Optimality of Spatially Inhomogeneous Search Strategies
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We consider random search processes alternating stochastically between diffusion and ballistic motion, in which the distribution function of ballistic motion directions varies from point to point in space. The specific space dependence of the directional distribution together with the switching rates between the two modes of motion establishes a spatially inhomogeneous search strategy. We show that the mean first passage times for several standard search problems—narrow escape, reaction partner finding, reaction escape—can be minimized with a directional distribution that is reminiscent of the spatial organization of the cytoskeleton filaments of cells with a centrosome: radial ballistic transport from the center to the periphery and back, and ballistic transport in random directions within a concentric shell of thickness \( \Delta_{\text{OPT}} \) along the domain boundary. The results suggest that living cells realize efficient search strategies for various intracellular transport problems economically through a spatial cytoskeleton organization that involves radial microtubules in the central region and only a narrow actin cortex rather than a cell body filled with randomly oriented actin filaments.

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in the periphery here, but our framework allows us to put any direction distribution—as for instance a nonisotropic filament distribution in the actin cortex, where filaments run prevalently along the cell membrane. For the scenarios that we study here results do not change much; details will be published elsewhere. Note that for $\Delta = R$ one obtains the homogeneous directional distribution $p_\Omega(r) = 1/4\pi$ considered in Ref. [6].

We model the random motion of the searcher by an intermittent search process [3,6,14,16], in which a particle performs random motion in two alternating modes: Brownian motion with diffusivity $D$, and ballistic motion with velocity $v$. Transitions between the modes occur stochastically with rates $k$ and $k'$, which we denote in the following, in reminiscence of molecular motor assisted transport, as the attachment and detachment rate, respectively. The underlying stochastic process is described by a Fokker-Planck equation for the time evolution of the probability distribution $P_\Omega(r,t)$ for the diffusing particle and $P_\Omega(r,t)$ for the particle that moves ballistically in the direction $\Omega$:

$$\frac{\partial P_\Omega(r,t)}{\partial t} = D \Delta P_\Omega(r,t) - k P_\Omega(r,t) + k' \int d\Omega P_\Omega(r,t),$$

$$\frac{\partial P_\Omega(r,t)}{\partial t} = -\nabla(v_\Omega P_\Omega(r,t)) + k P_\Omega(r,t) - k' P_\Omega(r,t).$$

The switching rates could also be space dependent functions $k(r)$ and $k'(r)$, thus establishing a further extension of spatially inhomogeneous search strategies. Here, we focus on constant rates.

We assume $v = |v_\Omega|$ to be constant throughout this study. At time $t = 0$ the particle starts diffusively at position $r_0$ [26]: $P_\Omega(r,t=0) = \delta(r - r_0)$, $P_\Omega(r,t) = 0$. Apart from the stochastic detachment with rate $k'$ a ballistically moving particle switches automatically to the diffusive mode at the MTOC ($|r| = 0$) since microtubules end there, at the inner border of the actin cortex ($|r| = R - \Delta$) since actin filaments end there, and at the cell membrane ($|r| = R$) since all filaments end there. Diffusing particles are reflected at the cell membrane ($|r| = R$), apart from small regions in the cell membrane in exit problems, where absorbing boundary conditions are applied. In the following we use the rescaled dimensionless spatial and temporal coordinates $\tilde{r} = r/R$ and $\tilde{t} = vt/R$, and the rescaled parameters $\tilde{D} = D/v R$, $\tilde{k} = R k/v$, and $\tilde{k}' = R k'/v$.

The efficiency of a search strategy, or a specific directional distribution, $p_\Omega(r)$ is measured in terms of a MFPT with respect to the events defined by the different search problems that we consider now.

An analytical determination of MFPTs in 2D and 3D bounded domains is feasible for homogeneous problems [27,28], but appears currently intractable for a spatially inhomogeneous problem like the one defined by Eq. (1). Here, we resort to high precision numerical methods and use an efficient Monte Carlo algorithm developed by us in Ref. [29] to generate the stochastic processes underlying Eq. (2); for details see Ref. [30]. We use of the order of $10^6$ realizations of the process for each parameter value such that the relative statistical error is below 0.1%.

**Narrow escape problem.**—First, we consider the search for a specific small area on the search domain boundary, the so-called narrow escape problem [23,24]. A concrete example in which the directional distribution (1) is relevant is the directed secretion by immune cells, which requires the formation of an immunological synapse [31,32] and the transport of vesicles containing secretion material towards the synapse involving the cytoskeleton [33,34].

We compute the MFPT for the various parameters $k, k'$, $\rho$, and $\Delta$ in Eqs. (1) and (2) for small escape regions of polar angle $\theta_{\text{abs}} = \arcsin(1/7) \approx 0.1433$ (0.51% of the spherical surface) as sketched in Fig. 1(a). In order to demonstrate the efficiency of a spatially inhomogeneous directional distribution [corresponding to $0 < \Delta < R$ in Eq. (1)] we first determine the optimal rates $\tilde{k}_{\text{opt}}(\tilde{D})$ and
\( \tilde{k}''(\tilde{D}) \) for a homogeneous directional distribution (\( \Delta = 1 \)). Figure 1(b) shows the MFPT as a function of \( \tilde{k} \) and \( \tilde{k}' \) for \( \tilde{D} = 0.05 \). The optimal detachment rate \( \tilde{k}_{\text{opt}}'' \) is zero, which holds for all \( \tilde{D} \). \( \tilde{k}_{\text{opt}}' = 0 \) means that uninterrupted ballistic transport to the cell membrane (and the subsequent switch to the diffusive mode) is optimal for the narrow escape problem, which is plausible, since the target area is on the membrane. The optimal attachment rate \( \tilde{k}_{\text{opt}}' \) decreases with increasing diffusivity \( \tilde{D} \) (Fig. S1a in Ref. [35]). For small diffusivities \( \tilde{D} < 0.1 \) the homogeneous intermittent search is always more efficient than the pure diffusive search. The MFPT of the latter diverges for \( \tilde{D} \rightarrow 0 \) as \( \tilde{T}_{\text{diff}} \approx 7.62/\tilde{D} \), for \( \theta_{\text{abs}} \) as above [36], whereas the MFPT for the homogeneous intermittent search \( \tilde{T}_{\text{opt}} \) stays finite (Fig. S1a in Ref. [35]).

Next, we take the optimal values \( \tilde{k}_{\text{opt}}'(\tilde{D}) \) and \( \tilde{k}_{\text{opt}}''(\tilde{D}) \) for \( \Delta = 1 \), and vary the width of the cortex \( \Delta \), but fix the value of \( p \) in Eq. (1) to 1 (only outward radial transport). The result is shown in Fig. 1(c): for small diffusivities \( \tilde{D} < 0.02 \) the MFPT is minimized for an inhomogeneous strategy \( \Delta < 0.2 \). For larger values (0.02 < \( \tilde{D} < 0.06 \)) the optimal strategy for the rates \( \tilde{k}_{\text{opt}}'(\tilde{D}) \) is a homogeneous one (\( \Delta = 1 \)). But if we vary the rate \( \tilde{k} \) superior inhomogeneous search strategies exist also in the range 0.02 < \( \tilde{D} < 0.06 \): minimizing the MFPT as a function of \( \tilde{k} \) and \( \Delta \) simultaneously the optimal strategy has a small, nonvanishing value for \( \Delta \) (Fig. S1b in Ref. [35]) for \( \tilde{D} = 0.04 \). For 0.06 < \( \tilde{D} < 0.1 \) a search strategy with a fully polarized network (\( \Delta = 0 \)) is optimal, and even more efficient general distributions \( \rho_{\text{opt}}(r) \) for this case exist. Finally, also for fixed attachment and detachment rates \( \tilde{k} \) and \( \tilde{k}' \), the MFPTs are minimized for small values of \( \Delta \) (Fig. S1c in Ref. [35]).

Enhanced reaction kinetic.—Next we consider the enhancement of the reaction kinetics between two reaction partners by motor assisted ballistic transport. It has already been demonstrated that spatially homogeneous and isotropic intermittent search strategies can decrease MFPTs substantially [6,16]. Such intermittent search strategies are only realized in those parts of a biological cell where cytoskeleton filaments are homogeneously and isotropically distributed, which is certainly not true for the whole cell body for which a spatial organization as defined by Eq. (1) is more realistic. In the following we study the efficiency of this strategy for the search for an immobile target of diameter \( d \) indicated by the gray circle. Trajectories are represented as in Fig. 1(a). (b) \( \tilde{T} \) as a function of \( \tilde{k} \) and \( \tilde{k}' \) for a spatially homogeneous directional distribution (\( \Delta = 1 \)) and a homogeneously distributed target position \( \tilde{r}_{\text{tar}} \) for \( \tilde{D} = 1/300 \), \( \tilde{d} = 0.025 \). (c) \( \tilde{T} \) for the inhomogeneous directional distribution with the optimal rates \( \tilde{k}_{\text{opt}}'(\tilde{D}, d) \) from the homogeneous case \( \Delta = 1 \) as function of \( \Delta \) for different values of the forward radial transport \( p \) and different target positions close to the center \( w \). (d) \( \tilde{T} \) as in (c) but now with fixed width \( \Delta = 0.1 \) as function of the forward probability \( p \) for different fixed rates \( \tilde{k} \) and \( \tilde{k}' \) and different values of \( w \).

\( \tilde{T}[10^4] \)

\( \tilde{T}[10^3] \)

\( \tilde{T}[10^2] \)

\( \tilde{T}[10] \)

\( \tilde{T}[1] \)

FIG. 2. (a) Sketch of the intermittent search for an immobile target of diameter \( d \) indicated by the gray circle. Trajectories are represented as in Fig. 1(a). (b) \( \tilde{T} \) as a function of \( \tilde{k} \) and \( \tilde{k}' \) for a spatially homogeneous directional distribution (\( \Delta = 1 \)) and a homogeneously distributed target position \( \tilde{r}_{\text{tar}} \) for \( \tilde{D} = 1/300 \), \( \tilde{d} = 0.025 \). (c) \( \tilde{T} \) for the inhomogeneous directional distribution with the optimal rates \( \tilde{k}_{\text{opt}}'(\tilde{D}, d) \) from the homogeneous case \( \Delta = 1 \) as function of \( \Delta \) for different values of the forward radial transport \( p \) and different target positions close to the center \( w \). (d) \( \tilde{T} \) as in (c) but now with fixed width \( \Delta = 0.1 \) as function of the forward probability \( p \) for different fixed rates \( \tilde{k} \) and \( \tilde{k}' \) and different values of \( w \).

Position \( \tilde{r}_{\text{tar}} \) with \( 0 \leq |\tilde{r}_{\text{tar}}| \leq 1 - \tilde{\Delta} \) will be either homogeneously distributed or it is predominantly located close to the center \( |\tilde{r}_{\text{tar}}| \leq 1/2 \) with probability \( w \).

Figure 2(b) shows the MFPT for the homogeneous direction distribution (\( \Delta = 1 \)) and the parameters \( \tilde{D} = 1/300 \) and \( \tilde{d} = 0.025 \), as a function of the rates \( \tilde{k} \) and \( \tilde{k}' \). In contrast to the narrow escape problem the optimum is not at \( \tilde{k} = 0 \) anymore, which is plausible since the target is not located on the boundary. The concentration of the target towards the center (\( w = 0.9 \)) does not change the MFPT significantly even for a rather large value of \( \tilde{d} \) (see Fig. S2a in Ref. [35]). In the biological context \( v \approx 1 \mu \text{m/s} \) for molecular motor assisted transport and \( R \approx 5 \mu \text{m} \) for T cells, so that the parameters in Fig. 2(b) correspond to \( D = 0.016 \mu \text{m}^2/\text{sec} \) and \( d = 0.26 \mu \text{m} \), which is typical for vesicles. The optimal homogeneous strategy according to Fig. 2(b) is \( \tilde{k}_{\text{opt}}' \approx 40 \) and \( \tilde{k}_{\text{opt}}'' \approx 25 \), corresponding to \( k_{\text{opt}}' \approx 8 \text{sec}^{-1} \) and \( k_{\text{opt}}'' \approx 5 \text{sec}^{-1} \), which is compatible with experimental observations [6,25].
Again we take the optimal values $\tilde{k}_{\text{opt}}(\tilde{D})$, $\tilde{k}'_{\text{opt}}(\tilde{D})$ from $\Delta = 1$ and calculate with these rates the MFPT for the inhomogeneous directional distribution for fixed values of the outward transport probability $p$ as a function of the cortex width $\Delta$. The result, shown in Fig. 2(c), demonstrates that again a thin cortex $\Delta \ll 1$ yields a much smaller search time for $p = 1/2$. Although the target is located with a high probability close to the center ($w = 0.75$ and $0.9$) the MFPT is not minimized for small values of $p$, corresponding to preferential radial transport towards the center, but for $p$ close to $1/2$. Similarly, for a fixed small cortex width $\Delta = 0.1$ the MFPT is minimized for $p$ close to $1/2$ even for large $w$ and also for fixed nonoptimal rates $\tilde{k}$, $\tilde{k}'$ as shown in Fig. 2(d). These results are confirmed for larger values of the parameters: $\tilde{D} = 0.01$ and $\tilde{d} = 0.1$ (see Figs. S2b and S2c in Ref. [35]).

