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TOPICAL REVIEW

Formation and computational implications of assemblies in neural circuits

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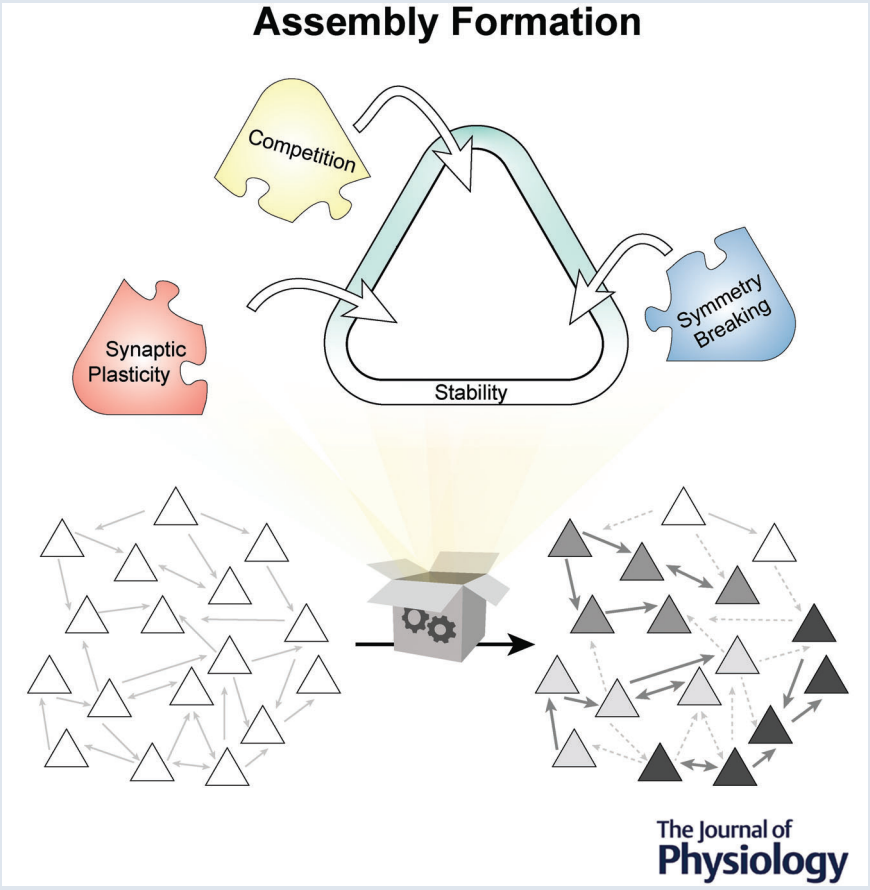

Abstract In the brain, patterns of neural activity represent sensory information and store it in non-random synaptic connectivity. A prominent theoretical hypothesis states that assemblies, groups of neurons that are strongly connected to each other, are the key computational units underlying perception and memory formation. Compatible with these hypothesised assemblies, experiments have revealed groups of neurons that display synchronous activity,

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either spontaneously or upon stimulus presentation, and exhibit behavioural relevance. While it remains unclear how assemblies form in the brain, theoretical work has vastly contributed to the understanding of various interacting mechanisms in this process. Here, we review the recent theoretical literature on assembly formation by categorising the involved mechanisms into four components: synaptic plasticity, symmetry breaking, competition and stability. We highlight different approaches and assumptions behind assembly formation and discuss recent ideas of assemblies as the key computational unit in the brain.

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Abstract figure legend Assembly formation. Assemblies are groups of strongly connected neurons formed by the interaction of multiple mechanisms and with vast computational implications. Four interacting components are thought to drive assembly formation: synaptic plasticity, symmetry breaking, competition and stability.

Introduction

Originating from the ideas of Lorente de Nó (1938) and Donald O. Hebb (1949), a prominent theoretical hypothesis proposed that groups of neurons instead of single neurons are the basic unit of perceptive integration (Buzsáki, 2010; Eichenbaum, 2018; Huyck & Passmore, 2013; Yuste, 2015). It is now widely accepted that groups of neurons that display synchronous activity represent key computational units and are often referred to as 'assemblies', 'ensembles' or 'engrams'. These terms are not always used consistently in the literature; therefore, in this review, we propose the following disambiguation. An 'ensemble' refers to multiple neurons that express a certain degree of synchronous activity without any hypothesis about their connectivity. An 'assembly,' on the other hand, is defined as a group of neurons that has stronger or denser synaptic connections (called the within-assembly weights) among the neurons that constitute it, as opposed to the weights going into or coming out of the assembly (called the across-assembly weights), without necessarily having highly synchronous activity. Finally, an 'engram' describes multiple ensembles or assemblies interconnected and spread across multiple layers and even brain areas.

Although it is often hypothesised that highly synchronous activity within a group of neurons (ensemble) follows from strong synaptic connectivity among these neurons (assembly), distinguishing between activity and connectivity is important. Experimental studies usually investigate ensembles. This is despite the development of new recording techniques which have made it possible to image and manipulate the activity of groups of neurons and link them to behaviour (Carrillo-Reid et al., 2017; Wenzel & Hamm, 2021), and is due to the challenge to directly measure synaptic connectivity between specific neurons experimentally. Despite recent efforts to show experimentally that an ensemble also consists of strong, connected neurons (e.g. Alejandre-García et al., 2022), a clear link is still missing.

Due to the readily accessible information about connectivity and activity in *in silico* network models, theoretical studies can bridge the gap between activity and connectivity, seeking a mechanistic understanding of assembly formation and stability. An early example is Hebb's suggestion that long-term synaptic plasticity mechanisms favour the formation of assemblies among neurons that activate synchronously (Hebb, 1949). In this review, we examine contemporary literature on

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assembly formation in recurrent networks, outlining the key components that, in addition to Hebb's basic principle where 'cells that fire together wire together' (Shatz, 1992), allow for the formation and stability of assembly structures. We identify four components: synaptic plasticity, symmetry breaking, competition and stability (Fig. 1*A*), and highlight how computational studies use different assumptions combining these four components in relation to experimental literature. Finally, we discuss recent ideas of how the concept of assemblies is useful in understanding how brains might 'compute' and we point towards open challenges and possible future research directions. Before diving into the computational perspective, we briefly review experimental findings on ensembles and assemblies.

Experimental evidence for ensembles, assemblies and their formation

Evidence of ensembles in neural activity. Ensembles of neurons have been identified by their temporally coordinated activity patterns in many species and across areas. These patterns appear upon stimulus presentation, such as in the mouse hippocampus (Harris et al., 2003) and visual cortex (Miller et al., 2014), the ferret visual cortex (Berkes et al., 2011) and the zebrafish (Romano et al., 2015). In addition, coordinated neural activity has been measured during spontaneous activity and even in *in vitro* preparations (Cossart et al., 2003; MacLean et al., 2005; Mao et al., 2001), hinting at the possibility that these patterns are generated by underlying local network structures (i.e. assemblies) rather than by common feedforward inputs. Therefore, one proposal supported by experimental evidence is that ensembles observed during spontaneous activity define the realm of possible activity patterns during stimulus presentation (Kenet et al., 2003; Luczak et al., 2009; Malvache et al., 2016; Miller et al., 2014; but see Avitan et al., 2021; Stringer et al., 2019).

