Supporting Information

Brian K. Mannakee[1] and Ryan N. Gutenkunst*[2]

[1]Division of Epidemiology and Biostatistics,
Mel and Enid Zuckerman College of Public Health, University of Arizona
[2]Department of Molecular and Cellular Biology, University of Arizona

Models considered

1 EGF/NGF signaling [1]

Brown et al. developed a dynamic model of the EGF/NGF signaling network in rat pheochromocytoma (PC12) cells. We downloaded the SBML file `BIOMD0000000033.xml` from the BioModels database and used it without modification. We simulated this model under two different conditions, 100 ng/ml EGF and 50 ng/ml NGF, as described in [1]. Protein domain, parameter, and reaction assignments are in S1 Dataset. In addition to our primary analysis, we calculated dynamical influence over a restricted subset of proteins containing only activated Erk.

2 Arachodonic acid signaling [2]

In order to gain insights related to anti-inflammatory drug interaction and design, Yang et al. created and studied a dynamic model of the arachadonic acid signaling network in human polymorphonuclear leukocytes. We downloaded the SBML file `BIOMD0000000106.xml` from the BioModels database and used it without modification, integrating the model between 0 and 60 minutes as in [2]. The model contains reactions that create and destroy each tracked biomolecule. We excluded these because they are not reactions between modeled proteins. Protein domain, parameter, and reaction assignments are in S1 Dataset. In addition to our primary analysis, we calculated dynamical influence over a restricted subset of proteins containing ω-LTB4 and 15-Hete.

3 EGF/NGF signaling [3]

Sasagawa et al. developed a model of ERK signaling networks, with parameters derived by fitting model dynamics to *in vivo* dynamics in PC12 cells, and studied network dynamics under a variety of stimulation conditions. We downloaded SBML file `BIOMD0000000049.xml` from the BioModels database and used it without modification. For all conditions simulated we integrated the network from 0 to 3600 seconds (60 minutes) as in [3]. The SBML file is coded for constant stimulation by 10 ng/ml EGF, and this is the first of the conditions we simulated. We simulated constant stimulation by 10 ng/ml NGF by using SloppyCell to set EGF concentration to 0 and NGF concentration to 10 ng/ml. Sasagawa et al. also investigate the effect of ramping the concentration of EGF (or NGF) from 0 to 1.5 ng/ml over the course of the simulation. To accomplish this we created assignment rules in SloppyCell which updated the EGF (or NGF) concentration at each time step of the integration, setting it equal to 1.5 * (time/3600) ng/ml. As in the fixed simulation conditions, the network was stimulated by EGF or NGF, but not both. Protein domain, parameter, and reaction assignments are in S1 Dataset. In addition to our primary analysis, we calculated dynamical influence over a restricted subset of proteins containing only activated Erk.

*To whom correspondence should be addressed. Email: rgutenk@email.arizona.edu

4 EGF/MAPK cascade [4]

Schoeberl et al. modeled the EGF signaling pathway, comparing simulated time courses with experimental time courses in HeLa cells under several experimental conditions. We downloaded the SBML file `BIOMD0000000019.xml` from the BioModels database. The model specifies the value of parameter `k5` as a piecewise function of another parameter `C`, and piecewise functions are not supported by SloppyCell, so we removed the piecewise function from the SBML file and used SloppyCell to create two SBML events that replicate it. We simulated the model under three experimental conditions from [4], namely stimulus with 50, 0.5, and 0.25 ng/ml EGF. For all conditions we simulated from 0 to 60 minutes. The model includes receptor internalization reactions which is not modeled mechanistically, and we excluded these reactions from our analysis. Protein domain, parameter, and reaction assignments are in S1 Dataset. In addition to our primary analysis, we calculated dynamical influence over a restricted subset of proteins containing only activated Erk.

