

Understanding neural circuit development through theory and models

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Abstract

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, theoretical and computational models have enabled us to test the adequacy of specific assumptions, explain experimental data and propose testable hypotheses. With the accumulation of larger data sets, theory and models will likely play an even more important role in understanding the development of neural circuits.

Introduction

Neural systems are tuned 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 double 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 diversity of mechanisms and structures unique to development characterize the self-organization into functioning circuits. Technological advancements in experimental techniques have made feasible to record and manipulate a number of circuit components. In parallel, data analysis techniques and theoretical 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, learn from and discriminate different sensory stimuli.

We highlight recent theoretical work on neural circuit organization during early stages of development (late prenatal or early postnatal) 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 single neuron properties, and the emergence of computations, we highlight the success of theoretical models to analyze different mechanisms and propose new hypotheses of neural circuit development.

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 are 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/*ephrins* (reviewed in [5, 9]), and are subsequently refined by spontaneous neural activity. We highlight three aspects of recent progress on map formation before we explore more computational aspects of development.

Recent models simulate not only the final map, but the **entire temporal evolution of map formation** from a combination of mechanisms: retinal axons initially arborize stochastically in the target region, synaptic connections are subsequently refined by Hebbian activity-dependent plasticity and regulated in strength through competition for a common source [10, 11, 12^{••}]. Despite the success of these models in reproducing experimental results, one disadvantage is their complexity – structure emerges from many interacting mechanisms making it difficult to infer which of the resulting properties are the product of any of the model ingredients; another disadvantage is their reproducibility since they take days to simulate.

With the accumulation of experimental data from normal and mutant animals, **new quantitative analysis methods of maps** have also been developed. One example is the ‘Lattice Method,’ which enables a quantitative assessment of the topographic ordering in the one-to-one map between two structures [13]. Fitting models to data from different types of mutants has suggested that that activity-dependent and molecular forces most likely act simultaneously (rather than sequentially) and stochastically to give rise to ordered connections as observed experimentally [13, 14].

To compare and unify different models aimed at capturing specific aspects of map formation, new frameworks now support the **unbiased and quantitative testing of computational models** on 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 equally consistent with existing data [16^{••}]. Despite the success in modeling map formation, the challenge remains to integrate maps with the emergence of other, more functional aspects of development.

Spontaneous activity: transient features and computational implications

Before the onset of sensory experience, many developing circuits can generate neural activity spontaneously. Spontaneous activity regulates many developmental processes, including neuronal migration, ion channel maturation and the establishment of precise connectivity [9, 17, 18]. In the retina, spontaneous activity is generated before the retina responds to light, and has been commonly implicated in the refinement of retinotopic maps between the retina and SC or LGN [18, 19]. The retina generates complex spatiotemporal waves of spontaneous activity during the first two weeks of postnatal development (in rodents) ([20], for models see [21, 22]). These propagate through the visual pathway to the SC, the thalamus, and the visual cortex [23, 24, 25[•]], which are themselves spontaneously active [26[•], 27]. We review several transient cellular properties and transient structures contributing to the generation and propagation of spontaneous activity in the cortex, and subsequently examine its computational implications and role in the refinement of connectivity to downstream targets.

Developing neurons express a unique configuration of ion channels and receptors to mediate

