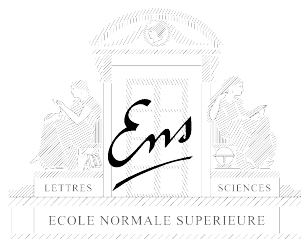# The search process for small targets in cellular microdomains

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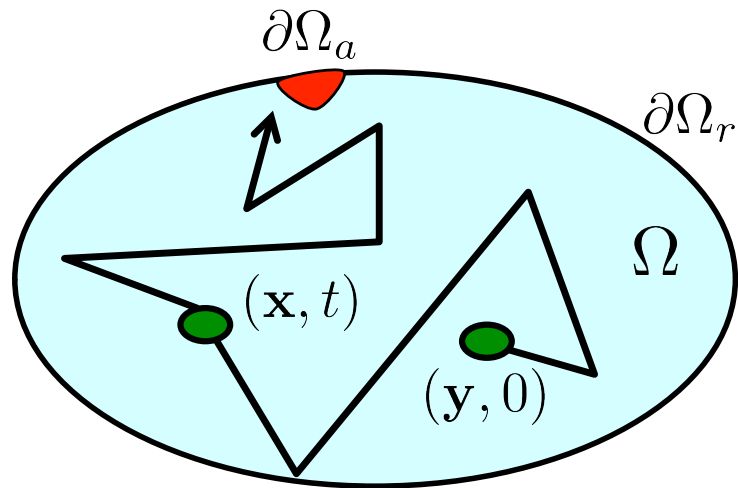
Outline

1. Search processes in cellular biology

2. Search of a Transcription Factor: Challenge of finding its DNA target within a large genome

3. Analysis of a Transcription Factor search process with conformational switching

4. Conclusions and Outlook

Narrow Escape: Finding a small target

Transition probability density:

$$p(\mathbf{x}, t | \mathbf{y}, 0) = Pr\{\mathbf{X}(t) = \mathbf{x} | \mathbf{X}(0) = \mathbf{y}\}$$

Initial condition: $\quad p(\mathbf{x}, 0 | \mathbf{y}, 0) = \delta(\mathbf{x} - \mathbf{y})$

Mixed Boundary Conditions:

$$p(\mathbf{x}, t | \mathbf{y}, 0) = 0, \ \ \mathbf{x} \in \partial\Omega_a$$

$$\frac{\partial}{\partial n} p(\mathbf{x}, t | \mathbf{y}, 0) = 0, \ \ \mathbf{x} \in \partial\Omega_r$$
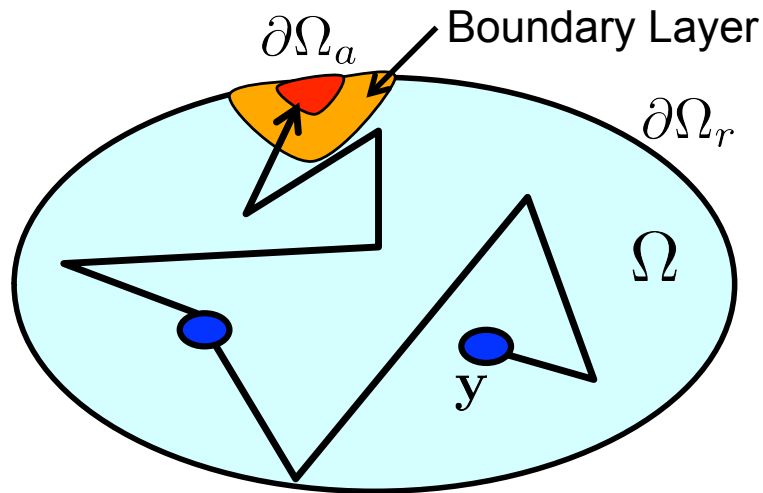
Fokker-Planck equation:

$$\frac{\partial p(\mathbf{x}, t | \mathbf{y} t')}{\partial t} = L(\mathbf{x}) p(\mathbf{x}, t | \mathbf{y} t')$$

Backward Kolmogorov equation:

$$\frac{\partial p(\mathbf{x}, t | \mathbf{y} t')}{\partial t'} = -L^*(\mathbf{y}) p(\mathbf{x}, t | \mathbf{y} t')$$

Narrow Escape Time

$\partial\Omega_a$ Boundary Layer

$\partial\Omega_r$

Ω

$\mathbf{y}$

First Passage Time (FPT)

$$\tau(\mathbf{y}) = \int_\Omega d\mathbf{x} \int_0^\infty dt\, p(\mathbf{x}, t | \mathbf{y}, 0)$$

Mean FPT (Narrow Escape Time)

$$\tau = \int_\Omega \tau(\mathbf{y}) d\mathbf{y}$$

FPT equation

$$D\Delta\tau(\mathbf{y}) = -1$$

Mixed Boundary Conditions

$$\tau(\mathbf{y}) = 0, \ \mathbf{y} \in \partial\Omega_a$$

$$\frac{\partial}{\partial n}\tau(\mathbf{y}) = 0, \ \mathbf{y} \in \partial\Omega_r$$

$$\tau \approx \frac{|\Omega|}{aD}\frac{1}{C} \longleftarrow \text{Capacitance of the exit surface}$$

Berg, Purcell, *Biophys J* (1977)
Zhou, Zwanzig, *J. Chem Phys* (1991)
Ward, Keller, *SIAM* (1993)
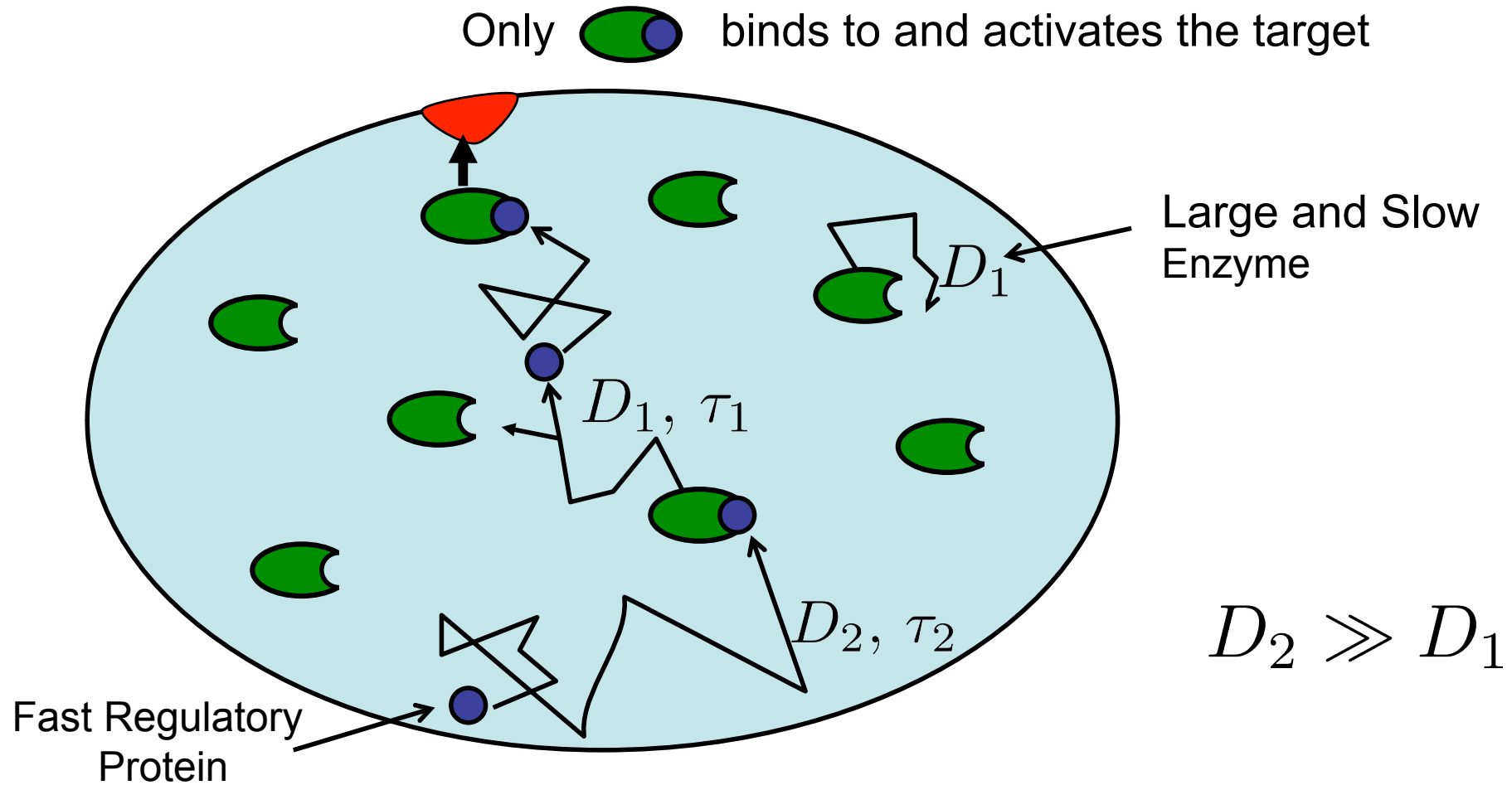Grigoriev et al, *J Chem Phys* (2002)
Holcman, Schuss, J. *Stat Phys* (2004)
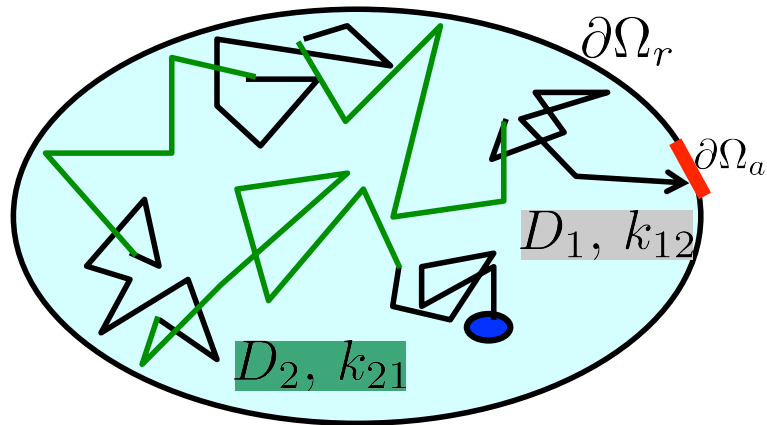Schuss et al, *PNAS* (2007)
Benichou, Voituriez, *PRL* (2008)
Reingruber et al, *J Chem Phys* (2009)

Gated Enzymatic Reaction

Only [green-blue] binds to and activates the target

Large and Slow Enzyme

D_1

D_1, τ_1

D_2, τ_2

$D_2 \gg D_1$

Fast Regulatory Protein

What is the optimal concentration of [green] needed to ensure fast target activation ?
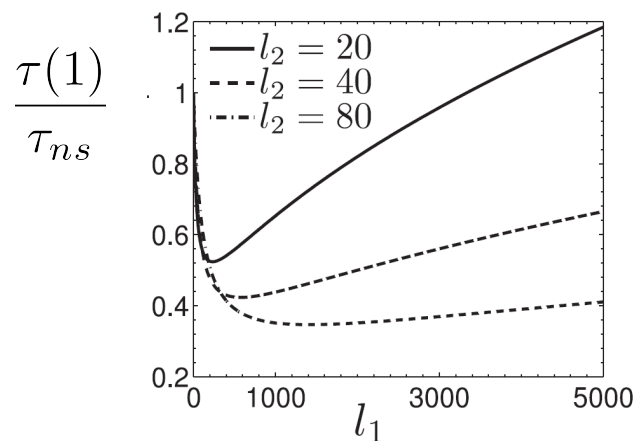
Gated Narrow Escape

Equations for the MFPT:

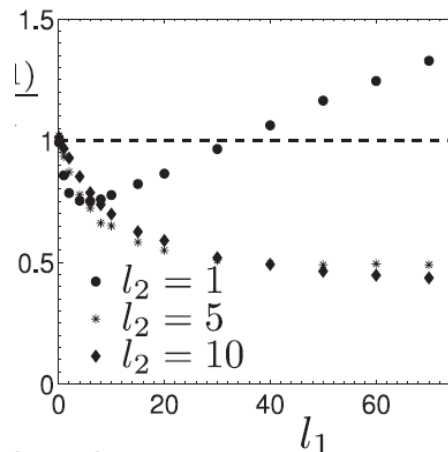$$D_1 \Delta \tau(y,1) - k_{12}(\tau(y,1) - \tau(y,2)) = -1$$
$$D_2 \Delta \tau(y,2) - k_{21}(\tau(y,2) - \tau(y,1)) = -1$$

(3D)

$$\tau = \left(1 + \frac{k_{12}}{k_{21}}\right) \begin{cases} \dfrac{|\Omega|}{4aD}, & l_1 \ll 1 \text{ or } l_2 \gg l_1 \\[3ex] \dfrac{|\Omega|}{\pi a^2 \sqrt{D_1 k_{12}}}, & l_1 \gg 1 \text{ and } \sqrt{l_1} \gg l_2 \end{cases}$$

$$l_1 = \frac{k_{12} a^2}{D_1} \quad l_2 = \frac{k_{21} a^2}{D_2}$$

$\dfrac{\tau(1)}{\tau_{ns}}$
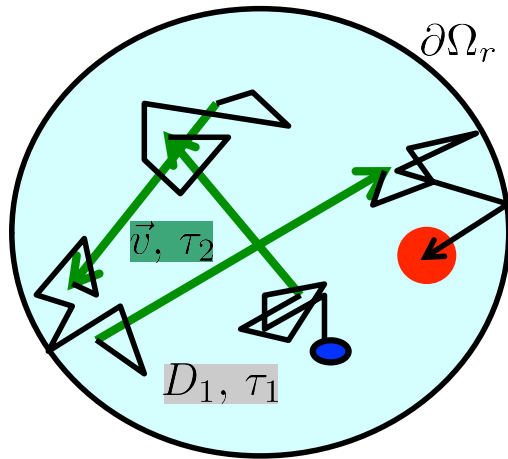

(1D)

(3D)

$$D_2 > D_1$$

Doering, Gadua, *PRL* (1992)
Reingruber, Holcman, *PRL* (2009)
Reingruber, Holcman, *J Cond Mat* (2010)

Intermittent search process with a ballistic phase

$\partial\Omega_r$

$\vec{v}, \tau_2$

D_1, τ_1

MFPT with ballistic motion in state 2

$$D\Delta_{\mathbf{r}}t_1 + \frac{1}{\tau_1}\int (t_2 - t_1)\,\rho(\omega_{\mathbf{v}})\,\mathrm{d}\omega_{\mathbf{v}} - kI_a(\mathbf{r})\,t_1 = -1$$
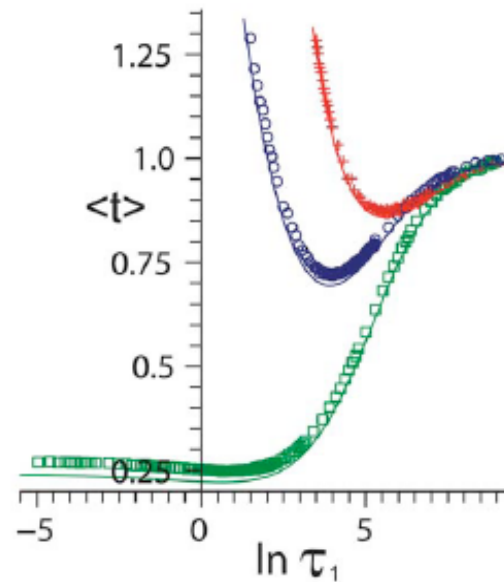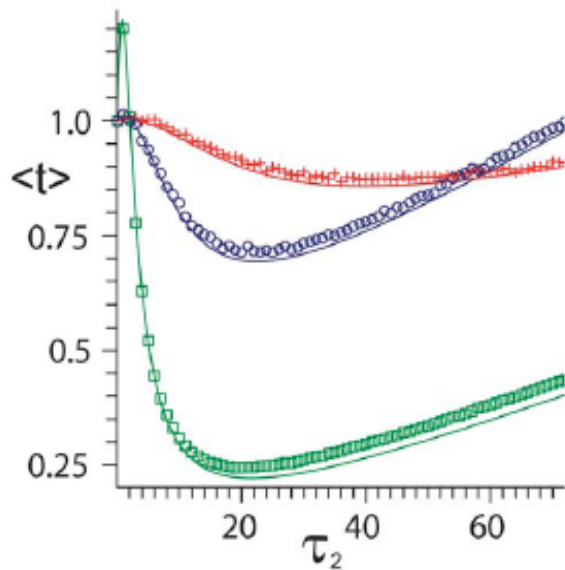
$$\mathbf{v}\cdot\nabla_{\mathbf{r}}t_2 - \frac{1}{\tau_2}(t_2 - t_1) = -1,$$

$$D_2 = \frac{v^2\tau_2}{2}$$
$$\delta x \sim \sqrt{D_2\tau_2} \sim v\tau_2$$

Regime where switching to state 2 can significantly speed up search search time:

$$v \gg \frac{D}{a}$$

(2D)

Global Minimum

$$\tau_{1,opt} \sim \frac{D}{v^2}$$
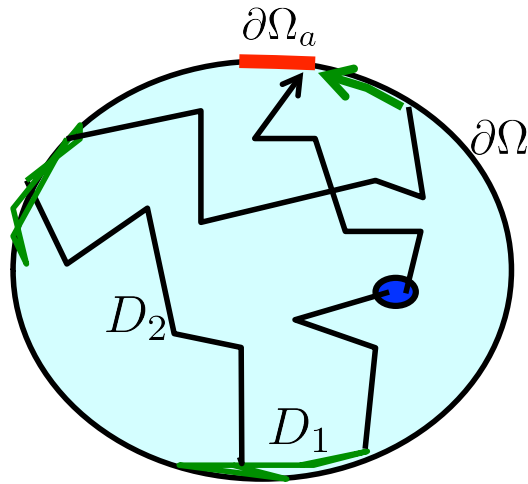
$$\tau_{2,opt} \sim \frac{a}{v}$$

(from Bénichou et al, *PRE* (2006))

Bénichou et al, *PRL* (2005)
Loverdo et al, *Nat Phys* (2008)
Bénichou et al, *Rev Mod Phys* (2011)
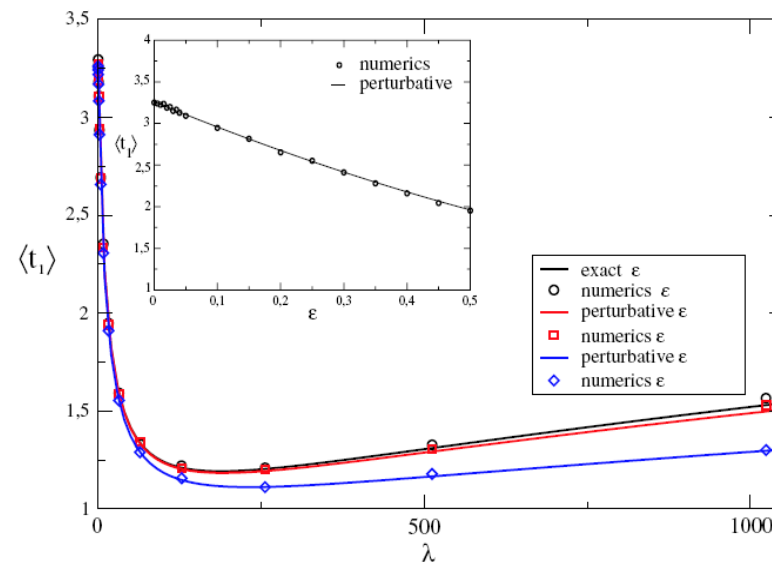
Search with bulk and surface diffusion

$$D_1 \Delta_{\partial S} t_1(\theta) + \lambda[t_2(R - a, \theta) - t_1(\theta)] = -1,$$

$$D_2 \Delta_S t_2(r, \theta) = -1,$$

Bulk excursions beneficial for $D_2 > \xi D_1$

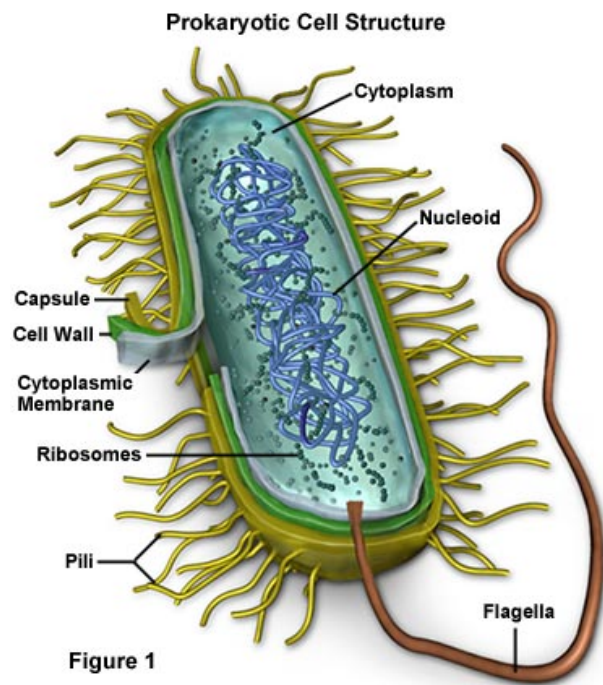(from Bénichou et al, *PRL* (2010))

(2D)

Berg, Blomberg, *Biophys Chem* (1976)
Berg, Ehrenberg, Biophys Chem (1981)
Tsaneva-Atanasova et al, *Biophys. J* (2009)
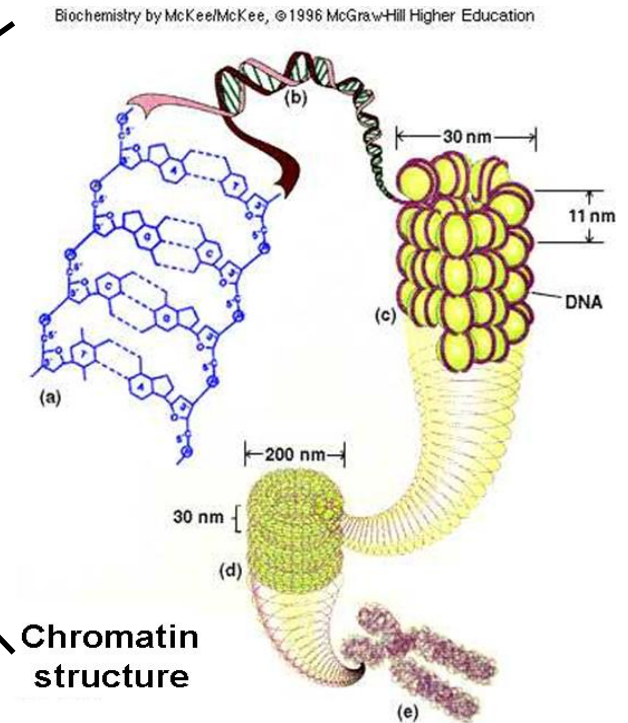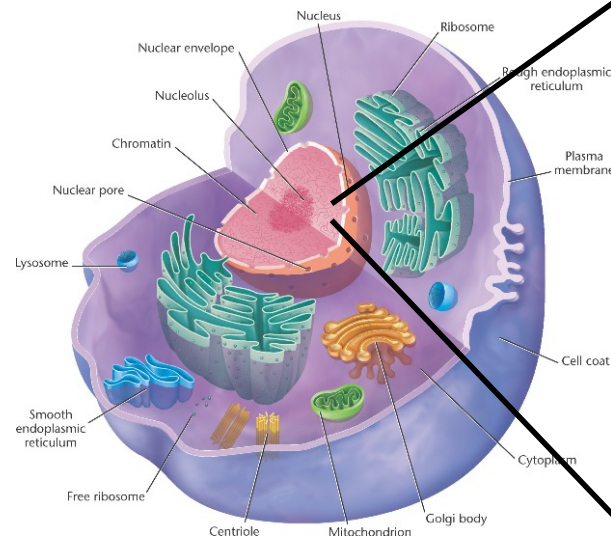Oshanin et al, *J. Chem Phys* (2010)

Transcription Factor Search and Gene Activation

What is the search mechanism by which Transcription Factors find a DNA promoter within a large genome ?

DNA in Prokaryote (Bacteria)

Bacteria DNA ~ 10^6 bps

DNA in Eukaryote

Human DNA ~ 10^9 bps

In Vitro Association Rate of Lac-I Repressor

Experiment: $\boxed{k \sim 10^{10}\, M^{-1}s^{-1}}$ Riggs et al, *Mol Biol*,1970

Theory: Pure 3D diffusion
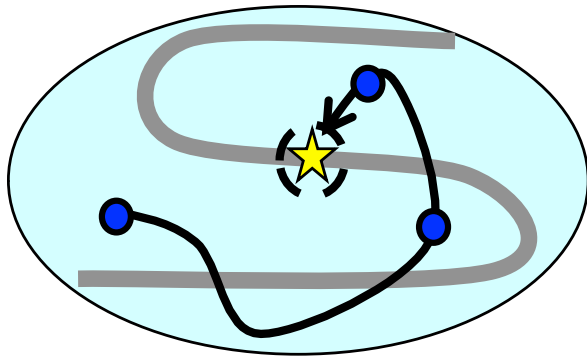
$$
\begin{aligned}
\tau_{3d} &= \frac{|V|}{4\pi D_3 a} \\[1em]
k_{3d} &= \frac{N_{Av}|V|}{\tau_{3d}} = N_{Av}4\pi D_3 a
\end{aligned}
$$

$$a \sim 5nm,\ |V| \sim 1\mu m^3,\ D_3 \sim 3\mu m^2/s \implies \tau_{3d} \sim 5s,\ \boxed{k_{3d} \sim 10^8 M^{-1}s^{-1}}$$

Theory: Pure sliding along DNA
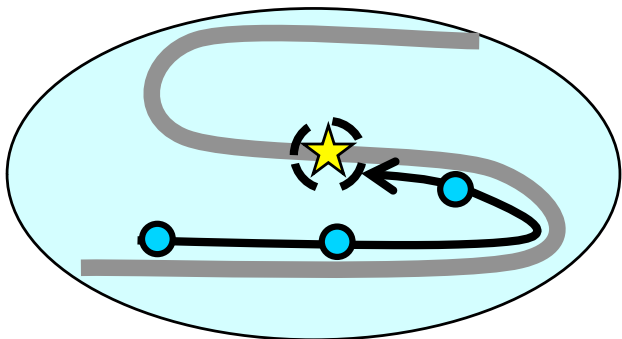
$$\tau_{1d} \sim \frac{L^2}{D_1} = \frac{(10^5 bp \times 0.3nm)^2}{1\mu m^2/s} \sim 900s \gg \tau_{3d}$$

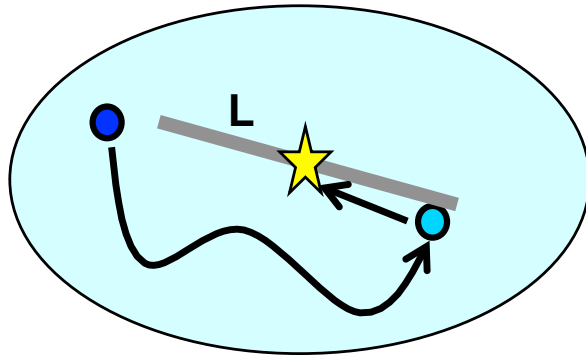# Facilitated Diffusion: 3D diffusion and 1D sliding

MFPT to a target with antenna of length L >> a:

$$\tau \approx \frac{|V|}{4\pi D_3 L} \ln\left(\frac{2L}{a}\right) \approx \frac{a}{L}\frac{|V|}{4\pi D_3 a} \ll \frac{|V|}{4\pi D_3 a}$$

DNA in diluted solution where 3D search dominates: $k_{3d} \ll k_{1d}$
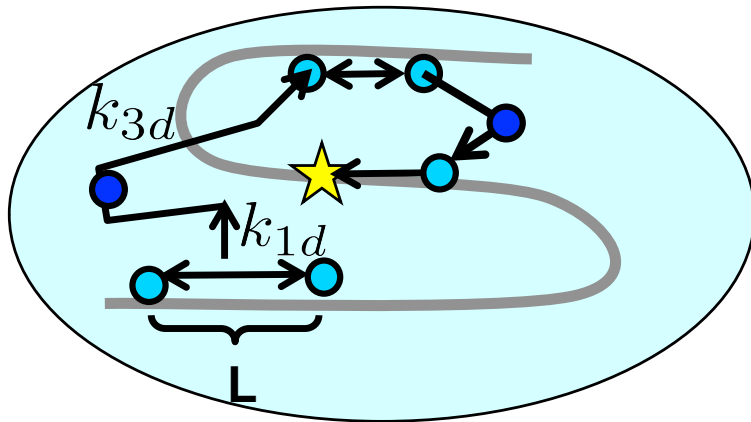
$$\tau \approx N_{sw}\left(\frac{1}{k_{3d}} + \frac{1}{k_{1d}}\right) \approx \frac{N_{sw}}{k_{3d}} \approx \frac{a}{L}\frac{|V|}{4\pi D_3 a}$$

$$\frac{L}{a} \sim 100 \implies k = 100 \times 10^8 M^{-1} s^{-1}$$

Richter, Eigen, *Biophys. Chem* (1974)
Berg, Blomberg, *Biophys Chem* (1976)
Berg, Winter, von Hippel, *Biochem* (1981)

In Vivo Association Rate of Lac-I Repressor

$$\tau \sim 350s \longrightarrow k \sim 10^6 M^{-1}s^{-1} \ll 10^8 M^{-1}s^{-1}$$

In vivo search time of
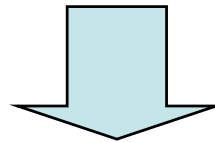Lac Repressor in E.Coli

Elf et al, *Science (2007)*

In vivo association rate is smaller
compared to pure 3D search !

Problem: Frequent bindings to DNA slow down the search
due to strong interactions with DNA base pairs !

Speed versus stability

Total number of DNA bps
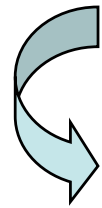
Search time: $\quad \tau \approx \dfrac{N_{bp}}{n}\left(\tau_{3d} + \tau_{1d}\right)$ $\qquad$ Berg, Winter, von Hippel, *Biochem (1981)*

$n \sim 2\sqrt{D_1 \tau_{1d}}$ $\quad$ Number of DNA bps scanned during a sliding event

$D_1 = D_0\left(1 + \dfrac{\sigma^2}{2}\right)e^{-\frac{7\sigma^2}{4}}$ $\quad$ Effective 1D diffusion constant as function of binding energy fluctuation

$\sigma < 2\,k_B T$ $\qquad$ Requirement for a search time that is compatible with reality
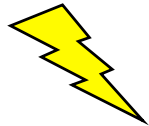
Slutsky, Mirny, *Biophys J* (2004)

$\sigma \sim 5\,k_B T$ $\qquad$ Estimations from binding energy measurements

Slutsky, Mirny, *Biophys J (*2004)
Gerland,Horoz,Hwa, *PNAS* (2002)

Search process with two sliding states
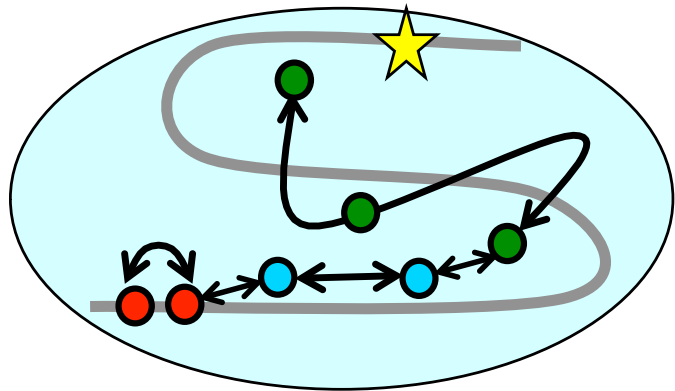
● - Free diffusion

◉ - Non-specific binding, fast diffusion along the DNA

● - Specific binding with DNA base pairs, slow diffusion

Berg, Winter, von Hippel, *Biochem (*1981)
Slutsky, Mirny, *Biophys. J.* (2004)

Experiment: Evidence for conformational switch of TF protein

free lac DBD   nonspecific complex   specific complex
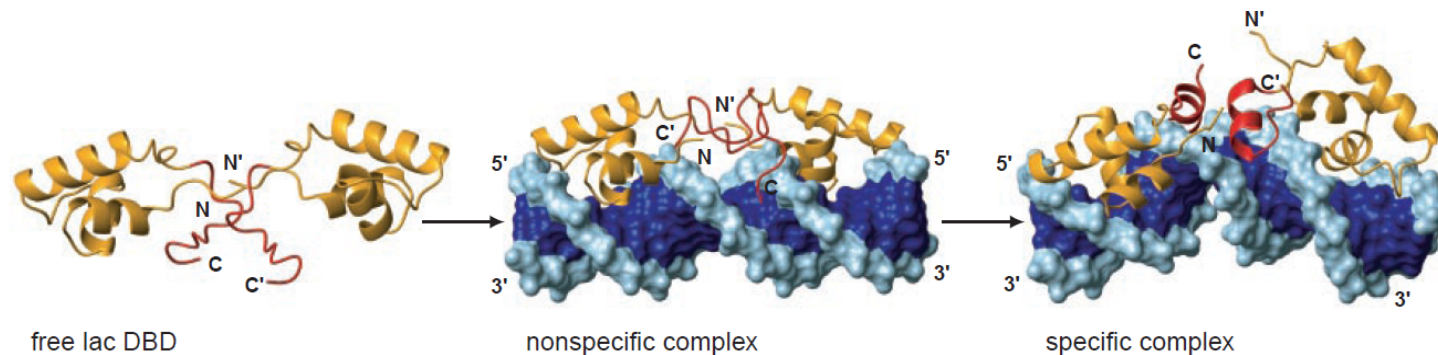
Kalodimos et al, *Science (*2004)

Transcription Factor search process with conformational switching

Search process with switching between 3 states
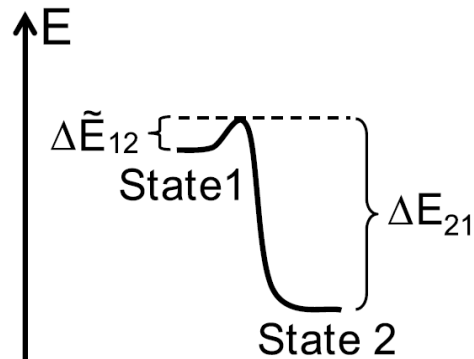
Free TF with a stable (State 1) and unstable (State 2) protein conformation
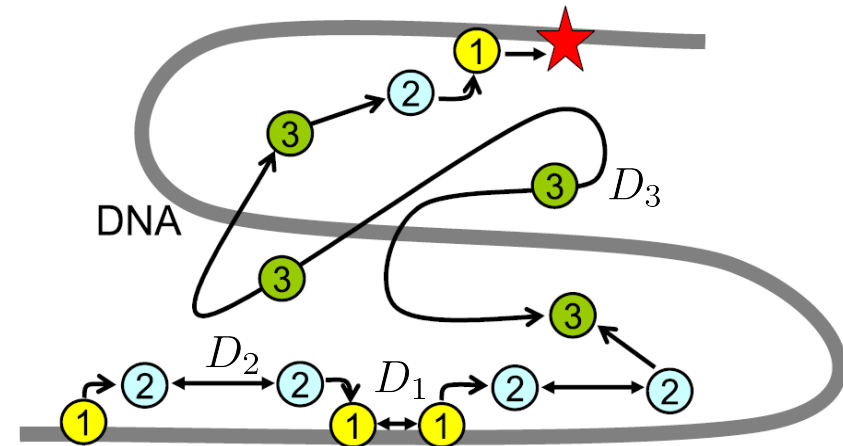
Schematic of the search process
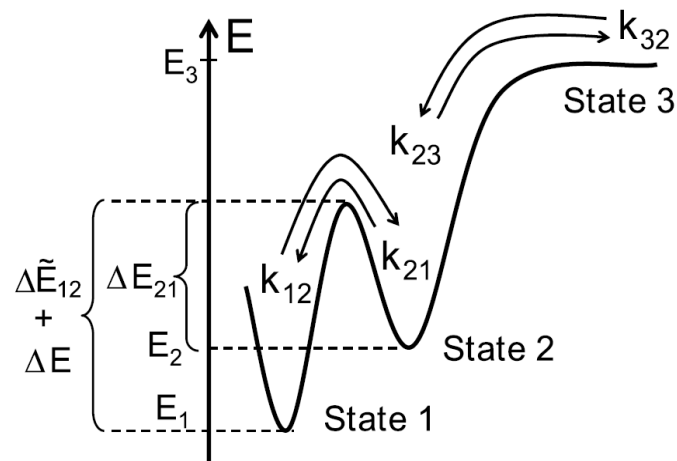
TF with additional conformation dependent DNA interactions in State 1 and 2

State 3: Free diffusion in the cytoplasm

State 2: Non-specific interaction with DNA backbone with fast diffusion in a smooth potential

State 1: Specific interaction with DNA base pairs with slow diffusion in a rough potential

Modeling Assumptions

1)
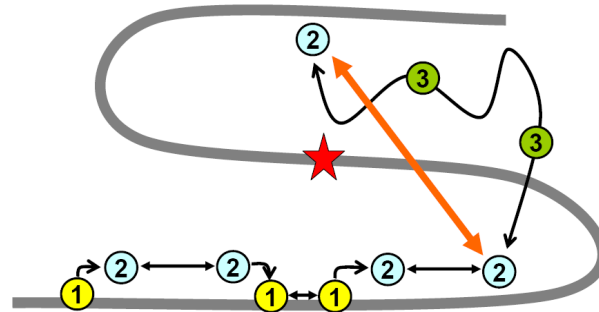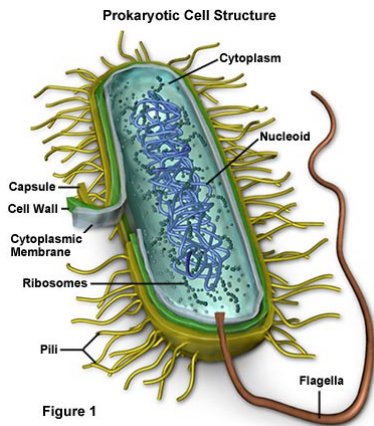
Highly coiled DNA

↓

Subsequent DNA attaching positions are uncorrelated

2) Uniform DNA strand (interaction does not dependent on the DNA position) of length 2L with a target located in the center

3) 3D motion is mapped onto an effective 1D motion along the DNA

D_3

D_2

D_1

L
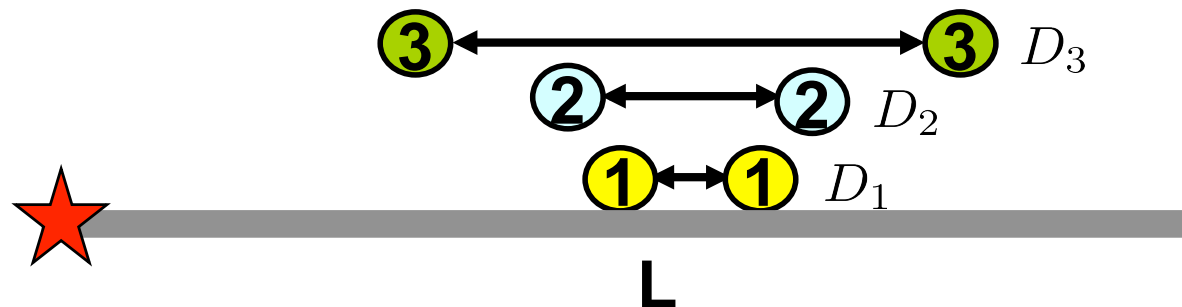
Consider equations for the Sojourn Times

Sojourn time spent in state n when starting initially in state m

$$t_n(y, m) = \int_0^L dx \int_0^\infty dt \, p(x, n, t | y, m)$$

MFPT when starting initially in state m :

$$t(x, m) = t_1(x, m) + t_2(x, m) + t_3(x, m)$$

Equations for the sojourn times

Sojourn times in state 1

$$D_1 t_1''(x, 1) - k_{12}(t_1(x, 1) - t_1(x, 2)) = -1$$

$$D_2 t_1''(x, 2) - k_{21}(t_1(x, 2) - t_1(x, 1)) - k_{23}(t_1(x, 2) - t_1(x, 3)) = 0$$

$$D_3 t_1''(x, 3) - k_{32}(t_1(x, 3) - t_1(x, 2)) = 0$$

Sojourn times in state 2 and 3

$$
\begin{pmatrix} t_2(x, 1) \\ t_2(x, 2) \\ t_2(x, 3) \end{pmatrix} = \frac{k_{12}}{k_{21}} \begin{pmatrix} t_1(x, 1) \\ t_1(x, 2) \\ t_1(x, 3) \end{pmatrix} + \frac{1}{k_{21}} \begin{pmatrix} 0 \\ 1 \\ 1 \end{pmatrix}
$$

$$
\begin{pmatrix} t_3(x, 1) \\ t_3(x, 2) \\ t_3(x, 3) \end{pmatrix} = \frac{k_{12} k_{23}}{k_{21} k_{32}} \begin{pmatrix} t_1(x, 1) \\ t_1(x, 2) \\ t_1(x, 3) \end{pmatrix} + \frac{1}{k_{21} k_{32}} \begin{pmatrix} 0 \\ k_{23} \\ k_{21} + k_{23} \end{pmatrix}
$$

MFPT as a function of the sojourn times

$$t(x,1) = t_1(x,1)\left(1 + \frac{k_{12}}{k_{21}} + \frac{k_{12}}{k_{21}}\frac{k_{23}}{k_{32}}\right)$$

$$t(x,2) = t_1(x,2)\left(1 + \frac{k_{12}}{k_{21}} + \frac{k_{12}}{k_{21}}\frac{k_{23}}{k_{32}}\right) + \frac{1}{k_{21}}\left(1 + \frac{k_{23}}{k_{32}}\right)$$

$$t(x,3) = t_1(x,3)\left(1 + \frac{k_{12}}{k_{21}} + \frac{k_{12}}{k_{21}}\frac{k_{23}}{k_{32}}\right) + \frac{1}{k_{21}}\left(1 + \frac{k_{23}}{k_{32}}\right) + \frac{1}{k_{32}}$$

Uniform initial distribution: $\langle t_1(x,1)\rangle = \langle t_1(x,2)\rangle = \langle t_1(x,3)\rangle = \tau_1(1)$
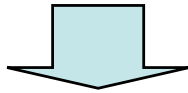
$$\tau(1) = \tau_1(1)\left(1 + \frac{k_{12}}{k_{21}} + \frac{k_{12}}{k_{21}}\frac{k_{23}}{k_{32}}\right) = n_{12}\left(\frac{1}{k_{12}} + \frac{1}{k_{21}} + \frac{1}{k_{21}}\frac{k_{23}}{k_{32}}\right)$$

$$\tau(2) = \tau(1) + \frac{1}{k_{21}}\left(1 + \frac{k_{23}}{k_{32}}\right),$$

$$\tau(3) = \tau(2) + \frac{1}{k_{32}},$$

$$n_{12} = k_{12}\tau_1(1) \qquad \text{Number of switching between states 1 and 2}$$

Uniform redistribution in state 3

$$D_1 t_1''(x, 1) - k_{12}(t_1(x, 1) - t_1(x, 2)) = -1$$

$$D_2 t_1''(x, 2) - k_{21}(t_1(x, 2) - t_1(x, 1)) - k_{23}(t_1(x, 2) - t_1(x, 3)) = 0$$

$$D_3 t_1''(x, 3) - k_{32}(t_1(x, 3) - t_1(x, 2)) = 0$$

$$D_3 \to \infty \quad \longrightarrow \quad t_1(x, 3) = const = \tau_1(1)$$
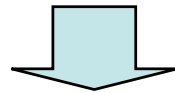
$$D_1 t_1''(x, 1) - k_{12}(t_1(x, 1) - t_1(x, 2)) = -1$$

$$D_2 t_1''(x, 2) - k_{21}(t_1(x, 2) - t_1(x, 1)) - k_{23}(t_1(x, 2) - t_1(1)) = 0$$

Exact solution for the search time

$$\tau = n_{12}\left(\frac{1}{k_{12}} + \frac{1}{k_{21}} + \frac{1}{k_{21}}\frac{k_{23}}{k_{32}}\right)$$

$$n_{12} = \frac{\xi_2 - \xi_1}{2\xi_2}\left(\sqrt{l_{12}}\frac{\coth(\sqrt{l_{12}}\mu_2)}{\mu_2} - \frac{1}{\mu_2^2}\right) + \frac{\xi_1 + \xi_2}{2\xi_2}\left(\sqrt{l_{12}}\frac{\coth(\sqrt{l_{12}}\mu_1)}{\mu_1} - \frac{1}{\mu_1^2}\right)$$

$$l_{12} = \frac{L^2 k_{12}}{D_1}$$

$$\xi_1 = -1 + \frac{D_1}{D_2}\frac{k_{21} + k_{23}}{k_{12}}, \qquad \xi_2 = \sqrt{\left(1 + \frac{D_1}{D_2}\frac{k_{21} + k_{23}}{k_{12}}\right)^2 - 4\frac{D_1}{D_2}\frac{k_{23}}{k_{12}}}$$

$$\mu_1^2 = 1 + \frac{\xi_1 - \xi_2}{2}, \qquad \mu_2^2 = 1 + \frac{\xi_1 + \xi_2}{2}.$$

Numerical evaluations suitable for E. Coli bacteria

Fixed input parameters:

$$L = 2.4 \times 10^6 \, bp$$ Length of E. Coli genome

$$D_2 = 2\frac{\mu m^2}{s}$$ Diffusion constant for fast sliding along DNA

$$k_{32} = 1.4ms$$ Average Time spent in 3D

Elf, *Science* (2007)
Malherbe, Holcman, *PLA* (2010))

Study of the search time as a function of physical parameters characterizing the TF interaction with the DNA:

$$l_{s1} = \sqrt{\frac{D_1}{k_{12}}}$$ Sliding distance in state 1 before switching to state 2

$$l_{s2} = \sqrt{\frac{D_2}{k_{21} + k_{23}}}$$ Sliding distance in state 2 before switching to 1 or 3

$$q = \frac{k_{23}}{k_{21} + k_{23}}$$ Probability to detach from the DNA

$$e^{-\chi} = \frac{D_1}{D_2}$$

Asymptotic for $q \ll 1$ and $\kappa = l_{s1}^2/l_{s2}^2 \ll 1$

MFPT to find the target

$$\tau \approx \sqrt{\frac{L^2}{D_2 k_{32}}} \left(1 + \sqrt{\frac{\kappa}{q}}\right) \left(\frac{e^\chi}{\alpha} + \frac{1}{\alpha\kappa} + q\alpha\right)$$

$$\alpha = \sqrt{\frac{D_2}{l_{s1}^2 k_{32}}}$$

Ratio of the time spent bound to the DNA to diffusing in the nucleus

$$r = \frac{k_{32}}{k_{23}} \left(1 + \frac{k_{21}}{k_{12}}\right) \approx \frac{1}{\alpha^2} \left(\frac{e^\chi}{q} + \frac{1}{q\kappa}\right)$$

Physical situation where binding in state 1 is such that a TF becomes immobilized

$$2\sqrt{\frac{D_1}{k_{12}}} = 2l_{s1} \sim 1$$

$\underbrace{\phantom{2\sqrt{\frac{D_1}{k_{12}}}}}$

Mean of maximal sliding distance in
state 1 (length in units of bp)

$$k_{12} = \xi e^{-\Delta E}$$ (Arrhenius) ΔE ~ Binding energy in state 1

$$D_1 = D_2 e^{-\chi} = l_{s1}^2 k_{12} = l_{s1}^2 \xi e^{-\Delta E} \longrightarrow \boxed{\chi \sim \Delta E}$$

(a)
$l_{s2}=2\text{bp}$
$l_{s2}=5\text{bp}$
$l_{s2}=10\text{bp}$
$l_{s2}=20\text{bp}$
time τ (sec)
$l_{s1} = 0.5,\ q = 0.01$
χ

(b)
$q=0.05$
$q=0.01$
$q=0.005$
$q=0.001$
τ
$l_{s1} = 0.5,\ l_{s2} = 10$
χ

(c)
$l_{s2}=2\text{bp}$
$l_{s2}=5\text{bp}$
$l_{s2}=10\text{bp}$
$l_{s2}=20\text{bp}$
time ratio r
$l_{s1} = 0.5,\ q = 0.01$
χ

(d)
τ
$q=0.05$
$q=0.01$
$q=0.005$
$q=0.001$
$q=0.0005$
$l_{s1} = 0.5,\ \chi = 7.5$
l_{s2}
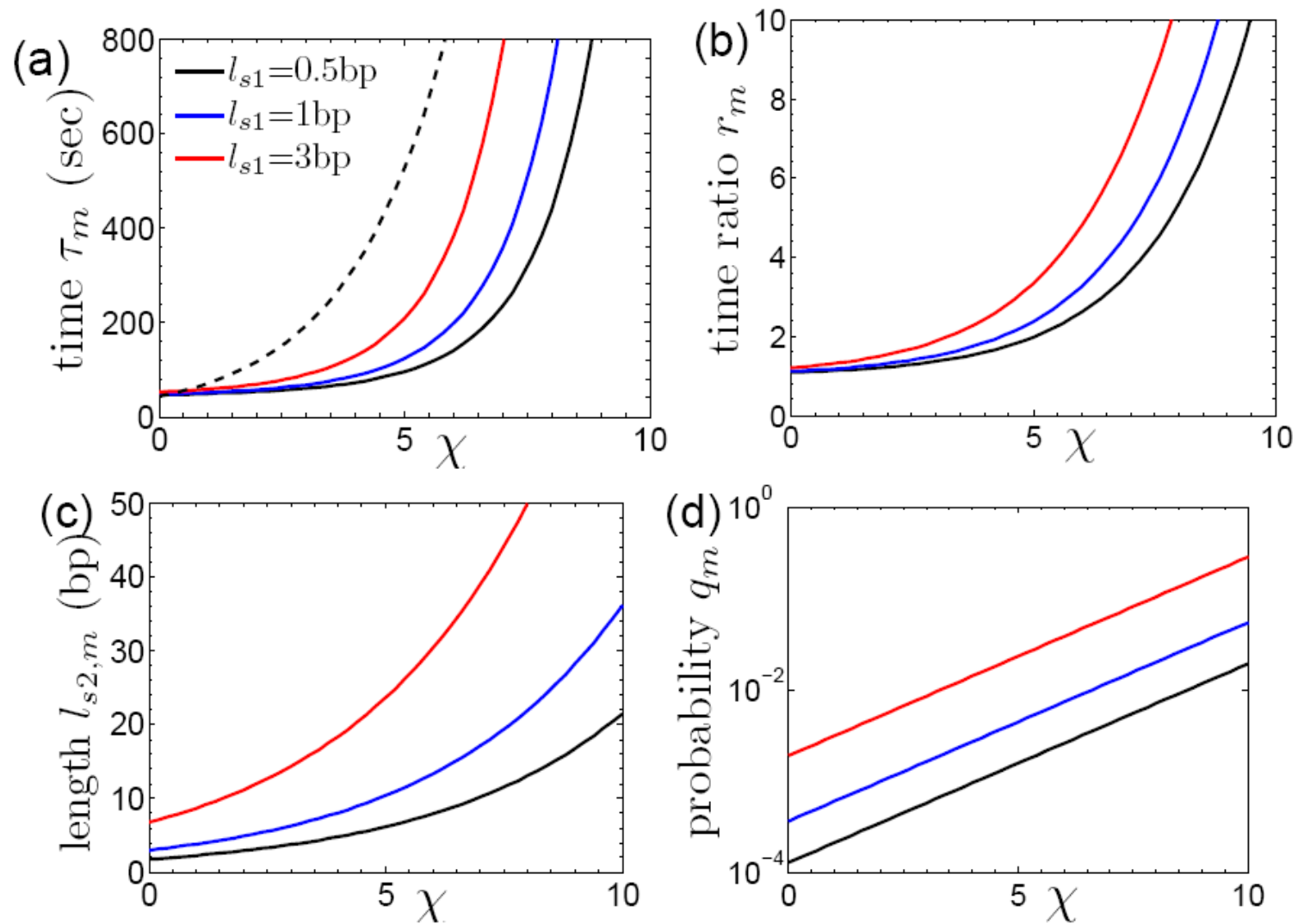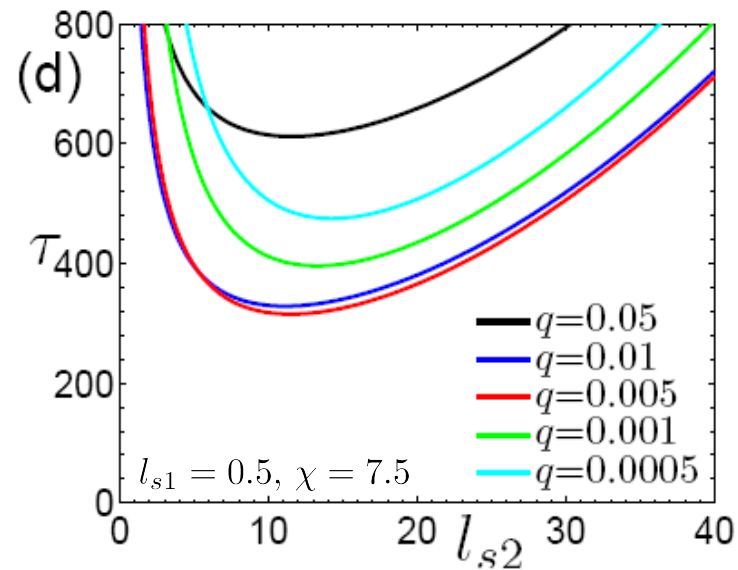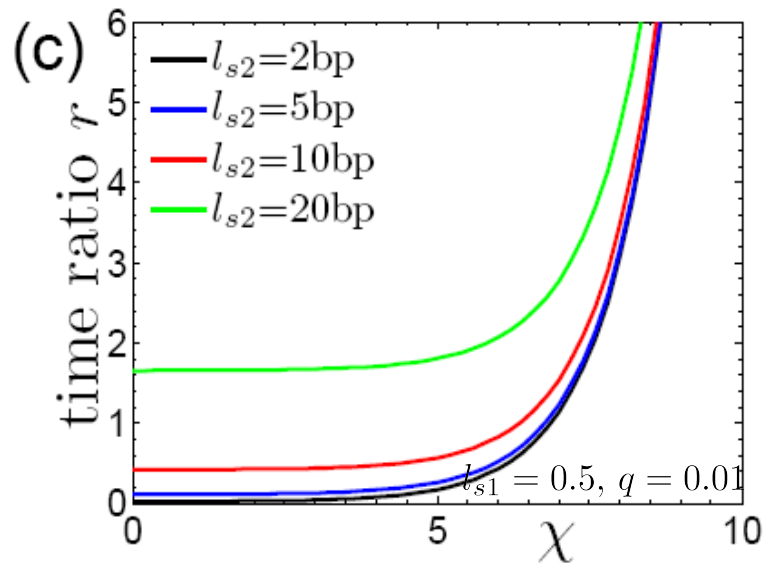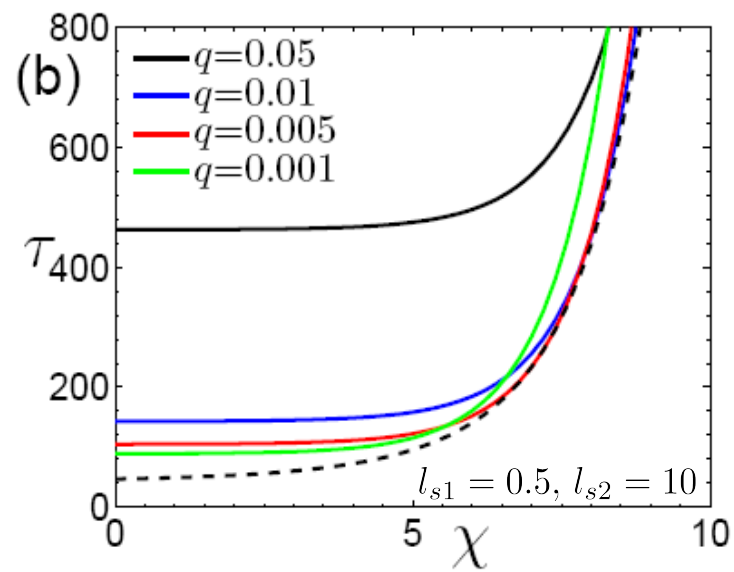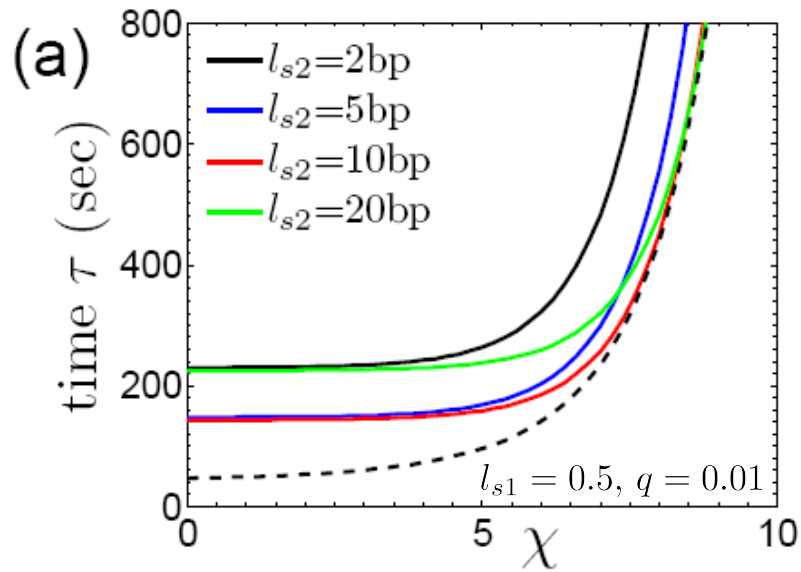
Binding energy and sliding distance

(e) — energy (k_BT) vs χ plot:
- $- - -$ E_1
- $E_b, l_{s2}=2\text{bp}$
- $E_b, l_{s2}=5\text{bp}$
- $E_b, l_{s2}=10\text{bp}$
- $E_b, l_{s2}=20\text{bp}$
- $l_{s1}=0.5,\ q=0.01$

(f) — distance δ (bp) vs l_{s2} plot:
- $q=0.05$
- $q=0.01$
- $q=0.005$

Energy diagram:
- E, E_3, E_2, E_1
- k_{32}, State 3
- k_{23}
- k_{12}, k_{21}, State 2
- State 1
- $\Delta\tilde{E}_{12} + \Delta E$, ΔE_{21}
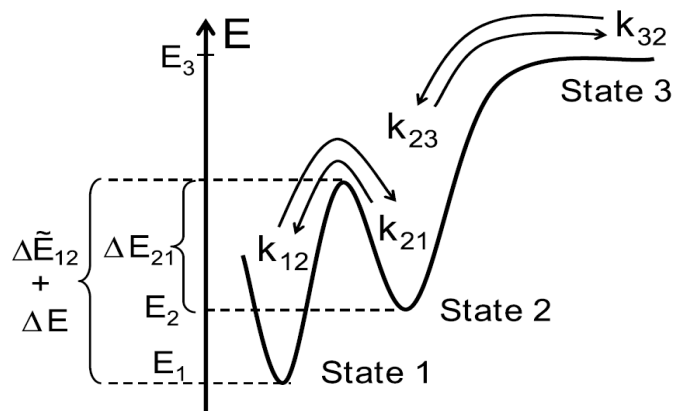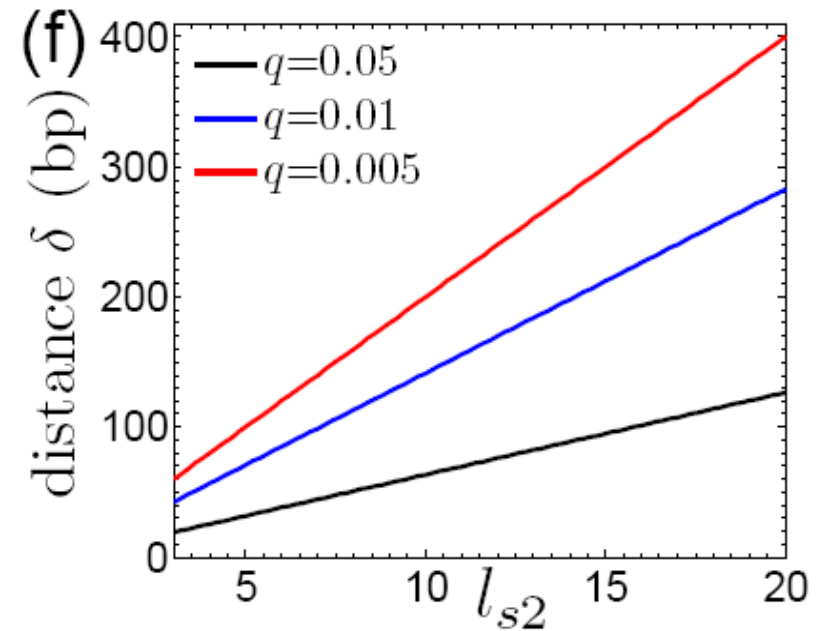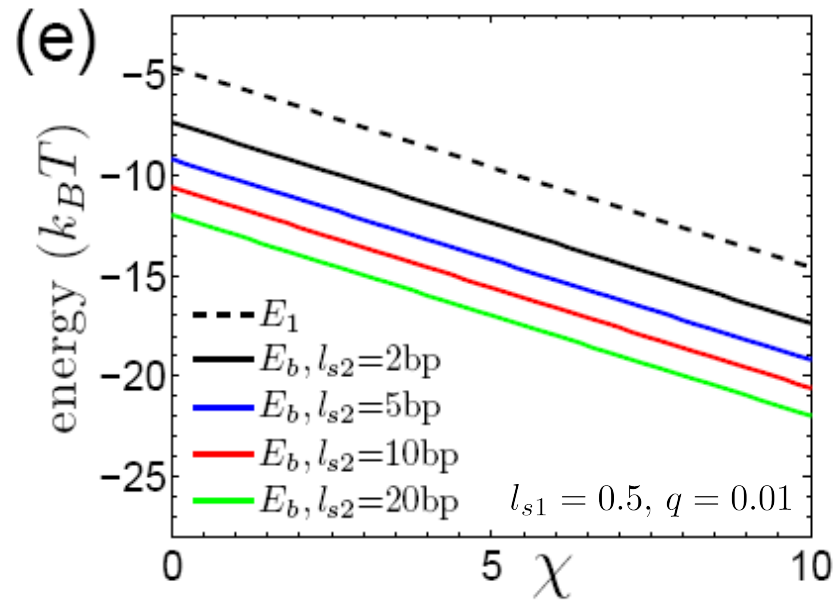
Conclusions and Outlook

➢ Search with conformational switch is faster and less sensitive to binding energy fluctuations compared to a single sliding state

➢ Fast search is possible even with strong TF-DNA interactions

➢ TF spends more time bound to the DNA compared to freely diffusing in the nucleus, in agreement with experiments

Outlook:

➢ Impact of binding energy fluctuations ?

➢ Better approximation for the search dynamics in state 3 (impact of DNA conformation and finite correlation length)

➢ Analysis of the switching process from a molecular model of the TF-DNA interaction

Acknowledgement

➢ I thank David Holcman for his continuous support

Thank you !

Gated Narrow Escape
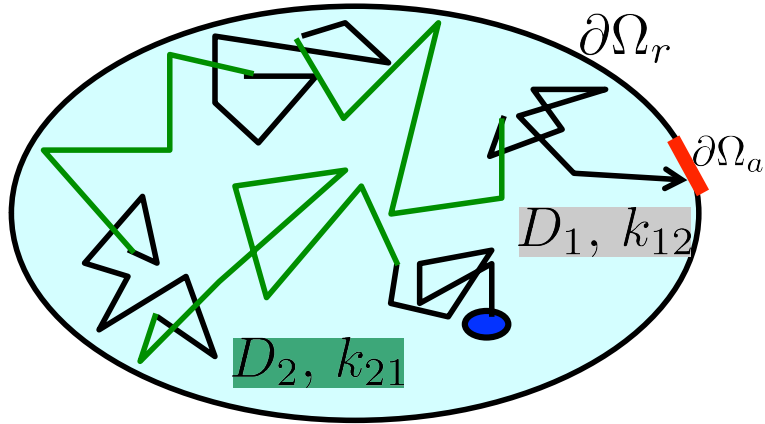
Equations for the MFPT:

$$D_1 \Delta \tau(y, 1) - k_{12}(\tau(y, 1) - \tau(y, 2)) = -1$$
$$D_2 \Delta \tau(y, 2) - k_{21}(\tau(y, 2) - \tau(y, 1)) = -1$$

(1D)

$$\tau(1) = \left(1 + \frac{k_{12}}{k_{21}}\right) \frac{L^2}{3D_1} \left(\frac{k_{21}D_1}{k_{12}D_2 + k_{21}D_1} + \frac{3k_{12}D_2}{k_{12}D_2 + k_{21}D_1} f\left(\frac{k_{12}L^2}{D_1} + \frac{k_{21}L^2}{D_2}\right)\right)$$

(3D)

$$\tau(1) = \left(1 + \frac{k_{12}}{k_{21}}\right) \begin{cases} \tau_{ns}, & l_1 \ll 1 \text{ or } l_2 \gg l_1 \\[2ex] \dfrac{|\Omega|}{|\partial\Omega_a|\sqrt{D_1 k_{12}}}, & l_1 \gg 1 \text{ and } \sqrt{l_1} \gg l_2 \end{cases}$$

$$l_1 = \frac{k_{12}a^2}{D_1} \quad l_2 = \frac{k_{21}a^2}{D_2}$$

Modeling Virus Trafficking in a Cell

What is the MFPT and Probability for a Virus to reach a nuclear pore ?

Microtubules

n **nuclear pores**

Cytoplasm

Diffusion: D

Nucleus

Killing Rate: k

Directed motion
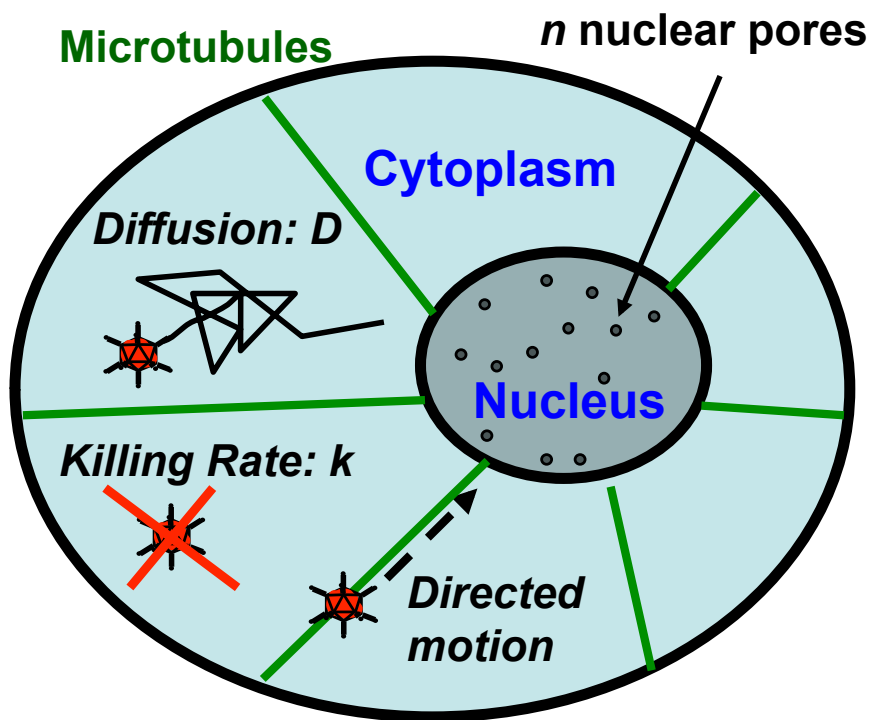
Fokker-Planck Equation:

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

diffusion   *drift*   *killing*

Mean time to find a pore:

$$\tau_n = \frac{\left(\dfrac{1}{4nD\epsilon} + \dfrac{1}{4\pi aD}\right)\displaystyle\int_\Omega e^{-\frac{\Phi(\mathbf{x})}{D}}d\mathbf{x}}{\dfrac{\int_{\partial\Sigma} e^{-\frac{\Phi(\mathbf{x})}{D}}d\mathbf{x}}{|\partial\Sigma|} + \left(\dfrac{1}{4nD\epsilon} + \dfrac{1}{4\pi aD}\right)\displaystyle\int_\Omega k(\mathbf{x})e^{-\frac{\Phi(\mathbf{x})}{D}}d\mathbf{x}}$$

Holcman, *J Stat. Phys* (2007)
Lagache, Holcman, *SIAM* (2008)
Lagache, Holcman, *PRE* (2008)
Lagache et al, *PRE* (2009)

Modeling viral trajectories

$$\dot{\mathbf{X}} = \begin{cases} \sqrt{2D}\dot{\mathbf{w}} & \textit{Free virus} \\ \\ \mathbf{V}(t) & \textit{Attached virus} \end{cases}$$

$$d\boldsymbol{X} = \boldsymbol{b}(\boldsymbol{X})\, dt + \sqrt{2D}\, d\boldsymbol{W}$$
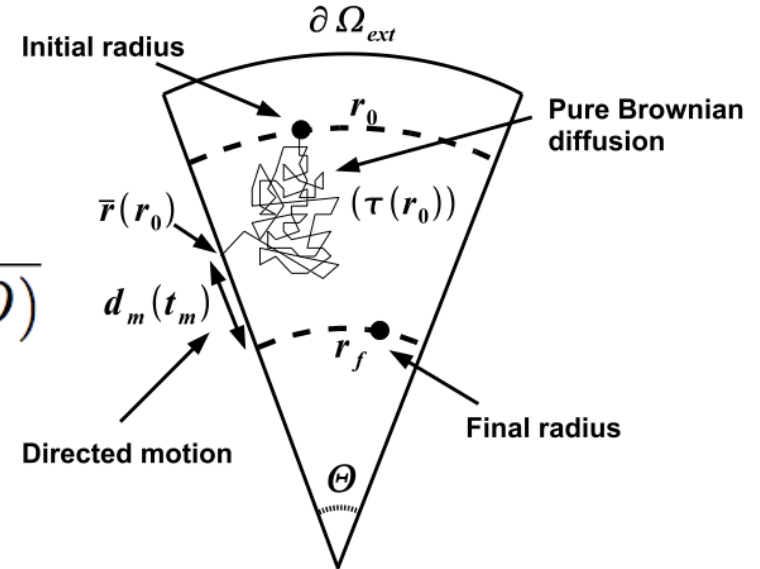
Calibration

+ degradation rate *k(X)*
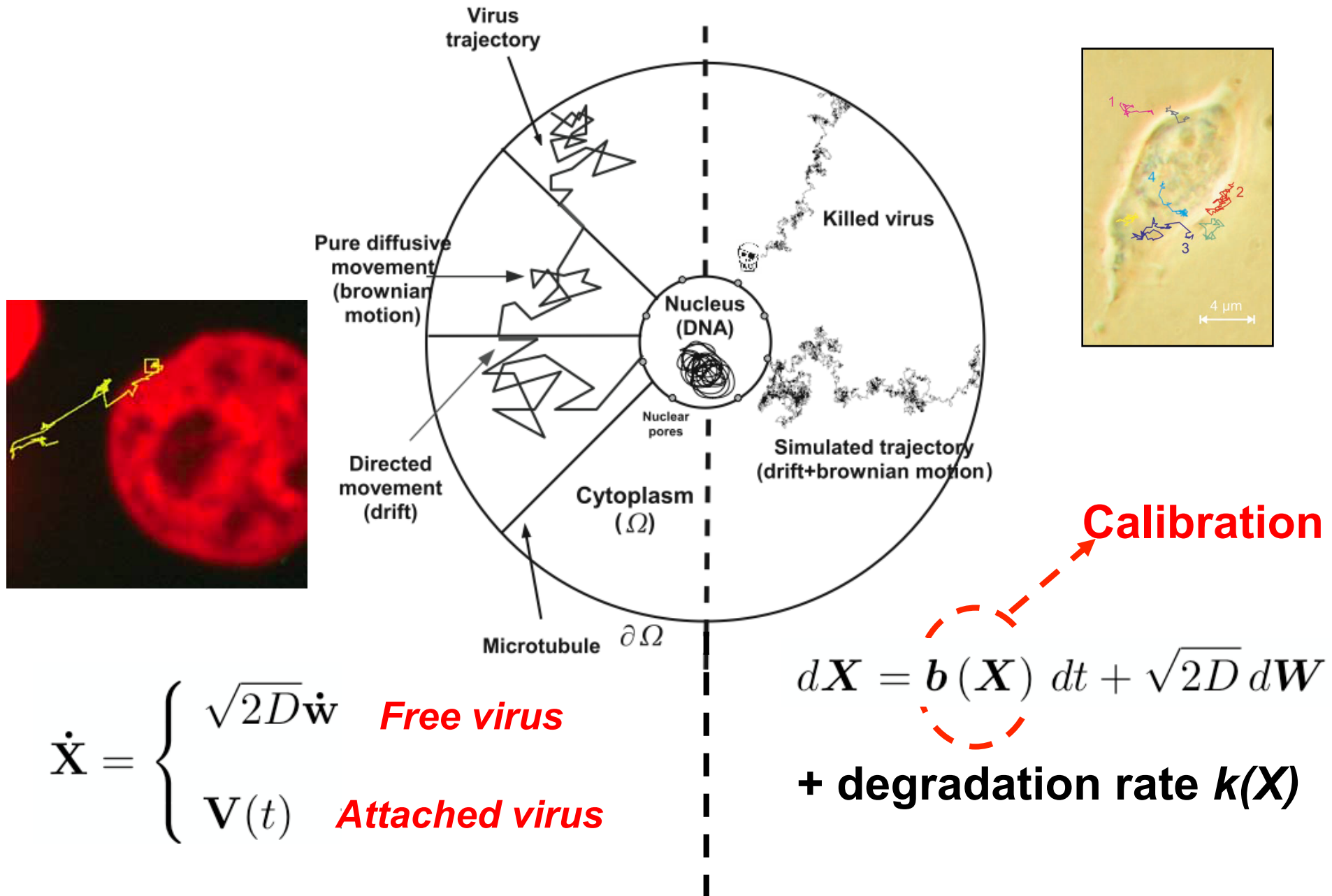
Calibration in the radial geometry

Asymptotic results (N microtubules)

$$b(r_0) = \frac{r_0 - (\bar{r}_0 - d_m)}{\tau(r_0) + t_m} \approx \frac{d_m - r_0\Theta^2/12}{t_m + r_0^2\Theta^2/(12D)}$$

$\Theta = 2\pi/N \ll 1$

Steady State Distribution
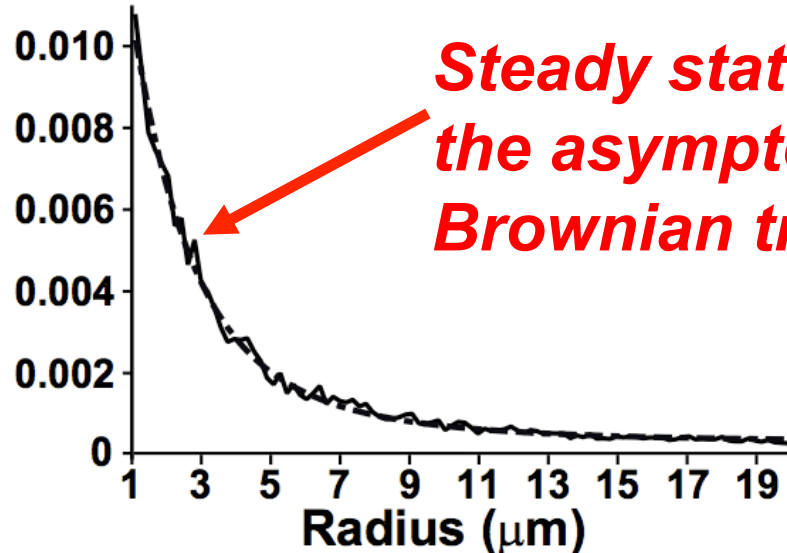
Steady state Langevin distribution (with the asymptotic b(r)) against intermittent Brownian trajectories

T. Lagache et D. Holcman, **SIAM J. Of Applied Maths** (2008) et **Phys. Rev. E** (2008).

D. Holcman, *J. of Stat. Phys.* 127 (2007)
T. Lagache et al., *Phys. Rev. E* 79 (2009)

Modeling Viral Trajectories

Biological observations:

- Average time ~ 15 min from endocytosis to nuclear entry **(Seisenberger et al, Science (2001))**

- Endosomal phase ~ 10 min **(Rink et al, Cell (2005))**

- Free trafficking phase ~ 5 min

Model predictions:

- Mean time for free virus to reach a nuclear pore ~ 3 min

- Infection efficiency ~ 94%

$$\tau_n = \frac{\left(\frac{1}{4nD\epsilon} + \frac{1}{4\pi aD}\right) \int_\Omega e^{-\frac{\Phi(\mathbf{x})}{D}} d\mathbf{x}}{\frac{\int_{\partial\Sigma} e^{-\frac{\Phi(\mathbf{x})}{D}} d\mathbf{x}}{|\partial\Sigma|} + \left(\frac{1}{4nD\epsilon} + \frac{1}{4\pi aD}\right) \int_\Omega k(\mathbf{x}) e^{-\frac{\Phi(\mathbf{x})}{D}} d\mathbf{x}}$$

Equations for the transition probabilities

$$p(x, n, t'|y, m, t') \qquad 0 \leq x, y \leq L \qquad 1 \leq n, m \leq 3$$

Forward Fokker-Planck equation

$$\frac{\partial p(x, n, t|y, m, t')}{\partial t} = D_n \Delta_x p(x, n, t|y, m, t') - \sum_{i=1}^{N} (k_{ni} p(x, n, t|y, m, t') - k_{in} p(x, i, t|y, m, t'))$$

$$p(x, n, t'|y, m, t') = \delta_{nm} \delta(x - y) \qquad \text{Initial condition}$$

Boundary conditions:
- State 2 and 3: Reflecting at x=0 and x=L
- State 1: Absorbing at x=0 (target) and reflecting at x=L

Backward Kolmogorov equation

$$\frac{\partial p(x, n, t|y, m, t')}{\partial t} = D_m \Delta_y p(x, n, t|y, m, t') - \sum_{i=1}^{N} k_{mi} (p(x, n, t|y, m, t') - p(x, n, t|y, i, t'))$$

MFPT to a nuclear pore

$$\tau_n = \frac{\int_\Omega \int_0^\infty p(\boldsymbol{x},t)dtd\boldsymbol{x} - \int_\Omega \int_0^\infty k(\boldsymbol{x})tp(\boldsymbol{x},t)dtd\boldsymbol{x}}{1 - \int_\Omega \int_0^\infty k(\boldsymbol{x})p(\boldsymbol{x},t)dtd\boldsymbol{x}}$$

Asymptotic Results

$$\tau_n = \frac{\dfrac{1}{4Dn\epsilon}\int_\Omega e^{-\frac{\Phi(\mathbf{x})}{D}}d\mathbf{x}}{\dfrac{1}{4Dn\epsilon}\int_\Omega e^{-\frac{\Phi(\mathbf{x})}{D}}k(\mathbf{x})d\mathbf{x} + \dfrac{\int_{\partial\Sigma} e^{-\frac{\Phi(\mathbf{x})}{D}}d\mathbf{x}}{|\partial\Sigma|}}$$
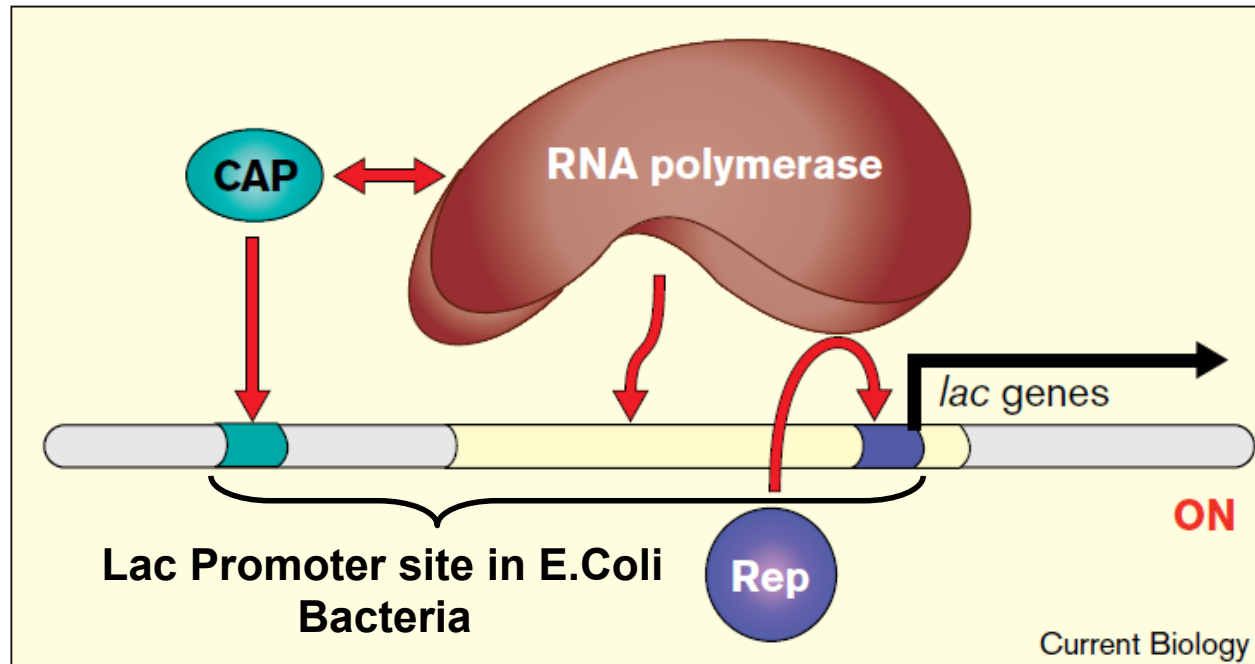
D. Holcman, *J. of Stat. Phys.*
127 (2007)
T. Lagache et al., *Phys. Rev. E*
79 (2009)

Problem

$$\lim_{n\to\infty,\, n\varepsilon^2 /|\partial\Sigma|<<1} \tau_n = 0$$

Transcription Factors and Gene Activation
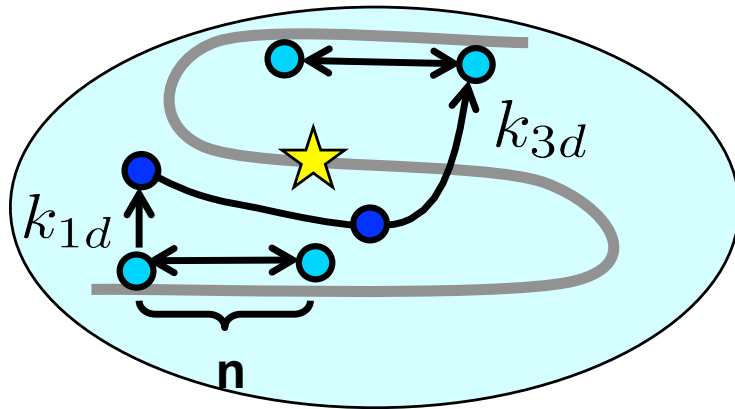

from Ptashne, *Curr Biol* (1998)

CAP: Transcriptional Activator of the Lac gene

Rep: Transcriptional Repressor of the Lac gene

3D and 1D Sojourn Times for optimal search

$$\tau = \frac{N_{bp}}{n}\left(\tau_{3d} + \tau_{1d}\right)$$

$$n \sim 2\sqrt{D_1 \tau_{1d}}$$

Minimal search time for given τ_{3d} : $\tau_{1d} = \tau_{3d}$

Experiment: TF spends 80-90% of the search time bound to DNA

Kalodimos et al, *Science* (2004)

Minimal search time

$$\tau_{min} = \sqrt{\frac{L^2}{D_2 k_{32}} \left(1 + \sqrt{\frac{2\alpha}{e^\chi}}\right)^2 \frac{e^\chi}{\alpha}} \qquad \alpha = \sqrt{\frac{D_2}{l_{s1}^2 k_{32}}}$$
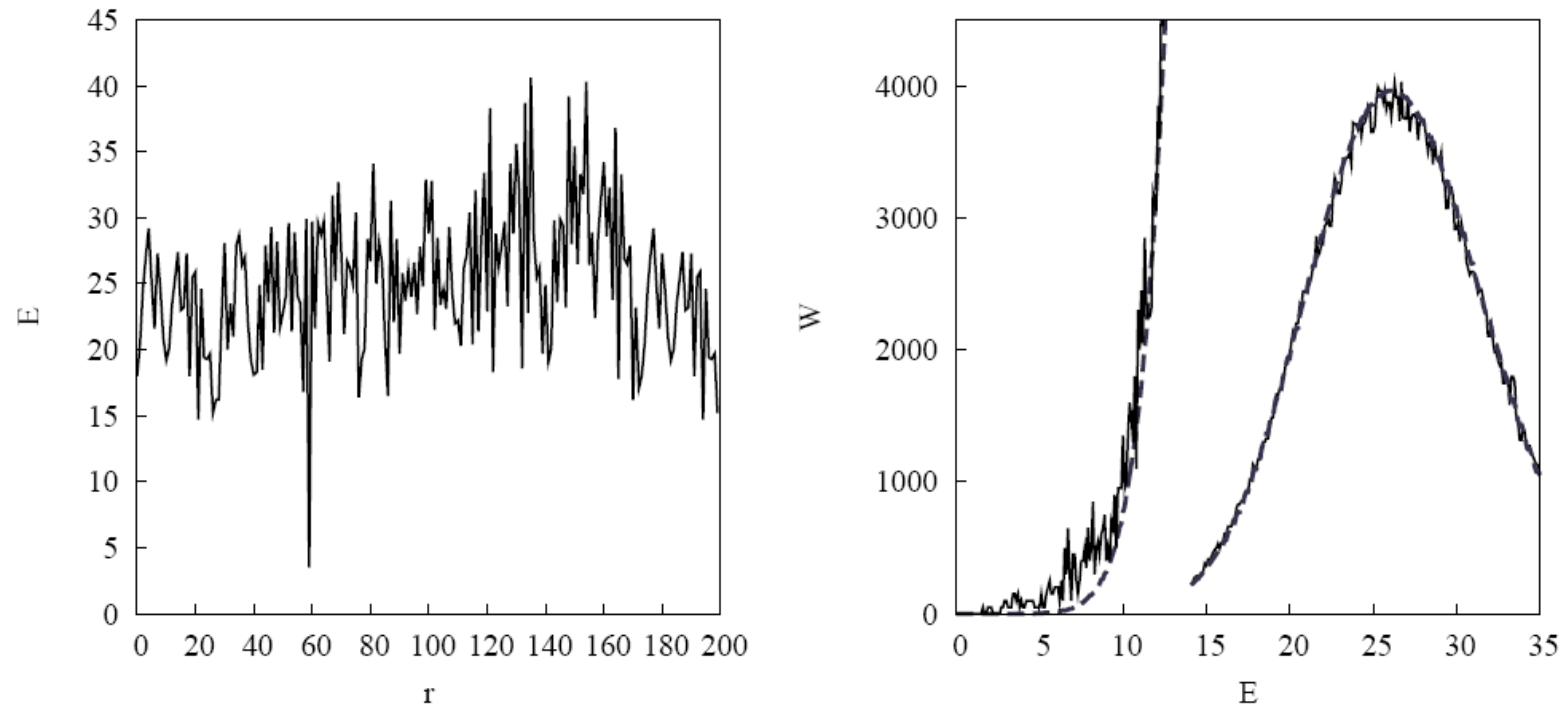
$$r_{min} = 1 + \sqrt{\frac{2e^\chi}{\alpha}}$$

Results for an optimal search process with a single sliding state

$$\tilde{\tau}_{min} = 2\sqrt{\frac{L^2}{D_2 k_{32}} e^{\frac{\chi}{2}}}$$

$$\tilde{r}_{min} = 1$$

TF binding energy

Figure 3
Transcription factor binding energies of the E. coli genome. (a) Energy "landscape" $E(r)$ for specific binding of the CRP factor at 200 consecutive positions r in an intergenic region, with a binding site at position 59. (b) Count histogram $W_{dat}(E)$ with energy bins of width 0.1 obtained from all intergenic regions, together with the distribution $W_0(E)$ for a random sequence (dashed line, shown with a 30 fold zoom into the region $E < 14$). From [16].

from Lässig, *BMC Bioinf.* (2007)