Technische Universität München
Zentrum Mathematik

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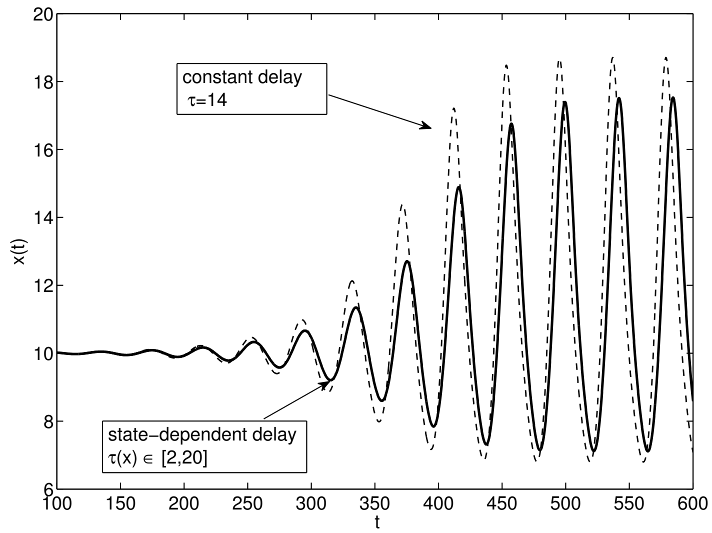
Maria Vittoria Barbarossa



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Abstract

This thesis introduces a new class of nonlinear neutral functional differential equations (abbreviated: NFDEs) with state-dependent delay for population dynamics. A neutral form of the *state-dependent blowfly equation* is obtained by formal derivation from a partial differential equations model of the Gurtin-MacCamy type. An extension of the existing theory for NFDEs with state-dependent delay is provided, thus allowing for results on existence, uniqueness and smoothness of solutions, as well as linearized stability of equilibria, of the new class of equations. The last part of the thesis presents a delay differential equations (DDEs) model for the dynamics of tumor growth, including proliferating tumor cells, phase-specific drugs and immunotherapy.

Zusammenfassung

Die vorliegende Doktorarbeit beschäftigt sich mit einer neuen Klasse nichtlinearer neutraler Differentialgleichungen (Englisch: Neutral functional differential equations, NFDEs) mit zustandsabhängiger Retardierung aus der Populationsdynamik. Ausgehend von einem System partieller Differentialgleichungen vom Gurtin-MacCamy Typ wird eine neutrale Form der *state-dependent blowfly equation* (Blowfly Gleichung mit zustandsabhängiger Retardierung) abgeleitet. Eine Erweiterung der existierenden Theorie nichtlinearer neutraler Differentialgleichungen mit zustandsabhängigen Retardierungen ist nötig für die Analyse der neuen Gleichungsklasse. Ergebnisse über Existenz, Eindeutigkeit und Glattheit der Lösungen, sowie über linearisierte Stabilität von Gleichgewichtslösungen werden hergeleitet. Der letzte Teil der Arbeit diskutiert ein Differentialgleichungsmodell mit Retardierung zur Abbildung der Interaktion proliferierender Tumorzellen, phasenspezifischer Chemotherapie und Immunotherapie.

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Contents

1. Preface

In all biological phenomena it is necessary to examine not only immediate actions but also those depending on the past, that is, on the changes which the species have undergone. These actions were first called hereditary actions*; but this name was not well chosen .... It was found preferable to use the term* historical actions *or* actions belonging to memory. *(V. Volterra, 1939 [121])*

In contrast to ordinary differential equations (ODEs), **delay differential equations (DDEs)** allow the inclusion of *historical actions* into mathematical models. A delay differential equation with **discrete delay** [1] is usually given in the form

$$\dot{x}(t) = f(t, x(t), x(t-\tau)), \tag{1.1}$$

with $f : \mathbb{R} \times \mathbb{R}^n \times \mathbb{R}^n \to \mathbb{R}^n$. Depending on the complexity of the problem, the delay τ may be a constant value ($\tau \geq 0$), a function of the time ($\tau(t) \geq 0$), or a function of the solution x itself ($\tau(x(t)) \geq 0$). Accordingly, equation (1.1) is called a differential equation with **constant delay**, **time-dependent delay**, or **state-dependent delay**, respectively.

When the right-hand side of the problem depends not only on the history of the solution x, but also on the history of the derivative $\dot{x}$, that is,

$$\dot{x}(t) = g(t, x(t), x(t-\tau), \dot{x}(t-\tau)),$$

we have a neutral delay differential equation or **neutral functional differential equation (NFDE)**. The same terminology applies to the case of multiple delays, i.e., when the problem has the form

$$\dot{x}(t) = f_p(t, x(t), x(t-\tau_1), \cdots, x(t-\tau_p)), \qquad f_p : \mathbb{R} \times \mathbb{R}^n \times (\mathbb{R}^n)^p \to \mathbb{R}^n.$$

The **initial value problem (IVP)** for a delay differential equation is defined by

$$\begin{aligned} \dot{x}(t) &= f(t, x(t), x(t-\tau)), & t &\geq t_0, \\ x(t) &= \phi(t), & t &\leq t_0, \end{aligned}$$

where ϕ is called the **history function** or the **initial data** of the IVP.

[1] Differential delay problems can be classified into equations with *discrete delay* and equations with *distributed delay*. In the latter case, the problem takes the form

$$\dot{x}(t) = f\left(t, x(t), \int_0^\infty k(s)x(t-s)\, ds\right).$$

The integral term in the right-hand side expresses a weighted average of the delay on $[0, \infty)$. In this thesis we do not discuss the case of distributed delays.

Introductory literature on delay differential equations can be found in Driver [43], MacDonald [85], and Cooke [32]. Among the first references that appeared in this field, we like to mention the books by Bellman and Cooke [15] and El'sgol'ts and Norkin [50]. Kuang [79] presents exhaustively the theory of DDEs with constant delays, paying particular attention to their application in population dynamics.

More and more in the last century, DDEs have been used to give a mathematical description of phenomena from different fields such as economics [23], physics [51, 112], and biology. A restriction to this last discipline yields a variety of models in physiology [17, 86], tumor growth [27, 40, 81, 120], epidemics [21, 26, 36, 83], ecology [11, 77, 84, 103], and population dynamics [7, 72, 100, 110, 134].

Perhaps the first example of a delay model in population dynamics was given in 1948 by Hutchinson, who tried to explain population oscillations by introducing a time lag ($r > 0$) into the classical *logistic equation*. The idea behind **Hutchinson's equation**,

$$\dot{x}(t) = bx(t)\left(1 - \frac{x(t-r)}{K}\right), \tag{1.2}$$

is that when the population size has reached the environmental capacity K, reproduction does not stop immediately, but only after a certain time $r > 0$.

Hutchinson's equation had an enormous impact on modeling population dynamics with delay equations and on the systematic study of the global behavior of differential equations with delays [74–76, 97, 134]. However, in spite of its mathematical relevance, Hutchinson's model (1.2) has been criticized by several authors [58, 61, 63, 100]. The main reason for disappointment is that if one interprets (1.2) as a birth-death equation, then one finds the delay in the death rate. From a biological point of view, it is difficult to motivate a delayed death term.

An alternative to Hutchinson's equation was given by Perez et al. [100], who proposed the so-called **blowfly equation**,

$$\dot{x}(t) = b(x(t-\tau))x(t-\tau) - \mu(x(t))x(t), \tag{1.3}$$

to explain the dynamics of Nicholson's populations of flies [93, 94]. This model describes the dynamics of a population x of mature individuals and the delay, $\tau > 0$, represents the time necessary for an individual to reach sexual maturity. That is, mature individuals produce offspring which stays a certain time τ in the juvenile class and enters the adult (or mature) class τ time units after birth.

After its first appearance in [100], the *blowfly equation* (1.3) has been rediscovered by several authors [7, 58]. Hadeler and Bocharov [20, 63] showed that (1.3) can be formally derived from a partial differential equation (PDE) system of the Gurtin-MacCamy type [60].

Both in (1.2) and (1.3), as well as in most of the above-mentioned references, the delay has been assumed to be a fixed value. It is only in the recent past, that authors started to describe more complex phenomena by including into the model a dependence of the delay on the solution itself [3, 13, 87, 91]. In several cases, models written in the form of DDEs with constant delay, such as

$$\dot{x}(t) = f(x(t-\tau)),$$

were extended to include a state-dependent delay,

$$\dot{x}(t) = f(x(t-\tau(x(t)))).$$

However, delays often belong, perhaps in an implicit manner, to the nature of real world phenomena. For example, in population dynamics delays arise naturally from *threshold phenomena*, which express the transition of an individual through different stages (cf. Section 2.2). So, one may wonder if it is formally (and physically) correct to replace a zero or a constant delay by a state-dependent one.

In this thesis, we shall present an example in which the simple substitution of a state-dependent delay for a constant one is not sufficient to represent the biological process. We shall consider the *blowfly equation* (1.3) and let the maturation time of individuals depend on the population size x. From a biological point of view, by this assumption we take into account so-called *compensatory responses*, which are based on density-dependent mechanisms [117]. For example, biological experiments suggest that declines in the age-at-maturity are caused by compensatory responses to declining population size. On the other side, a reduction in the (adult) population size may allow for larger intake of nutrients by immature individuals and therefore also for faster growth and shorter maturation time [29, 117].

Thus, it seems reasonable to let the delay τ depend on the population size. In a naive approach, one might substitute τ in (1.3) with a state-dependent delay $\tau(x(t))$ and obtain an equation of the form

$$\dot{x}(t) = b(x(t-\tau(x(t))))x(t-\tau(x(t))) - \mu(x(t))x(t). \tag{1.4}$$

However, one should be careful, because now the age-at-maturity τ is not a fixed value, but depends on the state of the system $x(t)$. Therefore, changes in the class of adult individuals cannot be only given by recruitment (juveniles who get older) or death, but should also take into account changes of the definition of adultness, that is, changes of $\tau(x(t))$.

As we show in Chapter 3, the correct extension of (1.3) has the form

$$\dot{x}(t) = \frac{\tilde{b}\big(x(t), x(t-\tau(x(t)))\big) - \mu(x(t))x(t)}{1 + \dot{\tau}(x(t))\tilde{b}\big(x(t), x(t-\tau(x(t)))\big)}. \tag{1.5}$$

This equation, which we shall call the **state-dependent blowfly equation**, can be derived from an age-structured population model, following similar lines to [20, 63]. The result (1.5) of a formal derivation is rather different from equation (1.4), which can be obtained by a simple "delay substitution". We will compare (1.4) and (1.5) from an analytical and a numerical point of view, and visualize the differences with the help of numerical examples.

In Section 3.2 we present a generalization of (1.5). The general model, which includes not only a state-dependent delay $\tau(x(t))$ but also a neutral term, has the form

$$\dot{x}(t) = \frac{\beta_{t,\tau} - \tilde{\mu}_1(x(t))}{1 + \dot{\tau}(x(t))\beta_{t,\tau}}, \tag{1.6}$$

with

$$\beta_{t,\tau} = \left[\tilde{b}_1(x(t-\tau)) + b_2(x(t-\tau))\frac{\dot{x}(t-\tau) + \tilde{\mu}_1(x(t-\tau))}{1 - \dot{\tau}(x(t-\tau))\dot{x}(t-\tau)}\right] e^{-\int_{t-\tau}^{t} \mu_0(x(\rho))d\rho}, \qquad \tau = \tau(x(t)).$$

This equation describes the evolution in time of a population of mature individuals, whose fertility is characterized by a peak, when individuals reach sexual maturity at age $\tau(x(t))$. Moreover, equation (1.6) can be compared to the neutral equation with constant delay $\hat{\tau}$,

$$\dot{x}_m(t) = (b_m + b_2\mu_m)e^{-\mu_i\hat{\tau}}x_m(t-\hat{\tau}) + b_2e^{-\mu_i\hat{\tau}}\dot{x}_m(t-\hat{\tau}) - \mu_m x_m(t), \qquad t > \hat{\tau},$$

introduced in [20, 62, 63] by Hadeler and Bocharov (see Section 2.1 for more details). To the best of our knowledge there is no example, other than (1.6), of neutral equations with state-dependent delay in population dynamics. However, one can find modifications of neutral equations with constant delays, which include non-constant delays [136].

Once we derived the *state-dependent blowfly equation* (1.5) and its neutral version (1.6), the natural continuation of the thesis lies in the analysis of these models. We are interested in existence, uniqueness, positivity and smoothness, as well as long-term behavior of solutions.

As we shall explain in Chapters 4 and 5, the *state-dependent blowfly equation* can be investigated with the help of the theory of Retarded Functional Differential Equations (RFDEs) [37, 64,66], and its application to the case of state-dependent delay problems [48,67,116,125–128].

Concerning neutral equations with state-dependent delay, there is less literature at our disposal. While NFDEs with constant delay can in part be investigated with the help of results in [15, 64, 66], there is no general theory for NFDEs with state-dependent delay.

A recent contribution to the theory of neutral equations with state-dependent delay is due to Walther [124, 129, 130]. In [124, 129], Walther constructed a set of hypotheses which yield smooth solutions and allow for linearized stability of a class of NFDEs with state-dependent delay and constant coefficients. This framework has been extended in [130] to investigate linearized stability of a more general class of NFDEs with state-dependent delay. We present Walther's work in Chapter 6.

In this context, the thesis contributes with three new results. The first one is related to a Lipschitz property for NFDEs, which can be applied to the case of neutral equations with state-dependent delay. The second result is a new hypothesis, which allows us to investigate linearized stability of a wider class of NFDEs with state-dependent delay. Finally we show how to linearize semiflows from neutral equations with state-dependent delays about nontrivial equilibria.

The achieved theoretical results allow for the analysis of two new classes of neutral equations with state-dependent delay, more general than those proposed by Walther in [124, 129, 130].

We will conclude our journey through the theory of (neutral) equations with state-dependent delay with the analysis of (1.6).

In the last part of the thesis we consider delay equations modeling cancer biology and tumor growth.

One of the main reasons for cancer seems to be a malfunction of the control system in the cell cycle, which leads to uncontrolled growth of a group of cells [119]. *Proliferating tumor cells* are responsible for extensions of the tumoral mass. It is nowadays possible to identify cells in the mitotic phase (where two new cells are generated from a mother cell), and to target and destroy them by *phase-specific drugs*. In this way medical doctors can reduce cell divisions and slow down or block tumor growth.

During the last three decades, mathematicians have been attempting to provide a description of tumor growth, contributing with a large variety of models [1, 16, 30, 104]. Many recent works in this direction include time delays. In most cases a constant time delay τ is introduced to represent the length of the *interphase* [25, 135], to describe the time it takes a cell to complete mitosis [27], or to indicate the time due to regulation processes [27, 105].

In Chapter 8 we introduce and analyze a mathematical model for tumor growth based on the dynamics of the cell cycle. Our delay differential equations model is essentially obtained by the methods we present in Chapter 3. Starting from a cell population structured by age, we derive a DDE system for proliferating tumor cells. Thanks to this approach, we are able to isolate cells in different phases of the cell cycle so that the effects of phase-specific drugs can be directly observed. Our model can be considered as an improvement of the approaches suggested in [81, 120].

Overview

This thesis is structured in three parts. The first part (Chapter 2 and Chapter 3) focuses on delay differential equations in population dynamics. We introduce a new class of neutral equations with state-dependent delay which describes the dynamics of an isolated population. The *state-dependent blowfly equation* is presented as a special case.

The second part of the thesis (Chapter 4 – Chapter 7) is devoted to the theory and analysis of (neutral) differential equations with state-dependent delay. The main goal of this part is to analyze the models introduced in Chapter 3.

The last part is concerned with a further biological application of DDEs with state-dependent and constant delays. We propose a DDE model for the cell cycle of proliferating tumor cells.

Chapter 2: Delays in Population Dynamics

In this chapter we give an overview of delay equations in mathematical models for the dynamics of isolated populations. Constant or state-dependent time delays allow for an accurate description of biological phenomena, e.g., they can explain population oscillations. We shall show that DDEs for population dynamics can be obtained from PDE models.

Chapter 3: A New Class of Equations

This chapter is dedicated to the central topic of the thesis, namely, a new class of equations with state-dependent delay for population dynamics.

In Section 3.1 we start with a Lotka-Sharpe model for an age-structured population. Introducing a *threshold age* τ (the age at which individuals are sexually mature), we distinguish juvenile individuals (y) from adult ones (x). In our assumptions, for a fixed time t, the threshold τ depends on the total adult population at time t, i.e., $\tau = \tau(x(t))$. By a formal derivation we obtain a system of DDEs with state-dependent delay and constant coefficients. In Section 3.2 we generalize the model of Section 3.1. On the one side, we let birth and death rates depend on the total adult population size x. On the other side, we assume that there is a peak in the fertility rate, when individuals reach maturity (at age $a = \tau$). The result is a class of autonomous nonlinear neutral equations with state-dependent delay. A special case of this class of equations is the *state-dependent blowfly equation*.

In Section 3.4 we show that our neutral state-dependent DDEs for population dynamics can be written in the form of a system of an ODE and a shift operator. This formulation has advantages from the numerical point of view. Numerical simulations of solutions to our equations with state-dependent delay are given in Section 3.5.

Chapter 4: Theory of Equations with State-Dependent Delay

We present an outline of the theory of RFDEs, which is the background for the theory of equations with state-dependent delays. We briefly report results from [37, 64, 66] on the stability of linear autonomous RFDEs and on the linearized stability of nonlinear equations.

Equations with state-dependent delay can in general be expressed in the RFDE formulation. However, the theory of retarded functional differential equations cannot be applied in a straightforward way. Walther and co-authors [67, 125–127] considered a class of DDEs with state-dependent delay and developed a set of hypotheses in order to guarantee existence, uniqueness and smoothness of solutions. In Section 4.2 we provide an outline of the works [125–127] and [67]. In particular, we report a principle of linearized stability for equations with state-dependent delay.

Chapter 5: A Class of Equations with State-Dependent Delay

We investigate solutions to (non-neutral) problems with state-dependent delay from Chapter 3. To this purpose, we introduce a general class of nonlinear equations with state-dependent delay of the form

$$\dot{x}(t) = \frac{\beta\left(x(t), x(t-\tau(x(t)))\right) - \delta(x(t))}{1 + \dot{\tau}(x(t))\beta\left(x(t), x(t-\tau(x(t)))\right)}.$$

With the help of the theory in Chapter 4, we investigate existence, uniqueness and long-term behavior of solutions to this class of delay equations. In this context, we present results on linearized stability of the *state-dependent blowfly equation*. To conclude the chapter, we show some qualitative differences between the problem with state-dependent delay and the corresponding one with constant delay.

Chapter 6: Theory of Neutral Equations with State-Dependent Delay

This chapter is devoted to the theory of neutral functional differential equations with state-dependent delays. In the first part we report from [124] several hypotheses, which guarantee existence and uniqueness of solutions of a class of NFDEs, $\dot{x}(t) = g(x_t, \partial x_t)$, with state-dependent delay. Under certain conditions, the solution segments of the NFDE generate semiflows on subspaces of the Banach spaces C^1 (of continuously differentiable functions) and C^2 (of twice continuously differentiable functions).

In Section 6.2 we present a new result on Lipschitz continuity of NFDEs, which can be applied to NFDEs with state-dependent delays. Section 6.3 is dedicated to results in [129, 130] about linearized stability of semiflows generated by neutral equations with state-dependent delay. We shall extend the framework in [130] to investigate semiflows from a wider class of equations. Further, we show how to rewrite a general neutral equation with state-dependent delay into the NFDE form and discuss linearization of semiflows at nontrivial equilibria.

Chapter 7: Two Classes of Neutral Equations with State-Dependent Delay

Here we introduce two classes of neutral equations with state-dependent delay,

$$\dot{x}(t) = \sum_{j=1}^{3} q_j\big(x(t), x(t-\tau(x(t))), \dot{x}(t-\tau(x(t)))\big),$$

and

$$\dot{x}(t) = \frac{\alpha\big(x(t), x(t-\tau(x(t))), \dot{x}(t-\tau(x(t)))\big) - \gamma(x(t))}{1 + \dot{\tau}(x(t))\alpha\big(x(t), x(t-\tau(x(t))), \dot{x}(t-\tau(x(t)))\big)}.$$

We use the theory in Chapter 6 to investigate existence, uniqueness and smoothness of solutions, as well as linearized stability of equilibria. For both classes of NFDEs, we present examples from biology. In this context, we study the neutral equation (1.6).

Chapter 8: Proliferating Tumor Cells

We introduce and analyze a mathematical model for tumor growth based on the dynamics of the cell cycle. The modeling technique of Chapter 3 allows us to isolate and describe cells in different phases of the cell cycle, distinguishing an immature cell population (cells in the interphase) from a mature one (mitotic cells). We use a constant delay, $\tau > 0$, to represent the length of the interphase, that is, the time between two consecutive cell divisions. Our DDE system can be compared to the models in [81, 120]. In Section 8.3 we discuss nonnegativity of solutions, look at the long term dynamics of the problem and investigate the stability of the tumor-free equilibrium. Section 8.4 presents numerical simulations of the interplay between tumor cells and immune system effectors. As the time between two consecutive cell divisions, i.e., the time a cell stays in the *interphase*, is affected by medicaments [107], we simulate the effects of different interphase durations on the dynamics of the tumor cell population. The content of this chapter has been recently published in [12].

To conclude the thesis, we summarize the achieved results and indicate directions for future research. The appendix provides details of all numerical simulations and minor analytical results.

Part I.

Populations and Delays

2. Delays in Population Dynamics

For over a century, one of the most challenging questions of mathematical biology has been the appropriate description of population dynamics. The classical Verhulst's model, also known as the *logistic equation*, was shown to be not always appropriate to explain certain phenomena, such as oscillations or chaotic behavior. For this reason mathematicians started to include time lags in their modeling approaches. The result is a variety of equations with constant or state-dependent delay for the dynamics of isolated populations. We collect few examples in Section 2.1.

Many delay models for population dynamics (some of them are presented in Section 2.1) have been obtained by introducing a constant or state-dependent delay in a known ordinary differential equation model. However, few authors showed that delay differential equations (DDEs) for population dynamics can be derived from partial differential equation (PDE) settings. Delays, indeed, arise from *threshold phenomena*, that is, phenomena which express the transition of an individual through different stages. In Section 2.2 we report an example from [96] for a population structured by age and show how to arrive at a system of DDEs.

2.1. Delay Equations in Population Biology

According to Hutchinson [73], scientific demography began in 1662 as Graunt's work *Natural and political observations mentioned in a following index and made upon the bills of mortality* appeared. Graunt studied birth and death registers of few quarters of London and predicted that the population in London would double every 64 years. His work was the starting point for further research in demography and population dynamics.

At the end of the eighteenth century, Malthus published anonymously *An essay on the principle of population* (republished in [89]), suggesting that "the power of population is indefinitely greater than the power in the earth to produce subsistence for man. A population, when unchecked, increases in a geometrical ratio. Subsistence increases only in an arithmetical ratio." In Malthus' opinion, population growth had to slow down, or a part of the population would have died for misery. On the other side, in a later and less pessimistic edition of his work, Malthus stated that "the power of the earth to produce subsistence is not unlimited, but it is strictly speaking indefinite" (cf. [73, Ch. 1]). Although there is no mathematical formulation in Malthus' work [89], his theory is expressed by the **exponential growth model**, or *Malthusian growth model* [92],

$$\dot{x}(t) = \tilde{b}x(t), \tag{2.1}$$

where $x(t)$ is the population size at time t and $\tilde{b} > 0$ the constant population net growth rate.

Almost half a century after Malthus, Verhulst reconsidered the problem and realized that population increase must be limited by “the size and fertility of the country” [9]. Verhulst [118] suggested that if a population has a constant growth rate $b > 0$ and the environment has a limited capacity $K > 0$, the population size at time t is regulated by the **logistic equation**,

$$\dot{x}(t) = bx(t)\left(1 - \frac{x(t)}{K}\right). \tag{2.2}$$

When x is small compared to K, the population size increases almost exponentially. The growth rate gets smaller, the closer x gets to the maximal capacity K (cf. Figure 2.1(a)) [92].

In 1920, the *logistic equation* (2.2) was rediscovered by Pearl and Read who modeled the population growth in the United States [98]. Moreover, during the twentieth century, experiments were performed to test the validity of Verhulst's model [78, Ch. 11]. In several cases, it turned out that (2.2) does not properly describe the dynamics of an isolated population [113].

Hutchinson [72, 73] argued that “the process of reproduction is not instantaneous” and that there is a time lag ($r > 0$) which should be included into (2.2).

Hutchinson's equation,

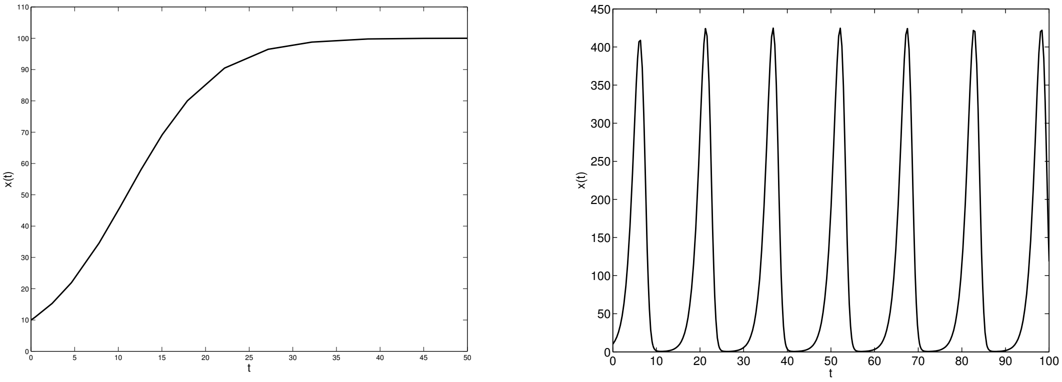
$$\dot{x}(t) = bx(t)\left(1 - \frac{x(t-r)}{K}\right), \tag{2.3}$$

is probably the first example of a delay model for population dynamics. The idea behind (2.3) is that when the population size x has reached the environmental capacity K, reproduction does not stop immediately, but only after a certain time $r > 0$. For this reason the derivative $\dot{x}(t)$ is proportional to $K - x(t-r)$. The time delay r can cause oscillations in solutions of (2.3), see Figure 2.1(b) for an example. Thus, Hutchinson's equation can explain the oscillatory behavior frequently observed in population dynamics. Among the best-known examples of population oscillations are Nicholson's experimental data obtained from cultures of the sheep blowfly *Lucilia cuprina* [93, 94], and Walters' data [123], from the planktonic crustacean *Daphnia*.

Letting $x(t) = K(1 - y(t))$ and changing time scale, from (2.3) one obtains

$$\dot{y}(t) = -\alpha y(t-1)\left(1 + y(t)\right), \tag{2.4}$$

with $\alpha = br \geq 0$. This equation had an enormous impact on the systematic study of the global behavior of differential equations with delays. Wright [134] proved that the zero solution of (2.4) is globally stable for $\alpha < \frac{3}{2}$ and that for $\alpha > \frac{\pi}{2}$ there exist undamped bounded oscillatory solutions. Wright's conjecture, that the zero solution of (2.4) is globally stable for $\alpha < \frac{\pi}{2}$, has not been proved yet. Kakutani and Markus [75] showed that all solutions of (2.4) oscillate if $\alpha > \frac{1}{e}$ and converge to zero (without oscillations) if $\alpha < \frac{1}{e}$. Jones [74] proved the global existence of periodic solutions for $\alpha > \frac{\pi}{2}$. Further results on existence of non-constant periodic solutions of (2.4) can be found in [76, 79, 97] and references thereof.



(a) *Logistic equation.* (b) Hutchinson's equation.

Figure 2.1: (a) Solutions of the *logistic equation* (2.2) increase up to the environmental capacity K. (b) The delay $r > 0$ can cause oscillations in solutions of (2.3). Parameter values in Appendix A, Table A.1.

Despite its oscillatory solutions, Hutchinson's model (2.3) has been criticized by several authors [58, 61, 63, 100]. The main reason for disappointment is that if one interprets Verhulst's model as a birth-death equation, $\dot{x} = b(x)x - \mu(x)x$, with constant birth rate $b(x) = b$ and linear death rate $\mu(x) = bx/K$, then Hutchinson's equation puts the delay in the death rate. From a biological point of view, it is difficult to motivate a delayed death term.

An alternative to Hutchinson's equation was given by Perez et al. [100], who proposed the so-called **blowfly equation**,

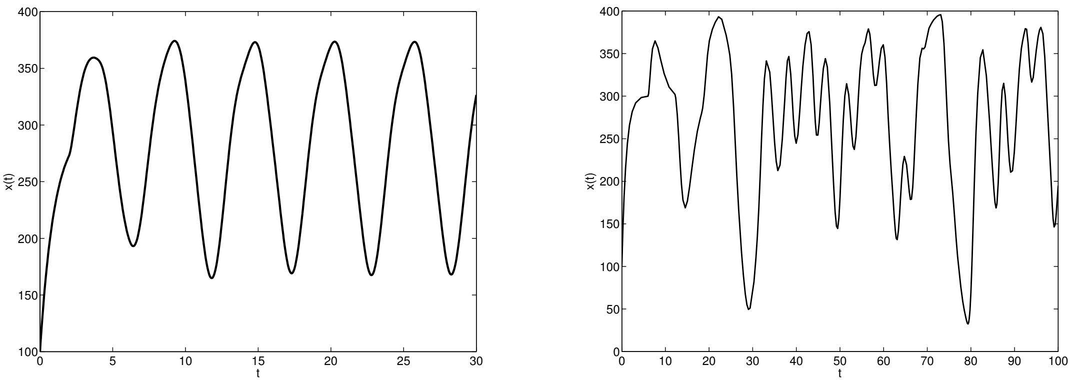
$$\dot{x}(t) = b(x(t-\tau))x(t-\tau) - \mu(x(t))x(t). \tag{2.5}$$

Here the delay $\tau > 0$ is meant to express the time necessary for an individual to reach maturity (in other words, individuals younger than τ age units cannot reproduce). Hence, equation (2.5) is supported by the biology. Moreover, this model can explain the observed oscillatory, almost chaotic, behavior of Nicholson's blowfly data (Figure 2.2).

Independent of Perez's work, Gurney, Blythe and Nisbet [58] arrived at a similar result. Beside objecting the fact that Hutchinson's equation does not accurately reproduce Nicholson's experimental data (the error between the best fit of the model and the data is large), Gurney and coauthors underlined that the model "mixes up time-lagged and not time-lagged contributions". They suggested that the delay should be in the birth term, rather than in the death term and that the dynamics of a sexually mature population x_m can be described by

$$\dot{x}_m(t) = R(x_m(t-\tau)) - \mu_m x_m(t),$$

where $R(x_m(t-\tau))$ is the recruitment term into the adult population, $\mu_m > 0$ is the death rate, and $\tau > 0$ are the time units necessary for a newborn to reach sexual maturity.



(a) $\tau = 2$. (b) $\tau = 6$.

Figure 2.2: Oscillatory solutions of the *blowfly equation* (2.5) for different values of τ. Parameter values in Appendix A, Table A.1.

Gurney and Nisbet choose the expression $R(y) = b_m y \exp(-y/x_\tau)$, where x_τ is defined as the population size at which maximal reproduction is possible. The resulting model,

$$\dot{x}_m(t) = b_m x_m(t-\tau)\exp(-x_m(t-\tau)/x_\tau) - \mu_m x_m(t), \tag{2.6}$$

shows a nontrivial stationary point $\bar{x} = x_\tau \ln(b_m/\mu_m)$. The stability of $\bar{x}$ is determined by the quantities $b_m\tau$ and $\mu_m\tau$, and both damped and sustained oscillations are possible [58].

Another model in this direction was proposed by Aiello and Freedman [2]. They considered a single species growth model for a population whose individuals go through an immature and a mature stage, and defined $\tau > 0$ as the time from birth to maturity of an individual. We denote by $x_i(t)$ and $x_m(t)$ the number of individuals in the immature and mature population, respectively. Let $b_m > 0$ be the fertility rate of the mature population and $\mu_i > 0$ be the death rate of the immature population. Further, let the mature population x_m be characterized by a non-constant death rate, $\mu_m(x_m) = \mu_m x_m,\ \mu_m > 0$. Under the assumption that the dynamics of x_i and x_m are known in the time interval $[-\tau, 0]$, Aiello and Freedman [2] proposed the following model:

$$\begin{cases} \dot{x}_i(t) &= b_m x_m(t) - \mu_i x_i(t) - e^{-\mu_i\tau}\phi(t-\tau), \\ \dot{x}_m(t) &= e^{-\mu_i\tau}\phi(t-\tau) - \mu_m x_m^2(t), \end{cases} \qquad 0 < t \le \tau, \tag{2.7a}$$

$$\begin{cases} \dot{x}_i(t) &= b_m x_m(t) - \mu_i x_i(t) - b_m e^{-\mu_i\tau} x_m(t-\tau), \\ \dot{x}_m(t) &= b_m e^{-\mu_i\tau} x_m(t-\tau) - \mu_m x_m^2(t), \end{cases} \qquad t > \tau, \tag{2.7b}$$

where $\phi(t)$ is the assumed birth rate of $x_i(t)$ at time $t \in [-\tau, 0]$.

It is interesting to notice the analogy with the system obtained by Hadeler and Bocharov [20,63] from a PDE model of the Lotka-Sharpe type [111]. For the same mature and immature population, the formal derivation in [20,63] yields

$$\begin{cases} \dot{x}_i(t) \;= b_m x_m(t) - \mu_i x_i(t) - e^{-\mu_i \tau} u_0(\tau - t), \\ \dot{x}_m(t) = e^{-\mu_i \tau} u_0(\tau - t) - \mu_m x_m(t), \end{cases} \qquad t \leq \tau, \tag{2.8a}$$

$$\begin{cases} \dot{x}_i(t) \;= b_m x_m(t) - \mu_i x_i(t) - b_m e^{-\mu_i \tau} x_m(t - \tau), \\ \dot{x}_m(t) = b_m e^{-\mu_i \tau} x_m(t - \tau) - \mu_m x_m(t), \end{cases} \qquad t > \tau, \tag{2.8b}$$

with $u_0(a) \geq 0$, $a \geq 0$, the initial age distribution of the PDE model. In (2.8), the death rate of adult individuals is a constant $\mu_m > 0$, which does not depend on the population size.

Neutral delay differential equations (NFDEs) have been less frequently used in population dynamics, possibly because the NFDE theory has been developed only in the last century. Perhaps the first example of a NFDE for population dynamics was given in 1988 by Gopalsamy and Zhang [56], who suggested a neutral version of Hutchinson's equation,

$$\dot{x}(t) = bx(t) \left(1 - \frac{x(t-r) + c\dot{x}(t-r)}{K} \right). \tag{2.9}$$

This equation resulted to be challenging from a mathematical point of view [53, 79], but its biological meaning is still unclear. In particular it seems difficult to motivate the neutral term in the death rate.

From a biological point of view, more meaningful than (2.9) is the model suggested by Hadeler and Bocharov [20, 62, 63], a neutral version of the *blowfly equation*,

$$\dot{x}_m(t) = (b_m + b_2 \mu_m) e^{-\mu_i \tau} x_m(t - \tau) + b_2 e^{-\mu_i \tau} \dot{x}_m(t - \tau) - \mu_m x_m(t), \qquad t > \tau. \tag{2.10}$$

This is a general version of the equation for x_m in (2.8b) and it is obtained under the assumption that at age $a = \tau > 0$, when individuals reach maturity, there exists a peak of weight $b_2 > 0$ in the fertility rate.

All models mentioned in this section are given in the form of delay differential equations with constant delay. However, in the last decades several authors suggested that the delay should rather depend on the population size itself.

State-Dependent Delays in Population Dynamics

In the context of population dynamics, the delay arises frequently as the maturation time from birth to adulthood, and this time is in some cases a function of the total population. (O. Arino et al., 2001 [8])

Once more we consider system (2.7b) from [2]. According to this model, at any time t and for any newborn, the time from birth to maturity is a fixed value ($\tau > 0$) and is not affected, e.g., by any changes in the population size.

In order to make the model closer to reality, Aiello, Freedman and Wu [3] substituted τ in (2.7b) by $\tau(x(t))$, where $x(t) = x_i(t) + x_m(t)$ is the total population at time t. It was assumed that $\tau(x)$ is a monotonically increasing function of x, bounded between two finite nonnegative values, that is,

$$\dot{\tau}(x) \geq 0, \qquad 0 < \tau_m \leq \tau(x) \leq \tau_M < \infty,$$

and that $t - \tau(x(t))$ is a monotonically increasing function of t. The model by Aiello et al. [3] is thus given by

$$\begin{cases} \dot{x}_i(t) \; = b_m x_m(t) - \mu_i x_i(t) - b_m e^{-\mu_i \tau(x(t))} x_m(t - \tau(x(t))), \\ \dot{x}_m(t) = b_m e^{-\mu_i \tau(x(t))} x_m(t - \tau(x(t))) - \mu_m x_m^2(t), \end{cases} \qquad t \geq 0, \tag{2.11}$$

with initial data $x_i(t) = \phi_i(t) \geq 0$ and $x_m(t) = \phi_m(t) \geq 0$ for $t \in [-\tau_M, 0]$. The authors showed that the mature population x_m is uniformly bounded away from zero and that, with some restrictions on the initial conditions, also the immature population x_i is nonnegative. The system with state-dependent delay (2.11) has a positive equilibrium, but unlike the constant delay case (2.7b), this equilibrium may not be unique [3].

System (2.11) was extended in [4] to include a more general birth function:

$$\begin{cases} \dot{x}_i(t) \; = b_m(x_m(t)) - \mu_i x_i(t) - e^{-\mu_i \tau(x(t))} b_m(x_m(t - \tau(x(t)))), \\ \dot{x}_m(t) = e^{-\mu_i \tau(x(t))} b_m(x_m(t - \tau(x(t)))) - \mu_m x_m(t), \end{cases} \qquad t \geq 0. \tag{2.12}$$

The birth rate $b_m(x_m)$ is assumed to be linear in x_m for small values of x_m and to tend toward zero for $x_m \to \infty$. The assumptions on the state-dependent delay $\tau(x)$ are the same as in [3].

Fathallah et al. [8] disagreed with both models in [3] and [4], arguing that if an individual reaches maturity at time t, the time τ from birth to maturity of the individual should not depend on the size of the population at time t, but on the population size x at the time of birth. In [8], the authors introduced the value $z(t)$ as the date of birth of an individual who becomes mature at time $t \geq 0$ and suggested that the maturation time τ is $\tau(x(z(t)))$. The resulting model for the total population (x) and the adult sub-population (x_m) is

$$\begin{cases} \dot{x}(t) \; = -\mu_i(x(t) - x_m) + b_m x_m(t) - \mu_m(x_m(t))x_m(t), \\ \dot{x}_m(t) = b_m e^{-\mu_i \tau(x(z(t)))} x_m(z(t))\dot{z}(t) - \mu_m(x_m(t))x_m(t), \end{cases} \qquad t \geq 0, \tag{2.13}$$

where $\mu_i > 0$ and $\mu_m(x_m)$ are the mortality rates of the immature and mature sub-population, respectively.

Instead of introducing a (state-dependent) delay as a maturation threshold, Bélair [13] assumed that the lifespan L of individuals in a population is a function of the population size x. The author let the birth rate b depend on x, too. Then the total number of individuals who were born and are still alive at time t is given by

$$x(t) = \int_{t-L(x(t))}^{t} b(x(s))\, ds,$$

and differentiation with respect to t yields

$$\dot{x}(t) = \frac{b(x(t)) - b(x(t - L(x(t))))}{1 - \dot{L}(x(t))b(x(t - L(x(t))))}. \tag{2.14}$$

With an appropriate set of initial data, Bélair [13] shows existence and uniqueness of solutions to (2.14). Further, by "freezing the delay" at an equilibrium solution $\bar{x}$ (cf. p. 70), the author associates a linear equation to the nonlinear problem (2.14). In Section 3.3 we present an equation, which may resemble (2.14). As we shall see, our equation is not introduced heuristically, but can be systematically derived from a PDE model for a population structured by age.

To the best of our knowledge, there is no example of neutral equations with state-dependent delay in population dynamics. In some recent literature one can find modifications of neutral equations with constant delay, which include non-constant delays, such as the one by Yang and Cao [136],

$$\dot{x}(t) = x(t)\Bigg(b(t) - \mu(t)x(t) - \sum_{j=1}^{n} d_j(t)x(t - r_j(t)) - \sum_{j=1}^{n} c_j(t)\dot{x}(t - s_j(t))\Bigg). \tag{2.15}$$

Here the functions $b(t)$, $\mu(t)$, $d_j(t)$, $r_j(t)$, $c_j(t)$, $s_j(t)$, $j = 1, \dots, n$, are assumed to be nonnegative, continuous, periodic functions. However, we regard (2.15) as a neutral equation with non-constant delay, rather than a neutral equation with state-dependent delay. Conditions for existence of periodic solutions to (2.15) are provided in [136].

As in some of the previous examples, many delay equations in biology have been obtained by taking an ordinary differential equation problem and inserting a constant or state-dependent delay into it [24, 40, 49, 71, 102, 136]. However, especially in population dynamics, one should be careful when introducing delay equations. MacDonald [85] observed that

> *in order to incorporate maturation data in a model, one has to start with an age-structured model, which is necessarily formulated in terms of partial differential equations, and to make sure that this model can reasonably be replaced by one formulated in terms of a functional differential equation.*

Hence, modeling population dynamics, one should start from a (e.g., age-) structured model and simplify the equations, replacing the "effects of the structure" by a delay. In the next section we briefly present some results on the connection between PDEs and delay equations that has already been thoroughly investigated in the past.

2.2. From Partial Differential Equations to Delay Differential Equations

In the attempt of achieving a mathematical description of the dynamics of an isolated population, it has been recognized that the life of an individual is characterized by many age-related factors, such as size, fecundity, growth, mortality [19]. Under the assumption that aging is a uniform phenomenon among individuals of the same population, several models have been formulated in terms of PDEs (for example, by Lotka and Sharpe [111], McKendrick [90], von Foerster [122], Gurtin and MacCamy [60]) or discrete-time analoga (e.g., by Leslie [80]).

The disadvantage of such detailed approaches is due to the fact that it is hard to get equivalently elaborate information from experiments. Further, in some cases the analysis or numerical simulation of a complex structured model is not easy to be carried on. Many mathematicians have thus been looking for a compromise, which should provide a good description of the phenomenon, while being comfortable to handle from the theoretical point of view. In this context, it became evident that there exists a connection between PDEs and delay differential equations. A large contribution in this direction comes from the population theory group at Strathclyde University (Glasgow, United Kingdom) and goes back to the 1980s [18, 19, 59, 95, 96]. In the following we present the method suggested in [96] to reduce a PDE model for a structured population to a system of delay differential equations.

Let us consider an age- and mass-dependent population dynamics and let $f(a, m, t)$ be the density of individuals of age a and mass m at time t. Then

$$\int_{a_1}^{a_2} \int_{m_1}^{m_2} f(a, m, t)\, dm\, da$$

is the number of individuals of age $a \in [a_1, a_2]$ and mass $m \in [m_1, m_2]$ at time t. The population dynamics can be described by the **balance equation**,

$$\frac{\partial}{\partial t} f(a, m, t) = -\frac{\partial}{\partial a} f(a, m, t) - \frac{\partial}{\partial m}(gf)(a, m, t) - \mu(a, m, t) f(a, m, t),$$

where $g(a, m, t)$ and $\mu(a, m, t)$ are growth rate, respectively death rate, of an individual of age a and mass m at time t. New individuals (of age $a = 0$) enter the population according to the **birth law**,

$$f(0, m, t) = \int_0^\infty \int_0^\infty b(a, \tilde{m}, m, t) f(a, \tilde{m}, t)\, d\tilde{m}\, da, \tag{2.16}$$

where $b(a, \tilde{m}, m, t)$ represents the per capita production rate of offspring of mass m at time t by individuals of mass $\tilde{m}$ and age a [96].

In a simpler approach, one could neglect the growth rate g and assume that birth and death rates do not depend on the mass, but only on the age of individuals. Then, the density $f(a, t)$ of individuals of age a at time t is regulated by the simpler balance equation,

$$\frac{\partial}{\partial t} f(a, t) = -\frac{\partial}{\partial a} f(a, t) - \mu(a, t) f(a, t). \tag{2.17}$$

An equivalent condition to the birth law (2.16) is given by the number of births at time t, that is,

$$B(t) = f(0,t) = \int_0^\infty b(a,t) f(a,t)\, da.$$

The probability that an individual born at time t survives at least to age a is given by

$$\sigma(t,a) = \exp\Big(- \int_t^{t+a} \mu(s-t,s)\, ds \Big).$$

Individuals of age a at time t are those born at time $t-a$, which survived from birth up to age a, that is,

$$f(a,t) = f(0,t-a)\sigma(t-a,a) = B(t-a)\sigma(t-a,a).$$

The last relation is well-defined only for $t > a$. It can be extended to all $t \leq 0$, assuming that the density $f(a,t)$ is known [59].

Let us now hypothesize that the species life can be approximated by a series of N stages (for example a butterfly has four stages: Egg, larva, pupa, adult) and that all individuals in the same stage have same growth, fertility and death rates. We can then assume that the transition from one stage to the next one occurs at a fixed age. Consequently, we define sub-populations,

$$x_j(t) = \int_{a_j}^{a_{j+1}} f(a,t)\, da, \tag{2.18}$$

that is, $x_j(t)$ is the number of individuals of age $a \in [a_j, a_{j+1}]$ at time t. The dynamics of x_j is given by

$$\dot{x}_j(t) = \underbrace{R_j(t)}_{\text{recruitment}} - \underbrace{M_j(t)}_{\text{maturation}} - \underbrace{\Delta_j(t)}_{\text{death}}, \tag{2.19}$$

where R_j is the recruitment rate into class j, M_j is the maturation rate from class j into class $j+1$ and Δ_j is the death rate of individuals in class j. On the other hand, from (2.18) we obtain

$$\begin{aligned}
\dot{x}_j(t) &= \frac{d}{dt} \int_{a_j}^{a_{j+1}} f(a,t)\, da \\
&= \int_{a_j}^{a_{j+1}} \frac{\partial}{\partial t} f(a,t)\, da \\
&\underset{(2.17)}{=} - \int_{a_j}^{a_{j+1}} \frac{\partial}{\partial a} f(a,t)\, da - \int_{a_j}^{a_{j+1}} \mu(a,t) f(a,t)\, da \\
&= -f(a_{j+1},t) + f(a_j,t) - \mu_j(t) x_j(t),
\end{aligned}$$

with death rate $\mu(a,t) = \mu_j(t)$ for all individuals in the age class $[a_j, a_{j+1}]$. Comparison with (2.19) yields

$$R_j(t) = f(a_j,t), \qquad \text{and} \qquad M_j(t) = f(a_{j+1},t) = R_{j+1}(t). \tag{2.20}$$

Newborns are produced by individuals in sub-population x_j at rate b_j, $j = 1, \ldots, N$, that is,

$$R_1(t) \;=\; f(0,t) \;=\; B(t) \;=\; \sum_{j=1}^{N} b_j(t)x_j(t).$$

Further, we have

$$\begin{aligned} R_j(t) &= B(t-a_j)\sigma(t-a_j,a_j), && j = 2,\ldots N,\\ M_j(t) &= B(t-a_{j+1})\sigma(t-a_{j+1},a_{j+1}), && j = 1,\ldots N-1,\\ M_N(t) &= 0. \end{aligned}$$

Let us now define $\tau_j = a_{j+1} - a_j$, the time an individual spends in developmental class j, and

$$P_j(t) = \frac{\sigma(t-a_{j+1},a_{j+1})}{\sigma(t-a_{j+1},a_j)},$$

the rate of individuals who entered class j at time $t-\tau_j$ and survived to class $j+1$, being recruited at time t. We find

$$\frac{M_j(t)}{R_j(t-\tau_j)} = \frac{B(t-a_{j+1})\sigma(t-a_{j+1},a_{j+1})}{B(t-\tau_j-a_j)\sigma(t-\tau_j-a_j,a_j)} = \frac{\sigma(t-a_{j+1},a_{j+1})}{\sigma(t-a_{j+1},a_j)} = P_j(t). \qquad (2.21)$$

Hence, we have simplified the dynamics of the age-structured population by assuming that individuals in the same stage, or age class, have same birth and death rates. We have defined the number x_j of individuals in age class j, that is, individuals of age $a \in [a_j, a_{j+1}]$, and we have shown that the dynamics of the sub-population x_j is regulated by

$$\begin{aligned} \dot{x}_j(t) &\;=\; R_j(t) - M_j(t) - \mu_j(t)x_j(t)\\ &\underset{(2.21)}{=} R_j(t) - R_j(t-\tau_j)P_j(t) - \mu_j(t)x_j(t), \end{aligned}$$

where

$$P_j(t) = \exp\Bigl(-\int_{t-\tau_j}^{t} \mu_j(s)\,ds\Bigr),$$

and

$$R_j(t) = \begin{cases} \sum\limits_{k=1}^{N} b_k(t)x_k(t), & j = 1,\\ \underset{(2.20)}{=} M_{j-1}(t) \underset{(2.21)}{=} R_{j-1}(t-\tau_{j-1})P_{j-1}(t), & j = 2,\ldots,N. \end{cases}$$

For example, let us consider a population with only two stages, that is, we have either immature (x_1) or mature individuals (x_2). Let $\tau = \tau_1 > 0$ be the time from birth to maturity of an individual. Let $\mu_1 > 0$ and $\mu_2 > 0$ be the death rate of immature individuals, respectively mature individuals. We assume that immature individuals do not reproduce ($b_1 = 0$) and that the fertility rate of mature individuals is $b_2 > 0$. Then we get

$$R_j(t) = \begin{cases} b_2 x_2(t), & j = 1, \\ R_{j-1}(t - \tau_{j-1}) P_{j-1}(t) = b_2 x_2(t - \tau) e^{-\mu_1 \tau}, & j = 2. \end{cases}$$

For the immature population x_1 we find

$$\begin{aligned} \dot{x}_1(t) &= R_1(t) - M_1(t) - \Delta_1(t) \\ &= b_2 x_2(t) - b_2 x_2(t - \tau) e^{-\mu_1 \tau} - \mu_1 x_1(t), \end{aligned}$$

and for the mature population,

$$\begin{aligned} \dot{x}_2(t) &= R_2(t) - \Delta_2(t) \\ &= b_2 x_2(t - \tau) e^{-\mu_1 \tau} - \mu_2 x_2(t). \end{aligned}$$

Similar results to those we have shown here could be obtained considering a size-structured population [69, 95].

The connection between partial differential equations and delay differential equations can be found in several other works [18–20, 59, 63, 87]. Hbid et al. [69] present examples of size- and age-structured models which can be reduced to delay differential equations with state-dependent delay. In Chapter 3 and Chapter 8 we shall derive differential equations with state-dependent delay from PDE models of the Gurtin-MacCamy type and of the Lotka-Sharpe type for age-structured populations.

3. A New Class of Equations

This chapter is devoted to a new class of equations with state-dependent delay for population dynamics.

In Section 3.1 we present the simplest of our models. We start with a Lotka-Sharpe model [111] for an age-structured population. In order to reduce the complexity of the structured model, we introduce a "threshold age" τ, which represents the age at which individuals become sexually mature. In this way we distinguish juvenile individuals (y) from adult ones (x). In particular, we assume that τ at time t depends on the size of the adult population, that is, $\tau(x(t))$. By a formal derivation we obtain a system of differential equations with state-dependent delay

$$\begin{aligned} \dot{y}(t) &= b_1 x(t) - b_1 x(t-\tau(x(t)))e^{-\mu_0 \tau(x(t))}\left(1 - \dot{\tau}(x(t))\dot{x}(t)\right) - \mu_0 y(t), \\ \dot{x}(t) &= \frac{b_1 x(t-\tau(x(t)))e^{-\mu_0 \tau(x(t))} - \mu_1 x(t)}{1 + \dot{\tau}(x(t)) b_1 x(t-\tau(x(t)))e^{-\mu_0 \tau(x(t))}}. \end{aligned}$$

Existence and uniqueness of solutions to this problem are investigated in Chapter 5.

In Section 3.2 we consider the Gurtin-MacCamy model [60], which describes an age-structured population whose birth and death rates depend on the total population size. Again, we distinguish juvenile (y) from adult (x) individuals and let birth and death rates depend on the adult population x. Further, we assume there is a peak in the fertility rate, when individuals reach maturity (at age $a = \tau$). Under these assumptions we obtain a class of autonomous neutral equations with state-dependent delay. The analysis of this kind of equations can be found in Chapter 7.

In Section 3.3 we provide the correct extension, by means of a state-dependent delay, of the classical *blowfly equation* (2.5). Our *state-dependent blowfly equation* is a special case of the class of equations derived in Section 3.2.

As we show in Section 3.4, (neutral) state-dependent DDEs for population dynamics can be written in the form of a system of an ODE and a shift operator. This reformulation of delay equations has been previously suggested by Hadeler and Bocharov [62, 63] and has advantages from the numerical point of view.

To conclude the chapter, we provide numerical simulations of solutions to our (neutral) equations with state-dependent delay. We aim to visualize qualitative differences between an equation with state-dependent delay and a corresponding one, with constant delay.

3.1. A Simple Model

The classical representation of an isolated population structured by age was introduced by Lotka and Sharpe [111]. Let $p = p(t,a)$ be the **population density** with respect to the age a at time t. Then the original Lotka-Sharpe model describes the dynamics of p by

$$p(t,a) = \gamma(a)c(t-a),$$

where $c(t)$ is the total number of individuals born at time t and $\gamma(a) = \gamma(a,0)$ is the probability that a newborn reaches age a. In general, the **survival probability** $\gamma(a_2, a_1)$ is the probability for an individual of age a_1 to live on to age a_2.

Nowadays the Lotka-Sharpe model is mostly given in its PDE representation, i.e., by the **balance equation**,

$$\frac{\partial p}{\partial t}(t,a) + \frac{\partial p}{\partial a}(t,a) = -\mu(a)p(t,a), \tag{3.1}$$

with age-dependent mortality rate $\mu : [0,\infty) \to [0,\infty)$.

The connection between the survival probability and the mortality rate is given by

$$\gamma(a_2,a_1) = \exp\left(-\int_{a_1}^{a_2} \mu(s)\,ds\right).$$

Newborns enter the population at time $t > 0$ according to the **birth law**,

$$p(t,0) = \int_0^\infty b(a)p(t,a)\,da, \tag{3.2}$$

with age-dependent fertility rate $b : [0,\infty) \to [0,\infty)$. The **initial age distribution** at $t = 0$ is given by a function $\psi : [0,\infty) \to [0,\infty)$,

$$p(0,a) = \psi(a). \tag{3.3}$$

Under the assumption that μ and b are continuous and bounded functions, the **intrinsic growth constant** $\tilde{\lambda}$, that is, the solution $\lambda (=: \tilde{\lambda})$ of

$$\int_0^\infty e^{-\lambda a} b(a)\gamma(a)\,da \;=\; 1,$$

determines the long term dynamics of the solutions to (3.1). If the **net reproductive rate**, $\sigma = \int_0^\infty b(a)\gamma(a)\,da$, is smaller than one, $\tilde{\lambda}$ is negative and the population becomes extinct. On the other hand, if $\sigma \geq 1$, the intrinsic growth rate is nonnegative and the population approaches a stable age distribution. This result, also known as *the Lotka-Sharpe theorem*, first appeared in [111] and was formalized years later with a rigorous proof by Feller [52]. The very same PDE (3.1) is also presented by von Foerster [122], who promotes the usage of age distributions in cell population studies. A deeper analysis of the model, as well as an alternative proof of the Lotka-Sharpe theorem can be found in Webb [131, 132].

The Lotka-Sharpe model (3.1) is our point of departure in this section. In order to reduce the complexity due to the age-structure, we introduce a *threshold age* $\tau > 0$ and distinguish juvenile individuals ($a < \tau$) from adult ones ($a > \tau$). The adult and juvenile populations at time $t \geq 0$ are thus, respectively,

$$y(t) = \int_0^\tau p(t,a)\,da, \qquad \text{and} \qquad x(t) = \int_\tau^\infty p(t,a)\,da. \tag{3.4}$$

Figure 3.1 shows the two populations at an arbitrary time point $t^* > 0$.

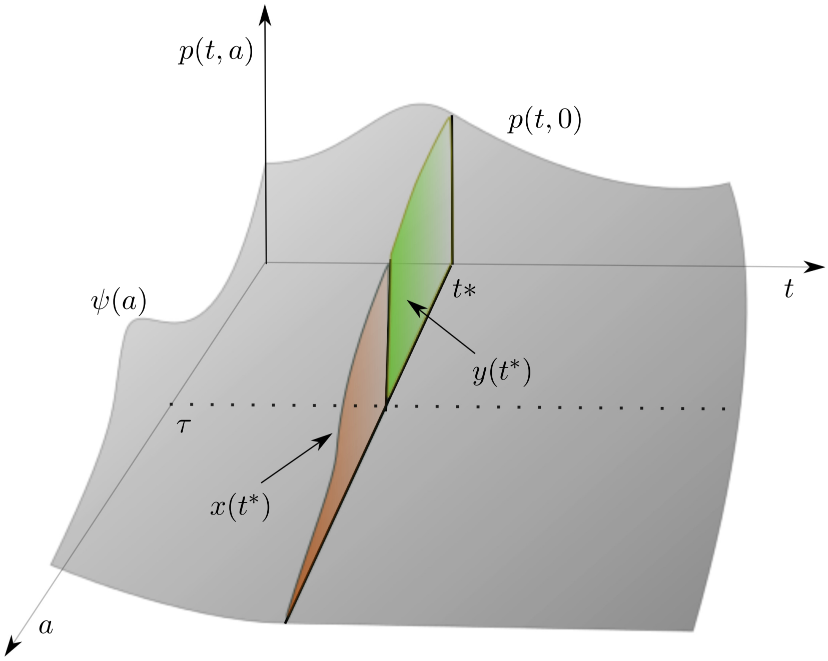


Figure 3.1: The gray surface represents the population density $p(t,a)$ in dependence on age of individuals (a) and time (t), given an initial age distribution $\psi(a)$. By integration we obtain the total number of juveniles y (green surface) and adults x (orange surface) at a fixed time $t^* > 0$.

