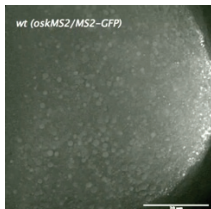# Molecular motor-based models of random intermittent search[1]
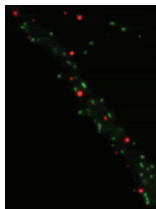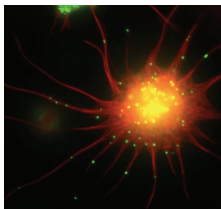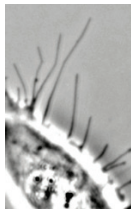
Paul C Bressloff
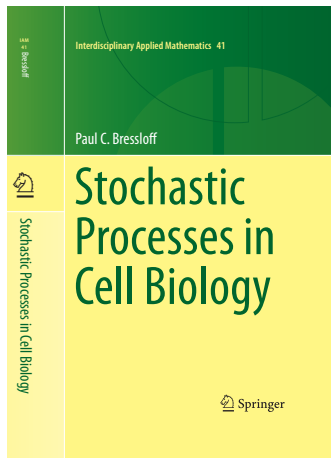
Department of Mathematics, University of Utah

June 4, 2014

SHAMELESS ADVERTISING!
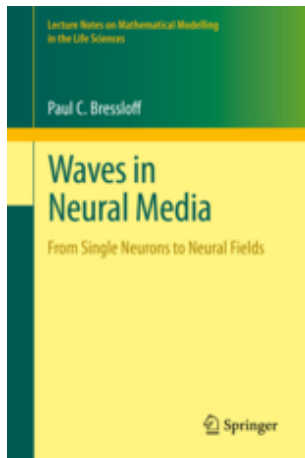
PLAN OF TALKS
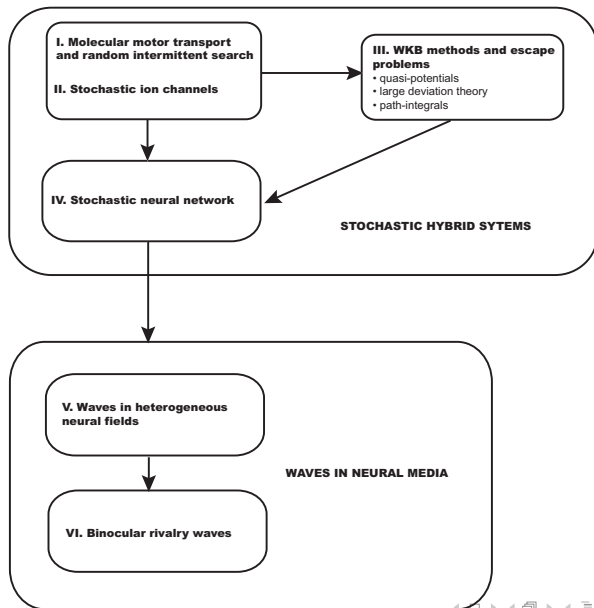
RANDOM INTERMITTENT SEARCH
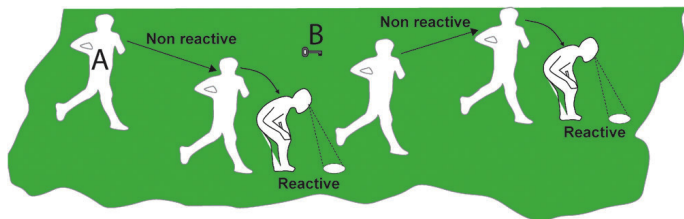
- Random search strategies are used throughout nature as a means of efficiently searching large areas for a target of unknown location

- An efficient stochastic search strategy is to alternate between
  (A) a slow motion (eg. diffusive) search phase and
  (B) a fast (eg. motor-assisted or ballistic) non-search phase

- Examples include foraging animals, a promoter protein searching for a specific target site on DNA, virus searching for the nucleus, **mRNA transport in neurons**

DNA/PROTEIN INTERACTIONS (BERG ET AL 1981)

(a) DNA, sliding, 3D diffusion, protein, target

(b) x=0
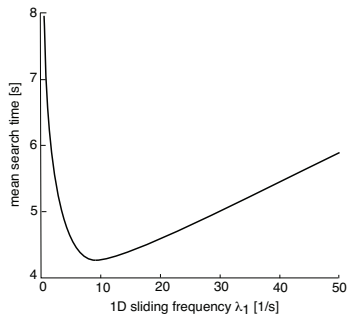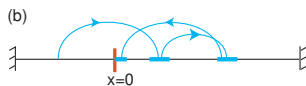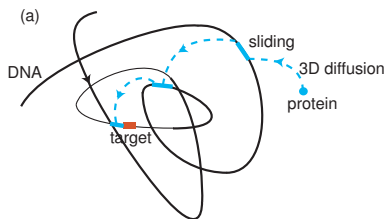
- Protein searching for a specific binding site on DNA with N base pairs executes sliding 1D diffusion for mean time τ_1

- Protein unbinds from DNA, executes 3D diffusion for mean time τ_3, rebinds at a random nonspecific site

$$\tau = \frac{N}{n}(\tau_1 + \tau_3), \quad n = 2\sqrt{D_1\tau_1}, \quad \tau_3^{-1} = 4\pi D_3 N b$$
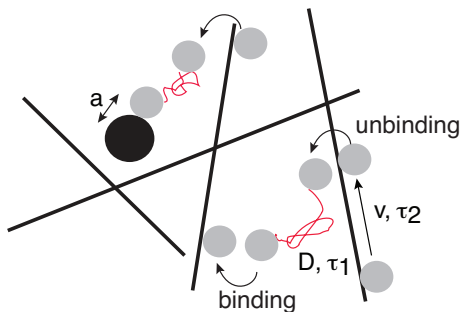
- A molecule searching for a reactant alternates between slow diffusion of duration τ_1 and ballistic motion of duration τ_2

- Ballistic motion consists of motor–driven transport along cytosokeletal filaments that form a 2D or 3D mesh within cell

