

Supporting Information

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SI Text

Proof of the Global Nature of Q_{\max} . The characteristic equation for the eigenvalues λ of the linear system defined by Eq. 2 of the main text is

$$\prod_{n=1}^N k_n = \prod_{n=1}^N (\lambda + k_n) \quad [\text{S1}]$$

in which k_n are the rate coefficients. The maximal quality factor Q_{\max} arises for the non-zero eigenvalue and its complex conjugate with an extremum of the phase $\arg \lambda = \arctan(\frac{\Im \lambda}{\Re \lambda}) = \arctan(Q)$, and always falls within the second and third quadrants ($\pi/2 < \arg \lambda < 3\pi/2$). We find the extrema of the phase by differentiating Eq. S1 with respect to k_i

$$\sum_{n=1}^N \frac{\delta_{ni}}{k_n} = \sum_{n=1}^N \frac{\frac{\partial \lambda}{\partial k_i} + \delta_{ni}}{\lambda + k_n} \quad [\text{S2}]$$

$$\frac{1}{k_i} = \frac{\partial \lambda}{\partial k_i} \sum_{n=1}^N \frac{1}{\lambda + k_n} + \frac{1}{\lambda + k_i},$$

which we rearrange to obtain

$$\left(\frac{\partial \lambda}{\partial k_i}\right)^{-1} \frac{\lambda}{k_i(\lambda + k_i)} = S. \quad [\text{S3}]$$

The quantity $S \equiv \sum_{n=1}^N \frac{1}{\lambda + k_n}$ is independent of the index i of the rate coefficient k_i .

When taking the derivative of λ with respect to k_i , consider the magnitude and phase separately: $\frac{\partial \lambda}{\partial k_i} = \frac{\partial \ln |\lambda|}{\partial k_i} \lambda + i \frac{\partial \arg \lambda}{\partial k_i} \lambda$. We can search for the extremum of the phase by setting $\frac{\partial \arg \lambda}{\partial k_i} = 0$. With this constraint, Eq. S2 becomes

$$\frac{\partial \ln |\lambda|}{\partial k_i} k_i (\lambda + k_i) = S^{-1} \quad [\text{S4}]$$

We equate the real and imaginary parts on both sides of Eq. S4 and find that

$$\frac{\Re \lambda + k_i}{\Im \lambda} = \frac{\Re \{S^{-1}\}}{\Im \{S^{-1}\}} \quad [\text{S5}]$$

This equation defines k_i implicitly and shows that all k_i must be equal at extrema of the phase, and hence at the maximal quality factor.

Time-Dependent Gillespie Algorithm. We used a time-dependent Gillespie method to perform exact stochastic simulations. Each state i in the Markov ring is associated with a reaction $i \rightarrow i + 1$. The Gillespie approach consists of sampling the timing and identity of reaction events, one after the other. Here we outline the derivation of the algorithm in the time-dependent case.

The probability density P at time t that reaction i occurs a time delay τ later may be expressed in terms of the probability P_0 that no reaction takes place during τ and the propensities a_i of the reactions. This results in the usual equation for the joint distribution of τ and i :

$$P(\tau, i | \mathbf{n}, t) = P_0(\tau | \mathbf{n}, t) a_i(t + \tau) \quad [\text{S6}]$$

This is the same equation as that obtained with the canonical Gillespie method except that the propensities here are time-dependent. To proceed, we require an expression for the probability that no reaction takes place. P_0 satisfies the differential equation

$$\frac{dP_0(\tau | \mathbf{n}, t)}{d\tau} = -P_0(\tau | \mathbf{n}, t) \sum_{i=1}^N a_i(t + \tau). \quad [\text{S7}]$$

After integrating with boundary condition $P_0(\tau = 0) = 1$, Eq. S7 can be combined with Eq. S6 to give the full joint distribution:

$$P(\tau, i | t) = a_i(t + \tau) \exp\left(-\sum_{i=1}^N b_i(t, \tau)\right), \quad [\text{S8}]$$

which involves the time integral of the propensities:

$$b_i(t, \tau) = \int_0^\tau a_i(t + t') dt' \quad [\text{S9}]$$

For the forcing scheme considered in the main text, the integral of the time-dependent propensity a_N is given by $b_N(t, \tau) = a_N|_{F=0} \cdot (\tau + [\cos(\omega t) - \cos(\omega t + \omega \tau)]F/\omega)$.

The simulation involves drawing pairs of τ and i to advance the state of the system. Drawing the time of the next reaction requires sampling from the marginal distribution of τ , $P(\tau | t) = \sum_{i=1}^N P(\tau, i | t)$. One way in which a sample can be obtained involves the inversion of the cumulative distribution function

$$F(\tau | t) = \int_0^\tau P(\tau' | t) d\tau' = 1 - \exp\left(-\sum_{i=1}^N b_i(t, \tau)\right) \quad [\text{S10}]$$

in order to find τ . If the propensities are constant, then $b_i = \tau a_i$ is linear in τ and this step requires simply taking the logarithm of a uniformly distributed random number. For time-dependent propensities, however, the inversion must be done iteratively. We implemented a hybrid method that makes Newton-Raphson iterations except at points where the derivative approaches zero, whereupon a robust bisection method supervenes.

Once the time to the next reaction, τ^* , has been sampled, the reaction channel can be determined by drawing from the categorical variable i , conditional on τ^* :

$$P(i | \tau^*, t) = \frac{a_i(t + \tau^*)}{\sum_{i'=1}^N a_{i'}(t + \tau^*)} \quad [\text{S11}]$$

Mathematica code that implements this algorithm is available at <http://tdgillespie.sourceforge.net>.

