Mathematical Optimization of Combination Therapy for Chronic Myeloid Leukemia (CML)

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Objective: To use mathematical modeling and control theory to predict optimal dosing regimens for patients with chronic myeloid leukemia (CML).

Methods: A semi-mechanistic ODE model for in-host CML-immune dynamics was developed starting from a previous model [1]. The leukemic cells were further differentiated into quiescent and proliferating sub-types. Imatinib, dasatinib, and nivolumab were incorporated into the model. Some parameter estimates were obtained from literature or in vitro experiments. Others were obtained by fitting data from the randomized Phase 3 DASISION trial [2] using nonlinear mixed effects modeling in Phoenix NLME (1.3, Pharsight). Treatment constraints and an objective functional incorporating leukemic cell populations and toxicity from therapeutic agents were specified, starting from previous work [3, 4]. The objective functional was minimized using TOMLAB packages (BASE 8.0, SNOPT 8.0, and PROPT, Tomlab Optimization) with MATLAB (R2015a, Mathworks).

Results: A combination therapy regimen predicted to achieve optimal clinical outcomes was computed, given the specified constraints and the goals quantified in the objective functional. The full mathematical system and quantitative constraints will be shown, along with graphical representations of optimal regimens (including which drugs, doses, and timing) in different settings.

Conclusion: Control theory applied to a mathematical model of CML-immune dynamics can predict regimens expected to achieve optimal outcomes. Such regimens can help inform trial design or can be tested experimentally themselves. They can also provide a benchmark for predictive comparison with other regimens of interest. This semi-mechanistic model is flexible enough to use in optimizing other therapies in the future.

References: