The maths of kidney, lung, and gland development: analyzing a branching instability driven by stochastic cell wiggling

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Branching morphologies are key to the functioning of kidneys, lungs and glands. Epithelial tissues, a type of tissues covering the cavities and surfaces of these and other organs, are thought to be central actors in the growth of such branching organs. From physical mechanisms forming branched structures, like crystal growth and a process called viscous fingering, we know that for a structure to branch it is essential to have some sort of curvature effect: the surface growth velocity must increase with the surface curvature. As a result, small surface irregularities can initiate a branch; an instability also known as the Mullins-Sekerka instability.

Interestingly, when isolated in cell cultures and placed in wells of curved geometry, the behavior of epithelial cells is curvature-dependent [3]. The cells display stochastic, amoeboid behavior at convex regions of the well, whereas they remain much more quiet at flat and concave regions of the well. Such curvature-dependent behavior is due to a self-secreted, diffusing inhibitor of cell motility, called TGF-β.

We tested the consequences of these experimental observations in a simulation model based on the Cellular Potts model [1, 2], and found that it easily produces self-avoiding branches with properties corresponding with biological epithelial branching systems. Interestingly, the thickness and number of these branches seems to depend on the extent to which the cells can "wiggle" randomly (see Figure 1—thus in this Monte-Carlo simulation, the degree of stochasticity may drive the morphological properties of the pattern, a rather unusual phenomenon.

In this project, you will analyze this stochastic branching instability in detail, using

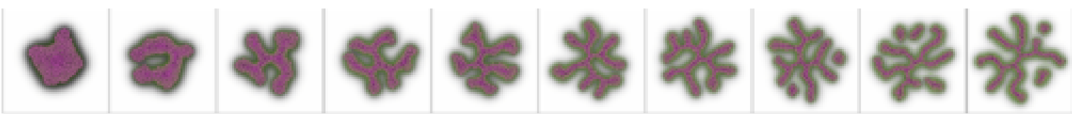

Figure 1: Simulation model of epithelial branching; increasing degree of stochastic cell motility from left to right

the simulation model and a mean field or continuous approximation of the model (e.g., level set methods), the details of which are open to discussion. The central question a) if our current intuition on this stochastic branching instability can be supported mathematically, and b) what is the relation between the stochastic parameter ("degree of cell motility") and the properties of the resulting branch morphologies.

References

[1] J. A. Glazier and F. Graner. Simulation of the differential adhesion driven rearrangement of biological cells. *Phys. Rev. E*, 47(3):2128–2154, Jan 1993.

[2] R. M. H. Merks, E. D. Perryn, A. Shirinifard, and J. A. Glazier. Contact-inhibited chemotaxis in de novo and sprouting blood-vessel growth. *PLoS Comp. Biol.*, 4(9):e1000163, Sep 2008.

[3] C. M. Nelson, M. M. VanDuijn, J. L. Inman, D. A. Fletcher, and M. J. Bissell. Tissue geometry determines sites of mammary branching morphogenesis in organotypic cultures. *Science*, 314:298–300, Jan 2006.