Mathematically Modeling Chronic Myelogenous Leukemia (CML)

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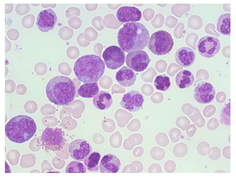
What is CML?

- **CML** results from the uncontrolled growth of white blood cells stemming from the bone marrow.
- A common treatment is **imatinib** (Gleevec), which enables most patients to achieve remission.
- Imatinib alone, however, is not sufficient for CML elimination; without continuous treatment, patients will relapse.
- Under prolonged use, CML develops **drug resistance**. Imatinib reliance leaves patients vulnerable to minor illnesses.



Model and Research Question

We use the DDE model in [1] to monitor CML dynamics under **drug resistance** & anti-leukemia **immune response**. We simulate the system in MATLAB using dde23.

Research Questions

1. **Which parameters** are most influential in altering the behavior of the CML system?
2. How do **strategic treatment interruptions** change parameter contributions to the system?

Metrics of Interest

Time to Remission

- Hematologic: $< 1.67\ k/\mu L$
- Cytogenetic: $< 1.67 \cdot 10^{-2}\ k/\mu L$
- **Molecular**: $< 1.67 \cdot 10^{-4}\ k/\mu L$
- Total Elimination*: $< 10^{-10}\ k/\mu L$

Minimum Cancer Concentration

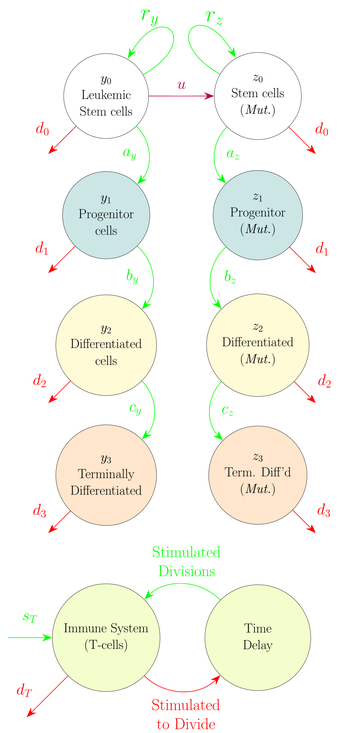
Maximum T-cell Concentration

Sum of Squared Residuals

$$SSE = \sum (T_i - \hat{T}_i)^2$$

T_i = patient T-cell conc.; $\hat{T}_i$ = simulated T-cell conc.

Delay Differential Equation Model (Kim *et al.*, 2008)



Non-Mutated

$$\begin{cases} \frac{dy_0}{dt} = (r_y(1-u) - d_0)y_0 - q_C p(C,T)y_0 \\ \frac{dy_1}{dt} = a_y y_0 - d_1 y_1 - q_C p(C,T)y_1 \\ \frac{dy_2}{dt} = b_y y_1 - d_2 y_2 - q_C p(C,T)y_2 \\ \frac{dy_3}{dt} = c_y y_2 - d_3 y_3 - q_C p(C,T)y_3 \end{cases}$$

Mutated (Rate u)

$$\begin{cases} \frac{dz_0}{dt} = (r_z - d_0)z_0 + r_y u y_0 - q_C p(C,T)z_0 \\ \frac{dz_1}{dt} = a_z z_0 - d_1 z_1 - q_C p(C,T)z_1 \\ \frac{dz_2}{dt} = b_z z_1 - d_2 z_2 - q_C p(C,T)z_2 \\ \frac{dz_3}{dt} = c_z z_2 - d_3 z_3 - q_C p(C,T)z_3 \end{cases}$$

