Supplementary Material: High chemical affinity increases the robustness of biochemical oscillations

Clara del Junco and Suriyanarayanan Vaikuntanathan
Department of Chemistry and The James Franck Institute, University of Chicago, Chicago, IL, 60637

I. THE FIRST NON-ZERO EIGENVALUE AS AN APPROXIMATION OF THE NUMBER OF COHERENT OSCILLATIONS AND PERIOD OF OSCILLATIONS

In a system such as the one pictured in Fig. 1 of the main text, we can define correlation function $C_{11}(t)$ as the conditional probability of the system being in state 1 at time t given that it began in state 1 at time 0. It is given by the solution of the master equation:

$$C_{11}(t) \equiv [\exp(\mathbf{W}t)\mathbf{P}(0)]_1 \tag{1}$$

$$= \sum_{j=0}^{N-1} P_j^{ss} e^{\phi_j t} \tag{2}$$

$$= \sum_{j=0}^{N-1} P_j^{ss} \exp[-\operatorname{Re}[\phi_j]t](\cos[\operatorname{Im}[\phi_j]t] + i\sin[\operatorname{Im}[\phi_j]t]) \tag{3}$$

where ϕ_j are the N eigenvalues of the $N \times N$ matrix $\mathbf{W}$, P_j^{ss} is the steady-state probability of finding the system in state j, and $[...]_1$ is the first element of the vector.

To see why the first non-zero eigenvalue ϕ_1, which we simply denote ϕ in the main text, is sufficient to approximate the number of coherent oscillations, we begin with the uniform case. In that case, Eq. 2 simplifies to:

$$C_{11}(t) = \frac{1}{N} \sum_{j=0}^{N-1} e^{\phi_j t} \tag{4}$$

As noted in the main text and illustrated in Fig. 1, the transition rate matrix $\mathbf{W}_0$ for this system is a circulant matrix whose eigenvalues lie in an ellipse in the complex plane with semi-major axis $a = k^+ + k^-$ and semi-minor axis $b = k^+ - k^-$ centered on the point $(-a, 0)$. When the affinity is large and $k^+/k^- \gg 1$, this effectively becomes a circle of radius $r = k^+$ centered at $(-r, 0)$.

The first eigenvalue is $\phi_0 = 0$, so the first term of the sum in Eq. 2 gives a constant contribution of $1/N$. The angle from the real axis to the jth eigenvalue ϕ_j is $2\pi j/N$. The imaginary part of ϕ_j is given by $r\sin(2\pi j/N)$, and the period of oscillations of the mth term in Eq. 3 is $T_j = 2\pi/(r\sin(2\pi j/N))$. The ratio of T_1 from the first non-zero eigenvalue to T_j from any subsequent eigenvalue is:

$$\frac{T_j}{T_1} = \frac{\sin(2\pi/N)}{\sin(2\pi j/N)} \approx \frac{2\pi/N}{2\pi j/N} = \frac{1}{j} \tag{5}$$

for $N \gg j$. The total period of the oscillations is therefore always T_1. Since $\operatorname{Re}[\phi_1] < \operatorname{Re}[\phi_j]$ for all $j > 1$, the number of oscillations of the correlation function $\mathcal{N}$ is given exactly by $|\operatorname{Im}[\phi_1]|/(-2\pi\operatorname{Re}[\phi_1]) = \mathcal{R}/2\pi$. Moreover, by the same reasoning the ratio of decay times τ_j/τ_1 where $\tau_i = -1/\operatorname{Re}[\phi_j]$ is j^2, so oscillations due to the second eigenvalue are damped out four times faster than the first, and the $j = 1$ term is the only important oscillating contribution to $C_{11}(t)$ for after a transient period.

When defects are added the eigenvalues will no longer lie on a perfect circle in the plane, and the arguments above will no longer hold exactly. For small perturbations (1 or 2 defect rates) it is reasonable to assume that the eigenvalues will not change very much and that $\mathcal{R}/2\pi \approx \mathcal{N}$. However, for large amounts of disorder it is not obvious that this will still be the case. T_j/T_1 may no longer be an integer, so that the total period of oscillations $T \neq T_1$, and moreover the period of the oscillations at short times ($T(1)$) and the period of oscillations at long times ($T(\tau)$) may not be the same. While $T(\tau)$ should be close to T_1, since all other contributions will have been damped out, $T(1)$ may not be. Yet, if the oscillator needs to be tuned to have the same period as an external signal to which it is entrained, T_1 (or T_j where j is a small integer) is likely to be the most relevant timescale.