- Active transport optimizes reaction rate if $a > D/v$

NEURONS ARE LARGE CELLS
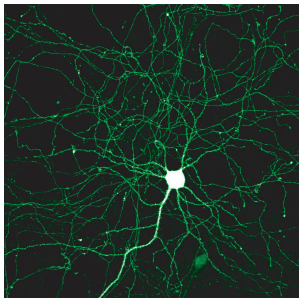
synapses located in mushroom-like dendrtic spines
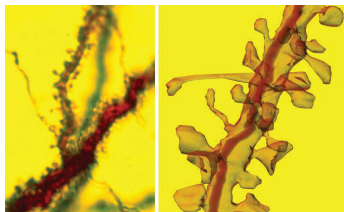
- Proteins and other molecules must be transported long distances along dendrites and axons
- Protein transport crucial in synapse formation and plasticity
- Defects underly various neurodegenerative diseases
- Diffusive transport is too slow: $\tau = L^2/D$ with $D = 1\mu m^2 s^{-1}$ and $L > 100\mu m$
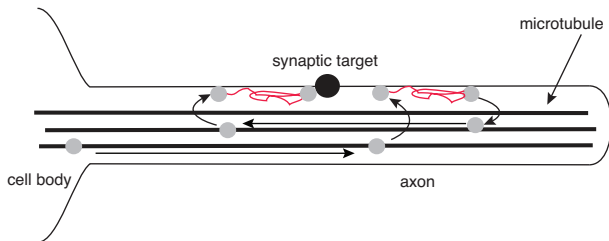
- Newly transcribed mRNA granules are transported into the dendrite by kinesin motors on microtubules.
- Following synaptic activation, mRNA is localized to synapses by actin-based myosin
- Motile mRNA particles in cultured hippocampal randomly switch between 3 states: stationary (or localized oscillations), anterograde and retrograde

MRNA TRANSPORT IS BIDIRECTIONAL
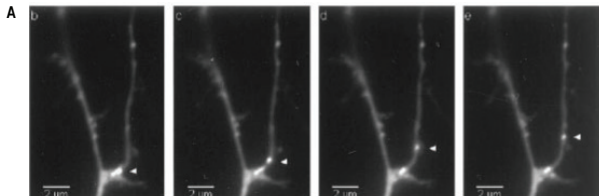
Rook et al J. Neurosci. (2000)
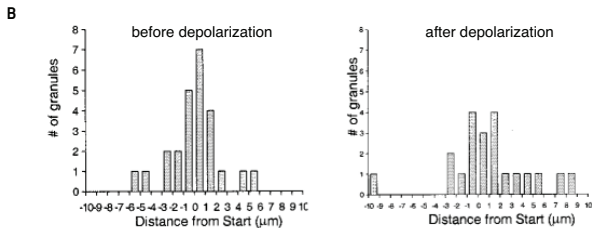
- Depolarization of cell increases anterograde bias

SPECIAL CHARACTERISTICS OF MRNA TRANSPORT

- Tends to be biased in anterograde direction – standard intermittent search models are unbiased

- Time for delivery is important - degradation of mRNA, synapses only primed for a limited period

- Non-zero probability of failure to find the target (eg. degradation, competition with other targets) - cost in resources

- Extensive dendritic branching

- Intracellular cargo is transported by a multiple motor complex

- Complex signalling mechanism involved in transferring mRNA to synaptic targets

Part I. Stochastic model of mRNA transport
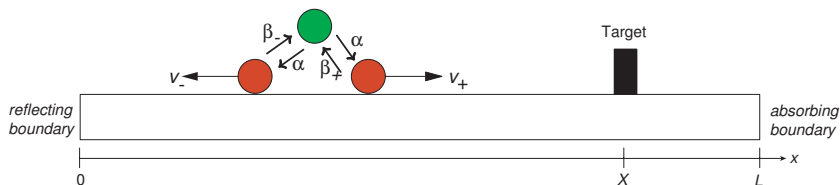
- Particle injected into dendrite at $x = 0$.

- Transitions between 3 states (left/right moving and stationary) given by a Markov process.

- In stationary state particle is absorbed at a rate k if within a distance l of target

STOCHASTIC MODEL OF MRNA TRANSPORT

- Chapman–Kolmogorov equation

$$\frac{\partial p_+}{\partial t} = -v\frac{\partial p_+}{\partial x} + \alpha p_0 - \beta_+ p_+$$

$$\frac{\partial p_-}{\partial t} = v\frac{\partial p_-}{\partial x} + \alpha p_0 - \beta_- p_-$$

$$\frac{\partial p_0}{\partial t} = -2\alpha p_0 + (\beta_+ p_+ + \beta_- p_-) - k\chi(x)p_0$$

  where $\chi(x) = 1$ if and only if $|x - X| < l$

- Boundary conditions (reflecting at $x = 0$, absorbing at $x = L$)

$$vp_-(0, t) = vp_+(0, t), \quad p_-(L, t) = 0$$

- Probability of finding target after time t is

$$\gamma(t) = k \int_t^\infty \int_{X-l}^{X+l} p_0(x, \tau)dxd\tau$$

OPTIMIZATION PROBLEM (UNBIASED SEARCH)

- Characterize efficiency of search in terms of the hitting probability Π and MFPT T:

$$\Pi = \gamma(0), \quad \text{MFPT } T = \int_0^\infty \frac{\gamma(t)}{\gamma(0)} dt$$

- First, consider unbiased search ($\beta_+ = \beta_- = \beta$) and reflecting boundaries at both ends ($\Pi = 1$)
- There then exists an optimal search strategy with respect to α, β
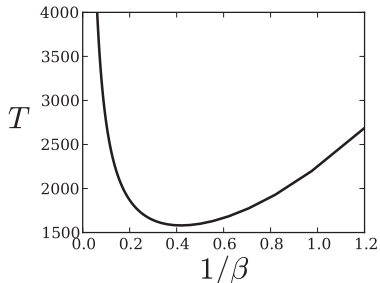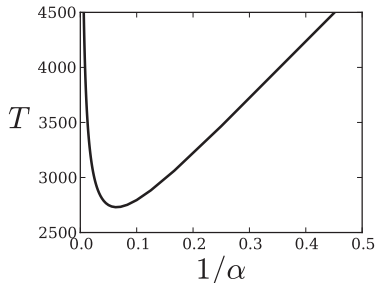
OPTIMIZATION PROBLEM (BIASED SEARCH)

