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Modeling cell response heterogeneity to cancer treatment

Tumor cells of a clonal population exhibit multiple levels of heterogeneity, from gene expression to drug response. Cell-to-cell variability in cell death dynamics after treatment is an emerging cause of drug resistance contributing to the reduced efficacies of cancer therapeutics (due to fractional killing). We developed a mathematical model of cell death based on mass-action kinetics, to represent a reaction cascade from drug-receptor interactions to caspase 8 activation, which controls the cell death decision. The model was fitted to a set of experimental single-cell trajectories obtained after treatment with a cancer drug. We obtained a family of parameter sets that represent the response variability observed within the population of clonal cells. Analysis of the parameters distributions helped identify critical reaction steps that distinguish sensitive from resistant cells, suggesting new regulatory reactions that can be targeted to improve cancer drugs efficacies.