

Exact results for noise power spectra in linear biochemical reaction networks

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We present a simple method for determining the exact noise power spectra in linear chemical reaction networks. We apply the method to networks which are representative of biochemical processes such as gene expression and signal detection. Our results clarify how noise is transmitted by signal detection motifs, and indicate how to coarse-grain networks by the elimination of fast reactions.

I. INTRODUCTION

It is now clear that chemical noise can sometimes play a significant role in the functioning of biochemical reaction networks [1]. Such noise is implicated in the spontaneous flipping of genetic switches [2], and has been shown to have an adverse effect on the functioning of a synthetic chemical oscillator [3]. In some circumstances it has also been argued that noise can have a beneficial effect, for example in stochastic focusing [4].

Chemical noise in reaction networks can be characterised by the root mean square (rms) deviation of number of molecules from the mean. Noise is important if the rms deviation is a significant fraction of the mean. This is typically associated with systems where the mean number of molecules is rather small. Such situations are characteristic of gene regulatory networks where the concentrations of regulatory proteins can be small enough for there to be only a few molecules in the cell volume. For example, for the lac operon in *E. coli*, the lac repressor is active at concentrations where there are only 10–20 molecules present in the cell volume [5].

The mean and the rms deviation are ‘point statistics’, and have frequently been used to characterise the stochastic properties of biochemical reaction networks. In the present paper, we focus on the noise power spectra, which are a more refined characterisation of the stochastic properties. We also focus on linear reaction networks for which the noise power spectra and point statistics can be calculated exactly. In the next section, we develop a general theory for computing the noise power spectra in linear reaction networks. We relegate technical details to the Appendix. In the following sections we apply the general theory to increasingly elaborate networks which model basic processes of biochemical interest, such as gene expression and signal detection.

II. GENERAL THEORY

We define a *linear reaction network* to be a network of chemical reactions which does not involve bimolecular or higher order reactions. For such a network, the chemical

rate equations can be written as

$$\frac{dN_i}{dt} = \sum_j K_{ij} N_j + b_i \quad (1)$$

where N_i is the number of molecules of species i , K_{ij} is a matrix of rate coefficients, and b_i are source terms. Eq. (1) is a set of linear ordinary differential equations, which explains the origin of the phrase ‘linear reaction network’. Appendix A1 indicates how K_{ij} and b_i are related to the stoichiometry matrix and reaction rates which specify the network.

Let $N_i(t)$ be the instantaneous number of molecules of species i in the system. Define the mean value of N_i in steady state to be $\langle N_i \rangle$, and the mean value out of steady state to be $\langle N_i \rangle_t$. By taking moments of the chemical master equation (see Appendix), one can prove that

$$\frac{d\langle N_i \rangle_t}{dt} = \sum_j K_{ij} \langle N_j \rangle_t + b_i. \quad (2)$$

Therefore, the chemical rate equations are *exact* for a linear reaction network, provided we work with the mean quantities $\langle N_i \rangle_t$. In steady state, the mean values therefore solve

$$\sum_j K_{ij} \langle N_j \rangle + b_i = 0. \quad (3)$$

This is a system of linear simultaneous equations which can be readily solved.

We now define the deviation away from the steady state mean values to be

$$\Delta N_i(t) = N_i(t) - \langle N_i \rangle \quad (4)$$

and introduce the steady-state variance-covariance matrix

$$S_{ij} = \langle \Delta N_i \Delta N_j \rangle. \quad (5)$$

The diagonal elements of this are the variances

$$\sigma_i^2 = S_{ii} = \langle \Delta N_i^2 \rangle. \quad (6)$$

The rms deviation mentioned in the introduction is σ_i . It is often the case that $\sigma_i^2 \sim \langle N_i \rangle$ and in fact some authors define the ‘noise strength’ to be $\sigma_i^2 / \langle N_i \rangle$ although we will not explicitly use this in the present paper. This scaling

means that the relative rms deviation $\sigma_i/\langle N_i \rangle \sim 1/\sqrt{\langle N_i \rangle}$ which indicates that the relative important of noise decreases inversely with the square root of the number of molecules involved. It is the basic reason why noise is important for systems where the number of molecules is small.

As many authors have noticed [6, 7, 8], the variance-covariance matrix at steady state can also be obtained by taking moments of the chemical master equation. The details are unimportant for our arguments, and are relegated to Appendix A 1. For the remainder of the main text, we assume that the means and variance-covariance matrix have been computed. We will say that these comprise the *point statistics* of the network.

To refine the description of the steady state beyond the point statistics, we introduce the set of correlation functions

$$C_{ij}(t) = \langle \Delta N_i(0) \Delta N_j(t) \rangle. \quad (7)$$

In steady state, the value chosen for the time origin is unimportant (therefore the average could be regarded as a time average over starting times, instead of an ensemble average). The correlation functions have the properties

$$\begin{aligned} C_{ij}(0) &\rightarrow S_{ij} \quad \text{as } t \rightarrow 0, \\ C_{ij}(t) &\rightarrow 0 \quad \text{as } t \rightarrow \infty, \\ C_{ij}(t) &= C_{ji}(-t) \end{aligned} \quad (8)$$

(the first of these is not always true; see section III C). The last property shows that the autocorrelation functions are time-symmetric, $C_{ii}(t) = C_{ii}(-t)$, but it does not follow that the cross-correlation functions are time-symmetric, as is illustrated by the example in section III A.

Closely related to the autocorrelation functions are the noise power spectra, which are the central topic of study in the present paper. These are defined to be

$$P_i(\omega) = \langle |\Delta N_i(\omega)|^2 \rangle = 2 \int_0^\infty dt \cos \omega t C_{ii}(t) \quad (9)$$

where $\Delta N_i(\omega)$ is the Fourier transform of $\Delta N_i(t)$. We shall use the second form in Eq. (9) to compute the noise power spectra.

Usually the noise power spectra obey the sum rule (for an exception, see section III C),

$$\sigma_i^2 = \frac{1}{2\pi} \int_0^\infty d\omega P_i(\omega). \quad (10)$$

Now we turn to the computation of the correlation functions and the noise power spectra. In Appendix A 2 we prove that the correlation functions satisfy

$$\frac{dC_{ki}}{dt} = \sum_j K_{ij} C_{kj}. \quad (11)$$

If we subtract Eq. (3) from Eq. (2), we find that the mean deviation out of steady state obeys

$$\frac{d\langle \Delta N_i \rangle_t}{dt} = \sum_j K_{ij} \langle \Delta N_j \rangle_t. \quad (12)$$

This shows that the correlation functions decay in exactly the same way as deviations away from steady state, so that Eq. (11) is an example of a regression theorem [9].

