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Current Opinion in Neurobiology

Understanding neural circuit development through theory and models

Leonidas MA Richter[1] and Julijana Gjorgjieva[1,2]

How are neural circuits organized and tuned to achieve stable function and produce robust behavior? The organization process begins early in development and involves a diversity of mechanisms unique to this period. We summarize recent progress in theoretical neuroscience that has substantially contributed to our understanding of development at the single neuron, synaptic and network level. We go beyond classical models of topographic map formation, and focus on the generation of complex spatiotemporal activity patterns, their role in refinements of particular circuit features, and the emergence of functional computations. Aided by the development of novel quantitative methods for data analysis, theory and computational models have enabled us to test the adequacy of specific assumptions, explain experimental data and propose testable hypotheses. With the accumulation of experimental data, theory and models will likely play an even more important role in understanding the development of neural circuits.

Addresses
[1] Computation in Neural Circuits Group, Max Planck Institute for Brain Research, Max-von-Laue-Str. 4, 60438 Frankfurt, Germany
[2] School of Life Sciences Weihenstephan, Technical University of Munich, 85354 Freising, Germany

Corresponding author: Gjorgjieva, Julijana (gjorgjieva@brain.mpg.de)

Current Opinion in Neurobiology 2017, **46**:39–47

This review comes from a themed issue on **Computational neuroscience**

Edited by **Adrienne Fairhall** and **Christian Machens**

http://dx.doi.org/10.1016/j.conb.2017.07.004

Introduction

Neural systems are organized to enable the efficient and stable processing of information across different brain regions and to generate robust behaviors. This requires a balance between flexibility, to learn from and adapt to new environments, and stability, to ensure reliable execution of behavior. Generating systems with this dual property is a non-trivial challenge and requires a prolonged period of development when multiple mechanisms are coordinated in a hierarchy of levels and timescales to establish a rich repertoire of computations. Studying this process is of fundamental importance for the understanding of normal brain function and the prevention, detection and treatment of brain disorders, including intellectual disabilities, autism, bipolar disorder, schizophrenia and epilepsy.

The developing brain is not merely an immature version of the adult brain. Even before sensory experience begins to sculpt connectivity, a myriad of mechanisms and structures unique to development characterize the self-organization into functioning circuits. Technological advancements in experimental techniques have made it feasible to record and manipulate a number of circuit components. In parallel, data analysis techniques, theory and computational models have enabled us to synthesize experimental data from multiple systems and to derive key principles for how neural circuits are built and organized into functional units, which can adapt to and learn from different environments, and make decisions based on sensory and internal drive.

We highlight recent theoretical work on neural circuit organization during early stages of development before sensory organs mature. We focus on activity-dependent mechanisms governing this process, after neuronal differentiation and migration have taken place, and use the visual system and the immature (undifferentiated) cortex as examples. By describing theoretical and modeling approaches for spontaneous activity generation, developmental refinements of connectivity and intrinsic neuronal properties, and the emergence of computations, we highlight the success of theoretical models to dissect existing mechanisms of neural circuit development and their capacity to propose and test new hypotheses.

Models of topographic map formation in the visual system

The initial stages of circuit development consist of establishing precise patterns of connectivity guided by matching molecular gradients and axonal targeting. One of the best studied models of organization of neural circuit connectivity is topographic maps in the visual system, whose orderly structure has made them an accessible model system for both theory and experiment. Retinotopic maps between the retina and higher visual centers, including the superior colliculus (SC), the lateral geniculate nucleus (LGN) and the cortex, have been the focus of intense study, elucidating general principles underlying neural circuit wiring [1-6,7•,8••]. Most models assume that topographic maps are formed by the interaction of molecular guidance cues, such

as Ephs/*ephrin*s (reviewed in [5,9]), and are subsequently refined by spontaneous neural activity. We highlight three aspects of recent progress on map formation.

Recent models simulate not only the final map, but the entire temporal evolution of map formation from a combination of mechanisms, including retinal axons that initially arborize stochastically in the target region, synaptic connections that are subsequently refined by Hebbian activity-dependent plasticity and are continuously regulated in strength through competition for a common source [10,11,12••]. Despite the success of these models in reproducing experimental results, due to the many interacting mechanisms it may be difficult to infer which of the resulting features is the product of any of the model ingredients. Furthermore, they take days to simulate which challenges their reproducibility.

With the accumulation of experimental data from normal and mutant animals, new quantitative analysis methods of maps have also been proposed, revealing novel aspects of map development. One new approach is the 'Lattice Method,' offering a quantitative assessment of the topographic ordering in the one-to-one map between two structures [13]. This method has shown that triple molecular knockouts, or double molecular knockouts with disrupted activity patterns, show a surprising amount of order, much higher than expected by chance. The topographic maps from these different mutants have suggested new experiments that examine the interplay of correlated activity and molecular guidance cues. A recent study has further built on this interaction finding that near equal contributions from molecular gradients and neural activity drive topographic mapping stochastically, resulting in the heterogeneous maps within and between individual animals measured experimentally [14]. Future work should examine the functional implications of this map heterogeneity.

Besides comparing different experimental maps, new frameworks also support the unbiased and quantitative testing of computational models on any available data from the mouse retinocollicular system [15••]. These enable us to go beyond comparing model output to known perturbations and towards predicting how these models would respond to novel manipulations. Such approaches are especially useful when several different models are similarly consistent with existing data [16••]. Despite the success in modeling map formation, the challenge remains to integrate maps with the emergence of other functional aspects of development.

Spontaneous activity: transient features and computational implications

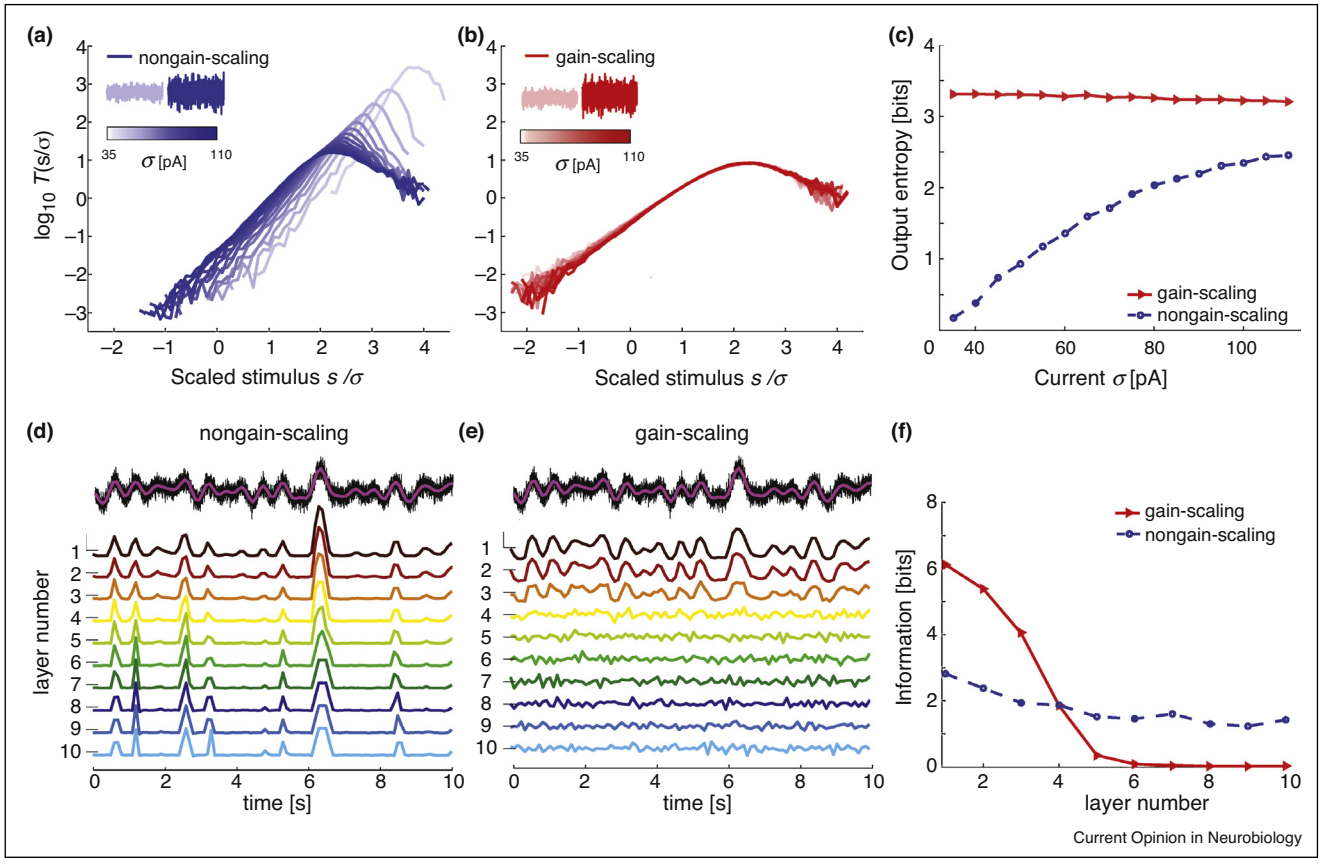
Before the onset of sensory experience, many developing circuits can spontaneously generate neural activity. Spontaneous activity regulates a range of developmental processes, including neuronal migration, ion channel maturation and the establishment of precise connectivity [9,17,18]. In the retina, spontaneous activity is generated in the form of spatiotemporal waves during the first two weeks of postnatal development (in rodents), before the retina responds to light ([19], for models see [20,21]). These waves propagate through the visual pathway to the SC, the thalamus, and the visual cortex [22,23,24•] (which are also spontaneously active [25•,26]), and guide the refinement of connectivity between the retina and its downstream targets [18,27]. Several transient cellular properties and structures contribute to the generation and propagation of spontaneous activity in the cortex.

