# Directed intermittent search for hidden targets

To cite this article: Paul Bressloff and Jay Newby 2009 *New J. Phys.* **11** 023033

View the article online for updates and enhancements.

## Related content

## Recent citations

# Directed intermittent search for hidden targets

## Paul Bressloff[1] and Jay Newby

Department of Mathematics, University of Utah, Salt Lake City,
UT 84112, USA
E-mail: bressloff@math.utah.edu

**Abstract.** We develop and analyze a stochastic model of directed intermittent search for a hidden target on a one-dimensional track. A particle injected at one end of the track randomly switches between a stationary search phase and a mobile, non-search phase that is biased in the anterograde direction. There is a finite possibility that the particle fails to find the target due to an absorbing boundary at the other end of the track or due to competition with other targets. Such a scenario is exemplified by the motor-driven transport of mRNA granules to synaptic targets along a dendrite. We first calculate the hitting probability and conditional mean first passage time (MFPT) for finding a single target. We show that an optimal search strategy does not exist, although for a fixed hitting probability, a unidirectional rather than a partially biased search strategy generates a smaller MFPT. We then extend our analysis to the case of multiple targets, and determine how the hitting probability and MFPT depend on the number of targets.

[1] Author to whom any correspondence should be addressed.

**Contents**

## 1. Introduction

There is increasing experimental evidence to suggest that local protein synthesis in the dendrites of neurons plays a crucial role in mediating persistent changes in synaptic structure and function, which are thought to be the cellular substrates of long-term memory [1]–[3]. This is consistent with the discovery that various mRNA species, as well as important components of the translational machinery such as ribosomes, are distributed in dendrites. Although many of the details concerning mRNA transport and localization are still unclear, a basic model is emerging. First, newly transcribed mRNA within the nucleus binds to proteins that inhibit translation, thus allowing the mRNA to be sequestered away from the protein-synthetic machinery within the cell body. The repressed mRNAs are then packaged into ribonucleoprotein granules that are subsequently transported into the dendrite via kinesin and dynein motors along microtubules[2]. Finally, the mRNA is localized to an activated synapse by actin-based myosin motor proteins, and local translation is initiated following neutralization of the repressive mRNA-binding protein. Details regarding the motor-driven transport of mRNA granules in dendrites have been obtained by fluorescently labeling either the mRNA or mRNA-binding proteins and using live-cell imaging to track the movement of granules in cultured neurons [4]–[6]. It has been found that under basal conditions the majority of granules in dendrites are stationary or exhibit small oscillations around a few synaptic sites. However, other granules exhibit rapid retrograde (towards the cell body) or anterograde (away from the cell body) motion consistent with bidirectional transport along microtubules [7]. These movements can be modified by neuronal activity as illustrated in figure 1. In particular, there is an enhancement of dendritically localized mRNA due to a combination of newly transcribed granules being transported into the dendrite, and the conversion of stationary or oscillatory granules already present in the dendrite into anterograde-moving granules.

The translocation of an mRNA granule to an activated synapse is an example of a general class of problems involving the search for a hidden target, that is, a target of unknown location

[2] Microtubules are polarized filaments with biophysically distinct plus and minus ends. In proximal dendrites (close to the cell body) microtubules have mixed orientation, so that bidirectional transport could be mediated by a plus-end motor such as kinesin. On the other hand, in distal dendrites microtubules have the same polarity (with the plus end oriented away from the cell body), so that bidirectional transport would require the combined action of kinesin and a minus-end motor such as dynein [7].
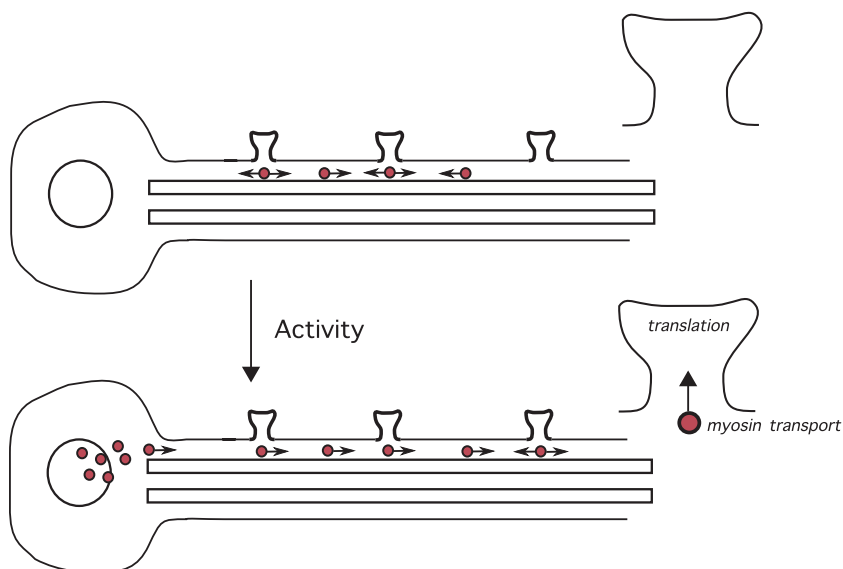
Activity

translation

myosin transport

**Figure 1.** Schematic diagram illustrating mRNA granule mobility in dendrites. Under basal conditions most granules are either stationary or exhibit localized oscillations, whereas a minority exhibit bidirectional transport. KCl depolarization activates transcription of mRNA at the cell body and converts existing stationary granules into anterograde granules [5].

which can only be detected when the searcher is within a certain range. Other striking examples include the behavior of foraging animals [8]–[11], the active transport of reactive chemicals in cells [12], and a promoter protein searching for a specific target site on DNA [13]–[16]. In all of these cases the searching object tends to alternate between an active search phase and a bulk displacement phase that is non-receptive to the target. In the case of DNA, it has been established that the search phase consists of one-dimensional diffusion during which the protein remains in contact with the DNA. This alternates with a three-dimensional diffusion phase in which a protein 'hops' from one site to another by dissociating from one site and then re-associating elsewhere in the same chain (see [14] for a review). A stochastic model of this process that is in good agreement with experiments suggests the existence of an optimal search strategy, which is achieved when both regimes have the same duration [15, 16]. In the case of foraging animals and active transport in cells, the searcher switches between a slow motion (diffusive) or stationary phase in which target detection can occur and a fast motion 'ballistic' phase. Recently, a stochastic model of the latter form of intermittent search process has been developed in which the optimal strategy is determined by calculating the durations of each phase that minimize the mean search time to find a single hidden target [12, 17, 18]. In these studies, it is assumed that (i) the motion of the searcher is unbiased, (ii) the searcher initiates its search at some random location within the physical domain, and (iii) the probability of finding the target is equal to unity. All of these assumptions are reasonable when considering the bidirectional transport of mRNA granules within the dendrite under basal conditions, see figure 1 (top). However, they break down when considering the directed transport of newly synthesized granules from the cell body to activated synapses as shown in figure 1 (bottom). Clearly assumptions (i) and (ii) no longer hold, since the motion is biased in the anterograde direction and the initial location
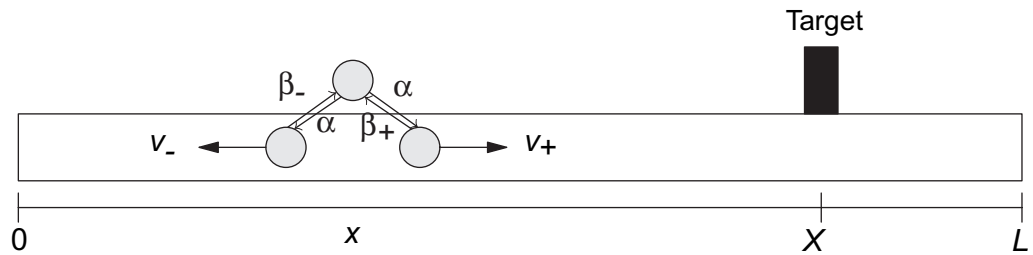
**Figure 2.** Stochastic model of directed intermittent search along a one-dimensional track of length $L$. A target is located at a fixed but unknown location $x = X$. The particle is injected at one end ($x = 0$) and its motion is biased in the anterograde direction (towards the end $x = L$).

is always at the cell body. Moreover, there is now a nonzero probability that the searcher does not find the target due to degradation at the distal end of the dendrites and possible absorption by another activated target (see assumption (iii)). It is also possible that an activated synaptic target may be only partially hidden in the sense that it might emit a signal that increases the probability of a granule stopping in a neighborhood of that target. However, we will not consider this possibility here because the details of such signaling mechanisms are currently unknown.

Motivated by the problem of mRNA transport, we present and analyze a stochastic model of directed intermittent search for a hidden target on a one-dimensional track. A particle injected at one end of the track randomly switches between a stationary search phase and a mobile, non-search phase that is biased in the anterograde direction. There is a finite possibility that the particle fails to find the target due to an absorbing boundary at the other end of the track or due to competition with other targets. The basic model is presented in section 2. We then calculate the hitting probability and conditional mean first passage time (MFPT) for finding a single target in the case of unidirectional search (section 3) and partially biased search (appendices A and B). We show that an optimal search strategy does not exist, although for a fixed hitting probability, a unidirectional rather than a partially biased search strategy generates a smaller MFPT (section 4). Finally, we analyze unidirectional search in the case of $n$ hidden targets, and determine the maximum hitting probability for finding the $n$th target given that the previous $n - 1$ targets are not found (section 5). We show that in the case of large $n$, it is preferable to spend more time in the mobile, non-search phase than in the stationary search phase.

