Quantifying Intermittent Transport in Cell Cytoplasm

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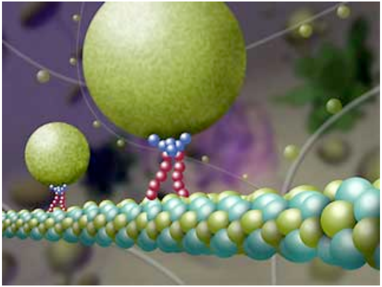
Cellular Transport

- Extra and Intracellular communication
- Intermittent transport: diffusion and active motion alternation
- Active motion along microtubules (MTs) via molecular motors



Intermittent Search Mechanism

Alternation between diffusion and directed motion to a target

- mRNA granules to synaptic targets along a dendrite.
- **DNA-viruses to nuclear pores**

Early steps of viral infection

- **1-2**: extracellular diffusion and membrane exploring
- **3**: Entry
- **3-4**: Intermittent transport: diffusion and directed motion along MTs
- **4**: Nuclear delivery of DNA

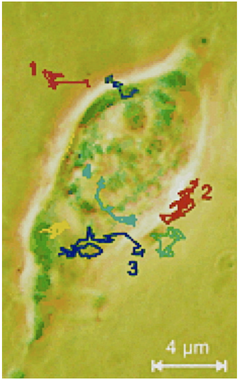
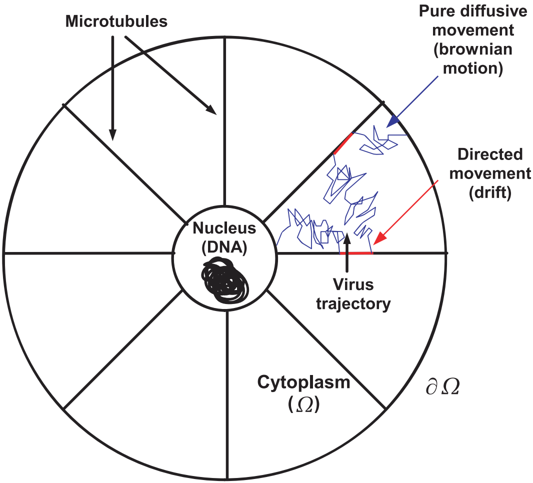


Figure: G. Seisengerger et al., Science **294**, 1929 (2001).

Scheme


Microtubules
Pure diffusive movement (brownian motion)
Directed movement (drift)
Nucleus (DNA)
Virus trajectory
Cytoplasm (Ω)
$\partial \Omega$

Motivations

- Deriving drift accounting for intermittent transport $\longrightarrow$ Langevin description of trajectories
- Application to viral infection analysis: possible degradation in cytoplasm $\longrightarrow$ Mean Time τ_e and Probability P_e a virus enters a nuclear pore ?

Langevin Description

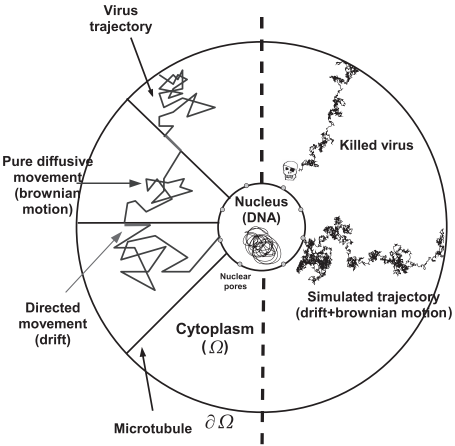
Left-Hand side: Intermittent Dynamics

$$\dot{\mathbf{x}} = \sqrt{2D}\dot{\mathbf{w}} \text{ Free Particle,}$$
$$\dot{\mathbf{x}} = \mathbf{V} \text{ Bound Particle.}$$

Right-Hand side: Langevin Dynamics

$$\dot{\mathbf{x}} = \mathbf{b}(\mathbf{x}) + \sqrt{2D}\dot{\mathbf{w}}$$

$+$killing field $k(\mathbf{x}) \longrightarrow$



Fokker-Planck Equation

Survival probability: $p(\mathbf{x}, \mathbf{y}, t) = Pr\{X(t) \in \mathbf{x} + d\mathbf{x} | X(0) = \mathbf{y}\}$

Forward Fokker-Planck Equation

$$\partial_t p = D \Delta p - \nabla \left(p \nabla b\left(\mathbf{x}\right)\right) - k\left(\mathbf{x}\right) p$$

boundary conditions: $p = 0$ on $\partial\Omega_a$ (nuclear pores) and $\frac{\partial p}{\partial n} = 0$ on $\partial\Omega - \partial\Omega_a$.