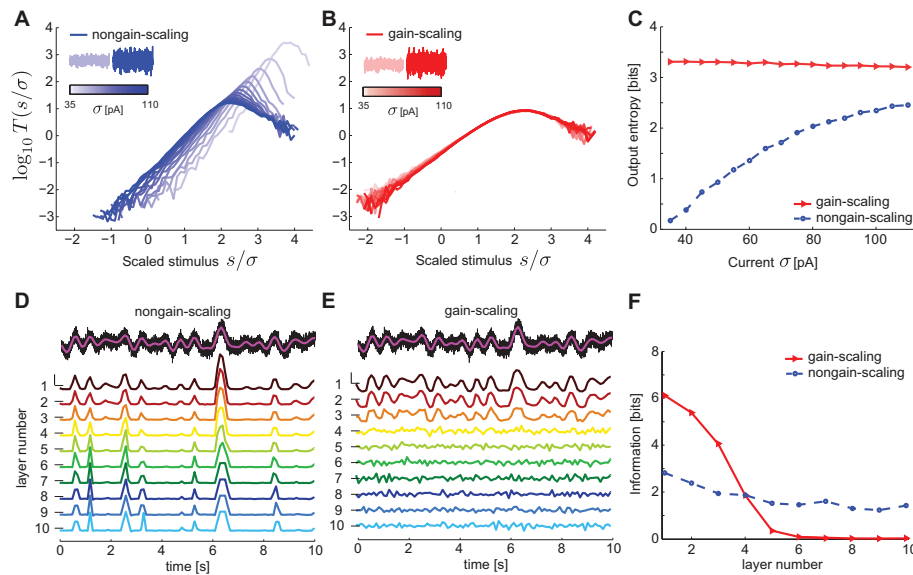


Figure 1: **A,B.** The nonlinearities in the LN model framework for a nongain-scaling (A) and a gain-scaling (B) Hodgkin-Huxley neuron stimulated with white noise with a range of variances σ^2 . The lack of gain scaling corresponds to cortical neurons recorded around birth, while the ability to gain scale matches cortical neurons after the first postnatal week. The nonlinearities were computed using Bayes' rule: $T(s) = P(\text{spike}|s)/r = P(s|\text{spike})/P(s)$ where r is the neuron's mean firing rate and s is the stimulus filtered by the spike-triggered average [29••]. The nonlinearities of gain-scaling neurons overlap over a wide range of σ . **C.** The output entropy as a function of the amplitude of fast fluctuations, σ , measures the information about fast fluctuations. **D,E.** Peristimulus time histograms (PSTHs) from each layer in feedforward networks of nongain-scaling (D) vs. 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 (D,E magenta, top) transmitted by the two networks in D and E. Figure adapted from [29••].

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) of single neurons change during the first postnatal week. This biophysical change enables single neurons to gain an ability to dynamically adjust their response range to the size of stimulus fluctuations [28]. This property is termed 'gain scaling' and can be extracted by building linear-nonlinear (LN) models from the response of single neurons to random noisy stimuli (Fig. 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 (Fig. 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 model cortical networks (Fig. 1D). This can be related to the ability of the cortical network to 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 (Fig. 1E) [29••]. These 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 (Fig. 1F). This example demonstrates that single neuron properties can influence network dynamics, thus bridging the gap between two levels of description, and makes predictions for the information processing capabilities of these networks which can be evaluated in experimental data.

To model cortical spontaneous activity in more biologically realistic set ups requires that

spontaneous transients are endogenously generated by the networks themselves, rather than provided as input to the network (as in Fig. 1E,F). To determine the source of these transients consistent with data, Baltz and colleagues proposed three different models implicating intrinsic bursts, spikes or accumulation of random synaptic input [30]. Although all models could generate propagating spontaneous events, networks where single neurons produced intrinsic bursts were most consistent with *in vitro* recordings of spontaneous network activity [30]. Barnett and colleagues distributed intrinsically bursting neurons along a gradient in a model network with recurrent synaptic connectivity and local gap junctions. The gradient of intrinsic bursting was sufficient to capture the direction of wave propagation in cortical slices [31•]. The models also predicted that wave activity persists near the site of initiation even after a wave has passed, which was confirmed experimentally [31•].