Developing neurons express a unique configuration of ion channels and receptors to mediate specific patterns of spontaneous activity, which may be incompatible with the information-processing functions of mature neurons [17]. In the developing mouse cortex, the proportions of the two main spike-generating conductances (sodium and potassium) in single neurons change during the first postnatal week. This biophysical change enables single neurons to acquire an ability to dynamically adjust their response range to the size of incoming stimulus fluctuations [28]. This property is termed 'gain scaling' and can be characterized by building linear-nonlinear (LN) models from the responses of single neurons to random noisy stimuli and examining the variability of the gains of the nonlinearities to different stimulus distributions (Figure 1a,b) [28]. Gain scaling in more mature neurons supports a high rate of information transmission about stimulus fluctuations in the face of changing stimulus amplitude, and is absent in immature neurons which respond to large amplitude events without adaptation (Figure 1c) [29••].

These single neuron changes in gain scaling during development can generate very different dynamics at the network level [29••]. The lack of gain-scaling early in development (around birth) allows slow activity transients to propagate through the model networks (Figure 1d). This enables cortical networks to amplify and propagate spontaneous waves at birth. The emergence of gain scaling a week later when spontaneous waves disappear, makes the networks better suited for the efficient representation (but not propagation) of information on fast timescales relevant for sensory stimuli (Figure 1e) [29••]. The different abilities of the two networks to transmit slow stimulus fluctuations can be captured in the mutual information between the slow stimulus and the average network response (Figure 1f). This example demonstrates that single neuron properties can influence developmental network dynamics in a powerful way, thus making predictions for the developmentally evolving information processing capabilities of these networks which can be evaluated in experimental data.

To model cortical spontaneous activity in more biologically realistic scenarios requires that spontaneous

Figure 1



(a,b) Nonlinear input–output relations in LN models of nongain-scaling **(a)** and gain-scaling **(b)** Hodgkin–Huxley (HH) neurons. The gain-scaling ability is determined by the common gain of nonlinearities obtained from neuronal responses to white noise stimuli with a range of variances σ^2 [29••]. A HH neuron with a small ratio of maximal conductances for sodium and potassium, $g_{Na}/g_K = 0.6$ shows more variable gains (a), while a neuron with $g_{Na}/g_K > 1$ shows nearly perfect gain-scaling (b). Real cortical neurons recorded around birth show lack of gain scaling (have variable gains), while more mature cortical neurons after the first postnatal week show nearly perfect gain scaling [28]. **(c)** The output entropy as a function of the stimulus standard deviation, σ, measures the information about fast fluctuations. (d,e) Peristimulus time histograms (PSTHs) from each layer in feedforward networks of nongain-scaling **(d)** versus gain-scaling **(e)** neurons showing the propagation of a slow-varying input (magenta, top) in the presence of background fast fluctuations (black, top). PSTHs were normalized to mean 0 (horizontal line) and variance 1 (vertical scalebar = 2). **(f)** Mutual information about the slow-varying input transmitted by the two networks in (d) and (e).
Figure adapted from [29••].