In Fig. 2 we show histograms of the relative difference $(T(1) - T_1)/T(1)$ for different realization of matrices of size $N = 100$ with reverse rates all equal to 1, random forward rates h_i^+ chosen from a Gaussian distribution with mean

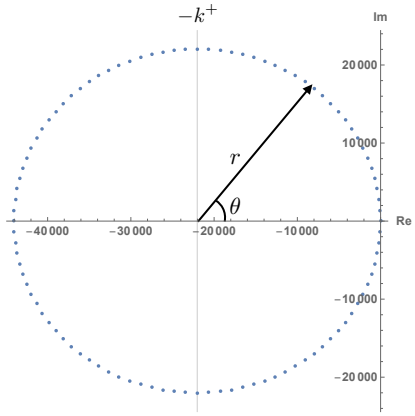

FIG. 1. Eigenvalues of a circulant matrix representing a network of size $N = 100$ with uniform rates $k^+ = e^{10}$ and $k^- = 1$.

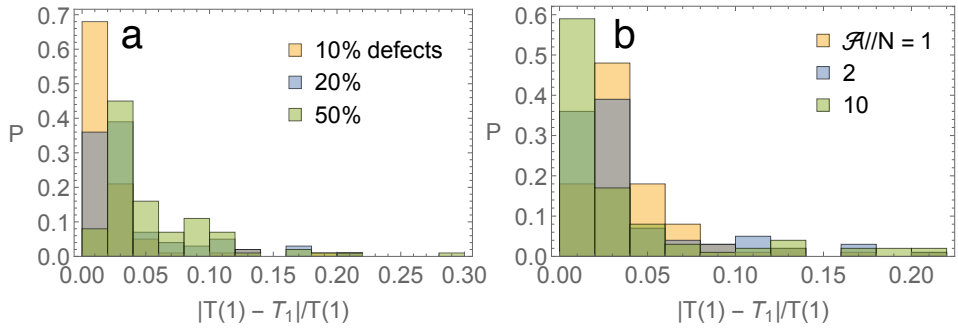

FIG. 2. Histograms of the relative difference between the first period of oscillations of the correlation function $C_{11}(t)$ ($T(1)$) and the period of oscillations due to the first eigenvalue $T_1 = 2\pi/\,\mathrm{Im}[\phi]$. $T(1)$ is the location of the first peak of $C_{11}(t)$ obtained by exponentiating the full transition rate matrix. T_1 was calculated from the first eigenvalue, which was also obtained numerically. The data for each set of parameters were obtained from 100 randomly generated matrices (a) At constant $\mathcal{A}/N = 2$ The agreement between $T(1)$ and T_1 gets worse with increasing disorder. (b) With the percent of defects held constant at 20%, the agreement between $T(1)$ and T_1 improves with increasing $\mathcal{A}/N$.

$\mu = \exp(\mathcal{A}/N)$ and variance $\sigma^2 = 0.25\exp(\mathcal{A}/N)$, and uniform forward rates k^+ set to maintain a constant $\mathcal{A}$. We emphasize that here we are considering the difference between the first term of Eq. 2 and the full correlation function, both of which are obtained by numerical diagonalization. The theory presented in the main text is another level of approximation of T_1 on top of this.

II. DETAILED CALCULATIONS

A. Transfer matrix formulation

To find the first non-zero eigenvalue ϕ of the transition matrix $\mathbf{W}$ in the disordered system, we will take advantage of the local nature of connections in this system to recast the eigenvalue problem in terms of transfer matrices.