The value τ is the **age-at-maturity** and corresponds to the time necessary for a newborn to reach full maturity. In our assumptions, for a fixed time t, the threshold τ depends on the total adult population at time t, i.e., $\tau = \tau(x(t))$. From a biological point of view, by this assumption we take into account so-called *compensatory responses*, which are based on density-dependent mechanisms [117]. For example, the length of the juvenile period can be substantially affected by the population size. Biological experiments suggest that declines in the age-at-maturity are caused by compensatory responses to declining population size. On the other side, a reduction in the (adult) population size may allow for larger intake of nutrients by immature individuals and therefore also for faster growth and shorter maturation time [29, 117]. For this reason, it is plausible to choose $\tau(x)$ as a monotonically increasing (not necessarily strictly increasing) function of x.

The age at which an individual becomes adult must be bounded both from above and from below. Whatever the size of the adult population is, there is definitively a minimum time to reach maturity and a maximal duration of the juvenile phase that would be biologically realistic. To have something concrete at hand, we assume that there are values h, τ_0, with $h > \tau_0 > 0$, such that

$$\tau : [0, \infty) \to [\tau_0, h] \subset (0, \infty)$$

is a monotonically increasing (not necessarily strictly increasing), (at least) continuously differentiable function (Figure 3.2).

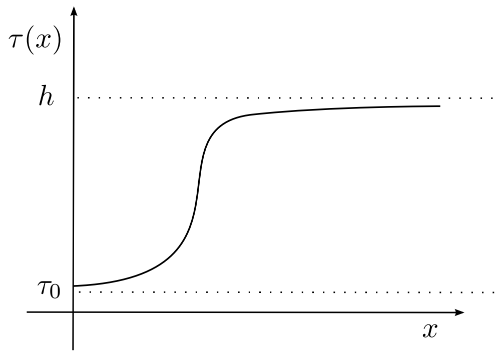


Figure 3.2: The age-at-maturity τ is a nonnegative, monotonically increasing (not necessarily strictly increasing), bounded function of the adult population x.

We restrict our investigation to the case in which $t-\tau(x(t))$ is a strictly increasing function of t (cf. model (2.11) in Section 2.1), i. e.,

$$1 - \frac{d\tau(x)}{dx}\frac{dx}{dt} = 1 - \frac{d\tau}{dt} > 0. \tag{3.5}$$

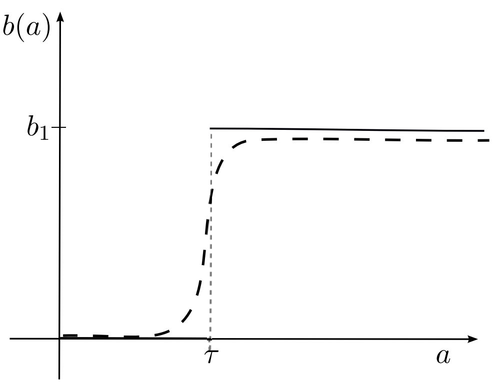
In other words, τ does not arbitrarily vary in time, but we assume that changes in the adulthood threshold are slower than changes in chronological time. The same assumption can be found in [3].

The population dynamics in (3.1)–(3.3) is characterized by age-dependent birth and death rates. Here we assume that birth (b) and death (μ) rates are piecewise constant functions of the age,

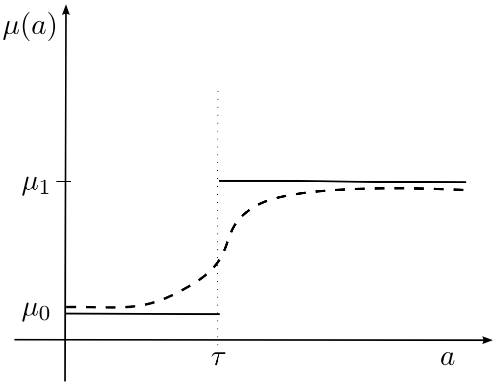
$$\begin{aligned} b(a) &= b_1 H_\tau(a), \\ \mu(a) &= \mu_0 + (\mu_1 - \mu_0) H_\tau(a), \end{aligned} \tag{3.6}$$

where $b_1 > \mu_1 > 0$ and $\mu_0 \geq 0$ are nonnegative constants and $H_z(s)$ is the Heaviside function with a jump at $s = z$,

$$H_z(s) = \begin{cases} 0, & s < z, \\ 1, & s \geq z. \end{cases}$$



(a) Birth function $b(a)$.



(b) Death function $\mu(a)$.

Figure 3.3: Birth and death rates are functions of the age a of an individual. Solid lines reflect the model assumptions. Juveniles have no offspring ($b_0 = 0$) and die at rate $\mu_0 \geq 0$. Fertility and death rate of adult individuals are $b_1 > 0$ and $\mu_1 > 0$, respectively. In particular, we assume $b_1 > \mu_1$. Dashed curves represent biologically realistic smooth functions.

The coefficients b_j, μ_j represent birth and death rates for juveniles ($j = 0$) and adults ($j = 1$). From a biological point of view, this means that juveniles have no offspring ($b_0 = 0$) and die at rate $\mu_0 \geq 0$. When individuals reach sexual maturity (at age $a = \tau$), they enter the adult population. Fertility and death rate of adult individuals are $b_1 > 0$ and $\mu_1 > 0$, respectively. In particular, we assume that the birth rate is larger than the death rate, that is, $b_1 > \mu_1$. Figure 3.3 shows the rates b and μ.

We consider the population density of adult individuals $p(\bar{t}, \bar{a})$ at time $\bar{t} > \bar{a} > \tau(x(\bar{t}))$. Because of $\bar{t} > \bar{a}$, the influence of initial data $\psi(a)$ is "forgotten" and we can trace back the value $p(\bar{t}, \bar{a})$ to $p(\bar{t} - \bar{a}, 0)$, according to the method of characteristics for PDEs (Figure 3.4).

Let us follow an individual born at time t_0. This individual runs with its cohort through all points (t, a), with $t - a = t_0$. Due to condition (3.5) on τ, there is a unique age $A(t_0)$ when it becomes adult and, because of $\frac{d\tau}{dt} < 1$, the observed individual never goes back to the juvenile phase. The age $A(t_0)$ is determined by the intersection of the "delay curve" $\tau(x(t))$ with the characteristic which originates in t_0, i.e., it is defined by the equations

$$t - a = t_0, \quad a = \tau(x(t)). \tag{3.7}$$

Thus, if $T = T(t_0)$ is the solution t to (3.7), then $A(t_0) = \tau(x(T))$. Figure 3.5 is meant to be a visual support to this result. In particular, we find the relation

$$A(t - \tau(x(t))) = \tau(x(t)). \tag{3.8}$$

Let us consider a point (t, a), with $t > a$. Assuming that the solution p of (3.1) exists on the interval $[0, \tau]$, we follow it from the point (t, a) along the characteristics and find

$$p(t, a) = p(t - a, 0) \exp\left(- \int_0^a \mu(\sigma) d\sigma \right).$$

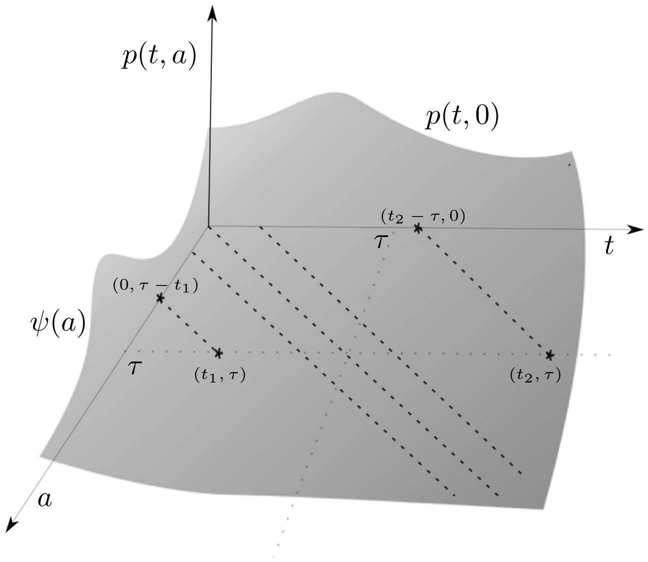


Figure 3.4: According to the method of characteristics for PDEs we associate to a point $p(t_1,\tau)$, with $t_1 < \tau$, the point $p(0,\tau-t_1) = \psi(\tau-t_1)$ and to $p(t_2,\tau)$, with $t_2 > \tau$, the point $p(t_2-\tau,0)$.

This means that for any (t,a) with $t > a > A(t-a)$, we have

$$\begin{aligned} p(t,a) &= p(t-a,0)\exp\left(-\int_0^{A(t-a)}\mu(\sigma)d\sigma - \int_{A(t-a)}^{a}\mu(\sigma)d\sigma\right) \\ &= p(t-a,0)e^{-\mu_0 A(t-a)-\mu_1(a-A(t-a))}. \end{aligned} \tag{3.9}$$

Computation of $p(t,a)$, requires the function A, which is not given explicitly. However, with result (3.9), the coefficient definition (3.6) and the relation (3.8), we get

$$p(t,\tau(x(t))) = p(t-\tau(x(t)),0)e^{-\mu_0\tau(x(t))}.$$

We now use the birth law (3.2) to express the population density at a point (t,a), with $t > a > \tau(x(t))$, and obtain

$$\begin{aligned} p(t,a) &= p(t-a,0)e^{-\int_0^a\mu(\sigma)d\sigma} \\ &= \int_{\tau(x(t-a))}^{\infty} b(s)p(t-a,s)ds\, e^{-\int_0^a\mu(\sigma)d\sigma} \\ &= b_1\int_{\tau(x(t-a))}^{\infty} p(t-a,s)ds\, e^{-\int_0^a\mu(\sigma)d\sigma} \\ &= b_1 x(t-a)e^{-\int_0^a\mu(\sigma)d\sigma}. \end{aligned} \tag{3.10}$$

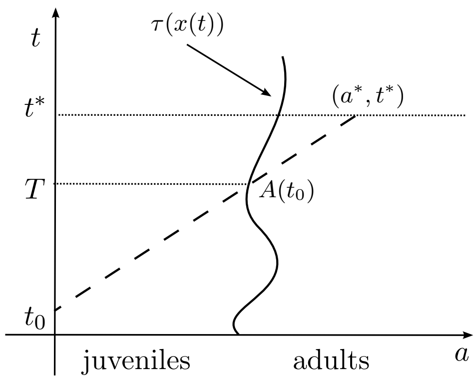


Figure 3.5: We observe an adult individual of age a^* at time t^*. This individual was born at time t_0 and reached maturity (i.e., age $A(t_0)$) at time $T = T(t_0)$. The age at maturity $A(t_0)$ is determined by the intersection of the curve $a = \tau(x(t))$ with the line $t - a = t_0$.

From this relation we can find an expression for the total adult population x. Unless otherwise explicitly mentioned, for simplicity we indicate the state-dependent delay $\tau(x(t))$ by τ only.

With (3.10) the total size of the adult population at time $t > \tau$ is given by

$$\begin{aligned} x(t) &= b_1 \int_{\tau}^{\infty} x(t-a) e^{-\int_0^a \mu(\sigma) d\sigma} \, da \\ &\underset{s=t-a}{=} b_1 \int_{-\infty}^{t-\tau} x(s) e^{-\int_0^{t-s} \mu(\sigma) d\sigma} \, ds \\ &\underset{\rho=\sigma+s}{=} b_1 \int_{-\infty}^{t-\tau} x(s) e^{-\int_s^t \mu(\rho - s) d\rho} \, ds. \end{aligned} \tag{3.11}$$

Differentiation with respect to the time yields a differential equation for $x(t)$,

$$\begin{aligned} \dot{x}(t) = {} & b_1 x(t-\tau) e^{-\int_{t-\tau}^t \mu(\rho-(t-\tau)) d\rho} \left(1 - \dot{\tau}(x(t))\dot{x}(t)\right) \\ & - b_1 \int_{-\infty}^{t-\tau} x(s) e^{-\int_s^t \mu(\rho - s) d\rho} \mu(t-s) \, ds. \end{aligned} \tag{3.12}$$

By (3.6), the age-dependent death rate $\mu(a)$ for adult individuals ($a > \tau$) is a constant $\mu_1 > 0$. Therefore, for the last term in (3.12) we get

$$\begin{aligned} b_1 \int_{-\infty}^{t-\tau} x(s) e^{-\int_s^t \mu(\rho - s) d\rho} \mu(t-s) \, ds &= b_1 \int_{\tau}^{\infty} x(t-z) e^{-\int_0^z \mu(u) du} \mu(z) \, dz \\ &\underset{(3.6)}{=} b_1 \int_{\tau}^{\infty} x(t-z) e^{-\int_0^z \mu(u) du} \mu_1 \, dz \\ &\underset{(3.11)}{=} \mu_1 x(t). \end{aligned}$$

In order to write the integral in the first term of (3.12) in a more explicit form, we define two sets

$$J_t = \{a \in \mathbb{R} : 0 \le a < t - \tau\} \qquad \text{and} \qquad A_t = \{a \in \mathbb{R} : a \ge t - \tau\}.$$

With J_t, A_t and the characteristic function $\chi_E(s)$ for a set $E \neq \emptyset$, we have

$$\int_{t-\tau}^{t} \mu(\rho - (t-\tau))\, d\rho = \int_{t-\tau}^{t} \big(\mu_0 \chi_{J_t}(\rho - t + \tau) + \mu_1 \chi_{A_t}(\rho - t + \tau)\big)\, d\rho = \mu_0 \tau.$$

Let us sum up and clarify our results. The point of departure has been a population structured by age, whose density $p(t,a)$ of individuals of age a at time t satisfies (3.1)–(3.3). A threshold age τ helped us distinguish immature (juvenile) from mature (adult) individuals, defined in (3.4). We have taken birth and death rates to be piecewise constant functions of the age and have assumed that $\tau : [0,\infty) \to [\tau_0, h] \subset (0,\infty)$, $0 < \tau_0 < h < \infty$ is a monotonically increasing (not necessarily strictly increasing) C^1-function of the adult population x, with property (3.5). An individual born at time t_0 becomes adult at time $T(t_0)$ and age $A(t_0)$, which are implicitly defined by (3.7). We have shown that we can derive a differential equation (3.12) for x. But this result is not satisfactory, as (3.12) holds for a time $t > A(t - \tau(x(t))) = \tau(x(t))$, which is implicitly defined. However, repeating the above considerations we observe that (3.12) holds for all $t > h = \max \tau(x(t))$.

Theorem 3.1. *Let $p(t,a)$ be a solution of (3.1)–(3.3), with coefficient functions (3.6) and let x be defined as in* (3.4)*, with $\tau : [0,\infty) \to [\tau_0, h] \subset (0,\infty)$ having property* (3.5)*. Assume that $p(t,a)$ exists for all times $t \le h$ and for all $a \ge 0$. Then, for all $t > h$, $x(t)$ satisfies the nonlinear equation*

$$\dot{x}(t) = \frac{b_1 x(t-\tau) e^{-\mu_0 \tau} - \mu_1 x(t)}{1 + \dot{\tau}(x(t)) b_1 x(t-\tau) e^{-\mu_0 \tau}}.$$

The same method can be used to describe the density $p(t,a)$ of juveniles, i.e., individuals of age $a < \tau$. Again, we observe these individuals at time $t > h$ and assume that the solution $p(t,a)$ of (3.1) exists for all times previous to t and all $a \ge 0$. With (3.10), the population size of juvenile individuals at time t is given by

$$y(t) = b_1 \int_0^{\tau} x(t-a) e^{-\int_0^a \mu(\sigma) d\sigma} da.$$

Differentiation with respect to the time yields a differential equation for the juvenile population

$$\dot{y}(t) = b_1 x(t) - b_1 x(t-\tau) e^{-\mu_0 \tau} \left(1 - \dot{\tau}(x(t)) \dot{x}(t)\right) - \mu_0 y(t).$$

In Appendix B we prove how to obtain the last equation. All in all, we can formulate the following result.

Corollary. *Let the hypotheses of Theorem 3.1 be satisfied. Then, for all $t > h$, the juvenile and the adult populations defined in (3.4) satisfy*

$$\dot{y}(t) = b_1 x(t) - b_1 x(t-\tau) e^{-\mu_0 \tau} \left(1 - \dot{\tau}(x(t)) \dot{x}(t)\right) - \mu_0 y(t), \tag{3.13a}$$

$$\dot{x}(t) = \frac{b_1 x(t-\tau) e^{-\mu_0 \tau} - \mu_1 x(t)}{1 + \dot{\tau}(x(t)) b_1 x(t-\tau) e^{-\mu_0 \tau}}. \tag{3.13b}$$

Now we briefly consider the case $t \le a$. To this purpose it will be convenient to have the explicit solution of (3.1)–(3.3) (cf. [131]),

$$p(t,a) = \begin{cases} \psi(a-t)\exp\left(-\int_0^t \mu(a-t+s)\,ds\right), & \text{if } a \ge t, \\ p(t-a,0)\exp\left(-\int_0^a \mu(s)\,ds\right), & \text{if } a < t. \end{cases} \tag{3.14}$$

When we consider $p(t,a)$ with $t \le a$, and trace it back along the characteristics, we arrive at a value $\psi(a-t)$ of the initial age distribution (3.3), as in Figure 3.4.

Repeating the same computations as for the case $t > h$, we can prove the following result. Details can be found in Appendix B.

Result 1. *Let $p(t,a)$ be a solution of (3.1)–(3.3), with coefficient functions (3.6) and let x, y be defined as in* (3.4)*, with $\tau : [0,\infty) \to [\tau_0, h] \subset (0,\infty)$ having property* (3.5)*. Then, for $t < \tau_0$ juvenile and adult populations satisfy*

$$\dot{y}(t) = b_1 x(t) - \psi(\tau - t)e^{-\mu_0 t}\left(1 - \dot{\tau}(x(t))\dot{x}(t)\right) - \mu_0 y(t), \tag{3.15a}$$

$$\dot{x}(t) = \frac{\psi(\tau - t)e^{-\mu_0 t} - \mu_1 x(t)}{1 + \dot{\tau}(x(t))\psi(\tau - t)e^{-\mu_0 t}}. \tag{3.15b}$$

The last result completes the formal derivation of DDEs with state-dependent delay from the Lotka-Sharpe model (3.1)–(3.3). We like to stress the fact that given a delay function $\tau : [0,\infty) \to [\tau_0, h]$, $0 < \tau_0 < h < \infty$, we can derive for $t > h$ a DDE system (3.13) with state-dependent delay $\tau(x(t))$, and for $t < \tau_0$ an ODE system (3.15). In the interval $[\tau_0, h]$, the dynamics is given either by (3.13) or by (3.15), depending on $t > \tau(x(t))$ or $t < \tau(x(t))$, which is implicitly determined. As we are interested in (well-defined) delay equations with state-dependent delay, we restrict ourselves to the case $t > h$.

In the next section we extend the derivation scheme to include DDEs of neutral type. However, we shall neglect the equation for juveniles (y) and focus on the autonomous equation for the adult population (x).

3.2. The Neutral Equation

In the Lotka and Sharpe model (3.1)–(3.3) it is assumed that birth and death processes do not depend on the total number of individuals. To overcome this simplistic hypothesis, Gurtin and MacCamy [60] introduced an explicit dependence on the total population size at time t,

$$P(t) = \int_0^\infty p(t,a)\,da.$$

The Gurtin-MacCamy model is given by

$$\begin{aligned} \frac{\partial}{\partial t}p(t,a) + \frac{\partial}{\partial a}p(t,a) &= -\mu(a, P(t))p(t,a), \\ p(t,0) &= \int_0^\infty b(a,P(t))p(t,a)\,da, \\ p(0,a) &= \psi(a). \end{aligned} \tag{3.16}$$

In contrast to the Lotka-Sharpe system (3.1)–(3.3), the birth function b and the death function μ may now also depend on the population size P. Given nonnegative and sufficiently smooth functions $\mu(a,P)$, $b(a,P)$, $\psi(a)$, for each point (t,a), solutions to (3.16) can be computed following the characteristic through (t,a),

$$p(t,a) = \begin{cases} \psi(a-t)\exp\left(-\int_0^t \mu(a-t+s, P(s))\,ds\right), & \text{if } a \geq t, \\ p(t-a,0)\exp\left(-\int_0^a \mu(s, P(t-a+s))\,ds\right), & \text{if } a < t. \end{cases}$$

Similarly to the Lotka-Sharpe model, the long-term dynamics can be predicted with help of the probability that a newborn reaches age a,

$$\gamma(a,P) = \exp\left(-\int_0^a \mu(s,P)\,ds\right),$$

and with the expected number of children born per unit of time when the population size is P,

$$\sigma(P) = \int_0^\infty b(a,P)\gamma(a,P)\,da.$$

Existence and uniqueness of solutions to (3.16), as well as exponential asymptotic stability of an equilibrium age distribution have been shown in [60].

As in Section 3.1, we use a "threshold age", the age-at-maturity $\tau > 0$, to distinguish juvenile (y) from adult (x) individuals,

$$y(t) = \int_0^\tau p(t,a)\,da, \qquad \text{and} \qquad x(t) = \int_\tau^\infty p(t,a)\,da,$$

and we assume that τ depends on the total adult population, i.e., $\tau = \tau(x(t))$. Further we assume that

$$\tau : [0,\infty) \to [\tau_0, h] \subset (0,\infty)$$

is a monotonically increasing, (at least) continuously differentiable function with property (3.5). For simplicity of notation we indicate the state-dependent delay $\tau(x(t))$ by τ. We let birth and death processes depend only on the size of the adult population x and build up a special case of the Gurtin-MacCamy model,

$$\frac{\partial}{\partial t}p(t,a) + \frac{\partial}{\partial a}p(t,a) = -\mu(a,x(t))p(t,a), \tag{3.17}$$

$$p(t,0) = \int_0^\infty b(a,x(t))p(t,a)\,da, \tag{3.18}$$

$$p(0,a) = \psi(a). \tag{3.19}$$

Fertility and mortality rates are taken to be piecewise continuous functions of the age. Other than in Section 3.1, we include a delta peak at $a = \tau$ in the fertility rate b,

$$\begin{aligned} b(a,x) &= b_1(x)H_\tau(a) + b_2(x)\delta_\tau(a), \\ \mu(a,x) &= \mu_0(x) + (\mu_1(x) - \mu_0(x))H_\tau(a). \end{aligned} \tag{3.20}$$

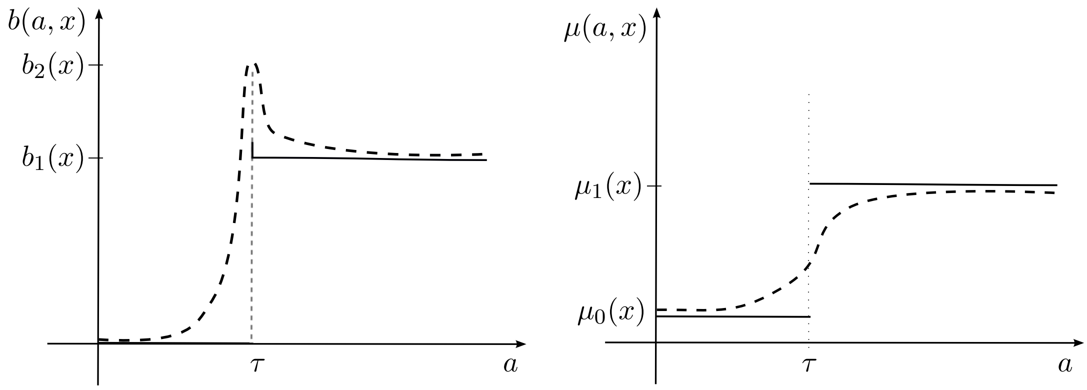
Here $H_\tau(a)$ is the Heaviside function with a jump at $a = \tau$ and $\delta_\tau(a)$ is the delta distribution with a peak at $a = \tau$. In biological terms, this means that juveniles have no offspring, whereas the birth rate of adults is a function $b_1(x)$, and that there is a fertility peak of weight $b_2(x) \not\equiv 0$ when individuals reach maturity at $a = \tau$, as in Figure 3.6. Such a peak has been observed, e.g., in the fecundity of loggerhead turtles [35]. Apparently, turtles are not fecund up to the age of 21 years, and produce a large number of eggs (127 per year) at age 22. When they are older, turtles lay a smaller number of eggs (80 eggs per year for turtles which are 24-54 years old). In view of the biological interpretation, it is realistic to assume that $b_1(x)$ and $b_2(x)$ are decreasing functions of the adult population size, with

$$\lim_{x\to\infty} b_1(x) = 0 \qquad \text{and} \qquad \lim_{x\to\infty} b_2(x) = 0.$$

The death rate of juveniles $\mu_0(x)$ is in general lower than the one of adults $\mu_1(x)$. Both are increasing functions of the population x, in particular we set

$$\lim_{x\to\infty} \mu_1(x) = \infty.$$

Further, we require that b_1 and μ_1 satisfy $b_1(0) > \mu_1(0)$ (cf. [100, 117]).



(a) Birth function $b(a, x)$.

(b) Death function $\mu(a, x)$.

Figure 3.6: Birth and death rates depend on the age of the individuals and on the total adult population. A fertility peak occurs for individuals of age $a = \tau$. Solid lines represent the model assumptions. Dashed curves indicate biological realistic smooth rate functions.

Consider the density of adult individuals $p(t,a)$ at a point $t > a > \tau$ and follow the characteristics of the PDE problem, as in Section 3.1. We obtain

$$
\begin{aligned}
p(t,a) &= p(t-a,0)\exp\left(-\int_0^a \mu(\sigma, x(t-a+\sigma))\,d\sigma\right)\\
&= \int_{\tau(x(t-a))}^{\infty} b(s,x(t-a))p(t-a,s)ds\ \exp\left(-\int_0^a \mu(\sigma, x(t-a+\sigma))\,d\sigma\right)\\
&= b_2(x(t-a))p(t-a,\tau(x(t-a)))\exp\left(-\int_0^a \mu(\sigma, x(t-a+\sigma))\,d\sigma\right)\\
&\quad + b_1(x(t-a))x(t-a)\exp\left(-\int_0^a \mu(\sigma, x(t-a+\sigma))\,d\sigma\right).
\end{aligned}
\tag{3.21}
$$

For a time $t \le a$ we would have similar computations and obtain $p(t,a)$ in dependence on the initial distribution $\psi(a)$ (cf. p. 31). However, we will only consider the case $t > a$.

To simplify the notation, in the sequel we write $\tilde{b}_1(z)$ and $\tilde{\mu}_1(z)$ for $b_1(z)z$ and $\mu_1(z)z$, respectively. The total adult population at time $t > \tau$ satisfies

$$
\begin{aligned}
x(t) &= \int_\tau^\infty p(t-a,0)e^{-\int_0^a \mu(\sigma,x(t-a+\sigma))\,d\sigma}\,da\\
&\underset{\substack{s=t-a\\(3.21)}}{=} \int_{-\infty}^{t-\tau}\left\{b_2(x(s))p(s,\tau(x(s))) + \tilde{b}_1(x(s))\right\}e^{-\int_0^{t-s}\mu(\sigma,x(s+\sigma))\,d\sigma}\,ds\\
&\underset{\xi=s+\sigma}{=} \int_{-\infty}^{t-\tau}\left\{b_2(x(s))p(s,\tau(x(s))) + \tilde{b}_1(x(s))\right\}e^{-\int_s^t \mu(\xi-s,x(\xi))\,d\xi}\,ds.
\end{aligned}
\tag{3.22}
$$

It might be useful to observe that

$$
\int_{t-\tau}^t \mu(\xi-t-\tau, x(\xi))\,d\xi = \int_0^\tau \mu(\sigma, x(t-\tau+\sigma))\,d\sigma = \int_0^\tau \mu_0(x(t-\tau+\sigma))\,d\sigma,
$$

and that for all $s \in (-\infty, t-\tau)$, we have $t-s \in (\tau,\infty)$ and $\mu(t-s, x(t)) = \mu_1(x(t))$.

Differentiation of (3.22) with respect to the time yields

$$
\dot{x}(t) = \frac{\left[\tilde{b}_1(x(t-\tau)) + b_2(x(t-\tau))p(t-\tau,\tau(x(t-\tau)))\right]e^{-\int_{t-\tau}^t \mu_0(x(\rho))d\rho} - \tilde{\mu}_1(x(t))}{1+\dot{\tau}(x(t))\left[\tilde{b}_1(x(t-\tau)) + b_2(x(t-\tau))p(t-\tau,\tau(x(t-\tau)))\right]e^{-\int_{t-\tau}^t \mu_0(x(\rho))d\rho}}.
\tag{3.23}
$$

Remark 3.2. Every nonnegative solution $p(t,a)$ of (3.17)–(3.19) satisfies the inequality

$$
\dot{\tau}(x(t))\dot{x}(t) < 1,
$$

where $x(t) = \int_\tau^\infty p(t,a)\,da$.

Indeed, differentiation of $x(t) = \int_\tau^\infty p(t,a)\,da$ yields

$$
\dot{x}(t) = -p(t,\tau(x(t)))\dot{\tau}(x(t))\dot{x}(t) + \int_\tau^\infty \frac{\partial}{\partial t}p(t,a)\,da,
$$

and from (3.17) we get

$$\dot{x}(t) = -p(t,\tau(x(t)))\dot{\tau}(x(t))\dot{x}(t) + p(t,\tau(x(t))) - \tilde{\mu}_1(x(t)).$$

Multiplying this equation by $\dot{\tau}(x(t))$ and solving for $\dot{\tau}(x(t))\dot{x}(t)$, we obtain

$$\dot{\tau}(x(t))\dot{x}(t) = \frac{p(t,\tau(x(t)))\dot{\tau}(x(t))}{1+\dot{\tau}(x(t))p(t,\tau(x(t)))} - \underbrace{\frac{\dot{\tau}(x(t))\tilde{\mu}_1(x(t))}{1+\dot{\tau}(x(t))p(t,\tau(x(t)))}}_{\geq 0 \quad (x(t)\geq 0)} < 1.$$

As in Section 3.1, we find an autonomous delay equation with state-dependent delay for the adult population x. The difference is that here we have an equation of neutral type.

Theorem 3.3. *Assume the solution $p(t,a)$ to (3.17)–(3.19) exists for all $t \leq h$ and all $a \geq 0$. Then, for all $t > h$, $x(t)$ satisfies the nonlinear neutral equation with state-dependent delay*

$$\dot{x}(t) = \frac{\beta_{t,\tau} - \tilde{\mu}_1(x(t))}{1+\dot{\tau}(x(t))\beta_{t,\tau}}, \tag{3.24}$$

with

$$\beta_{t,\tau} = \left[\tilde{b}_1(x(t-\tau)) + b_2(x(t-\tau))\frac{\dot{x}(t-\tau)+\tilde{\mu}_1(x(t-\tau))}{1-\dot{\tau}(x(t-\tau))\dot{x}(t-\tau)}\right] e^{-\int_{t-\tau}^{t}\mu_0(x(\rho))d\rho}, \quad \tau = \tau(x(t)).$$

Proof. The formal derivation of the delay equation (3.23) from the Gurtin-MacCamy model has been already shown above. However, it is not evident that (3.23) is a neutral equation.

Let $t > h > 0$ be given. In particular, we have $t \geq \tau(x(t))$. Then in view of equation (3.21) we have

$$p(t,\tau) = \left[\tilde{b}_1(x(t-\tau)) + b_2(x(t-\tau))p(t-\tau,\tau(x(t-\tau)))\right] e^{-\int_{t-\tau}^{t}\mu_0(x(\rho))d\rho}. \tag{3.25}$$

Substitution of (3.25) into (3.23) yields

$$\dot{x}(t) = \frac{p(t,\tau) - \tilde{\mu}_1(x(t))}{1+\dot{\tau}(x(t))p(t,\tau)}. \tag{3.26}$$

Then, solving for $p(t,\tau)$ we find

$$p(t,\tau) = \frac{\dot{x}(t) + \tilde{\mu}_1(x(t))}{1-\dot{\tau}(x(t))\dot{x}(t)},$$

which, by Remark 3.2, is well defined and nonnegative. It follows that

$$p(t-\tau,\tau(x(t-\tau))) = \frac{\dot{x}(t-\tau)+\tilde{\mu}_1(x(t-\tau))}{1-\dot{\tau}(x(t-\tau))\dot{x}(t-\tau)}. \tag{3.27}$$

Substitution into (3.23) completes the proof. □

When the delay is a constant value $\tau \equiv \hat{\tau}$, and $\mu_0(x) \equiv \mu_0 > 0$, equation (3.24) reduces to

$$\begin{aligned} \dot{x}(t) = &\tilde{b}_1(x(t-\hat{\tau}))e^{-\mu_0\hat{\tau}} - \tilde{\mu}_1(x(t)) \\ &+ b_2(x(t-\hat{\tau}))\left[\dot{x}(t-\hat{\tau}) + \tilde{\mu}_1(x(t-\hat{\tau}))\right] e^{-\mu_0\hat{\tau}}. \end{aligned} \tag{3.28}$$

This equation has been previously derived by Hadeler and Bocharov from a modified Gurtin-MacCamy model [20].

In conclusion, we have obtained a class of neutral equations of the form

$$\dot{x}(t) = \frac{\alpha\big(x(t), x(t-\tau), \dot{x}(t-\tau)\big) - \gamma(x(t))}{1 + \dot{\tau}(x(t))\alpha\big(x(t), x(t-\tau), \dot{x}(t-\tau)\big)},$$

with state dependent delay $\tau = \tau(x(t))$. For this kind of equations, in Chapter 7 we investigate existence and uniqueness of solutions, as well as linearized stability of equilibria. In Section 3.4 we show that the neutral equation (3.24) can be written as a system of an ODE and a shift operator. Next we present a particular case of (3.24).

3.3. The State-Dependent Blowfly Equation

In this section we take fertility and mortality rates to be given in the form

$$\begin{aligned} b(a,x) &= b_1(x)H_\tau(a), \\ \mu(a,x) &= \mu_0 + (\mu_1(x) - \mu_0)H_\tau(a), \end{aligned}$$

with b_1, μ_1 as in Section 3.2 and $\mu_0 \geq 0$. Looking back at the functions in (3.20), we note that here there is no delta peak in the fertility rate, i.e., $b_2 \equiv 0$.

By the same approach as in Section 3.2, we can derive an autonomous nonlinear equation,

$$\dot{x}(t) \quad = \quad \frac{\tilde{b}_1\big(x(t-\tau(x(t)))\big)e^{-\mu_0\tau(x(t))} - \tilde{\mu}_1(x(t))}{1 + \dot{\tau}(x(t))\tilde{b}_1\big(x(t-\tau(x(t)))\big)e^{-\mu_0\tau(x(t))}}, \tag{3.29}$$

with state-dependent delay $\tau(x(t)) \in [\tau_0, h]$. Once more, assuming that the solution p of the Gurtin-MacCamy model (3.17)–(3.19) has existed for a time interval of minimal length h, equation (3.29) describes the dynamics of the adult population x. All results in Section 3.2 are, of course, still valid for the simpler case (3.29).

If $\tau \equiv \hat{\tau}$ is a positive constant, then (3.29) is the *blowfly equation* (2.5) introduced in [100],

$$\dot{x}(t) = b(x(t-\hat{\tau}))x(t-\hat{\tau}) - \mu(x(t))x(t), \tag{3.30}$$

with $b(y) = b_1(y)e^{-\mu_0\hat{\tau}}$, $\mu(y) = \mu_1(y)$. This observation motivates us to call (3.29) the **state-dependent blowfly equation**.

If we omit the denominator in (3.29), while letting the delay τ still depend on x, then we get

$$\dot{x}(t) = \tilde{b}_1\big(x(t-\tau(x(t)))\big)e^{-\mu_0\tau(x(t))} - \tilde{\mu}_1(x(t)), \tag{3.31}$$

that could perhaps be seen as a state-dependent version of the *blowfly equation*. This equation, indeed, can be obtained from (3.30), substituting the constant delay by a state-dependent one. However, in (3.31) the change in the size of the adult population due to the change in τ has been neglected. In Section 3.5, we will visualize by some numerical examples how the behavior of the solution changes, if (3.31) is used instead of (3.29).

3.4. ODEs and Shifts

Hadeler and Bocharov [20,63] have shown that neutral equations with constant delay ($r > 0$) arising from population dynamics can be written in the form of a system of an ODE and a shift operator

$$\begin{aligned} \dot{y}(t) &= s(t) - d(y(t)), \qquad t \geq r \\ s(t) &= \tilde{S}(y(t-r), s(t-r)), \end{aligned}$$

with $d : \mathbb{R}^+ \to \mathbb{R}^+$, $\tilde{S} : \mathbb{R}^+ \times \mathbb{R}^+ \to \mathbb{R}^+$ and $s : \mathbb{R} \to \mathbb{R}^+$. Here, we present a similar result for the case of neutral equations with state-dependent delay and introduce three reformulations of equation (3.24), which can be motivated biologically.

The first system is given by an ODE for the adult population x and an equation for w, the *recruitment into the adult class*, that is,

$$w(t) = p(t, \tau(x(t))).$$

Once more, we omit arguments whenever confusion cannot arise and indicate the state-dependent delay $\tau(x(t))$ by τ.

Proposition 3.1. *For $t > h$, the neutral equation (3.24) is equivalent to the system*

$$w(t) = \left[\tilde{b}_1(x(t-\tau)) + b_2(x(t-\tau))w(t-\tau)\right] e^{-\int_{t-\tau}^{t} \mu_0(x(\rho))d\rho}, \tag{3.32a}$$

$$\dot{x}(t) = \frac{w(t) - \tilde{\mu}_1(x(t))}{1 + \dot{\tau}(x(t))w(t)}. \tag{3.32b}$$

Proof. 1) It is immediate to see that

$$\begin{aligned} w(t) &\underset{(3.25)}{=} \left[\tilde{b}_1(x(t-\tau)) + b_2(x(t-\tau))p(t-\tau, \tau(x(t-\tau)))\right] e^{-\int_{t-\tau}^{t} \mu_0(x(\rho))d\rho} \\ &= \left[\tilde{b}_1(x(t-\tau)) + b_2(x(t-\tau))w(t-\tau)\right] e^{-\int_{t-\tau}^{t} \mu_0(x(\rho))d\rho}. \end{aligned}$$

Substitution in (3.24) yields the system (3.32) of an ODE for x and a shift operator w.

2) Solving (3.32b) for w we obtain

$$w(t) = \frac{\dot{x}(t) - \tilde{\mu}_1(x(t))}{1 - \dot{\tau}(x(t))\dot{x}(t)}.$$

Using (3.32a) we obtain

$$\frac{\dot{x}(t)-\tilde{\mu}_1(x(t))}{1-\dot{\tau}(x(t))\dot{x}(t)} = \left[\tilde{b}_1(x(t-\tau)) + b_2(x(t-\tau))\frac{\dot{x}(t-\tau)-\tilde{\mu}_1(x(t-\tau))}{1-\dot{\tau}(x(t-\tau))\dot{x}(t-\tau)}\right] e^{-\int_{t-\tau}^{t}\mu_0(x(\rho))d\rho}.$$

Solving for $\dot{x}(t)$ we find (3.24).

□

Let the death rate of juveniles do not depend on the size of the adult populations, for example, $\mu_0(x) \equiv \mu_0 \geq 0$. Then (3.24) and (3.32) become, respectively,

$$\dot{x}(t) = \frac{\left[\tilde{b}_1(x(t-\tau)) + b_2(x(t-\tau))\frac{\dot{x}(t-\tau)+\tilde{\mu}_1(x(t-\tau))}{1-\dot{\tau}(x(t-\tau))\dot{x}(t-\tau)}\right] e^{-\mu_0\tau} - \tilde{\mu}_1(x(t))}{1+\dot{\tau}(x(t))\left[\tilde{b}_1(x(t-\tau)) + b_2(x(t-\tau))\frac{\dot{x}(t-\tau)+\tilde{\mu}_1(x(t-\tau))}{1-\dot{\tau}(x(t-\tau))\dot{x}(t-\tau)}\right] e^{-\mu_0\tau}} \tag{3.33}$$

and

$$\begin{aligned} w(t) &= \left[\tilde{b}_1(x(t-\tau)) + b_2(x(t-\tau))w(t-\tau)\right] e^{-\mu_0\tau}, \\ \dot{x}(t) &= \frac{w(t)-\tilde{\mu}_1(x(t))}{1+\dot{\tau}(x(t))w(t)}. \end{aligned} \tag{3.34}$$

For reasons of simplicity, all next results are given in terms of a constant death rate, $\mu_0(x) \equiv \mu_0$. Without difficulties they could be extended to the more general case of a non-constant juvenile death rate.

Equation (3.33) can be also written as a system of an ODE for x and a shift operator z, the *recruitment rate into the juvenile class*, defined by $z(t) = p(t, 0)$. Relation (3.18) and our choice of birth and death rates (3.20) yield

$$z(t) = \tilde{b}_1(x(t)) + b_2(x(t))p(t,\tau). \tag{3.35}$$

Corollary. *For $t > h$ the total adult population x and the recruitment into the juvenile class z satisfy*

$$\begin{aligned} \dot{x}(t) &= \frac{z(t-\tau)e^{-\mu_0\tau}-\tilde{\mu}_1(x(t))}{1+\dot{\tau}(x(t))z(t-\tau)e^{-\mu_0\tau}}, \\ z(t) &= \tilde{b}_1(x(t)) + b_2(x(t))z(t-\tau)e^{-\mu_0\tau}. \end{aligned} \tag{3.36}$$

Proof. For $t > h \geq \tau$ we have

$$p(t,\tau) = p(t-\tau, 0)e^{-\mu_0\tau} = z(t-\tau)e^{-\mu_0\tau}. \tag{3.37}$$

With (3.35) immediately follows

$$z(t) = \tilde{b}_1(x(t)) + b_2(x(t))z(t-\tau)e^{-\mu_0\tau}. \tag{3.38}$$

Insert expression (3.37) into equation (3.26). With (3.38) we get system (3.36). □

Finally, we introduce the *discounted recruitment into the adult class*,

$$v(t) = p(t, \tau)e^{\mu_0 \tau}. \tag{3.39}$$

Corollary. *For $t > h$ the total adult population x and the discounted recruitment rate v into the adult class satisfy*

$$\begin{aligned} \dot{x}(t) &= \frac{v(t)e^{-\mu_0\tau} - \tilde{\mu}_1(x(t))}{1 + \dot{\tau}(x(t))v(t)e^{-\mu_0\tau}}, \\ v(t) &= \tilde{b}_1(x(t-\tau)) + b_2(x(t-\tau))v(t-\tau)e^{-\mu_0\tau(x(t-\tau))}. \end{aligned} \tag{3.40}$$

Proof. The first equation is easily obtained from (3.26), with $p(t, \tau) = v(t)e^{-\mu_0\tau}$. The second equation follows observing that by (3.37) and (3.38) we have the relations

$$\begin{aligned} v(t) &= z(t-\tau), \\ z(t) &= \tilde{b}_1(x(t)) + b_2(x(t))v(t)e^{-\mu_0\tau}. \end{aligned}$$

□

From a biological point of view, all three systems (3.34), (3.36) and (3.40) are meaningful. Recruitment into the juvenile phase and (discounted) recruitment into the adult phase can both be observed, depending on the situation. On the other side, these systems might be used to investigate existence and uniqueness of solutions to the neutral equation (3.33) (cf. [10]). We shall use system (3.40) for the numerical computation of solutions to (3.33).

3.5. Numerical Insights

In this section we shortly discuss the numerics of neutral DDEs with state-dependent delay. Let $x \in \mathbb{R}$, $\phi : \mathbb{R} \to \mathbb{R}$ continuously differentiable, $f : [t_0, t_{end}] \times \mathbb{R} \times \mathbb{R} \times \mathbb{R} \to \mathbb{R}$ continuous, $\tau : \mathbb{R} \to [0, h]$, $h \in (0, \infty)$ and consider the initial value problem

$$\begin{aligned} \dot{x}(t) &= f(t, x(t), x(t-\tau(x_t)), \dot{x}(t-\tau(x_t))), \qquad t \geq t_0, \\ x(t) &= \phi(t), \qquad t \leq t_0, \end{aligned} \tag{3.41}$$

with $x_t(s) = x(t+s)$, $s \in [-h, 0]$. For this kind of problems, a possible discontinuity in the derivative of the solution at the initial point,

$$\lim_{t \to t_0^+} \dot{x}(t) \neq \lim_{t \to t_0^-} \dot{\phi}(t),$$

may generate a *cascade of discontinuities* [14]. Indeed, as soon as $s - \tau(x_s) = t_0$ for some $s > t_0$, the right-hand side f is discontinuous at s. This discontinuity is transferred to higher order derivatives along the whole integration interval, so that in some cases the solution may cease to exist or bifurcate at a discontinuity point [54]. However, we have to deal with a special case of (3.41) and indeed a much simpler scenario.

In our general problem (3.33), the delay value $\tau = \tau(x(t))$ is always given by the value of the solution at a certain point t. Further, we have smoothness and regularity assumptions on τ, as explained in Section 3.1. This means that the numerical computation of (3.33) is less challenging than expected. In particular we can solve (3.33) numerically by an implicit continuous Runge-Kutta method [14]. The code is implemented in MATLAB® and is based on an implicit ODE solver of order two [10, 108].

For $t \geq t_0$ we can directly solve (3.40). Indeed, given history functions for x and $\dot{x}$ on an interval $[t_0 - h, t_0]$, and the delay function τ, we can compute the values $\tau(x(t_0))$ and $x(t_0 - \tau(x(t_0)))$. The definition (3.39) of *discounted recruitment into the adult class* implies that initial data for v can be directly computed from (3.27), given x and $\dot{x}$ on $[t_0 - h, t_0]$. Thus we know the value $v(t_0 - \tau(x(t_0)))$, too. This allows the computation of $v(t_0)$ and $\dot{x}(t_0)$ and so on for all $t \geq t_0$. A smooth interpolant guarantees for the continuous extension of the solution after each integration.

In the following we show some numerical simulations of solutions to our (neutral) state-dependent delay problem. We shall visualize differences between the (neutral) equation with constant delay and the corresponding one with state-dependent delay. In particular we are interested in existence and qualitative behavior of oscillatory solutions.

First, let us consider the non-neutral case. For the numerical simulation of the *state-dependent blowfly equation* (3.29), we write the problem in the form (3.40), with $b_2 \equiv 0$. This system is autonomous, hence invariant under translations along the time axis (cf. Chapter 4). So we may shift the initial value to $t = 0$. We specify the coefficient functions in the form

$$b_1(x) = \alpha_1 e^{-\kappa_1 x}, \qquad \mu_1(x) = \gamma + \delta x,$$

and define the delay function by

$$\tau(x) = \tau_0 + (\tau_1 - \tau_0)\frac{x}{T + x}, \quad 0 < \tau_0 < \tau_1 < \infty,\ T > 0.$$

Parameter descriptions and values are given in Table 3.1, p. 45. We choose initial data $x(t) = 10$ and $\dot{x}(t) = 0$ for all $t \leq 0$ (constant history function). The same parameter values and initial data are chosen for simulations of the equation with constant delay (3.30). An example for an oscillatory solution x of (3.29) is shown in Figure 3.7.

If we look at the delay function $\tau(x(t))$ over time, represented in Figure 3.8(a), we notice that $\tau(x)$ does not take all values between τ_0 and τ_1, because it depends on the values of the solution x. Indeed, $\tau(x)$ takes values between $\tau_{min} = \tau(x_{min})$ and $\tau_{max} = \tau(x_{max})$, where x_{min}, x_{max} are the minimal value, respectively the maximal computed value for x. We estimate the mean value τ_{mean} of $\tau(x)$ and compare the solution of (3.29), with $\tau(x) \in [\tau_0, \tau_1]$, with the one of (3.30) for $\tau = \tau_{mean}$. An example for $\tau(x) \in [2, 20]$ and the corresponding $\tau_{mean} = 14.2574$ is shown in Figure 3.8(b). Although both solutions oscillate periodically, they do not show the same properties. Indeed, oscillation amplitude and period are smaller for the problem with state-dependent delay (3.29) than for the one with constant delay (3.30).

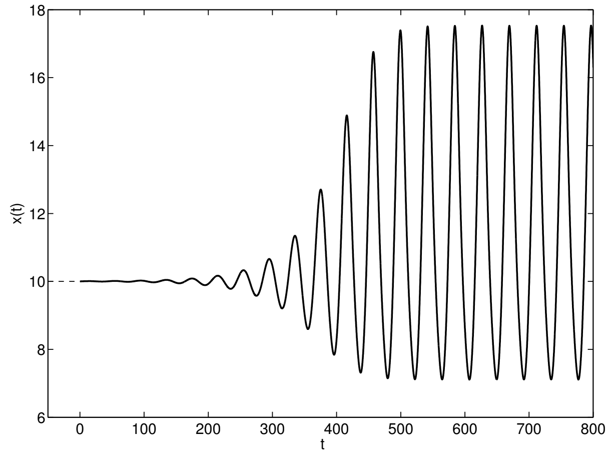
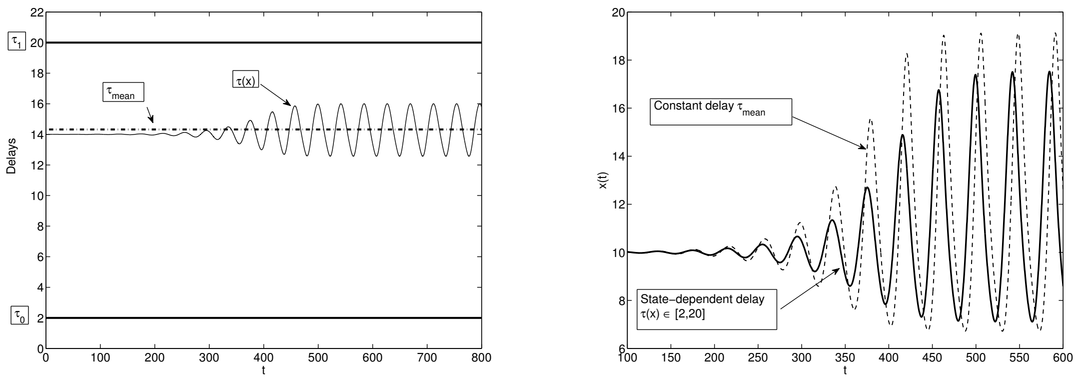


Figure 3.7: Oscillatory solution of the *state-dependent blowfly equation* (3.29). Here we have considered a state-dependent delay $\tau(x) \in [2, 20]$.



(a) Delays $\tau(x)$ and τ_{mean}.

(b) Numerical solutions $x(t)$.

Figure 3.8: (a) The delay function $\tau(x) \in [\tau_0, \tau_1]$ in time and its mean value τ_{mean}. The state-dependent delay $\tau(x)$ does not take all values between τ_0 and τ_1. (b) Dashed curve: Numerical solution of (3.30) for $\tau = \tau_{mean}$. Solid curve: Numerical solution of (3.29) with $\tau(x) \in [2, 20]$. Oscillation amplitude and period of the problem with state-dependent delay are smaller than those of the problem with constant delay.

What happens now, if we approximate the state-dependent delay, $\tau(x)$, by its value at the equilibrium solution, $\bar{\tau} = \tau(\bar{x})$? For $\bar{x} = 10$, we have $\bar{\tau} = 14$ and we compare the numerical solution of the state-dependent problem (3.29), with $\tau(x) \in [\tau_0, \tau_1]$, to the one of (3.30), with $\tau = \bar{\tau}$. The result is shown in Figure 3.9. On the one side, the constant delay does not completely resemble the dynamics of the state-dependent problem. On the other side, the state-dependent delay seems to have minimal effects on the oscillation period. The amplitude of the oscillatory solution of (3.29) is smaller than the one of the constant delay problem (3.30). This means that the state-dependent delay has a sort of damping effect on the solution. In Section 5.2 we will return on this topic from an analytical point of view.

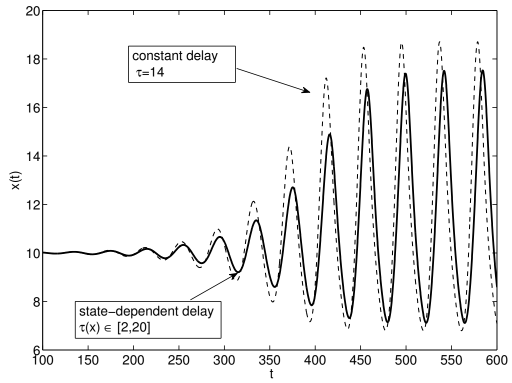


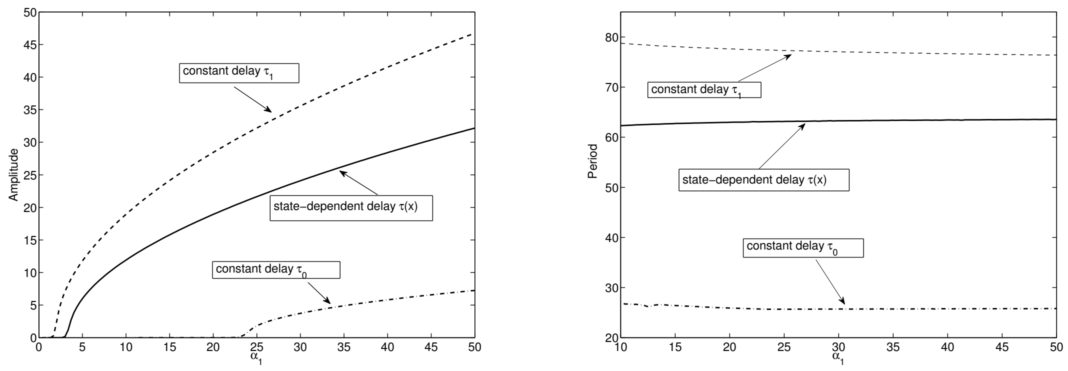
Figure 3.9: Dashed curve: Numerical solution of the *blowfly equation* (3.30) with constant delay $\tau = \bar{\tau} = 14$. Solid curve: Numerical solution of the *state-dependent blowfly equation* (3.29) with $\tau(x) \in [2, 20]$. Oscillations of solutions to (3.29) have smaller amplitude than those of (3.30).

In order to evidence further differences between a state-dependent and a constant delay, we perform a new numerical test. We choose α_1 as the bifurcation parameter and compare amplitude and period of oscillations for the problem with state-dependent delay (3.29) and the one with constant delay (3.30), with $\tau = \tau_0$ and $\tau = \tau_1$. As expected, solutions of the state-dependent DDE oscillate in a range between the two extremal constant cases (Figure 3.10). That is, the amplitude (respectively, period) of solutions to (3.29) is bounded from above by that of equation (3.30) with constant delay $\tau = \tau_1$, and from below by the amplitude of solutions to (3.30) with constant delay $\tau = \tau_0$.

Similar observations can be made for the neutral case. For the computation of solutions to (3.40), we define

$$b_2(x) = \alpha_2 e^{-\kappa_2 x}.$$

Parameter descriptions and values are given in Table 3.2, p. 45. Initial data are $x(t) = 10$ and $\dot{x}(t) = 0$ for all $t \leq 0$. An example for the solution x to (3.40) is shown in Figure 3.11.



(a) Oscillation amplitudes. (b) Oscillation periods.

Figure 3.10: Bifurcations with respect to α_1. Oscillation amplitudes (a) and periods (b) depend on the choice of the delay. We compare the state-dependent delay problem (3.29), with $\tau(x) \in [8, 30]$ (solid curve), and the constant delay problem (3.30), with $\tau_0 = 8$ and $\tau_1 = 30$ (dashed curves). Oscillatory solutions to (3.29) are bounded from above by those of equation (3.30) with delay $\tau = \tau_1$, and from below by solutions to (3.30) with $\tau = \tau_0$.

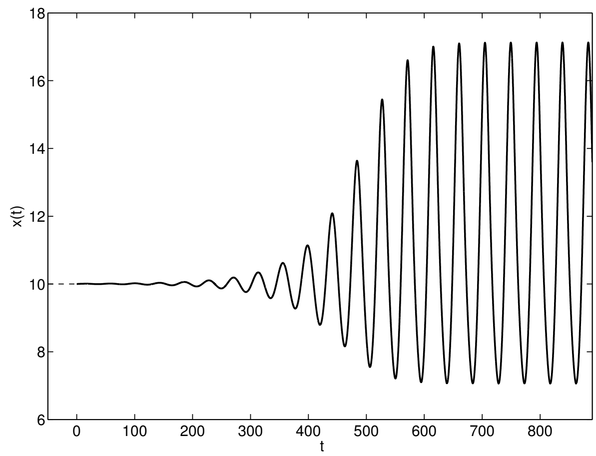
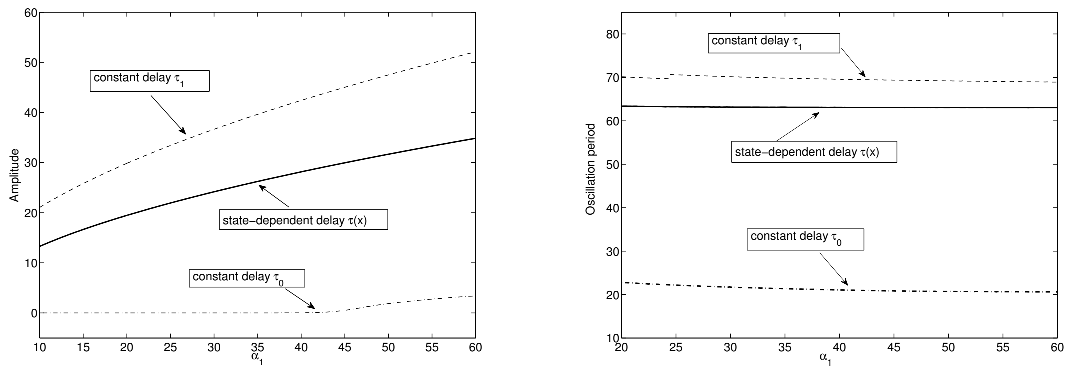


Figure 3.11: Oscillatory solution of the neutral equation (3.40). Here we have chosen a state-dependent delay $\tau(x) \in [2, 20]$.