- Now consider biased search $\beta \neq \beta_-$ and an absorbing boundary at $x = L$ ($\Pi < 1$)
- Now an optimal solution no longer exists, since increasing Π also increases T
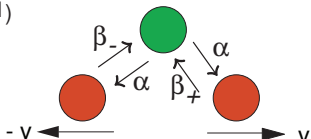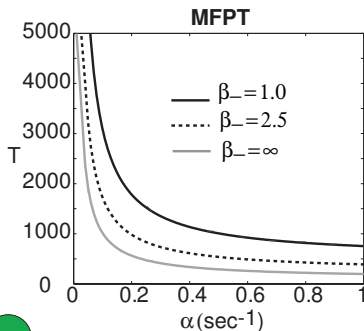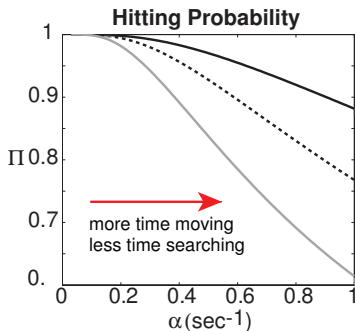
POPULATION OF SEARCHERS (PCB/JN 2012)

- Consider N independent, identical searchers that all start at the origin at time $t = 0$.

- Denote the MFPT to find the target of the jth searcher by T_j, $j = 1, \ldots, N$, with each T_j an independent, identically distributed random variable drawn from the single searcher first passage time (FPT) distribution

$$F(t) = \int_0^t J(s)ds, \quad J(s) = k \int_{X-l}^{X+l} p_0(x,s)dx.$$

- The random time T to find the target $T = \min(T_1, T_2, ..., T_N)$ has the distribution

$$\begin{aligned} F^{(N)}(t) &= \mathrm{Prob}(T < t) = 1 - \mathrm{Prob}(T > t) \\ &= 1 - \mathrm{Prob}(T_1 > t, T_2 > t, ..., T_N > t) \\ &= 1 - (1 - F(t))^N. \end{aligned}$$

MEAN-FIELD LIMIT

- Now suppose that the rate of detection for a single searcher scales as $k = \kappa/N$. Then

$$F^{(N)}(t) = 1 - \left(1 - \frac{\kappa}{N} \int_0^t \int_{X-l}^{X+l} p_0(x,s)ds\right)^N.$$

- In the mean-field limit $N \to \infty$, the detection rate $k \to 0$ so that the density function $p_0(x,t)$ is independent of the target.

- Moreover, in the large N limit,

$$\lim_{N\to\infty} F^{(N)}(t) = 1 - e^{-\mu(t)}, \quad \mu(t) = \kappa \int_0^t \int_{X-l}^{X+l} p_0(x,s)ds$$

with $p_0(x,t)$ the solution of the CK equation in the absence of a target.

EFFICIENCY OF SEARCH AS A FUNCTION OF N

- Plot of T against Π for various N in the case of biased search

- Upper curve is based on mean-field solution and lower curve on single searcher solution.

- Data points for finite N based on Monte-Carlo simulations
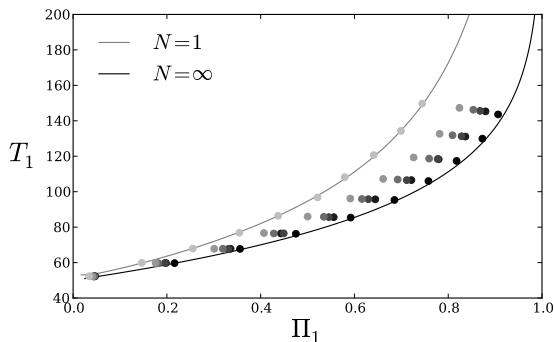
FPT DENSITY AS A FUNCTION OF N
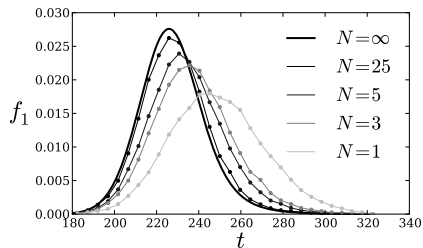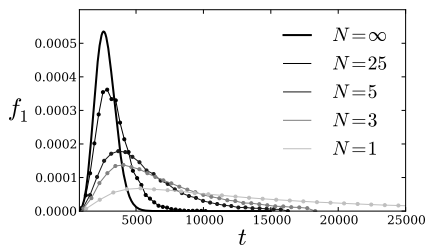
- LEFT: unbiased search RIGHT: biased search
- Asymptotic analysis shows that for an unbiased single searcher there is power-law scaling

$$F(t) \sim t^{-3/2}$$

whereas in the $N \to \infty$ limit there is a stretched exponential

$$F(t) \sim e^{-c\sqrt{t}}$$

Part II. Quasi-steady-state (QSS) diffusion approximation

MODEL REDUCTION (PCB/NEWBY 2010)

- 3-state model is simple to analyze directly.

- What about more complex search domains eg. dendritic trees, higher-dimensional microtubular networks?

- What about more complex biophysical models of motor–driven transport eg. tug–of–war model?

- QSS approximation reduces the Chapman-Kolomogorov equation to a Fokker-Planck equation in the regime of fast transition rates.

- Based on stochastic projection methods (Papanicolaou 1975, Gardiner 2009)

VELOCITY JUMP MARKOV PROCESS

- Consider a motor-complex having *N* internal velocity states:

$$\dot{x} = v_n, \quad n = 1, \ldots, N.$$

- Let $W(n, n'; x)dt/\epsilon$ be the probability that the system at x switches from n' at time t to the state n at time $t + dt$

- Introduce the probability density

$$\text{Prob}\{x(t) \in (x, x + dx), n(t) = n\} = p(x, n, t|x_0, n_0, 0)dx$$

- Differential Chapman-Kolmogorov (CK) equation

$$\frac{\partial p}{\partial t} = -v_n \frac{\partial [p(x, n, t)]}{\partial x} + \frac{1}{\epsilon} \sum_{n'} A(n, n'; x)p(x, n', t) - k_n \chi(x)p(x, n, t)$$

where

$$A(n, n'; x) = W(n, n'; x) - \sum_m W(m, n; x)\delta_{n', n}$$

MEAN-FIELD LIMIT

- Assume that for fixed x, the matrix $A(n, m; x)$ is irreducible and has a simple zero eigenvalue: $\sum_n A(n, m; x) = 0$ for all m.

