SUPPORTING MATERIAL FOR
The energy costs of insulators in biochemical networks

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Existence of periodic solutions in response to periodic input

For the system of ODEs in Eq. 10 in the main text, reproduced here,

$$\begin{aligned}
\frac{dZ}{dt} &= k(t) - \delta Z - \beta_1 Z\left(X_{\rm tot} - C_1 - C_2 - C - X^*\right) + \left(\beta_2 + k_1\right) C_1, \\
\frac{dC_1}{dt} &= \beta_1 Z\left(X_{\rm tot} - C_1 - C_2 - C - X^*\right) - \left(\beta_2 + k_1\right) C_1, \\
\frac{dC_2}{dt} &= \alpha_1 X^*\left(Y_{\rm tot} - C_2\right) - \left(\alpha_2 + k_2\right) C_2, \\
\frac{dX^*}{dt} &= k_1\, C_1 - \alpha_1 X^*\left(Y_{\rm tot} - C_2\right) + \alpha_2 C_2 - k_{\rm on} X^*\left(p_{\rm tot} - C\right) + k_{\rm off}\, C, \\
\frac{dC}{dt} &= k_{\rm on} X^*\left(p_{\rm tot} - C\right) - k_{\rm off}\, C.
\end{aligned} \tag{10}$$

there is always a periodic solution in response to any periodic input. Suppose that $k(t)$ is a continuous periodic signal with period T: $k(t+T) = k(t)$ for all $t \geq 0$, and let K be the largest value of $k(t)$. Then, the set $\mathcal{S}$ consisting of vectors (Z, C_1, C_2, X^*, C) with non-negative components for which

$$Z \leq (1/\delta)(K + (\beta_2 + k_1)X_{\rm tot}),\ X^* + C_1 + C_2 + C \leq X_{\rm tot},\ C_2 \leq Y_{\rm tot},\ C \leq p_{\rm tot},$$

is forward invariant: any solution that starts in the set $\mathcal{S}$ at time $t = 0$ stays in $\mathcal{S}$ for all $t > 0$. Moreover, this set is compact (closed and bounded) and convex.

Consider the mapping $\pi : \mathcal{S} \to \mathcal{S}$ with $\pi(\xi_0) = \xi(T)$, that is, the map that assigns to any initial state ξ_0 at time $t = 0$ the solution of Eq. 10 at time $t = T$. Since π is a continuous mapping, it follows as a consequence of Brouwer's Fixed-Point Theorem (1) that there exists at least one state ξ_0 for which $\pi(\xi_0) = \xi_0$. Periodicity of $k(t)$ then implies that the solution $\xi(t)$ starting from $\xi(0) = \xi_0$ is periodic with period T. Moreover, unless the input signal $k(t)$ is itself constant, the solution $\xi(t)$ is a true periodic solution (not a constant steady state), since $dZ/dt = 0$ for a constant $Z(t)$ would imply that $k(t)$ is equal to a constant.

Linear stability of solutions near equilibrium points

Here we show that, under very general physical assumptions, the solution of Eq. 10 is linearly stable around an equilibrium point, by proving that all eigenvalues of the Jacobian have negative real parts. For simplicity, we consider the system of equations with $W = Z + C_1$ and $V = X^* + C_2 + C$, given by

$$\begin{aligned}
\frac{dW}{dt} &= k(t) - \delta(W - C_1),\\
\frac{dC_1}{dt} &= \beta_1 (W - C_1)(X_{\text{tot}} - V - C_1) - (\beta_2 + k_1) C_1,\\
\frac{dC_2}{dt} &= \alpha_1 (V - C_2 - C)(Y_{\text{tot}} - C_2) - (\alpha_2 + k_2) C_2,\\
\frac{dC}{dt} &= k_{\text{on}}(V - C_2 - C)(p_{\text{tot}} - C) - k_{\text{off}} C\\
\frac{dV}{dt} &= k_1 C_1 - k_2 C_2.
\end{aligned} \tag{S1}$$

Here we initially take $k(t) = k$ to be constant. In the following analysis, it will be helpful to write expressions in terms of

$$\begin{aligned}
\Delta_1 &= \beta_1(W - C_1),\\
\Delta_2 &= \beta_1(X_{\text{tot}} - V - C_1),\\
\Delta_3 &= \alpha_2 + \alpha_1(V - C_2 - C),\\
\Delta_4 &= \alpha_1(Y_{\text{tot}} - C_2),\\
\Delta_5 &= k_{\text{off}} + k_{\text{on}}(V - C_2 - C),\\
\Delta_6 &= k_{\text{on}}(p_{\text{tot}} - C).
\end{aligned} \tag{S2}$$

All these quantities are evaluated at a positive equilibrium $(\bar{W}, \bar{C_1}, \bar{C_2}, \bar{C}, \bar{V})$. We will assume that all rate constants, such as β_1, β_2, and so forth, are strictly positive, as are the equilibrium concentrations for physically relevant solutions of Eq. 10. Note that under these assumptions all of the quantities listed in Eq. S2 will be strictly positive.