Eq. (11) is to be solved with the initial conditions $C_{ij}(0) = S_{ij}$. A convenient approach is by the use of the Laplace transform, which allows the initial conditions to be automatically incorporated. Taking the Laplace transform of Eq. (11) shows that

$$s\tilde{C}_{ki} - S_{ki} = \sum_j K_{ij} \tilde{C}_{kj} \quad (13)$$

where

$$\tilde{C}_{ij}(s) = \int_0^\infty dt e^{-st} C_{ij}(t). \quad (14)$$

Eq. (13) is a set of linear simultaneous equations which can readily be solved for $\tilde{C}_{ij}(s)$.

The power spectra now follow almost for free. Comparing Eq. (14) with Eq. (9) shows that

$$P_i(\omega) = \tilde{C}_{ii}(i\omega) + \tilde{C}_{ii}(-i\omega), \quad (15)$$

in other words $P_i(\omega)$ is twice the real part of the analytic continuation of $\tilde{C}_{ii}(s)$ to $s = i\omega$.

Eqs. (13) and (15) are the key results of this section. They indicate how exact results for the power spectra can be obtained for an arbitrary linear reaction network by purely algebraic methods. In Appendix A 3 we prove that the same results can be obtained from the chemical Langevin equations described by Gillespie [10].

It is interesting to note that the power spectra are simpler to obtain than the correlation functions themselves, which require an inverse Fourier or Laplace transform. To undertake such a step requires in general that a polynomial be factorised, which is not always possible. In fact the route to the power spectra, via Eqs (3), (13) and (A7) in the Appendix, just involves the solution of linear simultaneous equations.

III. APPLICATIONS

A. Gene expression models

We first consider a very simple model of gene expression



which represents a birth-death process in which n copies of A are generated each time the first (birth) reaction fires. This represents the ‘burstiness’ of gene expression in prokaryotes [8]. The point statistics are

$$\langle N_A \rangle = \frac{nk}{\gamma}, \quad \sigma_A^2 = \frac{n+1}{2} \langle N_A \rangle \quad (17)$$

The chemical rate equation is $dN_A/dt = nk - \gamma N_A$ so the autocorrelation function obeys $dC_{AA}/dt = -\gamma C_{AA}$.

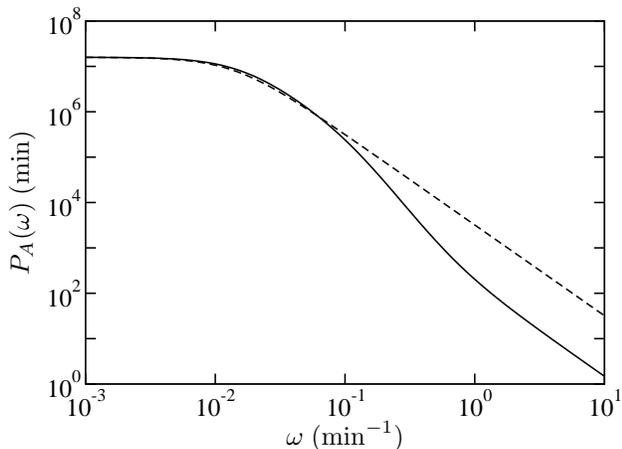


FIG. 1: Power spectra for the gene expression models in Eq. (16) (Eq. (19); dashed line) and Eq. (20) (Eq. (27); solid line). Parameters for the explicit mRNA model of Eq. (20) are $k = 2.76 \text{ min}^{-1}$, $\lambda = 0.12 \text{ min}^{-1}$, $\rho = 3.2 \text{ min}^{-1}$, and $\gamma = 0.016 \text{ min}^{-1}$. These correspond to cro in a recent model of phage lambda [11]. Parameters for the implicit mRNA model of Eq. (16) are $k = 1.36 \text{ min}^{-1}$, $n = 48.1$, $\gamma = 0.0142 \text{ min}^{-1}$. These are chosen so that the two models have matched point statistics, $\langle N_A \rangle = 4.6 \times 10^3$ and $\sigma_A / \langle N_A \rangle = 0.07$, and matching values of $P_A(0) = 1.6 \times 10^7 \text{ min}$.

The solution, and its Laplace transform, are

$$C_{AA}(t) = \sigma_A^2 e^{-\gamma t}, \quad \tilde{C}_{AA}(s) = \frac{\sigma_A^2}{s + \gamma}. \quad (18)$$

The corresponding power spectrum is

$$P_A(\omega) = \frac{2\gamma\sigma_A^2}{\omega^2 + \gamma^2}. \quad (19)$$

Now we turn to a more realistic representation of gene expression which explicitly includes mRNA, namely



The first two reactions represent generation and degradation of M which corresponds to mRNA. The second two reactions represent generation of the protein A from M and the degradation of A. This is a model which has been analysed by other workers [6, 7, 8], and we recover previously known results for the point statistics.

The mean values in steady state are

$$\langle N_M \rangle = \frac{k}{\lambda}, \quad \langle N_A \rangle = \frac{\rho}{\gamma} \langle N_M \rangle = \frac{bk}{\gamma}. \quad (21)$$

In this, $b = \rho/\lambda$ is the mean number of copies of A produced in the lifetime of one mRNA and can be taken to represent the ‘burstiness’ of gene expression. Comparing the last of Eq. (21) with the first of Eq. (17), it appears that b in the present model corresponds to n in the previous implicit mRNA model. As we shall see though,

this interpretation does not carry through to the other statistical properties.

The steady state variances and covariance are (see Appendix A 1)

$$\sigma_M^2 = \langle N_M \rangle, \quad \sigma_A^2 = \left(1 + \frac{\rho}{\gamma + \lambda}\right) \langle N_A \rangle, \quad (22)$$

$$S_{MA} = \frac{\rho \langle N_M \rangle}{\gamma + \lambda} = \frac{\gamma \langle N_A \rangle}{\gamma + \lambda}.$$

In this case, comparing Eq. (22) with Eq. (17), we see that the correspondence $b \leftrightarrow n$ fails for σ_A^2 .