- Perron-Frobenius Theorem $\implies$ continuous-time Markov process for fixed x,

$$\frac{dp(x, n, t)}{dt} = \frac{1}{\epsilon} \sum_m A(n, m; x) p(x, m, t),$$

has a globally attracting steady-state $\rho(x, n)$ such that $p(x, n, t) \to \rho(x, n)$ as $t \to \infty$.

- In the limit $\epsilon \to 0$ and $k_n = 0$, we obtain the mean-field equation

$$\frac{dx}{dt} = \mathcal{F}(x) \equiv \sum_n v_n \rho(x, n),$$

where $\rho(x, n)$ is the unique steady-state density:

$$\sum_m A(n, m; x) \rho(x, m) = 0$$

QUASI-STEADY-STATE DIFFUSION APPROXIMATION

- Decompose the probability density as

$$p(x, n, t) = C(x, t)\rho(x, n) + \epsilon w(x, n, t),$$

  where $\sum_n p(x, n, t) = C(x, t)$ and $\sum_n w(x, n, t) = 0$.

- Asymptotic expansion in ϵ yields FP equation

$$\frac{\partial C}{\partial t} = -\frac{\partial}{\partial x}(\mathcal{F}C) + \epsilon \frac{\partial}{\partial x}\left(\mathcal{D}\frac{\partial C}{\partial x}\right),$$

- Drift term given by mean-field equation, and diffusion coefficient

$$\mathcal{D}(x) = \sum_{m,n} Z(x, n)v_n,$$

- $Z(x, n)$ is the unique solution (for $\sum_m Z(x, m) = 0$)

$$\sum_m A(n, m; x)Z(x, m) = -[\mathcal{F}(x) - v_n]\rho(x, n)$$

3-STATE MODEL REVISITED

- Transition matrix is

$$\mathbf{A} = \begin{pmatrix} -\beta_+ & 0 & \alpha_+ \\ 0 & -\beta_- & \alpha_- \\ \beta_+ & \beta_- & -\alpha_+ - \alpha_- \end{pmatrix}, \quad \mathbf{v} = \begin{pmatrix} v \\ -v \\ 0 \end{pmatrix}, \quad \mathbf{k} = \begin{pmatrix} 0 \\ 0 \\ k \end{pmatrix}.$$

- The stationary density is

$$\boldsymbol{\rho} = \gamma^{-1}(\beta_+^{-1}, \beta_-^{-1}, \alpha^{-1})^T, \quad \gamma = \beta_+^{-1} + \beta_-^{-1} + \alpha^{-1}$$

- Drift and diffusion coefficient are

$$\mathcal{F} = \frac{1}{\gamma} \left(\frac{1}{\beta_+} - \frac{1}{\beta_-} \right) + \mathcal{O}(\varepsilon), \qquad \gamma = \frac{1}{\beta_-} + \frac{1}{\beta_+} + \frac{1}{\alpha}$$

$$\mathcal{D} = \epsilon \left(\frac{(1-\mathcal{F})^2}{\gamma\beta_+^2} + \frac{(1+\mathcal{F})^2}{\gamma\beta_-^2} \right) + \mathcal{O}(\varepsilon^2), \quad \lambda = \frac{k}{\alpha\gamma} + \mathcal{O}(\varepsilon)$$

MOMENT GENERATING FUNCTION

- Total probability flux into target is

$$J(t) = \lambda \int_{-1+X}^{1+X} u(x,t)dx.$$
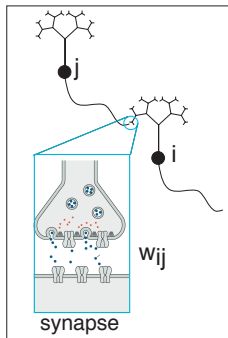
- Hitting probability and MFPT are given by

$$\Pi = \int_0^\infty J(t)dt = \Upsilon(0), \quad T = \frac{\int_0^\infty tJ(t)dt}{\int_0^\infty J(t)dt} = \frac{\Upsilon'(0)}{\Upsilon(0)}$$

- $\Upsilon(s)$ is moment generating function

$$\Upsilon(s) = \int_0^\infty e^{-st}J(t)dt = \lambda \int_{-1+X}^{1+X} \widetilde{U}(x,s)dx$$

Part III. Random intermittent search on a tree
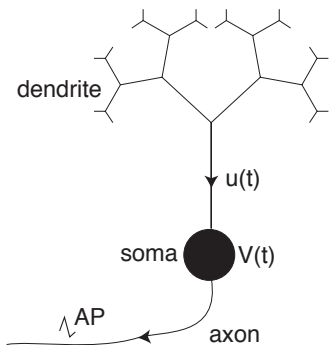
DENDRITIC TREE (PCB AND NEWBY 2009)

Target on jth branch

α

- *Interior branch nodes*
- *Open terminal nodes*
- *Closed terminal node*
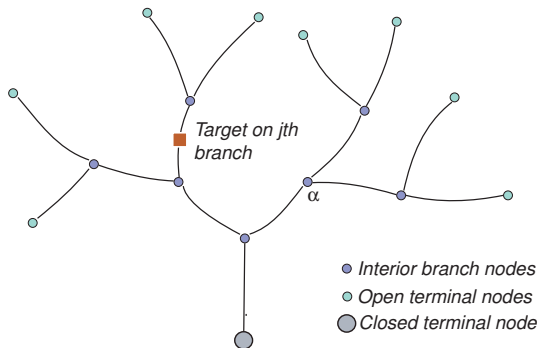
- Suppose that there is a hidden target on the *j*th branch of a tree Γ

- Let u_i denote probability density on *i*th segment of a tree under QSS approximation:

$$\frac{\partial u_i}{\partial t} = -\lambda \chi(x) \delta_{i,j} u_i - \mathcal{F}_i \frac{\partial u_i}{\partial x} + \mathcal{D}_i \frac{\partial^2 u_i}{\partial x^2}, \quad 0 < x < L_i$$

CONTINUITY AND CONSERVATION CONDITIONS

- Let $\mathcal{J}_i$ denote the probability current or flux

$$\mathcal{J}_i \equiv -\mathcal{D}_i \frac{\partial u_i}{\partial x} + \mathcal{F}_i u_i.$$

