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Active transport improves the precision of linear long distance molecular signalling

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Abstract

Molecular signalling in living cells occurs at low copy numbers and is thereby inherently limited by the noise imposed by thermal diffusion. The precision at which biochemical receptors can count signalling molecules is intimately related to the noise correlation time. In addition to passive thermal diffusion, messenger RNA and vesicle-engulfed signalling molecules can transiently bind to molecular motors and are actively transported across biological cells. Active transport is most beneficial when trafficking occurs over large distances, for instance up to the order of 1 metre in neurons. Here we explain how intermittent active transport allows for faster equilibration upon a change in concentration triggered by biochemical stimuli. Moreover, we show how intermittent active excursions induce qualitative changes in the noise in effectively one-dimensional systems such as dendrites. Thereby they allow for significantly improved signalling precision in the sense of a smaller relative deviation in the concentration read-out by the receptor. On the basis of linear response theory we derive the exact mean field precision limit for counting actively transported molecules. We explain how intermittent active excursions disrupt the recurrence in the molecular motion, thereby facilitating improved signalling accuracy. Our results provide a deeper understanding of how recurrence affects molecular signalling precision in biological cells and novel medical-diagnostic devices.

Keywords: noise in biochemical signalling, Brownian motion, active transport, linear response theory, fluctuation–dissipation theorem, generalised Langevin equation, recurrence

(Some figures may appear in colour only in the online journal)

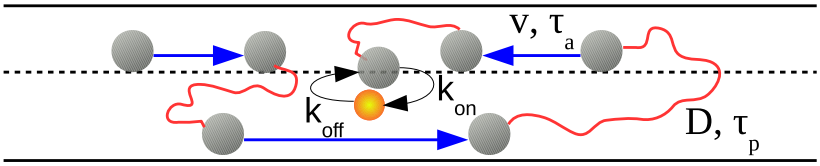

Figure 1. Model system: signalling particles (grey) perform passive thermal diffusion (red phases) interrupted by active ballistic excursions with constant speed and random direction (blue phases moving along the motor tracks). The duration of both phases is distributed exponentially with mean times $\tau_{p,a}$. When the particle reaches the receptor (orange sphere) it binds/dissociates with rates $k_{\rm on}$ and $k_{\rm off}$. Due to the specific geometry the system is effectively one-dimensional.

1. Introduction

In his seminal work on reaction-rate theory in the diffusion-controlled limit Smoluchowski established a quantitative connection between thermal fluctuations in the form of molecular diffusion and a macroscopically observable time evolution of the concentration of reactants and products [1]. Some 60 years later Berg and Purcell [2] showed that thermal diffusion also limits the accuracy of biochemical receptors and hence sets physical bounds to the precision of cellular signalling. Namely, cellular signalling typically involves low copy numbers of messenger molecules and is thereby inevitably subjected to appreciable fluctuations in the count of molecular binding events at biochemical receptors [2–7]. In a similar way counting noise limits the precision and sensitivity of modern microscopic diagnostic devices in medicine technology [8]. State-of-the-art single particle tracking techniques indeed highlight the inherent stochasticity of such molecular signalling events [10–13]. However, despite the significant sample-to-sample fluctuations cellular signalling operates at remarkable precision [14, 15]. Inside living cells some signalling molecules, typically entrapped in vesicles, do not only move by thermal diffusion alone but may also be actively transported along cellular filaments by molecular motors [16, 17] causing intermittent ballistic excursions [18]. Free molecules, such as messenger RNA, may as well attach to motors [19], or proteins may move in a directed fashion due to cytoplasmic drag [20]. Enhanced spreading may finally be facilitated by cytoplasmic streaming [21, 22]. A practical way to incorporate active motion in the stochastic dynamics of signalling molecules is the model of random intermittent search [23, 24] which was recently used to analyse reaction kinetics in active media [27] and the speed and precision of receptor signalling in three-dimensional media [6].

In a mean field picture of receptor signalling at equilibrium, developed by Bialek and Setayeshgar [3], signalling molecules diffuse in space and reversibly bind to the receptor in a Markovian fashion (figure 1). The central object of the theory is the so-called receptor-noise correlation time τ_c [2–4, 6, 7]. Namely, in a setting where the receptor measures the concentration over a period τ_m—much longer than any correlation time in the system—the noise in the receptor occupancy statistic will be Poissonian, and the concentration estimate will improve with the number $N_i \propto \tau_m/\tau_c$ of independent measurements. The correlation time is set by the thermal noise in the binding to the receptor and the thermal diffusion of the signalling molecules [2–4, 7] but can be altered by certain details of the transport, such as intermittent sliding along DNA in the so-called facilitated diffusion model of gene regulation [4] and intermittent active excursion by hitchhiking molecular motors [6]. In addition, τ_c depends on the dimensionality of the cell or domain in which it occurs [4, 7]. Moreover, when molecules explore their surrounding space in a compact manner—the motion is recurrent in

the sense of returning to already visited sites [25]—such as the one observed in one-dimensional diffusion, the recurrences prolong τ_c and thus reduce N_i within a given fixed τ_m [4]. Conversely, the interaction with a confining domain disrupts the positional correlations at long times [26] and thereby truncates τ_c, causing an improvement of the sensing precision especially in low dimensions [7].

It was shown in the case of chemical reactions coupled to active transport that the effect of active excursions is most pronounced in low dimensions since they act by disrupting the recurrence of one-dimensional Brownian motion [23, 24, 27]. Here we demonstrate that the effect of intermittent active motion in one-dimensional diffusive systems is even stronger when it comes to the sensing precision. We compute analytically the accuracy limit for receptor mediated concentration measurements in dimension 1 and argue that active excursions allow for enhanced precision of signalling in neurons.

2. Linear response theory of receptor noise coupled to active transport

We consider a signalling molecule (mRNA or protein) diffusing on the real line and randomly switching between a passive diffusion phase p with diffusivity D and an active ballistic phase a with velocity $\pm v$, see figure 1 and [6, 24, 27]. The duration of active/passive phases is exponentially distributed with mean $\tau_{a,p}$. The concentrations of freely diffusing and motor-bound signalling molecules are $c_p(x, t)$ and $c_a^{\pm}(x, t)$ and $\pm$ denotes motor-bound signalling molecules moving to the left/right, respectively. In addition, while passively diffusing the signalling molecule can reversibly bind to a receptor at x_0 in a Markov fashion. In a mean field description the fractional receptor occupancy $n(t)$ with on/off rates $k_{\mathrm{on/off}}$ evolves according to the coupled equations

$$\frac{\mathrm{d}n(t)}{\mathrm{d}t} = k_{\mathrm{on}} c_p(x_0, t)[1 - n(t)] - k_{\mathrm{off}} n(t), \tag{1a}$$

$$\frac{\partial c_p(x, t)}{\partial t} = D\partial_x^2 c_p + \frac{c_a^+(x, t) + c_a^-(x, t)}{\tau_a} - \frac{c_p(x, t)}{\tau_p} - \delta(x - x_0)\frac{\mathrm{d}n(t)}{\mathrm{d}t}, \tag{1b}$$

$$\frac{\partial c_a^{\pm}(x, t)}{\partial t} = \mp v\partial_x c_a^{\pm}(x, t) - \frac{c_a^{\pm}(x, t)}{\tau_a} + \frac{c_p(x, t)}{2\tau_p}, \tag{1c}$$

where detailed balance is fulfilled for the binding $k_{\mathrm{on}}\langle c_p\rangle/k_{\mathrm{off}} = \exp(F/k_BT)$ involving the binding free energy F. Equations (1*a*)–(1*c*) describe the motion of a molecule randomly switching between phases of passive diffusion and ballistic motion with rates τ_p^{-1} and τ_a^{-1}. Once the molecule locates the receptor at x_0 while being in the passive phase, it can bind to it. The total binding rate is proportional to the intrinsic rate k_{on}, the probability $c_p(x_0, t)$ to find the molecule at x_0 in the passive phase, and the probability $1 - n(t)$ that the receptor is unoccupied. Once being bound to the receptor the molecule unbinds with a first order rate proportional to the intrinsic unbinding rate k_{off} and the probability $n(t)$ to find the receptor occupied. Note that since c_p has units of 1/length and $n(t)$ is dimensionless, the rates $k_{\mathrm{on/off}}$ have different units, i.e. k_{on} has the units of length/time and k_{off} has units of 1/time.

