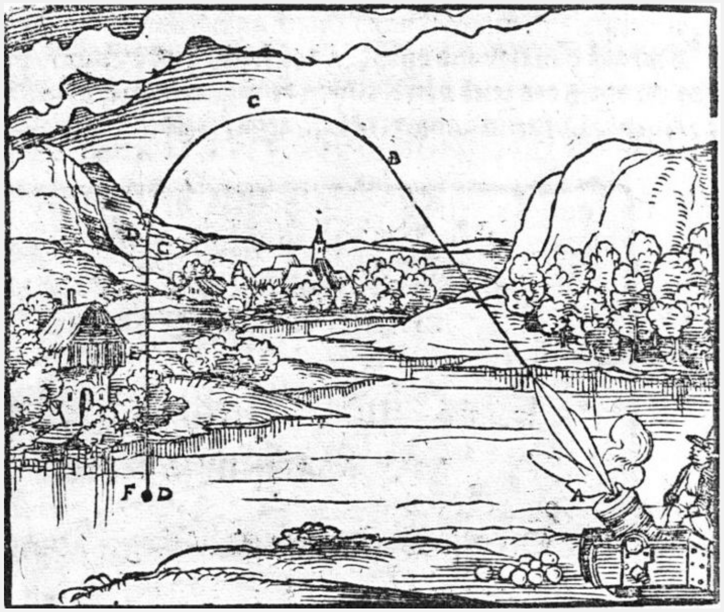
From facilitated diffusion to Lévy flights

— POSTECH Pohang, 6th February 2018 —

Hitting a visible target: an old science



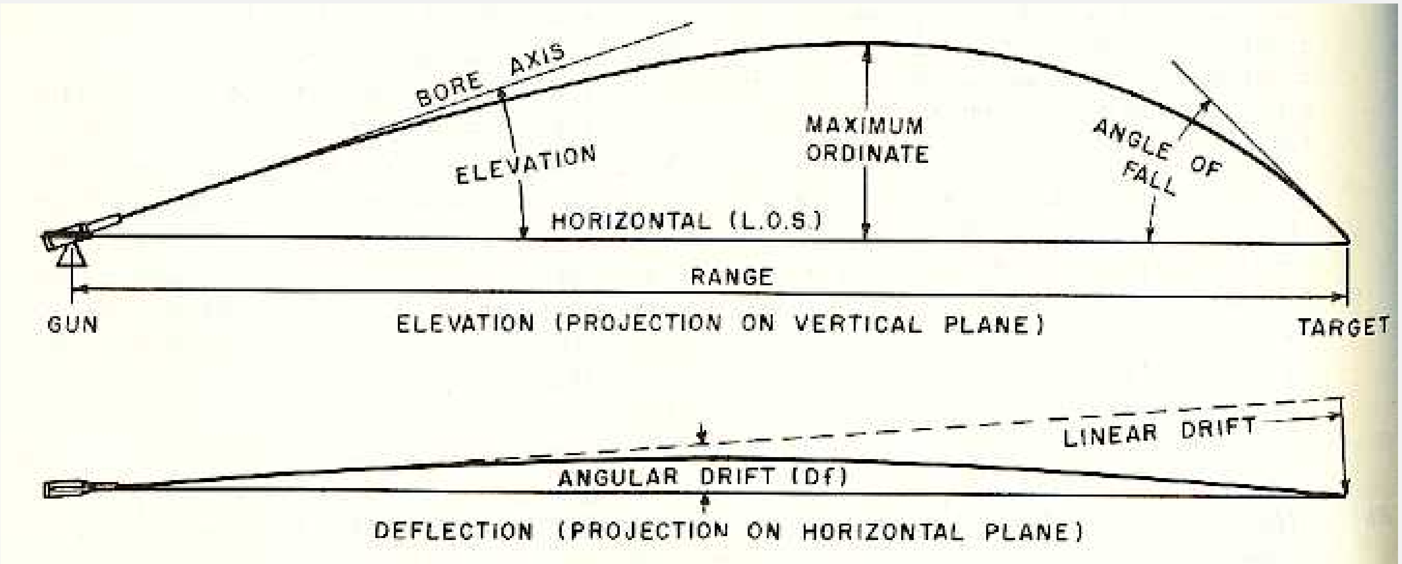
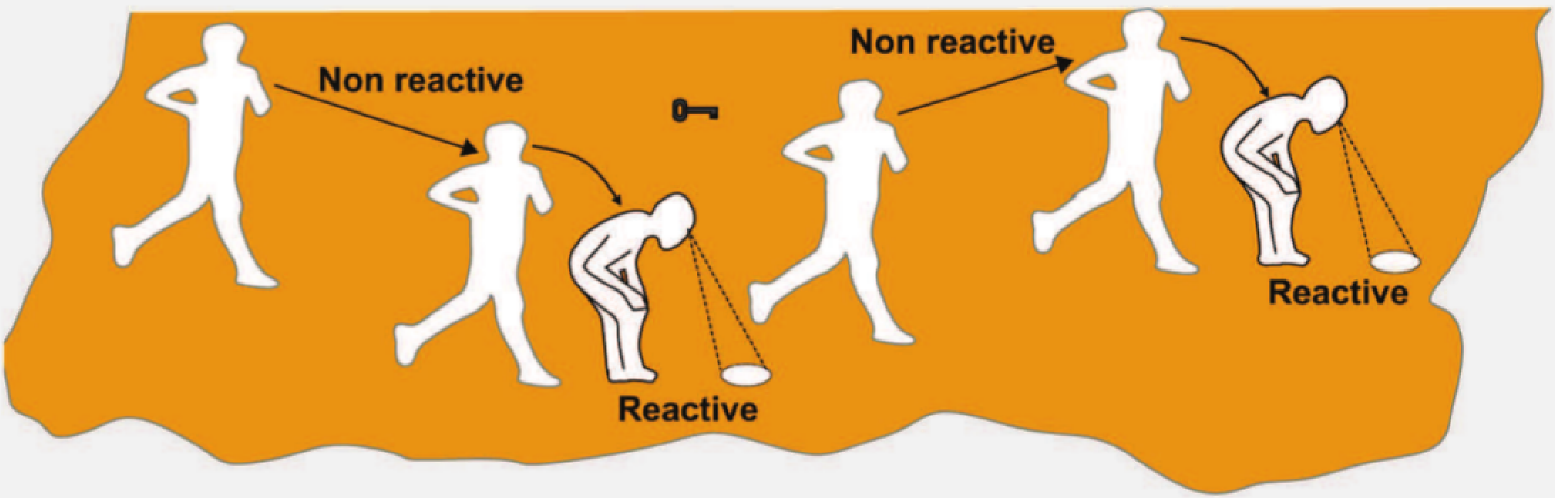


Figure 20A1.—A simple trajectory.

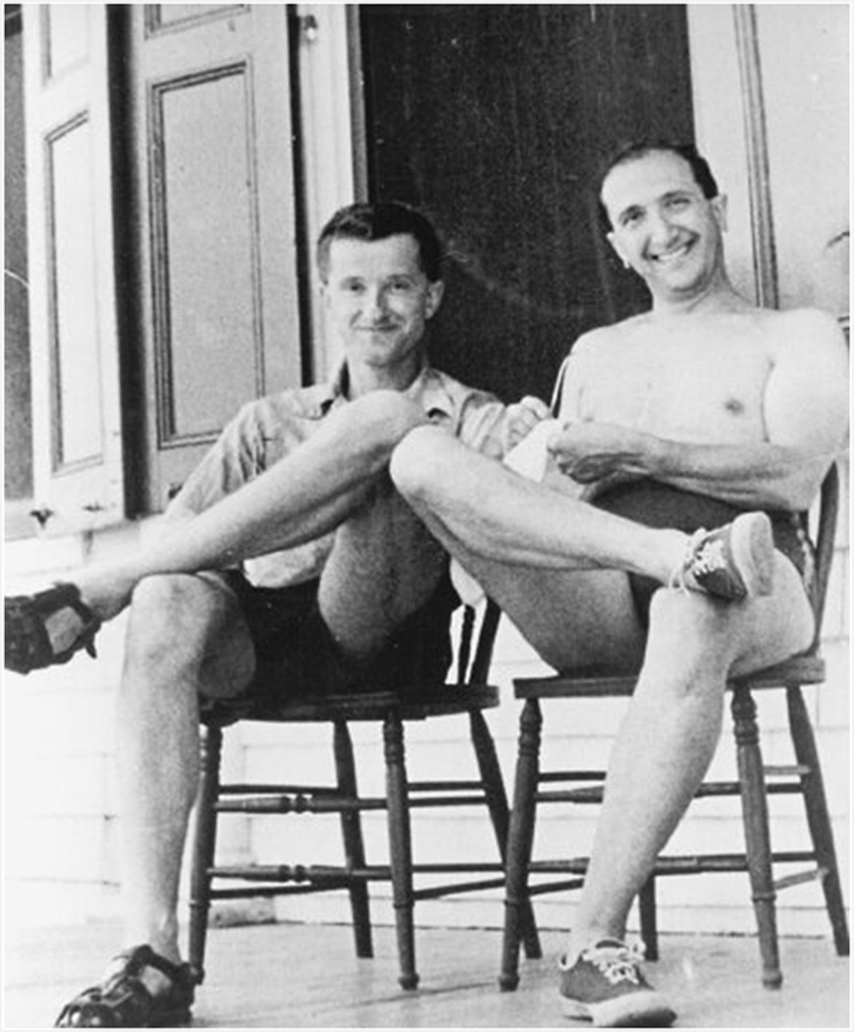
Random strategy for hidden target: intermittent search



O Bénichou, C Loverdo, M Moreau & R Voituriez, RMP (2011)

& now it's time for something completely different

Luria-Delbrück experiment (1943)

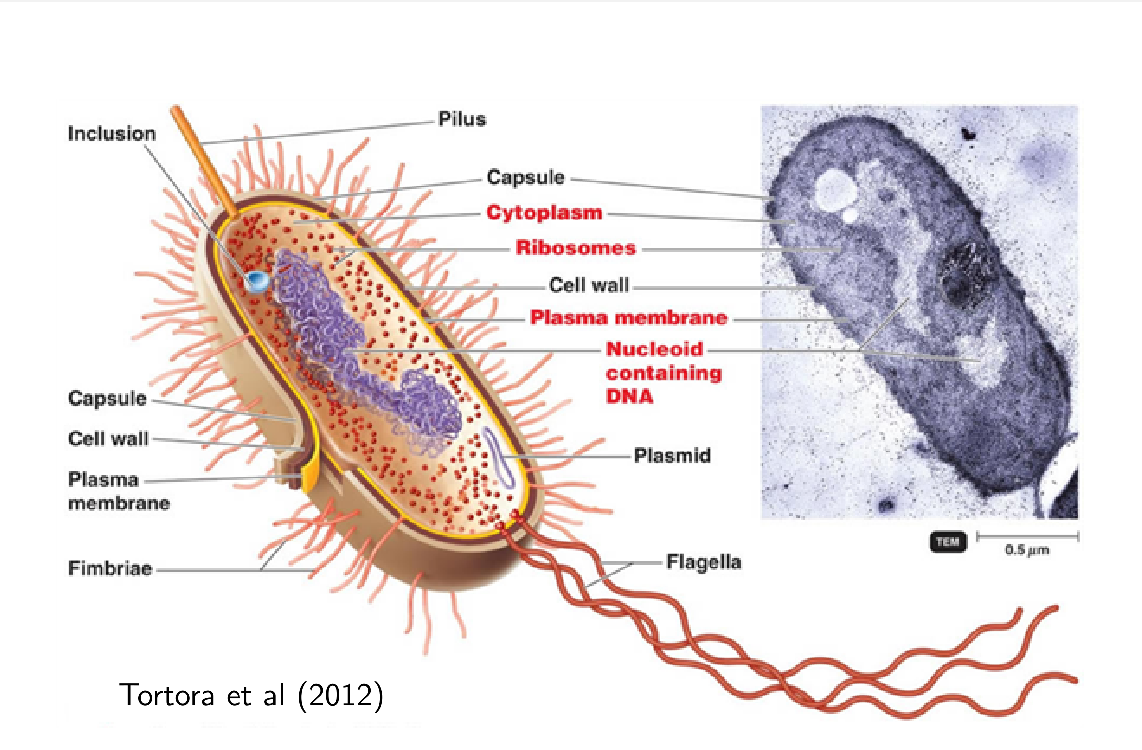


Max Delbrück and Salvador Luria (Nobel Prize, 1969)

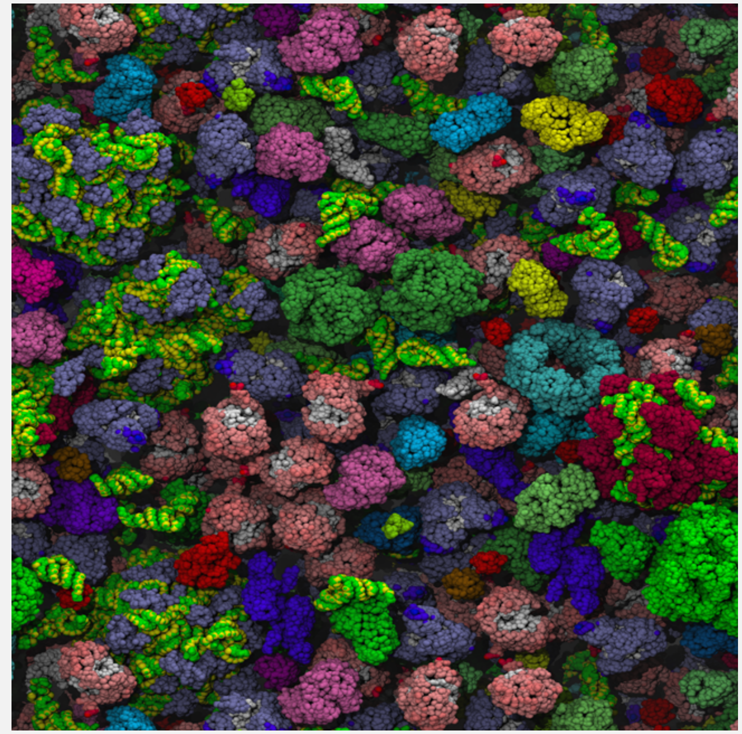
The Luria-Delbrück experiment or Fluctuation Test demonstrates that in bacteria mutations against a specific viral infection arise *randomly over time*, and are not induced by exposure to the virus itself. Those bacteria with the appropriately mutated genes will survive and proliferate the resistance.

SE Luria & M Delbrück, Genetics (1943)

Main protagonist: bacteria cells such as E.coli



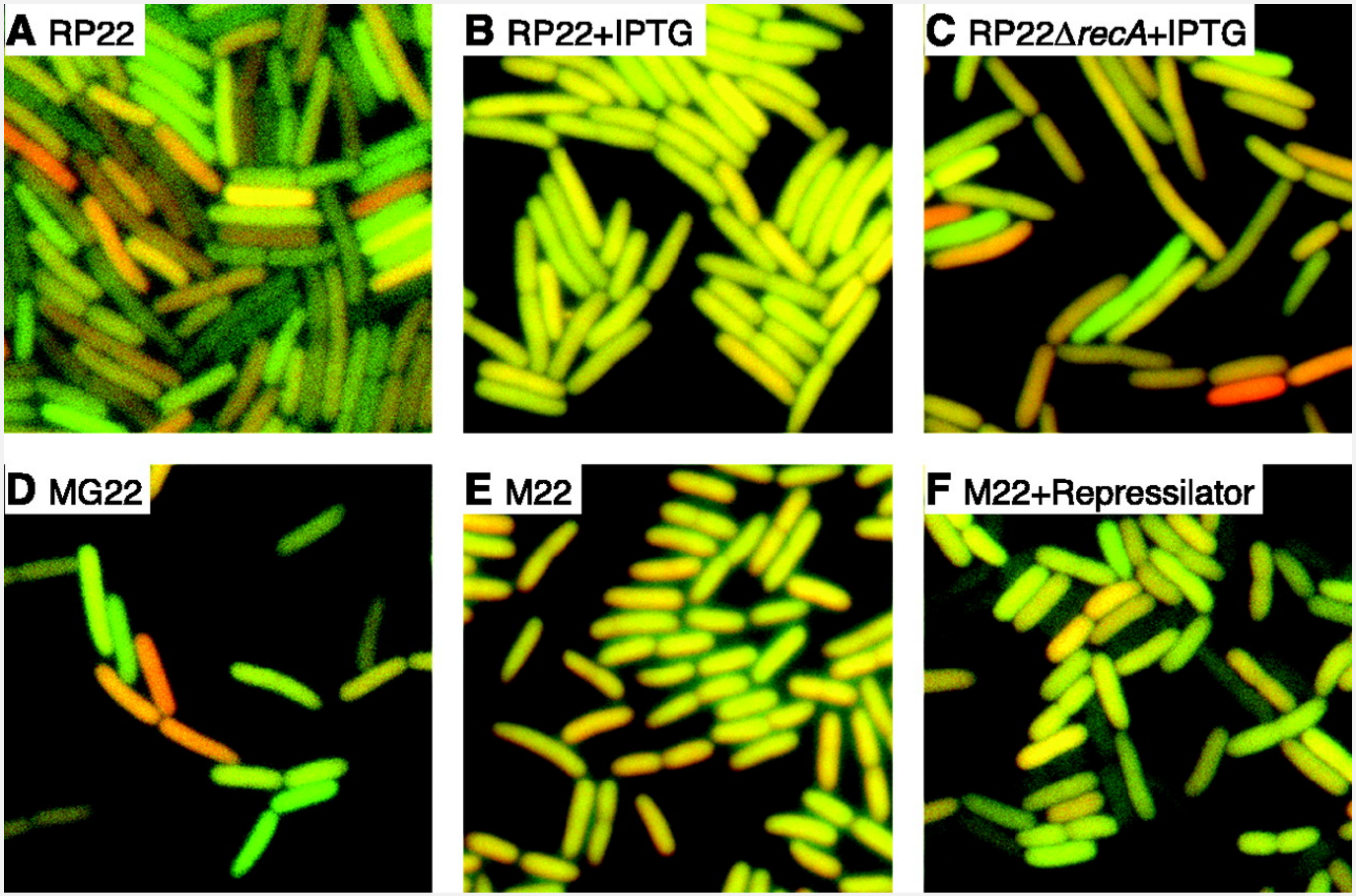
Tortora et al (2012)


McGuffee & Elcock, PLoS Comp Biol (2010)

(∃ also cells with fully delocalised chromatin)

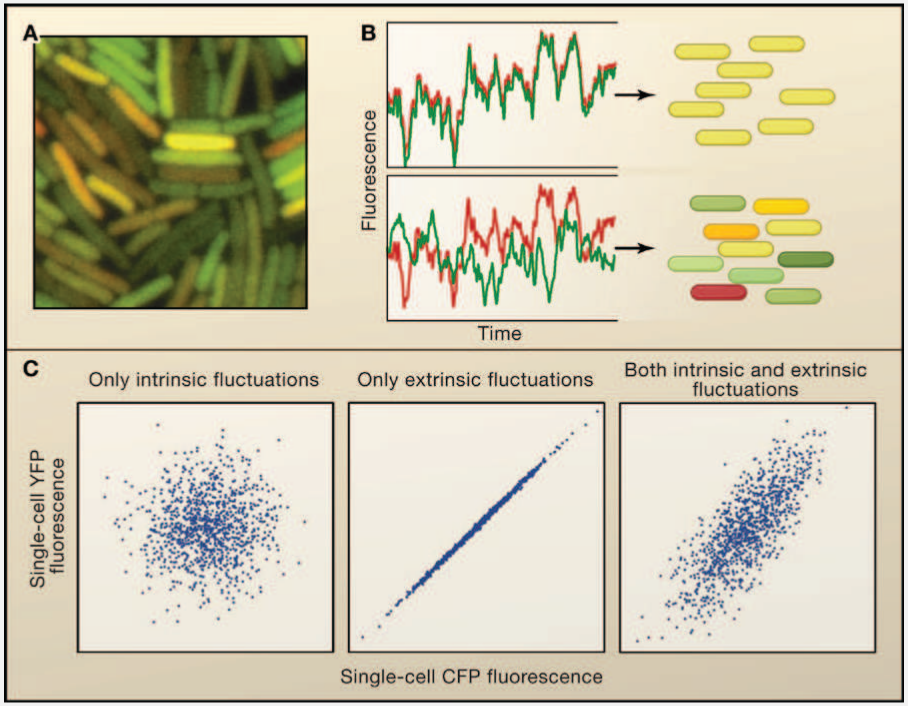
Gene regulation is intrinsically stochastic

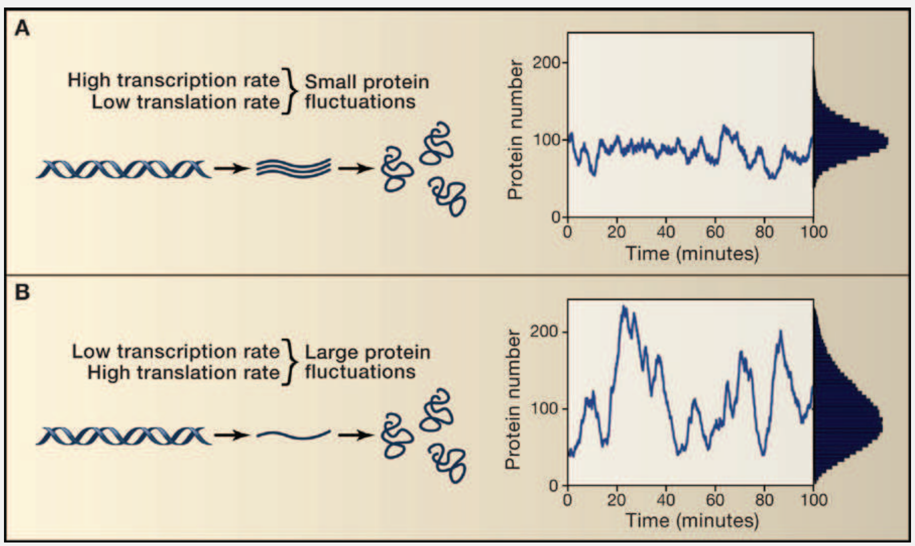
Phenotypic difference in a single cell line:

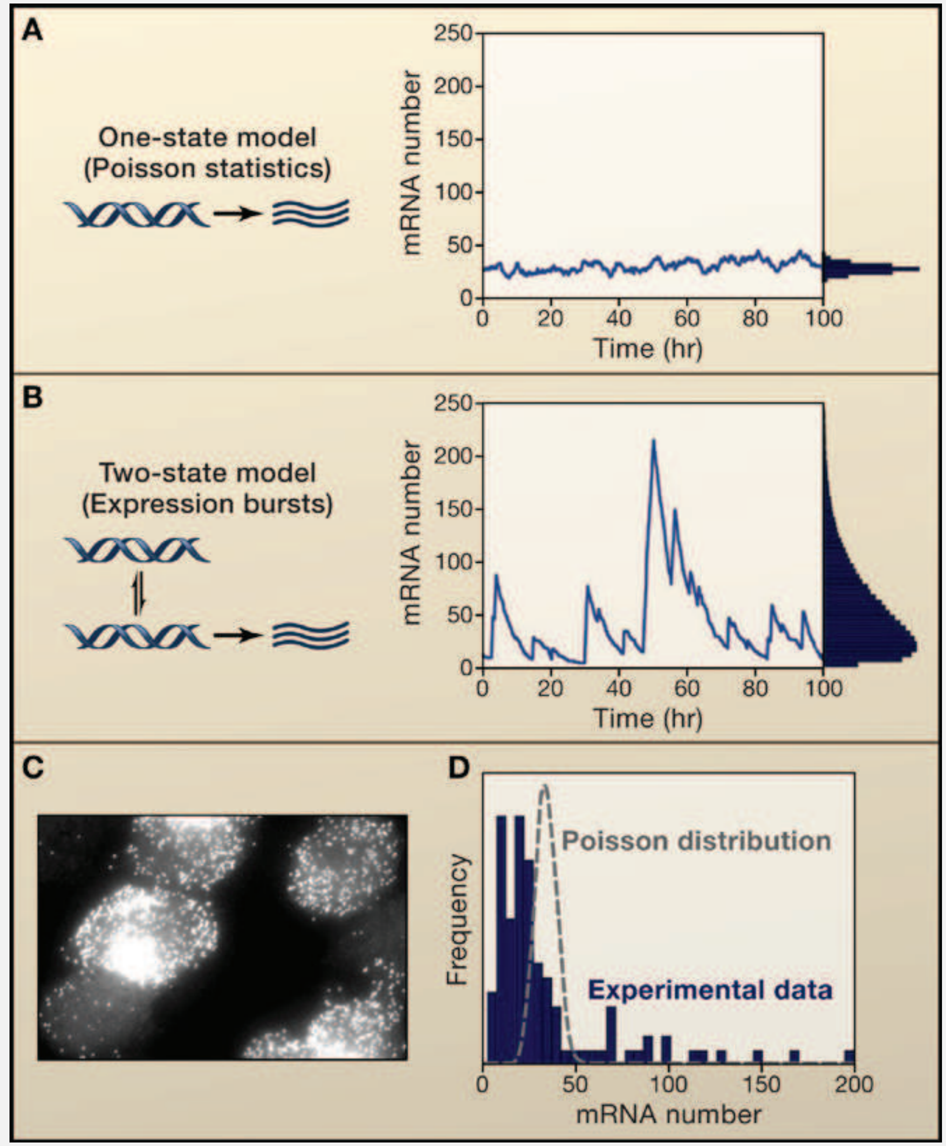


Elowitz et al, Science (2002)

Sources of cellular noisiness: chemical vs physical



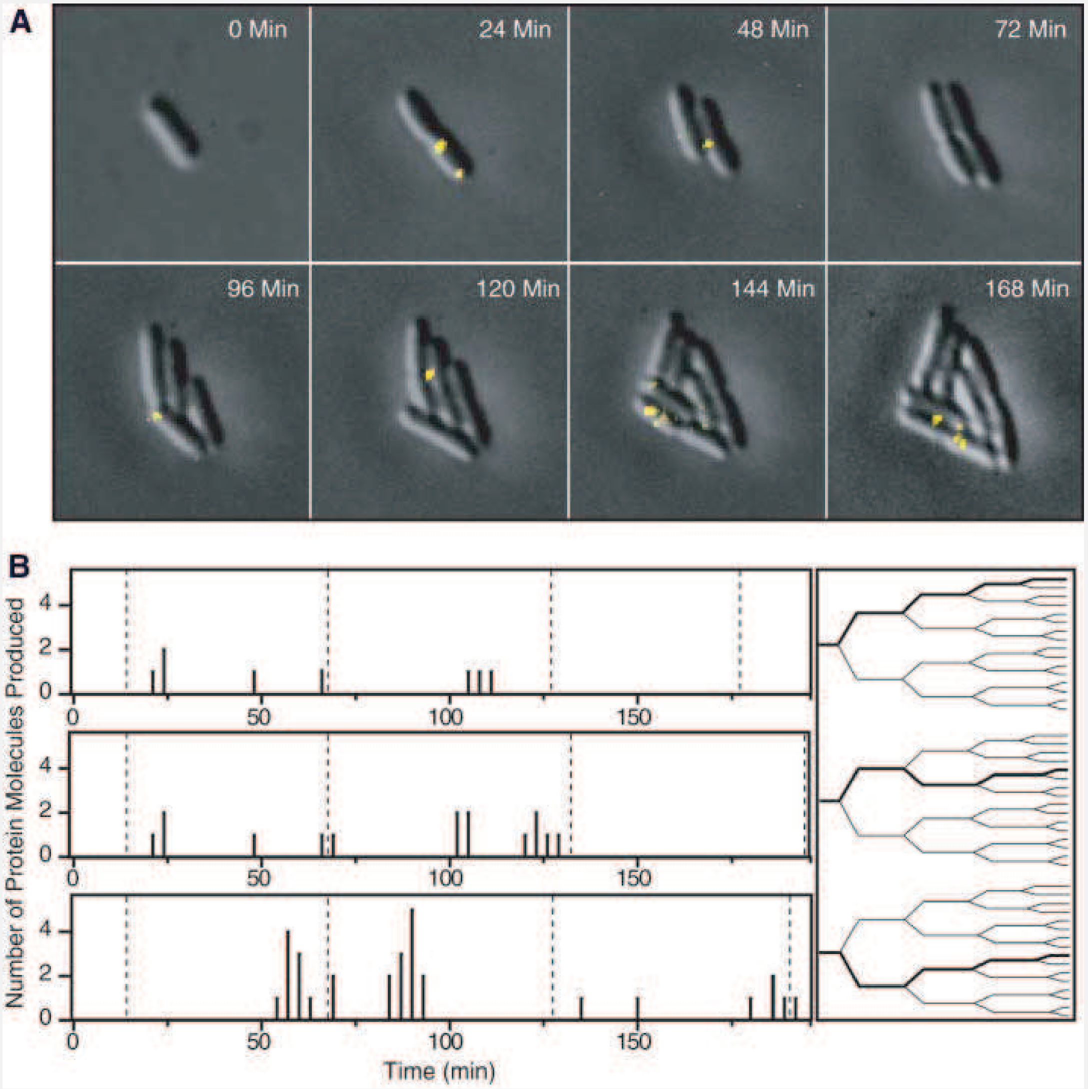




Plus noise due to spatial spreading of TFs!

A Raj & A van Oudenaarden, Cell (2008)

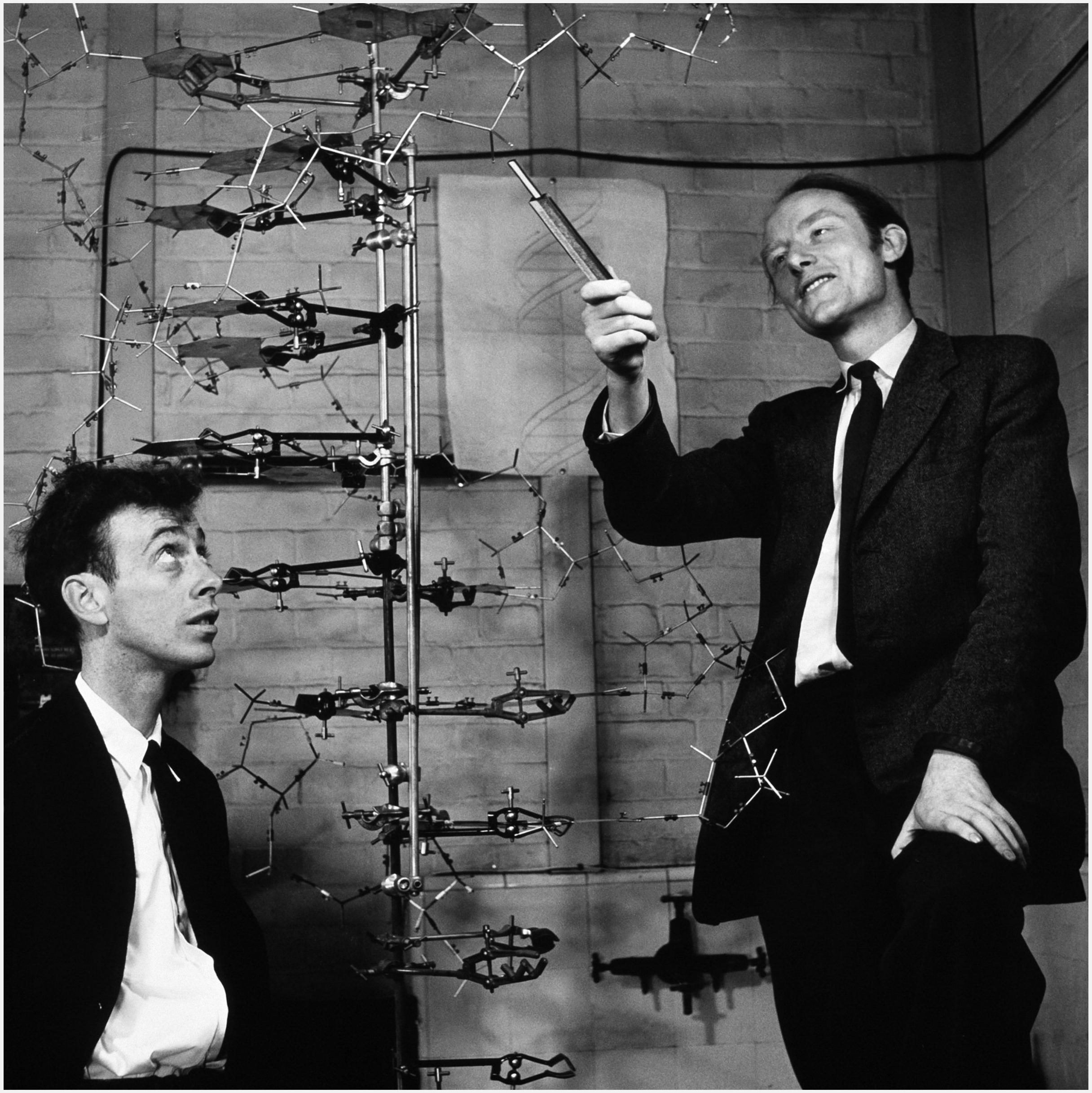
Gene expression one molecule at a time

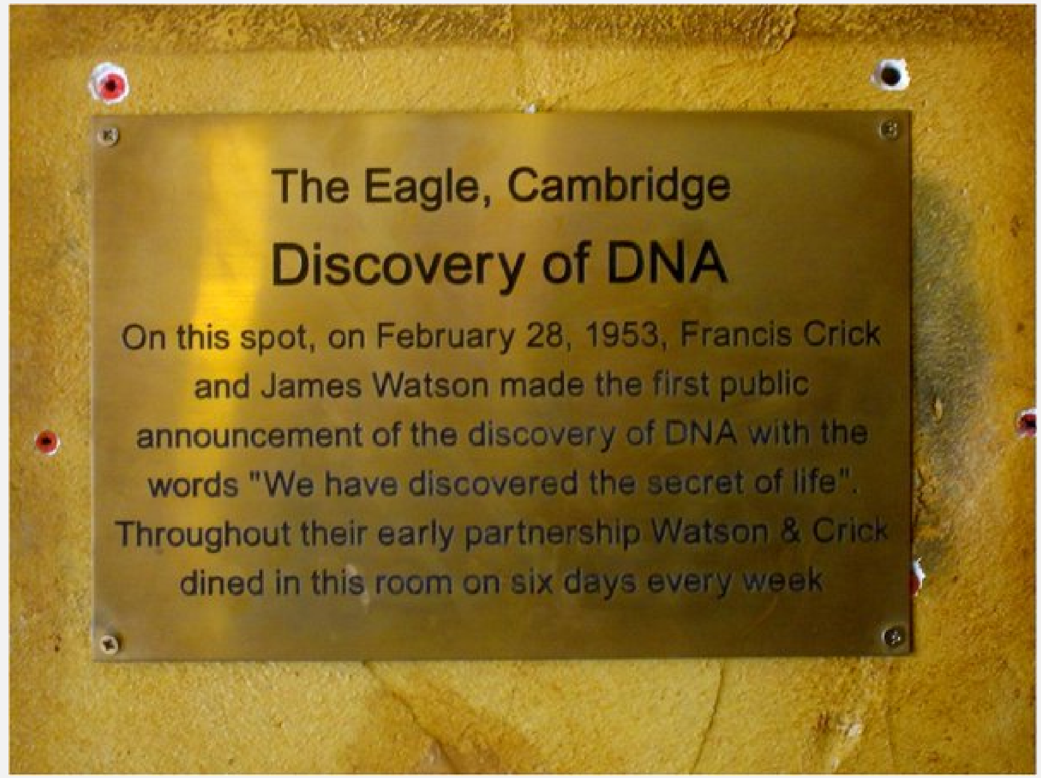


synthesised proteins (bursty) along three cell lineages, dashed lines marking cell divisions

Yu et al, Science (2006); I Golding et al, Cell (2005)

Genetic information is stored on DNA





The Eagle, Cambridge
Discovery of DNA
On this spot, on February 28, 1953, Francis Crick and James Watson made the first public announcement of the discovery of DNA with the words "We have discovered the secret of life".
Throughout their early partnership Watson & Crick dined in this room on six days every week

Central Dogma of Molecular Biology

by
FRANCIS CRICK
MRC Laboratory of Molecular Biology,
Hills Road,
Cambridge CB2 2QH

The central dogma of molecular biology deals with the detailed residue-by-residue transfer of sequential information. It states that such information cannot be transferred from protein to either protein or nucleic acid.