transients are endogenously generated by the networks themselves, rather than provided as input to the networks (as in Figure 1d,e). To determine the source of these transients, Baltz and colleagues proposed three different models dependent on intrinsic bursts, intrinsic spikes or accumulation of random synaptic input [30]. Although all models could initiate and propagate spontaneous events, networks where neurons produced intrinsic bursts were most consistent with *in vitro* recordings of spontaneous network activity [30]. Barnett and colleagues elaborated on this model to capture spontaneous wave propagation observed in coronal slices of mouse cortex. Here, intrinsically bursting neurons were distributed along a gradient in a network with long-range recurrent synaptic connectivity and local gap junctions. The gradient of intrinsic bursting ability was sufficient to capture the direction of wave propagation from ventral piriform regions to dorsal neocortical regions [31•]. Interestingly, the models also predicted that wave activity persists near the site of initiation even after a wave has passed, which was later confirmed experimentally [31•].

Other transient network features are also prominent in development and have profound implications for the emergence of circuit organization and function. One notable example is the depolarizing action of GABA in immature circuits (reviewed in [32]) which several models have utilized for the propagation of spontaneous activity [30,31•,33] in networks with immature neurons that have high excitability thresholds and weak and unreliable connectivity. While GABA also depolarizes immature cortical neurons *in vivo*, its action at the network level

appears to be inhibitory, calling for new models of GABAergic network control [34]. The subplate is a second example of a transient developmental structure with relatively mature properties, which serves as a scaffold to establish strong and precise connectivity between the thalamus and cortex, and then disappears [35,36]. As a third example, we mention the transient excitatory feedback connectivity between the thalamic reticular nucleus (TRN), thalamus and visual cortex, which appears necessary for the generation of feedforward connectivity along the developing visual pathway [37••]. The TRN and the subplate have so far not been modeled, except for a circuit subplate model with a single neuron at each relay stage (thalamus, subplate and cortex) [38], leaving open the question of how these transient structures orchestrate the development of large neural circuits with multiple convergent and divergent connections.

Network models incorporating these transient features could shed light on how developing circuits become spontaneously active even when cellular properties are immature and connectivity continuously refines. Thus, models offer the advantage of studying the action of any mechanism independently from the rest, as has been done with ion channel distributions and intrinsic excitability gradients.

Linking neural activity to the refinement of connectivity

How can developmental activity patterns, whether spontaneous or sensory-evoked, guide synaptic connectivity refinements? Quantitative analysis of the spatiotemporal structure of activity can provide insights into the nature of the operating rules of synaptic plasticity. During early development, patterns of spontaneous activity are 'sluggish' and characterized by long lasting events (bursts, spindle bursts, and calcium-dependent plateau-potentials) that have correlation timescales on the order of hundreds of milliseconds [22,25•,39,40]. Therefore, it is natural to assume that the plasticity rules that translate these patterns into circuit refinements should operate over long timescales [41–43].

Theoretical studies of phenomenological plasticity rules have illuminated which aspects of the spatiotemporal structure of activity guide the developmental evolution of connectivity. Activity patterns are typically interpreted into functional synaptic changes and circuit organization through Hebbian rules that use features of presynaptic and postsynaptic activity to increase or decrease synaptic strength. One of the best-studied forms of Hebbian plasticity in theoretical models is Spike-Timing-Dependent Plasticity (STDP), where potentiation and depression are induced by the precise timing and temporal order of presynaptic and postsynaptic spikes [44]. Because classical STDP integrates input correlations on the order of tens of milliseconds — much faster than firing patterns in development — more appropriate rules for developmental refinements have been analyzed. These include STDP rules which integrate more spikes or incorporate long temporal averages of the membrane potential (e.g. triplet STDP, voltage STDP) [45–47] and burst-based rules (e.g. BTDP) which evoke synaptic potentiation and depression based on the overlap (but not order) of bursts of spikes [41,42]. These plasticity rules have been studied in feedforward model networks where an array of input units projects to a single postsynaptic neuron, successfully explaining the emergence of various developmental receptive field features, including eye-specific segregation [41], ON–OFF segregation [42], and direction selectivity [47,48].

A recent study connected mechanistic connectivity refinements from known plasticity rules to normative models for the emergence of receptive field structures [49•]. By developing the concept of *nonlinear Hebbian learning*, the theory simultaneously satisfies the requirements for the final receptive field structure and the mechanisms for its development [49•]. This type of learning arises from the combination of plasticity with a neuron's input-output function and can be implemented by sparse coding and independent component analysis [50,51]. The entire space of possible stimuli can be represented by coupling neurons into recurrent networks, leading to the development of diverse receptive fields.

