

A Systems Approach for the Prediction of Wild Type MAPK Pathway Response to Targeted Drugs

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1 Abstract

In this paper we simulate the wild type MAPK pathway response to twelve *in silico* drugs that were previously found to reduce elevated phosphorylated ERK levels (ERK*) in 40 top ranked mutations in a model of the MAPK signal transduction pathway. We find that a subset of the simulated drugs (notably those targeting GEF and the $G_{\alpha\beta\gamma}$ G-protein trimer) were able to effectively inhibit the elevated ERK* levels of the mutated pathways, whilst simultaneously eliciting only minimal inhibition of the wild type pathway ERK* response to EGF stimulation.

2 Background and Methodology

In previous work [1, 2], we developed a ranked list of 40 mutations most likely to cause elevated ERK* levels in an ODE model of the MAPK signal transduction pathway [3]. Subsequently, we compiled a ranked list of inhibiting drugs that competitively bind to pathway participants, removing them from further pathway interaction and leading to reduction in steady state ERK* levels in these mutated pathways [4, 5].

In this work, we investigate balancing the effects of these ERK* reducing drugs on the mutated pathways with their effects on the non-perturbed wild type MAPK pathway, with the intention of finding a regime that still allows for normal growth factor (EGF) signaling functionality and ERK* response in the wild type pathway with minimal reduction in drug efficacy. The investigated drug targets consist of Raf, Ras, the $G_{\alpha\beta\gamma}$ G-protein, GEF, MEK, ERK, PLA2, PKC, PLC_{β} , PLC_{γ} , and two calcium channels. After running simulations of the drugged wild type pathway (under a 10 min, $3nM$ EGF stimulation) through a wide parameter space of drug dissociation constant $k_d = k_b/k_f$ and initial drug concentration C_0 , we extract the peak ERK* values for each simulation and compare them to the previously found steady state ERK* levels of the mutated pathways. ERK* levels below $0.002\mu M$ are considered basal, and pathways with steady state ERK* levels below this threshold are considered to be inactive, or non-signaling. Drugs that could deactivate the mutated pathways, yet imparted only minimal effect on the wild type pathway were ranked higher than drugs that could not as clearly distinguish between mutated and wild type pathways.

3 Results

While all drug targets demonstrated some ability to differentiate between mutated and wild type pathways, the most promising drug target in terms of its effect on the wild type pathway was GEF (Fig 1). At a concentration of $0.0316\mu M$, for all $k_d < 0.00316\mu M$, the drugs targeting GEF elicited the inactivation of 39 out of 40 mutated pathways. Simultaneously,

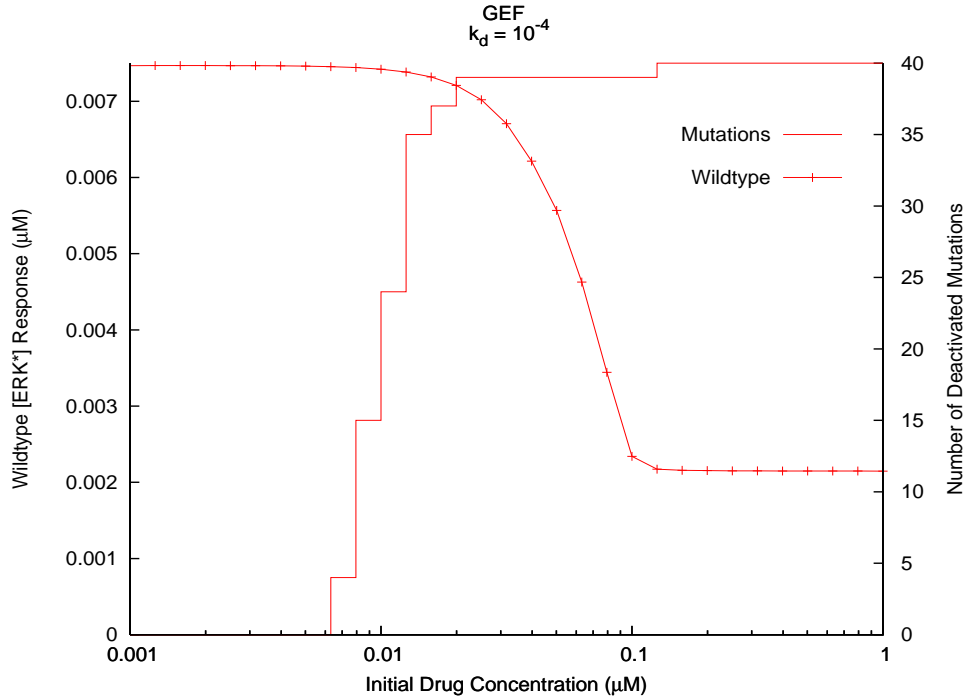


Figure 1: Comparison of simulated wild-type pathway ERK* response (crosses, left axis) and histogram of mutated pathway deactivation (stair step, right axis) by drugs targeting GEF. Simulations are run through the range of concentrations $10^{-3}\mu M$ to $1\mu M$. The dissociation constant of the drug/target interaction is $k_d = 10^{-4}\mu M$.

this drug reduced the wild type ERK* response peak to EGF stimulation by only $0.2nM$, a reduction of less than 3% from the non-drugged ERK* response.

The next highest performing drug target is the $G_{\alpha\beta\gamma}$ G-protein which, at a drug concentration of $C_0 = 0.2512\mu M$ for all $k_d < 0.01\mu M$, elicited the inactivation of 36 out of 40 mutated pathways. At the same C_0 value, the drug reduced the wild type ERK* response peak by $0.81nM$, or just under 11% of the peak value.

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