We consider the neutral problem (3.40), with state-dependent delay $\tau(x) \in [6, 30]$, as well as equation (3.28), with constant delay $\tau = \tau_0$ and $\tau = \tau_1$. We choose α_1 as bifurcation parameter and compare amplitude and period of oscillatory solutions of the two problems.

Computational results in Figure 3.12 show that oscillation amplitudes and periods of the state-dependent delay problem are bounded between those of the constant delay problems.



(a) Oscillation amplitudes. (b) Oscillation periods.

Figure 3.12: Bifurcations with respect to α_1. Oscillation amplitudes (a) and periods (b) depend on the choice of the delay. We compare solutions to the neutral equation (3.40), with state-dependent delay $\tau(x) \in [6, 30]$ (solid curve) and those of the constant delay equation (3.28) with $\tau_0 = 6$ and $\tau_1 = 30$ (dashed curves). Oscillation amplitudes (respectively, periods) of equation (3.40) are bounded from below by oscillation amplitudes (respectively, periods) of solutions of (3.28) with $\tau = \tau_0$ and from above by oscillation amplitudes (respectively, periods) of solutions of (3.28) with $\tau = \tau_1$.

A last numerical test shows what happens if we omit the denominator in the equation with state-dependent delay. We compare the numerical solution of the *state-dependent blowfly equation* (3.29) with the one of (3.31).

Equation (3.31) can be easily obtained, substituting the constant delay in (3.30) by a state-dependent one. In this sense, both equations may be considered as a state-dependent version of the classical *blowfly equation* (3.30) in [100]. However, a formal derivation (cf. Section 3.2) shows that changes of the delay function $\tau(x)$ with respect to its argument cannot be neglected, and that equation (3.29) is correct from a biological (and physical) point of view.

When choosing a modeling approach among (3.29) and (3.31), one should be aware of the qualitative differences between the two equations. As Figure 3.13 shows, solutions of (3.29) and (3.31) are not equivalent. We can observe, in particular on the short time scale, that oscillatory solutions of the simplified equation (3.31) are characterized by amplitudes larger than those of the *state-dependent blowfly equation* (3.29).

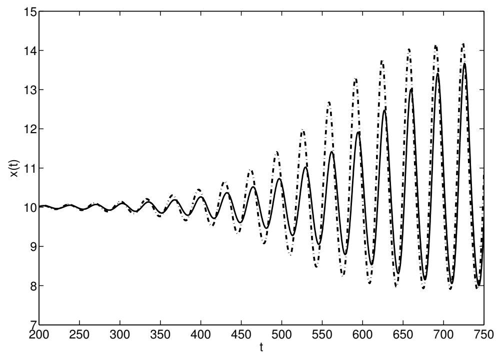


Figure 3.13: Oscillatory solution of the *state-dependent blowfly equation* (3.29) (solid line) and the simplified equation (3.31) (dashed line). Both equations may be considered "state-dependent" versions of the neutral equation in [20], but their solutions are not equivalent.

Table 3.1: Parameter values for numerical simulations of equations (3.29) and (3.30).

Symbol	**Description**	**Value**
α_1	Net fertility rate	21.2
κ_1	Discount rate due to adult population	0.6
γ	Death rate in absence of other individuals	0.001
δ	Death due to presence of other individuals	0.005
τ_0	Minimal age-at-maturity	2
τ_1	Maximal age-at-maturity	20
T	Threshold for $\tau(x)$	5
μ_0	Death rate of juveniles	0.002

Table 3.2: Parameter values for numerical simulations of the neutral equation (3.40).

Symbol	**Description**	**Value**
α_1	Net fertility rate	16.9
κ_1	Discount rate due to adult population	0.6
α_2	Net fertility rate (peak)	33.5
κ_2	Discount rate due to adult population (peak)	0.5
γ	Death rate in absence of other individuals	0.001
δ	Death due to presence of other individuals	0.005
τ_0	Minimal age-at-maturity	2
τ_1	Maximal age-at-maturity	20
T	Threshold for $\tau(x)$	5
μ_0	Death rate of juveniles	0.002

Part II.

Equations with State-Dependent Delay

4. Theory of Equations with State-Dependent Delay

The present chapter is meant to give an overview of the theory of equations with state-dependent delay.

We start by introducing the more general class of Retarded Functional Differential Equations (RFDEs), that is,

$$\dot{x}(t) = f(t, x_t), \tag{4.1}$$

where x_t is the "piece of solution" of (4.1) in a finite interval preceding t. This kind of equations has been largely investigated in the last century [37, 64, 66].

In Section 4.1 we recall basic notions on RFDEs. We briefly present results on stability of linear autonomous RFDEs [64,66] and on linearized stability of nonlinear equations [37,66].

In the second part of the chapter, we show that Delay Differential Equations (DDEs) with state-dependent delay can in general be expressed in the RFDE formulation (4.1). However, the theory of retarded functional differential equations does not apply in a straightforward way [127]. Walther and co-authors [67, 125–127] considered a class of DDEs with state-dependent delay,

$$\dot{x}(t) = g(x(t - \tau(x_t))), \tag{4.2}$$

and formulated hypotheses on the right-hand side of (4.2) which guarantee existence, uniqueness and smoothness of solutions. In Section 4.2 we provide an outline of the works [125–127] and [67]. A major result in Hartung et al. [67], here Theorem 4.4, states that solutions to (4.2) generate a semiflow F of continuously differentiable solution operators. Theorem 4.4 resolves the problem of linearization of state-dependent DDEs at stationary points, which was previously considered in [22, 33]. In the final part of the chapter, we report a principle of linearized stability for equations with state-dependent delay.

4.1. Retarded Functional Differential Equations

When changes in the state x of a physical system at a certain time t do not only depend on the state of the system at the current time ($x(t)$) but also on its past history, Ordinary Differential Equations (ODEs) are not suitable to describe the phenomenon. In this case, the appropriate tool is given by so-called Retarded Functional Differential Equations, which we shall formally define below.

Although early works on RFDEs are at least two hundred years old (cf. the examples reported in 1911 by Schmitt [109]), the theory of RFDEs has been systematically developed in the twentieth century. Traditional references in this field are the books by Hale [64], Hale and Verduyn Lunel [66] and Diekmann et al. [37]. In this section we present some notation and basic properties of RFDEs following Hale [64].

Let $h > 0$ and $n \in \mathbb{N}$. By $(\mathbb{R}^n)^{[-h,0]}$ we indicate the set of functions defined on the interval $[-h, 0]$ with values in $\mathbb{R}^n$,

$$(\mathbb{R}^n)^{[-h,0]} = \{\text{functions } \phi, \text{ s. t. } \phi : [-h, 0] \to \mathbb{R}^n\}.$$

Further, we define $C = C([-h, 0], \mathbb{R}^n)$, the set of continuous functions $\phi \in (\mathbb{R}^n)^{[-h,0]}$, together with the norm $\|\phi\|_C = \max_{-h \le t \le 0} |\phi(t)|$, and the set $C^1 = C^1([-h, 0], \mathbb{R}^n)$ of continuously differentiable functions $\psi \in (\mathbb{R}^n)^{[-h,0]}$, with the norm $\|\psi\|_{C^1} = \|\psi\|_C + \|\partial\psi\|_C$, where $\partial : C^1 \to C$ is the continuous linear operator of differentiation. Both $(C, \|\cdot\|_C)$ and $(C^1, \|\cdot\|_{C^1})$ are Banach spaces. By convenient abuse of notation, the same symbol is used for spaces of functions and for continuity properties of a function. Depending on the context, we shall be able to distinguish a continuous (C-), respectively a continuously differentiable (C^1-) function, from a subset of the Banach space C, respectively C^1.

The general RFDE has the form

$$\dot{x}(t) = f(t, x_t), \tag{4.3}$$

where $f : D \to \mathbb{R}^n$ is a map defined on D, an open subset of $\mathbb{R} \times C$. Here x_t, called **solution segment** or **state** of x at time t, indicates the piece of the solution x of (4.3) in the interval of length h preceding the time point t, that is, in $[t - h, t]$. If we select this piece of solution and shift it back to the interval $[-h, 0]$, as in Figure 4.1, we regard x_t as the function

$$x_t : [-h, 0] \to \mathbb{R}^n, \;\; s \mapsto x(t + s).$$

If x is a continuous function, then x_t is an element of C and $(t, x_t) \in D$. We like to underline the difference between the *segment* $x_t \in C$ and *the value* $x(t) \in \mathbb{R}^n$ of the solution x.

Depending on the right-hand side f, we say that (4.3) is a **linear equation** if there is a linear function L such that $f(t, \phi) = L(t)\phi + H(t)$; in particular, equation (4.3) is called **linear homogeneous** if $H \equiv 0$.

Given a continuous function $\phi \in C$, the **initial value problem** (IVP) associated to the RFDE (4.3) is given by

$$\begin{aligned} \dot{x}(t) &= f(t, x_t), \qquad \text{for } \; t \ge t_0, \\ x_{t_0} &= \phi. \end{aligned} \tag{4.4}$$

We say that a function x is a **solution** of (4.4) on an interval $[t_0 - h, t_m)$, $t_0 < t_m \le \infty$ if $x : [t_0 - h, t_m) \to \mathbb{R}^n$ is continuous, $(t, x_t) \in D$ for all $t \in [t_0, t_m)$, x satisfies (4.3) for all $t \in [t_0, t_m)$ and $x_{t_0} = \phi$. With a more compact notation, we indicate a **solution** of (4.3) **with initial data** ϕ **at** t_0 by $x(t_0, \phi, f)$. The map ϕ is also called **initial function** or **history function**.

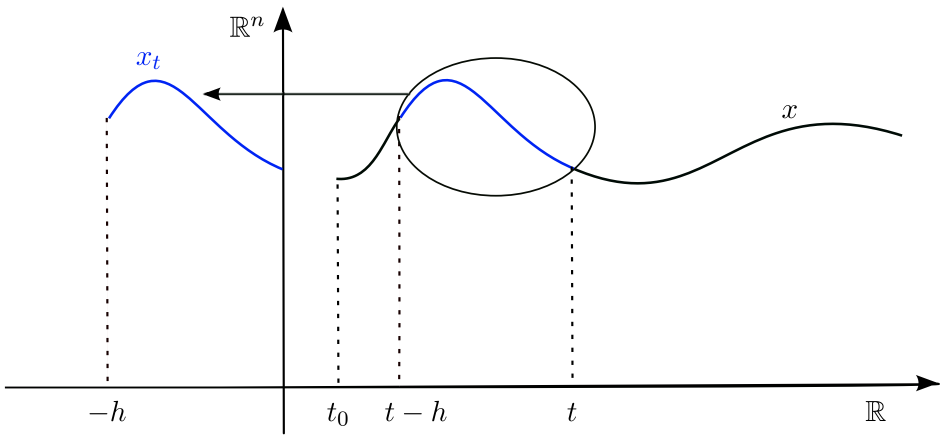


Figure 4.1: The state x_t of a solution x at time t is the segment of x in the time interval $[t-h,\, t]$. The function x_t maps the interval $[-h, 0]$ into $\mathbb{R}^n$.

If $f(t, \phi)$ is continuous, then there exists a t_m, $t_0 < t_m \leq \infty$, such that the IVP (4.4) has a solution $x : [t_0 - h, t_m) \to \mathbb{R}^n$, for any $(t_0, \phi) \in D$ and $x_t \in C$, for all $t \geq t_0$ [37, 64].

Uniqueness of solutions is guaranteed, provided that for each point $(t, \phi) \in D$ there exists an open neighborhood $K \subset D$ such that $f(t, \phi)$ is Lipschitz in ϕ on K, that is, there exists a constant $L_K > 0$ such that

$$\|f(z, \phi_1) - f(z, \phi_2)\|_{\mathbb{R}^n} \leq L_K \|\phi_1 - \phi_2\|_C \,,$$

for all (z, ϕ_1), $(z, \phi_2) \in K$. Further, solutions of (4.4) can be extended to a maximal interval of existence. These **noncontinuable solutions** are defined on intervals $[t_0, t_{max})$, with $t_{max} < \infty$, or on the whole $[t_0, \infty)$. However, solutions to (4.3) do not always behave nicely. For example, in general there is no (or no unique) solution for the backward initial value problem. That is, given initial data (t_0, ϕ) there is perhaps a solution x satisfying (4.4) in $[t_0 - h, t_0 + \delta]$, $\delta > 0$, but it might not be possible to extend this solution to the interval $[t_0 - h - \varepsilon, t_0 + \delta]$, for any $\varepsilon > 0$ [64].

In the development of the theory of RFDEs, the identification of "a good representation" of trajectories was not immediate. Let $x(t_0, \phi, f)$ be a noncontinuable solution of (4.4) and $D \subset C$. One candidate for the solution map could be

$$Q^t : D \to \mathbb{R}^n, \quad \phi \mapsto Q^t(\phi) = x(t_0, \phi, f)(t).$$

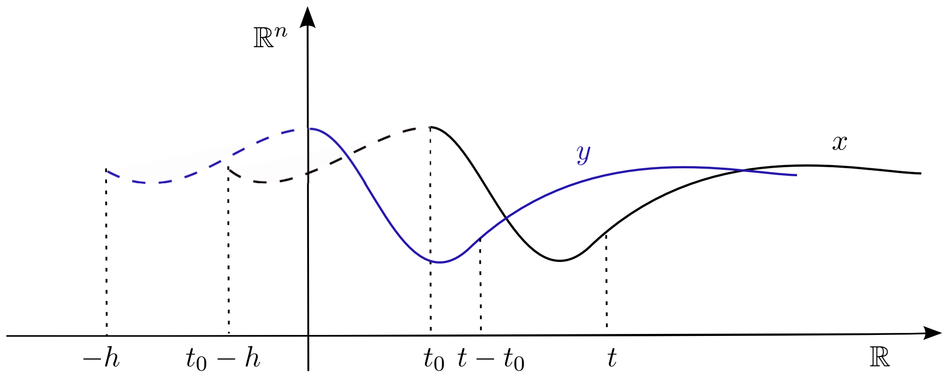


Figure 4.2: Invariance of solutions under translation for autonomous RFDEs. The solution x (black solid curve) with history on $[t_0 - h, t_0]$ (black dashed curve) and the shifted curve y (blue solid curve) with history on $[-h, 0]$ (blue dashed curve).

However, the map Q^t shows some unwanted properties, for example, it does not guarantee uniqueness of solutions [64]. Therefore we may consider the problem from a different point of view and look for a map between spaces of "the same kind". The proper operator should map an initial state ϕ at time t_0 to the state x_t at time t. Under this perspective, **the solution map** of the RFDE (4.4) is defined as

$$T_f(t, t_0) : C \supset D \to C, \quad \phi \mapsto T_f(t, t_0)\phi = x_t(t_0, \phi, f). \tag{4.5}$$

When necessary, we will present some features of the solution map (4.5). A complete description of the properties of $T_f(t, t_0)$ can be found in [66, Ch. 3].

In the following we will only consider **autonomous** retarded functional differential equations, i.e., RFDEs whose right-hand side does not explicitly depend on the time variable,

$$\dot{x}(t) = f(x_t), \tag{4.6}$$

where $f : U \to \mathbb{R}^n$ is a functional defined on an open subset U of C. Solutions of autonomous RFDEs are invariant under translation in time. Indeed, when $x : [t_0 - h, t_m) \to \mathbb{R}^n$ is a solution of (4.6) with initial data $x_{t_0} = \phi$ at t_0, then the map $y : [z + t_0 - h, t_m + z) \to \mathbb{R}^n,\ s \mapsto x(s - z)$ defines a solution of (4.6) with initial data $x_{t_0+z} = \phi$ at $t_0 + z$. From now on, we shift the initial point t_0 to the zero of the time axis and consider initial functions in the interval $[-h, 0]$, as shown in Figure 4.2.

One possibility to investigate the dynamics of a nonlinear RFDE problem is to consider the problem in proximity of an equilibrium and study the linearized problem. In the following sections we briefly present a few major results on linear RFDEs and linearized stability of RFDEs.

Linear Autonomous RFDEs

Let $L : C \to \mathbb{R}^n$ be a continuous linear map. This map extends uniquely to a continuous complex linear map $C^c \to \mathbb{C}^n$, with $C^c = C([-h,0],\mathbb{C}^n)$, which by abuse of notation we will also denote by L. Let us consider the linear autonomous equation

$$\dot{x}(t) = L(x_t), \qquad t \geq 0. \tag{4.7}$$

Given an initial value $\phi \in C^c$, if we identify $\mathbb{C}^n$ with $\mathbb{R}^{2n}$, then we can extend the results of the previous section to show existence and uniqueness of solutions to the linear problem (4.7), with $x_0 = \phi$. For each $\phi \in C^c$, let x^ϕ be the unique solution of (4.7) with initial function ϕ at zero. Then, for $t \geq 0$, the solution map (4.5) is defined by

$$T(t) : C^c \to C^c, \quad \phi \mapsto x_t^\phi.$$

For each $t \geq 0$, the solution operator $T(t)$ is a bounded, complex linear map such that

1. $T(0) = \mathrm{id}_{C^c}$,
2. $T(t)T(z) = T(t+z)$ for all t, $z \geq 0$,
3. $\lim\limits_{z\to t} |T(t)\phi - T(z)\phi| = 0$ for all $t \geq 0$ and all $\phi \in C^c$.

This means that the family $\{T(t)\}_{t\geq 0}$ is a **strongly continuous semigroup**, also called $\mathcal{C}_0$-semigroup, of transformations. In particular, the semigroup is **eventually compact**, as $T(t)$ is compact for all $t \geq h$ [32].

The **infinitesimal generator** of $\{T(t)\}_{t\geq 0}$ is the operator $A : C^c \to C^c$ defined by

$$A(\phi) = \lim_{t\to 0^+} \frac{T(t)\phi - \phi}{t}. \tag{4.8}$$

The **domain** $\mathcal{D}(A)$ of A is the set of all $\phi \in C^c$ for which the limit in (4.8) exists, in the sense of convergence in the norm in C^c. In case of the linear equation (4.6), it can be shown (cf. [64, Ch. 7]) that the generator A is given by

$$A\phi(s) = \begin{cases} \frac{d}{ds}\phi(s), & \text{if } s \in [-h,0), \\ L(\phi), & \text{if } s = 0, \end{cases} \tag{4.9}$$

and that its domain,

$$\mathcal{D}(A) = \Big\{\phi \in C^c \,:\, \phi \text{ is continuously differentiable on } [-h,0] \text{ and } \dot{\phi}(0) = L(\phi)\Big\},$$

is dense in C^c. In particular, for any $\phi \in \mathcal{D}(A)$, we have that

$$\frac{d}{dt}T(t)\phi = T(t)A\phi = AT(t)\phi. \tag{4.10}$$

The generator A in (4.9) reflects certain properties of the unknown operator $T(t)$. In the following we shortly motivate this point, whereas more details and proofs can be found in [64,66].

Next, we need some definitions. The **resolvent set** $\rho(X)$ of a linear operator $X : C^c \to C^c$ is the set of values $\lambda \in \mathbb{C}$ such that the **resolvent operator** $(\lambda I - X)^{-1}$ exists and is bounded, with domain dense in C^c. The **spectrum** of X, $\sigma(X)$, is the complement of $\rho(X)$ in the complex plane. The **point spectrum** $\sigma_P(X)$ is the part of $\sigma(X)$ which consists of those $\lambda \in \sigma(X)$ such that $\lambda I - X$ does not have an inverse. In this case, the point $\lambda \in \sigma_P(X)$ is called an **eigenvalue** of X and a nonzero ϕ, such that $(\lambda I - X)\phi = 0$, is called the **eigenvector** corresponding to λ.

Let us now consider a point $\lambda \in \sigma_P(X)$. The **null space** $\mathcal{N}(X)$ of X is the set of all $\phi \in C^c$ for which $X\phi = 0$. The null space $\mathcal{N}(\lambda I - X)$ is called **the eigenspace** of λ and its dimension is the geometric multiplicity of λ. The **generalized eigenspace** $\mathcal{M}_\lambda$ of λ is the smallest closed linear subspace that contains all null spaces $\mathcal{N}\left((\lambda I - X)^j\right)$, $j = 1, 2, \ldots$.

Now we go back to the linear problem (4.7). For the generator A in (4.9), it can be shown that the spectrum $\sigma(A)$ coincides with its point spectrum, $\sigma_P(A)$. Further, it is possible to give an explicit description of $\sigma(A)$. Let $\Delta(\lambda) : \mathbb{C}^n \to \mathbb{C}^n$ be the complex linear map defined by

$$\Delta(\lambda)(v) = \lambda v - L(\tilde{e}(\lambda, v)),$$

where, for each $\lambda \in \mathbb{C}$ and $v \in \mathbb{C}^n$, the map $\tilde{e}(\lambda, v) \in C^c$ is defined by

$$\tilde{e}(\lambda, v) : [-h, 0] \to \mathbb{C}^n, \quad t \mapsto \tilde{e}(\lambda, v)(t) = e^{\lambda t} v.$$

Then, a value $\lambda \in \mathbb{C}$ is in $\sigma(A)$ if and only if λ satisfies the **characteristic equation**

$$\det \Delta(\lambda) = 0. \tag{4.11}$$

Zeros of (4.11) are called **characteristic roots**. Hence, the eigenvalues of A are the characteristic roots of the linear RFDE (4.7).

A central result [64] on (4.9) states that there is a value $\gamma > 0$ such that no root of the characteristic equation (4.11) has real part greater than γ and that for each $\lambda \in \sigma(A)$ the generalized eigenspace is finite-dimensional. Moreover, there is a value $k \in \mathbb{Z}$ such that $\mathcal{M}_\lambda = \mathcal{N}\left((\lambda I - A)^k\right)$ and the space C^c is given by the direct sum of the null space $\mathcal{N}\left((\lambda I - A)^k\right)$ and of the range $\mathcal{R}\left((\lambda I - A)^k\right)$ of the operator $(\lambda I - A)^k$. Thus, for an eigenvalue λ of A, the generalized eigenspace $\mathcal{M}_\lambda$ is finite dimensional and $A\mathcal{M}_\lambda \subset \mathcal{M}_\lambda$ (as $\phi \in \mathcal{M}_\lambda$ implies $(\lambda I - A)^k \phi = 0$). Let us assume that $\dim \mathcal{M}_\lambda = d$, let $\phi_1^\lambda, \ldots, \phi_d^\lambda$ be a basis for $\mathcal{M}_\lambda$ and let $\Phi_\lambda = \left(\phi_1^\lambda, \ldots, \phi_d^\lambda\right)$. There is then a $d \times d$ constant matrix B_λ such that $A\Phi_\lambda = \Phi_\lambda B_\lambda$. With the explicit expression (4.9) of A, the above relation implies that

$$\Phi_\lambda(s) = \Phi_\lambda(0) e^{B_\lambda s}, \qquad \text{for } s \in [-h, 0].$$

From (4.10), we have that

$$(T(t)\Phi_\lambda)(s) = \Phi_\lambda(0)e^{B_\lambda(t+s)}, \qquad \text{for } s \in [-h, 0].$$

The last relation describes the operator $T(t)$ on the generalized eigenspace $\mathcal{M}_\lambda$ of an eigenvalue $\lambda \in \sigma(A)$. Hence, on $\mathcal{M}_\lambda$ the linear problem (4.7) has the same structure as an ODE. This result can be generalized to give more information on the solutions of (4.7).

Theorem 4.1 (Theorem 7.2.1 in [64]). *Let $\Lambda = \{\lambda_1, \ldots, \lambda_p\}$ be a finite set of eigenvalues of A and let $\Phi_\Lambda = (\Phi_{\lambda_1}, \ldots, \Phi_{\lambda_p})$ and $B_\Lambda = \operatorname{diag}(B_{\lambda_1}, \ldots, B_{\lambda_p})$, where Φ_{λ_j} is a basis for the generalized eigenspace of λ_j and B_{λ_j} is the matrix defined by $A\Phi_{\lambda_j} = \Phi_{\lambda_j} B_{\lambda_j}$, for all $j \in \{1, 2, \ldots, p\}$. Then the only eigenvalue of B_{λ_j} is λ_j and, for any vector a of the same dimension of Φ_Λ, the solution $T(t)\Phi_\Lambda a$, with initial value $\Phi_\Lambda a$ at $t = 0$, may be defined on $(-\infty, \infty)$ by the relation*

$$\begin{aligned} T(t)\Phi_\Lambda a &= \Phi_\Lambda e^{B_\Lambda t} a, \\ \Phi_\Lambda(s) &= \Phi_\Lambda(0) e^{B_\Lambda s}, \qquad \textit{for } s \in [-h, 0]. \end{aligned}$$

Moreover, the space C^c is given by the direct sum of two subspaces invariant under A and $T(t)$,

$$C^c = P_\Lambda \oplus Q_\Lambda,$$

where $P_\Lambda = \{\phi \in C^c : \phi = \Phi_\Lambda a, \text{ for some vector } a\}$.

Thus, the space C^c can be decomposed by Λ, that is, each element $\phi \in C^c$ can be written as the sum $\phi = \phi^{P_\Lambda} + \phi^{Q_\Lambda}$, with $\phi^{P_\Lambda} \in P_\Lambda$ and $\phi^{Q_\Lambda} \in Q_\Lambda$. From Theorem 4.1 we know how solutions to (4.7) behave on generalized eigenspaces of A. It is possible to have estimates of solutions on the complementary space Q_Λ, too. Indeed, given a value $\beta \in \mathbb{R}$ we can decompose C^c by the set

$$\Lambda = \Lambda_\beta = \{\lambda \in \sigma(A) : Re(\lambda) > \beta\}.$$

As it is shown in [37, 66], there exist positive constants γ and $K = K(\gamma)$ such that

$$\begin{aligned} \|T(t)\phi^{P_\Lambda}\| &\le K e^{(\beta+\gamma)t} \|\phi^{P_\Lambda}\|, \qquad \text{for } t \le 0, \\ \|T(t)\phi^{Q_\Lambda}\| &\le K e^{(\beta+\gamma)t} \|\phi^{Q_\Lambda}\|, \qquad \text{for } t \ge 0. \end{aligned}$$

Before moving on with the class of nonlinear RFDEs, we present a result about exponential stability of solutions to the linear equation (4.7).

Theorem 4.2 (Corollary 7.6.1 in [66]). *If all roots of the characteristic equation (4.11) have negative real parts, then there exist positive constants K and δ such that*

$$\|T(t)\phi\| \le K e^{-\delta t} \|\phi\|, \qquad \textit{for all } t \ge 0,$$

for all $\phi \in \mathbb{C}^c$.

Nonlinear RFDEs

Let us now consider a nonlinear RFDE

$$\dot{x}(t) = f(x_t), \qquad t \geq 0, \tag{4.12}$$

with $f : U \to \mathbb{R}^n$, $U \subset C$ open. Let $x^{eq} \in C$, $x^{eq}(t) \equiv \bar{x} \in \mathbb{R}^n$ be an **equilibrium solution** or **stationary state solution** of (4.12), that is, $f(x^{eq}) = 0$. In proximity of the equilibrium x^{eq} we can expand a solution x of (4.12),

$$x(t) = x^{eq} + y(t),$$

and the variable y satisfies

$$\dot{y}(t) = f(x^{eq} + y_t).$$

Assuming that there is a bounded linear map $L : C \to \mathbb{R}^n$ and a map $\nu : C \to \mathbb{R}^n$, such that $\lim_{\phi \to 0} \frac{|\nu(\phi)|}{\|\phi\|_C} = 0$, we can write

$$f(x^{eq} + \phi) = L(\phi) + \nu(\phi).$$

We can use the theory of the previous section to investigate the behavior of the linear system

$$\dot{z}(t) = L(z_t), \qquad t \geq 0. \tag{4.13}$$

Further, we have the following result on local stability of the nonlinear system (4.12).

Theorem 4.3 (Theorem 7.6.8 in [37])**.** *If all roots of the characteristic equation corresponding to the linear system (4.13) have negative real parts, then x^{eq} is a locally asymptotically stable equilibrium of (4.12).*

If $Re(\lambda) > 0$ for some characteristic root of (4.13), then x^{eq} is unstable for (4.12).

In most cases delay equations with constant, time-dependent or state-dependent delay can be expressed in the more general framework of RFDEs, as we explain in the next section.

4.2. Delay Equations and RFDEs

In general, a constant delay problem

$$\dot{x}(t) = g(x(t - r)),$$

with $g : \mathbb{R}^n \to \mathbb{R}^n$ and $r > 0$ can be rearranged in the form of an autonomous RFDE,

$$\dot{x}(t) = f_0(x_t), \tag{4.14}$$

with $f_0 : C \to \mathbb{R}^n$, $\phi \mapsto f_0(\phi) = g(\phi(-r))$, and $C = C([-r, 0], \mathbb{R}^n)$. Smoothness properties of f_0 are induced by those of g. For example, if g is Lipschitz continuous, f_0 is also Lipschitz continuous and for continuous initial data $\phi \in C$ there exists a unique solution to the IVP [37]. The situation is different for equations with state-dependent delays.

Given a map $g : \mathbb{R}^n \to \mathbb{R}^n$ and a delay functional $\tau : U_0 \to [0,h]$ on a subset $U_0 \subset (\mathbb{R}^n)^{[-h,0]}$, we consider a general DDE with state-dependent delay of the form

$$\dot{x}(t) = g(x(t - \tau(x_t))). \tag{4.15}$$

The map $f_0 : (\mathbb{R}^n)^{[-h,0]} \to \mathbb{R}^n$, defined by

$$f_0 = g \circ \operatorname{ev} \circ (\operatorname{id} \times (-\tau)),$$

with the evaluation

$$\operatorname{ev} : (\mathbb{R}^n)^{[-h,0]} \times [-h,0] \to \mathbb{R}^n, \quad (\phi, s) \mapsto \phi(s)$$

and the identity $\operatorname{id} = \operatorname{id}_{(\mathbb{R}^n)^{[-h,0]}}$ on $(\mathbb{R}^n)^{[-h,0]}$, is obviously suitable to rewrite the state-dependent delay problem (4.15) into the RFDE form (4.14). Unfortunately, this is not sufficient to apply results on RFDEs from Hale [64], Hale and Verduyn Lunel [66] or Diekmann et al. [37]. Indeed, independently of the smoothness of g and τ, the composition f_0 may not be locally Lipschitz continuous. This is because the evaluation map ev is in general not continuously differentiable, nor even locally Lipschitz continuous. These difficulties can be avoided by restricting the map ev to the space of continuously differentiable functions [125, 127]:

$$\operatorname{Ev} = \operatorname{ev}_{|_{C^1}} : C^1 \times [-h,0] \to \mathbb{R}^n.$$

The restricted map Ev is continuously differentiable with

$$D_1 \operatorname{Ev}(\phi, s)\xi = \xi(s), \qquad D_2 \operatorname{Ev}(\phi, s)1 = \dot{\phi}(s).$$

Given $g : \mathbb{R}^n \to \mathbb{R}^n$, $\tau : U \to [0,h]$ on an open subset $U \subset C^1$, and the identity $\operatorname{id} = \operatorname{id}_{C^1}$ on C^1, we consider the composition

$$U \ni \phi \underbrace{\mapsto}_{(\operatorname{id} \times (-\tau))} (\phi, -\tau(\phi)) \underbrace{\mapsto}_{\operatorname{Ev}} \phi(-\tau(\phi)) \underbrace{\mapsto}_{g} g(\phi(-\tau(\phi))) \in \mathbb{R}^n.$$

If g and τ are continuously differentiable, then the map $f : U \to \mathbb{R}^n$,

$$f = g \circ \operatorname{Ev} \circ (\operatorname{id} \times (-\tau)),$$

is continuously differentiable and for $\phi \in U$, $\xi \in C^1$, we have that

$$\begin{aligned} Df(\phi)\xi &= \dot{g}(\phi(-\tau(\phi)))\,[D_1 \operatorname{Ev}(\phi, -\tau(\phi))\xi + D_2 \operatorname{Ev}(\phi, -\tau(\phi))(-D\tau(\phi))\xi] \\ &= \dot{g}(\phi(-\tau(\phi)))\left[\xi(-\tau(\phi)) - \dot{\phi}(-\tau(\phi))D\tau(\phi)\xi\right]. \end{aligned}$$

Assume that $f : U \to \mathbb{R}^n$, $U \subset C^1$ open, is continuously differentiable and consider the IVP

$$\begin{aligned} \dot{x}(t) &= f(x_t), \qquad \text{for} \quad t \geq 0, \\ x_0 &= \phi. \end{aligned} \tag{4.16}$$

A solution $x : [-h, t_m) \to \mathbb{R}^n$, $0 < t_m \leq \infty$, of (4.16) is a continuously differentiable map and the curve $[0, t_m) \ni t \mapsto x_t \in C^1$ is continuous. Continuity at $t = 0$ implies

$$\dot{\phi}(0) = f(\phi).$$

The choice of initial data for (4.16) is thus restricted to the set

$$X_f = \{\phi \in U : \dot{\phi}(0) = f(\phi)\} \subset U \subset C^1.$$

The set X_f is also called **the solution manifold** of equation (4.14). In the next section we show that, under certain assumptions on f, the manifold X_f is continuously differentiable and that the solution segments x_t of (4.14) define a continuous semiflow on X_f.

4.2.1. The Semiflow on the Solution Manifold

In the sequel, a solution is meant to be a continuously differentiable function $x : [-h, t_m) \to \mathbb{R}^n$, $0 < t_m \leq \infty$ such that $x_t \in U$ for $t \in [0, t_m)$, $x_0 = \phi$ and $\dot{x}(t) = f(x_t)$ for $t \in (0, t_m)$.

We start with the IVP (4.16), for a given $\phi \in X_f$. When the functional $f : U \to \mathbb{R}^n$, $U \subset C^1$ is the right-hand side of a differential equation with state-dependent delay, it commonly satisfies Condition (S) below.

Definition 1 (Condition (S)). A functional $f : U \to \mathbb{R}^n$, defined on an open subset $U \subset C^1$, satisfies condition (S) provided that:

(S1) The map f is a C^1-functional.

(S2) Each derivative $Df(\phi)$, $\phi \in U$, has a linear extension $D_e f(\phi) : C \to \mathbb{R}^n$ which is continuous with respect to the norm in C.

(S3) The map $U \times C \to \mathbb{R}^n$, $(\phi, \chi) \mapsto D_e f(\phi)\chi$ is continuous.

In the following we quote without proof the main result from [67] about existence and differentiability of a semiflow on the solution manifold X_f.

Theorem 4.4 (Theorem 3.2.1 in [67]). *Suppose $U \subset C^1$ is open, $f : U \to \mathbb{R}^n$ has property (S) and $X_f \neq \emptyset$. It follows that:*

(i) The set X_f is a continuously differentiable submanifold of U with codimension n.

(ii) For each $\phi \in X_f$ there exists a unique $t_m(\phi) > 0$ and a unique noncontinuable solution $x^\phi : [-h, t_m(\phi)) \to \mathbb{R}^n$ of (4.14).

(iii) The solution segments $x_t^\phi \in X_f$ define a continuous semiflow

$$F : \Omega \to X_f, \quad (t, \phi) \mapsto x_t^\phi,$$

on the open subset

$$\Omega = \bigcup_{\phi \in X_f} [0, t_m(\phi)) \times \{\phi\}, \qquad \Omega \subset [0, \infty) \times X_f.$$

(iv) *For each* $t \geq 0$*, let* $\Omega_t = \{\phi \in X_f \, : \, (t, \phi) \in \Omega\}$*. Each map*

$$F_t : \Omega_t \to X_f, \quad \phi \mapsto F(t, \phi),$$

is continuously differentiable.

(v) *For* $\phi \in X_f$*, the tangent space of* X_f *at* ϕ *is*

$$T_\phi X_f = \{\chi \in C^1 \, : \, \dot{\chi}(0) = Df(\phi)\chi\}.$$

For all $(t, \phi) \in \Omega$ *and all* $\chi \in T_\phi X_f$ *it holds that*

$$D_2 F(t, \phi)\chi = DF_t(\phi)\chi = v_t^{\phi,\chi},$$

with the solution $v^{\phi,\chi} : [-h, t_m(\phi)) \to \mathbb{R}^n$ *of the initial value problem*

$$\begin{aligned} \dot{v}^{\phi,\chi} &= Df(F(t, \phi))v_t^{\phi,\chi}, \\ v_0^{\phi,\chi} &= \chi. \end{aligned}$$

(vi) *At each* $(t, \phi) \in [h, t_m(\phi)) \times X_f$ *the partial derivative* $D_1 F(t, \phi)$ *exists and satisfies*

$$D_1 F(t, \phi) = \partial(x_t^\phi).$$

(vii) *The restriction of* F *to the submanifold* $\{(t, \phi) \in \Omega \, : \, h < t\} \subset \mathbb{R} \times X_f$ *is continuously differentiable.*

Property (S2) was introduced as *almost Fréchet differentiability* by Mallet-Paret and co-authors [88]. Walther's initial works on state-dependent delay problems [125, 127] established that, when f has properties (S1) and (S2), the set X_f, if non-empty, is a continuously differentiable submanifold of C^1 with codimension n. The precursor of (S3) was a local Lipschitz condition on f:

Definition 2 (Condition (L))**.** For every $\phi \in U$ there is a neighborhood $V \in U$ and a constant $L \geq 0$ so that for all $\phi, \psi \in V$, we have

$$|f(\phi) - f(\psi)| \leq L\|\phi - \psi\|_C. \tag{L}$$

If f has properties (S1), (S2) and (L), then for each initial data $\phi \in X_f$, there is a unique maximal solution x^ϕ to (4.16). These maximal solutions x^ϕ define a continuous semiflow on X_f [127]. Introduced in [126], condition (S3) implies that $D_e f$ is locally bounded and, in turn, that (L) holds true for f. Condition (S3) is necessary to have the results *(vi)* and *(vii)* on the differentiability of the semiflow F. The complete proof of Theorem 4.4 can be found in Walther [126, 127], whereas an overview is given in [67].

Besides ensuring the continuous differentiability of the solution manifold, as well as the existence and differentiability of the semiflow F on X_f, Theorem 4.4 shows how to linearize semiflows defined by state-dependent delay differential equations.

4.2.2. Linearized Stability

Prior to publication of Theorem 4.4, a heuristic technique was used to address the "linearization problem". Given a nonlinear problem with state-dependent delay, the delay is "frozen" at an equilibrium $\bar{\phi}$, thus yielding a nonlinear problem with constant delay $\bar{\tau} = \tau(\bar{\phi})$, which can be linearized according to the theory of nonlinear equations with constant delay. The resulting auxiliary linear RFDE is defined on the space C of continuous functions.

However, this **"freezing-method"** applies only to equations in which the delay appears explicitly. On the other hand, there are many examples of interest in which the delay is given in an implicit form [3, 42, 67].

Theorem 4.4 guarantees that the maps $F_t : \Omega_t \to X_f$, $\phi \mapsto F(t,\phi)$ can be differentiated and that the corresponding derivatives are given by a variational equation on the tangent manifold $T_{\bar{\phi}}X_f$. In particular, the auxiliary linear RFDE, $\dot{v}^{\phi,\chi} = Df(\bar{\phi})v_t^{\phi,\chi}$, is the restriction to the tangent space $T_{\bar{\phi}}X_f$ of the auxiliary equation

$$\dot{v}^{\phi,\chi} = D_e f(\bar{\phi})v_t^{\phi,\chi}$$

on C, which is found by the heuristic technique [125]. We stress once more that the "true linearization" is the one on the tangent space $T_{\bar{\phi}}X_f$.

Let us assume that $f : U \to \mathbb{R}^n$, $U \subset C^1$ open, satisfies condition (S) and that $\bar{\phi} \in X_f$ is a stationary point of

$$\dot{x}(t) = f(x_t). \tag{4.17}$$

Let F be the semiflow generated by the solution segments of (4.17). By the heuristic (freezing) method, we would associate to (4.17) the linear IVP

$$\begin{aligned} \dot{v} &= D_e f\left(\bar{\phi}\right) v_t, \\ v_0 &= \chi, \end{aligned} \tag{4.18}$$

with $\chi \in C$. On the other hand, we know from Theorem 4.4 that the linearization of the semiflow F is given by the family $T_F = \{T_F(t)\}_{t\geq 0} = \{D_2F(t,\bar{\phi})\}_{t\geq 0}$ on $T_{\bar{\phi}}X_f$, which associates to each $\psi \in T_{\bar{\phi}}X_f$ the segment u_t of the solution u to the IVP

$$\begin{aligned} \dot{u} &= Df\left(\bar{\phi}\right) u_t, \\ u_0 &= \psi. \end{aligned} \tag{4.19}$$

Next we explain the relation between the two linear problems (4.18) and (4.19). Let us consider first the IVP (4.19). As for each $\psi \in T_{\bar{\phi}}X_f$, the solution $u = u^\psi$ is continuously differentiable, it can be shown that T_F is a $\mathcal{C}_0$-semigroup of operators on $T_{\bar{\phi}}X_f$. The generator of T_F is

$$G : \mathcal{D}(G) \to T_{\bar{\phi}}X_f, \quad \chi \mapsto \partial\chi,$$

and its domain is

$$\mathcal{D}(G) = \left\{\chi \in C^2 \,:\, \dot{\chi}(0) = Df\left(\bar{\phi}\right)\chi,\ \ddot{\chi}(0) = Df\left(\bar{\phi}\right)\partial\chi\right\}.$$

Let us now consider the IVP (4.18). Also in this case, the segments of solutions to (4.18) define a strongly continuous semigroup $T_e = \{T_e(t)\}_{t\geq 0}$ on C. The generator of T_e is

$$G_e : \mathcal{D}(G_e) \to C, \quad \chi \mapsto \partial\chi,$$

where

$$\mathcal{D}(G_e) = \left\{\chi \in C^1 \,:\, \dot{\chi}(0) = D_e f\left(\bar{\phi}\right)\chi\right\}.$$

Hence, we have that $\mathcal{D}(G_e) = T_{\bar{\phi}}X_f$ and, for all $t \geq 0$ and all $\phi \in \mathcal{D}(G_e)$,

$$T_F(t)\phi = T_e(t)\phi.$$

The connection between T_F and T_e is evident at spectral level. Let $\sigma(G)$ and $\sigma(G_e)$, denote the spectrum of the complexification of G, respectively of G_e. Then it can be shown (cf. [67, Ch. 3]) that $\sigma(G) = \sigma(G_e)$ and that for an eigenvalue $\lambda \in \sigma(G) = \sigma(G_e)$ the generalized eigenspaces coincide, that is, $\mathcal{M}(\lambda) = \mathcal{M}_e(\lambda)$. Further, for the spectral projections associated to λ it holds

$$\mathcal{P}(\lambda)\chi = \mathcal{P}_e(\lambda)\chi,$$

for $\chi \in (T_{\bar{\phi}}X_f)_{\mathbb{C}}$, the complexification of $T_{\bar{\phi}}X_f$. Going back to the realified generalized eigenspaces of G and G_e, similar relations can be obtained.

Let us define the sets

$$\begin{aligned}\sigma_u(G_e) &= \{\lambda \in \sigma(G_e) \,:\, Re(\lambda) > 0\}, \\ \sigma_c(G_e) &= \{\lambda \in \sigma(G_e) \,:\, Re(\lambda) = 0\}, \\ \sigma_s(G_e) &= \{\lambda \in \sigma(G_e) \,:\, Re(\lambda) < 0\},\end{aligned}$$

and let C_u, C_c, C_s denote the corresponding realified generalized eigenspaces. They are called the **unstable**, **center** and **stable space of** G_e, respectively.

A consequence of the connection between spectra, spectral projections and generalized eigenspaces of G and G_e is the fact that the unstable and center spaces of G coincide with C_u and C_c, respectively, whereas the stable space of G is $C_s \cap T_{\bar{\phi}}X_f$ [67].

We conclude the section with the **Principle of linearized stability** given in [67].

Theorem 4.5 (Theorem 3.6.1 in [67])**.** *If all eigenvalues of G_e have negative real part, then $\bar{\phi}$ is exponentially asymptotically stable for the semiflow F.*

Although it would be worth summarizing many more studies on DDEs with state-dependent delay, this would mislead the aim of this thesis. Our main reference in the last section was the exhaustive manuscript by Hartung et al. [67]. Going back in time to some pioneering results on state-dependent DDEs, we might have a look at Driver [41] about existence, uniqueness and dependence of solutions on initial data, as well as at the works by Brokate and Colonius [22] and Cooke and Huang [33], both related to the problem of linearization at equilibria. More recent are the contributions by Eichmann [48] on Hopf bifurcations and by Stumpf [116] on unstable center manifolds of state-dependent DDEs.

5. A Class of Equations with State-Dependent Delay

In this chapter we discuss existence, uniqueness and long-term behavior of solutions to (non-neutral) problems with state-dependent delay from Chapter 3. To this end we introduce a general class of nonlinear equations of the form

$$\dot{x}(t) = \frac{\beta\big(x(t), x(t-\tau(x(t)))\big) - \delta(x(t))}{1 + \dot{\tau}(x(t))\beta\big(x(t), x(t-\tau(x(t)))\big)}.$$

The theory presented in Chapter 4 is the instrument to analyze this kind of problems. We focus on the semi-dynamical system induced by the delay equation, investigate qualitative behavior of solutions and linearized stability of equilibria.

The analysis of the *state-dependent blowfly equation*

$$\dot{x}(t) = \frac{\tilde{b}_1\big(x(t-\tau(x(t)))\big)e^{-\mu_0\tau(x(t))} - \tilde{\mu}_1(x(t))}{1 + \dot{\tau}(x(t))\tilde{b}_1\big(x(t-\tau(x(t)))\big)e^{-\mu_0\tau(x(t))}}$$

and a comparison between the state-dependent problem and a correspondent one with constant delay conclude the chapter.

5.1. General Case

In Section 4.2 we have explained that a state-dependent delay problem, like

$$\dot{x}(t) = g(x(t-\tau(x(t)))) \tag{5.1}$$

can be written in the form of a RFDE. We noticed that when the functional f of a RFDE expresses the right-hand side of a state-dependent delay problem, it usually satisfies condition (S) (cf. Definition 1, p. 58) and, consequently, Theorem 4.4 and the Principle of linearized stability, Theorem 4.5, hold true.

In this section we study a class of nonlinear state-dependent delay equations arising from biology, which are more general than (5.1). In particular g shall be a function of two variables, as the right-hand side of our problem depends both on $x(t)$ and on $x(t-\tau(x(t)))$. A similar case has been recently considered in [116] for the analysis of an equation arising from economics.

In the following we present the general delay problem, investigate the solution semiflow and its linearization. With the achieved results, it is possible to analyze the *state-dependent blowfly equation* (3.29).

Our starting point is a general equation,

$$\dot{x}(t) = g\left(x(t), x(t - \tau(x(t)))\right), \tag{5.2}$$

with $g : \mathbb{R} \times \mathbb{R} \to \mathbb{R}$, $\tau : \mathbb{R} \to [0, h]$, $0 < h < \infty$. In the following C and C^1 denote the spaces $C([-h, 0], \mathbb{R})$ and $C^1([-h, 0], \mathbb{R})$, respectively. It is convenient to define the **evaluation at zero**,

$$\mathrm{ev}_0 : C \to \mathbb{R}, \qquad \phi \mapsto \mathrm{ev}_0(\phi) = \mathrm{ev}(\phi, 0),$$

and its restriction to the space of continuously differentiable functions

$$\mathrm{Ev}_0 : C^1 \to \mathbb{R}, \qquad \phi \mapsto \mathrm{Ev}_0(\phi) = \mathrm{Ev}(\phi, 0).$$

Here ev is the evaluation map on the space of continuous functions,

$$\mathrm{ev} : C \times [-h, 0] \to \mathbb{R}, \qquad (y, s) \mapsto y(s),$$

and Ev is the map

$$\mathrm{Ev} : C^1 \times [-h, 0] \to \mathbb{R}, \qquad (y, s) \mapsto y(s),$$

encountered previously in Section 4.2. With the properties of Ev immediately follows that $D\,\mathrm{Ev}_0(\psi)\xi = \xi(0)$.

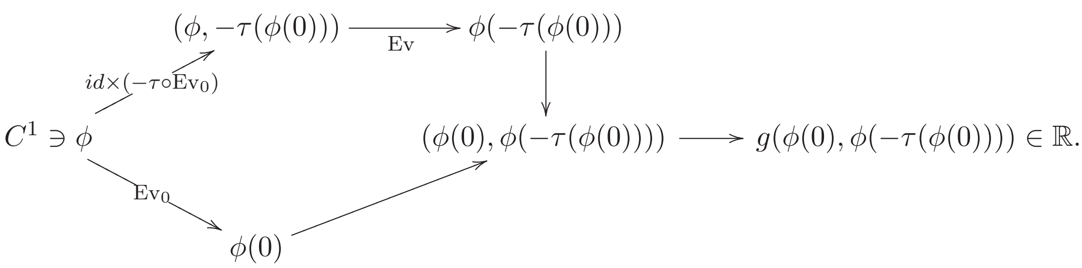
Equation (5.2) can be written in the RFDE notation,

$$\dot{x}(t) = f(x_t), \tag{5.3}$$

with $f : C^1 \to \mathbb{R}$, defined by

$$f = g \circ \big(\mathrm{Ev}_0 \times (\mathrm{Ev} \circ (\mathrm{id} \times (-\tau \circ \mathrm{Ev}_0)))\big).$$

The above composition of maps acts as follows on initial data $\phi \in C^1$:



Motivated by biological examples, which we shall discuss in the next section, we restrict ourselves to the class of g-functions

$$g : \mathbb{R} \times \mathbb{R} \to \mathbb{R},\ (w, y) \mapsto \frac{\beta(w, y) - \delta(w)}{1 + \dot{\tau}(w)\beta(w, y)}. \tag{5.4}$$

We assume that:

(a1) $\beta : \mathbb{R} \times \mathbb{R} \ni (w, y) \mapsto \beta(w, y) \in [0, \beta_M] \subset \mathbb{R}$, $\beta_M > 0$, is a nonnegative, continuously differentiable function and $\beta(0, 0) = 0$.

(a2) $\delta : \mathbb{R} \ni w \mapsto \delta(w) \in \mathbb{R}$ is a nonnegative, monotonically increasing (not necessarily strictly increasing) continuously differentiable function and $\delta(0) = 0$.

(a3) $\tau : \mathbb{R} \ni w \mapsto \tau(w) \in [0, h] \subset \mathbb{R}$, $h > 0$, is a nonnegative, monotonically increasing (not necessarily strictly increasing) C^2-function.

Hence, the map g is continuously differentiable with partial derivatives

$$\begin{aligned} \partial_1 g(w, y) = {} & \frac{\partial_1 \beta(w, y) - \dot{\delta}(w)}{1 + \dot{\tau}(w)\beta(w, y)} \\ & - (\beta(w, y) - \delta(w)) \frac{\ddot{\tau}(w)\beta(w, y) + \dot{\tau}(w)\partial_1\beta(w, y)}{(1 + \dot{\tau}(w)\beta(w, y))^2}, \\ \partial_2 g(w, y) = {} & \frac{\partial_2 \beta(w, y)\,(1 + \delta(w)\dot{\tau}(w))}{(1 + \dot{\tau}(w)\beta(w, y))^2}. \end{aligned} \tag{5.5}$$

As $g(0, 0) = 0$, the zero function is a solution of (5.2) and the solution manifold X_f of (5.3) is non-empty.

Proposition 5.1. *Consider a RFDE (5.3) with $f : C^1 \to \mathbb{R}$, defined by*

$$f = g \circ \big(\mathrm{Ev}_0 \times (\mathrm{Ev} \circ (\mathrm{id} \times (-\tau \circ \mathrm{Ev}_0)))\big),$$

where $\tau : \mathbb{R} \to [0, h]$, $h > 0$ and g is assumed as in (5.4), satisfying hypotheses (a1)–(a3).

Then, the map f satisfies condition (S).

Proof. We have to show that f satisfies properties (S1)–(S3) in Section 4.2.1.

(S1) The functional f is the composite of C^1-maps, hence continuously differentiable.

(S2) For $\phi, \chi \in C^1$, the derivative $Df(\phi)\chi$ is given by

$$\begin{aligned} Df(\phi)\chi = {} & D\Big(g \circ (\mathrm{Ev}_0 \times (\mathrm{Ev} \circ (\mathrm{id} \times (-\tau \circ \mathrm{Ev}_0))))\Big)(\phi)\chi \\ = {} & \partial_1 g\big(\phi(0), \phi(-\tau(\phi(0)))\big) D\,\mathrm{Ev}_0(\phi)\chi \\ & + \partial_2 g\big(\phi(0), \phi(-\tau(\phi(0)))\big) \big[D_1\,\mathrm{Ev}\big(\phi(0), \phi(-\tau(\phi(0)))\big)\chi \\ & \quad + D_2\,\mathrm{Ev}\,(\phi, -\tau(\phi(0)))\,[-\dot{\tau}(\phi(0)) D\,\mathrm{Ev}_0(\phi)\chi]\big] \\ = {} & \partial_1 g\big(\phi(0), \phi(-\tau(\phi(0)))\big)\chi(0) \\ & + \partial_2 g\big(\phi(0), \phi(-\tau(\phi(0)))\big) \big[\chi(-\tau(\phi(0))) - \dot{\phi}(-\tau(\phi(0)))\dot{\tau}(\phi(0))\chi(0)\big]. \end{aligned} \tag{5.6}$$

For $\chi \in C$ we define $D_e f(\phi)\chi$ by (5.6). It is now immediate to see that the map

$$\begin{aligned} C \to \mathbb{R},\ \chi \mapsto & \partial_1 g\big(\phi(0), \phi(-\tau(\phi(0)))\big) \operatorname{ev}_0(\chi) \\ & + \partial_2 g\big(\phi(0), \phi(-\tau(\phi(0)))\big) \big[\operatorname{ev}(\chi, -\tau(\phi(0))) - \dot{\phi}(-\tau(\phi(0)))\dot{\tau}(\phi(0)) \operatorname{ev}_0(\chi)\big] \end{aligned}$$

is continuous with respect to the norm in C (ev and ev_0 are continuous with respect to this norm).

(S3) Let pr_1 and pr_2 denote the projection on the first and second component, respectively. Then observe that the map

$$C^1 \times C \to \mathbb{R}, \quad (\phi, \chi) \mapsto D_e f(\phi)\chi$$

is given by sums and products of continuous maps. Indeed, for the assumptions on g and τ and for the properties of the evaluation maps ev, ev_0, Ev, Ev_0 we have that the maps $C^1 \times C \to \mathbb{R}$,

$$\begin{aligned} (\phi, \chi) \mapsto & (\operatorname{ev}_0 \circ \operatorname{pr}_2)(\phi, \chi) \\ & = \chi(0), \\ (\phi, \chi) \mapsto & \operatorname{ev} \circ (\operatorname{pr}_2 \times (-\tau \circ \operatorname{ev}_0 \circ \operatorname{pr}_1))(\phi, \chi) \\ & = \chi(-\tau(\phi(0))), \\ (\phi, \chi) \mapsto & \partial_1 g \circ \big((\operatorname{ev}_0 \circ \operatorname{pr}_1) \times (\operatorname{ev} \circ (\operatorname{pr}_1 \times (-\tau \circ \operatorname{ev}_0 \circ \operatorname{pr}_1)))\big)(\phi, \chi) \\ & = \partial_1 g(\phi(0), \phi(-\tau(\phi(0)))), \\ (\phi, \chi) \mapsto & \partial_2 g \circ \big((\operatorname{ev}_0 \circ \operatorname{pr}_1) \times (\operatorname{ev} \circ (\operatorname{pr}_1 \times (-\tau \circ \operatorname{ev}_0 \circ \operatorname{pr}_1)))\big)(\phi, \chi) \\ & = \partial_2 g(\phi(0), \phi(-\tau(\phi(0)))), \\ (\phi, \chi) \mapsto & D_2 \operatorname{Ev}(\operatorname{pr}_1 \times (-\tau \circ \operatorname{Ev}_0 \circ \operatorname{pr}_1))(\phi, \chi)1 \\ & = D_2 \operatorname{Ev}(\phi, -\tau(\phi(0)))1 \\ & = \dot{\phi}(-\tau(\phi(0))), \\ (\phi, \chi) \mapsto & \dot{\tau}(\operatorname{ev}_0 \circ \operatorname{pr}_1)(\phi, \chi) \\ & = \dot{\tau}(\phi(0)), \end{aligned}$$

are all continuous. Hence, f has property (S3).

□

By the previous theorem we have that the state-dependent delay equation (5.2), with g as in (5.4), satisfies all hypotheses of Theorem 4.4. Consequently, there exists a unique maximal solution of (5.2) and the solution manifold X_f is continuously differentiable. Further, the semiflow F defined by the solution segments can be linearized about a fixed point $\bar{\phi} \in X_f$.

By the Principle of linearized stability, Theorem 4.5, stability properties of an equilibrium $\bar{\phi}$, with respect to the semiflow F (of the nonlinear problem), can be deduced from those of

$\bar{\phi}$, with respect to the semiflow induced by the associated linear problem (cf. Chapter 4).