The activation of neural ensembles not only correlates with stimulus presentation but also plays an important role in expressing specific behaviours. Precise optogenetic manipulation of ensembles induces, enhances or impairs expressed behaviour, for example in the hippocampus

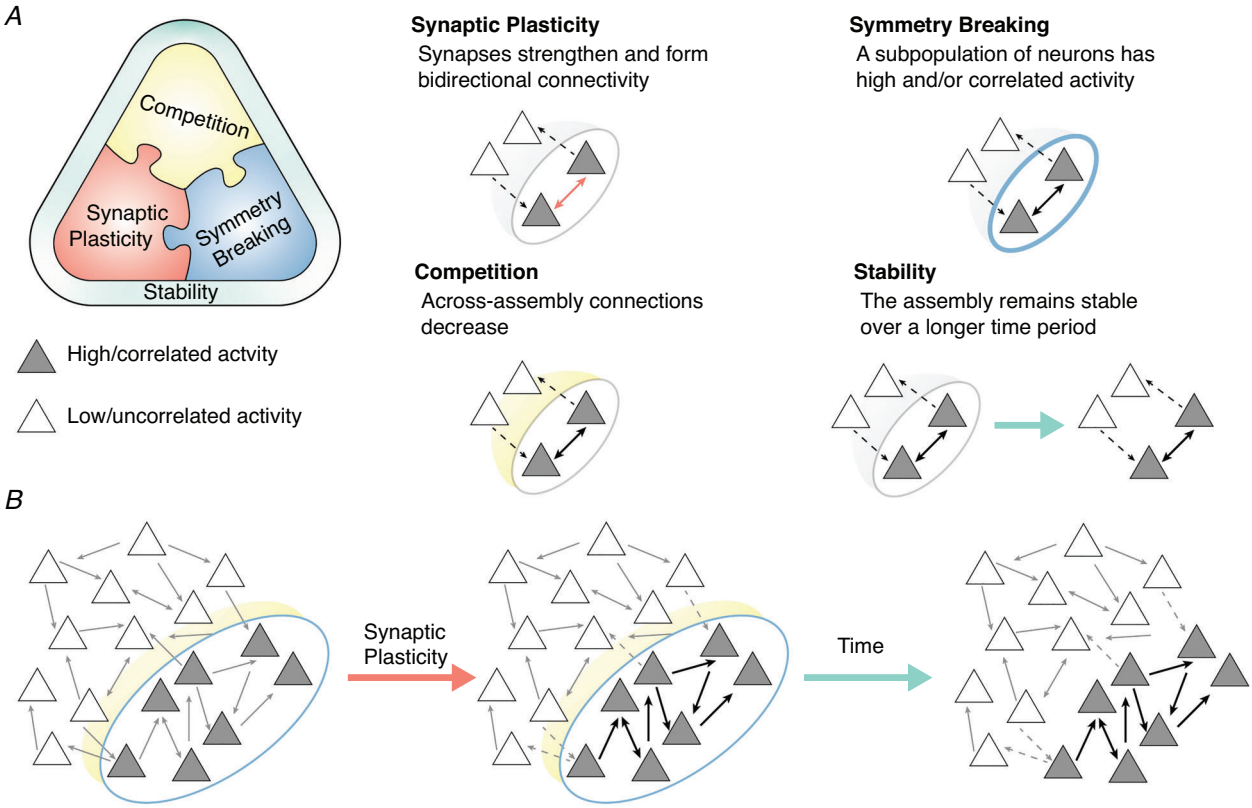

Figure 1. The basic building blocks of assembly formation
A, assembly formation is based on four key components in computational models: synaptic plasticity, symmetry breaking, competition and stability. *B*, due to symmetry breaking, a subpopulation of neurons fires at a high rate and/or with highly correlated activity compared to the remaining neurons. Synaptic plasticity promotes mutual connections within the assembly, while a competition mechanism decreases the across-assembly weights. The newly formed assembly structure is stable over time.

(Liu et al., 2012), the visual cortex (Carrillo-Reid et al., 2019; Marshel et al., 2019) and the orbitofrontal cortex (Jennings et al., 2019). Animals can also be trained to directly report the activation of a cell ensemble composed of fewer than 20 neurons in the barrel cortex and the olfactory bulb, even in the absence of a sensory stimulus (Dalgleish et al., 2020; Gill et al., 2020). However, it is unclear what generates the highly synchronous activity of the neurons within an ensemble: for example, whether the ensembles that lead to specific behaviours are strongly recurrently connected into assemblies or are strongly driven by common input. Additionally, it is unclear to what extent ensemble configuration and its function are preserved over longer time periods, such as days or months. Some recent work has shown that the cortical representation of natural images (Deitch et al., 2021) and odours (Schoonover et al., 2021) slowly shifts over time, a phenomenon termed 'representational drift' (Rule et al., 2019). Representational drift depends on the stimulus type (Marks & Goard, 2021) and is area-dependent, with representations in motor areas being especially stable (Jensen et al., 2022).

Evidence of assemblies in neural connectivity. Direct measures of neural connectivity based on electrophysiology, optogenetic stimulation and electron microscopy often reveal that network structure is far from random. In particular, bidirectional connections occur much more frequently compared to what would be expected if connections were random (Campagnola et al., 2022; Guzman et al., 2016; Jouhanneau et al., 2015; Song et al., 2005; Turner et al., 2022; but see Lefort et al., 2009). Although bidirectional connectivity does not uniquely define an assembly, it is consistent with the idea that neurons in the same assembly should have a denser and stronger mutual connectivity compared to the rest of the population.

Other studies have revealed that neurons are more likely to be connected when they share common neighbours (Perin et al., 2011; Turner et al., 2022), i.e. common input (Yoshimura et al., 2005) or common postsynaptic targets (Brown & Hestrin, 2009). Furthermore, highly correlated cells (Cossell et al., 2015; Ko et al., 2011) or cells that are tuned to the same stimuli have a higher probability of being connected (Ko et al., 2011; Lee et al., 2016; Rossi et al., 2020; Wertz et al., 2015). In the same vein, cells stemming from the same progenitor show similar selectivity for visual stimuli (Li et al., 2012; Ohtsuki et al., 2012) and display high connection probability as well as an increase in reciprocal connectivity (Tarusawa et al., 2016; Yu et al., 2009; but see Cadwell et al., 2020). The fact that functionally related neurons are more likely to be connected suggests that these groups of neurons can be considered assemblies.

Synaptic plasticity as a mechanism for assembly formation. It is widely believed that long-term synaptic plasticity is the underlying mechanism behind connectivity structure formation, including assembly formation (Abbott & Nelson, 2000; Brea & Gerstner, 2016; Feldman, 2009; Magee & Grienberger, 2020; Suvrathan, 2019). Multiple experimental studies have shown that the long-term plasticity of a synapse depends on firing rates and exact spike timing (Maffei, 2018). Long-term potentiation can be evoked by high firing rates (Kirkwood et al., 1996) or pairs of spikes which fire in a causal manner, whereby a postsynaptic spike follows a presynaptic spike (Bi & Poo, 1998; Markram et al., 1997). Therefore, groups of neurons firing at high rate and in a correlated manner (ensembles) should form strong synaptic connections among each other, forming an assembly.

However, experimentally it has been difficult to link synaptic plasticity directly to assembly formation. Recent findings in the mouse barrel cortex have suggested that the probability of neurons firing together increases when repeatedly activating them *in vivo*, tying this effect to long-lasting connectivity changes (Kim et al., 2016). Furthermore, fear memories could be artificially induced by stimulating neurons in the hippocampal region CA3 with a protocol that probably induces within-layer synaptic plasticity (Oishi et al., 2019).

A couple of experimental studies have attempted to imprint assemblies by repeatedly evoked spiking patterns in a selected subgroup of neurons (Carrillo-Reid et al., 2016; Zhang et al., 2020). While this increased correlated firing and spontaneous reactivations of the stimulated subgroup of neurons over days, the underlying mechanism has remained unclear. Long-term synaptic plasticity that leads to stronger recurrent inputs is one possibility (Zhang et al., 2020), but a change in the neuron's intrinsic excitability is also possible (Alejandre-García et al., 2022; Debanne et al., 2019; Zhang & Linden, 2003). Increased intrinsic excitability also plays an important role in memory formation. Studies in the hippocampus and amygdala have shown that cells with high intrinsic excitability during memory formation are likely to be part of the newly formed ensembles that correlate with the learned fear memories (Cai et al., 2016; Rashid et al., 2016). However, while recent studies suggest that memory formation requires changes in feedforward synapses between those ensembles (Abdou et al., 2018; Nabavi et al., 2014), it is unclear whether the same is true for recurrent synapses, i.e. whether memory formation relies on assembly formation.

Therefore, we conclude that despite the abundance of experimental data on the existence and formation of ensembles and assemblies, a clear link between how highly correlated activity and strong recurrent connectivity is still missing.

Formation of assemblies. To complement these experimental findings regarding the existence and relevance of neural ensembles and assemblies, computational studies have proven extremely useful in developing models linking synaptic plasticity to the formation of assemblies. We propose that the problem of stable assembly formation in neural circuits can be understood through four fundamental components (Fig. 1*A*).