To obtain a closed equation for the dynamics of $n(t)$ close to equilibrium, we linearise equations (1*a*)–(1*c*) around the respective equilibrium values $\langle n\rangle$, $\langle c_p\rangle$, and $\langle c_a^{\pm}\rangle$ [3] to obtain, in terms of small fluctuations, $n(t) = \langle n\rangle + \delta n(t)$ and $c_p(x, t) = \langle c_p\rangle + \delta c_p(x, t)$, and $c_a^{\pm}(x, t) = \langle c_a^{\pm}\rangle + \delta c_a^{\pm}(x, t)$. Moreover, the detailed balance condition imposes the constraint

$\delta k_{on}/k_{on} - \delta k_{off}/k_{off} = \delta F/k_B T$ on the free energy fluctuations. By Fourier transforming in time and in space, $\hat{\mathcal{F}}_t(t \to \omega)[\cdot] = \int_0^\infty e^{i\omega t}(\cdot)dt$, $\hat{\mathcal{F}}_x(x \to k)[\cdot] = \int_{-\infty}^\infty e^{-ikx}(\cdot)dx$, and solving the resulting system of ordinary equations we arrive at an exact generalised Langevin equation for the fluctuations around the equilibrium receptor occupancy within the linear regime [6]

$$\int_0^t \gamma(t-t')\frac{d\delta n(t')}{dt'} + \tau_b^{-1}d\delta n(t) = \frac{k_{off}\langle n\rangle \delta F(t)}{k_B T}. \tag{2}$$

Here τ_b denotes the correlation time of two-state Markov switching, $\tau_b = (k_{on}\langle c_p\rangle - k_{off})^{-1}$, and the noise in the form of the free energy fluctuations $\delta F(t)$ has zero mean $\langle \delta F(t)\rangle = 0$ and obeys the fluctuation–dissipation theorem $\langle \delta F(t)\delta F(t')\rangle = 2(k_B T/k_{off}\langle n\rangle)^2\gamma(t-t')$ [28]. The memory kernel $\gamma(t)$ in terms of an inverse Fourier transform operator reads

$$\gamma(t) = \delta(t) + \hat{\mathcal{F}}_t^{-1}\left[\lim_{a\to 0}\int_{-\pi/a}^{\pi/a} e^{ikx}\frac{dk}{2\pi}\frac{k_{on}(1-\langle n\rangle)}{-i\omega + Dk^2 + \Lambda_k(\tau_a, \tau_p; \omega)}\right], \tag{3}$$

and the contribution due to the intermittent active excursions is

$$\Lambda_k(\tau_a, \tau_p; \omega) = (\tau_a\tau_p)^{-1}\frac{\tau_a^{-1} - i\omega}{v^2k^2 + (\tau_a^{-1} - i\omega)^2}. \tag{4}$$

The limit in equation (3) is to be understood as a finite receptor size taken to zero after the integral is evaluated in order for the integral to converge. The memory term in the Langevin equation (2) reflects the fact that it takes a finite time before the receptor feels the effect of $\delta F(t)$ because the signalling molecule moves throughout space before (re)binding.