Now we turn to the computation of the correlation functions and the power spectra. The chemical rate equations are

$$\frac{dN_M}{dt} = k - \lambda N_M, \quad \frac{dN_A}{dt} = \rho N_M - \gamma N_A. \quad (23)$$

The correlation functions obey the homogeneous form of these equations. Taking the Laplace transform as indicated in the previous section, we find

$$\begin{aligned} s\tilde{C}_{MM} - \sigma_M^2 &= -\lambda\tilde{C}_{MM}, \\ s\tilde{C}_{AM} - S_{AM} &= -\lambda\tilde{C}_{AM}, \\ s\tilde{C}_{MA} - S_{MA} &= \rho\tilde{C}_{MM} - \gamma\tilde{C}_{MA}, \\ s\tilde{C}_{AA} - \sigma_A^2 &= \rho\tilde{C}_{AM} - \gamma\tilde{C}_{AA}. \end{aligned} \quad (24)$$

Because $C_{MA}(t) \neq C_{AM}(t)$, there are four different Laplace-transformed correlation functions (note though that $S_{MA} = S_{AM}$). The solutions are

$$\begin{aligned} \tilde{C}_{MM} &= \frac{\sigma_M^2}{s + \lambda}, \quad \tilde{C}_{AM} = \frac{S_{AM}}{s + \lambda}, \\ \tilde{C}_{MA} &= \frac{S_{MA}}{s + \gamma} + \frac{\rho\sigma_M^2}{(s + \lambda)(s + \gamma)}, \\ \tilde{C}_{AA} &= \frac{\sigma_A^2}{s + \gamma} + \frac{\rho S_{AM}}{(s + \lambda)(s + \gamma)}. \end{aligned} \quad (25)$$

In this particular case, the inverse Laplace transforms can easily be found by the method of partial fractions. We give only the result for the cross-correlation function, which exhibits the interesting time asymmetry mentioned above,

$$C_{MA}(t) = \begin{cases} S_{MA} e^{-\gamma t} + \rho\sigma_M^2 \frac{e^{-\gamma t} - e^{-\lambda t}}{\lambda - \gamma} & (t \geq 0) \\ S_{MA} e^{-\lambda|t|} & (t \leq 0) \end{cases} \quad (26)$$

(using $C_{MA}(-t) = C_{AM}(t)$ for the second line).

Finally, the power spectra are obtained. The power spectrum for M is $P_M(\omega) = 2\lambda\langle N_M \rangle / (\omega^2 + \lambda^2)$. This might have been anticipated as a special case of the previous model with $n = 1$, since as far as M is concerned

it is undergoing a simple birth-death process. The power spectrum for A is

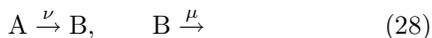
$$P_A(\omega) = \frac{2\gamma\langle N_A \rangle(\omega^2 + \lambda(\lambda + \rho))}{(\omega^2 + \lambda^2)(\omega^2 + \gamma^2)}. \quad (27)$$

With a suitable choice of n and rate coefficients k and μ , the point statistics of the previous model in Eq. (16) could be matched to the present model in Eq. (20). However, it is in general impossible to match the power spectra since the ω dependence is different. Fig. 1 shows the power spectra for the two models with matched point statistics. The presence of two correlation times in the explicit mRNA model compared to a single relaxation time for the implicit mRNA model is clearly seen.

We have gone through the calculations in some detail for these two model, but for the subsequent calculations we will only give the final results.

B. Signal detection

A very simple model of signal detection is the reaction



where A is the input signal and B is the output signal. Eq. (28) has a chemical rate equation

$$\frac{dN_B}{dt} = \nu N_A - \mu N_B + \eta. \quad (29)$$

We have included an additional noise term η in this, so it is actually a chemical Langevin equation. Taking the Fourier transform yields

$$i\omega N_B = \nu N_A - \mu N_B + \eta, \quad \text{or} \quad N_B = \frac{\nu N_A + \eta}{i\omega + \mu}. \quad (30)$$

The mean square modulus is then

$$\langle |N_B|^2 \rangle = \frac{\nu^2 \langle |N_A|^2 \rangle + \langle |\eta|^2 \rangle}{\omega^2 + \mu^2}. \quad (31)$$

We have assumed that η is uncorrelated with N_A . The theory of chemical Langevin equations [10] (see also Appendix A 3) shows that $\langle |\eta|^2 \rangle = 2\mu \langle N_B \rangle$, and for $\omega > 0$ one has $\langle |N_i|^2 \rangle = \langle |\Delta N_i|^2 \rangle$, thus finally

$$P_B(\omega) = \frac{\nu^2}{\omega^2 + \mu^2} P_A(\omega) + \frac{2\mu \langle N_B \rangle}{\omega^2 + \mu^2}. \quad (32)$$

This result has quite a striking interpretation. The total noise in the output signal is made up of an *extrinsic* contribution (first term) plus an *intrinsic* contribution (second term). Moreover, the extrinsic noise is equal the input signal noise multiplied by a low-pass filter function. This is analogous to the behaviour of a passive RC circuit element [12]. This result, in one form or another,

was derived by Paulsson [13], and by Shibata and Fujimoto [14]. We refer to it as the ‘spectral addition rule’. It is a potentially important result because it indicates that there is a trade-off between signal amplification by the detection motif and signal contamination by added intrinsic noise.

Our exact results for linear reaction networks enable us to test the spectral addition rule. We find that its validity is limited by the assumption that the intrinsic noise η is uncorrelated with the input signal N_A . In particular, if the detection motif consumes molecules of the input signal, a correlation can arise which spoils the spectral addition rule.

To demonstrate this, we now consider the effect of adjoining Eq. (28) onto the gene expression models in the previous section. We present results for the explicit mRNA model, but similar conclusions can be drawn for the implicit mRNA model too [15]. We therefore solve



We find that

$$\frac{P_A(\omega)}{\langle N_A \rangle} = \frac{2(\gamma + \nu)(\omega^2 + \lambda(\lambda + \rho))}{(\omega^2 + \lambda^2)(\omega^2 + (\gamma + \nu)^2)} \quad (34)$$

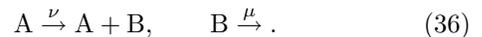
and

$$\frac{P_B(\omega)}{\langle N_B \rangle} = \frac{2\mu[(\omega^2 + \lambda^2)(\omega^2 + (\gamma + \nu)^2) + \lambda\nu\rho(\gamma + \nu)]}{(\omega^2 + \lambda^2)(\omega^2 + (\gamma + \nu)^2)(\omega^2 + \mu^2)} \quad (35)$$

with $\nu \langle N_A \rangle = \mu \langle N_B \rangle$. It is not hard to demonstrate that the spectral addition rule *fails* for these expressions.

