First semester report

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Introduction

In recent years, mathematical models of cancer have been developed. In these models, somatic evolution and accumulation of mutations are key in the development of cancer [1]. Hierarchical tissues provide a mechanism to limit the accumulation of driver mutations. This mechanism is manifested as a *wash out* effect for the mutations in the hierarchy. This *wash out* effect is sensitive to structural parameters of the hierarchy. These parameters are the number of levels in the hierarchy and the number of terminally differentiated cells. The ratio of total differentiation rates between consecutive levels also plays a crucial role in cancer progression. Using these parameters, an optimum hierarchy that minimizes the accumulation of mutations in the tissue has been found [5].

Chronic myeloid leukaemia (CML) is one of the most studied and well-known cancer types [2]. It was the first known human cancer that can be initiated by a single chromosomal abnormality [3]. CML evolves in three phases, these can be distinguished with a bone marrow biopsy or a blood test. The first is a chronic phase (CP) characterized by a long constant evolution estimated between 5 to 7 years. This initial phase is defined by an increased number of myeloid progenitors, despite this effect mature cells are still produced. The number of myeloid cell blast present in a blood test is around 5%. The second is a transition phase, called accelerated phase (AP), this phase presents an exaggerated number of myeloid progenitors and arrest of maturation. The final phase called blast crisis (BP) shows an overwhelming presence of myeloid blast in blood around 30%.

Many models show a sketch of the hematopoietic system and the development of CML [4]. Despite being able to reproduce the general behaviour of CML, these models fail to mimic the exact behaviour. Using the models described previously we ask the question: Is it possible to exactly simulate the behaviour of CML?

Research work

Using a hierarchical model for a tissue [5], we aim to reproduce the development of CML in a computer simulation. The simulation is written in Python, the simulation performs a stochastic update of the number of cells in each level in the hierarchy. Driver and neutral mutations were introduced into the model considering the rate of mutation as the error per cell division (μ). In each cell division, the probability of a daughter mutated cell arising is drawn from a binomial distribution. The average number of cells divisions in the level in a small time interval (Δt) is drawn from a Poisson distribution. At this point, we are assuming that the fitness of the driver mutated cell is proportional to the number of mutations present in the cell. The model parameters for the hematopoietic system was calculated

in many papers [6, 7]. The values for these parameters lie within an interval. It was our objective to input the values into the model trying to reproduce the behaviour of CML. The parameter values for the healthy hematopoietic system are the following: the number of levels $N \in [17, 31]$, $\gamma \in [2.45, 3.0]$ and the number of haematopoietic stem cells are estimated to be 10^4. The normal daily cell output of the haematopoietic system is around $3.5x10^{11}$, the major contribution from the myeloid cell lineage. We are still exploring the parameter space to find out the necessary assumptions or modifications to the parameters to accurately represent CML.

The necessary modification to simulate the development of CML is the modification of the amplification factor for the progenitor levels. Doing this modification, the number of driver mutations necessary to drive cancer progression is less in the progenitor levels, compared with the mature levels.

We will also go to evaluate other possible effects into the model, for instance, the inclusion of cell death or a drug to control the disease.

Attended courses

- Statistical physics of biological systems
- Statistical physics of polymers and membranes
- Reconstructing evolutionary history from molecular sequences 2

Conferences

Accepted to participate and present a poster in the GRC congress to be held from February 10 to 15 in Galveston, TX.

References

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[2] Provan, Drew & Gribben, John. (2018). Molecular hematology.

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[4] Dingli D, Traulsen A, Pacheco JM. PLoS ONE 2007; 2:e345.

[5] Dernyi, Imre & Szllsi, Gergely J. Nature Communications, 8 14545

[6] Jamieson CH, Ailles LE, Dylla SJ, et al. N Engl J Med 2004; 351:657-67.

[7] Primo D, Flores J, Quijano S, et al. Br J Haematol 2006; 135:43-51.