1. Background and motivation

Chronic myelogenous leukemia (CML) is a cancer of the blood, and the immune system is known to play an important role in the dynamics of CML [5]. Similarly, it is known that immune interactions are important for HIV [6]. My collaborators and I created models for each of these diseases, including immune system dynamics. We then applied statistical and mathematical techniques to compare and predict therapies and doses that appear to be most promising.

2. CML

Our work for CML began with the creation of a differential equation model that includes immune system dynamics by modeling three cell populations: naive T cells ($T_n$), effector T cells ($T_e$), and CML cells ($C$). The system of differential equations is the following:

\[
\begin{align*}
\frac{dT_n}{dt} &= s_n - d_n T_n - k_n T_n \left( \frac{C}{C + \eta} \right), \\
\frac{dT_e}{dt} &= \alpha_n k_n T_n \left( \frac{C}{C + \eta} \right) + \alpha_e T_e \left( \frac{C}{C + \eta} \right) - d_e T_e - \gamma_e C T_e, \\
\frac{dC}{dt} &= r_C \ln \left( \frac{C_{\text{max}}}{C} \right) - d_C - \gamma_e C T_e,
\end{align*}
\]

with $T_n(0) = 1510$ cells/$\mu$l, $T_e(0) = 20$ cells/$\mu$l, and $C(0) = 10,000$ cells/$\mu$l. There are twelve unspecified parameters in the system, which take different values for different patients/settings.

To compare various potential interventions, we considered changes to the parameter values in the system above and examined the effect on the maximum of $C$ over 750 days ($\hat{C}$). Figure 1 shows outcomes for 500 simulations plotted versus values of two of the parameters.
2.1 Results

We found that treatments directly affecting leukemic cell parameters ($r_c$ and $d_c$, the growth and death rates, respectively) are more likely to affect a patient’s outcome than treatments boosting a patient’s immune response in the ways we considered. More details and the statistical analysis appear in [3]. In [4], we incorporated drug therapy into the model, and used control theory to predict optimal doses over a set time period.

\begin{figure}
\centering
\begin{subfigure}{0.49\textwidth}
\centering
\includegraphics[width=\textwidth]{plot1}
\caption{Plots of 500 points for some parameters vs. $\hat{C}$, the maximum value of $C$ over a 750-day time period. All other parameters are varied simultaneously.}
\end{subfigure}
\begin{subfigure}{0.49\textwidth}
\centering
\includegraphics[width=\textwidth]{plot2}
\end{subfigure}
\end{figure}
3. HIV

We created and analyzed a model of HIV-immune dynamics in [2] that incorporates three types of drug resistance. We considered five cell populations: \( T = \) uninfected \( T \) cells, \( I_{00} = \) \( T \) cells infected with wild-type HIV, \( I_{01} = \) \( T \) cells infected with HIV resistant to a protease inhibitor \( \eta_1 \), \( I_{10} = \) \( T \) cells infected with HIV resistant to a reverse transcriptase inhibitor \( \eta_2 \), and \( I_{11} = \) \( T \) cells infected with HIV resistant to both \( \eta_1 \) and \( \eta_2 \). The following system gives the model with treatment by \( \eta_1 \) and \( \eta_2 \) included:

\[
\frac{dT}{dt} = s + p T \left( 1 - \frac{T + I_{00} + I_{01} + I_{10} + I_{11}}{T_{\text{max}}} \right) - \delta T T
\]

\[-[(1 - \eta_2)\beta_{00}I_{00} + (1 - \eta_2)\beta_{01}I_{01} + \beta_{10}I_{10} + \beta_{11}I_{11}] T\]

\[
\frac{dI_{00}}{dt} = (1 - \eta_2)\beta_{00}I_{00} T - \delta_{00}I_{00} + (1 - \eta_1)\kappa_{00}(1 - \mu_{01})(1 - \mu_{10})I_{00}
\]

\[+ \kappa_{01}\bar{\mu}_{10}(1 - \mu_{01})I_{01} + (1 - \eta_1)\kappa_{10}(1 - \mu_{01})\bar{\mu}_{10}I_{10} + \kappa_{11}\bar{\mu}_{10}\bar{\mu}_{11}I_{11} \]

\[
\frac{dI_{01}}{dt} = (1 - \eta_2)\beta_{01}I_{00} T - \delta_{01}I_{01} + \kappa_{01}(1 - \bar{\mu}_{01})(1 - \mu_{10})I_{01}
\]

\[+ (1 - \eta_1)\kappa_{00}\mu_{01}(1 - \mu_{10})I_{00} + (1 - \eta_1)\kappa_{10}\mu_{01}\bar{\mu}_{10}I_{10} + \kappa_{11}(1 - \bar{\mu}_{01})\bar{\mu}_{11}I_{11} \]

\[
\frac{dI_{10}}{dt} = \beta_{10}I_{10} T - \delta_{10}I_{10} + (1 - \eta_1)\kappa_{01}(1 - \mu_{01})(1 - \bar{\mu}_{10})I_{10}
\]

\[+ (1 - \eta_1)\kappa_{00}(1 - \mu_{01})\mu_{01}I_{00} + \kappa_{01}\bar{\mu}_{01}\mu_{01}I_{01} + \kappa_{11}\bar{\mu}_{01}(1 - \bar{\mu}_{10})I_{11} \]

\[
\frac{dI_{11}}{dt} = \beta_{11}I_{11} T - \delta_{11}I_{11} + \kappa_{11}(1 - \bar{\mu}_{01})(1 - \bar{\mu}_{10})I_{10}
\]

\[+ \kappa_{01}(1 - \bar{\mu}_{01})\mu_{01}I_{01} + (1 - \eta_1)\kappa_{00}\mu_{01}(1 - \bar{\mu}_{10})I_{10} \]

In [1], we applied control theory to predict optimal dosing regimens for \( \eta_1 \) and \( \eta_2 \). We used the following cost function, with higher weights for resistant strains:

\[
J(\eta_1, \eta_2) = \int_{t_{\text{initial}}}^{t_{\text{final}}} \left[ T(t) - w_{00}I_{00}(t) - w_{01}I_{01}(t) - w_{10}I_{10}(t) - w_{11}I_{11}(t) - B_1 \eta_1^2(t) - B_2 \eta_2^2(t) \right] dt
\]

A sample optimal therapy regimen for particular parameter values is shown on the left of Figure 2. A comparison constant-dose therapy regimen is shown on the right.
3.1 Results

For each simulation we ran, we found the same qualitative result: heavier doses at first lead to better outcomes when considering drug side effects and keeping T cell counts high.

4. Future work

We intend to continue to use control theory to explore various therapeutic options. Two of our top priorities include calculating optimal doses in the case of constraints on dose and developing models and code that can determine optimal dosing predictions for individuals in real time.

REFERENCES


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