Signal Detection, Modularity, and the Correlation between Extrinsic and Intrinsic Noise in Biochemical Networks

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We present an expression for the power spectrum of the output signal of a biochemical network, which reveals that the reactions that allow a network to detect biochemical signals, induce correlations between the extrinsic noise of the input signals and the intrinsic noise of the reactions that form the network. We show that anticorrelations between the extrinsic and intrinsic noise enhance the robustness of zero-order ultrasensitive networks to biochemical noise. We discuss the consequences for a modular description of noise transmission using the mitogen-activated protein kinase cascade.

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It is increasingly becoming recognized that understanding cell function requires an accurate description of noise propagation through biochemical networks [1]. The complete biochemical network of a living cell consists of a huge number of biochemical reactions. This precludes a detailed mesoscopic description of noise propagation. However, it is believed that biochemical networks are modular in design, which means that they can be decomposed into smaller, functionally independent units [2]. This is potentially useful, because it would make it possible to coarse grain the full network of individual reactions to a smaller network consisting of modules, where each module is described as a ''black box'' with input and output signals; the reactions that constitute each module would then be integrated into the input-output relations [3]. Here we address the question whether modularity can be exploited for developing a coarse-grained description of noise transmission.

Recently, several groups have derived analytical expressions for the noise in the output signal of a network as a function of the noise in the input signal, the extrinsic noise, and the noise in the biochemical reactions that constitute the network, the intrinsic noise [4–7]. These results suggest that the input-output relations for the noise of the individual modules of a network can be combined in a simple way to quantify the transmission of noise through the full network [4,5,7]. However, these studies assume that the extrinsic and intrinsic noise are independent sources of noise [4–7]. Here, we show that the biochemical reactions that allow a module to *detect* the incoming signals introduce correlations between the extrinsic and intrinsic noise. These correlations can strongly affect the propagation of noise through the network, as we illustrate for the mitogen-activated protein kinase (MAPK) cascade. Moreover, we show that correlations between extrinsic and intrinsic noise preclude a quantitative modular description of noise propagation through large scale biochemical networks. Our analysis also reveals the conditions under which the detection reactions do not introduce correlations between the extrinsic and intrinsic noise; under these conditions, a modular description of noise transmission can be developed.

Noise addition rule: Uncorrelated extrinsic and intrinsic noise.—We consider a module with one input and one output signal. We assume that the system is in steady state and that the fluctuations of the incoming and outgoing signals around their steady-state values are small; this allows us to linearize the coupling between them and to use the linear-noise approximation [8]. Moreover, we will here assume that the noise in the input is *uncorrelated* from that in the processing network and that the output signal relaxes exponentially with decay rate μ. This yields the following chemical Langevin equation

$$\dot{x} = \nu s(t) - \mu x + \eta(t). \tag{1}$$

Here, $s = S - \langle S\rangle$ is the deviation of the number of signaling molecules, S, from its mean, $\langle S\rangle$, and $x = X - \langle X\rangle$ is the corresponding quantity for the output signal; ν corresponds to the differential gain and the dot denotes a time derivative. The last term, $\eta(t)$, describes the noise in the reactions that constitute the processing unit. We model $\eta(t)$ as Gaussian white noise: $\langle\eta(t)\rangle = 0$ and $\langle\eta(t)\eta(t')\rangle = \langle\eta^2\rangle\delta(t - t')$. Fourier transforming Eq. (1) yields the power spectrum for the outgoing signal:

$$S_X^{\mathrm{sa}}(\omega) = \langle|\tilde{x}(\omega)|^2\rangle = \frac{2\sigma_{\mathrm{in}}^2\mu}{\mu^2 + \omega^2} + \tilde{g}(\omega)S_S(\omega), \tag{2}$$

where $\sigma_{\mathrm{in}}^2 = \langle\eta^2\rangle/(2\mu)$ is the intrinsic noise, $\tilde{g}(\omega) = \nu^2/(\mu^2 + \omega^2)$ is the frequency-dependent gain, and $S_S(\omega) = \langle|\tilde{s}(\omega)|^2\rangle$ is the power spectrum of the input. A similar expression has been obtained recently [4,7,9]. It suggests that the spectrum of the output can be written as a sum of an intrinsic (first term) and an extrinsic contribution (second term). We therefore refer to Eq. (2) as the spectral addition rule. It is a consequence of the assumption that $s(t)$ and $\eta(t)$ are *uncorrelated*.

