Extrinsic and intrinsic correlations in molecular information transmission

Vijay Singh,[1,2] Martin Tchernookov,[1,3] and Ilya Nemenman[1,4]

[1]*Department of Physics, Emory University, Atlanta, GA 30322, USA*
[2]*Computational Neuroscience Initiative, University of Pennsylvania, Philadelphia, PA 19104, USA*
[3]*Department of Physics, Lamar University, Beaumont, TX 77710*
[4]*Department of Biology, Emory University, Atlanta, GA 30322, USA*

Cells measure concentrations of external ligands by capturing ligand molecules with cell surface receptors. The numbers of molecules captured by different receptors co-vary because they depend on the same extrinsic ligand fluctuations. However, these numbers also counter-vary due to the intrinsic stochasticity of chemical processes because a single molecule randomly captured by a receptor cannot be captured by another. Such structure of receptor correlations is generally believed to lead to an increase in information about the external signal compared to the case of independent receptors. We analyse a solvable model of two molecular receptors and show that, contrary to this widespread expectation, the correlations have a small and *negative* effect on the information about the ligand concentration. Further, we show that measurements that average over multiple receptors are almost as informative as those that track the states of every individual one.

Keywords: sign rule, cellular information processing, two receptors

Introduction. Information processing is a crucial function of life [1]. It typically involves representing external signals by activities of biological elements, such as cell receptors, genes, or neurons. A lot is known about information processing by such individual elements [2–10]. However, the fascinating phenomena emerging in information processing by many interacting biological elements are only beginning to be uncovered [1, 11–17].

A particularly well-developed example of multivariate biological information processing is population coding by neurons [11, 16, 18–25]. Here many neurons (often heterogeneous and interacting) are treated as conveying information about the same stimulus. A celebrated general property of such networks is the "sign rule" [11, 16], which suggests that if fluctuations of neural activities due to changes in the signal are orthogonal to fluctuations due to intrinsic coupling among the neurons, then the collective of neurons has more information about the stimulus than a collective of noninteracting neurons would have.

Deriving the sign rule requires making serious (though often implicit) assumptions about the structure of fluctuations in populations of sensors. Verifying these assumptions is hard for networks as complex as those in the brain. In contrast, multiple receptors on the cell surface are a cellular biology equivalent of population coding in neuroscience, with an advantage that the structure of correlations among the sensors (receptors) does not have to be postulated *a priori*, but can be derived analytically from biophysically plausible molecular interactions. We use this advantage to study collective information processing in an analytically solvable model of two receptors interacting via binding to the same chemical ligand species. We show, in particular, that the sign rule is violated in this system, and the information gathered about the stimulus by the interacting receptors is smaller than in the noninteracting case. This suggests that studies of population codes based on correlations are insufficient (including in computational neuroscience, where they are common) since effects of the correlations depend on features of biophysical mechanisms that establish them.

In addition to its illumination of the limitations of the *general* sign rule, the two receptors model addresses an important question *specific* to cellular information processing. Estimation of a chemical signal concentration by cells has been studied since the seminal work of Berg and Purcell [26], with notable new recent results [17, 27–33]. However, most of these formulations consider the combined (or averaged) response of all receptors on the cell surface for estimating the concentration. Keeping track of responses of individual receptors would provide extra information about the concentration stored in the receptor-to-receptor variability. Our model quantifies how useful it is for the cell to keep track of such data. We show that, for large observation times, the average population response is almost as informative about the stimulus as the set of activities of all individual receptors.

Background. We introduce the sign rule with the following simple yet instructive model [11, 16]. Imagine a Gaussian signal s with the mean $\bar{s}$ and the variance σ_s^2. It is measured by two responses, r_1 and r_2 (firing rates of neurons or receptor activity). For simplicity, these are assumed linearly and equivalently dependent on s (or the response to small fluctuations is linearized), such that

$$r_1 = as + \eta_1, \quad r_2 = as + \eta_2, \tag{1}$$

where a is the gain, and $\eta_{1,2}$ are Gaussian noises with $\langle \eta_i \rangle = 0$, and $\mathrm{var}\,\eta_i \equiv \langle \eta_i^2 \rangle = \sigma_\eta^2$.

We estimate the signal from the responses as $s_{\mathrm{est}} = (r_1 + r_2)/(2a)$. Then the estimation error variance is

$$\mathrm{var}\,(s_{\mathrm{est}} - s) \equiv \sigma_{\mathrm{err}}^2 = \frac{\sigma_\eta^2(1+\rho_\eta)}{2a^2}. \tag{2}$$

Here $\rho_\eta \sigma_\eta^2 = \mathrm{cov}\,(\eta_1, \eta_2)$ stands for the covariance of the two noises, or the *noise-induced* covariance [11], and

ρ_η is the corresponding correlation coefficient. By analogy with the intrinsic noise in systems biology [34], ρ_η can also be called the *intrinsic noise correlation*. When $\rho_\eta = 0$, Eq. (2) reduces to the usual decrease of the error variance by a factor of two for two independent measurements. However, when $\rho_\eta < 0$, the error variance is smaller. In particular, if $\rho_\eta \to -1$, the signal can be estimated with no error. Generalizing this simple observation, one can define the *stimulus-induced response covariance* [11] or the *extrinsic noise covariance* [34], as the covariance between mean responses to stimuli, averaged over all stimuli, $\mathrm{cov}\,(\bar{r}_1, \bar{r}_2) \equiv \rho_s a^2 \sigma_s^2$. Then our example illustrates the *sign rule* [16]: if ρ_s and ρ_η are of opposite signs, then the stimulus can be inferred from the two responses with a smaller error compared to the (conditionally) independent responses, $\rho_\eta = 0$. The same result can restated using *mutual information* between the two responses and the stimulus [1, 9, 35, 36] :

$$I[r_1, r_2; s] = \frac{1}{2} \ln \left[1 + \frac{a^2 \sigma_s^2}{(1+\rho_\eta)\sigma_\eta^2} \right]. \qquad (3)$$

For Eq. (1), $\rho_s = 1 > 0$, and then $\rho_\eta < 0$ corresponds to increase in the information.