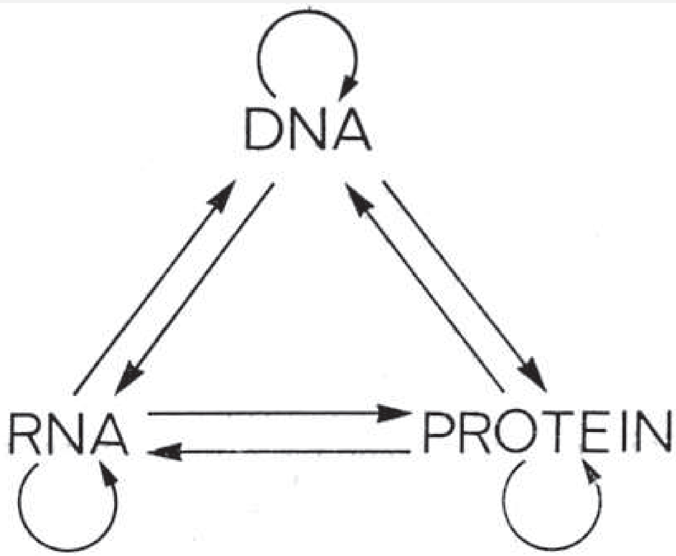


Fig. 1. The arrows show all the possible simple transfers between the three families of polymers. They represent the directional flow of detailed sequence information.

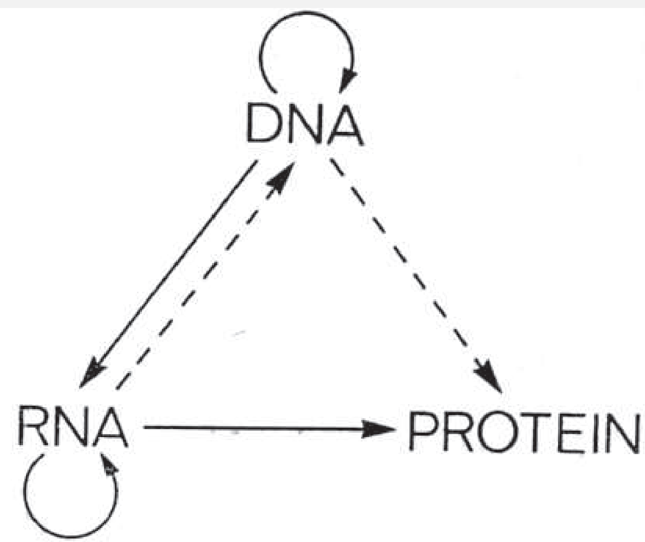
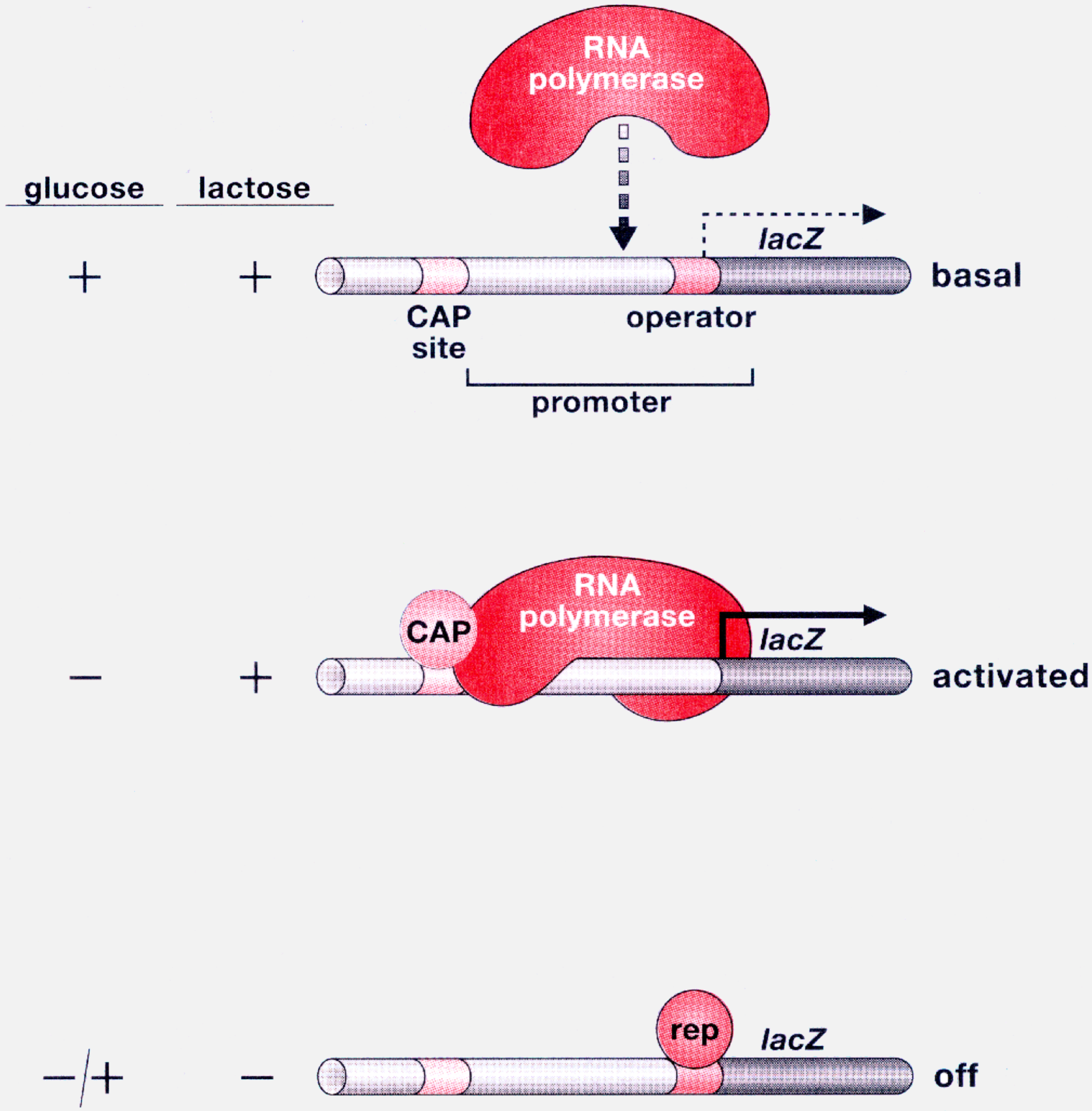


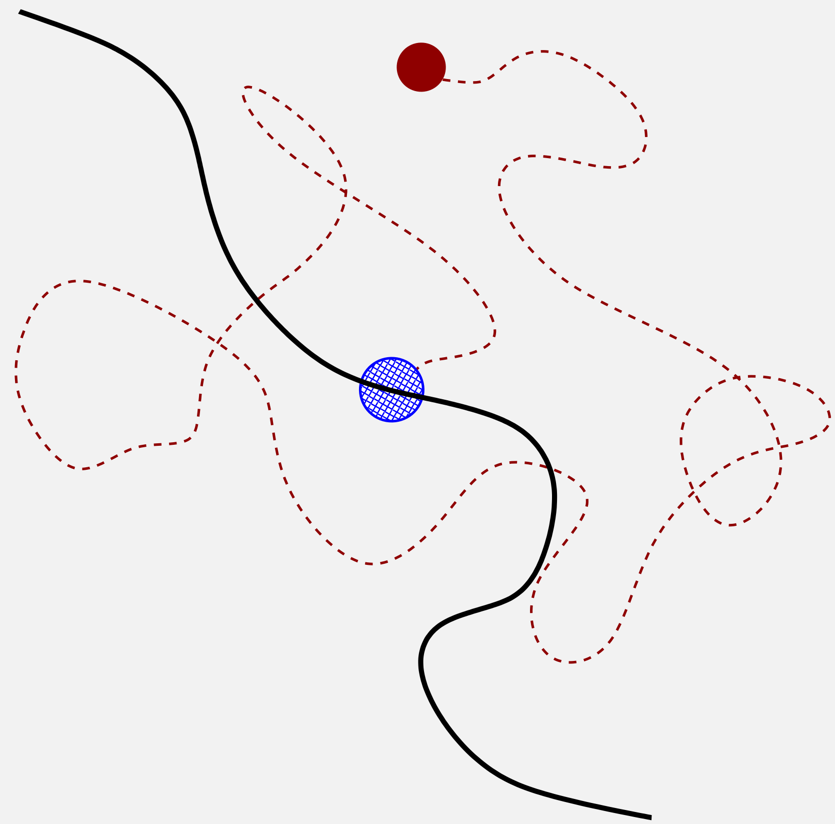
Fig. 2. The arrows show the situation as it seemed in 1958. Solid arrows represent probable transfers, dotted arrows possible transfers. The absent arrows (compare Fig. 1) represent the impossible transfers postulated by the central dogma. They are the three possible arrows starting from protein.

Gene regulation by transcription factors: Lac repressor



M Ptashne, A genetic switch

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

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

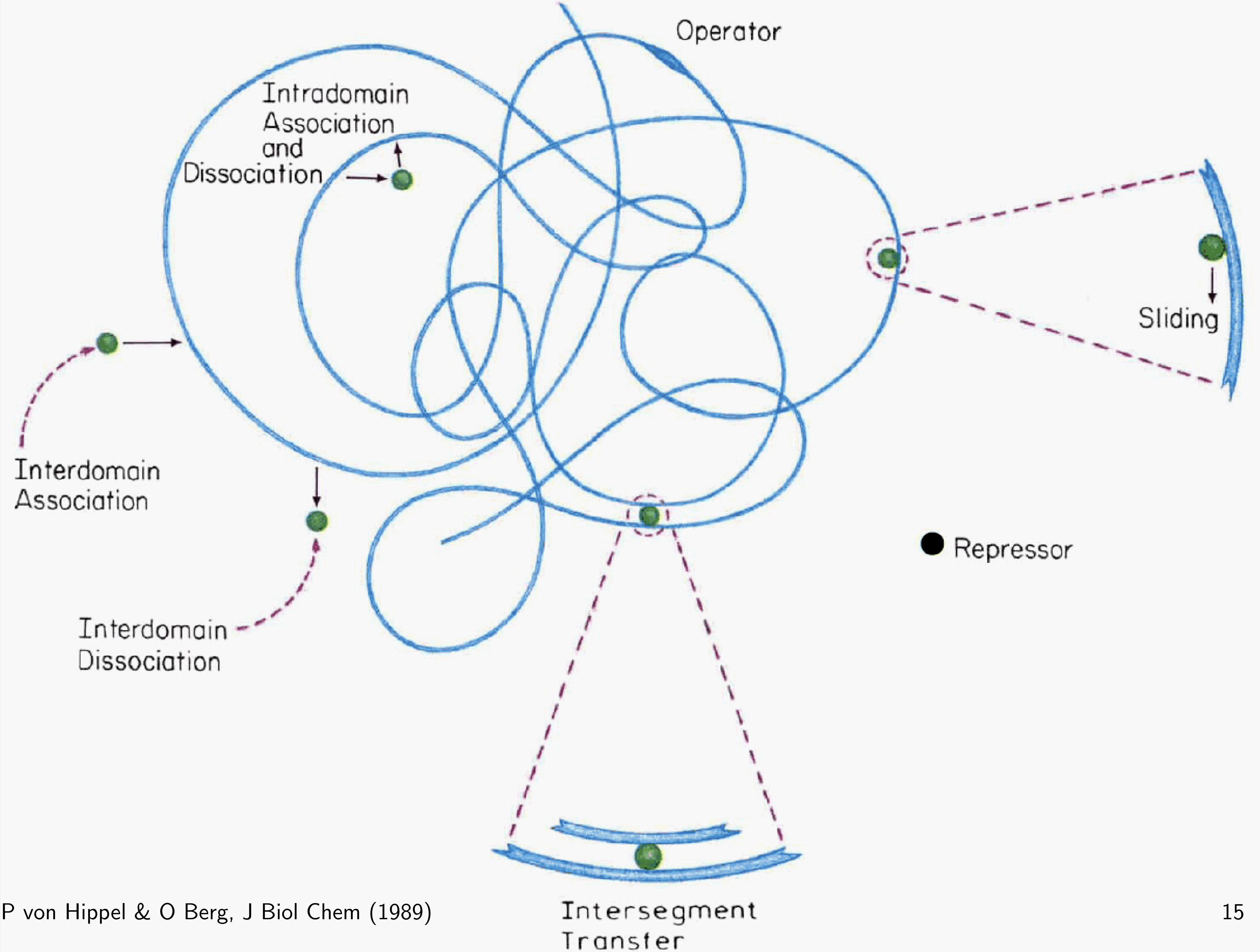
Lac repressor [AD Riggs, S Bourgeois, M Cohn, J Mol Biol 53, 401 (1970)]:

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

$\rightarrow$ Facilitated diffusion picture

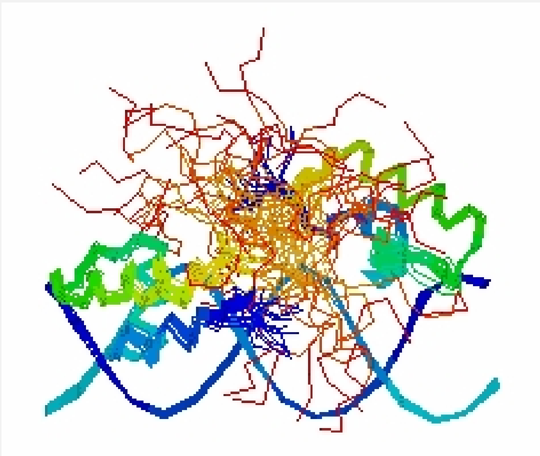
M v Smoluchowski, Physikal. Zeitschr. (1916); P von Hippel and O Berg, J Biol Chem (1989)

Facilitated diffusion: the Berg-von Hippel model

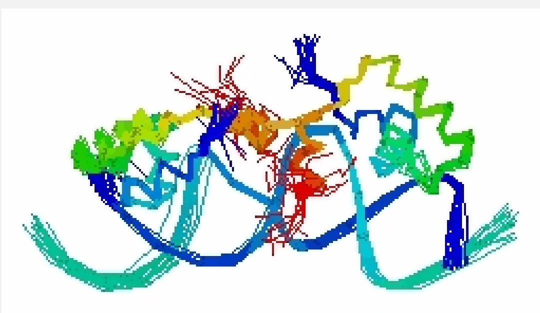


P von Hippel & O Berg, J Biol Chem (1989)

Non-specific binding energy based on *in vivo* data



Lac repressor, nonspecific binding

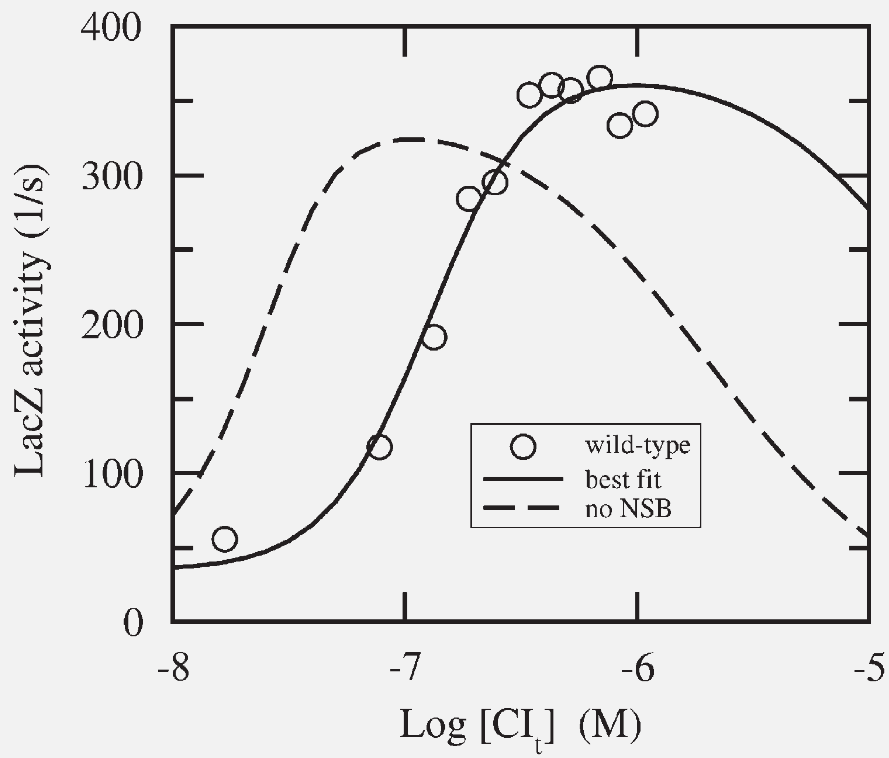


Lac repressor, specific binding

$$[\mathrm{X}] = [\mathrm{X}_{\mathrm{free}}] + \left[\mathrm{X}_{@\mathrm{O_P}}\right] + [\mathrm{X}_{\mathrm{NSB}}]$$

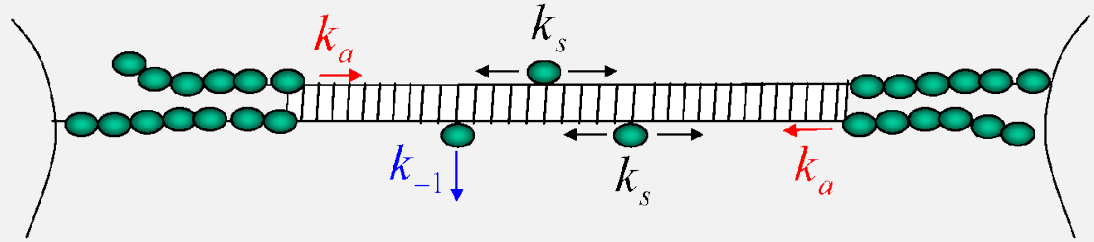
$$\Delta G_{\mathrm{NSB}}(\mathrm{CI}) = -4.1 \pm 0.9\,\mathrm{kcal/mol},$$

$$\Delta G_{\mathrm{NSB}}(\mathrm{Cro}) = -4.2 \pm 0.8\,\mathrm{kcal/mol}$$



A Bakk & RM, FEBS Lett (2004); J Theoret Biol (2004)