In these studies synaptic refinements are derived based on low-order correlations measured in spontaneous activity and early sensory-evoked responses. However, developmental activity patterns contain much more structure on several temporal and spatial scales, and activity itself refines during brain maturation [24•,25•,52•]. At the same time, these activity-dependent refinements interact nontrivially with molecular mechanisms as discussed earlier [10,12••,14]. A future challenge is to determine how more complex activity patterns could shape network connectivity and sensory representations in models which are still analytically tractable.

Simultaneous to our renewed appreciation for the complexity of spontaneous and sensory-evoked activity, we need to re-examine the ultimate purpose of these activity patterns. Existing research has focused on understanding the emergence of simple receptive fields, typically generated through feedforward plastic interactions. With the reinvention of the concept of 'receptive field' [53], we might also need to adjust the end goal of theoretical models driven by developmental activity patterns. Furthermore, foundational theoretical work is also needed to study complex receptive fields in primary visual cortex [54], or the coexistence of multiple feature-selectivities [55], as well as response features of neurons in higher visual areas that build on low-order representations [56,57]. Such complex scenarios may be linked to the nonlinear interactions among neurons in plastic, recurrent networks [58].

The emergence of systems-level organization

Understanding the implications of realistic developmental activity patterns requires appropriate models of plasticity in recurrent networks of spiking neurons. To capture experimentally measured features of network connectivity, Clopath and colleagues proposed a biologically motivated plasticity rule for spiking neurons, voltage STDP [46], because classical pair-based STDP failed to generate the prevalence of bi-directional connections in recurrent networks due to its asymmetric nature in evoking potentiation versus depression. Introducing nonlinear high-order interactions of presynaptic and postsynaptic activity can give rise to the firing rate dependence of STDP [59], and enable the formation of synfire chains or self-connected assemblies depending on the inputs [46]. This firing rate dependence was described originally in a classical model of nonlinear Hebbian plasticity, the Bienenstock-Cooper-Munro rule of synaptic plasticity [60] and has since been elaborated in more biologically realistic models that include higher-order spike interactions [47] and voltage [46].

Voltage STDP was successfully applied to a developmental scenario for the emergence of functional specificity in recurrent connections among similarly tuned neurons in mouse primary visual cortex [61••]. The functional specificity of recurrent connections only emerges after eye-opening, building on feature preference of individual neurons which is already present at eye-opening [61••]. To capture the additional aspect of feature preference before eye-opening, the same plasticity rule was implemented at feedforward synapses preceding any recurrent plasticity. The presence of gap junctions among specific cortical neurons was used to establish initial selectivity biases that were eventually amplified by recurrent plasticity and redistribution of recurrent synaptic connections [61••]. Therefore, the action of a single phenomenological plasticity rule successfully captured the experimentally observed sequence of developmental events from feedforward feature preference acquisition, to the emergence of recurrent connection specificity among similarly tuned neurons.

