Mathematical Modeling of Chronic Myelogenous Leukemia (CML)

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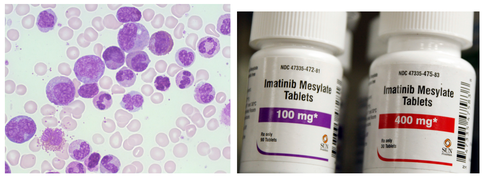
What is CML?

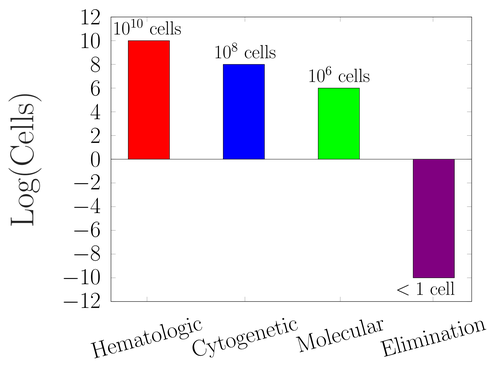
- **CML** results from uncontrolled growth of white blood cells.
- A common treatment is **imatinib** (Gleevec).
- Imatinib alone is not a cure/sufficient for CML elimination.
- Under prolonged use, CML develops **drug resistance**.



Research Questions

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

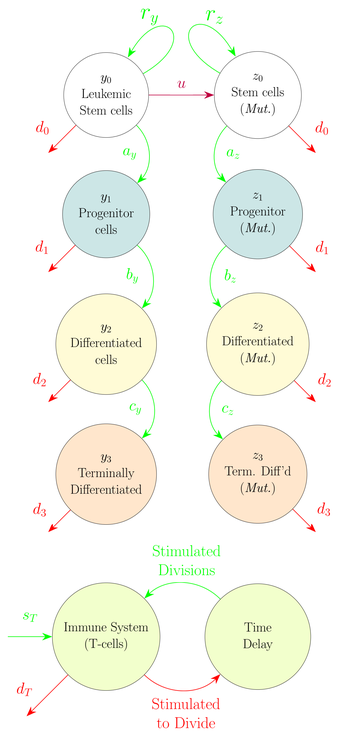
Remission Stages



Immune Response Parameters*

- q_C: Probability of T-cell killing CML cell
- q_T: Probability of T-cell surviving CML encounter
- $e^{-c_n C}$: Immune down-regulation

Delay Differential Equations 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

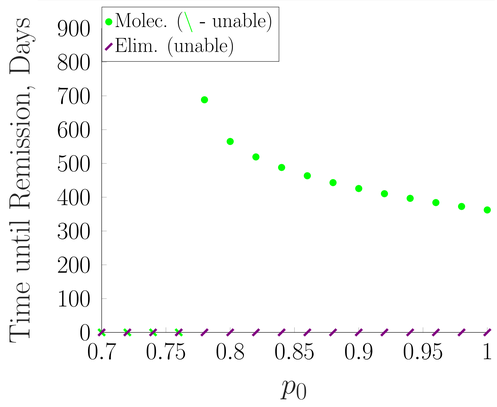
$$\begin{cases} \frac{dT}{dt} = s_T - d_T T - p(C,T)C + 2^n p(C_{n\tau}, T_{n\tau}) q_T C_{n\tau} \end{cases}$$

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: p_0

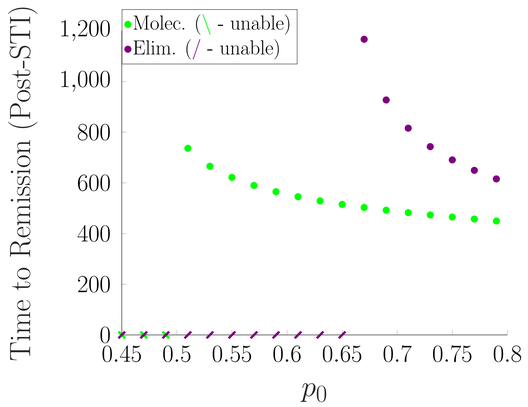
p_0 = Probability of T-cell encountering cancer cell



Thresholds: $p_0 \approx 0.77$ (Molecular); No Elimination.

Effect of STIs on Thresholds

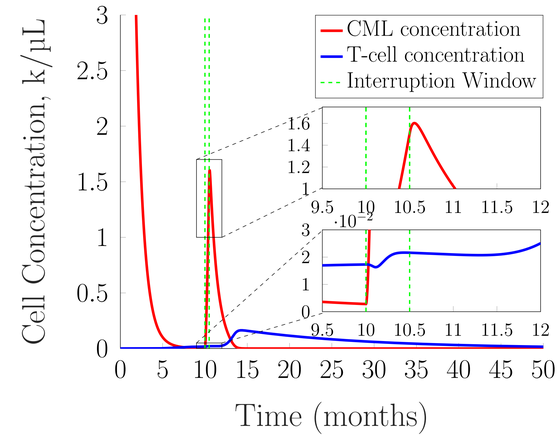
Incorporate 1×15-day STI at $t = 300$:



Thresholds: $p_0 \approx 0.5$ (Molecular), 0.8 (Elimination)

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

Best STI Implementation:

Best timing/duration/quantity for total elimination?

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?

Analytic Behavior:

Connection between stability analysis of critical points with patient stability toward remission?

References and Acknowledgements

MBE Publication

Paquin, D., Gross, L., Stewart, A., Thai, G. (2024). Numerical Analysis of Critical Parameter Values for Remission During Imatinib Treatment of Chronic Myelogenous Leukemia. Accepted to Mathematical Biosciences and Engineering: Special Issue on Models and Applications of Delay Differential Equations.

[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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