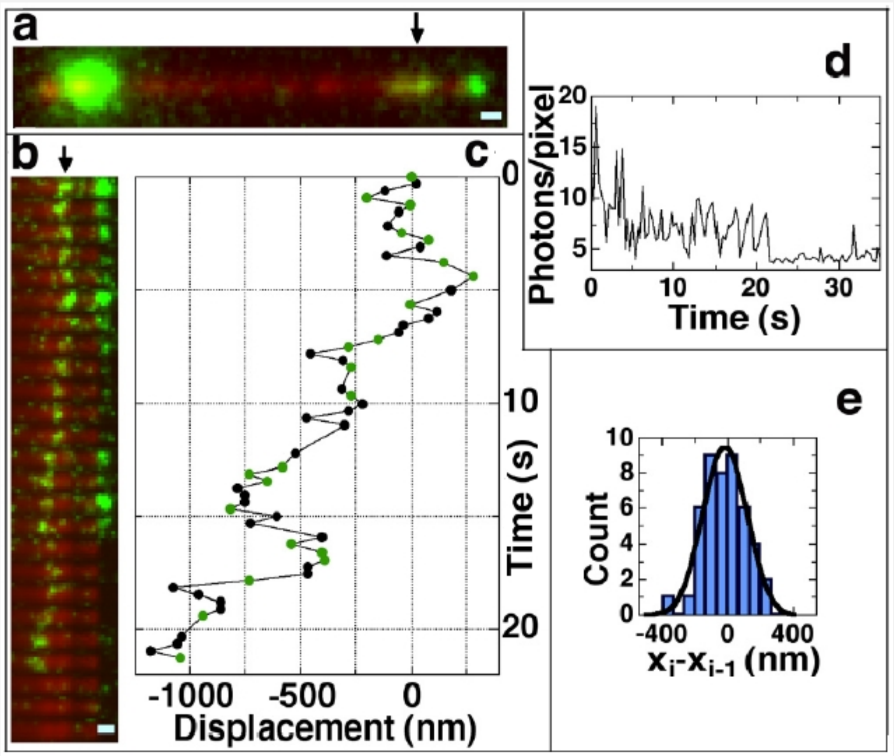
Proof of 1D search mode

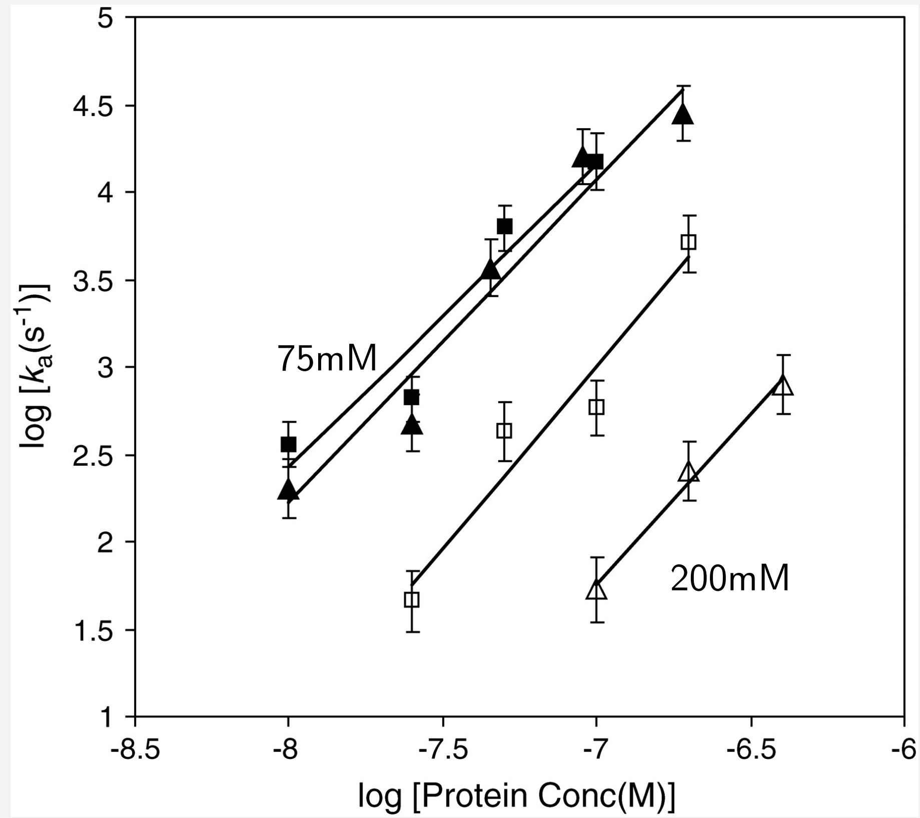


McGhee & von Hippel isotherm

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

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





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

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

Calculating facilitated diffusion (our version): manifestation of intermittency

$$\frac{\partial n(x,t)}{\partial t} = \left(D_{1d}\frac{\partial^2}{\partial x^2} - k_{\rm off}\right) n(x,t) - j(t)\delta(x) + G(x,t)$$
$$+k_{\rm off}\int_{-\infty}^{\infty} dx' \int_0^t dt' \, W_{\rm bulk}(x-x', t-t')$$

n: line density of TFs

x: chemical co-ordinate along DNA

$k_{\rm off}$: unbinding rate of non-specifically bound TFs

D_{1d}: 1D diffusion constant ($\sim 10^{-2} D_{3d}$)

$j(t)$: flux into target (δ sink @ $x = 0$)

G: virgin flux of previously unbound TFs

$W_{\rm bulk}$: 3D diffusion propagator

Long chain, fast dynamics: Lévy flights

M Lomholt, T Ambjörnsson & RM, PRL (2005)

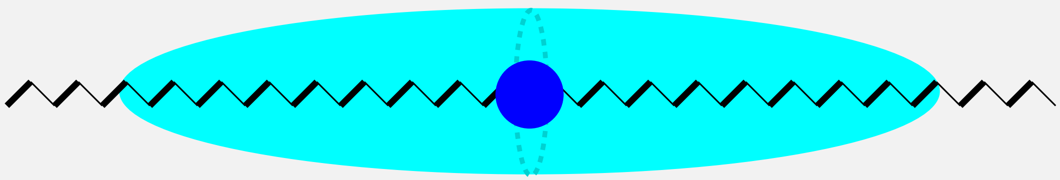
The antenna effect

Target search rate for cylindrical DNA model:

$$k_{\rm on} \sim 4\pi D_{3d}\ell_{\rm sl}^{\rm eff} \times \frac{1}{\sqrt{\ln(\ell_{\rm sl}^{\rm eff}/r_{\rm int})}}$$

Sliding length:

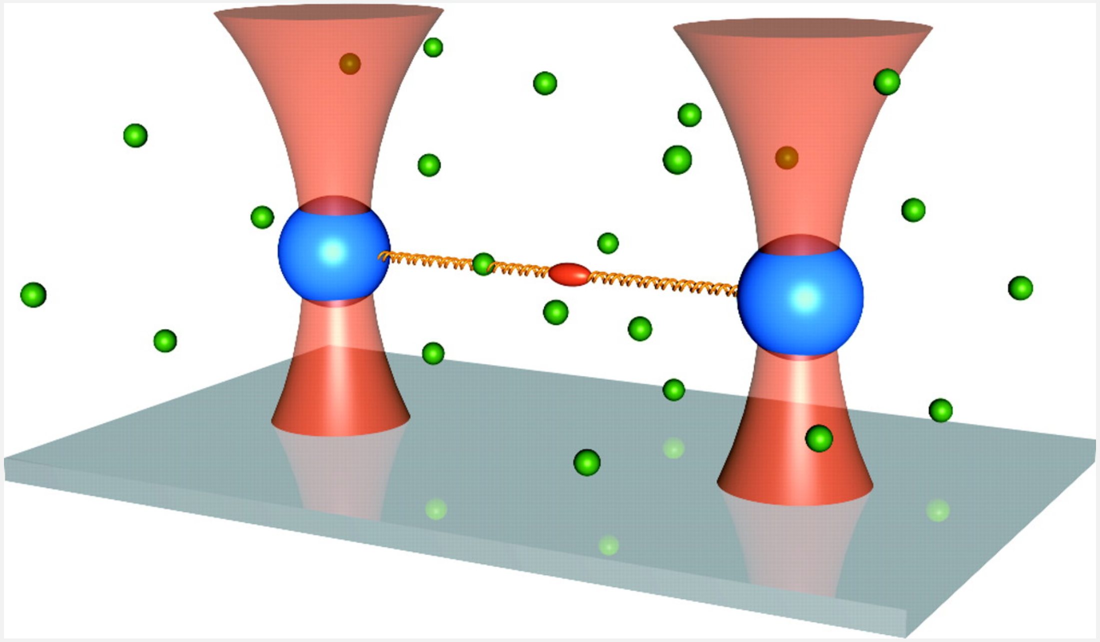
$$\ell_{\rm sl} = \sqrt{\frac{D_{1d}}{k_{\rm off}}}$$

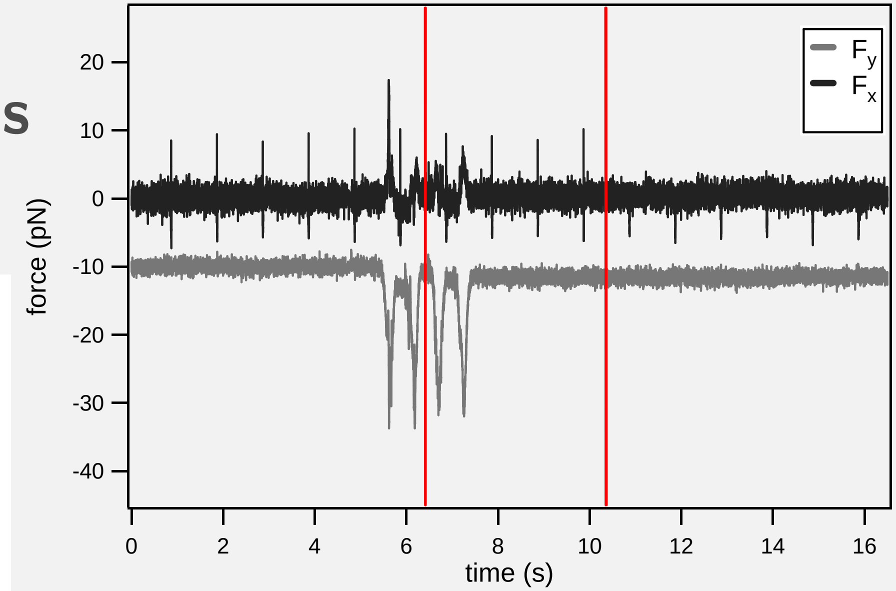


Effective sliding length:

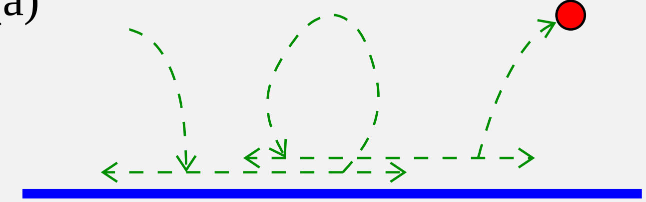
$$\ell_{\rm sl}^{\rm eff} = \sqrt{\frac{k_{\rm on}}{2\pi D_{3d}}} \times \ell_{\rm sl}$$ microhop correction: $$\sqrt{\frac{k_{\rm on}}{2\pi D_{3d}}}$$

The rôle of DNA conformations

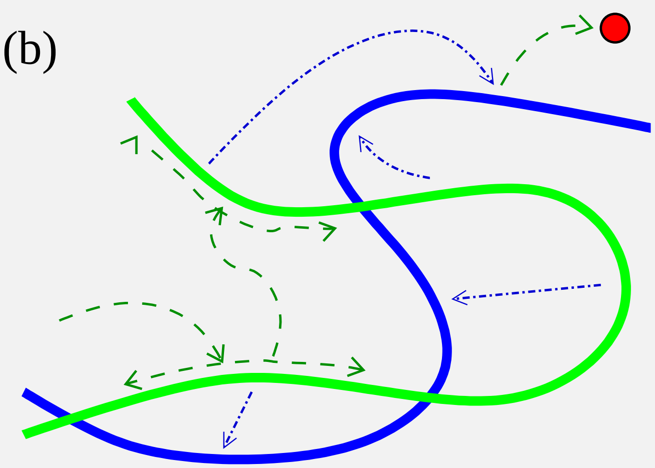




(a)



(b)



pCco5 plasmid DNA: 6538bp $\approx 2.2\mu$m $\approx 45\ell_p$

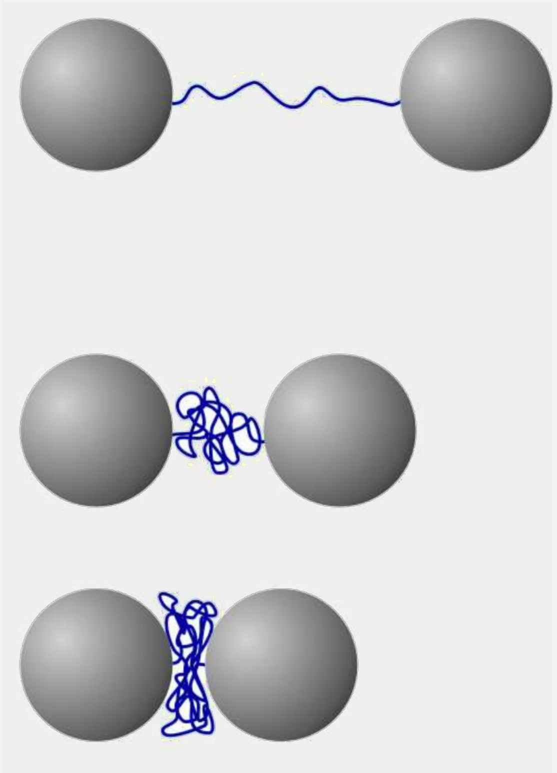
[comp λ DNA 48.5kbp]

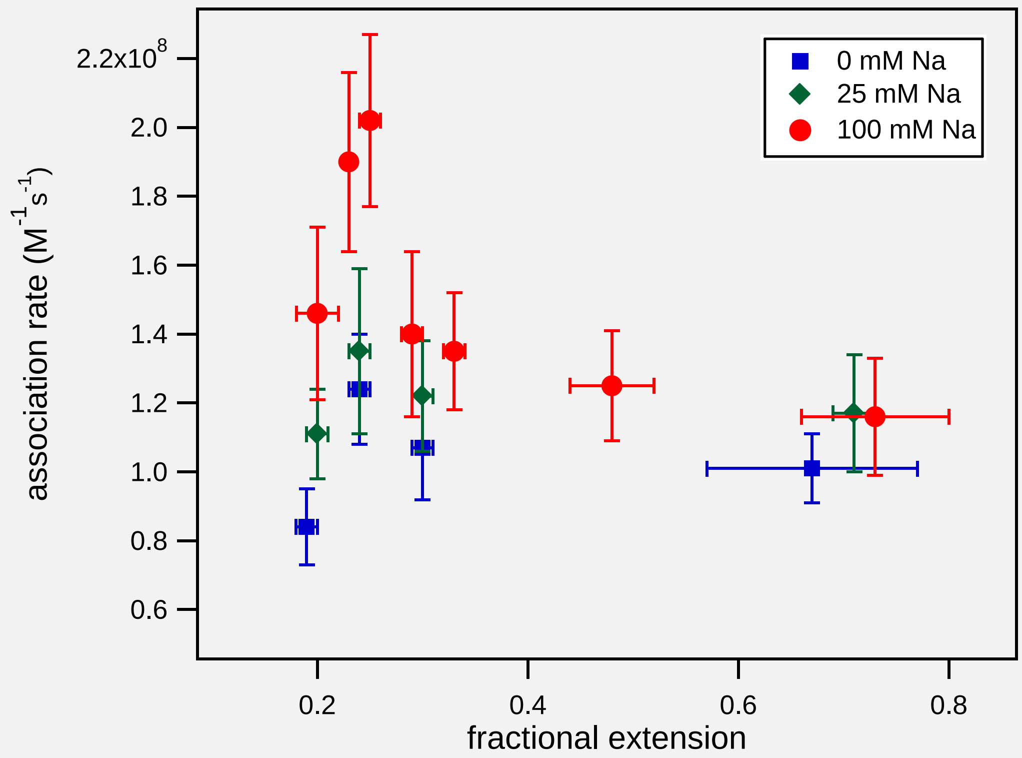
B van den Broek, MA Lomholt, S-M Kalisch, RM & GJL Wuite, PNAS (2008)

More compact DNA conformations speed up the search

[NaCl]	$k_{\rm on}^{\rm straight}$ [Ms]	$l_{\rm sl}^{\rm eff}$ [bp]	$1/\sqrt{l_{\rm DNA}}$ [bp]	ℓ_p [bp]	$R_{\rm theory}$	$R_{\rm measured}$
0 mM	0.8×10^8	195	518	188	1.18	1.3 ± 0.2
25 mM	1.0×10^8	250	485	175	1.23	1.1 ± 0.2
100 mM	1.0×10^8	250	150	159	1.67	1.7 ± 0.3
150 mM	0.9×10^9	15.5	120	153	1.15	1.3 ± 0.4