According to linear response theory [3, 28] we can write $\delta n(t) = \int_0^t \alpha(t')\delta F(t-t')dt'$ where the generalised susceptibility becomes

$$\alpha(t) = \hat{\mathcal{F}}_t^{-1}[\tilde{\alpha}(\omega)] = \hat{\mathcal{F}}_t^{-1}\left[\frac{\delta\tilde{n}(\omega)}{\delta\tilde{F}(\omega)}\right], \tag{5}$$

and the power spectrum of $\delta n(t)$ is in turn obtained according to the fluctuation–dissipation theorem from the imaginary part of $\tilde{\alpha}(\omega)$,

$$S_{\delta n}(\omega) = \frac{2k_B T}{\omega}\,\mathrm{Im}[\tilde{\alpha}(\omega)]. \tag{6}$$

Since the receptor's sensitivity is limited to frequencies $|\omega| \leqslant \tau_m^{-1}$, the uncertainty in measuring the occupation fraction will be

$$\overline{\delta n^2} = \int_{-1/\tau_m}^{1/\tau_m} S_{\delta n}(\omega)d\omega. \tag{7}$$

Moreover, a change in concentration is equivalent to a change in F, $\delta c_p/\langle c_p\rangle = \delta F/k_B T$. Using this one can also show that [3]

$$S_{\delta c_p}(\omega) = \left(\frac{\langle c_p\rangle}{k_B T}\right)^2\left|\frac{\delta\tilde{n}(\omega)}{\delta\tilde{F}(\omega)}\right|^{-2} S_{\delta n}(\omega), \tag{8}$$

and use this to relate the uncertainty in δn to the precision at which the receptor can determine c_p.

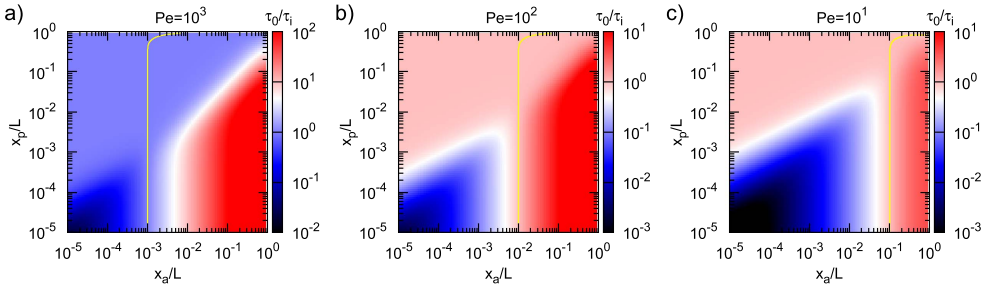

Figure 2. Ratio τ_0/τ_i of equilibration times for passive diffusion (subscript 0) and intermittent active motion (subscript i) as a function of the typical lengths of active (x_a) and passive (x_p) displacements for various Péclet numbers $\mathrm{Pe} = Lv/D$. The yellow line corresponds to $\tau_0/\tau_i = 1$. Whenever $\tau_0/\tau_i > 1$ active motion leads to faster equilibration.

3. Equilibration rate

We split the signalling process into an equilibration phase, during which the system equilibrates to a new concentration, and the measurement phase, during which the receptor reads out this equilibrium concentration. Moreover, we assume that the equilibration time corresponds to the time during which the signalling molecules move a distance L of the order of the size of the cell or a cellular compartment. The equilibration time τ_i is then defined implicitly by the mean squared displacement via $\langle x(\tau_i)^2\rangle = L^2$.

We here neglect the binding to the receptor given by equation (1*a*) and adopt a probabilistic interpretation of equations (1*b*) and (1*c*), which we solve by Laplace transforming in time and Fourier transforming in space. The mean squared displacement for a particle starting at the origin in the passive phase is obtained from the Laplace transform $\langle x^2(s)\rangle = -\partial_k^2[c_a^+(k,s) + c_a^-(k,s) + c_p(k,s)]_{k=0}$ and after Laplace inversion reads

$$\langle x(t)^2\rangle = 2\Big\{(v\tau_a)^2\mathrm{e}^{-t/\tau_a} - \frac{v^2 + D\tau_p^{-1}}{(\tau_a^{-1}+\tau_p^{-1})^2}\mathrm{e}^{-t(\tau_a+\tau_p)/\tau_a\tau_p} + \frac{(v\tau_a)^2 + D\tau_p}{\tau_p(1+\tau_a/\tau_p)}t + \frac{D\tau_p - (v\tau_a)^2(1+2\tau_p/\tau_a)}{(1+\tau_p/\tau_a)^2}\Big\}. \tag{9}$$

