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Functioning of a metabolic flux sensor in *Escherichia coli*

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Supporting Information

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SI Text 1: Model Describing System Without Feedforward Activation

The mathematical model containing two metabolites (X and Y) and two enzymatic reactions (E_1 and E_2) can be described by a set of two ordinary differential equations:

$$\frac{dX}{dt} = v - v_{E1} \quad [S1]$$

$$\frac{dY}{dt} = v_{E1} - v_{E2}, \quad [S2]$$

where v denotes the influx (input of the system) and v_{E1} and v_{E2} denote the reaction rates of E_1 and E_2 , respectively. At steady state, the differential expressions are zero, simplifying Eqs. **S1** and **S2** to the following:

$$v_{E1} = v_{E2} = v. \quad [S3]$$

The rates through the two reactions v_{E1} and v_{E2} can be described with the following equations, assuming a reversible Michaelis–Menten-type kinetic for E_1 and an irreversible Michaelis–Menten-type kinetic for E_2 :

$$v_{E1} = v = \frac{v_{\max,E1} \cdot \left(X - \frac{Y}{K_{\text{eq}}} \right)}{K_{m,X,E1} \cdot \left(1 + \frac{Y}{K_{m,Y,E1}} \right) + X} \quad [S4]$$

$$v_{E2} = v = \frac{v_{\max,E2} \cdot Y}{K_{m,Y,E2} + Y} \quad [S5]$$

$K_{m,X,E1}$, $K_{m,Y,E1}$, and $K_{m,Y,E2}$ denote the K_m values for X and Y of E_1 and for Y of E_2 , respectively. K_{eq} denotes the equilibrium constant of E_1 , and $v_{\max,E1}$ and $v_{\max,E2}$ denote the maximal possible fluxes of E_1 and E_2 , respectively.

To obtain an analytical solution of the relationship of X and the flux v , Eqs. **S4** and **S5** can be rearranged for X and Y , respectively. Replacing Y in Eq. **S4** (and assuming that $K_{m,X,E1} =$

$K_{m,Y,E1}$ to reduce the number of parameters), one obtains the following:

$$X = \frac{v \cdot K_{m,X,E1}}{v_{\max,E1} - v} + \frac{v \cdot K_{m,Y,E2} \cdot v_{\max,E1}}{K_{\text{eq}} \cdot (v_{\max,E1} - v) \cdot (v_{\max,E2} - v)} + \frac{v^2 \cdot K_{m,Y,E2}}{(v_{\max,E1} - v) \cdot (v_{\max,E2} - v)}. \quad [S6]$$

For $v \ll v_{\max,E1}$ and $v \ll v_{\max,E2}$ (which is equivalent to an influx that is much lower than the maximal possible fluxes for E_1 and E_2), this equation simplifies to the following:

$$X = \frac{v \cdot K_{m,X,E1}}{v_{\max,E1}} + \frac{v \cdot K_{m,Y,E2}}{K_{\text{eq}} \cdot v_{\max,E2}}. \quad [S7]$$

This equation describes the analytical solution for the relationship of X and flux v .

SI Text 2: Model Describing System with Feedforward Activation of E_2 by X

Here, we use the same ordinary differential equations as above. In contrast to the previous model, we use a Monod–Wyman–Changeux (MWC) kinetic for E_2 in accordance to previous studies on pyruvate kinase I (PYK I) (1–3):

$$v_{E2} = v = \frac{v_{\max,E2} \cdot \frac{Y}{K_{m,Y,E2}} \cdot \left(1 + \frac{Y}{K_{m,Y,E2}} \right)^{n-1}}{L \cdot \left(1 + \frac{X}{K_{mA,X,E2}} \right)^{-n} + \left(1 + \frac{Y}{K_{m,Y,E2}} \right)^n}. \quad [S8]$$

L , n , and $K_{mA,X,E2}$ in Eq. **S8** denote allosteric equilibrium constant, cooperativity constant, and affinity constant of X for E_2 , respectively. We chose values for L and n in accordance to parameter values that were obtained for PYK I in previous studies: PYK I is inactive in absence of its allosteric activator FBP (1, 4), which corresponds to $L \gg 1$, and several studies have determined n to be equal to 4 (1, 5). Because $n > 1$, it is not possible to derive an analytical solution for the relationship of X and flux v , and thus we solve this model equation as specified in the main text.

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