Probality P_e and mean time τ_e to a nuclear pore

P_e and τ_e

$$P_e = 1 - \int_0^\infty \int_\Omega k(\mathbf{x})\tilde{p}(\mathbf{x},t)d\mathbf{x}dt$$

$$\tau_e = \frac{\int_0^\infty \int_\Omega \tilde{p}(\mathbf{x},t)d\mathbf{x}dt - \int_0^\infty \int_\Omega k(\mathbf{x})t\tilde{p}(\mathbf{x},t)d\mathbf{x}dt}{P_e}$$

where $\tilde{p}(\mathbf{x},t) = \int_\Omega p(\mathbf{x},\mathbf{y},t)p_i(\mathbf{y})d\mathbf{y}$

Asymptotic Results

Nuclear pores $(\partial\Omega_a)$= small holes $\longrightarrow \frac{|\partial\Omega_a|}{|\partial\Omega|} = \epsilon \ll 1$

Asymptotic Results in ϵ

$$\begin{cases} P_e = \dfrac{\frac{1}{|\partial\Omega|}\int_{\partial\Omega} e^{-\frac{\Phi(\mathbf{x})}{D}} dS_{\mathbf{x}}}{\frac{ln\left(\frac{1}{\epsilon}\right)}{D\pi}\int_{\Omega} e^{-\frac{\Phi(\mathbf{x})}{D}} k(\mathbf{x})d\mathbf{x} + \frac{1}{|\partial\Omega|}\int_{\partial\Omega} e^{-\frac{\Phi(\mathbf{x})}{D}} dS_{\mathbf{x}}}, \\ \tau_e = \dfrac{\frac{ln\left(\frac{1}{\epsilon}\right)}{D\pi}\int_{\Omega} e^{-\frac{\Phi(\mathbf{x})}{D}} d\mathbf{x}}{\frac{ln\left(\frac{1}{\epsilon}\right)}{D\pi}\int_{\Omega} e^{-\frac{\Phi(\mathbf{x})}{D}} k(\mathbf{x})d\mathbf{x} + \frac{1}{|\partial\Omega|}\int_{\partial\Omega} e^{-\frac{\Phi(\mathbf{x})}{D}} dS_{\mathbf{x}}}, \end{cases}$$

for $\mathbf{b} = -\nabla\Phi$

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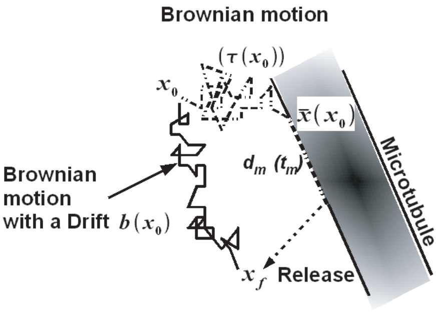
PROBLEM: **b**?

Principle

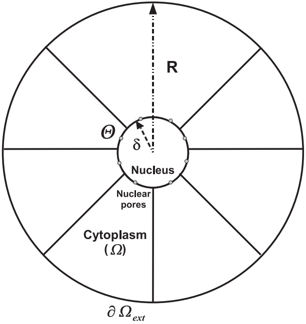
MFPTs from $\mathbf{x_0}$ to $\mathbf{x_f}$ are equal. In the small diffusion limit:

$$\frac{||\mathbf{x_f} - \mathbf{x_0}||}{\mathbf{b}(\mathbf{x_0})} = \tau(\mathbf{x_0}) + t_m$$

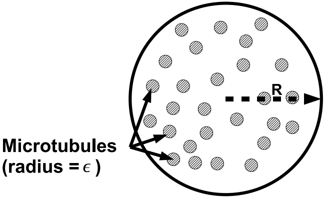


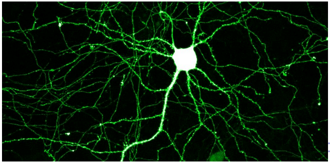
Cell representation

Two-dimensional radial cell with N uniformly distributed microtubules:

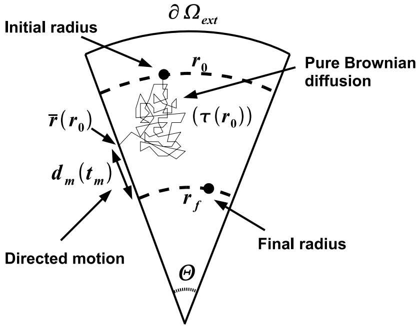


Neurite cross section with N thin cylindrical MTs





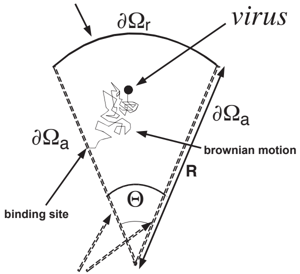
Two-dimensional representation



In the small diffusion limit

$$\frac{r_0 - r_f}{b(r_0)} = \frac{r_0 - (\bar{r}(r_0) - d_m)}{b(r_0)} = \tau(r_0) + t_m$$

MFPT to a microtubule



Dynkin's system

$$
\begin{aligned}
D\Delta u(r,\theta) &= -1 \text{ in } \Omega \\
u(r,0) = u(r,\Theta) &= 0, \\
\frac{\partial u}{\partial r}(R,\theta) &= 0.
\end{aligned}
$$

For $\Theta << 1$

$$
\tau(r_0) = \frac{1}{\Theta}\int_0^{\Theta} u(r_0,\theta)d\theta \approx r_0^2\frac{\Theta^2}{12D}
$$

Mean binding radius (1)

Heat equation

$$
\begin{aligned}
D\Delta p(r,\theta,t) &= \frac{\partial p}{\partial t}(r,\theta,t) \text{ in } \Omega \\
p(r,0,t) = p(r,\Theta),t &= 0, \\
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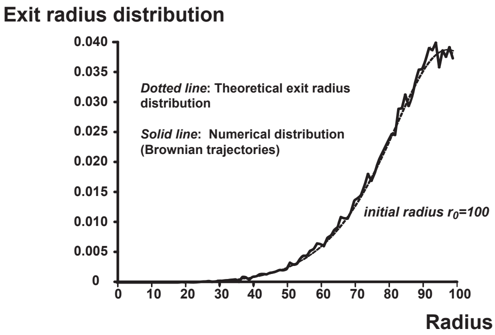
Indeed,

$$\bar{r}(r_0) = \frac{1}{\Theta}\int_0^{\Theta}\int_0^{R} r\epsilon(r|r_0,\theta_0)d\theta_0$$

with $\epsilon(r|r_0,\theta_0) = \int_0^{\infty} j(r,t|r_0,\theta_0)dt = -D\int_0^{\infty}\frac{\partial p}{\partial n}(r,t|r_0,\theta_0)dt.$

Mean binding radius (2)



For $\Theta << 1$

$$\bar{r}(r_0) \approx r_0 \left(1 + \frac{\Theta^2}{12}\right)$$

Results

Effective drift amplitude

$$b(r_0) = \frac{r_0 - (\bar{r}(r_0) - d_m)}{\tau(r_0) + t_m} = \frac{d_m - r_0 \frac{\Theta^2}{12}}{t_m + r_0^2 \frac{\Theta^2}{12D}}.$$

$$\Phi(r) = \frac{d_m\sqrt{12Dt_m}}{t_m\Theta} \arctan\left(\frac{\Theta r}{\sqrt{12Dt_m}}\right) - \frac{D}{2} \ln\left(12Dt_m + r^2\Theta^2\right)$$

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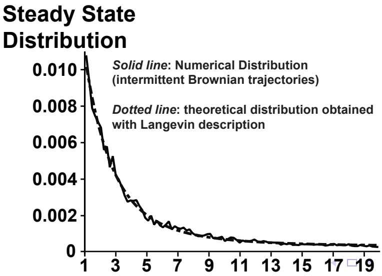
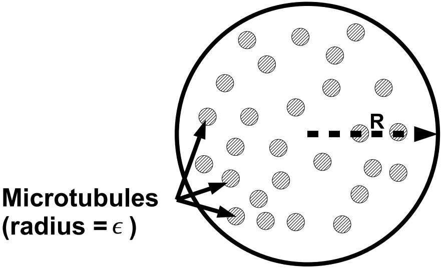


Cylindrical neurite case

Cross section of a neurite



In the small diffusion limit

$$b = \frac{d_m}{t_m + \tau}$$

with $\tau \approx \frac{1}{\lambda_1} = \frac{|\Omega| ln\left(\frac{1}{\epsilon}\right)}{2\pi N}$ the MFPT to a microtubule.