In the case of a chemical ligand being absorbed by two identical receptors, the mean values of r_1 and r_2 change in the same way with the ligand concentration, so that $\rho_\mathrm{s} = 1 > 0$. At the same time, a molecule absorbed at one receptor cannot be absorbed at the other, which should give $\rho_\eta < 0$, and hence will increase the measured information according to the sign-rule. However, in computational neuroscience, where these ideas originated, noise (co)-variances are inferred empirically and are, in principle, unconstrained. In contrast, in cell biology, intrinsic noises are generated from the discreteness and stochasticity of individual chemical reaction events [37–39], which constrains relations among these quantities. In particular, ρ_η may depend on σ_η, and then it is unclear if the sign rule would hold in Eq. (3). Indeed, the primary contribution of this Letter is to show that measuring the ligand concentration with two identical receptors does not obey the sign rule.

The Model. We consider two identical receptors that can bind ligand molecules with a rate k_in (Fig. 1). No more than one molecule can be bound to each receptor at the same time (with no restrictions on the number of bound molecules, the dynamics is linear, the receptors are conditionally independent). The bound molecule can be absorbed/deactivated with the rate k_abs, freeing the receptor (absorbing receptors collect more information about the stimulus compared to binding-unbinding receptors [29]). Alternatively, it can unbind and leave the vicinity of receptors with the rate k_off. Finally, it can leave one receptor and diffuse to the other. We model this as a hop between the receptors with the rate k_hop, which in reality would depend on the diffusion constant and the distance between the receptors. The number of molecules absorbed on both receptors over time t, $\{Q_1(t), Q_2(t)\}$, carries information about the binding rate k_in. Since, k_in is proportional to the ligand concentration, such counting of the absorbed molecules measures the concentration.

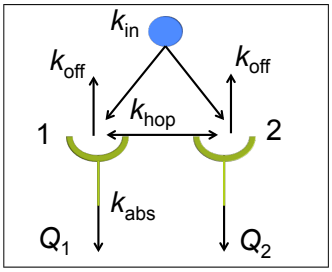

FIG. 1: Model schematics. Receptors 1 and 2 bind ligands with rate k_in, and the bound molecules can detach and diffuse away to infinity with the rate k_off. The bound ligands also can be absorbed with the rate k_abs, or they can dissociate and diffuse to the other receptor (hop) with the rate k_hop. Q_i is the number of ligands absorbed at the receptor i.

Within this setup, we investigate how the ligand-induced interaction between the two receptors affects the information about the concentration, $I[Q_1, Q_2; k_\mathrm{in}]$, cf. Eq. (3). Note that the hopping can change the conditional distribution $P(Q_1, Q_2|k_\mathrm{in})$, which can affect the information, but it cannot change the conditional distribution of the total number of captured molecules $Q_+ = Q_1 + Q_2$. Thus the change in the information, if any, can come only from the dependence between $Q_- = Q_1 - Q_2$ and k_in. This expands the molecular sensing literature [26, 28, 29], where one typically estimates k_in based only on the integrated number of observed ligands, Q_+. In other words, together with our main question, we will quantify if the set of individual responses of all receptors, $\{Q_1, Q_2\}$ or $\{Q_+, Q_-\}$, is more informative about the concentration than the integrated response alone.

Solution. To calculate the distribution $P(Q_1, Q_2|k_\mathrm{in})$, we start with the master equation describing the dynamics of the vector of probabilities of having 0 or 1 molecules bound to each of the receptors, $\mathbf{P} = \{P_{ij};\, i, j = 0, 1\}^T = \{P_{00}, P_{01}, P_{10}, P_{11}\}^T$,

$$\dot{\mathbf{P}}(t) = -H\,\mathbf{P}(t). \qquad (4)$$

Here the generator matrix is

$$H = \begin{bmatrix} 2k_\mathrm{in} & -k_\mathrm{off} - k_\mathrm{abs} & -k_\mathrm{off} - k_\mathrm{abs} & 0 \\ -k_\mathrm{in} & k_\mathrm{tot} & -k_\mathrm{hop} & -k_\mathrm{abs} - k_\mathrm{off} \\ -k_\mathrm{in} & -k_\mathrm{hop} & k_\mathrm{tot} & -k_\mathrm{abs} - k_\mathrm{off} \\ 0 & -k_\mathrm{in} & -k_\mathrm{in} & 2k_\mathrm{off} + 2k_\mathrm{abs} \end{bmatrix}, \qquad (5)$$

with $k_\mathrm{tot} = k_\mathrm{in} + k_\mathrm{off} + k_\mathrm{abs} + k_\mathrm{hop}$.

To find the probability distribution of Q_1 and Q_2, we use the generating functional technique [36, 40–44]. Namely, we separate out the parts of H that correspond

to the absorption events

$$H \equiv H_0 + H_{\mathrm{abs},1} + H_{\mathrm{abs},2}, \tag{6}$$

$$H_{\mathrm{abs},1} = \begin{bmatrix} 0 & -k_{\mathrm{abs}} & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -k_{\mathrm{abs}} \\ 0 & 0 & 0 & 0 \end{bmatrix}, \tag{7}$$

$$H_{\mathrm{abs},2} = \begin{bmatrix} 0 & 0 & -k_{\mathrm{abs}} & 0 \\ 0 & 0 & 0 & -k_{\mathrm{abs}} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}. \tag{8}$$

Then we tag the terms corresponding to the absorption reactions by counting fields e^{χ_1} and e^{χ_2}, forming the tagged generator matrix,

$$\tilde{H}(\chi_1, \chi_2) \equiv H_0 + H_{\mathrm{abs},1} e^{\chi_1} + H_{\mathrm{abs},2} e^{\chi_2}. \tag{9}$$

Finally we realize that the vector of moment generating functions (or the Laplace transforms) of $P(Q_1, Q_2|k_{\mathrm{in}}, i, j)$, denoted as $\mathbf{Z}(\chi_1, \chi_2, t) = \{Z_{00}, Z_{01}, Z_{10}, Z_{11}\}$, satisfies the tagged master equation

$$\dot{\mathbf{Z}}(\chi_1, \chi_2, t) = -\tilde{H}(\chi_1, \chi_2)\mathbf{Z}(\chi_1, \chi_2, t). \tag{10}$$

