Homeostatic Expansion: MATLAB to Python

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ABSTRACT

Autoimmune disease is a condition that attacks the body of a host immune system. Even though there are several mechanisms to counter this attack, sometimes they fail to do so, and autoimmune disease develops. Interaction of cells within this process can be shown by a system of differential equations. A mathematical model, along with experimental testing can be contracted to define the process of homeostatic expansion in healthy and autoimmune mice, with its limitations. My graduate mentor has designed a mathematical model to assess various components of the interactions between CD4 T cells, activated CD4 T cells, T regulatory cells (Tregs), and the cytokine IL-2 in a developing system using a MATLAB code. This model allows a prediction for how autoimmune disease develops along with the cellular interactions and regulation. My goal for this particular project was to translate this mathematical code from MATLAB to Python.

Cell Expansion in Mice

We utilized two mouse models to study homeostasis, wild type (WT; normal homeostasis) and IL-2 deficient (IL-2KO; autoimmune mouse). IL-2KO mice spontaneously develop autoimmune disease providing a potential model for homeostatic dysregulation. In a healthy mouse (WT), Tregs leave the thymus by day 4 providing regulation to the system. A fully developed immune is present by adolescence (at 4-5 weeks of age). T cells originate in the thymus and IL-2KO T cells are normal, similar with WT T cells. In the periphery IL-2KO T cells develop as they would in WT until about day 9. At day 10 we see the expansion of activated IL-2KO T cells and by day 12 the immune system is targeting and killing the red blood cells. By day 12, the immune system is no longer in homeostasis, and the mice succumb to autoimmunity begin on day 18.

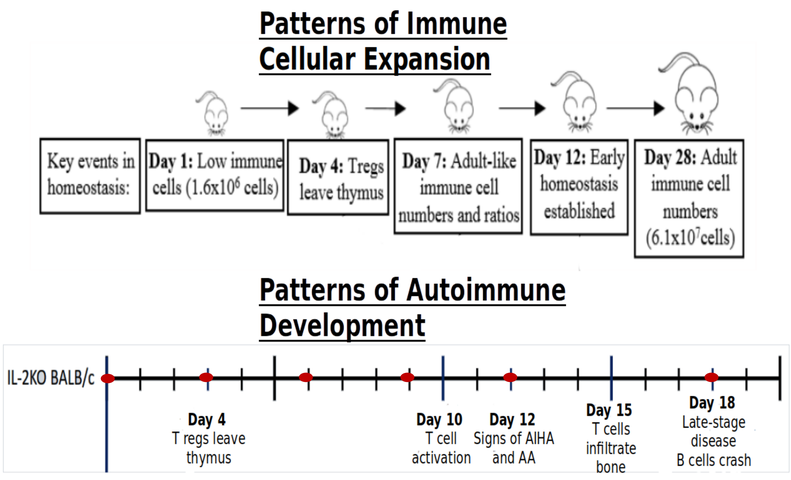

Figure 1. Data shows key events in immunity development of healthy versus autoimmune mice.

Model Diagram

T cells mature in the thymus and become either Tregs or naive T cells. Naive T cells self replicate at high rates to generate activated T cells which produce IL-2. IL-2 cytokine acts a survival signal for Tregs, which then allows Tregs to suppress activated T cells. Our model indicates that the rate at which naive T cells replicate controls the balance of the system and contains especially sensitive parameters. When IL-2 is not present the Tregs begin to die off, which allows expanded naïve T cell replication causing an over abundance in naive T cells. This is essentially the issue when IL-2 is deficient as IL-2 normally maintains Treg survival and function. The absence of Tregs allows uncontrolled homeostatic expansion of activated T cells leading to autoimmune disease.

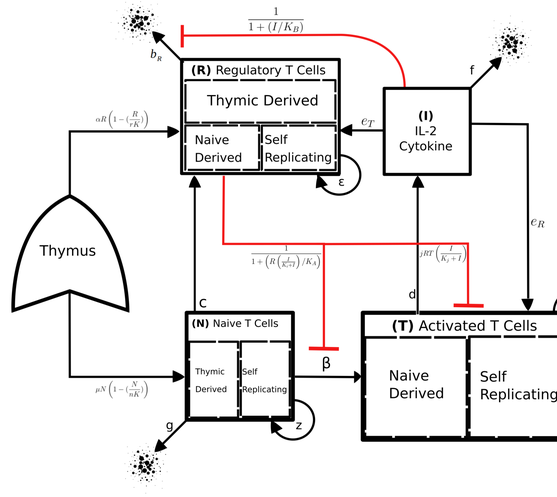

Figure 2. Diagram shows various aspects of homeostatic expansion model. Includes parameters, self replication, balance of the system. Round arrows indicate self-replication. Black dots indicate cell death. Line arrows indicate cell interactions or transitions. Red lines indicate regulation.