Results(1)

with the two-dimensional potential

$$\Phi(r) = \frac{d_m\sqrt{12Dt_m}}{t_m\Theta}\arctan\left(\frac{\Theta r}{\sqrt{12Dt_m}}\right) - \frac{D}{2}\ln\left(12Dt_m + r^2\Theta^2\right)$$

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Probability and mean time to a nuclear pore

$$P_e \approx \frac{d_m}{d_m + K}\left(1 - \frac{K\delta\left(d_m\delta + Dt_m\right)}{12Dt_m d_m\left(d_m + K\right)}\Theta^2\right)$$

$$\tau_e \approx \frac{K}{k\left(d_m + K\right)}\left(1 + \frac{\delta\left(d_m\delta + Dt_m\right)}{12Dt_m\left(d_m + K\right)}\Theta^2\right).$$

where $K = 2k_0\delta t_m \ln\left(\frac{1}{\epsilon}\right)$ and $\alpha = \left(1 + \frac{R+\delta}{d_m}\right)\frac{1}{24}$.

Results (2)

with biological data:

Probability and mean time to a nuclear pore

$$P_e \approx 95\%$$
$$\tau_e \approx 3min.$$

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coherent with the reported total entry time of $15min$. (G. Seisengerger et al., Science **294**, 1929 (2001)).

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without drift: $\tau_e \approx 15min$.

Conclusion

- General framework to analyze intermittent search processes
- Application to viral entry modelling

Perspectives

- Other steps of viral infection (endosome escape . . .)
- Asymptotics for structured targets (many nuclear pores on a spherical nuclear pore . . .)

Asymptotics for structured targets (pure diffusion $\mathbf{b} = 0$)

n disks (nuclear pores) of radius η located on a microdomain (capacitance C_S: for a spherical nucleus of radius δ, $C_S = 4\pi\delta$)

Old Asymptotics

$$\tau_e = \frac{\left(\frac{|\Omega|}{4Dn\eta}\right)}{1 + \left(\frac{\int_\Omega k(\mathbf{x})d\mathbf{x}}{4Dn\eta}\right)}$$

Problem:
$\lim_{n\to\infty, n\epsilon^2 \ll 1} \tau_e = 0$

New Asymptotics

$$\tau_e = \frac{\left(\frac{|\Omega|}{D\tilde{C}}\right)}{1 + \left(\frac{\int_\Omega k(\mathbf{x})d\mathbf{x}}{D\tilde{C}}\right)}$$

where $\frac{1}{\tilde{C}} \approx \frac{1}{C_S} + \frac{1}{4n\eta}$

New asymptotics with a drift??

The lab

http://www.biologie.ens.fr/bcsmcbs/
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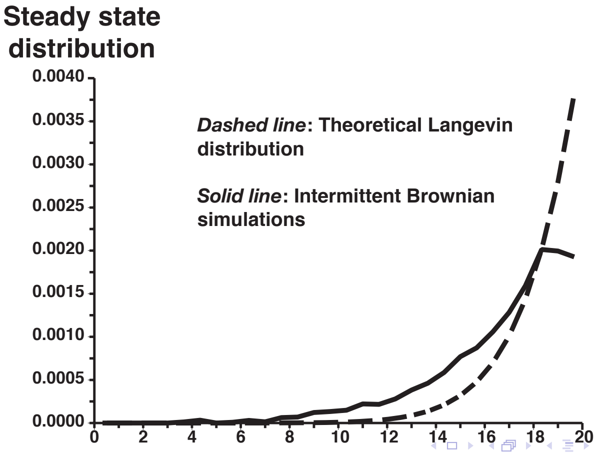
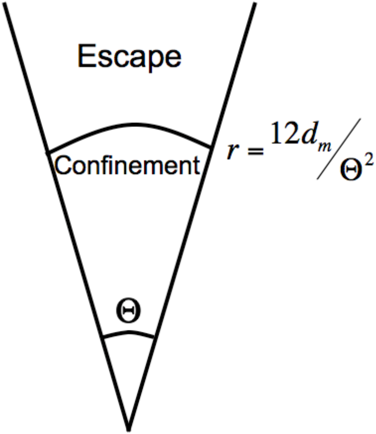
Negative drift