- Impose closed boundary condition on primary terminal branch and open boundary conditions at all other terminal segments

$$\mathcal{J}_0(0, t) = 0, \quad u_i(L_i, t) = 0$$

- At all branch nodes α with set of segments $\mathcal{I}_\alpha$ impose continuity

$$u_i(x(\alpha), t) = \Phi_\alpha(t), \quad \text{for all } i \in \mathcal{I}_\alpha,$$

and current conservation

$$\sum_{i \in \mathcal{I}_\alpha} \mathcal{J}_i(x(\alpha), t) = 0.$$

GREEN'S FUNCTION ON A TREE

- Laplace transforming FP equation on a tree we find that

$$\widetilde{U}_i(x,s) - \lambda \int_{-1}^{1} \mathcal{G}_{i,j}(x, y + X; s)\widetilde{U}_i(y,s)dy = -\mathcal{G}_{i,0}(x,0;s)$$

- $\mathcal{G}_{i,j}(x,y;s)$ is Green's function satisfying boundary conditions and

$$\left[\mathcal{D}_i\partial_x^2 - \mathcal{F}_i\partial_x - s\right]\mathcal{G}_{i,j}(x,y;s) = \delta_{i,j}\delta(x-y)$$

- Given a target on the jth branch, the generating function for the hitting probability and MFPT is then

$$\Upsilon_j(s) = \lambda \int_{-1}^{1} \widetilde{U}_j(x + X, s)dx.$$

STEPS IN CALCULATION OF Π AND T

1. Solve Green's function on each line segment in terms of unknown functions $\widetilde{\Phi}_\alpha(s)$

2. Match solutions of line segments meeting at a branch node using current conservation

3. Working from the open terminal nodes inwards, generate an iterative equation for $\widetilde{\Phi}_\alpha(s)$ which can be solved as a finite continued fraction

4. Substitute solution for Green's function into integral equation and solve for $\widetilde{U}_j$ numerically

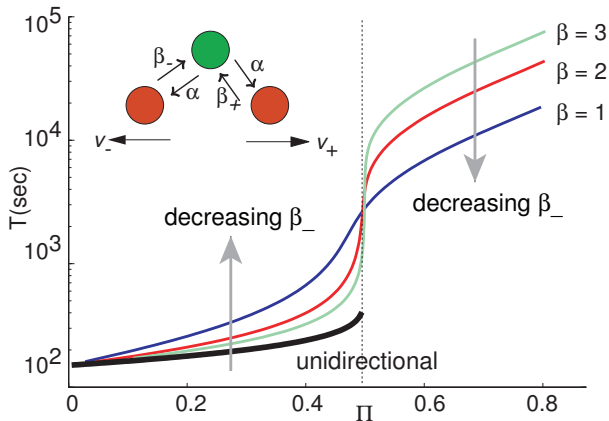5. Construct generating function and take limit $s \to 0$.

EXAMPLE: SEMI–INFINITE CAYLEY TREE
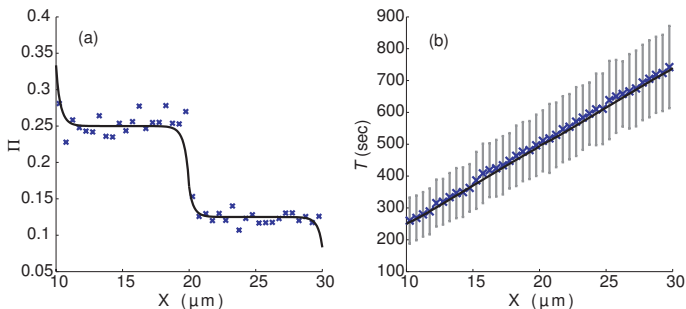
- Semi–infinite Cayley tree ($z = 3$) with identical branches of length $L = 10\mu m$.

- Plot of Π and T vs. target distance X from soma.

- Solid curves (analytical), points 'x' (Monte Carlo)

- Boundary layer at each branch node where

$$\Pi \to \Pi' \approx \Pi/(z-1)$$

TWO PHASES OF RANDOM SEARCH ON A TREE

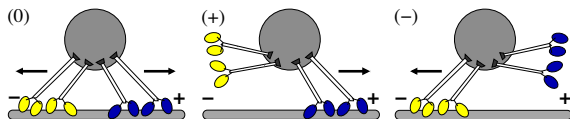- $n = 1$ branch node between target and soma

- Hit Prob $\Pi < 0.5$: resources cheap, unidirectional strategy

- Hit Prob $\Pi > 0.5$: resources costly, bidirectional strategy

Part IV. Tug–of–war model of random intermittent search

TUG-OF-WAR MODEL OF BIDIRECTIONAL TRANSPORT (KLUMPP ET AL 2005)

- Microtubule are polarized filaments with biophysically distinct $+$ and $-$ ends.

- Polarity determines preferred direction of motion of individual motors: kinesin (dynein) moves towards the $+$ $(-)$ end

- Multiple kinesin (antegrograde) and dynein (retrograde) motors form a protein complex with vesicular cargo.

- Individual motors randomly attach to and detach from microtubule track resulting in bidirectional transport

SINGLE MOTOR PROPERTIES

- Consider a cargo complex with $M_{\pm}$ kinesin/dynein motors.

- Suppose that $m_{\pm}(t)$ kinesin/dynein motors attached to microtubule at time t

- Load on each kinesin (dynein) motor is F/m_+ $(-F/m_-)$ where F is the total cargo force.

- Load reduces velocity of each motor according to
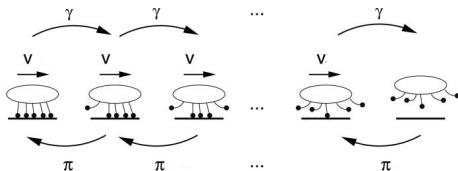
$$v = \overline{v}(1 - F/mF_S)$$

  where F_S is the stall force.