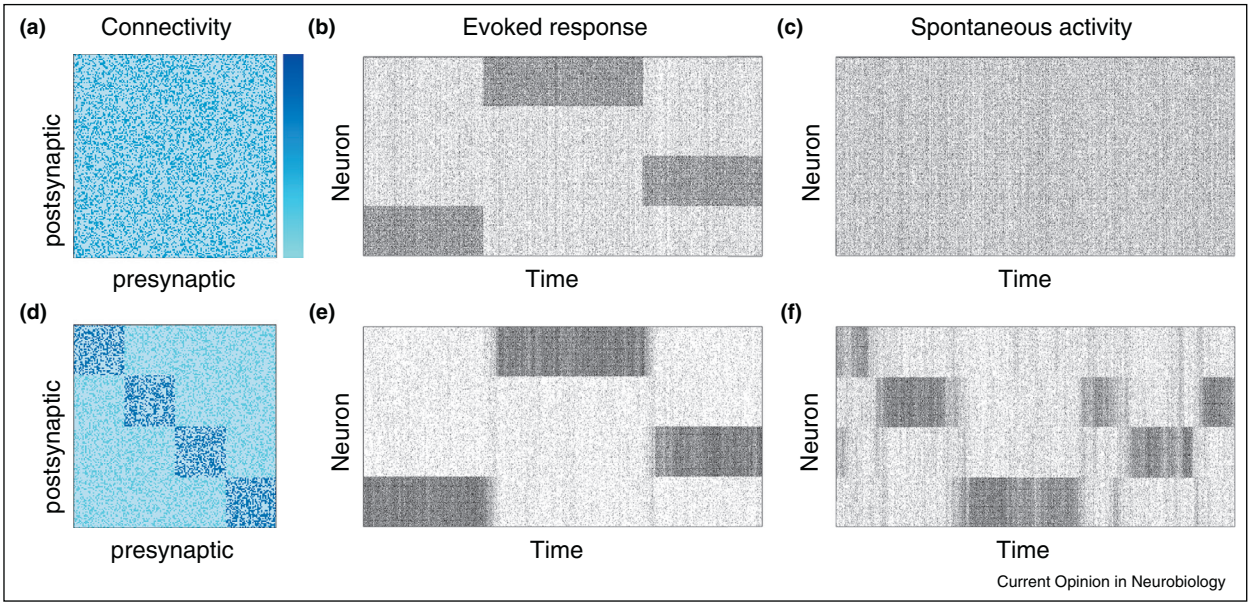
Sadeh and colleagues studied a comparable process in large recurrent networks of spiking neurons with balanced excitation and inhibition, where the dominant input to a neuron is not feedforward but comes from the local recurrent network into which the neuron is embedded [62•]. This recurrent input sharpened the initially weak orientation selectivity of single neurons, while plasticity at both recurrent excitatory and inhibitory synapses produced adult connection specificity [62•]. Additionally, the neurons also sparsified their responses as observed experimentally around eye-opening [52•,63]. One caveat of these models [61••,62•] is that they do not explicitly represent orientation selectivity: the emergence of this feature selectivity is realized by the selective potentiation of feedforward inputs from a group of correlated neurons which represent a given orientation. Related models, however, can give rise to biphasic, oriented receptive fields localized in space under certain conditions [64•].

More broadly, preferentially strong connectivity among groups of neurons in recurrent network models with balanced excitation and inhibition can emerge without reference to the feature preference (or sensory tuning) of these neurons [64•,65•,66]. These preferentially connected groups are called *Hebbian assemblies*; the attractor dynamics they can give rise to [64•,67] could be the substrate of different neural computations, including predictive coding through the spontaneous retrieval of evoked response patterns (Figure 2) [64•,65•,66] and decreased variability during sensory stimulation [65•]. Interestingly, in some of these models recurrent attractor dynamics and biphasic, oriented receptive fields localized in space emerge only when the networks are trained with natural image stimuli, but not with white noise [64•].

Innovative theoretical analysis has also derived the conditions for the spontaneous, devoid of feedforward patterning of inputs, emergence of different types of assemblies through pair-based STDP at recurrent synapses [68]. This could be a good model for the development of network connectivity by spontaneous activity generated intrinsically in the network. Changing the shape of the plasticity rule and the biophysical properties of synaptic transmission can result in the emergence of either self-connected assemblies or synfire chains [68]. Curiously, the same structures emerge upon training in models with feedforward and recurrent plasticity under voltage STDP, where the determining feature of the output structure is the nature of the inputs (random inputs versus temporal sequences) [46].

The development of functional recurrent circuitry in models often relies on the interplay between Hebbian and homeostatic forms of plasticity. Classical Hebbian-style plasticity rules alone induce a positive feedback instability, harvesting and reinforcing co-activity of cells in the circuit, induced by either shared input or recurrent connectivity. To combat this problem and bring circuit function to a normal operating regime, the above models implement a myriad of homeostatic mechanisms based on experimental observations [69]: (1) normalization of synaptic weights, (2) metaplasticity where the amplitude and sign of Hebbian synaptic change is modulated ((1) and (2) reviewed in [70••]) (3) plasticity at inhibitory synapses [64•,65•,66] and (4) shifts in intrinsic excitability [71•,72], or a combination of these mechanisms [73,74•]. Such homeostatic mechanisms can be either added to simple Hebbian rules or be implicit in more complex rules, such as triplet STDP with a sliding threshold [47] or voltage STDP [46]. A key insight from these models has been