## 2. Stochastic model of cargo transport in a dendrite

Consider a single motor-driven particle moving along a one-dimensional track of length $L$, see figure 2. The particle could represent an mRNA granule and the track could be a microtubular filament running the length of a dendrite; for simplicity, we ignore any branching. Suppose that at time $t = 0$ the particle enters one end of the track, which we take to be at $x = 0$. Within the interior of the track, $0 < x < L$, the particle can be in one of three states labeled by $n = 0, \pm$: stationary ($n = 0$), moving to the right (anterograde) with speed $v_+$ ($n = +$), or moving to the left (retrograde) with speed $v_-$ ($n = -$). Transitions between the three states are governed by a discrete Markov process. We further assume that there is a hidden (synaptic) target at a fixed but unknown location $x = X$. If the particle is within a distance $a$ of the target and is in the

stationary state, then the particle can detect or, equivalently, be absorbed by the target at a rate $k$. We assume throughout that $a < X$ and $a < L - X$ so the domain of detectability lies fully within the interval $[0, L]$.

Let $Z(t)$ and $N(t)$ denote the random position and state of the particle at time $t$ and define $\mathbb{P}(x, t, n \mid y, 0, m) \, dx$ as the joint probability that $x \leqslant Z(t) < x + dx$ and $N(t) = n$ given that initially the particle was at position $Z(0) = y$ and was in state $N(0) = m$. Setting

$$P_n(x, t) \equiv \mathbb{P}(x, t, n | y, 0, +) \tag{2.1}$$

with initial condition $P_n(x, 0) = \delta(x - y)\delta_{n,+}$, we have the following master equation describing the evolution of the probability densities for $t > 0$:

$$\partial_t P_+(x, t) = -v_+ \partial_x P_+(x, t) - \beta_+ P_+(x, t) + \alpha P_0(x, t), \tag{2.2a}$$

$$\partial_t P_-(x, t) = v_- \partial_x P_-(x, t) - \beta_- P_-(x, t) + \alpha P_0(x, t), \tag{2.2b}$$

$$\partial_t P_0(x, t) = \beta_+ P_+(x, t) + \beta_- P_-(x, t) - 2\alpha P_0(x, t) - k\chi(x - X) P_0(x, t). \tag{2.2c}$$

Here $\alpha, \beta_\pm$ are the transition rates between the stationary and mobile states as indicated in figure 2. We have introduced the indicator function $\chi$ according to

$$\chi(x) = \begin{cases} 1 & \text{if } |x| < a, \\ 0 & \text{otherwise.} \end{cases} \tag{2.3}$$

Equations (2.2a)–(2.2c) are supplemented by a reflecting boundary condition at $x = 0$ and an absorbing boundary condition at $x = L$. That is,

$$v_- P_-(0, t) = v_+ P_+(0, t), \qquad P_-(L, t) = 0. \tag{2.4}$$

The absorbing boundary takes into account the fact that granules can be degraded or absorbed by other targets downstream to the given target (see also section 5). Finally, we assume that the transport is partially biased in the anterograde direction by taking

$$\vartheta_- \equiv \frac{\beta_+}{v_+} - \frac{\beta_-}{v_-} < 0.$$

If the velocities in the two directions are equal, $v_+ = v_- = v$, then this condition implies that the particle spends more time in the anterograde state than the retrograde state. Unidirectional transport is obtained in the limit $\beta_- \to \infty$.

Let $J(t)$ denote the probability flux due to absorption by the target at $X$:

$$J(t) = k \int_{X-a}^{X+a} P_0(x, t) \, dx. \tag{2.5}$$

Define the hitting probability $\Pi$ to be the probability that the particle eventually finds the target, that is, it is absorbed somewhere in the interval $X - a \leqslant x \leqslant X + a$ rather than at the end $x = L$:

$$\Pi = \int_0^\infty J(t) \, dt. \tag{2.6}$$

The conditional mean first passage time [19] (MFPT) $T$ is then defined to be the mean time it takes for the particle to find the target given that it is not absorbed at $x = L$:

$$T = \frac{\int_0^\infty t\,J(t)\,\mathrm{d}t}{\int_0^\infty J(t)\,\mathrm{d}t}. \tag{2.7}$$

The two quantities $T$ and $\Pi$ characterize the efficiency of the stochastic search process. Clearly, it would be advantageous for the particle to minimize the search time $T$ and maximize the hitting probability $\Pi$. However, as we show in this paper, these two requirements compete with each other so that, in contrast to previous studies of intermittent search for which $\Pi = 1$ and the motion is unbiased [12, 17, 18], there is not a single optimal search strategy. This can be seen heuristically in the case of unidirectional transport where the particle is either stationary or undergoes anterograde motion. Here the particle can reach the target more quickly by having a higher probability of being in the mobile state. However, this also increases the chance of overshooting the target without detecting it and thus reduces the hitting probability. For the particular application to mRNA transport, it could be argued that the only important factor is minimizing the MFPT irrespective of the hitting probability, since many mRNA granules are synthesized in the nucleus and transported into the dendrite for delivery to synaptic targets. However, as we explore further in section 5, synaptic targets compete for resources so that one expects mRNA transport to be biased towards targets closer to the nucleus. This could be important when considering the role of protein synthesis in synaptic plasticity. Hence, it is important to keep track of both the hitting probability and the MFPT.

## 3. Calculation of $\Pi$ and $T$

There are two alternative methods for calculating the hitting probability $\Pi$ and the conditional MFPT $T$ defined by equations (2.6) and (2.7), one based on Laplace transforming the forward master equation and the other based on solving the corresponding backward equation [19]. We will follow [12, 17, 18] and use the latter approach here. For the sake of illustration, we will focus on the simpler problem of unidirectional intermittent search, for which equations (2.2a)–(2.2c) reduce to the two-state Markov process

$$\partial_t P_+ = -v\partial_x P_+ + \alpha P_0 - \beta P_+, \tag{3.1a}$$

$$\partial_t P_0 = \beta P_+ - \alpha P_0 - k\chi(x - X)P_0. \tag{3.1b}$$

In this case there is no need to introduce any supplementary boundary conditions, since the particle cannot return to the origin nor find the target once it has crossed the point $x = X + a < L$. Starting from the associated Chapman–Kolmogorov equation, it can be shown that the backward master equation for the two-state model is given by

$$\partial_t Q_+ = v\partial_y Q_+ - \beta[Q_+ - Q_0], \tag{3.2a}$$

$$\partial_t Q_0 = \alpha[Q_+ - Q_0] - k\chi(y - X)Q_0, \tag{3.2b}$$

where $Q_m(y, t) = \mathbb{P}(x, t, 0|y, 0, m)$. For notational convenience, we have dropped the subscript $+$ on the velocity $v$ and transition rate $\beta$. Let $\gamma_m(y, t)$ be the total probability that the particle is absorbed by the target after time $t$ given that it started at $y$ in state $m$. That is,

$$\gamma_m(y, t) = k \int_t^\infty \int_{X-a}^{X+a} \mathbb{P}(x, t', 0|y, 0, m) \, \mathrm{d}x \, \mathrm{d}t'. \tag{3.3}$$

Integrating equations (3.2$a$) and (3.2$b$) with respect to $x$ and $t$ and using $\partial_t \gamma_m(y, t) = -k \int_{X-a}^{X+a} \mathbb{P}(x, t, 0|y, 0, m) \, \mathrm{d}x$, we find that

$$\partial_t \gamma_+ = v \partial_y \gamma_+ + \beta(\gamma_0 - \gamma_+), \tag{3.4a}$$

$$\partial_t \gamma_0 = \alpha[\gamma_+ - \gamma_0] - k\chi(y - X)\gamma_0. \tag{3.4b}$$

The probability $\gamma_m(y, t)$ can be used to define two important quantities that characterize the efficiency of the search process. The first is the hitting probability

$$\pi_m(y) = \gamma_m(y, 0) \tag{3.5}$$

and the second is the conditional MFPT $T_m(y)$,

$$T_m(y) = -\int_0^\infty t \frac{\partial_t \gamma_m(y, t)}{\gamma_m(y, 0)} \, \mathrm{d}t = \frac{\int_0^\infty \gamma_m(y, t) \, \mathrm{d}t}{\gamma_m(y, 0)} \tag{3.6}$$

after integration by parts. It follows from definitions (2.6) and (2.7) that

$$\Pi = \pi_+(0), \quad T = T_+(0). \tag{3.7}$$

We first calculate the hitting probability $\pi_m(y)$. Setting $t = 0$ in equations (3.4$a$) and (3.4$b$), and using $\partial_t \gamma_m(y, 0) = -k\chi(y - X)\delta_{0,m}$ shows that

$$0 = v \partial_y \pi_+ + \beta(\pi_0 - \pi_+), \tag{3.8a}$$

$$-k\chi(y - X) = \alpha[\pi_+ - \pi_0] - k\chi(y - X)\pi_0. \tag{3.8b}$$

Solving equation (3.8$b$) for $\pi_0(y)$ gives

$$\pi_0(y) = \frac{\alpha \pi_+(y) + k\chi(y - X)}{\alpha + k\chi(y - X)}. \tag{3.9}$$

Substituting this into equation (3.8$a$) then yields

$$\partial_y \pi_+(y) = \frac{\beta}{v} \frac{k}{\alpha + k}(\pi_+(y) - 1)\chi(y - X). \tag{3.10}$$

This equation can be solved separately in the three domains $0 < x < X - a$, $X - a < x < X + a$ and $X + a < x < L$. Continuity across the boundaries at $x = X \pm a$ together with the condition $\pi_+(y) = 0$ for $y \geqslant X + a$ yields the solution

$$\pi_+(y) = \begin{cases} 1 - \mathrm{e}^{-2\lambda a}, & y < X - a, \\ 1 - \mathrm{e}^{-\lambda(X+a-y)}, & X - a < y < X + a, \\ 0, & y > X + a, \end{cases} \tag{3.11}$$

where

$$\lambda = \frac{\beta}{v}\frac{k}{\alpha + k}. \tag{3.12}$$

In order to calculate the MFPT $T_m(y)$, we integrate equations (3.4a) and (3.4b) with respect to $t$, using the identity $\int_0^\infty \partial_t \gamma_m(y,t)\, dt = -\pi_m(y)$:

$$-\pi_+ = v\frac{\partial(\pi_+ T_+)}{\partial y} + \beta(\pi_0 T_0 - \pi_+ T_+), \tag{3.13a}$$

$$-\pi_0 = \alpha[\pi_+ T_+ - \pi_0 T_0] - k\chi(y - X)\pi_0 T_0. \tag{3.13b}$$

Solving equation (3.13b) for $T_0$ in terms of $T_+$, substituting the result into equation (3.13a) and setting $S_+(y) \equiv T_+(y)\pi_+(y)$ leads to the equation

$$\partial_y S_+(y) = \frac{\beta}{v}\frac{k\chi(y-X)}{\alpha + k\chi(y-X)}S_+(y) - \frac{1}{v}\left(\frac{\beta}{\alpha + k\chi(y-X)}\pi_0(y) + \pi_+(y)\right). \tag{3.14}$$

This can be solved along similar lines to equation (3.10) by matching solutions in the three domains $0 < x < X - a$, $X - a < x < X + a$ and $X + a < x < L$, and requiring that $S_+(X + a) = 0$. After some algebra we obtain the result

$$T_+(y) = \begin{cases} (X - a - y)\mu_1 - \dfrac{2a\mu_2}{e^{2\lambda a} - 1} + \mu_3, & y < X - a, \\[2ex] \mu_3 - \dfrac{(X + a - y)\mu_2}{e^{\lambda(X+a-y)} - 1}, & |y - X| < a, \end{cases} \tag{3.15}$$

where

$$\mu_1 = \frac{1}{v}\left(1 + \frac{\beta}{\alpha}\right), \qquad \mu_2 = \frac{1}{v}\left(1 + \frac{\alpha\beta}{(\alpha + k)^2}\right), \qquad \mu_3 = \frac{\alpha + \beta + k}{\beta k}. \tag{3.16}$$

Note that as expected $T_+(y) \to \infty$ as $y \to X + a$. Finally, combining equations (3.7), (3.11) and (3.15),

$$\Pi = 1 - e^{-2\lambda a}, \quad T = (X - a)\mu_1 - \frac{2a\mu_2}{e^{2\lambda a} - 1} + \mu_3. \tag{3.17}$$

The calculation of $\Pi$ and $T$ proceeds in a similar fashion for the full three-state model given by equations (2.2a)–(2.2c). The details are presented in the appendices. In figures 3 and 4, we plot $\Pi$ and $T$ as functions of $\alpha$ and $\beta_+$ with $\beta_-$ and $v_+ = v_- = v$ fixed. The special case of unidirectional transport is recovered by taking the limit $\beta_- \to \infty$. It can be seen that increasing the parameter $\alpha$, which controls how much time the particle spends in the stationary search mode, decreases both the hitting probability and the conditional MFPT, see figure 3. Similarly, increasing the parameter $\beta_+$, which controls how much time the particle spends in the anterograde mobile state, increases both the hitting probability and the MFPT, see figure 4.
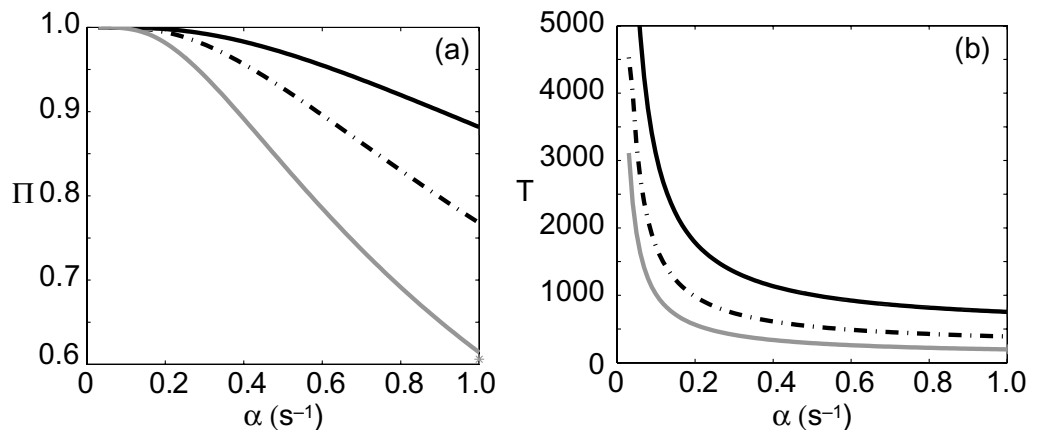
**Figure 3.** Partially biased anterograde transport. (a) The hitting probability $\Pi$ and (b) the MFPT $T$ are plotted as functions of the parameter $\alpha$ for fixed $\beta_+ = 1\,\text{s}^{-1}$ and various values of $\beta_-$: solid black curve ($\beta_- = 1.5\,\text{s}^{-1}$), dashed curve ($\beta_- = 2.5\,\text{s}^{-1}$) and solid gray curve (unidirectional). Other parameter values are $X = 10\,\mu\text{m}$, $L = 20\,\mu\text{m}$, $a = 1\,\mu\text{m}$, $k = 0.05\,\text{s}^{-1}$, $v_\pm = 0.1\,\mu\text{m}\,\text{s}^{-1}$.
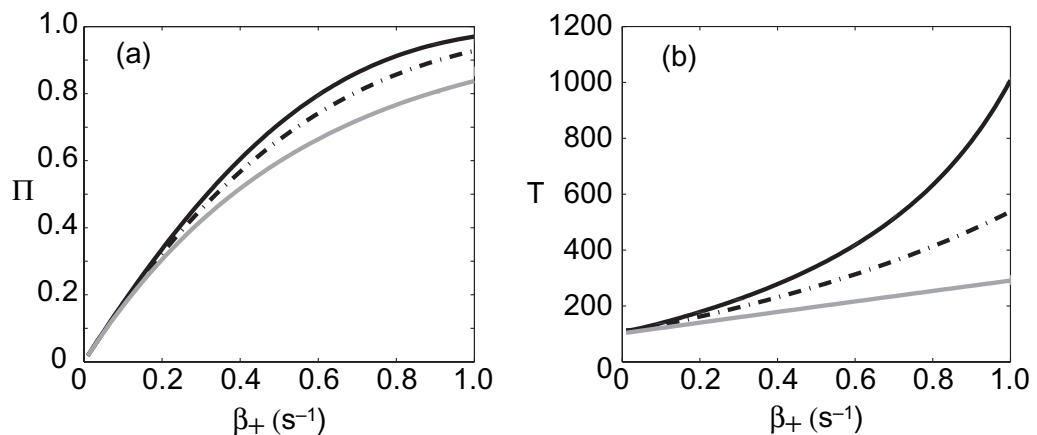


**Figure 4.** Same as figure 3 except (a) the hitting probability $\Pi$ and (b) the conditional MFPT $T$ are now plotted as functions of $\beta_+$ with fixed $\alpha = 0.5\,\text{s}^{-1}$.

Our results are consistent with the intuitive picture that one cannot simultaneously maximize the hitting probability and minimize the MFPT. Note that we take parameter values consistent with experimental studies of mRNA transport [4]–[6]. During unidirectional motion average velocities are found in the range $0.05$–$0.2\,\mu\text{m}\,\text{s}^{-1}$, whereas the duration of a moving phase tends to be in the range 1–10 s. Dendrites in cultured cells range in length from 10–100 $\mu\text{m}$.