Differential Equations of System

$$\frac{dN}{dt} = \mu N\left(1-\left(\frac{N}{nK}\right)\right) + zN - \beta N\left(\frac{1}{1+\left(R\left(\frac{I}{K_i+I}\right)/K_A\right)^n}\right) - cN - gN$$

$$\frac{dT}{dt} = \beta N\left(\frac{1}{1+\left(R\left(\frac{I}{K_i+I}\right)/K_A\right)^n}\right) + aT - jRT\left(\frac{I}{K_j+I}\right) - b_T T$$

$$\frac{dR}{dt} = \alpha R\left(1-(\frac{R}{rK})\right) + \epsilon R + cN - b_R R\left(\frac{1}{1+(I/K_B)^n}\right)$$

$$\frac{dI}{dt} = dT - e_T IT - e_R IR - fI$$

Figure 3. First-order differential equations that simulate the population growth of each type of cell. (Top to bottom: Naive, T cells, Activated T cells, Regulatory T cells, IL-2 cytokine)

Original MATLAB plots vs. Python translations

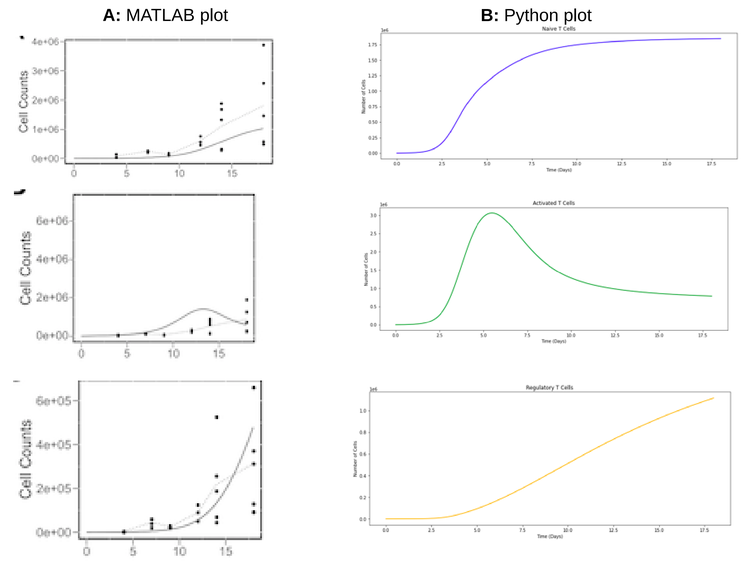

Figure 4. Plots show a comparison of the original MATLAB plots generated by my mentor (left column) and my translation to Python (right column). A) Dots indicate experimentally collected data from WT splenic T cells. Dotted line indicates trend line. Solid line indicates population growth? B) Python plots from WT splenic T cells (Top row: Naive T cells, Middle row: Activated T cells, Bottom row: Regulatory T cells)

CONCLUSION

Overall, we found that the self-replicating of naive T cells are vital to this system, and with only a slight change of its parameters, particularly mu, the entire system is thrown off balance. The entire model is interconnected, and we use the mathematical differential equations to understand how it functions and how we can make further predictions to understand the development of autoimmune diseases in the host.

- I successfully learned Python and applied my programming skills to this model to generate figures that are mostly similar the original MATLAB plots.
- I successfully learned to debug and modify my code for it to run
- I learned basic T cell immunology outside of my major studies
- I received mentoring and exposure to multiple projects and graduate student experiences
- I was exposed to programs such as Joint Genome Institute and Lawrence Livermore National Lab

Recognition

I'd like to thank the Molecular and Cell Biology Department, as well as the members of the Hoyer Lab for inspiring me with their research and progression in their academic journeys. A special thank you also goes out to Prof. Katrina Hoyer and Jonathan Anzules who have been devoted mentors to me throughout this internship, guiding and rearing me through my academic and career goals.
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