We are interested in the long-time asymptotic, where each receptor has had many absorption events, $Q_1, Q_2 \gg 1$. Then the solution of Eq. (10) can be approximated as

$$\mathbf{Z}(\chi_1, \chi_2, t) \approx \mathbf{Z}(0) \exp[-\tilde{\lambda}_{\min}(\chi_1, \chi_2)\, t], \tag{11}$$

where $\tilde{\lambda}_{\min}$ is the smallest real part eigenvalue of $\tilde{H}$. From here, one can read off the cumulant generating functions conditional on the occupancy of the receptors, to the leading order in t, $F_{ij}(\chi_1, \chi_2, t) \approx -\tilde{\lambda}_{\min}(\chi_1, \chi_2)\, t$. As expected, the leading order is the same for any value of i, j. Thus the means and the (co)variances of the numbers of absorbed molecules, conditional on k_{in} all scale linearly with time. They can be obtained by differentiating $\tilde{\lambda}_{\min}(\chi_1, \chi_2)$ with respect to χ_1 and χ_2. Denoting by $\langle \ldots | k_{\mathrm{in}} \rangle$ expectations conditional on k_{in}, we write:

$$\langle Q_i | k_{\mathrm{in}} \rangle = t \left. \frac{\partial \tilde{\lambda}_{\min}(\chi_1, \chi_2, t)}{\partial \chi_i} \right|_{\chi_1, \chi_2 = 0}, \tag{12}$$

$$\langle \delta Q_i \delta Q_j | k_{\mathrm{in}} \rangle = t \left. \frac{\partial^2 \tilde{\lambda}_{\min}(\chi_1, \chi_2, t)}{\partial \chi_i \partial \chi_j} \right|_{\chi_1, \chi_2 = 0}. \tag{13}$$

In its turn, the eigenvalue $\tilde{\lambda}_{\min}$ can be obtained using non-Hermitian perturbation theory considering χ_i as the perturbation parameters around the eignevalue $\lambda_{\min} = 0$ of the unperturbed Hamiltonian [36]. For compactness of notation, we define $k_{\mathrm{ioa}} = k_{\mathrm{in}} + k_{\mathrm{off}} + k_{\mathrm{abs}}$. This gives:

$$\langle Q_i | k_{\mathrm{in}} \rangle = \frac{k_{\mathrm{in}} k_{\mathrm{abs}}\, t}{k_{\mathrm{ioa}}}, \tag{14}$$

$$\langle \delta Q_i \delta Q_i | k_{\mathrm{in}} \rangle = \langle Q_i | k_{\mathrm{in}} \rangle \times \left(1 - \frac{2 k_{\mathrm{in}} k_{\mathrm{abs}}}{k_{\mathrm{ioa}}^2} + \frac{2 k_{\mathrm{hop}} k_{\mathrm{in}} k_{\mathrm{abs}}}{k_{\mathrm{ioa}}^2 (k_{\mathrm{tot}} + k_{\mathrm{hop}})} \right), \tag{15}$$

$$\langle \delta Q_1 \delta Q_2 | k_{\mathrm{in}} \rangle = -2 \langle Q_i | k_{\mathrm{in}} \rangle \frac{k_{\mathrm{hop}} k_{\mathrm{in}} k_{\mathrm{abs}}}{k_{\mathrm{ioa}}^2 (k_{\mathrm{tot}} + k_{\mathrm{hop}})}. \tag{16}$$

These expressions fully define the conditional distribution $P(Q_1, Q_2|k_{\mathrm{in}})$ to the leading, Gaussian order. Notice that $\langle \delta Q_1 \delta Q_2 | k_{\mathrm{in}} \rangle < 0$ as long as $k_{\mathrm{hop}} \neq 0$, and thus, according to the sign rule, we expect more information from the two correlated receptors than the two independent ones with $k_{\mathrm{hop}} = 0$.

In the basis of $Q_\pm = Q_1 \pm Q_2$, the covariance matrix diagonalizes, and we get

$$\langle Q_+ | k_{\mathrm{in}} \rangle = \frac{2\, k_{\mathrm{in}} k_{\mathrm{abs}}\, t}{k_{\mathrm{ioa}}}, \tag{17}$$

$$\langle Q_- | k_{\mathrm{in}} \rangle = 0, \tag{18}$$

$$\left\langle \delta Q_+^2 | k_{\mathrm{in}} \right\rangle = \langle Q_+ | k_{\mathrm{in}} \rangle \frac{[k_{\mathrm{ioa}}^2 - 2 k_{\mathrm{in}} k_{\mathrm{abs}}]}{k_{\mathrm{ioa}}^2}, \tag{19}$$

$$\left\langle \delta Q_-^2 | k_{\mathrm{in}} \right\rangle = \langle Q_+ | k_{\mathrm{in}} \rangle \frac{k_{\mathrm{ioa}}^2 - 2 k_{\mathrm{in}} k_{\mathrm{abs}} + 2 k_{\mathrm{hop}} k_{\mathrm{ioa}}}{k_{\mathrm{ioa}} (k_{\mathrm{tot}} + k_{\mathrm{hop}})}, \tag{20}$$

$$\langle \delta Q_+ \delta Q_- | k_{\mathrm{in}} \rangle = 0. \tag{21}$$

Since neither $\langle Q_+ | k_{\mathrm{in}} \rangle$ nor $\left\langle \delta Q_+^2 | k_{\mathrm{in}} \right\rangle$ depend on k_{hop}, these expressions clearly show that the total number of molecules absorbed by the two receptors is not affected by the interaction parameter k_{hop}, as we alluded to previously. The coupling between the receptors only affects the variance of the difference of the number of molecules coming from each receptor.

