

Modelling cell response to cancer drug treatment identifies dynamic features of efficient cell death initiation, enabling prediction and control of therapeutic response heterogeneity

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Abstract Poster: Cell response heterogeneity upon drug treatment is a leading cause of **reduced drug efficacy** in preclinical **cancer research**. Although single-cell studies have revealed the depth of cellular heterogeneity observed between in tumor cells, the regulatory impact of cell variability on therapeutic response remains unclear.

In this study, we integrated single-cell data and dynamical features of an **ODE system** modelling the **extrinsic apoptosis** triggered by death receptor ligands, to determine an cell response predictor that enabled the discovery of key regulators of the cell death initiation. This model, calibrated on **single-cell FRET ratio time-trajectories of clonal HeLa cells** treated with TNF-related apoptosis-inducing ligand (**TRAIL**), produces **two distinct response phenotypes** (sensitive and resistant) that allows accurate cell fate prediction.

Analysing the timeline of the core reactions and the dynamic properties of the model, we identified regulatory steps of the cell decision, **locating a first resolution upon TRAIL binding**, but also the existence of a ruling time frame during which the sensitive cells benefit from additional regulation at the receptor level, before cell death commitment.

Finally, our cell fate predictor was tested on experimental data sets (treated with different doses of TRAIL) and served determining the dynamic **origins of fractional killing**. Here, we emphasised the role of key regulatory dynamics, revealing measurable factors such as Caspase 8 degradation and activation rates, allowing single-cell isolation for molecular profiling with the **fate-seq workflow** developed by our group.