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Supplemental Information

Criticality and Adaptivity in Enzymatic Networks

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Criticality and adaptivity in enzymatic networks

Supporting Material

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1 Serial enzymatic network with reversible binding

Correlation resonance also occurs in enzymatic networks with reversible binding of enzyme to substrate. To demonstrate this, we simulated the serial enzymatic network shown in Figure 1B of the main text with $\eta^+ = 100$, $\eta^- = 10$ (Supp. Fig. S1). We also fixed $\lambda = 10.9$ and varied η^+ and η^- while keeping their ratio fixed at $K_m = \eta^-/\eta^+ = 0.1$ (Supp. Fig.S2).

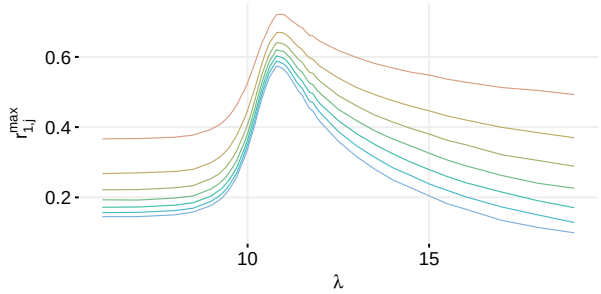

Figure S1: Maximal correlations between X_1 and $X_j, j = 2, ..., 8$ for a serial enzymatic network with reversible binding with $\eta^+ = 100$ and $\eta^- = 10$, giving $K_m = 0.1$. As in Figure 1 of the Main Text, correlation resonance is observed near the balance point $\lambda = 10$, slightly offset by finite dilution rate. Other parameters were $\mu = 1$, $\gamma = 0.01$, and $L = 80$.

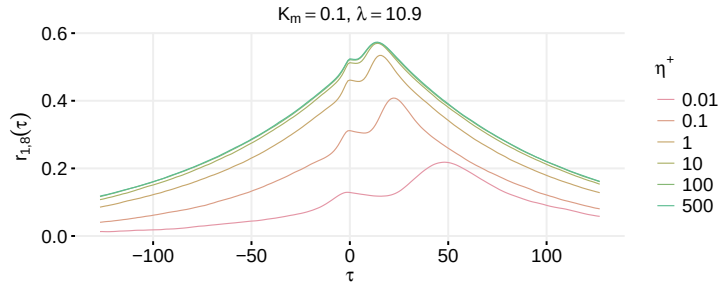

Figure S2: Correlation between X_1 and X_8 as a function of the time delay τ for different η^+ with $K_m = \eta^-/\eta^+$ held constant. The correlations are nearly independent of η^+ for $\eta^+ > 10$, but decrease for very small η^+. Other parameters were $\lambda = 10.9$, $\mu = 1$, $\gamma = 0.01$, and $L = 80$.

2 Parallel enzymatic network with different values of η^+ and η^- for each species

We tested the correlation properties of the parallel 8-node network when binding and unbinding constants of different species to the protease $\eta^\pm$ are different. Our simulations show that the correlation resonance still occurs near the same value of $\lambda \approx \mu L/n$ (see Fig. S3,A), however the magnitudes of the correlation peaks among different species vary significantly. This variability can be explained by the fact that species with higher binding and lower unbinding rate are processed preferentially and more effectively than those that have lower binding and higher unbinding rates because a higher fraction of proteases is bound to them on average. Thus the queues of the former are shorter than of the latter. This is indeed confirmed by the Fig. S3,B where the mean queue lengths $\langle Q_i \rangle$ are plotted against the individual Michaelis constants in the Briggs-Haldane form $K_i = (\mu + \eta_i^-)/\eta_i^+$. Queues with intermediate lengths are closest to criticality and should have higher cross-correlation than very short or very long queues. Figure S3,C indeed shows a strong

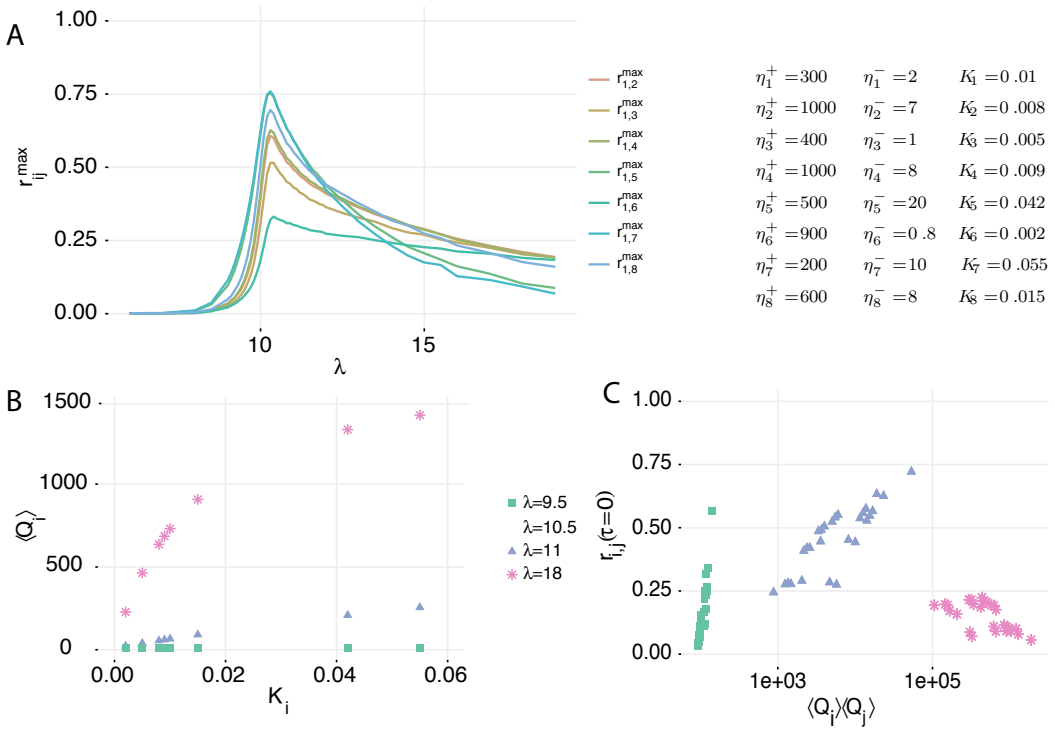

Figure S3: A. Maximum correlations $r_{1,j}^{\max}$ vs. λ in a parallel 8-node network where each protein has different values of η^+ and η^- given on the right together with corresponding $K_i = (\mu + \eta_i^-)/\eta_i^+$. Correlation resonance is still observed near the balance point $\lambda = \mu L/n$, but species with lower K_i have lower cross-correlations near the peak. B. Mean queue lengths of different species $\langle Q_i \rangle$ as functions of K_i. C. Maximum cross-correlation coefficients between different species versus the product of their mean queue lengths for different λ.

correlation between the mean queue lengths and the cross-correlation coefficients with the maximum near $\langle Q_i \rangle \approx 100$.

3 Correlation resonance in a branching network with multiple cofactors

To further test the generality of the correlation resonance phenomenon, we simulated a more complex branching network (Fig. S4A). Rather than a single cofactor, reactions in this network required one of three different cofactors C_1, C_2, C_3 which are assumed to be produced with rates $\lambda_{C_1}, \lambda_{C_2}, \lambda_{C_3}$, respectively. Furthermore, each reaction $X_i + C_k \to X_j$ had its own rate μ_{ij} . Despite these changes, the network still exhibited strong correlation resonance for the subset of species that required the limiting cofactor for processing.

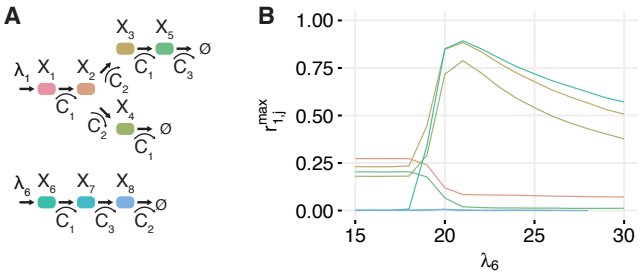

Figure S4: Correlation resonance in a branching network with multiple shared cofactors. (A) A branching network using three different shared cofactors. In this model, each reaction has its own rate rather than all rates being the same. (B) The correlation between a number of species peaks for a particular value of λ_6 with constant $\lambda_1 = 10$. For the parameters used, the cofactor C_1 is limiting, so all species processed by enzymes requiring C_1, *viz.* X_1, X_3, X_4, and X_6, are highly correlated near the balance point. Simulation parameters are $\gamma = 0.01$, $\lambda_{C_1} = \lambda_{C_2} = \lambda_{C_3} = 40$, $\eta^+ = 1000$, $\eta^- = 0$, $\mu_{12} = 1$, $\mu_{23} = 2$, $\mu_{24} = 1$, $\mu_{35} = 3$, $\mu_{4\emptyset} = 1$, $\mu_{5\emptyset} = 2$, $\mu_{67} = 2$, $\mu_{78} = 3$, and $\mu_{8\emptyset} = 2$.

4 Correlation length in a serial enzymatic network

Because the distance between enzymatic "nodes" in the serial network is a discrete variable, we use linear interpolation to define the position along the chain where the maximum correlations drops to $r_0 = 0.5$. For this, suppose $r^{\max}_{1,j+1} \le r_0 < r^{\max}_{1,j}$. Then the correlation length is defined as

$$L_c = j - 1 + \frac{r^{\max}_{1,j} - r_0}{r^{\max}_{1,j} - r^{\max}_{1,j+1}} \tag{S1}$$

When the maximum correlation between the first species and the last species exceeds the threshold (i.e., $r^{\max}_{1,n} > r_0 = 0.5$), the correlation length is assumed to have the maximum possible value $n - 1$.