Consider the eigenvalue equation for the circulant matrix $\mathbf{W}_0$:

$$\begin{bmatrix} -(k^- + k^+) & k^- & \dots & k^+ \\ k^+ & -(k^- + k^+) & k^- & \dots \\ \vdots & & \ddots & \\ k^- & \dots & k^+ & -(k^- + k^+) \end{bmatrix} \begin{bmatrix} f_1 \\ f_2 \\ \vdots \\ f_N \end{bmatrix} = \phi^{(0)} \begin{bmatrix} f_1 \\ f_2 \\ \vdots \\ f_N \end{bmatrix} \tag{6}$$

We can then write:

$$-(k^- + k^+)f_1 + k^- f_2 + k^+ f_N = \phi^{(0)} f_1 \tag{7}$$

$$-(k^- + k^+)f_2 + k^- f_3 + k^+ f_1 = \phi^{(0)} f_2 \tag{8}$$

and so forth, with

$$\phi^{(0)} = -(k^- + k^+) + k^- \exp(-2\pi i/N) + k^+ \exp(2\pi i/N). \tag{9}$$

Solving for f_1 in Eq. 8 gives:

$$f_1 = \frac{\phi^{(0)} + k^- + k^+}{k^+} f_2 - \frac{k^-}{k^+} f_3 \tag{10}$$

which we can also write as:

$$\begin{bmatrix} f_1 \\ f_2 \end{bmatrix} = \begin{bmatrix} \frac{\phi^{(0)}+k^-+k^+}{k^+} & -\frac{k^-}{k^+} \\ 1 & 0 \end{bmatrix} \begin{bmatrix} f_2 \\ f_3 \end{bmatrix} \equiv \mathbf{B} \begin{bmatrix} f_2 \\ f_3 \end{bmatrix}. \tag{11}$$

Thus, $\mathbf{B}$ maps the eigenvector magnitudes (f_{i-1}, f_i) to (f_i, f_{i+1}). Because the matrix $\mathbf{B}$ is the same for each link in the unicyclic network with uniform rates, we have:

$$\begin{bmatrix} f_1 \\ f_2 \end{bmatrix} = \mathbf{B}^N \begin{bmatrix} f_1 \\ f_2 \end{bmatrix} \tag{12}$$

so that $\mathbf{B}^N$ must have an eigenvalue of 1. Solving for the eigenvalues of $\mathbf{B}^N$ will give a polynomial of order $(\phi^{(0)})^N$, the N roots of which are the N eigenvalues of the transition matrix $\mathbf{W}_0$. This gives us an alternative to Eq. 6 for finding $\phi^{(0)}$.

B. One defect rate

We first consider the case of adding one set of "defect" rates $h^\pm$. To do so we replace one of the $\mathbf{B}$ matrices in the product in Eq. 12 by

$$\mathbf{A} \equiv \begin{bmatrix} \frac{\phi+h^-+h^+}{h^+} & -\frac{h^-}{h^+} \\ 1 & 0 \end{bmatrix}. \tag{13}$$

which maps the eigenvector elements on either side of the link with the defect rates. The new product of transfer matrices is:

$$\begin{bmatrix} f_1 \\ f_2 \end{bmatrix} = \mathbf{A}\mathbf{B}^{N-1} \begin{bmatrix} f_1 \\ f_2 \end{bmatrix}. \tag{14}$$

Now the $\mathbf{B}$ matrix has changed, since modifying the rates changes the value of ϕ. We write ϕ in the most general way as:

$$\phi = \phi^{(0)} + C\gamma \tag{15}$$

where C is a constant to be determined, which implies

$$\mathbf{B} = \mathbf{B}_0 + \begin{bmatrix} C\gamma/(k^+) & 0 \\ 0 & 0 \end{bmatrix} \equiv \mathbf{B}_0 + \mathbf{B}_1 \tag{16}$$

with $\mathbf{B}_0$ given by equation 11.