The first component, synaptic plasticity, promotes assemblies by strengthening bidirectional connections of within-assembly neurons. The second component, symmetry breaking, represents a form of bias that influences neural activity, and thus can be used by synaptic plasticity to refine and shape assemblies. The third component, competition, strengthens synaptic connections within an assembly and weakens connections across assemblies. Lastly, stability prescribes that learned assemblies remain resilient to fluctuations and keep their connectivity structure intact over time.

Synaptic plasticity. To describe synaptic plasticity, computational models have defined phenomenological descriptions of the interactions between pre- and postsynaptic spikes in the form of learning rules. We first consider one of the best studied rules: Hebbian pairwise spike timing-dependent plasticity (STDP), where a presynaptic spike followed by a postsynaptic spike leads to long-term potentiation (LTP), whereas a postsynaptic spike followed by a presynaptic spike leads to long-term depression (Bi & Poo, 1998). The magnitude of the synaptic change depends on the time difference between the spikes, increasing as the events occur closer in time (Fig. 2*A*). At the circuit level, this rule does not favour the formation of neural assemblies, but rather it disrupts them (Ravid Tannenbaum & Burak, 2016), as it tends to cancel bidirectional connections between neurons (Abbott & Nelson, 2000; Clopath et al., 2010; Song & Abbott, 2001; Song et al., 2000) including synaptic loops that involve multiple neurons (Kozloski & Cecchi, 2010). This is due to the potentiation/depression profile of the rule (Fig. 2*A*). For example, if neuron j spikes before neuron i the synaptic weight that goes from j to i, w_{ij}, will increase; however, the reciprocal connection from neuron i to neuron j, w_{ji}, will decrease (Fig. 2*A*, red vertical lines). Therefore, synaptic plasticity rules with an anti-symmetric profile, as in the Hebbian case, can produce a continuous competition between reciprocal connections, resulting in a 'winner-take-all' mechanism that leaves only one direction intact (Abbott & Nelson, 2000; Song et al., 2000; Song & Abbott, 2001).

To understand the effect of STDP rules on bidirectional connections more generally, computational models describe the dependency between synaptic weight changes, firing statistics and plasticity rule parameters. The firing rates of single neurons and the pairwise correlations between the neurons' spike trains together with the parameters of the STDP rule determine the mean weight change (Kempter et al., 1999; Fig. 2*B*). However, any change of synaptic weights can, in turn, produce changes in the neurons' firing rates and correlation structure. Decomposing synaptic plasticity into structural motifs is a widely used theoretical approach that captures this complex relationship (Hu et al., 2013, 2014; Jovanović & Rotter, 2016; Montangie et al., 2020; Ocker, Hu et al., 2017; Ocker, Josić et al., 2017; Pernice et al., 2011; Ravid Tannenbaum & Burak, 2016; Trousdale et al., 2012). The structural motif framework is based on two assumptions: first, synaptic plasticity occurs on a much slower timescale than the dynamics of neural firing; and second, the neural dynamics follows an approximately linear behaviour. When the first assumption holds, the (slow) weight update does not depend on specific realisations of neural firing, but is instead determined by mean firing rates and by the correlation structure between the neurons' spike trains (Kempter et al., 1999). The second assumption of linearity allows us to compute the full firing statistics analytically from the network weights (Jovanović et al., 2015). This leads to a self-consistent solution (Ocker et al., 2015), where at each iteration first the firing statistics are derived from fixed weights, and then the weights are updated following the interaction between those statistics and synaptic plasticity. While this framework applies to any synaptic plasticity rule, for simplicity here we explain it in the context of the pairwise STDP rule.

Structural motifs are defined as the connectivity paths that a given spike from neuron k in a network travels to neuron j and neuron i, consequently affecting the correlation between neuron j and i. Using this framework, we can formulate the mean synaptic weight change of a synapse from neuron j to neuron i, $\langle \dot{w}_{ij} \rangle$, as a sum of terms which depend on structural motifs with a certain 'order of interaction' (Montangie et al., 2020; Ravid Tannenbaum & Burak, 2016; Fig. 2*C*). The order of interaction refers to the total number of synapses a spike from any neuron in a network needs to travel to affect the mean connection strength $\langle w_{ij} \rangle$ between presynaptic neuron j and postsynaptic neuron i, indicated below with the number in the superscript:

$$\langle \dot{w}_{ij} \rangle = \langle \dot{w}_{ij} \rangle^{(0)} + \langle \dot{w}_{ij} \rangle^{(1)} + \langle \dot{w}_{ij} \rangle^{(2)} + \langle \dot{w}_{ij} \rangle^{(3)} + \cdots \quad (1)$$

Hence, each of the terms of different orders of interaction consists of the product of different activity statistics (rates, correlations) and motif coefficients that scale each term's contribution. The first term in eqn (1) represents the zero-order structural motif (order of interaction 0), also referred to as the rate motif. This term describes the

mean weight change as a function of only the pre- and postsynaptic firing rates (r_j, r_i):

$$\langle \dot{w}_{ij} \rangle^{(0)} = r_i r_j M_0 \tag{2}$$

where M_0 is the zero-order motif coefficient and can be calculated as the area under the plasticity rule (Fig. 2*A*). The second term in eqn (1) represents the first-order structural motif (order of interaction 1), describing how a spike in either the pre- or the postsynaptic neuron can affect $\langle w_{ij} \rangle$:

$$\langle \dot{w}_{ij} \rangle^{(1)} = r_j w_{ij} M_{1,0} + r_i w_{ji} M_{0,1}. \tag{3}$$

The first-order motif coefficients, $M_{1,0}$ and $M_{0,1}$, and in general other higher-order motif coefficients, can be calculated based on the shape of the excitatory postsynaptic current (EPSC) and the STDP parameters (Fig. 2*D*). As the order of the interaction increases, the contributions on the weight dynamics become smaller because more synapses are involved, and therefore higher orders of interaction are often truncated (Montangie et al., 2020; Ravid Tannenbaum & Burak, 2016).

Given the importance of bidirectional connections for the formation of assemblies, the above mathematical framework can be used to describe the mean weight