5 Susceptibility of a serial enzymatic network

We computed the susceptibility of the enzymatic cascade to external perturbations using a deterministic model of an eight-species serial network, Eqs. (14)-(15) of the Main Text with $\bar{L}$ fixed. We switched the input from λ to $\lambda + \Delta\lambda$ for a certain time and computed the changes in $\bar{Q}_i$. The susceptibility is defined as $S_i = \frac{\Delta \bar{Q}_i \lambda}{\bar{Q}_{i0} \Delta\lambda}$, where $\bar{Q}_{i0}$ is the stationary value of $\bar{Q}_i$ at the input rate λ, and $\Delta\bar{Q}_i$ is the maximum change of $\bar{Q}_i$ from the baseline value $\bar{Q}_{i0}$ reached during or after the increase of λ. Similar to the cross-correlation function, the susceptibility as a function of λ exhibits a peak-like shape. For very short pulses, the maximum susceptibility occurs below the balance point. But for longer pulses and for a step function, the maximum susceptibility is achieved very close to the balance point $\lambda = 10$ (figure S5).

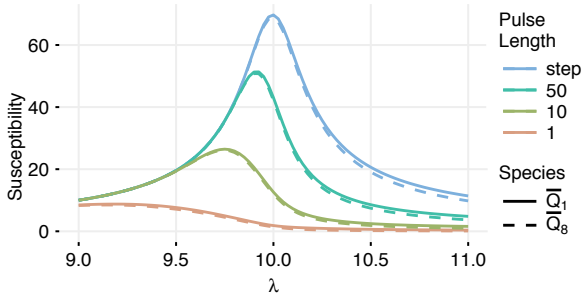

Figure S5: Susceptibility in a deterministic model of a serial enzymatic network of eight species with fixed number of shared enzymes as a function of λ. The value of λ was increased by $\Delta\lambda = 0.1$ for time intervals of length 1, 5, 50, or ∞, and the maximum changes in proteins $\bar{Q}_1, \bar{Q}_8$ were calculated. Parameters used in simulations were $L = 80$, $\gamma = 0.01$, $K_m = 0.1$, $\mu = 1$.

We also computed susceptibility for an adaptive serial network which is described by Eqs. (14)-(16) of the Main Text. Figure S6A shows that the susceptibility becomes nearly independent of λ in analogy with the cross-correlation functions. However, the absolute values of susceptibility become lower. As in stochastic simulations of adaptive networks, for values of α that are small relative to γ, the enzyme synthesis is weak, and the network remains overloaded even with adaptation. For very large α, the feedback is too quick, and the response becomes weak. This produces a trade-off between robustness to changes in λ (due to adaptation) and sensitivity to input signals, which results in an optimal value of adaptation rate α (see Fig. S6B).

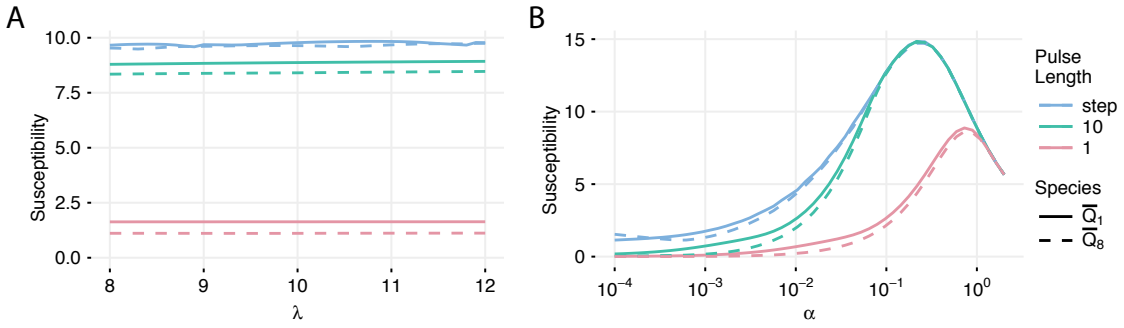

Figure S6: Susceptibility in a deterministic model of an adaptive serial enzymatic network of eight species as a function of λ with $\alpha = 0.05$ (A) and as a function of α for $\lambda = 10$ (B). The value of λ was transiently increased by $\Delta\lambda = 0.1$ for time intervals of length 1, 10, or ∞, and the sensitivity was calculated as described. Parameters used in simulations were $\gamma = 0.01$, $K_m = 0.1$, $\mu = 1$.

6 Steady-state distribution for a serial network with common enzymatic processing

Here we obtain an analytical formula for the steady-state distribution of a Markov chain associated with the serial network with shared enzymatic processing described by the reactions in Eq. 2 of the Main Text, under the instant irreversible binding assumption ($\eta^+ = +\infty, \eta^- = 0$) and in the absence of dilution ($\gamma = 0$).

For $i = 1, \ldots, n$, Q_i^b (resp. Q_i^u) denotes the number of copies of protein X_i that are bound (resp. unbound) to enzyme and L is the (fixed) total number of copies of the enzyme E, whether bound or unbound. The $(2n)$-dimensional process $\mathbf{Q} = (Q_1^u, Q_1^b, \ldots, Q_n^u, Q_n^b)$ is a continuous-time Markov chain. Under our assumptions, we will always have that the total number of bound copies of the proteins is no more than L, i.e., $Q^b = \sum_{i=1}^n Q_i^b \leq L$, and if $Q^b < L$, then $Q^u = 0$. For convenience, we denote the total number of unbound copies of the proteins by $Q^u = \sum_{i=1}^n Q_i^u$ and the total number of copies of all proteins, whether bound or unbound, by $Q = Q^b + Q^u$. We let $\mathcal{Q}$ denote the state space for $\mathbf{Q}$ and $\mathbf{q} = (q_1^u, q_1^b, \ldots, q_n^u, q_n^b)$ will denote a generic value in $\mathcal{Q}$.

We assume that the system is underloaded, i.e., $n\lambda < L\mu$, so that the average load on the enzymatic processing machinery is less than the average processing capacity. Under this assumption, the Markov chain $\mathbf{Q}$ does not explode in finite time, and indeed it will have a unique steady-state distribution.

The infinitesimal generator Γ for $\mathbf{Q}$ is given by the following for $\tilde{\mathbf{q}}, \mathbf{q} \in \mathcal{Q}$:

$$\Gamma(\tilde{\mathbf{q}}, \mathbf{q}) = \begin{cases} \lambda & \text{if } \tilde{\mathbf{q}} = \mathbf{q}^{1,u-} \text{ and } q_1^u > 0, \text{ or} \\ & \quad \text{if } \tilde{\mathbf{q}} = \mathbf{q}^{1,b-} \text{ and } q^u = 0, q_1^b > 0; \\ \mu(q_i^b + 1_{\{i \neq j\}}) \left(\frac{q_j^u + 1_{\{j \neq i+1\}}}{q^u + 1_{\{i=n\}}} \right) & \text{if } \tilde{\mathbf{q}} = \mathbf{q}^{i,b,j,u} \text{ for some } i, j \in \{1, \ldots, n\}, \text{ where} \\ & \quad q_j^b > 0, \ q^b = L \text{ and } \ q_{i+1}^u > 0 \text{ if } i < n; \\ \mu(q_i^b + 1) & \text{if } \tilde{\mathbf{q}} = \mathbf{q}^{i,b,i+1} \text{ for some } i \in \{1, \ldots, n\}, \text{ where} \\ & \quad q^u = 0, \text{ and either } i < n \text{ and } q_{i+1}^b > 0, \\ & \quad \text{or } i = n \text{ and } q^b < L; \\ 0 & \text{for all other } \tilde{\mathbf{q}} \neq \mathbf{q}; \\ -(\lambda + \mu q^b) & \text{if } \tilde{\mathbf{q}} = \mathbf{q}. \end{cases}$$