As an aside, one can show $\sigma_B^2 / \langle N_B \rangle < \sigma_A^2 / \langle N_A \rangle$. Since the $A \rightarrow B$ reaction in Eq. (33) can be regarded as post-translational modification step, this shows that post-translational modification can reduce the noise associated with gene expression. The reason is that the post-translational modification reaction smoothes the ‘burstiness’ of gene expression by acting as a low-pass filter.

To appreciate the influence of coupling the detection reaction to the input signal noise, we now change the detection scheme so that the signal molecules A are *not* consumed, by replacing Eq. (28) with



As far as B is concerned, it is important to note that the *same* chemical Langevin equation Eq. (29) holds for this detection scheme as for the previous scheme. For this variant we find $P_A(\omega)$ is as given in Eq. (27) and

$$\frac{P_B(\omega)}{\langle N_B \rangle} = \frac{2\mu[(\omega^2 + \lambda^2)(\omega^2 + \gamma(\gamma + \nu)) + \gamma\nu\rho\lambda]}{(\omega^2 + \gamma^2)(\omega^2 + \lambda^2)(\omega^2 + \mu^2)} \quad (37)$$

One can check that in this case $P_A(\omega)$ and $P_B(\omega)$ do obey the spectral addition rule.

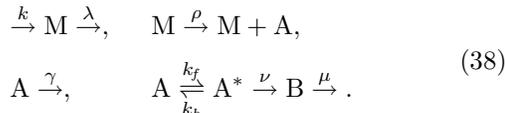
Whilst we have only demonstrated the failure of the spectral addition rule for one particular case, the result is

suggestive of the general conclusion that the spectral addition rule will only hold for detection schemes which do not consume input signal molecules. These conclusions can also be reached by analysing the chemical Langevin equations for the whole network [15].

C. Fast reactions

There is a growing literature on the adiabatic elimination of fast reactions for stochastic chemical kinetics [16, 17, 18, 19, 20, 21, 22, 23, 24, 25]. For example Kepler and Elston [16], and Shibata [18, 19], have a formalism that permits a systematic approach to the problem, involving the identification of the fast and slow variables in the system. In a similar example, Bundschuh *et al* present simulation results which support the general strategy of elimination of fast variables in terms of slow variables [20]. Here we examine the procedure for elimination of a fast equilibration reaction in the context of the *exact* results for a linear reaction network. Our results shed light on the way in which fast equilibration reactions can be systematically eliminated from a reaction network, whilst preserving the noise attributes.

To make a concrete example, we suppose that the signal detection motif of the previous section consists of a fast binding-unbinding step, followed by a slower detection step. We replace $A \rightarrow B$ by $A \rightleftharpoons A^* \rightarrow B$ where A^* represents the bound state. We suppose that the substrate which binds A is in excess, so that our reaction network is still a linear network. The reaction scheme in its totality is now



The noise statistics for this network can be solved but the expressions are rather lengthy. We therefore focus on the limit of a fast binding-unbinding reaction.

The equilibrium constant K for the binding-unbinding reaction is defined via

$$k_f = K k_b. \quad (39)$$

To take the limit of fast equilibration, we keep K finite and allow $k_b \rightarrow \infty$. The results are as follows. Let us first consider the final product species B . We find $P_B(\omega)$ is given by Eq. (37) but with ‘renormalised’ reaction rates

$$\gamma_R = \frac{\gamma}{K+1}, \quad \nu_R = \frac{K\nu}{K+1} \quad (40)$$

The same is true of the variance σ_B^2 .

We can rationalise this as follows. The chemical rate equations which involve the species in the fast equilibra-

tion reaction (A and A^*) are

$$\begin{aligned} dN_A/dt &= \rho N_M - (\gamma + k_f)N_A + k_b N_{A^*}, \\ dN_{A^*}/dt &= k_f N_A - (\nu + k_b)N_{A^*}, \\ dN_B/dt &= \nu N_{A^*} - \mu N_B. \end{aligned} \quad (41)$$

We now make a linear transformation from N_A and N_{A^*} to new variables N_X and N_Y :

$$\begin{aligned} N_X &= N_A + N_{A^*}, \\ N_Y &= K N_A - N_{A^*}. \end{aligned} \quad (42)$$

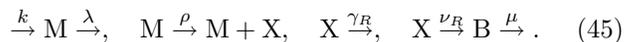
These are chosen because N_X is a *slow* variable which is conserved by the equilibration reaction, and N_Y is a *fast* variable which vanishes in steady state. In terms of these concentration variables, the chemical rate equations become

$$\begin{aligned} dN_X/dt &= \rho N_M - \frac{\gamma + K\nu}{K+1} N_X - \frac{\gamma - \nu}{K+1} N_Y, \\ dN_Y/dt + (K+1)k_b N_Y &= K\rho N_M - \frac{\gamma - \nu}{K+1} N_X, \\ dN_B/dt &= \frac{K\nu}{K+1} N_X - \frac{\nu}{K+1} N_Y - \mu N_B. \end{aligned} \quad (43)$$

The second of these shows that N_Y relaxes at a rate $\sim k_b$ to a constant $\sim 1/k_b$, for large k_b . This formalises the separation of timescales between N_Y and all the other concentration variables. In the large k_b limit therefore, $N_Y = 0$ and Eqs. (43) become

$$\begin{aligned} dN_X/dt &= \rho N_M - (\gamma_R + \nu_R)N_X, \\ dN_B/dt &= \nu_R N_X - \mu N_B. \end{aligned} \quad (44)$$

with the reaction rates given by Eq. (40). These are (a subset of) the chemical rate equations for the following reaction network



This is the same as the previously discussed scheme in Eq. (33), with the replacement $A \leftrightarrow X$. The power spectra follow from Eqs. (37) accordingly. The important point to note is that this scheme not only has the correct chemical rate equations but also has the correct noise power spectra.

Now let us turn to the power spectra for A and A^* in the original network. We find that

$$P_A(\omega) = \frac{1}{(K+1)^2} P_X(\omega), \quad P_{A^*}(\omega) = K^2 P_A(\omega). \quad (46)$$

Again these results are easy to rationalise, since inverting Eqs. (42) and setting $N_Y = 0$ shows that

$$N_A = \frac{1}{K+1} N_X, \quad N_{A^*} = K N_A \quad (47)$$

(the proportionality factors become squared when computing the noise power spectra).