We now proceed with the matrix perturbation of $\mathbf{B}$. First we compute the eigenvalues (β_i) and normalized eigenvectors of $\mathbf{B}_0$. Note that since $\mathbf{B}_0$ is non-Hermitian, its right and left eigenvectors ($\langle i|$ and $|i\rangle$) are not the same and we need to compute them separately in order to get an orthonormal basis set [1]. The left eigenvectors of $\mathbf{B}_0$ are the right eigenvectors of $\mathbf{B}_0^\dagger$ (the conjugate transpose of $\mathbf{B}_0$). We obtain:

$$\beta_1^0 = e^{2\pi i/N} \qquad \beta_2^0 = (k^-/k^+)e^{-2\pi i/N} \tag{17}$$

$$|1_0\rangle = \frac{1}{c_1}(e^{2\pi i/N}, 1) \qquad |2_0\rangle = \frac{1}{c_2}((k^-/k^+)e^{-2\pi i/N}, 1) \tag{18}$$

$$\langle 1_0| = \frac{1}{c_1}(-(k^+/k^-)e^{2\pi i/N}, 1) \qquad \langle 2_0| = \frac{1}{c_2}(-e^{-2\pi i/N}, 1) \tag{19}$$

$$c_1^2 = 1 - (k^+/k^-)e^{4\pi i/N} \qquad c_2^2 = 1 - (k^-/k^+)e^{-4\pi i/N} \tag{20}$$

(it is easy to verify that this is an orthonormal basis set). Now we compute the first-order correction to the eigenvalues:

$$\beta_1^{(1)} = \langle 1_0|\mathbf{B}_1|1_0\rangle = -\frac{e^{4\pi i/N}}{c_1^2}\frac{C\gamma}{k^-}. \tag{21}$$

We choose

$$C = -c_1^2 k^- e^{-2\pi i/N} \tag{22}$$

so that

$$\beta_1^{(1)} = e^{2\pi i/N}\gamma \tag{23}$$

giving

$$\beta_1 = e^{2\pi i/N}(1+\gamma). \tag{24}$$

Similarly,

$$\beta_2 = \frac{k^-}{k^+}e^{-2\pi i/N}(1+\gamma) = e^{-\mathcal{A}/N}e^{-2\pi i/N}(1+\gamma). \tag{25}$$

We can now compute $\mathbf{B}^{N-1}$ using:

$$\mathbf{B}^{N-1} = \sum_i \beta_i^{N-1}\mathbf{X}_i^0 \tag{26}$$

where $\mathbf{X}_i^0 \equiv |i_0\rangle\langle i_0|$ is the outer product of zero-order eigenvectors. Since $\beta_2 \propto e^{-\mathcal{A}/N} < 1$, we can see that if $\mathcal{A}$ is sufficiently large, all of the terms containing β_2 will vanish. Then, Eq. 14 reduces to:

$$\begin{bmatrix} f_1 \\ f_2 \end{bmatrix} = \beta_1^{N-1}\mathbf{A}\mathbf{X}_1^{(0)}\begin{bmatrix} f_1 \\ f_2 \end{bmatrix} \tag{27}$$

where $\mathbf{X}_1^{(0)}$ is:

$$\mathbf{X}_1^{(0)} = \frac{1}{c_1^2}\begin{bmatrix} -e^{4\pi i/N}k^+/k^- & e^{2\pi i/N} \\ -e^{2\pi i/N}k^+/k^- & 1 \end{bmatrix} \tag{28}$$

1. *Comparing to exact eigenvalues of* $\mathbf{B}$

Since $\mathbf{B}$ is a two by two matrix, we can compute its exact eigenvalues and check how the error in our perturbative approximations of β_1 and β_2 scales. This will reveal what the 'perturbative parameter' in our theory is. The exact eigenvalues of $\mathbf{B}$ are:

$$\beta_{\text{exact}}^{\pm} = \frac{e^{-2\pi i/N}}{2}\left(\frac{k^-}{k^+}(1-\gamma) + e^{4\pi i/N}(1+\gamma) \pm \left[-4e^{4\pi i/N}\frac{k^-}{k^+} + \left(\frac{k^-}{k^+}(1-\gamma) + e^{4\pi i/N}(1+\gamma)\right)^2\right]^{1/2}\right) \tag{29}$$

$$= \frac{e^{-2\pi i/N}}{2}\left(e^{-\mathcal{A}/N}(1-\gamma) + e^{4\pi i/N}(1+\gamma) \pm \left[-4e^{4\pi i/N}e^{-\mathcal{A}/N} + \left(e^{-\mathcal{A}/N}(1-\gamma) + e^{4\pi i/N}(1+\gamma)\right)^2\right]^{1/2}\right) \tag{30}$$