The off-diagonal entries in Γ indicate the infinitesimal rates for all possible transitions from other states into $\mathbf{q}$. To describe these, let $\mathbf{q} = (q_1^u, q_1^b, \ldots, q_n^u, q_n^b)$ and $q^u = \sum_{i=1}^n q_i^u$, $q^b = \sum_{i=1}^n q_i^b$. The first case in the description of Γ covers transitions associated with production of a new copy of protein X_1. There are two sub-cases to consider, corresponding to the possibilities for the system state $\tilde{\mathbf{q}}$ just before the transition, where in this state, either (i) all copies of the enzyme are bound to copies of the proteins, or (ii) at least one copy of the enzyme is free. For the first sub-case, $\mathbf{q}^{1,u-}$ denotes the modification of $\mathbf{q}$ obtained by subtracting one from q_1^u; note that $q_1^u > 0$ is required for this sub-case to be permissible. For the second sub-case, under our instant binding assumption, a newly produced copy of the protein X_1 will instantly bind to a copy of the enzyme. For this, $\mathbf{q}^{1,b-}$ denotes the modification of $\mathbf{q}$ obtained by subtracting one from q_1^b; note that $q_1^b > 0$ and $q^u = 0$ are required for this sub-case to be permissible. The second and third cases cover transitions due to completion of enzymatic processing of a bound copy of a protein X_i, production of a new unbound copy of protein X_{i+1} (if $i < n$) and instant binding of the freed copy of the enzyme to a copy of some protein (provided there are unbound copies available), where the protein copy is chosen at random from the pool of unbound copies of all of the proteins available just prior to the transition, unless there are no such copies, in which case the enzyme copy binds to the newly produced copy of the protein (if there is one). The second case covers such transitions when there is at least one unbound copy of a protein immediately prior to the transition, and the third case covers transitions in which there are no unbound copies of protein immediately prior to the transition. In the latter case, either a copy of protein X_i for $i < n$ completes its processing and produces a new copy of protein X_{i+1} which instantly binds to the newly freed copy of the enzyme, or a copy of protein X_n completes its processing and a copy of the enzyme becomes free and the total number of proteins shrinks by one. In the second case, assuming $q^u > 0$ or $q^u = 0$, $q^b = L$, $i = n$, the state immediately prior to a transition in which a copy of protein X_i finishes being processed and a copy of protein X_j becomes newly bound, is given by $\mathbf{q}^{i,b,j,u}$. This is obtained from $\mathbf{q}$ by adding one to q_i^b, then subtracting one from q_{i+1}^u if $i < n$, then adding one to q_j^u, and finally, subtracting one from q_j^b. For this transition to be possible, $q_{i+1}^u > 0$ is needed if $i < n$, and $q_j^b > 0$ is needed. For the transitions in the third case, assuming $q^u = 0$ and either $i < n$ or $i = n, q^b < L$, the state immediately prior to a transition, in which a copy of protein X_i finishes being processed, and a copy of protein X_{i+1} is produced and immediately binds to enzyme (if $i < n$), is denoted by $\mathbf{q}^{i,b,i+1}$. This is obtained from $\mathbf{q}$ by adding one to q_i^b and subtracting one from q_{i+1}^b if $i < n$. The latter requires $q_{i+1}^b > 0$.

We now describe the steady-state distribution for $\mathbf{Q}$. For this, given $\mathbf{q} = (q_1^u, q_1^b, \ldots, q_n^u, q_n^b) \in \mathcal{Q}$, $q^u = \sum_{i=1}^n q_i^u$, $q^b = \sum_{i=1}^n q_i^b$, and $q = q^u + q^b$, let

$$\vartheta(\mathbf{q}) \quad = \quad \pi(q)\chi_q(\mathbf{q}), \tag{S2}$$

where

$$\chi_q(\mathbf{q}) \quad = \quad \frac{q^b!}{q_1^b! \cdots q_n^b!} \frac{q^u!}{q_1^u! \cdots q_n^u!} \left(\frac{1}{n} \right)^q \tag{S3}$$

$$\pi(q) \quad = \quad c \frac{(n\lambda)^q}{\prod_{l=1}^q \phi(l)}, \tag{S4}$$

for

$$\phi(l) = \min(l, L)\mu, \tag{S5}$$

$$c^{-1} = \sum_{q=0}^{\infty} \frac{(n\lambda)^q}{\prod_{l=1}^{q} \phi(l)} = \sum_{q=0}^{L-1} \frac{\zeta^q}{q!} + \frac{\zeta^L}{L!(1-\rho)}, \tag{S6}$$

and $\zeta = \frac{n\lambda}{\mu}$, $\rho = \frac{n\lambda}{L\mu} < 1$.

Remark. In the expressions above, x^0 for $x > 0$, $0!$ and a product over an empty set of indices are all defined to equal 1. Also, note that since enzymes will be bound whenever there are sufficiently many copies of proteins to bind to, q^b, q^u can be recovered from q: $q^b = \min(q, L)$ and $q^u = (q - L)^+$.

Theorem 6.1. *Assuming $n\lambda < L\mu$, the probability distribution ϑ is the unique steady-state distribution for* $\mathbf{Q}$. *In other words, in steady-state, the distribution for Q is the same as that for the birth-death process describing the total number of molecules in an L-server first-come-first-served queue with Poisson arrivals at rate $n\lambda$, independent exponentially distributed service times with a mean of $1/\mu$, and, conditioned on Q, the distribution of the protein types is as if each molecule in the system, whether bound or unbound, independently chooses its type, where the probability that it chooses type i is $\frac{1}{n}$, $i = 1, \ldots, n$.*

Remark. It turns out that the steady-state distribution for $\mathbf{Q}$ is the same as for the enzymatic processing model in [4] when the different types of proteins there are all produced independently at rate λ and the dilution parameter γ is set to zero. Our result is almost a special case of a result for multi-class queueing networks described in Corollary 3.5 of Kelly [3]. However, the derivation in Kelly does not allow for immediate feedback to a queue as we have here. One can think of our result as a formal "limit" of Kelly's result for a two-station queueing network, in which the first station is an enzymatic processing queue and the second station is a quick service station that quickly returns a newly produced copy of protein to the enzymatic processing queue. The "limit" is as this quick service time tends to zero. Alternatively, as suggested in Exercise 5 on page 64 of Kelly [3], one can try to extend Kelly's result to a single queue with immediate feedback. That is what we do here. We note however, that for this to be true, it is important for the proof that an enzyme does not immediately bind to the copy of protein that it just produced, unless there are no other copies of protein to bind to. In other words, a newly produced copy of protein is not inserted into the queue of waiting proteins until after the freed enzyme tries to select from the pool of waiting proteins. Only if the pool is empty, does the enzyme bind to the protein just produced.

Proof. Since the Markov chain associated with $\mathbf{Q}$ is irreducible and does not explode in finite time, it suffices to show that ϑ given by (S2) satisfies the following equation (see Theorems 3.5.3 and 3.5.5 of [6]):

$$\sum_{\tilde{\mathbf{q}} \in \mathcal{Q}} \vartheta(\tilde{\mathbf{q}}) \Gamma(\tilde{\mathbf{q}}, \mathbf{q}) = 0 \quad \text{for all } \mathbf{q} \in \mathcal{Q}. \tag{S7}$$

We now verify this. In the following, in the first equality, for the sums over i and j, any term for which $\mathbf{q}^{i,b,j,u}$ or $\mathbf{q}^{i,b,i+1}$ is not in $\mathcal{Q}$ is considered to be zero. Also, indicator functions are suppressed when they

are not needed, e.g., due to the factor multiplying them being zero. For any $\mathbf{q} \in \mathcal{Q}$,

$$
\begin{aligned}
&\sum_{\tilde{\mathbf{q}} \in \mathcal{Q}} \vartheta(\tilde{\mathbf{q}}) \Gamma(\tilde{\mathbf{q}}, \mathbf{q}) \\
&= (\vartheta(\mathbf{q}^{1,u-}) 1_{\{q_1^u > 0\}} + \vartheta(\mathbf{q}^{1,b-}) 1_{\{q^u = 0, q_1^b > 0\}}) \lambda \\
&\quad + 1_{\{q^u > 0\}} \sum_{i=1}^{n} \sum_{j=1}^{n} \vartheta(\mathbf{q}^{i,b,j,u}) \mu(q_i^b + 1_{\{i \neq j\}}) \left(\frac{q_j^u + 1_{\{j \neq i+1\}}}{q^u + 1_{\{i=n\}}} \right) \\
&\quad + 1_{\{q^u = 0, q^b = L\}} \mu \left(\sum_{i=1}^{n-1} \vartheta(\mathbf{q}^{i,b,i+1})(q_i^b + 1)) + \sum_{j=1}^{n} \vartheta(\mathbf{q}^{n,b,j,u})(q_n^b + 1_{\{j \neq n\}}) \right) \\
&\quad + 1_{\{q^b < L\}} \mu \sum_{i=1}^{n} \vartheta(\mathbf{q}^{i,b,i+1})(q_i^b + 1) \\
&\quad - \vartheta(\mathbf{q})(\lambda + \mu q^b) \\
&= \lambda \pi(q-1) (\chi_{q-1}(\mathbf{q}^{1,u-}) 1_{\{q_1^u > 0\}} + \chi_{q-1}(\mathbf{q}^{1,b-}) 1_{\{q^u = 0, q_1^b > 0\}}) \\
&\quad + 1_{\{q^u > 0\}} \frac{\mu \pi(q)}{q^u} \sum_{i=1}^{n-1} \Big(\sum_{j \neq i, i+1} 1_{\{q_j^b > 0, q_{i+1}^u > 0\}} \chi_q(\mathbf{q}^{i,b,j,u})(q_i^b + 1)(q_j^u + 1) \\
&\qquad + 1_{\{q_{i+1}^u > 0\}} \chi_q(\mathbf{q}^{i,b,i,u}) q_i^b (q_i^u + 1) + 1_{\{q_{i+1}^b > 0\}} \chi_q(\mathbf{q}^{i,b,i+1,u})(q_i^b + 1) q_{i+1}^u \Big) \\
&\quad + 1_{\{q^u > 0\}} \frac{\mu \pi(q+1)}{q^u + 1} \Big(\sum_{j \neq n} 1_{\{q_j^b > 0\}} \chi_{q+1}(\mathbf{q}^{n,b,j,u})(q_n^b + 1)(q_j^u + 1) + \chi_{q+1}(\mathbf{q}^{n,b,n,u}) q_n^b (q_n^u + 1) \Big) \\
&\quad + 1_{\{q^u = 0, q^b = L\}} \mu \pi(q) \sum_{i=1}^{n-1} 1_{\{q_{i+1}^b > 0\}} \chi_q(\mathbf{q}^{i,b,i+1})(q_i^b + 1) \\
&\quad + 1_{\{q^u = 0, q^b = L\}} \mu \pi(q+1) \left(\sum_{j=1}^{n-1} 1_{\{q_j^b > 0\}} \chi_{q+1}(\mathbf{q}^{n,b,j,u})(q_n^b + 1) + \chi_{q+1}(\mathbf{q}^{n,b,n,u}) q_n^b \right) \\
&\quad + 1_{\{q^b < L\}} \mu \left(\pi(q) \sum_{i=1}^{n-1} 1_{\{q_{i+1}^b > 0\}} \chi_q(\mathbf{q}^{i,b,i+1})(q_i^b + 1) + \pi(q+1) \chi_{q+1}(\mathbf{q}^{n,b,n+1})(q_n^b + 1) \right) \\
&\quad - \pi(q) \chi_q(\mathbf{q})(\lambda + \mu q^b) \\
&= \lambda \pi(q-1) \chi_q(\mathbf{q}) n \left(\frac{q_1^u}{q^u} 1_{\{q_1^u > 0\}} + \frac{q_1^b}{q^b} 1_{\{q^u = 0, q_1^b > 0\}} \right) \\
&\quad + 1_{\{q^u > 0\}} \frac{\mu \pi(q) \chi_q(\mathbf{q})}{q^u} \sum_{i=1}^{n-1} \Big(\sum_{j \neq i, i+1} q_j^b q_{i+1}^u + q_{i+1}^u q_i^b + q_{i+1}^b q_{i+1}^u \Big) \\
&\quad + 1_{\{q^u > 0\}} \frac{\mu \pi(q+1) \chi_q(\mathbf{q})}{n} \Big(\sum_{j \neq n} q_j^b + q_n^b \Big) \\
&\quad + 1_{\{q^u = 0, q^b = L\}} \mu \chi_q(\mathbf{q}) \left(\pi(q) \sum_{i=1}^{n-1} q_{i+1}^b + \frac{\pi(q+1)}{n} \left(\sum_{j=1}^{n-1} 1_{\{q_j^b > 0\}} q_j^b + q_n^b \right) \right) \\
&\quad + 1_{\{q^b < L\}} \mu \chi_q(\mathbf{q}) \left(\pi(q) \sum_{i=1}^{n-1} 1_{\{q_{i+1}^b > 0\}} q_{i+1}^b + \frac{\pi(q+1)}{n} (q^b + 1) \right) \\
&\quad - \pi(q) \chi_q(\mathbf{q})(\lambda + \mu q^b)
\end{aligned}
$$