If the noise in the input signal has an amplitude σ_s^2 and decays monoexponentially with a relaxation rate λ, then

the output noise, obtained by integrating Eq. (2), is

$$\sigma_{\rm tot}^2 = \sigma_{\rm in}^2 + g^2 \frac{\langle X\rangle^2}{\langle S\rangle^2} \frac{\mu}{\lambda+\mu} \sigma_{\rm s}^2 \equiv \sigma_{\rm in}^2 + \sigma_{\rm ex}^2. \quad (3)$$

Here, $g \equiv \partial \ln\langle X\rangle / \partial \ln\langle S\rangle$ is the logarithmic gain and $\sigma_{\rm ex}^2$ is the extrinsic noise. This ''noise addition'' rule has been derived by Paulsson [6] and Shibata and Fujimoto [7]. It is only valid if the input signal has a single exponential relaxation time and if the spectral addition rule, Eq. (2), holds, which means that the extrinsic and intrinsic noise must be uncorrelated [10].

Equation (2) suggests that the extrinsic contribution to the power spectrum of the output signal can be *factorized* into a function that only depends upon intrinsic properties of the module, namely $\tilde{g}(\omega)$, and one that only depends upon the input signal, $S_{\rm S}(\omega)$. This would be highly useful, because it would allow a modular description of noise propagation. If, for instance, the network consists of a number of modules connected in series, then, once the intrinsic noise of each of the modules is known, the propagation of noise through the network could be obtained for *arbitrarily varying* input signals by a recursive application of the spectral addition rule, Eq. (2), to the successive modules [4,5]. However, this approach requires that the spectral addition rule holds for each of the individual modules. Below, we will show that the detection reactions can introduce correlations between the extrinsic and intrinsic noise. These obscure the distinction between the two noise sources and lead to a break down of the spectral addition rule, thereby impeding a modular description of noise propagation.

Correlated extrinsic and intrinsic noise.—We consider a module that consists of one component only. This component X, both detects the input S and provides the output signal. Below, we discuss more complex modules. To capture the correlations, we explicitly describe the detection of the signal by studying the *coupled* Langevin equations for the interacting species, S and X:

$$\dot{s} = -\lambda s + \kappa x + \xi(t), \qquad \dot{x} = \nu s - \mu x + \eta(t). \quad (4)$$

Here, κ describes how the fluctuations of the input signal are affected by those of the detection component; we model the noise in s, $\xi(t)$, also as a Gaussian white noise, $\langle\xi(t)\rangle = 0$, $\langle\xi(t)\xi(t')\rangle = \langle\xi^2\rangle\delta(t-t')$, correlated with the noise in x: $\langle\xi(t)\eta(t')\rangle = \langle\xi\eta\rangle\delta(t-t')$ [10]. Equation (4) can be solved using Fourier transformation, which gives

$$S_{\rm S}(\omega) = \frac{\kappa^2\langle\eta^2\rangle + 2\kappa\mu\langle\xi\eta\rangle + (\mu^2+\omega^2)\langle\xi^2\rangle}{(\kappa\nu-\lambda\mu)^2 + (\lambda^2+2\kappa\nu+\mu^2)\omega^2+\omega^4}, \quad (5a)$$

$$S_{\rm X}(\omega) = \frac{\langle\eta^2\rangle(\lambda^2+\omega^2) + 2\lambda\nu\langle\xi\eta\rangle + \nu^2\langle\xi^2\rangle}{(\kappa\nu-\lambda\mu)^2 + (\lambda^2+2\kappa\nu+\mu^2)\omega^2+\omega^4}. \quad (5b)$$

In contrast to Eqs. (2), Eqs. (5) take into account the correlations between the extrinsic and intrinsic noise.