Equation (9) is a transcendental equation for τ_i and depends only on three parameters: the typical distance covered in the active and passive phases, $x_a = v\tau_a$ and $x_p = \sqrt{D\tau_p}$, and the dimensionless Péclet number $\mathrm{Pe} = Lv/D$. Moreover, it states that over a period of duration $\tau_a + \tau_p$ the directional persistence in the active phase causes a nonlinear time dependence of $\langle x^2(t)\rangle$. Upon this transient regime an effective diffusive regime $\langle x^2(t)\rangle \sim D_{\mathrm{eff}}t$ is established with an effective diffusion coefficient $D_{\mathrm{eff}} = (D\tau_p + [v\tau_a]^2)/(\tau_p + \tau_a)$. To estimate the equilibration rate of active transport with respect to diffusion we compare τ_i with the purely passive equilibration time $\tau_0 \equiv L^2/(2D)$. Figures 2(a)–(c) show results for various biologically relevant Péclet numbers.

From figure 2 we find that active transport is more efficient for larger Pe values. More precisely, the required typical displacement in the active phase needed to enhance the equilibration with respect to bare diffusion is smaller for larger Pe. In the biologically relevant setting the molecular motor speed $v \sim 1\ \mu\mathrm{m\ s}^{-1}$ is widely independent of the particle size

[15] and the values for the diffusion coefficients span a scale between $D \lesssim 10^{-2}\ \mu\mathrm{m}^2\ \mathrm{s}^{-1}$ corresponding to large cargo such as vesicles, and $D \sim 10\ \mu\mathrm{m}^2\ \mathrm{s}^{-1}$ corresponding to smaller proteins. Conversely, the dimension of effectively linear cells such as neurons or their substructures (i.e. dendrites) falls between 10 μm and $\lesssim$1 m, which means that Pe $\gtrsim 10 - 100$ values are in fact robustly expected. Therefore, according to figure 2 it is quite plausible that intermittent active motion indeed enhances signalling speed *in vivo*.

The physical principle underlying the enhancement is rooted in the fundamental difference in the time scaling of diffusive and active motion, $\simeq t$ versus $\simeq t^2$. For example, comparing only purely passive and active motion we find that for Pe > 2 active motion is more efficient. In the intermittent case the motion has a transient period of duration $\tau_a + \tau_p$, which corresponds to a parameter dependent combination of both regimes. After this transient period the effective diffusive regime is established with diffusivity D_{eff}, which may or may not be larger than the bare D. τ_i can therefore be smaller or larger than τ_0. Shuttling of large cargo therefore almost universally profits from active motion, whereas active motion of smaller proteins will only be more efficient over sufficiently large distances. The observed features thus provide a simple explanation why experimentally active transport is observed mostly in the trafficking of larger particles [14, 29]. Similarly, active diagnostics [8, 9] can also be faster and hence could enable for a higher diagnostic throughput.

4. Signalling precision with thermal diffusion alone

We now address the signalling precision and focus first on the situation, where molecules move in space by thermal diffusion alone. In this case $\Lambda_k = 0$ and the k-integral in equation (3) is evaluated exactly, after taking the limit $a \to 0$ yielding

$$\gamma(t) = \delta(t) + \hat{\mathcal{F}}_t^{-1}\left[\frac{k_{\mathrm{on}}(1 - \langle n\rangle)}{2}\sqrt{\frac{-\mathrm{i}}{D\omega}}\right]. \tag{10}$$