$$
\begin{aligned}
&= \pi(q)\chi_q(\mathbf{q})\phi(q)\left(\frac{q_1^u}{q^u}1_{\{q_1^u>0\}} + \frac{q_1^b}{q^b}1_{\{q^u=0,q_1^b>0\}}\right)\\
&\quad +1_{\{q^u>0\}}\frac{\mu\pi(q)\chi_q(\mathbf{q})q^b}{q^u}\left(\sum_{i=1}^{n-1} q_{i+1}^u + \frac{\lambda}{\phi(q+1)}q^u\right)\\
&\quad +1_{\{q^u=0,q^b=L\}}\mu\pi(q)\chi_q(\mathbf{q})\Big(q^b - q_1^b + \frac{\lambda}{\phi(q+1)}q^b\Big)\\
&\quad +1_{\{q^b<L\}}\mu\pi(q)\chi_q(\mathbf{q})\Big(q^b - q_1^b + \frac{\lambda}{\phi(q+1)}(q^b+1)\Big)\\
&\quad -\pi(q)\chi_q(\mathbf{q})(\lambda+\mu q^b)\\
&= \mu\pi(q)\chi_q(\mathbf{q})\Bigg(L\frac{q_1^u}{q^u}1_{\{q_1^u>0\}} + q_1^b 1_{\{q^u=0\}} + 1_{\{q^u>0\}}\left(L\frac{q^u-q_1^u}{q^u}+\frac{\lambda}{\mu}\right)\\
&\qquad\qquad +1_{\{q^u=0,q^b=L\}}\left(q^b - q_1^b + \frac{\lambda}{\mu}\right) + 1_{\{q^b<L\}}\Big(q^b - q_1^b + \frac{\lambda}{\mu}\Big) - \Big(\frac{\lambda}{\mu}+q^b\Big)\Bigg)\\
&= 0.
\end{aligned}
$$

In the above derivation, we have used the forms of π and χ in deriving the string of equalities. In particular, we have used the fact that $\frac{\pi(q+1)}{n} = \frac{\lambda}{\phi(q+1)}\pi(q)$ and that $\phi(q+1) = L\mu$ when $q^u > 0$ or $q^u = 0$, $q^b = L$, and $\phi(q+1) = (q^b+1)\mu$ when $q^b < L$. □

The preceding result leads to the following formulas for the steady-state moments of the total number of copies of protein i, $Q_i = Q_i^u + Q_i^b$, in terms of those for the total number of copies of all proteins, Q. Here overline denotes the mean value, SCV indicates the squared coefficient of variation (the variance divided by the square of the mean), and Var denotes the variance.

Corollary 6.1. *Suppose that the assumptions of Theorem 6.1 hold. Then, in steady-state we have the following for $i = 1, \ldots, n$,*

$$
\begin{aligned}
\overline{Q}_i &= \frac{\overline{Q}}{n}, &\text{(S8)}\\
SCV(Q_i) &= SCV(Q) - \frac{1}{\overline{Q}} + \frac{1}{\overline{Q}_i}, &\text{(S9)}
\end{aligned}
$$

and the steady-state correlation between Q_i and Q_j for $j \neq i$ is given by

$$
\begin{aligned}
r_{ij}(\tau=0) &= \frac{\overline{Q_iQ_j} - \overline{Q}_i\overline{Q}_j}{\sqrt{Var(Q_i)Var(Q_j)}}\\
&= \frac{F-1}{F-1+n}, &\text{(S10)}
\end{aligned}
$$

where $F = Var(Q)/\overline{Q}$ is the steady-state Fano factor for Q.

Proof. From Theorem 6.1, we know that conditioned on $Q = q$, since $q^b = \min(q, L)$ and $q^u = (q-L)^+$, $Q_i^b, i = 1, \ldots, n$, have a multinomial distribution with parameters $(\min(q, L); p_1, \ldots, p_n)$, independent of $Q_i^u, i = 1, \ldots, n$, which have a multinomial distribution with parameters $((q-L)^+; p_1, \ldots, p_n)$, and hence $Q_i, i = 1, \ldots, n$ have a multinomial distribution with parameters $(q; p_1, \ldots, p_n)$, where $p_i = \frac{1}{n}$ for $i = 1, \ldots, n$. The formulas for the moments and correlations of the Q_i, expressed in terms of the moments of Q, then follow from computations using the multinomial distributions. These computations are very similar to those performed in [4]. We leave the details to the reader. □

Formulas for the steady-state moments of Q, which are the steady-state moments for a one-dimensional birth-death process that describes the total number of jobs in an $M/M/L$ queue with arrival rate $n\lambda$ and

service rate μ, can be readily computed. In particular, the following formula for the steady-state mean for Q is from (2.29) in [2]. Here $\zeta = \frac{n\lambda}{\mu}$, $\rho = \frac{n\lambda}{L\mu}$ and c is the normalizing constant for the steady-state distribution of Q, as before.

$$\overline{Q} \;=\; \zeta + c\frac{\zeta^L \rho}{L!(1-\rho)^2},$$

and the second moment can be obtained using the sum of the geometric series of powers of ρ and derivatives thereof as follows:

$$\overline{Q^2} \;=\; c\left\{\sum_{q=1}^{L-1}\frac{q\zeta^q}{(q-1)!} + \frac{\zeta^L}{L!}\left(\frac{2\rho^2}{(1-\rho)^3} + \frac{(2L+1)\rho}{(1-\rho)^2} + \frac{L^2}{1-\rho}\right)\right\}.$$

7 Correlations in a serial enzymatic network below balance

We approximate the underloaded regime by the situation where the number of enzymes is truly unlimited and they bind their substrates infinitely quickly (the strong binding approximation). In this situation, all proteins are always bound to enzymes and the master equation is

$$\begin{aligned}\frac{d}{dt}P(\mathbf{q},t) &= \lambda[P(\mathbf{q}_1,t) - P(\mathbf{q},t)] \\ &+\mu\sum_{i=1}^{n}[(q_i+1)P(\mathbf{q}^i_{i+1},t) - q_i P(\mathbf{q},t)] \\ &+\gamma\sum_{i=1}^{n}[(q_i+1)P(\mathbf{q}^i,t) - q_i P(\mathbf{q},t)]\end{aligned} \tag{S11}$$

where $\mathbf{q}$ stands for a vector of numbers of substrates $(q_1,...,q_n)$. The subscript i in $\mathbf{q}_i$ or $\mathbf{q}^j_i$ indicates that the i-th component of $\mathbf{q}$ (if $i \in \{1,...,n\}$) is replaced by $q_i - 1$, and the superscript j in $\mathbf{q}^j$ or q^j_i means that q_j (if $j \in \{1,...,n\}$) is replaced by $q_j + 1$. For example, $\mathbf{q}^1_2$ denotes the vector $(q_1+1, q_2-1, q_3, ..., q_n)$.

From this master equation, it is straightforward to derive expressions for the steady-state means $\overline{Q}_i$ and same-time covariances $\mathrm{cov}(Q_i,Q_j) = \overline{Q_iQ_j} - \overline{Q}_i\overline{Q}_j$,

$$\overline{Q}_i = \frac{\alpha\mu^{i-1}}{(\mu+\gamma)^i} \tag{S12}$$

$$\mathrm{cov}(Q_i,Q_j) = \overline{Q}_i\delta_{i,j} \tag{S13}$$

where $\delta_{i,j}$ is the Kronecker symbol.