5 Myosin phosphorylation [5]

Maeda et al. developed a computational model of thrombin-dependent Rho-kinase activation and myosin light chain phosphorylation in human umbilical vein endothelial cells. We downloaded the SBML file `BIOMD0000000088.xml` for this model from the BioModels database. Some parameter names were duplicated, so we modified the model SBML file to assign unique parameter names and used the published parameter values (see S1 Dataset). The only simulation condition we considered was the $0.01\mu M$ thrombin stimulation published in the SBML file, and we integrated the model from 0 to 3600 seconds as in [5]. We ignored reactions occurring in the extra-cellular compartment, particularly thrombin/thrombin-receptor interactions, and assigned all other reactions to protein domains as outlined in S1 Dataset. We did not calculate a sensitivity for the parameter `ratio`, because it is always multiplied by another parameter `V_max` whose sensitivity we did calculate. SloppyCell interprets rate laws in terms of changes in concentration rather than changes in amount as called for by the SBML specification, so we adjusted reaction stoichiometries by a factor of 1/(compartment size) for reactants in compartment `c2`, the only compartment in all the models we consider with size not equal to 1. In addition to our primary analysis, we calculated dynamical influence over a restricted subset of proteins containing phosphorylated myosin light chain (pMLC) and phosphorylated myosin phosphatase targeting subunit 1 (pMYPT1).

6 Extrinsic apoptosis [6]

Albeck et al. developed a model of TRAIL-induced apoptosis and used it to analyze extrinsic apoptosis in HeLa cells. We downloaded the SBML file `BIOMD0000000220.xml` from the BioModels database and used it without modification. We simulated the model for 10 hours under the 50 ng/ml TRAIL stimulus condition encoded in the SBML file. We excluded extra-cellular reactions involving TRAIL, as well as intra-cellular reactions involving DISC and the TRAIL-DISC complex, because the protein components of the DISC are not specified in the model. We also excluded transport across the mitochondrial membrane and binding of proteins to the inner mitochondrial membrane, because these reactions are not mechanistically specified in the model. Protein domain, parameter, and reaction assignments are in S1 Dataset. In addition to our primary analysis, we calculated dynamical influence summing over a restricted subset of proteins containing Caspase 3, Caspase 8, cytosolic Smac, and cytosolic Cytochrome C.

7 EGF/Insulin crosstalk [7]

Borisov et al. developed a model of the Ras/Erk signaling system that incorporates mechanisms of cross-talk between the EGF and Insulin signaling pathways and tested it in HEK293 cells. We downloaded the SBML file `BIOMD0000000223.xml` from the BioModels database and used it without modification. This SBML model, however, was altered slightly from the originally published model by adding an extra-cellular compartment of size 34. While the model page on the BioModels website says this allows for the use of the original concentrations of EGF we found that this did not create the correct dynamics. Rather than altering the model by changing the size of the extra-cellular compartment we multiplied the desired concentrations of EGF by 34, which produced the correct model dynamics. We

simulated the model under four different experimental conditions, 0.01nM or 1 nM EGF with 0 or 100 nM Insulin, as described in [7]. This model contains a reaction in which Akt1 activates mTor via a chain reaction among a number of proteins that are not included in the model. As a result we only applied this reaction's sensitivity κ to the Akt1 kinase domain, but not to mTor. This is the only reaction in the model in which mTor appears, so mTor was excluded from our analysis of this model. Protein domain, parameter, and reaction assignments are in S1 Dataset. In addition to our primary analysis, we calculated dynamical influence summing over a restricted subset of proteins containing active (doubly phosphorylated) Erk and phosphorylated Akt.

8 G1 cell cycle progression [8]

Haberichter et al. constructed a dynamical model of mammalian G1 cell cycle progression in order to simulate cell cycle progression dynamics in proliferating cells continuously exposed to growth factors. We downloaded the SBML file `BIOMD0000000109.xml` from the BioModels database and used it without modification. We simulated the model under the experimental conditions encoded in the SBML file, integrating for 1000 minutes. The model includes reactions that create and destroy proteins, which we excluded from our analysis because they do not involve interaction with any other protein in the model. Protein domain, parameter, and reaction assignments are in S1 Dataset. In addition to our primary analysis, we calculated dynamical influence summing over a restricted subset of proteins containing the two activation states, hypo- and hyper-phosphorylated, of retinoblastoma tumor suppressor protein pRb.