Reaction-escape problem.—Finally, we consider the combination of the reaction and escape problem, where cargo has first to bind to a reaction partner before it can be delivered or dock at a specific area on the cell boundary as, for instance, a synapse. A prominent example is the docking of lytic granules at the immunological synapse of cytotoxic T lymphocytes that requires the pairing with a CD3 endosome beforehand [38].

Figure 3(a) shows a sketch of the process, now involving two particles, a searcher and a target, each one executing a random intermittent motion described by a Fokker-Planck equation analogous to (2) with additional boundary conditions: the searcher and the target react and build a pair once they get closer than a distance $d$ and are both in the diffusive mode. $\tilde{T}_{\text{reac}}$, $\tilde{T}_{\text{esc}}$, and $\tilde{\tau} = \tilde{T}_{\text{reac}} + \tilde{T}_{\text{esc}}$ denote the MFPT for the reaction event, the MFPT for the pair escape, and the total MFPT, respectively.

Figure 3(b) shows $\tilde{T}$ for the homogeneous directional distribution ($\Delta = 1$) as a function of the rates $\tilde{k}$, $\tilde{k}'$ for $\tilde{D} = 0.01$, $\tilde{d} = 0.1$, $\tilde{d}_{\text{abs}} = \arcsin(1/7)$, ($\tilde{T}_{\text{reac}}$ and $\tilde{T}_{\text{esc}}$ are shown separately in Fig. S3a in Ref. [35]). $\tilde{T}_{\text{reac}}$ is minimized by a nonvanishing rate $\tilde{k}'$, whereas $\tilde{T}_{\text{esc}}$ is again minimized for $\tilde{k}' = 0$. $\tilde{T}$ is also minimized by $\tilde{k}' = 0$. It should be noted that for a purely diffusive target the total MFPT is minimized by a nonvanishing rate $\tilde{k}' > 0$. In Fig. 3(c) we show the MFPTs for the inhomogeneous directional distribution (1) as a function of the cortex width $\Delta$, with the optimal rates for the homogeneous case for $\tilde{D} = 1/300$ for $p = 1/2$ (outward and inward radial transport equally probable) and for $p = 1$ (only outward radial transport). The data show that $p = 1/2$ and a small cortex width $\Delta$ reduce the total MFPT by 70% in comparison with the homogeneous strategy $\Delta = 1$. For $\tilde{D} > 0.01$ one can reduce $\Delta$ down to zero without changing $\tilde{T}$ substantially (see Fig. S3b in Ref. [35]). Even if one fixes the attachment and detachment rates to nonoptimal values, $\tilde{T}$ is again reduced by at least 50% for small cortex widths (see Fig. S3c in Ref. [35]).

To conclude, we have studied for the first time the efficiency of spatially inhomogeneous intermittent search strategies defined by the directional distribution $P_{\Omega}(r)$ in the Fokker-Planck equation (2) together with the rates $\tilde{k}$, $\tilde{k}'$. For the narrow escape problem it turns out to be a superior strategy to allow only radial outward ballistic transport from the center towards a thin sheet of thickness $\Delta$ underneath the boundary, where ballistic transport in all directions is possible. This thin boundary layer allows an accelerated random motion along the boundary to find the escape region, somewhat reminiscent of a purely diffusive search with an accelerated surface mediated diffusion [20]. A similar result holds for the reaction kinetics problem, in which the target is not located on the boundary: here again optimal strategies with a small thickness $\Delta$ exist, in particular better than the homogeneous strategy [6], but the optimal probability for forward or backward radial transport is now around $p = 1/2$. This result is reminiscent of an acceleration of purely diffusive search kinetics by following boundaries with an increased diffusivity [21].
problem combines both scenarios and the optimal forward or backward radial transport probability depends on the size ratio of the target and escape region. In passing we note that qualitatively similar results are obtained when the searcher can find the target also during the ballistic motion [39].

