

## Mathematical modeling methods

Biochemical reactions and associated parameters related to signal transduction were taken from prior publications ([41] and [42]), and initial concentrations of protein species were taken as median values from quantitative mass spectrometry measurements across a panel of cancer cell lines (Shi et al., 2016). The *KRAS*<sup>G12V</sup> mutation was implemented via 10-fold reduced binding rate of the active (GTP) form to RAS-GAP. The core model contains 101 reactions and 75 parameters, including the canonical enzymatic cascade (48 parameters) with multiple feedback regulatory loops (27 parameters). An additional 59 reactions related to drug-target interactions were included, and 14 drug-specific parameters were fixed to experimentally measured values. Parameters related to feedback regulatory loops were estimated by fitting *in vitro* phospho-MEK and phospho-ERK dose responses to cobimetinib and GDC-0623 treatments [22] via particle swarm optimization. An empirical relationship was used to transform relative steady state ppERK to cell viability ( $1 - e^{-4 \cdot (\text{relative ppERK})}$ ). The model was simulated for 24-hours (to quasi-steady state), followed by drug treatments for 72 hours. The model was coded in SimBiology® and simulated using MATLAB R2016a. Model equations, parameters values, and initial conditions are specified in Supplemental Table 1.

## References

- Hatzivassiliou, G., J.R. Haling, H. Chen, K. Song, S. Price, R. Heald, J.F.M. Hewitt, M. Zak, A. Peck, C. Orr, M. Merchant, K.P. Hoefflich, J. Chan, S.-M. Luoh, D.J. Anderson, M.J.C. Ludlam, C. Wiesmann, M. Ultsch, L.S. Friedman, S. Malek, and M. Belvin. 2013. Mechanism of MEK inhibition determines efficacy in mutant KRAS- versus BRAF-driven cancers. *Nature*. 501:232–6. doi:10.1038/nature12441.
- Schoeberl, B., C. Eichler-Jonsson, E.D. Gilles, and G. Müller. 2002. Computational modeling of the dynamics of the MAP kinase cascade activated by surface and internalized EGF receptors. *Nat. Biotechnol.* 20:370–375. doi:10.1038/nbt0402-370.
- Shi, T., M. Niepel, J.E. McDermott, Y. Gao, C.D. Nicora, W.B. Chrisler, L.M. Markillie, V.A. Petyuk, R.D. Smith, K.D. Rodland, P.K. Sorger, W.-J. Qian, and H.S. Wiley. 2016. Conservation of protein abundance patterns reveals the regulatory architecture of the EGFR-MAPK pathway. *Sci. Signal.* 9:1–14.
- Sturm, O.E., R. Orton, J. Grindlay, M. Birtwistle, V. Vyshemirsky, D. Gilbert, M.

Calder, A. Pitt, B. Kholodenko, and W. Kolch. 2010. The mammalian MAPK/ERK pathway exhibits properties of a negative feedback amplifier. *Sci. Signal.* 3:ra90. doi:10.1126/scisignal.2001212.

**Supplemental Table 1. Mathematical modeling of the MAPK pathway**

<b>Parameter</b>	<b>Value</b>	<b>Units</b>
k1f	2.49087E-05	cell/molecule/second
k1r	1.3	1/second
k2	0.5	1/second
k3f	0.0000131	cell/molecule/second
k3r	0.3	1/second
k4	0.023	1/second
k5f	1.6667E-08	cell/molecule/second
k5r	0.0053	1/second
k6f	1.6667E-06	cell/molecule/second
k6r	0.0053	1/second
k7	1	1/second
k8f	0.000118333	cell/molecule/second
k8r	0.2	1/second
k9	1	1/second
k10f	0.000118333	cell/molecule/second
k10r	0.2	1/second
k11	1	1/second
k14	3.5	1/second
k15f	0.00000045	cell/molecule/second
k15r	0.5	1/second
k16	0.058	1/second
k19	2.9	1/second
k20f	2.38333E-05	cell/molecule/second
k20r	0.8	1/second
k21	0.058	1/second
k22f	8.90722E-05	cell/molecule/second
k22r	0.033	1/second
k23	16	1/second
k24f	8.33333E-06	cell/molecule/second
k24r	0.5	1/second
k25	0.246	1/second
k26f	8.90722E-05	cell/molecule/second
k26r	0.033	1/second
k27	5.7	1/second
k28f	0.0000235	cell/molecule/second
k28r	0.6	1/second
k29	0.246	1/second
k30f	0.000000001	cell/molecule/second
k30r	99.20374868	1/second

k31	998.7677413	1/second
k32f	0.003270023	cell/molecule/second
k32r	2.339375737	1/second
k33	29.97830381	1/second
k34f	0.0000099	cell/molecule/second
k34r	1.249296869	1/second
k35	995.6270947	1/second
k36	49.98376987	1/second
k37f	0.000000954	cell/molecule/second
k37r	45.26487127	1/second
k38	20.0666884	1/second
k39f	0.0000005	cell/molecule/second
k39r	11.05212178	1/second
k40	0.005	1/second
k44	0.00001	1/second
k45	0.001	1/second
k46	0.029595942	1/second
k47	0.001072136	1/second
k48f	0.00000211	cell/molecule/second
k48r	65.75095587	1/second
k49f	0.00000244	cell/molecule/second
k49r	49.92687244	1/second
k50	0	1/second
k51f	1.31186E-06	cell/molecule/second
k51r	0.3	1/second
k43	0.002	1/second
k42	0.098260953	1/second
k41	0.005607279	1/second
k401f	3.73E-07	cell/molecule/second
k401r	0.0042	1/second
k402f	4.36E-07	cell/molecule/second
k402r	0.0042	1/second
k13f	7.02424E-07	cell/molecule/second
k13r	0.0162	1/second
k12f	4.0352E-07	cell/molecule/second
k12r	0.0134	1/second
k18f	7.02424E-07	cell/molecule/second
k18r	0.0162	1/second
k17f	4.0352E-07	cell/molecule/second
k17r	0.0134	1/second
k301f	1.66E-06	cell/molecule/second
k301r	5.00E-05	1/second

k302f	1.66E-06	cell/molecule/second
k302r	1.80E-04	1/second
k303f	4.04E-07	cell/molecule/second
k303r	0.67	1/second
k304f	7.02E-07	cell/molecule/second
k304r	0.81	1/second
k305	0.35	1/second
k308f	4.04E-07	cell/molecule/second
k308r	0.67	1/second
k309f	7.02E-07	cell/molecule/second
k309r	0.81	1/second
k310	0.29	1/second
k306f	0	cell/molecule/second
k306r	0	1/second
k307	0	1/second
k311f	0	cell/molecule/second
k311r	0	1/second
k312	0	1/second