Let $\bar{\phi} \in X_f$ be an equilibrium of (5.3), i.e., there exists a $\bar{x} \in \mathbb{R}$ such that $\bar{\phi} : [-h, 0] \to \mathbb{R}$, $s \mapsto \bar{\phi}(s) = \bar{x}$ and $f\left(\bar{\phi}\right) = g(\bar{x}, \bar{x}) = 0$. The linearized equation associated to (5.2) is

$$\dot{v}(t) = \partial_1 g\left(\bar{x}, \bar{x}\right) v(t) + \partial_2 g\left(\bar{x}, \bar{x}\right) v\left(t - \tau\left(\bar{x}\right)\right). \tag{5.7}$$

This equation has the form of a classical linear equation,

$$\dot{y}(t) = -Ay(t) - By(t - r),$$

with one constant delay $r > 0$ and constant coefficients. In (5.7), we have $r = \tau\left(\bar{x}\right)$ and coefficients

$$A = -\frac{\partial_1 \beta\left(\bar{x}, \bar{x}\right) - \dot{\delta}\left(\bar{x}\right)}{1 + \dot{\tau}\left(\bar{x}\right) \beta\left(\bar{x}, \bar{x}\right)}, \qquad B = -\frac{\partial_2 \beta\left(\bar{x}, \bar{x}\right)\left(1 + \delta\left(\bar{x}\right) \dot{\tau}\left(\bar{x}\right)\right)}{\left(1 + \dot{\tau}\left(\bar{x}\right) \beta\left(\bar{x}, \bar{x}\right)\right)^2}.$$

We will return to this linear equation and its properties in a moment. Next, we use the results in this section to investigate the *state-dependent blowfly equation*.

5.2. The State-Dependent Blowfly Equation

The last section was devoted to the analysis of a class of equations with state-dependent delay,

$$\dot{x}(t) = g(x(t), x(-\tau(x(t)))),$$

with $g : \mathbb{R} \times \mathbb{R} \to \mathbb{R}$ as in (5.4). Here we apply the general results and investigate the *state-dependent blowfly equation*,

$$\dot{x}(t) = \frac{\tilde{b}_1\big(x(t - \tau(x(t)))\big)e^{-\mu_0 \tau(x(t))} - \tilde{\mu}_1(x(t))}{1 + \dot{\tau}(x(t))\tilde{b}_1\big(x(t - \tau(x(t)))\big)e^{-\mu_0 \tau(x(t))}}. \tag{5.8}$$

From Chapter 3 we report the assumptions:

1. We have defined $\tilde{b}_1(z) = b_1(z)z$ and $\tilde{\mu}_1(z) = \mu_1(z)z$, $z \in \mathbb{R}$.
2. The birth rate $b_1 : \mathbb{R} \to [0, B_1] \subset \mathbb{R}$, $B_1 > 0$ is a continuously differentiable, nonnegative, monotonically decreasing (not necessarily strictly decreasing) function and $b_1(0) > \mu_1(0)$.
3. The death rate $\mu_0 > 0$ is a positive constant.
4. The death rate $\mu_1 : \mathbb{R} \to \mathbb{R}$ is a continuously differentiable, nonnegative, monotonically increasing (not necessarily strictly increasing) function.
5. The age-at-maturity $\tau : \mathbb{R} \to [0, h]$, $h > 0$ is a nonnegative, monotonically increasing (not necessarily strictly increasing) twice continuously differentiable function.

When writing the *state-dependent blowfly equation* (5.8) in the RFDE form, it is immediate to recognize that the right-hand side is an element of the class (5.4),

$$g : \mathbb{R} \times \mathbb{R} \to \mathbb{R}, \quad (w, y) \mapsto \frac{\beta(w, y) - \delta(w)}{1 + \dot{\tau}(w)\beta(w, y)},$$

with

$$\beta(w, y) = \tilde{b}_1(y)e^{-\mu_0\tau(w)}, \qquad \text{and} \qquad \delta(w) = \tilde{\mu}_1(w).$$

We compute the derivatives

$$\begin{aligned} \partial_1\beta(w, y) &= -\mu_0\dot{\tau}(w)\tilde{b}_1(y)e^{-\mu_0\tau(w)}, \\ \partial_2\beta(w, y) &= \dot{\tilde{b}}_1(y)e^{-\mu_0\tau(w)}, \\ \dot{\delta}(w) &= \dot{\tilde{\mu}}_1(w), \end{aligned}$$

and from (5.5) we obtain

$$\begin{aligned} \partial_1 g(w, y) = &-\frac{\mu_0\dot{\tau}(w)\tilde{b}_1(y)e^{-\mu_0\tau(w)} + \dot{\tilde{\mu}}_1(w)}{1 + \dot{\tau}(w)\tilde{b}_1(y)e^{-\mu_0\tau(w)}} \\ &- \left(\tilde{b}_1(y)e^{-\mu_0\tau(w)} - \tilde{\mu}_1(w)\right) \frac{\left(\ddot{\tau}(w) - \mu_0\dot{\tau}(w)^2\right)\tilde{b}_1(y)e^{-\mu_0\tau(w)}}{\left(1 + \dot{\tau}(w)\tilde{b}_1(y)e^{-\mu_0\tau(w)}\right)^2}, \\ \partial_2 g(w, y) = &\ \dot{\tilde{b}}_1(y)e^{-\mu_0\tau(w)} \frac{(1 + \tilde{\mu}_1(w)\dot{\tau}(w))}{\left(1 + \dot{\tau}(w)\tilde{b}_1(y)e^{-\mu_0\tau(w)}\right)^2}. \end{aligned}$$

By Proposition 5.1, the right-hand side of (5.8) satisfies property (S). Further, the solution manifold X_f is not empty, as it contains at least the trivial solution $x \equiv 0$. Applying Theorem 4.4, we guarantee that X_f is a continuous differentiable sub-manifold of C^1 of codimension one, and we can linearize (5.8) about an equilibrium solution.

Due to the assumptions on the birth rate $b_1(x)$ (monotonically decreasing function) and on the death rate $\mu_1(x)$ (monotonically increasing function), there exists a nonzero equilibrium solution $\bar{x} \in \mathbb{R}$, $\bar{x} \neq 0$ of (5.8). That is, there is a function $\bar{\phi} \in X_f$, such that $\bar{\phi} : [-h, 0] \to \mathbb{R}, s \mapsto \bar{\phi}(s) = \bar{x}$ and $f\left(\bar{\phi}\right) = g\left(\bar{x}, \bar{x}\right) = 0$. It follows that

$$\tilde{b}_1\left(\bar{x}\right)e^{-\mu_0\tau(\bar{x})} = \tilde{\mu}_1\left(\bar{x}\right). \tag{5.9}$$

The partial derivatives of g at $(\bar{x}, \bar{x}) \in \mathbb{R}^2$ are

$$\begin{aligned} \partial_1 g\left(\bar{x}, \bar{x}\right) &= -\frac{\mu_0\dot{\tau}\left(\bar{x}\right)\tilde{b}_1\left(\bar{x}\right)e^{-\mu_0\tau(\bar{x})} + \dot{\tilde{\mu}}_1\left(\bar{x}\right)}{1 + \dot{\tau}\left(\bar{x}\right)\tilde{b}_1\left(\bar{x}\right)e^{-\mu_0\tau(\bar{x})}} = -\frac{\mu_0\dot{\tau}\left(\bar{x}\right)\tilde{\mu}_1\left(\bar{x}\right) + \dot{\tilde{\mu}}_1\left(\bar{x}\right)}{1 + \dot{\tau}(\bar{x})\tilde{\mu}_1\left(\bar{x}\right)}, \\ \partial_2 g\left(\bar{x}, \bar{x}\right) &= \frac{\dot{\tilde{b}}_1\left(\bar{x}\right)e^{-\mu_0\tau(\bar{x})}}{1 + \dot{\tau}\left(\bar{x}\right)\tilde{\mu}_1\left(\bar{x}\right)}. \end{aligned}$$

So, for $\chi \in C$ we have

$$Df\left(\bar{\phi}\right)\chi = \left[\frac{\dot{\tilde{b}}_1\left(\bar{x}\right)e^{-\mu_0\tau(\bar{x})}}{1+\dot{\tau}(\bar{x})\tilde{\mu}_1\left(\bar{x}\right)}\right]\chi(-\tau\left(\bar{x}\right)) - \left[\frac{\mu_0\dot{\tau}\left(\bar{x}\right)\tilde{\mu}_1\left(\bar{x}\right)+\dot{\tilde{\mu}}_1(\bar{x})}{1+\dot{\tau}\left(\bar{x}\right)\tilde{\mu}_1\left(\bar{x}\right)}\right]\chi(0).$$

For an initial function φ in the tangent space $T_{\bar{\phi}}X_f = \left\{\varphi \in C^1 : \dot{\varphi}(0) = Df\left(\bar{\phi}\right)\varphi\right\}$, we associate to the nonlinear *state-dependent blowfly equation* (5.8) the linear problem

$$\dot{v}(t) = \left[\frac{\dot{\tilde{b}}_1\left(\bar{x}\right)e^{-\mu_0\tau(\bar{x})}}{1+\dot{\tau}\left(\bar{x}\right)\tilde{\mu}_1\left(\bar{x}\right)}\right]v(t-\tau\left(\bar{x}\right)) - \left[\frac{\mu_0\dot{\tau}\left(\bar{x}\right)\tilde{\mu}_1\left(\bar{x}\right)+\dot{\tilde{\mu}}_1\left(\bar{x}\right)}{1+\dot{\tau}\left(\bar{x}\right)\tilde{\mu}_1\left(\bar{x}\right)}\right]v(t). \tag{5.10}$$

This linear equation can also be found by means of a Taylor expansion about a stationary solution, as we show below.

Let x be a solution of (5.8) and let us consider a nontrivial equilibrium $\bar{x} \neq 0$, whose existence has been motivated above. We expand the solution x about the fixed point $\bar{x}$ and get

$$x(t) = \bar{x} + \eta(t),$$

with a small error $\eta(t)$. Similarly, we expand the delay at the equilibrium,

$$\begin{aligned}\tau(x(t)) &= \tau\left(\bar{x}+\eta(t)\right)\\ &= \tau(\bar{x}) + \dot{\tau}(\bar{x})\eta(t) + o(\|\eta\|).\end{aligned}$$

Fixing the delay at $\bar{x}$, we eliminate the state-dependency and obtain a constant value, $\bar{\tau} = \tau(\bar{x})$. Now we linearize the delayed term,

$$\begin{aligned}x(t-\tau) &= \bar{x} + \eta(t-\tau(\bar{x}+\eta(t)))\\ &= \bar{x} + \eta(t-(\bar{\tau}+\dot{\tau}(\bar{x})\eta(t)+o(|\eta(t)|)))\\ &= \bar{x} + \eta(t-\bar{\tau}) + o(\|\eta\|).\end{aligned}$$

For birth and death terms we have

$$\begin{aligned}\tilde{b}_1(x(t)) &= b_1\left(\bar{x}+\eta(t-\bar{\tau})+o(\|\eta\|)\right)\left(\bar{x}+\eta(t-\bar{\tau})+o(\|\eta\|)\right)\\ &= \tilde{b}_1(\bar{x}) + \dot{\tilde{b}}_1(\bar{x})\eta(t-\bar{\tau}) + o(\|\eta\|),\end{aligned}$$

respectively,

$$\tilde{\mu}_1(x(t)) = \tilde{\mu}_1(\bar{x}) + \dot{\tilde{\mu}}_1(\bar{x})\eta(t) + o(\|\eta\|).$$

The exponential term in (5.8) can be written as

$$e^{-\mu_0\tau(x(t))} = e^{-\mu_0\bar{\tau}}\left(1-\mu_0\dot{\tau}(\bar{x})\eta(t)+o(\|\eta\|)\right).$$

Finally, for the derivative of τ we obtain

$$\begin{aligned}\dot{\tau}(x(t)) &= \dot{\tau}(\bar{x}+\eta(t))\\ &= \dot{\tau}(\bar{x}) + \ddot{\tau}(\bar{x})\eta(t) + o(\|\eta\|).\end{aligned}$$

For simplicity of notation, we write η_0 for $\eta(t)$ and $\eta_{\bar{\tau}}$ for $\eta(t-\bar{\tau})$. The previous steps yield the differential equation

$$\dot{\eta}(t) = \frac{\left[\tilde{b}_1(\bar{x}) + \dot{\tilde{b}}_1(\bar{x})\eta_{\bar{\tau}} + o(\|\eta\|)\right] e^{-\mu_0\bar{\tau}} \left(1 - \mu_0\dot{\tau}(\bar{x})\eta_0 + o(\|\eta\|)\right)}{1 + \left(\dot{\tau}(\bar{x}) + \ddot{\tau}(\bar{x})\eta_0 + o(\|\eta\|)\right) \left[\tilde{b}_1(\bar{x}) + \dot{\tilde{b}}_1(\bar{x})\eta_{\bar{\tau}} + o(\|\eta\|)\right] e^{-\mu_0\bar{\tau}} \left(1 - \mu_0\dot{\tau}(\bar{x})\eta_0 + o(\|\eta\|)\right)}$$
$$- \frac{\left[\tilde{\mu}_1(\bar{x}) + \dot{\tilde{\mu}}_1(\bar{x})\eta_0 + o(\|\eta\|)\right]}{1 + \left(\dot{\tau}(\bar{x}) + \ddot{\tau}(\bar{x})\eta_0 + o(\|\eta\|)\right) \left[\tilde{b}_1(\bar{x}) + \dot{\tilde{b}}_1(\bar{x})\eta_{\bar{\tau}} + o(\|\eta\|)\right] e^{-\mu_0\bar{\tau}} \left(1 - \mu_0\dot{\tau}(\bar{x})\eta_0 + o(\|\eta\|)\right)}.$$

With the condition at equilibrium (5.9), we find that

$$\begin{aligned}
\dot{\eta}(t) &= \frac{\dot{\tilde{b}}_1(\bar{x})e^{-\mu_0\bar{\tau}}\eta_{\bar{\tau}} - \left(\tilde{b}_1(\bar{x})\mu_0\dot{\tau}(\bar{x})e^{-\mu_0\bar{\tau}} + \dot{\tilde{\mu}}_1(\bar{x})\right)\eta_0 + o(\|\eta\|)}{\left(1 + \dot{\tau}(\bar{x})\tilde{b}_1(\bar{x})\right) + \left(\dot{\tau}(\bar{x})\left(\dot{\tilde{b}}_1(\bar{x})\eta_{\bar{\tau}} - \tilde{b}_1(\bar{x})\mu_0\eta_0\right) + \ddot{\tau}(\bar{x})\tilde{b}_1(\bar{x})\eta_0\right) e^{-\mu_0\bar{\tau}} + o(\|\eta\|)} \\
&= \frac{\left(\dot{\tilde{b}}_1(\bar{x})e^{-\mu_0\bar{\tau}}\eta_{\bar{\tau}} - \left(\tilde{b}_1(\bar{x})\mu_0\dot{\tau}(\bar{x})e^{-\mu_0\bar{\tau}} + \dot{\tilde{\mu}}_1(\bar{x})\right)\eta_0\right) + o(\|\eta\|)}{\left(1 + \dot{\tau}(\bar{x})\tilde{b}_1(\bar{x})\right) + \left(\dot{\tau}(\bar{x})\left(\dot{\tilde{b}}_1(\bar{x})\eta_{\bar{\tau}} - \tilde{b}_1(\bar{x})\mu_0\eta_0\right) + \ddot{\tau}(\bar{x})\tilde{b}_1(\bar{x})\eta_0\right) e^{-\mu_0\bar{\tau}} + o(\|\eta\|)} \\
&\quad \cdot \frac{\left(1 + \dot{\tau}(\bar{x})\tilde{b}_1(\bar{x})e^{-\mu_0\bar{\tau}}\right) - \left(\dot{\tau}(\bar{x})\left(\dot{\tilde{b}}_1(\bar{x})\eta_{\bar{\tau}} - \tilde{b}_1(\bar{x})\mu_0\eta_0\right) + \ddot{\tau}(\bar{x})\tilde{b}_1(\bar{x})\eta_0\right) e^{-\mu_0\bar{\tau}} + o(\|\eta\|)}{\left(1 + \dot{\tau}(\bar{x})\tilde{b}_1(\bar{x})e^{-\mu_0\bar{\tau}}\right) - \left(\dot{\tau}(\bar{x})\left(\dot{\tilde{b}}_1(\bar{x})\eta_{\bar{\tau}} - \tilde{b}_1(\bar{x})\mu_0\eta_0\right) + \ddot{\tau}(\bar{x})\tilde{b}_1(\bar{x})\eta_0\right) e^{-\mu_0\bar{\tau}} + o(\|\eta\|)}.
\end{aligned}$$

Eventually, the linearized equation for (5.8) is given by

$$\dot{\eta}(t) = \frac{\dot{\tilde{b}}_1(\bar{x})e^{-\mu_0\bar{\tau}}}{1 + \dot{\tau}(\bar{x})\tilde{\mu}_1(\bar{x})}\eta(t-\bar{\tau}) - \frac{\dot{\tilde{\mu}}_1(\bar{x}) + \mu_0\dot{\tau}(\bar{x})\tilde{\mu}_1(\bar{x})}{1 + \dot{\tau}(\bar{x})\tilde{\mu}_1(\bar{x})}\eta(t). \tag{5.11}$$

The technique we used to linearize the state-dependent delay problem has been introduced by Cooke and Huang [33] and it is known as the method of *freezing the delay at an equilibrium point*. In practice, we consider a nontrivial equilibrium $\bar{x}$ of (5.8) and expand the solution at $\bar{x}$. The delay is fixed at $\bar{x}$ and the nonlinear equation with constant delay $\bar{\tau} = \tau(\bar{x})$ can be linearized. The linear equation (5.11) that we obtain by the "freezing method" is formally the same as the result (5.10) of the analysis in Section 5.1. However, the linear RFDE (5.11) is defined on the whole space C of continuous functions. As argued by Walther and coauthors [67, 126, 127], the true linearization of a state-dependent problem at an equilibrium $\bar{\phi}$ is defined on the tangent space $T_{\bar{\phi}}X_f$. The "correct" linearization of (5.8) is given by (5.10).

To conclude the chapter, we discuss the linearized stability of the *state-dependent blowfly equation*.

Linearized Stability

Equation (5.10) is a classical linear equation

$$\dot{y}(t) = -Ay(t) - By(t-r), \tag{5.12}$$

with one constant delay $r = \bar{\tau} > 0$ and constant coefficients

$$A = \frac{\dot{\tilde{\mu}}_1(\bar{x}) + \mu_0 \dot{\tau}(\bar{x})\tilde{\mu}_1(\bar{x})}{1 + \dot{\tau}(\bar{x})\tilde{\mu}_1(\bar{x})}, \qquad B = -\frac{\dot{\tilde{b}}_1(\bar{x})e^{-\mu_0\bar{\tau}}}{1 + \dot{\tau}(\bar{x})\tilde{\mu}_1(\bar{x})}. \tag{5.13}$$

The corresponding *characteristic equation* is given by

$$\lambda = -A - Be^{-\lambda r}. \tag{5.14}$$

Remarkable results on zeros of this transcendental equation are due to Hayes [68] and allow for the determination of the stability of the steady state $y = 0$ in (5.12). In the following we sketch an idea of the stability analysis of (5.14). Further results on zeros of transcendental equations and their influence on the stability of delay equations can be found in the classical literature on DDEs [15, 37, 64, 79].

Let λ be a complex root of (5.14), $\lambda = w + iv$, with $w, v \in \mathbb{R}$. Substitution in (5.14) yields

$$w + A + B\cos(rv)e^{-rw} = 0, \qquad v - B\sin(rv)e^{-rw} = 0,$$

and, for $v \neq k\frac{\pi}{r}, k \in \mathbb{Z}$, we obtain

$$A = -w - \frac{v\cos(rv)}{\sin(rv)}, \qquad B = \frac{v}{\sin(rv)}e^{rw}.$$

In the parameter plane (A, B) we find a line

$$\mathcal{R}_0 = \{(A,B) \,:\, A = -B\},$$

at which $\lambda = 0$ is a root of the characteristic equation (5.14).

Now we look for purely imaginary roots. For $w = 0$, $A(v)$ and $B(v)$ are even functions in v, so we can consider only the case $v \geq 0$. Purely imaginary roots $\lambda = iv$ can be found on the curves $\mathcal{C}_k$ in the parameter plane (A, B),

$$\mathcal{C}_k = \left\{ (A,B) = \left(-\frac{v\cos(rv)}{\sin(rv)}, \frac{v}{\sin(rv)} \right) \,:\, k\frac{\pi}{r} < v < (k+1)\frac{\pi}{r},\ k \in \mathbb{N} \right\}.$$

The curve

$$\mathcal{C}_0 = \left\{ (A,B) = \left(-\frac{v\cos(rv)}{\sin(rv)}, \frac{v}{\sin(rv)} \right) \,:\, 0 \leq v < \frac{\pi}{r} \right\}$$

and the line $\mathcal{R}_0$ meet at $(-1/r,\ 1/r)$, where $\lambda = 0$ is a double root of (5.14). Figure 5.1 shows the parameter plane (A, B) with the line $\mathcal{R}_0$ and the curves $\mathcal{C}_k$. The region delimited by $\mathcal{R}_0$ and $\mathcal{C}_0$ is the stability region of the steady state $y = 0$. We notice that the curve $\mathcal{C}_0$ is always above the bisector $A - B = 0$.

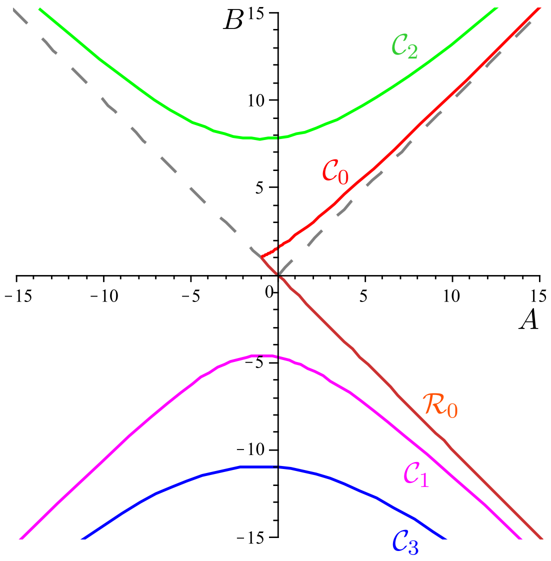


Figure 5.1: Parameter plane (A, B) with curves $\mathcal{C}_k$, on which purely imaginary roots $\lambda = iv$ exist. The curve $\mathcal{C}_0$ (always above the bisector $A - B = 0$) and the line $\mathcal{R}_0$ meet at the point $(-1/r,\, 1/r)$. The stability region is delimited by $\mathcal{R}_0$ and $\mathcal{C}_0$.

A result (cf. [64, 68, 115]) concerning the stability of the linear equation (5.12) asserts the following.

(i) If $A + B < 0$, then $y = 0$ is unstable.

(ii) If $A + B > 0$ and $B \leq A$, then $y = 0$ is asymptotically stable.

(iii) If $A+B > 0$ and $B > A$, then there exists a value $r^* > 0$ such that $y = 0$ is asymptotically stable for $0 < r < r^*$ and unstable for $r > r^*$.

We are now interested in the effects of a state-dependent delay $\tau(x)$. We consider a fixed point $\bar{x}$ of (5.8). The linearization of equation (5.8) about $\bar{x}$ is given by (5.10), which is an equation of the standard form (5.12). The stability of $\bar{x}$ with respect to (5.8) can be deduced from the stability of $v = 0$ in (5.10).

A stationary state $\bar{x}$ of (5.8) is also a stationary state of an equation with constant delay $\bar{\tau} = \tau(\bar{x})$, namely,

$$\dot{x}(t) = \tilde{b}_1(x(t - \bar{\tau}))e^{-\mu_0 \bar{\tau}} - \tilde{\mu}_1(x(t)). \tag{5.15}$$

This equation can be linearized at $\bar{x}$, yielding

$$\dot{z}(t) = -\overline{A}z(t) - \overline{B}z(t - \bar{\tau}), \tag{5.16}$$

with

$$\overline{A} = \dot{\tilde{\mu}}_1(\bar{x}), \quad \overline{B} = -\frac{\dot{\tilde{b}}_1(\bar{x})}{\tilde{b}_1(\bar{x})}\tilde{\mu}_1(\bar{x}). \tag{5.17}$$

The characteristic equation associated to (5.16) is given by

$$\lambda = -\overline{A} - \overline{B}e^{-\lambda\bar{\tau}}. \tag{5.18}$$

The stability region of $z = 0$ in the the parameter plane $(\overline{A}, \overline{B})$ is delimited by the line

$$\overline{\mathcal{R}}_0 = \left\{(\overline{A}, \overline{B}) \,:\, \overline{A} = -\overline{B}\right\},$$

and the curve

$$\overline{\mathcal{C}}_0 = \left\{(\overline{A}, \overline{B}) = \left(-\frac{v\cos(\bar{\tau}v)}{\sin(\bar{\tau}v)}, \frac{v}{\sin(\bar{\tau}v)}\right) \,:\, 0 \le v < \frac{\pi}{\bar{\tau}}\right\}.$$

The coordinates $(\overline{A}, \overline{B})$ of a point on $\overline{\mathcal{C}}_0$ satisfy

$$\begin{aligned}
&\overline{A} + \overline{B}\cos\left(\bar{\tau}\sqrt{\overline{B}^2 - \overline{A}^2}\right) \\
&= -\frac{v\cos(\bar{\tau}v)}{\sin(\bar{\tau}v)} + \frac{v}{\sin(\bar{\tau}v)}\cos\left(\bar{\tau}\sqrt{v^2}\right) \\
&= 0,
\end{aligned}$$

and $\overline{A} \ge -\frac{1}{\bar{\tau}}$, $\overline{B} \ge \frac{1}{\bar{\tau}} > 0$.

In order to compare (5.12) to (5.16), we write A and B in (5.13) as perturbations of $\overline{A}$ and $\overline{B}$ in (5.17). Define

$$\kappa = \frac{1}{1 + \dot{\tau}(\bar{x})\tilde{\mu}_1(\bar{x})} \in (0, 1), \tag{5.19}$$

and observe that

$$A = \kappa\overline{A} + \mu_0(1 - \kappa), \qquad B = \kappa\overline{B}. \tag{5.20}$$

Indeed, we have

$$A \underset{(5.9)}{=} \frac{\dot{\tilde{\mu}}_1(\bar{x}) + \mu_0\dot{\tau}(\bar{x})\tilde{\mu}_1(\bar{x})}{1 + \dot{\tau}(\bar{x})\tilde{\mu}_1(\bar{x})} \underset{(5.19)}{=} \kappa\dot{\tilde{\mu}}_1(\bar{x}) + \kappa\mu_0\left(\frac{1}{\kappa} - 1\right) \underset{(5.17)}{=} \kappa\overline{A} + \mu_0\left(1 - \kappa\right),$$

and

$$B \underset{(5.9)}{=} -\frac{\dot{\tilde{b}}_1(\bar{x})}{1 + \dot{\tau}(\bar{x})\tilde{\mu}_1(\bar{x})}\frac{\tilde{\mu}_1(\bar{x})}{\tilde{b}_1(\bar{x})} \underset{(5.19)}{=} \kappa\dot{\tilde{b}}_1(\bar{x})\frac{\tilde{\mu}_1(\bar{x})}{\tilde{b}_1(\bar{x})} \underset{(5.17)}{=} \kappa\overline{B}.$$

For $\kappa = 1$, the coefficients (A, B) in (5.13) of the characteristic equation (5.14) coincide with those of (5.18), and $\mathcal{C}_0 \equiv \overline{\mathcal{C}}_0$. Let us indicate by $\overline{\Sigma}$ the stability region of the problem (5.15) with constant delay $\bar{\tau}$. Then we can show the following theorem.

Theorem 5.1. *Consider the state-dependent blowfly equation (5.8). Its linearization (5.10) about a nontrivial equilibrium $\bar{x}$ is an equation with constant delay $\bar{\tau} = \tau(\bar{x})$.*

If for $\bar{x}$ the coefficients $(\overline{A}, \overline{B})$ of (5.16) are on the boundary $\overline{\mathcal{C}}_0$ of $\overline{\Sigma}$, then the coefficients (A, B) of (5.12), obtained from $(\overline{A}, \overline{B})$ according to (5.20), are in the interior of $\overline{\Sigma}$, that is, (A, B) is in $\overline{\Sigma}$ but not on $\overline{\mathcal{C}}_0$.

Proof. First, we consider a point $\overline{P} = \left(\overline{A}, \overline{B}\right)$ on $\overline{\mathcal{C}}_0$ (see Figure 5.2). The normal vector (pointing to the left) to the curve $\overline{\mathcal{C}}_0$ at $\overline{P}$ is

$$N_{\overline{P}} = \begin{pmatrix} \frac{-\partial \overline{B}(v)}{\partial v} \\ \\ \frac{\partial \overline{A}(v)}{\partial v} \end{pmatrix} = \begin{pmatrix} \frac{\bar{\tau} v \cos(\bar{\tau} v) - \sin(\bar{\tau} v)}{\sin^2(\bar{\tau} v)} \\ \\ \frac{\bar{\tau} v - \cos(\bar{\tau} v)\sin(\bar{\tau} v)}{\sin^2(\bar{\tau} v)} \end{pmatrix} = \frac{1}{\sqrt{\overline{B}^2 - \overline{A}^2}} \begin{pmatrix} -\overline{B}(1+\overline{A}\bar{\tau}) \\ \\ \overline{A} + \bar{\tau}\overline{B}^2 \end{pmatrix}.$$

Further, we consider the point

$$P = (A, B) = (\kappa \overline{A} + \mu_0(1-\kappa), \kappa \bar{B}),$$

such that for $\kappa = 1$, $P \equiv \overline{P}$. For the assumptions on the state-dependent delay, we have $\dot{\tau}(\bar{x}) > 0$, which corresponds to $\kappa < 1$. The point $P = (A, B)$ is on a curve parametrized by κ. The tangent vector at $\kappa = 1$ is

$$T_{\overline{P}} = \begin{pmatrix} \overline{A} - \mu_0 \\ \overline{B} \end{pmatrix}.$$

The sign of the scalar product of $N_{\overline{P}}$ and $T_{\overline{P}}$ indicates in which direction, with respect to $\overline{\mathcal{C}}_0$, the point P moves for $\kappa < 1$.

As the curve $\overline{\mathcal{C}}_0$ lies above the bisector of the first quadrant angle, the coordinates $(\overline{A}, \overline{B})$ of $\overline{P}$ satisfy $\overline{B} > \overline{A}$, with $\overline{A} \geq -\frac{1}{\bar{\tau}}$. Thus we find that:

$$\begin{aligned} &\operatorname{sign}\left(\frac{1}{\sqrt{\overline{B}^2 - \overline{A}^2}} \left(-\overline{B}\left(1+\overline{A}\bar{\tau}\right)\left(\overline{A} - \mu_0\right) + \overline{B}\left(\overline{A} + \bar{\tau}\overline{B}^2\right)\right)\right) \\ &= \operatorname{sign}\left(-\overline{B}(1+\overline{A}\bar{\tau})\left(\overline{A} - \mu_0\right) + \overline{B}\left(\overline{A} + \bar{\tau}\overline{B}^2\right)\right) \\ &= \operatorname{sign}\left(\bar{\tau}\overline{B}\left(\overline{B}^2 - \overline{A}^2\right) + \mu_0 \overline{B}\left(1 + \bar{\tau}\overline{A}\right)\right) \\ &= +1. \end{aligned}$$

Hence, for $\kappa < 1$, the point P moves down with respect to the curve $\overline{\mathcal{C}}_0$, as in Figure 5.3. □

Theorem 5.1 seems to suggest that

> A point $\bar{x}$, marginally stable for the *classical blowfly equation* (5.15), is asymptotically stable for the *state-dependent blowfly equation* (5.8).

This observation is also supported by the numerics, as simulations in Section 3.5 show. Observe that our remark is meant in terms of linearized stability. Indeed, we consider the classical *blowfly equation* (5.15) and its linearization (5.16) about $\bar{x}$. A state-dependent version of (5.15) is given by equation (5.8), which can be linearized about the equilibrium $\bar{x}$, yielding (5.10). This equation has the standard form (5.12), the same one of equation (5.16), and its coefficients (A, B) depend on the derivative $\dot{\tau}(x)$ of the state-dependent delay, evaluated at $\bar{x}$. With (5.20), the coefficients (A, B) of (5.12) can be related to $(\overline{A}, \overline{B})$ in (5.16). Similarly, a point P in the (A, B)-plane can be represented in the $\left(\overline{A}, \overline{B}\right)$-plane.

So, we start from a point $\overline{P} \in \overline{\mathcal{C}}_0$, as in Figure 5.2. A state-dependent delay $\dot{\tau}(x) > 0$ (corresponding to $\kappa < 1$) moves the point $\overline{P}$ to a point P, in the stability region $\overline{\Sigma}$ of the problem with constant delay, as Figure 5.3 shows. In other words, the point P, associated to $\bar{P}$ by means of (5.20), is in $\overline{\Sigma}$ but not on the boundary $\overline{\mathcal{C}}_0$.

Assume that for the linear equation (5.16), with constant delay $\bar{\tau}$ and coefficients $\left(\overline{A}, \overline{B}\right)$, the solution $\bar{x}$ is marginally stable. When the delay depends on the state, the associated linear equation (5.10) at $\bar{x}$ has the form (5.12) and can be compared to an equation with constant delay $\bar{\tau} = \tau(\bar{x})$. Let the coefficients $\left(\overline{A}, \overline{B}\right)$ in (5.16) lie on the stability boundary $\overline{\mathcal{C}}_0$ of $\overline{\Sigma}$. Then, the pair (A, B) of coefficients of (5.12), which can be obtained from $\left(\overline{A}, \overline{B}\right)$ using (5.20), is in the stability domain $\overline{\Sigma}$, but not on the boundary.

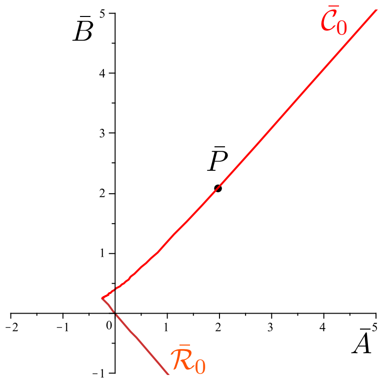


Figure 5.2: Parameter plane $\left(\overline{A}, \overline{B}\right)$. The stability region $\overline{\Sigma}$ is bounded by the line $\overline{\mathcal{R}}_0$ and the curve $\overline{\mathcal{C}}_0$. We consider a point $\overline{P}$ on $\overline{\mathcal{C}}_0$.

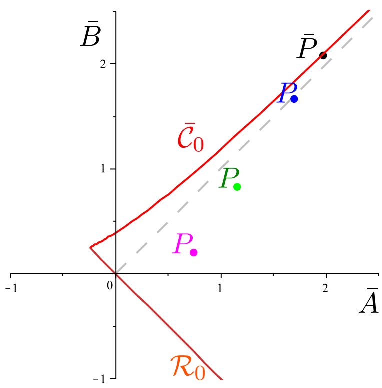


Figure 5.3: For $\kappa = 1$ (i.e., constant delay), the point $P \equiv \overline{P}$ is on the stability boundary $\overline{\mathcal{C}}_0$ of $\overline{\Sigma}$. For $\kappa < 1$ (i.e., state-dependent delay), the point P moves into the stability domain $\overline{\Sigma}$. Few numerical examples, with $\kappa = 0.8$ (blue), $\kappa = 0.4$ (green), $\kappa = 0.1$ (magenta).

6. Theory of Neutral Equations with State-Dependent Delay

This chapter is devoted to the theory of neutral functional differential equations with state-dependent delay. Roughly speaking, a functional differential equation of neutral type, or **neutral functional differential equation (NFDE)** is characterized by the fact that the state of the system at a certain time depends not only on its history (that is, on the state of the system at a previous time), but also on the derivative of the past history. For example,

$$3\dot{x}(t) - 4x^3(t-\tau)\dot{x}(t-\tau) = \sin(x(t-\tau)),$$

with $x : [-\tau, \infty) \to \mathbb{R}$ and $\tau > 0$, is an autonomous nonlinear NFDE. This equation can also be written in an *implicit form*, frequently used by Hale, Meyer and Henry [64, 65, 70],

$$\frac{d}{dt}D(x_t) = g(x_t),$$

with $D : \Omega_0 \to \mathbb{R}$, $\phi \mapsto 3\phi(0) - \phi^4(-\tau)$ and $g : \Omega_0 \to \mathbb{R}, \phi \mapsto \sin(\phi(-\tau))$, $\Omega_0 \subseteq C^1([-\tau, 0], \mathbb{R})$ open. However, in this thesis we shall write NFDEs in an explicit form.

We start by introducing some necessary notation. Given values $h > 0$ and $n \in \mathbb{N}$, we denote by C and C^1 the Banach spaces of all continuous, respectively continuously differentiable functions $\phi : [-h, 0] \to \mathbb{R}^n$ (cf. p. 49). Further we introduce the Banach space $C^2 = C^2([-h, 0], \mathbb{R}^n)$ of twice continuously differentiable functions $\psi : [-h, 0] \to \mathbb{R}^n$, together with the norm $\|\psi\|_{C^2} = \|\psi\|_C + \|\partial\psi\|_C + \|\partial\partial\psi\|_C$.

Given normed vector spaces Y_1, Y_2, an open subset $M \subset Y_1$ and a map $u : M \to Y_2$, we indicate by $Lip(u)$ the Lipschitz constant of u, that is, the value

$$Lip(u) = \sup_{\substack{a,\, b \in M, \\ a \neq b}} \frac{|u(a) - u(b)|}{|a - b|} \leq \infty.$$

The norm on the Cartesian product $Y_1 \times Y_2$ of the spaces Y_1 and Y_2 is given by addition, i.e., $\|(y_1, y_2)\|_{Y_1 \times Y_2} = \|y_1\|_{Y_1} + \|y_2\|_{Y_2}$.

Given Banach spaces B, B_1, we denote by $L_c(B, B_1)$ the Banach space of linear continuous maps from B to B_1. The norm of $u \in L_c(B, B_1)$ is defined by

$$\|u\|_{L_c(B,B_1)} = \sup_{\|s\|_B \leq 1} \|u(s)\|_{B_1}.$$

From now on we consider a class of NFDEs

$$\dot{x}(t) = f_0(x_t, \partial x_t), \tag{6.1}$$

where $f_0 : W_0 \to \mathbb{R}^n$ is defined on an open subset $W_0 \subset C^1 \times C$. A continuously differentiable function $x : [-h, t_m) \to \mathbb{R}^n$, with $0 < t_m \leq \infty$ is a **solution** of (6.1) if x satisfies (6.1) for all $t \in (0, t_m)$ and $(x_t, \partial x_t) \in W_0$ for all $t \in [0, t_m)$.

In Section 6.1 we report from [124] a framework, which guarantees existence and uniqueness of solutions to (6.1). Under certain conditions, the solution segments of (6.1) generate semiflows on subspaces of the Banach spaces C^1 and C^2 [124].

In Section 6.2 we present a new result about Lipschitz continuity of NFDEs with state-dependent delays.

Section 6.3 is dedicated to results in [129,130] about linearized stability of semiflows generated by neutral equations with state-dependent delay. We shall extend the framework in [130] to investigate semiflows from a wider class of equations.

To conclude the chapter, in Section 6.4 we show how to rewrite a general neutral equation with state-dependent delay into the NFDE form (6.1), so that results in Sections 6.1–6.3 can be applied. Further, we discuss linearization of semiflows at nontrivial equilibria.

6.1. Semiflows from NFDEs with State-Dependent Delay

Analogously to the case of non-neutral equations with state-dependent delay (cf. Chapter 4), we shall construct smooth semiflows of solutions to (6.1).

If $x : [-h, t_m) \to \mathbb{R}^n$ is a solution of (6.1), then all solution segments x_t are elements of the open subset

$$U_1 = \{\phi \in C^1 : (\phi, \partial\phi) \in W_0\} \subset C^1. \tag{6.2}$$

Further, if $f_0 : W_0 \to \mathbb{R}^n$, $W_0 \subset C^1 \times C$ open, is continuous, then all segments x_t, $t \in [0, t_m)$, of a solution $x : [-h, t_m) \to \mathbb{R}^n$ of (6.1) belong to the set

$$X_1 = \Big\{\phi \in U_1 \,:\, \dot{\phi}(0) = f_0(\phi, \partial\phi)\Big\} \subset U_1 \subset C^1.$$

Indeed, the above definition of solution implies that $x_t \in X_1$ for all $t \in (0, t_m)$. Further, as both f_0 and the map $[0, t_m) \to C^1 \times C$, $t \to (x_t, \partial x_t)$ are continuous, we find

$$\dot{x}_0(0) \;=\; \dot{x}(0) \;=\; \lim_{s\to 0^+} \dot{x}(s) \;=\; \lim_{s\to 0^+} f_0(x_s, \partial x_s) \;=\; f_0(x_0, \partial x_0).$$

In the following we present a framework which allows for the construction of semiflows generated by solutions of the IVP

$$\begin{aligned} \dot{x}(t) &= f_0(x_t, \partial x_t), \\ x_0 &= \phi, \end{aligned} \tag{6.3}$$

and report without proof central results from [124] on existence, uniqueness and smoothness of solutions to (6.3). The first set of assumptions is given by:

(g0) *Continuity.*
The function f_0 is continuous.

(g1) *The delay in the neutral term never vanishes (cf. Figure 6.1).*
For every $\phi \in U_1 \subset C^1$ there exists a value $\Delta \in (0, h)$ and a neighborhood N of $(\phi, \partial\phi)$, $N \subset W_0 \subset C^1 \times C$, such that for all $(\rho, \xi_1), (\rho, \xi_2)$ in N, with

$$\xi_1(t) = \xi_2(t), \text{ for all } t \in [-h, -\Delta],$$

it follows that

$$f_0(\rho, \xi_1) = f_0(\rho, \xi_2).$$

(g2) *Local estimates for f_0*
For every $\phi \in U_1 \subset C^1$ there exists a constant $L \geq 0$ and a neighborhood N of $(\phi, \partial\phi)$, $N \subset W_0 \subset C^1 \times C$, such that for all $(\phi_1, \xi_1), (\phi_2, \xi_2)$ in N, it follows that

$$|f_0(\phi_2, \xi_2) - f_0(\phi_1, \xi_1)| \leq L \left(\|\xi_2 - \xi_1\|_C + (Lip(\xi_2) + 1) \|\phi_2 - \phi_1\|_C \right).$$

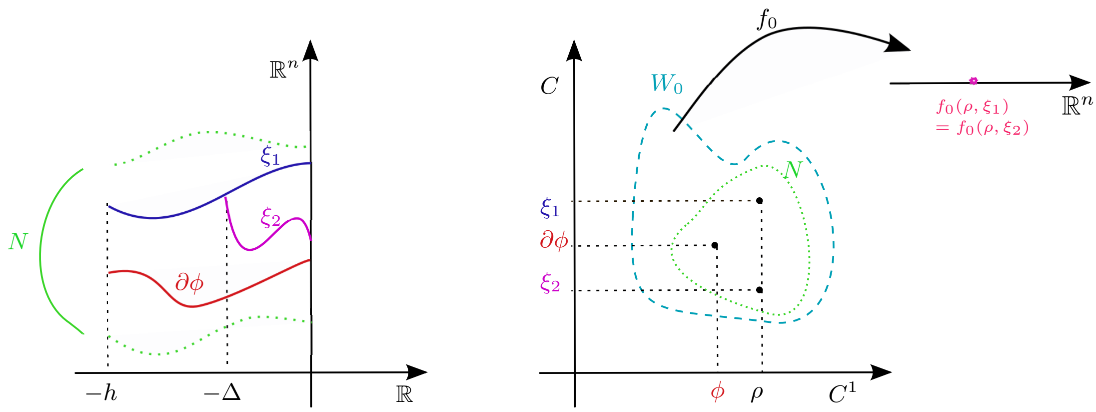


Figure 6.1: Condition (g1): For each $\phi \in U_1$ we find a neighborhood N of $(\phi, \partial\phi)$, $N \subset W_0$ and a value $\Delta \in (0, h)$ such that, for all (ρ, ξ_1), (ρ, ξ_2) in N, as long as the functions ξ_1, ξ_2 coincide in $[-h, -\Delta]$, we have $f_0(\rho, \xi_1) = f_0(\rho, \xi_2)$. By (g1) we formally neglect the small interval $[-\Delta, 0]$ for the second component of f_0, i.e., we neglect the possibility that the delay in the neutral term of (6.1) becomes zero.

Now define the set

$$X_{1+} = \{\phi \in X_1 \, : \, Lip(\partial\phi) < \infty\} \subset X_1 \subset C^1.$$

If f_0 satisfies (g0)–(g2) and ϕ is an element of the set X_{1+}, then there is a solution $x : [-h, t_m) \to \mathbb{R}^n$, $0 < t_m \leq \infty$ of the IVP (6.3), with initial data $x_0 = \phi$, which is unique on the interval $[-h, t_m)$. That is, if $y : [-h, t_m) \to \mathbb{R}^n$, $0 < t_m \leq \infty$ is a solution of the IVP (6.3) with initial data $y_0 = x_0$, then $x = y$. The proof of this result can be found in [124, Sec. 4].

With (g1) and (g2) one can prove that for every solution $x : [-h, t_m) \to \mathbb{R}^n$, $0 < t_m \leq \infty$ of (6.3), with $x_0 = \phi \in X_{1+}$, the derivative $\dot{x} : [-h, t_m) \to \mathbb{R}^n$ is locally Lipschitz continuous. For every initial data $\phi \in X_{1+}$ we define the value

$$t_\phi = \sup \{t_m > 0 \, : \, \text{ there is a solution } x : [-h, t_m) \to \mathbb{R}^n \text{ to (6.3)}\} \leq \infty.$$

Then, the maximal solution $x^\phi : [-h, t_\phi) \to \mathbb{R}^n$ to (6.3), with $x^\phi_0 = \phi$, is defined by the solutions on intervals $[-h, t_m)$, with $t_m < t_\phi$. All segments of the maximal solution x^ϕ_t are in X_{1+} and generate a semiflow

$$G_1 : \Omega_1 \to X_{1+}, \quad (t, \phi) \mapsto G_1(t, \phi) = x^\phi_t, \tag{6.4}$$

where $\Omega_1 = \bigcup_{\phi \in X_{1+}} [0, t_\phi) \times \{\phi\}$. Proposition 4.6 in [124] shows that Ω_1 is an open subset of $[0, \infty) \times X_{1+}$ with respect to the topology induced by $\mathbb{R} \times C^1$ and that the semiflow G_1 is continuous with respect to the topology induced by C^1.

Semiflows with better smoothness properties than G_1 can be found by making further assumptions on the right-hand side of the IVP (6.3). To this purpose, it is necessary to consider the restriction $f = f_0|_W$ of f_0 to the open subset $W = W_0 \cap (C^1 \times C^1)$ and to have the following condition.

(g3) *Linear extension of the derivative Df*
The map $f : W \to \mathbb{R}^n$ is continuously differentiable and every derivative

$$Df(\phi, \xi) : C^1 \times C^1 \to \mathbb{R}^n,$$

with $(\phi, \xi) \in W$, has a linear extension,

$$D_e f(\phi, \xi) : C \times C \to \mathbb{R}^n.$$

In addition, the map

$$W \times C \times C \ni (\phi, \xi, \rho, \chi) \mapsto D_e f(\phi, \xi)(\rho, \chi) \in \mathbb{R}^n$$

is continuous.

Now let us assume that the set $X_2 = X_1 \cap C^2$ is non-empty. If f_0 has properties (g1) and (g3), then X_2 is a continuously differentiable submanifold of codimension n in C^2 with tangent space

$$T_\phi X_2 = \left\{ \chi \in C^2 \,:\, \dot\chi(0) = Df(\phi, \partial\phi)(\chi, \partial\chi) \right\}$$

at $\phi \in X_2$ (cf. Proposition 5.1 in [124]). For $\phi \in X_2$ we define the extended tangent space

$$T_{e,\phi} X_2 = \left\{ \chi \in C^1 \,:\, \dot\chi(0) = D_e f(\phi, \partial\phi)(\chi, \partial\chi) \right\} \subset C^1.$$

Again, let $f_0 : W_0 \to \mathbb{R}^n$, $W_0 \subset C^1 \times C$ open, be given with properties (g0)–(g3). Section 6 of [124] contains the proof that, under the above assumptions, solutions to (6.3) define a continuous semiflow on the subset

$$X_{2*} = \{ \phi \in X_2 \,:\, \partial\phi \,\in\, T_{e,\phi} X_2 \} \tag{6.5}$$

of the manifold X_2. Indeed, for each $\phi \in X_{2*}$ there is a maximal solution $x^\phi : [-h, t_\phi) \to \mathbb{R}^n$ of (6.3), which is twice continuously differentiable and all segments x_t^ϕ, $t \in [0, t_\phi)$ are in X_{2*} (cf. Proposition 6.1 in [124]). The solution segments of x^ϕ define a map,

$$G_2 : \Omega_2 \to X_{2*}, \quad (t, \phi) \mapsto G_2(t, \phi) = x_t^\phi,$$

with

$$\Omega_2 = \{ (t, \phi) \in [0, \infty) \times X_{2*} \,:\, t < t_\phi \}.$$

It is easy to verify that G_2 is a semiflow, as $G_2(0, \phi) = x_0^\phi = \phi$ and G_1 in (6.4) is a semiflow. Moreover, it is possible to show that the semiflow G_2 is continuous with respect to the norms on $\mathbb{R} \times C^2$ and C^2 (cf. Proposition 6.2 in [124], for a local result, and Corollary 6.3 in [124], for continuity on Ω_2).

For $\phi \in X_{2*}$, $\chi \in T_{e,\phi} X_2$ consider the IVP

$$\dot v(t) = D_e f(x_t^\phi, \partial x_t^\phi)(v_t, \partial v_t), \tag{6.6}$$

$$v_0 = \chi. \tag{6.7}$$

A solution of this IVP is a continuously differentiable function $v : [-h, t^*) \to \mathbb{R}^n$, with $t^* \in (0, t_\phi]$, which satisfies (6.6)–(6.7) for $t \in (0, t^*)$. For such a solution, equation (6.6) holds also at $t = 0$ and all segments v_t are in $T_{e, G_2(t,\phi)} X_2$ for all $t \in [0, t^*)$.

Conditions (g0)–(g3) guarantee that for any $\phi \in X_{2*}$ and any $\chi \in T_{e,\phi} X_2$, there is a unique maximal solution $v^{\phi,\chi} : [-h, t_\phi) \to \mathbb{R}^n$ of (6.6)–(6.7).

The formulation of this linear IVP is the first step to investigate differentiability properties of the solution operator

$$G_2(t, \cdot) : \Omega_{2,t} \to X_{2*}, \quad \phi \mapsto G_2(t, \phi),$$

with $\Omega_{2,t} = \{ \phi \in X_{2*} \,:\, t < t_\phi \} \subset X_{2*}$, and linear stability of neutral equations with state-dependent delays.

The next two hypotheses allow for more results on smoothness properties of solutions to (6.3).

(g4) The map $f : W \to \mathbb{R}^n$ is continuously differentiable and for every $(\phi_0, \xi_0) \in W$ there exists a constant $c \geq 0$ and a neighborhood N of (ϕ_0, ξ_0), $N \subset W \subset C^1 \times C^1$ such that, for all $(\phi_1, \xi_1), (\phi_2, \xi_2)$ in N and for all $\chi \in C^1$, we have

$$|(Df(\phi_2, \xi_2) - Df(\phi_1, \xi_1))\,(0, \chi)| \leq c\,\|\partial\chi\|_C\,\|\phi_2 - \phi_1\|_C\,.$$

(g5) The map $f : W \to \mathbb{R}^n$ is continuously differentiable and every derivative

$$Df(\phi, \xi) \,:\, C^1 \times C^1 \to \mathbb{R}^n, \quad (\phi, \xi) \in W \subset C^1 \times C^1,$$

has a linear extension

$$D_e f(\phi, \xi) : C \times C \to \mathbb{R}^n.$$

Moreover, for every $(\phi_0, \xi_0) \in W$ there exist a value $c \geq 0$ and a neighborhood $N \subset W$ of (ϕ_0, ξ_0) in $C^1 \times C^1$, such that for all $(\phi_1, \xi_1), (\phi_2, \xi_2)$ in N and for all $(\rho, \chi) \in C \times C$, with $\|(\rho, \chi)\|_{C\times C} = 1$, we have

$$\begin{aligned}&|(D_e f(\phi_2, \xi_2) - D_e f(\phi_1, \xi_1))\,(\rho, \chi)|\\ &\qquad \leq c\,(Lip(\chi) + Lip(\partial\xi_2) + 1)\,\|(\phi_2, \xi_2) - (\phi_1, \xi_1)\|_{C^1\times C^1}.\end{aligned}$$

The set of hypotheses (g0)–(g5) allows for differentiability properties of the solution operators $G_2(t, \cdot)$, which we shall not discuss at this point. Main results are contained in Sections 8 and 9 of [124].

Hypotheses (g0)–(g5) are satisfied for a prototype equation

$$\dot{x}(t) = a\dot{x}(t - \tau_a(x(t))) + u(x(t)), \tag{6.8}$$

with $a > 0$, $\tau_a : \mathbb{R} \to (0, h)$, $u : \mathbb{R} \to \mathbb{R}$, τ_a and u continuously differentiable and $\dot{\tau}_a$, $\dot{u}$ Lipschitz continuous. However, not every neutral equation with state-dependent delay satisfies (g4). As we shall explain in Section 6.3, a substitute for hypothesis (g4) has already been introduced in [129, 130].

Before proceeding to results on linearized stability of NFDEs with state-dependent delay, we present a consequence of hypothesis (g3).

6.2. Condition (g3) and Lipschitz Continuity

For a general RFDE

$$\dot{x}(t) = f_1(x_t),$$

with $f_1 : V_1 \to \mathbb{R}^n, V_1 \subset C^1$, the following result was shown in [126].

Proposition (Corollary 1 in [126]). *Consider $f_1 : V_1 \to \mathbb{R}^n$, with $V_1 \subset C^1$ open subset. Assume that:*

(i) The map f_1 is continuously differentiable.

(ii) The derivative $Df_1(\phi) : C^1 \to \mathbb{R}^n$, $\phi \in C^1$ has a linear extension $D_e f_1(\phi) : C \to \mathbb{R}^n$.

(iii) The map $C^1 \times C \ni (\phi, \chi) \mapsto D_e f_1(\phi)\chi \in \mathbb{R}^n$ is continuous.

Then f_1 is locally Lipschitz continuous with respect to the norm of C, i.e., for every $\phi \in V_1$ there are an open neighborhood $O_1 \subset V_1$ and a constant $c \geq 0$ so that, for all $\psi, \chi \in O_1$, we have $|f_1(\psi) - f_1(\chi)| \leq c\,\|\psi - \chi\|_C$.

In the following we show a similar result for NFDEs.

Proposition 6.1. *Consider a neutral equation*

$$\dot{x}(t) = f_0(x_t, \partial x_t)$$

with $f_0 : W_0 \to \mathbb{R}^n$, $W_0 \subset C^1 \times C$ open subset. Assume that

(i) The restriction f of f_0 to the open subset $W = W_0 \cap (C^1 \times C^1)$ of the space $C^1 \times C^1$ is continuously differentiable.

(ii) For all $(\phi, \xi) \in W$, the derivative $Df(\phi, \xi) : C^1 \times C^1 \to \mathbb{R}^n$ has a linear extension $D_e f(\phi, \xi) : C \times C \to \mathbb{R}^n$.

(iii) The map

$$W \times C \times C \ni (\phi, \xi, \rho, \chi) \mapsto D_e f(\phi, \xi)(\rho, \chi) \in \mathbb{R}^n$$

is continuous.

Then, for every $(\phi, \xi) \in W$ there is a neighborhood N of (ϕ, ξ), $N \subset W \subset C^1 \times C^1$ and a constant $L > 0$ such that, for all (ϕ_1, ξ_1), $(\phi_2, \xi_2) \in N$ we have

$$|f(\phi_2, \xi_2) - f(\phi_1, \xi_1)| \leq L\|(\phi_2, \xi_2) - (\phi_1, \xi_1)\|_{C\times C}.$$

Proof. 1) (cf. Proposition 2.6 in [124].) Let a point $(\phi^*, \xi^*) \in W \subset C^1 \times C^1$ be given. For hypothesis (iii), there is a neighborhood $N \subset W \subset C^1 \times C^1$ of (ϕ^*, ξ^*) and a value $r > 0$ such that, for every $(\phi, \xi) \in N$ and every $(\rho, \chi) \in C \times C$, with $\|(\rho, \chi)\|_{C\times C} < r$, we have

$$|D_e f(\phi, \xi)(\rho, \chi) - D_e f(\phi^*, \xi^*)(0, 0)| = |D_e f(\phi, \xi)(\rho, \chi)| < 1.$$

So, for all $(\phi,\xi)\in N$ we get

$$\|D_e f(\phi,\xi)\|_{L(C\times C,\mathbb{R}^n)} \le \frac{1}{r}.$$

2) Thus, for all $(\phi,\xi)\in W\subset C^1\times C^1$ there is a convex neighborhood $N\subset W$ and a constant $L>0$ such that $D_e f$ is bounded by L on N. Hence, for (ϕ_1,ξ_1), $(\phi_2,\xi_2)\in N$, we obtain

$$\begin{aligned}
&|f(\phi_2,\xi_2)-f(\phi_1,\xi_1)|\\
&=\left|\int_0^1 Df\big((\phi_1,\xi_1)+s\big((\phi_2,\xi_2)-(\phi_1,\xi_1)\big)\big)\,\big[(\phi_2,\xi_2)-(\phi_1,\xi_1)\big]\,ds\right|\\
&=\left|\int_0^1 D_e f\big((\phi_1,\xi_1)+s\big((\phi_2,\xi_2)-(\phi_1,\xi_1)\big)\big)\big[(\phi_2,\xi_2)-(\phi_1,\xi_1)\big]\,ds\right|\\
&\le \int_0^1 \big|D_e f\big((\phi_1,\xi_1)+s\big((\phi_2,\xi_2)-(\phi_1,\xi_1)\big)\big)\big[(\phi_2,\xi_2)-(\phi_1,\xi_1)\big]\,\big|\,ds\\
&\le L\|(\phi_2,\xi_2)-(\phi_1,\xi_1)\|_{C\times C}.
\end{aligned}$$

□

It may not be straightforward to consider Proposition 6.1 as an analogon for NFDEs of Corollary 1 in [126], therefore we briefly comment these two results.

