Second Semester Report

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Thesis title: Understanding somatic evolution and development based on genome-scale sequence data

1. Introduction

During the second semester of my PhD studies, I worked on a side project involving both theoretical mathematical analysis and stochastic simulations related to stem cell dynamics. The goal was to estimate the probability of cancer arising in various tissues.

2. Description of research carried out in the current semester

In the human body, stem cells are typically found in specialized compartments called stem cell niches. These niches are homeostatic systems that regulate stem cell activity, maintaining a balance between self-renewal and differentiation to preserve tissue integrity.

Each time a cell divides, its DNA is replicated. While this replication process is highly accurate and supported by efficient repair mechanisms, the accumulation of mutations over time is inevitable. Among these mutations, some rare ones (called driver mutations) can disrupt key regulatory genes, such as those controlling the cell cycle, apoptosis, or DNA repair. Only 5 to 7 such driver mutations are enough for a cell to become cancerous.

Within a niche, each stem cell gives rise to its own lineage. Most stem cell divisions are asymmetric, producing one stem cell and one differentiated progenitor cell. However, symmetric divisions also occur in certain tissues, but less frequently. These divisions can either produce two stem cells (symmetric renewal) or two differentiated cells (symmetric differentiation). To maintain the number of stem cells within a niche, a symmetric differentiation event must be followed by a symmetric renewal in another stem cell. Unlike asymmetric division, which maintains existing lineages, symmetric division can lead to the elimination or expansion of specific cell lineages.

To model the risk of cancer, we assume that driver mutations are acquired according to a Poisson distribution. The question then becomes: what is the probability that a stem cell acquires at least m mutations? Derényi, Imre, et al. [1] developed a model to calculate this probability for a single stem cell following its lineage. In my project, I applied this model to a population of N stem cells, representing an entire niche. I used stochastic simulations

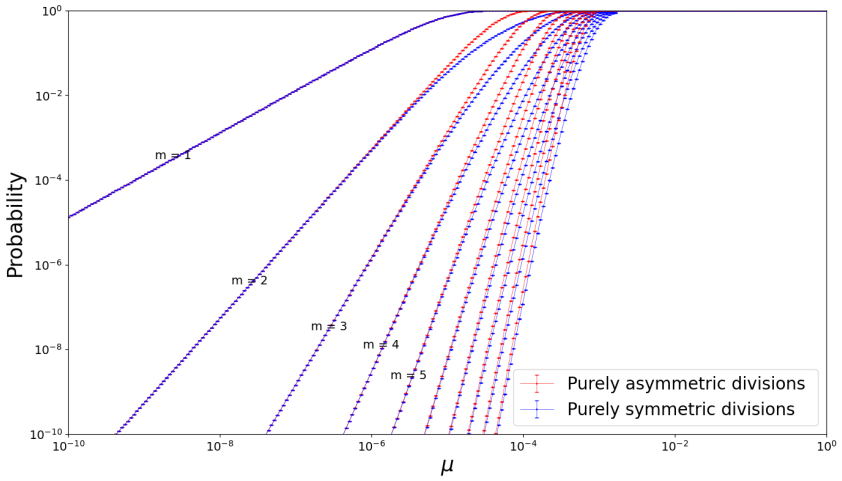

Figure 1: Stochastic simulations for a stem cell niche, with $N = 8$ stem cell and $L = 2^{16}$ progenitor cells. The plot shows the probability of acquiring at least m mutations in the entire niche. The model is based on Derényi et al. [1] [1]

under multiple distinct modes of division: where all stem cells divide asymmetrically, where all divide symmetrically and between.

I also investigated whether symmetric divisions offer any evolutionary advantage over asymmetric divisions in the colonic crypt and other tissues. In the latter part of the semester, we extended the model to account for non-Poisson mutation rates, allowing mutation probabilities to vary.

This work has led to a manuscript that is now nearly complete and will soon be ready for submission.

3. Studies in the current semester

During the semester, I registered the following classes:

- Bioinformatics (INFPHD412-N) - graded with a 5
- Graphs in the bioinformatics (FIZ/3/063E) - ongoing

4. Conferences, Summer Schools

During this semester, I submitted an abstract to the XXX. Congress in Biophysics, which was accepted for oral presentation. I was also accepted to participate in a summer school organized by the Hungarian Centre of Excellence for Molecular Medicine (HCEMM), titled Mathematical Modelling in Cancer Research, held in Szeged from June 10 to 14. The summer school was a valuable experience, both professionally and personally. I had the opportunity to attend lectures presenting state-of-the-art methods and models; I learned about theoretical approaches and agent-based software tools that may prove useful in the future. Additionally, I worked as part of an international team on a group project, which was a great experience.

5. Teaching Activities

I was one of the instructors for the Modern Physics Laboratory course, teaching the ”biolfiz” measurements in 4×45 minutes for 7 weeks.

References

[1] Derényi, Imre, et al. ”How mutation accumulation depends on the structure of the cell lineage tree.” Physical Review E 109.4 (2024): 044407.