Stochastic Simulation of Progress Toward Equilibrium in a Multi Compartment Cell Structure

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June 2024

1 Introduction

Many cell structures in the body rely on a multi compartment system to maintain cell numbers. From a single stem cell population, numerous non-stem cell compartments are filled through random differentiations and divisions, which eventually result in a final developed cell population.

In this project, this general process will be applied to hematopoiesis, where useful assumptions can be made. We'll assume that there is no cell death, an exponentially increasing proliferation rate, and a constant differentiation rate. Specifically, from past research, we know that a good model for hematopoiesis includes an initial stem cell population of 400 cells ($N_0 = 400$), a division probability of 0.85 ($\varepsilon = 0.85$), a death rate of 0 ($\lambda = 0$), and an exponentially increasing proliferation rate given by $r_i = \gamma^i r_0$ (where i denotes the ith non stem cell compartment, $\gamma = 1.26$, and $r_0 = 1/365$).

The deterministic elements of such a process have already been determined in Dynamics of Mutant Cells in Hierarchical Organized Tissues by Werner, Dingli, Lenaerts, Pacheco, and Traulsen. The stochasistic side, however, has not been fully explored. In this project, the primary goal is to determine through simulation the variance in cell populations at given times.

2 Methods

A Gillespie algorithm was used to model this random process. This algorithm calculates a random distribution for the waiting time until the next cell event (differentiation, division, or death) over all compartments and repeatedly samples from this distribution to determine the next cell actions. By sampling a waiting time, performing the necessary adjustments to the cell populations, and adding this time to a counter, the Gillespie algorithm can simulate the growth of the compartments for any arbitrary amount of time. In this project, the publicly available Gillespie Stochastic Simulation Algorithm by Nezar was used.

In this experiment, it was decided to run each simulation to 4000 days while collecting population sizes at every 200 day increment. Additionally, to maintain a reasonable run time, we contained the simulation to only seven non stem cell compartments. On a technical note, the population of the ith non stem cell compartment has no effect on the $(i-1)$th compartment or any previous compartment so a cut off of seven non stem cell compartments has no adverse effect on our data. It should also be noted that our simulation was coded so that cells in the final compartment (the seventh non stem cell compartment) could differentiate into a higher compartment, it is just that we did not simulate the growth of such cells.

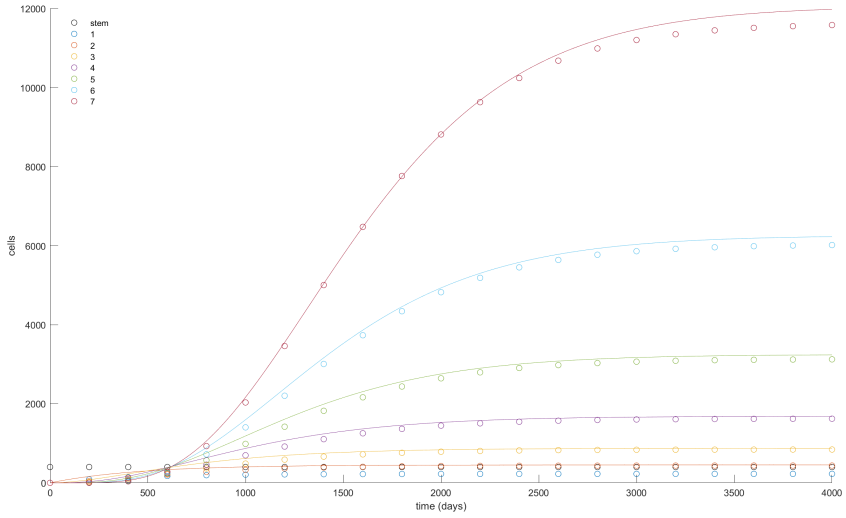
We condensed each simulation into a single row and appended it to a master sheet, which is formatted as such:

1	2	3	4	5	6	7	8 to 28	$8+21i$ to $28+21i$
Time of day of run completion (minutes)	Day of year of run completion	Year of run completion	ε	λ	γ	r_0	# of cells in stem cell compartment across time	# of cells in ith non stem cell compartment across time

