Urszula Ledzewicz
Southern Illinois University Edwardsville, USA
Łódź University of Technology, Poland
Heinz Schättler
Washington University, St. Louis, USA

Optimal control in biomedical problems

We discuss a variety of optimal control problems that arise from biomedical problems with a focus on mathematical models for cancer treatments. We consider the optimization of drug administration schedules (dosage, frequency and sequencing of therapeutic agents) with the aim to minimize an objective that makes a compromise between minimizing the tumor burden and pharmacologically relevant quantities which measure side effects of the drugs. Using the Pontryagin maximum principle and tools of geometric optimal control theory insights can be gained into the optimality of bang-bang controls (representing medically maximum tolerated doses, MTD) and singular controls (corresponding to biologically optimal doses, BOD). Simple answers are not always the best ones as there is mounting medical evidence that "more is not necessarily better" and a properly calibrated dose can lead to a better outcome (metronomic therapies).

In this talk, several models will be discussed that model tumor heterogeneity and various aspects of the tumor microenvironment (anti-angiogenic treatment and immunotherapies) with emphasis on combination therapies. A continuing thread in all models is the role of pharmacometrics, i.e., how the structure of optimal controls depends on whether a pharmacokinetic model (PK) for the drug action is included in the dynamics or not and how the effects of the drugs are modelled through a pharmacodynamic (PD) relation, e.g., log-kill assumption or Michaelis–Menten type kinetics.

For a specific example, the treatment of chronic myeloid leukemia (CML) through a combination of tyrosine kinase inhibitors and immuno-modulatory therapies, we compare optimal solutions with best-in class solutions that only allow the use of a limited range of dosages and a priori specified timing changes.

On a separate topic, a mathematical model for the selective spiking of integrate-and-fire neurons is considered from an optimal control point of view. Its analysis reveals fundamental limits on the spiking sequences that can be achieved time-optimally.