Equations (5) reveal that the correlations between extrinsic and intrinsic noise can have two distinct origins, corresponding to a nonzero value of κ and $\langle\xi\eta\rangle$. To elucidate their effects on noise transmission, we consider the difference $\Delta S_{\rm X}(\omega) \equiv S_{\rm X}(\omega) - S_{\rm X}^{\rm sa}(\omega)$ between the full result of Eq. (5b) and the spectral addition rule of Eq. (2). In the linear limit of small κ and $\langle\xi\eta\rangle$, this is given by

$$\Delta S_{\rm X}(\omega) \simeq \frac{2\nu}{\lambda^2+\omega^2}\left(\frac{\langle\xi\eta\rangle\lambda}{\mu^2+\omega^2} + \frac{\kappa\langle\eta^2\rangle(\lambda\mu-\omega^2)}{(\mu^2+\omega^2)^2}\right). \quad (6)$$

The first source of correlations, quantified via κ, is present when the dynamics of the processing unit (intrinsic noise) acts back on that of the input signal (extrinsic noise). This happens in the first of the three elementary detection motifs presented in Table I. Here, a negative feedback arises from the unbinding of signaling molecules from the detection molecules ($\kappa = \mu$). Equation (6) reveals that this feedback decreases the low-frequency fluctuations, while transferring part of the noise to the high-frequency regime of the power spectrum. This could be advantageous, because high-frequency fluctuations are usually filtered more effectively by the network downstream.

The second source, quantified via $\langle\xi(t)\eta(t')\rangle$, is the *correlated fluctuations* in the number of signaling and detection molecules, due to the detection reactions. This source is present in schemes I and II of Table I, where, each time a detection reaction fires, a signaling molecule is consumed and *simultaneously* a molecule of the processing module is produced (or activated). Additionally, for scheme I, the unbinding reactions also lead to cross correlations in $\xi(t)$ and $\eta(t)$. For I, $\langle\xi\eta\rangle = -(\nu\langle S\rangle + \mu\langle X\rangle)$, while for II, $\langle\xi\eta\rangle = -\nu\langle S\rangle$ [11]. Equation (6), which, incidentally, is exact when $\kappa = 0$, shows that these negative cross correlations reduce the output noise, especially in the low-frequency regime.

For detection motif III, κ and $\langle\xi\eta\rangle$ are zero. Here, the detection reactions do not affect the signal in any way. The extrinsic and intrinsic noise are therefore uncorrelated and

TABLE I. Three elementary detection motifs. X is the output and S is the input signal; in I, W is the inactive (unbound) state of the detection component and X the active (bound) state. While all schemes obey $d\langle X\rangle/dt = \nu\langle S\rangle - \mu\langle X\rangle$, the noise is transmitted differently, due to the different sources of correlations between extrinsic and intrinsic noise.

	Scheme	Examples
(I)	$S + W \overset{\nu=k_f W}{\underset{\mu}{\rightleftarrows}} X$	ligand-receptor binding, enzyme-substrate binding, transcription factor-DNA binding
(II)	$S \overset{\nu}{\rightarrow} X \overset{\mu}{\rightarrow} \varnothing$	post-translational modification, endocytosis of activated trans-membrane receptors
(III)	$S \overset{\nu}{\rightarrow} S + X$, $X \overset{\mu}{\rightarrow} \varnothing$	coarse-grained models, enzymatic reactions, and gene expression

the spectral addition rule, Eq. (2), holds. Since, in this example, the input signal relaxes monoexponentially, also the noise addition rule, Eq. (3), holds.

The above analysis can be generalized to modules that consist of an arbitrary number of linear(ized) reactions and that have more than one input [10]. If and only if all the input signals are detected via detection motif III, a spectral addition rule analogous to Eq. (2) can be derived, allowing for a modular description [10]. Finally, spatial fluctuations, which have been ignored here, will change the power spectra [12]. If, however, their nontrivial effects in the high-frequency regime are not important, because they are filtered by the network, then it might be possible to include the consequences of diffusion in a ''well-stirred'' model, by describing the low-frequency effects via renormalizing the reaction rates [12].

Zero-order ultrasensitivity.—We illustrate the consequences of correlated extrinsic and intrinsic noise for the amplification mechanism of zero-order ultrasensitivity [13]. This operates in push-pull networks, where two enzymes covalently modify a component (see also Fig. 2):

$$\mathrm{E_a} + \mathrm{W} \underset{d_1}{\overset{a_1}{\rightleftarrows}} \mathrm{E_a W} \xrightarrow{k_1} \mathrm{E_a} + \mathrm{X}, \qquad \mathrm{E_d} + \mathrm{X} \underset{d_2}{\overset{a_2}{\rightleftarrows}} \mathrm{E_d X} \xrightarrow{k_2} \mathrm{E_d} + \mathrm{W}. \tag{7}$$

$\mathrm{E_a}$ is the activating enzyme that provides the input and $\mathrm{E_d}$ is the deactivating enzyme, the unmodified component W serves as the detection component, and the modified component X provides the output. When the substrate concentration is increased, the enzymes become more saturated with substrate, and the (de)modification rates become more ''zero order'' in substrate concentration [13]. This increases the sharpness of the response (the gain) markedly [13], as Figs. 1(a)–1(c) show. The amplification mechanism of zero-order ultrasensitivity thus relies on enzyme saturation, which means that the signaling molecules $\mathrm{E_a}$ must be strongly bound to the detection molecules W. This has important consequences for the transmission of noise, as we will now discuss.

