Supplementary Material (ESI) for Molecular BioSystems

Supplementary Materials

Sloppy Models, Parameter Uncertainty, and the Role of Experimental Design

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List of Supplementary Figures and Tables

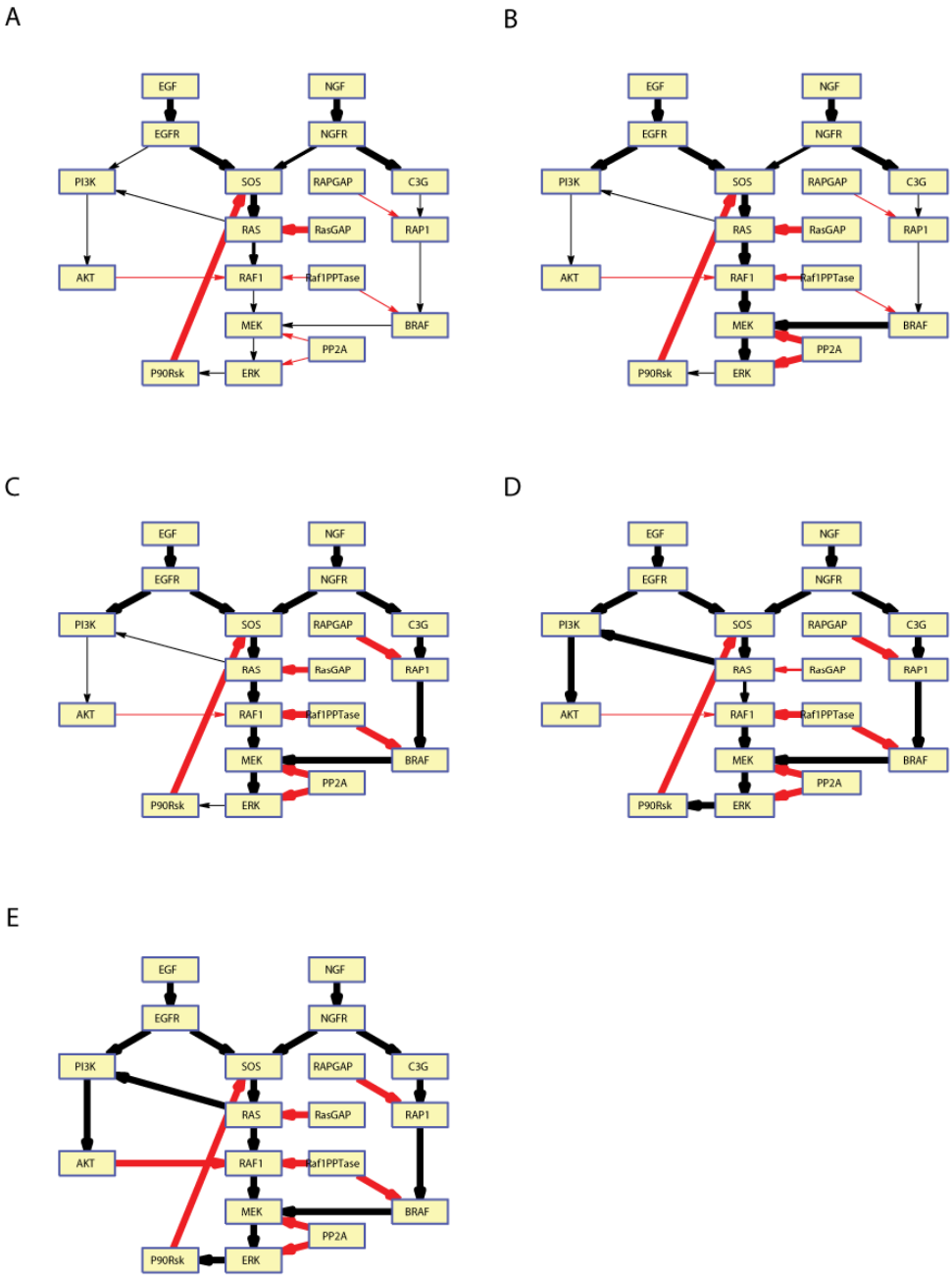

Figure S1. Parameter elucidation determined by greedy search. Thick lines indicate both parameters associated with the reaction were determined to within 10% by the bounding box metric. Medium lines indicate that one of the two parameters accociated with the reaction were determined to within 10%. Thin line indicate that neither were determined to within 10%. (A) Experiment 1 only, (B) Experiments 1 and 2. (C) Experiments 1–3 (D) Experiments 1–4, (E) Experiments 1–5. Overall the first parameters discovered were in the core SOS to ERK pathway followed by the C3G to BRAF then the PI3K, AKT pathway.