If we ignore terms of order $e^{-\mathcal{A}/N}$ compared to terms of order 1, the expressions above simplify to:

$$\lim_{\exp(-\mathcal{A}/N)\to 0}\beta_{\text{exact}}^{\pm} = \frac{e^{2\pi i/N}}{2}\left((1+\gamma) \pm (1+\gamma)\right) \tag{31}$$

giving

$$\lim_{\exp(-\mathcal{A}/N)\to 0}\beta_{\text{exact}}^{+} = e^{2\pi i/N}(1+\gamma) = \beta_1 \qquad \lim_{\exp(-\mathcal{A}/N)\to 0}\beta_{\text{exact}}^{-} = 0 \tag{32}$$

In the limit of very high affinity, Eq. 27 is exact. Therefore, the small parameter in our theory is $\exp(-\mathcal{A}/N)$.

2. Solving for γ

We can now compute the matrix product in Eq. 27 and set its eigenvalue equal to 1 in order to solve for ϕ. Recall that $\mathbf{A}$ is also a function of ϕ, so we will also include γ in $\mathbf{A}$. In the case of a single defect, where γ is small, this effect is likely to be insignificant and it would be sufficient to approximate $\mathbf{A}$ as a function of $\phi^{(0)}$ only. However, below we will add multiple defects to the network and in that case, including γ in $\mathbf{A}$ is important. We find:

$$\mathbf{A}\mathbf{X}_1^{(0)} \equiv \mathbf{Z} = \frac{1}{c_1^2}\begin{bmatrix} da & db \\ a & b \end{bmatrix} \tag{33}$$

where

$$d(h^{\pm}) = \frac{\gamma + e^{-2i\pi/N}(k^- - h^-) + k^+e^{2i\pi/N} + h^- + h^+ - k^- - k^+}{h^+} \tag{34}$$

$$a = -e^{4\pi i/N}k^+/k^- \tag{35}$$

$$b = e^{2\pi i/N} \tag{36}$$

Since the two rows of $\mathbf{Z}$ are related by a constant, $\mathbf{Z}$ has a zero eigenvalue. The non-trivial eigenvalue ζ of $\mathbf{Z}$ is:

$$\zeta = \frac{e^{2\pi i/N}\left(k^+e^{2\pi i/N}(-C\gamma - h^- - h^+ + k^- + k^+) + h^-k^+ + h^+k^- - k^-k^+ - e^{4\pi i/N}{k^+}^2\right)}{c_1^2h^+k^-}. \tag{37}$$

We can now solve for γ using:

$$1 = \beta_1^{N-1}\zeta \tag{38}$$

$$= e^{-2\pi i/N}(1+\gamma)^{N-1}\zeta \tag{39}$$

For notational simplicity we absorb the $e^{-2\pi i/N}$ term in to ζ, letting

$$\zeta' = e^{-2\pi i/N}\zeta. \tag{40}$$

Rearranging, we have:

$$(1+\gamma) = {\zeta'}^{1/(1-N)} \tag{41}$$

We now rewrite ${\zeta'}^{1/(1-N)}$ as $\exp\big(\log\big({\zeta'}^{1/(1-N)}\big)\big) = \exp\Big(\Big(\frac{1}{1-N}\Big)\log(\zeta')\Big)$ and expand:

$$\exp\left(\left(\frac{1}{1-N}\right)\log(\zeta')\right) \approx 1 + \frac{1}{1-N}\log(\zeta') + \frac{1}{2(1-N)^2}(\log(\zeta'))^2 + \cdots, \tag{42}$$

giving

$$1 + \gamma \approx 1 + \frac{1}{1-N}\log(\zeta') + \frac{1}{2(1-N)^2}(\log(\zeta'))^2 \tag{43}$$

The 1's cancel and we get:

$$\gamma \approx \frac{1}{1-N}\log(\zeta') + \frac{1}{2(1-N)^2}(\log(\zeta'))^2. \tag{44}$$

