

Dynamical Grammar Modeling of Cellular Proliferative Dynamics in the Olfactory Epithelium

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The olfactory epithelium (OE) is one of a few regions of the vertebrate nervous system that undergoes neurogenesis, or *de novo* production of neurons, throughout life. Under normal circumstances, a small population of stem and progenitor cells replenishes slow, continual neuron loss; but when the OE is injured, proliferation increases dramatically until proper neuron number is restored. What strategies are used to achieve robust size control in the face of environmental and genetic perturbations? How do such strategies impact the speed and stability of regeneration?

Experimental studies have shown that proliferative cells in the OE are organized into discrete lineage stages. Secreted molecules, such as growth and differentiation factor 11 (GDF11), are produced by cells at particular stages in the neuronal lineage and feed back to inhibit proliferation at earlier stages [1]. Additional diffusible proteins, such as Follistatin, are produced in and around the OE, and act as competitive inhibitors of GDF11 and its homologs.

In principle, mathematical or computational modeling can help us to explore how such molecules and lineage stages contribute to regenerative dynamics and size control in the OE. Simple ODE models can be constructed [2], but require assuming that the system is "well-stirred", continuous, and deterministic. In fact, OE cells at different lineage stages are distributed in a non-uniform manner in space, and length scales associated with such spatial inhomogeneity may be large compared with the length scales over which molecules such as GDF11 and Follistatin diffuse before being captured and destroyed. To account for such effects, and indeed to determine whether spatial inhomogeneity is important for proliferative control, a different approach to modeling is needed.

Here we employ a Dynamical Grammar (DG) formulation. The DG provides a multiscale modeling framework in which a system can be comprised of continuous and discrete elements, and evolves as a stochastic process. The transition probability operator is defined by stochastic rules (reactions) with corresponding rate functions, and continuous rules (ODE or PDE) that act on groups of parameterized objects. Each DG has a well-defined semantics expressed in terms of operator algebra, in which parallel-acting processes are mapped to the sum of their time-evolution operators [3]. To simulate such a hybrid system we use a hybrid ODE/stochastic process simulation algorithm, derived from an expansion of the exponential function using operator algebra, that generalizes Gillespie's Stochastic Simulation

Algorithm.

In our application the objects are cells parameterized by type, size, and location. Grammar reactions describe events such as cell differentiation, division or death, while continuous rules depict cell growth and movement, and diffusion of secreted molecules. Rate functions for differentiation depend on cell type and spatiotemporally varying concentrations of extracellular molecules. The cell division rule has a stochastic rate, and orientations of divisions follow a probability distribution. Rules governing tissue mechanics and growth involve weak (breakable) springs.

We will present data on the ability of such modeling to capture regulated proliferation, growth, differentiation and spatial organization in small domains of the OE during its initial development.

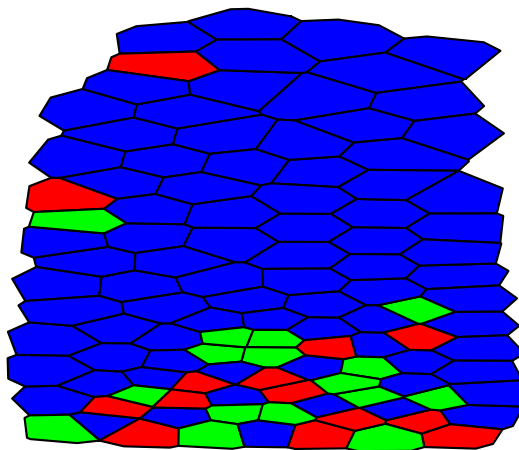


Figure 1: A Voronoi diagram representation of a stochastic simulation output at $t = 500$ hours. Red regions represent stem cells, green are immediate neuronal precursors and blue are olfactory receptor neurons. The simulation starts with only 3 stem cells. Cells move under the influence of the weak spring connections to neighboring cells or the basal lamina. The springs may be connected or disconnected according to cell movement and division, while the spring constants are based on the cells' adhesion properties. The DG interpreter and simulation algorithm runs in our "Plenum" package written for the Mathematica computer algebra system

References

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