Using equation (10) in equations (6)–(8) we arrive at the power spectrum of concentration fluctuations experienced by the receptor

$$S_{\delta c_p}(\omega) = \frac{2\langle c_p\rangle}{k_{\mathrm{on}}(1 - \langle n\rangle)} - \frac{\langle c_p\rangle}{\sqrt{D}}\frac{\sqrt{|\omega|}}{\omega}\sin\left(\frac{\mathrm{Arg}(-\mathrm{i}\omega)}{2}\right), \tag{11}$$

where Arg denotes the principal value of the argument. Integrating over the frequency range $(-\tau_m^{-1}, \tau_m^{-1})$ we obtain the final result for the variance of the concentration measured by the receptor

$$\overline{\delta c_p^2} = \frac{2\langle c_p\rangle}{k_{\mathrm{on}}(1 - \langle n\rangle)\tau_m} + \frac{\langle c_p\rangle}{\pi}\sqrt{\frac{2}{D\tau_m}}, \tag{12}$$

where the first part describes the noise due to the two-state Markov switching (i.e. the binding alone) and the second term stands for the noise due to diffusion. Note that for the recurrent nature of one-dimensional diffusion and the fact that the receptor is point-like, we *cannot* approximate the precision at which the receptor can determine c_p with $\int_{-1/\tau_m}^{1/\tau_m} S_{\delta c_p}(\omega)\mathrm{d}\omega \sim S_{\delta c_p}(\omega \to 0)/\tau_m$ as in the three-dimensional case (see e.g. [3]). More precisely, in contrast to the Lorentzian shape of $S_{\delta c_p}(\omega \to 0)$ in the three-dimensional case, $S_{\delta c_p}(\omega)$ diverges as $\omega \to 0$. The integral over ω nevertheless converges and leads to equation (12). Moreover, in contrast to the three-dimensional case where the squared measurement error $\overline{\delta c_p^2}$ decreases as $1/\tau_m$, for one-dimensional diffusion we find the much

slower decay $\overline{\delta c_p^2} \propto 1/\sqrt{\tau_m}$. That is, $N_i^{1D}/N_i^{3D} \propto 1/\sqrt{\tau_m}$ and the receptor measurement is thus much less efficient in one-dimension.

5. Signalling precision with active motion

As we are interested in the signalling precision at equilibrium and hence consider τ_m values which are much longer than any correlation time in the motion [3, 4, 6] such that $\tau_m \gg \tau_a, \tau_p$, we may take the limit in $\Lambda_k(\tau_a, \tau_p; \omega \to 0)$ as well as in equation (3). This way we recover, after performing the integral over k in equation (3) and taking the limit $a \to 0$, an effective white noise asymptotic on the slow time scale $t \gg \tau_a, \tau_p$,

$$\gamma(t) \sim \delta(t)\left[1 + \frac{k_{\rm on}(1 - \langle n\rangle)}{D^2\tau_p([D\tau_p]^{-1} + [v\tau_a]^{-2})^{3/2}}\right], \tag{13}$$

and correspondingly an effectively Lorentzian fluctuation spectrum $S_{\delta n}(\omega)$ at small frequencies (see [6]). From equation (8) we obtain also the low frequency region of the power spectrum concentration fluctuations

$$S_{\delta c_p}(\omega) \sim \frac{2\langle c_p\rangle}{k_{\rm on}(1 - \langle n\rangle)} + \frac{\langle c_p\rangle}{Dx_p^2(x_p^{-2} + x_a^{-2})^{3/2}}, \tag{14}$$

for $\omega \ll \tau_b^{-1}, \tau_a^{-1}, \tau_p^{-1}$, where we introduced the typical distance the signalling molecule moves in the passive $x_p = \sqrt{D\tau_p}$ and motor bound phases $x_a = v\tau_a$. As before, the first term in equation (14) corresponds to the two-state switching noise and the second term to the noise due to spatially extended intermittent dynamics. Note that in contrast to the three-dimensional setting, where the active excursions merely rescale the correlation time [6], we here find a qualitative change in the properties of the noise, compare equations (11) and (14).