In Proposition 6.1 we start with an open subset W_0 of $C^1\times C$ and $f_0: W_0\to\mathbb{R}^n$, the right-hand side of the NFDE (6.1). If f_0, together with its restriction f to the subset $W=W_0\cap(C^1\times C^1)$, satisfies property (g3), then it also satisfies the following property.

(g2') For every $\phi\in C^2$, with $(\phi,\partial\phi)\in W\subset C^1\times C^1$, there exists a constant $L>0$ and a neighborhood N of $(\phi,\partial\phi)$, $N\subset W$, such that for all $(\phi_1,\xi_1),(\phi_2,\xi_2)$ in N, we have

$$|f(\phi_2,\xi_2)-f(\phi_1,\xi_1)|\le L\|(\phi_2,\xi_2)-(\phi_1,\xi_1)\|_{C\times C}.$$

Corollary 1 in [126] asserts that, if the right-hand side f_1 of the RFDE is continuously differentiable and the map $C^1\times C\ni(\phi,\chi)\mapsto D_e f_1(\phi)\chi\in\mathbb{R}^n$ is continuous, then f_1 is locally Lipschitz continuous with respect to the norm in C. In the notation of Section 4.2.1, this means that when f_1 has properties (S1) and (S3), it also has property (S2).

In the proof of Proposition 6.1 we consider the restriction f of f_0 to the space of continuously differentiable functions. Accordingly, the estimate in (g2') expresses a local Lipschitz condition for the map f. On the other hand, property (g2) gives a local Lipschitz condition for f_0. In this sense, we cannot say that when f in (6.1) has property (g3), it has also property (g2).

However, let us consider applications of NFDEs. In applications, one is mostly interested in linearized stability of semiflows from neutral equations with state-dependent delays. Thus, in the end, one deals with NFDEs whose right-hand side is restricted to some open subset of $C^1\times C^1$, or of $C^2\times C^1$, and considers initial data in $X_2\subset C^2$. This does not mean that the above conditions (and in particular condition (g3), related to the derivative of the right-hand side) have to be understood in the topology of $C^2\times C^1$, but only that the right-hand side is defined on some thinner subset. In this sense condition (g3) applies directly to the right-hand side of the NFDE and so does condition (g2'). Hence, by Proposition 6.1, we find that (g3) implies a local Lipschitz condition for the right-hand side of the problem. We shall make use of this result in the next chapter.

6.3. Linearized Stability

In [129,130], the above framework has been extended to prove a principle of linearized stability for neutral equations. Beside properties (g0)–(g4), two more conditions have been introduced in order to have linearization at equilibria. On the other hand, hypothesis (g5) is not relevant for this purpose. In this section, we summarize major results in [129, 130].

Let $f_0 : W_0 \to \mathbb{R}^n$, $W_0 \subset C^1 \times C$ open subset. Recall the definition (6.5) of the set X_{2*}. We assume that $(0, 0) \in W_0$ and $f_0(0, 0) = 0$, so that $0 \in X_{2*}$ is a stationary point of the semiflow G_2. In the previous sections we have seen that under the hypotheses (g0)-(g3), for every $\phi \in X_{2*}$ there is a unique maximal solution $x^\phi : [-h, t_\phi) \to \mathbb{R}^n$ of the IVP (6.3).

It is possible to associate to (6.3) a linear variational equation along the zero solution, namely

$$\dot{v}(t) = D_e f(0, 0)(v_t, \partial v_t), \tag{6.9}$$

where $f = f_0\big|_W$ is the restriction of f_0 to $W = W_0 \cap (C^1 \times C^1)$. As we shall show below, the connection between the nonlinear equation (6.3) and the linear variational equation (6.9) is given by the **remainder map** of f, i.e., the continuously differentiable map

$$r : \left\{\phi \in C^2 \,:\, (\phi, \partial\phi) \in W\right\} \to \mathbb{R}^n,\ \phi \mapsto f(\phi, \partial\phi) - Df(0, 0)(\phi, \partial\phi). \tag{6.10}$$

In order to understand the results in [129, 130] about linearized stability for neutral equations with state-dependent delay, we consider the problem from the point of view of NFDEs. Adopting the notation used, e.g., by Hale [64,66], we write (6.9) in the form of a homogeneous linear NFDE,

$$\frac{d}{dt}\left(v - L \circ V\right)(t) = R v_t, \tag{6.11}$$

where $L, R \in L_c(C, \mathbb{R}^n)$ are continuous linear operators

$$L = D_e f(0, 0)(0, \cdot), \qquad R = D_e f(0, 0)(\cdot, 0),$$

and V is defined by $[0, t_m) \to C$, $t \mapsto V(t) = v_t$, for any continuous function $v : [-h, t_m) \to \mathbb{R}^n$.

Proposition 6.2. *Any twice continuously differentiable solution $v : [-h, t_m) \to \mathbb{R}^n$ of (6.9), with initial data $v_0 \in T_{e,0}X_2$, is also a solution* [1] *of (6.11).*

Proof. The map $V : [0, t_m) \to C$, $t \mapsto v_t$ is continuously differentiable with $DV(t)1 = \partial v_t$, for $t \in [0, t_m)$. Hence, the composite $L \circ V$ is continuously differentiable. Moreover, the map $[0, t_m) \to \mathbb{R}^n$, $t \mapsto v(t) - L \circ V(t)$ is continuously differentiable and for all $t \in (0, t_m)$ we have

$$\begin{aligned}\frac{d}{dt}\left(v - L \circ V\right)(t) &= \dot{v}(t) - L(\partial v_t) \\ &= \dot{v}(t) - D_e f(0,0)(0, \partial v_t) \\ &= D_e f(0,0)(v_t, \partial v_t) - D_e f(0,0)(0, \partial v_t) \\ &= D_e f(0,0)(v_t, 0) \\ &= R v_t.\end{aligned}$$

The same holds at $t = 0$ with the right derivative of $[0, t_m) \to \mathbb{R}^n$, $t \mapsto v(t) - L \circ V(t)$. □

Analogously, we can associate the original problem (6.3) to an inhomogeneous NFDE. Let $x : [-h, t_m) \to \mathbb{R}^n$ be a noncontinuable twice continuously differentiable solution of (6.3) with initial data $x_0 \in X_{2*}$, and define the map

$$r_x : [0, t_m) \to \mathbb{R}^n, \quad t \mapsto r_x(t) = r(x_t). \tag{6.12}$$

Then, x solves the inhomogeneous NFDE

$$\frac{d}{dt}\left(x - L \circ X\right)(t) = R x_t + r_x(t), \tag{6.13}$$

in the sense that the map $[0, t_m) \to \mathbb{R}^n$, $t \mapsto x(t) - L \circ X(t)$ is continuously differentiable for all $t \in (0, t_m)$ and at $t = 0$ only with the right derivative (cf. Proposition 3.3 in [129]).

We go back to the linear NFDE (6.11). Every continuous initial function $\chi \in C$ uniquely determines a continuous solution $v : [-h, \infty) \to \mathbb{R}^n$ of (6.11), with $v_0 = \chi$. To indicate explicitly that v is the solution to (6.11) with initial data χ, we denote v by v^χ. As, for $\chi \in C$, the map $[-h, \infty) \to C$, $t \mapsto v_t^\chi$ is continuous, the solutions v^χ form a strongly continuous semigroup $\{S(t)\}_{t \geq 0}$, where

$$S(t) : C \to C, \quad \chi \mapsto v_t^\chi.$$

This $\mathcal{C}_0$-semigroup gives information on the behavior of solutions of the inhomogeneous NFDE (6.13) (cf. Proposition 6.3 in [129]). Given a continuous map $I : [-h, \infty) \to \mathbb{R}^n$ and constant values $b \geq 1$, $a \in \mathbb{R}$ such that

$$\|S(t)\chi\|_C \leq b e^{at} \|\chi\|_C, \qquad \forall\, t \geq 0,\ \chi \in C,$$

[1] In the sense that the map $[0, t_m) \to \mathbb{R}^n$, $t \mapsto v(t) - L \circ V(t)$ is continuously differentiable for all $t \in (0, t_m)$ and at $t = 0$ only with the right derivative.

for every continuous solution $y : [-h, \infty) \to \mathbb{R}^n$ of the inhomogeneous NFDE

$$\frac{d}{dt}\,(y - L \circ Y)\,(t) = Ry_t + I(t),$$

we have

$$|y(t)| \leq b \left(e^{at}|y_0| + n \int_0^t e^{a(t-s)} |I(s)|\, ds \right), \qquad t \geq 0.$$

Notice that the map r_x in (6.13) is continuous, as the curve $[0, t_m) \ni t \mapsto x_t \in C^2$ is continuous. With $I = r_x$, the last result can be used to investigate solutions of (6.13). Thus, in order to associate the linear problem (6.9) to the original IVP (6.3), we shall estimate r_x. We recall (6.12) and consider the remainder map (6.10). For $\phi \in C^2$ we have the equality

$$\begin{aligned}
r(\phi) &= f(\phi, \partial\phi) - Df(0,0)(\phi, \partial\phi) \\
&= f(\phi, \partial\phi) - \underbrace{f(0,0)}_{=0} - Df(0,0)(\phi, \partial\phi) \\
&= \int_0^1 \left(Df(s\phi, s\partial\phi) - Df(0,0) \right) (\phi, \partial\phi)\, ds \\
&= \int_0^1 \left(Df(s\phi, s\partial\phi) - Df(0,0) \right) (0, \partial\phi)\, ds \\
&\quad + \int_0^1 \left(Df(s\phi, s\partial\phi) - Df(0,0) \right) (\phi, 0)\, ds.
\end{aligned}$$

Consequently we find

$$\begin{aligned}
|r(\phi)| \leq & \max_{0 \leq s \leq 1} |\left(Df(s\phi, s\partial\phi) - Df(0,0) \right) (0, \partial\phi)| \\
& + \max_{0 \leq s \leq 1} |\left(Df(s\phi, s\partial\phi) - Df(0,0) \right) (\phi, 0)|.
\end{aligned} \tag{6.14}$$

Now we introduce two more hypotheses on f_0.

(g6) The point $(0,0)$ is in W_0 and $f_0(0,0) = 0$. Further, condition (g3) holds and the map

$$W \ni (\phi, \xi) \mapsto \|D_e f(\phi, \xi)(0, \cdot)\|_{L_c(C, \mathbb{R}^n)} \in \mathbb{R}$$

is upper semicontinuous at $(0,0)$.

(g7) The point $(0,0)$ is in W_0, it is $f_0(0,0) = 0$ and $f = f_0\big|_W$ is differentiable. Further there exist constants $c \geq 0$, $m > 0$ and a function $\zeta : [0, \infty) \to [0, \infty)$, which is continuous at $0 = \zeta(0)$, such that for all $(\phi, \xi) \in W$, with $\|\phi\|_C + \|\xi\|_C < m$, and for all $\rho \in C^1$, we have

$$|\left(Df(\phi, \xi) - Df(0,0) \right) (\rho, 0)| \;\leq\; c \left\{ \zeta \left(\|\phi\|_{C^1} + \|\xi\|_{C^1} \right) \|\rho\|_C + \|\rho\|_{C^1} \|\xi\|_C \right\}.$$

The main result in [129] is about asymptotic stability of solutions of (6.3).

Theorem 6.1 (Theorem 1.1 in [129]). *Let $f_0 : W_0 \to \mathbb{R}^n$, $W_0 \subset C^1 \times C$ an open set, be given with properties (g0)–(g4), (g6) and (g7). Consider the restriction $f = f_0|_W$ of f_0 to the open subset $W = W_0 \cap (C^1 \times C^1)$. Assume that*

$$\|D_e f(0,0)(0,\cdot)\|_{L_c(C,\mathbb{R}^n)} < 1,$$

and that there exist $c \geq 1$, $\alpha < 0$ such that

$$\|S(t)\chi\|_C \leq ce^{\alpha t} \|\chi\|_C \,, \quad \text{for all} \ \ t \geq 0, \, \chi \in C.$$

Then, the semiflow G_2 is exponentially attracting, that is, there exist values $\delta > 0, \kappa \geq 1$ and $\beta < 0$ such that, for all $\phi \in X_{2*}$, with $\|\phi\|_{C^2} < \delta$ and for all $t \geq 0$,

$$\|G_2(t,\phi)\|_{C^2} \leq \kappa e^{\beta t} \|\phi\|_{C^2} \,.$$

On the whole, the proof of Theorem 6.1 is based on the following facts:

(I) Assumptions (g0)–(g4), (g6) and (g7) allow for the determination of a convex open neighborhood $N_1 \subset W$ of $(0,0)$ in $C^1 \times C^1$ and a value $c_1 \geq 0$, such that for all $\phi \in C^2$ with $(\phi, \partial\phi) \in N_1$,

$$|r(\phi)| \leq \left(c_1 \|\partial\partial\phi\|_C + c_1 \max_{0\leq s\leq 1} \left(\zeta\left(\|s\partial\phi\|_{C^1} + \|s\phi\|_{C^1}\right) + \|\phi\|_{C^1}\right)\right) \|\phi\|_C \,,$$

with the function $\zeta : [0,\infty) \to [0,\infty)$, as in (g7).

(II) If all hypotheses of Theorem 6.1 are satisfied, then one can determine a neighborhood $N_2 \subset N_1$ of $(0,0)$ in $W \subset C^1 \times C^1$ such that

$$\|D_e f(\phi,\xi)(0,\cdot)\|_{L_c(C,\mathbb{R}^n)} \leq q_1, \ \ \text{for all} \ \ (\phi,\xi) \in N_2,$$

with $q_1 \in \left(\|D_e f(0,0)(0,\cdot)\|_{L_{c(C,\mathbb{R}^n)}}, 1\right)$. Moreover, following estimates hold.

Proposition 6.3. *Let $\varepsilon > 0$ be given. Then there exist values $\kappa_1 \geq 1$, $\beta_1 < 0$, $\kappa_2 \geq 1$, $\beta_2 \in (\beta_1, 0)$, $\kappa_3 \geq 1$ and $\beta_3 = \beta_3(\beta_2) < 0$ such that for a noncontinuable twice continuously differentiable solution $x : [-h, t_m) \to \mathbb{R}^n$ of (6.3), with initial data $x_0 \in X_{2*}$ and with*

$$|r_x(t)| \leq \varepsilon \|x_t\|_C \,, \ \ \text{for all} \ t \in [0, t_m),$$

we have $\|x_t\|_C \leq \kappa_1 e^{\beta_1 t} \|x_0\|_C$ and $\|\partial x_t\|_C \leq \kappa_2 e^{\beta_2 t} \|x_0\|_{C^1}$, for all $t \in [0, t_m)$.

Further, if $(x_t, \partial x_t) \in N_2$ for all $t \in [0, t_m)$, then $\|\partial\partial x_t\|_C \leq \kappa_3 e^{\beta_3 t} \|x_0\|_{C^2}$, for all $t \in [0, t_m)$.

The proof of Proposition 6.3 is given in Walther [129, Sec. 4].

(III) Set $k = k_1 + k_3 + k_4$, and $\beta = \max\{\beta_1, \beta_2, \beta_3\}$ and notice that $k \geq 1$ and $\beta < 0$. With the results in (I) and (II), given $\varepsilon > 0$ we can determine a value $\delta_0 > 0$ such that, for all $\phi \in C^2$ with $\|\phi\|_{C^2} < \delta_0$, we have $(\phi, \partial\phi) \in N_2$ and

$$c_1 \|\partial\partial\phi\|_C + c_1\big(\zeta\left(\|s\partial\phi\|_{C^1} + \|s\phi\|_{C^1}\right) + \|\phi\|_{C^1}\big) < \varepsilon, \qquad \text{for all } s \in [0,1].$$

Then we also have

$$|r(\phi)| \leq \varepsilon \|\phi\|_C .$$

Choose a value $\delta \in (0, \delta_0)$. For a noncontinuable twice continuously differentiable solution $x : [-h, t_m) \to \mathbb{R}^n$ of (6.3), with $x_0 \in X_{2*}$ and with $\|x_0\|_{C^2} < \delta$, the estimates in (II) yield

$$\|x_t\|_{C^2} \leq k e^{\beta t} \|x_0\|_{C^2}, \qquad \text{for all} \quad t \in [0, t_m).$$

Proposition 5.2 in [129] finally shows that $t_m = \infty$.

The prototype equation (6.8) satisfies all properties (g0)–(g4), (g6) and (g7) and Theorem 6.1 can be used to determine linearized stability of semiflows generated by solutions of this neutral equation [129]. Unfortunately, the same does not hold for every neutral equation with state-dependent delay.

When the right-hand side f_0 is more complex than the one in (6.8), certain hypotheses of Theorem 6.1 might not be satisfied. In [130] the set of assumptions has been modified to investigate NFDEs of the form

$$\dot{x}(t) = A\left(\dot{x}(t - \tau_b(x(t)))\right) + g(x(t - \tau_c(x(t)))), \tag{6.15}$$

with $A : \mathbb{R} \to \mathbb{R}$, $\tau_b : \mathbb{R} \to (0, h)$, $g : \mathbb{R} \to \mathbb{R}$, $\tau_c : \mathbb{R} \to [0, h]$ all continuously differentiable and $A(0) = 0 = g(0)$. This kind of equations satisfies conditions (g0)–(g3), but not (g4). Thus, for the prototype equation (6.15) a weaker hypothesis has been formulated. To this purpose it might be useful to recall the definition of the set U_1 in (6.2).

(g8) The point $(0,0)$ is in W_0, it is $f_0(0,0) = 0$ and f is differentiable. Further there exist a convex neighborhood $U_2 \subset U_1 \cap C^2$ of 0 in C^2, a constant $c > 0$, a continuous function $\alpha : \mathbb{R} \to \mathbb{R}$ and a value $\Delta \in (0, h)$ such that, for all $\phi \in U_2$ we have

$$\max_{0 \leq s \leq 1} |(Df(s\phi, s\partial\phi) - Df(0,0))(0, \partial\phi)| \leq c \|\partial\partial\phi\|_C \|\phi\|_C + \max_{|\xi| \leq \|\partial\phi\|_C} |\alpha(\xi) - \alpha(0)| \max_{\Delta \leq u \leq h} |\dot{\phi}(-u)|.$$

Condition (g6) was kept unchanged, whereas (g7) was modified into the following hypothesis.

(g9) The point $(0,0)$ is in W_0, it is $f_0(0,0) = 0$ and f is differentiable. Further there exist a convex neighborhood $U_2 \subset U_1 \cap C^2$ of 0 in C^2, a constant $c > 0$ and a function $\zeta : [0, \infty) \to [0, \infty)$ which is continuous at $0 = \zeta(0)$, so that for all $\phi \in U_2$ we have

$$\max_{0 \leq s \leq 1} |(Df(s\phi, s\partial\phi) - Df(0,0))(\phi, 0)| \leq c \max_{0 \leq s \leq 1} \left\{\zeta\left(\|s\phi\|_{C^2}\right) \|\phi\|_C + \|\phi\|_{C^1} \|s\phi\|_C\right\}.$$

The set of hypotheses, (g0)–(g3), (g6), (g8) and (g9), yields a new principle of linearized stability for neutral equations with state-dependent delays.

Theorem 6.2 (Theorem 1.3 in [130]). *Let $f_0 : W_0 \to \mathbb{R}^n$, $W_0 \subset C^1 \times C$ open, be given with properties (g0)–(g3), (g6), (g8) and (g9). Consider the restriction $f = f_0|_W$ of f_0 to the open subset $W = W_0 \cap (C^1 \times C^1)$. Suppose*

$$\|D_e f(0,0)(0,\cdot)\|_{L_c(C,\mathbb{R}^n)} < 1, \tag{6.16}$$

and assume that there exist $c \geq 1$, $\alpha < 0$ such that

$$\|S(t)\chi\|_C \leq ce^{\alpha t}\,\|\chi\|_C\,, \quad \text{for all} \;\; t \geq 0,\, \chi \in C.$$

Then the stationary point 0 of the semiflow G_2 is stable and attracting:

(i) For every $\varepsilon > 0$, there exists a $\delta > 0$ such that for all $\phi \in X_{2*}$ with $\|\phi\|_{C^2} < \delta$, we have $t_\phi = \infty$ and $\|G_2(t,\phi)\|_{C^2} < \varepsilon$ for all $t \geq 0$.

(ii) There exists a $\delta_f > 0$ such that for all $\phi \in X_{2*}$ with $\|\phi\|_{C^2} < \delta_f$, we have $t_\phi = \infty$ and $\lim\limits_{t\to\infty} \|G_2(t,\phi)\|_{C^2} = 0$.

This principle of linearized stability, however, is weaker than the one in Theorem 6.1. On the one hand it is still possible to show asymptotic stability, on the other hand there is no way to guarantee exponential convergence to the stationary state.

For the proof of Theorem 6.1 we refer to Walther [130, Sec. 3-5]. The only part of the proof we shall explicitly mention here is concerned with hypotheses (g8) and (g9).

Let r denote the remainder map (6.10) of f. If all hypotheses of Theorem 6.2 are fulfilled, then for every $\varepsilon > 0$ it is possible (cf. Proposition 3.1 (v) in [130]) to determine a value $\Delta \in (0,h)$ and a neighborhood V_ε of 0 in C^2 such that, for all $\phi \in V_\varepsilon$ we have

$$|r(\phi)| \leq \varepsilon \left(\|\phi\|_C + \max_{\Delta \leq u \leq h} |\dot{\phi}(-u)| \right).$$

This estimate is obtained from (6.14) under the assumption that the estimates in (g8) and (g9) hold.

In Chapter 7 we shall present two classes of neutral equations with state-dependent delays, which are both more general than the prototype equations considered in [130]. In both cases we find that hypothesis (g8) is not satisfied. As we are interested in linearized stability of semiflows generated by our neutral equations, we have to either look for an alternative stability result or change hypothesis (g8) into a weaker condition and show that the proof of Theorem 6.2 still holds. We choose the latter strategy and introduce a new hypothesis (g8*) to replace (g8) in the proof of Proposition 3.1 (v) of [130].

A New Hypothesis

We require a new condition for f_0 in (6.3).

(g8*) The point $(0,0)$ is in W_0, it is $f_0(0,0) = 0$ and f is differentiable. Further there exist a convex neighborhood $U_2 \subset U_1 \cap C^2$ of 0 in C^2, values c_1, $c_2 > 0$ and $\Delta \in (0,h)$, a function $\vartheta : [0,\infty) \to [0,\infty)$ continuous at $0 = \vartheta(0)$ such that, for all $\phi \in U_2$,

$$\max_{0\le s\le 1} |(Df(s\phi, s\partial\phi) - Df(0,0))\,(0,\partial\phi)| \le c_1 \,\|\partial\partial\phi\|_C \,\|\phi\|_C + c_2 \max_{0\le s\le 1} \vartheta\left(\|s\phi\|_{C^1}\right) \max_{\Delta\le u\le h} |\dot\phi(-u)|.$$

We assume that the hypotheses of Theorem 6.2 are fulfilled, with (g8*) instead of (g8). Then the following proposition holds true.

Proposition 6.4 (Proposition 3.1. in [130])**.** *There are a convex open neighborhood U_2 of 0 in C^2, a neighborhood $N_1 \subset W$ of $(0,0)$ in $C^1 \times C^1$, constants $c \ge 1$, $\alpha < 0$ with*

$$\|S(t)\|_{L_c(C,C)} \le ce^{\alpha t}, \quad \textit{for all } \; t \ge 0,$$

and $q \in (0,1)$ and $\Delta \in (0,h)$ with the following properties.

(i) For all $\phi \in U_2$, $(\phi, \partial\phi) \in N_1$.

(ii) For all (ϕ,ξ) and (ϕ,ξ_1) in N_1, with $\xi(t) = \xi_1(t)$ on $[-h,-\Delta]$ and for all ρ, χ, χ_1 in C with $\chi(t) = \chi_1(t)$ on $[-h,-\Delta]$ we have

$$D_e f(\phi,\xi)(\rho,\chi) = D_e f(\phi,\xi_1)(\rho,\chi_1).$$

(iii) For all $\phi \in U_2$,

$$\|D_e f(\phi,\partial\phi)\|_{L_c(C\times C,\mathbb{R}^n)} \le c.$$

(iv) For all $\phi \in U_2$,

$$\|D_e f(\phi,\partial\phi)(\cdot,0)\|_{L_c(C,\mathbb{R}^n)} < q.$$

(v) For every $\varepsilon > 0$ there is a neighborhood $V_\varepsilon \subset U_2$ of 0 in C^2 such that, for all $\phi \in V_\varepsilon$ we have

$$|r(\phi)| \le \varepsilon \left(\|\phi\|_C + \max_{\Delta\le u\le h} |\dot\phi(-u)| \right).$$

Proof. The proof of (i)-(iv) stays unchanged and can be found in [130, Sec. 3].

Proof of (v): We choose a convex open neighborhood U_2 of 0 in C^2 so small that for all $\phi \in U_2$ we have $(\phi,\partial\phi) \in N_1$, and the estimates in (g8*) and (g9) hold, with functions $\vartheta : [0,\infty) \to [0,\infty)$ continuous at $0 = \vartheta(0)$, and $\zeta : [0,\infty) \to [0,\infty)$ continuous at $0 = \zeta(0)$.

The values $\Delta \in (0,h)$ and $c \geq 1$ (which might be taken from the first part of the proof) can be chosen so that for all $\phi \in U_2$,

$$|(Df(\phi,\partial\phi) - Df(0,0))\,(0,\partial\phi)| \leq\, c\,\|\partial\partial\phi\|_C\,\|\phi\|_C + c\vartheta\,(\|\phi\|_{C^1})\,\max_{\Delta\leq u\leq h}|\dot{\phi}(-u)|,$$

and

$$|(Df(\phi,\partial\phi) - Df(0,0))\,(\phi,0)|\,\leq\, c\,\{\zeta\,(\|\phi\|_{C^2})\,\|\phi\|_C + \|\phi\|_{C^1}\,\|\phi\|_C\}\,.$$

Then for $\phi \in U_2$, with (6.14) and conditions (g8*) and (g9), we obtain

$$\begin{aligned}|r(\phi)| \leq\ &\max_{0\leq s\leq 1}|\,(Df(s\phi,s\partial\phi) - Df(0,0))\,(0,\partial\phi)|\\&+\max_{0\leq s\leq 1}|\,(Df(s\phi,s\partial\phi) - Df(0,0))\,(\phi,0)|\\ \leq\ & c\Big(\|\partial\partial\phi\|_C\,\|\phi\|_C + \max_{0\leq s\leq 1}\vartheta\,(\|s\phi\|_{C^1})\,\max_{\Delta\leq u\leq h}|\dot{\phi}(-u)|\\&\qquad+\max_{0\leq s\leq 1}\{\zeta\,(\|s\phi\|_{C^2})\,\|\phi\|_C + \|\phi\|_{C^1}\,\|s\phi\|_C\}\Big).\end{aligned}$$

For $\varepsilon > 0$ we can find a value $\delta_\varepsilon > 0$ such that, for all $\phi \in U_2 \subset C^2$ with $\|\phi\|_{C^2} < \delta_\varepsilon$ we have $(\phi,\partial\phi) \in N_1$ and

$$c\,\{\|\partial\partial\phi\|_C + \vartheta\,(\|s\phi\|_{C^1}) + \zeta\,(\|s\phi\|_{C^2}) + \|\phi\|_{C^1}\} < \varepsilon, \qquad \text{for all}\ \ s \in [0,1].$$

□

We have thus introduced a new condition to replace (g8) in the set of hypotheses for linearized stability of neutral equations with state-dependent delay. An alternative condition was necessary, as (g8) turned out to be not satisfied by equations more general than those proposed in [130]. Because of the C^1-norm, the estimate in condition (g8*) is weaker that the one in (g8). Still, with (g8*) instead of (g8), the key result in Proposition 6.4 (v) and, consequently, Theorem 6.2 hold true. With this result, in Chapter 7 we shall study two classes of NFDEs with state-dependent delay more general than the class of equations (6.15).

At present there is no general theory for neutral equations with state-dependent delay. All results in [124, 129, 130] and in this thesis have been tested just on some classes of neutral equations with state-dependent delays. In the future it might happen that working on some more general examples, one has to further modify the above conditions or improve existing results.

6.4. Neutral Equations in Practice

In this section we consider a general class of neutral equations with state-dependent delay, given in an explicit form, as can be usually found in applications. We shall first show how to write these equations in the NFDE form, so that the results in Sections 6.1–6.3 can be applied. In the last part we discuss linearization of semiflows at nontrivial equilibria.

Without loss of generality in the sequel we consider the scalar case, $n = 1$. This means that we denote by C the space of continuous maps $\phi : [-h, 0] \to \mathbb{R}$ (analogously for C^1 and C^2).

6.4.1. Reduction to NFDEs

Let a value $h > 0$ and continuously differentiable functions $g : \mathbb{R}^3 \to \mathbb{R}$ and $\tau : \mathbb{R} \to (0, h)$ be given. Consider the class of neutral equations with state-dependent delay,

$$\dot{x}(t) = g(x(t), x(t - \tau(x(t))), \dot{x}(t - \tau(x(t)))). \tag{6.17}$$

Introducing the evaluation maps

$$\begin{aligned} \mathrm{ev} : C \times [0, h] \to \mathbb{R}, \quad (\xi, s) \mapsto \xi(s), \qquad & \mathrm{ev}_0 : C \to \mathbb{R}, \quad \phi \mapsto \phi(0), \\ \mathrm{Ev} : C^1 \times (0, h) \to \mathbb{R}, \quad (\phi, s) \mapsto \phi(s), \qquad & \mathrm{Ev}_0 : C^1 \to \mathbb{R}, \quad \phi \mapsto \phi(0), \end{aligned}$$

we define $f_0 : C^1 \times C \to \mathbb{R}$ by

$$f_0 = g \circ \big((\mathrm{Ev}_0 \circ \mathrm{pr}_1) \times (\mathrm{Ev} \circ (\mathrm{pr}_1 \times (-\tau \circ \mathrm{Ev}_0 \circ \mathrm{pr}_1))) \times (\mathrm{ev} \circ (\mathrm{pr}_2 \times (-\tau \circ \mathrm{Ev}_0 \circ \mathrm{pr}_1))) \big), \tag{6.18}$$

with the projections pr_1 and pr_2, onto the first and second component, respectively. Then, equation (6.17) can be rearranged in the form of a NFDE,

$$\dot{x}(t) = f_0(x_t, \partial x_t), \tag{6.19}$$

with f_0 in (6.18). However, as we have explained in Chapter 4, the map ev, defined on the space of continuous functions C, is not continuously differentiable. This fact prevents any result on the continuous differentiability of f_0. In order to analyze semiflows generated by a neutral equation with state-dependent delay, we restrict f_0 to the space $C^1 \times C^1$ and define $f = f_0\big|_{C^1 \times C^1}$. We use the evaluation map Ev, which is the restriction of ev to the space of continuously differentiable functions (cf. Chapter 4) and write (6.17) in the NFDE form (6.19), with right-hand side

$$f = g \circ \big((\mathrm{Ev}_0 \circ \mathrm{pr}_1) \times (\mathrm{Ev} \circ (\mathrm{pr}_1 \times (-\tau \circ \mathrm{Ev}_0 \circ \mathrm{pr}_1))) \times (\mathrm{Ev} \circ (\mathrm{pr}_2 \times (-\tau \circ \mathrm{Ev}_0 \circ \mathrm{pr}_1))) \big).$$

For future purposes it will be convenient to observe that, as g, τ and the evaluation maps Ev_0, Ev are continuously differentiable, f is continuously differentiable, too.

To simplify the notation, we set $\phi^0 = \phi(0)$ and $\tau^{\phi^0} = \tau(\phi^0) = \tau(\phi(0))$. Let $\partial_j g$ indicate the partial derivative of g with respect to the j-th component, $j = 1, 2, 3$. Then, for $\phi, \rho, \xi, \chi \in C^1$, the derivative $Df(\phi, \xi)(\rho, \chi)$ is given by

$$
\begin{aligned}
&Df(\phi,\xi)(\rho,\chi)\\
&= \partial_1 g\left(\phi^0, \phi(-\tau^{\phi^0}), \xi(-\tau^{\phi^0})\right) \cdot D(\mathrm{Ev}_0 \circ \mathrm{pr}_1)(\phi,\xi)(\rho,\chi)\\
&\quad + \partial_2 g\left(\phi^0, \phi(-\tau^{\phi^0}), \xi(-\tau^{\phi^0})\right) \cdot D\left[\mathrm{Ev} \circ (\mathrm{pr}_1 \times (-\tau \circ \mathrm{Ev}_0 \circ \mathrm{pr}_1))\right](\phi,\xi)(\rho,\chi)\\
&\quad + \partial_3 g\left(\phi^0, \phi(-\tau^{\phi^0}), \xi(-\tau^{\phi^0})\right) \cdot D\left[\mathrm{Ev} \circ (\mathrm{pr}_2 \times (-\tau \circ \mathrm{Ev}_0 \circ \mathrm{pr}_1))\right](\phi,\xi)(\rho,\chi)\\
&= \partial_1 g\left(\phi^0, \phi(-\tau^{\phi^0}), \xi(-\tau^{\phi^0})\right) \cdot D\,\mathrm{Ev}_0(\phi)\rho\\
&\quad + \partial_2 g\left(\phi^0, \phi(-\tau^{\phi^0}), \xi(-\tau^{\phi^0})\right) \cdot D\,\mathrm{Ev}(\phi, -\tau^{\phi^0}) \circ (\mathrm{pr}_1 \times ((-\dot\tau(\phi^0)) \cdot \mathrm{Ev}_0 \circ \mathrm{pr}_1))(\rho,\chi)\\
&\quad + \partial_3 g\left(\phi^0, \phi(-\tau^{\phi^0}), \xi(-\tau^{\phi^0})\right) \cdot D\,\mathrm{Ev}(\xi, -\tau^{\phi^0}) \circ (\mathrm{pr}_2 \times ((-\dot\tau(\phi^0)) \cdot \mathrm{Ev}_0 \circ \mathrm{pr}_1))(\rho,\chi)\\
&= \partial_1 g\left(\phi^0, \phi(-\tau^{\phi^0}), \xi(-\tau^{\phi^0})\right) \rho(0)\\
&\quad + \partial_2 g\left(\phi^0, \phi(-\tau^{\phi^0}), \xi(-\tau^{\phi^0})\right) D\,\mathrm{Ev}(\phi, -\tau^{\phi^0})(\rho, -\dot\tau(\phi^0)\rho(0))\\
&\quad + \partial_3 g\left(\phi^0, \phi(-\tau^{\phi^0}), \xi(-\tau^{\phi^0})\right) D\,\mathrm{Ev}(\xi, -\tau^{\phi^0})(\chi, -\dot\tau(\phi^0)\rho(0))\\
&= \partial_1 g\left(\phi^0, \phi(-\tau^{\phi^0}), \xi(-\tau^{\phi^0})\right) \rho(0)\\
&\quad + \partial_2 g\left(\phi^0, \phi(-\tau^{\phi^0}), \xi(-\tau^{\phi^0})\right) \left[D_1\,\mathrm{Ev}(\phi, -\tau^{\phi^0})\rho + D_2\,\mathrm{Ev}(\phi, -\tau^{\phi^0})\left[-\dot\tau(\phi^0)\rho(0)\right]\right]\\
&\quad + \partial_3 g\left(\phi^0, \phi(-\tau^{\phi^0}), \xi(-\tau^{\phi^0})\right) \left[D_1\,\mathrm{Ev}(\xi, -\tau^{\phi^0})\chi + D_2\,\mathrm{Ev}(\xi, -\tau^{\phi^0})\left[-\dot\tau(\phi^0)\rho(0)\right]\right]\\
&= \partial_1 g\left(\phi^0, \phi(-\tau^{\phi^0}), \xi(-\tau^{\phi^0})\right) \rho(0)\\
&\quad + \partial_2 g\left(\phi^0, \phi(-\tau^{\phi^0}), \xi(-\tau^{\phi^0})\right) \left[\rho(-\tau^{\phi^0}) - \dot\phi(-\tau^{\phi^0})\dot\tau(\phi^0)\rho(0)\right]\\
&\quad + \partial_3 g\left(\phi^0, \phi(-\tau^{\phi^0}), \xi(-\tau^{\phi^0})\right) \left[\chi(-\tau^{\phi^0}) - \dot\xi(-\tau^{\phi^0})\dot\tau(\phi^0)\rho(0)\right].
\end{aligned} \tag{6.20}
$$

6.4.2. Nontrivial Equilibria

Section 6.3 provides a principle of linearized stability for semiflows generated by NFDEs with state-dependent delay, under the assumption that $0 \in X_{2*} \subset C^2$ is a stationary point of the semiflow G_2 (cf. p. 81). However, in applications one is often also interested in the stability properties of nontrivial stationary points.

In the following we consider a nontrivial stationary point $\bar\phi \in X_{2*} \subset C^2$ and show that Theorem 6.2 can be applied as well in order to determine linearized stability of the semiflow G_2.

Consider again equation (6.17), with continuously differentiable functions $g : \mathbb{R}^3 \to \mathbb{R}$ and $\tau : \mathbb{R} \to (0, h)$, $h > 0$. We write (6.17) the form of a NFDE,

$$\dot{x}(t) = f(x_t, \partial x_t), \tag{6.21}$$

with $f : C^1 \times C^1 \to \mathbb{R}$ defined by

$$f(\phi, \xi) = g \circ \big((\mathrm{Ev}_0 \circ \mathrm{pr}_1) \times (\mathrm{Ev} \circ (\mathrm{pr}_1 \times (-\tau \circ \mathrm{Ev}_0 \circ \mathrm{pr}_1))) \times (\mathrm{Ev} \circ (\mathrm{pr}_2 \times (-\tau \circ \mathrm{Ev}_0 \circ \mathrm{pr}_1)))\big)(\phi, \xi).$$

Assume that f satisfies (g0)-(g3), (g6), (g8*) and (g9), and that all the hypotheses of Theorem 6.2 are fulfilled. Then, for Theorem 6.2 the trivial equilibrium $0 \in X_{2*} \subset C^2$ of the semiflow G_2 (generated by solution of (6.21)) is stable and attracting.

Let us now assume that there exists a nontrivial equilibrium $\bar{\phi} \in X_{2*} \subset C^2$ of the semiflow G_2. This means that there is a value $\bar{x} \in \mathbb{R}$ such that $\bar{\phi} : [-h, 0] \ni s \to \bar{\phi}(s) = \bar{x} \in \mathbb{R}$, $\partial \bar{\phi} \equiv 0$ and

$$f(\bar{\phi}, 0) = g(\bar{x}, \bar{x}, 0) = 0.$$

We are interested in stability properties of the nontrivial equilibrium $\bar{\phi}$ of G_2.

To this purpose, we define the map

$$\bar{f} : C^1 \times C^1 \to \mathbb{R}, \quad (\phi, \xi) \mapsto \bar{f}(\phi, \xi) = f(\phi + \bar{\phi}, \xi). \tag{6.22}$$

Proposition 6.5. *The map $\bar{f}$ in (6.22) satisfies (g0)–(g3), (g6), (g8*) and (g9).*

Proof. To make the notation less cumbersome, we define

$$\phi^{\bar{x}} := \phi(0) + \bar{x}, \quad \tau^{\bar{x}} := \tau(\phi^{\bar{x}}) = \tau(\phi(0) + \bar{x}),$$

$$\phi^{\bar{x}}_s := s\phi(0) + \bar{x}, \quad \tau^{\bar{x}}_s := \tau(\phi^{\bar{x}}_s) = \tau(s\phi(0) + \bar{x}).$$

Before proceeding with the proof we make some useful observations. First we notice that for ψ, $\rho \in C^1$, $z \in [-h, 0]$, we have

$$D_1 \mathrm{Ev}(\psi + \bar{\phi}, z)\rho = \rho(z), \;\; D_2 \mathrm{Ev}(\psi + \bar{\phi}, z)1 = \dot{\psi}(z),$$

and $D\,\mathrm{Ev}_0(\psi + \bar{\phi})\rho = \rho(0)$. We introduce the map $\sigma = \sigma_{\bar{\phi}}$,

$$\sigma : C^1 \times C^1 \to C^1 \times C^1, \quad (\phi, \xi) \mapsto (\phi + \bar{\phi}, \xi),$$

which is obviously continuously differentiable. Next we observe that the maps $C^1 \times C^1 \to \mathbb{R}$,

$$\begin{aligned}
(\phi, \xi) &\mapsto \big(\mathrm{Ev}_0 \circ \mathrm{pr}_1 \circ \sigma\big)(\phi, \xi) = \phi^{\bar{x}}, \\
(\phi, \xi) &\mapsto \big(\mathrm{Ev} \circ \big(\mathrm{pr}_1 \times (-\tau \circ \mathrm{Ev}_0 \circ \mathrm{pr}_1)\big) \circ \sigma\big)(\phi, \xi) = \phi(-\tau^{\bar{x}}) + \bar{x}, \\
(\phi, \xi) &\mapsto \big(\mathrm{Ev} \circ \big(\mathrm{pr}_2 \times (-\tau \circ \mathrm{Ev}_0 \circ \mathrm{pr}_1)\big) \circ \sigma\big)(\phi, \xi) = \xi(-\tau^{\bar{x}}),
\end{aligned}$$

are all continuously differentiable with

$$\begin{aligned}
&D\big(\mathrm{Ev}_0\circ\mathrm{pr}_1\circ\sigma\big)(\phi,\xi)(\rho,\chi)\\
&\qquad = D\,\mathrm{Ev}_0(\phi+\bar\phi)\rho=\rho(0),\\
&D\big(\mathrm{Ev}\circ\big(\mathrm{pr}_1\times(-\tau\circ\mathrm{Ev}_0\circ\mathrm{pr}_1)\big)\circ\sigma\big)(\phi,\xi)(\rho,\chi)\\
&\qquad = D\,\mathrm{Ev}\big(\phi+\bar\phi,-\tau^{\bar x}\big)\circ\big(\mathrm{pr}_1,-\dot\tau(\phi^{\bar x})D\,\mathrm{Ev}_0(\phi+\bar\phi)\circ\mathrm{pr}_1\big)(\rho,\chi)\\
&\qquad = D\,\mathrm{Ev}\big(\phi+\bar\phi,-\tau^{\bar x}\big)\big(\rho,-\dot\tau(\phi^{\bar x})\rho(0)\big),\\
&D\big(\mathrm{Ev}\circ\big(\mathrm{pr}_2\times(-\tau\circ\mathrm{Ev}_0\circ\mathrm{pr}_1)\big)\circ\sigma\big)(\phi,\xi)(\rho,\chi)\\
&\qquad = D\,\mathrm{Ev}\big(\xi,-\tau^{\bar x}\big)\circ\big(\mathrm{pr}_2,-\dot\tau(\phi^{\bar x})D\,\mathrm{Ev}_0(\phi+\bar\phi)\circ\mathrm{pr}_1\big)(\rho,\chi)\\
&\qquad = D\,\mathrm{Ev}\big(\xi,-\tau^{\bar x}\big)\big(\chi,-\dot\tau(\phi^{\bar x})\rho(0)\big),
\end{aligned}\tag{6.23}$$

for all ϕ, ξ, ρ, $\chi\in C^1$.

Now we verify the hypotheses on the right-hand side.

(g0) Condition (g0) is satisfied, $\bar f$ being the composite of continuous maps:

$$C^1\times C^1\ni(\phi,\xi)\mapsto\bar f(\phi,\xi)=f\circ\sigma(\phi,\xi)\in\mathbb{R}.$$

(g1) We notice that this condition involves only the second argument of the right-hand side. For all $(\phi,\xi)\in C^1\times C^1$ we have $\bar f(\phi,\xi)=f(\phi+\bar\phi,\xi)$. Hence, $\bar f$ and f have the same second argument. We assumed that f has property (g1), consequently also $\bar f$ has property (g1).

(g2) For Proposition 6.1, it suffices to prove that $\bar f$ satisfies (g3).

(g3) For ϕ, ξ, ρ, $\chi\in C^1\times C^1$, with (6.20) and (6.23) we get

$$\begin{aligned}
&D\bar f(\phi,\xi)(\rho,\chi)\\
&= Df(\phi+\bar\phi,\xi)\cdot D\sigma(\phi,\xi)(\rho,\chi)\\
&= Df(\phi+\bar\phi,\xi)(\rho,\chi)\\
&= \partial_1 g\big(\phi^{\bar x},\phi(-\tau^{\bar x})+\bar x,\xi(-\tau^{\bar x})\big)\rho(0)\\
&\quad+\partial_2 g\big(\phi^{\bar x},\phi(-\tau^{\bar x})+\bar x,\xi(-\tau^{\bar x})\big)\Big[\rho(-\tau^{\bar x})-\dot\phi(-\tau^{\bar x})\dot\tau(\phi^{\bar x})\rho(0)\Big]\\
&\quad+\partial_3 g\big(\phi^{\bar x},\phi(-\tau^{\bar x})+\bar x,\xi(-\tau^{\bar x})\big)\Big[\chi(-\tau^{\bar x})-\dot\xi(-\tau^{\bar x})\dot\tau(\phi^{\bar x})\rho(0)\Big].
\end{aligned}\tag{6.24}$$

Then for $(\rho,\chi)\in C\times C$ we define $D_e\bar f(\phi,\xi)(\rho,\chi)$ by (6.24). The map

$$C^1\times C^1\times C\times C\ni(\phi,\xi,\rho,\chi)\mapsto D_e\bar f(\phi,\xi)(\rho,\chi)\in\mathbb{R}$$

is continuous, being a composite of continuous maps.

(g6) $\bar{f}(0,0) = f \circ \sigma(0,0) = f(\bar{\phi},0) = 0$, as we assumed that $(\bar{\phi},0)$ is a fixed point of f.

For all $(\phi,\xi) \in C^1 \times C^1$ and all $\chi \in C$, we have

$$D_e\bar{f}(\phi,\xi)(0,\chi) = \partial_3 g\big(\phi^{\bar{x}}, \phi(-\tau^{\bar{x}}) + \bar{x}, \xi(-\tau^{\bar{x}})\big)\chi(-\tau^{\bar{x}}).$$

Consequently,

$$\begin{aligned}\|D_e\bar{f}(\phi,\xi)(0,\cdot)\|_{L_c(C,\mathbb{R})} &= \big|\partial_3 g\big(\phi^{\bar{x}}, \phi(-\tau^{\bar{x}}) + \bar{x}, \xi(-\tau^{\bar{x}})\big)\big| \\ &= \Bigg|\Bigg(\partial_3 g\big((\mathrm{Ev}_0 \circ \mathrm{pr}_1) \times (\mathrm{Ev} \circ (\mathrm{pr}_1 \times (-\tau \circ \mathrm{Ev}_0 \circ \mathrm{pr}_1))) \\ &\qquad \times (\mathrm{Ev} \circ (\mathrm{pr}_2 \times (-\tau \circ \mathrm{Ev}_0 \circ \mathrm{pr}_1)))\big) \circ \sigma\Bigg)(\phi,\xi)\Bigg|.\end{aligned}$$

As f has property (g6), the map $C^1 \times C^1 \to \mathbb{R}$,

$$\begin{aligned}(\phi,\xi) \mapsto \partial_3 g\big(&(\mathrm{Ev}_0 \circ \mathrm{pr}_1) \times (\mathrm{Ev} \circ (\mathrm{pr}_1 \times (-\tau \circ \mathrm{Ev}_0 \circ \mathrm{pr}_1))) \\ &\times (\mathrm{Ev} \circ (\mathrm{pr}_2 \times (-\tau \circ \mathrm{Ev}_0 \circ \mathrm{pr}_1)))\big)\,(\phi,\xi)\end{aligned}$$

is upper semicontinuous at $(0,0)$. With the continuity of σ the proof of (g6) is completed.

(g8*) For all $\phi \in C^2$, with $\|\phi\|_{C^2} \le 1$ and for $s \in [0,1]$, from (6.24) we obtain

$$\begin{aligned}&\big|\big(D\bar{f}(s\phi, s\partial\phi) - D\bar{f}(0,0)\big)(0,\partial\phi)\big| \\ &= \big|\partial_3 g\big(\phi_s^{\bar{x}}, s\phi(-\tau_s^{\bar{x}}) + \bar{x}, s\dot{\phi}(-\tau_s^{\bar{x}})\big)\dot{\phi}(-\tau_s^{\bar{x}}) - \partial_3 g(\bar{x},\bar{x},0)\dot{\phi}(-\tau(\bar{x}))\big| \\ &\le \big|\partial_3 g\big(\phi_s^{\bar{x}}, s\phi(-\tau_s^{\bar{x}}) + \bar{x}, s\dot{\phi}(-\tau_s^{\bar{x}})\big)\big|\big|\dot{\phi}(-\tau_s^{\bar{x}}) - \dot{\phi}(-\tau(\bar{x}))\big| \\ &\quad + \Big[\big|\partial_3 g\big(\phi_s^{\bar{x}}, s\phi(-\tau_s^{\bar{x}}) + \bar{x}, s\dot{\phi}(-\tau_s^{\bar{x}})\big) - \partial_3 g\big(\phi_s^{\bar{x}}, s\phi(-\tau_s^{\bar{x}}) + \bar{x}, 0\big)\big| \\ &\qquad + \big|\partial_3 g\big(\phi_s^{\bar{x}}, s\phi(-\tau_s^{\bar{x}}) + \bar{x}, 0\big) - \partial_3 g\big(\phi_s^{\bar{x}}, \bar{x}, 0\big)\big| \\ &\qquad + \big|\partial_3 g\big(\phi_s^{\bar{x}}, \bar{x}, 0\big) - \partial_3 g\big(\bar{x}, \bar{x}, 0\big)\big|\Big] \max_{\tau(\bar{x}) \le u \le h} |\dot{\phi}(-u)| \\ &\le \max_{\substack{|\nu|, |\nu_1| \le \|s\phi\|_C \\ |\eta| \le \|s\partial\phi\|_C}} \big|\partial_3 g\big(\nu + \bar{x}, \nu_1 + \bar{x}, \eta\big)\big| \, \|\partial\partial\phi\|_C \max_{|u| \le \|s\phi\|_C} |\dot{\tau}(u + \bar{x})| \, \|s\phi\|_C \\ &\quad + \Bigg[\max_{\substack{|\nu|, |\nu_1| \le \|s\phi\|_C \\ |\eta| \le \|s\partial\phi\|_C}} \big|\partial_3 g(\nu + \bar{x}, \nu_1 + \bar{x}, \eta) - \partial_3 g(\nu + \bar{x}, \nu_1 + \bar{x}, 0)\big| \\ &\qquad + \max_{\substack{|\nu| \le \|s\phi\|_C \\ |\nu_1| \le \|s\phi\|_C}} \big|\partial_3 g(\nu + \bar{x}, \nu_1 + \bar{x}, 0) - \partial_3 g(\nu + \bar{x}, \bar{x}, 0)\big| \\ &\qquad + \max_{|\nu| \le \|s\phi\|_C} \big|\partial_3 g(\nu + \bar{x}, \bar{x}, 0) - \partial_3 g(\bar{x}, \bar{x}, 0)\big|\Bigg] \max_{\tau(\bar{x}) \le u \le h} |\dot{\phi}(-u)|.\end{aligned}$$

For $c_1 = \max_{\substack{|y_j| \le 1 \\ j=1,2,3}} \big|\partial_3 g(y_1 + \bar{x}, y_2 + \bar{x}, y_3)\big| \max_{|u| \le 1} |\dot{\tau}(u + \bar{x})|, \quad \Delta = \tau(\bar{x}) \in (0,h)$

and $\vartheta : [0, \infty) \to [0, \infty)$ given by

$$\vartheta(z) = \Bigg[\max_{\substack{|y_j| \le z \\ j=1,2,3}} \big|\partial_3 g(y_1 + \bar{x}, y_2 + \bar{x}, y_3) - \partial_3 g(y_1 + \bar{x}, y_2 + \bar{x}, 0)\big|$$

$$+ \max_{\substack{|y_j| \le z \\ j=1,2}} \big|\partial_3 g(y_1 + \bar{x}, y_2 + \bar{x}, 0) - \partial_3 g(y_1 + \bar{x}, \bar{x}, 0)\big| + \max_{|y_1| \le z} \big|\partial_3 g(y_1 + \bar{x}, \bar{x}, 0) - \partial_3 g(\bar{x}, \bar{x}, 0)\big| \Bigg],$$

we obtain the estimate in (g8*).

(g9) For all $\phi \in C^2$, with $\|\phi\|_{C^2} \le 1$ and for $s \in [0, 1]$, from (6.24) we obtain

$$\begin{aligned}
&\big|\big(D\bar{f}(s\phi, s\partial\phi) - D\bar{f}(0,0)\big)(\phi, 0)\big| \\
&\le \big|\partial_1 g\big(\phi_s^{\bar{x}}, s\phi(-\tau_s^{\bar{x}}) + \bar{x}, s\dot{\phi}(-\tau_s^{\bar{x}})\big)\phi(0) - \partial_1 g(\bar{x}, \bar{x}, 0)\phi(0)\big| \\
&\quad + \big|\partial_2 g\big(\phi_s^{\bar{x}}, s\phi(-\tau_s^{\bar{x}}) + \bar{x}, s\dot{\phi}(-\tau_s^{\bar{x}})\big)\phi(-\tau_s^{\bar{x}}) - \partial_2 g(\bar{x}, \bar{x}, 0)\phi(-\tau(\bar{x}))\big| \\
&\quad + \big|\partial_2 g\big(\phi_s^{\bar{x}}, s\phi(-\tau_s^{\bar{x}}) + \bar{x}, s\dot{\phi}(-\tau_s^{\bar{x}})\big)s\dot{\phi}(-\tau_s^{\bar{x}})\dot{\tau}(\phi_s^{\bar{x}})\phi(0)\big| \\
&\quad + \big|\partial_3 g\big(\phi_s^{\bar{x}}, s\phi(-\tau_s^{\bar{x}}) + \bar{x}, s\dot{\phi}(-\tau_s^{\bar{x}})\big)s\ddot{\phi}(-\tau_s^{\bar{x}})\dot{\tau}(\phi_s^{\bar{x}})\phi(0)\big| \\
&\le \Bigg[\max_{\substack{|\nu|, |\nu_1| \le \|s\phi\|_C \\ |\eta| \le \|s\partial\phi\|_C}} \big|\partial_1 g(\nu + \bar{x}, \nu_1 + \bar{x}, \eta) - \partial_1 g(\nu + \bar{x}, \nu_1 + \bar{x}, 0)\big| \\
&\qquad + \max_{\substack{|\nu| \le \|s\phi\|_C \\ |\nu_1| \le \|s\phi\|_C}} \big|\partial_1 g(\nu + \bar{x}, \nu_1 + \bar{x}, 0) - \partial_1 g(\nu + \bar{x}, \bar{x}, 0)\big| \\
&\qquad + \max_{|\nu| \le \|s\phi\|_C} \big|\partial_1 g(\nu + \bar{x}, \bar{x}, 0) - \partial_1 g(\bar{x}, \bar{x}, 0)\big| \Bigg] \|\phi\|_C \\
&\quad + \max_{\substack{|\nu|, |\nu_1| \le \|s\phi\|_C \\ |\eta| \le \|s\partial\phi\|_C}} \big|\partial_2 g\big(\nu + \bar{x}, \nu_1 + \bar{x}, \eta\big)\big| \, \|\partial\phi\|_C \max_{|u| \le \|s\phi\|_C} |\dot{\tau}(u + \bar{x})| \, \|s\phi\|_C \\
&\quad + \Bigg[\max_{\substack{|\nu|, |\nu_1| \le \|s\phi\|_C \\ |\eta| \le \|s\partial\phi\|_C}} \big|\partial_2 g(\nu + \bar{x}, \nu_1 + \bar{x}, \eta) - \partial_2 g(\nu + \bar{x}, \nu_1 + \bar{x}, 0)\big| \\
&\qquad + \max_{\substack{|\nu| \le \|s\phi\|_C \\ |\nu_1| \le \|s\phi\|_C}} \big|\partial_2 g(\nu + \bar{x}, \nu_1 + \bar{x}, 0) - \partial_2 g(\nu + \bar{x}, \bar{x}, 0)\big| \\
&\qquad + \max_{|\nu| \le \|s\phi\|_C} \big|\partial_2 g(\nu + \bar{x}, \bar{x}, 0) - \partial_2 g(\bar{x}, \bar{x}, 0)\big| \Bigg] \|\phi\|_C \\
&\quad + \max_{\substack{|\nu|, |\nu_1| \le \|s\phi\|_C \\ |\eta| \le \|s\partial\phi\|_C}} \big|\partial_2 g\big(\nu + \bar{x}, \nu_1 + \bar{x}, \eta\big)\big| \, \|s\partial\phi\|_C \max_{|u| \le \|s\phi\|_C} |\dot{\tau}(u + \bar{x})| \, \|\phi\|_C \\
&\quad + \max_{\substack{|\nu|, |\nu_1| \le \|s\phi\|_C \\ |\eta| \le \|s\partial\phi\|_C}} \big|\partial_3 g\big(\nu + \bar{x}, \nu_1 + \bar{x}, \eta\big)\big| \, \|s\partial\partial\phi\|_C \max_{|u| \le \|s\phi\|_C} |\dot{\tau}(u + \bar{x})| \, \|\phi\|_C \,.
\end{aligned}$$

To obtain the desired estimate define the value

$$c = \left(\max_{\substack{|z_j|\le 1\\ j=1,2,3}} |\partial_2 g(z_1+\bar{x}, z_2+\bar{x}, z_3)| + \max_{\substack{|z_j|\le 1\\ j=1,2,3}} |\partial_3 g(z_1+\bar{x}, z_2+\bar{x}, z_3)| \right) \max_{|z|\le 1} |\dot{\tau}(z+\bar{x})| + 1,$$

and the function $\zeta : [0,\infty) \to [0,\infty)$ given by

$$\begin{aligned}
\zeta(y) =& y + \Bigg[\max_{\substack{|\nu_j|\le y\\ j=1,2,3}} \left|\partial_1 g(\nu_1+\bar{x}, \nu_2+\bar{x}, \nu_3) - \partial_1 g(\nu_1+\bar{x}, \nu_2+\bar{x}, 0)\right| \\
&\quad + \max_{\substack{|\nu_j|\le y\\ j=1,2}} \left|\partial_1 g(\nu_1+\bar{x}, \nu_2+\bar{x}, 0) - \partial_1 g(\nu_1+\bar{x}, \bar{x}, 0)\right| \\
&\quad + \max_{|\nu_1|\le y} \left|\partial_1 g(\nu_1+\bar{x}, \bar{x}, 0) - \partial_1 g(\bar{x}, \bar{x}, 0)\right| \Bigg] \\
&+ \Bigg[\max_{\substack{|\nu_j|\le y\\ j=1,2,3}} \left|\partial_2 g(\nu_1+\bar{x}, \nu_2+\bar{x}, \nu_3) - \partial_2 g(\nu_1+\bar{x}, \nu_2+\bar{x}, 0)\right| \\
&\quad + \max_{\substack{|\nu_j|\le y\\ j=1,2}} \left|\partial_2 g(\nu_1+\bar{x}, \nu_2+\bar{x}, 0) - \partial_2 g(\nu_1+\bar{x}, \bar{x}, 0)\right| \\
&\quad + \max_{|\nu_1|\le y} \left|\partial_2 g(\nu_1+\bar{x}, \bar{x}, 0) - \partial_2 g(\bar{x}, \bar{x}, 0)\right| \Bigg].
\end{aligned}$$

□

Consider the neutral equation

$$\dot{x}(t) = \bar{f}(x_t, \partial x_t), \tag{6.25}$$

with $\bar{f} : C^1 \times C^1 \to \mathbb{R}$, defined by (6.22). Proposition 6.5 states that $\bar{f}$ satisfies all properties (g0)-(g3), (g6), (g8*) and (g9). Let condition (6.16) hold for $\bar{f}$, that is,

$$\|D_e \bar{f}(0,0)(0,\cdot)\|_{L_c(C,\mathbb{R})} = \left|\partial_3 g(\bar{x},\bar{x},0)\right| < 1.$$

Further, assume that there are values $c \ge 1$ and $\alpha < 0$ such that

$$\|S_{\bar{f}}(t)\chi\|_C \le c e^{\alpha t} \|\chi\|_C, \quad \text{for all } t \ge 0,\ \chi \in C,$$

with the operator $S_{\bar{f}}(t)$, defined by the linear problem associated to (6.25) (cf. p. 86).