## 4. Suboptimal search

A useful way to characterize the efficiency of the search strategy is to determine the minimum MFPT (if it exists) for a fixed hitting probability. Let us first consider the unidirectional case. Using equation (3.17) to express $\beta$ as a function of $\alpha$ and $\Pi$ (with all other parameters fixed),
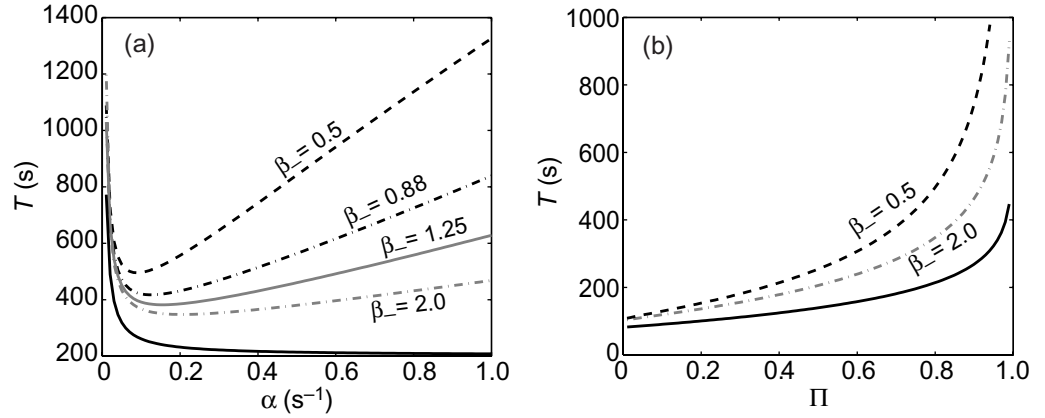
**Figure 5.** (a) Plot of MFPT $T$ as a function of $\alpha$ for fixed $\Pi = 0.8$ and various $\beta_-$. Other parameters are $v_\pm = 0.1\,\mu\mathrm{m\,s^{-1}}$, $X = 10\,\mu\mathrm{m}$, $a = 1\,\mu\mathrm{m}$, $k = 0.05\,\mathrm{s^{-1}}$, $L = 20\,\mu\mathrm{m}$. Unidirectional case is shown as a solid black curve. (b) Corresponding plot of minimum search time $T$ (with respect to variation in $\alpha$) as a function of the hitting probability $\Pi$ for $\beta_- = 1\,\mathrm{s^{-1}}$. Unidirectional case (black curve) is plotted for $\alpha_{\max} = 0.5\,\mathrm{s^{-1}}$.

we find that

$$\beta = \mathcal{B}(\alpha, \Pi) \equiv -\frac{v(\alpha + k)\ln(1 - \Pi)}{2ak}. \tag{4.1}$$

Substituting into the corresponding formula for the MFPT we obtain a function of the form $T = \mathcal{T}(\alpha, \mathcal{B}(\alpha, \Pi))$. Solving the equation $\partial_\alpha \mathcal{T}(\alpha, \mathcal{B}(\alpha, \Pi)) = 0$ for $\alpha$ formally yields two solutions

$$\alpha_\pm(\Pi) = k\frac{-(X - a)\Pi \pm \sqrt{-2a(X - a)(1 - \Pi)\Pi}}{(X - a)\Pi + 2a(1 - \Pi)}. \tag{4.2}$$

However, it is evident that $-2a(X - a)(1 - \Pi)\Pi < 0$ and therefore $\alpha_\pm(\pi)$ will always be complex valued. Thus no global minimum or maximum exists. This means we can choose any hitting probability $\Pi \in [0, 1]$ and the corresponding MFPT $\mathcal{T}(\alpha, \mathcal{B}(\alpha, \pi))$ will always be a decreasing function $\alpha$. This suggests that for fixed $\Pi$, the MFPT could be minimized by taking the limit $\alpha \to \infty$. However, this limit is not physically reasonable, since there will be a minimum time that the particle has to spend in the stationary state, that is, there exists an upper bound $\alpha \leqslant \alpha_{\max}$. It follows that the minimum search time for fixed $\Pi$ is $\mathcal{T}(\alpha_{\max}, \mathcal{B}(\alpha_{\max}, \Pi))$.

We can proceed in a similar fashion for partially biased anterograde transport by eliminating the transition rate $\beta_+$ in terms of $\Pi, \alpha, \beta_-$. We now find that for fixed $\Pi$ and $\beta_-$, the MFPT is a unimodal function of $\alpha$ with a unique minimum at $\alpha = \alpha_{\mathrm{opt}}(\beta_-, \Pi)$, see figure 5(a). However, the minimum search time is larger than that found for unidirectional transport ($\beta_- \to \infty$) at the same value of $\alpha$. This is further illustrated in figure 5(b), where we plot $\mathcal{T}(\alpha_{\mathrm{opt}}, \beta_-, \Pi)$ as a function of $\Pi$ for various values of $\beta_-$. Our results are nontrivial, since allowing a nonzero probability of moving in the retrograde direction might have enhanced the hitting probability without extracting too high a cost in terms of the conditional MFPT. We conclude from our analysis that in one dimension an effective strategy is to perform
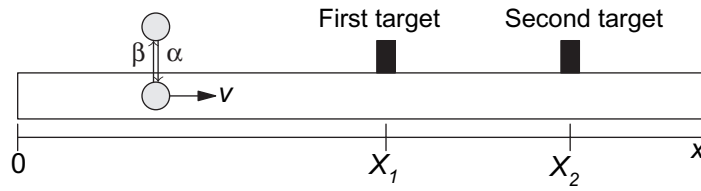
**Figure 6.** Schematic diagram of unidirectional search with multiple targets.

unidirectional intermittent search with fast switching between the mobile and immobile states. This is consistent with experimental observations regarding the activity-dependent anterograde transport of mRNA granules to unknown synaptic targets on a dendrite, see figure 1.

Note that the results depend weakly on the track length $L$, see appendices. For it can be checked that $\Pi$ and $T$ depend on $L$ through terms dominated by the factor $e^{\vartheta_-(L-X)}$. If $\vartheta_- < 0$ then these terms vanish in the limit $L \to \infty$ for fixed target position $X$. Hence, the absorbing boundary does not contribute significantly to $\Pi$ and $T$ unless the target is in the neighborhood of the boundary; the size of this neighborhood shrinks as the bias $\vartheta_-$ increases. In other words, once the particle has moved sufficiently beyond the target, its probability of returning to the target is negligible. It follows that one could replace the absorbing boundary by a population of downstream targets, for example, without significantly altering the results (see section 5).

## 5. Multiple targets and competition

So far we have considered anterograde intermittent search for a single hidden target, under the assumption that additional targets are further downstream. As long as the downstream targets are sufficiently far from the upstream target and transport is biased in the anterograde direction, they will have little effect on the hitting probability and conditional MFPT of the upstream target. However, an upstream target will have a significant effect on the search for downstream targets. In order to explore this phenomenon, let us consider two identical targets at positions $x = X_1$ and $X_2$ where the distance between the two targets is $l = X_2 - X_1 > 2a$, see figure 6. Since unidirectional transport is more effective than partially biased transport (see section 4) and is simpler to analyze, we will consider the former here. In this case the downstream target has no influence on the upstream target.

First, recall from section 3 that the hitting probability $\pi_+(y)$ for a single target at $X$ is independent of the starting position $y$ provided that $y < X - a$. That is, $\pi_+(y) = \Pi$ with $\Pi$ given by equation (3.17). The probability that the particle will miss the first target and then find the second target is simply

$$\hat{\Pi} = (1 - \Pi)\Pi. \tag{5.1}$$

This is easily generalized to the case of multiple targets by considering a series of trials that have probability $\Pi$ of success and $1 - \Pi$ of failure. In particular, the probability of missing the first $n$ targets and finding the $(n+1)$th target is

$$\hat{\Pi} = (1 - \Pi)^n \Pi. \tag{5.2}$$

Note that the hitting probability is independent of the spacing between the targets.

Let $\hat{T}$ denote the conditional MFPT to find the second target. It can be decomposed into two parts, $\hat{T} = \hat{T}_1 + \hat{T}_2$, where $\hat{T}_1$ is the conditional MFPT that the particle reaches $x = X_1 + a$ without finding the first target and $\hat{T}_2$ is the conditional MFPT that the particle finds the second target starting at a distance $l - a$ from it. The latter can be written down directly using our results from section 3, see equation (3.17), namely

$$\hat{T}_2 = (X_2 - X_1 - 2a)\mu_1 - \frac{2a\mu_2}{e^{2\lambda a} - 1} + \mu_3. \tag{5.3}$$

The calculation of $\hat{T}_1$ follows along similar lines to the analysis of section 3.1. Let $\pi_m^c(y) = 1 - \pi_m(y)$ be the probability of missing the first target given that the particle starts at position $y$ in state $m$. Clearly $\pi_m^c(y) = 1$ for $y \geqslant X_1 + a$. Let $\gamma_m^c(y)$ denote the corresponding probability that the particle passes the first target after a time $t$,

$$\gamma_m^c(y, t) = v \int_t^\infty \mathbb{P}(X_1 + a, t', + \mid y, 0, m) \, dt', \tag{5.4}$$

where $v$ is the velocity in the anterograde direction. It follows that $\pi_m^c(y) = \gamma_m^c(y, 0)$ and the conditional MFPT for reaching $X_1 + a$ without finding the first target is

$$T_m^c(y) = \frac{\int_0^\infty \gamma_m^c(y, t) \, dt}{\gamma_m^c(y, 0)}. \tag{5.5}$$