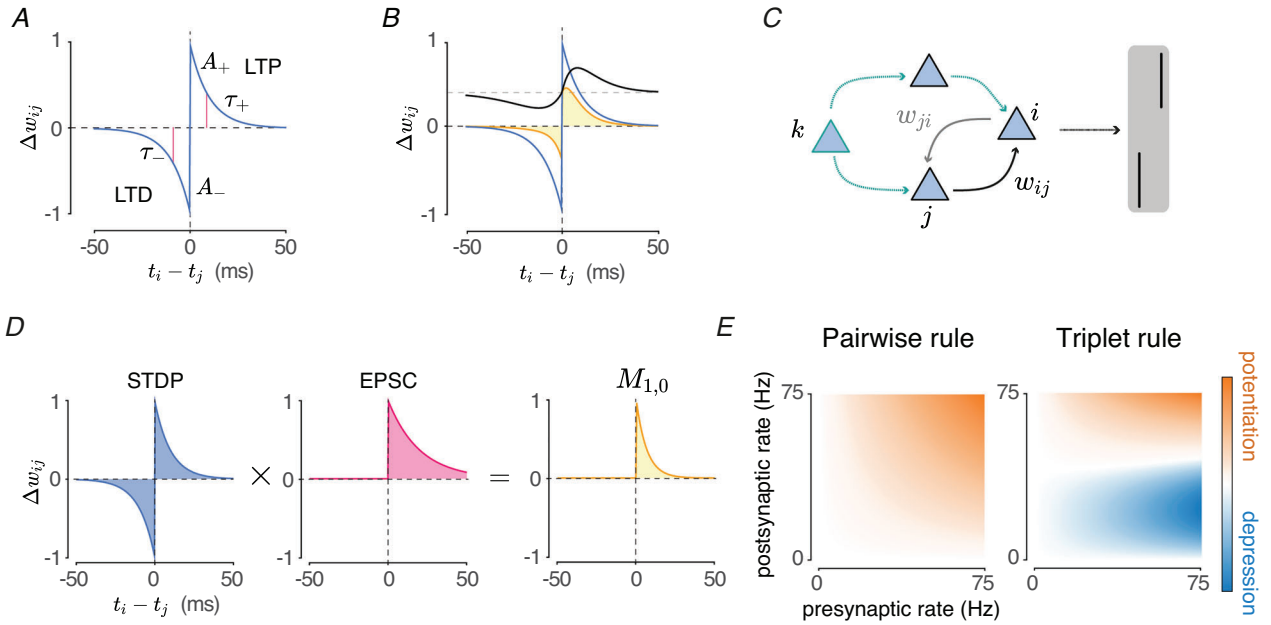

Figure 2. The effect of spike timing-dependent plasticity (STDP) on the formation of bidirectional connections
A, weight change of the synapse from neuron *j* to neuron *i*, Δw_{ij}, via the pairwise STDP rule as a function of the time difference between post- (t_i) and presynaptic spike (t_j), with long-term potentiation (LTP) parameters A_+ and τ_+ and long-term depression (LTD) parameters A_- and τ_-. Red vertical lines indicate weight change of reciprocal connections for one time difference of spikes in neuron *j* and *i*. The total area under the STDP rule is $A_+\tau_+ + A_-\tau_-$. *B*, the mean synaptic weight change (yellow area) can be computed as the area under the product of two curves: the pairwise STDP rule as in *A* (blue line) and the correlation density (black line). *C*, example of a structural motif with order of interaction 3 as one part of the decomposition of synaptic weight change ($\langle \dot{w}_{ij} \rangle^{(3)}$, see eqn 1). A spike in neuron *k* travels through one synapse to the presynaptic neuron *j* and through two synapses to the postsynaptic neuron *i*, influencing the correlation between neuron *j* and neuron *i* and therefore the weight change at synapse w_{ij} (adapted from Montangie et al., 2020). *D*, the structural motif with order of interaction 1 (also called the first-order motif) contributes to the mean weight change of synapse w_{ij} with two terms, $M_{1,0}$ and $M_{0,1}$ (see eqn 3). The first-order motif coefficient $M_{1,0}$ can be calculated by multiplication of the STDP area (blue) with the EPSC area (magenta). The EPSC here is defined as $E(t) = \exp(-t/\tau_e)$ for $t > 0$ with decay time constant τ_e. The first-order motif coefficients are $M_{1,0} = A_+ \tau_+ \tau_e/(\tau_+ + \tau_e)$ (yellow area under the curve in the right panel), and $M_{0,1} = A_- \tau_- \tau_e/(\tau_- + \tau_e)$ (not shown) (adapted from Montangie et al., 2020). *E*, weight change as a function of the pre- and postsynaptic firing rates for a pairwise STDP rule (left, see also *A*) with dominant potentiation, i.e. positive total area under the STDP rule $A_+\tau_+ + A_-\tau_- > 0$ (meaning that the zero-order motif coefficient is positive $M_0 > 0$), and the mean weight dynamics depend on pre- and postsynaptic firing rates. Weight change as a function of the pre- and postsynaptic firing rates for a triplet (right) STDP rule which has a rate-dependent zero-order contribution that depends non-linearly on the postsynaptic firing rate and depends linearly on the presynaptic rate. In both panels, the pre- and postsynaptic neurons fire independently. Potentiation (orange) and depression (blue) are normalised to their respective maximum value (adapted from Litwin-Kumar & Doiron, 2014).

dynamics for the reciprocal weights between neuron j and i as follows, considering only the zero- and first-order structural motifs (eqns 2 and 3):

$$\langle \dot{w}_{ij} \rangle^{(0,1)} = r_i r_j M_0 + r_j w_{ij} M_{1,0} + r_i w_{ji} M_{0,1}, \quad (4)$$

$$\langle \dot{w}_{ji} \rangle^{(0,1)} = r_i r_j M_0 + r_i w_{ji} M_{1,0} + r_j w_{ij} M_{0,1}. \quad (5)$$

Simplifying this for the case where the pairwise STDP plasticity rule has the same area of long-term depression (LTD) and LTP (i.e. $A_+ \tau_+ = -A_- \tau_-$, see Fig. 2*A*), the motif coefficients can be calculated as $M_0 = 0$ and $M_{0,1} = -M_{1,0}$, which we call simply M, yielding:

$$\langle \dot{w}_{ij} \rangle^{(0,1)} = \left(r_j w_{ij} - r_i w_{ji} \right) M, \quad (6)$$

$$\langle \dot{w}_{ji} \rangle^{(0,1)} = \left(r_i w_{ji} - r_j w_{ij} \right) M. \quad (7)$$

Therefore, it is easy to see that an increase of w_{ij} leads to a decrease of the reciprocal connection w_{ji} and vice versa. Furthermore, the weight changes depend on the weight strength, leading to a 'winner-take-all mechanism', where only one synaptic weight 'wins.' However, this is only true in the case of approximately equal areas of LTD and LTP and has been pointed out by multiple computational studies as the inability of the asymmetric pair-based STDP rule to generate bidirectional connections and, as a result, assemblies (Abbott & Nelson, 2000; Clopath et al., 2010; Song et al., 2000; Song & Abbott, 2001). For an STDP rule which has dominant potentiation, the zero-order motif coefficient is positive ($M_0 > 0$), and the mean weight dynamics depend on pre- and postsynaptic firing rates (Fig. 2*E*, left). Notably, this can lead to bidirectional connectivity (Babadi & Abbott, 2013).

Another way to promote bidirectional connections is using a symmetric STDP rule which has dominant depression (Manz & Memmesheimer, 2022) or without any LTD (Ravid Tannenbaum & Burak, 2016). In this setting, synaptic weights grow linearly with the pre- and postsynaptic rates, and further increase bidirectionally when neurons fire close in time, regardless of the firing order. Finally, a third possibility is to introduce synaptic delays (Babadi & Abbott, 2013; Gilson, Burkitt & van Hemmen et al., 2010; Ravid Tannenbaum & Burak, 2016). It is likely that a combination of multiples of these mechanisms operates in real biological circuits and here the computational models provide a principled mathematical investigation of each contribution.

While the pairwise STDP rule describes excitatory plasticity in the case of specific induction protocols, other plasticity rules have been proposed that can capture plasticity induced by more naturalistic induction protocols or directly resulting from well-defined molecular components. For example, to explain plasticity in response to increasing stimulation frequencies during classical pre–post pairing, Pfister and Gerstner (2006) proposed that triplets of spikes, in addition to pairs of spikes, contribute to synaptic plasticity. As a result, this triplet STDP rule is sensitive to higher-order firing statistics (Gjorgjieva et al., 2011). In the motif expansion framework, the rule adds a positive zero-order contribution that grows quadratically with the post-synaptic firing rate and linearly with the presynaptic rate (Montangie et al., 2020). This non-linear component generates a threshold between LTD and LTP that depends on presynaptic and postsynaptic firing rates (Litwin-Kumar & Doiron, 2014; Fig. 2*E*, right): when two neurons fire above threshold, both synaptic weights between them increase, promoting the bidirectionality needed for assemblies. Other computational models of assembly formation use similar non-linear dependencies of the weight change on the postsynaptic firing rate in the plasticity rules they implement, including the voltage-based STDP rule (Clopath et al., 2010; Ko et al., 2013; Miconi et al., 2016), the calcium rule (Graupner & Brunel, 2012) and the nearest-neighbour implementation of the pairwise STDP rule (Izhikevich & Desai, 2003; Izhikevich et al., 2004). The strong rate dependency in plasticity rules (Fig. 2*E*) justifies modelling neuronal dynamics based purely on the firing rate to study assembly formation (Eckmann & Gjorgjieva, 2022; Mackwood et al., 2021; Miehl & Gjorgjieva, 2022; Sadeh & Clopath, 2021).

Besides synaptic plasticity, assembly formation may also emerge from other mechanisms. We highlight structural plasticity, which refers to the activity-dependent pruning and sprouting of synapses (Gallinaro & Rotter, 2018; Gallinaro et al., 2022; Lu et al., 2019). A structural plasticity mechanism aiming to stabilise excitatory firing rates can lead to the formation of assemblies in which the number of connections, rather than connection strength, is increased among neurons within the assembly (Gallinaro et al., 2022).