Figures 1(b)–1(d) show the noise in the output X of the network in Eq. (7); the input $\mathrm{E_a}$ is modeled as a birth-death process, corresponding to (de)activation of $\mathrm{E_a}$. The analysis has been performed using the linear-noise approximation [8,10]. Figure 1(d) shows that as the substrate concentration is increased, the noise in the output also increases. This has been observed before [7,14]: the higher gain [see Fig. 1(c)], not only amplifies the mean, but also the noise of the input signal $\mathrm{E_a}$, the extrinsic noise [see Eq. (2)] [7]; in addition, when the (de)modification reactions become more zero order, their intrinsic fluctuations also increase [14]. However, Fig. 1(d) also shows that the actual increase in the output noise is much smaller than that predicted by the spectral addition rule. This is a result of the anticorrelations between the extrinsic and intrinsic noise. These reduce the noise, but are neglected by the spectral addition rule. Moreover, they become more significant as the network moves deeper into the zero-order regime: as the enzymes become more saturated, the input signal $\mathrm{E_a}$ is increasingly being affected by its interaction with the detection component W. While it has been known that fluctuations can adversely affect the performance of push-pull networks [1,14], our results reveal that anticorrelated fluctuations between different noise sources can enhance their performance by increasing the signal-to-noise ratio.

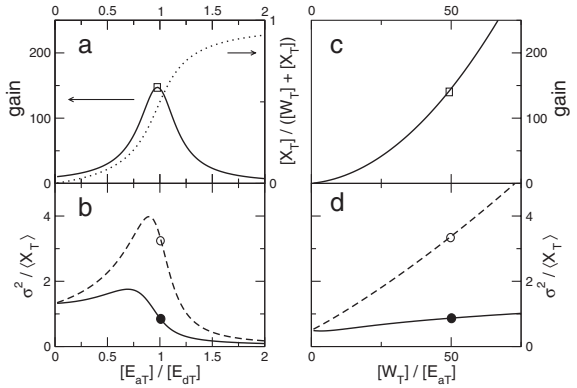

FIG. 1. Gain $\partial\langle X\rangle/\partial\langle E_{aT}\rangle$ and output noise $\sigma_X^2/\langle X\rangle$ for the network of Eq. (7). The response (dotted curve), gain (a) and output noise (b) as a function of $[\mathrm{E_{aT}}]/[\mathrm{E_{dT}}]$, for $[\mathrm{W_T}]+[\mathrm{X_T}] = 10\ \mu\mathrm{M}$ and $[\mathrm{E_{dT}}] = 0.1\ \mu\mathrm{M}$ (subscript T denotes total species concentration). The gain (c) and output noise (d) as a function of $[\mathrm{W_T}]/[\mathrm{E_{aT}}]$, for $[\mathrm{E_{aT}}] = [\mathrm{E_{dT}}] = 0.1\ \mu\mathrm{M}$ and $[\mathrm{W_T}] = [\mathrm{X_T}]$. In (b) and (d), the dashed curves correspond to the predictions of the spectral addition rule [Eq. (2)], and the solid lines correspond to the analysis that takes into account the correlations between extrinsic and intrinsic noise. Panel (d) shows that the actual increase in output noise due to enzyme saturation is much lower than that predicted by the spectral addition rule. $K_{\mathrm{M,E_a}} = K_{\mathrm{M,E_d}} = 1\ \mu\mathrm{M}$; the decay rate of $\mathrm{E_a}$ is $\lambda = 30k_1$, and $a_1 = a_2 = 0.1k_1$.