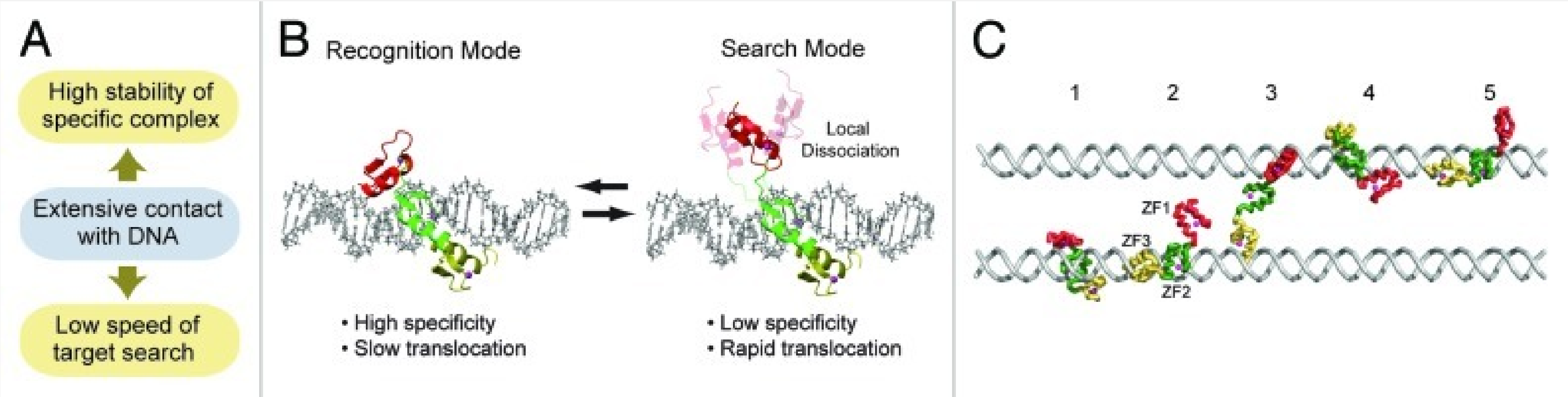
$R = k_{\rm on}^{\rm max}/k_{\rm on}^{\rm straight}$: enhancement ratio of attachment rates @ max and straight configuration)





MA Lomholt, B van den Broek, S-M Kalisch, GJL Wuite & RM, PNAS (2009)

Speed-stability paradox in TF search along DNA

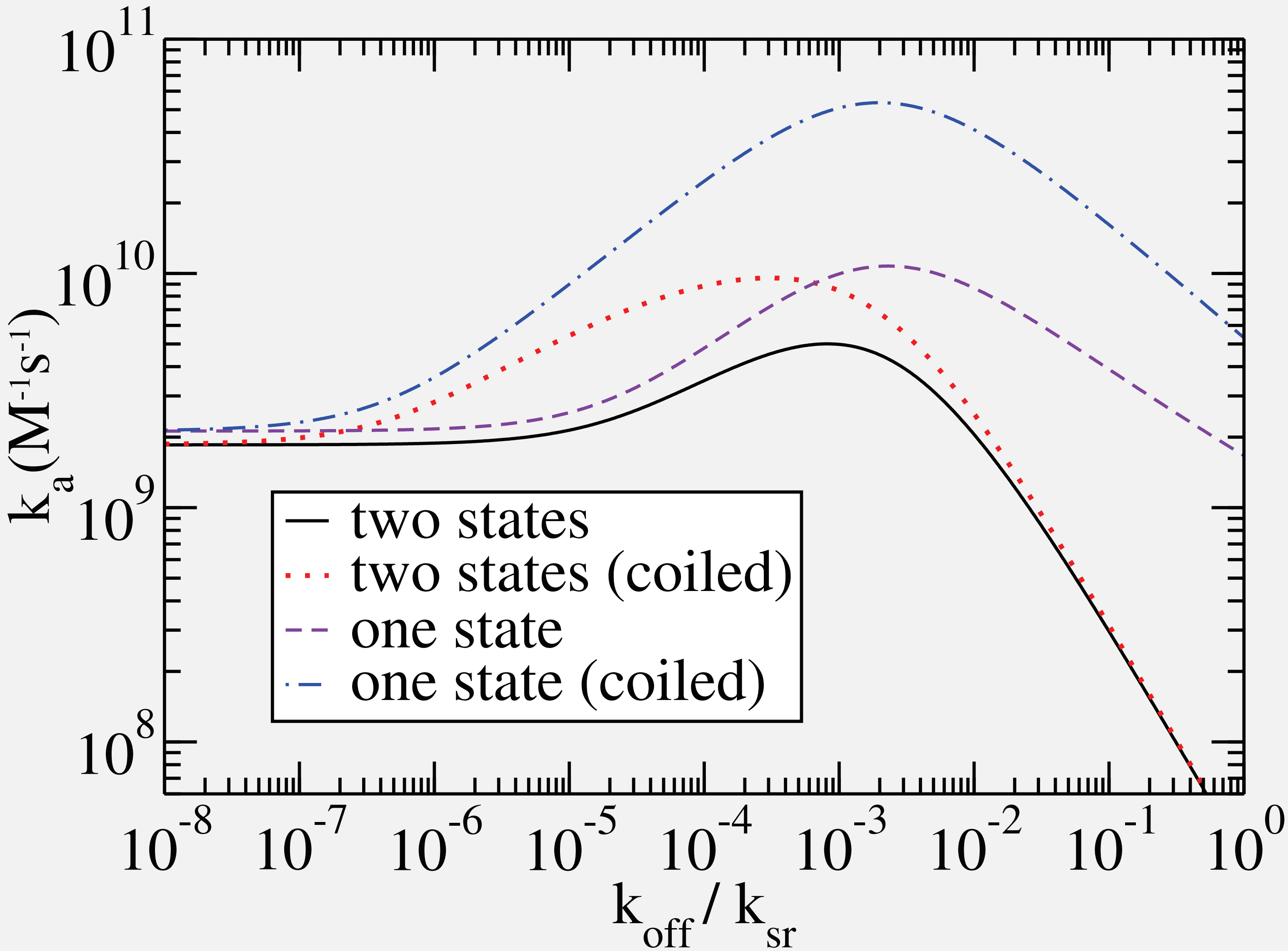


From simulations:

B: Search & recognition modes for a zinc finger protein

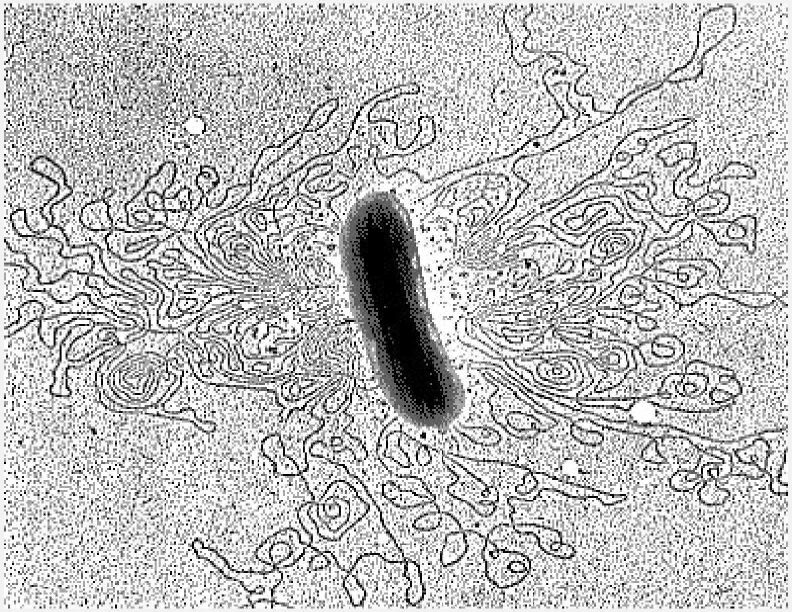
C: Intersegmental transfer of the protein

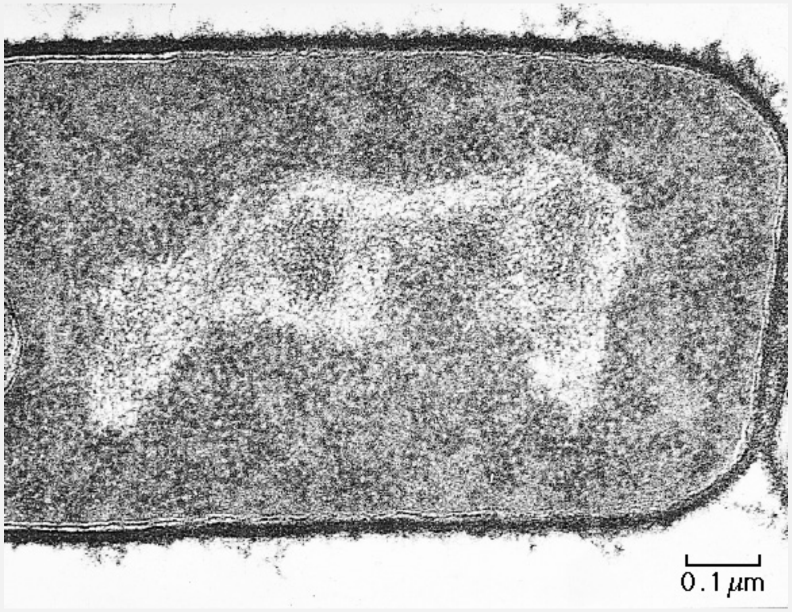
Facilitated diffusion: rate with search & recognition states



M Bauer & RM, Biophys J (2012)

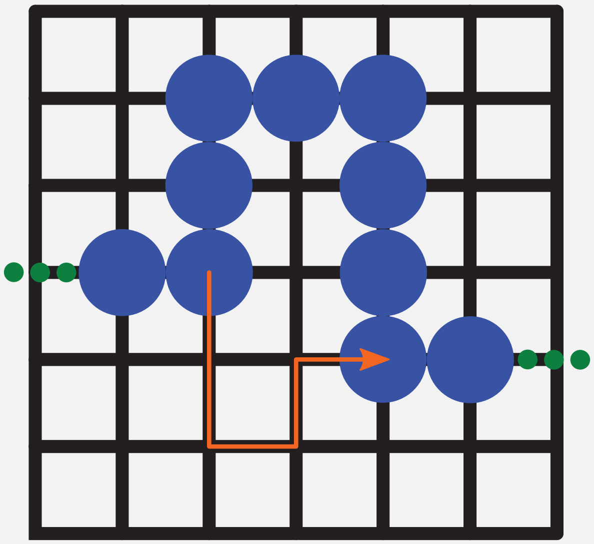
In vivo bacterial gene regulation: E.coli





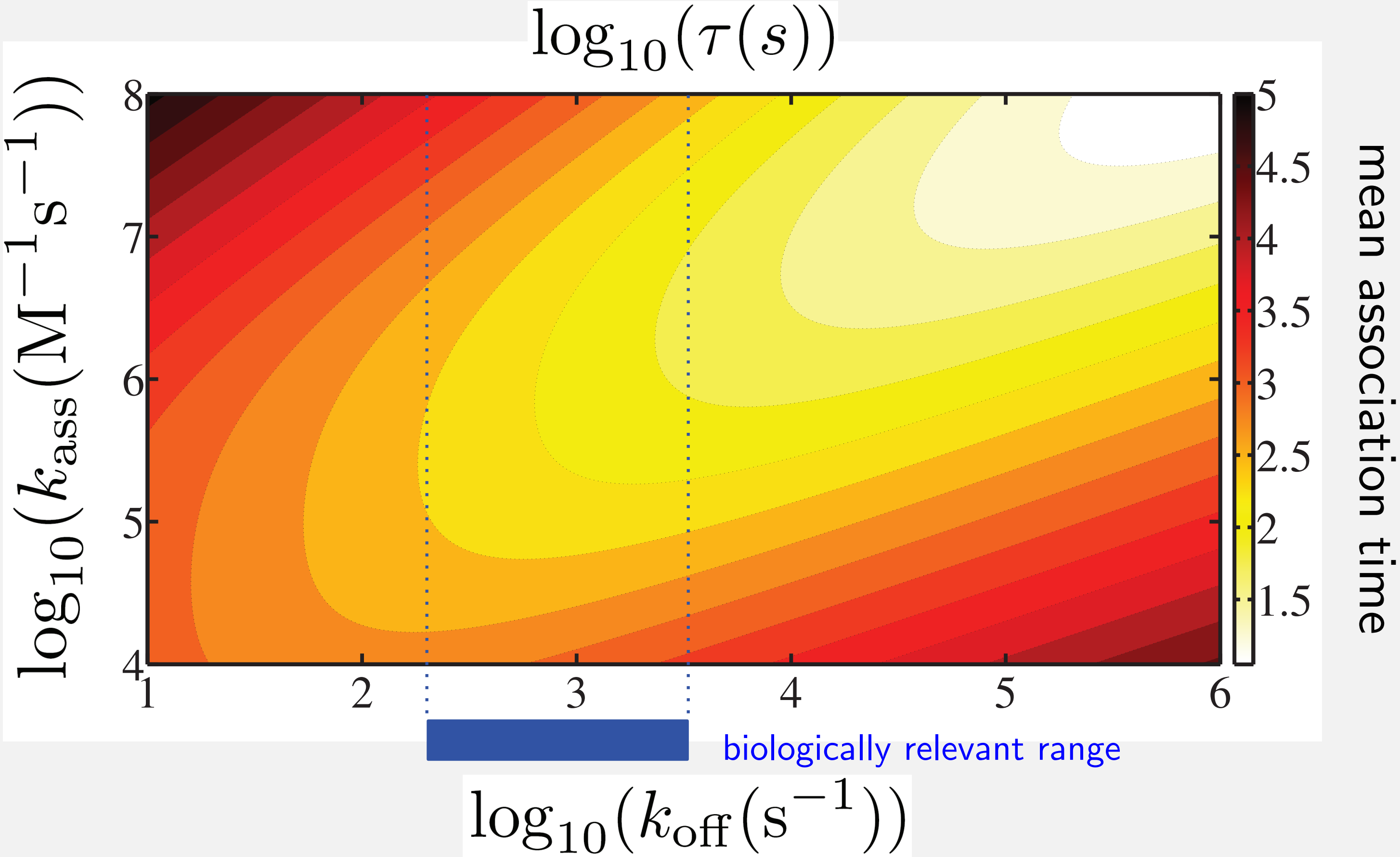
Chromosome is approx an SAW

[M Buenemann & P Lenz, PLoS ONE (2010)]



M Bauer & RM, PLoS ONE (2013)

In vivo gene regulation consistent with facilitated diffusion



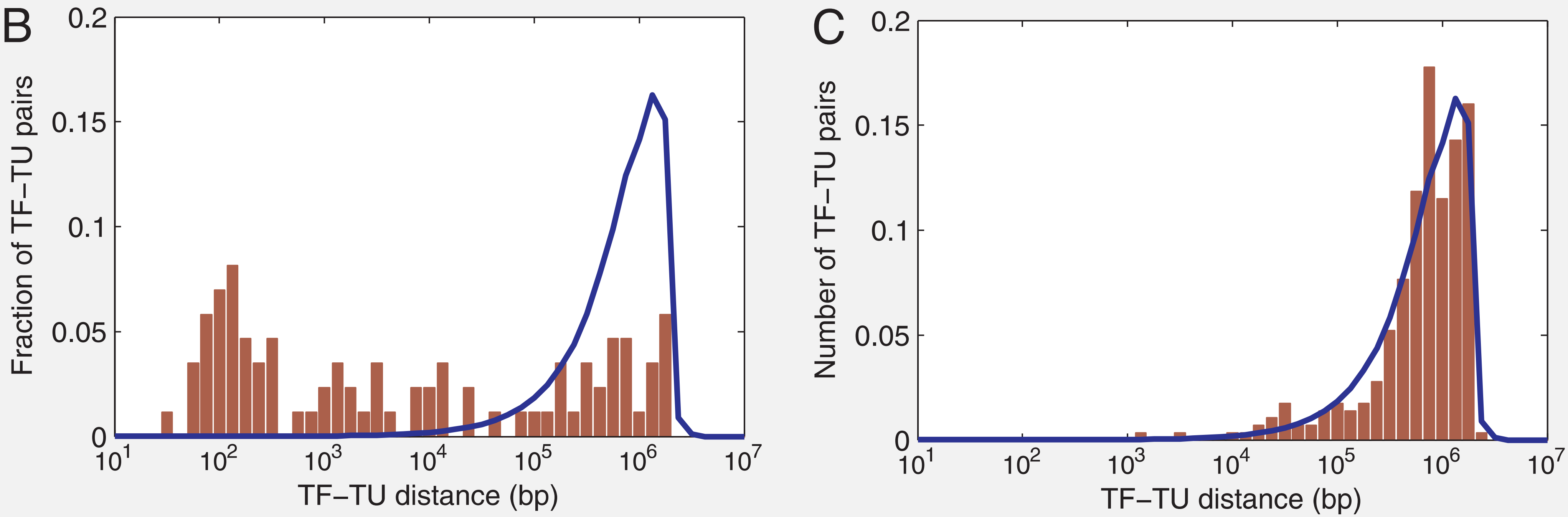
@ optimum the target association time is $\tau \approx 311$sec (no fit parameter)

single molecule experiment: $\tau_{\text{exp}} = 354$sec [Elf et al, Science (2007)]