We now define the absorption currents $J_\pm = Q_\pm / t$, so that $\langle J_\pm | k_{\mathrm{in}} \rangle = \langle Q_\pm | k_{\mathrm{in}} \rangle / t$, and $\left\langle \delta J_\pm^2 | k_{\mathrm{in}} \right\rangle = \left\langle \delta Q_\pm^2 | k_{\mathrm{in}} \right\rangle / t^2$. Now assuming a Gaussian marginal distribution of k_{in}, with the mean $\bar{k}_{\mathrm{in}}$ and the variance $\sigma_{k_{\mathrm{in}}}^2$, we write down the marginal distribution of absorption currents averaged over the external signal concentrations

$$P(J_+, J_-) = \int \frac{dk_{\mathrm{in}}}{\sqrt{2\pi}\sigma_{k_{\mathrm{in}}}} \exp\left[-\frac{(k_{\mathrm{in}} - \bar{k}_{\mathrm{in}})^2}{2\sigma_{k_{\mathrm{in}}}^2} \right] \times \frac{\exp\left[-\frac{(J_+ - \langle J_+ | k_{\mathrm{in}} \rangle)^2}{2\left\langle \delta J_+^2 | k_{\mathrm{in}} \right\rangle} - \frac{J_-^2}{2\left\langle \delta J_-^2 | k_{\mathrm{in}} \right\rangle} \right]}{2\pi \sqrt{\left\langle \delta J_+^2 | k_{\mathrm{in}} \right\rangle \left\langle \delta J_-^2 | k_{\mathrm{in}} \right\rangle}}. \tag{22}$$

Note that $\left\langle \delta J_\pm^2 | k_{\mathrm{in}} \right\rangle \propto 1/t$ for large t. This is the usual manifestation of the law of large numbers, so that the ratio of the standard deviation of the currents to their means decreases as $\propto 1/t^{1/2}$.

Both $\langle J_+ | k_{\mathrm{in}} \rangle$ and $\left\langle \delta J_\pm^2 | k_{\mathrm{in}} \right\rangle$ depend on k_{in}. We assume that $\sigma_{k_{\mathrm{in}}}^2$ is small, so that this dependences can be written to the first order in $\delta k_{\mathrm{in}} = k_{\mathrm{in}} - \bar{k}_{\mathrm{in}}$. Then the dependence of the mean currents on k_{in} preserves the Gaussian form of Eq. (22), while the dependence of the

variance manifests itself in sub-Gaussian orders. To the leading order in small $\sigma^2_{k_{\rm in}}$, the marginal distribution of the currents is still a product of two Gaussians,

$$P(J_+,J_-)=\frac{1}{2\pi\sigma_+\sigma_-}e^{-\frac{(J_+-\langle J_+\rangle)^2}{2\sigma_+^2}-\frac{J_-^2}{2\sigma_-^2}},\ \text{with} \quad (23)$$

$$\langle J_+\rangle=\frac{2\,\bar{k}_{\rm in}k_{\rm abs}}{\bar{k}_{\rm ioa}}, \quad (24)$$

$$\sigma_+^2=\left\langle\delta J_+^2|\bar{k}_{\rm in}\right\rangle\left[1+\left(\frac{\partial\langle J_+\rangle}{\partial k_{\rm in}}\right)^2_{\bar{k}}\frac{\sigma^2_{k_{\rm in}}}{\left\langle\delta J_+^2|\bar{k}_{\rm in}\right\rangle}\right], \quad (25)$$

$$\sigma_-^2=\left\langle\delta J_-^2|\bar{k}_{\rm in}\right\rangle. \quad (26)$$

The mutual information we are seeking is $I[Q_1,Q_2;k_{\rm in}]=S[Q_1,Q_2]-\langle S[Q_1,Q_2|k_{\rm in}]\rangle_{k_{\rm in}}$, where S are the marginal and the conditional entropies. In the limit of small σ^2_k, entropies are given by logarithms of the corresponding variances, so that

$$I[Q_1,Q_2;k_{\rm in}]=\frac{1}{2}\ln\left[1+\left(\frac{\partial\langle J_+\rangle}{\partial k_{\rm in}}\right)^2_{\bar{k}}\frac{\sigma^2_k}{\left\langle\delta J_+^2|\bar{k}_{\rm in}\right\rangle}\right], \quad (27)$$

which is independent of $k_{\rm hop}$.

The mutual information in Eq. (27) is independent of the interaction between the receptors, *violating* the sign rule. The reason for the violation is easy to trace: although the intrinsic receptor correlations are negative, the quantity $(1+\rho_\eta)\sigma^2_\eta=\left\langle\delta J_+^2|k_{\rm in}\right\rangle$ in Eq. (3) is independent of $k_{\rm hop}$! The biophysics of the problem conspires to ensure that the variance of the number of the absorbed ligands on the individual receptors increases by exactly the amount to counteract the receptor correlations to the Gaussian order in fluctuations. The effect of the correlations can only be seen in the higher order corrections. This answers our main question about the generality of the sign rule. Further, we note that the information in Eq. (27) is independent of J_-. This answers the second question: to the Gaussian order and for large t, keeping track of differences between the individual receptors does not change the amount of available information.

To study non-Gaussian effects of hopping we evaluate $\Delta I(\bar{k}_{\rm in},k_{\rm abs},k_{\rm hop})=I_{\bar{k}_{\rm in},k_{\rm abs},k_{\rm hop}}[Q_1,Q_2;k_{\rm in}]-I_{\bar{k}_{\rm in},k_{\rm abs},0}[Q_1,Q_2;k_{\rm in}]$, where the second term is equivalent to two independent receptors. We simulate the system using the Gillespie algorithm [45]. As illustrated in Fig. 2, $\Delta I<0$, so that the receptor coupling through hopping *reduces* the mutual information, contradicting the very sign of the sign rule. This is because the hopping introduces another stochastic process into the system, increasing the overall noise. Further, at $t\to\infty$, $\Delta I\to 0$ for all hopping rates, indicating that the receptor coupling does not provide extra information at large t compared to independent receptors even to non-Gaussian orders.

Discussion. We have analyzed a simple model of two identical receptors that are coupled through interactions with the same ligand. Our main finding is that, in this system, the variance and the co-variance of the receptor activities both depend on the interactions between the receptors in such a way that the interactions do not affect the amount of information between the receptor activities and the ligand concentration to the Gaussian order in fluctuations. We additionally discovered that the interactions have a *negative* effect on the amount of available information in sub-Gaussian orders, though the effect disappears at long observation time. These observations violate the well-known "sign rule" [11, 16]. In contrast, in most previous analyses, the variances of the individual sensors have been *assumed* independent of the interactions between the sensors [11, 18, 20, 21, 47], leading to the sign rule. We show that biophysical interactions do not necessarily obey such assumptions. We expect that similar concerns will be valid beyond receptors in individual cells, in applications such as neural population coding or multicellular molecular communication [17, 48]. Thus such mechanistic considerations must enter analyses of multivariate information processing.