For the variances, σ_A^2 and $\sigma_{A^*}^2$, we find a different story though. In fact, in the limit $k_b \rightarrow \infty$, we find a *breakdown* of the sum rule in Eq. (10). The reason is that

$$\lim_{k_b \rightarrow \infty} \int_0^\infty d\omega P_i(\omega) \neq \int_0^\infty d\omega \lim_{k_b \rightarrow \infty} P_i(\omega) \quad (48)$$

for $i = A$ and A^* . The sum rule always holds for the left hand side of Eq. (48), but the limiting power spectra are defined in terms of the right hand side of Eq. (48). (As an aside, we find that the sum rule is satisfied for $P_{A+A^*}(\omega)$, which is equal to $P_X(\omega)$, confirming that the effect is confined to the individual species in the fast equilibration reaction.) To handle this kind of situation, we define a ‘sum rule deficit’

$$\Delta\sigma_i^2 \equiv \sigma_i^2 - \frac{1}{2\pi} \int_0^\infty d\omega P_i(\omega). \quad (49)$$

For the present situation, we find that

$$\Delta\sigma_A^2 = \Delta\sigma_{A^*}^2 = \frac{\langle N_{A^*} \rangle}{K+1}. \quad (50)$$

Interestingly, the same result is found for *all* situations involving a fast equilibration reaction which we have examined.

The origin of the sum rule deficit lies in the noise generated by the fast equilibration reaction. Formally, at any finite k_b we can define the contribution of the equilibration reaction to the total noise of species i to be

$$\Delta P_i(\omega) = P_i(\omega) - \lim_{k_b \rightarrow \infty} P_i(\omega). \quad (51)$$

For $i = A$ and A^* , one has that $\Delta P_i(\omega) \rightarrow 0$ as $k_b \rightarrow \infty$, at any finite value of ω , but that $\int_0^\infty \Delta P_i(\omega) \rightarrow 2\pi\Delta\sigma_i^2$. The reason is that, whilst $\Delta P_i(\omega)$ vanishes as $1/k_b$, it extends over a frequency range $0 < \omega \lesssim k_b$, so the total integrated contribution does not vanish in the limit $k_b \rightarrow \infty$. In words, the equilibration reaction contributes high-frequency noise which vanishes at any particular finite frequency in the limit of infinitely fast equilibration, but makes a net non-zero contribution to the total integrated noise.

The universal magnitude of the sum rule deficit can be understood by analysing the simplest of all equilibration reactions, namely



Solving for the point statistics in this system one has $K\langle N_A \rangle = \langle N_{A^*} \rangle$ and, from Eqs. (A7) in the Appendix,

$$\begin{aligned} -K\sigma_A^2 + S_{AA^*} + \langle N_{A^*} \rangle &= 0 \\ -KS_{AA^*} + \sigma_{A^*}^2 + K\sigma_A^2 - S_{AA^*} - 2\langle N_{A^*} \rangle &= 0 \\ KS_{AA^*} - \sigma_{A^*}^2 + \langle N_{A^*} \rangle &= 0 \end{aligned} \quad (53)$$

These equations are linearly dependent and cannot by themselves be solved for the elements of the variance-covariance matrix. The reason is that the slow variable

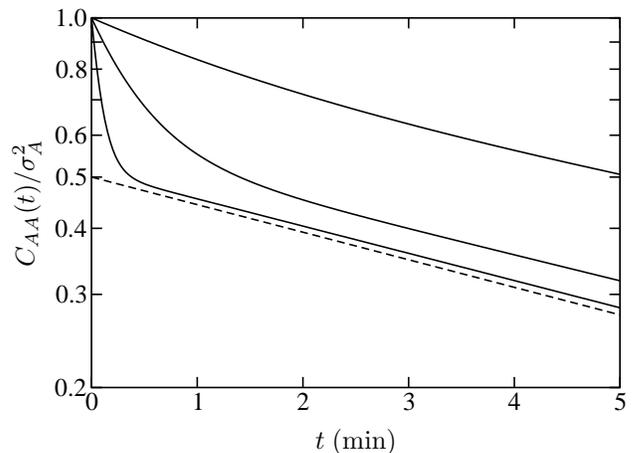


FIG. 2: Correlation function for the model in Eq. (57), with $\gamma_R = K\gamma/(K+1) = 0.12 \text{ min}^{-1}$ and $K = 1$. The lines are for $k_b = 0.2, 1.0, 5.0 \text{ min}^{-1}$, and $k_b \rightarrow \infty$ (dashed line).

$N_A + N_{A^*}$ is exactly conserved by the reaction scheme in Eq. (52). However this implies that $\Delta N_A = -\Delta N_{A^*}$ and so $\sigma_A^2 = \sigma_{A^*}^2 = -S_{AA^*}$. These are consistent with Eqs. (53), which can now be solved to get

$$\sigma_A^2 = \sigma_{A^*}^2 = -S_{AA^*} = \frac{\langle N_{A^*} \rangle}{K+1}. \quad (54)$$

This explains the universal value found for the sum rule deficit above.

To complete the discussion, we turn finally to the correlation functions where the analogue of Eq. (48) is

$$\lim_{k_b \rightarrow \infty} \lim_{t \rightarrow 0} C_{ii}(t) \neq \lim_{t \rightarrow 0} \lim_{k_b \rightarrow \infty} C_{ii}(t) \quad (55)$$

for $i = A$ and A^* . The left hand side is always equal to σ_i^2 . One can show that the difference between the two sides gives an alternative expression for the sum rule deficit,

$$\Delta\sigma_i^2 = \sigma_i^2 - \lim_{t \rightarrow 0} C_{ii}(t). \quad (56)$$

This can be made clear by another example. Consider



The steady state point statistics, which hold for arbitrary k_b , are $\langle N_A \rangle = (k_b + \gamma)\langle N_{A^*} \rangle/k_f$, $\langle N_{A^*} \rangle = k/\gamma$, $\sigma_A^2/\langle N_A \rangle = \sigma_{A^*}^2/\langle N_{A^*} \rangle = 1$, $S_{AA^*} = 0$. We solve for the correlation functions using the methods described in section II. Similar results are obtained for both A and A^* so we report results only for species A . The Laplace-transformed autocorrelation function is

$$\tilde{C}_{AA}(s) = \frac{\sigma_A^2(s + \gamma + k_b)}{s^2 + (\gamma + k_f + k_b)s + \gamma k_f}. \quad (58)$$

Writing

$$s^2 + (\gamma + k_f + k_b)s + \gamma k_f = (s + k_+)(s + k_-) \quad (59)$$

allows us to perform the inverse Laplace transform by the method of partial fractions. The decay rates k_{\pm} are given by

$$k_{\pm} = \frac{(\gamma + k_f + k_b) \pm \sqrt{(\gamma + k_f + k_b)^2 - 4\gamma k_f}}{2}. \quad (60)$$

The net result is

$$C_{AA}(t) = \sigma_A^2 (Ae^{-k_+t} + Be^{-k_-t}) \quad (61)$$

with

$$A = \frac{(\gamma + k_b) - k_-}{k_+ - k_-}, \quad B = 1 - A. \quad (62)$$

For any finite value of k_b , it is clear from this that $C_{AA}(0) = \sigma_A^2$ and there is no sum rule deficit.

