Simulation of within-host dynamics in patients infected by HIV

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The goal of this project is to model the “viral dynamics” of HIV infection and examine the effectiveness of antiretroviral drug when used to treat HIV patients. Generally, HIV disease progression consist of three main phases: acute, chronic and AIDS. Each of these phases are characterized by changes in *$CD4^+$ T-cell* count and the plasma viral load. The first part of this project includes simulating the first phase of virus spread using stochastic agent-based modeling of HIV transmission. We used “cell-to-cell transmission” hypothesis for this reason to simulate the T-cell dynamics in acute phase. In the second part of the project, we extended the analysis by discrete time modeling of differential equations which used to explain the HIV infection kinetics in AIDS phase as well as system’s behavior when undergoes a long-term treatment. Finally, we opt reinforcement learning approach to determine optimal treatment strategy for patients with HIV and use a ODE simulation model to generate the patient clinical data. This ODE model takes into account drug combinations and we compare the performance of RL-based model with optimal control method for tracking their physiological response to separate classes of treatments and determine the optimal drug level to be administered to the patient.

Description of the system

The immune response to any virus is generated by a complex web of interactions among different types of white blood cells (monocytes, T and B cells). The time scale to develop a specific immune response may vary from days to weeks. In the case of HIV, the entire course of infection involves two different time scales.

The primary infection exhibits the same characteristics as any other viral infection: a dramatic increase of the virus population during the first 2–6 weeks, followed by a sharp decline, due to the action of the immune system. However, instead of being completely eliminated after the primary infection, as many other viruses, a low HIV concentration is detected for a long asymptomatic time: the clinical latency period. This period may vary from one to ten (or more) years. Besides the low virus burden detected during this period, a gradual deterioration of the immune system is manifested by the reduction of CD4+T-cell populations in the peripheral blood. The third phase of the disease is achieved when the concentration of the T cells is lower than a critical value (~30%), leading to the development of AIDS. As a consequence, the patient normally dies from opportunistic diseases (Figure 1).

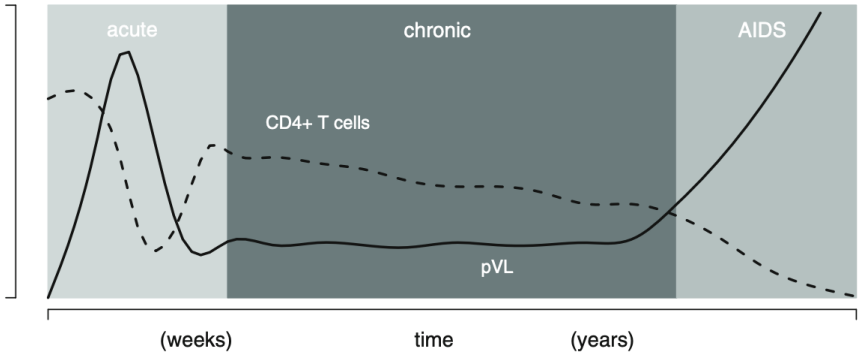

Figure 1 HIV disease progression (adopted from [1]).

Expected approaches that would be used to study the system

In the first section, our aim is to simulate the first phase of HIV infection (acute phase) and show how an arbitrary initial infection in a lattice like cell population can lead in progression of virus within a host body [1]. In the second section, we focus on modeling the spread of virus in third phase (AIDS) and try to simulate the HIV growth dynamics using the concept of ordinary differential equations (ODEs) [2,3]. We examine the effect of treatment on our simulations and see how this can slow down and even decrease the growth of infection within a host. Finally, we opt for reinforcement learning to find optimal treatment plan and use a ODE model proposed by [5] to simulate patients with HIV tracking their physiological response to drug combinations [4]. Previous studies[5][6] have explored using mathematical models of HIV infection dynamics for addressing the problem of designing STI treatments. These models are usually represented by a set of Ordinary Differential Equations(ODEs) and control theory is applied to deduce STI strategies. Modeling the HIV infection dynamics is a complex task and along with selecting the right parametric system of ODEs, one must fit their parameters to reflect quantitatively biological observations. Control theory based studies first state an optimality criterion and then search for control strategies optimizing this criterion. Wodarz and Nowak [9] employed a mathematical model representing uninfected CD4+ T-cells, infected CD4+ T-cells, CTL precursors (immune memory), and CTL effectors. Bonhoeffer et al. [10] used a model incorporating uninfected, actively infected, and latently infected T-cells, as well as immune response. Both thse models offer important theoretical insights into immune control of virus based on treatment strategies. Reinforcement Learning(RL) computes control strategy directly from the measured trajectories and does not need the apriori identification of model of system dynamics. Ernst et. al.[4] first introduced RL techniques in computing STI strategies using the mathematical model proposed by Adams et. al. [5] to artificially generate the clinical data. They applied Bayesian RL (FIQ-ERT) with Q-learning to learn an optimal drug prescription strategy and derived STI strategy with a cycling between the two main anti-HIV drugs: Reverse Transcriptase Inhibitors(RTI) and Protease Inhibitors(PI). Parbhoo et. al.[8] used the same mathematical model

and compared three BRL methods, FQI-ERT, neural FQI and LSPI with varying performances. Parbhoo et. al. [7] also proposed a mixture-of-experts approach to combine the strengths of both kernel-based regression and model-based bayesian PORL for HIV therapy selection. Kernel-based regression methods are more suitable for modeling related patients while model-based RL are more suitable for reasoning about future outcomes and they designed a method for automatic selection of either of these model based on the patient.

Platform of development

Python, Jupyter Notebook

Package Dependencies: seaborn, jdc, pandas, matplotlib, scipy

Show of progress

We completed first section of the project, which concentrated on simulating acute phase of HIV progression in a host body using cellular automata concept. We also finished implementing second section of the project, ODE-based implementation of virus infection in its final phase and effect of treatment in controlling the disease. The results of these two sections are available online on our github repository. Additionally, we also implemented the simulation model and control theory based optimization model for HIV treatment in third section. The model is based on ODE model proposed by [5] and expands upon the ODE model in section 2 by taking into account the effect of drug combinations (reverse transcriptase inhibitors and protease inhibitors). Currently, we have simulated the model for patients with weak and strong immune systems and verified our equilibria state with the results indicated in [5]. We will be working on implementing Bayesian Reinforcement Learning model using the clinical data derived from simulated model we have developed. We plan to implement Fitted Q-iteration model for learning treatment strategy.

Division of labor

Farshad Rafiei: Cellular Automata
Aslihan Celik: ODE implementation
Anirudh Choudhary: ODE implementation + (Control Theory based optimization & Reinforcement Learning)
Literature review is divided equally between the members of the group and each person contributed a part of literature review which is relevant to their coding section.

Github repository

https://github.gatech.edu/frafiei3/CSE6730

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