In summary, theoretical frameworks have made important progress in explaining how the properties of the synaptic plasticity rule affect the formation of different connectivity structures, especially assemblies. We have focused on pair-based or triplet-based STDP rules, with the requirement that they should promote, and not hinder, the formation of bidirectional connections, a fundamental building block for the formation of assemblies. Bidirectional connections alone, however, do not guarantee an assembly-like structure. Consider, for example, the degenerate case of an all-to-all connected network, or a network with prominent bidirectional connectivity, but still no clear separation among groups of neurons. The two closely related principles of symmetry breaking and competition tackle this issue. As we discuss below, the former imposes an intrinsic or external bias that induces heterogeneity in the circuit and acts as a

learning signal. The latter provides a mechanism for consolidating within-assembly weights while reducing across-assembly weights.

Symmetry breaking. The most straightforward way to induce symmetry breaking for assembly formation is to train network weights via synaptic plasticity by structured external input. One possibility is to simultaneously stimulate neurons expected to be in one assembly with a high input rate, and neurons which are not part of the assembly with a low input rate (Fig. 3*A*). A synaptic plasticity rule dominated by firing rates will then potentiate bidirectional connections within the stimulated subpopulation (Clopath et al., 2010; Litwin-Kumar & Doiron, 2012, 2014; Schulz et al., 2021). Another possibility is to maintain constant firing rates across the neural population, but drive neurons expected to be in the same assembly by correlated inputs (Gilson et al., 2009a; Ocker & Doiron, 2019; Wu et al., 2020; Fig. 3*B*). Both of these assembly training paradigms are similar in that they impose a structure on the network via an external input. During the training protocol subpopulations of neurons (the future assemblies) are sequentially stimulated multiple times (Fig. 3*C*). In the correlation-based approach it is also possible to stimulate subpopulations of neurons in parallel (Ocker & Doiron, 2019).

Besides assuming an already selective external feedforward input performing symmetry breaking, input synapses can also be plastic and the external selectivity can be learned in parallel with the formation of assemblies (Clopath et al., 2010; Gilson et al., 2009a; Gilson, Burkitt, Grayden et al., 2010; Miconi et al., 2016; Zenke et al., 2015). This is in line with experimental studies suggesting that feedforward input becomes stimulus specific before strong recurrent connections form (Ko et al., 2011, 2013). The formation of feedforward selectivity could potentially be guided by recurrent gap junctions (as modelled by Crodelle & McLaughlin, 2021; Ko et al., 2013). These connections are observed during early development preferentially between cells that stem from the same progenitor and seem to play a crucial role in the formation of chemical synapses between these cells (Yu et al., 2009, 2012).

Experiments in the sensory deprived zebrafish larvae have shown that assemblies can also form without external input, only due to network-intrinsic activity (Pietri et al., 2017). Such assembly formation without structured input has been obtained in computational models with different forms of STDP based on the two frameworks discussed above: either mainly driven by the rate contribution (zero-order motif) (Babadi & Abbott, 2013; Burkitt et al., 2007; Gilson et al., 2009b; Ocker et al., 2015; Ocker & Doiron, 2019), or by higher-order motifs arising from internal correlation structure with the rate contribution minimised (Montangie et al., 2020; Ocker et al., 2015; Ocker & Doiron, 2019; Ravid Tannenbaum & Burak, 2016), or a combination thereof (Manz & Memmesheimer, 2022). When network-intrinsic correlations contribute significantly to assembly formation, symmetry breaking in

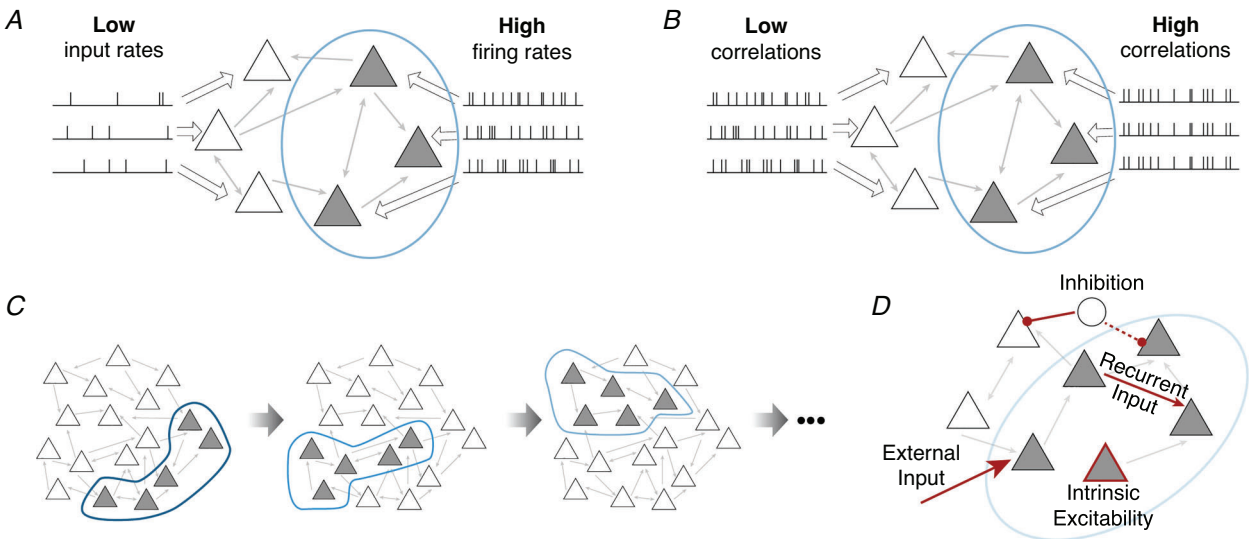

Figure 3. Symmetry breaking via external input
A, strong external input onto a subpopulation of neurons (blue ellipse) leads to high firing of the targeted neurons (grey triangles). *B*, same as *A*, but for strongly correlated external input. *C*, training protocol in which three distinct subpopulations of neurons (blue outlines) are stimulated sequentially. *D*, different mechanisms can contribute to symmetry breaking: structured external input, recurrent input that reflects existing structures, inhibition and changes in intrinsic excitability.

the network develops either due to random fluctuations in an otherwise symmetric network, or due to an initial bias in the connectivity matrix (Ocker & Doiron, 2019; Triplett et al., 2018).

Experimental studies have suggested additional mechanisms that might drive symmetry breaking: for example, neurons which become part of an engram during memory formation first have a higher excitability during the memory-encoding phase that seems to be partially due to cell-intrinsic mechanisms (Alejandre-García et al., 2022; Josselyn & Tonegawa, 2020). This highlights that the effect of symmetry breaking is probably a result of many interacting mechanisms: structured external input, recurrent input from already existing structures, intrinsic excitability, and also local inhibition or disinhibition (Fig. 3*D*).

In summary, the symmetry breaking mechanism is necessary to enable the potentiation of synapses by synaptic plasticity within the assembly. However, while successfully promoting weight potentiation within each assembly, symmetry breaking does not guarantee that weights across assemblies do not also increase, due to random rate fluctuations, or due to synaptic plasticity rules biased towards potentiation. Hence, the overall increase in synaptic strength might eventually lead to unstable dynamics, preventing the formation of desired assembly structure, as the assemblies tend to merge together. Below, we outline how competition can solve this problem.

Competition. Competition describes a mechanism to decrease across-assembly weights while increasing within-assembly weights. Competition therefore enables a clear separation of assembly from non-assembly neurons and prevents assemblies from merging. In some configurations, symmetry breaking driven by external inputs together with a plasticity rule is sufficient to induce competition between the synapses within and across assemblies. When a plasticity rule depends non-linearly on firing rates, such as the triplet STDP rule (Pfister & Gerstner, 2006), it is possible to choose the firing rates of external inputs such that within-assembly weights potentiate while across-assembly weights depress (Ocker & Doiron, 2019).