The parameters for the optimal strategies that we find are biologically relevant, as discussed in Refs. [6] and [35]. For intracellular reaction kinetics our results therefore suggest that the spatial organization of the cytoskeleton of cells with a centrosome does not only minimize the characteristic time necessary for various random search tasks but does so in an economic way: instead of supporting a resource demanding and isotropic homogeneous filament network it is sufficient, and almost always even more efficient, to establish just a thin actin cortex underneath the cell membrane.

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[26] Results do not change significantly if the searcher starts in the ballistic mode since the time that the searcher stays in the diffusive mode (maximally until reaching the boundary where an automatic switch to the diffusive mode occurs) is much smaller than the overall MFPT.
[37] If both reaction partners are mobile an obvious suitable strategy would be to transport both of them towards the MTOC to bring them into contact.
FIG. S1: Narrow escape problem. a) MFPT for the purely diffusive, $\widetilde{T}_{\text{diff}}$ (red line), and intermittent search, $\widetilde{T}_{\text{opt}}$ (green line), with a homogeneous filament density ($\widetilde{\Delta} = 1$) with optimal transition rates, as functions of the diffusion constant $\widetilde{D}$. The optimal attachment rate $\widetilde{k}_{\text{opt}}(\widetilde{D})$ is represented by the blue line (and right y-axis), the optimal detachment rate is $\widetilde{k'}_{\text{opt}} = 0$. b) MFPT as a function of $\widetilde{k}$ and $\widetilde{\Delta}$ for $\widetilde{D} = 0.04$, $\widetilde{k'} = 0$ and $p = 1$. The red dot indicates the global minimum, and the green dot (top left) indicates the minimum for the homogeneous case ($\widetilde{\Delta} = 1$). c) $\widetilde{T}$ as a function of $\widetilde{\Delta}$ for fixed rates $\widetilde{k} = \widetilde{k'} = 10$ for different $\widetilde{D}$ and $p = 1$. 
FIG. S2: Enhanced reaction kinetic. b) Homogeneous filament density: MFPTs as a function of $\hat{k}$ and $\hat{k}'$ for a spatially homogeneous filament density ($\hat{\Delta} = 1$), for (left) $\hat{D} = 0.01, \hat{d} = 0.1$, homogeneously distributed target position $\hat{r}_{\text{tar}}$; (right) $\hat{D} = 0.01, \hat{d} = 0.1$, target position $\hat{r}_{\text{tar}} \leq 0.5$ with probability $w = 0.9$. c) MFPT for the inhomogeneous filament density with the optimal rates $\hat{k}_{\text{opt}}(\hat{D}, \hat{d})$ from the homogeneous case $\hat{\Delta} = 1$ as function of $\hat{\Delta}$ for different values of the forward radial transport $p$ and different target positions close to the center $w$. d) MFPT as in c) but now with fixed width $\hat{\Delta} = 0.1$ as function of the forward probability $p$ for different fixed rates $k$ and $k'$ different values of $w$. 
FIG. S3: a) Homogeneous filament density ($\tilde{\Delta} = 1$): MFPTs for reaction ($\tilde{T}_{\text{reac}}$, left), pair escape ($\tilde{T}_{\text{esc}}$, right) as a function of $\tilde{k}$ and $\tilde{k}'$ for $\tilde{D} = 0.01, \tilde{d} = 0.1, \theta_{\text{abs}} = \arcsin(1/7)$. The red dots represents the minimum. b) Inhomogeneous filament density: The MFPTs $\tilde{T}_{\text{reac}}, \tilde{T}_{\text{esc}}, \tilde{T}$ for the optimal attachment / detachment rates ($k, k'$) from figure Fig.2b) as a function of the actin cortex width ($\Delta$) for symmetric radial microtubule transport ($p = 1/2$) in the left panel, and purely outward transport microtubule transport ($p = 1$) in the right panel. c) The MFPTs $\tilde{T}_{\text{reac}}, \tilde{T}_{\text{esc}}, \tilde{T}$ for fixed, non-optimal attachment / detachment rates $\tilde{k} = 5, \tilde{k}' = 10$ for ($\tilde{D} = 1/300, \tilde{d} = 0.025$).
Biologically relevant parameters

