Second semester report

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Ph. D. Thesis title: **Reverse-engineering of molecular biological processes of ageing**

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1 Introduction

Unfortunately, our previous inquiry into protein interaction networks has proven unfruitful due to the lack of transposon data. We needed to change our approach. Due to the uncertainty of information on biological systems, we chose a more statistical approach. We decided to look at it from a population dynamics standpoint. We decided to construct a population dynamics model and simulation which had an ageing mechanism to study the emergent population dynamics of biological ageing.

The primary aim of our inquiry in this simulation is to understand why the ageing process is so prevalent as a phenotype. We seek to unveil the causation of the selection pressure that preserves this pernicious phenotype. Our main source of inspiration is [1].

2 Research work

We constructed a bottom-up population dynamics model that infers organism and population ageing from cellular ageing. As a "zeroeth order" approach we tried to construct the simplest toy model that captures the main properties of ageing emergent from the genetic damage induced by the retrotransposon proliferation. Our model simulates the following levels of biological organisation: cells, organs, organisms, population.

The cellular ageing is the atomic and microscopic ageing mechanism in our model. At this level, we directly simulated the damage incurred by the retrotransposon proliferation process for each cell with time. The time step of our model is the retrotransposon proliferation cycle. The retrotransposon copying and insertion process are stochastic. The disabling insertion probability depends on the base pair length of the sensitive parts of genes and the length of the insertion accessible segments of the genome. Retrotransposon copies can be inserted into retrotransposons and disable them as well.

At the organ level, we infer the functionality of an organ from the number of functional cells. In the simplest case, it is the Heaviside step function of functional cells, i.e. the organ becomes dysfunctional after the loss of the majority of the cells. In a more sophisticated model, we would use a sigmoid function.

At the organism, the functionality or aliveness depends on the functionality of its vital organs. If one of the essential organs becomes dysfunctional, then the organism dies.

One critical challenge we face with this simulation is the problem of falsification due to the inherent uncertainty of information about biological systems. The cornerstone of our model is the cellular ageing mechanism. We need to be able to determine whether the complexity of our model is sufficient. We do not want to introduce a speculative ageing mechanism. A direct falsification would be a periodic harvest of the cells of specimens and a measure of the number of retrotransposon copies on the genome or the genome length with time. However, such a procedure is expensive and time-consuming. So it is out of our scope. Fortunately, since our inquiry is inherently statistical, we can exploit the macroscopic observables for falsification, which are easy to measure. One such easy-to-observe macroscopic quantity is lifespan. It allows us to falsify our model via a survival analysis since our model must be able to predict the lifespan statistics of a population up to a time-scaling factor. The time scaling factor describes in-model time. So, I am going to implement this survival analysis.

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Nevertheless, there are still open questions about whether retrotransposon proliferation is the sole cause of biological ageing that we need to sort out. I found the most glaring one when I studied the genome project of the Hydra Vulgaris [2, 3]. Hydra species are renowned for the lack of an ageing process. Yet, the genome project of Hydra Vulgaris suggests that their genome contains a staggering amount of transposons. This fact is highly paradoxical.

3 Studies

This semester, I wrapped up the in-programme course requirement. I have participated in the following courses:

- I completed the "Genetic analysis (progressive level)" (BIO/05/01E) course.
- I completed the "Sensory biophysics II: Bioacoustics" (FIZ/3/045E) course.

The genetics analysis course had crucial importance for me to attain a rudimentary level of literacy in genetics. Building familiarity with the terminology and nomenclature of genetics allows seamless interoperation with geneticists whose expertise is invaluable in ageing research. At this level, we directly simulated the damage incurred by the retrotransposon proliferation process for each cell with time. The time step of our model is the retrotransposon proliferation cycle. We constructed simple rules for the senescence of a cell. We defined vital and metabolic genes. If a retrotransposon insertion disables an essential gene, that cell becomes senescent. If such insertions disable all the metabolic genes, the cell becomes senescent.

References

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