To conceptualise this, we consider a toy example with three neurons, of which only two belong to an assembly (Fig. 4*A*, red). We use a plasticity rule where potentiation and depression depend on firing rates, as for example the triplet STDP rule introduced in Fig. 2*E* (right). During the training protocol (see Fig. 3*C*), neurons within the assembly have high firing rates, while the outside neuron has low firing rates (Fig. 4*B*, left). The plasticity rule then leads to strong potentiation of within-assembly weights (Fig. 4*C*, left, purple star) and weak potentiation of weights into the assembly (Fig. 4*C*, left, green star). If the outside neuron joins another assembly at a later time, the situation reverses, with high rates outside the assembly (green neuron) and low rates within it (Fig. 4*B*, right). In this scenario, the weights into the assembly decrease more (Fig. 4*C*, right, green star) than the within-assembly weights (Fig. 4*C*, right, purple star). The weights out of the assembly always change in an opposite manner to the weights into the assembly when the pre- and postfiring rates are reversed (Fig. 4*C*, black star). Averaged throughout the whole training protocol, this leads to an increase in the within-assembly weights (Fig. 4*A*, purple arrow). In contrast, the weights onto the neuron outside the assembly decrease (Fig. 4*A*, black dashed arrow). However, the weights into the assembly only decrease if the connected outside neuron is part of a distinct assembly that is trained at a later time point (Fig. 4*A*, green dashed arrow). In this example, synaptic competition follows directly from the plasticity rule in combination with the symmetry breaking of the training protocol with different input firing rates. A pairwise symmetric STDP rule dominated by depression can also induce competition without such structured external input (Manz & Memmesheimer, 2022). Here, the relative contributions of the zero- and higher-order motifs regulate assembly size.

Many computational studies include additional mechanisms for more robust and flexible assembly formation. A widely used mechanism is synaptic weight normalisation (Fiete et al., 2010; Tetzlaff et al., 2011, 2013, 2015), which is often linked to synaptic scaling, suggesting that synaptic weights are down- (up-) regulated if the firing rates of the neurons are high (low) (Turrigiano et al., 1998; Turrigiano, 2008), and heterosynaptic plasticity, where the induction of potentiation (depression) in synapses is accompanied by depression (potentiation) at nearby synapses (Chistiakova et al., 2015; Field et al., 2020; Lynch et al., 1977).

Weight normalisation keeps the sum (or sum of squares) of all outgoing or incoming weights (or both) constant for each neuron. This mechanism, first introduced in the context of feedforward receptive-field formation (Miller & MacKay, 1994; Miller, 1996), induces synaptic competition. Any increase in a group of synaptic weights due to synaptic plasticity leads to a decrease in the remaining connections due to normalisation. To emphasise this point, we revisit the toy example mentioned above with the additional constraint that the sum of the incoming weights remains constant (Fig. 4*D*). Here, we consider subtractive normalisation that affects all incoming weights by subtracting an equal amount independent of their strength. This mechanism introduces competition by depressing the weights into the assembly despite the potentiation induced by synaptic plasticity (Fig. 4*D*, left) or potentiating in the within-assembly weights despite the depression

by synaptic plasticity (Fig. 4*D*, right). Subtractive normalisation results in a winner-take-all competition (Miller & MacKay, 1994), whereby at the fixed point, i.e. the point at which synaptic weights no longer change, the weight with the highest potentiation (or equivalently the lowest depression) rate will 'win' (Fig. 4*D*, yellow diamond). Including weight normalisation enables synaptic plasticity rules that do not introduce competition themselves – like symmetric pairwise STDP – to generate assembly structures (Ravid Tannenbaum & Burak, 2016) because the normalisation mechanism amplifies small asymmetries in the weight dynamics. At the same time, weight normalisation also enables more reliable assembly formation even in cases where it is not explicitly needed to generate assemblies (Litwin-Kumar & Doiron, 2014; Schulz et al., 2021; Wu et al., 2020; Zenke et al., 2015).

In contrast to subtractive normalisation, divisive normalisation induces less competition and does not lead to a winner-take-all mechanism, but to a stable fixed point where weights are proportional to their respective potentiation strengths (Miller & MacKay, 1994; Fig. 4*E*, yellow diamond; compare with Fig. 4*D*, left). A divisive effect is in line with the biological idea that synapses compete for molecular resources (Triesch et al., 2018), and it has been used, for example, in a model of assembly formation that can disambiguate input features (Eckmann & Gjorgjieva, 2022).

Metaplasticity, a dynamic change of the plasticity mechanism itself (Abraham, 2008), can also induce competition. A stimulus which results in a high postsynaptic firing rate leads to an increase in the LTD/LTP threshold, hence making it harder for a subsequent stimulus to induce LTP. A classic rate-based

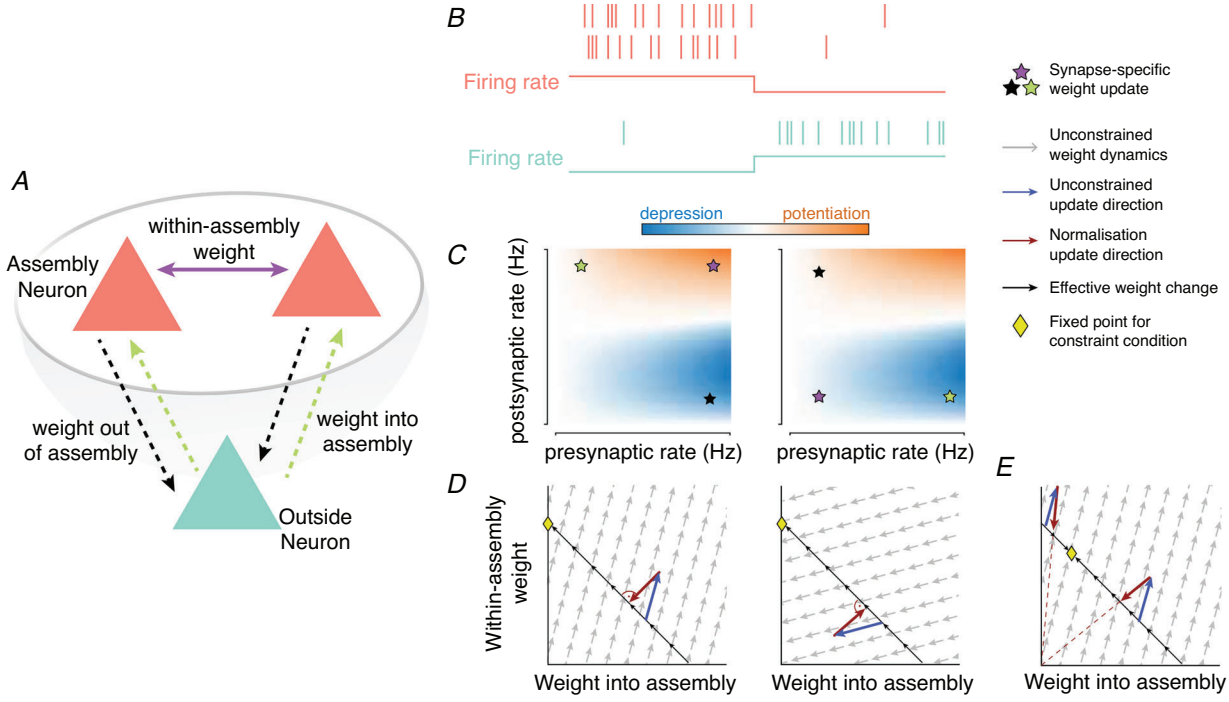

Figure 4. Competition between within- and across-assembly weights
A, a toy model schematic to explain the concept of competition. Two neurons (red) are part of an assembly, one neuron (mint) is not. The neurons are connected by synapses within the assembly (purple), into the assembly (green) and out of the assembly (black). The dotted line indicates the weights, which should decrease due to competition to form the assembly. *B*, firing rates and spikes for the three neurons in *A*, for two scenarios when training assemblies (left and right). Left: the within-assembly neurons have a high firing rate while the outside neuron fires with a low firing rate. Right: the firing rates of the within-assembly *vs*. outside-assembly neurons are reversed relative to the left (adapted from Ocker & Doiron, 2019). *C*, weight change as a function of the pre- and postsynaptic firing rates for the triplet STDP rule (as in Fig. 2*E*). The stars correspond to the pre- and postsynaptic rates in the scenarios sketched in *B*, with filling colour matching the scheme in *A* (adapted from Ocker & Doiron, 2019). *D*, phase plane of weight dynamics, showing weight into the assembly (*x*-axis, green arrow in *A*) *versus* within-assembly-weight (*y*-axis, purple arrow in *A*). The dynamics follow from the weight changes depicted in *C*, induced by the scenario in *B*. Grey arrows indicate the unconstrained weight dynamics, the blue arrow shows the weight change following the unconstrained synaptic plasticity dynamics, the red arrow shows the counteracting effect of the subtractive normalisation, the black arrow indicates the net weight change and the yellow diamond indicates the fixed point of the constrained weight evolution (adapted from Clopath et al., 2016). *E*, same scenario as in *D* (left) but with divisive normalisation.

plasticity rule implementing metaplasticity is the Bienenstock–Cooper–Munro (BCM) rule, which has been studied extensively in the context of competition in feedforward networks (Bienenstock et al., 1982; Yger & Gilson, 2015), and can be linked to the triplet STDP rule if one of the rule's parameters changes with ongoing activity (Gjorgjieva et al., 2011). Metaplasticity in the context of assembly formation is an important part of the voltage-based STDP rule (Clopath et al., 2010; Miconi et al., 2016), and adding metaplasticity to STDP ensures assembly formation over a broader range of parameters (Zenke et al., 2015).