Noise due to reflecting external membrane

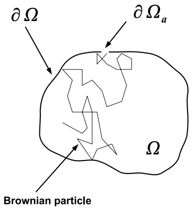


Limit radius



In cell of radius $50\mu m$, positive drift for $d_m \geq 1\mu m$

Escape through a small hole (1)



How long it takes for a brownian particle confined to a domain Ω to escape through a small opening $\partial\Omega_a$ $(\epsilon = \frac{|\partial\Omega_a|}{|\partial\Omega|} << 1)$?

Mean escape time

$$\tau = \frac{|\Omega|}{\pi D} ln\left(\frac{1}{\epsilon}\right) \text{ (2-dimensional case)},$$

$$\tau = \frac{|\Omega|}{4\epsilon D} \text{ (3-dimensional case)},$$

Escape through a small hole (2)

Dynkin's system

$$\begin{aligned} \Delta u(\mathbf{x}) &= -\frac{1}{D} \text{ in } \Omega \\ u(\mathbf{x}) &= 0 \text{ on } \partial\Omega_a \\ \frac{\partial u}{\partial n}(\mathbf{x}) &= 0 \text{ on } \partial\Omega_r = \partial\Omega - \partial\Omega_a. \end{aligned}$$

Neumann Function $\mathcal{N}(\mathbf{x}, \xi)$

$$\begin{aligned} \Delta \mathcal{N}(\mathbf{x}, \xi) &= -\delta(\mathbf{x} - \xi) \text{ for } \mathbf{x}, \xi \in \Omega \\ \frac{\partial \mathcal{N}}{\partial n}(\mathbf{x}, \xi) &= -\frac{1}{|\partial\Omega|} \text{ for } \mathbf{x} \in \partial\Omega, \xi \in \Omega. \end{aligned}$$

Escape through a small hole (3)

$$\int_{\Omega} \mathcal{N}(\mathbf{x},\xi)\Delta u(\mathbf{x}) - \Delta\mathcal{N}(\mathbf{x},\xi)u(\mathbf{x})d\mathbf{x} = \int_{\partial\Omega_a} \mathcal{N}(\mathbf{x},\xi)\frac{\partial u}{\partial n}(\mathbf{x})d\mathbf{x} + \frac{1}{|\partial\Omega|}\int_{\partial\Omega} u(\mathbf{x})d\mathbf{x}$$

and

$$\int_{\Omega} \mathcal{N}(\mathbf{x},\xi)\Delta u(\mathbf{x}) - \Delta\mathcal{N}(\mathbf{x},\xi)u(\mathbf{x})d\mathbf{x} = u(\xi) - \frac{1}{D}\int_{\Omega} \mathcal{N}(\mathbf{x},\xi)d\mathbf{x}$$

thus

$$u(\xi) - \frac{1}{D}\int_{\Omega} \mathcal{N}(\mathbf{x},\xi)d\mathbf{x} = \int_{\partial\Omega_a} \mathcal{N}(\mathbf{x},\xi)\frac{\partial u}{\partial n}(\mathbf{x})d\mathbf{x} + \frac{1}{|\partial\Omega|}\int_{\partial\Omega} u(\mathbf{x})d\mathbf{x}$$

Escape through a small hole (4)

For $\xi \in \partial\Omega_a$, C_0 the constant leading order in ϵ of $u(\mathbf{x})$ and $g(s) = \frac{g_0}{\sqrt{\epsilon^2 - s^2}}$ the local expansion of $\frac{\partial u}{\partial n}$ on the boundary:

$$-\frac{1}{D}\int_{\Omega} \mathcal{N}(\mathbf{x},\xi)d\mathbf{x} = \int_{\partial\Omega_a} \mathcal{N}(s)g(s)ds + C_0$$

$\mathcal{N}(s) = \frac{1}{4\pi|s|} + \ \textit{regular function}$, $-\frac{1}{D}\int_{\Omega}\mathcal{N}(\mathbf{x},\xi)d\mathbf{x}$ is bounded and $g_0 = \frac{|\Omega|}{2\pi\epsilon D}$ (compatibility condition). Thus:

$$u(\mathbf{x}) \approx C_0 = \frac{|\Omega|}{4\epsilon D}$$