Then, Theorem 6.2 holds and $0 \in X_{2*,\bar{f}}$ is a stable and attracting fixed point of the semiflow $G_{2,\bar{f}}$ generated by solutions of (6.25). This means that $\bar{\phi} \in X_{2*}$ is a stable and attracting fixed point of the semiflow $G_2 = G_{2,f}$, generated by solutions of the neutral equation (6.21). Hence, we have shown that Theorem 6.2 can be used for linearization at nontrivial fixed points of semiflows generated by neutral equations with state-dependent delay.

7. Two Classes of Neutral Equations with State-Dependent Delay

In this chapter we introduce two classes of neutral equations with state-dependent delay and use the theory in Chapter 6 to investigate existence, uniqueness and smoothness, as well as linearized stability of solutions. Our equations are more general than the classes of equations (6.8) and (6.15) in [129, 130]. We shall show that both our classes of neutral equations satisfy hypotheses (g0)-(g3), (g6), (g9) and the newly introduced condition (g8*), instead of (g8). For both classes of NFDEs we will present examples inspired by biology. In this context we analyze solution semiflows generated by the neutral equation (3.24) in Chapter 3.

In the sequel, whenever the notation gets too cumbersome, we shall use the abbreviations ϕ^0, ϕ^0_s, τ^{ϕ^0}, $\tau^{\phi^0}_s$ for $\phi(0)$, $s\phi(0)$, $\tau(\phi(0))$ and $\tau(s\phi(0))$, respectively.

7.1. First Class of Neutral Equations

In this section we consider neutral equations with state-dependent delay of the form

$$\dot{x}(t) = \sum_{j=1}^{3} q_j\big(x(t), x(t-\tau(x(t))), \dot{x}(t-\tau(x(t)))\big), \tag{7.1}$$

with $\tau : \mathbb{R} \to (0, h)$ continuously differentiable. Inspired by an example from biology (cf. Section 7.1.3), we have chosen a right-hand side which is the sum of three terms. A similar analysis could be done if the right-hand side is a sum of n terms. The terms $q_j : \mathbb{R}^3 \to \mathbb{R}$, $j \in \{1, 2, 3\}$ are defined by

$$(w, y, z) \mapsto p_{j,1}(w)p_{j,2}(y)p_{j,3}(z),$$

with continuously differentiable components $p_{j,i} : \mathbb{R} \to \mathbb{R}$, such that for all $j \in \{1, 2, 3\}$, $p_{j,k}(0) = 0$ for some $k \in \{1, 2, 3\}$ and $p_{j,l}(0) \neq 0$ for $l \in \{1, 2, 3\}$, $l \neq k$.

Equation (7.1) can be written in the NFDE form,

$$\dot{x}(t) = f(x_t, \partial x_t),$$

with

$$f : C^1 \times C^1 \ni (\phi, \xi) \mapsto f(\phi, \xi) = \sum_{j=1}^{3} q_j\big(\phi(0), \phi(-\tau(\phi(0))), \xi(-\tau(\phi(0)))\big) \in \mathbb{R}. \tag{7.2}$$

7.1.1. An Intermediate Step

The analysis of (7.2) is easier if we first investigate the case in which f has only one component.

Theorem 7.1. *Consider a function* $q : \mathbb{R}^3 \to \mathbb{R}$,

$$(w, y, z) \mapsto q(w, y, z) = p_1(w)p_2(y)p_3(z),$$

with continuously differentiable factors $p_j : \mathbb{R} \to \mathbb{R}$, $j \in \{1, 2, 3\}$, *such that* $p_j(0) = 0$ *for some* $j \in \{1, 2, 3\}$ *and* $p_l(0) \neq 0$ *for* $l \in \{1, 2, 3\}$, $l \neq j$. *Let* $\tau : \mathbb{R} \to (0, h)$ *be continuously differentiable.*

Then the map $f : C^1 \times C^1 \to \mathbb{R}$, *given by*

$$(\phi, \xi) \mapsto f(\phi, \xi) = q\big(\phi(0), \phi(-\tau(\phi(0))), \xi(-\tau(\phi(0)))\big), \tag{7.3}$$

satisfies (g0)–(g3), (g6), (g8) and (g9).*

Proof. For the definition of f we have

$$f = q \circ \big((\mathrm{Ev}_0 \circ \mathrm{pr}_1) \times (\mathrm{Ev} \circ (\mathrm{pr}_1 \times (-\tau \circ \mathrm{Ev}_0 \circ \mathrm{pr}_1))) \times (\mathrm{Ev} \circ (\mathrm{pr}_2 \times (-\tau \circ \mathrm{Ev}_0 \circ \mathrm{pr}_1)))\big).$$

(g0) The map f in (7.3) is continuous as q (which is the product of continuous functions), the delay function τ and the evaluation maps Ev_0, Ev are continuous.

(g1) Let $\phi \in C^1$ be given. There is a value $\Delta \in (0, h)$ such that $\tau(\mathrm{Ev}_0(\phi)) = \tau(\phi(0)) \in (\Delta, h)$. For the continuity of τ and Ev_0, there exists a neighborhood V of ϕ, $V \subset C^1$, such that for all $\psi \in V$ we have $\tau(\mathrm{Ev}_0(\psi)) = \tau(\psi(0)) \in (\Delta, h)$.

Then for all $\psi \in V$ and all $\xi_1, \xi_2 \in C^1$, such that $\xi_1(t) = \xi_2(t)$ for $t \in [-h, -\Delta]$ we get

$$\begin{aligned} f(\psi, \xi_1) &= q\big(\psi(0), \psi(-\tau(\psi(0))), \xi_1(-\tau(\psi(0)))\big) \\ &= p_1(\psi(0))p_2(\psi(-\tau(\psi(0))))p_3(\xi_1(-\tau(\psi(0)))) \\ &= p_1(\psi(0))p_2(\psi(-\tau(\psi(0))))p_3(\xi_2(-\tau(\psi(0)))) \\ &= q\big(\psi(0), \psi(-\tau(\psi(0))), \xi_2(-\tau(\psi(0)))\big) \\ &= f(\psi, \xi_2). \end{aligned}$$

(g2) With Proposition 6.1 and the proof of (g3) below, condition (g2') holds for f. It is not further necessary to verify (g2).

(g3) For ϕ, ξ, χ, $\rho \in C^1$ we have (cf. p. 94)

$$\begin{aligned}
&Df(\phi,\xi)(\rho,\chi)\\
&= \partial_1 q\left(\phi^0, \phi(-\tau^{\phi^0}), \xi(-\tau^{\phi^0})\right)\cdot D(\mathrm{ev}_0\circ \mathrm{pr}_1)(\phi,\xi)(\rho,\chi)\\
&\quad + \partial_2 q\left(\phi^0, \phi(-\tau^{\phi^0}), \xi(-\tau^{\phi^0})\right)\cdot D\left[\mathrm{ev}\circ(\mathrm{pr}_1\times(-\tau\circ \mathrm{ev}_0\circ \mathrm{pr}_1))\right](\phi,\xi)(\rho,\chi)\\
&\quad + \partial_3 q\left(\phi^0, \phi(-\tau^{\phi^0}), \xi(-\tau^{\phi^0})\right)\cdot D\left[\mathrm{ev}\circ(\mathrm{pr}_2\times(-\tau\circ \mathrm{ev}_0\circ \mathrm{pr}_1))\right](\phi,\xi)(\rho,\chi)\\
&= \partial_1 q\left(\phi^0, \phi(-\tau^{\phi^0}), \xi(-\tau^{\phi^0})\right)\cdot \mathrm{ev}_0\circ \mathrm{pr}_1(\rho,\chi)\\
&\quad + \partial_2 q\left(\phi^0, \phi(-\tau^{\phi^0}), \xi(-\tau^{\phi^0})\right)\cdot D\,\mathrm{Ev}(\phi,-\tau^{\phi^0})\circ(\mathrm{pr}_1,\times(-\dot\tau(\phi^0)\cdot \mathrm{ev}_0\circ \mathrm{pr}_1))(\rho,\chi)\\
&\quad + \partial_3 q\left(\phi^0, \phi(-\tau^{\phi^0}), \xi(-\tau^{\phi^0})\right)\cdot D\,\mathrm{Ev}(\xi,-\tau^{\phi^0})\circ(\mathrm{pr}_2\times(-\dot\tau(\phi^0)\cdot \mathrm{ev}_0\circ \mathrm{pr}_1))(\rho,\chi)\\
&= \partial_1 q\left(\phi^0, \phi(-\tau^{\phi^0}), \xi(-\tau^{\phi^0})\right)\cdot \mathrm{ev}_0(\rho)\\
&\quad + \partial_2 q\left(\phi^0, \phi(-\tau^{\phi^0}), \xi(-\tau^{\phi^0})\right)\cdot D\,\mathrm{Ev}(\phi,-\tau^{\phi^0})\circ(\rho,-\dot\tau(\phi^0)\rho(0))\\
&\quad + \partial_3 q\left(\phi^0, \phi(-\tau^{\phi^0}), \xi(-\tau^{\phi^0})\right)\cdot D\,\mathrm{Ev}(\xi,-\tau^{\phi^0})\circ(\chi,-\dot\tau(\phi^0)\rho(0))\\
&= \dot p_1(\phi^0)p_2(\phi(-\tau^{\phi^0}))p_3(\xi(-\tau^{\phi^0}))\rho(0)\\
&\quad + p_1(\phi^0)\dot p_2(\phi(-\tau^{\phi^0}))p_3(\xi(-\tau^{\phi^0}))\left[\rho(-\tau^{\phi^0}) - \dot\phi(-\tau^{\phi^0})\dot\tau(\phi^0)\rho(0)\right]\\
&\quad + p_1(\phi^0)p_2(\phi(-\tau^{\phi^0}))\dot p_3(\xi(-\tau^{\phi^0}))\left[\chi(-\tau^{\phi^0}) - \dot\xi(-\tau^{\phi^0})\dot\tau(\phi^0)\rho(0)\right].
\end{aligned} \tag{7.4}$$

For $\phi,\xi \in C^1$ and $\rho,\chi \in C$ we define the map $D_e f(\phi,\xi)$ by (7.4). Recall that the delay function τ and the factors p_j, $j \in \{1,2,3\}$ are continuously differentiable, the evaluation maps Ev, Ev_0, ev_0 are continuous. Hence, the map

$$C^1\times C^1\times C\times C \ni (\phi,\xi,\rho,\chi)\mapsto D_e f(\phi,\xi)(\rho,\chi)\in\mathbb{R}$$

is continuous (indeed, each component of the sum in $D_e f(\phi,\xi)(\rho,\chi)$ is continuous).

(g6) As $p_j(0) = 0$ for some $j \in \{1,2,3\}$, we have $f(0,0) = q(0,0,0) = 0$.

For all $\phi,\xi \in C^1$ and all $\chi \in C$, we get

$$D_e f(\phi,\xi)(0,\chi) = p_1(\phi^0)p_2(\phi(-\tau^{\phi^0}))\dot p_3(\xi(-\tau^{\phi^0}))\chi(-\tau^{\phi^0}).$$

Thus, for all $\phi, \xi \in C^1$,

$$\begin{aligned}
&\|D_e f(\phi,\xi)(0,\cdot)\|_{L_c(C,\mathbb{R})}\\
&= \sup_{\|\chi\|_C \le 1} \left| p_1(\phi^0) p_2(\phi(-\tau^{\phi^0})) \dot p_3(\xi(-\tau^{\phi^0}))\chi(-\tau^{\phi^0}) \right|\\
&= \left| p_1(\phi^0) p_2\big(\phi(-\tau^{\phi^0})\big) \dot p_3\big(\xi(-\tau^{\phi^0})\big) \right|\\
&= \left| p_1\big(\mathrm{Ev}_0(\phi)\big) p_2\big(\mathrm{Ev}(\phi, -\tau(\mathrm{Ev}_0(\phi)))\big) \dot p_3\big(\mathrm{Ev}(\xi, -\tau(\mathrm{Ev}_0(\phi)))\big) \right|.
\end{aligned}$$

The factors $p_j, j = 1,2,3$, and the delay τ are continuously differentiable functions, whereas the evaluation maps Ev, Ev_0 are continuous. It follows that the map

$$C^1 \times C^1 \to \mathbb{R},\ (\phi,\xi) \mapsto \|D_e f(\phi,\xi)(0,\cdot)\|_{L_c(C,\mathbb{R})}$$

is the product of maps, which are continuous at $(0,0)$, therefore continuous (in particular, upper semicontinuous) at $(0,0)$.

(g8*) For all $\phi \in C^2$, with $\|\phi\|_{C^2} \le 1$ and for $s \in [0,1]$, with (7.4) we obtain

$$\begin{aligned}
&\left|\left(Df(s\phi, s\partial\phi) - Df(0,0)\right)(0,\partial\phi)\right|\\
&\quad \le \left| p_1(\phi^0_s)\, p_2(s\phi(-\tau_s^{\phi^0}))\, \dot p_3(s\dot\phi(-\tau_s^{\phi^0}))\, \dot\phi(-\tau_s^{\phi^0}) - p_1(0)p_2(0)\dot p_3(0)\dot\phi(-\tau(0)) \right|.
\end{aligned}$$

We easily verify that, if $p_1(0) = 0$ and $p_2(0) \ne 0 \ne p_3(0)$,

$$\begin{aligned}
&\left|\left(Df(s\phi, s\partial\phi) - Df(0,0)\right)(0,\partial\phi)\right|\\
&\le \left| p_1(\phi^0_s) p_2(s\phi(-\tau_s^{\phi^0})) \dot p_3(s\dot\phi(-\tau_s^{\phi^0})) \dot\phi(-\tau_s^{\phi^0}) \right|\\
&\le \max_{|\nu| \le \|s\phi\|_C} |p_1(\nu)| \max_{|\nu| \le \|s\phi\|_C} |p_2(\nu)| \max_{|\eta| \le \|s\partial\phi\|_C} |\dot p_3(\eta)| \max_{|z| \le \|s\phi\|_C} |\dot\phi(-\tau(z))|\\
&\le \max_{|\nu| \le \|s\phi\|_C} |p_1(\nu) - p_1(0)| \max_{|\nu| \le \|s\phi\|_C} |p_2(\nu)| \max_{|\eta| \le \|s\partial\phi\|_C} |\dot p_3(\eta)| \max_{|z| \le \|s\phi\|_C} |\dot\phi(-\tau(z))|.
\end{aligned}$$

Define the values

$$c_2 = \max_{|\nu|\le 1} |p_2(\nu)| \max_{|\eta|\le 1} |\dot p_3(\eta)|,$$

and $\Delta = \min\{\tau(\nu) : |\nu| \le \|s\phi\|_C, 0 \le s \le 1\}$. In view of the above definition of the delay function, $\Delta \in (0,h)$. The estimate in (g8*) holds with

$$\vartheta : [0,\infty) \to [0,\infty), \quad z \mapsto \max_{|y|\le z} |p_1(y) - p_1(0)|.$$

Analogously, if $p_2(0) = 0$ and $p_1(0) \ne 0 \ne p_3(0)$, we obtain the estimate in (g8*) with the above value $\Delta \in (0,h)$,

$$c_2 = \max_{|\nu|\le 1} |p_1(\nu)| \max_{|\eta|\le 1} |\dot p_3(\eta)|,$$

and the function

$$\vartheta : [0,\infty) \to [0,\infty), \quad z \mapsto \max_{|y|\le z} |p_2(y) - p_2(0)|.$$

Otherwise, in the case $p_3(0) = 0$ and $p_1(0) \neq 0 \neq p_2(0)$, we have

$$\begin{aligned}
&\big|(Df(s\phi, s\partial\phi) - Df(0,0))\,(0,\partial\phi)\big| \\
&\quad\le \big|p_1(\phi_s^0)p_2(s\phi(-\tau_s^{\phi^0}))\dot p_3(s\dot\phi(-\tau_s^{\phi^0}))\dot\phi(-\tau_s^{\phi^0}) - p_1(0)p_2(0)\dot p_3(0)\dot\phi(-\tau(0))\big| \\
&\quad\le \sum_{j=1}^{4} M_j,
\end{aligned}$$

with

$$\begin{aligned}
M_1 &= |p_1(\phi_s^0)p_2(s\phi(-\tau_s^{\phi^0}))\dot p_3(s\dot\phi(-\tau_s^{\phi^0}))\dot\phi(-\tau_s^{\phi^0}) \\
&\qquad - p_1(\phi_s^0)p_2(s\phi(-\tau_s^{\phi^0}))\dot p_3(s\dot\phi(-\tau_s^{\phi^0}))\dot\phi(-\tau(0))|, \\
M_2 &= |p_1(\phi_s^0)p_2(s\phi(-\tau_s^{\phi^0}))\dot p_3(s\dot\phi(-\tau_s^{\phi^0}))\dot\phi(-\tau(0)) \\
&\qquad - p_1(\phi_s^0)p_2(s\phi(-\tau_s^{\phi^0}))\dot p_3(0)\dot\phi(-\tau(0))|, \\
M_3 &= |p_1(\phi_s^0)p_2(s\phi(-\tau_s^{\phi^0}))\dot p_3(0)\dot\phi(-\tau(0)) - p_1(\phi_s^0)p_2(0)\dot p_3(0)\dot\phi(-\tau(0))|, \\
M_4 &= |p_1(\phi_s^0)p_2(0)\dot p_3(0)\dot\phi(-\tau(0)) - p_1(0)p_2(0)\dot p_3(0)\dot\phi(-\tau(0))|.
\end{aligned}$$

Hence we obtain

$$\begin{aligned}
&\big|(Df(s\phi, s\partial\phi) - Df(0,0))\,(0,\partial\phi)\big| \\
&\le \max_{|\nu|\le\|s\phi\|_C}|p_1(\nu)| \max_{|\nu|\le\|s\phi\|_C}|p_2(\nu)| \max_{|\eta|\le\|s\partial\phi\|_C}|\dot p_3(\eta)|\,\|\partial\partial\phi\|_C \max_{|\nu|\le\|s\phi\|_C}|\dot\tau(\nu)|\,\|s\phi\|_C \\
&\quad + \Big[\max_{|\nu|\le\|s\phi\|_C}|p_1(\nu)| \max_{|\nu|\le\|s\phi\|_C}|p_2(\nu)| \max_{|\eta|\le\|s\partial\phi\|_C}|\dot p_3(\eta) - \dot p_3(0)| \\
&\qquad + \max_{|\nu|\le\|s\phi\|_C}|p_1(\nu)| \max_{|\nu|\le\|s\phi\|_C}|p_2(\nu) - p_2(0)|\,|\dot p_3(0)| \\
&\qquad + \max_{|\nu|\le\|s\phi\|_C}|p_1(\nu) - p_1(0)|\,|p_2(0)|\,|\dot p_3(0)|\Big] \max_{\tau(0)\le z\le h}|\dot\phi(-z)|.
\end{aligned}$$

The desired estimate holds with $\Delta = \tau(0) \in (0,h)$, the values

$$c_1 = \max_{|\nu|\le1}|p_1(\nu)| \max_{|\nu|\le1}|p_2(\nu)| \max_{|\eta|\le1}|\dot p_3(\eta)| \max_{|\nu|\le1}|\dot\tau(\nu)|,$$

$$c_2 = \max_{|\nu|\le1}|p_1(\nu)| \left(\max_{|\nu|\le1}|p_2(\nu)| + \max_{|\nu|\le1}|\dot p_3(\nu)|\right) + \max_{|\nu|\le1}|p_2(\nu)| \max_{|\nu|\le1}|\dot p_3(\nu)|,$$

and the function

$$\vartheta : [0,\infty) \to [0,\infty),\ z \mapsto \max_{|y|\le z}|p_1(y) - p_1(0)| + \max_{|y|\le z}|p_2(y) - p_2(0)| + \max_{|y|\le z}|\dot p_3(y) - \dot p_3(0)|.$$

(g9) For all $\phi \in C^2$, with $\|\phi\|_{C^2} \leq 1$ and $s \in [0,1]$, from (7.4) we obtain

$$\begin{aligned}
&\left|(Df(s\phi, s\partial\phi) - Df(0,0))(\phi, 0)\right| \\
&= \Big|\dot{p}_1(\phi_s^0)p_2(s\phi(-\tau_s^{\phi^0}))p_3(s\dot{\phi}(-\tau_s^{\phi^0}))\phi(0) \\
&\quad + p_1(\phi_s^0)\dot{p}_2(s\phi(-\tau_s^{\phi^0}))p_3(s\dot{\phi}(-\tau_s^{\phi^0}))\left[\phi(-\tau_s^{\phi^0}) - s\dot{\phi}(-\tau_s^{\phi^0})\dot{\tau}(\phi_s^0)\phi(0)\right] \\
&\quad - p_1(\phi_s^0)p_2(s\phi(-\tau_s^{\phi^0}))\dot{p}_3(s\dot{\phi}(-\tau_s^{\phi^0}))\, s\ddot{\phi}(-\tau_s^{\phi^0})\dot{\tau}(\phi_s^0)\phi(0) \\
&\quad - \dot{p}_1(0)p_2(0)p_3(0)\phi(0) - p_1(0)\dot{p}_2(0)p_3(0)\phi(-\tau(0))\Big| \\
&\leq \Big[\max_{|\nu|\leq\|s\phi\|_C}|\dot{p}_1(\nu)| \max_{|\nu|\leq\|s\phi\|_C}|p_2(\nu)| \max_{|\eta|\leq\|s\partial\phi\|_C}|p_3(\eta) - p_3(0)| \\
&\qquad + \max_{|\nu|\leq\|s\phi\|_C}|\dot{p}_1(\nu)| \max_{|\nu|\leq\|s\phi\|_C}|p_2(\nu) - p_2(0)||p_3(0)| \\
&\qquad + \max_{|\nu|\leq\|s\phi\|_C}|\dot{p}_1(\nu) - \dot{p}_1(0)||p_2(0)||p_3(0)|\Big]\|\phi\|_C \\
&\quad + \max_{\substack{|\nu|\leq\|s\phi\|_C \\ |\nu_1|\leq\|s\phi\|_C \\ |\eta|\leq\|s\partial\phi\|_C}}|p_1(\nu)\dot{p}_2(\nu_1)p_3(\eta)|\,\|\partial\phi\|_C \max_{|\nu|\leq\|s\phi\|_C}|\dot{\tau}(\nu)|\,\|s\phi\|_C \\
&\quad + \Big[\max_{|\nu|\leq\|s\phi\|_C}|p_1(\nu)| \max_{|\nu|\leq\|s\phi\|_C}|\dot{p}_2(\nu)| \max_{|\eta|\leq\|s\partial\phi\|_C}|p_3(\eta) - p_3(0)| \\
&\qquad + \max_{|\nu|\leq\|s\phi\|_C}|p_1(\nu)| \max_{|\nu|\leq\|s\phi\|_C}|\dot{p}_2(\nu) - \dot{p}_2(0)||p_3(0)| \\
&\qquad + \max_{|\nu|\leq\|s\phi\|_C}|p_1(\nu) - p_1(0)||\dot{p}_2(0)||p_3(0)|\Big]\|\phi\|_C \\
&\quad + \max_{\substack{|\nu|\leq\|s\phi\|_C \\ |\nu_1|\leq\|s\phi\|_C \\ |\eta|\leq\|s\partial\phi\|_C}}|p_1(\nu)\dot{p}_2(\nu_1)p_3(\eta)|\,\|s\partial\phi\|_C \max_{|\nu|\leq\|s\phi\|_C}|\dot{\tau}(\nu)|\,\|\phi\|_C \\
&\quad + \max_{\substack{|\nu|\leq\|s\phi\|_C \\ |\nu_1|\leq\|s\phi\|_C \\ |\eta|\leq\|s\partial\phi\|_C}}|p_1(\nu)p_2(\nu_1)\dot{p}_3(\eta)|\,\|s\partial\partial\phi\|_C \max_{|\nu|\leq\|s\phi\|_C}|\dot{\tau}(\nu)|\,\|\phi\|_C\,.
\end{aligned} \tag{7.5}$$

It will be convenient to define the values

$$c_0 = \max_{|\nu|\leq 1}|p_1(\nu)| \max_{|\nu|\leq 1}|\dot{\tau}(\nu)| \left(\max_{|\nu|\leq 1}|\dot{p}_2(\nu)| \max_{|\nu|\leq 1}|p_3(\nu)| + \max_{|\nu|\leq 1}|p_2(\nu)| \max_{|\nu|\leq 1}|\dot{p}_3(\nu)|\right),$$

$$c_1 = \max_{|\nu|\le 1}|\dot{p}_1(\nu)|\left(\max_{|\nu|\le 1}|p_2(\nu)| + \max_{|\nu|\le 1}|p_3(\nu)|\right) + \max_{|\nu|\le 1}|p_2(\nu)|\max_{|\nu|\le 1}|p_3(\nu)|,$$

and

$$c_2 = \max_{|\nu|\le 1}|p_1(\nu)|\left(\max_{|\nu|\le 1}|\dot{p}_2(\nu)| + \max_{|\nu|\le 1}|p_3(\nu)|\right) + \max_{|\nu|\le 1}|\dot{p}_2(\nu)|\max_{|\nu|\le 1}|p_3(\nu)|.$$

From the relation (7.5), we obtain

$$\begin{aligned}
&\left|\left(Df(s\phi, s\partial\phi) - Df(0,0)\right)(\phi, 0)\right| \\
&\le c_1\left[\max_{|\eta|\le\|s\partial\phi\|_C}|p_3(\eta) - p_3(0)| + \max_{|\nu|\le\|s\phi\|_C}|p_2(\nu) - p_2(0)| + \max_{|\nu|\le\|s\phi\|_C}|\dot{p}_1(\nu) - \dot{p}_1(0)|\right]\|\phi\|_C \\
&\quad + c_0\,\|\partial\phi\|_C\,\|s\phi\|_C \\
&\quad + c_2\left[\max_{|\eta|\le\|s\partial\phi\|_C}|p_3(\eta) - p_3(0)| + \max_{|\nu|\le\|s\phi\|_C}|\dot{p}_2(\nu) - \dot{p}_2(0)| + \max_{|\nu|\le\|s\phi\|_C}|p_1(\nu) - p_1(0)|\right]\|\phi\|_C \\
&\quad + c_0\left(\|s\partial\phi\|_C + \|s\partial\partial\phi\|_C\right)\|\phi\|_C\,.
\end{aligned}$$

The estimate in (g9) follows with $c = c_0 + c_1 + c_2 + 1$ and the function $\zeta : [0,\infty) \to [0,\infty)$ given by

$$\begin{aligned}
\zeta(y) = y &+ \max_{|z|\le y}|\dot{p}_1(z) - \dot{p}_1(0)| + \max_{|z|\le y}|p_2(z) - p_2(0)| \\
&+ \max_{|z|\le y}|p_1(z) - p_1(0)| + \max_{|z|\le y}|\dot{p}_2(z) - \dot{p}_2(0)| + 2\cdot\max_{|z|\le y}|p_3(z) - p_3(0)|.
\end{aligned}$$

□

The previous proof shows that the map $f : C^1 \times C^1 \to \mathbb{R}$ in (7.3) satisfies (g0)–(g3), (g6), (g9) and (g8*). That is, the first hypothesis of Theorem 6.2 is satisfied, with (g8*) instead of (g8). We notice that the second hypothesis of Theorem 6.2, condition (6.16), is satisfied if

$$|p_1(0)p_2(0)\dot{p}_3(0)| < 1.$$

This is trivial in the cases $p_1(0) = 0$, $p_2(0) \neq 0 \neq p_3(0)$, and $p_2(0) = 0$, $p_1(0) \neq 0 \neq p_3(0)$. Now we continue with the analysis of (7.2).

7.1.2. The Class of Equations (7.2)

Thanks to the results of the previous section, it is now immediate to analyze the right-hand side f in (7.2).

Theorem 7.2. *For $j = 1, 2, 3$, let the map $f_j : C^1 \times C^1 \to \mathbb{R}$ be defined by*

$$(\phi, \xi) \mapsto f_j(\phi, \xi) = q_j\big(\phi(0), \phi(-\tau(\phi(0))), \xi(-\tau(\phi(0)))\big).$$

The function $q_j : \mathbb{R}^3 \to \mathbb{R}$, given by

$$q_j(w, y, z) = p_{j,1}(w)p_{j,2}(y)p_{j,3}(z),$$

has continuously differentiable components $p_{j,i} : \mathbb{R} \to \mathbb{R}$, such that for all $j \in \{1, 2, 3\}$, $p_{j,k}(0) = 0$ for some $k \in \{1, 2, 3\}$ and $p_{j,l}(0) \neq 0$ for $l \in \{1, 2, 3\}$, $l \neq k$. Further, let $\tau : \mathbb{R} \to (0, h)$ be continuously differentiable.

Then the map $f : C^1 \times C^1 \to \mathbb{R}$,

$$(\phi, \xi) \mapsto f(\phi, \xi) = \sum_{j=1}^{3} f_j(\phi, \xi),$$

satisfies (g0)–(g3), (g6), (g8) and (g9).*

Proof. In view of Theorem 7.1, each f_j, $j \in \{1, 2, 3\}$ satisfies (g0)–(g3), (g6), (g8*) and (g9). One by one, we verify these conditions for f.

(g0) Continuity of f is trivial (f is the sum of continuous functions).

(g1) The proof of Theorem 7.1 (g1) implies that for each $\phi \in C^1$ and each function f_j, $j \in \{1, 2, 3\}$, there is a value $\Delta_j \in (0, h)$ and a neighborhood $V_j \subset C^1$ of $\phi \in C^1$, such that for all $\psi \in V_j$ we have $\tau(\psi(0)) \in (\Delta_j, h)$. Further, for all $\psi \in V_j$ and all $\xi_1, \xi_2 \in C^1$ such that $\xi_1(t) = \xi_2(t)$ for $t \in [-h, -\Delta_j]$, we have $f_j(\psi, \xi_1) = f_j(\psi, \xi_2)$.

We define $\Delta = \max\{\Delta_1, \Delta_2, \Delta_3\}$ and $V = \bigcap_{j=1}^{3} V_j$. Then $\Delta \in (0, h)$ and for all $\psi \in V$ and all $\xi_1, \xi_2 \in C^1$, with $\xi_1(t) = \xi_2(t)$ for $t \in [-h, -\Delta]$, we obtain

$$f(\psi, \xi_1) = \sum_{j=1}^{3} f_j(\psi, \xi_1) = \sum_{j=1}^{3} f_j(\psi, \xi_2) = f(\psi, \xi_2).$$

(g2) In view of Proposition 6.1 and the proof of (g3) below, it is not further necessary to verify this property.

(g3) For ϕ, ξ, ρ, $\chi \in C^1$ we have

$$Df(\phi,\xi)(\rho,\chi) \;=\; D\left[\sum_{i=1}^{3} f_i(\phi,\xi)\right](\rho,\chi) \;=\; \sum_{i=1}^{3} Df_i(\phi,\xi)(\rho,\chi).$$

For the proof of Theorem 7.1, the extension $D_e f_j(\phi,\xi)$ of $Df_j(\phi,\xi)$ to the space $C\times C$ is well-defined, for all $j \in \{1,2,3\}$. It is immediate to see that $Df(\phi,\xi)$ has a linear extension $D_e f(\phi,\xi)$ to $C\times C$, as well. Due to the continuity of

$$C^1\times C^1\times C\times C \ni (\phi,\xi,\rho,\chi)\mapsto D_e f_j(\phi,\xi)(\rho,\chi)\in\mathbb{R}, \qquad j\in\{1,2,3\},$$

also the map

$$C^1\times C^1\times C\times C \ni (\phi,\xi,\rho,\chi)\mapsto D_e f(\phi,\xi)(\rho,\chi)\in\mathbb{R}$$

is continuous.

(g6) As $f_j(0,0)=0$, for all $j\in\{1,2,3\}$, we have that $f(0,0)=0$. For all ϕ, $\xi\in C^1$ and all $\chi\in C$ we have

$$D_e f(\phi,\xi)(0,\chi) = \sum_{j=1}^{3} D_e f_j(\phi,\xi)(0,\chi).$$

It follows that

$$\|D_e f(\phi,\xi)(0,\cdot)\|_{L_c(C,\mathbb{R})} = \sup_{\substack{\chi\in C\\ \|\chi\|_C\le 1}} \left|\sum_{j=1}^{3} D_e f_j(\phi,\xi)(0,\chi)\right|.$$

For the proof of Theorem 7.1 (g6), the map

$$C^1\times C^1\to L_c(C,\mathbb{R}), \quad (\phi,\xi)\mapsto D_e f_j(\phi,\xi)(0,\cdot)$$

is continuous at $(0,0)$, for all $j\in\{1,2,3\}$. Hence we have that, also the map

$$C^1\times C^1\to\mathbb{R}, \qquad (\phi,\xi)\mapsto \|D_e f(\phi,\xi)(0,\cdot)\|_{L_c(C,\mathbb{R})}$$

is continuous at $(0,0)$, in particular upper semicontinuous.

(g8*) By Theorem 7.1 we know that, for each $j\in\{1,2,3\}$ there exist a convex neighborhood $U_{2,j}$ of 0 in C^2, values $c_{j,1}>0$, $c_{j,2}>0$, $\Delta_j\in(0,h)$, and a function $\vartheta_j:[0,\infty)\to[0,\infty)$ continuous at $0=\vartheta_j(0)$ such that, for all $\phi\in U_{2,j}$,

$$\begin{aligned}&\max_{0\le s\le 1}\left|\left(Df_j(s\phi,s\partial\phi)-Df_j(0,0)\right)(0,\partial\phi)\right|\\ &\le\; c_{j,1}\,\|\partial\partial\phi\|_C\,\|\phi\|_C + c_{j,2}\max_{0\le s\le 1}\vartheta_j\left(\|s\phi\|_{C^1}\right)\max_{\Delta_j\le u\le h}|\dot{\phi}(-u)|.\end{aligned}$$

Let $U_2^* = \bigcap_{j=1}^{3} U_{2,j} \subset C^2$, a convex neighborhood of 0 in C^2. Then for all $\phi \in U_2^*$ we have

$$\begin{aligned}
&\max_{0\le s\le 1} \left|(Df(s\phi, s\partial\phi) - Df(0,0))\,(0,\partial\phi)\right| \\
&\le \max_{0\le s\le 1}\left\{\sum_{j=1}^{3}\left|\Big(Df_j(s\phi, s\partial\phi) - Df_j(0,0)\Big)(0,\partial\phi)\right|\right\} \\
&\le \sum_{j=1}^{3}\left[c_{j,1}\,\|\partial\partial\phi\|_C\,\|\phi\|_C + c_{j,2}\max_{0\le s\le 1}\vartheta_j\left(\|s\phi\|_{C^1}\right)\max_{\Delta_j\le u\le h}|\dot\phi(-u)|\right] \\
&\le k_1\,\|\partial\partial\phi\|_C\,\|\phi\|_C + k_2\max_{0\le s\le 1}\vartheta\left(\|s\phi\|_{C^1}\right)\max_{\Delta\le u\le h}|\dot\phi(-u)|,
\end{aligned}$$

with values $k_1 = \sum_{j=1}^{3} c_{j,1}$, $k_2 = \sum_{j=1}^{3} c_{j,2}$, and $\Delta = \min_{j=1,2,3}\Delta_j$, and the function $\vartheta : [0,\infty) \to [0,\infty)$ defined by $\vartheta(y) = \sum_{j=1}^{3}\vartheta_j(y)$. Notice that ϑ is continuous at $0 = \sum_{j=1}^{3}\vartheta_j(0) = \vartheta(0)$ and $\Delta \in (0,h)$.

(g9) For each $j = 1,2,3$, there exists a convex neighborhood $V_{2,j}$ of 0 in C^2, a value $c_j > 0$, and a function $\zeta_j : [0,\infty) \to [0,\infty)$ continuous at $0 = \zeta_j(0)$ such that, for all $\phi \in V_{2,j}$ we have

$$\max_{0\le s\le 1}|(Df_j(s\phi, s\partial\phi) - Df_j(0,0))\,(\phi,0)| \le c_j\max_{0\le s\le 1}\left\{\zeta_j\left(\|s\phi\|_{C^2}\right)\|\phi\|_C + \|\phi\|_{C^1}\,\|s\phi\|_C\right\}.$$

Define $V_2 = \bigcap_{j=1}^{3} V_{2,j} \subset C^2$, a convex neighborhood of 0 in C^2. For all $\phi \in V_2$ we obtain

$$\begin{aligned}
&\max_{0\le s\le 1}\left|(Df(s\phi, s\partial\phi) - Df(0,0))\,(\phi,0)\right| \\
&\le \sum_{j=1}^{3}\max_{0\le s\le 1}\left\{\left|\Big(Df_j(s\phi, s\partial\phi) - Df_j(0,0)\Big)(\phi,0)\right|\right\} \\
&\le \sum_{j=1}^{3}\left[c_j\max_{0\le s\le 1}\left\{\zeta_j\left(\|s\phi\|_{C^2}\right)\|\phi\|_C + \|\phi\|_{C^1}\,\|s\phi\|_C\right\}\right] \\
&\le c\max_{0\le s\le 1}\left\{\zeta\left(\|s\phi\|_{C^2}\right)\|\phi\|_C + \|\phi\|_{C^1}\,\|s\phi\|_C\right\},
\end{aligned}$$

with $c = c_1 + c_2 + c_3$, $c > 0$ and $\zeta : [0,\infty) \to [0,\infty)$, $y \mapsto \sum_{j=1}^{3}\zeta_j(y)$, continuous at $0 = \sum_{j=1}^{3}\zeta_j(0) = \zeta(0)$.

□

We have shown that the map f in (7.2) satisfies (g0)-(g3), (g6), (g8*) and (g9). When also condition (6.16) and the hypothesis about boundedness of $\|S(t)\chi\|_C$ are satisfied, we can use Theorem 6.2 to investigate linearized stability of the solution semiflow generated by (7.2). The next section shows an example for (7.2) from population dynamics.

7.1.3. An Example from Biology

Let us consider the following neutral problem with state-dependent delay:

$$\begin{aligned}\dot{x}(t) &= \tilde{b}_1(x(t-\tau(x(t))))e^{-\mu_0\tau(x(t))} - \tilde{\mu}_1(x(t)) \\ &\quad + b_2(x(t-\tau(x(t))))\left[\dot{x}(t-\tau(x(t))) + \tilde{\mu}_1(x(t-\tau(x(t))))\right] e^{-\mu_0\tau(x(t))}.\end{aligned} \tag{7.6}$$

In population biology, this equation may express the dynamics of a population x of *adult* individuals, under the assumption that the *age-at-maturity* τ (that is, the age at which an individual becomes adult and is able to reproduce) depends on the total number of adult individuals. Biological motivation of the relation between age-at-maturity and population size can be found, e.g., in [117]. Going back to Section 3.2, equation (7.6) can be seen as a simpler form of (3.24), or can be obtained from (3.28), if the constant delay $\hat{\tau}$ is directly replaced by a state-dependent one. For this reason, we assume that the components of (7.6) satisfy the assumptions, which we have made in Section 3.2:

(i) $\tau : \mathbb{R} \to (0, h)$, is a nonnegative, monotonically increasing (not necessarily strictly increasing) C^2-function.

(ii) $\tilde{b}_1(y) = b_1(y)y$, with $b_1 : \mathbb{R} \to [0, B_1]$, $B_1 < \infty$ is a nonnegative, monotonically decreasing (not necessarily strictly decreasing) continuously differentiable function.

(iii) $b_2 : \mathbb{R} \to [0, B_2]$, $B_2 \in (B_1, \infty)$, is a nonnegative, monotonically decreasing (not necessarily strictly decreasing) C^1-function.

(iv) $\mu_0 > 0$ is a constant value.

(v) $\tilde{\mu}_1(y) = \mu_1(y)y$, with $\mu_1 : \mathbb{R} \to [0, \infty)$, is a nonnegative, monotonically increasing (not necessarily strictly increasing) C^1-function.

Equation (7.6) is an example from the class (7.2), with $f : C^1 \times C^1 \to \mathbb{R}$ and

$$\begin{aligned} q_1(w, y, z) &= e^{-\mu_0\tau(w)}\big(\tilde{b}_1(y) + b_2(y)\tilde{\mu}_1(y)\big), \\ q_2(w, y, z) &= e^{-\mu_0\tau(w)}b_2(y)z, \\ q_3(w, y, z) &= -\tilde{\mu}_1(w), \end{aligned}$$

or equivalently,

$$\begin{aligned} &p_{1,1}(w) = e^{-\mu_0\tau(w)}, && p_{1,2}(y) = \tilde{b}_1(y) + b_2(y)\tilde{\mu}_1(y), && p_{1,3}(z) = 1, \\ &p_{2,1}(w) = e^{-\mu_0\tau(w)}, && p_{2,2}(y) = b_2(y), && p_{2,3}(z) = z, \\ &p_{3,1}(w) = -\tilde{\mu}_1(w), && p_{3,2}(y) = 1, && p_{3,3}(z) = 1. \end{aligned}$$

By Theorem 7.2 we know that the right-hand side f of the neutral equation (7.6) satisfies hypotheses (g0) –(g3), (g6), (g8*) and (g9). With the results in Section 7.1.2, we associate to (7.6) the linear variational equation along the zero solution,

$$\begin{aligned}\dot v(t) &= D_e f(0,0)(v_t,\partial v_t)\\ &= \sum_{i=1}^{3} D_e f_i(0,0)(v_t,\partial v_t)\\ &= \sum_{i=1}^{3}\Big[\dot p_{j,1}(0)p_{j,2}(0)p_{j,3}(0)\,v_t(0)+p_{j,1}(0)\dot p_{j,2}(0)p_{j,3}(0)\,v_t(-\tau(0))\\ &\qquad\qquad + p_{j,1}(0)p_{j,2}(0)\dot p_{j,3}(0)\,\dot v_t(-\tau(0))\Big]\\ &= -\mu_1(0)v(t)+(b_1(0)+b_2(0)\mu_1(0))\,e^{-\mu_0\tau(0)}v(t-\tau(0))\\ &\quad + b_2(0)e^{-\mu_0\tau(0)}\dot v(t-\tau(0)).\end{aligned}$$

The zero equilibrium corresponds to the (trivial) case of no living adult individual. However, in mathematical biology we are mostly interested in the persistence of a population. For this reason, we consider a positive[1] equilibrium of the dynamical system and investigate its linearized stability.

Let $\bar x \in (0,\infty)$ be a nontrivial equilibrium of (7.6), then

$$b_1(\bar x)+b_2(\bar x)\mu_1(\bar x)=\mu_1(\bar x)e^{\mu_0\bar\tau}, \tag{7.7}$$

with $\bar\tau=\tau(\bar x)$. In other words, we assume that there exists a nonzero solution $\bar\phi\in C^2$ of $\dot x(t)=f(x_t,\partial x_t)$, such that $\bar\phi:\,[-h,0]\to\mathbb{R},\ s\mapsto\bar\phi(s)=\bar x$, and $f\big(\bar\phi,0\big)=\sum_{j=1}^{3} q_j(\bar x,\bar x,0)=0$. The considerations in Section 6.4.2 and Proposition 6.5 show that $\big(\bar\phi,0\big)\in C^2\times C^1$ is an equilibrium of (7.6) and that we can associate to (7.6) a linear variational equation along $(\bar\phi,0)$, namely

$$\begin{aligned}\dot v(t) &= D_e f(\bar\phi,0)(v_t,\partial v_t)\\ &= -\Big(\dot{\tilde\mu}_1(\bar x)+\mu_0\dot\tau(\bar x)e^{-\mu_0\bar\tau}\Big[\tilde b_1(\bar x)+b_2(\bar x)\tilde\mu_1(\bar x)\Big]\Big)\,v(t)\\ &\quad+\Big[\dot{\tilde b}_1(\bar x)+\dot b_2(\bar x)\tilde\mu_1(\bar x)+b_2(\bar x)\dot{\tilde\mu}_1(\bar x)\Big]\,e^{-\mu_0\bar\tau}v(t-\bar\tau)\\ &\quad+b_2(\bar x)e^{-\mu_0\bar\tau}\dot v(t-\bar\tau),\end{aligned}\tag{7.8}$$

with $\bar\tau=\tau(\bar x)$. In view of the Principle of linearized stability, Theorem 6.2, we consider the IVP associated to (7.8) with initial data in C and are interested in exponential stability of the zero solution. Notice that (7.8) has the form

$$\dot\eta(t)+A\dot\eta(t-\bar\tau)+B\eta(t)+C\eta(t-\bar\tau)=0, \tag{7.9}$$

[1]For biological reason we are interested only in nonnegative solutions.

with coefficients

$$\begin{aligned} A &= -b_2(\bar{x})e^{-\mu_0\bar{\tau}}, \\ B &= \dot{\tilde{\mu}}_1(\bar{x}) + \mu_0\dot{\tau}(\bar{x})\tilde{\mu}_1(\bar{x}), \qquad \text{(we have used (7.7))} \\ C &= -\left[\dot{\tilde{b}}_1(\bar{x}) + \dot{b}_2(\bar{x})\tilde{\mu}_1(\bar{x}) + b_2(\bar{x})\dot{\tilde{\mu}}_1(\bar{x})\right] e^{-\mu_0\bar{\tau}}. \end{aligned}$$

The characteristic equation corresponding to (7.9) is

$$\lambda + A\lambda e^{-\lambda\bar{\tau}} + B + Ce^{-\lambda\bar{\tau}} = 0. \tag{7.10}$$

The fundamental theory of linear NFDEs, existence and uniqueness of solutions to equations of the class (7.9), as well as the analysis of the characteristic equation (7.10) can be found, e.g., in [79]. Here, we only report from [79] the main result about the stability of the zero solution of (7.9).

The roots of the characteristic equation (7.10), and therefore the stability of the trivial equilibrium of (7.9), depend on the parameters A, B, C and on the delay $\bar{\tau}$ as follows.

(i) If $|A| > 1$, then (7.9) is unstable, for all $\bar{\tau} > 0$.

(ii) If $|A| < 1$ and $C^2 < B^2$ or $C = B \neq 0$, an increase in $\bar{\tau}$ does not change the stability of the equation, i. e., the stability properties do not change with respect to the case $\bar{\tau} = 0$.

(iii) If $|A| < 1$ and $C^2 > B^2$, with $B + C < 0$, the equation is unstable for all $\bar{\tau} > 0$.

(iv) If $|A| < 1$ and $C^2 > B^2$, with $B + C > 0$, there exists a $\bar{\tau}^* > 0$ such that (7.9) is asymptotically stable for all $\bar{\tau} < \bar{\tau}^*$ and is unstable for $\bar{\tau} > \bar{\tau}^* = \vartheta/\sigma$, with

$$\vartheta = \operatorname{arccot}\left(-\frac{A\sigma^2 + BC}{\sigma(C - BA)}\right), \qquad \sigma = \sqrt{\frac{C^2 - B^2}{1 - A^2}}.$$

(v) If $|A| < 1$ and $B + C = 0$, then (7.9) is stable (but not asymptotically stable) if $B \geq 0$. If $B < 0$, it is unstable.

(vi) If $A = +1$ and $B = C$, then (7.9) is stable (but not asymptotically stable) if $B \geq 0$. Otherwise if $B < 0$, it is unstable for all $\bar{\tau} > 0$.

(vii) If $A = +1$ and $B > |C|$, then equation (7.9) is asymptotically stable for all $\bar{\tau} > 0$.

(viii) If $A = +1$ and $-|B| > C$, then (7.9) is always unstable.

(ix) If $A = -1$ and $B + C = 0$, then if $B \geq 0$, equation (7.9) is stable (but not asymptotically stable). If $B < 0$, it is unstable for all $\bar{\tau} > 0$.

(x) If $A = -1$ and $B > |C|$, then (7.9) is asymptotically stable for all $\bar{\tau} > 0$.

(xi) If $A = -1$ and $|B| < C$, then (7.9) is always unstable.

The local stability of the nontrivial equilibrium $\bar{x}$ of (7.6) can be investigated with the above scheme. For the condition at equilibrium (7.7), it follows that

$$\underbrace{b_1(\bar{x})}_{>0} = \underbrace{\mu_1(\bar{x})e^{\mu_0\bar{\tau}}}_{>0}(1 - b_2(\bar{x})e^{-\mu_0\bar{\tau}}).$$

Consequently,

$$b_2(\bar{x})e^{-\mu_0\bar{\tau}} < 1.$$

Hence, for the linear equation (7.8) we always have $|A| < 1$ and are in one of the cases (ii), (iii), (iv) or (v). In order to determine the stability of $\bar{x}$, one has to check the sign of $B^2 - C^2$. This sign depends explicitly on the choice of the functions b_1, b_2, μ_1 and τ, and we do not analyze the problem further at this stage. We rather move to a second, more challenging class of neutral equations with state-dependent delay.

7.2. A More General Case

More general than the class of neutral equations introduced in Section 7.1, is the one we present here. In the following we consider neutral equations with state-dependent delay of the form

$$\dot{x}(t) = \frac{\alpha\big(x(t), x(t-\tau(x(t))), \dot{x}(t-\tau(x(t)))\big) - \gamma(x(t))}{1 + \dot{\tau}(x(t))\alpha\big(x(t), x(t-\tau(x(t))), \dot{x}(t-\tau(x(t)))\big)}, \tag{7.11}$$

where

(i) $\alpha : \mathbb{R}^3 \to [0, \infty)$ is a nonnegative, C^1-function and $\alpha(0, 0, 0) = 0$.

(ii) $\gamma : \mathbb{R} \to [0, \infty)$ is a nonnegative, C^1-function and $\gamma(0) = 0$.

(iii) $\tau : \mathbb{R} \to (0, h)$, $h > 0$, is a nonnegative, monotonically increasing (not necessarily strictly increasing), C^2-function.

Equation (7.11) can be written in the NFDE form,

$$\dot{x}(t) = f(x_t, \partial x_t),$$

where $f : C^1 \times C^1 \to \mathbb{R}$ is the map

$$(\phi, \xi) \mapsto f(\phi, \xi) = g\left(\phi(0), \phi(-\tau(\phi(0))), \xi(-\tau(\phi(0)))\right), \tag{7.12}$$

and

$$g : \mathbb{R}^3 \ni (w, y, z) \mapsto \frac{\alpha(w, y, z) - \gamma(w)}{1 + \dot{\tau}(w)\alpha(w, y, z)} \in \mathbb{R}.$$

Theorem 7.3. *The map f in (7.12) satisfies (g0)–(g3), (g6), (g8*) and (g9).*

Proof. (g0) The continuity of f follows from the continuity of the functions α, γ, the delay function τ, together with its derivative $\dot{\tau}$ and the evaluation maps Ev_0, Ev.

(g1) Let $\phi \in C^1$ be fixed. There is a value $\Delta \in (0,h)$ such that $\tau^{\phi^0} = \tau(\mathrm{Ev}_0(\phi)) \in (\Delta, h)$. Further, there exists a neighborhood $V \subset C^1$ of ϕ in C^1, such that for all $\psi \in V$, we have $\tau(\psi(0)) = \tau(\mathrm{Ev}_0(\psi)) \in (\Delta, h)$.
For simplicity of notation we write ψ^0 for $\psi(0)$. Then, for all $\psi \in V$ and all $\xi_1, \xi_2 \in C^1$, such that $\xi_1(t) = \xi_2(t)$ for all $t \in [-h, -\Delta]$, we have

$$\begin{aligned} f(\psi, \xi_1) &= \frac{\alpha\big(\psi^0, \psi(-\tau(\psi^0)), \xi_1(-\tau(\psi^0))\big) - \gamma(\psi^0)}{1 + \dot{\tau}(\psi^0)\alpha\big(\psi^0, \psi(-\tau(\psi^0)), \xi_1(-\tau(\psi^0))\big)} \\ &= \frac{\alpha\big(\psi^0, \psi(-\tau(\psi^0)), \xi_2(-\tau(\psi^0))\big) - \gamma(\psi^0)}{1 + \dot{\tau}(\psi^0)\alpha\big(\psi^0, \psi(-\tau(\psi^0)), \xi_2(-\tau(\psi^0))\big)} \\ &= f(\psi, \xi_2). \end{aligned}$$

(g2) In view of Proposition 6.1, with the proof of (g3) below, it is not further necessary to verify this hypothesis (cf. Section 7.1.1)

(g3) In view of the assumptions on α, γ and τ, all partial derivatives of g,

$$\begin{aligned} \partial_1 g(w,y,z) = \big[&\partial_1\alpha(w,y,z) - \dot{\gamma}(w) - \dot{\gamma}(w)\dot{\tau}(w)\alpha(w,y,z) + \gamma(w)\dot{\tau}(w)\partial_1\alpha(w,y,z) \\ &- (\alpha(w,y,z) - \gamma(w))\ddot{\tau}(w)\alpha(w,y,z)\big] / \left(1 + \dot{\tau}(w)\alpha(w,y,z)\right)^2, \\ \partial_2 g(w,y,z) &= \frac{\partial_2\alpha(w,y,z)(1 + \gamma(w)\dot{\tau}(w))}{(1 + \dot{\tau}(w)\alpha(w,y,z))^2}, \\ \partial_3 g(w,y,z) &= \frac{\partial_3\alpha(w,y,z)(1 + \gamma(w)\dot{\tau}(w))}{(1 + \dot{\tau}(w)\alpha(w,y,z))^2}, \end{aligned}$$

are continuous. With this result and the properties of the evaluation maps Ev_0, Ev, also f is continuously differentiable. For ϕ, ξ, ρ, $\chi \in C^1$, we obtain (cf. p. 94)

$$\begin{aligned} Df(\phi,\xi)(\rho,\chi) = {} & \partial_1 g\left(\phi^0, \phi(-\tau^{\phi^0}), \xi(-\tau^{\phi^0})\right)\rho(0) \\ & + \partial_2 g\left(\phi^0, \phi(-\tau^{\phi^0}), \xi(-\tau^{\phi^0})\right)\left[\rho(-\tau^{\phi^0}) - \dot{\phi}(-\tau^{\phi^0})\dot{\tau}(\phi^0)\rho(0)\right] \\ & + \partial_3 g\left(\phi^0, \phi(-\tau^{\phi^0}), \xi(-\tau^{\phi^0})\right)\left[\chi(-\tau^{\phi^0}) - \dot{\xi}(-\tau^{\phi^0})\dot{\tau}(\phi^0)\rho(0)\right]. \end{aligned} \tag{7.13}$$

Then for ϕ, $\xi \in C^1$ and ρ, $\chi \in C$ we define $D_e f(\phi,\xi)(\rho,\chi)$ by (7.13). With the assumptions on α, γ and τ, and the continuity of Ev_0, Ev, ev_0, the map

$$C^1 \times C^1 \times C \times C \ni (\phi,\xi,\rho,\chi) \mapsto D_e f(\phi,\xi)(\rho,\chi) \in \mathbb{R}$$

is continuous (cf. p. 103).