For a system of only zero- and first-order Markovian reactions, the regression theorem dictates that the time-delayed covariance is given by (see [1])

$$\mathrm{cov}(\mathbf{Q}(t),\mathbf{Q}(t+\tau)) = e^{\mathbf{B}\tau}\overline{\tilde{\mathbf{Q}}(t)\tilde{\mathbf{Q}}^T(t)} \tag{S14}$$

where $\mathbf{B}$ is the Jacobian of the corresponding linear system for the means, $\overline{\mathbf{Q}} = -\mathbf{B}^{-1}\mathbf{A}$, and $\tilde{\mathbf{Q}} = \mathbf{Q} - \overline{\mathbf{Q}}$.

For this system the Jacobian $\mathbf{B}$ has the bi-diagonal form

$$\mathbf{B} = \begin{pmatrix} -\mu-\gamma & 0 & 0 & \dots & 0 \\ \mu & -\mu-\gamma & 0 & \dots & 0 \\ 0 & \mu & -\mu-\gamma & \dots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \mu & -\mu-\gamma \end{pmatrix} \tag{S15}$$

Since $\mathbf{B}$ is a sum of commuting diagonal matrix $\mathbf{B}_0$ with elements $-(\mu+\gamma)\delta_{i,j}$ and the lower shift matrix $\mathbf{L}$ with elements $\mu\delta_{i,j+1}$, the matrix exponential $\exp(\mathbf{B}\tau)$ can be written as

$$\exp(\mathbf{B}\tau) = e^{-(\mu+\gamma)\tau}\left(\mathbf{I} + \mathbf{L}\tau + \frac{1}{2}\mathbf{L}^2\tau^2 + \ldots + \frac{1}{(n-1)!}\mathbf{L}^{n-1}\tau^{n-1}\right) \tag{S16}$$

Taking advantage of the properties of powers of shift matrices, we can easily compute the covariance

$$\mathrm{cov}(Q_1(t), Q_j(t+\tau)) = \frac{\mu^{j-1}\tau^{j-1}}{(j-1)!}\frac{\alpha}{\mu+\gamma}e^{-(\mu+\gamma)\tau} \tag{S17}$$

Then the expression for the correlation coefficient between $Q_1(t)$ and $Q_j(t+\tau)$ is

$$r_{1j}(\tau) = \frac{[\mu(\mu+\gamma)]^{\frac{j-1}{2}}\tau^{j-1}}{(j-1)!}e^{-(\mu+\gamma)\tau}. \tag{S18}$$

8 Factorized steady-state distributions for a parallel network with adaptive enzymatic processing

Here we establish a factorization result for the steady-state distribution of the $(2n+1)$-dimensional Markov chain associated with the parallel network with shared enzymatic processing and adaptation described by Eq. 8 in the Main Text. Under irreversible, instant binding ($\eta_- = 0, \eta_+ = +\infty$), when the adaptation rate ν depends only on the sum of all protein counts, this means that the steady-state correlation coefficient r_{ij} (for $\tau = 0$) can be computed from the steady-state distribution for the two-dimensional Markov chain associated with the total number of protein copies and the total number of copies of the enzyme.

For $i = 1, \ldots, n$, we let Q_i^b (resp. Q_i^u) denote the number of copies of protein X_i that are bound (resp. unbound) to enzyme and let L denote the total number of copies of the enzyme E, whether bound or unbound. Note that L is no longer constant, it is a stochastic process. Let $Q^b = \sum_{i=1}^n Q_i^b$ and $Q^u = \sum_{i=1}^n Q_i^u$, the total number of copies of bound and unbound protein, respectively, and let $Q = Q^b + Q^u$, the total number of copies of all proteins, whether bound or unbound. Note that since L denotes the total number of copies of the enzyme (bound plus unbound), we will always have that the total number of bound copies of proteins is no more than L, i.e., $Q^b \leq L$. We assume that ν is a measurable function of (Q^u, Q^b, L), in particular, this covers the case where ν just depends on Q. The $(2n+1)$-dimensional process

$$\mathbf{Z} = (Q_1^u, Q_1^b, \ldots, Q_n^u, Q_n^b, L)$$

is a continuous-time Markov chain. We let $\mathcal{Z}$ denote the state space for $\mathbf{Z}$ and $\mathbf{z} = (q_1^u, q_1^b, \ldots, q_n^u, q_n^b, \ell)$ will denote a generic value in $\mathcal{Z}$. In addition, because of our assumptions that η^+, η^-, μ and γ do not depend on i, and that ν depends only on (Q^u, Q^b, L), we have that the three-dimensional process

$$\mathbf{W} = (Q^u, Q^b, L)$$

is a continuous-time Markov chain. We denote the state space for $\mathbf{W}$ by $\mathcal{W}$ and a generic element of this space by $\mathbf{w} = (q^u, q^b, \ell)$.

We assume that the function ν is such that $\mathbf{Z}$ is irreducible and does not explode in finite time and is such that $\mathbf{W}$ has a steady-state distribution. Then $\mathbf{Z}$ has a unique steady-state distribution. We will show that the steady-state distribution for $\mathbf{Z}$ can be expressed in terms of that for $\mathbf{W}$.

The infinitesimal generator for $\mathbf{Z}$ is given by the following for $\tilde{\mathbf{z}}, \mathbf{z} \in \mathcal{Z}$:

$$\Gamma(\tilde{\mathbf{z}}, \mathbf{z}) = \begin{cases} \lambda_i & \text{if } \tilde{\mathbf{z}} = \mathbf{z}^{i,u-} \text{ for some } i \in \{1, \ldots, n\} \text{ and } q_i^u > 0, \\ \gamma(q_i^u + 1) & \text{if } \tilde{\mathbf{z}} = \mathbf{z}^{i,u+} \text{ for some } i \in \{1, \ldots, n\}, \\ \eta^+(\ell - q^b + 1)(q_i^u + 1) & \text{if } \tilde{\mathbf{z}} = \mathbf{z}^{i,u+,b-} \text{ for some } i \in \{1, \ldots, n\} \text{ and } q_i^b > 0, \\ \eta^-(q_i^b + 1) & \text{if } \tilde{\mathbf{z}} = \mathbf{z}^{i,u-,b+} \text{ for some } i \in \{1, \ldots, n\} \text{ and } q_i^u > 0, \\ \mu(q_i^b + 1) & \text{if } \tilde{\mathbf{z}} = \mathbf{z}^{i,b+} \text{ for some } i \in \{1, \ldots, n\}, \\ \gamma(q_i^b + 1) & \text{if } \tilde{\mathbf{z}} = \mathbf{z}^{i,b+,\ell+} \text{ for some } i \in \{1, \ldots, n\}, \\ \nu(q^u, q^b, \ell - 1) & \text{if } \tilde{\mathbf{z}} = \mathbf{z}^{\ell-} \text{ and } \ell > 0, \\ \gamma(\ell - q^b + 1) & \text{if } \tilde{\mathbf{z}} = \mathbf{z}^{\ell+}, \\ 0 & \text{for all other } \tilde{\mathbf{z}} \neq \mathbf{z}, \\ -(\Lambda + \gamma(q^u + \ell) & \\ \quad + \mu q^b + \eta^+ q^u(\ell - q^b) & \\ \quad + \eta^- q^b + \nu(q^u, q^b, \ell)) & \text{if } \tilde{\mathbf{z}} = \mathbf{z}. \end{cases}$$

The off-diagonal entries in Γ indicate the infinitesimal rates for all possible transitions from other states into $\mathbf{z}$. To describe these, let $\mathbf{z} = (\mathbf{q}, \ell)$ for $\mathbf{q} = (q_1^u, q_1^b, \ldots, q_n^u, q_n^b)$, and let $q^u = \sum_{i=1}^n q_i^u$, $q^b = \sum_{i=1}^n q_i^b$. The first case in the description of Γ covers transitions associated with production of a new copy of a protein. For this, $\mathbf{z}^{i,u-}$ denotes the modification of $\mathbf{z}$ obtained by subtracting one from q_i^u. Note that $q_i^u > 0$ is needed for this transition to be possible. The second case covers transitions due to dilution of an unbound copy of a protein. For this, $\mathbf{z}^{i,u+}$ denotes the modification of $\mathbf{z}$ obtained by adding one to q_i^u. The third case covers transitions due to binding of an unbound copy of a protein to an unbound copy of the enzyme. For this, $\mathbf{z}^{i,u+,b-}$ denotes the modification of $\mathbf{z}$ obtained by adding one to q_i^u and subtracting one from q_i^b, and $\ell - q^b + 1$ is the number of unbound copies of the enzyme associated with $\mathbf{z}^{i,u+,b-}$. The fourth case covers transitions due to unbinding of a copy of a protein bound to a copy of the enzyme. For this, $\mathbf{z}^{i,u-,b+}$ denotes the modification of $\mathbf{z}$ obtained by subtracting one from q_i^u and adding one to q_i^b. The fifth case covers transitions due to completion of enzymatic degradation of a bound copy of a protein. For this, $\mathbf{z}^{i,b+}$ denotes the modification of $\mathbf{z}$ obtained by adding one to q_i^b. The sixth case covers transitions due to dilution of a copy of a protein bound to a copy of the enzyme. For this, $\mathbf{z}^{i,b+,\ell+}$ denotes the modification of $\mathbf{z}$ obtained by adding one to q_i^b and to ℓ. The seventh case covers a transition due to production of a new copy of the enzyme. For this, $\mathbf{z}^{\ell-}$ denotes the modification of $\mathbf{z}$ obtained by subtracting one from ℓ. The eighth case covers a transition due to dilution of an unbound copy of the enzyme. For this, $\mathbf{z}^{\ell+}$ denotes the modification of $\mathbf{z}$ obtained by adding one to ℓ.

