The Boolean Kinetics of Signal Transduction: Supplementary Material

Equations of the LAC_SIM model of the E.coli Lac operon (Figure 1):
\[
v_1 = \frac{V_{m1}}{1 + \left(\frac{RPF}{K_{i1}}\right)^{n1}}
\]
where RPF is free (unbound) concentration of lac repressor
\[
v_2 = \beta-Gal \ast k_2
\]
where \(\beta-Gal\) is concentration of \(\beta\)-galactosidase
\[
v_3 = V_{m3} \ast lactoseC / (lactoseC + Km3)
\]
where lactoseC is cellular lactose concentration; \(V_{m3} = \beta-Gal \ast TO3\)
\[
v_4 = lactoseE \ast k_4
\]
where lactoseE is extracellular lactose concentration
\[
v_5 = permease \ast k_5
\]
where permease is concentration of galactoside permease
\[
v_6 = \frac{V_{m6} \ast lactoseE}{(lactoseE + Km6) \ast (1 + I/Ki6)}
\]
where \(V_{m6} = permease \ast TO6\) and \(I\) is an inhibitor of facilitated transport.
\[
v_7 = lactoseC \ast k_7
\]
\(k_2, k_4, k_5\) and \(k_7\) are first-order rate constants for their respective reactions. \(V_{m1}, V_{m3}\) and \(V_{m6}\) are maximal velocities; \(V_{m1}\) is a constant, and \(V_{m3}\) and \(V_{m6}\) 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 lactoseC is constant
\[
d[lactoseC]/dt = v_4 + v_6 - v_3 - v_7
\]
\[
d[\beta-Gal]/dt = v_1 - v_2
\]
\[
d[permease]/dt = v_1 - v_5
\]
\[
RPF = \frac{RPT}{1 + (lactoseC/Ki3)^{n3}}
\]
where \(RPT\) is total (free + alloactose-bound) concentration of lac repressor.

Parameter values used for the simulations discussed in the main text were: \(k_2=1.0; k_4=0.05; k_5=4.5; k_7=0.05; V_{m1}=100; TO3=0.167; TO6=0.98; Km3=0.2; Km6=0.05; Ki1=1.0.\)

Equations of the MAPK_SIM model of the human MAPK signalling pathway (see figure 4):
\[
v_1 = \frac{V_{m1} \ast cfos}{(cfos + Km1) \ast (1 + cyclinD/Ki1)}
\]
\[
v_2 = cyclinD \ast k_2
\]
\[
v_3 = \frac{V_{m3} \ast (ras/Km3)^{n3}}{1 + (ras/Km3)^{n3}}
\]
where ras indicates the ras-GTP complex.
\[
v_4 = \frac{V_{m4} \ast EGF/Km4}{(1 + EGF/Km4) \ast (1 + spr/Ki4) \ast (1 + I_4/Kinc)}
\]
where spr is the sprouty protein [25], and \(I_4\) is an inhibitor of the EGF receptor tyrosine kinase, e.g. erlotinib [26].
\[
v_5 = \frac{V_{m5} \ast Grb2/Km5}{1 + Grb2/Km5}
\]
\[
v_6 = Grb2 \ast k_6
\]
\[
v_7 = \frac{V_{m7} \ast MEKP/Km7}{(1 + MEKP/Km7) \ast (1 + spr/Ki7)}
\]
where MEKP is the active, phosphorylated form of MEK.
\[
v_8 = ras \ast k_8
\]
\[
v_9 = \frac{V_{m9} \ast raf/Km9}{(1 + raf/Km9) \ast (1 + ERKP/Ki9) \ast (1 + I_9/Ki8)}
\]
where ERKP is the phosphorylated form of ERK and \(I_9\) is a raf kinase inhibitor, e.g. sorafenib [27].
\[
v_{10} = \frac{V_{m10} \ast MEKP/Km10}{1 + MEKP/Km10}
\]
\[ v_{11} = \text{ERK} \times k_{11} \]

\[ k_2, k_6, k_8 \text{ and } k_{11} \text{ are first-order rate constants for their respective reactions. } V_m1, V_m3, V_m4, V_m5, V_m7, V_m9 \text{ and } V_m10 \text{ are maximal velocities; } K_m1, K_m3, K_m4, K_m5, K_m7, K_m9 \text{ and } K_m10 \text{ are Michaelis constants; } K_i1, K_i4, K_i7, K_i8, K_i9 \text{ and } K_{inc} \text{ are noncompetitive inhibition constants; } n_3 \text{ is a Hill constant.} \]