(g6) As $\alpha(0,0,0) = 0 = \gamma(0)$, we have $f(0,0) = 0$. For all $\phi, \xi \in C^1$ and all $\chi \in C$, from (7.13) we obtain

$$D_e f(\phi,\xi)(0,\chi) = \frac{\partial_3\alpha(\phi^0, \phi(-\tau^{\phi^0}), \xi(-\tau^{\phi^0}))\left(1+\gamma(\phi^0)\dot\tau(\phi^0)\right)}{\left(1+\dot\tau(\phi^0)\alpha(\phi^0,\phi(-\tau^{\phi^0}),\xi(-\tau^{\phi^0}))\right)^2}\chi(-\tau^{\phi^0}).$$

Hence, for all ϕ, $\xi \in C^1$, we have

$$\begin{aligned}
&\|D_e f(\phi,\xi)(0,\cdot)\|_{L_c(C,\mathbb{R})}\\
&= \left|\frac{\partial_3\alpha\big(\phi^0, \phi(-\tau^{\phi^0}), \xi(-\tau^{\phi^0})\big)\left(1+\gamma(\phi^0)\dot\tau(\phi^0)\right)}{\left(1+\dot\tau(\phi^0)\alpha\big(\phi^0,\phi(-\tau^{\phi^0}),\xi(-\tau^{\phi^0})\big)\right)^2}\right|\\
&= \left|\frac{\partial_3\alpha\big(\mathrm{Ev}_0(\phi), \mathrm{Ev}(\phi,-\tau(\mathrm{Ev}_0(\phi))), \mathrm{Ev}(\xi,-\tau(\mathrm{Ev}_0(\phi)))\big)\left(1+\gamma(\mathrm{Ev}_0(\phi))\dot\tau(\mathrm{Ev}_0(\phi))\right)}{\left(1+\dot\tau(\mathrm{Ev}_0(\phi))\alpha\big(\mathrm{Ev}_0(\phi), \mathrm{Ev}(\phi,-\tau(\mathrm{Ev}_0(\phi))), \mathrm{Ev}(\xi,-\tau(\mathrm{Ev}_0(\phi)))\big)\right)^2}\right|.
\end{aligned} \tag{7.14}$$

We observe that the maps $C^1 \times C^1 \to \mathbb{R}$,

$(\phi,\xi) \mapsto \alpha\big((\mathrm{Ev}_0 \circ \mathrm{pr}_1) \times (\mathrm{Ev} \circ (\mathrm{pr}_1 \times (-\tau \circ \mathrm{Ev}_0 \circ \mathrm{pr}_1))) \times (\mathrm{Ev} \circ (\mathrm{pr}_2 \times (-\tau \circ \mathrm{Ev}_0 \circ \mathrm{pr}_1)))\big)(\phi,\xi)$,

$(\phi,\xi) \mapsto \partial_3\alpha\big((\mathrm{Ev}_0 \circ \mathrm{pr}_1) \times (\mathrm{Ev} \circ (\mathrm{pr}_1 \times (-\tau \circ \mathrm{Ev}_0 \circ \mathrm{pr}_1))) \times (\mathrm{Ev} \circ (\mathrm{pr}_2 \times (-\tau \circ \mathrm{Ev}_0 \circ \mathrm{pr}_1)))\big)(\phi,\xi)$,

$(\phi,\xi) \mapsto \gamma \circ (\mathrm{Ev}_0 \circ \mathrm{pr}_1)(\phi,\xi)$,

$(\phi,\xi) \mapsto \dot\tau \circ (\mathrm{Ev}_0 \circ \mathrm{pr}_1)(\phi,\xi)$,

are continuous, as α, γ and τ are C^1-functions and the evaluation maps Ev, Ev_0 are continuous. If follows that also the map

$$C^1 \times C^1 \to \mathbb{R},\ (\phi,\xi) \mapsto \|D_e f(\phi,\xi)(0,\cdot)\|_{L_c(C,\mathbb{R})},$$

defined by (7.14), is continuous.

(g8*) For all $\phi \in C^2$, with $\|\phi\|_{C^2} < 1$, and for $s \in [0,1]$, we have

$$\begin{aligned}
&\big|(Df(s\phi, s\partial\phi) - Df(0,0))\,(0,\partial\phi)\big|\\
&= \left|\partial_3 g\left(\phi_s^0, s\phi(-\tau_s^{\phi^0}), s\dot\phi(-\tau_s^{\phi^0})\right)\dot\phi(-\tau_s^{\phi^0}) - \partial_3 g(0,0,0)\dot\phi(-\tau(0))\right|\\
&\le \left|\partial_3 g\left(\phi_s^0, s\phi(-\tau_s^{\phi^0}), s\dot\phi(-\tau_s^{\phi^0})\right)\right|\left|\dot\phi(-\tau_s^{\phi^0}) - \dot\phi(-\tau(0))\right|\\
&\quad + \left|\partial_3 g\left(\phi_s^0, s\phi(-\tau_s^{\phi^0}), s\dot\phi(-\tau_s^{\phi^0})\right) - \partial_3 g(0,0,0)\right|\left|\dot\phi(-\tau(0))\right|\\
&\le \max_{\substack{|\nu|,\,|\nu_1|\le\|s\phi\|_C\\ |\eta|\le\|s\partial\phi\|_C}} \left|\partial_3 g(\nu,\nu_1,\eta)\right| \|\partial\partial\phi\|_C \max_{|\nu|\le\|s\phi\|_C} |\dot\tau(\nu)|\ \|s\phi\|_C\\
&\quad + \Bigg[\max_{\substack{|\nu|,\,|\nu_1|\le\|s\phi\|_C\\ |\eta|\le\|s\partial\phi\|_C}} |\partial_3 g(\nu,\nu_1,\eta) - \partial_3 g(\nu,\nu_1,0)| + \max_{|\nu|,\,|\nu_1|\le\|s\phi\|_C} |\partial_3 g(\nu,\nu_1,0) - \partial_3 g(\nu,0,0)|\\
&\qquad + \max_{|\nu|\le\|s\phi\|_C} |\partial_3 g(\nu,0,0) - \partial_3 g(0,0,0)|\Bigg] \max_{\tau(0)\le|z|\le h} |\dot\phi(-z)|.
\end{aligned}$$

Define now the value

$$c_1 = \max_{\substack{|z_j|\le 1\\ j=1,2,3}} |\partial_3 g(z_1,z_2,z_3)| \max_{|\nu|\le 1} |\dot\tau(\nu)|,$$

and the function $\vartheta : [0,\infty) \to [0,\infty)$, given by

$$\begin{aligned} y \mapsto \vartheta(y) = &\max_{\substack{|z_j|\le y\\ j=1,2,3}} |\partial_3 g(z_1,z_2,z_3) - \partial_3 g(z_1,z_2,0)| + \max_{\substack{|z_j|\le y\\ j=1,2}} |\partial_3 g(z_1,z_2,0) - \partial_3 g(z_1,0,0)| \\ &+ \max_{|z|\le y} |\partial_3 g(z,0,0) - \partial_3 g(0,0,0)|. \end{aligned}$$

The function ϑ is continuous (indeed, $\partial_3 g$ is continuous) and $\vartheta(0)=0$. The estimate in (g8*) holds with $\Delta = \tau(0) \in (0,h)$.

(g9) For all $\phi \in C^2$, with $\|\phi\|_{C^2} < 1$ and $s \in [0,1]$ we have

$$\begin{aligned} &\left|(Df(s\phi, s\partial\phi) - Df(0,0))(\phi,0)\right| \\ &= \big|\partial_1 g(\phi_s^0, s\phi(-\tau_s^{\phi^0}), s\dot\phi(-\tau_s^{\phi^0}))\phi(0) - \partial_1 g(0,0,0)\phi(0) \\ &\quad + \partial_2 g(\phi_s^0, s\phi(-\tau_s^{\phi^0}), s\dot\phi(-\tau_s^{\phi^0}))\phi(-\tau_s^{\phi^0}) - \partial_2 g(0,0,0)\phi(-\tau(0)) \\ &\quad + \partial_2 g(\phi_s^0, s\phi(-\tau_s^{\phi^0}), s\dot\phi(-\tau_s^{\phi^0}))\, s\dot\phi(-\tau_s^{\phi^0})\dot\tau(\phi_s^0)\phi(0) \\ &\quad + \partial_3 g(\phi_s^0, s\phi(-\tau_s^{\phi^0}), s\dot\phi(-\tau_s^{\phi^0}))\, s\ddot\phi(-\tau_s^{\phi^0})\dot\tau(\phi_s^0)\phi(0)\big| \\ &\le \Bigg[\max_{\substack{|\nu|,|\nu_1|\le\|s\phi\|_C\\ |\eta|\le\|s\partial\phi\|_C}} |\partial_1 g(\nu,\nu_1,\eta) - \partial_1 g(\nu,\nu_1,0)| + \max_{|\nu|,\,|\nu_1|\le\|s\phi\|_C} |\partial_1 g(\nu,\nu_1,0) - \partial_1 g(\nu,0,0)| \\ &\quad + \max_{|\nu|\le\|s\phi\|_C} |\partial_1 g(\nu,0,0) - \partial_1 g(0,0,0)|\Bigg] \|\phi\|_C \\ &\quad + \Bigg[\max_{\substack{|\nu|,\,|\nu_1|\le\|s\phi\|_C\\ |\eta|\le\|s\partial\phi\|_C}} |\partial_2 g(\nu,\nu_1,\eta) - \partial_2 g(\nu,\nu_1,0)| + \max_{|\nu|,\,|\nu_1|\le\|s\phi\|_C} |\partial_2 g(\nu,\nu_1,0) - \partial_2 g(\nu,0,0)| \\ &\quad + \max_{|\nu|\le\|s\phi\|_C} |\partial_2 g(\nu,0,0) - \partial_2 g(0,0,0)|\Bigg] \|\phi\|_C \\ &\quad + \max_{\substack{|\nu|,\,|\nu_1|\le\|s\phi\|_C\\ |\eta|\le\|s\partial\phi\|_C}} |\partial_2 g(\nu,\nu_1,\eta)|\ \|\partial\phi\|_C \max_{|\nu|\le\|s\phi\|_C} |\dot\tau(\nu)|\,\|s\phi\|_C \\ &\quad + \max_{\substack{|\nu|,\,|\nu_1|\le\|s\phi\|_C\\ |\eta|\le\|s\partial\phi\|_C}} |\partial_2 g(\nu,\nu_1,\eta)|\,\|s\partial\phi\|_C \max_{|\nu|\le\|s\phi\|_C} |\dot\tau(\nu)|\,\|\phi\|_C \\ &\quad + \max_{\substack{|\nu|,\,|\nu_1|\le\|s\phi\|_C\\ |\eta|\le\|s\partial\phi\|_C}} |\partial_3 g(\nu,\nu_1,\eta)|\,\|s\partial\partial\phi\|_C \max_{|\nu|\le\|s\phi\|_C} |\dot\tau(\nu)|\,\|\phi\|_C\,. \end{aligned}$$

At this point one could introduce the explicit expression of the partial derivatives of g (cf. the proof of (g3) above) and find better estimates, but this would only make the computation more bulky. The estimate in (g9) can be obtained by defining the value

$$c = \max_{|z|\le 1} |\dot{\tau}(z)| \left(\max_{\substack{|z_j|\le 1\\ j=1,2,3}} |\partial_2 g(z_1,z_2,z_3)| + \max_{\substack{|z_j|\le 1\\ j=1,2,3}} |\partial_3 g(z_1,z_2,z_3)| \right) + 1,$$

and the function $\zeta : [0,\infty) \to [0,\infty)$,

$$\begin{aligned} y \mapsto{}& y + \max_{\substack{|z_j|\le y\\ j=1,2,3}} |\partial_1 g(z_1,z_2,z_3) - \partial_1 g(z_1,z_2,0)| + \max_{\substack{|z_j|\le y\\ j=1,2}} |\partial_1 g(z_1,z_2,0) - \partial_1 g(z_1,0,0)| \\ &+ \max_{|z|\le y} |\partial_1 g(z,0,0) - \partial_1 g(0,0,0)| + \max_{\substack{|z_j|\le y\\ j=1,2,3}} |\partial_2 g(z_1,z_2,z_3) - \partial_2 g(z_1,z_2,0)| \\ &+ \max_{\substack{|z_j|\le y\\ j=1,2}} |\partial_2 g(z_1,z_2,0) - \partial_2 g(z_1,0,0)| + \max_{|z|\le y} |\partial_2 g(z,0,0) - \partial_2 g(0,0,0)|. \end{aligned}$$

It is now easy to see that ζ is continuous (the derivatives $\partial_j g$, $j = 1,2$ are continuous) and $\zeta(0) = 0$.

□

7.3. The Neutral Equation (3.24)

In Section 3.2 we have presented the neutral equation (3.24), with state-dependent delay $\tau = \tau(x(t))$. Here we consider a special case of (3.24) with constant death rate for juveniles, $\mu_0(x) \equiv \mu_0 > 0$,

$$\dot{x}(t) = \frac{\beta_{t,\tau} - \tilde{\mu}_1(x(t))}{1 + \dot{\tau}(x(t))\beta_{t,\tau}}, \tag{7.15}$$

with

$$\beta_{t,\tau} = \left[\tilde{b}_1(x(t-\tau)) + b_2(x(t-\tau)) \frac{\dot{x}(t-\tau) + \tilde{\mu}_1(x(t-\tau))}{1 - \dot{\tau}(x(t-\tau))\dot{x}(t-\tau)} \right] e^{-\mu_0 \tau(x(t))}.$$

All results below could be extended without difficulties to the general case (3.24). Equation (7.15) expresses the dynamics of a population x of adult individuals, under the assumption that the length of the juvenile period (τ) depends on the number of adults. For more details about equation (7.15), we refer to Section 3.2. Here, we simply report few assumptions.

(i) $\tau : \mathbb{R} \to (0,h)$ is a nonnegative, monotonically increasing (not necessarily strictly increasing), C^2-function with property (3.5).

(ii) $\tilde{b}_1(y) = b_1(y)y$, and $b_1 : [0,\infty) \to [0,B_1]$, $B_1 < \infty$ is a nonnegative, monotonically decreasing (not necessarily strictly decreasing), continuously differentiable function.

(iii) $b_2 : [0,\infty) \to [0,B_2]$, $B_2 \in (B_1,\infty)$ is a nonnegative, monotonically decreasing (not necessarily strictly decreasing), C^1-function and $b_2 \not\equiv 0$ (otherwise, we have no neutral term in the equation).

(iv) $\mu_0 > 0$ is a nonnegative constant.

(v) $\tilde{\mu}_1(y) = \mu_1(y)y$, and $\mu_1 : [0,\infty) \to [0,\infty)$ is a nonnegative, monotonically increasing (not necessarily strictly increasing), C^1-function.

Equation (7.15) is an example[2] from the class of equations (7.12), with

$$\alpha(w,y,z) = \left(\tilde{b}_1(y) + b_2(y)\frac{z+\tilde{\mu}_1(y)}{1-\dot{\tau}(y)z}\right) e^{-\mu_0\tau(w)} \qquad \text{and} \qquad \gamma(w) = \tilde{\mu}_1(w).$$

Analogously to the case considered in Section 7.1.3, we are interested here in the stability properties of a nonzero equilibrium $\bar{x} \in \mathbb{R}$ of (7.15). In the NFDE notation, we assume that there exists a nonzero function $\bar{\phi} \in C^2$, $\bar{\phi} : [-h,0] \ni s \mapsto \bar{\phi}(s) = \bar{x} \in \mathbb{R}$, such that

$$f(\bar{\phi},0) = 0 \;\Leftrightarrow\; \alpha(\bar{x},\bar{x},0) = \gamma(\bar{x}).$$

Equivalently, the point $\bar{x} \neq 0$ satisfies

$$\tilde{b}_1(\bar{x}) + b_2(\bar{x})\tilde{\mu}_1(\bar{x})e^{-\mu_0\bar{\tau}} = \tilde{\mu}_1(\bar{x}), \tag{7.16}$$

with $\bar{\tau} = \tau(\bar{x})$. By Theorem 7.3 and Proposition 6.5, we associate to (7.15) a linear variational equation along $(\bar{\phi},0)$,

$$\dot{v}(t) = D_e f(\bar{\phi},0)(v_t,\partial v_t).$$

By (7.13), we find

$$\dot{v}(t) = \partial_1 g\,(\bar{x},\bar{x},0)\,v(t) + \partial_2 g\,(\bar{x},\bar{x},0)\,v(t-\tau(\bar{x})) + \partial_3 g\,(\bar{x},\bar{x},0)\,\dot{v}(t-\tau(\bar{x})),$$

with

$$\begin{aligned}
\partial_1 g(\bar{x},\bar{x},0) &= \frac{\partial_1\alpha(\bar{x},\bar{x},0)}{1+\dot{\tau}(\bar{x})\alpha(\bar{x},\bar{x},0)} - \frac{\dot{\gamma}(\bar{x})}{1+\dot{\tau}(\bar{x})\alpha(\bar{x},\bar{x},0)},\\
\partial_2 g(\bar{x},\bar{x},0) &= \frac{\partial_2\alpha(\bar{x},\bar{x},0)(1+\gamma(\bar{x})\dot{\tau}(\bar{x}))}{(1+\dot{\tau}(\bar{x})\alpha(\bar{x},\bar{x},0))^2},\\
\partial_3 g(\bar{x},\bar{x},0) &= \frac{\partial_3\alpha(\bar{x},\bar{x},0)(1+\gamma(\bar{x})\dot{\tau}(\bar{x}))}{(1+\dot{\tau}(\bar{x})\alpha(\bar{x},\bar{x},0))^2}.
\end{aligned}$$

With the partial derivatives of α,

$$\begin{aligned}
\partial_1\alpha(w,y,z) &= -\mu_0\dot{\tau}(w)\alpha(w,y,z),\\
\partial_2\alpha(w,y,z) &= \left(\dot{\tilde{b}}_1(y) + \frac{\dot{b}_2(y)(z+\tilde{\mu}_1(y)) + b_2(y)\dot{\tilde{\mu}}_1(y)}{1-\dot{\tau}(y)z} + b_2(y)\frac{(z+\tilde{\mu}_1(y))\ddot{\tau}(y)z}{(1-\dot{\tau}(y)z)^2}\right) e^{-\mu_0\tau(w)},\\
\partial_3\alpha(w,y,z) &= \frac{b_2(y)(1+\dot{\tau}(y)\tilde{\mu}_1(y))}{(1-\dot{\tau}(y)z)^2}e^{-\mu_0\tau(w)},
\end{aligned}$$

[2]Concerning the nonnegativity of $\alpha(w,y,z)$, notice that $\tilde{b}_1(y) \geq 0$, $b_2(y) \geq 0$ for all $y \in [0,\infty)$. Further, in Section 3.2 we had found the connection (3.27) between the population density $p(t,a) \geq 0$ and the neutral equation (7.15).

and the condition at equilibrium (7.16), we find the linear equation

$$\begin{aligned}\dot{v}(t) = &-\frac{\tilde{\mu}_1(\bar{x})\mu_0\,\dot{\tau}(x)\big|_{x=\bar{x}} + \dot{\tilde{\mu}}_1(x)\big|_{x=\bar{x}}}{1+\dot{\tau}(x)\big|_{x=\bar{x}}\,\tilde{\mu}_1(\bar{x})}v(t)\\ &+\frac{\dot{\tilde{b}}_1(x)|_{x=\bar{x}} + \frac{d}{dx}\big(b_2(x)\tilde{\mu}_1(x)\big)|_{x=\bar{x}}}{1+\dot{\tau}(x)\big|_{x=\bar{x}}\,\tilde{\mu}_1(\bar{x})}e^{-\mu_0\bar{\tau}}v(t-\bar{\tau})\\ &+b_2(\bar{x})e^{-\mu_0\bar{\tau}}\dot{v}(t-\bar{\tau}),\end{aligned} \tag{7.17}$$

with $\bar{\tau} = \tau(\bar{x})$. Similarly to the case presented in Section 7.1.3, equation (7.17) is a standard linear neutral equation with one constant delay $\bar{\tau}$,

$$\dot{\eta}(t) + A\dot{\eta}(t-\bar{\tau}) + B\eta(t) + C\eta(t-\bar{\tau}) = 0,$$

and constant coefficients

$$\begin{aligned} A &= -b_2(\bar{x})e^{-\mu_0\bar{\tau}},\\ B &= \frac{\tilde{\mu}_1(\bar{x})\mu_0\,\dot{\tau}(x)\big|_{x=\bar{x}} + \dot{\tilde{\mu}}_1(x)\big|_{x=\bar{x}}}{1+\dot{\tau}(x)\big|_{x=\bar{x}}\,\tilde{\mu}_1(\bar{x})},\\ C &= -\frac{\dot{\tilde{b}}_1(x)|_{x=\bar{x}} + \frac{d}{dx}\big(b_2(x)\tilde{\mu}_1(x)\big)|_{x=\bar{x}}}{1+\dot{\tau}(x)\big|_{x=\bar{x}}\,\tilde{\mu}_1(\bar{x})}e^{-\mu_0\bar{\tau}}.\end{aligned}$$

The stability of the equilibrium $\bar{x}$ can be investigated with help of the scheme in Section 7.1.3. For example, let us consider the same birth, death, and delay functions as in Section 3.5,

$$b_1(x) = \alpha_1 e^{-\kappa_1 x}, \quad \mu_1(x) = \gamma + \delta x, \quad b_2(x) = \alpha_2 e^{-\kappa_2 x}, \quad \tau(x) = \tau_0 + (\tau_1 - \tau_0)\frac{x}{T+x},$$

with parameter values as in Table 7.1 and initial data $x(t) = 10, t < 0$. In this setting, there exists a nontrivial equilibrium $\bar{x} \approx 8.7074$ and the delay at the equilibrium is $\bar{\tau} = \tau(\bar{x}) \approx 10.25$. The coefficients of the linear equation (7.17) can be determined by direct computation: $A \approx -0.384$, $B \approx 0.08324$, and $C \approx 0.1469$. So, we have $|A| < 1$, $C^2 > B^2$ and $C + B > 0$. According to the scheme in Section 7.1.3, there exists a value $\tau^* > 0$ at which a stability change occurs. A simple calculation yields $\tau^* \approx 13.706$. Thus, we have $\bar{\tau} < \tau^*$ and the solution converges asymptotically to the nontrivial equilibrium $\bar{x}$, as it is shown by the numerical simulation in Figure 7.1. For the numerics of NFDEs we refer to Section 3.5.

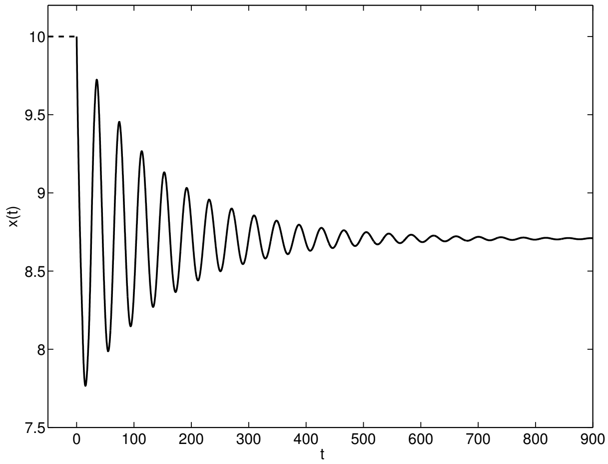


Figure 7.1: Numerical simulation of a solution of (7.15). With initial data $x(t) = 10$, $t < 0$, and parameter values in Table 7.1, we find a nontrivial equilibrium $\bar{x} \approx 8.7074$ and we have that $\bar{\tau} < \tau^*$. Thus, the solution converges asymptotically to $\bar{x}$.

Table 7.1: Parameter values for numerical simulations of the neutral equation (7.15).

Symbol	**Description**	**Value**
α_1	Net fertility rate	5.2
κ_1	Discount rate due to adult population	0.6
α_2	Net fertility rate (age-at-maturity)	30.5
κ_2	Discount rate due to adult population (age-at-maturity)	0.5
γ	Death rate in absence of other individuals	0.001
δ	Death due to presence of other individuals	0.005
τ_0	Minimal age-at-maturity	2
τ_1	Maximal age-at-maturity	15
T	Threshold for $\tau(x)$	5
μ_0	Death rate of juveniles	0.002

Part III.

Cell populations

8. Proliferating Tumor Cells

This part of the thesis is concerned with biological applications of delay equations (DDEs) with state-dependent and constant delays. With the help of the results in Chapters 3 and 4 we put up and analyze a model for tumor growth, based on the dynamics of the cell cycle.

In Section 8.1, a short presentation of the biological background highlights the complexity of tumoral cell proliferation.

The model we introduce in Section 8.2 is essentially obtained by the methods we presented in Chapter 3. We derive a DDE system for proliferating tumor cells from a PDE model for an age-structured cell population. Thanks to this approach, we are able to isolate phases of the cell cycle, so that the effects of, e.g., phase-specific drugs can be directly observed.

In Section 8.3 we discuss nonnegativity of solutions, look at the long term dynamics of the problem and investigate the stability of the tumor-free equilibrium.

The last section presents numerical simulations of the interplay between tumor cells and immune system effectors. Our aim is to investigate the dynamics of a solid tumor cured with mitosis-specific drugs and immunotherapy. As it was observed in [107], the time between two consecutive cell divisions (i.e., the time a cell stays in the *interphase*) is affected by medicaments. When drug concentration is high, tumor cells stay longer in the interphase. We shall observe the effects of different interphase durations on the dynamics of the tumor cell population.

8.1. Mathematical Biology of Cancer

In the last thirty years, beside the efforts in medicine and radiology [119], several contributions to the description of tumor growth have been given by mathematical biology. A broad overview of mathematical approaches, from age structures [101] to multiscale modeling [28], is summed up in the book by Bellomo [16]. Further references on mathematical modeling of cancer can be found in [1, 30, 104].

One recurrent factor in the mathematical modeling of tumor growth is the classification of tumor cells in three groups: **Necrotic cells** (are dead), **quiescent cells** (are not dead, but have not enough nutrients for cell growth or division), **proliferating cells** (the active part, they undergo mitosis) [106]. A large class of models focuses on the dynamics of proliferating cells, which are responsible for the extension of the tumoral mass. In particular cell aging and cell cycle have been considered in many references [45–47, 81, 120].

When a cell divides, two new (daughter) cells of age zero are generated. The age of each one of these cells can be quantified with respect to the time at birth. The aging process carries a cell through many stages, until it is ready to divide itself into two daughter cells. More precisely, the **cell cycle** is a sequence of four phases [6,82]. The initial G_1 **phase** is necessary for the cell to grow up, before the DNA is replicated in the **S phase**. A second growth phase (G_2) follows and the **mitotic phase** (**M**) completes the cycle, with division of nucleus and cytoplasm. As a result of a completed sequence, two daughter cells enter the cycle in G_1. The first three phases are often summed up together and referred to as **interphase**. In order to guarantee an error-free replication there is a biochemical control system, which verifies at different **checkpoints** whether the processes at each phase of the cycle have been accurately completed, before progression into the next phase. If anything did not work properly, the cycle stops. Cells may also enter the G_0 **state**, or **quiescence**, in which they live in a resting state, neither growing nor dividing. It usually happens that cells lacking growth factors stop at a checkpoint, move from G_1 to G_0 and start the cycle again after a certain time [34]. Figure 8.1 presents the sequence of phases we just described.

One of the main reasons for cancer seems to be a malfunction of the control system in the cell cycle, which leads to the uncontrolled growth of groups of cells. Phase-specific drugs are designed to target cells in the mitotic phase, thus preventing from new division. Based on these facts, we set up a model which takes into account the cell cycle and describes the dynamics of tumor cells in different phases. For more realistic perspectives, the basic model is extended to include phase-specific drugs and immunotherapy.

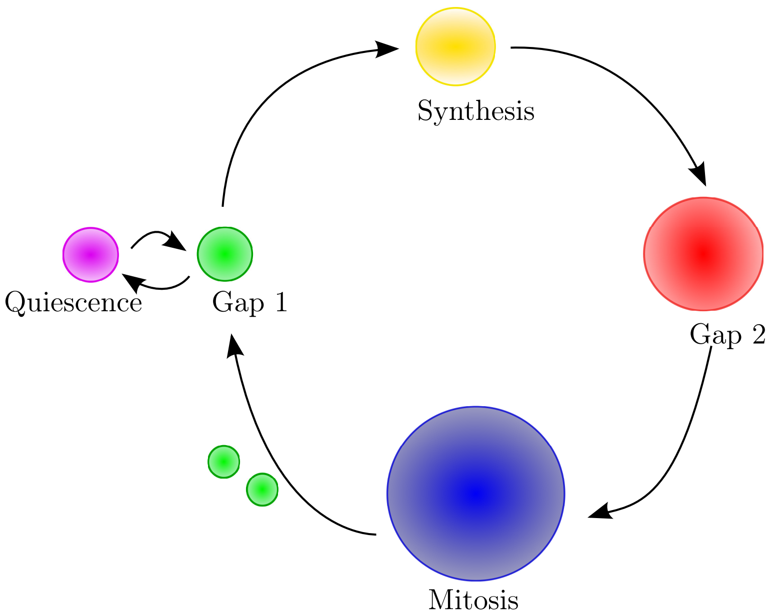


Figure 8.1: The cell cycle consists of four phases: Gap 1 (G_1), Synthesis (S), Gap 2 (G_2), Mitosis (M). Cells may also enter the quiescent state, G_0.

8.2. Mathematical Model

In this section we introduce a mathematical model for proliferating tumor cells. We start taking into account cell aging and end up with a system of delay differential equations.

Many recent works give a mathematical description of tumor growth incorporating time delays. In most cases, a constant time delay τ is introduced to accomplish one of the following tasks:

- To represent the *interphase* (the three phases G_1, S, and G_2) as the time interval in which a cell is not ready for division [25, 135].
- To describe the time it takes a cell to complete mitosis [27].
- To skip some processes [27, 105]. The delay is used to replace a chain of ODEs, as in the *linear chain trick* [85].

Concerning the use of state-dependent delays in modeling cancer biology, there have been very few published works. A recent example has been suggested by Alarcón et al. [5].

We do not really start with a delay problem, but rather use once more the connection between PDEs and DDEs (cf. Section 2.2) to derive our equations. PDE models for tumor growth have been extensively used by Dyson and coauthors [44–47], who consider proliferating and quiescent cells as populations structured by age, space and size. However, the setting we shall use is simpler and takes into account the age structure only.

8.2.1. Why Looking for a New Approach

To the best of our knowledge, two mathematical models with delay have been written to date to describe the effects of phase-specific drugs on a solid tumor. The first approach by Villasana and Radunskaya [120] describes proliferating tumor cells which undergo chemotherapy and interact with immune system effectors. Liu et al. [81] modified and extended the model in [120] including a resting state for tumoral cells.

As we have explained in Section 2.2, the standard model for an immature population (x_1) and a mature one (x_2) has the form

$$\begin{aligned} \dot{x}_1(t) &= R_1(t) - M_1(t) - \Delta_1(t), \\ \dot{x}_2(t) &= R_2(t) - M_2(t) - \Delta_2(t), \end{aligned} \tag{8.1}$$

where R_i, M_i, Δ_i are respectively recruitment, maturation and death factors of the population x_i. Recruitment into x_1 is mostly given by a birth function, whereas into x_2 it occurs by maturation only [96]. Nisbet and coauthors [19, 58, 96] showed that $M_1(t) = R_2(t)$ is indeed a function of $x_2(t-\tau)$, where $\tau > 0$ is the maturation time (cf. p. 20).

Although describing basically an immature (interphase cells) and a mature (mitotic cells) population, the model by Liu et al. does not show the standard setting (8.1). Indeed, the basic system for interphase (x_1), mitotic (x_2) and quiescent (z) cells in [81] reads

$$\begin{aligned}\dot{z}(t) &= 2\alpha_2 x_2(t) - \alpha_3 z(t) - \delta_3 z(t),\\ \dot{x}_1(t) &= \alpha_3 z(t) - \alpha_1 x_1(t) - \delta_1 x_1(t),\\ \dot{x}_2(t) &= \alpha_1 x_1(t-\tau) - \alpha_2 x_2(t) - \delta_2 x_2(t).\end{aligned}$$

According to this model, $M_1(t) = \alpha_1 x_1(t)$ cells reach maturity at time t and leave the interphase. At the same time there are $R_2(t) = \alpha_1 x_1(t-\tau)$ cells which enter the mitotic phase. Thus, $M_1(t) \neq R_2(t)$, contradicting Nisbet's results. From a biological point of view, it seems there is an inconsistency in the model, as some cells are at the same time both in the compartment of mitotic cells and in the one of immature cells.

In the following we derive a delay model of the form (8.1) for interphase and mitotic cells.

8.2.2. Deriving the Equations

Our point of departure is a tumoral cell population structured by age. Let $p(t,a)$ be the density of proliferating cells of age a at time t. The dynamics of $p(t,a)$ can be described by the Lotka-Sharpe model (cf. Chapter 3),

$$\begin{aligned}\frac{\partial p}{\partial t}(t,a) + \frac{\partial p}{\partial a}(t,a) &= -\mu(a)p(t,a),\\ p(t,0) &= \int_0^\infty b(a)p(t,a)\,da,\\ p(0,a) &= \psi(a).\end{aligned} \tag{8.2}$$

As we did in Section 3.1, we assume that birth and death rates are piecewise constant functions of the age,

$$\begin{aligned}b(a) &= b_1 H_\tau(a),\\ \mu(a) &= \mu_0 + (\mu_1 - \mu_0)H_\tau(a),\end{aligned} \tag{8.3}$$

where $H_\tau(a)$ is the Heaviside function with a jump at $a = \tau$, and $b_1 > 0$, $\mu_0 \geq 0$, $\mu_1 > 0$ are real, nonnegative constants. The positive constant τ corresponds to the length in time of the interphase. Thus, equation (8.3) says that interphase cells do not divide ($b_0 = 0$) and die at rate μ_0, whereas mitotic cells divide at rate b_1 and die at rate μ_1. The biology suggests that τ is nonnegative and bounded, e.g.,

$$0 < \tau_{min} \leq \tau \leq \tau_{max} < \infty.$$

A cell, indeed, needs a certain time before it is ready for division. On the other side, it does not stay an infinite time in the first three phases of the cell cycle (the possibility that a cell becomes quiescent is considered separately).

According to the method presented in Section 3.1, we define three sub-populations of cells:

- $V(t) = \int_0^\tau p(t,a)\,da$, the total number of cells in the interphase. Interphase cells cannot divide, become quiescent at rate $\mu_Q > 0$, die at rate $\mu_0 \geq 0$.

- $U(t) = \int_\tau^\infty p(t,a)\,da$, the total number of mitotic cells. These cells divide at rate b_1 and die at rate μ_1. When division occurs, two new cells are generated and a mother cell formally dies. We include both the "natural death rate" of mitotic cells and the "death rate due to division" into μ_1 and require that $\mu_1 > b_1$.

- $Q(t)$, the total number of quiescent cells at time t. Quiescent cells do not age, do not divide [82]. They die at rate $\mu_{G_0} \geq 0$ or enter the cycle again (at rate b_Q), starting from G_1 [34].

Without loss of generality, we consider a point $(t,a) \in \mathbb{R}^+ \times \mathbb{R}^+$ with $t > a$. Because of mitosis, the number of newborn cells at time t is exactly twice the number of dividing cells at time t (cf . [133]). Further, quiescent cells which restart the cycle are considered to be of age zero. Hence, the number of cells which enter the cycle at time t is given by

$$p(0,t) = \underbrace{2\int_0^\infty b(a)p(t,a)\,da}_{\text{result of mitosis}} + \underbrace{b_Q Q(t).}_{\text{from quiescence}}$$

If follows that the density of cells of age a at time $t > a$ is given by

$$p(t,a) = \begin{cases} [2b_1 U(t-a) + b_Q Q(t-a)]\, e^{-(\mu_0+\mu_Q)a}, & \text{if} \quad a < \tau, \\ [2b_1 U(t-a) + b_Q Q(t-a)]\, e^{-(\mu_0+\mu_Q)\tau} e^{-\mu_1(a-\tau)}, & \text{if} \quad a > \tau. \end{cases}$$

An integral equation for U can be obtained by applying the method of Section 3.1. Then for $t > a > \tau$ we find

$$U(t) = \int_{-\infty}^{t-\tau} [2b_1 U(s) + b_Q Q(s)]\, e^{-(\mu_0+\mu_Q)\tau} e^{-\mu_1(t-s-\tau)}\, ds, \tag{8.4}$$

and the total mitotic population satisfies

$$\dot{U}(t) = \underbrace{[2b_1 U(t-\tau) + b_Q Q(t-\tau)]\, e^{-(\mu_0+\mu_Q)\tau}}_{\text{from interphase}} - \underbrace{\mu_1 U(t).}_{\text{death}} \tag{8.5}$$

Equation (8.5) explains the evolution in time of the mitotic cell population: A cell is in the mitotic phase at time t if it entered the cycle (i.e., it either was generated by mitosis or left the quiescent phase) at time $t-\tau$, and did not die nor become quiescent in $[t-\tau, t]$.

In Section 3.1 we obtained (3.13a) for the juvenile population (see also Appendix B). Analogously we get a DDE for interphase cells,

$$\begin{aligned}\dot V(t) &= \underbrace{2b_1U(t)}_{\text{by mitosis}} + \underbrace{b_QQ(t)}_{\text{from } G_0} - \underbrace{\big(2b_1U(t-\tau)+b_QQ(t-\tau)\big)e^{-(\mu_0+\mu_Q)\tau}}_{\text{maturation}} \\ &\quad - \underbrace{\mu_0V(t)}_{\text{death}} - \underbrace{\mu_QV(t)}_{\text{quiescence}}.\end{aligned} \tag{8.6}$$

The dynamics of quiescent cells is not characterized by age-dependent factors and we easily find

$$\dot Q(t) = \underbrace{\mu_QV(t)}_{\text{from } G_1} - \underbrace{b_QQ(t)}_{\text{enter } G_1} - \underbrace{\mu_{G_0}Q(t)}_{\text{death}}. \tag{8.7}$$

Altogether we have a system of two DDEs (8.5)–(8.6) and an ODE (8.7) for proliferating tumor cells. If we neglect quiescence, system (8.5)–(8.6) reduces to

$$\begin{aligned}\dot U(t) &= 2b_1U(t-\tau)e^{-\mu_0\tau} - \mu_1U(t)\\ \dot V(t) &= 2b_1\big(U(t)-U(t-\tau)e^{-\mu_0\tau}\big) - \mu_0V(t),\end{aligned}$$

which has the form (8.1).

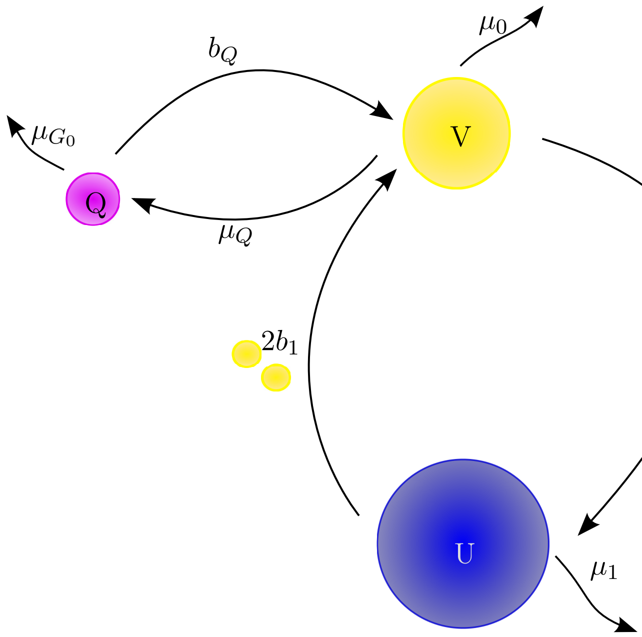


Figure 8.2: Schematic illustration of model (8.5)–(8.7) for quiescent (Q), mitotic (U) and interphase (V) cells.

As in Section 3.1, we could have chosen a state-dependent delay τ. For example, we may assume that the interphase duration at time t depends on the total number of mitotic cells at time t, and that $\tau = \tau(U(t))$ is a monotonically increasing, nonnegative, bounded, continuously differentiable function. From a biological point of view, this means that more adult cells consume more nutrients and can slow down the growth process of new cells. In other words, the more mitotic cells we have, the longer a new generated cell remains in the interphase.

By a formal derivation (cf. Section 3.1), we obtain the following nonlinear system

$$\begin{aligned}
\dot{U}(t) &= \frac{\big[2b_1U(t-\tau(U(t))) + b_QQ(t-\tau(U(t)))\big]e^{-(\mu_0+\mu_Q)\tau(U(t))} - \mu_1U(t)}{1+\dot{\tau}(U(t))\big[2b_1U(t-\tau(U(t))) + b_QQ(t-\tau(U(t)))\big]e^{-(\mu_0+\mu_Q)\tau(U(t))}},\\
\dot{V}(t) &= 2b_1\big[U(t) - U(t-\tau(U(t)))e^{-(\mu_0+\mu_Q)\tau(U(t))}\big]\\
&\quad + b_Q\big[Q(t) - Q(t-\tau(U(t)))e^{-(\mu_0+\mu_Q)\tau(U(t))}\big] - (\mu_0+\mu_Q)V(t)\\
&\quad + \dot{\tau}(U(t))\dot{U}(t)\big[2b_1U(t-\tau(U(t))) + b_QQ(t-\tau(U(t)))\big]e^{-(\mu_0+\mu_Q)\tau(U(t))},\\
\dot{Q}(t) &= \mu_QV(t) - (b_Q+\mu_{G_0})Q(t).
\end{aligned} \tag{8.8}$$

To be precise, nutrient consumption is due to all kind of cells, not only to mitotic cells. Consequently, the delay should be a function of the total cell population, that is, $\tau = \tau(N(t))$, where $N(t) = U(t) + Q(t) + V(t)$. Further, external factors, such as drugs, were found out to affect the interphase duration [107]. So one could choose $\tau = \tau(D(t))$, $D(t)$ being the drug concentration at time t.

However, system (8.8) is not really easy to handle and a more complicate delay function would make the model almost inaccessible to the analysis. As a mathematical model should stay simple, while being as detailed as necessary, we opt for the easiest approach and choose a constant delay $\tau > 0$. At the same time, we extend the basic model (8.5)–(8.7) by including drug concentration (D) and immune system effector cells (I) and obtain

$$\begin{aligned}
\dot{Q}(t) &= \mu_QV(t) - b_QQ(t) - \mu_{G_0}Q(t) - k_QI(t)Q(t),\\
\dot{U}(t) &= \big(2b_1U(t-\tau) + b_QQ(t-\tau)\big)e^{-(\mu_0+\mu_Q)\tau - k_0\int_0^\tau I(t-\tau+\sigma)d\sigma}\\
&\qquad - U(t)\big(\mu_1 + k_2I(t) + k_5(1-e^{-k_3D(t)})\big),\\
\dot{V}(t) &= 2b_1U(t) + b_QQ(t) - V(t)\big(\mu_0 + \mu_Q + k_0I(t)\big)\\
&\qquad - \big(2b_1U(t-\tau) + b_QQ(t-\tau)\big)e^{-(\mu_0+\mu_Q)\tau - k_0\int_0^\tau I(t-\tau+\sigma)d\sigma},\\
\dot{I}(t) &= k + \rho I(t)\frac{(Q(t)+U(t)+V(t))^n}{\alpha + (Q(t)+U(t)+V(t))^n} - \delta_4I(t)\\
&\qquad - \big(c_1Q(t) + c_2U(t) + c_3V(t)\big)I(t) - k_6(1-e^{-k_7D(t)})I(t),\\
\dot{D}(t) &= -\gamma D(t).
\end{aligned} \tag{8.9}$$

Once again, this model is derived by the method presented in Section 3.1. With respect to (8.5)–(8.7), we changed the death rates of quiescent, interphase and mitotic cells by including the effects of drugs and immune system effectors. Table 8.1 gives an overview of variables and parameters in (8.9), whereas Figure 8.3 shows the model compartments.

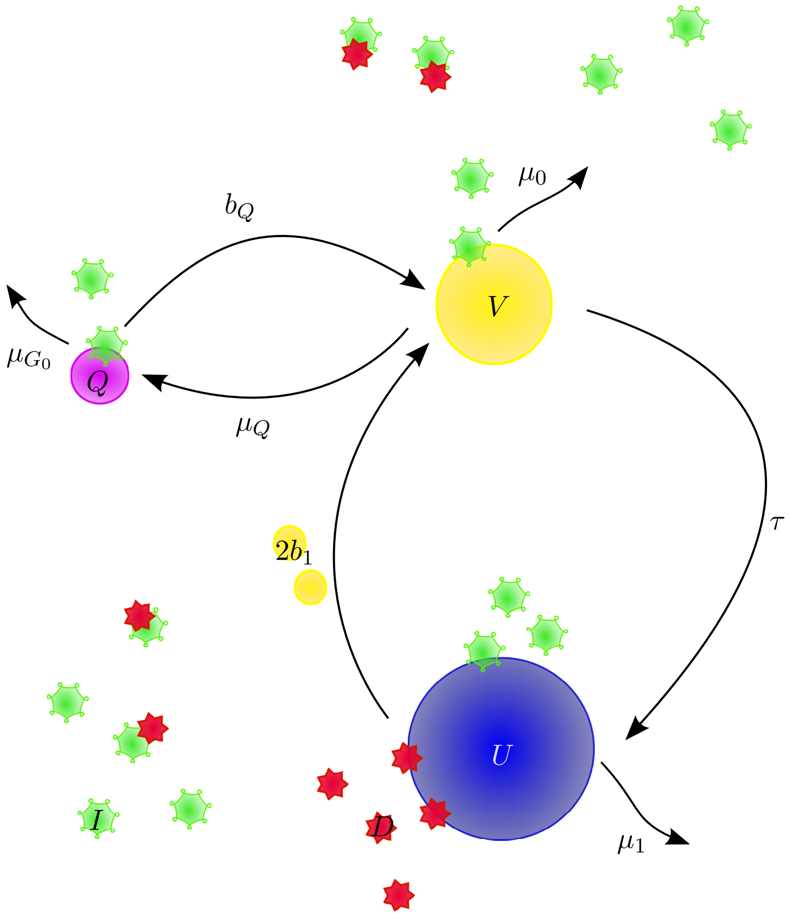


Figure 8.3: Schematic illustration of model (8.9) for interphase (V), quiescent (Q) and mitotic (U) tumoral cells, immune system effectors (I) and drugs (D).

Immune system effectors (also called *lymphocytes*) are introduced into the body at a hypothetical constant rate $k > 0$. In Section 8.4 we will modify k by a periodic immunotherapy. When lymphocytes detect tumor cells, they are activated (at rate $\rho > 0$) and start to defend the body. Quiescent, mitotic and interphase cells are killed by immune system effectors at rate $k_Q > 0$, $k_2 > 0$ and $k_0 > 0$, respectively. Unfortunately, lymphocytes do not always survive an aggression to the tumoral mass. We assume that lymphocytes die at constant rate $c_1 \geq 0$, $c_2 \geq 0$, $c_3 \geq 0$ when they encounter quiescent, mitotic and interphase cells, respectively. Natural death of lymphocytes occurs at rate $\delta_4 > 0$. Further, we assume that there is a phase-specific drug, injected once at time $t = 0$, which targets mitotic cells only. The drug-induced death rate of mitotic cells, $k_5(1 - e^{-k_3 D(t)})$, depends on drug concentration at time t, with $k_3 > 0$, $k_5 > 0$. Lymphocytes (and also cells of the healthy tissue, which we do not consider here) may be killed by drugs as well (at rate $k_6(1 - e^{-k_7 D(t)})$, with $k_6 > 0$, $k_7 > 0$). Drug usage and decay occur at constant loss rate $\gamma > 0$, as in [81, 120].

The biology of the human immune system and its interplay with tumoral cells are actually two complex topics, and we shall discuss none of them in the thesis. Biological references in this field can be found in [55, 99]. Concerning the mathematical modeling of the competition between immune system effector cells and tumor, besides the above-mentioned books [16, 104], we like to indicate the works by D'Onofrio [38–40] which have been inspiring for the setting we shall present in Section 8.4.

Table 8.1: Description of variables and parameters in system (8.9).

Symbol	Description of the variable
$V(t)$	Number of interphase cells at time t
$U(t)$	Number of mitotic cells at time t
$Q(t)$	Number of quiescent cells at time t
$I(t)$	Immune system effector cells (ISE) at time t
$D(t)$	Drug concentration at time t
τ	Time duration of the interphase
μ_0	Death rate of interphase cells
μ_Q	Transition rate from G_1 to G_0
b_1	Division rate of mitotic cells
μ_1	Death rate of mitotic cells
μ_{G_0}	Death rate of quiescent cells
b_Q	Transition rate from G_0 to G_1
k	Basic ISE production
ρ	Tumor-induced ISE activation rate
n	Nonlinearity of tumor-immune system competition
α	Threshold for the immune system activation
c_1	Loss of lymphocytes due to interaction with quiescent cells
c_2	Loss of lymphocytes due to interaction with mitotic cells
c_3	Loss of lymphocytes due to interaction with interphase cells
δ_4	Death rate of lymphocytes
k_0	Effectiveness of immune system on interphase cells
k_Q	Effectiveness of immune system on quiescent cells
k_2	Effectiveness of immune system on mitotic cells
k_3	Effectiveness of drugs on mitotic cells
k_5	Drug-induced death rate of mitotic cells (maximum value)
k_6	Drug-induced death rate of lymphocytes (maximum value)
k_7	Effectiveness of drugs on lymphocytes
γ	Drug degradation rate

8.3. Analytical Results

In this section we consider (8.9) from an analytical point of view. First we focus on positivity of solutions and provide an ODE system, which describes the dynamics of proliferating tumor cells in the interval $[0, \tau]$. Further we identify fixed points of (8.9) and give criteria for the stability of the disease-free steady state.

8.3.1. Nonnegativity of Solutions and Proper Initial Data

A recurrent challenge in mathematical biology is due to the fact that solutions are not allowed to leave the positive cone, or a part of it. In this context it is important to mention that, despite nonnegative initial data, systems of delay equations may show negative solutions [115]. Nonnegativity of solutions of DDE systems for population dynamics has been previously considered, e.g., in [4, 20].

The first delay model for tumor growth, given in [120], was questioned by Liu et al. [81] mainly because it was showing negative solutions in positive time. Liu et al. [81] introduced an alternative model whose structure guarantees positive solutions (cf. [115]). We have explained in Section 8.2 the reasons why also this second model needs to be improved and have proposed new delay models, which can be obtained by a PDE setting. Unluckily, neither our simple model (8.5)–(8.7), nor its extended version (8.9) can a priori ensure positivity of solutions. However, we can derive a system of differential equations, which provides information in the time interval $[0, \tau]$, as we show below.

Let us consider the simple delay model (8.5)–(8.7) for tumoral cells only. Without difficulties, all results could be extended to the larger model (8.9). System (8.5)–(8.7) holds for all $t \geq \tau$. The challenge is to define what happens for a time $t < \tau$. To this purpose, it will be convenient to consider once more the Lotka-Sharpe model (8.2). For $t < \tau$, the solution of the balance equation depends on the initial distribution $\psi(a)$ (cf. p. 31). Define

$$u_0(s) = \psi(s), \ s < \tau,$$

and indicate by $u_0(\tau - t)$ the density of cells of age $\tau - t$ at time 0. At time t these cells are of age τ and, consequently, enter the class of mitotic cells. Being related to the initial distribution of the age-structured population, the last consideration holds for interphase and mitotic cells, but not for quiescent cells. These cells, indeed, do not age [82]. Quiescent cells enter the cycle from G_1 and we believe them to be of "age zero" when they restart cycling. A quiescent cell which reenters the cycle must spend a time τ in the interphase, before passing to the mitotic phase. This transition does not occur as long as $t < \tau$.

The above thoughts suggest that for $t < \tau$ we have

$$\begin{aligned} \dot{V}(t) &= 2b_1 U(t) + b_Q Q(t) - u_0(\tau - t)e^{-(\mu_0+\mu_Q)t} - (\mu_0 + \mu_Q)V(t), \\ \dot{U}(t) &= u_0(\tau - t)e^{-(\mu_0+\mu_Q)t} - \mu_1 U(t), \\ \dot{Q}(t) &= \mu_Q V(t) - (b_Q + \mu_{G_0})Q(t). \end{aligned} \tag{8.10}$$

Analogously to (3.15), which was derived from the Lotka-Sharpe model (3.1)–(3.3), the last system can be obtained from (8.2). System (8.10) describes the cell dynamics in $[0, \tau]$ and represents the correct expression of initial data for (8.5)–(8.7).

However, the solution of (8.10) depends on the initial age distribution $\psi(a)$ of the PDE model (8.2). When $\psi(a)$ is known, one can compute the solution of (8.10) and use it as history function for the DDE problem (8.5)–(8.7). In this case positivity of solutions is preserved and guaranteed by the well-posedness of the PDE problem [111,131] and by the formal derivation of the ODE (8.10) and DDE (8.5)–(8.7) problems. In case ψ is unknown things get more challenging. Although we shall not further consider the question in this thesis, it is probably possible to identify a set of "good" history functions, which guarantee positivity of solutions of the delay model. In [20], Bocharov and Hadeler defined such a set of initial data for a simpler problem.

8.3.2. Stability of Equilibria

In the sequel we provide a qualitative investigation of the models introduced in Section 8.2. First we consider the ODE system ($\tau = 0$) corresponding to (8.9) and simplifications thereof. To this purpose we make use of well-known results on linear and nonlinear dynamics, which can be found in the standard literature on dynamical systems [57]. In the second part of this section we consider the problem with delay.

Simple ODE model: Tumor cells, no immunotherapy, no chemotherapy

We observe tumor cells only, neglecting both, immunotherapy and chemotherapy. The simple model is given by

$$\begin{aligned} \dot{Q}(t) &= \mu_Q V(t) - (b_Q + \mu_{G_0})Q(t), \\ \dot{U}(t) &= 2b_1 U(t) + b_Q Q(t) - \mu_1 U(t), \\ \dot{V}(t) &= -(\mu_0 + \mu_Q)V(t). \end{aligned} \tag{8.11}$$

This is a linear system with the single stationary state $P_3^* = (0, 0, 0)$.

Result 2. *The stationary state P_3^* is locally asymptotically stable, if $b_1 < \frac{\mu_1}{2}$.*

Proof. The stability of P_3^* is determined by the eigenvalues

$$\lambda_1 = -b_Q - \mu_{G_0}, \qquad \lambda_2 = 2b_1 - \mu_1, \qquad \lambda_3 = -\mu_0 - \mu_Q,$$

of the coefficient matrix

$$A = \begin{pmatrix} -(b_Q + \mu_{G_0}) & 0 & \mu_Q \\ b_Q & 2b_1 - \mu_1 & 0 \\ 0 & 0 & -(\mu_0 + \mu_Q) \end{pmatrix}.$$

As $\lambda_1 < 0$ and $\lambda_3 < 0$, the point P_3^* is locally asymptotically stable if $\lambda_2 < 0$. □

In other words, if the death rate μ_1 of the mitotic cells is large, compared to the division rate b_1, then the tumor will vanish at a point.

ODE model with immunotherapy, no chemotherapy

Inclusion of immunotherapeutic effects into the basic ODE model (8.11) yields

$$\begin{aligned}
\dot{Q}(t) &= \mu_Q V(t) - b_Q Q(t) - \mu_{G_0} Q(t) - k_Q I(t) Q(t),\\
\dot{U}(t) &= 2b_1 U(t) + b_Q Q(t) - U(t)(\mu_1 + k_2 I(t)),\\
\dot{V}(t) &= -V(t)(\mu_0 + \mu_Q + k_0 I(t)),\\
\dot{I}(t) &= k + \rho I(t) \frac{(Q(t)+U(t)+V(t))^n}{\alpha + (Q(t)+U(t)+V(t))^n}\\
&\quad - \delta_4 I(t) - (c_1 Q(t) + c_2 U(t) + c_3 V(t)) I(t).
\end{aligned}$$

As we are particularly interested in long term growth (or eradication) of the tumor, we investigate the stability of the cancer-free equilibrium $P_4^* = \left(0,0,0,\frac{k}{\delta_4}\right)$.

Result 3. *If the parameter values satisfy*

$$\delta_4(\mu_1 - 2b_1) + k_2 k > 0,$$

then the tumor-free equilibrium P_4^* is locally asymptotically stable.

Proof. We linearize the system at P_4^* and get the Jacobian matrix, $B = J(P_4^*)$,

$$B = \begin{pmatrix} -\left(b_Q + \mu_{G_0} + \frac{k_Q k}{\delta_4}\right) & 0 & \mu_Q & 0\\ b_Q & 2b_1 - \mu_1 - \frac{k_2 k}{\delta_4} & 0 & 0\\ 0 & 0 & -\left(\mu_0 + \mu_Q + \frac{k_1 k}{\delta_4}\right) & 0\\ -\frac{c_1 k}{\delta_4} & -\frac{c_2 k}{\delta_4} & -\frac{c_3 k}{\delta_4} & -\delta_4 \end{pmatrix}, \tag{8.12}$$

with eigenvalues

$$\begin{aligned}
\lambda_1 &= -\delta_4,\\
\lambda_2 &= -\frac{1}{\delta_4}(\mu_1 \delta_4 + k_2 k - 2b_1 \delta_4),\\
\lambda_3 &= -\frac{1}{\delta_4}(k_1 k + \mu_0 \delta_4 + \mu_Q \delta_4),\\
\lambda_4 &= -\frac{1}{\delta_4}(k_Q k + b_Q \delta_4 + \mu_{G_0} \delta_4).
\end{aligned}$$

All eigenvalues are real and λ_1, λ_3 and λ_4 are negative. Hence, P_4^* is stable if $\lambda_2 < 0$. □

So, when $\mu_1 - 2b_1 > 0$, we have $\delta_4(\mu_1 - 2b_1) + k_2 k > 0$ and the tumor would be defeated, even without immune system interaction (cf. Result 2). In case of $\mu_1 - 2b_1 < 0$, either a low death rate (δ_4) of the lymphocytes, high lymphocytes production (k) or high immune system effectiveness (k_2) are necessary for tumor eradication. The stability condition for the tumor-free steady state can be written in the form: $k > \frac{\delta_4}{k_2}(2b_1 - \mu_1)$. It is indeed practical to have a stability condition in terms of k, as this parameter can be controlled from outside, for example by immunotherapeutic treatments (cf. Section 8.4).

ODE model with immuno- and chemotherapy

Finally we consider the complete model (8.9), for $\tau = 0$. The tumor-free steady state is

$$P_5^* = \left(0, 0, 0, \frac{k}{\delta_4}, 0\right).$$

The corresponding Jacobian matrix is

$$C = J_5\left(P_5^*\right) = \begin{pmatrix} & & B & & 0 \\ & & & & 0 \\ & & & & 0 \\ & & & & -\frac{k_6 k}{\delta_4} \\ 0 & 0 & 0 & 0 & -\gamma \end{pmatrix},$$

where B is the Jacobian matrix (8.12).
Thus, the spectrum of C is

$$\sigma(C) = \sigma(B) \cup \{-\gamma\}.$$

Because of $\gamma > 0$, the stability conditions in Result 3 stay unchanged, even when chemotherapy is included in the model.