Since $\gamma_m^c(y, t)$ satisfies equations identical in form to $\gamma_m(y, t)$, see equations (3.4a) and (3.4b), we can integrate with respect to $t$ to obtain the following equations for $S_m^c(y) = \pi_m^c(y) T_m^c(y)$:

$$-\pi_+^c = v \frac{d}{dy}(S_+^c) + \beta(S_0^c - S_+^c), \tag{5.6a}$$

$$-\pi_0^c = \alpha S_+^c - (\alpha + k\chi(y - X_1))S_0^c, \tag{5.6b}$$

which are supplemented by the boundary conditions $S_+(X_1 + a) = 0$ and $\pi_+^c(X_1 + a) = 1$. Eliminating $S_0^c$ we obtain the single equation

$$\partial_y S_+^c(y) = \frac{\beta}{v} \frac{k\chi(y - X)}{\alpha + k\chi(y - X)} S_+^c(y) - \frac{1}{v}\left(\frac{\beta}{\alpha + k\chi(y - X)}\pi_0^c(y) + \pi_+^c(y)\right), \tag{5.7}$$

where $\pi_m^c(y) = 1 - \pi_m(y)$ with $\pi_m(y)$ given by equations (3.9) and (3.11). Solving the above equation along similar lines to (3.14)), we obtain the solution

$$\hat{T}_1 = \frac{S_+^c(0)}{\pi_+^c(0)} = A e^{2a\lambda}$$
$$= 2\mu_2 a + \mu_1(X_1 - a). \tag{5.8}$$

Finally, adding this to equation (5.3) gives us the conditional MFPT $\hat{T}$ to the second target in the full two target system

$$\hat{T} = 2a\mu_2\left(1 - \frac{1}{e^{2\lambda a} - 1}\right) + \mu_1(X_2 - 3a) + \mu_3. \tag{5.9}$$
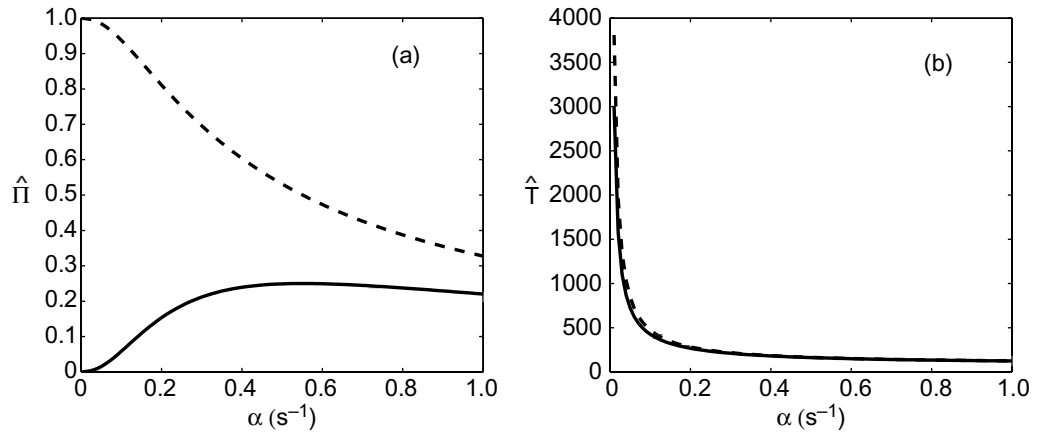
**Figure 7.** Anterograde unidirectional transport with two targets located at $X_1 = 5\,\mu\text{m}$ and $X_2 = 10\,\mu\text{m}$. (a) The hitting probability $\hat{\Pi}$ and (b) the MFPT $\hat{T}$ of the downstream target are plotted as functions of the parameter $\alpha$ for fixed $\beta = 0.5\,\text{s}^{-1}$. The dashed curves show the corresponding results when the upstream target is absent. Other parameter values are $X = 10\,\mu\text{m}$, $a = 1\,\mu\text{m}$, $k = 0.5\,\text{s}^{-1}$ and $v = 0.12\,\mu\text{m}\,\text{s}^{-1}$.
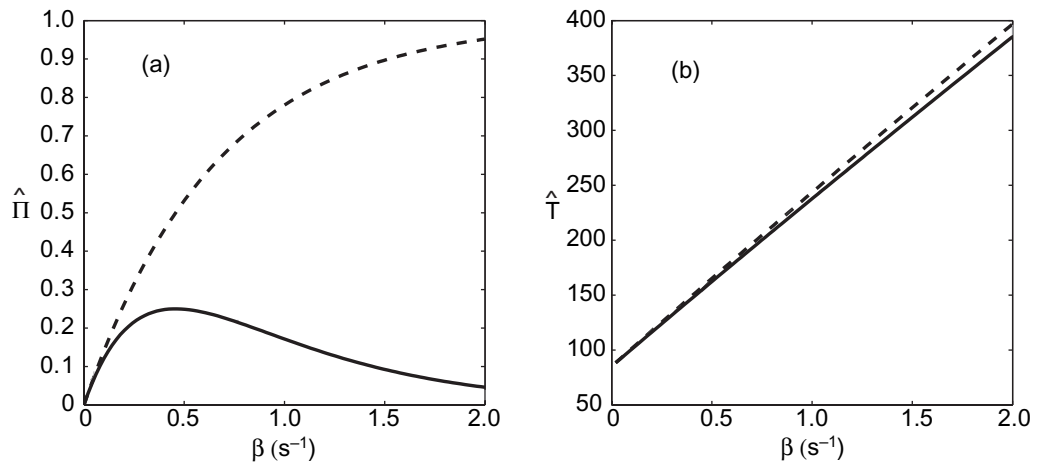


**Figure 8.** Same as figure 7 except that $\hat{\Pi}$ and $\hat{T}$ are plotted as functions of $\beta$ for fixed $\alpha = 0.5\,\mu\text{m}$.

We are interested in how the behavior of the search as a function of the state transition rates changes when additional targets are present. As seen in figures 7 and 8, the addition of a target between a searcher and its intended target qualitatively changes the behavior of the hitting probability as a function of the state transition rates. The hitting probability now has a maximum value when either $\alpha$ or $\beta$ is held fixed. Suppose that we maximize $\hat{\Pi}$ with respect to $\beta$ for $\alpha$ fixed. In the case of $n + 1$ targets, equations (3.17) and (5.2) show that $\hat{\Pi} = e^{-2na\lambda} - e^{-2(n+1)a\lambda}$ with $\lambda$ given by equation (3.12). The condition $\partial\hat{\Pi}/\partial\beta = 0$ then implies that the maximum hitting probability is achieved when $\alpha$ and $\beta$ satisfy the linear relationship

$$\beta_{\max}(\alpha) = \frac{\ln(1 + 1/n)\,v}{2ka}(\alpha + k). \tag{5.10}$$
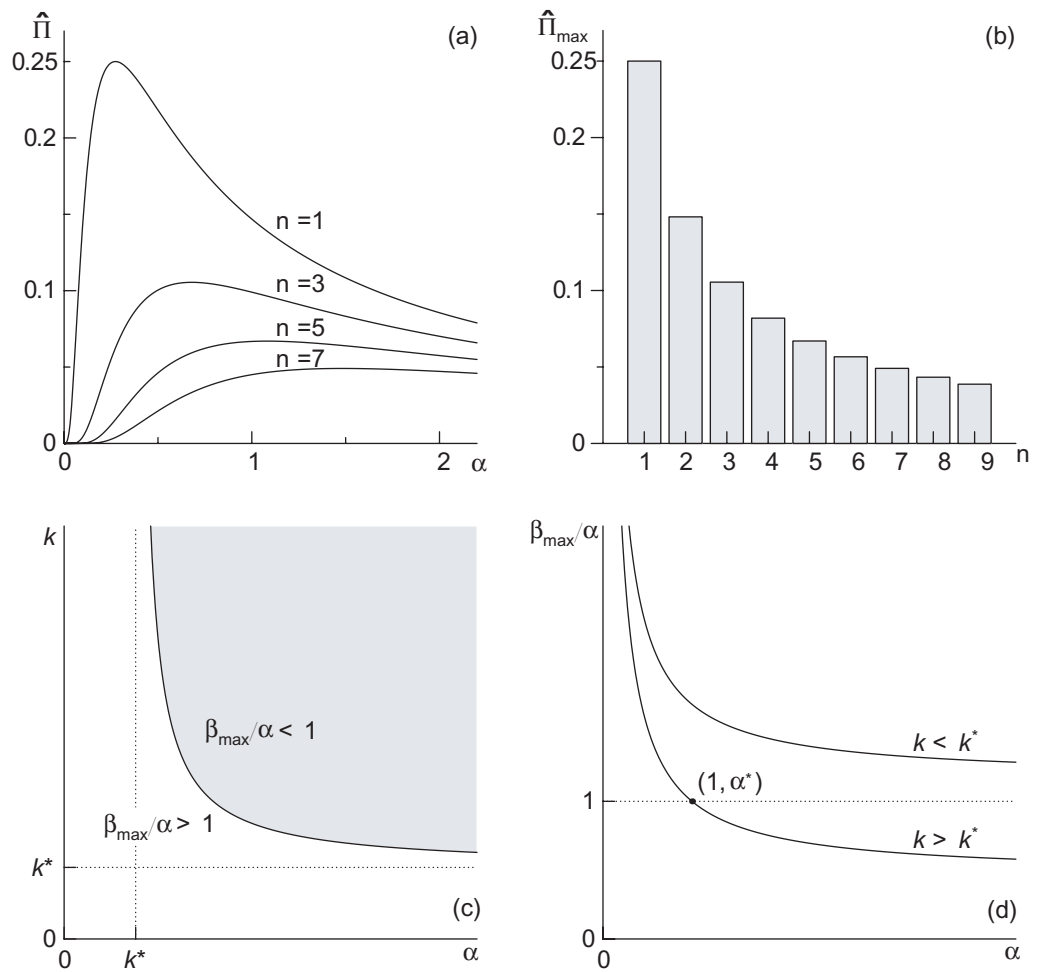
**Figure 9.** (a) The hitting probability as a function of $\alpha$ for various values of $n$. (b) The maximum hitting probability as a function of $n$. (c) The curve $\beta_{\max}/\alpha^* = 1$ separating the $\alpha$–$k$ plane into two regions for $n = 1$. (d) The ratio $\beta_{\max}/\alpha$ as a function of $\alpha$ for two different values of $k$.