The infinitesimal generator for $\mathbf{W}$ is given by the following for $\tilde{\mathbf{w}}, \mathbf{w} \in \mathcal{W}$:

$$\Delta(\tilde{\mathbf{w}}, \mathbf{w}) = \begin{cases} \Lambda & \text{if } \tilde{\mathbf{w}} = \mathbf{w}^{u-} \text{ and } q^u > 0, \\ \gamma(q^u + 1) & \text{if } \tilde{\mathbf{w}} = \mathbf{w}^{u+}, \\ \eta^+(\ell - q^b + 1)(q^u + 1) & \text{if } \tilde{\mathbf{w}} = \mathbf{w}^{u+,b-} \text{ and } q^b > 0, \\ \eta^-(q^b + 1) & \text{if } \tilde{\mathbf{w}} = \mathbf{w}^{u-,b+} \text{ and } q^u > 0, \\ \mu(q^b + 1) & \text{if } \tilde{\mathbf{w}} = \mathbf{w}^{b+}, \\ \gamma(q^b + 1) & \text{if } \tilde{\mathbf{w}} = \mathbf{w}^{b+,\ell+}, \\ \nu(q^u, q^b, \ell - 1) & \text{if } \tilde{\mathbf{w}} = \mathbf{w}^{\ell-} \text{ and } \ell > 0, \\ \gamma(\ell - q^b + 1) & \text{if } \tilde{\mathbf{w}} = \mathbf{w}^{\ell+}, \\ 0 & \text{for all other } \tilde{\mathbf{w}} \neq \mathbf{w}, \\ -\left(\Lambda + \gamma(q^u + \ell)\right. & \\ \quad + \mu q^b + \eta^+ q^u(\ell - q^b) & \\ \quad \left. + \eta^- q^b + \nu(q^u, q^b, \ell)\right) & \text{if } \tilde{\mathbf{w}} = \mathbf{w}. \end{cases} \tag{S19}$$

Here $\Lambda = \sum_{i=1}^n \lambda_i$. The cases for $\Delta(\tilde{\mathbf{w}}, \mathbf{w})$, $\tilde{\mathbf{w}} \neq \mathbf{w}$, correspond to the possible transitions into $\mathbf{w}$. Writing

$\mathbf{w} = (q^u, q^b, \ell)$, these can be described as follows. The first case corresponds to a transition due to production of a new copy of a protein. For this, $\mathbf{w}^{u-}$ denotes the modification of $\mathbf{w}$ obtained by subtracting one from q^u. The second, sixth and eighth cases correspond to transitions due to dilution of an unbound copy of a protein, a protein-enzyme complex or an unbound copy of the enzyme, respectively. For this, $\mathbf{w}^{u+}$ denotes the modification of $\mathbf{w}$ obtained by adding one to q^u, $\mathbf{w}^{b+,\ell+}$ denotes the modification of $\mathbf{w}$ obtained by adding one to q^b and to ℓ, and $\mathbf{w}^{\ell+}$ denotes the modification of $\mathbf{w}$ obtained by adding one to ℓ. The third and fourth cases correspond to transitions due to binding and unbinding of a copy of a protein to a copy of the enzyme. For this, $\mathbf{w}^{u+,b-}$ denotes the modification of $\mathbf{w}$ obtained by adding one to q^u and subtracting one from q^b and $\mathbf{w}^{u-,b+}$ denotes the modification obtained by subtracting one from q^u and adding one to q^b. The fifth case corresponds to a transition due to the completion of enzymatic degradation of a bound copy of a protein. For this, $\mathbf{w}^{b+}$ denotes the modification of $\mathbf{w}$ obtained by adding one to q^b. The seventh case covers a transition due to production of a new copy of the enzyme. For this, $\mathbf{w}^{\ell-}$ denotes the modification of $\mathbf{w}$ obtained by subtracting one from ℓ.

For $i = 1, \ldots, n$, let

$$p_i = \frac{\lambda_i}{\Lambda}.$$

For each $\mathbf{z} = (\mathbf{q}, \ell) \in \mathcal{Z}$, where $\mathbf{q} = (q_1^u, q_1^b, \ldots, q_n^u, q_n^b)$, let $\mathbf{w} = (q^u, q^b, \ell)$ where $q^u = \sum_{i=1}^n q_i^u$, $q^b = \sum_{i=1}^n q_i^b$, and let

$$\chi_{\mathbf{w}}(\mathbf{q}) = \frac{q^u!}{q_1^u! \cdots q_n^u!} \frac{q^b!}{q_1^b! \cdots q_n^b!} \prod_{i=1}^n p_i^{q_i^u + q_i^b}.$$

Theorem 8.1. *Assume that π is a steady-state distribution for $\mathbf{W}$. Then the steady-state distribution for $\mathbf{Z}$ has the following factorized form:*

$$\zeta(\mathbf{z}) = \pi(\mathbf{w}) \chi_{\mathbf{w}}(\mathbf{q}), \quad \mathbf{z} \in \mathcal{Z}. \tag{S20}$$

In other words, in steady-state, conditioned on the value of $\mathbf{W}$, the distribution of the protein types is as if each protein molecule in the system, whether bound or unbound, independently chooses its type, where the probability that it chooses type i is p_i, $i = 1, \ldots, n$.

Proof. Since we assumed that $\mathbf{Z}$ is irreducible and does not explode in finite time, it suffices to show that ζ given by (S20) satisfies the following:

$$\sum_{\tilde{\mathbf{z}} \in \mathcal{Z}} \zeta(\tilde{\mathbf{z}}) \Gamma(\tilde{\mathbf{z}}, \mathbf{z}) = 0 \quad \text{for all } \mathbf{z} \in \mathcal{Z}.$$

We now verify this. In the following, $\mathbf{q}^{i,u-}$ denotes the modification of $\mathbf{q}$ obtained by subtracting one from q_i^u, $\mathbf{q}^{i,u+}$ denotes the modification of $\mathbf{q}$ obtained by adding one to q_i^u, $\mathbf{q}^{i,u+,b-}$ denotes the modification of $\mathbf{q}$ obtained by adding one to q_i^u and subtracting one from q_i^b, $\mathbf{q}^{i,u-,b+}$ denotes the modification of $\mathbf{q}$ obtained by subtracting one from q_i^u and adding one to q_i^b, $\mathbf{q}^{i,b+}$ denotes the modification of $\mathbf{q}$ obtained by adding one to q_i^b.

For any $\mathbf{z} \in \mathcal{Z}$,

$$
\begin{aligned}
&\sum_{\tilde{\mathbf{z}} \in \mathcal{Z}} \zeta(\tilde{\mathbf{z}}) \Gamma(\tilde{\mathbf{z}}, \mathbf{z}) \\
&= \sum_{i=1}^{n} \pi(\mathbf{w}^{u-}) \chi_{\mathbf{w}^{u-}}(\mathbf{q}^{i,u-}) 1_{\{q_i^u > 0\}} \lambda_i + \sum_{i=1}^{n} \pi(\mathbf{w}^{u+}) \chi_{\mathbf{w}^{u+}}(\mathbf{q}^{i,u+}) \gamma(q_i^u + 1) \\
&\quad + \sum_{i=1}^{n} \pi(\mathbf{w}^{u+,b-}) \chi_{\mathbf{w}^{u+,b-}}(\mathbf{q}^{i,u+,b-}) \eta^+(\ell - q^b + 1)(q_i^u + 1) 1_{\{q_i^b > 0\}} \\
&\quad + \sum_{i=1}^{n} \pi(\mathbf{w}^{u-,b+}) \chi_{\mathbf{w}^{u-,b+}}(\mathbf{q}^{i,u-,b+}) \eta^-(q_i^b + 1) 1_{\{q_i^u > 0\}} \\
&\quad + \sum_{i=1}^{n} \pi(\mathbf{w}^{b+}) \chi_{\mathbf{w}^{b+}}(\mathbf{q}^{i,b+}) \mu(q_i^b + 1) + \sum_{i=1}^{n} \pi(\mathbf{w}^{b+,\ell+}) \chi_{\mathbf{w}^{b+,\ell+}}(\mathbf{q}^{i,b+}) \gamma(q_i^b + 1) \\
&\quad + \pi(\mathbf{w}^{\ell-}) \chi_{\mathbf{w}}(\mathbf{q}) \nu(q^u, q^b, \ell - 1) 1_{\{\ell > 0\}} + \pi(\mathbf{w}^{\ell+}) \chi_{\mathbf{w}}(\mathbf{q}) \gamma(\ell - q^b + 1) \\
&\quad - \pi(\mathbf{w}) \chi_{\mathbf{w}}(\mathbf{q}) (\Lambda + \gamma(q^u + \ell) + \mu q^b + \eta^+ q^u (\ell - q^b) + \eta^- q^b + \nu(q^u, q^b, \ell)) \\
&= \chi_{\mathbf{w}}(\mathbf{q}) \left[\sum_{i=1}^{n} \pi(\mathbf{w}^{u-}) \frac{q_i^u}{q^u p_i} \lambda_i 1_{\{q_i^u > 0\}} + \sum_{i=1}^{n} \pi(\mathbf{w}^{u+}) p_i (q^u + 1) \gamma \right. \\
&\quad + \sum_{i=1}^{n} \pi(\mathbf{w}^{u+,b-}) \frac{(q^u + 1) q_i^b}{q^b} \eta^+(\ell - q^b + 1) 1_{\{q_i^b > 0\}} \\
&\quad + \sum_{i=1}^{n} \pi(\mathbf{w}^{u-,b+}) \frac{(q^b + 1) q_i^u}{q^u} \eta^- 1_{\{q_i^u > 0\}} \\
&\quad + \sum_{i=1}^{n} \pi(\mathbf{w}^{b+}) (q^b + 1) p_i \mu + \sum_{i=1}^{n} \pi(\mathbf{w}^{b+,\ell+}) (q^b + 1) p_i \gamma \\
&\quad + \pi(\mathbf{w}^{\ell-}) \nu(q^u, q^b, \ell - 1) 1_{\{\ell > 0\}} + \pi(\mathbf{w}^{\ell+}) \gamma(\ell - q^b + 1) \\
&\quad \left. - \pi(\mathbf{w}) (\Lambda + \gamma(q^u + \ell) + \mu q^b + \eta^+ q^u (\ell - q^b) + \eta^- q^b + \nu(q^u, q^b, \ell)) \right] \\
&= \chi_{\mathbf{w}}(\mathbf{q}) \left[\pi(\mathbf{w}^{u-}) \Lambda 1_{\{q^u > 0\}} + \pi(\mathbf{w}^{u+}) (q^u + 1) \gamma \right. \\
&\quad + \pi(\mathbf{w}^{u+,b-}) (q^u + 1) \eta^+(\ell - q^b + 1) 1_{\{q^b > 0\}} \\
&\quad + \pi(\mathbf{w}^{u-,b+}) (q^b + 1) \eta^- 1_{\{q^u > 0\}} \\
&\quad + \pi(\mathbf{w}^{b+}) (q^b + 1) \mu + \pi(\mathbf{w}^{b+,\ell+}) (q^b + 1) \gamma \\
&\quad + \pi(\mathbf{w}^{\ell-}) \nu(q^u, q^b, \ell - 1) 1_{\{\ell > 0\}} + \pi(\mathbf{w}^{\ell+}) \gamma(\ell - q^b + 1) \\
&\quad \left. - \pi(\mathbf{w}) (\Lambda + \gamma(q^u + \ell) + \mu q^b + \eta^+ q^u (\ell - q^b) + \eta^- q^b + \nu(q^u, q^b, \ell)) \right] \\
&= \chi_{\mathbf{w}}(\mathbf{q}) \sum_{\tilde{\mathbf{w}} \in \mathcal{W}} \pi(\tilde{\mathbf{w}}) \Delta(\tilde{\mathbf{w}}, \mathbf{w}) = 0,
\end{aligned}
$$