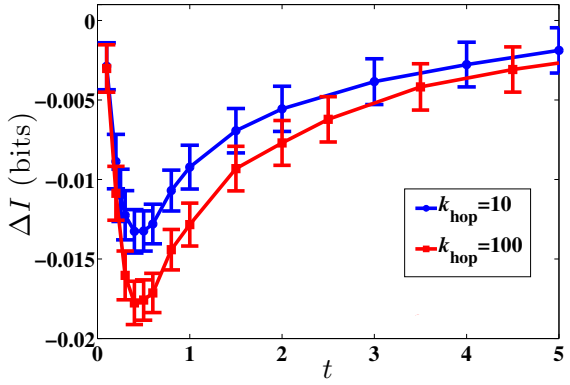

FIG. 2: Correlations due to molecular hopping reduce information about the signal. We plot the reduction in the information compared to two non-interacting receptors for $k_{\rm in}=k_{\rm abs}=10$. We use Gillespie [45] algorithm for simulations and NSB entropy estimator [46] to evaluate information from data. Each point is obtained from 10^6 samples from the steady state of the system dynamics for 17 values of $k_{\rm in}$.

In studies of cellular sensing, one often make an assumption that cells are only affected by the population-averaged activities of their receptors. In principle, additional information about the external ligand can be encoded in differences of activities of individual receptors since these differences depend on the concentrations, $Q_1-Q_2\sim\sqrt{k_{\rm in}}$. Our analysis provides a solid basis for this assumption by showing that, for long observation times, the cell has as much information about the signal when it tracks the sum of activities of its receptors as if it were to track activities of every individual receptor.

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Extrinsic and intrinsic correlations in molecular information transmission

Vijay Singh[1,2] Martin Tchernookov[1,3] and Ilya Nemenman[1,4]
[1]Department of Physics, Emory University, Atlanta, GA 30322, USA
[2]Computational Neuroscience Initiative, University of Pennsylvania, Philadelphia, PA 19104, USA
[3]Department of Physics, Lamar University, Beaumont, TX 77710
[4]Department of Biology, Emory University, Atlanta, GA 30322, USA

1. DERIVATION OF EQUATION 3

MUTUAL INFORMATION BETWEEN SIGNAL AND RESPONSE OF TWO INTERACTING UNITS

Assume that the signal s and the responses of the two units r_1 and r_2 conditional on s are all Gaussian, i.e.,

$$P(s) = \mathcal{N}\left(\bar{s}, \sigma_s^2\right)$$
$$P(r_1, r_2 \mid s) = \mathcal{N}\left((\bar{r}_1, \bar{r}_2), \Sigma\right),$$

here,
$\bar{s}$ and σ_s^2 are the mean and variance of the signal,
$(\bar{r}_1, \bar{r}_2)$ are the mean responses given the signal s,
$\Sigma = \sigma_\eta^2 \begin{pmatrix} 1 & \rho_\eta \\ \rho_\eta & 1 \end{pmatrix}$,
σ_η^2 is the response variance conditional on the stimulus s, and
ρ_η is the conditional correlation coefficient of the two responses.

Assuming that σ_s^2 is small, such that Σ can be regarded as a constant, and

$$r_i(s) = r_i(\bar{s}) + \partial_s r_i(\bar{s})\,(s - \bar{s}),$$

the joint distribution is:

$$P(r_1, r_2) = \int ds\, P(r_1, r_2 \mid s)\, P(s) = \mathcal{N}\left((\bar{r}_1(\bar{s}), \bar{r}_2(\bar{s})), \tilde{\Sigma}\right)$$

where

$$\tilde{\Sigma} = \Sigma\left(1 + \sigma_s^2 \begin{bmatrix} \partial_s \bar{r}_1(s) \\ \partial_s \bar{r}_2(s) \end{bmatrix} \Sigma^{-1} \left[\partial_s \bar{r}_1(s),\ \partial_s \bar{r}_2(s)\right]\right)_{\bar{s}}$$

For a normal distribution, $\mathcal{N}(\mu, \Sigma)$, the entropy is $\frac{1}{2}\log|\Sigma|$ up to an additive constant, so we have the mutual information as

$$I[r_1, r_2; s] = S[r_1, r_2] - \langle S[r_1, r_2 \mid s] \rangle_{\bar{s}} = \frac{1}{2}\log\left[1 + \frac{(\partial_s \bar{r}(s))^2\, \sigma_s^2}{(1+\rho_\eta)\,\sigma_\eta^2}\right]_{\bar{s}},$$

where we have chosen $\bar{r}_1 = \bar{r}_2 = \bar{r}$ for identical units.

For response linearly depending on s, this is equivalent to Eq. (4) in the main text.

2. Solution of the model using perturbation theory

1. The Generator Matrix and its Eigen-system

The tagged generator matrix is given as

```
TildeH[χ1_, χ2_, kin_, koff_, kabs_, khop_] := (−1) {{−2 kin, kabs Exp[ χ1] + koff, kabs Exp[ χ2] + koff, 0},
    {kin, −kin − kabs − koff − khop, khop, kabs Exp[ χ2] + koff},
    {kin, khop, −kin − kabs  − koff − khop, koff + kabs Exp[ χ1]}, {0, kin, kin, −2 kabs − 2 koff}};
MatrixForm[TildeH[χ1, χ2, kin, koff, kabs, khop]]
```

$$\begin{pmatrix} 2\,kin & -e^{\chi 1}\,kabs - koff & -e^{\chi 2}\,kabs - koff & 0 \\ -kin & kabs + khop + kin + koff & -khop & -e^{\chi 2}\,kabs - koff \\ -kin & -khop & kabs + khop + kin + koff & -e^{\chi 1}\,kabs - koff \\ 0 & -kin & -kin & 2\,kabs + 2\,koff \end{pmatrix}$$

The original generator matrix is:

```
H  = TildeH[0, 0, kin, koff, kabs, khop]; MatrixForm[H]
```

$$\begin{pmatrix} 2\,kin & -kabs - koff & -kabs - koff & 0 \\ -kin & kabs + khop + kin + koff & -khop & -kabs - koff \\ -kin & -khop & kabs + khop + kin + koff & -kabs - koff \\ 0 & -kin & -kin & 2\,kabs + 2\,koff \end{pmatrix}$$