- Unbinding rate of a motor increases exponentially with load

$$\gamma(F/m) = \overline{\gamma}e^{F/mF_d}$$

  where F_d is detachment force. Binding rate π is constant

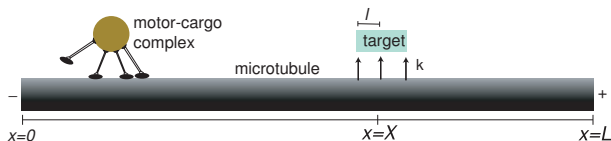# TRANSITION RATES BETWEEN INTERNAL STATES

- Transition rates for $m = m_{\pm}$

  $$\beta(m) = m\gamma(F/m) \text{ for } m \to m-1, \quad \alpha(m) = (M-m)\pi \text{ for } m \to m+1$$

- Equating velocities of kinesin/dynein motors determines F and v:

  $$F = F(m_+, m_-), \quad v = v(m_+, m_-) = \frac{m_+ F_{S+} - m_- F_{S-}}{m_+ F_{S+}/\overline{v}_+ + m_- F_{S-}/\overline{v}_-}$$

- Divide internal states into slowly moving search phases ($m_+ = m_-$) and faster non–search phases ($m_+ \neq m_-$).

CHAPMAN-KOLMOGOROV EQUATION

- Let $p(x, m_+, m_-, t)$ be probability density that cargo complex is in internal state (m_+, m_-) and has position x at time t

- Convert to general velocity jump Markov process by setting

$$n(m_+, m_-) = (M_+ + 1)m_- + (m_+ + 1)$$

$$p(x, n, t) = p(x, m_+, m_-, t), \quad v_n = v(m_+, m_-), \quad k_n = \delta_{m_+, m_-}$$

- Differential Chapman-Kolmogorov (CK) equation

$$\frac{\partial p}{\partial t} = -v_n \frac{\partial [p(x, n, t)]}{\partial x} + \frac{1}{\epsilon} \sum_{n'} A(n, n'; x) p(x, n', t) - k_n \chi(x) p(x, n, t)$$
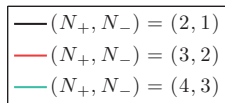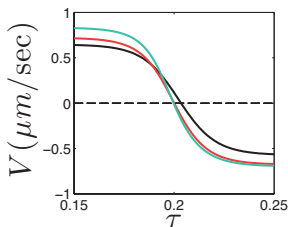
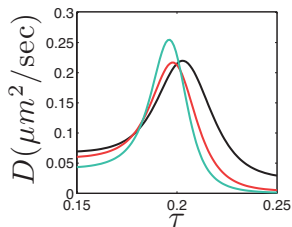# MICROTUBULE-ASSOCIATED PROTEINS (MAPS)

- MAPs (tau, MAP2) can bind to microtubules and reduce the binding rate of kinesin:

$$\pi_0(\tau) = \frac{\pi_0^{max}}{1 + e^{-\gamma(\tau_0 - \tau)}},$$

- Use QSS reduction to derive Fokker–Planck equation with $[\tau]$-dependent parameters:

$$\frac{\partial u}{\partial t} = -\lambda \chi(x) u - V \frac{\partial u}{\partial x} + D \frac{\partial^2 u}{\partial x^2}$$

LOCAL SIGNALING ENHANCES SEARCH PROCESS
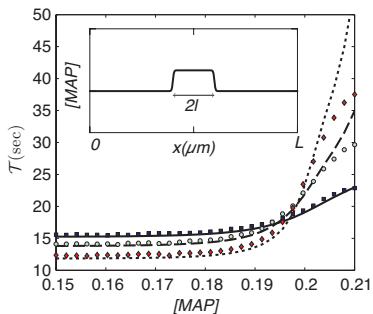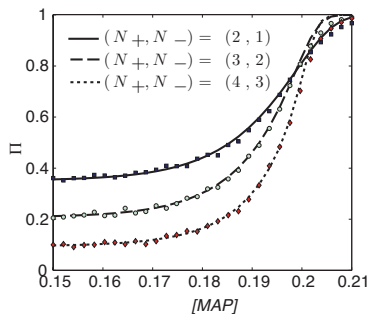
- Increasing [MAP] in the target domain can sharply increase hitting probability Π with only a relatively small increase in the MFPT

τ-INDUCED OSCILLATIONS
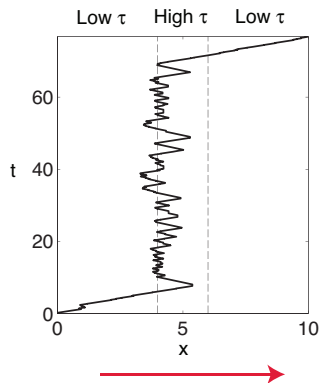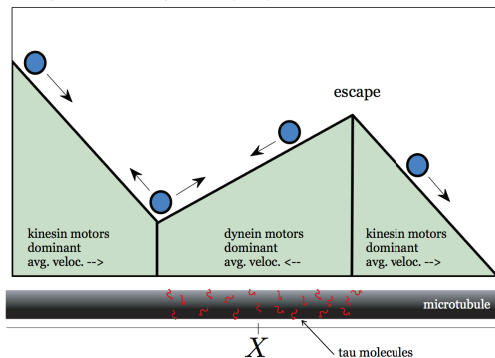
- Provides a possible explanation for experimentally observed oscillatory motion of motor complexes
- Breakdown of QSS approximation

METASTABILITY

- Mean-field equation with local signaling:

$$\frac{dx}{dt} = \mathcal{F}(x) = -\frac{d\Psi}{dx}$$

- Outside target domain $\mathcal{F}(x) = \bar{v}$
- Inside target domain $\mathcal{F}(x)$ changes sign $\implies$ potential $\Psi(x)$ has two fixed points: stable/unstable pair

enhanced MAP
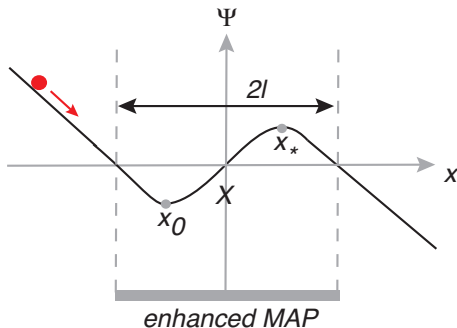
FIRST-PASSAGE TIME (FTP) PROBLEM