Then

\[ \frac{d[\text{Grb2}]}{dt} = v_4 - v_6 \]
\[ \frac{d[\text{ras}]}{dt} = v_5 + v_{21} - v_8; \text{ note: } v_21 \text{ is a cross-talk signal from the PI3K pathway, discussed below.} \]
\[ \frac{d[\text{raf}]}{dt} = v_3 - v_9 \]
\[ \frac{d[\text{MEKP}]}{dt} = v_9 - v_{10} \]
\[ \frac{d[\text{ERKP}]}{dt} = v_{10} - v_7 - v_{11} \]
\[ \frac{d[\text{cfos}]}{dt} = v_7 - v_1 \]

\[ k_2, k_6, k_8 \text{ and } k_{11} \text{ are first-order rate constants for their respective reactions. } V_m1, V_m3, V_m4, V_m5, V_m7, V_m9 \text{ and } V_m10 \text{ are maximal velocities; } K_m1, K_m3, K_m4, K_m5, K_m7, K_m9 \text{ and } K_m10 \text{ are Michaelis constants; } K_i1, K_i4, K_i7 \text{ and } K_i9 \text{ are noncompetitive inhibition constants; } n_3 \text{ is a Hill constant.} \]

\[ k_2 = 1.6; \quad k_6 = 0.05; \quad k_8 = 0.028; \quad k_{11} = 0.02; \quad V_m1 = 19.4; \quad V_m3 = 10; \quad V_m4 = 33; \quad V_m5 = 50; \quad V_m7 = 20; \quad V_m9 = 10; \quad V_m10 = 20; \quad K_m1 = 1; \quad K_m3 = 30; \quad K_m4 = 1; \quad K_m5 = 3.5; \quad K_m7 = 10; \quad K_m9 = 2; \quad K_i1 = 0; \quad K_i3 = 1; \quad K_i4 = 1; \quad K_i5 = 1; \quad K_i7 = 1; \quad K_i9 = 400; \quad K_{inc} = 1; \quad n_3 = 4. \]

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

\[ v_{12} = \frac{V_m12 \times \text{PDGF}}{K_m12} \times (1 + \text{PDGF}/K_m12) \]
\[ v_{13} = \text{PI3K} \times k_{13} \]
\[ v_{14} = \frac{V_m14 \times \text{PI3K}/K_m14}{(1 + \text{PI3K}/K_m14)} \times (1 + I_{14}/K_{i14}) \]
where \( I_{14} \) is an inhibitor of PI3 kinase, e.g. LY294002 [28].
\[ v_{15} = \frac{V_m15 \times \text{Akt}/K_m15}{(1 + \text{Akt}/K_m15)} \]
\[ v_{16} = \frac{V_m16 \times \text{mTOR}/K_m16}{(1 + \text{mTOR}/K_m16)} \]
\[ v_{17} = \frac{e\text{IF4E} \times k_{17}}{1} \]
\[ v_{18} = \frac{V_m18 \times \text{mTOR}/K_m18}{(1 + \text{mTOR}/K_m18)} \]
\[ v_{19} = \frac{p70S6K \times k_{19}}{1} \]
\[ v_{20} = \frac{V_m20 \times e\text{IF4E}/K_{a20}}{(1 + e\text{IF4E}/K_{a20}) \times p70S6K/K_{b20}} \times (1 + p70S6K/K_{b20}) \]
\[ v_{21} = \frac{\text{PI3K} \times k_{21}}{1} \]
\[ v_{22} = \frac{\text{ras} \times k_{22}}{1} \]

\[ k_{13}, k_{17}, k_{19}, k_{21} \text{ and } k_{22} \text{ are first-order rate constants for their respective reactions. } V_m12, V_m14, V_m15, V_m16, V_m18 \text{ and } V_m20 \text{ are maximal velocities; } K_m12, K_m14, K_m15, K_m16 \text{ and } K_m18 \text{ are Michaelis constants; } K_{a20} \text{ and } K_{b20} \text{ are dissociation constants for binding of eIF4E and p70S6K respectively; } K_{i14} \text{ is a noncompetitive inhibition constant.} \]

Then

\[ \frac{d[\text{PI3K}]}{dt} = v_{12} + v_{22} - v_{13} \]
\[ \frac{d[\text{Akt}]}{dt} = v_{14} - v_{15} \]
\[ \frac{d[\text{mTOR}]}{dt} = v_{15} - v_{16} - v_{18} \]
\[ \frac{d[e\text{IF4E}]}{dt} = v_{16} - v_{17} \]
\[ \frac{d[p70S6K]}{dt} = v_{18} - v_{19} \]

Parameter values used for the simulations used in the main text were:

\[ k_{13} = 0.05; k_{17} = 2; k_{19} = 0.1; k_{21} = 0.01; V_m12 = 0.66; V_m14 = 2; V_m15 = 4; V_m16 = 5; V_m18 = 3; V_m20 = 6; K_m12 = 1; K_m14 = 5; K_m15 = 5; K_m16 = 5; K_m18 = 4; K_m20 = 1. \]