This gives a self-consistent equation for γ (since ζ' is a function of γ). To obtain the results in the main text, we solved eq. 44 numerically by searching for roots of the equation in the neighborhood of the analytical approximation that we can obtain from expanding the logarithms in eq. 44 to first order. To obtain this analytical approximation we rewrite ζ' as:

$$\zeta' = \zeta_0' - \gamma\frac{k^+e^{2\pi i/N}C}{c_1^2h^+k^-} = \zeta_0' - \gamma\frac{k^+}{h^+} \tag{45}$$

where ζ_0' is independent of γ. We then expand the logarithm as:

$$\log(\zeta') = \log\left(\zeta_0' - \gamma\frac{k^+}{h^+}\right) \tag{46}$$

$$= \log\left(\zeta_0'\left(1 - \gamma\frac{k^+}{h^+\zeta_0'}\right)\right) \tag{47}$$

$$\approx \log(\zeta_0') - \gamma\frac{k^+}{h^+\zeta_0'} \tag{48}$$

where in the last line we have used $\log(1+x) \approx x$ for $x \ll 1$. Plugging this back in to Eq. 44 and keeping only the term linear in $1/(1-N)$ gives:

$$\gamma \approx \frac{1}{1-N}\left[\log(\zeta_0') - \gamma\frac{k^+}{h^+\zeta_0'}\right]. \tag{49}$$

C. Many Defect Rates

Now we extend our results to the case where many (m) of the rates are 'defects'. The product of transfer matrices in this case is:

$$\begin{bmatrix} f_1 \\ f_2 \end{bmatrix} = \mathbf{A}_1\mathbf{B}^{L_1}\cdots\mathbf{A}_j\mathbf{B}^{L_j}\cdots\mathbf{A}_m\mathbf{B}^{L_m}\begin{bmatrix} f_1 \\ f_2 \end{bmatrix}. \tag{50}$$

where L_j is the distance between neighboring defect rates and $\sum_j L_j = N - m$.

1. *Defect spacing $L_j \geq 1$*

Recall that

$$\mathbf{B}^{L_j} = \left(e^{-2\pi i/N}(1+\gamma)\right)^{L_j}\mathbf{X}_1^0 + \left(e^{-\mathcal{A}/N}e^{-2\pi i/N}(1+\gamma)\right)^{L_j}\mathbf{X}_2^0. \tag{51}$$

Generally, this means that eq. 50 has 2^m terms. However, if $e^{-L_j\mathcal{A}/N}$ is sufficiently large, we can ignore β_2 as we did in the case of one defect above. Then, eq. 50 reduces to a single term from which we can factorize β_1, giving:

$$\begin{bmatrix} f_1 \\ f_2 \end{bmatrix} = \beta_1^{N-m}\mathbf{A}_1\mathbf{X}_1^{(0)}\cdots\mathbf{A}_j\mathbf{X}_1^{(0)}\cdots\mathbf{A}_m\mathbf{X}_1^{(0)}\begin{bmatrix} f_1 \\ f_2 \end{bmatrix} \tag{52}$$

The affinity thus sets a correlation length for the defects; if the affinity per site ($\mathcal{A}/N$) is sufficiently large, the spacing between them does not matter. In principle, the order of the matrices in the matrix product in Eq. 52 is however still important and hence the values of ϕ and $\mathcal{R}$ depend on the order of the defects. However, our calculations are simplified due to the special symmetry of $\mathbf{Z}_j \equiv \mathbf{A}_j\mathbf{X}_1^{(0)}$ (given explicitly by Eq. 33 with the defect rates $h^\pm$ now indexed $h_j^\pm$, etc.). It turns out that the non-trivial eigenvalue of the product $\mathbf{Z}_i\mathbf{Z}_j$ is the product of the non-trivial eigenvalues of $\mathbf{Z}_i$ and $\mathbf{Z}_j$. As a result, the expression for ϕ is simply determined by the product of the non-trivial eigenvalues of the $\mathbf{Z}_j$ matrices. Therefore, as long as $L_j \geq 1 \forall j$, the order in which the defects are placed and the spacing between them becomes irrelevant as far as ϕ is concerned. We can simply extend our results for one defect to write:

$$\gamma \approx \frac{1}{m-N}\sum_{j=1}^{m}\log(\zeta_j') + \frac{1}{2(m-N)^2}\left(\sum_{j=1}^{m}\log(\zeta_j')\right)^2. \tag{53}$$

where ζ_j' is a function of $k^+, k^-, h_j^+, h_j^-, N$ given by eq. 37 and 40 but is independent of any of the other defect rates. The corresponding analytical approximation is:

$$\gamma \approx \frac{1}{m-N}\left[\sum_{j=1}^{m}\log(\zeta_{0,j}') - \gamma\frac{k^+}{\sum_{j=1}^{m}h_j^+\zeta_{0,j}'}\right]. \tag{54}$$