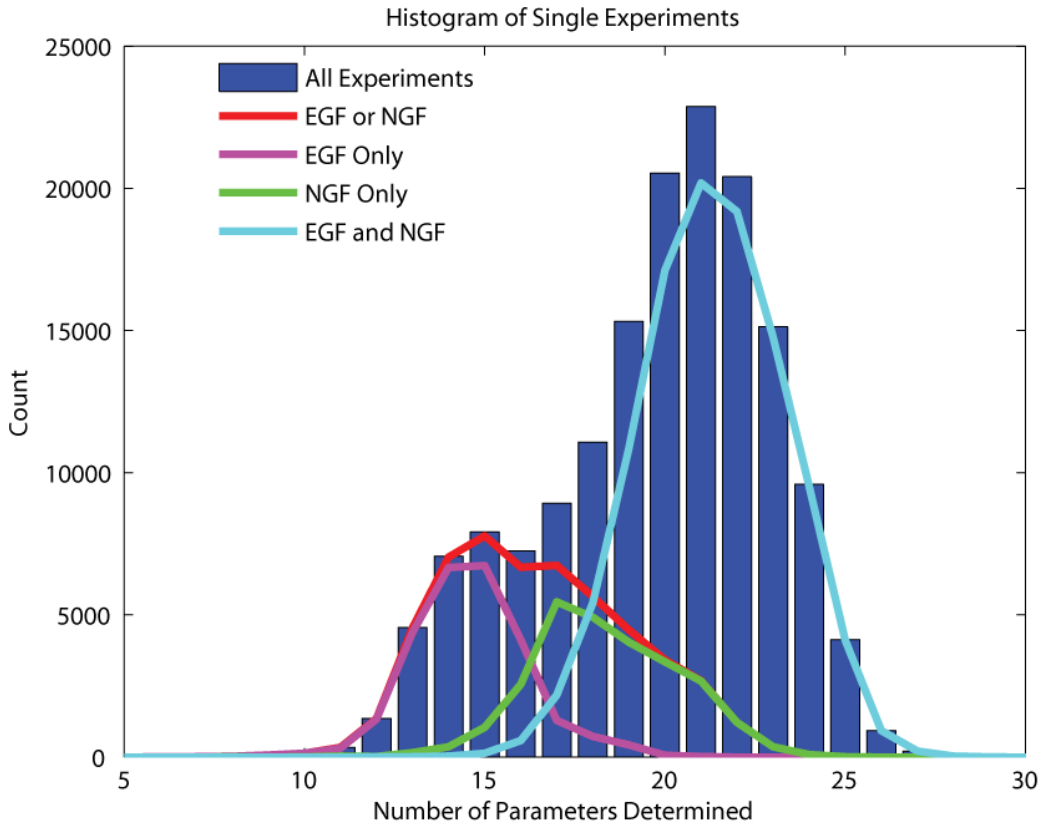

Figure S2. Histogram of the number of parameters determined to 10% relative error for each individual experiment. The blue bars show the results for all experiments; the cyan line is the subset of experiments that used an EGF and an NGF stimulus; the red line is the subset that used only one stimulus (EGF or NGF); the magenta line is for EGF alone; and the green line is for NGF alone. In general, the double stimuli performed better than the singles, but not twice as good, and there is a long tail to the singles subset.