9 ErbB signaling [9]

Birtwistle et al. built a model of ErbB signaling that describes the response of the signaling network to stimulus of all four ErbB receptors with EGF and HRG (heregulin), comparing model dynamics to dynamics in MCF-7 human breast cancer cells. We downloaded SBML file `BIOMD0000000175.xml` from the BioModels database and used it without modification. Experimental conditions in the paper include stimulation with 0 nM, 0.5 nM, and 10 nM EGF and HRG in each possible combination of those three stimuli, for a total of 12 experimental conditions, and we simulate each of these 12 conditions for 2000 seconds. As in other models we excluded receptor internalization reactions that are not mechanistically described in the model. Protein domain, parameter, and reaction assignments are in S1 Dataset. In addition to our primary analysis, we calculated dynamical influence summing over a restricted subset of proteins containing active (doubly phosphorylated) Erk and phosphorylated Akt. In particular, we used the normalized active Erk and Akt concentrations described in [9].

10 Wnt/Erk crosstalk [10]

Kim et al. created a model of the Erk and Wnt pathways to investigate the effect of a positive feedback loop resulting from crosstalk between Wnt and Erk signaling, and they compared model dynamics with experimental results in HEK293 cells. We downloaded the SBML file `BIOMD0000000149.xml` from the BioModels database and used it without modification. This model includes a protein `X` which is postulated to mediate the feedback between the two pathways; it is transcribed as a result Wnt signaling and activates B-raf in the Erk network. We did not include reactions for transcription and degradation of protein `X`, because they are not mechanistically specified. We did, however, include the reaction in which protein `X` activates B-raf, which occurs on the Ras-binding domain (RBD) of B-raf, because binding at the RBD is the mode of activation of B-raf, and the reaction is modeled in the same way as Ras activation of B-raf. We excluded creation and destruction of β-catenin as well as degradation of Axin, since they are not mechanistically described in the model. Protein domain, parameter, and reaction assignments are in S1 Dataset. In addition to our primary analysis, we calculated dynamical influence summing over a restricted subset of proteins containing active (doubly phosphorylated) Erk and the β-catenin/TCF complex.

11 Rod phototransduction [11]

Dell'Orco et al. developed a model of rod phototransduction specifically aimed at describing the mechanism of light adaptation in rod cells, verifying it by reproducing the results of several pre-

vious light adaptation response experiments in mouse rod cells. We downloaded the SBML file `BIOMD0000000326.xml` from the BioModels database and used it with minor modification. We removed two piecewise assignment rules, because SloppyCell does not handle piecewise rules, and replaced them with SBML events. We simulated six flash intensities, replicating those used to create Figure 7 in the publication, by setting the parameter `flash0Mag` to 1.54, 12.5, 45.8, 184, 800, and 2000. The parameter `kP1_rev` represents the rate of dissociation of phosphodiesterase from activated G-alpha molecules, and is set to zero in this model, so we excluded it from our analysis. Protein domain, parameter, and reaction assignments are in S1 Dataset. In addition to our primary analysis, we calculated dynamical influence summing over a restricted subset of molecular species containing only cyclic GMP.

12 IL-6 signaling [12]

Singh et al. developed a model of IL-6 signaling encompassing the Jak/STAT as well as MAP kinase pathways in human hepatocytes. We downloaded the SBML file `BIOMD0000000151.xml` from the BioModels database and used it without modification. We simulated the experimental conditions encoded in the model, 10 ng/ml IL-6 stimulus and an initial Shp2 concentration of 100 nM. The model includes transcription, translation, and mRNA translocation for the protein SOCS which are not mechanistically detailed, so we excluded them. Protein domain, parameter, and reaction assignments are in S1 Dataset. In addition to our primary analysis, we calculated dynamical influence summing over a restricted subset of proteins containing only active STAT3 dimers in the nucleus.

13 Trehalose biosynthesis [13]

Smallbone et al. created a model of the trehalose biosynthesis pathway in *Sa. cerevisiae*. We downloaded the SBML file `BIOMD0000000380.xml` from the BioModels database and used it without modification. This model reaches a steady state, and the model was validated by comparing the steady state concentrations of the metabolites in the model with experimental results in yeast experiencing heat shock. We simulated the model under the heat shock condition used in the publication, and ran the model for 50000 seconds, at which point all metabolites had reached steady state concentrations. The model creates `Clb2` in a reaction that is not mechanistically specified, and we excluded this reaction from our analysis. Protein domain, parameter, and reaction assignments are in S1 Dataset. In addition to our primary analysis, we calculated dynamical influence summing over only the metabolite of interest, trehalose-6-phosphate.

