Developing a data-integrated simulation framework to predict responsiveness to targeted cancer therapeutics

Fabian Klötzer[1], Lara Hundsdorfer[1], Cristiano Guttà[1], Gavin Fullstone[1,2], Markus Rehm[1,2]

[1]) Institute of Cell Biology and Immunology, University of Stuttgart, Germany
fabian.kloetzer@izi.uni-stuttgart.de
[2]) Stuttgart Research Center Systems Biology, University of Stuttgart, Germany

The wide variety of cancer types represents a big challenge for cancer therapy. Case-to-case heterogeneity demands individualized treatments that can vary in choice, dosing and combination of anti-cancer agents. Modeling the sensitivity of tumor cells to anti-cancer therapeutics can provide a cost effective in silico estimation of treatment efficacy. Therefore, we are developing a data-integrated, mechanistic ODE model to predict mitochondrial outer membrane permeabilization (MOMP) within cancer cells. MOMP is a crucial step in executing apoptotic cell death, resulting from complex interactions of the druggable BCL-2 protein family. Simulating BCL-2 protein interactions allows for introduction of mechanistic domain knowledge into the model. This improves the model specificity, allows to investigate regulatory mechanisms that have not been fully understood yet, and can test for the sensitivity to anti-cancer agent combinations (BH3 mimetics). As a first step, we determined treatment recommendations for 325 different cancer cell lines using a prototype model implementation. Input data were averaged protein amounts from cell populations, thus so far neglecting the heterogeneity between individual cells of the same population. To incorporate heterogeneity in the model, we will use in house experimental single cell data to re-parameterize the model to simulate cell populations at single cell resolution. This interplay between data-based modeling and model-based experimental design is hoped to increase the explanatory power of the model and the accuracy of optimal treatment predictions.