Recent work has proposed that inhibition and the plasticity of inhibitory-to-excitatory synapses also play an important part in the competition between assemblies (Herpich & Tetzlaff, 2019; Lagzi et al., 2021; Miehl & Gjorgjieva, 2022; Sadeh & Clopath, 2021). Specifically, inhibitory plasticity can be linked to BCM-like metaplasticity and therefore can control the induction of LTD or LTP at excitatory synapses (Clopath et al., 2016; Miehl & Gjorgjieva, 2022).

In summary, multiple mechanisms to induce competition between within- and across-assembly weights have been suggested, including weight normalisation, metaplasticity and inhibitory plasticity. While all these mechanisms aid reliable formation of assemblies, the last outstanding question pertains to maintaining stable assemblies in the face of ongoing synaptic plasticity.

Stability of representations. Maintaining stable assemblies, or representations in general, faces two main challenges: first, how to control synaptic weight changes to prevent pathological firing rates in the network; and second, how to preserve the difference between within- and across-assembly weight strength so that the learned structure does not disappear over time (Fig. 5*A*).

Synaptic plasticity mechanisms lead to unbounded growth of the synaptic weights due to positive feedback between activity and plasticity, termed 'Hebbian runaway dynamics' (Turrigiano & Nelson, 2004). Solutions to this problem are weight normalisation (Fig. 4), metaplasticity mechanisms or applying upper bounds on the weights. Two types of upper bounds are often considered, 'hard' and 'soft'. Soft upper bounds implement 'weight-dependent' plasticity assuming that the weights change proportionally to the inverse of their strength (Gütig et al., 2003; Rossum et al., 2000; Rubin et al., 2001). Although soft bounds ensure stability, they can lead to unimodal weight distributions and, therefore, might counteract the formation of assemblies (Morrison et al., 2007). Similarly, metaplasticity and normalisation mechanisms might also stabilise weight growth at the expense of reducing competition (Yger & Gilson, 2015). Theoretical work has proposed that the key aspect to ensuring stable weight dynamics is the relative timescales of synaptic plasticity *versus* stabilising mechanisms (Zenke et al., 2013).

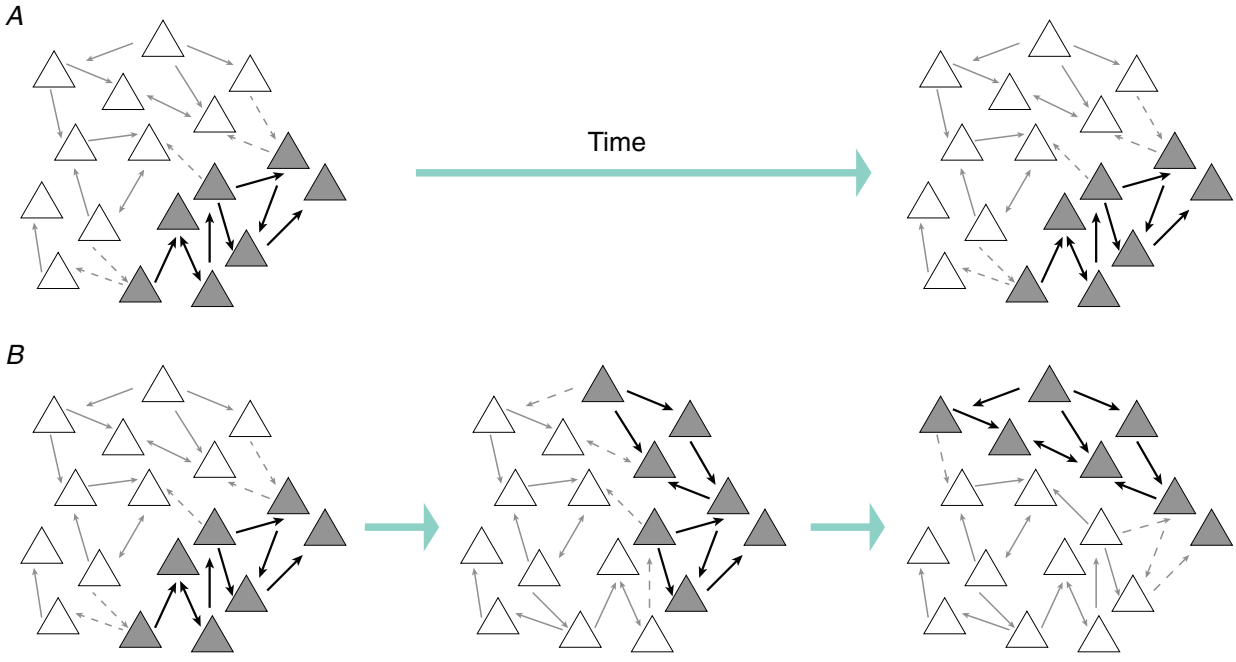

Figure 5. Stability of representations
A, the neurons of a given assembly remain the same over time, providing a stable representation of a sensory percept. *B*, the neurons of a given assembly change over time, leading to a representational drift.

When a network remains plastic after learning assemblies, learning additional assemblies or ongoing spontaneous activity alone can degrade the learned structure. Therefore, the network 'forgets' these representations (Fusi, 2017). It has been suggested that reactivation of the learned structure through the high activity of assembly neurons can reinforce the assembly structure (Fauth & van Rossum, 2019; Litwin-Kumar & Doiron, 2014). Essentially, the network transitions from learning due to external input to learning due to internal structure (see section Symmetry Breaking) and thus self-stabilises. Additional mechanisms, such as short-term plasticity, have also been suggested to keep the firing rates in the network in a healthy regime (Fauth & van Rossum, 2019; Hiratani & Fukai, 2014; Mongillo et al., 2005; Vasilaki & Giugliano, 2014; Zenke et al., 2015). An alternative to self-stabilisation via high firing rate reactivation is self-stabilisation via spiking statistics, for example when storing assemblies in a 'silent' fashion. In this framework, plasticity at inhibitory-to-excitatory synapses can maintain a stable balance of excitation and inhibition after learning, such that assembly neurons have similar firing rates to other neurons in the network (Barron et al., 2017; Ramaswami, 2014). Despite this, assembly neurons show higher correlations and spiking irregularities during spontaneous activity, which can stabilise and improve the long-term storage of the imprinted assemblies (Gallinaro & Clopath, 2021; Ocker & Doiron, 2019). The assemblies can then be accessed by disinhibitory mechanisms (Barron et al., 2016), or even be read out in seemingly quiet stages, by downstream neurons through synapses with short-term plasticity (Gallinaro & Clopath, 2021).

However, should the goal be to maintain stable assemblies at all? Experimental work suggests that assemblies may change over time, known as 'representational drift' (Rule et al., 2019). In computational models, ongoing synaptic plasticity after assembly formation results in single neurons dropping in and out of assemblies, leading to a drift of the assembly structure (Kossio et al., 2021; Manz & Memmesheimer, 2022; Raman & O'Leary, 2021; Triplett et al., 2018; Fig. 5*B*). Hence, an important question is how such unstable neuronal representations can lead to stable task performance (Mau et al., 2020; Rule et al., 2019). Current solutions to this problem propose that assemblies should be considered in conjunction with their readouts, for example by assuming that the connections from assemblies to downstream neurons can be also plastic. This leads to a constant readout despite changing assemblies (Kossio et al., 2021; Rule & O'Leary, 2022).