Our derivation depends on the distance between defect rates in the networks being at least one ($L_j \geq 1$). Nonetheless, our numerical results in the main text show that these expressions accurately predict the eigenvalues of the oscillator even when $L_j = 0$ for nearly all of the defects. We now discuss how high affinity makes this possible.

2. Defect spacing $L_j = 0$

The reason we require $L_j \geq 1$ is that the non-trivial eigenvalue of the product $\mathbf{Z}_i\mathbf{Z}_j$, where $\mathbf{Z}_j \equiv \mathbf{A}_j\mathbf{X}_1^{(0)}$, is the product of the non-trivial eigenvalues of $\mathbf{Z}_i$ and $\mathbf{Z}_j$. However, the eigenvalue of the product of $\mathbf{A}_i\mathbf{A}_j$ is *not* the product of their eigenvalues. Therefore, Eq. 53 should not be valid if there are defect rates on either side of the same node in the network. In this case we need to consider the products $\mathbf{A}_i\mathbf{A}_j$, $\mathbf{A}_i\mathbf{A}_j\mathbf{A}_k$, etc., for clusters of 2, 3, etc. defects. We find that the matrices

$$\mathbf{Z}_2^{ij} \equiv \mathbf{A}_j\mathbf{A}_i\mathbf{X}_1^{(0)} \tag{55}$$

$$\mathbf{Z}_3^{ijk} \equiv \mathbf{A}_j\mathbf{A}_i\mathbf{A}_k\mathbf{X}_1^{(0)} \tag{56}$$

$$\cdots \tag{57}$$

$$\mathbf{Z}_m^{ij\cdots} \equiv \mathbf{A}_j\mathbf{A}_i\cdots\mathbf{A}_m\mathbf{X}_1^{(0)} \tag{58}$$

have the same properties as the $\mathbf{Z}$ matrices, i.e. the eigenvalue of the product $\prod \mathbf{Z}_m^{ij\cdots}\mathbf{Z}_n^{kl\cdots}$ is the product of the eigenvalues of $\mathbf{Z}_{m,ij\cdots m}$ and $\mathbf{Z}_{n,kl\cdots n}$. Clearly there is a way of including higher and higher order correlations, but as soon as we include *any* coupling of the defects we need a lot more information about their positions. In order for the defects to be completely decoupled from one another, as indeed we find that they are even at moderate affinities $\mathcal{A}/N \approx 2$, we need the eigenvalue of the product of $\mathbf{A}_i\mathbf{A}_j$ to be the product of their eigenvalues. Let us write $\mathbf{A}_j$ as

$$\mathbf{A}_j = \begin{bmatrix} x_j & -y_j \\ 1 & 0 \end{bmatrix} \tag{59}$$

where

$$x_j = \frac{\phi + h_j^- + h_j^+}{h_j^+} = \frac{h_j^- e^{-2\pi i/N} + h_j^+ e^{-2\pi i/N} + C\gamma/N}{h_j^+} \qquad y_j = \frac{h_j^-}{h_j^+} \tag{60}$$

In the limit of large N, we have:

$$\lim_{N\to\infty} x_j = \frac{h_j^- + h_j^+}{h_j^+} = 1 + \frac{h_j^-}{h_j^+} \qquad y_j = \frac{h_j^-}{h_j^+}. \tag{61}$$

The eigenvalues of $\mathbf{A}_j$ are

$$\alpha_1^j = \frac{1}{2}\left(\sqrt{{x_j}^2 + 4y_j} + x_j\right), \alpha_2^j = 0. \tag{62}$$