DDE model

As in Villasana [120], we neglect the quiescent phase and consider a model for interphase and mitotic cells only,

$$\dot{U}(t) = 2b_1 U(t-\tau)e^{-\mu_0\tau} - \mu_1 U(t), \tag{8.13a}$$

$$\dot{V}(t) = 2b_1\left(U(t) - U(t-\tau)e^{-\mu_0\tau}\right) - \mu_0 V(t). \tag{8.13b}$$

In this case the only stationary point is $P^* = (U^*, V^*) = (0, 0)$. To determine stability, it is not necessary to investigate the roots of the characteristic equation of the system. Indeed, the equation for U, (8.13a), is autonomous. Due to the structure of equation (8.13b), it is sufficient to determine stability conditions for $U^* = 0$, to have the corresponding conditions for the trivial equilibrium. Equation (8.13a) is linear and has a "positivity structure", that is, whenever $U(t) = 0$, the right hand-side is nonnegative (cf. [114]). In this case, the dominant root of the characteristic equation must be real [114, 115]. Thus it is sufficient to investigate real roots of

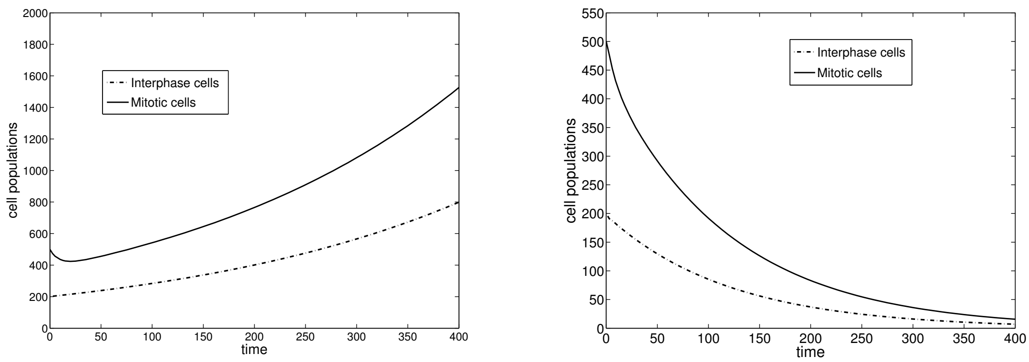
$$z + \mu_1 - 2b_1 e^{-\mu_0\tau}e^{-z\tau} = 0. \tag{8.14}$$

Real roots $z \in \mathbb{R}$ of (8.14) are given by intersections of the line $y = z + \mu_1$ with the curve $y = 2b_1 e^{-\mu_0\tau - z\tau}$. If $2b_1 e^{-\mu_0\tau} < \mu_1$, then there is no intersection in the positive half-plane, hence there is no characteristic root z, with $Re(z) > 0$. If the parameter values are such that $2b_1 e^{-\mu_0\tau} > \mu_1$, then the two curves intersect at some point z, with $Re(z) > 0$ and the fixed point P^* becomes unstable. An equivalent condition for instability can be formulated in terms of the delay.

Proposition 8.1. *Consider the delay system (8.13) for mitotic and interphase tumor cells. The stability of the tumor-free steady state P^* depends on the parameters as follows.*

- *For all $\tau > \widehat{\tau} = \frac{1}{\mu_0} \ln\left(\frac{2b_1}{\mu_1}\right)$, the dominant characteristic root of (8.14) lies in the negative half-plane and P^* is stable.*
- *For $\tau < \widehat{\tau}$ the point P^* is unstable.*

In other words, if cells divide too often, or, equivalently, the interphase is very short, the tumor size will explode because of the large number of mitotic cells. Numerical simulations in Figure 8.4 show an application of the above result. With parameter values and initial data chosen as in Appendix A, Table A.2, a stability switch occurs at $\widehat{\tau} \approx 5.27$. For $\tau = 5$ the cancer-free equilibrium is unstable (Figure 8.4(a)), whereas for $\tau = 6$ it is stable (Figure 8.4(b)).



(a) Instability of P^* for $\tau = 5$. (b) Stability of P^* with $\tau = 6$.

Figure 8.4: A stability switch occurs at $\widehat{\tau} \approx 5.27$. For $\tau = 5$ the cancer-free equilibrium P^* is unstable (a), whereas for $\tau = 6$ it is stable (b). In this numerical simulation we have moved the starting point to $t = 0$ (the shifting is possible because of time-invariance of autonomous systems). Parameter values and initial data are given in Appendix A Table A.2.

8.4. Effects of Periodic Immunotherapy

In this section we focus on cancer treatments, in particular on immunotherapy. Cancer immunotherapy aims to stimulate the immune system and provides a support for the body, in order to better fight the tumor. More and more immunotherapeutic treatments are preferred over chemotherapy, since the effectors of the immune system are more specific than drugs in their actions: They target cancer cells only and leave the vast majority of healthy cells untouched [31].

As suggested by d'Onofrio [39], a constant immunotherapy is not applicable in practice, and it is rather an idealization of a periodic treatment. To simulate the effects of immunotherapy, we generalize the equation for I in (8.9) by introducing a function ϑ for the stimulation of the immune system over time,

$$\begin{aligned}\dot{I}(t) = \vartheta(t) + \rho I(t) \frac{(Q(t)+U(t)+V(t))^n}{\alpha + (Q(t)+U(t)+V(t))^n} - \delta_4 I(t) \\ - (c_1 Q(t) + c_2 U(t) + c_3 V(t)) I(t).\end{aligned}$$

We choose three different expressions for ϑ from those proposed in [38–40]:

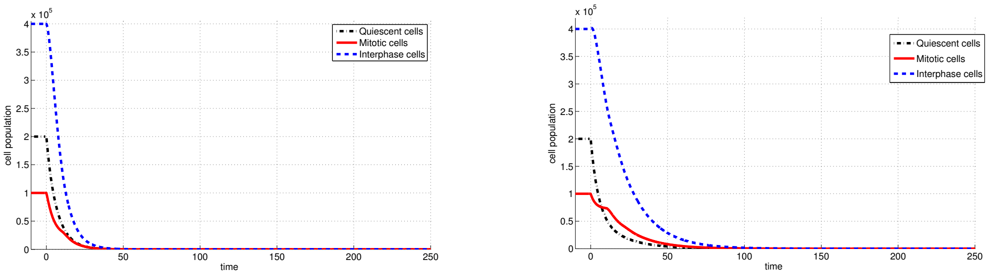
- $\vartheta(t) = \vartheta_0(t) = k$, constant immunotherapy, as considered in the previous sections.
- $\vartheta(t) = \vartheta_1(t) = k\left(1 + \cos\left(\frac{2\pi}{T} t\right)\right)$, an idealized T-periodic therapy, which is reminiscent of periodic forcing.
- $\vartheta(t) = \vartheta_2(t) = k \exp\left(-\frac{1}{\gamma_I} \mathrm{Mod}(t, T)\right)$ is a more realistic T-periodic therapy. Here k is the delivered drugs concentration, γ_I the degradation rate of drugs in the body and T the time between two consecutive deliveries. $\mathrm{Mod}(t, T)$ is the result of $t \bmod T$.

Numerical simulations help us to visualize the effects of each one of the above treatments on a tumoral mass. We assume that the patient undergoes immunotherapy from the very beginning. Unless other specifications are made, we use parameter values and initial data, as in Appendix A, Tables A.3 and A.4. Parameter values are mostly taken from [81, 120] or derived from these works. In all our plots, the time scale is shifted of τ, i.e., we move the starting point to $t = 0$. This shifting is possible because of time-invariance of autonomous systems (cf. Chapter 4).

Constant Treatment $\vartheta_0(t)$

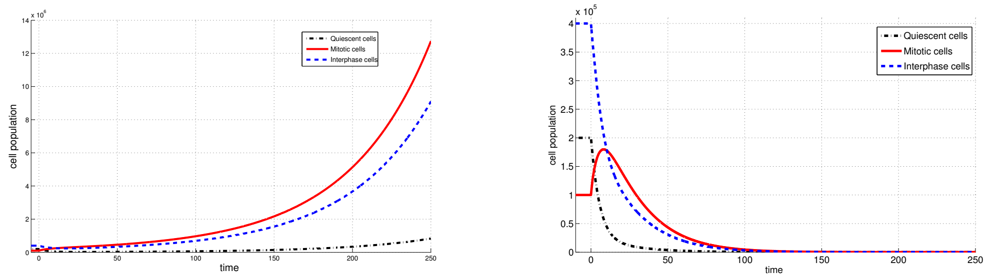
We start with the numerical simulation of a constant therapy $\vartheta(t) = \vartheta_0(t)$. We may observe (Figure 8.5) that when the time between one mitosis and the next one is large (that is, the delay τ) and the division rate is small, the tumor vanishes independent of the delivered dose (cf. Section 8.3).

However, cancer is due to the uncontrolled growth of cells, so a large division rate ($b_1 = 0.20$) is plausible. Further, we assume that the interphase duration is short ($\tau = 2$) and we look at the effects of constant immunotherapy. Increasing the dose can be a winning strategy: The tumor vanishes when the immune system is highly stimulated (Figure 8.6).



(a) $\vartheta_0 : \; k = 2 \cdot 10^6$. (b) $\vartheta_0 : \; k = 2 \cdot 10^4$.

Figure 8.5: Effects of a constant therapy ϑ_0 on mitotic (red), interphase (blue) and quiescent cells (black). When the time between one mitosis and the next one is large ($\tau = 10$) and the division rate is small ($b_1 = 0.12$), the tumor vanishes independent of the delivered immunotherapy dose.



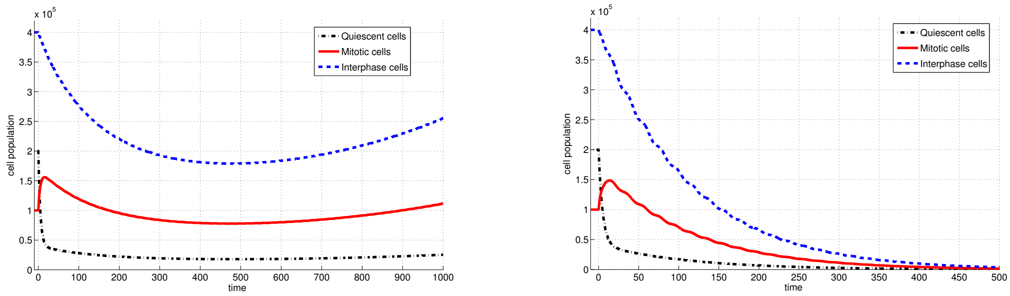
(a) $\vartheta_0 : \; k = 2 \cdot 10^4$. (b) $\vartheta_0 : \; k = 2 \cdot 10^6$.

Figure 8.6: Effects of a constant therapy ϑ_0 on mitotic (red), interphase (blue) and quiescent cells (black). Short interphase duration ($\tau = 2$) and (a) large cell division rate ($b_1 = 0.20$) lead to tumor growth. (b) Immunotherapy can stop cell proliferation.

Periodic Treatment

As a constant immunotherapy is not possible in practice [39], we shall look at the effects of an idealized periodic treatment, $\vartheta(t) = \vartheta_1(t) = k\left(1 + \cos\left(\frac{2\pi}{T}t\right)\right)$, where k is the mean value of ϑ over one period of length T.

If we consider the simple model (8.13) with parameter values as in Table A.4, we find a stability switch at $\widehat{\tau} \approx 5.97$. For $\tau < \widehat{\tau}$ the tumor-free stationary point P^* is unstable. So we choose $\tau = 5.5$ and investigate the effects of therapies on the tumor. Let us assume a time $T = 20$ (days) between one therapy delivery and the next one, and choose $k = 2 \cdot 10^4$ as the mean value for the therapy. This strategy is not effective and the tumor escapes the immunosurveillance (Figure 8.7(a)). However, when we administer a larger dose, e.g., $k = 2 \cdot 10^6$, tumor proliferation can be stopped (Figure 8.7(b)). Similar happens when applying an intermediate drug concentration ($k = 5 \cdot 10^4$) at larger time intervals ($T = 50$), see Figure 8.8.



(a) $\vartheta_1:\ T = 20,\ k = 2 \cdot 10^4$.

(b) $\vartheta_1:\ T = 20,\ k = 2 \cdot 10^6$.

Figure 8.7: Effects of a periodic immunotherapy $\vartheta_1(t)$ on mitotic (red), interphase (blue) and quiescent cells (black). We fix the time, $T = 20$ days, between two consecutive deliveries. (a) With $k = 2 \cdot 10^4$ the tumor escapes immunosurveillance. (b) Large immunotherapy dose ($k = 2 \cdot 10^6$) can stop tumor proliferation.

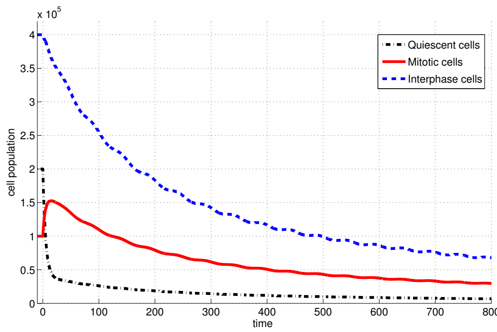


Figure 8.8: Effects of a periodic immunotherapy $\vartheta_1(t)$ on mitotic (red curve), interphase (blue curve) and quiescent cells (black curve). We can achieve a compromise: Therapy delivered at intervals of $T = 50$ (days), with intermediate drug concentration ($k = 5 \cdot 10^4$), reduces cell proliferation.

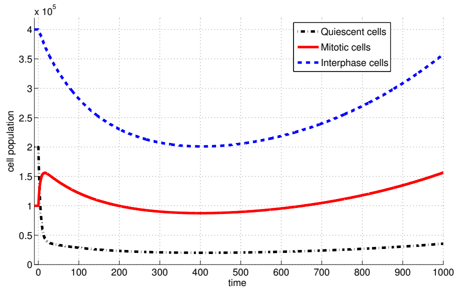
Similar results hold for a T-periodic treatment in the form $\vartheta(t) = \vartheta_2(t)$. This expression is more correct than the one given by $\vartheta_1(t)$, as it takes into account degradation of drugs over time. Here, k describes the immunotherapy dose at time $t = nT$, for $n \in \mathbb{N}_0$. Drug decay occurs at constant rate $1/\gamma_I$, and $\gamma_I \approx 0$ corresponds to a very fast decay. For $\gamma_I \to \infty$, the function $\vartheta_2(t)$ approaches a constant therapy. The mean value of ϑ_2 is given by $[\vartheta] = k\gamma_I\big(1 - \exp(-T/\gamma_I)\big)/T$.

From a medical point of view, varying the decay parameter γ_I might be difficult, thus for our numerical simulations, we fix the value of γ_I and investigate the effects of T and k on the cell populations. For $T = 20$ and $k = 2 \cdot 10^4$ (Figure 8.9(a)) or $k = 4 \cdot 10^4$ (Figure 8.9(b)) the tumor grows larger (cf. the previous case and Figure 8.7(a)). Reducing the gap between two consecutive deliveries or administering a larger dose to the patient, tumor eradication would be possible, as in the limit the constant therapy ϑ_0 is approached. However, we would like to achieve a compromise (not too much medicament, nor too often), as in the case of the ϑ_1-therapy. This is indeed possible. For example, a weekly ($T = 7$ days) dose of $k = 4 \cdot 10^4$ is sufficient to reduce the tumor size (Figure 8.10(a)). Similar results can be achieved by giving to the patient a larger dose ($k = 6 \cdot 10^4$) every 15 days (Figure 8.10(b)).

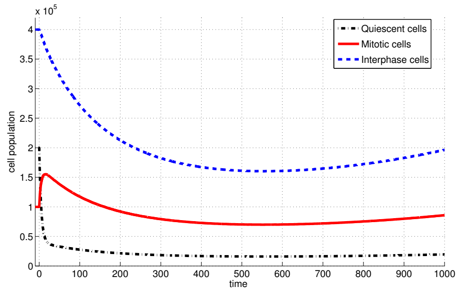
As it was observed by Santiago-Mozos et al. [107], the time between two consecutive divisions (i.e., the interphase duration) is affected by medicaments. When the drug concentration is high, tumor cells stay longer in the interphase (or perhaps in a quiescent state). Our results suggest that, if we manage to extend the interphase duration up to a certain time interval, then the tumor can be defeated by chemotherapy or by a combination of chemotherapy and immunotherapy.

One could possibly extend (8.9) by including into the model a state-dependent delay $\tau(D)$, where $D(t)$ is the drug concentration at time t.

It is true that we have not achieved complete eradication of the tumoral mass, but only its reduction. This is often the aim of medical doctors, when complete eradication of the tumor is not possible.

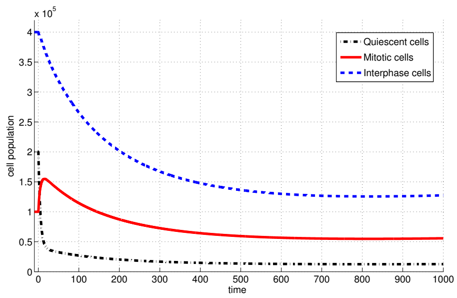


(a) $\vartheta_2: \ T = 20, \ k = 2 \cdot 10^4$.

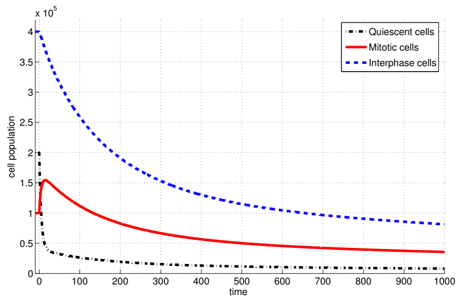


(b) $\vartheta_2: \ T = 20, \ k = 4 \cdot 10^4$.

Figure 8.9: Effects of a periodic immunotherapy $\vartheta_2(t)$ on mitotic (red), interphase (blue) and quiescent cells (black). We fix the time, $T = 20$ days, between two consecutive therapy deliveries. With $k = 2 \cdot 10^4$ or $k = 4 \cdot 10^4$ the tumor escapes immunosurveillance.



(a) $\vartheta_2: \ T = 7, \ k = 4 \cdot 10^4$.



(b) $\vartheta_2: \ T = 15, \ k = 6 \cdot 10^4$.

Figure 8.10: Effects of a periodic immunotherapy $\vartheta_2(t)$ on mitotic (red), interphase (blue) and quiescent cells (black). We observe that weekly ($T = 7$) or biweekly ($T = 15$) drug delivery, with intermediate drug concentration ($k = 4 \cdot 10^4$, respectively $k = 6 \cdot 10^4$), notably reduces cell proliferation.

9. Conclusion

To conclude the thesis we summarize our results and suggest directions for future research.

9.1. Summary

In this thesis we have introduced a new class of neutral differential equations (NFDEs) with state-dependent delay for the dynamics of an isolated population. Possibly, this is the first application of NFDEs with state-dependent delay in mathematical population biology.

The point of departure was a system of partial differential equations (PDEs) of the Gurtin-MacCamy type for a population structured by age. From the point of view of experimentalists, it is almost impossible to collect data for a continuum of age classes. For many species, however, members life cycle can be classified into few stages (e.g., eggs, larvae, pupae, adults), so that biologists are often able to determine the number of individuals in each stage (that is, the size of each sub-population).

To reduce the complexity of the structured model, we have distinguished the sub-population of immature individuals from the one of mature individuals, by introducing an age threshold, dependent on the adult population size. We have assumed that there is a peak in the fertility rate of individuals when they reach maturity, and have shown that we can derive an autonomous NFDE, equation (3.24), with state-dependent delay for the adult sub-population. Further, we have proved that there is a connection between the solutions of the PDE model and those of the neutral equation.

The *state-dependent blowfly equation* is a special case of the class of NFDEs, which we have considered. A comparison between this equation and the well-known *blowfly equation* has shown that a state-dependent delay, with respect to a constant one, might have a stabilizing effect. The last result could be verified both from an analytical and a numerical point of view. It is worth noticing that the *state-dependent blowfly equation*, which we have obtained by a formal derivation from the age-structured model, is different from the equation one would get by replacing the constant delay by a state-dependent one.

To the theory of neutral functional differential equations contributes the thesis with three new results. First, we have proved that, under certain smoothness conditions on the derivative of the right-hand side of the NFDE, we obtain local Lipschitz continuity of the right-hand side itself. A similar result did already exist for retarded functional differential equations. We have provided an extension to the class of NFDEs. Our result seems to be useful in applications, in particular for the investigation of linearized stability of semiflows generated by neutral equations with state-dependent delays.

The recent works [129, 130] provide methods for linearization of semiflows of certain classes of NFDEs with state-dependent delay about the zero solution. In Section 6.4.2 we have generalized these results, showing how to linearize semiflows from neutral equations with state-dependent delays about nontrivial equilibria. This result is also important in applications of NFDEs. Indeed, in applications one is mostly interested in the stability properties of nontrivial stationary points.

Perhaps the most relevant contribution of the thesis is the new hypothesis (g8*) which extends Walther's framework, allowing for the analysis of a wider class of neutral equations with state-dependent delay. Importantly, with the newly introduced hypothesis, the principle of linearized stability from [130] for semiflows of solutions generated by NFDEs with state-dependent delay still holds. We like to remark that, at present there is no general theory for neutral equations with state-dependent delay. All results in this thesis and in [124, 129, 130] have been tested only on few classes of neutral equations with state-dependent delays. In the future it might happen that working on some more general examples, one has to further modify existing results.

With help of the achieved results we have provided a qualitative analysis of two new classes of nonlinear NFDEs with state-dependent delay. In particular, we have discussed existence, uniqueness, smoothness and long term behavior of solutions of equation (3.24).

In the last part of the thesis, we have presented a system of delay differential equations for proliferating tumor cells. Our model allows to simulate the effects of phase-specific drugs, which target cells in the mitotic phase, and immunotherapeutic treatments on a tumoral mass. The result has significantly improved the models in [81, 120], both from a mathematical and a biological point of view.

Although this might be an oversimplification of the real-life phenomenon, we have chosen a constant delay approach. Our aim was to give results for the dynamics of a solid tumor cured with mitosis-specific drugs and immunotherapy. As it has been observed in [107], the time between two consecutive cell divisions (i.e., the length of the interphase) is affected by medicaments. At high drug concentration tumor cells stay longer in the interphase. Our results suggest that, if we manage to prolong the interphase duration, we can reduce tumor growth by drugs only, or with the parallel support of immunotherapy. In a future approach, a state-dependent delay $\tau(D)$, where $D(t)$ is the drug concentration at time t, might be included into the model.

We have briefly discussed nonnegativity of solutions. In general, for systems of delay equations, nonnegative initial data do not guarantee nonnegativity of solutions. We have determined an ODE system on the interval $[0, \tau]$, whose solutions are proper initial data for the delay system, in the sense that they guarantee nonnegativity of solutions. It might still be possible to identify a larger set of "good" history functions, which guarantee nonnegativity of solutions of the delay model.

In the future we would like to verify and validate the model through a comparison to medical data. This would allow for a better understanding of tumor growth and perhaps for the definition of criteria for tumor reduction or, in the best case, eradication.

9.2. Perspectives

An immediate continuation of this thesis could be a deeper analysis of the neutral equation (3.24) with state-dependent delay for population dynamics. Indeed, we have first derived the equation from a PDE model and have then moved to the analysis of more general classes of problems. It would be interesting to go back to the original problem, consider it again in the context of population dynamics and investigate, e.g., effects of model parameters on the dynamics of the system. A comparison to possible experimental data would be of interest. Further, one could extend the modeling approach to describe interacting species. This would lead to systems of NFDEs with state-dependent delay and perhaps to further theoretical questions.

Concerning the theory of neutral equations with state-dependent delay, there is much work which could be done. To the best of our knowledge, there are no results on global stability of NFDEs with state-dependent delay. A potential starting point could be the investigation of global stability conditions for the two classes of NFDEs discussed in Chapter 7.

From the point of view of dynamical systems, Eichmann [48] proved a local Hopf bifurcation theorem for equations with state-dependent delay. The achievement of an analogous result for NFDEs with state-dependent delay is one of our future goals. Also in this case, the starting point could be a special class of NFDEs with state-dependent delay, perhaps an example from physics or biology.

We have not particularly emphasized that the numerics of (neutral) equations with state-dependent delay is a challenging topic. For the numerical simulation of all models in this thesis, we implemented a simple solver (essentially an implicit continuous Runge-Kutta method) in MATLAB®. Among the existing solvers for delay equations, not many are suitable to solve neutral state-dependent or stiff problems. This is the reason why we have chosen to write our own solver. In the future, it could be possible to extend the code to compute numerical solutions to more general classes of (neutral) problems with state-dependent delay. Thinking of applications, e.g., in biology, the solver might be used in the framework of parameter identification.

A. Setting for Numerical Simulations

This part contains details, such as parameter values and initial conditions, of all numerical simulations in the thesis. The content is organized as follows:

1) Table A.1: Parameter values for numerical simulations in Figure 2.1 and Figure 2.2, p. 13.

2) Table A.2: Parameter values for numerical simulations in Figure 8.4, p. 138.

3) Table A.3: Main setting for numerical simulations in Chapter 8.

4) Table A.4: Parameter values and initial data for numerical simulations in Section 8.4.

Table A.1: Parameter values and initial data for simulations in Figures 2.1 and 2.2.

Symbol	**Description**	**Value**
$x(0)$	Initial value for equation (2.2)	10
b	Reproduction rate in (2.2)	0.2
K	Environment capacity in (2.2)	100
$x(t) \equiv \phi_x$, $t \leq 0$	History function for equation (2.3)	10
b	Reproduction rate in (2.3)	0.8
K	Environment capacity in (2.3)	100
r	Time delay in (2.3)	3
$x(t) \equiv \phi_x$, $t \leq 0$	History function for (2.5) (cf. [100])	100
$b(x)$	Reproduction rate in (2.5) (cf. [100])	$\begin{cases} \hat{b}_0 - \hat{b}_1 x, \text{ if } \hat{b}_0/\hat{b}_1 > x, \\ 0, \text{ if } \hat{b}_0/\hat{b}_1 < x \end{cases}$
$\hat{b}_0$	Basic reproduction rate (cf. [100])	4
$\hat{b}_1$	Population-dependent reproduction rate (cf. [100])	0.01
$\mu(x) \equiv \mu$	Death rate in (2.5) (cf. [100])	1
τ	Time from birth to maturity	2 and 6

Table A.2: Parameter values and history functions for numerical simulation in Figure 8.4.

Symbol	**Description**	**Dimension**	**Value**
b_1	Division rate of mitotic cells	$[\text{time}]^{-1}$	0.25
- - -	All other parameter values	- - -	as in Table A.3
$V(0) = V_0$	Initial value for V	[cells]	200
$U(t) \equiv U_0$, $t \leq 0$	Constant history function for U	[cells]	500

Table A.3: Parameter values for numerical simulations in Chapter 8.

Symbol	Description	Dimension	Value
μ_0	Death rate of interphase cells	$[\text{time}]^{-1}$	0.11
μ_Q	Transition rate from G_1 to G_0	$[\text{time}]^{-1}$	0.02
b_1	Division rate of mitotic cells	$[\text{time}]^{-1}$	in text
μ_1	Death rate of mitotic cells	$[\text{time}]^{-1}$	0.28
μ_{G_0}	Death rate of quiescent cells	$[\text{time}]^{-1}$	$0.1 \cdot 10^{-4}$
b_Q	Transition rate from G_0 to G_1	$[\text{time}]^{-1}$	0.2
k	Basic ISE production rate	$[\text{cells}] \cdot [\text{time}]^{-1}$	$0.15 \cdot 10^{6}$
ρ	Tumor induced ISE activation rate	$[\text{time}]^{-1}$	0.2
n	Nonlinearity of tumor-IS competition	no dimension	3
α	Threshold for ISE activation	$[\text{cells}]^{n}$	$0.5 \cdot 10^{6}$
c_1	Loss of lymphocytes due to Q-cells	$[\text{cells} \cdot \text{time}]^{-1}$	$0.2 \cdot 10^{-6}$
c_2	Loss of lymphocytes due to U-cell	$[\text{cells} \cdot \text{time}]^{-1}$	$0.8 \cdot 10^{-7}$
c_3	Loss of lymphocytes due to V-cell	$[\text{cells} \cdot \text{time}]^{-1}$	$0.108 \cdot 10^{-6}$
δ_4	Death rate of lymphocytes	$[\text{time}]^{-1}$	0.3
k_0	Effectiveness of ISE on V-cells	$[\text{cells} \cdot \text{time}]^{-1}$	$0.1 \cdot 10^{-7}$
k_Q	Effectiveness of ISE on Q-cells	$[\text{cells} \cdot \text{time}]^{-1}$	$0.1 \cdot 10^{-8}$
k_2	Effectiveness of ISE on U-cells	$[\text{cells} \cdot \text{time}]^{-1}$	$0.4 \cdot 10^{-8}$
k_3	Effectiveness of drug on U-cells	$[\text{concentration}]^{-1}$	$0.25 \cdot 10^{-3}$
k_5	Drug-induced death rate of U-cells	$[\text{time}]^{-1}$	0.7
k_6	Drug-induced death rate of ISE	$[\text{time}]^{-1}$	0.3
k_7	Effectiveness of drug on ISE	$[\text{concentration}]^{-1}$	$0.5 \cdot 10^{-2}$
γ	Drug degradation rate	$[\text{time}]^{-1}$	$0.3 \cdot 10^{-2}$

Table A.4: Parameter values and initial data for numerical simulations in Section 8.4.

Symbol	Description	Dimension	Value
b_1	Division rate of mitotic cells	$[\text{time}]^{-1}$	0.27
τ	Interphase duration	[time]	5.5
k	Maximal immunotherapy dose	$[\text{cells}] \cdot [\text{time}]^{-1}$	in text
T	Time between two consecutive deliveries	[time]	20
γ	Drug degradation rate	$[\text{time}]^{-1}$	20
- - -	All other parameter values	- - -	as in Table A.3
	Initial Data		
$Q(t) \equiv Q_0,\ t \in [-20, 0]$	Constant history function for Q	[cells]	$2 \cdot 10^{5}$
$U(t) \equiv U_0,\ t \in [-20, 0]$	Constant history function for U	[cells]	$1 \cdot 10^{5}$
$V(0) = V_0$	Initial value for V	[cells]	$4 \cdot 10^{5}$
$I(0) = I_0$	Initial value for I	[cells]	$3 \cdot 10^{5}$
$D(0) = D_0$	Initial value for D	[concentration]	100

B. Further Analytical Results

In the sequel we provide results related to Section 3.1, which have not been included in the main part of the thesis. To ease the notation, we denote the state-dependent delay $\tau(x(t))$ by τ only.

Equation for juveniles in Section 3.1

In the following we show how to derive equation (3.13a).

Recall the definition (3.4) of $y(t)$, the population size of juveniles at time t. We consider a time $t > h$ and assume that the solution $p(t, a)$ of (3.1) exists for all times previous to t and all $a \geq 0$. With (3.10), the population size of juvenile individuals at time t satisfies

$$\begin{aligned} y(t) &= b_1 \int_0^{\tau} x(t-a) e^{-\int_0^a \mu(\sigma) d\sigma} da \\ &= b_1 \int_{t-\tau}^{t} x(s) e^{-\int_0^{t-s} \mu(\sigma) d\sigma} ds. \end{aligned}$$

Differentiation with respect to the time yields

$$\begin{aligned} \dot{y}(t) = b_1 &\left[x(t) - x(t-\tau) e^{-\int_0^{\tau} \mu(\sigma) d\sigma} \big(1 - \dot{\tau}(x(t)) \dot{x}(t)\big) \right] \\ &- b_1 \int_{t-\tau}^{t} x(s) e^{-\int_0^{t-s} \mu(\sigma) d\sigma} \mu(t-s) ds. \end{aligned}$$

Observe that for $s \in [t-\tau, t]$ we have $t - s \in [0, \tau]$. With the definition of death rate in (3.6), we find

$$b_1 \int_{t-\tau}^{t} x(s) e^{-\int_0^{t-s} \mu(\sigma) d\sigma} \mu(t-s)\, ds = b_1 \int_{t-\tau}^{t} x(s) e^{-\int_0^{t-s} \mu(\sigma) d\sigma} \mu_0 \, ds = \mu_0 y(t).$$

All in all, we have obtained a differential equation for y, namely,

$$\dot{y}(t) = b_1 \left[x(t) - x(t-\tau) e^{-\mu_0 \tau} \big(1 - \dot{\tau}(x(t)) \dot{x}(t)\big) \right] - \mu_0 y(t).$$

Dynamics in the case $t < \tau_0$

Recall the definition (3.4) of $x(t)$, the population size of adult individuals at time t. In the following we show how to derive (3.15b). Analogously, one can obtain (3.15a).

We consider the case $t \leq a$ and recall the explicit solution (3.14) of (3.1)–(3.3).

The population size of adult individuals at time $t < \tau$ is given by

$$\begin{aligned} x(t) &= \int_{\tau}^{\infty} \psi(a-t) \exp\left(-\int_0^t \mu(a-t+s)\,ds\right) da \\ &= \int_{\tau-t}^{\infty} \psi(z) \exp\left(-\int_0^t \mu(z+s)\,ds\right) dz. \end{aligned}$$

It is biologically plausible to assume $p(t,\infty) = 0$, for all $t \geq 0$. Hence $\psi(\infty) = 0$. Differentiation with respect to the time yields a differential equation for $x(t)$,

$$\begin{aligned} \dot{x}(t) = &-\psi(\tau-t) \exp\left(-\int_0^t \mu(\tau-t+s)\,ds\right) \big(\dot{\tau}(x(t))\dot{x}(t) - 1\big) \\ &- \int_{\tau-t}^{\infty} \psi(z) \exp\left(-\int_0^t \mu(z+s)\,ds\right) \mu(z+t)\,dz. \end{aligned} \tag{B.1}$$

With (3.6), the age-dependent death rate $\mu(a)$ of adult individuals ($a > \tau$) is a constant $\mu_1 > 0$. So we have

$$\int_{\tau-t}^{\infty} \psi(z) \exp\left(-\int_0^t \mu(z+s)ds\right) \mu(z+t)dz = \int_{\tau-t}^{\infty} \psi(z) \exp\left(-\int_0^t \mu(z+s)ds\right) \mu_1 dz = \mu_1 x(t).$$

Further we observe that

$$\int_0^t \mu(\tau-t+s)\,ds = \int_{\tau-t}^{\tau} \mu(z)\,dz = \int_{\tau-t}^{\tau} \mu_0\,dz = \mu_0 t.$$

Substitution into (B.1) yields

$$\dot{x}(t) = -\psi(\tau-t)e^{-\mu_0 t}\big(\dot{\tau}(x(t))\dot{x}(t) - 1\big) - \mu_1 x(t).$$

Now solve for $\dot{x}(t)$ and obtain

$$\dot{x}(t) = \frac{\psi(\tau-t)e^{-\mu_0 t} - \mu_1 x(t)}{1 + \dot{\tau}(x(t))\psi(\tau-t)e^{-\mu_0 t}}.$$

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List of Symbols

Abbreviations

DDE	Delay Differential Equation
IVP	Initial Value Problem
ODE	Ordinary Differential Equation
NFDE	Neutral Functional Differential Equation
PDE	Partial Differential Equation
RFDE	Retarded Functional Differential Equation

Mathematical Symbols

$\emptyset$	Empty set
$\mathbb{N}$	Set of natural numbers $\{1, 2, 3, \ldots\}$
$\mathbb{Z}$	Set of integers $\{\ldots, -2, -1, 0, 1, 2, \ldots\}$
$\mathbb{R}$	Set of real numbers
$\mathbb{R}_0^+$	Set of nonnegative real numbers
$\mathbb{R}^+$	Set of positive real numbers
$\mathbb{R}^n$	Set of n-dimensional vectors over $\mathbb{R}$
$\mathbb{C}$	Set of complex numbers
$\mathbb{C}^n$	Set of n-dimensional vectors over $\mathbb{C}$
$(\mathbb{R}^n)^{[-h,0]}$	Set of functions $\phi : [-h, 0] \to \mathbb{R}^n$, $n \in \mathbb{N}$ and $h > 0$, Definition p. 50
C	Set of continuous $\phi \in (\mathbb{R}^n)^{[-h,0]}$, Definition p. 50
C^1	Set of continuously differentiable $\phi \in (\mathbb{R}^n)^{[-h,0]}$, Definition p. 50
C^2	Set of twice continuously differentiable $\phi \in (\mathbb{R}^n)^{[-h,0]}$, Definition p. 77
C^c	Set of continuously differentiable $\phi : [-h, 0] \to \mathbb{C}^n$, Definition p. 53

$\lVert \cdot \rVert_C$	Norm on C, Definition p. 50
$\lVert \cdot \rVert_{C^1}$	Norm on C^1, Definition p. 50
$\lVert \cdot \rVert_{C^2}$	Norm on C^2, Definition p. 77
t	Time variable
$\dot{x}(t)$	Derivative of x with respect to t
$\ddot{x}(t)$	Second derivative of $x(t)$ with respect to t
∂	Differentiation operator, $\partial : C^1 \to C$
$\frac{\partial}{\partial x} g(x,y)$	Partial derivative of $g(x,y)$ with respect to x
$\partial_j g(x_1, \ldots, x_n)$	Partial derivative of g with respect to x_j, $j = 1, \ldots, n$
Du	Derivative of a continuously differentiable map u
$D_e u$	Extended derivative of a continuously differentiable map u, Definition p. 58
$D_1 v$	Derivative of a map v with respect to the first variable
$D_2 v$	Derivative of a map v with respect to the second variable
$H_z(s)$	Heaviside function with discontinuity at $s = z$
$\chi_E(s)$	Characteristic function of a set $E \neq \emptyset$
$\delta_z(s)$	Delta distribution with peak at $s = z$
ev	Evaluation map on the space $(\mathbb{R}^n)^{[-h,0]}$ or C, Definition p. 57
ev_0	Evaluation at zero on the space C, Definition p. 64
Ev	Restriction of ev to the space C^1, Definition p. 57
Ev_0	Restriction of ev_0 to the space C^1, Definition p. 64
id, id_Y	Identity map (on the space Y)
pr_1	Projection onto the first component
pr_2	Projection onto the second component
x_t	Segment of a solution x, Definition p. 50
X_f	Solution manifold of RFDE (4.14), Definition p. 58
X	Linear operator
$\rho(X)$	Resolvent set of X, Definition p. 54

$\sigma(X)$	Spectrum of X, Definition p. 54
$\sigma_P(X)$	Point spectrum of X, Definition p. 54
$\mathcal{N}(X)$	Nullspace of X, Definition p. 54
$\mathcal{M}_\lambda$	Generalized eigenspace of an eigenvector λ of X, Definition p. 54
$\mathcal{R}(X)$	Range of X
Y_1, Y_2	Normed vector spaces
$Lip(u)$	Lipschitz constant of $u : M \to Y_2$, $M \subset Y_1$, Definition p. 77
$\\|\cdot\\|_{Y_1 \times Y_2}$	Norm on the Cartesian product $Y_1 \times Y_2$, Definition p. 77
B, B_1	Banach spaces
$L_c(B, B_1)$	Space of linear continuous maps $B \to B_1$, Definition p. 77
$\\|\cdot\\|_{L_c(B,B_1)}$	Norm on $L_c(B, B_1)$, Definition p. 77
$\exp(z) = e^z$	Exponential function
$Im(z)$	Imaginary part of $z \in \mathbb{C}$
max, min	Maximum and minimum of a function or a set
$\mathrm{Mod}(t, T)$	$\mathrm{Mod}(t, T) = t - T\lfloor \frac{t}{T} \rfloor$
$o(f)$	"Small o" of f. It is $g \in o(f)$ if $\lim\limits_{x\to\infty} \frac{\lvert f(x)\rvert}{\lvert g(x)\rvert} = 0$
$\varphi\big\rvert_U$	Restriction of a function φ to the set U
$Re(z)$	Real part of $z \in \mathbb{C}$
sign	Sign function
sup	Supremum of a function or a set
$\oplus$	Direct sum
$\cdot$	Dot product
$\times$	Cartesian product
$\circ$	Function composition

Model Notation in Chapter 3 and Sections 5.2, 7.1.3 and 7.3

$y(t)$	Number of juvenile individuals at time t, p. 25, 32
$x(t)$	Number of adult individuals at time t, p. 25, 32
$\tau(x)$	Age-at-maturity, p. 26, 32
τ_0	Minimal age-at-maturity, p. 26, 32
h	Maximal age-at-maturity, p. 26, 32
μ_0	Death rate of juveniles (constant), p. 26
b_1	Fertility rate of adult individuals (constant), p. 26
μ_1	Death rate of adult individuals (constant), p. 26
$\mu_0(x)$	Death rate of juveniles (dependent on adult population), p. 32
$b_1(x)$	Fertility rate of adult individuals (dependent on adult population), p. 32
$\mu_1(x)$	Death rate of adult individuals (dependent on adult population), p. 32
$b_2(x)$	Fertility peak at maturity (dependent on adult population), p. 32
$\tilde{b}_1(x)$	Short notation for $b_1(x)x$, p. 34
$\tilde{\mu}_1(x)$	Short notation for $\mu_1(x)x$, p. 34

Chapter-specific Notation

Chapter 2

x	Number of individuals, in models (2.1), (2.2), (2.3), (2.5), (2.9), (2.11), (2.12), (2.13), (2.14) and (2.15)
$\tilde{b}$	Net growth rate, in model (2.1)
b	Constant birth rate, in models (2.2), (2.3) and (2.9)
K	Capacity of the environment, in models (2.2), (2.3) and (2.9)
r	Time units after which reproduction stops, in equations (2.3) and (2.9)
y	Variable for writing (2.3) in the form (2.4)
α	Parameter for writing (2.3) in the form (2.4)
τ	Constant time from birth to maturity, in models (2.5), (2.6), (2.7), (2.8) and (2.10), and in the example at p. 21

$b(x)$	Size-dependent birth rate, in equations (2.5) and (2.14)
$\mu(x)$	Size-dependent death rate, in equation (2.5)
x_m	Number of mature individuals, in models (2.6), (2.7), (2.8), (2.10), (2.11), (2.12) and (2.13)
$b_m(x_m)$	Fertility rate of mature individuals dependent on adult population, in models (2.6) and (2.12)
μ_m	Constant death rate of mature individuals, in (2.6), (2.8), (2.10) and (2.12)
x_τ	Population size at which maximal fertility rate is achieved, in equation (2.6)
b_m	Constant fertility rate of mature individuals, in models (2.7), (2.8), (2.10), (2.11) and (2.13)
$\mu_m(x_m)$	Death rate of mature individuals dependent on adult population, in models (2.7), (2.11) and (2.13)
x_i	Number of immature individuals, in models (2.7), (2.8), (2.11) and (2.12)
μ_i	Constant death rate of immature individuals, in models (2.7), (2.8), (2.10), (2.11), (2.12) and (2.13)
$\phi(t)$	Birth rate for $x_i(t)$ at time $t \in [-\tau, 0]$, in model (2.7a)
$u_0(a)$	Initial age distribution of the PDE system, in model (2.8a)
c	Influence of previous density changes on population density, in equation (2.9)
b_2	Fertility peak at age $a = \tau$, in equation (2.10)
$\tau(x)$	Population-dependent time from birth to maturity, in models (2.11) and (2.12)
τ_m	Minimal value of $\tau(x)$, in model (2.11)
τ_M	Maximal value of $\tau(x)$, in model (2.11)
$z(t)$	Date of birth of an individual who matures at time t, in model (2.13)
$\tau(x(z(t)))$	Population-dependent time from birth to maturity, in model (2.13)
$L(x)$	Population-dependent lifespan of individuals, in equation (2.14)
$b(t)$	Time-dependent birth rate, in equation (2.15)
$\mu(t)$	Time-dependent death rate, in equation (2.15)
$d_j(t)$	Time-dependent coefficients of delayed term, in equation (2.15)
$c_j(t)$	Time-dependent coefficients of neutral term, in equation (2.15)

$r_j(t)$	Time-dependent delay, in equation (2.15)
$s_j(t)$	Time-dependent delay in neutral term, in equation (2.15)
a	Age of individuals (structured population)
m	Mass (or size) of individuals (structured population)
$f(a, m, t)$	Density of individuals of age a, mass m at time t
$g(a, m, t)$	Growth rate of individuals of age a, mass m at time t
$\mu(a, m, t)$	Death rate of individuals of age a, mass m at time t
$b(a, \tilde{m}, m, t)$	Production of offspring of mass m by parents of mass $\tilde{m}$ and age a at time t
$f(a, t)$	Density of individuals of age a at time t
$\mu(a, t)$	Death rate of individuals of age a at time t
$b(a, t)$	Fertility rate of individuals of age a at time t
$B(t)$	Number of births at time t
$\sigma(t, a)$	Probability that an individual born at time t survives at least to age a
N	Number of stages in a species life
$x_j(t)$	Number of individuals of age $a \in [a_j, a_{j+1}]$ at time t
$R_j(t)$	Recruitments into age class j
$M_j(t)$	Maturations from age class j to age class $j+1$
$\Delta_j(t)$	Deaths in age class j
$\mu_j(t)$	Death rate of individuals of age $a \in [a_j, a_{j+1}]$ at time t
$b_j(t)$	Birth rate of individuals of age $a \in [a_j, a_{j+1}]$ at time t
τ_j	Time an individual spends in developmental class j
$P_j(t)$	Individuals who entered class j at time $t - \tau_j$ and enter class $j+1$ at time t
$x_1(t)$	Immature individuals at time t
$x_2(t)$	Mature individuals at time t
μ_1	Death rate of immature individuals
μ_2	Death rate of mature individuals
b_2	Fertility rate of mature individuals in the example at p. 21

Chapter 3

a	Age of individuals
$p(t,a)$	Density of individuals of age a at time t
$c(t)$	Total number of individuals born per unit of time at time t
$\gamma(a_2,a_1)$	Survival probability from age a_1 to age a_2
$b(a)$	Age-dependent fertility rate
$\mu(a)$	Age-dependent death rate
$\psi(a)$	Initial age distribution
$\tilde{\lambda}$	Intrinsic growth constant
σ	Net reproductive rate
$A(t_0)$	Age-at-maturity of an individual born at time t_0
$T(t_0)$	Time at which an individual born at time t_0 reaches maturity
J_t	The set $\{a \in \mathbb{R} : 0 \leq a < t-\tau\}$
A_t	The set $\{a \in \mathbb{R} : a \geq t-\tau\}$
$P(t)$	Total population at time t in model (3.16)
$\gamma(a,P)$	Survival probability from birth to age a
$b(a,P)$	Age- and population-dependent fertility rate in (3.16)
$\mu(a,P)$	Age- and population-dependent death rate in (3.16)
$\sigma(P)$	Expected offspring by population size P
w	Recruitment into the adult class
z	Recruitment into the juvenile class
v	Discounted recruitment into the adult class
x_{min}	Minimal value of numerical solution for x, Section 3.5
x_{max}	Maximal value of numerical solution for x, Section 3.5
τ_{min}	The value $\tau(x_{min})$
τ_{max}	The value $\tau(x_{max})$
τ_{mean}	Mean value of τ_{max} and τ_{min}

$\bar{\tau}$	Value of τ at equilibrium solution $\bar{x}$
α_1	Net fertility rate
κ_1	Discount rate due to adult population
α_2	Net fertility rate (in the fertility peak)
κ_2	Discount rate due to adult population (in the fertility peak)
γ	Death rate in absence of other individuals
δ	Death due to presence of other individuals
τ_0	Minimal age-at-maturity
τ_1	Maximal age-at-maturity
T	Threshold for population size in age-at-maturity $\tau(x)$

Chapter 4

f	Right-hand side of the general RFDE (4.3)
D	Domain of f, $D \subset \mathbb{R} \times C$ open
$x(t_0, \phi, f)$	Solution of (4.3) with initial data ϕ at t_0
$[t_0, t_{max})$	Definition interval of a noncontinuable solution
ϕ	History function of the IVP (4.4), $\phi \in C$
$T_f(t, t_0)$	Solution map of $x(t_0, \cdot, f)$, for a fixed t
f	Right-hand side of the autonomous RFDE (4.6)
U	Domain of f in (4.6), $U \subset C$ open
L	Right-hand side of the linear autonomous RFDE (4.7)
$T(t)$	Solution map of a linear autonomous RFDE for a fixed t
$\{T(t)\}_{t\geq 0}$	Family of solution operators
$\mathcal{C}_0$	Strongly continuous (semigroup)
A	Infinitesimal generator of the semigroup $\{T(t)\}_{t\geq 0}$
$\mathcal{D}(A)$	Domain of A
$\Delta(\lambda)$	Complex linear map for characteristic equation
P_Λ, Q_Λ	Spaces for decomposition of C^c

x^{eq}	Stationary state of the nonlinear RFDE (4.12)
x^{ϕ}	Noncontinuable solution of (4.14)
F	Semiflow of solution segments
Ω	Domain of F, $\Omega \subset [0,\infty) \times X_f$ open
F_t	The map $\phi \mapsto F(t,\phi)$, for a fixed t
Ω_t	Domain of F_t
$T_\phi X_f$	Tangent space of X_f at ϕ
L	Constant for estimate in Condition (L)
$\bar{\phi}$	Equilibrium solution of a RFDE
$\bar{\tau}$	Delay function at equilibrium
T_F	Semigroup of linear operators (linearization of semiflow F)
$T_{\bar{\phi}} X_f$	Tangent space of X_f at $\bar{\phi}$
G	Generator of T_F
$\mathcal{D}(G)$	Domain of G
T_e	Semigroup of operators defined by solution segments of IVP (4.18)
G_e	Generator of T_e
$\mathcal{D}(G_e)$	Domain of G_e
$\sigma_u(G_e)$	Set of eigenvalues of G_e with $Re(\lambda) > 0$
$\sigma_c(G_e)$	Set of eigenvalues of G_e with $Re(\lambda) = 0$
$\sigma_s(G_e)$	Set of eigenvalues of G_e with $Re(\lambda) < 0$
C_u	Unstable space of G_e
C_c	Center space of G_e
C_s	Stable space of G_e

Chapter 5

g	Right-hand side of a general state-dependent delay equation
f	Right-hand side of a general autonomous RFDE
β	Nonnegative, bounded C^1-function in (5.4)

δ	Nonnegative, monotonically increasing C^1-function in (5.4)
$\bar{\phi}$	Equilibrium of the RFDE (5.3)
$\bar{x}$	Equilibrium of g
A, B	Coefficients of a linear RFDE
$\overline{A}$, $\overline{B}$	Coefficients of the linear RFDE (5.16)
η	Variable for linearization of (5.8)
η_0	Short notation for $\eta(t)$
$\eta_{\bar{\tau}}$	Short notation for $\eta(t-\bar{\tau})$
$\mathcal{R}_0$	Bisector of second and fourth quadrant in the (A, B)-plane
$\overline{\mathcal{R}}_0$	Bisector of second and fourth quadrant in the $(\overline{A}, \overline{B})$-plane
$\mathcal{C}_k$	Curves with imaginary roots in the (A, B)-plane
$\overline{\mathcal{C}}_k$	Curves with imaginary roots in the $(\overline{A}, \overline{B})$-plane
$\overline{\Sigma}$	Stability region of the problem with constant delay $\bar{\tau}$

Chapter 6

f_0	Functional of the NFDE defined on W_0
W_0	Domain of f_0, $W_0 \subset C^1 \times C$
U_1	The set $\{\phi \in C^1 : (\phi, \partial\phi) \in W_0\} \subset C^1$
X_1	The set $\left\{\phi \in U_1 \,:\, \dot{\phi}(0) = f_0(\phi, \partial\phi)\right\} \subset U_1$
X_{1+}	The set $\{\phi \in X_1 \,:\, Lip(\partial\phi) < \infty\} \subset X_1$
t_ϕ	Maximal time at which a solution to (6.3) exists
x^ϕ	Maximal solution to the IVP with initial data ϕ
G_1	Semiflow generated by segments of x^ϕ
Ω_1	Domain of G_1
W	The set $W_0 \cap (C^1 \times C^1)$
f	Restriction of f_0 to the set W
X_2	The set $X_1 \cap C^2$

$T_\phi X_2$	Tangent space defined by Df
$T_{e,\phi} X_2$	Tangent space defined by $D_e f$
X_{2*}	The set $\{\phi \in X_2 : \partial\phi \in T_{e,\phi} X_2\}$
G_2	Semiflow generated by segments of C^2-solutions
Ω_2	Domain of G_2
$G_2(t,\cdot)$	Solution operator $\phi \mapsto G_2(t,\phi)$
$\Omega_{2,t}$	Domain of $G_2(t,\cdot)$
$v^{\phi,\chi}$	Maximal solution to the IVP (6.6)–(6.7)
a	Constant coefficient in (6.8)
τ_a	State-dependent delay in (6.8)
u	Continuously differentiable function in (6.8)
f_1	Right-hand side of the RFDE at p. 83
V_1	Domain of f_1, p. 83
r	Remainder map
L, R	Continuous linear operators
V	The map $[0,t_m) \to C$, $t \mapsto V(t) = v_t$ for a continuous $v : [-h,t_m) \to \mathbb{R}^n$
r_x	The map $[0,t_m) \to \mathbb{R}^n$, $t \mapsto r_x(t) = r(x_t)$
$\{S(t)\}_{t\geq 0}$	Semigroup generated by segments of solutions to (6.11)
A, g	Continuously differentiable functions in (6.15)
τ_b, τ_c	State-dependent delays in (6.15)
$\bar\phi$	Nontrivial equilibrium of f
$\bar f$	The map $C^1 \times C^1 \to \mathbb{R}$, $\quad (\phi,\xi) \mapsto f(\phi+\bar\phi,\xi)$
$\phi^{\bar x}$	Short notation for $\phi(0)+\bar x$
$\phi^{\bar x}_s$	Short notation for $s\phi(0)+\bar x$
$\tau^{\bar x}$	Short notation for $\tau(\phi(0)+\bar x)$
$\tau^{\bar x}_s$	Short notation for $\tau(s\phi(0)+\bar x)$
σ	The map $C^1 \times C^1 \ni (\phi,\xi) \mapsto (\phi+\bar\phi,\xi) \in C^1 \times C^1$

Chapter 7

τ	State-dependent delay, $\tau : \mathbb{R} \to (0, h),\ h > 0$
f	Right-hand side of the NFDE defined on $C^1 \times C^1$
q_j	Components of the right-hand side of (7.1)
$p_{j,k}$	Components of q_j
ϕ^0	Short notation for $\phi(0)$
ϕ^0_s	Short notation for $s\phi(0)$
τ^{ϕ^0}	Short notation for $\tau(\phi(0))$
$\tau^{\phi^0}_s$	Short notation for $\tau(s\phi(0))$
v	Variable for linearization of (7.6)
$\bar{\phi}$	Nontrivial equilibrium of f
$\bar{x}$	The value $\bar{x} \in \mathbb{R}$, such that $\bar{\phi}(s) = \bar{x}$ for all $s \in [-h, 0]$
A, B, C	Coefficients of the linear NFDE (7.9)
$\bar{\tau}^*$	Delay at which a stability change occurs
α	Nonnegative C^1-function in (7.11)
γ	Nonnegative C^1-function in (7.11)

Chapter 8

a	Age of a cell
$p(t, a)$	Density of proliferating cells of age a at time t
$b(a)$	Age-dependent fertility rate
$\mu(a)$	Age-dependent death rate
$\psi(a)$	Initial age distribution
$u_0(a)$	Initial age distribution for $a < \tau$
τ	Duration of the interphase
τ_{min}	Lower bound for τ
τ_{max}	Upper bound for τ

$V(t)$	Number of interphase cells at time t
$U(t)$	Number of mitotic cells at time t
$Q(t)$	Number of quiescent cells at time t
$I(t)$	Immune system effector cells at time t
$D(t)$	Drug concentration at time t
μ_0	Death rate of interphase cells
μ_Q	Transition rate from G_1 to G_0
b_1	Division rate of mitotic cells
μ_1	Death rate of mitotic cells
μ_{G_0}	Death rate of quiescent cells
b_Q	Transition rate from G_0 to G_1
k	Basic immune system effectors production
ρ	Tumor-induced immune system effectors activation rate
n	Nonlinearity of tumor-immune system competition
α	Threshold for the immune system activation
c_1	Loss of lymphocytes due to interaction with quiescent cells
c_2	Loss of lymphocytes due to interaction with mitotic cells
c_3	Loss of lymphocytes due to interaction with interphase cells
δ_4	Death rate of lymphocytes
k_0	Effectiveness of immune system on interphase cells
k_Q	Effectiveness of immune system on quiescent cells
k_2	Effectiveness of immune system on mitotic cells
k_3	Effectiveness of drugs on mitotic cells
k_5	Drug-induced death rate of mitotic cells (maximum value)
k_6	Drug-induced death rate of lymphocytes (maximum value)
k_7	Effectiveness of drugs on lymphocytes
γ	Drug degradation rate

List of Figures

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List of Publications

Following articles have been published prior to submission of this thesis:

- M. V. Barbarossa, C. Kuttler, A. Fekete, M. Rothballer. A delay model for quorum sensing of *Pseudomonas putida*. *BioSystems Elsevier* 102, pp. 148–156, 2010.
- M. V. Barbarossa, C. Kuttler, J. Zinsl. Delay equations modeling the effects of phase-specific drugs and immunotherapy on proliferating tumor cells. *AIMS Mathematical Biosciences and Engineering* 9(2), pp. 241–257, 2012.

Following preprints have been published prior to submission of this thesis:

- M. V. Barbarossa, C. Kuttler, A. Fekete, M. Rothballer. Delay models for quorum sensing of *Pseudomonas putida*: Analysis and Numerical Simulation. *IBB Preprint Series*, Abstract nr. 09–31, 2009.
- M. V. Barbarossa, C. Kuttler, J. Zinsl. Delay models for the cell cycle of tumoral cells. *IBB Preprint Series*, Abstract nr. 11–08, 2011.

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