Other transient network features are also prominent in developing circuits. The depolarizing action of GABA in immature circuits (reviewed in [32, 33]) is an example of a transient developmental feature which several models have utilized for the propagation of spontaneous activity [30, 31•] – this feature seems to be important to support spontaneous activity in networks where immature neurons have high excitability thresholds, and weak and unreliable connectivity. The subplate is a transient structure with relatively mature properties, which serves as a scaffold to establish strong and precise connectivity between the thalamus and cortex and then disappears [34, 35]. 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 [36••]. 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) [37], leaving open the question of how these transient structures support the organization 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 is still forming. Models offer the advantage of studying the action of any mechanism independently from the rest, allowing us to identify the relative influence of each, 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 (spontaneous or sensory-evoked) guide synaptic connectivity refinements? Detailed 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 [23, 26•, 38–41]. Therefore, it is natural to assume that the plasticity rules that translate these patterns into circuit refinements should operate over long timescales.

Theoretical studies of phenomenological plasticity rules have helped us understand the implications of different spatiotemporal structure of activity on the temporal evolution of connectivity. The activity patterns are typically interpreted into functional synaptic changes and circuit organization through Hebbian rules that use pre- 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 pre- and postsynaptic spikes [42]. Because this classical STDP rule integrates input correlations on the order of tens of milliseconds – much faster than firing in development – more appropriate rules for developmental refinements have been analyzed. These include STDP rules which integrate more spikes or long temporal averages of the membrane potential (e.g. triplet STDP, voltage STDP) [43–45] and burst-based

rules (e.g. BTD) which evoke synaptic potentiation and depression based on the overlap (but not order) of bursts of spikes [38, 39]. 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 [38], ON-OFF segregation [39], and direction selectivity [45, 46].

A recent study connected these mechanistic connectivity refinements from known plasticity rules to normative models for the emergence of receptive field structures [47[•]]. By developing the concept of *nonlinear Hebbian learning*, the theory simultaneously satisfied the requirements for final receptive field structure and the mechanisms for its development [47[•]]. 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 [48, 49]. Coupling neurons into recurrent networks resulted in the development of diverse receptive fields through nonlinear Hebbian learning, which was necessary to represent the entire space of possible stimuli. Going one step further, it would be interesting to extend this theory to link bottom-up and top-down approaches for plasticity in recurrent synapses.

These theoretical studies drive synaptic refinements based on low-order correlations measured in spontaneous activity and early evoked responses. However, developmental activity patterns contain much more structure on several temporal and spatial scales, and activity itself refines during brain maturation [25[•], 26[•], 50[•]]. At the same time, these activity-dependent refinements interact nontrivially with molecular mechanisms as discussed earlier [10, 12^{••}]. 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.

The emergence of systems-level organization

One major challenge for modeling the implications of realistic developmental patterns is plasticity in recurrent networks of spiking neurons; this problem has been recently approached in numerical simulation studies. Clopath and colleagues introduced a biologically motivated plasticity rule for spiking neurons, voltage STDP, to model plasticity in spiking recurrent networks with different input configurations [44]. Although the assumed input patterns were abstract groups of correlated neurons, unrelated to experimentally recorded activity, plasticity in the networks generated different functional network structures including synfire chains and self-connected assemblies accompanied by prevalence of bidirectional connections [44].

Voltage STDP was also applied to a developmental scenario of the emergence of functional specificity of recurrent connections among similarly-tuned neurons in mouse V1 [51^{••}]. This specificity of recurrent connections only emerges after eye-opening, building on feature preference of individual neurons which is already present at eye-opening [51^{••}]. 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 [51^{••}]. 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 [52[•]]. This recurrent input sharpened the initially weak orientation selectivity of single neurons. Plasticity at both recurrent excitatory and inhibitory synapses produced adult connection specificity [52[•]]. In addition to sharpening orientation selectivity, the neurons also sparsified their responses as observed experimentally around eye opening [53, 50[•]]. One caveat of both