In terms of these variables, the Jacobian corresponding to Eq. 10 is

$$J = \begin{pmatrix}
-\delta & \delta & 0 & 0 & 0\\
\Delta_2 & -k_1 - \beta_2 - \Delta_1 - \Delta_2 & 0 & 0 & -\Delta_1\\
0 & 0 & -k_2 - \Delta_3 - \Delta_4 & -\Delta_4 & \Delta_4\\
0 & 0 & -\Delta_6 & -\Delta_5 - \Delta_6 & \Delta_6\\
0 & k_1 & -k_2 & 0 & 0
\end{pmatrix}.$$

All eigenvalues of the Jacobian will have negative real part provided that the Routh-Hurwitz stability criterion (2) is satisfied. The stability criterion consists of a set of conditions on the coefficients of the characteristic polynomial $P(\lambda) = \lambda^5 + a_1\lambda^4 + a_2\lambda^3 + a_3\lambda^2 + a_4\lambda + a_5$ of the Jacobian matrix.

For our system these conditions take the form

$$a_1, a_2, a_3, a_4, a_5 > 0, \tag{S3}$$

$$a_1 a_2 a_3 - a_3^2 - a_1^2 a_4 > 0, \tag{S4}$$

$$(a_1 a_4 - a_5)(a_1 a_2 a_3 - a_3^2 - a_1^2 a_4) - a_5(a_1 a_2 - a_3)^2 - a_1 a_5^2 > 0. \tag{S5}$$

A simple expansion of the coefficients of the characteristic polynomial, written in terms of the variables introduced in Eq. S2, shows that the conditions given by Eq. S3 and Eq. S4 are satisfied for any physical choice of parameters, as defined above. The left-hand side of Eq. S5 can be written in terms of the variables in Eq. S2 as well as the rate constants k_1, k_2, β_2, and δ, but this expansion includes both positive and negative terms, and it is not immediately clear that the inequality always holds. We note that the actual expressions for Eq. S3, Eq. S4, and Eq. S5 written out in full are long and unenlightening, thus we omit them here.

There are two *separate* physical limits in which we can show that Eq. S5 is satisfied: when the production rate k and degradation rate δ of Z are small, and when the catalytic rates k_1 and k_2 for the phosphorylation and dephosphorylation reactions are large. We emphasize that both of these limits, individually, reflect conditions that we expect to be satisfied generically in the biochemical systems that we are modeling, as noted in Section 1 of the main paper.

To prove linear stability in the first case, we first observe that all of the negative terms in the expansion of the LHS of Eq. S5 are multiplied by factors of δ, whereas some of the positive terms are not. Each rate constant appears as an independent parameter, and the equilibrium concentrations appearing in Eq. S2 only depend upon the parameters k, δ through the ratio k/δ, which sets the equilibrium value of Z, $\bar{Z} = \beta_1 k/\delta$. Thus for every choice of the rate constants $\alpha_1, \alpha_2, \beta_1, \beta_2, k_1, k_2, k_{\text{on}}$, and k_{off}, and the equilibrium concentration $\bar{Z}$, there exists some $\delta_0 > 0$ such that for all δ with $\delta_0 > \delta > 0$, and with k chosen such that $\beta_1 k/\delta = \bar{Z}$, the negative terms in the expansion of Eq. S5 are small enough, compared to the positive terms, that the inequality is satisfied. This proves the linear stability of such an equilibrium solution of Eq. 10 for all positive $\delta < \delta_0$ with $k = \bar{Z}\delta/\beta_1$.

For the second case, we note that the positive terms in the expansion of Eq. S5 include terms with higher powers of k_1 and k_2 than in the negative terms. Holding all other rate constants fixed, we note that as k_1 and k_2 are varied the equilibrium concentrations are bounded and positive. Thus for large enough k_1 and k_2, the positive terms in the expansion of Eq. S5 dominate the negative terms, and the inequality is satisfied.

We can extend these results for the linear stability of equilibrium solutions of Eq. 10 with constant input to the case where $k(t)$ is time-varying using the following theorem (a special case of Theorem 10.3 in (3)): Consider the forced system of differential equations, written in vector form,

$$\frac{dx}{dt} = f(x) + \kappa(t) \tag{S6}$$

with $f = (f_1, \ldots, f_n)$ a continuously differentiable vector field, $\kappa(t) = \bar{u} + \epsilon u(t)$, where $\bar{u}$ is a constant vector in $\mathbb{R}^n$ and $u(t)$ is continuous and T-periodic: $u(t+T) = u(t)$ for all $t \geq 0$. Let $\bar{x}$ denote a steady state for the forced system when $\epsilon = 0$, that is, $f(\bar{x}) + \bar{u} = 0$, and assume that all the eigenvalues of the Jacobian matrix $J = \partial f / \partial x|_{x=\bar{x}}$ have negative real part. Then, for each small enough $\epsilon > 0$, there exists a solution $x(t)$ of Eq. S6 which is T-periodic, with $x(0)$ close to $\bar{x}$. Moreover, this solution is asymptotically stable: it attracts all close-by solutions, and solutions starting near $x(0)$ stay uniformly close to $x(t)$ for all times.

In our case the vectors are five-dimensional, with $x = (W, C_1, C_2, C, V)$, f given by the vector of derivatives of Eq. S1, and $\kappa(t) = (k(t), 0, 0, 0, 0)$.

Supporting References

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