Another possible solution to the stability problem is to break free from the assumption that synaptic plasticity is 'on' at all times, continuously changing learned structures. To turn off, or gate, synaptic plasticity several mechanisms have been suggested, including inhibition of the inhibitory population, i.e. disinhibition as a gating signal (Froemke et al., 2007; Letzkus et al., 2011) or 'three-factor plasticity rules', where neuromodulators that convey a learning signal can regulate weight change in addition to the pre- and postsynaptic activity (Frémaux & Gerstner, 2016). Another mechanism is synaptic tagging and capture, where activity-dependent synaptic plasticity needs an additional stabilising internal signal to allow persistent connectivity changes (Luboeinski & Tetzlaff, 2021; Redondo & Morris, 2011).

In summary, multiple solutions have been proposed to ensure the stability of the learned assemblies: from self-stabilisation by activity (Litwin-Kumar & Doiron, 2014) or spiking statistics (Gallinaro & Clopath, 2021; Ocker & Doiron, 2019), to plastic downstream readouts despite drifting representation (Rule et al., 2019) and gating of synaptic plasticity.

Conclusions and outlook. Inspired by the wealth of experimental results on the existence and computational relevance of neural ensembles and assemblies, various computational models have investigated how synaptic plasticity mediates their formation and stability. In this review, we have identified four fundamental computational principles behind this process (Fig. 1). First, synaptic plasticity can lead to strong, bidirectional connectivity among neurons, but it needs to be accompanied by a second component, a symmetry breaking signal, to break up neurons into multiple assemblies. To prevent distinct assemblies from merging requires a third component, competition. Finally, the last component ensures the stability of assembly structures or of their representations.

While recent experimental work has made great advances in understanding synchronous activity (ensembles), a clear link between ensembles, assemblies and the formation of assemblies via synaptic plasticity mechanisms is still lacking. Computational models have proven indispensable in providing the missing link because they allow multiple mechanisms to be studied one at a time or in combination. An outstanding question that we did not address pertains to the functional and computational consequences of learned assemblies, which remains an important future direction. Nonetheless, we include a short overview on the functional relevance of assemblies.

The idea of assemblies, or ensembles, as the basic units of cognition has recently replaced the neuron-centric view (Buzsáki, 2010; Eichenbaum, 2018; Huyck & Passmore, 2013; Yuste, 2015). An emergent core assumption from this framework is that each ensemble represents a specific concept or feature, acting as the fundamental unit for

memory storage (Neves et al., 2008). One advantage of having strong recurrent connectivity (assembly) compared to only considering correlated rates (ensemble) is stimulus amplification (Peron et al., 2020), thus enabling weaker stimuli to elicit a recognisable response and to increase robustness whereby the malfunction or death of single neurons or synapses will not affect the represented concept. Consequently, an incomplete stimulus can be sufficient to evoke the complete assembly – a phenomenon named pattern completion, which is especially relevant for memory retrieval (Guzman et al., 2016). Moreover, recurrent interactions alone may be sufficient to keep an assembly active after stimulation, thus enabling the brain to decouple intrinsic activity from external stimulation and modify learned concepts independently from specific external inputs (Harris, 2005).

One can think of assemblies as the basis of any computation (Byrne & Huyck, 2010; Herpich & Tetzlaff, 2019; Ranhel, 2012), also referred to as 'assembly calculus' (Papadimitriou et al., 2020; Papadimitriou & Friederici, 2022). In this view, plastic changes of within- and across-assembly weights are abstracted in mathematically tractable basic operations. These basic operations describe how new assemblies are formed and how existing assemblies can be combined with each other. This framework allows us, for example, to build the full architecture of language syntax (Papadimitriou et al., 2020; Papadimitriou & Friederici, 2022). In general, assemblies can be combined in two distinct ways. First, chains of assemblies can form directed sequences, which has been suggested specifically in the hippocampus, and lead to reliable and even reversed reactivation after learning (Holtmaat & Caroni, 2016). For example, it has been shown that learning assemblies in a sequence can generate clock-like neuronal dynamics, enabling the learning of different spatiotemporal patterns (Maes et al., 2020, 2021). Second, assemblies can be associated with each other. Association models can be based on chaining models, where the association is encoded in the connection strength between the assemblies. Another option to encode associations is hierarchical models, where the associated concept is encoded in a newly formed assembly that only activates if both pre-existing assemblies are active (Pokorny et al., 2020).

Although most computational studies on assembly formation begin with an unstructured network from which assemblies and associations between assemblies are learned, this probably is not the case in the adult brain. There are two possibilities. First, assemblies might be formed in early development, and be later used as a 'backbone' to learn new sequences or associate new features (Holtmaat & Caroni, 2016). Cortical areas generate stereotypical structured 'spontaneous activity' during early development that is important for connectivity refinement (Richter & Gjorgjieva, 2017) and can drive assembly formation without structured external input (Loidolt et al., 2020; Montangie et al., 2020; Ravid Tannenbaum & Burak, 2016). Second, new assemblies might also form in the adult brain, where they should be integrated into an existing network structure without 'forgetting' previously learned representations and potentially allowing overlap between assemblies. This possibility is closely related to the existence of engrams, large-scale representations potentially spanning multiple brain regions. Experimental studies have identified various mechanisms of engram formation, such as plastic changes in synapses between regions, or modulated intrinsic excitability of recruited neurons (Holtmaat & Caroni, 2016; Josselyn & Tonegawa, 2020). Going one step further, Buzsáki (2010) suggested that assemblies should be defined from the perspective of a readout mechanism, as done, for example, in the context of drifting assemblies (Kossio et al., 2021; Rule & O'Leary, 2022). Future work needs to carefully study assembly formation and association in the context of existing network structures.

Once established, assembly structures shape ongoing network activity and generate distinct activity patterns often called discrete attractor dynamics (Aljadeff et al., 2021; Hopfield, 1982). These dynamics can also show sustained elevated activity independent of external cues which links to working memory tasks (Amit et al., 1994; Durstewitz et al., 2000). When multiple assemblies are embedded in a network, their activation can switch stochastically between different assemblies (Mazzucato et al., 2015). The resulting activity patterns are termed 'metastable dynamics', and closely relate to experimental findings (Abeles et al., 1995; La Camera et al., 2019). In the rat gustatory cortex, they have been linked to expectation: by reducing the stability of attractors via an external cue, the switching rate increases and stimuli can be detected faster (Mazzucato et al., 2019). Discrete attractor dynamics are also investigated in more abstract models called associative memory models and support the view of ensembles as computing units. As advanced significantly by Hopfield (1982), patterns of neuronal activation are imprinted in the network connectivity and can be activated even with incomplete stimuli, due to the attractor dynamics. Interestingly, the abstract assumptions correspond, especially as formulated for example by Tsodyks (1989), to the four components we identified when reviewing the literature on assembly formation: a Hebbian learning rule establishes bidirectional connections within an assembly based on well-defined memory patterns, which when imprinted, determine which neurons should be active, hence acting as a symmetry breaking mechanism. The abstractions in these models have enabled extensive theoretical results related to these attractor networks, including the theoretical limit for the number of patterns or concepts stored in a recurrent network (Amit et al., 1985; Gardner, 1988).

Various aspects in the models have also been made more biologically realistic, for example sparse coding (Amari, 1989; Gripon et al., 2016), asymmetric connections (Tsodyks, 1989) or context dependency (Podlaski et al., 2020). It is interesting to compare the abstracted learning rules of associative memory models with their more biologically plausible local and dynamic learning counterparts, as they are used in studies on assembly formation. These associative memory models have an advantage in the clear benchmarks they provide, such as the number of stored patterns, thus making it easier to compare different modelling approaches. Such a comparison is still an open research direction for assembly formation with more biologically inspired mechanisms. A formal integration of these two concepts will yield further insights, as initial efforts are already gaining some traction (Aljadeff et al., 2021).

In this review, we have focused on assemblies as a prominent type of connectivity structure described in many neural circuits in the brain. Beyond assemblies, at a smaller scale, specific connectivity motifs are either over- or under-represented than expected by chance (Song et al., 2005). At a larger scale, synfire chains, hub networks and other structures have been described in network neuroscience (Bassett & Sporns, 2017). Future work needs to show how these different, small- and large-scale, connectivity structures are related and how they can be learned via synaptic plasticity, leading to diverse activity dynamics and complex computations.

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Additional information

Competing interests

None.

Author contributions

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