Now let us take the limit $k_b \rightarrow \infty$ with $K = k_f/k_b$ being held constant. To leading order we have

$$\begin{aligned} k_+ &\rightarrow (K + 1)k_b, & k_- &\rightarrow \frac{K\gamma}{K + 1}, \\ A &\rightarrow \frac{K}{K + 1}, & B &\rightarrow \frac{1}{K + 1}, \end{aligned} \quad (63)$$

and thus

$$\lim_{k_b \rightarrow \infty} C_{AA}(t) = \frac{\sigma_A^2}{K + 1} \exp\left[-\frac{K\gamma t}{K + 1}\right]. \quad (64)$$

Apart from the amplitude, this correlation function is characteristic of $\overset{k}{\rightleftharpoons} X \xrightarrow{\gamma_R}$ with $\gamma_R = K\gamma/(K + 1)$. This is entirely in accord with rewriting the original scheme in terms of the relevant slow variable.

The analysis shows that in the limit $k_b \rightarrow \infty$, we have $C_{AA}(0) < \sigma_A^2$. Thus there is a non-zero sum rule deficit

$$\Delta\sigma_A^2 = \sigma_A^2 \left(1 - \frac{1}{K + 1}\right) = \frac{\langle N_{A^*} \rangle}{K + 1} \quad (65)$$

where we have used $\sigma_A^2 = \langle N_A \rangle = \langle N_{A^*} \rangle / K$. Again, the universal value for the sum rule deficit is recovered.

Our analysis shows what happens to the correlation functions in the limit of fast equilibration (similar results are found for $C_{A^*A^*}$). At any finite k_b there are two decay rates in the correlation function. In the limit $k_b \rightarrow \infty$ one of these decay rates diverges whilst the other saturates to a finite value. The diverging decay rate carries with it a finite amplitude and it is this that gives rise to the sum rule deficit. The phenomenology is illustrated in Fig. 2 which shows typical results for $C_{AA}(t)$ at several increasing values of the equilibration rate.

The results in this section are supportive of the general strategy of elimination of the fast variables in terms of the appropriate slow variables. To be specific, the strategy is to rewrite the chemical rate equations in terms of fast

and slow variables, eliminate the fast variables, and interpret the reduced rate equations in terms of a reduced reaction network, possibly involving new chemical species (in the present example, X replaces A and A*). Our study has provided examples where one can rigorously prove that this strategy is successful.

IV. DISCUSSION

Firstly, let us make some general remarks about the use of noise power spectra to characterise the stochastic properties of chemical reaction networks. As we have shown, the noise power spectra are straightforward to calculate once one has the point statistics (the mean values and the variance-covariance matrix), for a linear network, or for a linearisation of a non-linear network. In fact, the power spectra are *easier* to calculate than the autocorrelation functions, which in general require the factorisation of a polynomial, unless one is satisfied with stopping at the Laplace-transformed autocorrelation functions. Because the power spectra are functions of frequency, they are a more refined measure than the point statistics, and can be used for instance as a sensitive test of whether two reaction networks can be mapped onto one another.

Let us comment briefly on the situation for experiments and simulations. Both face similar difficulties in measuring the power spectra. A signal of sufficiently long duration needs to be captured at sufficiently fine resolution in order to be able to estimate the power spectrum. Event-driven simulations though, such as those based on the Gillespie algorithm [26], have an advantage since in principle the exact moments when a signal changes its value are known.

Secondly, we discuss the biological relevance of our results. Our results indicate that the way noise is transmitted through a signal detection motif may be more complicated than previously thought [13, 14, 15]. In particular, if the detection motif consumes the input signal molecules, a correlation can be set up between the intrinsic noise generated by the detection motif, and the input signal noise. We have examined this in the context of a post-translational modification reaction attached to the output of a gene expression module. Our analysis shows incidentally that post-translational modification can ameliorate the noise of gene expression, by smoothing out the ‘burstiness’ of the translation step.

We also examined the effect of a fast equilibration reaction interposed in the network. We find that, in the limit of infinitely fast equilibration, such a network can be exactly mapped onto a reduced or coarse-grained network through the use of suitably chosen slow variables. This result supports the use of slow variables as a general strategy for model-order reduction by elimination of fast reactions.

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APPENDIX A: TECHNICAL DETAILS

Technical details and proofs are relegated to this Appendix. For further reading we recommend Gardiner [9], van Kampen [27], Gillespie [10, 26], and Swain [28].

1. Point statistics

We first describe the chemical master equation and present a useful moment relation. As a preliminary step we need to define some basic quantities. The stoichiometry matrix is a non-square matrix $\nu_{i\alpha}$ equal to the change in species i due to the firing of reaction α in the network. We shall use roman indices to label chemical species and the greek symbol α to label reactions. In terms of $\nu_{i\alpha}$, the chemical rate equations can be written

$$\frac{dN_i}{dt} = \sum_{\alpha} \nu_{i\alpha} a_{\alpha} \quad (\text{A1})$$

where a_{α} is the flux through reaction channel α . The quantity a_{α} is usually dependent on the current values of N_i and is referred to by Gillespie as the ‘propensity function’. The propensity functions for a linear reaction network will be described shortly.

In these terms, the probability P_{N_i} of being in the state characterised by N_i molecules of species i obeys

$$\frac{\partial P_{N_i}}{\partial t} = \sum_{\alpha} \left\{ a_{\alpha}(N_i - \nu_{i\alpha}) P_{N_i - \nu_{i\alpha}} - a_{\alpha}(N_i) P_{N_i} \right\}. \quad (\text{A2})$$

If a reaction channel is impossible, for instance where $N_i - \nu_{i\alpha} < 0$, we set $a_{\alpha} = 0$. Eq. (A2) is the chemical master equation.

Multiplying Eq. (A2) by a general function $f(N_i)$ and summing over all N_i yields

$$\frac{d\langle f \rangle_t}{dt} = \sum_{\alpha} \langle a_{\alpha}(N_i) [f(N_i + \nu_{i\alpha}) - f(N_i)] \rangle_t. \quad (\text{A3})$$

This is particularly useful for deriving equations for moments.