Optimal homogeneous search strategies for the enhanced reaction kinetics in biological cells have been studied in [6], where also the biological relevance of the parameters and the resulting optimal homogeneous strategies have been discussed. For heavy cargo, like vesicles (diameter ca. 100 nm) and other organelles, the diffusion constant is around or even below $10^{-2}\mu m^2/sec$ and therefore molecular motor assisted transport and intermittent search strategies are essential. Consequently in this type of cargo one also finds optimal search strategies [6]. For light cargo like small to intermediate proteins intermittent search strategies are not efficient in intracellular reaction kinetics and this is also what we obtain for all other search problems considered: for large diffusion constants purely diffusive search is always optimal (see Fig S1).

In [6] it was argued that for plausible values of the velocity ($v \sim 1\mu m/sec$) and diffusion constants for vesicles ($\sim 10^{-2}\mu m^2/sec$) the optimal attachment and detachment rates turned out to be of the order of $k, k' \sim 10 sec^{-1}$ for reaction radii $d \sim 0.1\mu m$ and thus compatible with experimental observations [25].

For the inhomogeneous search strategies we take the optimal rates for the homogeneous case, which were already found to be biologically relevant [6], and vary the cortex width $\Delta$ and the radial forward probability $p$. The width of the actin cortex of cells is of the order of 0.2-0.4 $\mu m$, and the radial forward probability depends on the equipment of cargo with the forward and backward motors, kinesin and dynein, respectively. The optimal widths we find vary from case to case between zero and 0.2 $R$, where $R$ is the cell radius. When considering T-cells the radius is around 5 $\mu m$. In the following we fix $R = 5\mu m$ and $v = 1\mu m/sec$ and consider the three search problems treated in the main text separately.

**Narrow escape problem:** As shown in Fig. S1a the optimal attachment rate $\tilde{k}_{opt}$ for the homogeneous search strategy decreases with increasing diffusion constant $\tilde{D}$. With $R = 5\mu m$, $v = 1\mu m/sec$ and $D = 0.05\mu m^2/sec$ one has $\tilde{D} = 0.02$ and from Fig. S1a $\tilde{k}_{opt} \approx 10$ and thus $k_{opt} \approx 2 sec^{-1}$. For smaller diffusion constants $k_{opt}$ increases further. In the inhomogeneous case we take these optimal values, as shown in Fig. 1c in the main text and show the MFPT as a function of the cortex width $\Delta$. For diffusion constants smaller than $\tilde{D} = 0.02$, i.e. $D < 0.1\mu m^2/sec$ there is a minimum, which moves towards $\tilde{\Delta} \approx 0.1$ for further decreasing diffusion constant. $\tilde{\Delta} \approx 0.1$ corresponds to $\Delta \approx 0.5\mu m$, close to the actual width of the actin cortex in cells. Fig. S1c shows that one can also fix the detachment and attachment rates to biologically relevant values (here $k = k' = 2 sec^{-1}$) and one still gets a minimal MFPT for small cortex widths.

**Enhanced reaction kinetics:** The optimal switch rates for the homogeneous search for $\tilde{D} = 1/300$ and reaction distance $\tilde{d} = 0.025$, corresponding to $D = 0.016\mu m^2/sec$ and $d = 0.125\mu m$, are according to Fig. 2b $\tilde{k}_{opt} \approx 40$ and $\tilde{k'}_{opt} \approx 25$, which corresponds to...
$k_{\text{opt}} \approx 8\sec^{-1}$ and $k'_{\text{opt}} \approx 5\sec^{-1}$. For the inhomogeneous case Fig. 2c shows that for $p = 0.5$ (equal probability for forward and backward radial transport) a thin cortex yields the smaller MFPTs (actually the minimum is at $\Delta = 0$). Fig. S2 yields similar numbers.

**Reaction-escape problem:** Fig. S3c shows again for the inhomogeneous case that for switch rates fixed to biologically relevant values (here $k = 0.5k' = 1\sec^{-1}$) a thin cortex yields smaller MFPTs than the homogeneous search strategies (minimum smaller than $\tilde{\Delta} = 0.1$, i.e. $\Delta < 0.5\mu m$).