The left and right Eigen-systems of the generator matrix is

```
ER = Eigensystem[H]
EL = Eigensystem[Transpose[H]]
```

$$\left\{\{0,\ kabs + kin + koff,\ 2\,(kabs + kin + koff),\ kabs + 2\,khop + kin + koff\},\right.$$
$$\left\{\left\{-\frac{-kabs^2 - 2\,kabs\,koff - koff^2}{kin^2}, -\frac{-kabs - koff}{kin}, -\frac{-kabs - koff}{kin}, 1\right\},\right.$$
$$\left.\left.\left\{-\frac{kabs + koff}{kin}, -\frac{-kabs + kin - koff}{2\,kin}, -\frac{-kabs + kin - koff}{2\,kin}, 1\right\}, \{1, -1, -1, 1\}, \{0, -1, 1, 0\}\right\}\right\}$$

$$\left\{\{0,\ kabs + kin + koff,\ 2\,(kabs + kin + koff),\ kabs + 2\,khop + kin + koff\},\right.$$
$$\left\{\{1, 1, 1, 1\}, \left\{-\frac{kin}{kabs + koff}, -\frac{-kabs + kin - koff}{2\,(kabs + koff)}, -\frac{-kabs + kin - koff}{2\,(kabs + koff)}, 1\right\},\right.$$
$$\left.\left.\left\{\frac{kin^2}{(kabs + koff)^2}, -\frac{kin}{kabs + koff}, -\frac{kin}{kabs + koff}, 1\right\}, \{0, -1, 1, 0\}\right\}\right\}$$

The perturbative part to the original generator matrix can be obtained by taking the difference between the tagged generator matirix and the original generator martrix. The difference defined as “delTildeH” is

```
delTildeH = TildeH[χ1, χ2, kin, koff, kabs, khop] − TildeH[0, 0, kin, koff, kabs, khop]; MatrixForm[delTildeH]
```

$$\begin{pmatrix} 0 & kabs - e^{\chi 1}\,kabs & kabs - e^{\chi 2}\,kabs & 0 \\ 0 & 0 & 0 & kabs - e^{\chi 2}\,kabs \\ 0 & 0 & 0 & kabs - e^{\chi 1}\,kabs \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

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2. Corrected Eigenvalues and Eigenvectors

Using the eigensystem of the generator matrix and delTildeH, we can get the correction to the eigenvalues and eigenvectors usign pertuebation theory. The corrected eigenvalues are:

```
Do[λi = Simplify[Part[ER, 1, i] + 1/(Part[EL, 2, i].Part[ER, 2, i])
    ((Part[EL, 2, i].delTildeH.Part[ER, 2, i]) + Sum[((Part[EL, 2, i].delTildeH.Part[ER, 2, j]) *
        (Part[EL, 2, j].delTildeH.Part[ER, 2, i]))/(Part[EL, 2, j].Part[ER, 2, j]) *
    (If[j == i, 0, 1/(Part[ER, 1, i] - Part[ER, 1, j])]), {j, 1, 4}])], {i, 1, 4}]
```

Similarly the corrected left and right eigen-vectors are:

```
Do[{Ri = Simplify[1/Sqrt[Part[EL, 2, i].Part[ER, 2, i]]
    (Part[ER, 2, i] + Sum[(Part[ER, 2, j] * (Part[EL, 2, j].delTildeH.Part[ER, 2, i]))/
        (Part[EL, 2, j].Part[ER, 2, j]) * If[j == i, 0, 1/((Part[ER, 1, i] - Part[ER, 1, j]))], {j, 1, 4}])],
  Li = Simplify[1/Sqrt[Part[EL, 2, i].Part[ER, 2, i]] (Part[EL, 2, i] +
    Sum[((Part[EL, 2, i].delTildeH.Part[ER, 2, j]) * Part[EL, 2, j])/(Part[EL, 2, j].Part[ER, 2, j]) *
      If[j == i, 0, 1/((Part[ER, 1, i] - Part[ER, 1, j]))], {j, 1, 4}])}, {i, 1, 4}]
```

---

3. Steady state occupation of the receptors (Equilibrium conditions)

The probability of occupation is given by the vector $\{P_{00},P_{01},P_{10},P_{11}\}$. In steady state the probabity of occupation can be determined by solving the equation

$$P(t)\,H = 0$$

The solution is:

```
P0 = Simplify[Part[{P00, P01, P10, P11} /. Solve[{2 kin P00 + (-kabs - koff) P01 + (-koff - kabs) P10 == 0,
      -kin P00 + (koff + khop + kin + kabs) P01 - khop P10 + (-koff - kabs) P11 == 0,
      -kin P01 - kin P10 + (2 koff + 2 kabs) P11 == 0,
      P00 + P01 + P10 + P11 == 1}, {P00, P01, P10, P11}], 1]]
```

$$\left\{\frac{(kabs+koff)^2}{(kabs+kin+koff)^2}, \frac{kin\,(kabs+koff)}{(kabs+kin+koff)^2}, \frac{kin\,(kabs+koff)}{(kabs+kin+koff)^2}, \frac{kin^2}{(kabs+kin+koff)^2}\right\}$$

---

4. Probablity generating function for (Q_1, Q_2)

```
GenFun = Simplify[{1, 1, 1, 1}.(Sum[Exp[-λi * t] Li.P0 Ri, {i, 1, 4}])];
```

---

5. Mean and Variance of (Q_1, Q_2)

By taking the derivative of the cumulant generating function, Log[GenFun], one can get the mean and the variances.

Mean number of accumulated molecules. $< Q_1| k_{in}>$ or $< Q_2| k_{in}>$

```
Qmean = Simplify[D[Log[GenFun], χ1] /. {χ1 → 0, χ2 → 0}]
```

$$\frac{\text{kabs kin t}}{\text{kabs + kin + koff}}$$

Variance $< \delta Q^2_1 | k_{in} >$ or $< \delta Q^2_2 | k_{in} >$

```
δQsq11 = FullSimplify[D[D[Log[GenFun], χ1], χ1] /. {χ1 → 0, χ2 → 0}]
```