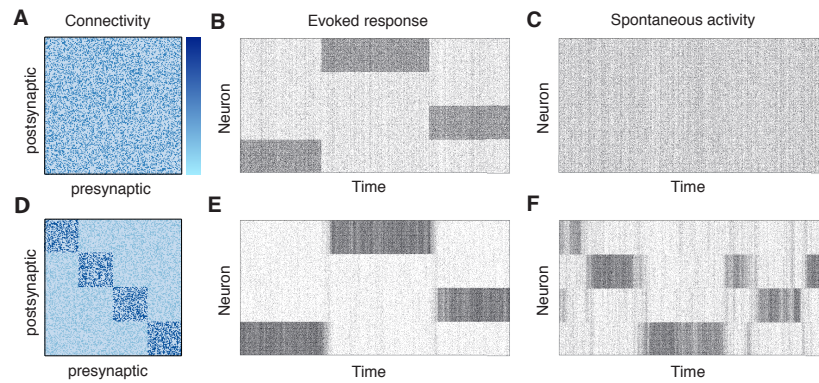


Figure 2: **A.** Excitatory connectivity matrix of an unstructured recurrent network of excitatory and inhibitory spiking neurons [52[•], 57]. **B.** Spike rasters of the evoked response in the network by driving three different subsets of excitatory neurons with stronger external input compared to the other neurons, as indicated by the elevated firing rates. **C.** Activity in the network in response to 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 [54[•], 55[•], 56]. **E.** Spike rasters of the evoked response as in B. **F.** In response to uniform external input to all excitatory neurons, the network spontaneously activates subsets of neurons with stronger connectivity [55[•], 56]. These could be interpreted as attractors of the network dynamics, giving rise to spontaneous retrieval of evoked activity patterns. This behavior is absent in the unstructured network (C).

models [51^{••}, 52[•]] 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. Related models, however, can give rise to biphasic, oriented receptive fields localized in space under certain conditions [54[•]].

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 [55[•], 56, 54[•]]. These preferentially connected groups are called *Hebbian assemblies*; the attractor dynamics they can give rise to in networks [54[•], 57] could be the substrate of different neural computations, including predictive coding through the spontaneous retrieval of evoked response patterns (Fig. 2) [54[•], 55[•], 56] and decreased variability during sensory stimulation [55[•]]. 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 [54[•]].

Innovative theoretical analysis has also derived the conditions for the spontaneous emergence of different types of assemblies through STDP at recurrent synapses, in the absence of feedforward patterned inputs [58]. By changing the shape of the plasticity rule and the biophysical properties of synaptic transmission, the authors demonstrated the emergence of self-connected assemblies vs. synfire chains [58]. Interestingly, the same structures emerged upon training with random vs. temporal sequences of inputs (respectively) in models with feedforward and recurrent plasticity under voltage STDP [44].

The development of functional recurrent circuitry in these models often relies on an interplay of Hebbian and homeostatic forms of plasticity. Classical Hebbian-style plasticity rules alone induce a positive feedback instability whereby neurons that are frequently co-active will increase their connectivity and future co-activity. To combat this problem and bring circuit function to a normal operating regime, the above models implement diverse homeostatic mechanisms based on experimental observations [59]: (1) normalization of synaptic weights, (2) metaplasticity where the amplitude and sign of Hebbian synaptic change is modulated ((1) and (2) reviewed in [60^{••}]) (3) plasticity at inhibitory synapses [54[•], 55[•], 56] and (4) shifts in intrinsic excitability [61[•], 62], or a combination of them [63, 64[•]]. A key insight from these models has been 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 [60^{••}, 65].

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. [66]), and to relate them to the detailed map formation models discussed earlier [67[•]]. Moreover, it would be interesting 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 [68].

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 more comprehensive models which can explain larger 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 [26[•], 50[•], 24, 25[•]], 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 what its role is in sculpting 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 [38, 39, 69]. This will enable us to link theoretical descriptions of plasticity at the level of neuron pairs to network connectivity refinements, explaining the emergence of functional units such as synfire chains, assemblies and memory attractors [54[•], 55[•], 58]. The observation that the same network structures emerge either intrinsically through the properties of the plasticity rule, or externally through the nature of the input patterns, 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 [70[•]]. In some cases, the same solution might emerge for different problems, but often different solutions might be beneficial to ensure robustness and variability of responses.

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 and population activity patterns, and the

behaviorally relevant computations these 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.

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