TF regulation effects gene proximity

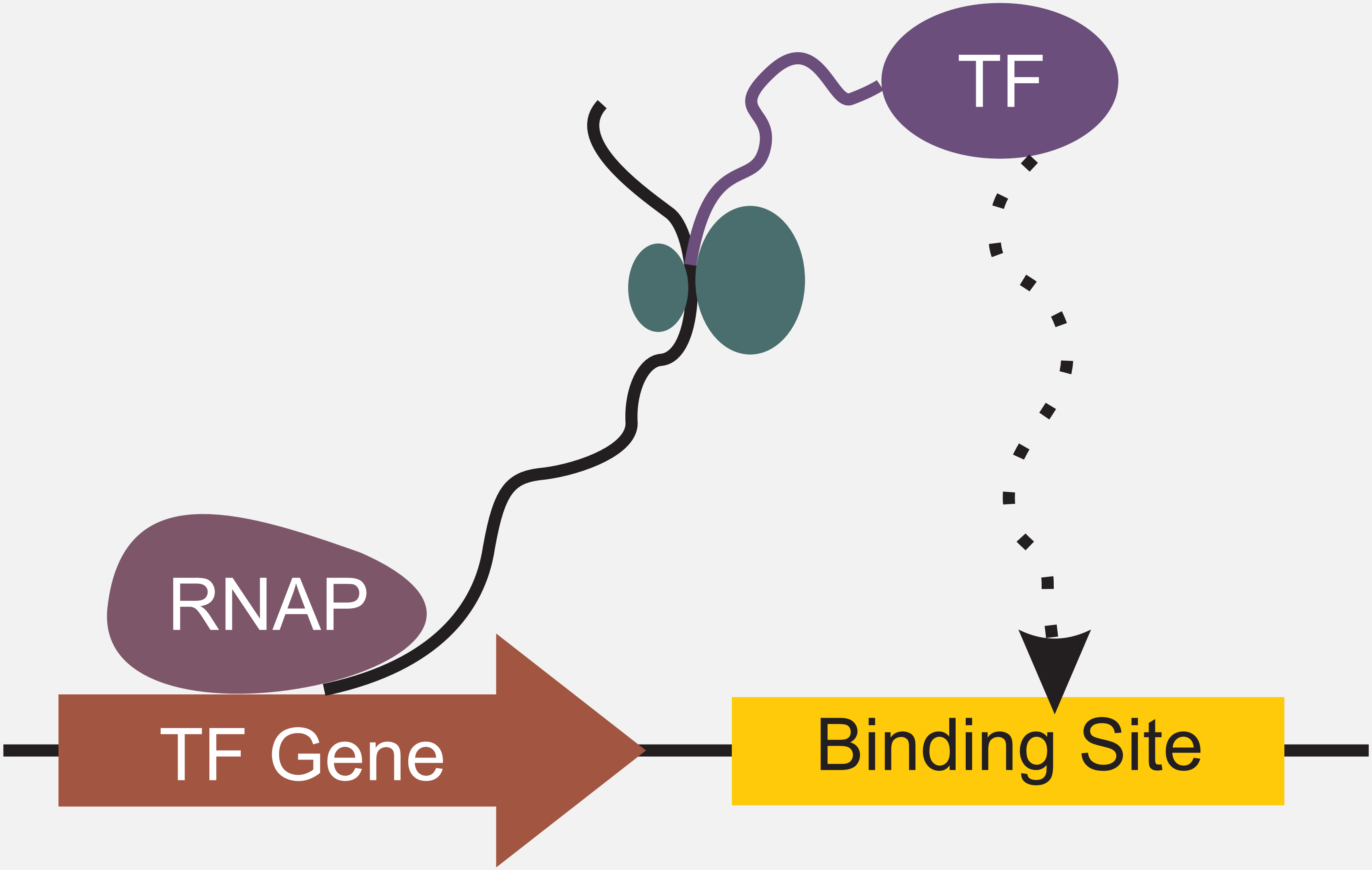
Does distance between genes interacting via TFs matter?

Gene-gene distance distribution for local TFs (regulate < 4 operons, left) and global (regulate ≥ 4 operons, right). Blue line: random location of genes



Kolesov et al, PNAS (2007)

Rapid search hypothesis

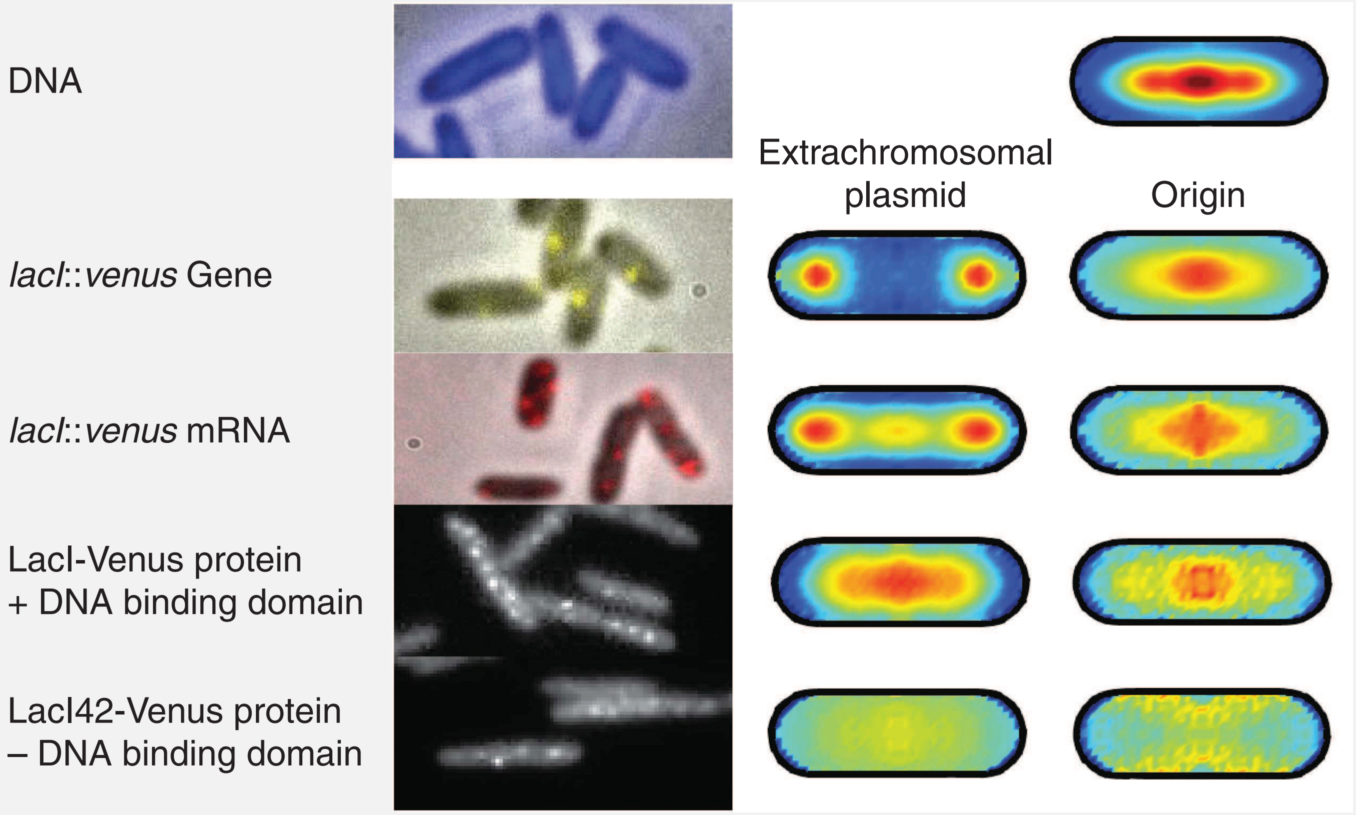


Kolesov et al, PNAS (2007)

Spatial aspects: do gene locations matter?

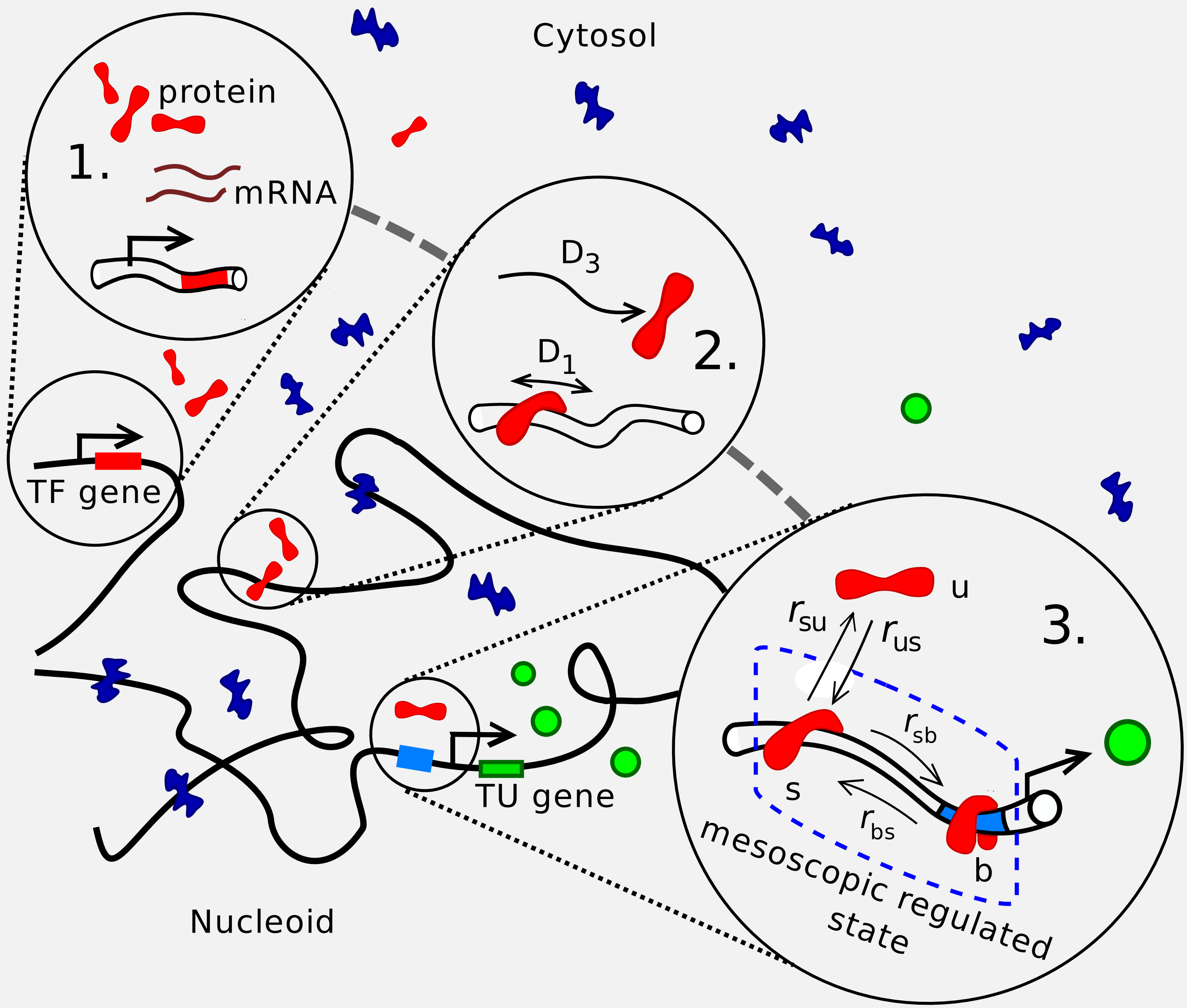
Képès: TF targets are typically located next to or at regular distances from the TF gene $\rightarrow$ TF gene-target pairs close in 3D

Kuhlman & Cox: • localisation of TF near TF gene • TF distribution highly heterogeneous • TF gene influences distribution



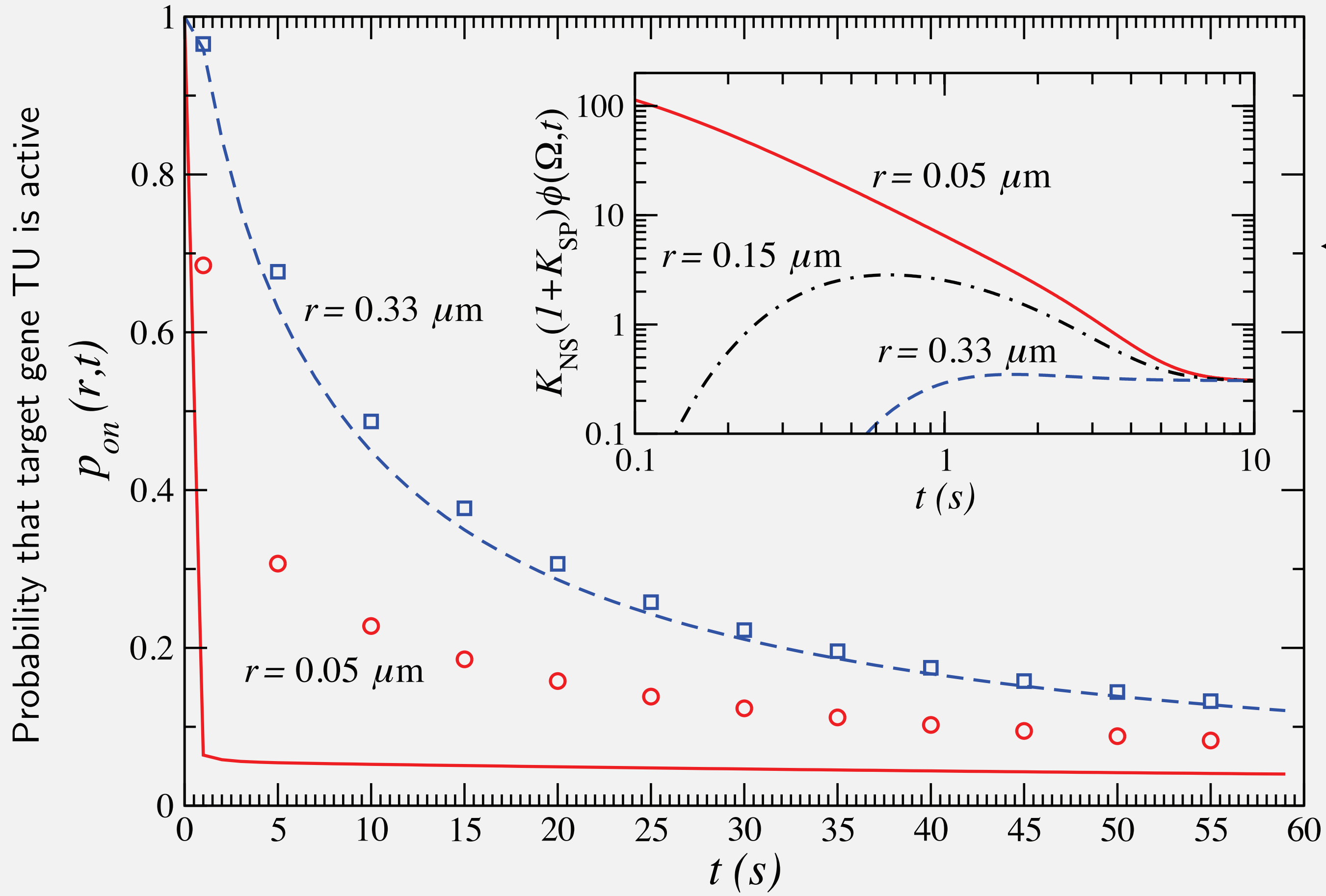
Kepes et al, J Mol Biol (2004); Kuhlman & Cox, Mol Syst Biol (2012)

Transient intracellular signalling is diffusion controlled



O Pulkkinen & RM, PRL (2013)

Result 1: transient response to repression



← TF concentration @ TU

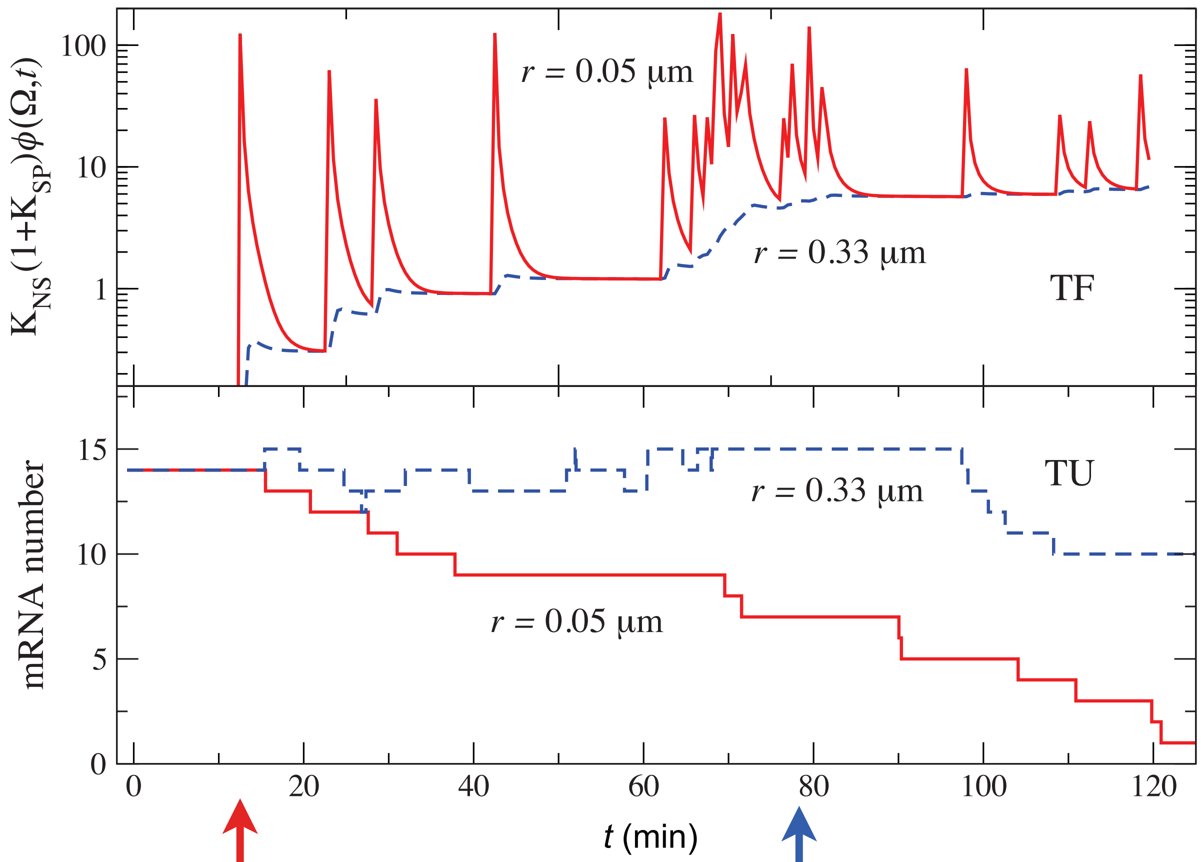
Mean field approximation (full & dashed lines):

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

O Pulkkinen & RM, PRL (2013)

Result 2: time dependence of gene response

Sample paths from MC simulations:



First repressor binding at $r = 0.05$ μm

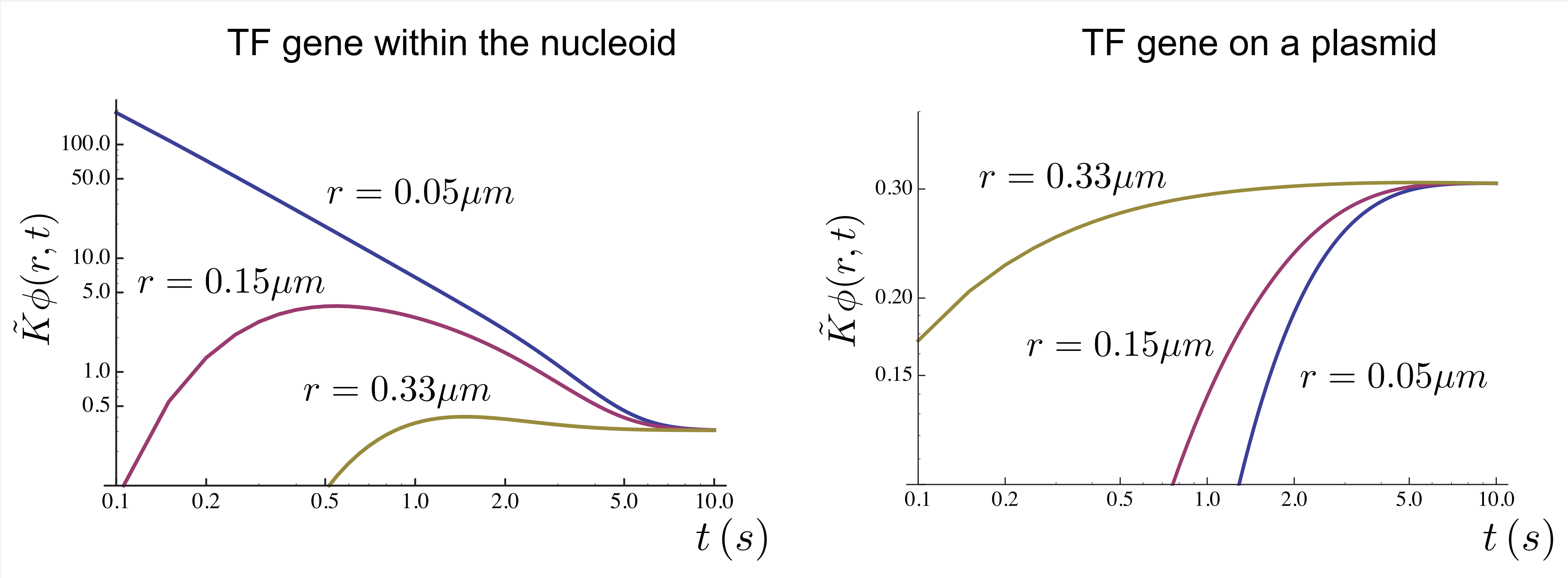
First repressor binding at $r = 0.33$ μm

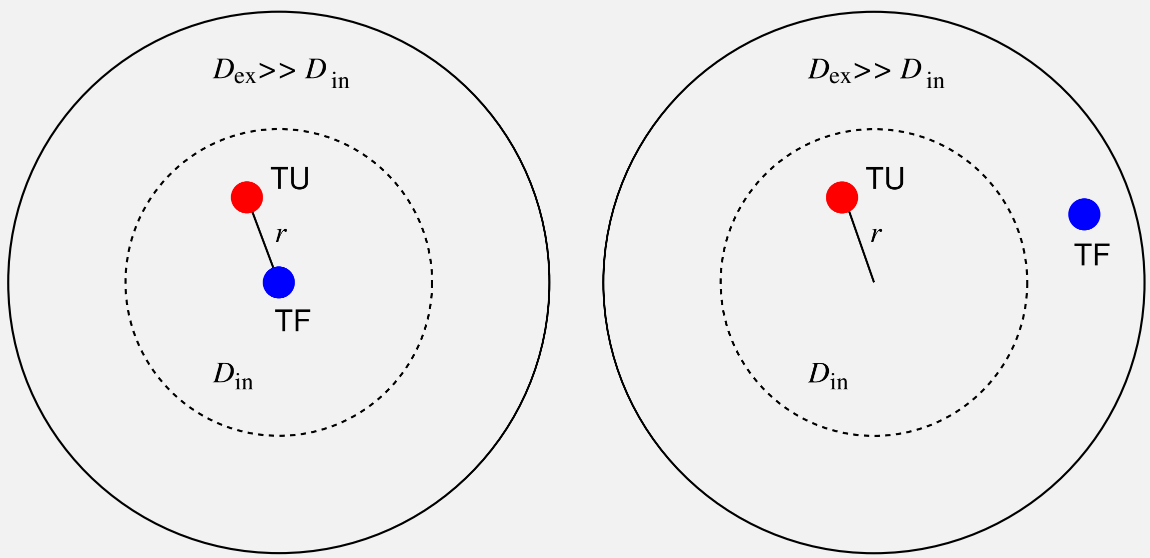
TF density at the target operator

Target expression

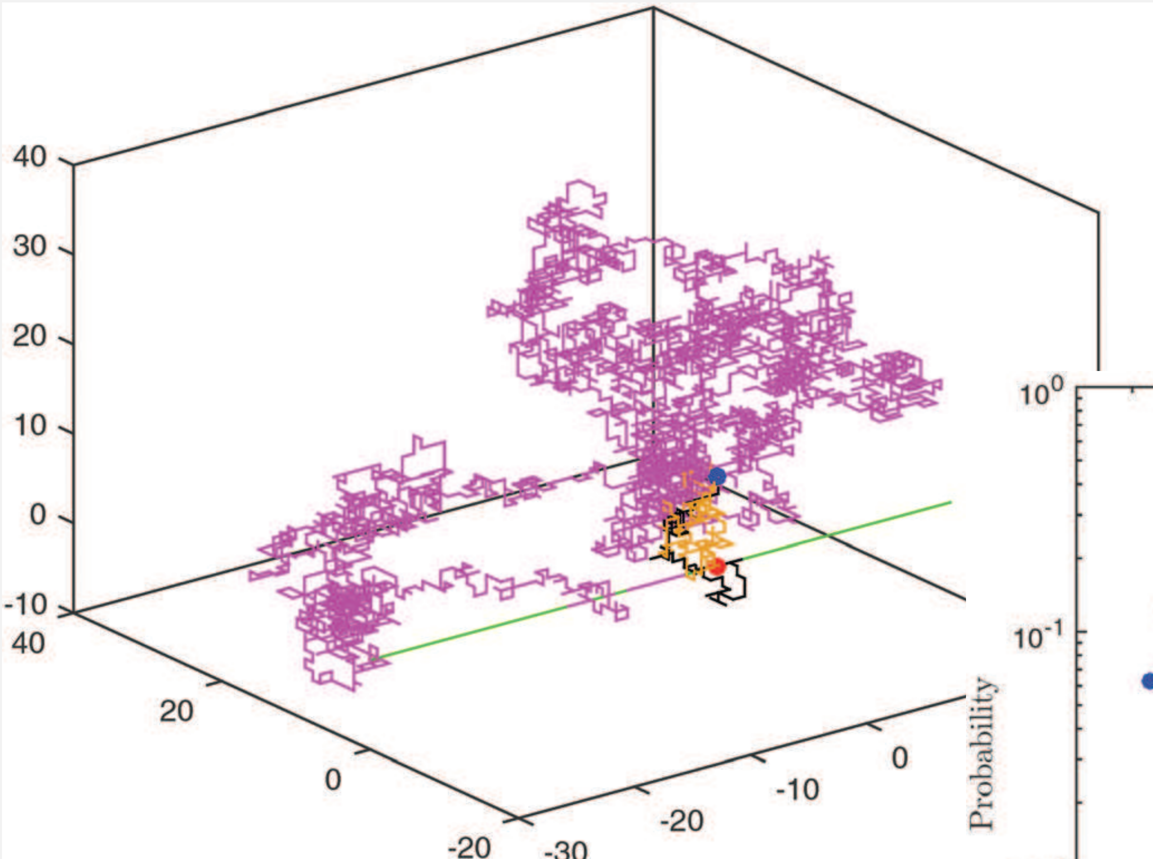
O Pulkkinen & RM, PRL (2013)

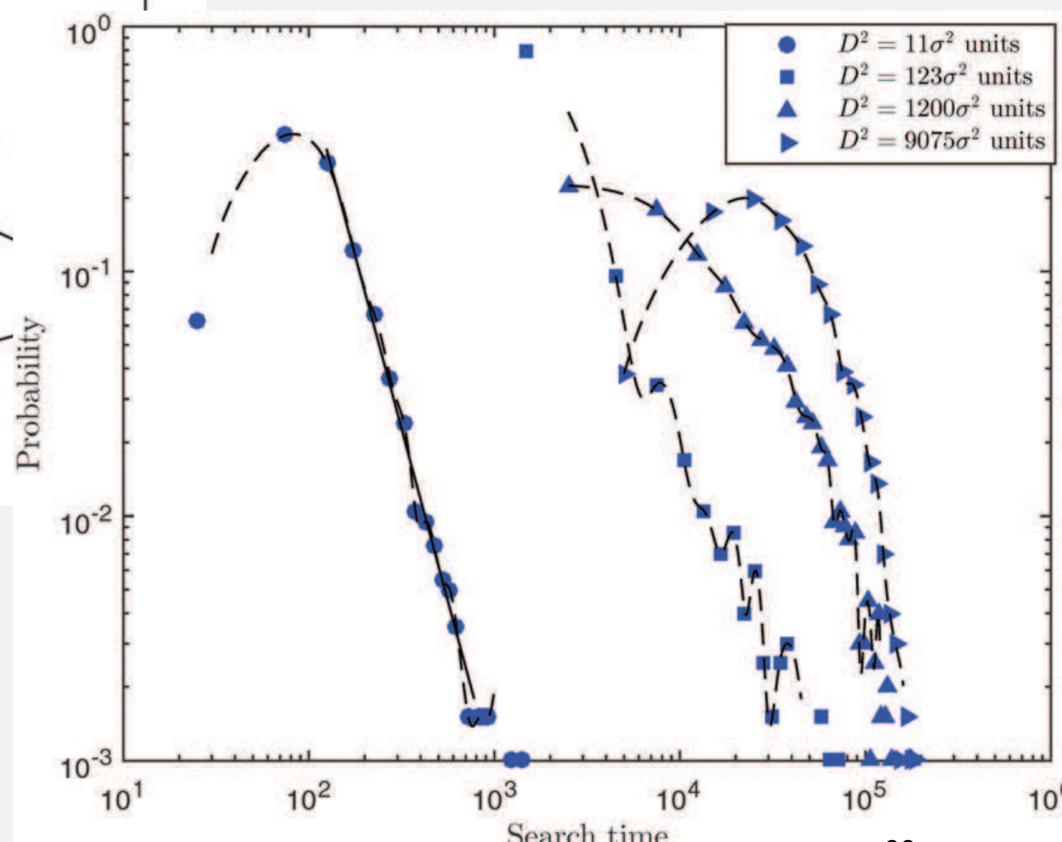
Result 3: gene location matters





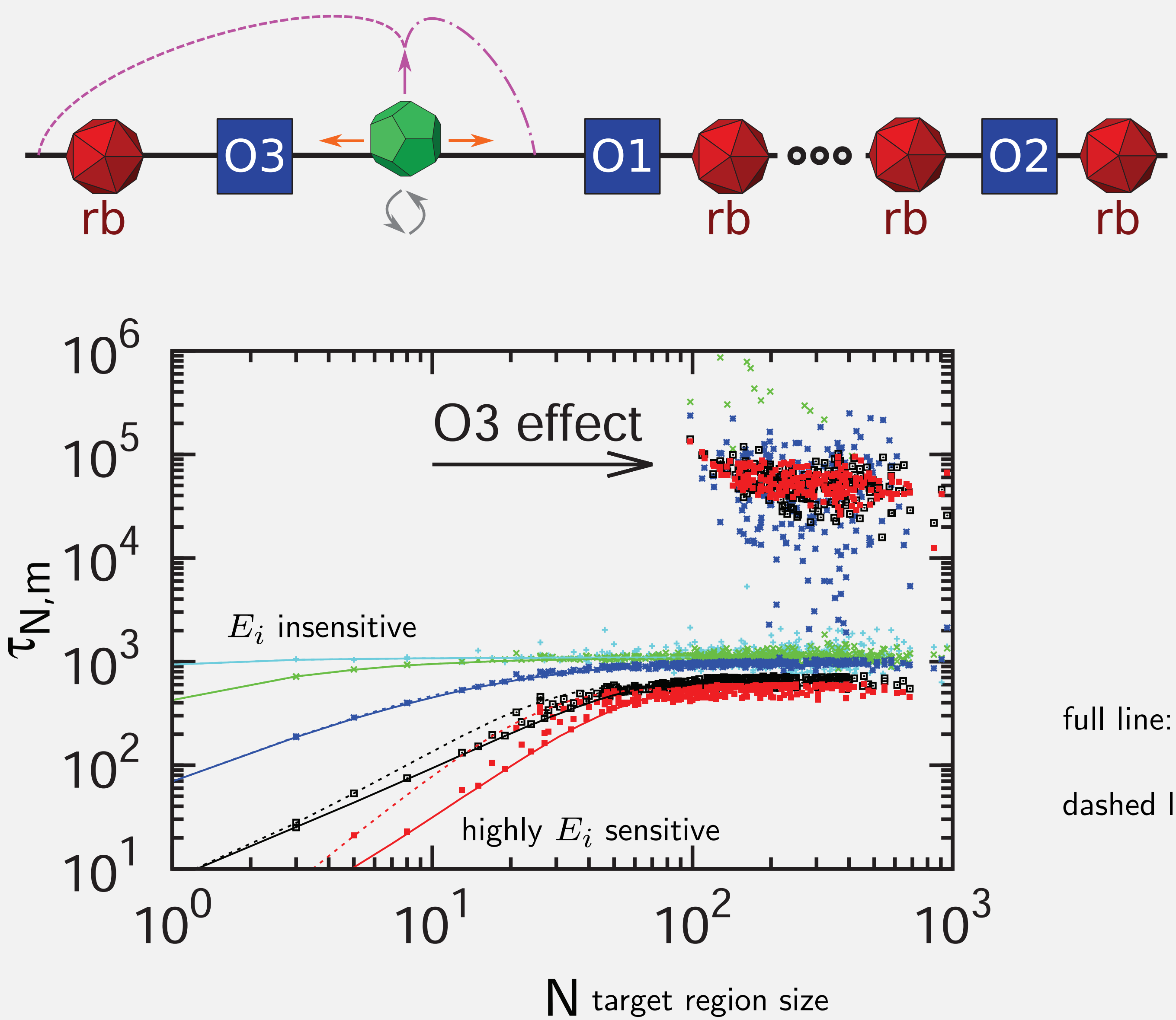
Numerical analysis confirms relevance of proximity effect





P Kar, AV Cherstvy & RM, PCCP (2018)

Sequence (binding energy) effects on target search time

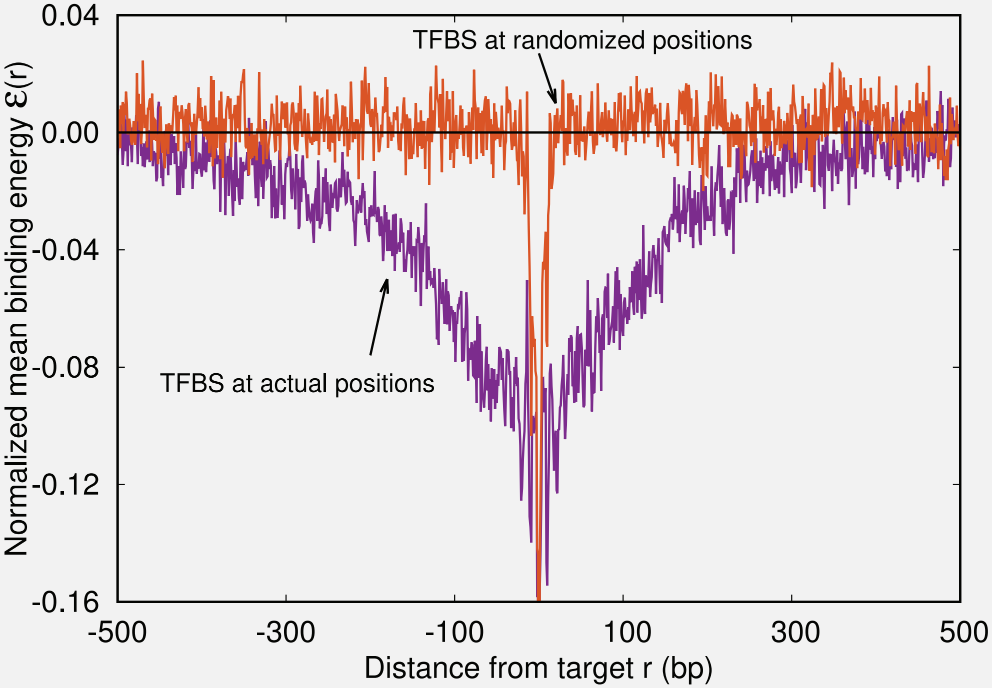


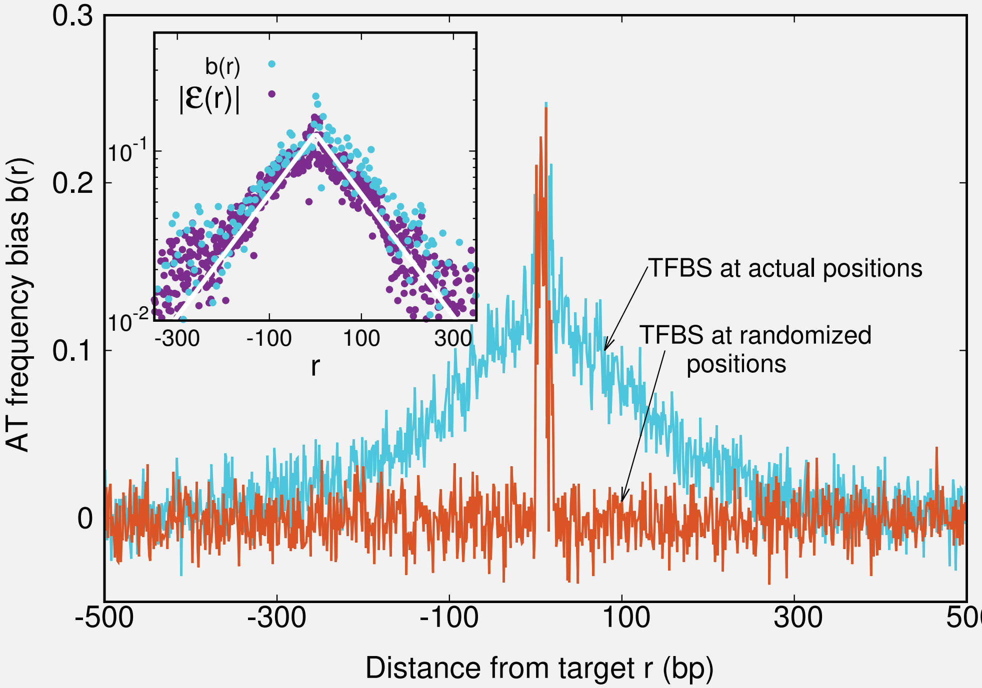
full line: centred target

dashed line: target @ boundary

M Bauer & RM, Sci Rep (2015)