We now indicate how the point statistics and in particular the variance-covariance matrix can be found for an arbitrary linear reaction network. The results follow as particular cases of Eq. (A3).

First we need to specify in more detail the propensity functions for a linear reaction network. We distinguish between zeroth- and first-order reactions in the network.

The former are pure generating reactions of the form ‘ \rightarrow products’. The latter are monomolecular reactions and comprise the rest of the network (in a linear reaction network, all reactions are either zeroth- or first-order). The set of zeroth-order reactions is denoted by $\{0\}$ and the set of first-order reactions by $\{1\}$.

The propensity function for a zeroth-order reaction is

$$a_{\alpha} = k_{\alpha}, \quad \alpha \in \{0\}. \quad (\text{A4})$$

where k_{α} is the reaction rate. For the first order reactions, we introduce an indicator matrix $\epsilon_{i\alpha}$, such that $\epsilon_{i\alpha} = 1$ if the reaction α involves species i as the reactant, and $\epsilon_{i\alpha} = 0$ otherwise. Armed with this, the propensity function for a first-order reaction is

$$a_{\alpha} = k_{\alpha} \sum_i \epsilon_{i\alpha} N_i \quad \alpha \in \{1\}. \quad (\text{A5})$$

Inserting Eqs. (A4) and (A5) into Eq. (A1) obtains Eq. (1) in the main text, with

$$b_i = \sum_{\alpha \in \{0\}} k_{\alpha} \nu_{i\alpha}, \quad K_{ij} = \sum_{\alpha \in \{1\}} k_{\alpha} \nu_{i\alpha} \epsilon_{j\alpha}. \quad (\text{A6})$$

The first moment of the chemical master equation is found by setting $f(N_i) = N_i$ in Eq. (A3). It is easy to show that this gives Eq. (2) in the main text, with the above definitions of b_i and K_{ij} .

The second moment of the chemical master equation is found by setting $f(N_i) = N_i N_j$ in Eq. (A3). This gives a closed set of equations for the elements of the variance-covariance matrix. In steady state, these equations can be reduced to

$$\sum_k (K_{ik} S_{kj} + K_{jk} S_{ki}) + H_{ij} = 0 \quad (\text{A7})$$

where

$$H_{ij} = \sum_{\alpha \in \{0\}} k_{\alpha} \nu_{i\alpha} \nu_{j\alpha} + \sum_k \left(\sum_{\alpha \in \{1\}} k_{\alpha} \nu_{i\alpha} \nu_{j\alpha} \epsilon_{k\alpha} \right) \langle N_k \rangle \quad (\text{A8})$$

Eq. (A7) is a set of linear simultaneous equations for the elements S_{ij} of the variance-covariance matrix.

As an example of the application of this machinery, consider the model for gene expression in Eq. (20) in the main text. There are two species, M and A, and four reactions. The stoichiometry matrix is

$$\nu_{i\alpha} = \left(\begin{array}{c|ccc} 1 & -1 & 0 & 0 \\ 0 & 0 & 1 & -1 \end{array} \right). \quad (\text{A9})$$

The reaction rates are

$$k_{\alpha} = (k \mid \lambda \ \rho \ \gamma). \quad (\text{A10})$$

The indicator matrix is

$$\epsilon_{i\alpha} = \left(\begin{array}{c|cc} \cdot & 1 & 1 \\ \cdot & 0 & 0 \end{array} \right). \quad (\text{A11})$$

In these, the reactions to the left of the vertical line correspond to $\alpha \in \{0\}$ and the reactions to the right of the

line correspond to $\alpha \in \{1\}$ (the indicator matrix is only defined for the latter reactions).

From these one computes

$$K_{ij} = \begin{pmatrix} -\lambda & 0 \\ \rho & -\gamma \end{pmatrix}. \quad (\text{A12})$$

Obviously this could have been written down by inspection. Less trivially, one also finds

$$\begin{aligned} H_{ij} &= \begin{pmatrix} k + \lambda \langle N_M \rangle & 0 \\ 0 & \rho \langle N_M \rangle + \gamma \langle N_A \rangle \end{pmatrix} \\ &= \begin{pmatrix} 2\lambda \langle N_M \rangle & 0 \\ 0 & 2\gamma \langle N_A \rangle \end{pmatrix}. \end{aligned} \quad (\text{A13})$$

Eqs. (A7) simplify to

$$\begin{aligned} -2\lambda\sigma_M^2 + 2\lambda\langle N_M \rangle &= 0, \\ \rho\sigma_M^2 - \gamma S_{MA} - \lambda S_{MA} &= 0, \\ 2\rho S_{MA} - 2\gamma\sigma_A^2 + 2\gamma\langle N_A \rangle &= 0. \end{aligned} \quad (\text{A14})$$

There are only three equations since Eq. (A7) is symmetric in i and j . These are solved to get Eqs. (22) in the main text.

2. Regression theorem

The proof of the regression theorem Eq. (11) in the main text is straightforward and parallels the development in Gardiner [9]. We start by writing out an explicit expression for the correlation function

$$C_{ij}(t) = \int d\{N_{i,0}\} d\{N_{i,t}\} \Delta N_{i,0} \Delta N_{j,t} \times P_s(N_{i,0}) P(N_{i,t}|N_{i,0};t). \quad (\text{A15})$$

In this, $P_s(N_{i,0})$ is the steady state probability distribution for the starting point $N_i = N_{i,0}$, and $P(N_{i,t}|N_{i,0};t)$ is the conditional probability distribution for $N_i = N_{i,t}$ at time t , given that the system started with $N_i = N_{i,0}$ at $t = 0$. These probability distributions could in principle be found by solving the chemical master equation. We now define two kinds of averages

$$\begin{aligned} \langle f(N_i) \rangle_{t|0} &= \int d\{N_{i,t}\} f(N_{i,t}) P(N_{i,t}|N_{i,0};t), \\ \langle f(N_i) \rangle_0 &= \int d\{N_{i,0}\} f(N_{i,0}) P_s(N_{i,0}). \end{aligned} \quad (\text{A16})$$

In words, the first is the average value of a function of $N_i = N_{i,t}$ at time t , given that the system started with $N_i = N_{i,0}$ at $t = 0$. The second is the average value of a function of $N_i = N_{i,0}$ in steady state conditions. In terms of these, Eq. (A15) can be written as

$$C_{ij}(t) = \langle \Delta N_i \langle \Delta N_j \rangle_{t|0} \rangle_0. \quad (\text{A17})$$

This result is completely general [9].