where the last equality holds because π is a steady-state distribution for $\mathbf{W}$. □

Under the assumption of Theorem 8.1, we have the following steady-state moment formulas. Let $Q_i = Q_i^u + Q_i^b$ for $i = 1, \ldots, n$. Then $Q = \sum_{i=1}^{n} Q_i$, the total number of copies of proteins in the system.

Corollary 8.1. *In steady-state, for $i = 1, \ldots, n$,*

$$\overline{Q}_i = p_i \overline{Q}, \tag{S21}$$

$$SCV(Q_i) = SCV(Q) - \frac{1}{\overline{Q}} + \frac{1}{\overline{Q}_i}, \tag{S22}$$

and the correlation between Q_i and Q_j for $j \neq i$ is given by

$$\begin{aligned} r_{ij}(\tau = 0) &= \frac{\overline{Q_i Q_j} - \overline{Q}_i \overline{Q}_j}{\sqrt{Var(Q_i) Var(Q_j)}} \\ &= \frac{F-1}{(F-1+\frac{1}{p_i})^{1/2}(F-1+\frac{1}{p_j})^{1/2}}, \end{aligned} \tag{S23}$$

where $F = Var(Q)/\overline{Q}$ is the steady-state Fano factor for Q.

Proof. From Theorem 8.1, in steady-state, conditioned on $\mathbf{W} = (Q^u, Q^b, L) = (q^u, q^b, \ell)$, we have that $(Q_i^u, i = 1, \ldots, n)$ has a multinomial distribution with parameters $(q^u; p_1, \ldots, p_n)$, independent of $(Q_i^b, i = 1, \ldots, n)$ which has a multinomial distribution with parameters $(q^b; p_1, \ldots, p_n)$, and hence $(Q_i, i = 1, \ldots, n)$ has a multinomial distribution with parameters $(q^u + q^b; p_1, \ldots, p_n)$. The formulas for the moments and correlations then follow from computations using these multinomial distributions. These computations are similar to those performed in [4]. We leave the details to the reader. □

Remarks.

1. Note that in order to compute the steady-state Fano factor for Q, one needs to know the steady-state distribution of the three-dimensional Markov chain $\mathbf{W} = (Q^u, Q^b, L)$. However, the dimension can be reduced from three to two, by assuming irreversible, instant binding ($\eta_- = 0, \eta_+ = +\infty$) and that ν depends only on Q. Then (Q, L) is a two-dimensional Markov chain.

2. The reactions in Eq. 3 of the Main Text are nearly the same as those in Eq. 6 of the Main Text when the enzyme E is replaced by the cofactor C, $\nu = \lambda_C$ and $\gamma_C = \gamma$. The only difference is that $X_i C$ degrades to nothing, whereas $X_i E$ degrades to E. Indeed, with a very slight change to the proof of Theorem 8.1, one can show that the factorization result of Theorem 8 and Corollary 8.1 hold when $\mathbf{Z}$ is the Markov chain associated with Eq. 3 of the Main Text. The only difference in the proof is that the infinitesimal generator for $\mathbf{Z}$ associated with Eq. 3 of the Main Text has $\mathbf{z}^{i,b+,\ell+}$ in place of $\mathbf{z}^{i,b+}$ in the fifth line of the description of Γ, and for the infinitesimal generator of $\mathbf{W}$ associated with Eq. 3, in the fifth line of the description of Δ, $\mathbf{w}^{b+}$ is replaced with $\mathbf{w}^{b+,\ell+}$.

3. The result of Theorem 8.1 can be generalized to time-dependent distributions in a similar manner to that in [5] to yield the following: if $\mathbf{Z}$ is initialized with a distribution of factorized form (i.e., conditioned on $\mathbf{W}$, the types of the proteins are distributed as if each protein molecule in the system chooses its type independently of the other protein molecules and such that it is of type i with probability p_i, $i = 1, \ldots, n$), then the distribution of $\mathbf{Z}$ at time t also is of factorized form.

9 Adaptive parallel queueing network with $\nu = \alpha Q_1^u$

We simulated an adaptive parallel enzymatic network with two species where the production rate of the enzyme was proportional to only the unbound molecules of one species. This network exhibited strong correlations for a wide range of λ values and for a large range of the proportionality constant α (Fig. S7).

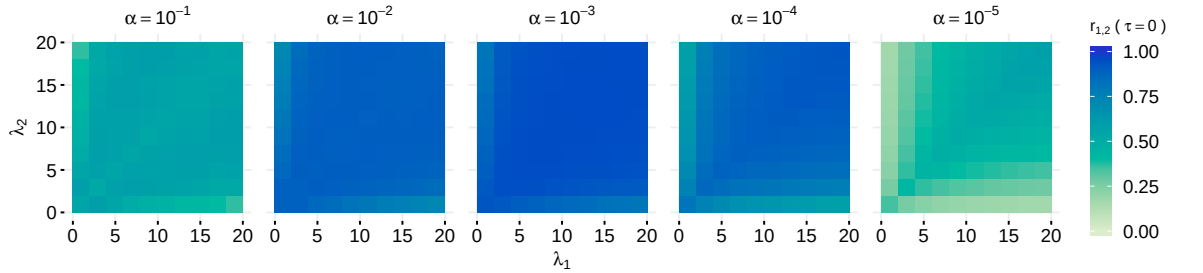

Figure S7: Adaptive parallel network with $\nu = \alpha Q_1^u$ (unbound X_1 only). In the range $10^{-4} < \alpha < 10^{-2}$, adaptation generates strong correlations for nearly all combinations of input rates λ_1 and λ_2. This includes combinations for which λ_1 is an order of magnitude greater or smaller than λ_2. Other parameters were $\mu = 1$, $\eta^+ = 1000$, $\eta^- = 0$, $\gamma = 0.01$

10 Adaptive serial queueing network with $\nu = \alpha Q_1$

We simulated a serial enzymatic adaptive queueing network where production rate of the enzyme was proportional to only one of the proteins. This network also exhibited strong correlations for a wide range of λ values (Fig. S8).

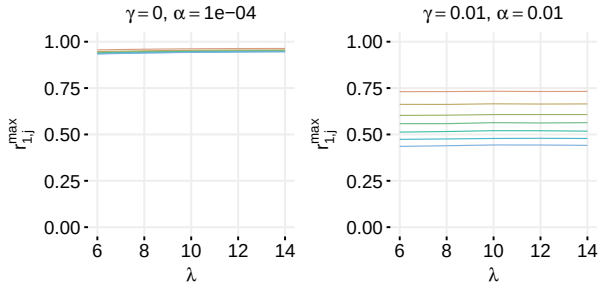

Figure S8: Maximal correlations for an adaptive serial enzymatic network with $\nu = \alpha Q_1$. In this network the synthesis rate of the enzyme is proportional to the total (enzyme-bound and unbound) number of X_1 molecules. Adaptation generates strong correlations for all values of the input rate λ shown without dilution (left) and with dilution (right). Parameters not shown are $\mu = 1$, $\eta^+ = 1000$, $\eta^- = 0$, and the dilution rate for enzymes in both cases is 0.01.

