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Modeling isogenic cancer cell response upon TRAIL treatment in multi-omics studies

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Cell response heterogeneity upon treatment is the main obstacle in developing efficacious cancer drugs in preclinical 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.

To gain a deeper understanding on the multivariate mechanisms giving rise to these heterogeneous commitments to apoptosis, our team presented in 2020, a new workflow called **fate-seq**, that combines 3 single-cell techniques [2], see Fig.1. First, a predictive measure of single-cell response by **live-cell microscopy is associated to a cell drug response (resistant or sensitive) predictor**, based on FRET signal dynamic [1, 3]. Then, a **laser-capture micro-dissection** to separate the predicted resistant cells from the predicted sensitive ones, and finally, a **single-cell RNA sequencing** to profile each cell. We also provided an example of application with the analysis of TNF-related apoptosis-inducing ligand (TRAIL) transcriptional signature. Since this example illustrated some perspectives in drug-target discovery, we now propose to increase the pipeline throughput by tackling the following limitations.

First of all, the live-microscopy steps are carried out by hand. It's time-consuming, expensive, and prone to manipulations errors. Hence, in this work, we present a new workflow that uses **machine learning image processing methods** to perform dynamic image analysis, detecting single cell events in label-free time-lapse microscopy experiments of drug pharmacological profiling. Our analysis framework is an open source and adaptable workflow that automatically predicts cell division and cell death times from each single cell trajectory, along with other classic cellular features of cell image analyses.

The second main limitation in the pipeline, is the number of cells accurately predicted from the FRET signal (barely 20 cells over 70 [2]). Here, we tackle that challenge in a original way, coupling a mechanistic approach with a machine learning learning model to analyse the FRET signal. We first introduce a new **ODE model of the key-reactions involved in extrinsic apoptosis initiation by death-ligands**. This model is calibrated on the FRET time-trajectories of hundreds of clonal HeLa cells treated with TRAIL. By analyzing the different steps in the regulation of apoptosis, and the associated timeline according to the drug response, we can place an initial decision on cell fate just after TRAIL binding. This lethal resolution is highlighted by the presence of additional regulation at the receptor level that only benefits the drug-sensitive population until their death. By this mean, we also show how to reduce our mechanistic model to obtain an explicit solution that correctly describes the observed FRET signals. Using only 3 parameters of this explicit solution as input features for a

machine learning model, we finally demonstrate that it is possible to **predict the drug response** for almost each cell.

In conclusion, our work brings **innovative solutions** based on **modeling cell response to TRAIL with machine learning methods**, and illustrates how computational biology can be integrated in a single-cell analyses pipeline to upgrade the workflow throughput.

Key-words: Apoptosis, Pharmacodynamics, Fractional killing, Oncology, Single-cell, Machine learning, ODE models.

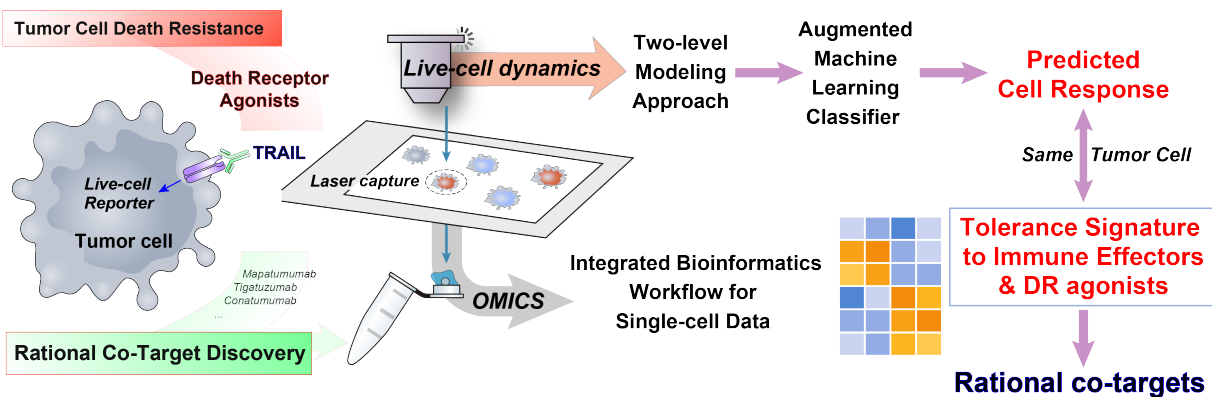


Figure 1: **Upgrading fate-seq pipeline by integrating machine learning models of TRAIL drug-response:** Step 1 - single-cell *in vitro* experiment: clonal cancer cells are treated with TRAIL at IC50; Step 2 - using live-cell microscopy, cells are automatically observed for 50 min using machine learning image processing and each cell FRET signal is recorded; Step 3 - based on FRET signal, the parameters of an approximated explicit solution of a mechanistic model describing TRAIL triggering apoptosis are used as input for a machine learning classifier that predicts each cell drug response; Step 4 - based on this prediction, cells are separated into 2 groups: drug-sensitive and drug-tolerant, by micro-dissection; Step 5 - Omics analyses for the two groups (RNA, proteomics, etc); Step 6 - differential expression analyses based the two groups (and in the future unsupervised machine learning). In the first run of fate-seq, we used RNA-sequencing and identified 6 genes differently expressed according to the drug response that were validated experimentally, as potent drug-target in TRAIL combination treatment.

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