Using equation (14) we can now approximate the precision at which the receptor can determine c_p with $\int_{-1/\tau_m}^{1/\tau_m} S_{\delta c_p}(\omega){\rm d}\omega \sim S_{\delta c_p}(\omega \to 0)/\tau_m$ and obtain our main result

$$\overline{\delta c_p^2} \sim \frac{2\langle c_p\rangle}{k_{\rm on}(1 - \langle n\rangle)\tau_m} + \frac{\langle c_p\rangle}{Dx_p^2(x_p^{-2} + x_a^{-2})^{3/2}\tau_m}. \tag{15}$$

Here we are interested in the transport-controlled sensing [3, 4, 6]. Comparing the noise due to the spatially extended motion for passive and active intermittent motion we find that that active motion allows for more precise absolute concentration measurements as soon as the inequality

$$\tau_m > \tau_p \frac{\pi^2}{2(1 + (x_p/x_a)^2)^3} \tag{16}$$

holds such that in the limit of long active excursions $x_a \gg x_p$ we end up with the condition $\tau_m > \tau_p\frac{\pi^2}{2}$. Note that the right-hand side of this inequality is essentially the characteristic time of the asymptotic exponential decay of the first passage time density of a one-dimensional random walk in a domain of length L if we set $L^2/D = \tau_p$ [30]. In other words, for active signalling to be more precise in one-dimension the receptor needs to measure long enough for the particle to find the target in the passive phase, which is an intuitive result.

In order to be more concrete we compare the scaled variances of measurement errors for active $\sigma_i = \overline{\delta c_{p,i}^2}/\langle c_{p,i}\rangle^2$ and passive $\sigma_0 = \overline{\delta c_{p,0}^2}/\langle c_{p,0}\rangle^2$ motion. In the transport-controlled regime we have $\langle c_{p,i}\rangle \sim c_{\rm tot}/(1 + \tau_a/\tau_p)$ for intermittent active motion and $\langle c_{p,0}\rangle \sim c_{\rm tot}$, where $c_{\rm tot}$ denotes the total concentration of molecules. Note that here and throughout the

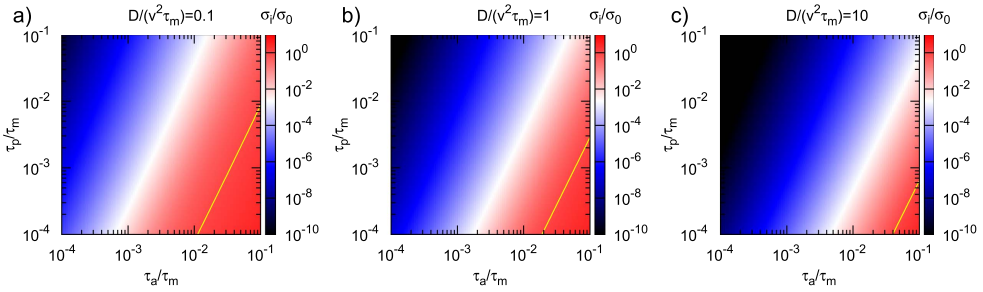

Figure 3. Precision ratio of scaled variances of $\sigma_k = \overline{\delta c_{p,k}^2}/\langle c_{p,k}\rangle^2$ with $k = 0, i$ for active intermittent (subscript i) versus passive (subscript 0) transport as a function of the relative duration of active (τ_a/τ_m) and passive (τ_a/τ_m) phases with respect to the measurement time τ_m for various values of dimensionless ratio between the squared typical length of passive $x_{p,m}^2 = D\tau_m$ versus active $x_{a,m}^2 = (v\tau_m)^2$ displacements during the measurement time τ_m. Whenever $\sigma_i/\sigma_0 < 1$ active motion leads to more precise signalling. Note that $\tau_a/\tau_m \leqslant 0.1$ and $\tau_p/\tau_m \leqslant 0.1$ in order to assure equilibrium sensing conditions.

entire paper we implicitly assume that the number of molecules exceeds the number of receptors [3]. The relative precision ratio reads

$$\frac{\sigma_i}{\sigma_0} = \pi\sqrt{\frac{\tau_p^*}{2}}\,\frac{(1+\tau_a^*/\tau_p^*)}{(1+Q\tau_p^*/[\tau_a^*]^2)^{3/2}}, \tag{17}$$

where we introduced dimensionless times $\tau_p^* = \tau_p/\tau_m$ and $\tau_a^* = \tau_a/\tau_m$ as well as $Q = D/(v^2\tau_m)$, the dimensionless ratio between the squared typical lengths of passive $x_{p,m} = \sqrt{D\tau_m}$ versus active $x_{a,m} = v\tau_m$ displacements during the measurement time τ_m. The results for various values of Q are presented in figure 3.

