The Boolean Kinetics of Signal Transduction: Supplementary Material

Equations of the LAC_SIM model of the *E.coli* Lac operon (Figure 1):

v1 = Vm1/(1 + (RPf/Ki1) ^ n1)

where RPf is free (unbound) concentration of lac repressor

v2 = β-Gal * k2

where β-Gal is concentration of β-galactosidase

v3 = Vm3 * lactoseC / (lactoseC + Km3)

where lactoseC is cellular lactose concentration; Vm3 = β-Gal * TO3

v4 = lactoseE * k4

where lactoseE is extracellular lactose concentration

v5 = permease * k5

where permease is concentration of galactoside permease

v6 = Vm6 * lactoseE /(lactoseE + Km6) /(1 + I/Ki6)

where Vm6 = permease * TO6 and I is an inhibitor of facilitated transport.

v7 = lactoseC * k7

k2, k4, k5 and k7 are first-order rate constants for their respective reactions. Vm1, Vm3 and Vm6 are maximal velocities; Vm1 is a constant, and Vm3 and Vm6 are the product of the respective enzyme concentrations and their turnover numbers, TO3 and TO6, respectively; Km3 and Km6 are Michaelis constants; Ki1 and Ki6 are noncompetitive inhibition constants; n1 and n3 are Hill constants.

Then lactoseE is constant

d[lactoseC]/dt = v4 + v6 – v3 – v7

d[β-Gal]/dt = v1 – v2

d[permease]/dt = v1 – v5

RPf = RPt / (1 + (lactoseC/Ki3)^n3)

where RPt is total (free + alloactose-bound) concentration of lac repressor.

Parameter values used for the simulations discussed in the main text were: k2=1.0; k4=0.05; k5=4.5; k7=0.05; Vm1=100; TO3=0.167; TO6=0.98; Km3=0.2; Km6=0.05; Ki1=1.0.

Equations of the MAPK_SIM model of the human MAPK signalling pathway (see figure 4):

v1 = Vm1 * cfos /(cfos + Km1) / (1 + cyclinD/Ki1)

v2 = cyclinD * k2

v3 = Vm3 * (ras/Km3)^n3 /(1 + (ras/Km3)^n3)

where ras indicates the ras-GTP complex.

v4 = Vm4 * EGF/Km4 / (1 + EGF/Km4) / (1 + spr/Ki4) / (1 + I4/Kinc)

where spr is the sprouty protein [25], and I4 is an inhibitor of the EGF receptor tyrosine kinase, e.g.erlotinib [26].

v5 = Vm5 * Grb2/Km5 / (1 + Grb2/Km5)

v6 = Grb2 * k6

v7 = Vm7 * MEKP/ Km7 / (1 + MEKP/Km7) / (1 + spr/Ki7)

where MEKP is the active, phosphorylated form of MEK.

v8 = ras * k8

v9 = Vm9 * raf/Km9 / (1 + raf/Km9) / (1 + ERKP/Ki9) / (1 + I9/Ki8)

where ERKP is the phosphorylated form of ERK and I9 is a raf kinase inhibitor, e.g. sorafenib [27].

v10 = Vm10 * MEKP /Km10 /(1 + MEKP/Km10)

v11 = ERKP * k11

k2, k6, k8 and k11 are first-order rate constants for their respective reactions. Vm1, Vm3, Vm4, Vm5, Vm7, Vm9 and Vm10 are maximal velocities; Km1, Km3, Km4, Km5, Km7, Km9 and Km10 are Michaelis constants; Ki1, Ki4, Ki7, Ki8, Ki9 and Kinc are noncompetitive inhibition constants; n3 is a Hill constant.

Then

d[Grb2]/dt = v4 – v6

d[ras]/dt = v5 + v21 – v8; note: v21 is a cross-talk signal from the PI3K pathway, discussed below.

d[raf]/dt = v3 – v9

d[MEKP]/dt = v9 – v10

d[ERKP]/dt = v10 – v7 – v11

d[cfos]/dt = v7 – v1

k2, k6, k8 and k11 are first-order rate constants for their respective reactions. Vm1, Vm3, Vm4, Vm5, Vm7, Vm9 and Vm10 are maximal velocities; Km1, Km3, Km4, Km5, Km7, Km9 and Km10 are Michaelis constants; Ki1, Ki4, Ki7 and Ki9 are noncompetitive inhibition constants; n3 is a Hill constant.

k2=1.6; k6=.05; k8=.028; k11=.02; Vm1=19.4; Vm3=10; Vm4=.33; Vm5=50; Vm7=20; Vm9=10; Vm10=20; Km1=1; Km3=30; Km4=1; Km5=3.5; Km7=10; Km9=2; Km10=1; Ki1=10; Ki3=1; ki4=1; Ki5=1; Ki7=1; Ki9=400; Ki10=1; n3=4.

Equations of the Akt_SIM model of the human Akt (PI3K) signalling pathway (Figure 7):

v12 = Vm12 * PDGF/Km12 /(1 + PDGF/Km12)

v13 = PI3K * k13

v14 = Vm14 * PI3K/Km14 /(1 + PI3K/Km14) / (1+ I14/Ki14)

where I14 is an inhibitor of PI3 kinase, e.g. LY294002 [28].

v15 = Vm15 * Akt/Km15 /(1 + Akt/Km15)

v16 = Vm16 * mTOR/Km16 /(1 + mTOR/Km16)

v17 = eIF4E * k17

v18 = Vm18 * mTOR/Km18 /(1 + mTOR/Km18)

v19 = p70S6K * k19

v20 = Vm20 * eIF4E/Ka20 /(1 + eIF4E/Ka20) * p70S6K/Kb20 / (1 + p70S6K/Kb20)

v21 = PI3K * k21

v22 = ras * k22

k13, k17, k19, k21 and k22 are first-order rate constants for their respective reactions. Vm12, Vm14, Vm15, Vm16, Vm18 and Vm20 are maximal velocities; Km12, Km14, Km15, Km16 and Km18 are Michaelis constants; Ka20 and Kb20 are dissociation constants for binding of eIF4E and p70S6K respectively; Ki14 is a noncompetitive inhibition constant.

Then

d[PI3K]= v12 + v22 -v13

d[Akt] = v14 – v15

d[mTOR] = v15 – v16 – v18

d[eIF4E] = v16 – v17

d[p70S6K] = v18 – v19

Parameter values used for the simulations used in the main text were: k13=.05; k17=.2; k19=.1; k21=.01; k22=.01; Vm12=.66; Vm14=2; Vm15=4; Vm16 =5; Vm18=3; Vm20=6; Km12=1; km14=5; Km15=5; Km16=5; Km18=4; Km20 = 1.