Changes in T-cell Population

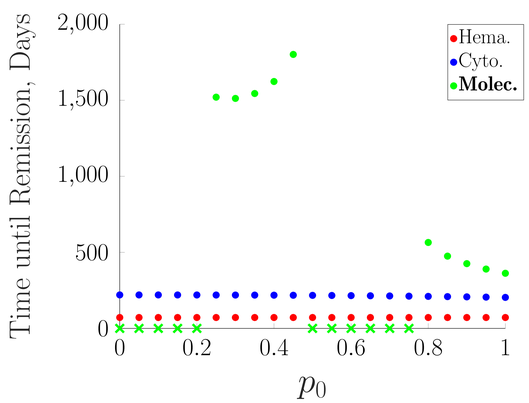
$$\begin{cases} \frac{dT}{dt} = s_T - d_T T - p(C,T)C + 2^n p(C_{n\tau}, T_{n\tau}) q_T C_{n\tau} \end{cases}$$

Immune Response

$$\begin{cases} p(C,T) = p_0 e^{-c_n C} kT \\ C(t) = \sum y_i(t) + \sum z_i(t) \\ C_{n\tau} = C(t - n\tau),\ T_{n\tau} = T(t - n\tau) \end{cases}$$

Parameter Analysis: No Mutations

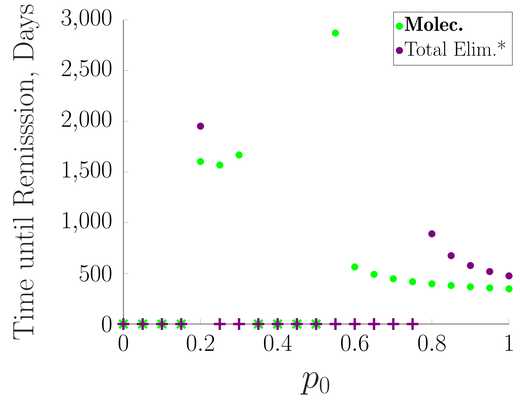
p_0 = Probability of T-cell encountering cancer cell



Note: Unable to attain total cancer elimination.

Effect of STIs on Thresholds

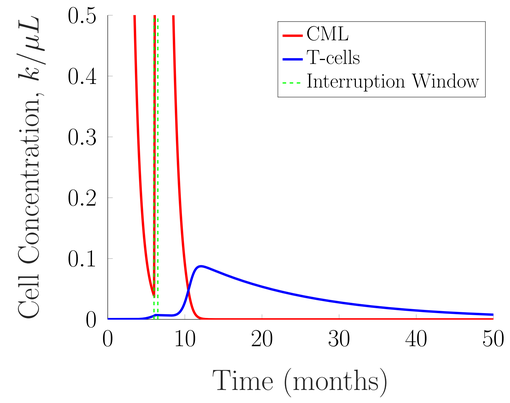
Incorporate 1×15-day STI at $t = 180$:



Total Elim. Threshold: $p_0 \approx 0.8$

Strategic Treatment Interruptions (STIs)

In [2], Paquin *et al.* implements a **15-day** STI at **6 months** to re-activate immune response and enable total cancer elimination:



Future Research

Goodness-of-Fit Metric:

How to build on SSE to capture best fit to patient data?

$$SSP = |t_{peak} - \hat{t}_{peak}|$$

$$SSDQ = \sum \left[\left(\frac{T_{i+1} - T_i}{t_{i+1} - t_i} \right) - \left(\frac{\hat{T}_{i+1} - \hat{T}_i}{\hat{t}_{i+1} - \hat{t}_i} \right) \right]^2$$

Best STI Implementation:

Best timing/duration/quantity for total elimination?

Patient-Dependent Parameters: (n, c_n, s_T, d_T)

Find biologically feasible ranges to vary over.

Incorporating Resistance: $u = 4 \cdot 10^{-8},\ z_0(0) = 10^{-9}$

How does imatinib resistance affect the timing/duration/quantity of STIs needed for total elimination?

References and Acknowledgements

[1] Kim PS, Lee PP, Levy D. (2008) Dynamics and Potential Impact of the Immune Response to Chronic Myelogenous Leukemia. PLOS Computational Biology 4(6): e1000095. https://doi.org/10.1371/journal.pcbi.1000095

[2] Paquin, D., Kim, P.S., Lee, P.P. et al. Strategic Treatment Interruptions During Imatinib Treatment of Chronic Myelogenous Leukemia. Bull Math Biol 73, 1082–1100 (2011). https://doi.org/10.1007/s11538-010-9553-0

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