



## **SINGLE CELLS VS. CELL POPULATIONS – FROM A BINARY DECISION TO A CONTINUOUS RESPONSE**

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In many situations of biological relevance individual cells within a clonal population show different responses upon a common stimulus. One example are populations of cancer cells where some cells die upon a death signal and others survive. Although the decision at the single cell level is binary a continuous response can be observed at the population scale.

Within this project a population of NCI-H460 tumor cells is studied. This population is highly heterogeneous as single cells of this population differ in protein expression levels and sensitivities with respect to the cytokine TRAIL. To achieve a better understanding of TRAIL-induced apoptosis in a cell population a multi-scale model is developed.

This mathematical model describes TRAIL signaling in single-cells on the basis of mechanistic ordinary differential equations, whereas the population is modeled by an ensemble of individual cells. This leads to a partial differential equation governing the population dynamics. Cell-to-cell variability is introduced by differences in protein synthesis rates among individual cells, interpretable as epigenetic differences. The distribution of the synthesis rates is estimated from data obtained by flow cytometry.

We show that epigenetic differences can explain the distribution of death instances observed in experiments. Plausible markers for the survival or death of individual cells could be determined. The model indicates that e.g. for high TRAIL concentrations mainly differences in procaspase 3 and XIAP expression levels play crucial roles for the cell fate decision, whereas for low TRAIL concentrations also the procaspase 8 expression level might represent an important marker. Variability within the mitochondrial pathway appears negligible, which is in accordance with experimental data. The comparison of the model predictions with the experimental data supports the predictive power achieved by the combination of the single-cell model and cell population heterogeneity.

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