Optimal Protocols for a Mathematical Model for Combination Therapy of CML

Urszula Ledzewicz
Dept. of Mathematics and Statistics, Southern Illinois University, Edwardsville Il 62026 USA
and Institute of Mathematics, Lodz University of Technology, 90-924 Lodz, Poland.
uledzew@siue.edu

Helen Moore
Quantitative Clinical Pharmacology, Bristol-Myers Squibb, Princeton, NJ 08540 USA.

Abstract

In the talk we introduce a mathematical model for the treatment of chronic myeloid leukemia (CML) which was developed in collaboration with Helen Moore from the pharmaceutical company Bristol-Myers Squibb. The goal is to create a minimally parameterized model which would still capture the effects of combination of tyrosine kinase inhibitors and immuno-modulatory therapies; these are introduced in the model as controls. The pharmacodynamics of the drugs is modelled using Michaelis-Menten terms and since the model focuses on the long term therapies drug dosages are identified with their concentrations. We first analyze the problem as a dynamical system in the case when these concentrations are constant. We show how increasing levels of therapies affect the equilibrium solutions and their stability. In particular, we illustrate how, depending on the parameter values, the model is able to replicate chronic, accelerated and blast phases typical of the disease. The model is then analyzed as an optimal control problem with the aim to minimize an objective functional that takes into account the tumor burden and the total pharmacologically relevant quantities which measure side effects of the drugs given. We first pursue this analysis for control sets that are intervals, i.e., allow arbitrary dosing regimens within certain limits, but also compute the best-in class solutions when a limited range of dosages and timing changes are specified a priori, a common limitation in the practical administration of drug schedules. We show that excellent approximations of optimal protocols can be achieved even within such limited scheduling options. We will also discuss challenges and computational limitations arising in searching for optimal long horizon treatments which are of particular interest for pharmaceutical companies in the case of CML.

Keywords: mathematical model, chronic myeloid leukemia, combination therapy, optimal control

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