Modularity and the MAPK cascade.—We discuss the implications of the correlations between the extrinsic and intrinsic noise for a modular description of noise transmission using the Mos/MEK/p42 MAPK cascade

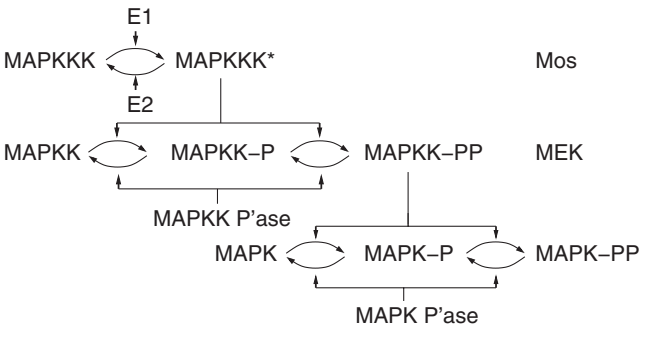

FIG. 2. The Mos/MEK/p42 MAPK cascade. This network consists of three tiers, which, from a topological point of view, could be regarded as modules. The tiers consists of push-pull networks, where the activity of an enzyme is covalently modified by the action of two opposing enzymes [see Eq. (7)].

TABLE II. Noise in the Mos/MEK/p42 MAPK cascade (see Fig. 2). In I, the transmission of noise was computed by studying all the reactions together. In II, the spectral addition rule has been applied iteratively to the successive layers, thus assuming they form independent modules. In III (IV) the first (last) two layers were considered to form one module, while the other layer was assumed to form an independent module. Note that the correlations between the noise in active Mos and the intrinsic fluctuations of MEK strongly affect the transmitted noise. The concentrations are: [Mos] = 3 nM; [MEK] = 1200 nM; [MAPK] = 300 nM (see also [3,10,15]).

	$\sigma^2_{\mathrm{Mos}^*}/[\mathrm{Mos}^*]$	$\sigma^2_{\mathrm{MEK-PP}}/[\mathrm{MEK-PP}]$	$\sigma^2_{\mathrm{MAPK-PP}}/[\mathrm{MAPK-PP}]$
I: Fully coupled	0.643	90.3	2.25
II: All uncoupled	0.727	168.0	3.75
III: Coupled Mos & MEK	0.643	91.1	2.26
IV: Coupled MEK & MAPK	0.727	166.0	3.72

[3,10,15] (see Fig. 2). From a topological point of view, this network consists of three push-pull modules that are connected in series. Table II shows the noise in the output signals of the three modules, as predicted by an iterative application of the spectral addition rule [Eq. (2)], and as revealed by an analysis that takes into account the correlations between the extrinsic and intrinsic noise of each module [10]. The spectral addition rule significantly overestimates the propagation of noise: the noise in MAPK, the output of the cascade, is about 50% lower than that predicted by the spectral addition rule. This supports our conclusion that anticorrelations between the extrinsic and intrinsic noise can make biochemical networks more robust against biochemical noise.

Table II also illustrates under which conditions modularity can be exploited for a coarse-grained description of noise transmission. Analysis III refers to a calculation that takes into account the correlations between the noise in the output signal of the first layer, Mos^*, and the intrinsic noise of the second layer, the fluctuations in the (de)modification reactions of MEK; however, it ignores the correlations between the output signal of the second layer and the intrinsic noise of the third layer. Similarly, analysis IV corresponds to a description, in which the first layer forms one module, whereas the second and third layer form a second, independent module. It is seen that while the former description is fairly accurate, the latter significantly overestimates the noise in the output signal of the cascade. This shows that while the correlations between extrinsic and intrinsic noise are not very important for the transmission of noise from the second to the third layer, these correlations do affect the propagation of noise from the first to the second layer. The reason for this is that active Mos is more saturated with its substrate, MEK, than active MEK is with its substrate, MAPK (see also Fig. 1).

In summary, our analysis demonstrates that, from the perspective of noise transmission, a network can be decomposed into modules only if the signals that connect them are detected via reactions that do not introduce significant correlations between the noise in these signals and the intrinsic noise of the modules. When these correlations are important, then the propagation of noise can only be quantified accurately if the correlated subnetworks are regrouped into independent modules. Finally, we believe that the predictions of our analysis could be tested by performing fluorescence resonance energy transfer (FRET) or fluorescence correlation spectroscopy experiments [16]. By putting a FRET donor on MEK, and a FRET acceptor on both the enzyme of the upstream module, Mos, and that of the downstream module, MAPK, it should be possible to study the effect of correlations between extrinsic and intrinsic noise on the transmission of noise in signal transduction cascades.

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