For a linear reaction network, taking the first moment of the chemical master equation proves an analogue to Eq. (12), namely

$$\frac{d\langle \Delta N_i \rangle_{t|0}}{dt} = \sum_j K_{ij} \langle \Delta N_j \rangle_{t|0}. \quad (\text{A18})$$

Combining this with Eq. (A17) demonstrates that $C_{ij}(t)$ obeys Eq. (11) in the main text.

3. Chemical Langevin equations

We prove that the power spectra obtained from the chemical Langevin equations for a linear reaction network are equivalent to the exact results obtained from the chemical master equation. As the first step, Gillespie has shown that the chemical Langevin equations for a general network are [10]

$$\frac{dN_i}{dt} = \sum_\alpha \nu_{i\alpha} a_\alpha + \sum_\alpha \nu_{i\alpha} a_\alpha^{1/2} \Gamma_\alpha. \quad (\text{A19})$$

In this, Γ_α are independent unit Gaussian white noise functions, one for each reaction channel. Applying this to a linear reaction network obtains

$$\frac{dN_i}{dt} = \sum_j K_{ij} N_j + b_i + \eta_i \quad (\text{A20})$$

with

$$\eta_i = \sum_{\alpha \in \{0\}} k_\alpha^{1/2} \nu_{i\alpha} \Gamma_\alpha + \sum_{\alpha \in \{1\}} (k_\alpha \sum_j \epsilon_{j\alpha} N_j)^{1/2} \nu_{i\alpha} \Gamma_\alpha. \quad (\text{A21})$$

It follows that the η_i are Gaussian white noise functions with the following statistics

$$\langle \eta_i \rangle = 0, \quad \langle \eta_i(t) \eta_j(t') \rangle = H_{ij} \delta(t - t'). \quad (\text{A22})$$

The correlation matrix H_{ij} is *identical* to the matrix that features in the computation of the variance-covariance matrix, given by Eq. (A8) above, which can be interpreted in this context as a fluctuation-dissipation theorem.

Working in terms of the deviation from steady state, and taking the Fourier transform of the chemical Langevin equations, obtains

$$i\omega \Delta N_i = \sum_j K_{ij} \Delta N_j + \eta_i. \quad (\text{A23})$$

We conclude

$$P_i(\omega) = \langle |\Delta N_i|^2 \rangle = \sum_{jk} B_{ij} H_{jk} B_{ki}^\dagger \quad (\text{A24})$$

where $B_{ij}(i\omega)$ is the inverse of $i\omega\delta_{ij} - K_{ij}$ and $B_{ij}^\dagger(i\omega) = B_{ji}(-i\omega)$ is the adjoint. Our task is to prove that Eq. (A24) is equivalent to Eqs. (13) and (15) in the main text.

The problem is made easier if we rewrite everything in abstract matrix notation. The result we have just obtained can be written as

$$\mathbf{P}_1 = \mathbf{B} \cdot \mathbf{H} \cdot \mathbf{B}^\dagger \quad (\text{A25})$$

with

$$\mathbf{B} = (i\omega\mathbf{I} - \mathbf{K})^{-1}, \quad \mathbf{B}^\dagger = (-i\omega\mathbf{I} - \mathbf{K}^\text{T})^{-1} \quad (\text{A26})$$

(\mathbf{K}^T is the transpose of \mathbf{K}). The diagonal elements of \mathbf{P}_1 are the power spectra from the chemical Langevin equation route.

We now similarly rewrite the results from the analysis of the chemical master equation. Eqs. (A7), (13) and (15) can be written respectively as

$$\begin{aligned} \mathbf{K} \cdot \mathbf{S} + \mathbf{S} \cdot \mathbf{K}^\text{T} + \mathbf{H} &= 0, \\ i\omega\mathbf{C} - \mathbf{S} &= \mathbf{K} \cdot \mathbf{C}, \quad \text{or} \quad \mathbf{C} = \mathbf{B} \cdot \mathbf{S}, \\ \mathbf{P}_2 &= \mathbf{C} + \mathbf{C}^\dagger = \mathbf{B} \cdot \mathbf{S} + \mathbf{S} \cdot \mathbf{B}^\dagger \end{aligned} \quad (\text{A27})$$

(note that \mathbf{S} is real and symmetric). The diagonal elements of \mathbf{P}_2 are the power spectra from the chemical master equation route.

Eliminate \mathbf{H} between the first of Eqs. (A27) and Eq. (A25) to get

$$\mathbf{P}_1 = -(\mathbf{B} \cdot \mathbf{S} \cdot \mathbf{K}^\text{T} \cdot \mathbf{B}^\dagger + \mathbf{B} \cdot \mathbf{K} \cdot \mathbf{S} \cdot \mathbf{B}^\dagger). \quad (\text{A28})$$

It follows from Eq. (A26) that

$$\mathbf{B} \cdot \mathbf{K} = i\omega\mathbf{B} - \mathbf{I}, \quad \mathbf{K}^\text{T} \cdot \mathbf{B}^\dagger = -i\omega\mathbf{B}^\dagger - \mathbf{I}. \quad (\text{A29})$$

On substituting these into Eq. (A28), there is a cancellation of terms, and one finds

$$\mathbf{P}_1 = \mathbf{B} \cdot \mathbf{S} + \mathbf{S} \cdot \mathbf{B}^\dagger. \quad (\text{A30})$$

Comparison with the last of Eqs. (A27) shows that $\mathbf{P}_1 = \mathbf{P}_2$. This contains our desired result, and proves that the power spectra obtained by the chemical Langevin equation route are the same as those obtained by the (exact) chemical master equation route. Actually, we have a slightly stronger result, since it follows that $\langle |\Delta N_X|^2 \rangle = \mathbf{x}^\text{T} \cdot \mathbf{P}_1 \cdot \mathbf{x} = \mathbf{x}^\text{T} \cdot \mathbf{P}_2 \cdot \mathbf{x}$, for any linear combination $N_X = \sum_i x_i N_i$.

Swain has presented an analysis of the chemical Langevin equations for, effectively, a general linear reaction network [28]. He obtains general results for the correlation functions and the variance-covariance matrix in terms of the eigenvalues of K_{ij} . The present section can be read as proving that the variance-covariance matrix can be found by a simpler route, by solving Eq. (A7) in terms of the noise correlation matrix. For the correlation functions though, our route involves an inverse Laplace transform which in general requires that a polynomial be factorised, and is equivalent to solving the secular equation for K_{ij} . So our methods do not provide any additional simplification compared to Swain for the correlation functions. As we have emphasised in the main text though, our results demonstrate that the power spectra are much easier to calculate than the correlation functions.

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