Substitution of this into equation (5.2) yields the maximum hitting probability

$$\hat{\Pi}_{\max} = \frac{n^n}{(n+1)^{n+1}}.\tag{5.11}$$

Interestingly the maximum hitting probability depends only on the number of targets, as illustrated in figures 9(a) and (b).

The ratio $\beta/\alpha$ tells us how much time is spent moving relative to how much time is spent searching. At the maximum hitting probability, this ratio can be characterized as follows. Let $\alpha^*$ satisfy $\beta_{\max}/\alpha^* = 1$. Then

$$\alpha^*(k) = \frac{kv \ln(1+1/n)}{2ak - v \ln(1+1/n)}.\tag{5.12}$$

**IOP** Institute of Physics ⬥ DEUTSCHE PHYSIKALISCHE GESELLSCHAFT

Since $\alpha$ must be positive it follows that $\alpha^*(k)$ only exists for certain values of $k$. Let

$$k^* = \frac{v \, \ln(1 + 1/n)}{2a}. \tag{5.13}$$

If $k < k^*$ then $\alpha^*(k)$ does not exist and the ratio $\beta_{\max}/\alpha$ is always greater than one so that more time is spent searching than moving. On the other hand, if $k > k^*$ then the curve $\alpha = \alpha^*(k)$ exists and is a phase boundary separating the parameter regimes $\beta_{\max}/\alpha > 1$ and $\beta_{\max}/\alpha < 1$, see figures 9(c) and (d). Moreover, for large $n$

$$k^* = \frac{1}{n}\frac{v}{2a} + O(n^{-2}), \tag{5.14}$$

and the condition $k > k^*$ can be written as

$$\frac{1}{k} < \frac{2an}{v}. \tag{5.15}$$

This is nothing more than the statement that the average time necessary to find the target on entering the searching state is less than the time necessary to traverse the $n$ target intervals prior to reaching the intended target. Finally, in the limit $n \to \infty$, we see that $k^* \to 0$ and the maximum hitting probability occurs for $\beta_{\max}/\alpha < 1$. In other words, when many targets compete for a particle intended for a specific target, the hitting probability is maximized when more time is spent moving than searching. This is consistent with experimental observations of the motor-driven transport of mRNA granules, which suggest that unidirectional transport is characterized by long periods of continuous motion interrupted by brief pauses.

## 6. Discussion

In this paper, we have extended recent work on stochastic models of intermittent search in order to allow for both biased directed transport and failure to find a target. In the case of a one-dimensional directed search problem, there are conflicting demands of minimizing the conditional MFPT and maximizing the hitting probability. We showed that for a fixed hitting probability, a unidirectional search strategy yields a smaller MFPT than one that is partially biased in the same direction. We also determined in the unidirectional case how the hitting probability for a specific target decreases with the number of competing targets. A major motivation for our study was the experimental observation that activation of synaptic targets can signal the nucleus to transcribe new mRNA, which is then packaged within ribonucleoprotein granules and transported in an anterograde direction along the microtubules of a neuron's dendrite.

There are a number of interesting extensions of our work. First, the example of mRNA transport suggests that it would be worthwhile exploring directed intermittent search on a tree-like branching structure. One way to approach this problem would be to carry out a quasi-steady-state reduction of the full model along the lines of Reed et al [20], in order to derive an effective advection–diffusion equation for motor-driven transport on a dendritic tree. Such a model could also be used to develop a population-level description of mRNA transport, in which there are multiple mRNA granules searching for multiple synaptic targets. Incorporating both global and local signaling mechanisms from synaptic targets would then allow us to explore the role of mRNA transcription, translation and transport in long-term synaptic plasticity [2].

**IOP** Institute of Physics **Φ** DEUTSCHE PHYSIKALISCHE GESELLSCHAFT

Although our modeling and analysis were motivated by the problem of mRNA transport, directed or biased intermittent search arises in a wide range of phenomena including many forms of chemotaxis, in which an organism searches for a food source by moving up a chemical concentration gradient [21]. One apparent difference between chemotaxis and mRNA transport (besides the spatial dimension of the search) is that the target emits a diffusing signal in the former case. However, it is also possible that an activated synaptic target is only partially hidden, in the sense that it might emit a short-range signal that increases the probability of a granule stopping in the neighborhood of that target. Finally, it would be interesting to extend our analysis of directed intermittent search to higher spatial dimensions where there is a much weaker spatial correlation between the slow and fast phases.

### Appendix A. Hitting probability for partially biased anterograde transport

For the full three-state model, the hitting probabilities $\pi_m(y)$, $m = 0, \pm$, satisfy the equations (cf equations (3.8a) and (3.8b))

$$0 = v_+\partial_y\pi_+ + \beta_+(\pi_0 - \pi_+), \tag{A.1}$$

$$0 = -v_-\partial_y\pi_- + \beta_-(\pi_0 - \pi_-), \tag{A.2}$$

$$-k\chi(y-X) = \alpha(\pi_+ + \pi_- - 2\pi_0) - k\chi(y-X)\pi_0. \tag{A.3}$$

Solving (A.3) for $\pi_0$ and substituting the result into (A.1) and (A.2) gives

$$\partial_y\pi_+(y) + v_+((u(y)-1)\pi_+(y) + u(y)\pi_-(y)) = -v_+w(y), \tag{A.4}$$

$$\partial_y\pi_-(y) - v_-(u(y)\pi_+(y) + (u(y)-1)\pi_-(y)) = v_-w(y), \tag{A.5}$$

where

$$v_\pm = \frac{\beta_\pm}{v_\pm}, \quad u(y) = \frac{\alpha}{2\alpha + k\chi(y-X)}, \quad w(y) = \frac{k\chi(y-X)}{2\alpha + k\chi(y-X)}. \tag{A.6}$$

Equations (A.4) and (A.5) are supplemented by a reflecting boundary condition at $y = 0$ and an absorbing boundary at $y = L$:

$$\pi_+(0) = \pi_-(0), \quad \pi_+(L) = 0. \tag{A.7}$$

Following along similar lines to the unidirectional case, we must solve for $\pi_\pm(y)$ in three different regions: $0 < y < X - a$, $X - a < y < X + a$ and $X + a < y < L$. The solution in each of these regions will have two unknown integration constants so that we require six conditions. Two are given by the boundary conditions, whereas the other four are obtained by requiring continuity in $\pi_+(y)$ and $\pi_-(y)$ at $y = X \pm a$.

In region I ($0 \leqslant y \leqslant X - a$) we have $\chi(y - X) = 0$ so that $u(y) = 1/2$, $w(y) = 0$, and equations (A.4) and (A.5) become

$$\partial_y\pi_+(y) + \frac{v_+}{2}(-\pi_+(y) + \pi_-(y)) = 0, \tag{A.8}$$

$$\partial_y\pi_-(y) + \frac{v_-}{2}(-\pi_+(y) + \pi_-(y)) = 0. \tag{A.9}$$

Introducing the transformations $s = \frac{1}{2}(\pi_+ + \pi_-)$ and $d = \frac{1}{2}(\pi_+ - \pi_-)$,

$$\partial_y s(y) - \vartheta_+ d(y) = 0, \quad \partial_y d(y) - \vartheta_- d(y) = 0, \tag{A.10}$$

where $\vartheta_+ = \frac{1}{2}(\nu_+ + \nu_-)$ and $\vartheta_- = \frac{1}{2}(\nu_+ - \nu_-)$. Solutions to these equations have the form

$$s(y) = A_I \frac{\vartheta_+}{\vartheta_-} e^{\vartheta_- y} + B_I, \quad d(y) = A_1 e^{\vartheta_- y},$$

where $A_1$ and $B_1$ are unknown constants. The reflecting boundary condition $\pi_+(0) = \pi_-(0)$ implies that $A_I = 0$ so that solution is a constant region I, which is the desired hitting probability $\Pi$:

$$\pi_\pm(y) = \Pi. \tag{A.11}$$

The equations in region III ($X + a \leqslant y \leqslant L$) are the same as in region I so that we have solutions of the form

$$\pi_+(y) = A_{III}\nu_+ e^{\vartheta_- y} + B_{III}, \quad \pi_-(y) = A_{III}\nu_- e^{\vartheta_- y} + B_{III}.$$