The eigenvalues of the product $\mathbf{A}_j\mathbf{A}_i$ are:

$$\alpha_1^{ij} = \frac{1}{2}\left(-\sqrt{(x_ix_j + y_i + y_j)^2 - 4y_iy_j} + x_ix_j + y_i + y_j\right) \tag{63}$$

$$\alpha_2^{ij} = \frac{1}{2}\left(\sqrt{(x_ix_j + y_i + y_j)^2 - 4y_iy_j} + x_ix_j + y_i + y_j\right) \tag{64}$$

If we can ignore the y terms compared to the x terms, then these reduce to:

$$\lim_{y/x\to 0} \alpha_1^{ij} = 0 \tag{65}$$

$$\lim_{y/x\to 0} \alpha_2^{ij} = x_ix_j \tag{66}$$

and the eigenvalues of $\mathbf{A}_i$ become $\alpha_1^j = x_j, \alpha_2^j = 0$. Clearly, in this limit the eigenvalue of the product of transfer matrices is equal to the product of eigenvalues, as required, and the order of the defects will no longer matter even if they are adjacent. The limit is fulfilled when the affinity is high so that $h^-/h^+ \sim \exp(-\mathcal{A}/N)$.

Following the derivation above using x_j as the eigenvalue for the defect transfer matrices, we obtain the same result as in eqs. 53 and 54 with ζ replaced by x. Indeed, we see that in the limit that $h^-/h^+ \to 0$ and $k^-/k^+ \to 0$, ζ reduces to x. This explains how our theory can handle many adjacent defects.

III. CONSTANT AFFINITY RESULTS

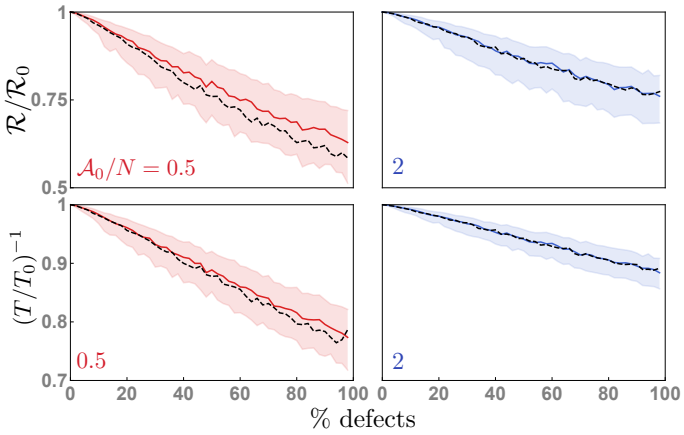

FIG. 3. Coherence $\mathcal{R}$ and period T of an oscillator with $N = 100$ states as a function of the percent of defect rates. All counterclockwise rates are set to 1. We restrict ourselves to even numbers of defect rates. Half of the clockwise defect rates $\{h_j^+\}$ are drawn from a Gaussian distribution with mean $k^+ = \exp(\mathcal{A}_0/N)$ and standard deviation $0.4k^+$, and with a lower cutoff at 0.1 so that we do not select rates that are very close to zero or negative. We set the other half of the defect rates to $\{\exp(\mathcal{A}_0/N)^2/h_j^+\}$. This prescription ensures that the affinity remains constant and equal to $\mathcal{A}_0$, while also allowing the rates to vary over at least an order of magnitude. Red curves are for $\mathcal{A}_0/N = 0.5$; blue curves $\mathcal{A}_0/N = 2$. Because the distributions of $\mathcal{R}$ and T are asymmetric, rather than plotting the mean and standard deviation of the data we plot the median (solid line) $\pm$ one quartile (shaded region) of the numerical values for 500 samples of defect rates. The dashed lines are the median theoretical predictions for 500 samples of defect rates. Our results confirm the bound in Ref. [2], as the value of $\mathcal{R}/\mathcal{R}_0$ is never greater than 1. For $\mathcal{A}_0/N = 2$, our theory is accurate even when % defects ≈ 100. Our results confirm the bound in Ref. [2], as the value of $\mathcal{R}/\mathcal{R}_0$ is never greater than 1, and show that $\mathcal{R}$ and T become more robust (spread of values decreases) and predictable at high affinity.

[1] R. A. Marcus, J. Phys. Chem. A **105**, 2612 (2001).
[2] A. C. Barato and U. Seifert, Phys. Rev. E **95**, 062409 (2017).