11 Adaptive serial network with $\nu = \nu_0 + \alpha Q_8$

Next we simulated an adaptive serial network with the enzyme synthesized with the rate ν proportional to the amount of total (unbound and enzyme-bound) X_8. In this network, it is possible for enzyme production to permanently cease if enzyme levels and levels of Q_8 are both zero at the same time. To avoid this scenario, we added a small basal level of enzyme production, $\nu_0 = 0.1$, which contributes a mean of $\nu_0/\gamma = 10$ enzymes. The number of enzymes required for adaptation is closer to 80, so this effect is minor. For this network, we again saw adaptation to the critical state. However, the range of usable α values is much narrower (Fig. S9).

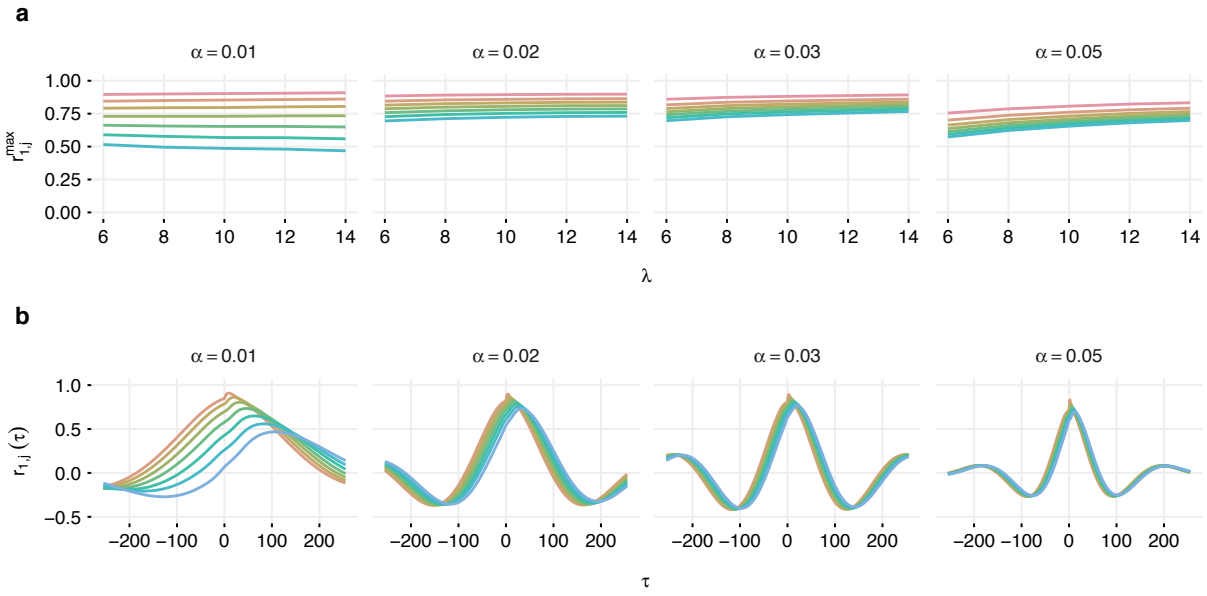

Figure S9: Adaptive serial network with $\nu = \nu_0 + \alpha Q_8$. (a) Maximum correlations between Q_1 and Q_i as a function of λ for different values of the feedback parameter α. For α near 0.02-0.03, correlations between all species are high. (b) Time dependence of correlations for different α with $\lambda = 12$. Negative correlations indicate oscillations of a frequency dependent on α. Other parameter values were $\mu = 1$, $\eta^+ = 1000$, $\eta^- = 0$, $\gamma = 0.01$, $\nu_0 = 0.01$.

12 Serial network adapting to unbound proteins

We also simulated an adaptive serial network with enzyme synthesis rate proportional only to unbound protein (i.e. $\nu = \alpha \sum_i Q_i^u$). Figure S10 illustrates that this network shows very similar behavior to the

network with rate proportional to total protein described in the Main Text.

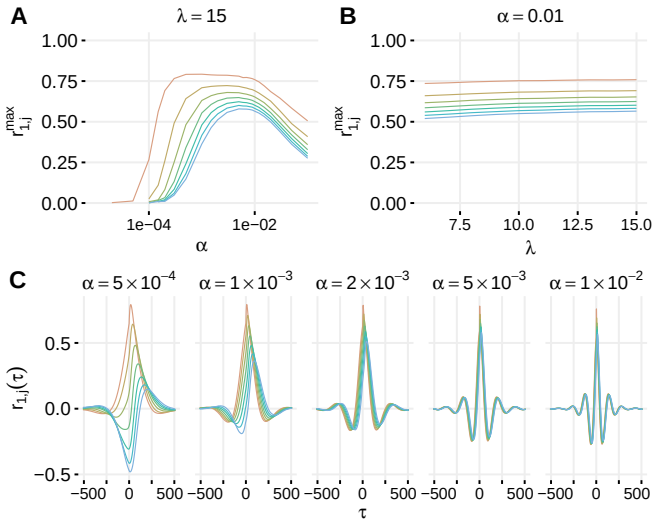

Figure S10: Adaptive serial network with enzyme synthesis proportional to total unbound protein. (A) Maximum correlations between the first species and other species for different values of α when $\lambda = 15$. (B) Maximum correlations between the first species and other species for different values of λ when $\alpha = 0.01$. (C) Time-dependence of correlations for different values of α with $\lambda = 15$. Oscillations increase in frequency as alpha is increased. Parameters for all simulations were $\gamma = 0.01$, $\mu = 1$, $\eta^+ = 1000$, and $\eta^- = 0$.

13 Power spectra of species levels

We computed the power spectral densities of species levels in serial networks. In the constant-enzyme case, there is a large DC component above balance (corresponding to the large nonzero mean of species levels in this regime) and a low DC component below balance. All three cases display similar high frequency power spectra (figure S11).

In order to compare the adaptive case to the non-adaptive case, we modified the non-adaptive network. Enzymes E were produced at a rate λ_E and diluted with other species at the rate γ, giving a mean number of enzymes $\bar{L} = \lambda_E/\gamma$. For $\bar{L} = 80$, this network had a maximum correlation at $\lambda = 11.5$. We then simulated an adaptive network with $\lambda = 11.5$ for various values of the feedback parameter α and computed power spectra (figure S12). We observed apparent amplification of very low frequencies and attenuation of slightly higher frequencies in the adaptive power spectrum, consistent with the oscillations observed in correlations of the adaptive system.

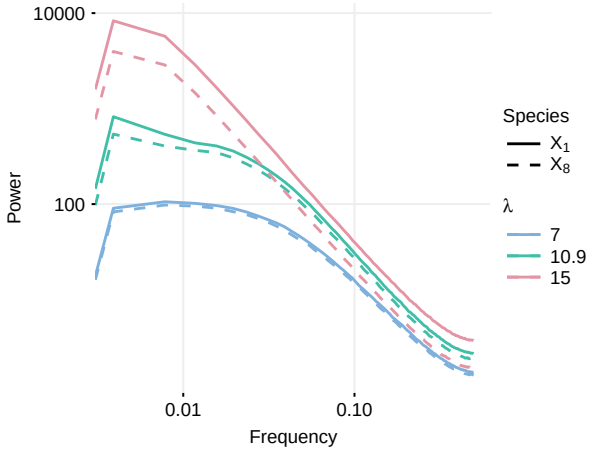

Figure S11: Power spectra in a non-adaptive serial networks below, at, and above balance ($\lambda = 7, 10.9, 15$, respectively). The DC components increase as balance is reached and surpassed, corresponding to the increase in mean species levels. All cases display similar high frequency power spectra. The spectra were estimated using Welch's method. Parameters were $L = 80$, $\gamma = 0.01$, $\mu = 1$, $\eta^+ = 1000$, and $\eta^- = 0$.

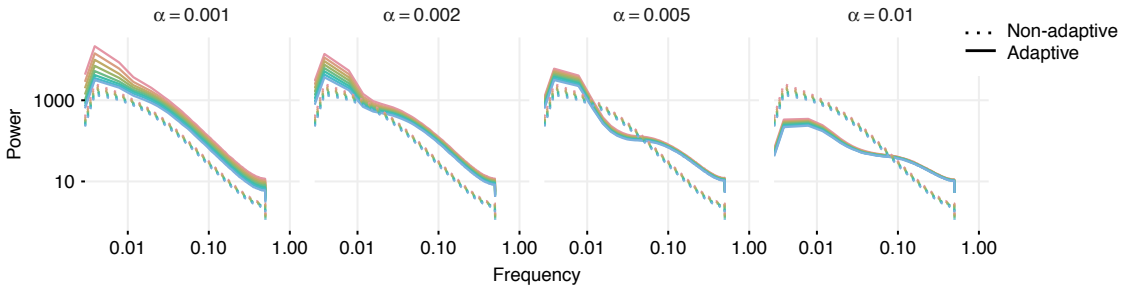

Figure S12: Power spectra in non-adaptive (with stochastic levels of enzyme, see text) and adaptive networks. Adaptive networks for four different values of α are shown; the non-adaptive spectrum is repeated on each plot for reference. The spectra were estimated using Welch's method. Parameters were $\lambda = 11.5$, $\lambda_E = 0.8$, $\gamma = 0.01$, $\mu = 1$, $\eta^+ = 1000$, and $\eta^- = 0$.

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