Figure 2



(a) Excitatory connectivity matrix of an unstructured recurrent network of excitatory and inhibitory spiking neurons [62•,67]. Darker shades of blue indicate stronger connections. **(b)** Spike rasters of the evoked response in the network by driving three different subsets of excitatory neurons with stronger external input compared to the other neurons, as indicated by the elevated firing rates. **(c)** Activity in the network in response to weak uniform external input to all excitatory neurons. **(d)** Excitatory connectivity matrix of a structured recurrent network of excitatory and inhibitory spiking neurons. Neurons are more strongly connected within a cluster, which could be imprinted through plasticity mechanisms in simulated networks [64•,65•,66]. **(e)** Spike rasters of the evoked response as in b. **(f)** In response to weak uniform external input to all excitatory neurons, the network spontaneously activates subsets of neurons with stronger connectivity [65•,66]. These could be interpreted as attractors of the network dynamics, giving rise to spontaneous retrieval of evoked activity patterns, which in turn reinforce and maintain the imprinted structure through STDP. This behavior is absent in the unstructured network (c).

that experimental forms of homeostatic plasticity are too slow to stabilize Hebbian plasticity; stability in the models requires faster forms of homeostatic plasticity that have yet to be identified experimentally [70••,75].

Taken together, these studies highlight the importance of theory and models to understand how functional connectivity in recurrent networks emerges from Hebbian and homeostatic plasticity giving rise to stable dynamics and computations. A future challenge would be to interpret these findings in the context of specific biophysical mechanisms that might implement them (e.g. [76]), and to relate them to the map formation models discussed earlier [77•]. Moreover, it would be worthwhile to examine the emergence of functional organization under realistic developmental patterns of activity, which as discussed earlier are sluggish and might utilize different plasticity rules than those that rely on precise spike timing [78].

Conclusion

Theoretical and computational approaches have contributed in powerful ways to our understanding of how neuronal circuits develop to establish precise connectivity and tuned single neuron responses, and to give rise to adult computations. Retinotopic map formation represents perhaps the most successful example of models of development (apart from orientation maps): starting from phenomenological models, theorists have proposed comprehensive models which can explain large data sets and make interesting predictions. However, this represents only one aspect of neural development. Going forward, we should use this example to build modeling frameworks which capture the diversity of mechanisms unique to this period, their timescales and spatial scales of operation and their coordinated action to generate adult computations.

In addition to the detailed analysis of spontaneous and sensory-evoked activity in developing circuits *in vitro*, we still need to understand the generation and function of this activity in the intact animal. With the recent spur of *in vivo* recordings [23,24•,25•,52•], theoretical neuroscience can contribute to the quantitative analysis of longitudinal recordings of single neuron and network activity in novel ways. This analysis can provide us with necessary assumptions and constraints for new models of how this activity is generated, how it changes over development, and how it sculpts developing networks.

Analyzing this activity can also help us infer the appropriate developmental plasticity rules from the potentially different correlational structure in the juvenile and the adult [41,42,79]. This will enable us to link theoretical

descriptions of plasticity at the level of neuron pairs (triplets, etc.) to network connectivity refinements, explaining the emergence of functional units such as synfire chains, assemblies and memory attractors [64•,65•,68]. The observation that the same network structures emerge either intrinsically through the properties of the plasticity rule [68], or externally through the nature of the input patterns [46], suggests that these issues should be examined experimentally under specific developmental scenarios where the derived model structures are observed.

While it seems natural that models should explore novel hypotheses and make predictions to direct future experiments, we also point out another important role. Existing models should be tested on paradigms and data different from those on which the models were initially based. This has the value of testing the generality and utility of models and avoids overfitting. Theory and models hold the potential to uncover common underlying principles (or differences) in the development of different circuits, for instance sensory and motor [80•]. In some cases, the same solution might emerge for different problems, but often different solutions might be beneficial to satisfy different computational requirements.

With the accumulation of experimental data, theory and models need to play a larger role in understanding the development of neural circuits with its diversity of interacting instructive signals guiding self-organization. We have proposed that the new focus should be on the developmental emergence of single cell properties, the generation of spatio-temporal population activity patterns and the plasticity they induce, to understand the functionally relevant computations they might reflect. As many developmental processes are carefully orchestrated, theoretical and modeling approaches are necessary to tease apart the relative importance and role of each process.

Conflict of interest statement

Nothing declared.

Acknowledgements

This work was supported by funding from the Max Planck Society. JG holds a Career Award at the Scientific Interface from the Burroughs Wellcome Fund. The authors thank Matthias Kaschube, Tatjana Tchumatchenko and Stephen Eglen for comments on the manuscript.

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