- Assume particle starts at stable fixed point x_0
- Absorbing boundary conditions at x_*:

$$p(x_*, n, t) = 0 \quad \text{for all } n \text{ such that } v_n < 0$$

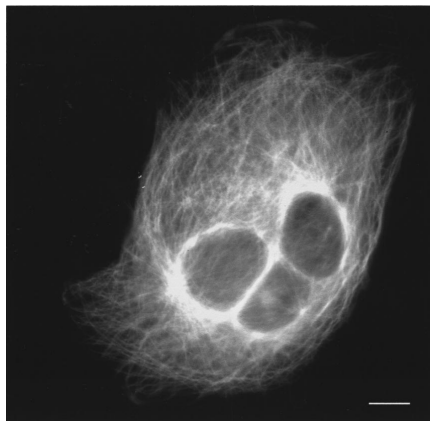- Let T be FPT with density $f(t)$
- Introduce survival probability

$$S(t) = \int_{-\infty}^{x_*} \sum_n p(x, n, t) dx \equiv \text{Prob}\{t > T\}.$$

- It follows that (for $v_n \to F(x, n)$)

$$f(t) = -\frac{dS}{dt} = -\int_{-\infty}^{x_*} \sum_n \frac{\partial p}{\partial t}(x, n, t) dx$$
$$= \sum_n F(x, n) p(x_*, n, t),$$

Part VI. Higher–dimensional transport networks

MICROTUBULAR NETWORKS

1. Axons and dendrites: microtubles tend to be aligned in parallel so that transport process is effectively 1D

2. Intracellular transport within the cell body of neurons and most non–polarized animal cells occurs along a microtubular network that projects radially from an organizing center (centrosome) with outward polarity

3. Often the delivery of cargo from the cell membrane or nucleus to other localized cellular compartments requires a non–radial path involving several tracks.

4. Microtubules bend due to large internal stresses, resulting in a locally disordered network.

5. *In vivo* transport on relatively short length scales may be similar to transport observed *in vitro*, where microtubular networks are not grown from a centrosome and thus exhibit orientational and polarity disorder.

2D RANDOM INTERMITTENT SEARCH (PCB/NEWBY 2011)
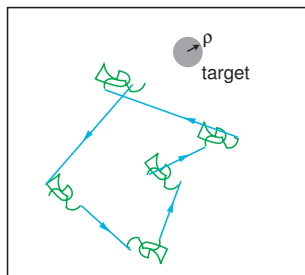
1. 2 types of behavior: Brownian motion with diffusivity D_0 or ballistic motion with velocity $\mathbf{v}(\theta) = (v\cos\theta, v\sin\theta)$, $\theta \in [0, 2\pi)$.

2. Target is at unknown location $\mathbf{r}_0 = (x_0, y_0)$ and radius ρ

3. Transition rate β from a ballistic state to the diffusive state is independent of θ

4. Reverse transition rate taken to be $\alpha q(\theta)$ with $\int_0^{2\pi} q(\theta)d\theta = 1$

QSS REDUCTION OF MASTER EQUATION

- Chapman-Kolmogorov equation is

$$\frac{\partial p}{\partial t} = -\boldsymbol{\nabla} \cdot (\mathbf{v}(\theta)p) - \beta p + \alpha q(\theta)p_0$$

$$\frac{\partial p_0}{\partial t} = D_0 \boldsymbol{\nabla}^2 p_0 + \beta \int_0^{2\pi} p(\mathbf{r}, \theta', t)d\theta' - \alpha p_0 - k\chi(\mathbf{r})p_0,$$

  with $\mathbf{r} = (x, y)$ and the indicator function $\chi(\mathbf{r}) = 1$ if and only if $|\mathbf{r} - \mathbf{r}_0| < \rho$.

- Perform the rescalings $\alpha \to \alpha/\epsilon$, $\beta \to \beta/\epsilon$ and $D_0 \to \epsilon D_0$.

- Carry out a QSS reduction so that to leading order

$$p(\mathbf{r}, \theta, t) = u(\mathbf{r}, t)\frac{\alpha q(\theta)}{\alpha + \beta} \quad p_0(\mathbf{r}, t) = u(\mathbf{r}, t)\frac{\beta}{\alpha + \beta},$$

EFFECTIVE FOKKER–PLANCK EQUATION

$$\frac{\partial u}{\partial t} = -\boldsymbol{\nabla} \cdot (\mathbf{V}u) + \epsilon b D_0 \boldsymbol{\nabla}^2 u + \epsilon \boldsymbol{\nabla} \cdot (\mathbf{D}\boldsymbol{\nabla}u) - \lambda \chi(\mathbf{r})u.$$

- The diffusion tensor $\mathbf{D}$ has leading order components

$$\mathcal{D}_{xx} \sim \frac{\alpha\beta^{-1}}{\alpha + \beta} \left(\left\langle v_x^2 \right\rangle - \left\langle v_x \right\rangle^2 + b^2 \left\langle v_x \right\rangle^2 \right)$$

$$\mathcal{D}_{xy} \sim \frac{\alpha\beta^{-1}}{\alpha + \beta} \left(\left\langle v_x v_y \right\rangle - \left\langle v_x \right\rangle \left\langle v_y \right\rangle + b^2 \left\langle v_x \right\rangle \left\langle v_y \right\rangle \right)$$

$$\mathcal{D}_{yy} \sim \frac{\alpha\beta^{-1}}{\alpha + \beta} \left(\left\langle v_y^2 \right\rangle - \left\langle v_y \right\rangle^2 + b^2 \left\langle v_y \right\rangle^2 \right),$$

- The effective drift velocity and detection rate are given by

$$\mathbf{V} \sim \frac{\alpha}{\alpha + \beta} \left\langle \mathbf{v} \right\rangle, \quad \lambda \sim \frac{\beta k}{\alpha + \beta}, \quad \left\langle f \right\rangle = \int q(\theta)f(\theta)d\theta$$

ISOTROPIC DIFFUSION IN A SQUARE DOMAIN WITH A SMALL HOLE

- Backwards equation for MFPT T is

$$-1 = \epsilon D \boldsymbol{\nabla}^2 T - \lambda \chi(\mathbf{r}) T, \quad q(\theta) = \frac{1}{2\pi}, \quad D_0 = 0$$

- Target radius $\rho \ll L$. Use matched asymptotics to solve for T. Outer solution is

$$T(\mathbf{r}) = -\frac{L^2}{D} G(\mathbf{r}, \mathbf{r}_0) + T_{\text{av}}, \quad D = \epsilon \frac{\alpha v^2}{2\beta(\alpha + \beta)}$$

