Modeling contact inhibition of growth using Glazier-Graner-Hogeweg (GGH) approach

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Contact inhibition of growth is achieved through homophilic cell surface adhesion proteins called cadherins. Overexpression of cadherins increases the thickness of a confluent monolayer and vice versa, showing that cadherins influence the extent of cell-cell contact. On the other hand, overexpression of cadherins also arrests cell growth and its disruption increases secretion of growth factors, indicating that cadherins are able to influence growth as well. Thus, cadherins seem to be influencing cell growth, possibly by altering the extent of cell-cell contact. Therefore, we hypothesize that the extent of cell-cell contact can be considered as a *constitutive property* of the number of cadherin junctions and show that it can be effectively used to control cell growth and proliferation. We use this approach to model contact inhibition of growth in cell cultures, wound healing and tissue morphogenesis.

***Keywords* — contact inhibitions, cadherins, constitutive property, growth and proliferation, epithelial cells**

I. Background

Contact inhibition is a fundamental mechanism by which cells arrest their growth when they come into contact with each other. In epithelial cell cultures, contact inhibition of proliferation is a key factor in achieving confluence. In proliferating wounded tissues, growth is finally arrested through contact inhibition. In developing tissues contact inhibition is overcome by signal from growth morphogens. The underlying cell property that brings about contact inhibition is the cell-cell adhesion, which is achieved through homophilic cell adhesion proteins called cadherins that are situated at the surface of the cell.

In epithelial cell cultures, overexpression of cadherins increases the thickness of the monolayer showing that cadherins directly increases the extent of cell-cell contact [1]. Similarly disruption of cadherins, results in highly flattened cells. On the other hand, overexpression of cadherins also arrests cell proliferation and disruption of cadherins initiates secretion of growth factors [2,3]. Thus, cadherins are able to influence extracellular property namely the cell-cell contact as well as intracellular events including initiation of cell proliferation events and growth.

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These experimental results suggests that cadherins influencing growth events may be a direct consequence of the extent of cell-cell contact, which is a result of the amount of cadherins on the surface of the cell. This leaves us with following fundamental questions which I will be answering in my talk: *Can we consider the extent of cell-cell contact as a constitutive property of the number of cadherin junctions at the surface? If so, is it possible to use this formalism to model the mechanism of contact inhibition and thereby collective tissue properties such as confluence, tissue morphogenesis, and wound healing?*

II. Conclusions

Based on the experimental evidences, we hypothesize that the extent of cell-cell contact – *cell-cell contact area*, can be treated as a constitutive property of the number of cadherin junctions. We show that this approach can be effectively used to model contact inhibition of growth in confluent monolayers, wound healing and tissue morphogenesis. We use Glazier-Graner-Hogeweg model [4] to implement our hypothesis in a cell based modeling environment. In addition to modeling these properties, we also mathematically reproduce a recent experimental result [5] showing the opposing effects of growth factors and cell-cell adhesion molecules in establishing contact inhibition.

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