Master Equation and its Connection to Macroscopic Dynamics. We commence with the master equation for the occupancies \mathbf{n} of the states

$$\frac{\partial P(\mathbf{n}, t)}{\partial t} = \sum_{i=1}^N \{a^{(i)}(\mathbf{n} - \mathbf{s}^{(i)}, t)P(\mathbf{n} - \mathbf{s}^{(i)}, t) - a^{(i)}(\mathbf{n}, t)P(\mathbf{n}, t)\} \quad [\text{S12}]$$

in which the sum is over the transitions (also called reaction channels) i and

$$a^{(i)}(\mathbf{n}, t) = n_i k_i(\mathbf{n}, t) \quad [\text{S13}]$$

are the propensities constructed from the occupancy n_i and the corresponding rate coefficient $k_i(\mathbf{n}, t)$. The vectors $\mathbf{s}^{(i)}$ are the columns of the stoichiometry matrix \mathbf{S} , the stoichiometric changes of the transitions. In the $N = 4$ case,

$$\mathbf{S} = \begin{bmatrix} +1 & 0 & 0 & -1 \\ -1 & +1 & 0 & 0 \\ 0 & -1 & +1 & 0 \\ 0 & 0 & -1 & +1 \end{bmatrix}. \quad [\text{S14}]$$

The conservative nature of the dynamics is clear from the fact that the columns of \mathbf{S} sum to zero. As discussed in the main text, all rates are equal to unity except the first and last. We assert that the first rate has cooperativity,

$$k_1(\mathbf{n}, t) = k_0 \left[1 + \frac{\varepsilon}{\nu} \left\{ \left(c \frac{n_1}{n_1^*} + (1-c) \frac{n_2}{n_2^*} \right)^\nu - 1 \right\} \right], \quad [\text{S15}]$$

and the last has time dependence,

$$k_N(\mathbf{n}, t) = 1 + F \sin(\omega t). \quad [\text{S16}]$$

The macroscopic limit then follows (1) by considering the ensemble average, defined as the average over all possible occupancies satisfying the constraint $\sum_{i=1}^N n_i = R$:

$$\langle X \rangle = \sum_{n_1, \dots, n_N} X P(\mathbf{n}, t). \quad [\text{S17}]$$

Taken over the master equation, we find

$$\frac{\partial \langle \mathbf{n} \rangle}{\partial t} = \sum_{n_1, \dots, n_N} \mathbf{n} \sum_{i=1}^N \{a^{(i)}(\mathbf{n} - \mathbf{s}^{(i)}, t)P(\mathbf{n} - \mathbf{s}^{(i)}, t) - a^{(i)}(\mathbf{n}, t)P(\mathbf{n}, t)\} \quad [\text{S18}]$$

$$\begin{aligned} &= \sum_{n_1, \dots, n_N} \sum_{i=1}^N \{(\mathbf{n} + \mathbf{s}^{(i)} - \mathbf{n})a^{(i)}(\mathbf{n}, t)P(\mathbf{n}, t)\} \\ &= \sum_{i=1}^N \mathbf{s}^{(i)} \langle a^{(i)}(\mathbf{n}, t) \rangle. \end{aligned}$$

In the macroscopic limit,

$$\frac{\partial \langle \mathbf{n} \rangle}{\partial t} = \sum_{i=1}^N \mathbf{s}^{(i)} a^{(i)}(\langle \mathbf{n} \rangle, t) \quad [\text{S19}]$$

in general (1).

All the rates k , including the nonlinear cooperative one defined in Eq. S15 above, are invariant under a rescaling of \mathbf{n} : $a^{(i)}(\langle \mathbf{n} \rangle, t) = a^{(i)}(\gamma \langle \mathbf{n} \rangle, t)$ for an arbitrary scaling factor γ . By defining a dynamical variable $\mathbf{x} = \langle \mathbf{n} \rangle / R$, we therefore retain the functional form of the cooperativity and arrive at Eq. 4 in the main text.

Stability Analysis About the Fixed Point. The unforced ($F = 0$) dynamical equations are:

$$\dot{\mathbf{x}} = (\mathbf{A} + \varepsilon g(x_1, x_2) \mathbf{B}) \mathbf{x} = \mathbf{h}(\mathbf{x}). \quad [\text{S20}]$$

We expand about \mathbf{x}^* :

$$\begin{aligned} \dot{\mathbf{x}} &= \mathbf{h}(\mathbf{x}^*) + \nabla \mathbf{h}(\mathbf{x}^*) [\mathbf{x} - \mathbf{x}^*] + h.o.t. \\ &= \mathbf{A} \mathbf{x}^* + (\mathbf{A} + \varepsilon \mathbf{B} \mathbf{x}^* \otimes \nabla g(x_1^*, x_2^*)) [\mathbf{x} - \mathbf{x}^*] = \mathbf{A} \mathbf{x}^* + \mathbf{J} [\mathbf{x} - \mathbf{x}^*], \end{aligned} \quad [\text{S21}]$$

in which the symbol \otimes represents the outer product of two vectors. The Jacobian is therefore

$$\mathbf{J} = \begin{bmatrix} -k_0(1+c\varepsilon) & -(1-c)\varepsilon & 0 & 1 \\ k_0(1+c\varepsilon) & (1-c)\varepsilon - 1 & 0 & 0 \\ 0 & 1 & -1 & 0 \\ 0 & 0 & 1 & -1 \end{bmatrix}, \quad [\text{S22}]$$

in which we have used the solution to \mathbf{x}^* that relates $x_2^* = k_0 x_1^*$.

1. van Kampen N (2007) *Stochastic Processes in Physics and Chemistry*, 3rd Ed. (North Holland).