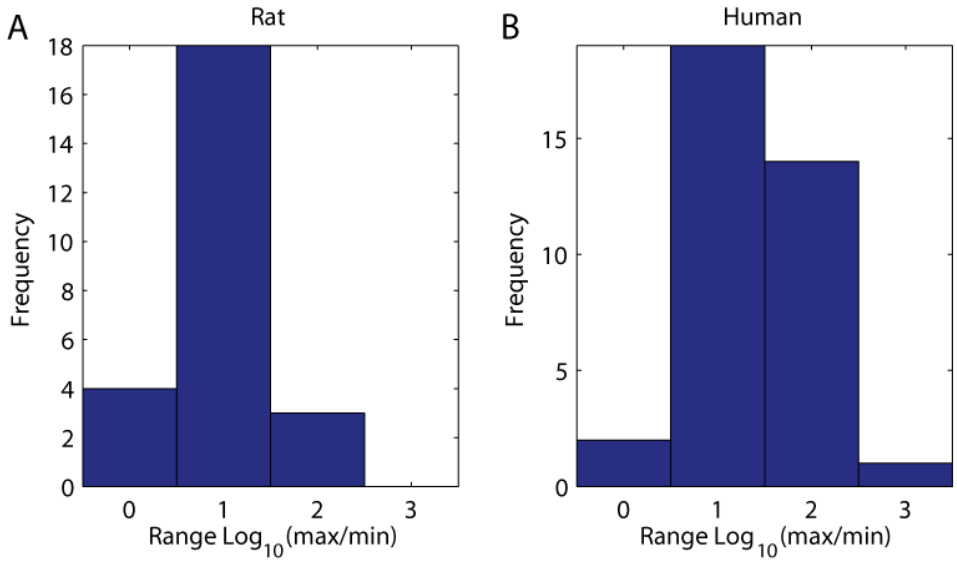

Figure S3. Histogram of expression levels for genes that code for the proteins in the model. (A) Results from different cell types and tissues in rats. (B) Results for various cell types and tissues in humans. The expression levels of almost all of the genes vary by 10 fold or more with about half varying 100 fold.

