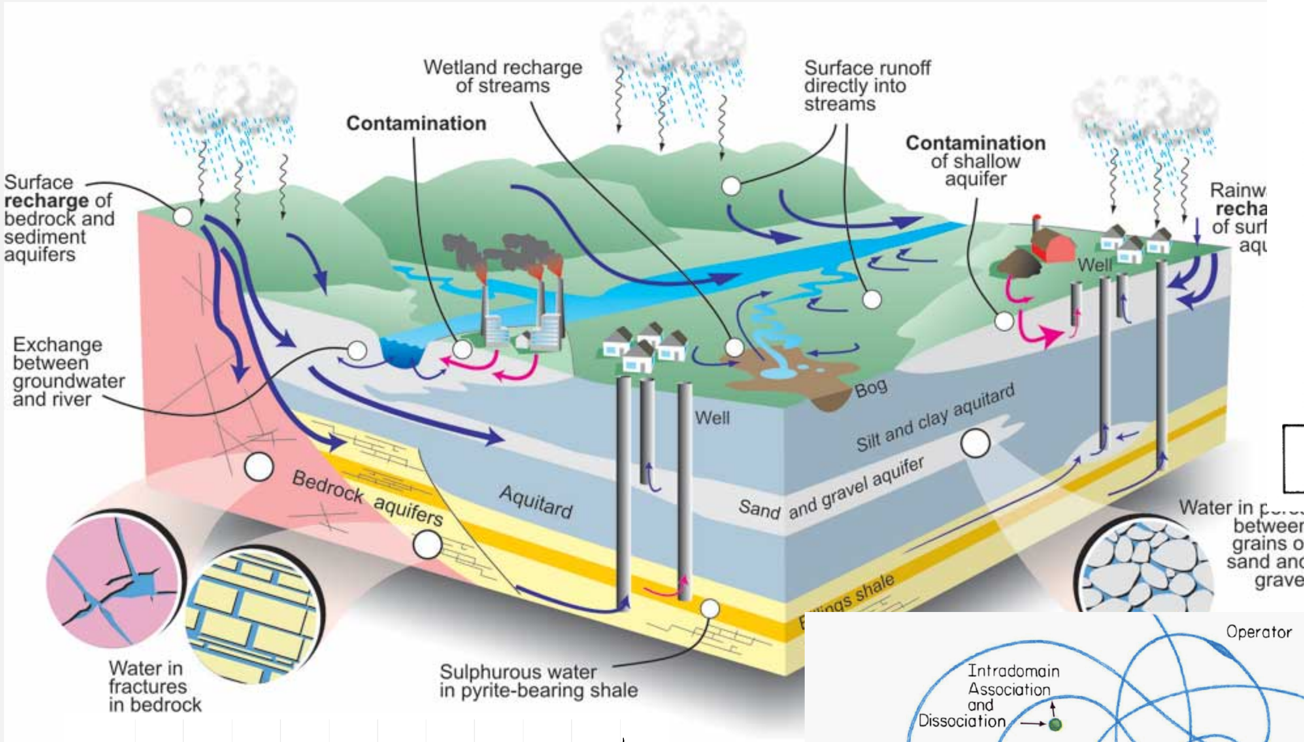
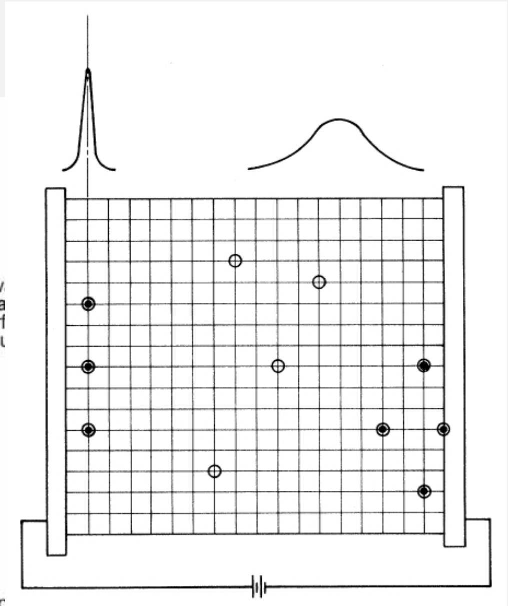
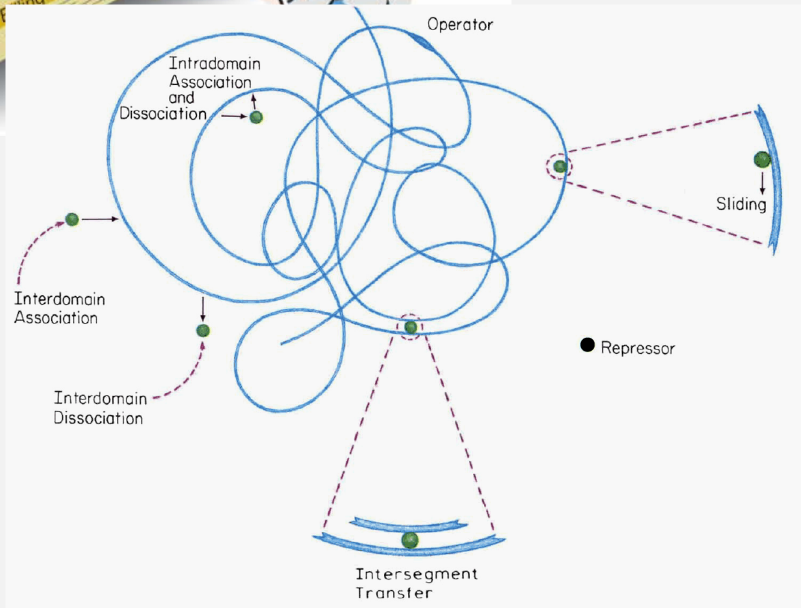
LANZHOU COURSE: First-passage phenomena

—online, 15th July 2021—

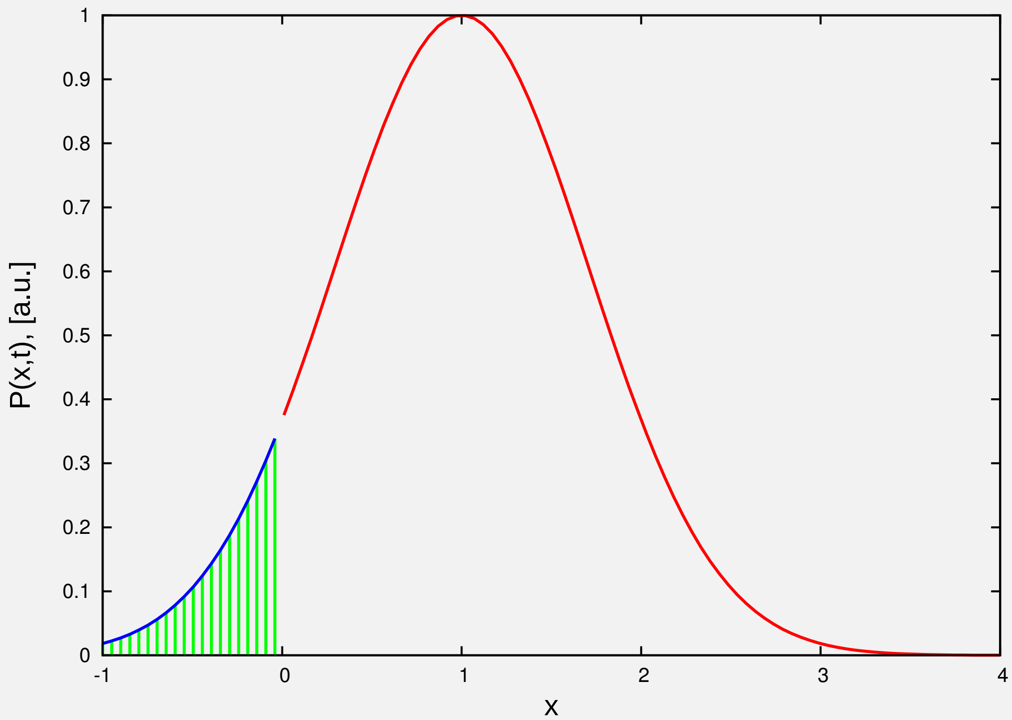
First passage time problems







First passage time problems



Boundary value problem: absorbing boundary condition (Cauchy problem)

$$\frac{\partial}{\partial t}P(x,t) = K\frac{\partial^2}{\partial x^2}P(x,t) \;\therefore\; P(0,t) = 0$$

Redner, A guide to first-passage processes, CUP (2001)

First passage time problems: Images method

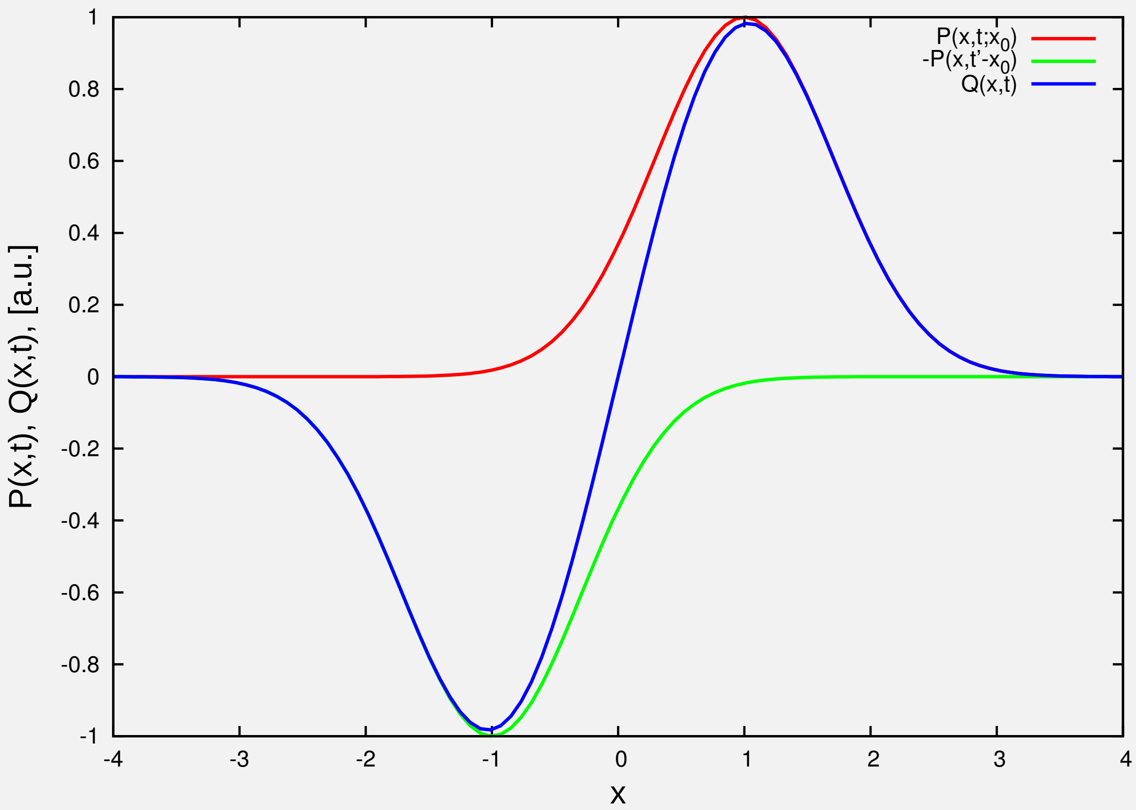


Image solution:

$$Q(x,t) = P(x,t;x_0) - P(x,t;-x_0)$$

Redner, A guide to first-passage processes, CUP (2001)

First passage time problems: Images method

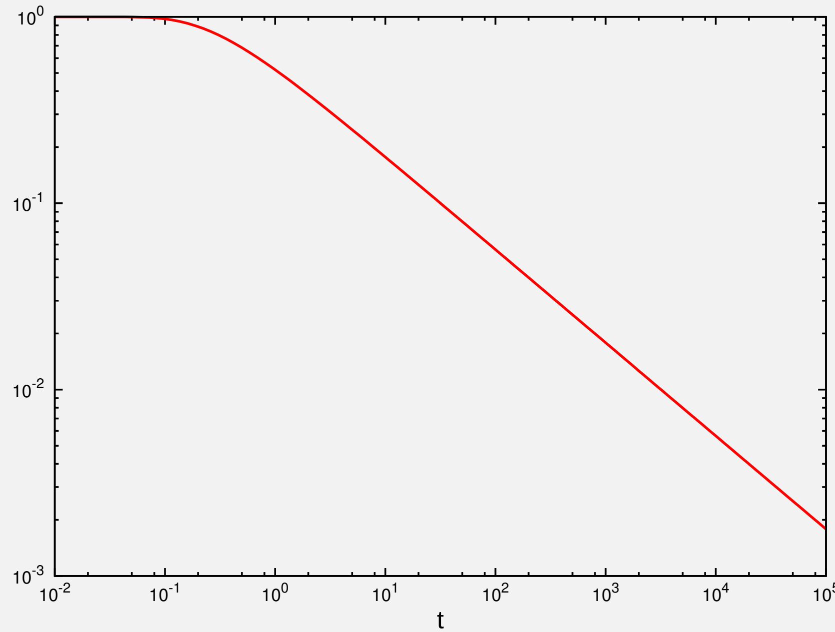
Image solution

$$Q(x,t) = \frac{1}{\sqrt{4\pi K t}} \left\{ \exp\left(-\frac{(x-x_0)^2}{4Kt} \right) - \exp\left(-\frac{(x+x_0)^2}{4Kt} \right) \right]$$

Survival probability:

$$\mathscr{S}(t) = \int Q(x,t)dx = \mathrm{erf}\left(\frac{x_0}{\sqrt{4Kt}} \right)$$

$$\mathscr{S}(0) = 1; \;\; \mathscr{S}(t) \simeq t^{-1/2}$$

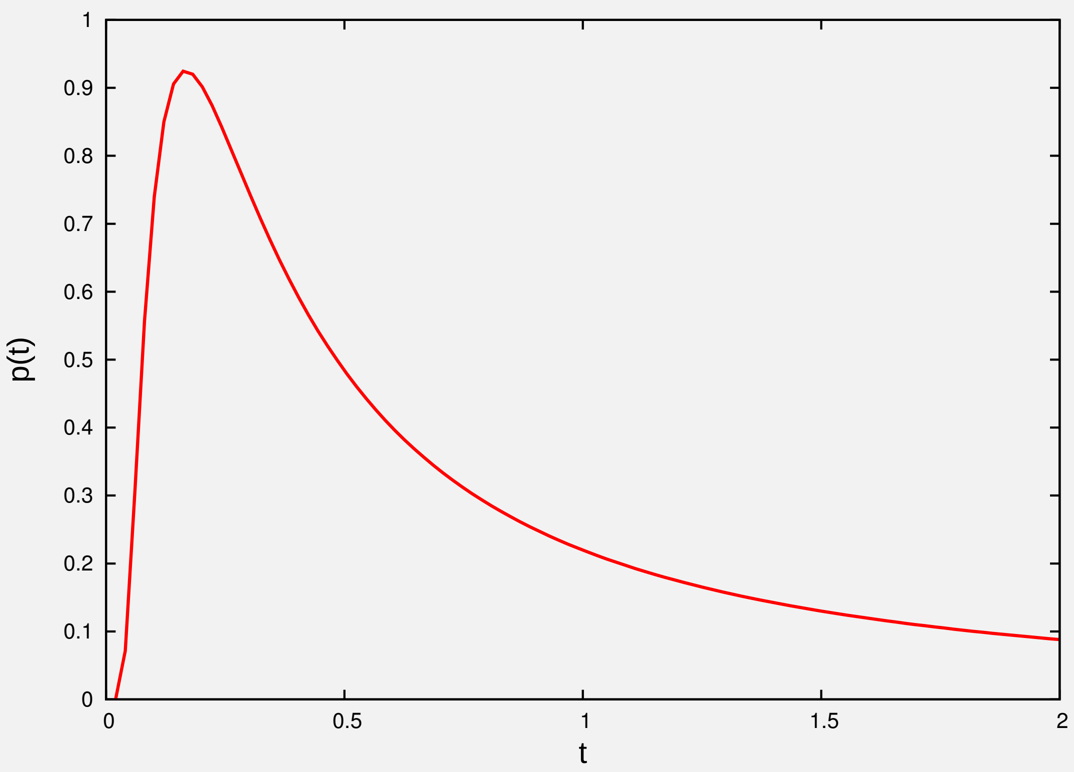


Redner, A guide to first-passage processes, CUP (2001)

First passage time problems: Images method

First passage time density:

$$\wp(t) = -\frac{d\mathscr{S}(t)}{dt} = \frac{x_0}{\sqrt{4\pi K t^3}} \exp\left(-\frac{x_0^2}{4Kt}\right) \simeq t^{-3/2}$$



Redner, A guide to first-passage processes, CUP (2001)

First passage time problems: First arrival

Removal of probability at $x = 0$ (arrival)

$$\frac{\partial}{\partial t}P(x,t) = K\frac{\partial^2}{\partial x^2}P(x,t) - \wp_{\rm fa}(t)\delta(x) \;\; \therefore \;\; P(0,t) = 0$$

First arrival density

$$\wp_{\rm fa}(t) = -\frac{d}{dt}\int_{-\infty}^{\infty} P(x,t)dx$$

Solving the diffusion equation with sink and initial condition $P(x,0) = \delta(x - x_0)$:

$$P(k,u) = \frac{\exp(ikx_0) + \wp_{\rm fa}(u)}{u + Kk^2}$$

Such that

$$P(-x_0,t) = \int_0^t \wp_{\rm fa}(\tau)P(0,t-\tau)d\tau \implies \wp_{\rm fa}(u) = \frac{P(-x_0,u)}{P(0,u)}$$

The solution for $\wp_{\rm fa}(t)$ matches the first passage density

BD Hughes, Random Walk and Random Environments, Oxford (2000)