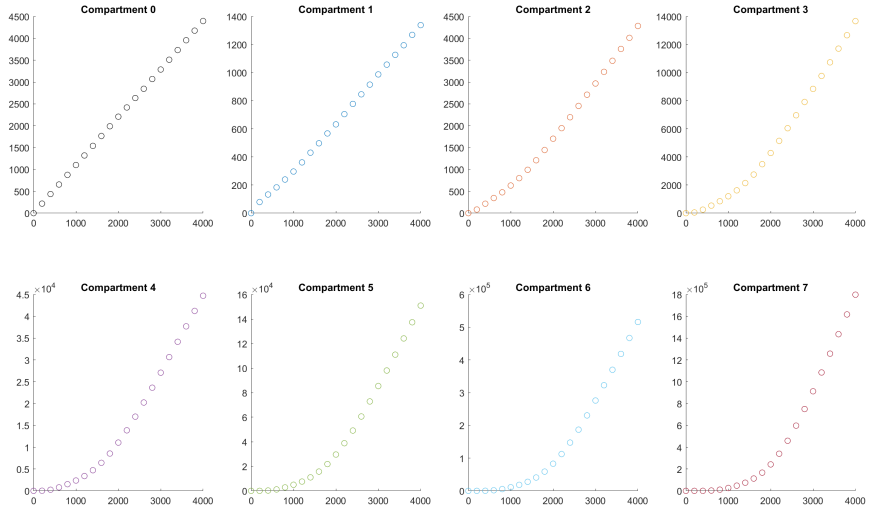
This simulation was run over 250,000 times to produce the data sheet that our results are derived from.

3 Results

Here is a plot comparing the average cell populations for each compartment from our data and from the theoretical equations proposed in the reference paper.

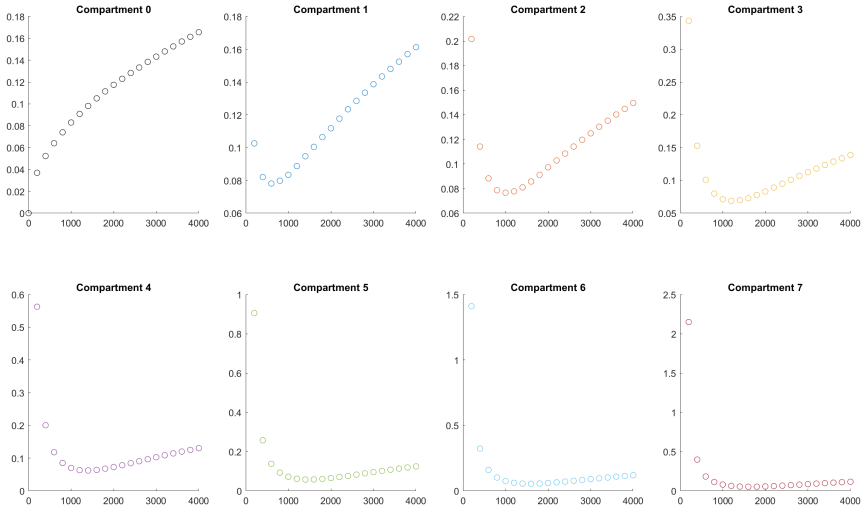


A particularly interesting result is that our simulation found an additional compartment that is not mentioned in the reference paper. Further analysis is required to deduce why this compartment was excluded.
Here is an array of plots showing the variance over time for each of the eight compartments.



Note that is it expected that the variance of compartment 0 (the stem cell compartment) has a linear dependence on time because the stem cell population follows a simple birth-death process. It should also be noted that there were no stem cell extinction events observed.

Here is an array of plots showing the coefficient of variation over time for each of the eight compartments.



4 Conclusion

There is still much work to be done to fully quantify the stochastic elements of multi compartment cell structures. However, this project provides a glimpse into the stochastic processes involved and can be used in the future as a validation method for calculated results. There are many potential future avenues to explore, such as simulation of the proliferation of a mutant cell in the population, as an analogue to the second part of the the reference paper. Additionally, simulating the result of tweaking a particular parameter could also give interesting results.

5 References

The Gillespe algorithm code can be found at this link:
`https://www.mathworks.com/matlabcentral/fileexchange/34707-gillespie-stochastic-simulation-algorithm`

The reference paper that this project is built upon:
Werner B, Dingli D, Lenaerts T, Pacheco JM, Traulsen A (2011) Dynamics of Mutant Cells in Hierarchical Organized Tissues. PLoS Comput Biol 7(12): e1002290. doi:10.1371/journal.pcbi.1002290

A folder containing all my code, along with the data sheet produced as part

of this project, can be found here:
https://drive.google.com/drive/folders/1zQE4uSxtAE9jqoo_bBJ1SinZqphlp34u?usp=sharing