The absorbing boundary condition $\pi_+(L) = 0$ implies that $B_{III} = -A_{III}\nu_+ e^{\vartheta_- L}$. Thus the solution in region III is

$$\pi_+(y) = A_{III}\nu_+(e^{\vartheta_- y} - e^{\vartheta_- L}), \quad \pi_-(y) = A_{III}(\nu_- e^{\vartheta_- y} - \nu_+ e^{\vartheta_- L}). \tag{A.12}$$

In region II ($X - a \leqslant y \leqslant X + a$) we have $\chi(y - X) = 1$ so that $u(y) = \sigma \equiv \alpha/(2\alpha + k)$ and $w(y) = \delta \equiv k/(2\alpha + k)$. Hence, (A.4) and (A.5) can be written as the matrix equation

$$\begin{pmatrix} \partial_y \pi_+(y) \\ \partial_y \pi_-(y) \end{pmatrix} + \mathbf{N} \begin{pmatrix} \pi_+(y) \\ \pi_-(y) \end{pmatrix} = \begin{pmatrix} -\nu_+\delta \\ \nu_-\delta \end{pmatrix}, \tag{A.13}$$

where

$$\mathbf{N} = \begin{pmatrix} \nu_+(\sigma - 1) & \nu_+\sigma \\ -\nu_-\sigma & -\nu_-(\sigma - 1) \end{pmatrix}. \tag{A.14}$$

This matrix equation can be solved in terms of the eigenvalues $\lambda_j$ and eigenvectors $(\xi_j, 1)^T$ of $N$, $j = 1, 2$:

$$\begin{pmatrix} \pi_+(y) \\ \pi_-(y) \end{pmatrix} = \Phi(y) \begin{pmatrix} A_{II} \\ B_{II} \end{pmatrix} + \begin{pmatrix} 1 \\ 1 \end{pmatrix}, \tag{A.15}$$

where $\Phi(y)$ is the fundamental solution matrix

$$\Phi(y) = \begin{pmatrix} \xi_1 e^{-\lambda_1 y} & \xi_2 e^{-\lambda_2 y} \\ e^{-\lambda_1 y} & e^{-\lambda_2 y} \end{pmatrix}, \quad \lambda_{1,2} = \vartheta_-(\sigma - 1) \pm \Delta, \tag{A.16}$$

and

$$\Delta = \sqrt{\vartheta_-^2 \sigma^2 + \vartheta_+^2(1 - 2\sigma)}, \quad \xi_{1,2} = \frac{1}{\nu_-\sigma}(\vartheta_+(1 - \sigma) \mp \Delta). \tag{A.17}$$

**IOP** Institute of Physics $\Phi$ DEUTSCHE PHYSIKALISCHE GESELLSCHAFT

Finally, we match the three solutions (A.11), (A.12) and (A.15) to determine the unknown constants $\Pi$, $A_{II}$, $B_{II}$, and $A_{III}$ by requiring continuity at $y = X - a$ and $X + a$:

$$\Pi = 1 - \frac{2\vartheta_-(\xi_1 - \xi_2)}{\Omega}, \tag{A.18}$$

$$A_{II} = \frac{2\vartheta_-}{\Omega}(\xi_2 - 1)e^{\lambda_1(X-a)}, \tag{A.19}$$

$$B_{II} = -\frac{2\vartheta_-}{\Omega}(\xi_1 - 1)e^{\lambda_2(X-a)}, \tag{A.20}$$

$$A_{III} = \frac{1}{\Omega}(\xi_1 - 1)(\xi_2 - 1)(e^{-2a\lambda_1} - e^{-2a\lambda_2})e^{-\vartheta_-(X+a)}, \tag{A.21}$$

where

$$\Omega = -\nu_+(\xi_2 - 1)(\xi_1 - 1)(e^{-2a\lambda_1} - e^{-2a\lambda_2})e^{\vartheta_-(L-X-a)} \tag{A.22}$$
$$+ (\xi_2 - 1)(\nu_-\xi_1 - \nu_+)e^{-2a\lambda_1} - (\xi_1 - 1)(\nu_-\xi_2 - \nu_+)e^{-2a\lambda_2}.$$

Equation (A.18) is the desired result.

## Appendix B. Conditional MFPT for partially biased anterograde transport

The equations for the conditional MFPT take the form (cf equations (3.13*a*) and (3.13*b*))

$$\nu_+\partial_y(T_+\pi_+) + \beta_+(T_0\pi_0 - T_+\pi_+) = -\pi_+, \tag{B.1}$$

$$\nu_-\partial_y(T_-\pi_-) - \beta_-(T_0\pi_0 - T_-\pi_-) = \pi_-, \tag{B.2}$$

$$\alpha(T_+\pi_+ + T_-\pi_-) - (2\alpha + k\chi(y - X))T_0\pi_0 = -\pi_0. \tag{B.3}$$

Let $S_m \equiv T_m\pi_m$ and solve (B.3) for $S_0$. This yields

$$S_0(y) = u(y)(S_+(y) + S_-(y)) + \frac{\pi_0 u(y)}{\alpha}. \tag{B.4}$$

Substituting (B.4) into (B.1) and (B.2) gives

$$\partial_y S_+(y) + \nu_+((u(y) - 1)S_+(y) + u(y)S_-(y)) = -\left(\frac{\pi_+(y)}{\nu_+} + \frac{\nu_+u(y)\pi_0(y)}{\alpha}\right), \tag{B.5}$$

$$\partial_y S_-(y) - \nu_-(u(y)S_+(y) + (u(y) - 1)S_-(y)) = \left(\frac{\pi_-(y)}{\nu_-} + \frac{\nu_-u(y)\pi_0(y)}{\alpha}\right). \tag{B.6}$$

Equations (B.5) and (B.6) are solved by imposing the boundary conditions

$$S_+(0) = S_-(0), \quad S_+(L) = 0, \tag{B.7}$$

along with requiring continuity in $S_+(y)$ and $S_-(y)$ at $y = X \pm a$. Given the solution for $S_m(y)$, the conditional MFPT is $T = S_+(0)/\Pi$.

The calculation of the conditional MFPT for biased bidirectional transport proceeds along similar lines to the hitting probability in appendix A. In region I we have $u(y) = \frac{1}{2}$ and $w(y) = 0$ so that (B.5) and (B.6) become

$$\partial_y S_+(y) + \frac{v_+}{2}(S_-(y) - S_+(y)) = -\left(\frac{1}{v_+} + \frac{v_+}{4\alpha}\right)\pi_+(y) - \frac{v_+}{4\alpha}\pi_-(y), \tag{B.8}$$

$$\partial_y S_-(y) + \frac{v_-}{2}(S_-(y) - S_+(y)) = \left(\frac{1}{v_-} + \frac{v_-}{4\alpha}\right)\pi_-(y) + \frac{v_-}{4\alpha}\pi_+(y). \tag{B.9}$$

Performing the transformation $S = \frac{1}{2}(S_- + S_+)$ and $D = \frac{1}{2}(S_- S_+)$ and exploiting the fact that $\pi_\pm(y) = \Pi$ in region I,

$$\partial_y D(y) - \vartheta_- D(y) = \frac{\Pi}{2}\rho_1, \tag{B.10}$$

$$\partial_y S(y) + \vartheta_+ D(y) = \frac{\Pi}{2}\rho_2, \tag{B.11}$$

where

$$\rho_1 = \frac{1}{v_-} + \frac{1}{v_+} + \frac{\vartheta_+}{\alpha}, \qquad \rho_2 = \frac{1}{v_-} - \frac{1}{v_+} - \frac{\vartheta_-}{\alpha}. \tag{B.12}$$

The solution to (B.10) is

$$D(y) = \frac{\Pi}{2\vartheta_-}\rho_1(e^{\vartheta_- y} - 1), \tag{B.13}$$

where we have imposed the reflecting boundary condition at $x = 0$. The solution to (B.11) is then

$$S(y) = \frac{\Pi}{2}\left([\rho_2 + \frac{\vartheta_+}{\vartheta_-}\rho_1]y - \frac{\vartheta_+}{\vartheta_-^2}\rho_1 e^{\vartheta_- y}\right) + \hat{B}_{\mathrm{I}}. \tag{B.14}$$

Equations (B.8) and (B.9) also hold in region III with $\pi_\pm(y)$ given by equation (A.12). We find that

$$D(y) = \hat{A}_{\mathrm{III}}e^{\vartheta_- y} + H_D(y) \tag{B.15}$$

with

$$H_D(y) = \frac{A_{\mathrm{III}}}{2}\left(\left(\frac{v_+}{v_+} + \frac{v_-}{v_-} + \frac{\vartheta_+^2}{\alpha}\right)ye^{\vartheta_- y} + \frac{v_+}{\vartheta_-}\rho_1 e^{\vartheta_- L}\right), \tag{B.16}$$

and

$$S(y) = -\frac{\vartheta_+}{\vartheta_-}\hat{A}_{\mathrm{III}}e^{\vartheta_- y} + H_S(y) + \hat{B}_{\mathrm{III}} \tag{B.17}$$

with

$$H_S(y) = \frac{A_{\text{III}}}{2} \left( \left( \frac{\nu_+}{\vartheta_- \nu_-} - \frac{\nu_-}{\vartheta_- \nu_-} - \frac{\vartheta_+}{\alpha} \right) e^{\vartheta_- y} - \nu_+ \rho_2 y e^{\vartheta_- L} \right) - \vartheta_+ \int^y H_D(y') \, dy'. \tag{B.18}$$