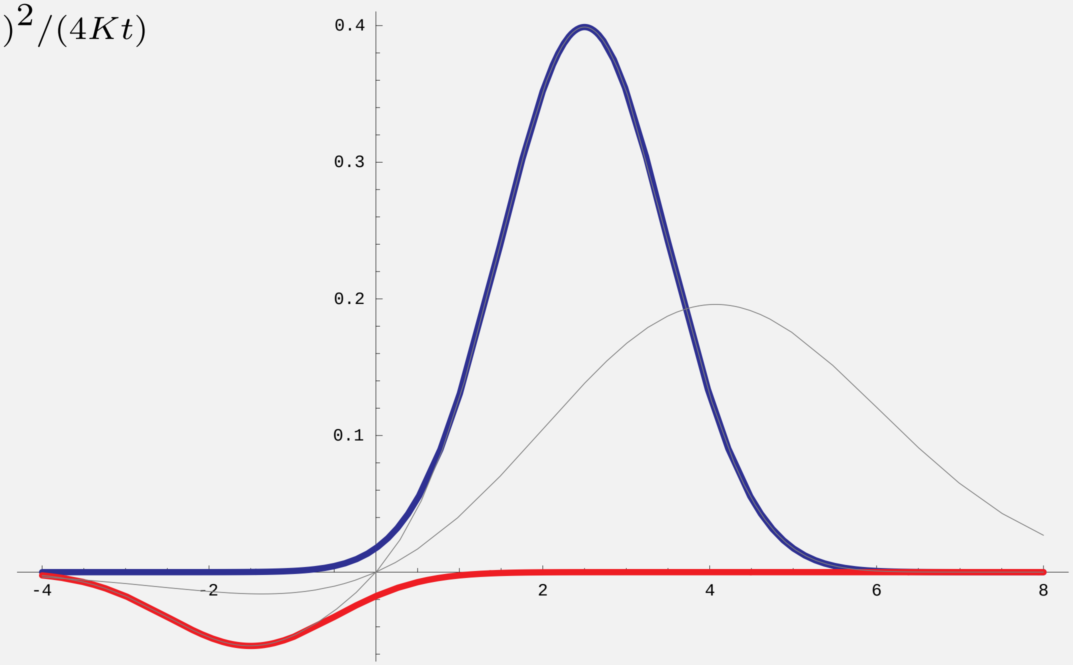
Method of images in presence of drift

$$\frac{\partial}{\partial t}P(x,t) = V\frac{\partial}{\partial x}P(x,t) + K\frac{\partial^2}{\partial x^2}P(x,t)$$ NB: V towards boundary

$$Q(x,t) = \frac{1}{\sqrt{4\pi K t}}\left[e^{-(x-x_0-Vt)^2/(4Kt)} - e^{Vx/K}e^{-(x+x_0-Vt)^2/(4Kt)}\right]$$

$$\wp(t) = \frac{x_0}{\sqrt{4\pi K t^3}}e^{-(x_0+Vt)^2/(4Kt)}$$

$$T = \frac{V}{x_0}$$



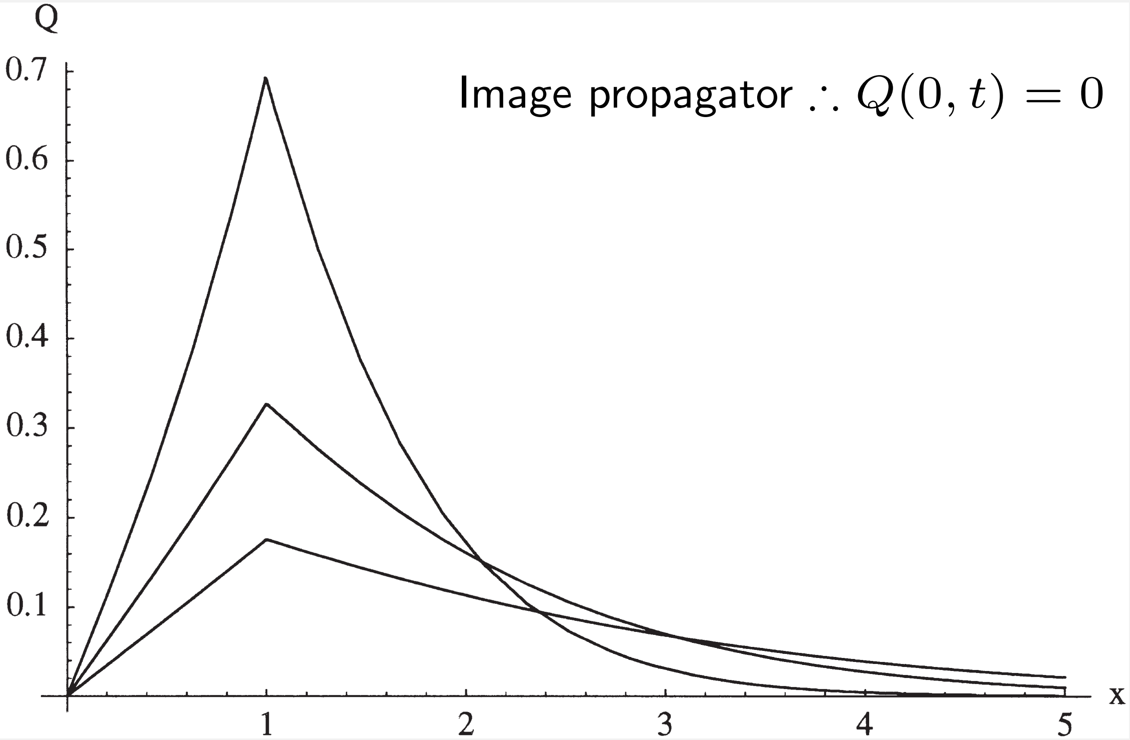
First passage behaviour for subdiffusive CTRW

Finite domain:

$$\wp_1(t) \simeq \exp\left(-\frac{t}{\tau}\right) \quad \curvearrowright \quad \wp_\alpha(t) \simeq \frac{1}{t^{1+\alpha}} \qquad \text{always long retention!}$$

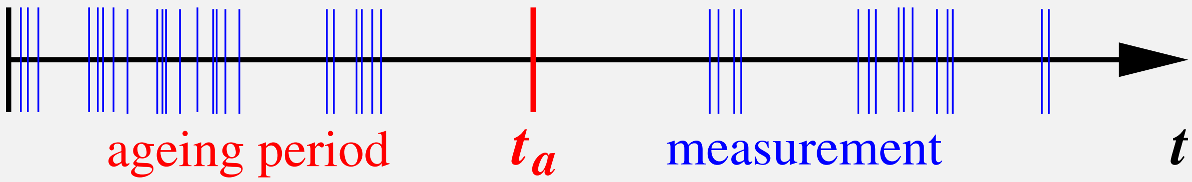
Semi-infinite domain:

$$\wp_1(t) \simeq \frac{x_0}{t^{1+1/2}} \quad \curvearrowright \quad \wp_\alpha(t) \simeq \frac{x_0}{t^{1+\alpha/2}}$$



RM & J Klafter, Physica A (2000)

Ageing effects in single trajectory time averages

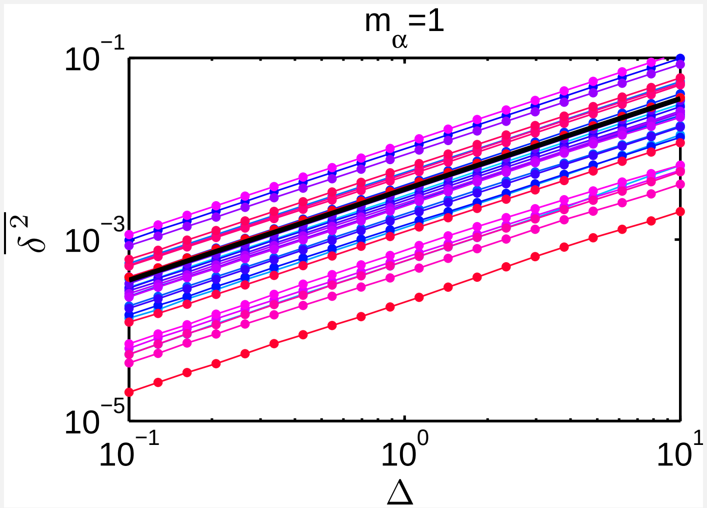


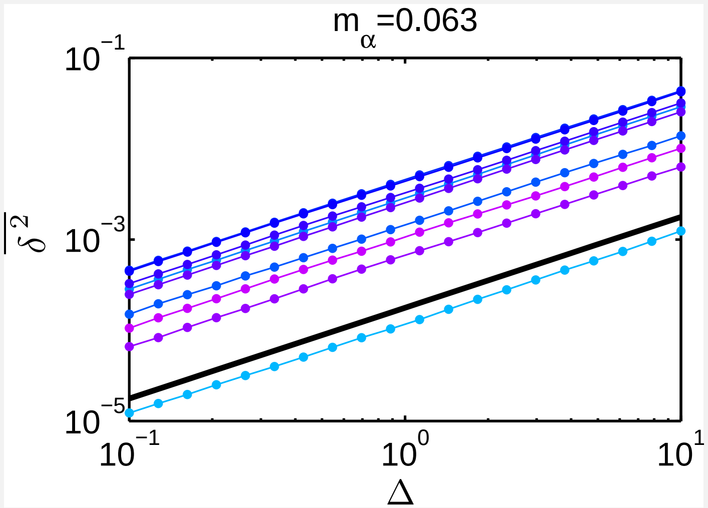
Ageing mean squared displacement ($\Lambda(z) = (1+z)^\alpha - z^\alpha$)

$$\left\langle \overline{\delta^2(\Delta)} \right\rangle_a = \frac{\Lambda_\alpha(t_a/T)}{\Gamma(1+\alpha)} \frac{g(\Delta)}{T^{1-\alpha}} \qquad \not\Leftrightarrow \qquad \langle x^2(t)\rangle_a \simeq \begin{cases} t^\alpha, & t_a \ll t \\ t_a^{\alpha-1} t, & t_a \gg t \end{cases}$$

Probability to make at least one step during $[t_a, t_a + T]$: *population splitting*

$$m_\alpha(T/t_a) \simeq (T/t_a)^{1-\alpha}, \quad T \ll t_a$$

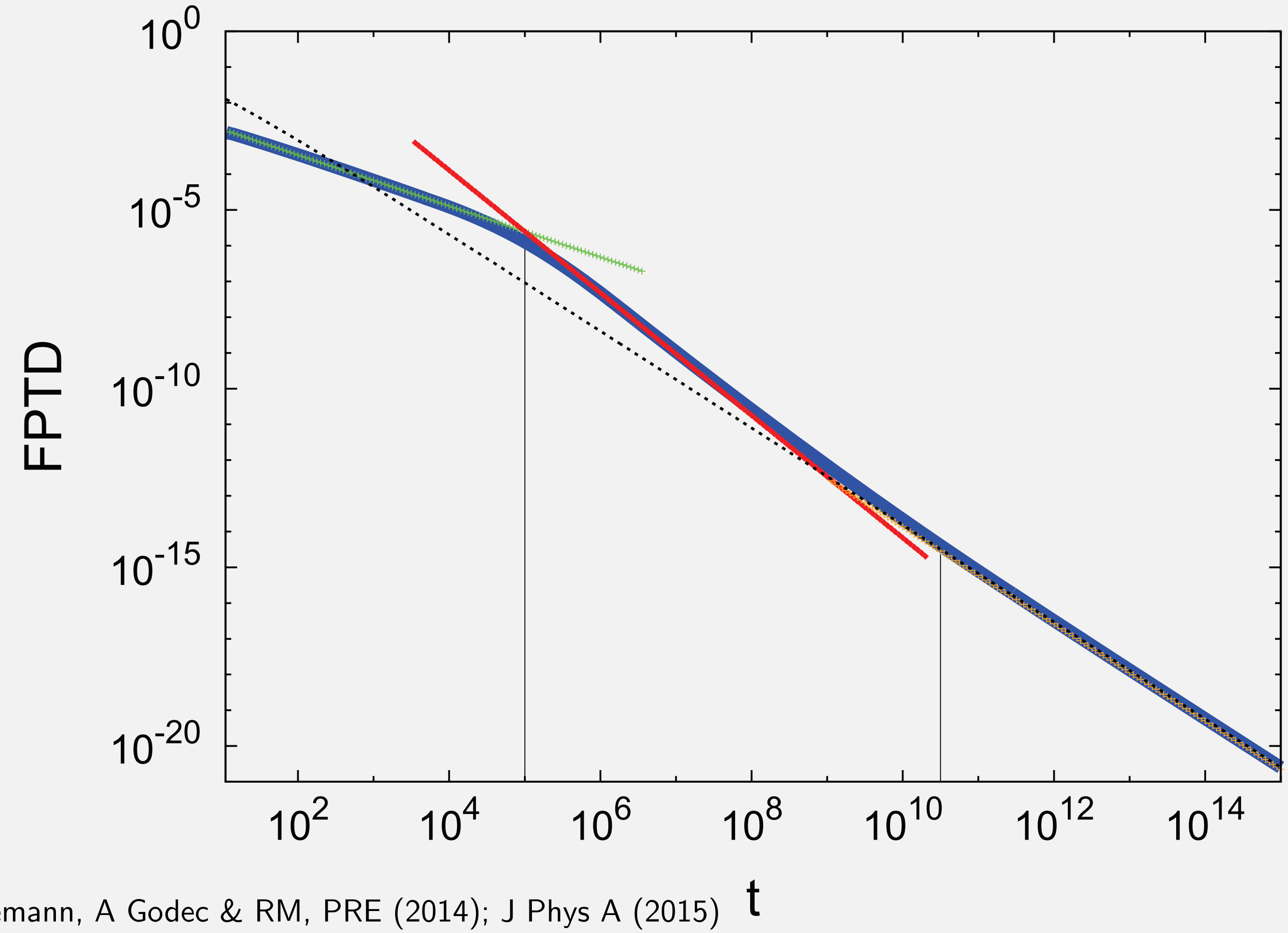




J Schulz, E Barkai & RM, PRL (2013), PRX (2014)

Ageing induces crossovers in the first passage dynamics

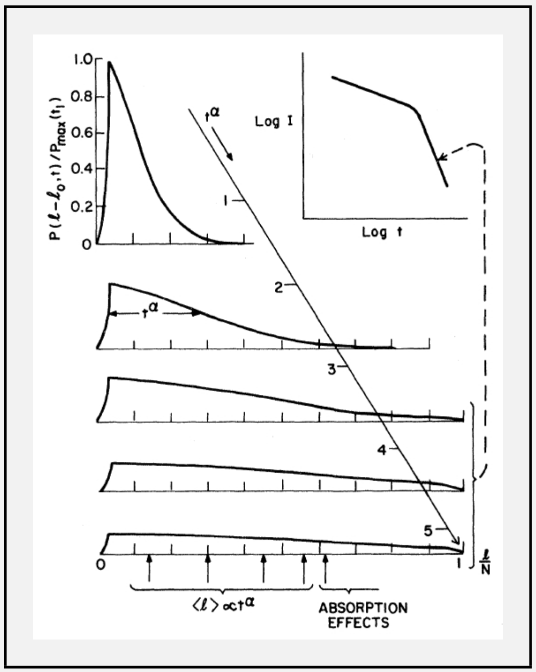
$$\wp_a(t_a,t)\simeq\begin{cases} t_a^{\alpha-1}t^{-\alpha}, & t_a\gg t\\ t_a^{\alpha}t^{-1-\alpha}, & t_a\ll t\ll t_a^2\\ x_0K_\alpha^{-1/2}t^{-1-\alpha/2}, & t_a^2\ll t\end{cases}$$

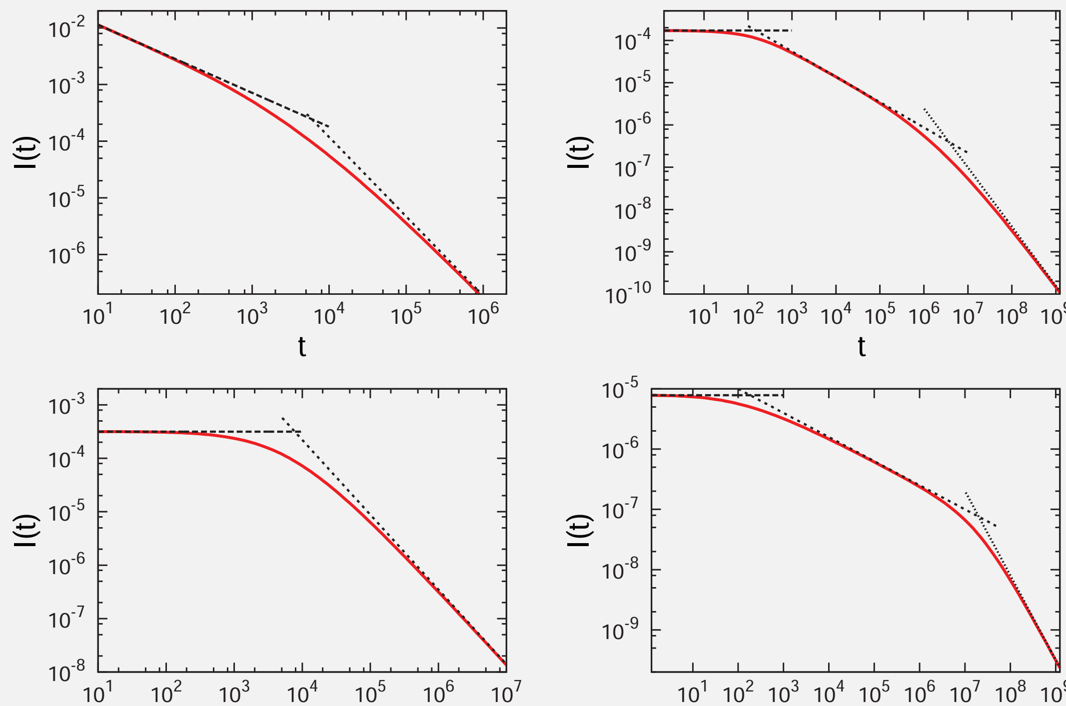


H Krüsemann, A Godec & RM, PRE (2014); J Phys A (2015)

Ageing current for scale free waiting times

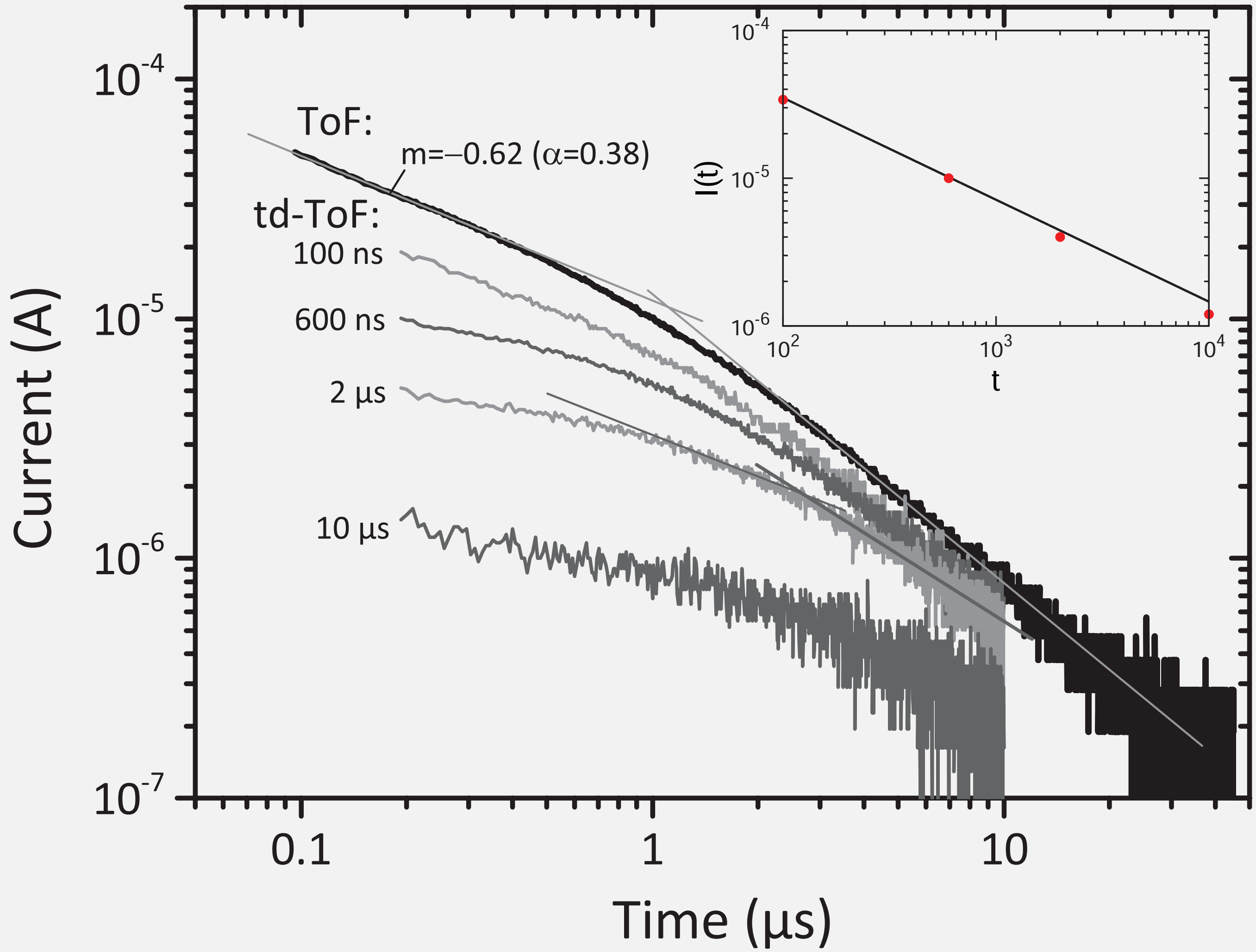
$$I(t_a,t) \sim \begin{cases} \dfrac{FK_\alpha}{k_BT}\dfrac{t_a^{\alpha-1}}{\Gamma(\alpha)}, & t \ll t_a, t_c \\ \dfrac{FK_\alpha}{k_BT}\dfrac{t^{\alpha-1}}{\Gamma(\alpha)}, & t_a \ll t \ll t_c \\ a\dfrac{t_a^{\alpha-1}t^{-\alpha}}{\Gamma(\alpha)\Gamma(1-\alpha)}, & t_c \ll t \ll t_a \\ \left[\dfrac{a\alpha(k_BT)^2}{F^2K_\alpha} + \dfrac{a^2\alpha k_BT}{2FK_\alpha} + \dfrac{a\alpha t_a^\alpha}{\Gamma[1+\alpha]}\right]\dfrac{t^{-1-\alpha}}{\Gamma(1-\alpha)}, & t \gg t_a, t_c \end{cases}.$$





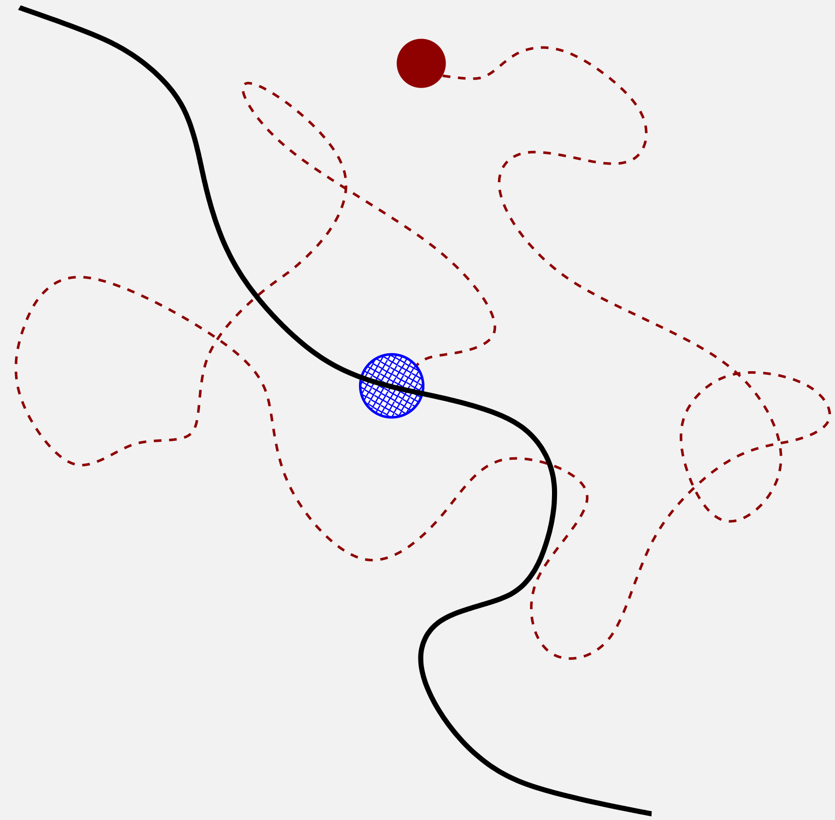
A Krüsemann, R Schwarzl & RM, Transp Por Med (2016)

Ageing charge carrier motion in polymeric semiconductors



M Schubert, . . . & D Neher, Phys Rev B (2013); H Krüsemann, A Godec & RM, PRE (2014), JPA (2015), TiPM (2016)

Smoluchowski search picture



Search rate for a particle with diffusivity $D_{3\mathrm{d}}$ to find an immobile target of radius a (assuming immediate binding):

$$k_{\mathrm{on}}^{S} = 4\pi D_{3\mathrm{d}} a$$

Protein-DNA interaction: $a \approx$ {few bp} $\approx$ 1nm
$D_{3\mathrm{d}} \approx 10\mu\mathrm{m}^2/\mathrm{sec}$ (typically $\varnothing_{\mathrm{TF}} \approx$ 5nm):

$$k_{\mathrm{on}}^{S} \approx \frac{10^8}{(\mathrm{mol/l}) \times \mathrm{sec}}$$

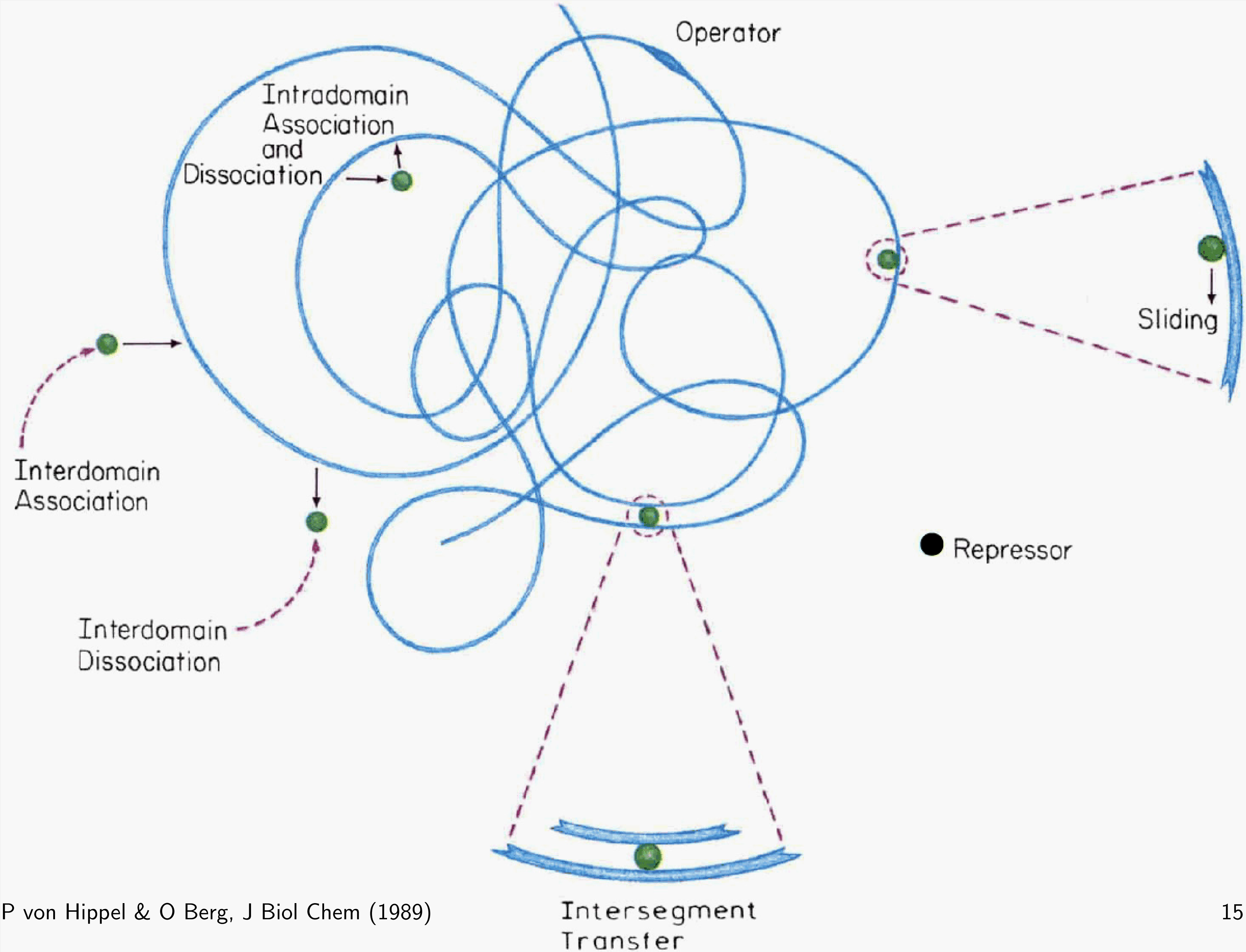
Lac repressor [AD Riggs, S Bourgeois, M Cohn, J Mol Biol 53, 401 (1970)]:

$$k_{\mathrm{on}} \approx \frac{10^{10}}{(\mathrm{mol}/l) \times \mathrm{sec}}$$

$\rightarrow$ Facilitated diffusion picture

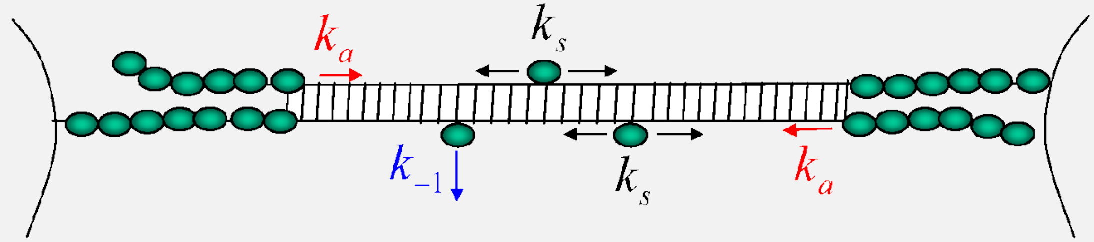
M v Smoluchowski, Physikal. Zeitschr. (1916); P von Hippel and O Berg, J Biol Chem (1989)

Facilitated diffusion: the Berg-von Hippel model



P von Hippel & O Berg, J Biol Chem (1989)

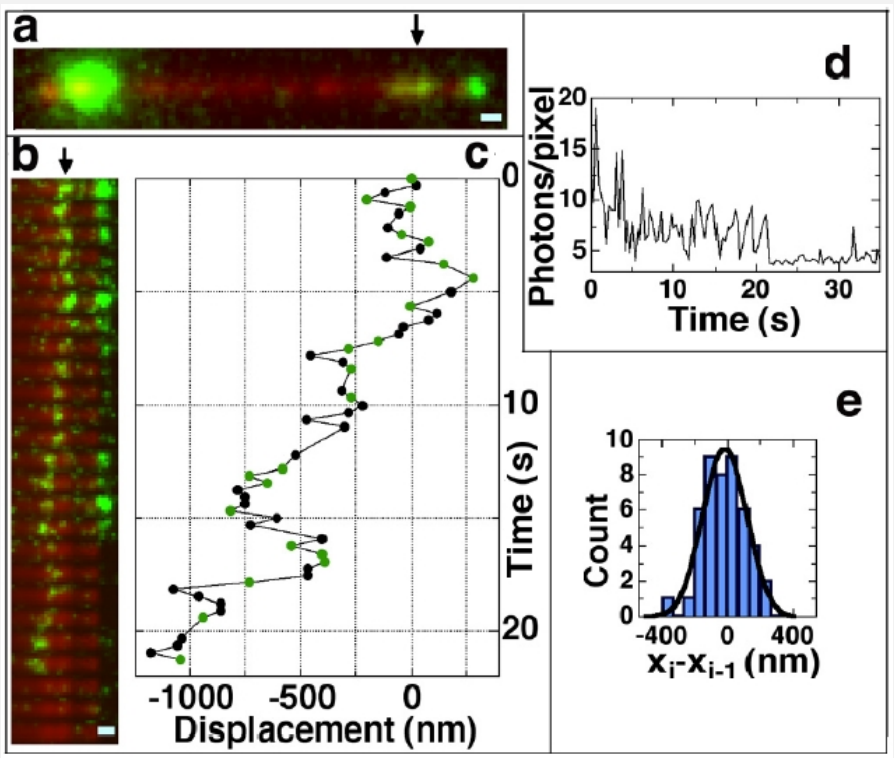
Proof of 1D search mode

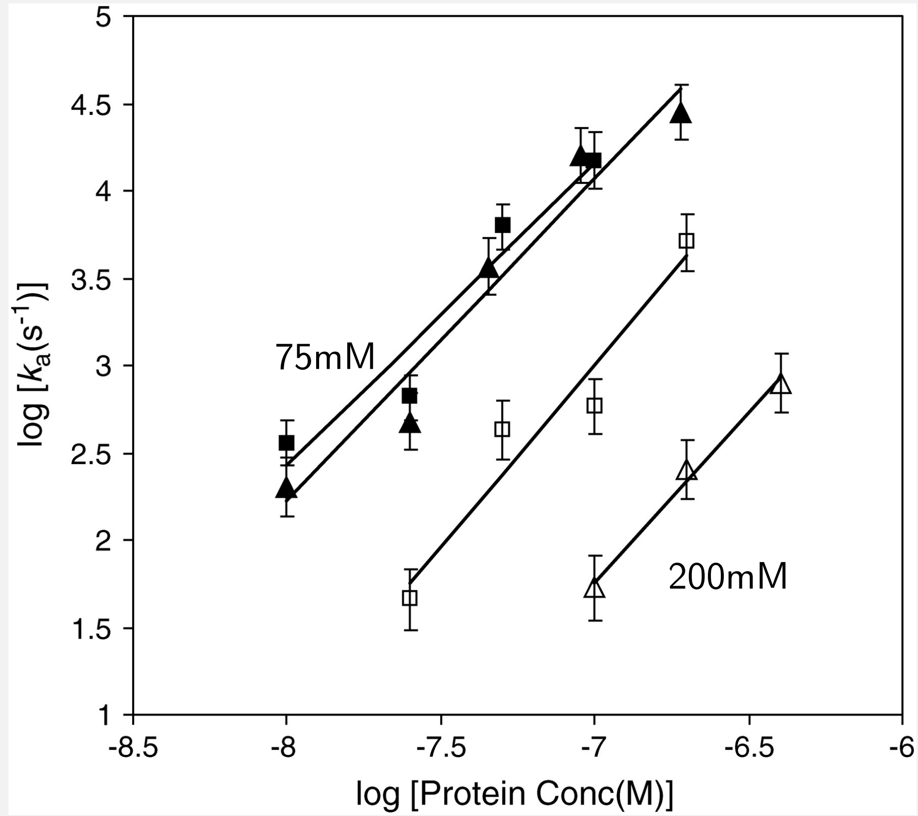


McGhee & von Hippel isotherm

$$f = \frac{N\lambda}{L} \simeq K_{\rm ns}\lambda C, \;\; f \ll 1$$

$$k_a \simeq \begin{cases} C, & \text{1D/3D Berg \& von Hippel} \\ C^2, & \text{Pure 1D search} \end{cases}$$



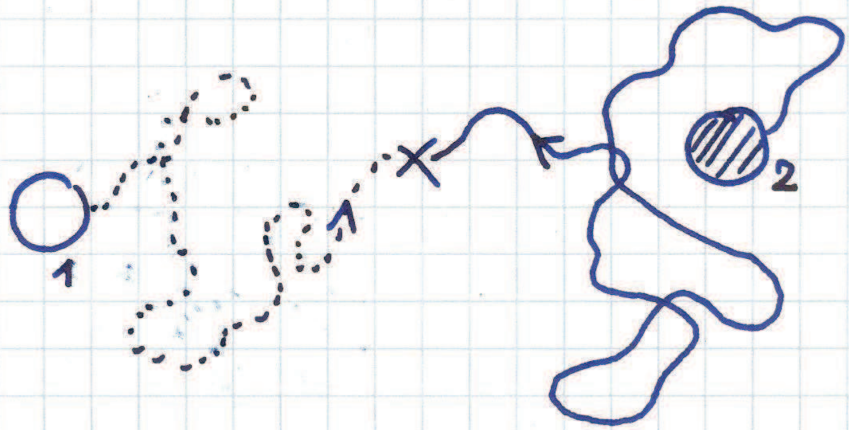


$\Delta = 1.74 \pm 0.35,\ 1.85 \pm 0.24,\ 2.08 \pm 0.39,\ 1.95 \pm 0.17$

YM Wang, RH Austin & EC Cox, PRL (2006); IM Sokolov, RM, K Pant & MC Williams, Biophys J (2005)

Smoluchowski approach to diffusion limited reactions

We consider a two-body reaction. Once the particles meet, they react with infinite rate:



Diffusivities D_1 & D_2 & $\langle x_i^2(t)\rangle = 2D_i t$ Brownian motion

The encounter requires that the relative co-ordinate vanishes: effective relative diffusivity?

$$R^2 = \langle (x_1 - x_2)^2 \rangle = \langle x_1^2 \rangle - \underbrace{2\langle x_1 x_2 \rangle}_{\longrightarrow 0} + \langle x_2^2 \rangle = 2(D_1 + D_2)t$$

$\Rightarrow D_{rel} = D_1 + D_2$

In $d=3$ according to Stokes: $D_i = \frac{k_B T}{6\pi \eta a_i}$

Consider now the volume density $n(\underline{r},t)$ of transcription factors searching for a reaction centre of radius $b = a_1 + a_2$

$$\frac{\partial n}{\partial t} = D_{rel} \frac{1}{r^2} \frac{\partial}{\partial r} r^2 \frac{\partial n}{\partial r}$$ for radial symmetry

Boundary condition: $\lim_{r \to \infty} n = n_{bulk}$; $n|_{r=b} = 0$ absorption

Stationary state:

$$\frac{\partial n}{\partial t} = 0 = D_{rel} \frac{1}{r^2} \frac{\partial}{\partial r} r^2 \frac{\partial n}{\partial r}$$

$$\Rightarrow n_{st}(r) = n_{bulk} \left(1 - \frac{b}{r}\right).$$

Rate constant for binding yields from stationary flux:

$$\underline{\underline{k_a}} = \frac{\dot{j}_{st}}{n_{bulk}} = \frac{1}{n_{bulk}} 4\pi b^2 D_{rel} \left.\frac{\partial n_{st}}{\partial r}\right|_{r=b} = \underline{\underline{4\pi D_{rel} b.}}$$

Berg & von Hippel refine this result (J. Biol. Chem. 264, 675 (1989))

$$k_a = 4\pi \kappa a f \frac{D_{TF} + D_{DNA}}{1000} N_A$$

κ: unitless interaction parameter measuring fraction of surfaces, that are reactive

a: interaction distance in cm

f: dimensionless factor reflecting increase/decrease of diffusional rate due to electrostatic attraction or repulsion of particles

N_A: Avogadro's number

1000: factor to normalize units of k_a to $M^{-1}\,sec^{-1}$, $[D_i] = cm^2/sec$

$a_{TF} \approx 40\,\text{Å}$, $a_{DNA\ cylinder} \approx 10\,\text{Å}$ $\sim$ $a \approx 5 \times 10^{-8}\,cm$

f estimated to ≈ 1 (TF & DNA carry negative charge but $\exists$ salt and TF has positive binding domain)

$\kappa \approx 0.05$ ($\approx 1/5$ of TF surface represents active site, $\approx 1/4$ of cylindrical DNA surface interacts with TF)

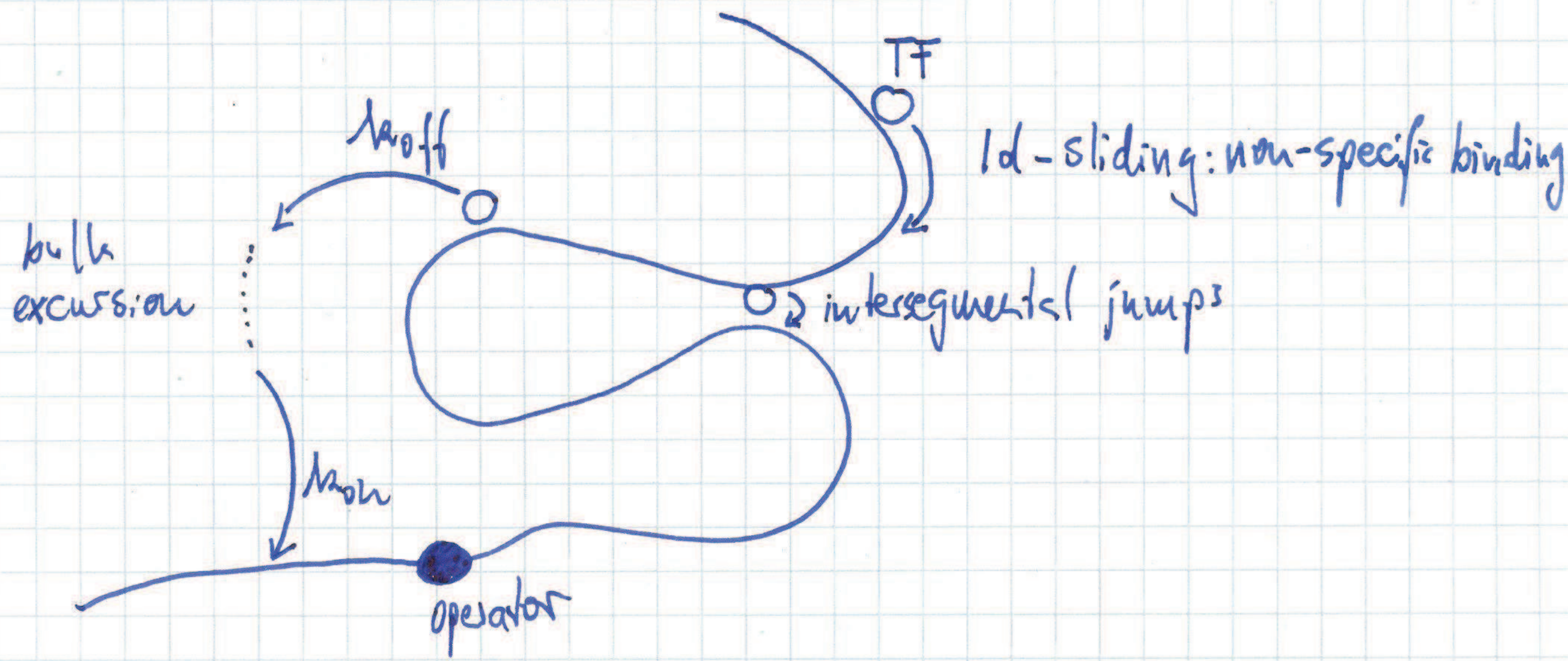
$\Rightarrow$ $\underline{\underline{k_a \approx 10^{8}\ M^{-1}\,sec^{-1}.}}$

Measurements: $k_a \approx 5 \times 10^{10}\ M^{-1}\,sec^{-1}$ $\lightning$

(Riggs et al, J. Mol. Biol. 53, 401 (1970)
Winter et al, Biochem. 20, 6961 (1981))

Adam & Delbrück (1968): idea of <u>facilitated diffusion</u>

Richter & Eigen (1974): first mathematical description



Pólya problem: 1d diffusion is recurrent, 3d diffusion is transient

advantage of sliding: if operator in vicinity, it will be located with high fidelity advantage of bulk excursions: they decorrelate the search, i.e., there $\exists$ a high probability, that the TF lands on a previously unexplored part of the DNA

disadvantage sliding: oversampling $\Rightarrow$ needs to be limited by k_{off}

disadvantage bulk excursion: location of small target in 3d difficult

$\Rightarrow$ <u>optimisation of TF-search by facilitated diffusion!</u>

$\exists$ many different approaches to calculate k_{ea} for this Berg-von Hippel model

We use the diffusion eq. for the 1d line density of TF on the DNA:

$$\frac{\partial n(x,t)}{\partial t} = \left(D_{1d}\frac{\partial^2}{\partial x^2} - k_{off}\right) n(x,t) - j(t)\,\delta(x) + G(x,t)$$

$$+ k_{off}\int_{-\infty}^{\infty} dx' \int_0^t dt'\, W_{bulk}(x-x', t-t')\, n(x', t').$$

x: "chemical co-ordinate" along DNA

k_{off}: unbinding rate from non-specifically bound state

D_{1d}: 1d diffusion constant along DNA

$j(t)$: flux into the target, represented by δ-sink: $n(x=0,t)=0$

G: "virgin" flux of TFs from bulk that have not previously bound to DNA

W_{bulk}: 3d diffusion kernel for bulk excursion from x' to x during time span $t-t'$

In steady state the flux defines the association rate: $j_{st} = k_{1d} \times n_{st}$

$W_{bulk}(x,t)$ is the solution (Green's fct.) of the diffusion eq.

From above dynamic eq:

$$\frac{1}{k_{1d}} = \int_{-\infty}^{\infty} \frac{dq}{2\pi} \frac{1}{D_{1d} q^2 + k_{off}\left[1-\lambda_{bulk}(q)\right]}$$

$$\lambda_{bulk}(q) = \int_0^{\infty} dt \int_{-\infty}^{\infty} dx \; e^{iqx} \, W_{bulk}(x,t)$$

Finally $k_{on} = \dfrac{j_{st}}{n_{bulk}}$

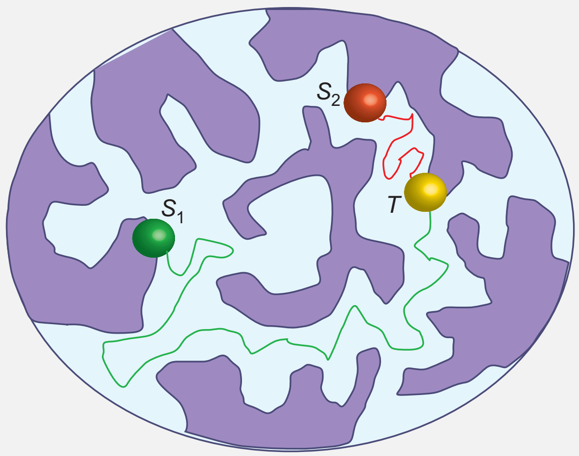
For a cylindrical DNA:

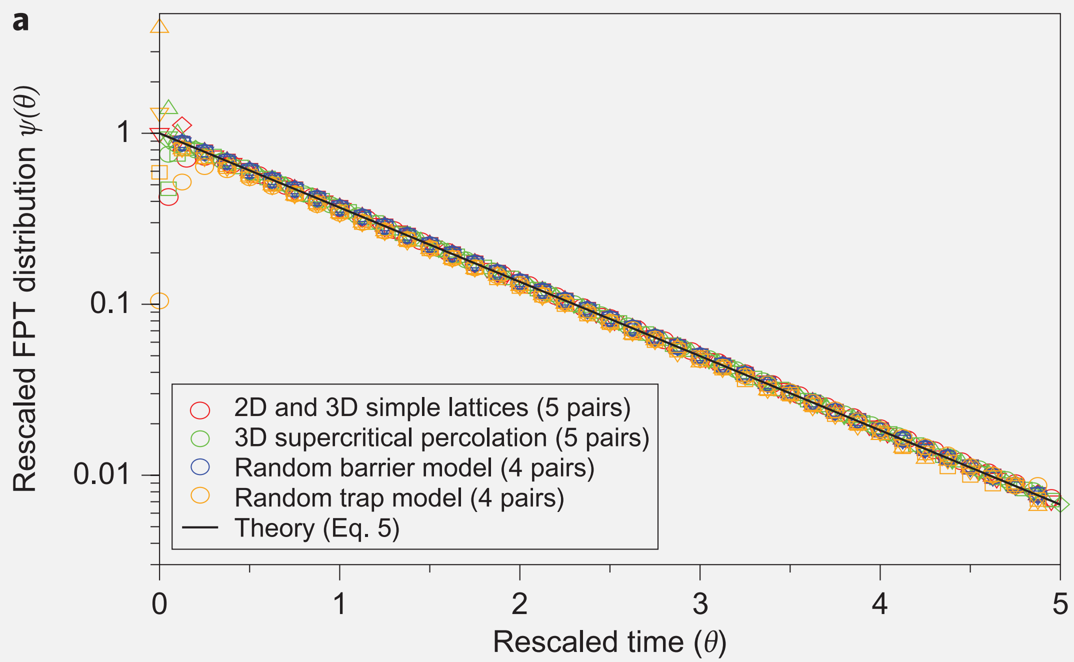
$$k_{on} \sim 4\pi D_{3d}\, l_{sl}^{eff} \cdot \frac{1}{\left[\ln\left(l_{sl}^{eff}/r_{int}\right)\right]^{1/2}}$$

$$\underbrace{l_{sl}^{eff} = \sqrt{\frac{k_{on}}{2\pi D_{3d}}}\; l_{sl}} \quad \therefore \quad l_{sl} = \sqrt{D_{1d}/k_{off}} \text{ sliding length (antenna)}$$

effective sliding length: l_{sl}
corrected by immediate rebinding
events

Finite domain: (global) MFPT in (non-)compact domains



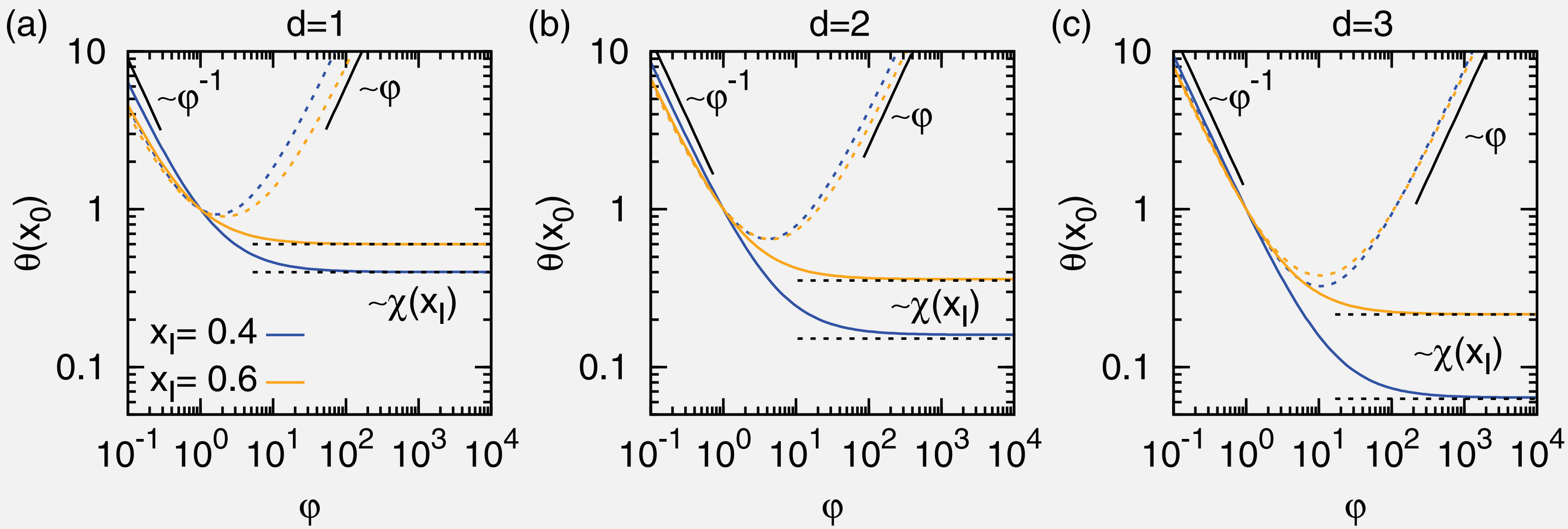


Key results: distance r from initial point of release to target matters in "compact systems" (i.e., when $d_w > d_f$)

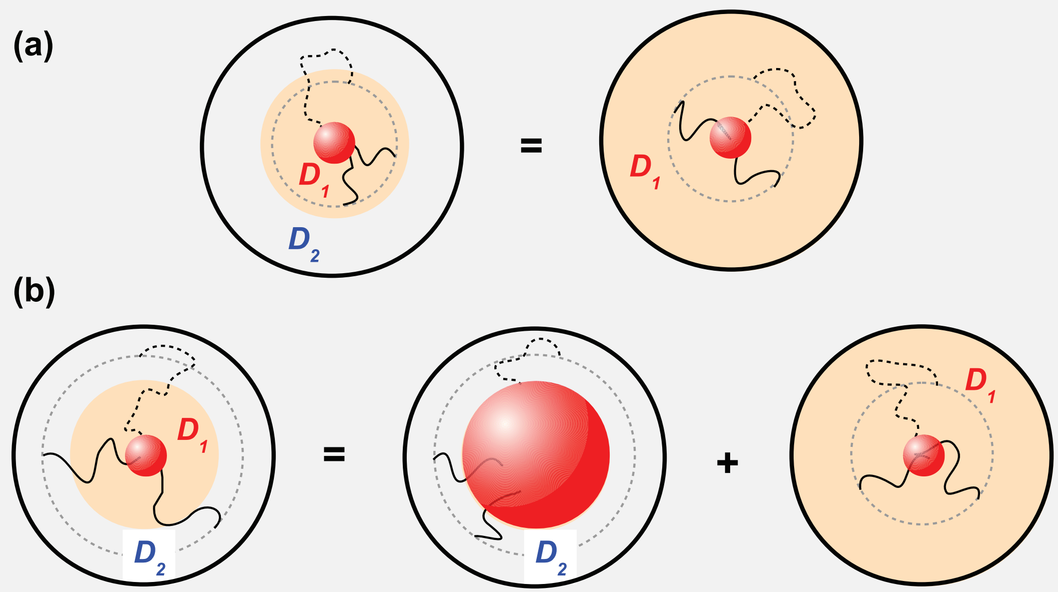
Fluctuations of the FPT for system size R: $\propto (R/r)^{d_w - d_f}$ become large for $r \ll R$ when $d_w > d_f$ (i.e., in compact case).

O Bénichou, C Chevalier, J Klafter, B Meyer & Voituriez, Nature Chem (2010)

Optimisation & universality of FPT in quenched media

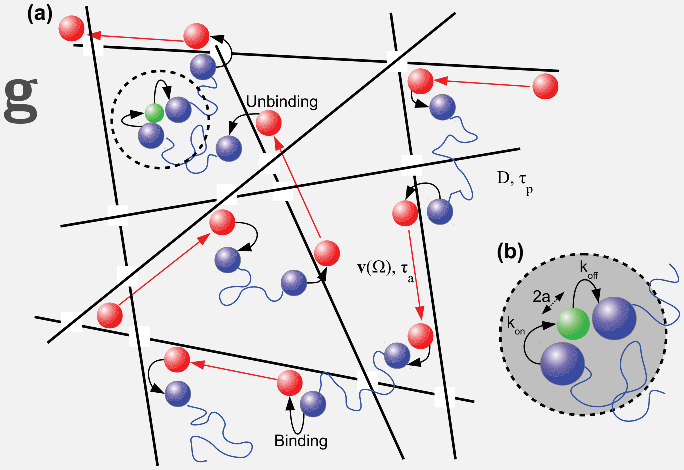


MFPT versus $\varphi = D_1/D_2$ for initial radii $x_0 = 0.3$ (dashed) & $x_0 = 0.8$ (full)

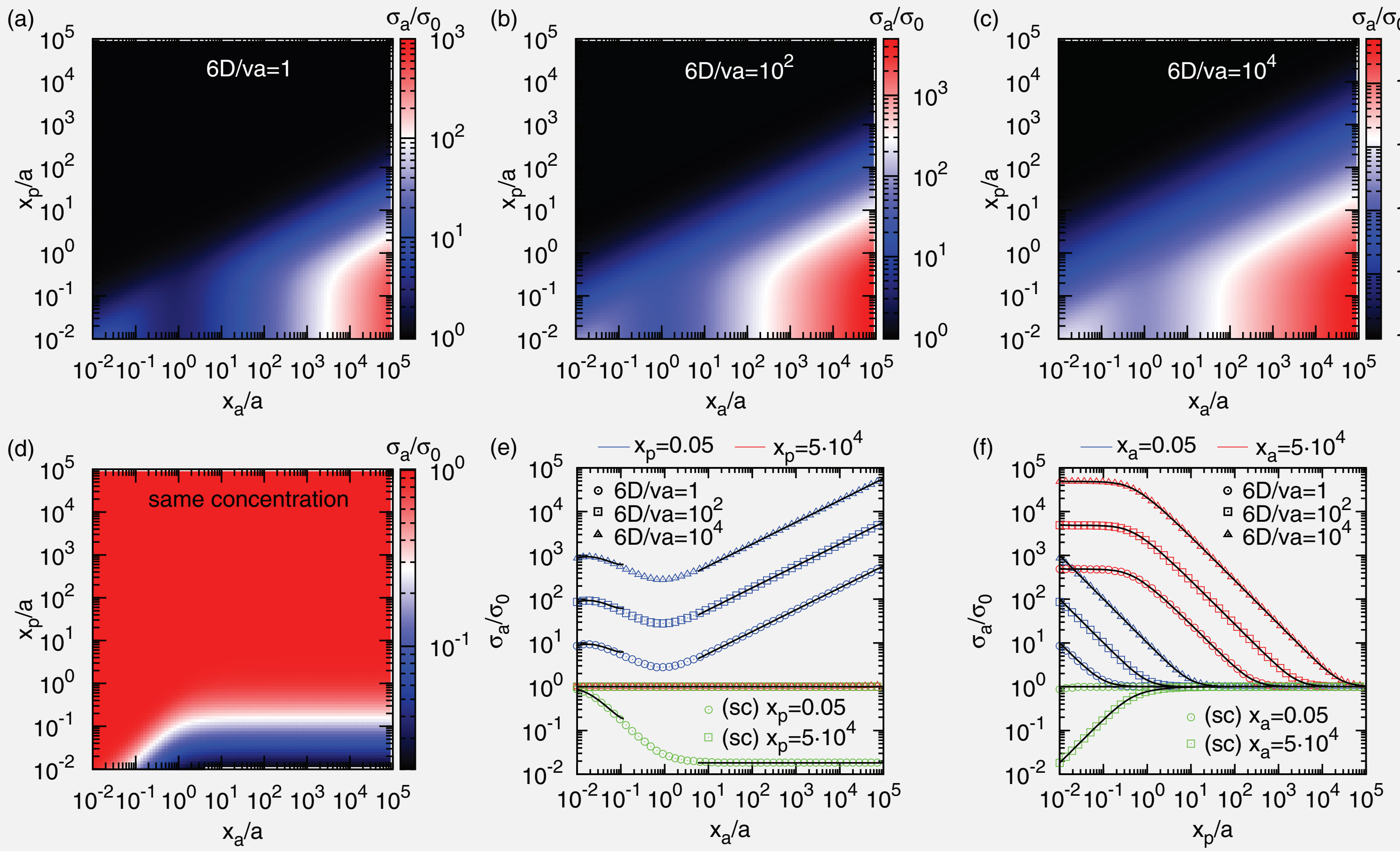


Direct trajectories dominate ↷ addition theorem for MFPT

Speed & precision in active signalling

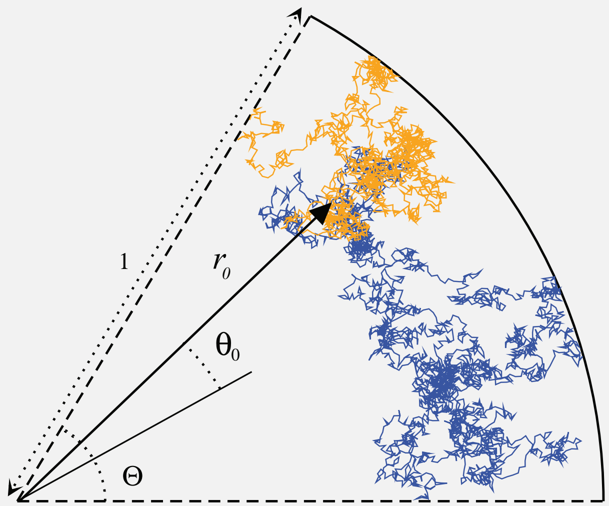


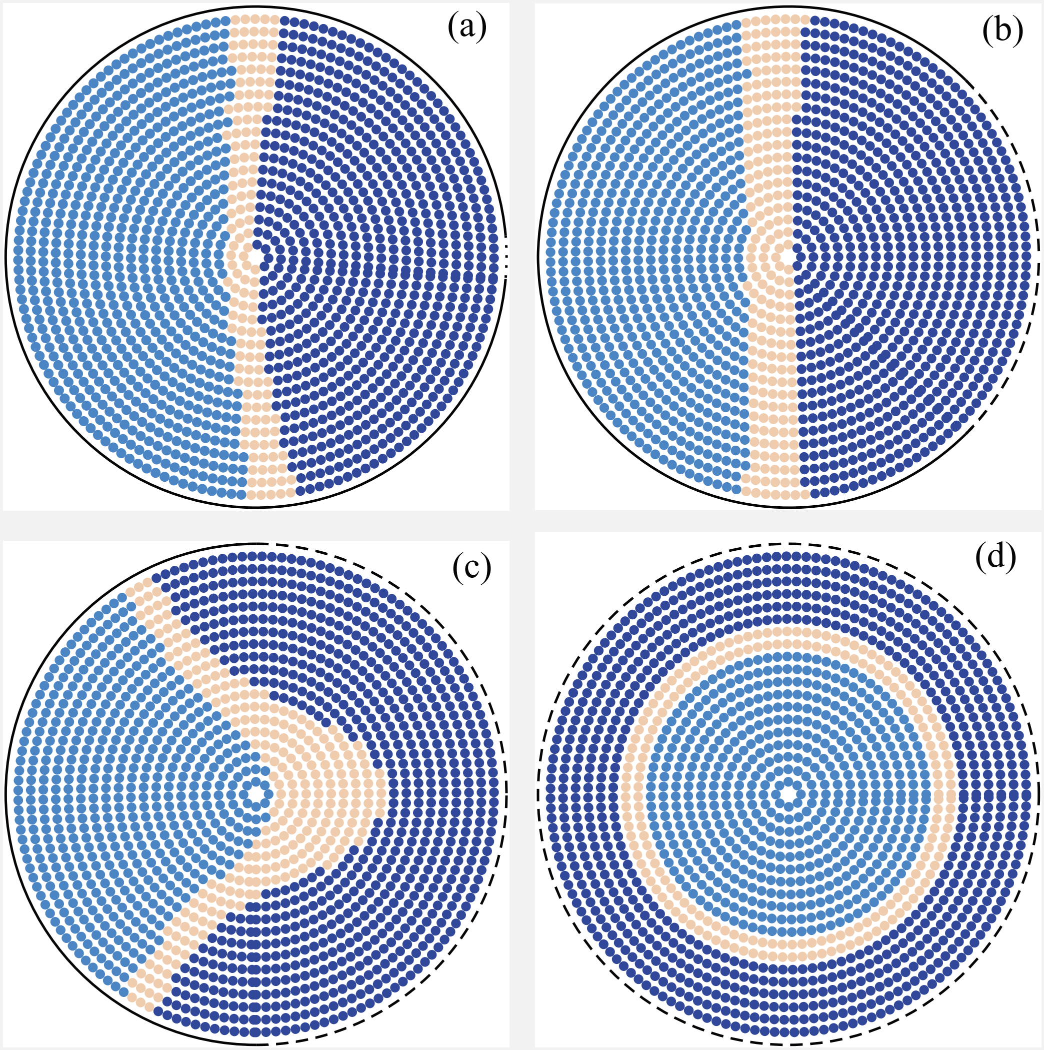
Exact results for MFPT & precision $\sigma_a = [\overline{\delta c_p^2}/\langle c_p \rangle]^{-1/2}$ of concentration fluctuations @ receptor site compared to thermal diffusion $\sigma_0 = [\pi D a c_{\text{tot}} \tau_m]^{-1/2}$

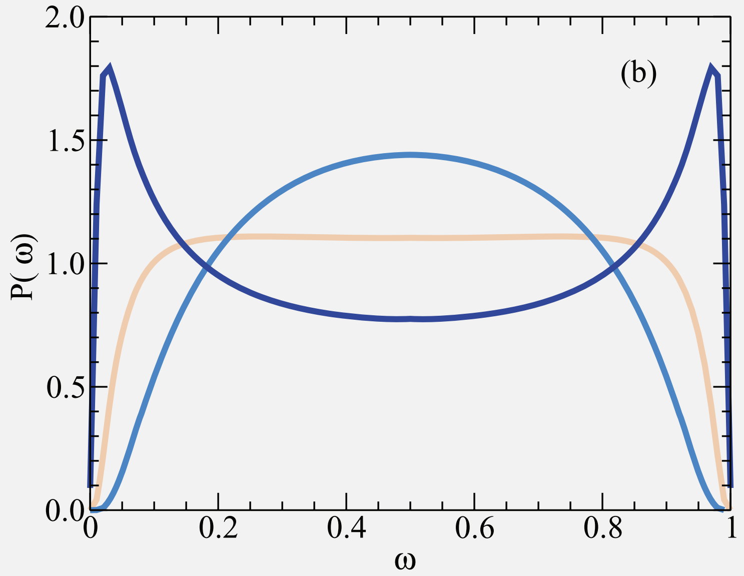


A Godec & RM, PRE (2015)

First-past-the-post: when the MFPT is meaningful

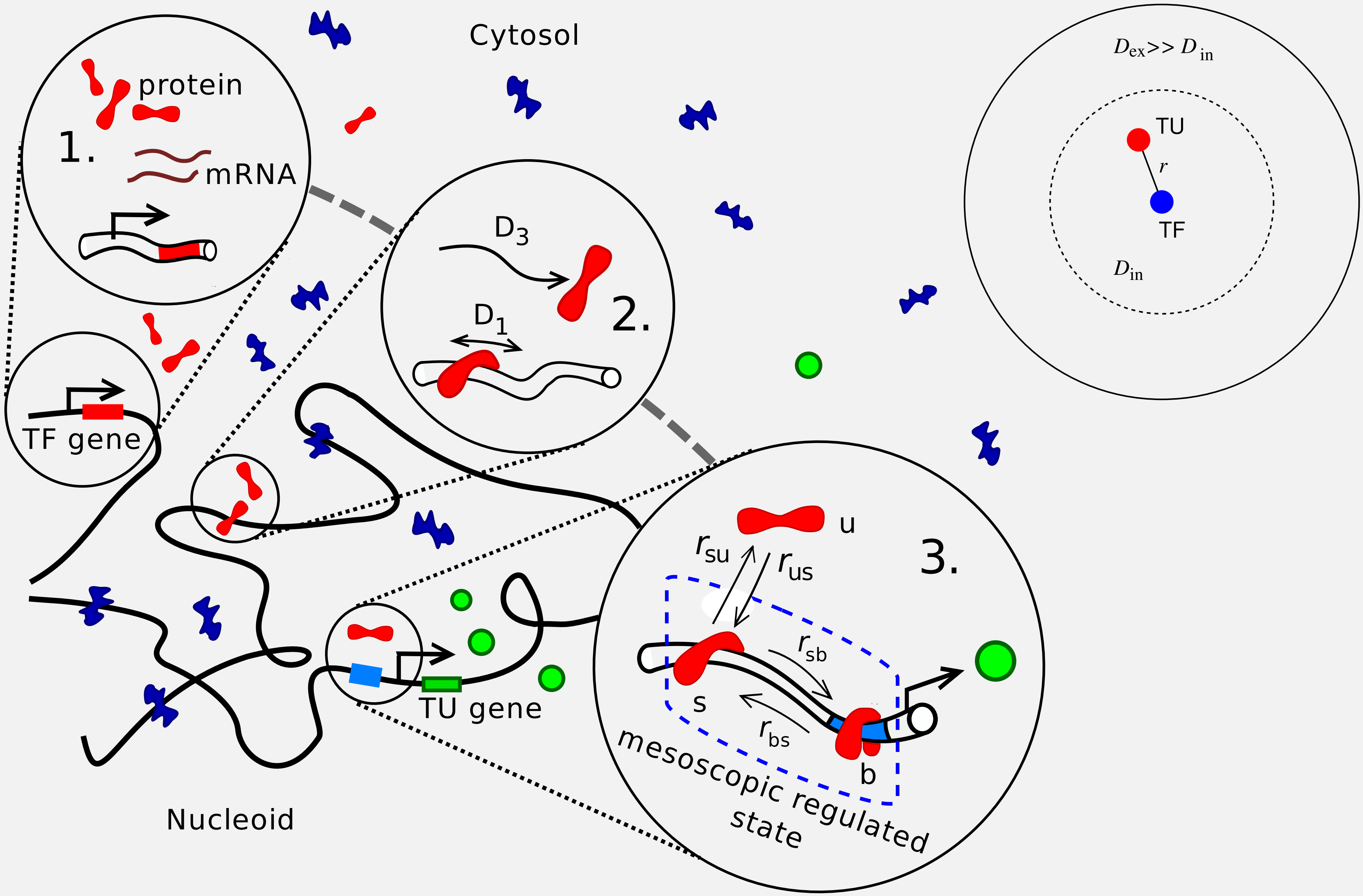




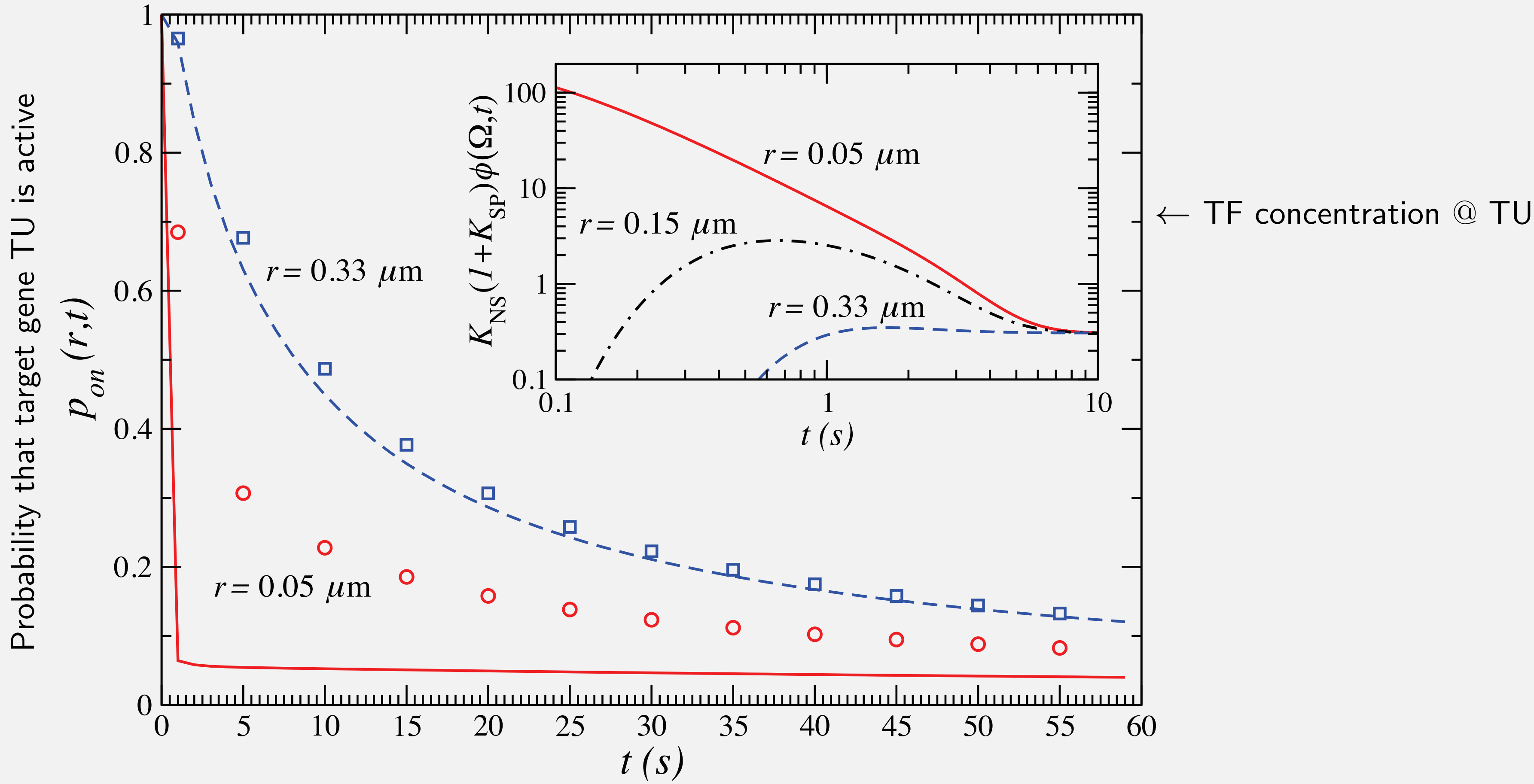


T Mattos, C Mejía-Monasterio, RM & G Oshanin, PRE (2012)

Transient intracellular signalling is geometry-controlled



Result 1: transient response to repression



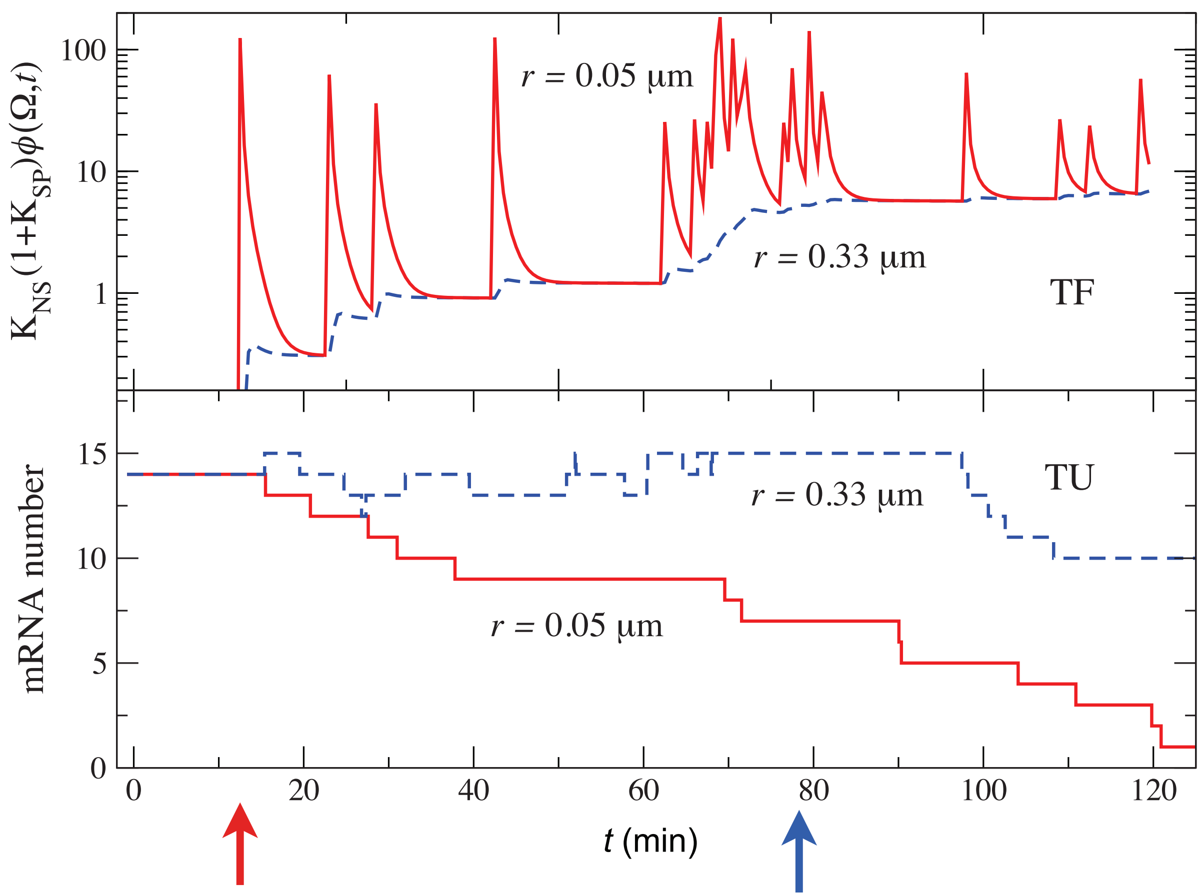
Mean field approximation (full & dashed lines):

$$p_{on}(r,t) = \left\langle \frac{1 + K_{\mathrm{NS}}\rho_{\mathrm{TF}}(r,t)}{1 + \tilde{K}\rho_{\mathrm{TF}}(r,t)} \right\rangle \approx \frac{1 + K_{\mathrm{NS}}\langle\rho_{\mathrm{TF}}(r,t)\rangle}{1 + \tilde{K}\langle\rho_{\mathrm{TF}}(r,t)\rangle}$$

O Pulkkinen & RM, PRL (2013)

Result 2: time dependence of gene response: bursts!

Sample paths from MC simulations:



TF density at the target operator

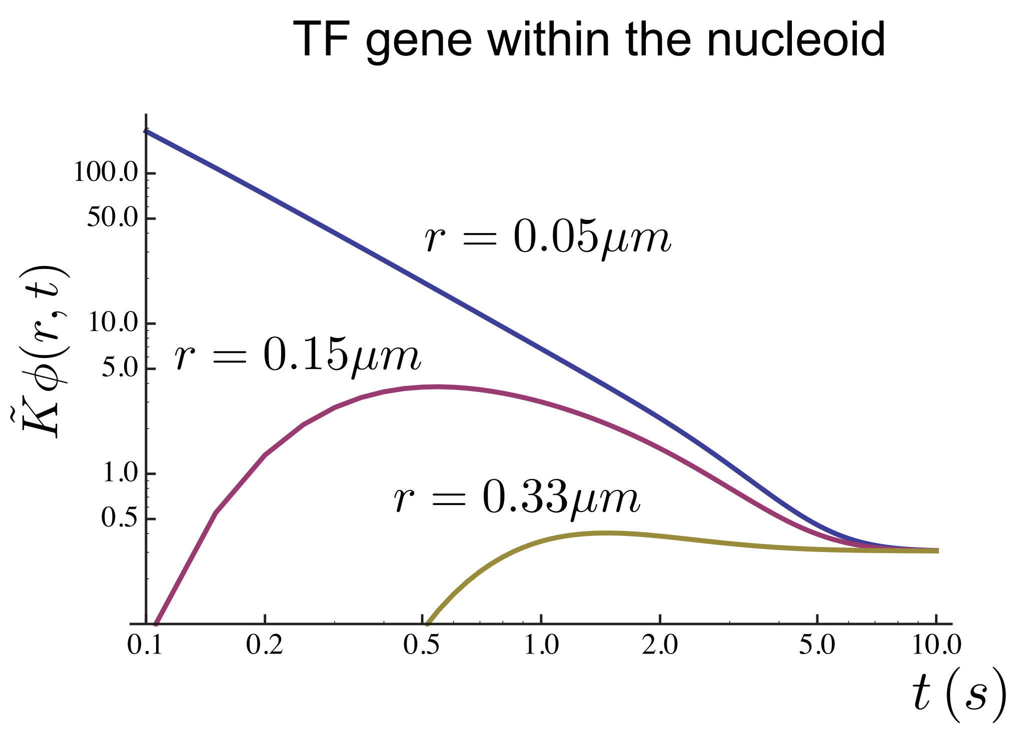
Target expression

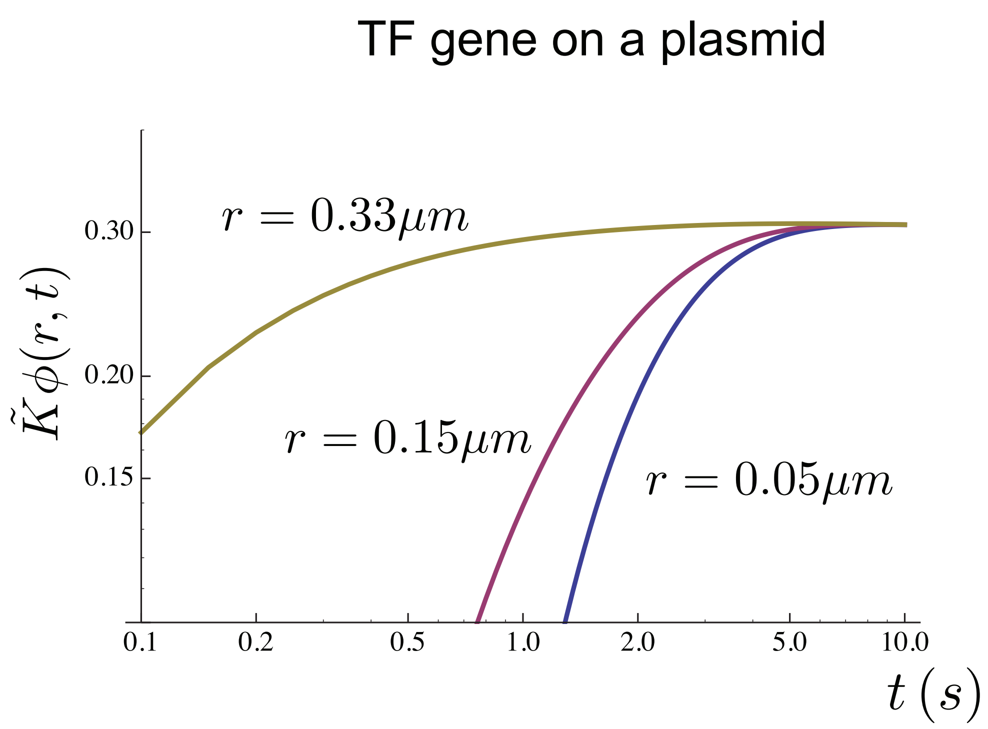
First repressor binding at r = 0.05 μm

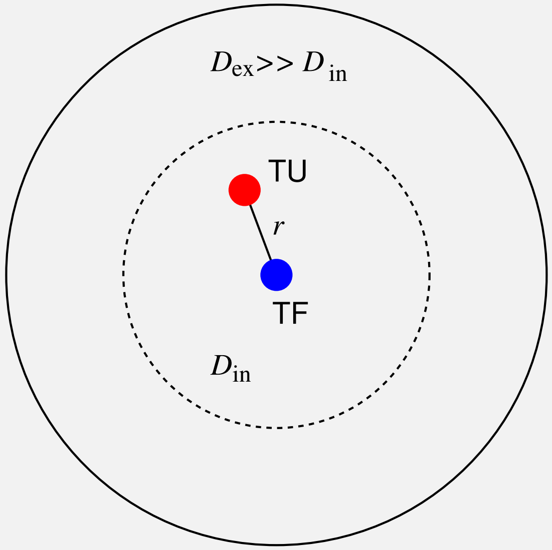
First repressor binding at r = 0.33 μm

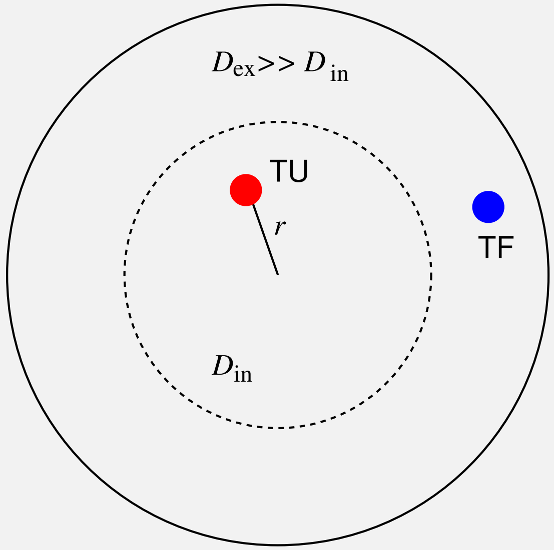
O Pulkkinen & RM, PRL (2013)

Result 3: gene location matters



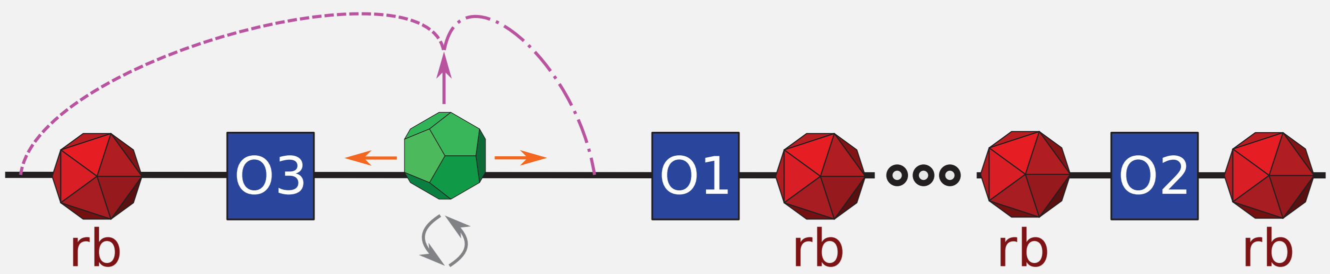


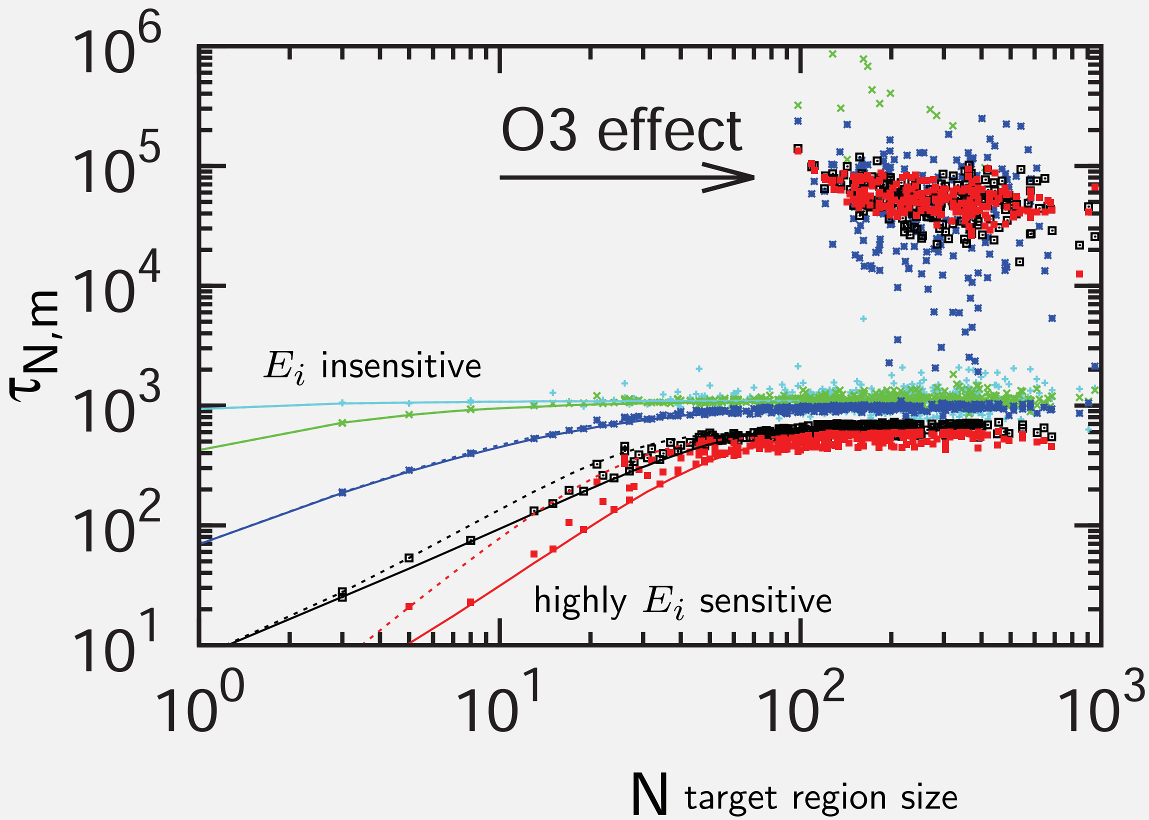




O Pulkkinen & RM, PRL (2013)

Sequence (binding energy) effects on target search time

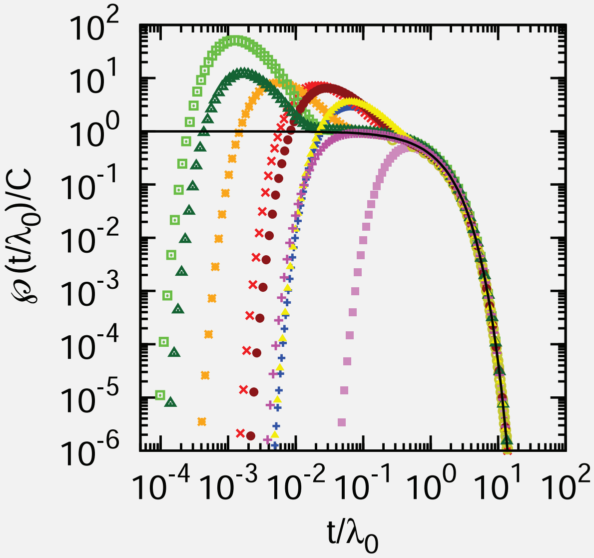


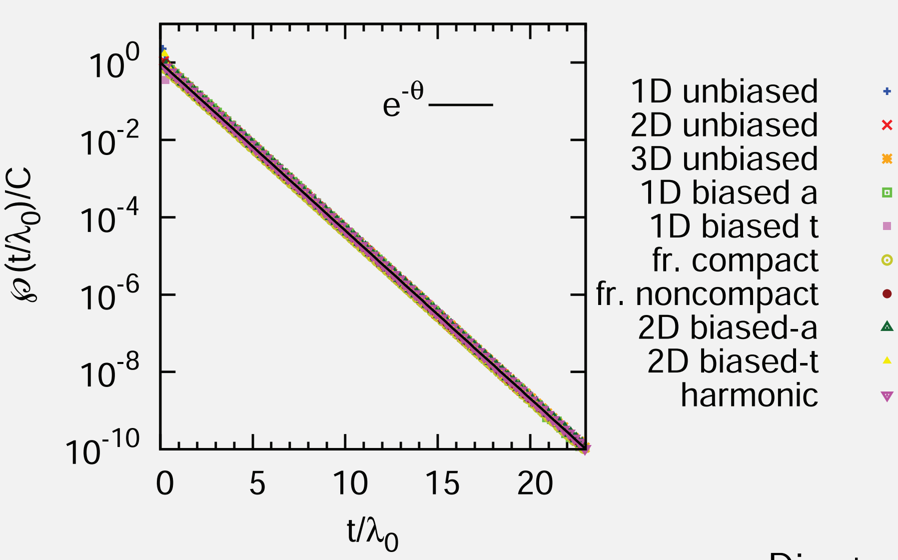


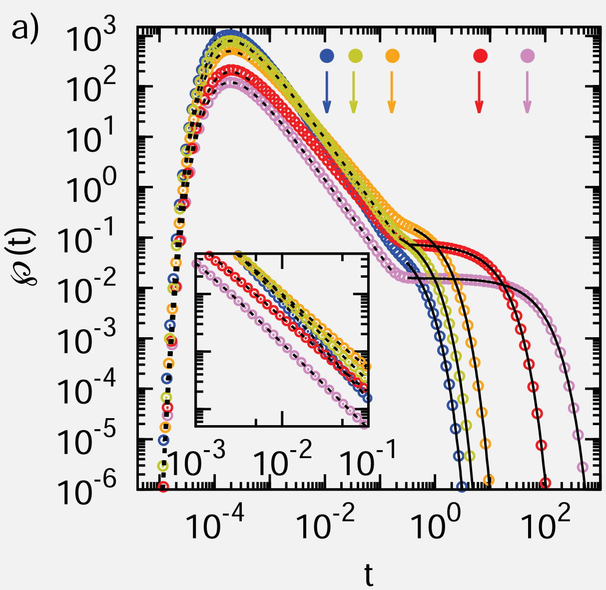
full line: centred target

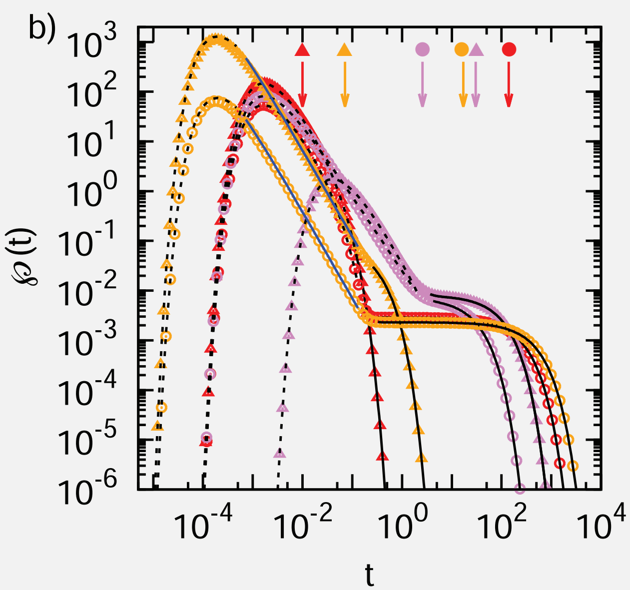
dashed line: target @ boundary

Universal proximity effect in few encounter limit

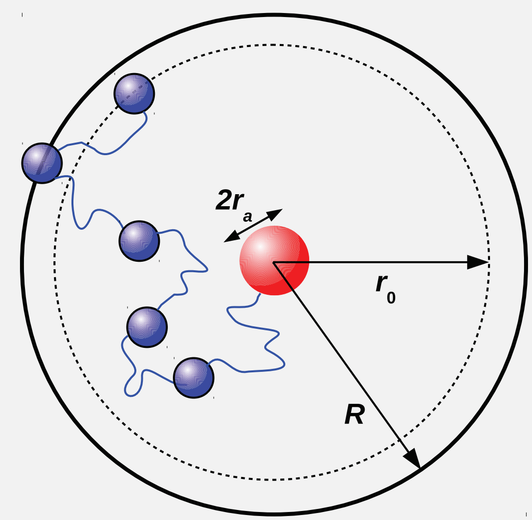






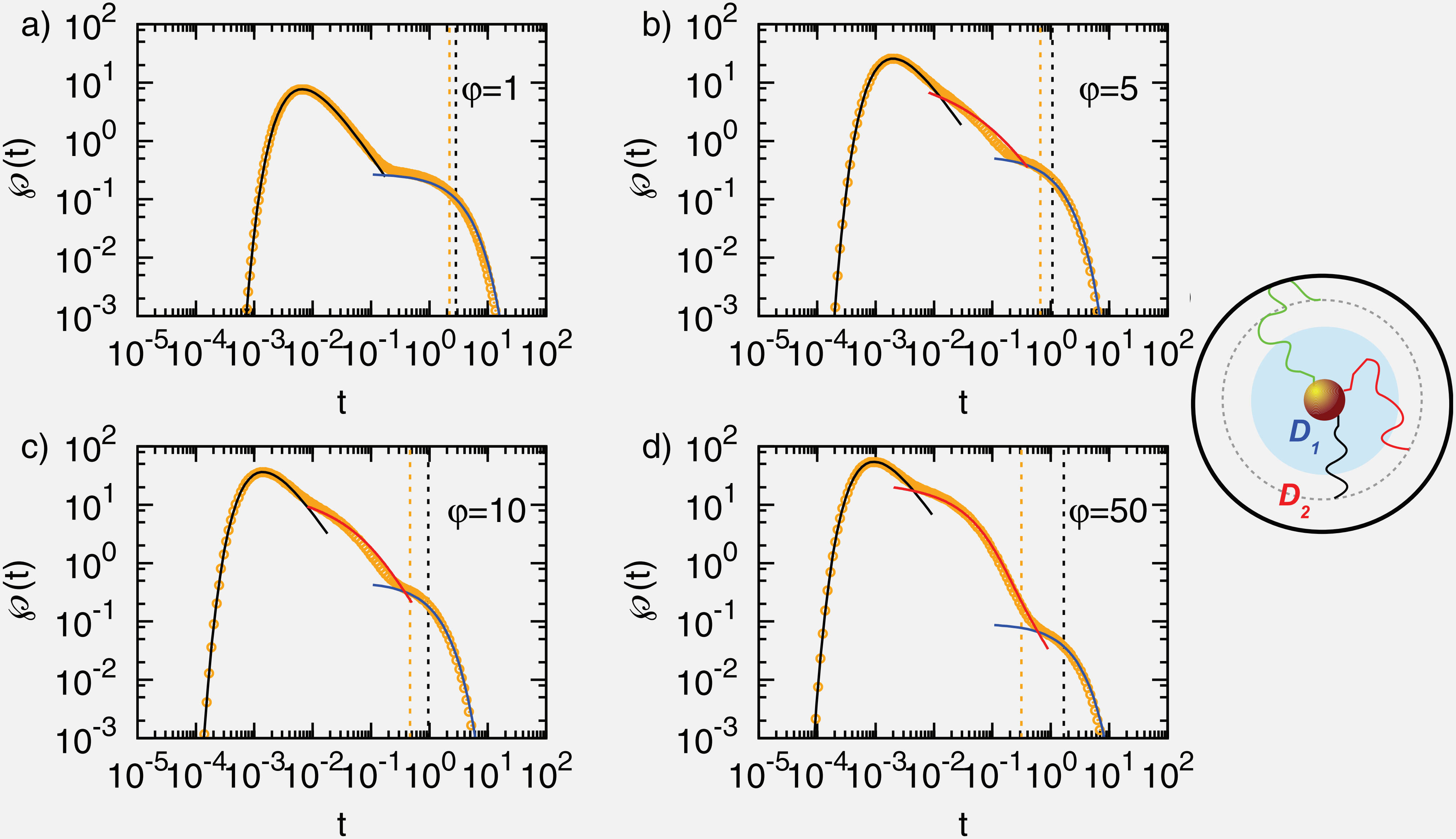


Direct vs indirect trajs:



A Godec & RM, PRX (2016); Sci Rep (2016)

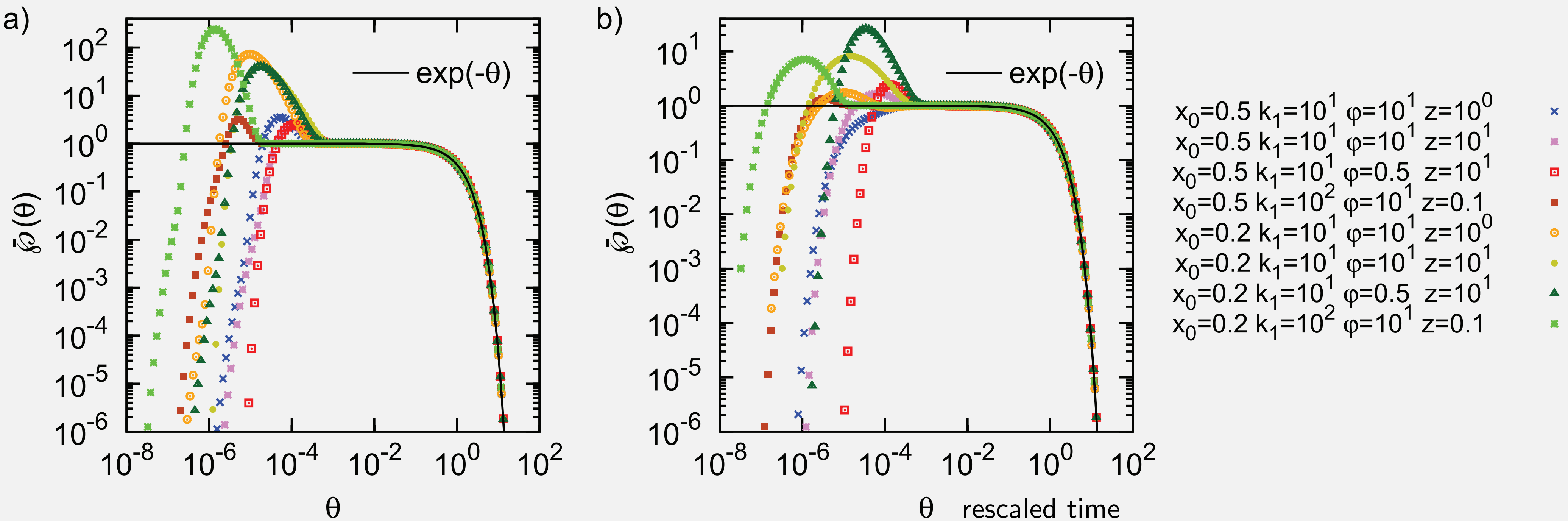
Emergence of a new time scale in heterogeneous diffusion

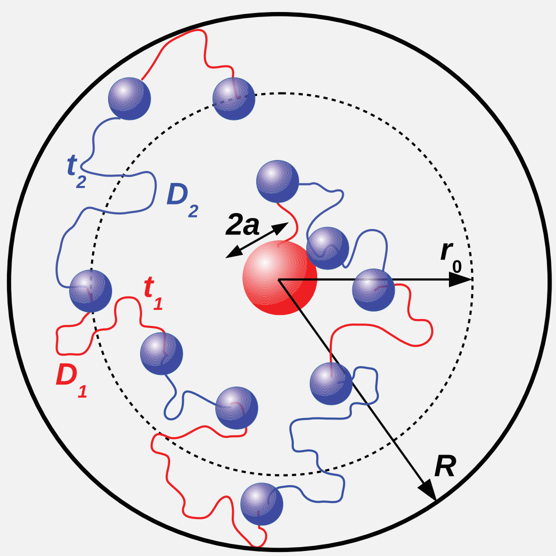


Dashed lines: MFPT from x_0 (orange) & outer boundary $x = 1$ (black); $\varphi = D_1/D_2$

A Godec & RM, Sci Rep (2016)

First-past-the-post for 2-channel diffusion



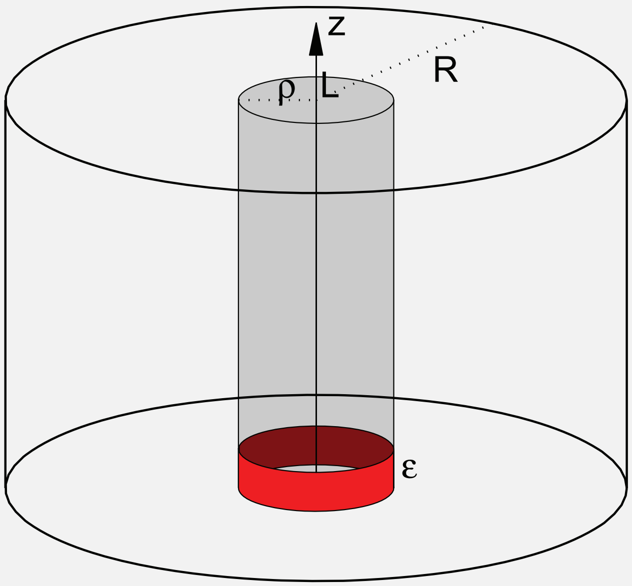


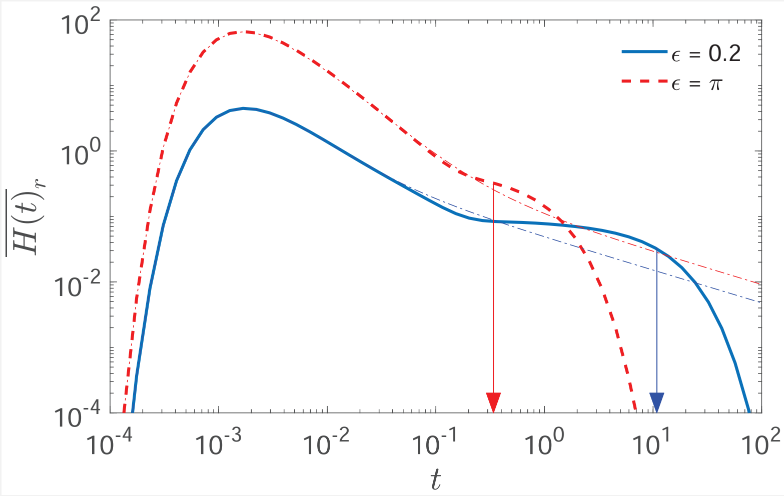
Search mode /w D_1

& recognition mode /w D_2

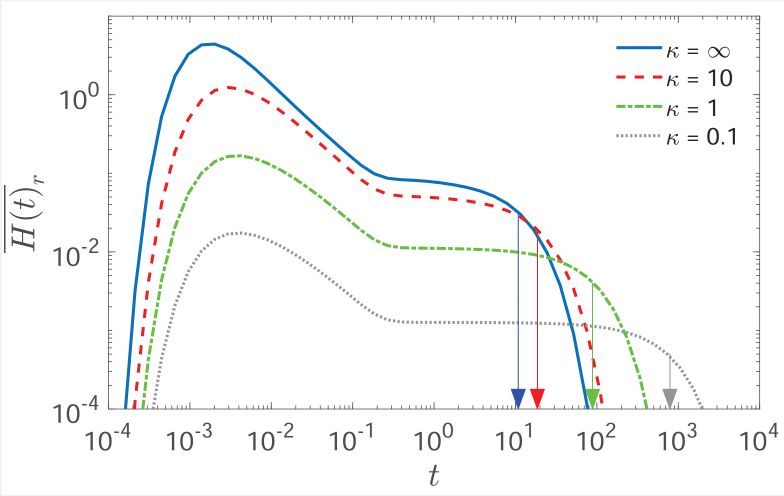
A Godec & RM, JPA (2017)

Few-encounter effect in cylindrical domain /w finite reactivity





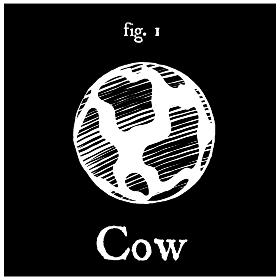
perfect reactivity $\kappa = \infty$



target size $\epsilon = 0.2$

D Grebenkov, RM & G Oshanin, NJP (2017)

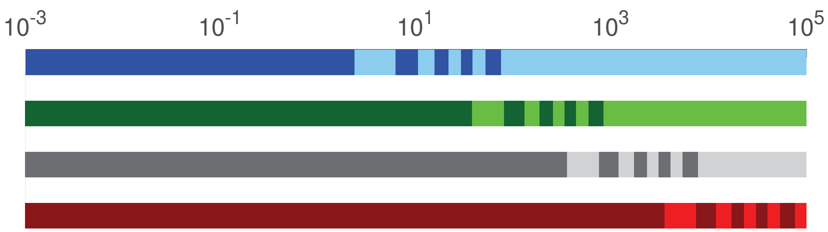
Strongly defocused (fluctuating) reaction times

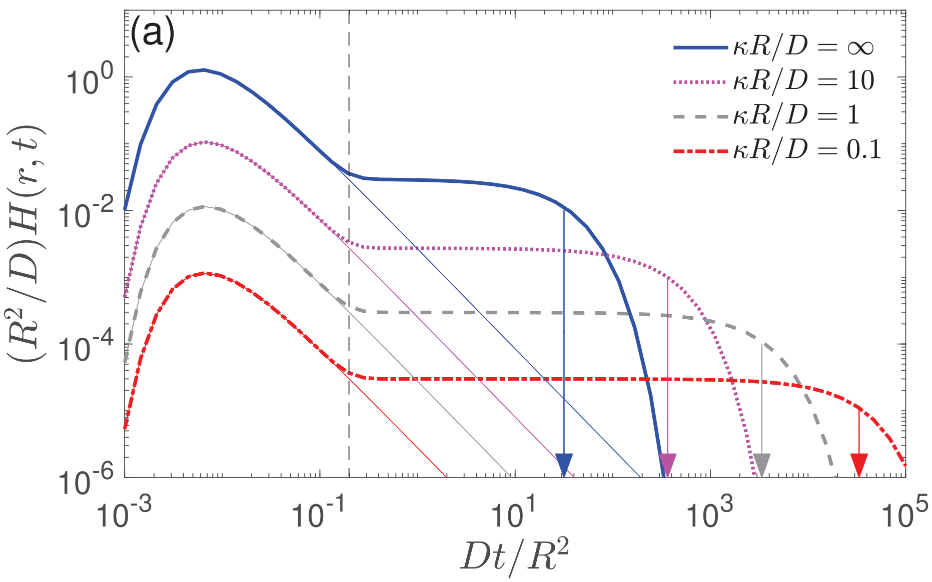


Geometry control: direct trajectories independent of outer boundary

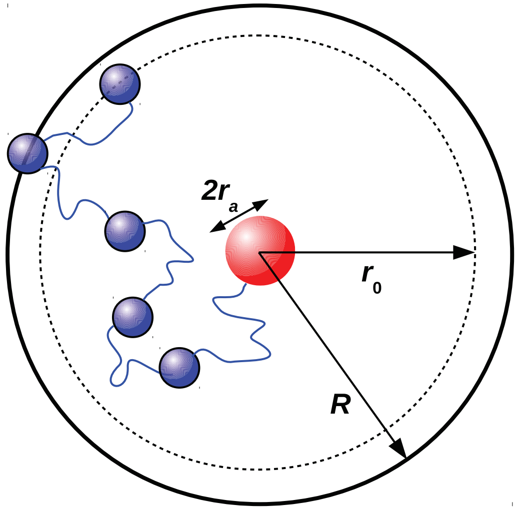
Reaction control: finite reactivity requires multiple collisions

Full first passage time density:





Direct vs indirect trajectories:



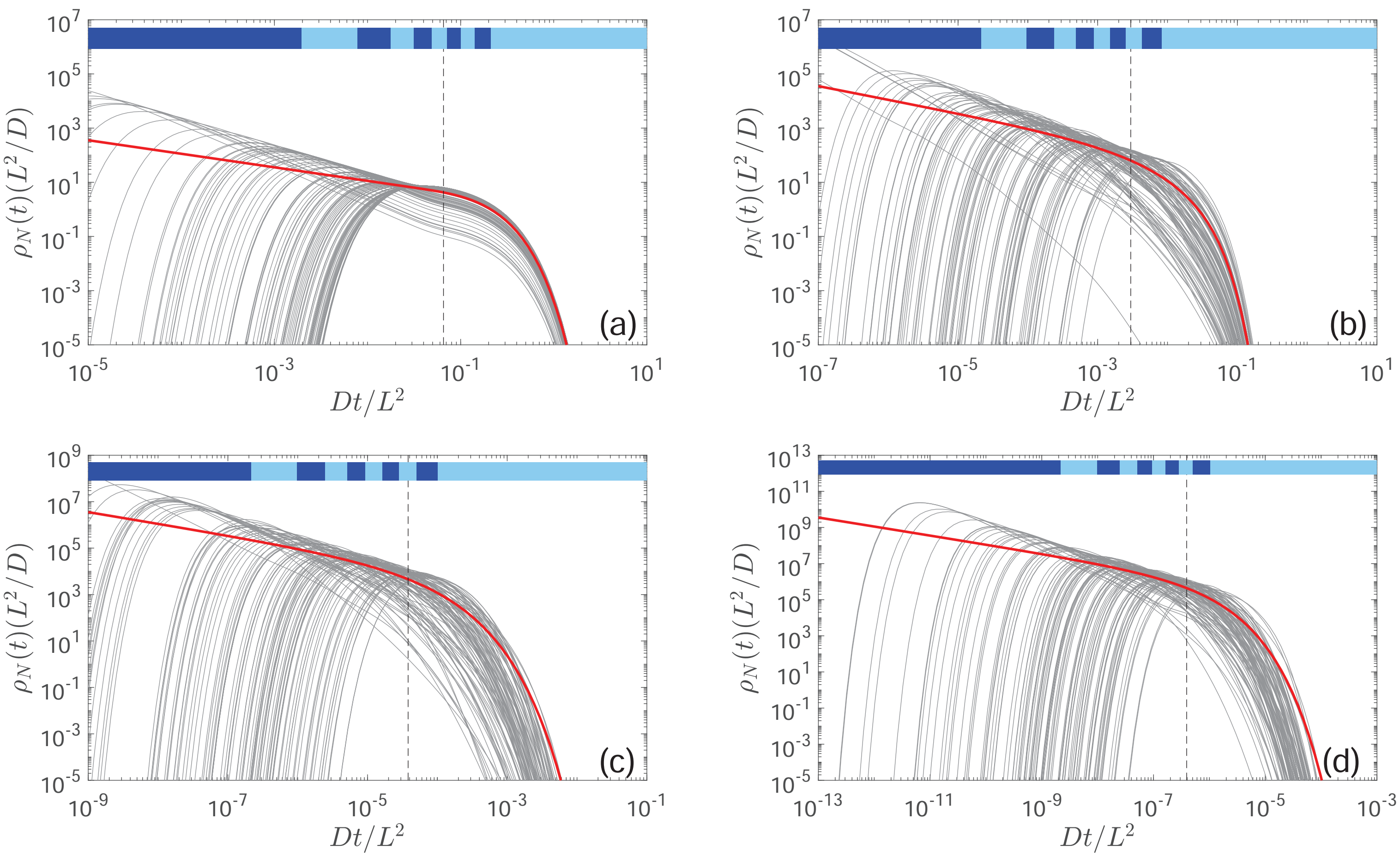
$$\langle t\rangle = \frac{(r_0-r_a)(2R^3-r_0r_a[r_0+r_a])}{6Dr_0r_a} + \frac{R^3-r_a^3}{3\kappa r_a}$$

D Grebenkov, RM & G Oshanin, Comm Chem (2019), PCCP (2018); A Godec & RM, PRX (2016), Sci Rep (2016)

Reaction/search speedup for N "molecules" in parallel

Fixed starting point: fastest FPT $\langle t \rangle \simeq 1/\ln N$

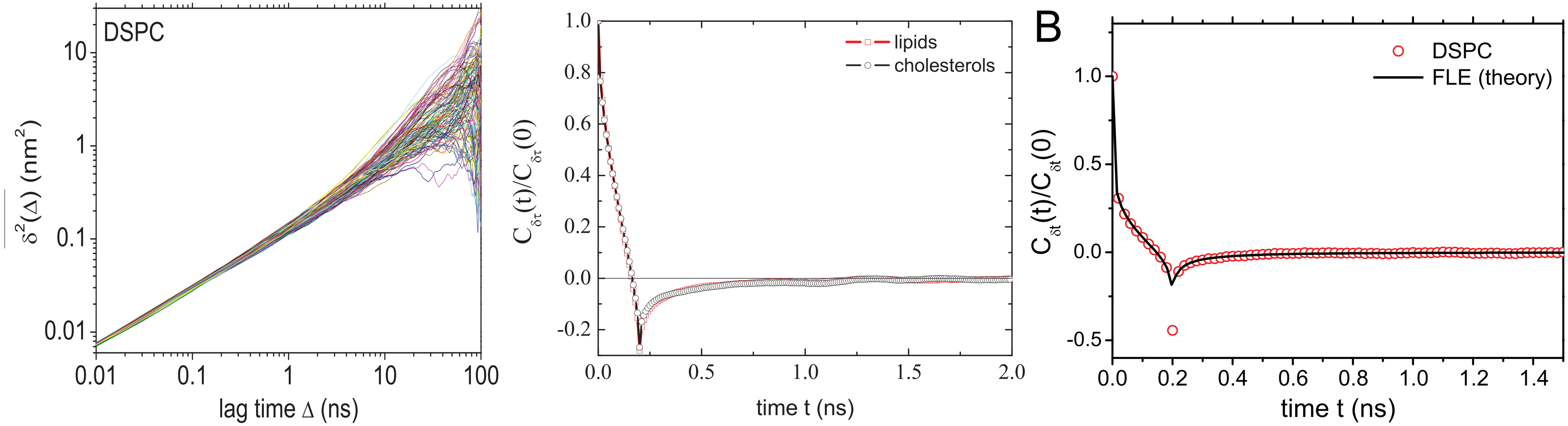
Uniformly distributed initial conditions: $\langle t \rangle \simeq \begin{cases} 1/N^2, & \text{perfect reactivity} \\ 1/N, & \text{partial reactivity} \end{cases}$



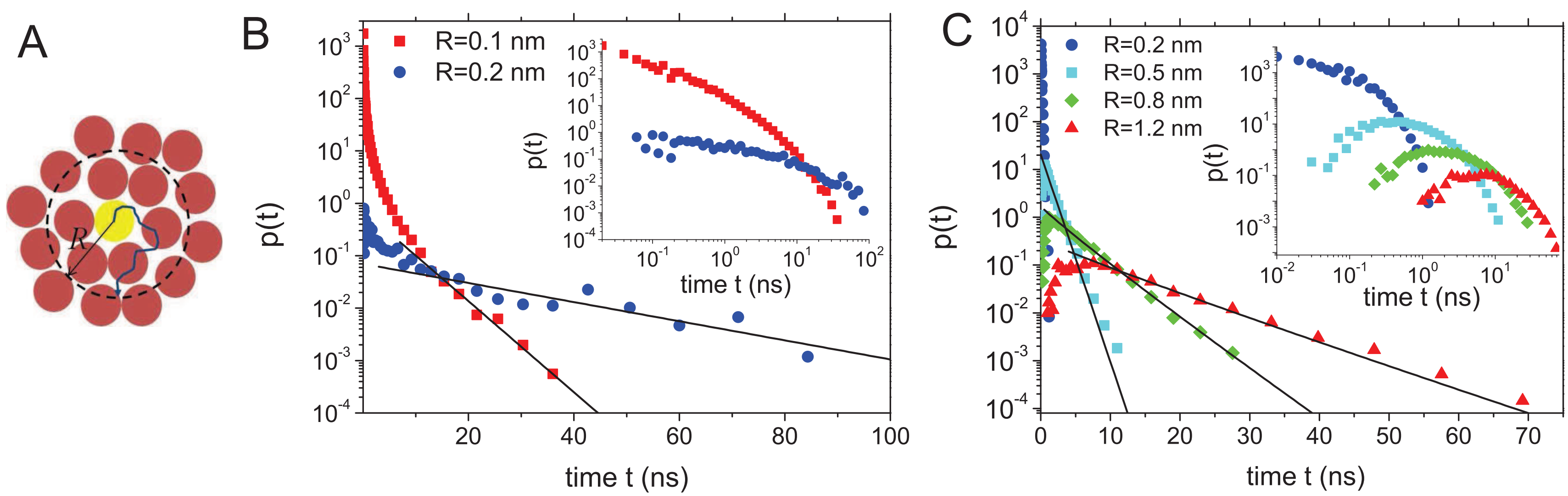
Grey lines: 100 random initial positions

D Grebenkov, RM & G Oshanin, NJP (2020)

Reproducible TA MSD & antipersistent correlations



Rattling dynamics: exptl first passage PDF ↷ FLE motion



D Grebenkov, RM & G Oshanin, NJP (2020)

First passage statistic of fractional Brownian motion

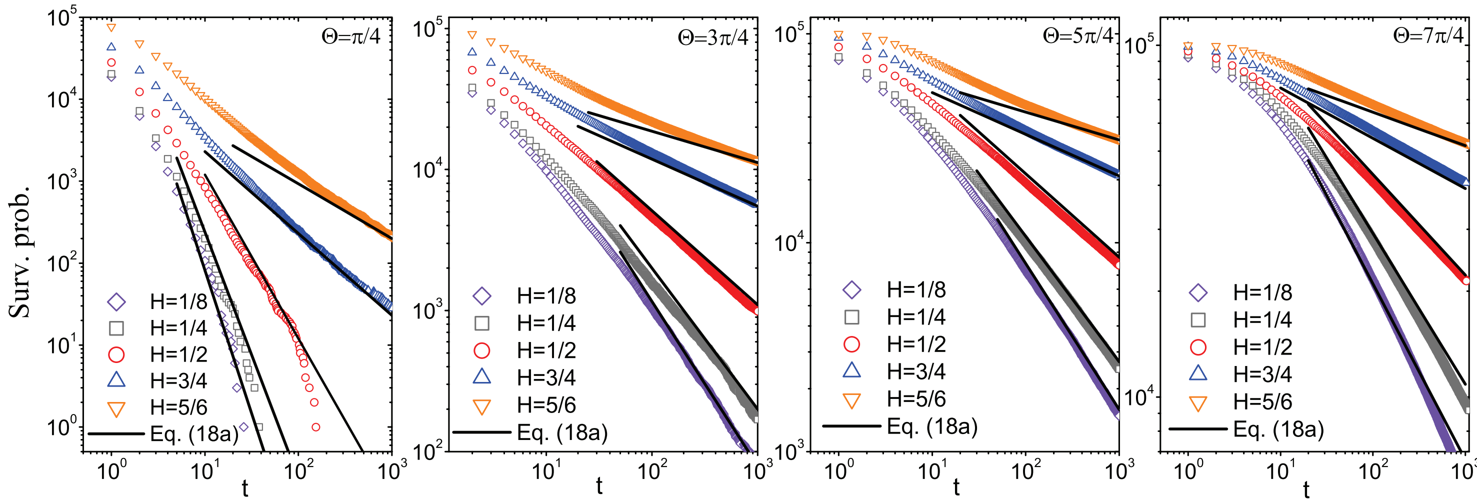
Naïve solution using the method of images:

$$P(x,t) = \frac{1}{\sqrt{4\pi K_\alpha t^\alpha}} \exp\left(-\frac{x^2}{4K_\alpha t^\alpha}\right) \quad \curvearrowright \quad \wp(t) \simeq t^{-1-\alpha/2}$$

Contradicts scaling argument (Ding & Wang) and Molchan's analytical result:

$$\wp(t) \simeq t^{\alpha/2-2}$$

Conjecture for wedge domain with opening angle Θ: $\wp(t) \simeq t^{\pi(\alpha-2)/(2\Theta)-1}$

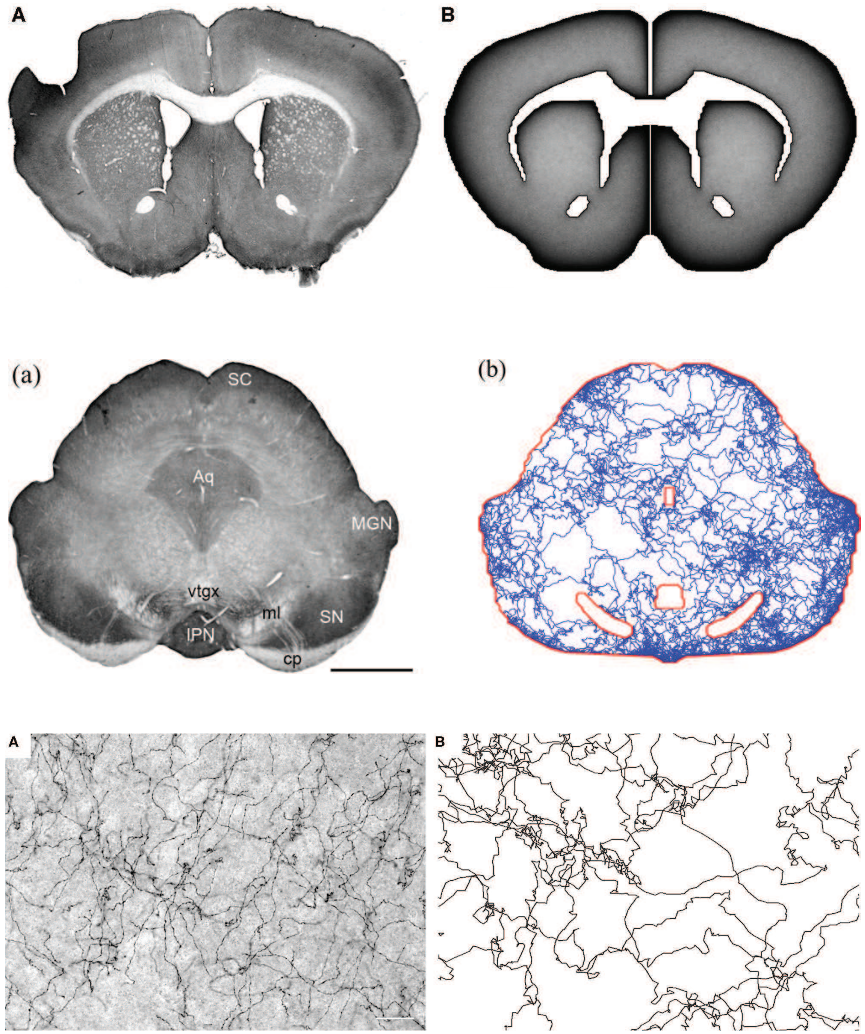


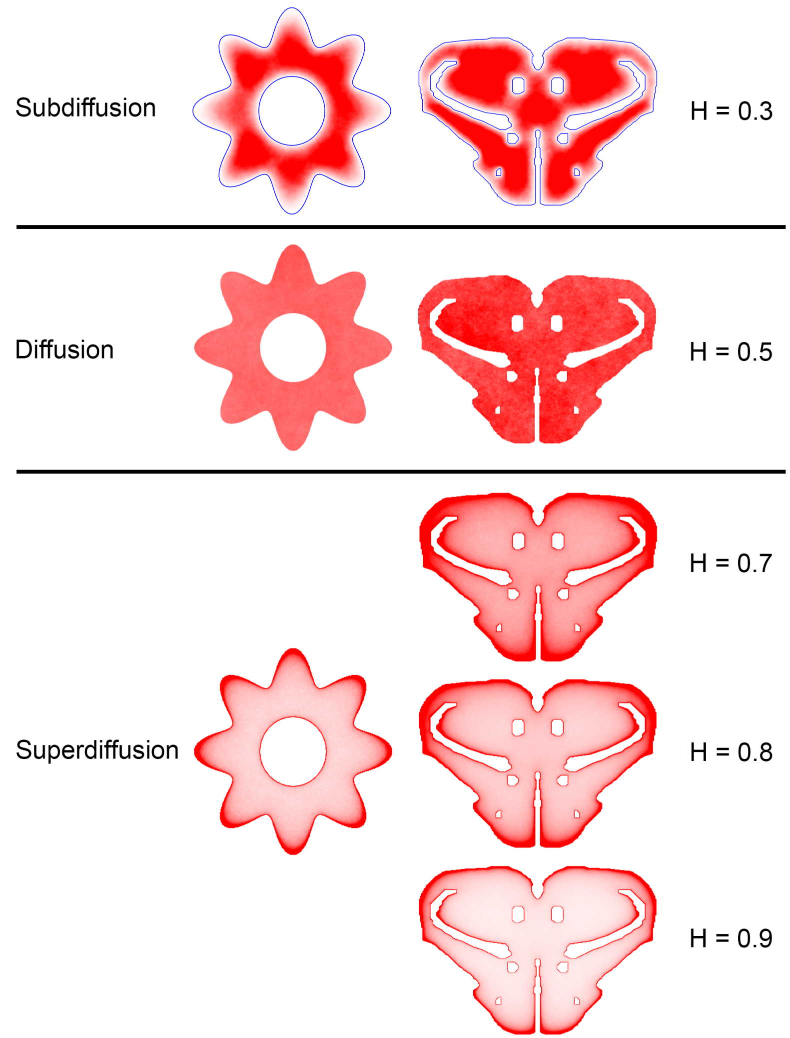
JH Jeon, AV Chechkin & RM, EPL (2011); GM Molchane, Comm Math Phys (1999); M Ding & W Yang, PRE (1997)

Brain serotonergic axons as FBM paths

DIVERSION AHEAD

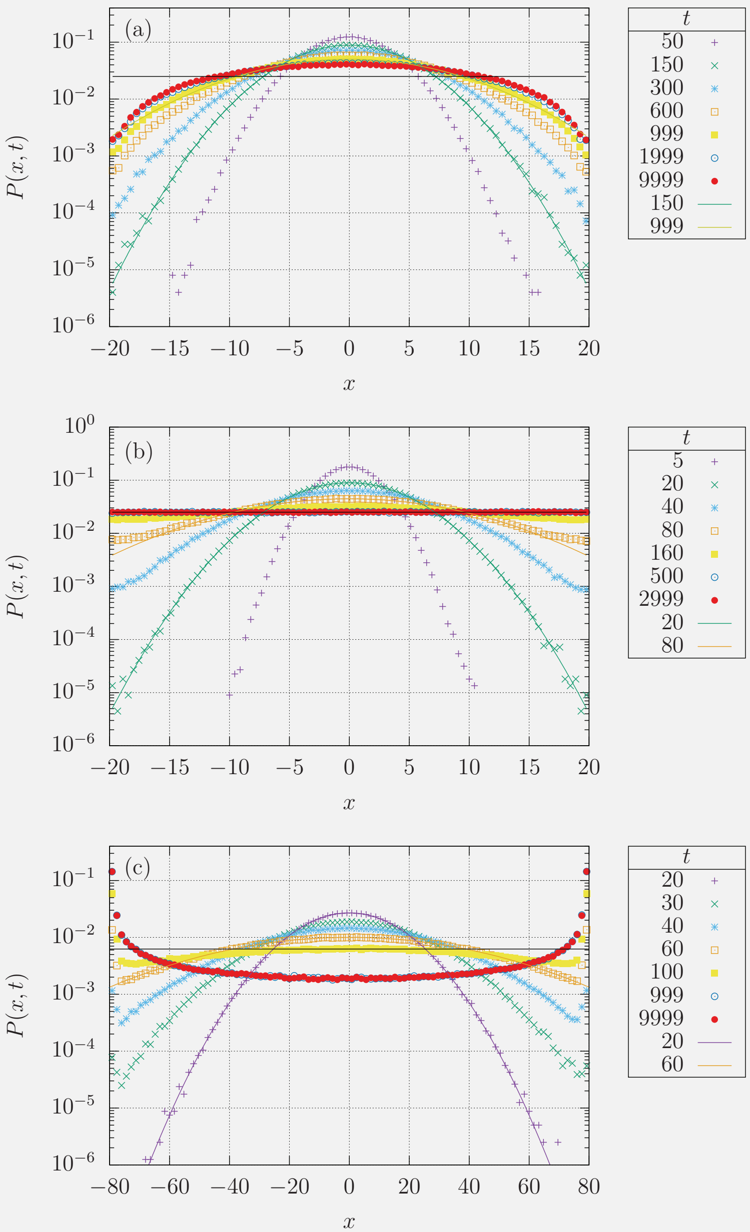
Correlated fluctuations effect non-flat profile

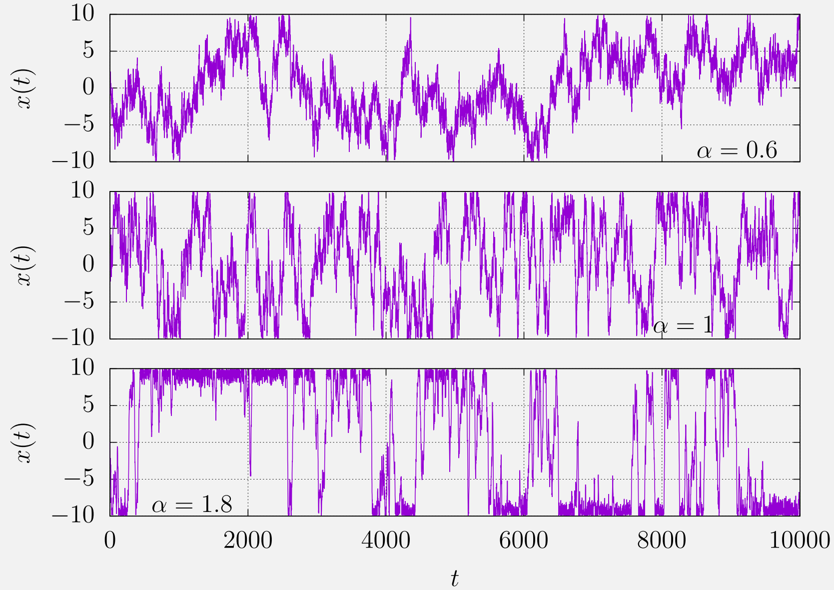


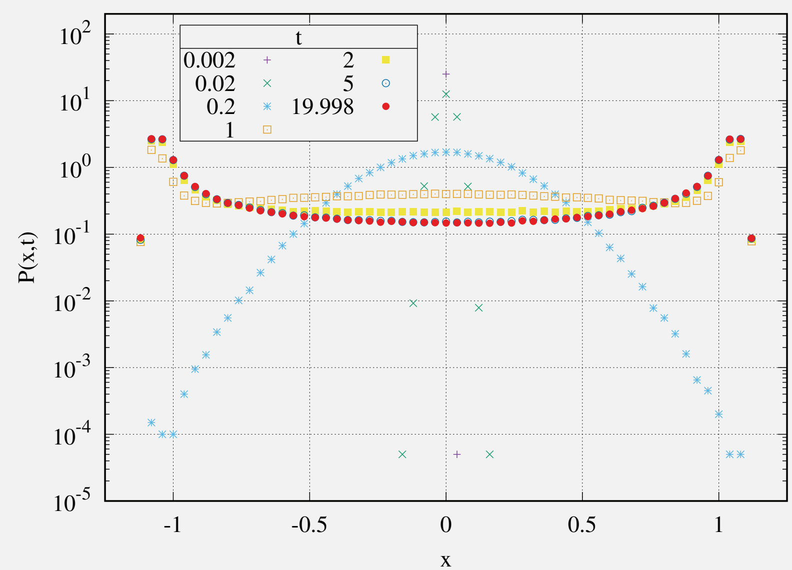


S Janušonis, N Detering, RM & T Vojta, Front Comp Neurosc (2020); T Guggenberger, T Vojta & RM, NJP (2019)

FBM: accretion & depletion effects near boundaries







FBM in superharmonic potentials