Synthesis of a Combined Neutropenia and Lymphopenia Model in Response to Chemotherapy

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Objectives: To build a biologically-motivated model of neutrophil and lymphocyte response to a standard dose of [DRUG] chemotherapy. The model structure is derived from the interactions in the hematopoiesis lineage tree, allowing the simultaneous assessment of mono- or combination chemotherapy that results in multiple hematological toxicities.

Methods: The model was built similarly to Friberg et al. [1] where a set of ordinary differential equations use a transit rate parameter to mimic the lifespan of the cell type. Changes in circulating cell count signal a feedback response to the progenitor cells as cell count drops post chemotherapy. This model joins the neutrophils and lymphocytes under one common progenitor state, consistent with biology. Any pharmacokinetic model and dosing schedule can be used as an input to the model. The model was built in Pyomo and can be fit to data using IPOPT [2].

Results: Fifteen differential equations capture the dynamics behind chemotherapy-induced neutropenia and lymphopenia. The nadirs of both neutrophils and lymphocytes occur around 7 days post chemotherapy. The model can be fit to data by independently changing the transit rate parameters for neutrophils and lymphocytes. Independent chemotherapy kill effects can additionally act in N1 or L1 based on the neutropenic or lymphopenic potential of the drug(s), respectively (Figure 1).

Conclusions: The joint model of two hematological toxicities can be used to assess multiple drug combination effects with mixed or overlapping toxicity. The model is easily tailored to individual patient response fitting individual parameters (via IPOPT), and exogenous rescue agents (e.g., G-CSF) that impact recovery and drug dosing can be incorporated into the parameterization or as additional blocks into the model diagram.

References: