Viral Infection Analysis

Thibault Lagache

Ecole Normale Supérieure, département de biologie

October 22^{nd} 2007

Virology principles

Virology principles

- Cell=cytoplasm+nucleus

Virology principles

- Cell=cytoplasm+nucleus
- Virus enters external membrane...

Virology principles

- Cell=cytoplasm+nucleus
- Virus enters external membrane...
- and has to reach a small nuclear pore...

Virology principles

- Cell=cytoplasm+nucleus
- Virus enters external membrane...
- and has to reach a small nuclear pore...
- to enter the nucleus and replicates.

Viral Dynamics in the Cytoplasm

- Virus can either diffuse

Viral Dynamics in the Cytoplasm

- Virus can either diffuse
- or be actively transported along microtubules

Viral Dynamics in the Cytoplasm

- Virus can either diffuse
- or be actively transported along microtubules
- to ultimately reach a nuclear pore

Monitoring *in vivo* of viral trajectories

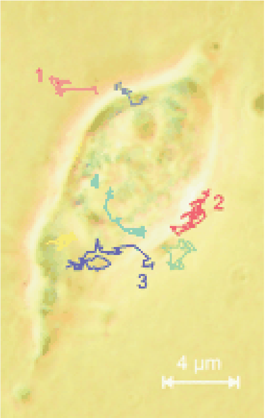
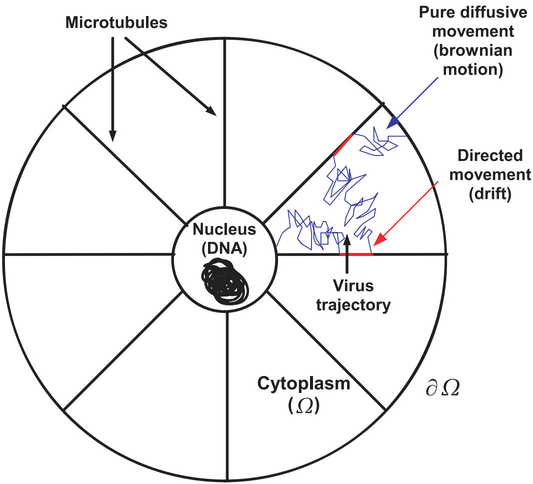


Figure: G. Seisengerger et al., Science **294**, 1929 (2001).

Scheme



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

Modeling Motivations

Modeling Motivations

- Degradation activity occurs in cell cytoplasm

Modeling Motivations

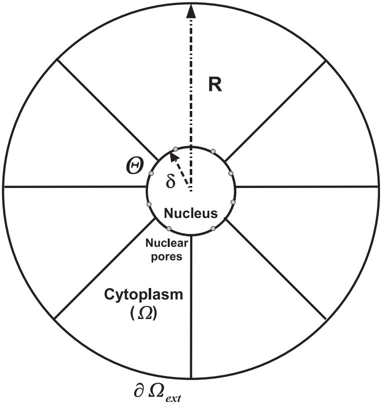
- Degradation activity occurs in cell cytoplasm
- We want to derive the Mean Time τ_N and the Probability P_N a virus hits a nuclear pore

Modeling Motivations

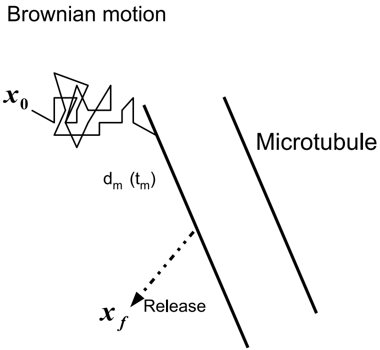
- Degradation activity occurs in cell cytoplasm
- We want to derive the Mean Time τ_N and the Probability P_N a virus hits a nuclear pore
- Application to efficient vectors design in gene therapy

Cell representation

Two-dimensional radial cell with N uniformly distributed microtubules:

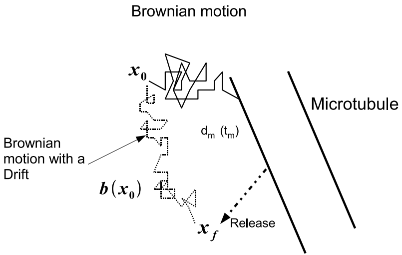


Intermittent Dynamics of the Virus



Viral Dynamics Equations

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

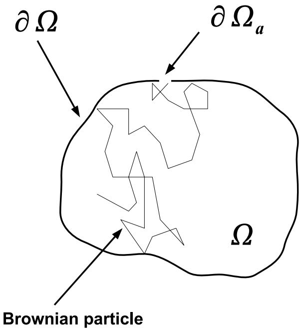


Homogenized Description

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

Homogenization Interest

Application of the small hole theory: computation of P_N and τ_N



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

$$\tau = \frac{|\Omega|}{\pi D} ln \left(\frac{1}{\epsilon} \right)$$

Assumptions

Assumptions

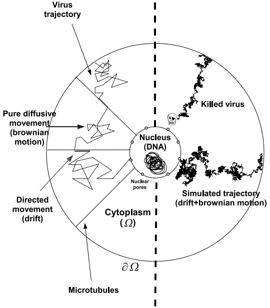
- We model the degradation activity with a steady state killing field $k(\mathbf{x})$.

Assumptions

- We model the degradation activity with a steady state killing field $k(\mathbf{x})$.
- We assume the drift $\mathbf{b}$ derived from a potential Φ: $\mathbf{b} = -\nabla\Phi$.

Assumptions

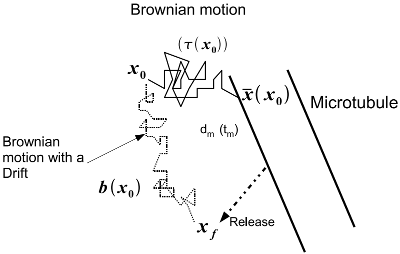
- We model the degradation activity with a steady state killing field $k(\mathbf{x})$.
- We assume the drift $\mathbf{b}$ derived from a potential Φ: $\mathbf{b} = -\nabla\Phi$.
- The n nuclear pores occupy a small fraction of the nuclear membrane



Theoretical Results

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

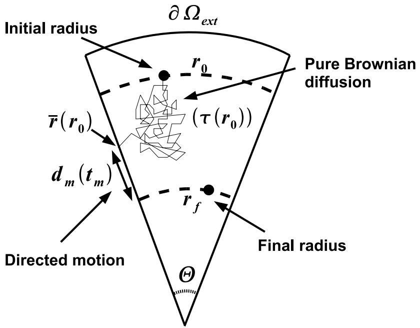
MFPTs from $\mathbf{x_0}$ to $\mathbf{x_f}$ are equal in both intermittent and homogenized trajectories



In the small diffusion limit

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

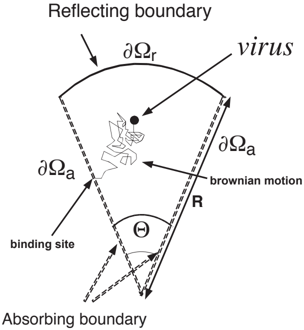
Two-dimensional radial case



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)

We solve the heat equation in the pie wedge domain Ω:

Heat equation

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

Mean binding radius (1)

We solve the heat equation in the pie wedge domain Ω:

Heat equation

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

Indeed,

Mean binding radius (1)

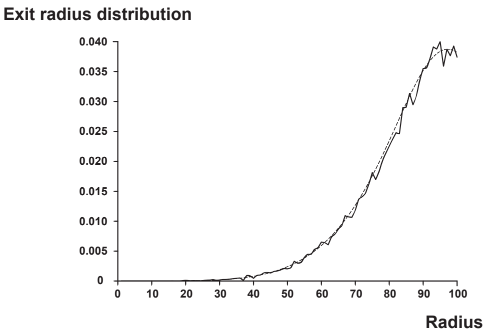
We solve the heat equation in the pie wedge domain Ω:

Heat equation

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

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 $\Theta << 1$

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

Results (1)

Effective drift amplitude

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

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

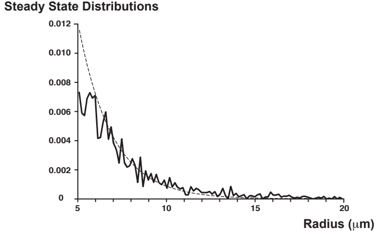
Results (1)

Effective drift amplitude

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

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

Steady state distributions for both intermittent brownian simulations (solid line) and theoretical homogenized trajectories (dashed line)



Probability and mean time to a nuclear pore

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

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

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

Conclusion

Conclusion

- An homogenized description for P_N and τ_N derivation.

Conclusion

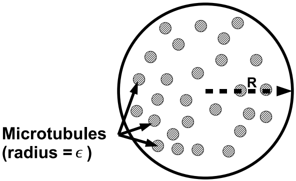
- An homogenized description for P_N and τ_N derivation.
- Generalization a three-dimensional (spherical) level ?

Conclusion

- An homogenized description for P_N and τ_N derivation.
- Generalization a three-dimensional (spherical) level ?
- Other steps of viral infection..

Drift computation in a neuron

Cylindrical geometry



In the small diffusion limit

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

with $\tau = \frac{1}{\lambda_1} = \frac{|\Omega| ln(\frac{1}{\epsilon})}{2\pi N}$