$$\left(e^{-(\text{kabs}+2\,\text{khop}+\text{kin}+\text{koff})\,t}\,\text{kabs kin}\right.$$
$$\left(e^{(\text{kabs}+2\,\text{khop}+\text{kin}+\text{koff})\,t}\,\text{kabs}^5\,t + e^{(\text{kabs}+2\,\text{khop}+\text{kin}+\text{koff})\,t}\,(\text{kin}+\text{koff})^3\,(2\,\text{khop}+\text{kin}+\text{koff})^2\,t + \right.$$
$$e^{(\text{kabs}+2\,\text{khop}+\text{kin}+\text{koff})\,t}\,\text{kabs}^4\,(4\,\text{khop}+3\,\text{kin}+5\,\text{koff})\,t -$$
$$\text{kabs}\left(\text{kin}\,(\text{kin}+\text{koff})^2 + e^{2\,\text{khop}\,t}\,\text{kin}\,(2\,\text{khop}+\text{kin}+\text{koff})^2 - e^{(\text{kabs}+2\,\text{khop}+\text{kin}+\text{koff})\,t}\,(\text{kin}+\text{koff})\right.$$
$$\left.(2\,\text{khop}+\text{kin}+\text{koff})\,((\text{kin}+\text{koff})\,(3\,\text{kin}+5\,\text{koff}) + \text{khop}\,(4\,\text{kin}+6\,\text{koff}))\,t\right) -$$
$$2\,\text{kabs}^2\left(\text{kin}\,(\text{kin}+\text{koff}) + e^{2\,\text{khop}\,t}\,\text{kin}\,(2\,\text{khop}+\text{kin}+\text{koff}) - e^{(\text{kabs}+2\,\text{khop}+\text{kin}+\text{koff})\,t}\right.$$
$$\left.\left(6\,\text{khop}\,(\text{kin}+\text{koff})\,(\text{kin}+2\,\text{koff}) + (\text{kin}+\text{koff})^2\,(2\,\text{kin}+5\,\text{koff}) + \text{khop}^2\,(4\,\text{kin}+6\,\text{koff})\right)t\right) +$$
$$\text{kabs}^3\left(-\left(1+e^{2\,\text{khop}\,t}\right)\text{kin} + 2\,e^{(\text{kabs}+2\,\text{khop}+\text{kin}+\text{koff})\,t}\left(2\,\text{khop}^2 + (\text{kin}+\text{koff})\,(2\,\text{kin}+5\,\text{koff}) + \right.\right.$$
$$\left.\left.\left.\text{khop}\,(5\,\text{kin}+8\,\text{koff})\right)t\right)\right)\Big/\left((\text{kabs}+\text{kin}+\text{koff})^4\,(\text{kabs}+2\,\text{khop}+\text{kin}+\text{koff})^2\right)$$

Covariance $< \delta Q_1 \, \delta Q_2 | k_{in} >$.

```
δQsq12 = FullSimplify[D[D[Log[GenFun], χ1], χ2] /. {χ1 → 0, χ2 → 0}]
```

$$\left(e^{-(\text{kabs}+2\,\text{khop}+\text{kin}+\text{koff})\,t}\,\text{kabs}^2\,\text{kin}^2\right.$$
$$\left((\text{kin}+\text{koff})^2 - e^{2\,\text{khop}\,t}\,(2\,\text{khop}+\text{kin}+\text{koff})^2 - 2\,e^{(\text{kabs}+2\,\text{khop}+\text{kin}+\text{koff})\,t}\,\text{khop}\,(\text{kin}+\text{koff})\right.$$
$$(2\,\text{khop}+\text{kin}+\text{koff})\,t - \text{kabs}^2\left(-1 + e^{2\,\text{khop}\,t} + 2\,e^{(\text{kabs}+2\,\text{khop}+\text{kin}+\text{koff})\,t}\,\text{khop}\,t\right) +$$
$$\left.2\,\text{kabs}\left(\text{kin}+\text{koff} - e^{2\,\text{khop}\,t}\,(2\,\text{khop}+\text{kin}+\text{koff}) - 2\,e^{(\text{kabs}+2\,\text{khop}+\text{kin}+\text{koff})\,t}\,\text{khop}\,(\text{khop}+\text{kin}+\text{koff})\,t\right)\right)\Big/$$
$$\left.\left((\text{kabs}+\text{kin}+\text{koff})^4\,(\text{kabs}+2\,\text{khop}+\text{kin}+\text{koff})^2\right)\right.$$

Covariance matrix.

```
Sig = {{δQsq11, δQsq12}, {δQsq12, δQsq11}};
```

---

6. Transformation from (Q_1, Q_2) to (Q_+, Q_-)

Let us first express (Q_1, Q_2) in terms of (Q_+, Q_-).

```
Solve[{δQ+ == Q1 + Q2 − 2 Qmean, Q− == Q1 − Q2}, {Q1, Q2}]
```

$$\left\{\left\{\text{Q1} \to \frac{\text{kabs kin t}}{\text{kabs + kin + koff}} + \frac{\text{Q}_-}{2} + \frac{\delta\text{Q}_+}{2},\ \text{Q2} \to \right.\right.$$
$$\left.\left.-((-2\,\text{kabs kin t} + \text{kabs Q}_- + \text{kin Q}_- + \text{koff Q}_- - \text{kabs}\,\delta\text{Q}_+ - \text{kin}\,\delta\text{Q}_+ - \text{koff}\,\delta\text{Q}_+)/(2\,(\text{kabs} + \text{kin} + \text{koff})))\right\}\right\}$$

Now the term inside the exponential of the gaussian can be written as

```
exponent = {Q1 − Qmean, Q2 − Qmean}.Inverse[Sig].{Q1 − Qmean, Q2 − Qmean} /.
```

$$\left\{\left\{\text{Q1} \to \frac{\text{kabs kin t}}{\text{kabs + kin + koff}} + \frac{\text{Q}_-}{2} + \frac{\delta\text{Q}_+}{2},\ \text{Q2} \to -((-2\,\text{kabs kin t} + \text{kabs Q}_- + \text{kin Q}_- + \right.\right.$$
$$\left.\left.\text{koff Q}_- - \text{kabs}\,\delta\text{Q}_+ - \text{kin}\,\delta\text{Q}_+ - \text{koff}\,\delta\text{Q}_+)/(2\,(\text{kabs} + \text{kin} + \text{koff})))\right\}\right\};$$

