The R8 Race: Patterning neurogenesis during *Drosophila* development

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***Short Abstract* — We present a quantitative model of the formation of the R8 photoreceptor lattice in *Drosophila* development. In our model, R8 induction proceeds through the flipping of cell-autonomous switches, with existing R8's providing a template for the placement of new photoreceptors. This novel patterning mechanism has the dramatic consequence that, depending on initial conditions, both the normal triangular lattice and stripes of R8 cells can appear in genetically identical tissue. These predictions are confirmed experimentally by manipulation of the *Notch* and *scabrous* genes. Our model suggests an alternative to the textbook version of neural fate specification through lateral inhibition.**

I. Background

The *Drosophila melanogaster* eye imaginal disc is a classic example of the *de novo* generation of periodic order during development. The adult eye comprises ~750 ommatidia, each composed of 8 photoreceptors and assorted support cells, packed in a crystalline array [1]. These ommatidia are founded by R8 cells, which are specified in an orderly array in the wake of the morphogenetic furrow (MF) that moves across the developing retina. The earliest marker of R8 fate is the transcription factor Atonal (Ato). As cells enter the MF, regularly-spaced intermediate groups (IG's) of ~10 cells raise their *ato* level, and *ato* expression is lost in the other cells. Over about 2 hours, Ato then progressively disappears from the IG until only a single cell, the R8, is left expressing it. The network that controls this dynamical evolution involves at least three kinds of interaction. Hedgehog (Hh), secreted by differentiating R8's posterior to the MF, starts the cascade of events leading to *ato* induction. Cell-autonomous self-activation can then sustain *ato* expression once it reaches a critical level. Ato also activates several signaling molecules that repress its expression in nearby cells. The emergence of a single neural precursor cell from within a proneural group is a common feature shared by many examples of neural development [2,3].

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II. Results

Based on experimentally verified interactions, we develop a mathematical model of R8 specification. Mathematical biologists have often assumed that patterns in activator-inhibitor systems of the sort present in the eye disc arise via a Turing instability [4]. We find, however, that the fact that self-activation in this system is cell-autonomous leads to a very different pattern formation mechanism, in which bistable switches in each cell play a central role. Our model reproduces a number of real-world observations, such as the consistent location of the R8 at the posterior apex of the IG's [5], that had previously been difficult to explain. Moreover, it predicts several novel phenotypes that we have verified experimentally, most strikingly a transition from a hexagonal to a striped pattern in certain genotypes after a transient perturbation. The model also suggests that the selection of the individual R8's is a consequence of the timing of initial *ato* activation rather than of interactions among cells in the fully-developed proneural group, as had been thought to be the case both in eye discs and in many other proneural regions [2,3,6]; it may thus have broader implications for neural fate specification. In the half-century since spacing patterns in biology were first modeled, it has become clear that cell-autonomous auto-regulation is a widespread feature of cell determination networks. Our work emphasizes that this ubiquity of complex feedbacks within individual cells requires models that treat cells as discrete objects; such models can have behavior quite different from those that smear the cells into a uniform continuum.

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