Control of Cell Fraction and Population Recovery during Tissue Regeneration in Stem Cell Lineages

Alexandra Jilkine (University of Notre Dame)

Multicellular tissues are continually turning over, and homeostasis is maintained through regulated proliferation and differentiation of stem cells and progenitors. Following tissue injury, a dramatic increase in cell proliferation is commonly observed, resulting in rapid restoration of tissue size. This regulation is thought to occur via multiple feedback loops acting on cell self-renewal or differentiation. Prior modeling studies of the cell lineage system have suggested that loss of homeostasis and initiation of tumorigenesis can be contributed to the loss of control of these processes, and the rate of symmetric versus asymmetric division of the stem cells may also be altered.

Here, we compare three variants of hierarchical stem cell lineage tissue models with different combinations of negative feedbacks and use sensitivity analysis to examine what are the possible strategies for the cells to achieve certain performance objectives. Our results suggest that multiple negative feedback loops must be present in the stem cell lineage the fractions of stem cells to differentiated cells in the total population as robust as possible to variations in cell division parameters, and to minimize the time for tissue recovery in a non-oscillatory manner. When one of these negative feedback loops on stem cell division been knocked out, most of the stem cell lineage population will be in the form of stem cells, suggestive of ``pre-cancerous'' tissue. Furthermore, modeling suggests that positive feedback loops in stem cell homeostasis may also be required. We contrast and compare the differences between deterministic and stochastic versions of the models.