Introduction to the Special Issue on From Maps to Circuits: Models and Mechanisms for Generating Neural Connections

This Special Issue grew out of the meeting “From Maps to Circuits: Models and Mechanisms for Generating Neural Connections” held at the University of Edinburgh in July 2014 (see maps2014.org for more details). It brings together work presented at the meeting along with other closely related contributions.

Neural maps form a key organizing principle of wiring in the nervous system. While understanding the development of these maps has been a critical target for both experimental and theoretical work for many decades, the meeting and this Special Issue highlight many key questions that remain only partially answered. Neural maps can take a variety of forms in different systems. In the retinotectal/retinocollicular projection, neighboring points in the retina map to the neighboring points in the tectum. While the same is true on a broad scale for the mapping from the retina to the thalamus to the primary visual cortex, on a finer scale maps of higher order features emerge, including ocular dominance and orientation preference, which in many higher-order mammals have a complex spatial structure. In contrast, in the olfactory system, widely dispersed olfactory sensory neurons expressing the same odorant receptor project axons which converge on the same glomerulus in the optic bulb.

A key feature of the neural mapping field has been an unusually tight interplay between experimental and theoretical work. Beginning with pioneering mathematical work by David Willshaw, Christoph Von der Malsburg, and others in the 1970s, productive theoretical paradigms have been established which have made important contributions to interpreting and guiding experimental work across many areas of neural map formation. One of the key goals of the meeting was to bring people together who have shown an interest at combining theoretical and experimental techniques. Experimental and theoretical work spanning many of the different model mapping systems is presented in this Special Issue.

The reviews by Kita et al. (2015a) and Hunter et al. (2015) emphasize the importance of zebrafish as a model system for studying neural maps. Due to their ease of manipulation, and their accessibility and optical transparency during early development, they offer many opportunities for probing mechanisms of map formation. (Kita et al., 2015a) introduce in a zebrafish context some of the basic principles that are then developed in the other contributions, most importantly the role of both molecular and activity-dependent cues in driving map formation. The main focus of (Hunter et al., 2015) is the potential of zebrafish for large-scale brain mapping, including gene expression mapping, understanding the functional classes of retinal ganglion cells, and the retinal projectome, and understanding the relationships between neural activity, neural circuits and behavior. They also discuss some of the big data problems involved, and possible approaches to resolving those.

A variety of molecular cues are critical for the initial formation of maps in many different neural systems. Missaire and Hindges (2015) review the critical role of cell adhesion molecules (CAMs) in several different aspects of map formation in the visual system. CAMs are initially important for promoting neurite outgrowth, both by cytoskeletal remodeling and modulation of gene activation. They then play a key role in target selection. This includes the decision of retinal axons whether or not to cross the midline, and topographic targeting in the tectum, where CAMs can act in concert with graded tectal cues such as the ephrins. CAMs also play an important role in dendrite self-avoidance, helping ensure the even spread of neural resources.

While the role of ephrin gradients in guiding map formation is well established, it has been unclear whether they affect the targeting of different types of retinal ganglion cells equally. In the research contribution of (Sweeney et al., 2015) the authors study the laminar organization of targeting in the superior colliculus in ephrin-A2/A5 double mutant mice. Intriguingly they find a misalignment between the maps of different retinal ganglion cell types, suggest- ing map formation proceeds somewhat independently depending on retinal cell type. This raises many inter- esting questions for future work.

The olfactory system provides another key model for understanding neural map formation, showing both some similarities but also marked differences with visual maps. The review by Nishizumi and Sakano (2015) summarizes recent work from the Sakano lab on how olfactory maps form in mouse. Key issues include how each olfactory sensory neu- ron manages to express only one type of odorant receptor, and how odorant receptors instruct axon projections. For the latter, recent results suggest that receptor-identity-dependent Cyclic adenosine mono- phosphate (cAMP) levels play a critical role in deter- mining targeting along the anterior-posterior axis, while in contrast graded levels of Neuropilin 2 pro- vide positional information along the dorsal-ventral axis. The authors then discuss the influence of neural activity on map development, in particular how activ- ity refines the initial glomerular map set up by purely molecular cues.

The influence of activity on visual map formation is explored in the two research contributions of (Kita et al., 2015b; and Xu et al., 2015). Recent work has suggested that axonal branching plays a critical role in the navigation of retinal ganglion cell axons to their targets in the tectum in zebrafish, but the extent to which this process is regulated by activity was unclear. By blocking activity in the retina (Kita et al., 2015b) found that while some aspects of branching-based navigation were unaf- fected, other aspects were, suggesting that there may not be a clean temporal separation between molecularly-guided and activity-dependent map development. (Xu et al., 2015) address the long- standing question of whether activity plays an instructive or merely permissive role in retinocollic- ular map formation. They used a novel approach to genetically disrupt spontaneous retinal waves in mice using a manipulation specific to the retina, reducing overall levels of activity but leaving its correlational structure unchanged. Eye-specific seg- regation but not retinotopic refinement was dis- rupted, providing support for an instructive role for neural activity in map formation.

Finally, two theoretical papers address the capa- bility of models to explain some of the main exper- imental data from the map formation field. (Hjorth et al., 2015) present the first thorough comparison of the performance of computational models of reti- nocollicular map formation, by comparing the abil- ity of four prominent models to explain the maps seen in a number of recently characterized mouse mutants. The basic finding was that all the models failed in one way or another, suggesting there is still plenty of work to be done in this area. How- ever, partial recovery of some of the models could be achieved by hypothesizing that a weak, as yet unidentified, gradient is still present when all ephrin-A ligands are removed from the tectum, sug- gesting an interesting direction for future experi- mental work. Wilson and Bednar (2015) compare four different models of feature map development in the visual cortex, and address what light they shed on the functional significance of spatial pat- terning in cortical maps. In addition to providing an accessible introduction to these models, the authors argue that none of them provide a compelling explanation for why we have maps, and thus that maps may in fact be an epiphenomenon.

Epiphenomenon or not, the articles in this Special Issue show that the study of neural map development remains a strong and productive area. Indeed a follow-up meeting is planned in 2015 (see maps2015. org). It is clear that future discoveries regarding this paradigmatic example of patterned neural wiring have the potential to have a critical impact on not only our understanding of brain development in gen- eral, but also on how problems with neural wiring could underlie many common neurodevelopmental disorders.

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