- G is Neumann Green's function

$$\boldsymbol{\nabla}^2 G(\mathbf{r}, \mathbf{r}') = \frac{1}{L^2} - \delta(\mathbf{r} - \mathbf{r}'), \quad r \in \Sigma$$
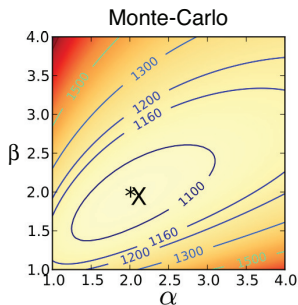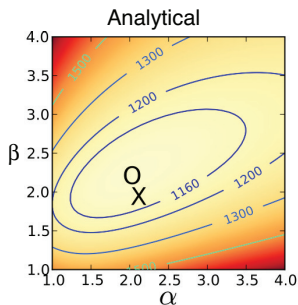
$$\partial_n G(\mathbf{r}, \mathbf{r}') = 0, \quad \mathbf{r} \in \partial\Sigma, \quad \int_\Sigma G(\mathbf{r}, \mathbf{r}') dr = 0.$$

OPTIMIZING MFPT FOR ISOTROPIC DIFFUSION

- Determine T_{av} by matching with inner solution around disc - requires determining regular part of Green's function

$$G(\mathbf{r}, \mathbf{r}') = -\frac{1}{2\pi} \left(\log |\mathbf{r} - \mathbf{r}'| - R(\mathbf{r}, \mathbf{r}') \right)$$

- In the case of reflecting boundary conditions (no other targets) there exists a unique pair of transition rates $(\alpha_{\mathrm{opt}}, \beta_{\mathrm{opt}})$ for which the MFPT T is minimized (optimal search strategy)

# Part VII. Model of cell polarization

CELL POLARIZATION IN BUDDING YEAST

- Many cellular processes depend critically on the establishment and maintenance of polarized distributions of signaling proteins on the plasma membrane.

- Well known example is budding yeast during mating or cell mitosis
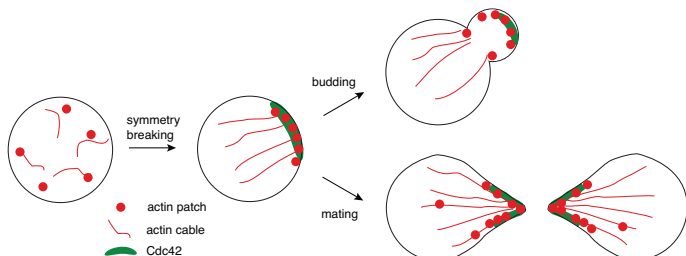
CELL POLARIZATION IN NEURONS (3 STAGES)

1. Breaking of spherical geometry by actin-rich structures including lamellipodia and filopodia
2. Lamellipodia then coalesce to form *growth cones*, followed by the establishment of several short processes, called *neurites*
3. One of the neurites grows more rapidly to become the axon – other neurites remain short and later develop into dendrites

Stage 1 *Stage 2* *Stage 3*

neurites

axon

growth cone
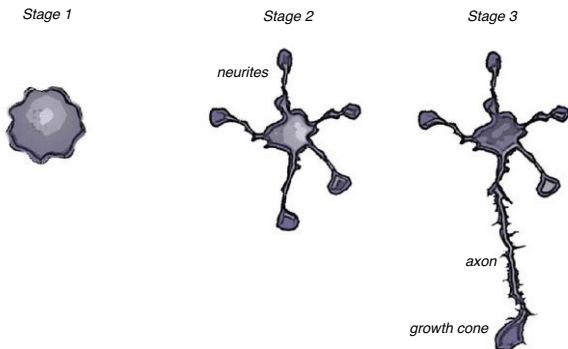
ACTIVE TRANSPORT MODEL

- Signaling molecules attach and orient filaments that deliver vesicles carrying the signaling molecule from the cytoplasm to the plasma membrane.

- The additional signaling molecules orient more filaments that transport more molecules in a positive feedback loop, resulting in a polarization region of higher molecule density.
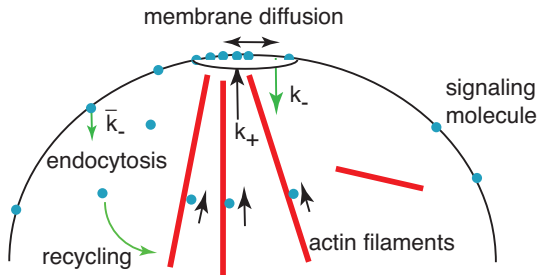
- Spontaneous cell polarization can occur if filaments are nucleated at sites on the cell membrane (the actin cytoskeleton)
- Cell only polarizes in response to an external chemical gradient if the filaments nucleate from organizing sites within the cytoplasm (microtubule asters).
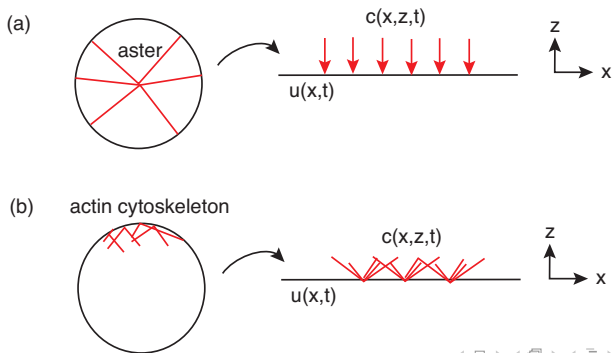
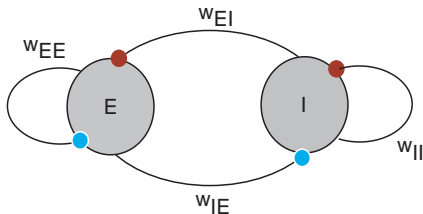# OTHER EXAMPLES OF STOCHASTIC HYBRID SYSTEMS

Gene networks (Newby)

Stochastic ion channels
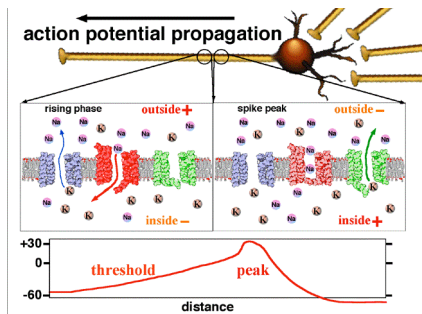
PCB/Keener/Newby

Stochastic neural population dynamics (PCB/Newby)

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