We find that the minimal value of τ_a that is required for improved sensing precision with respect to bare diffusion (i.e. for $\sigma_i/\sigma_0 < 1$, which corresponds to the region to the left of the yellow curve in figure 3) decreases with decreasing Q. In other words, for large particles with a smaller D the active displacements can become arbitrarily short. Given that the typical measurement times lie between $\simeq 1$ s and $\simeq 1$ min [3] the conditions for improved signalling accuracy appear to be robustly satisfied.

To understand this we need to recall that, while larger τ_a monotonically leads to lower absolute read-out errors (see equation (15)), it simultaneously decreases $\langle c_p\rangle$ and hence renormalises σ_i. The improved accuracy in figure 3 is thus a result of a trade-off between a decreases of the absolute concentration fluctuations and a lower equilibrium probability to be at the receptor site. This result is striking as it suggests that even the slightest active displacements can disrupt the recurrence and improve the read-out precision as long as their length is larger than the receptor size.

Physically, this observation is due to the fact that the receptor collects new information only from statistically independent binding events. Correlations between consecutive measurements arise due to a finite Markov binding time τ_b and due to the return and rebinding of a previously bound molecule. Moreover, we assume that only freely diffusing molecules can bind to the receptor. Therefore, the receptor necessarily experiences the binding of those molecules, which are ballistically swept towards the binding site over a distance larger than the receptor size, as statistically independent. In turn, molecules which are ballistically flushed

away from the receptor after unbinding will also contribute statistically independent binding events, regardless of how they return to the receptor. The nonexistence of a lower-bound on τ_a is thus an artefact of assuming a point-like receptor.

Note that in an alternative setting, in which we compare the precision to determe the same concentration of passively moving molecules, which corresponds to a higher $c_{\rm tot}$ in the intermittent active case (i.e. $\langle c_{p,i}\rangle \to c_{\rm tot}$ [6]), the signalling precision would be improved unconditionally. Therefore, in contrast to the three-dimensional case, where active motion only improves sensing precision for certain values of parameters [6], active transport can robustly and much more efficiently improve sensing accuracy in one-dimensional systems for sufficiently long measurement times.

6. Conclusion

The degree of recurrence of spatial exploration is essential for random target search processes [23, 24]. For example, in the facilitated diffusion model of gene regulation the topological coupling of one- and three-dimensional diffusion allows for a more efficient search (e.g. [31]). In a similar manner intermittent active excursions can significantly speed up random search [23, 24].

In contrast, the topological coupling of one- and three-dimensional diffusion does not appreciably improve the signalling precision [4]. In addition, we showed previously that in a three-dimensional setting active motion only conditionally improves the signalling accuracy, by decreasing the correlation time of the counting noise in a process called active focusing [6]. Here we find, strikingly, that active excursions effect qualitative changes in the power spectrum of concentration fluctuations experienced by the receptor in one-dimensional systems such as neurons. By adding the active component the power spectrum changes from $1/\sqrt{\omega}$ for thermal diffusion alone to a Lorentzian shape with a finite plateau. This Lorentzian shape is also observed for passive signalling in three-dimensions [3, 4, 6]. Therefore, active excursions disrupt the recurrent nature of one-dimensional diffusion.

Existing studies provide insight into how receptor clustering [3] and cooperativity [32], dimensionality [4], spatial confinement [7], receptor diffusion [33] and active transport [6] affect the precision of receptor signalling. The overall dependence of the counting noise on the manner the signalling molecules explore their surrounding space suggests that a heterogeneous diffusivity profile [26, 34] and spatial disorder [35] would alter the signalling precision as well. Both have been observed in experiments [36]. In addition, signalling molecules or transport versicles often exhibit anomalous diffusion [37], both in the form of passive [38] and active [22, 39] motion. It would therefore be interesting to investigate the impact of these features on the sensing precision in the future.

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