14 Glycolysis [14]

Talser et al. created a model of carbohydrate flux under oxidative stress conditions in *Sa. cerevisiae*. We downloaded the SBML file `BIOMD0000000247.xml` from the BioModels database and used it with substantial modification. The model file in the BioModels database included unfitted parameter values, but model author Markus Ralser generously provided us with the parameter values they obtained by fitting the model to experimental data, and we reparameterized the SBML file accordingly. We simulated the wild-type experimental conditions encoded in the model for 100 minutes. Protein domain, parameter, and reaction assignments are in S1 Dataset. In addition to our primary analysis, we calculated dynamical influence summing over the ratio of NADH to NADPH, the quantity of interest.

15 Cell cycle regulation [15]

Chen et al. developed a model of the cell cycle in *Sa. cerevisiae* in order to investigate the complex mechanisms of cell cycle control. We downloaded the SBML file `BIOMD0000000056.xml` from the BioModels database and used it with substantial modification. This model was constructed with some reactions combined into assignment rules, making it impossible to use SloppyCell to calculate dynamical influence for individual reaction parameters. We separated these assignment rules into individual reactions and added those reactions to the model file, replacing the assignment rules. In order to verify that the modified model was correct we replicated Figures 3 and 6 from the publication. The model contains reactions causing the degradation of various proteins by SCF, which is not included in the model, and these reactions are not mechanistically described, so we excluded them from our analysis. We simulated the wild-type experimental conditions encoded in the paper for 200 minutes

as in Figures 3 and 6 of the publication. Protein domain, parameter, and reaction assignments are in S1 Dataset. In addition to our primary analysis, we calculated dynamical influence summing over measures of the timing of cell cycle events; MASS, BUD, ORI, and SPN.

16 Mitotic exit [16]

Queralt et al. developed a model of the initiation of mitotic exit in *Sa. cerevisiae* induced by down-regulation of the phosphatase Cdc50. We downloaded the SBML file `BIOMD0000000409.xml` from the BioModels database and used it without modification. This model contains reactions creating and destroying proteins Clb2, Cdc20, securin, separase, Cdc5, and Cdc15 which are not mechanistically described in the model, and we excluded these reactions from our analysis. We simulated the wild type conditions encoded in the model for 50 minutes, as in Figure 7 of the publication. Protein domain, parameter, and reaction assignments are in S1 Dataset. In addition to our primary analysis, we calculated dynamical influence summing over only the concentration of active separase.

17 Mitotic exit [17]

Vinod et al. created a computational model of mitotic exit in *Sa. cerevisiae* aimed at investigating the role of separase and Cdc14 endocycles. We downloaded the SBML file `BIOMD0000000370.xml` from the BioModels database and used it with substantial modification. This model was constructed using rate rules rather than reactions in SBML. Because SloppyCell our analysis is focused on reactions, we converted the rate rules to reactions, ensuring that the model remained correct by using it to generate Figure 2 from the publication. The model includes reactions creating, destroying, or (de)activating proteins Clb2, Sic1, Cln1, Cdc20, Cdh1, Swi5, Pds1, Esp1, Cdc5, Polo, and MBF which are not mechanistically detailed, and we excluded these reactions from our analysis. We simulated the wild-type experimental conditions encoded in the model for 120 minutes as in Figure 2 of the publication. Protein domain, parameter, and reaction assignments are in S1 Dataset. In addition to our primary analysis, we calculated dynamical influence summing over only the concentration of active separase.

18 Pheromone pathway [18]

Kofahl and Klipp modelled the dynamics of the *Sa. cerevisiae* pheromone pathway. We downloaded the SBML file `BIOMD0000000037.xml` from the BioModels database and used it without modification. The model includes reactions for the destruction of `Ste2` and the export of `Bar` that are not mechanistically detailed, and we excluded them from our analysis. We simulated the wild-type experimental conditions encoded in the model for 30 minutes, as in [18]. Protein domain, parameter, and reaction assignments are in S1 Dataset. In addition to our primary analysis, we calculated dynamical influence summing over only the concentration of complexes M and N, which include Far1 and are required for polarized growth and cell cycle arrest respectively.

S1 Dataset

References are [19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 16, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170].

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