Next we express the term inside the exponential in terms of Q_+ and Q_-, and collect the terms corresponding to Q^2_+ and Q^2_-

exponentSimplified = Simplify[Normal[Series[exponent, {δQ_+, 0, 3}]]]

$$\left\{\frac{1}{2\,\text{kabs}\,\text{kin}}\,e^{(\text{kabs}+2\,\text{khop}+\text{kin}+\text{koff})\,t}\,(\text{kabs}+\text{kin}+\text{koff})^2\right.$$
$$\left(\left((\text{kabs}+2\,\text{khop}+\text{kin}+\text{koff})^2\,Q_-^2\right)\Big/\left(e^{(\text{kabs}+2\,\text{khop}+\text{kin}+\text{koff})\,t}\,\text{kabs}^3\,t+e^{(\text{kabs}+2\,\text{khop}+\text{kin}+\text{koff})\,t}\,(\text{kin}+\text{koff})\right.\right.$$
$$(2\,\text{khop}+\text{kin}+\text{koff})^2\,t+e^{(\text{kabs}+2\,\text{khop}+\text{kin}+\text{koff})\,t}\,\text{kabs}^2\,(4\,\text{khop}+\text{kin}+3\,\text{koff})\,t+$$
$$\text{kabs}\left(e^{(\text{kabs}+2\,\text{khop}+\text{kin}+\text{koff})\,t}\,\text{kin}^2\,t+e^{(\text{kabs}+2\,\text{khop}+\text{kin}+\text{koff})\,t}\left(4\,\text{khop}^2+8\,\text{khop}\,\text{koff}+3\,\text{koff}^2\right)t+\right.$$
$$\left.\left.\text{kin}\left(-2+4\,e^{(\text{kabs}+2\,\text{khop}+\text{kin}+\text{koff})\,t}\,(\text{khop}+\text{koff})\,t\right)\right)\right)+$$
$$\left((\text{kabs}+\text{kin}+\text{koff})^2\,\delta Q_+^2\right)\Big/\left(-2\,e^{2\,\text{khop}\,t}\,\text{kabs}\,\text{kin}+e^{(\text{kabs}+2\,\text{khop}+\text{kin}+\text{koff})\,t}\right.$$
$$\left.\left.\left(\text{kabs}^3+(\text{kin}+\text{koff})^3+\text{kabs}^2\,(\text{kin}+3\,\text{koff})+\text{kabs}\left(\text{kin}^2+4\,\text{kin}\,\text{koff}+3\,\text{koff}^2\right)\right)t\right)\right)\Big\}$$

$< \delta Q^2{}_+ \mid k_{\text{in}} >$ can be obtained as the inverse of the coefficient of the term corresponding to $\delta Q^2{}_+$.

varδQsum = 1 / Coefficient[exponentSimplified, $\delta Q_+{}^2$]

$$\left\{\frac{1}{(\text{kabs}+\text{kin}+\text{koff})^4}\,2\,e^{-(\text{kabs}+2\,\text{khop}+\text{kin}+\text{koff})\,t}\,\text{kabs}\,\text{kin}\left(-2\,e^{2\,\text{khop}\,t}\,\text{kabs}\,\text{kin}+\right.\right.$$
$$\left.\left.e^{(\text{kabs}+2\,\text{khop}+\text{kin}+\text{koff})\,t}\left(\text{kabs}^3+(\text{kin}+\text{koff})^3+\text{kabs}^2\,(\text{kin}+3\,\text{koff})+\text{kabs}\left(\text{kin}^2+4\,\text{kin}\,\text{koff}+3\,\text{koff}^2\right)\right)t\right)\right\}$$

$< \delta Q^2{}_- \mid k_{\text{in}} >$ can be obtained as the inverse of the coefficient of the term corresponding to $Q^2{}_-$.

varδQdiff = 1 / Coefficient[exponentSimplified, $Q_-{}^2$]

$$\left\{\left(2\,e^{-(\text{kabs}+2\,\text{khop}+\text{kin}+\text{koff})\,t}\,\text{kabs}\,\text{kin}\right.\right.$$
$$\left(e^{(\text{kabs}+2\,\text{khop}+\text{kin}+\text{koff})\,t}\,\text{kabs}^3\,t+e^{(\text{kabs}+2\,\text{khop}+\text{kin}+\text{koff})\,t}\,(\text{kin}+\text{koff})\,(2\,\text{khop}+\text{kin}+\text{koff})^2\,t+\right.$$
$$e^{(\text{kabs}+2\,\text{khop}+\text{kin}+\text{koff})\,t}\,\text{kabs}^2\,(4\,\text{khop}+\text{kin}+3\,\text{koff})\,t+$$
$$\text{kabs}\left(e^{(\text{kabs}+2\,\text{khop}+\text{kin}+\text{koff})\,t}\,\text{kin}^2\,t+e^{(\text{kabs}+2\,\text{khop}+\text{kin}+\text{koff})\,t}\left(4\,\text{khop}^2+8\,\text{khop}\,\text{koff}+3\,\text{koff}^2\right)t+\right.$$
$$\left.\left.\left.\text{kin}\left(-2+4\,e^{(\text{kabs}+2\,\text{khop}+\text{kin}+\text{koff})\,t}\,(\text{khop}+\text{koff})\,t\right)\right)\right)\right)\Big/$$
$$\left.\left((\text{kabs}+\text{kin}+\text{koff})^2\,(\text{kabs}+2\,\text{khop}+\text{kin}+\text{koff})^2\right)\right\}$$

In the long time limit, t -> ∞, these can be written as

Assuming[kin > 0 && kabs > 0 && khop > 0 && koff > 0, Limit[varδQsum/t, t $\to \infty$]]

$$\left\{\left(2\,\text{kabs}\,\text{kin}\left(\text{kabs}^2+2\,\text{kabs}\,\text{koff}+(\text{kin}+\text{koff})^2\right)\right)\Big/(\text{kabs}+\text{kin}+\text{koff})^3\right\}$$

Assuming[kin > 0 && kabs > 0 && khop > 0 && koff > 0, Limit[varδQdiff/t, t $\to \infty$]]

$$\left\{\left(2\,\text{kabs}\,\text{kin}\left(\text{kabs}^2+2\,\text{kabs}\,(\text{khop}+\text{koff})+(\text{kin}+\text{koff})\,(2\,\text{khop}+\text{kin}+\text{koff})\right)\right)\Big/\right.$$
$$\left.\left((\text{kabs}+\text{kin}+\text{koff})^2\,(\text{kabs}+2\,\text{khop}+\text{kin}+\text{koff})\right)\right\}$$

The last two expressions are the variance of J_+ and J_- as given in the main text.