The absorbing boundary condition at $y = L$ requires $D(L) = S(L)$ so that we can eliminate the constant $\hat{B}_{\text{III}}$ and

$$S(y) = \frac{\hat{A}_{\text{III}}}{\vartheta_-} (\nu_+ e^{\vartheta_- L} - \vartheta_+ e^{\vartheta_- y}) + H_D(L) + H_S(y) - H_S(L). \tag{B.19}$$

In region II, we have $u(y) = \sigma$ and $w(y) = \delta$ so that equations (B.5) and (B.6) can be written in the matrix form

$$\begin{pmatrix} \partial_y S_+(y) \\ \partial_y S_-(y) \end{pmatrix} + \mathbf{N} \begin{pmatrix} S_+(y) \\ S_-(y) \end{pmatrix} = \mathbf{F(y)} \tag{B.20}$$

with $N$ defined in equation (A.10),

$$\mathbf{F}(y) = \begin{pmatrix} -\dfrac{\pi_+(y)}{\nu_+} - \dfrac{\nu_+ \sigma}{\alpha} \left[ \sigma \left( \pi_+(y) + \pi_-(y) \right) + \delta \right] \\ \dfrac{\pi_-(y)}{\nu_-} + \dfrac{\nu_- \sigma}{\alpha} \left[ \sigma \left( \pi_+(y) + \pi_-(y) \right) + \delta \right] \end{pmatrix}, \tag{B.21}$$

and $\pi_\pm(y)$ are given by equation (A.15). Using variation of constants, we obtain the solution

$$\begin{pmatrix} S_+(y) \\ S_-(y) \end{pmatrix} = \Phi(y) \begin{pmatrix} \hat{A}_{II} \\ \hat{B}_{II} \end{pmatrix} + \Phi(y) \int \Phi^{-1}(s) F(s) \, ds, \tag{B.22}$$

where the fundamental matrix $\Phi(y)$ is defined in equation (A.16). It follows that

$$D(y) = \frac{\hat{A}_{\text{II}}}{2} (1 - \xi_1) e^{-\lambda_1 y} + \frac{\hat{B}_{\text{II}}}{2} (1 - \xi_2) e^{-\lambda_2 y} + g_-(y), \tag{B.23}$$

$$S(y) = \frac{\hat{A}_{\text{II}}}{2} (1 + \xi_1) e^{-\lambda_1 y} + \frac{\hat{B}_{\text{II}}}{2} (1 + \xi_2) e^{-\lambda_2 y} + g_+(y), \tag{B.24}$$

where

$$g_\mp(y) = \pm \left( \frac{\kappa_{1,1}\phi_{2,2}}{2\Delta} + \kappa_{1,2}\phi_{1,2} y \right) e^{\lambda_1(X - a - y)} \mp \left( \frac{\kappa_{2,2}\phi_{1,1}}{2\Delta} - \kappa_{2,1}\phi_{2,1} y \right) e^{\lambda_2(X - a - y)}$$
$$\pm (\omega_1 (\xi_2 \mp 1) - \omega_2 (\xi_1 \mp 1)) \tag{B.25}$$

and

$$\kappa_{i,j} = \frac{\vartheta_-}{(\xi_1 - \xi_2)\Omega} \left( \frac{\sigma^2}{\alpha} (\xi_i + 1)(\xi_j \nu_- + \nu_+) + \frac{\xi_i}{\nu_+} + \frac{\xi_j}{\nu_-} \right), \tag{B.26}$$

$$\omega_i = \frac{\lambda_i \left((\sigma/\alpha)(\xi_i v_- + v_+) + \xi_i/v_- + 1/v_+\right)}{2(\xi_1 - \xi_2)v_+ v_- (1 - 2\sigma)}, \tag{B.27}$$

$$\phi_{i,j} = (\xi_i \mp 1)(\xi_j - 1). \tag{B.28}$$

Finally, the four unknown constants $\hat{B}_I$, $\hat{A}_{II}$, $\hat{B}_{II}$, $\hat{A}_{III}$ can be calculated by imposing continuity of $S(y)$ and $D(y)$ at $y = X - a$ and $X + a$. After some lengthy algebra, we find that the conditional MFPT is

$$T = \frac{S(0)}{\Pi} = -\frac{1}{2}\frac{\vartheta_+}{\vartheta_-^2}\rho_1 + \frac{\hat{B}_I}{\Pi}. \tag{B.29}$$

with

$$\hat{B}_I = -\frac{\Pi}{2}\left(\left[\rho_2 + \frac{\vartheta_+}{\vartheta_-}\rho_1\right](X-a) - \frac{\vartheta_+}{\vartheta_-^2}\rho_1 e^{\vartheta_-(X-a)}\right) + \tau(\xi_1 - 1)(\xi_2 - 1)(D(X+a) - g_-(X+a))$$

$$- \eta_{2,1}(S(X+a) - g_+(X+a)) + g_+(X-a). \tag{B.30}$$

Here $D(X+a)$ and $S(X+a)$ are determined from equations (B.15) and (B.17) with

$$\hat{A}_{III} = \vartheta_-\left[\frac{\pi_1}{2}\rho_1(e^{\vartheta_-(X-a)} - 1) - g_-(X-a) + \eta_{1,2}(g_-(X+a) - H_D(X+a))\right.$$

$$\left. + \tau(\xi_1 - 1)(\xi_2 - 1)\{g_+(X+a) - H_D(L) - H_S(X+a) + H_S(L)\}\right]$$

$$\times \left[(\vartheta_-\eta_{1,2} - \vartheta_+\tau(\xi_1 - 1)(\xi_2 - 1))e^{\vartheta_-(X+a)} + v_+\tau(\xi_1 - 1)(\xi_2 - 1)e^{\vartheta_- L}\right]^{-1} \tag{B.31}$$

and

$$\eta_{i,j} = \frac{(\xi_i - 1)(\xi_j + 1)e^{2\lambda_1 a} - (\xi_j - 1)(\xi_i + 1)e^{2\lambda_2 a}}{2(\xi_1 - \xi_2)}, \tag{B.32}$$

$$\tau = \frac{e^{2\lambda_1 a} - e^{2\lambda_2 a}}{2(\xi_1 - \xi_2)}. \tag{B.33}$$

## References

[1] Steward O and Schuman E M 2001 *Annu. Rev. Neurosci.* **24** 299
[2] Kelleher R L, Govindarajan A and Tonegawa S 2004 *Neuron* **44** 59
[3] Bramham C R and Wells D G 2007 *Nat. Rev. Neurosci.* **8** 776
[4] Knowles R B, Sabry J H, Martone M E, Deerinck T J, Ellisman M H, Bassell G J and Kosik K S 1996 *J. Neurosci.* **16** 7812
[5] Rook M S, Lu M and Kosik K S 2000 *J. Neurosci.* **20** 6385
[6] Dynes J L and Steward O 2007 *J. Comp. Neurol.* **500** 433
[7] Welte M A 2004 *Curr. Biol.* **14** 525
[8] Bell J W 1991 *Searching Behaviour, The Behavioural Ecology of Finding Resources* (London: Chapman and Hall)

[9] Viswanathan G M, Afanasyev V, Buldyrev S V, Murphy E J, Prince H A and Stanley H E 1996 *Nature* **381** 413

[10] Viswanathan G M, Buldyrev S V, Havlin S, da Luz M G E, Raposo E P and Stanley H E 1999 *Nature* **401** 911

[11] Bartumeus F, Catalan J, Fulco U L, Lyra M L and Viswanathan G M 2002 *Phys. Rev. Lett.* **88** 097901

[12] Loverdo C, Benichou O, Moreau M and Voituriez R 2008 *Nat. Phys.* **4** 134

[13] Berg O G and Blomberg C 1976 *Biophys. Chem.* **4** 367

[14] Halford S E and Marko J F 2004 *Nucleic Acids Res.* **32** 3040

[15] Slutsky M and Mirny L A 2004 *Biophys. J.* **87** 4021

[16] Coppey M, Benichou O, Voituriez R and Moreau M 2004 *Biophys. J.* **87** 1640

[17] Benichou O, Coppey M, Moreau M, Suet P H and Voituriez R 2005 *Phys. Rev. Lett.* **19** 198101

[18] Benichou O, Loverdo C, Moreau M and Voituriez R 2007 *J. Phys.: Condens. Matter* **19** 065141

[19] Redner S 2001 *A Guide to First Passage Time Processes* (Cambridge: Cambridge University Press)

[20] Reed M C, Venakides S and Blum J J 1990 *SIAM J. Appl. Math.* **50** 167

[21] Berg H C and Purcell E M 1977 *Biophys. J.* **20** 193