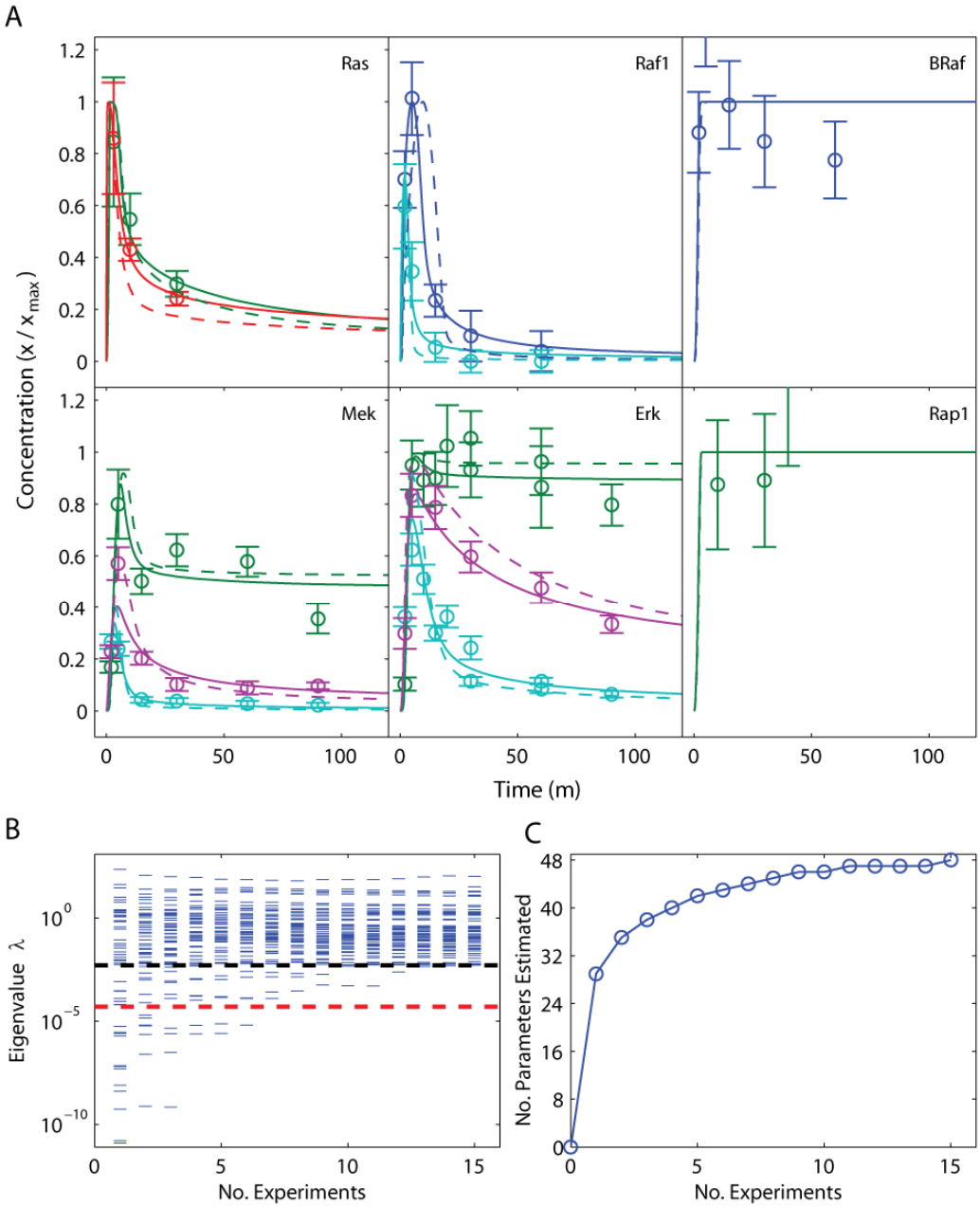

Figure S4. Design with single genetic perturbations at another feasible parameterization. The parameters of the model were changed such that K_M for each enzyme could not be greater than three times its maximum substrate concentration. (A) The results of simulating the model at the original parameterization (solid lines) the modified parameterization (dashed lines), and experimental data (circles with error bars). The line colors indicate the experimental condition: 100 ng/mL NGF (blue), 50 ng/mL NGF (green), 30 ng/mL EGF (red), 100 ng/mL EGF (cyan), 100 ng/mL EGF with 50× EGFR overexpression (magenta). The experimental design methodology was applied with EGF/NGF doses and single gene changes. (B) Eigenspectra of experiments. (C) Number of parameters determined to within 10% relative error (R.E.) by each step of the search. With the modified parameterization all 48 of the parameters could be determined to 10% R.E. (black dashed line) with 15 experiments, and to within 100% R.E with seven experiments (red dashed line).

Table SI: Parameter-Defining Experimental Set for Alternative Parameterization

Exp	EGF (mol./cell)	NGF (mol./cell)	Over Expressed	Knocked Down
1	1.00×10^{7}	4.56×10^{7}		PP2A
2	1.00×10^{1}	4.56×10^{3}		RasGap
3	1.00×10^{7}	4.56×10^{3}	P90Rsk	
4	0.00	4.56×10^{5}		RapGap
5	1.00×10^{7}	4.56×10^{5}	Sos	
6	1.00×10^{7}	4.56×10^{5}	Akt	
7	0.00	4.56×10^{3}	PI3K	
8	1.00×10^{3}	4.56×10^{1}	BRaf	
9	1.00×10^{7}	0.00		Mek
10	1.00×10^{7}	4.56×10^{5}	Raf1	
11	1.00×10^{7}	0.00	PI3K	
12	1.00×10^{7}	4.56×10^{1}	Erk	
13	1.00×10^{7}	4.56×10^{1}	PP2A	
14	1.00×10^{7}	4.56×10^{3}	Mek	
15	1.00×10^{7}	4.56×10^{7}	Sos	

Table SII. Modified Parameters at Alternative Parameterization[a]

	Parameter Value	
Parameter Name	Original	Modified
kEGF	694.731	41.0944
KmEGF	6.09×10^{6}	3.60×10^{5}
kdSos	1611.97	647.019
KmdSos	8.96896×10^{5}	3.60×10^{5}
kRasGap	1509.36	77.6942
KmRasGap	1.43×10^{6}	73733.3
kpRaf1	185.759	70.122
KmpRaf1	4.77×10^{6}	1.80×10^{6}
kpMekCytoplasmic	9.85367	7.652
KmpMekCytoplasmic	1.01×10^{6}	782264
kdErk	8.8912	4.14072
KmdErk	3.50×10^{6}	1.63×10^{6}
kpP90Rsk	0.0213697	0.0100758
KmpP90Rsk	7.63523×10^{5}	3.60×10^{5}
kAkt	0.0566279	0.0311737
KmAkt	6.53951×10^{5}	3.60×10^{5}
kdRaf1ByAkt	15.1212	1.99935
KmRaf1ByAkt	1.19355×10^{5}	15781.3
kRapGap	27.265	4.04006
KmRapGap	2.9599×10^{5}	43859.1
kRap1ToBRaf	2.20995	0.775829
KmRap1ToBRaf	1.03×10^{6}	3.60×10^{5}
kdBRaf	441.287	0.0832448
KmdBRaf	1.09×10^{7}	2052.32

[a] Catalytic rates start with a ‘k’ and are in units of molecules·(cell-volume)$^{-1}$·s^{-1}. Michaelis constants start with a ‘Km’ and have units of molecules·(cell-volume)$^{-1}$.