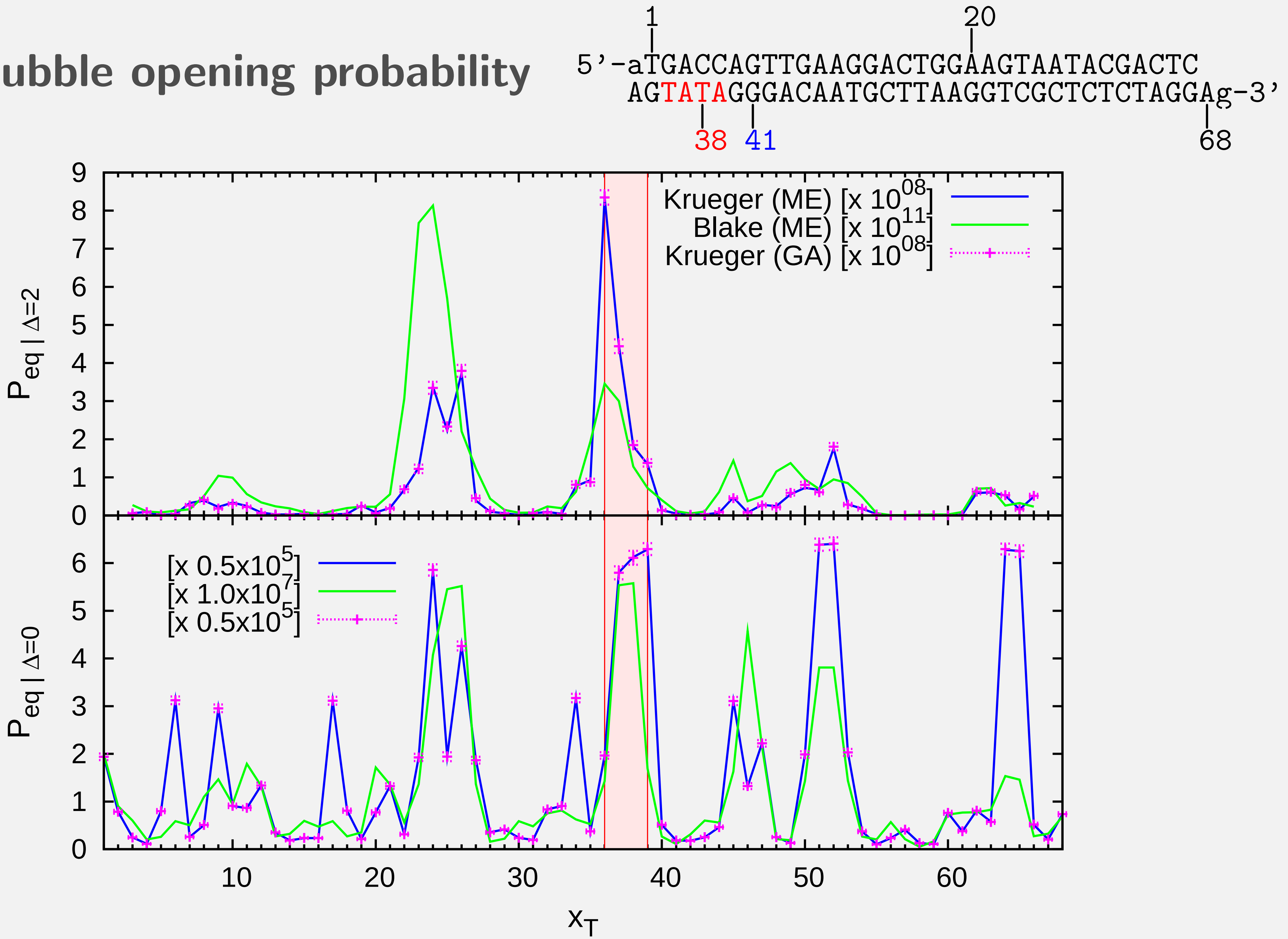
Energetic funnel facilitated diffusion



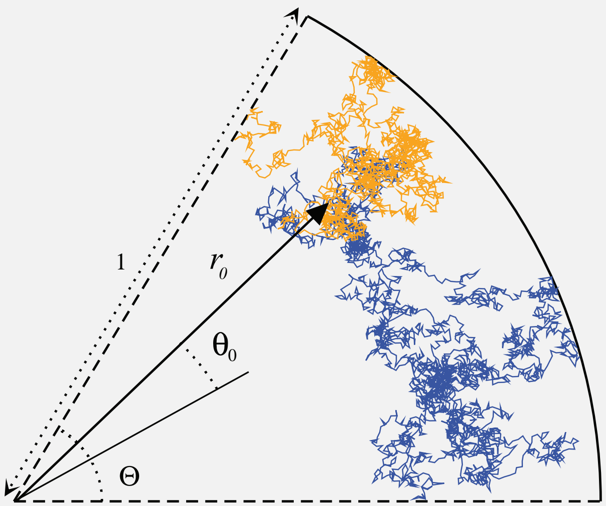


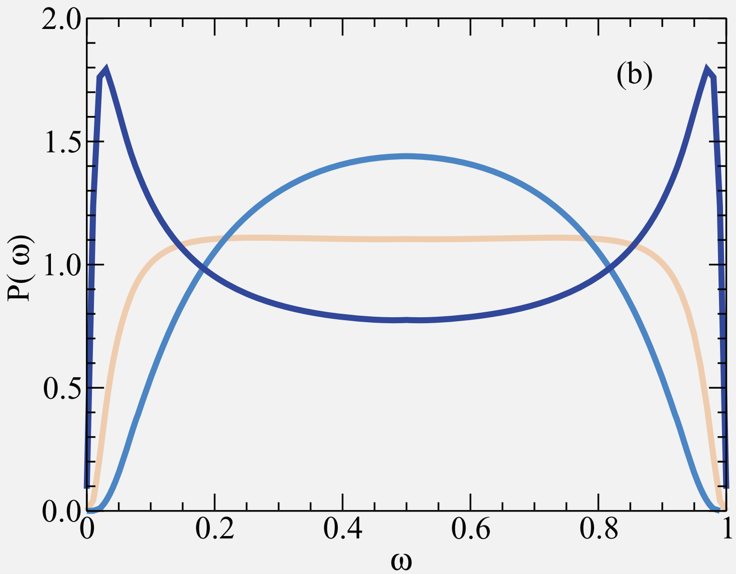
M Cencini & S Pigolotti, NAR (2017)

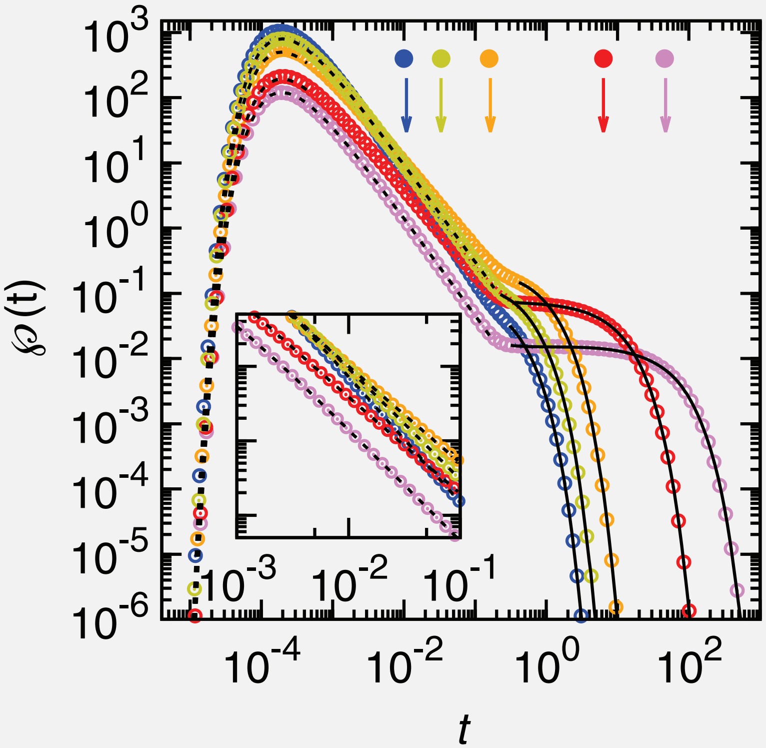
Bubble opening probability

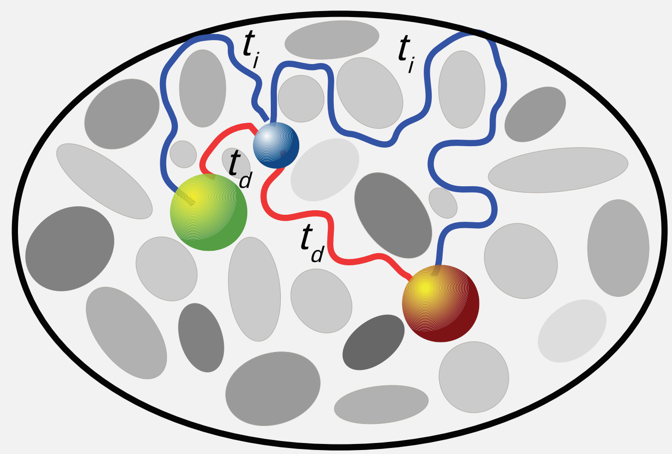


First-past-the-post: few-encounter limit & geometry control



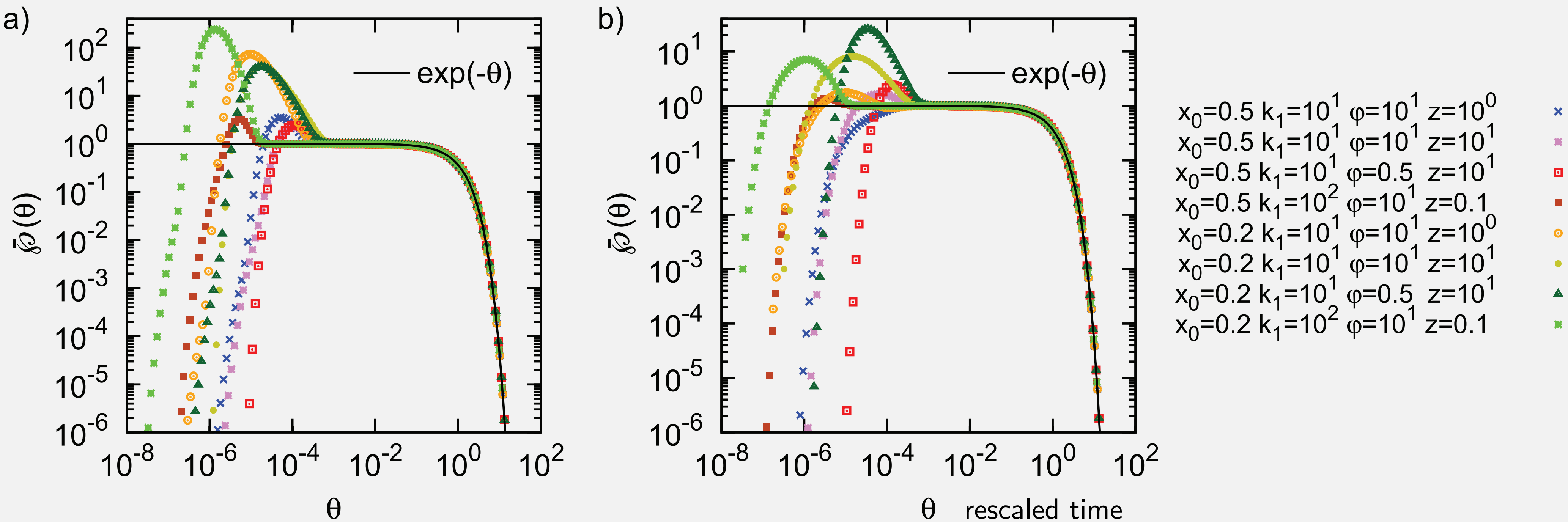


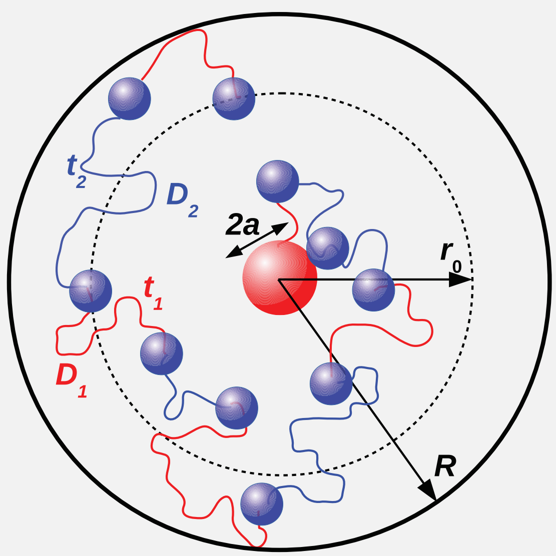




T Mattos, C Mejía-Monasterio, RM & G Oshanin, PRE (2012); A Godec & RM, PRX (2016); Sci Rep (2016)

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



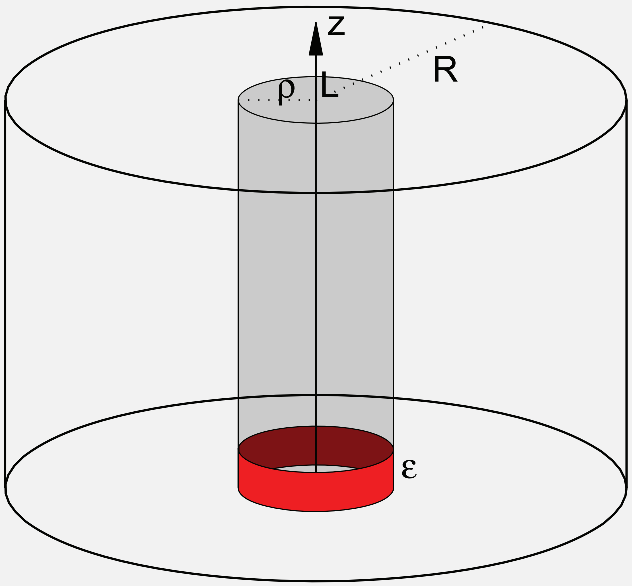


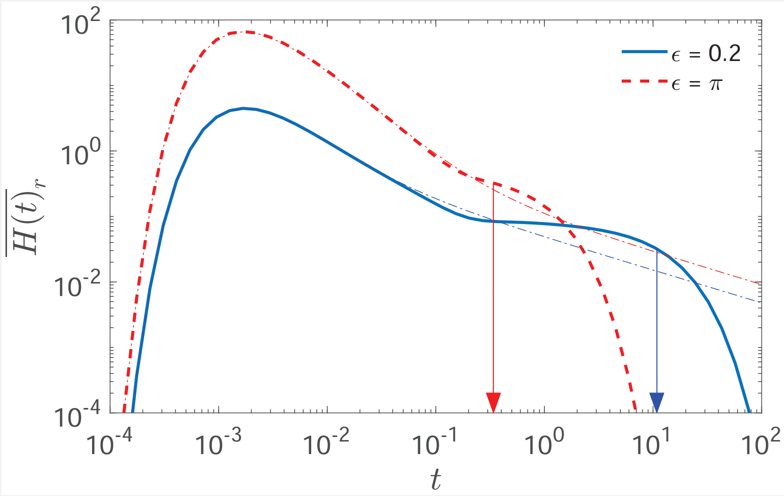
Search mode /w D_1

& recognition mode /w D_2

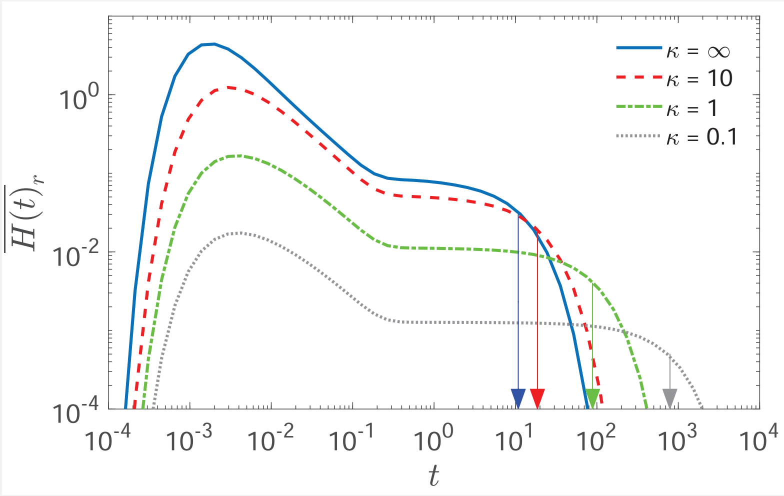
A Godec & RM, JPA (2017)

Few-encounter effect in cylindrical domain /w finite reactivity





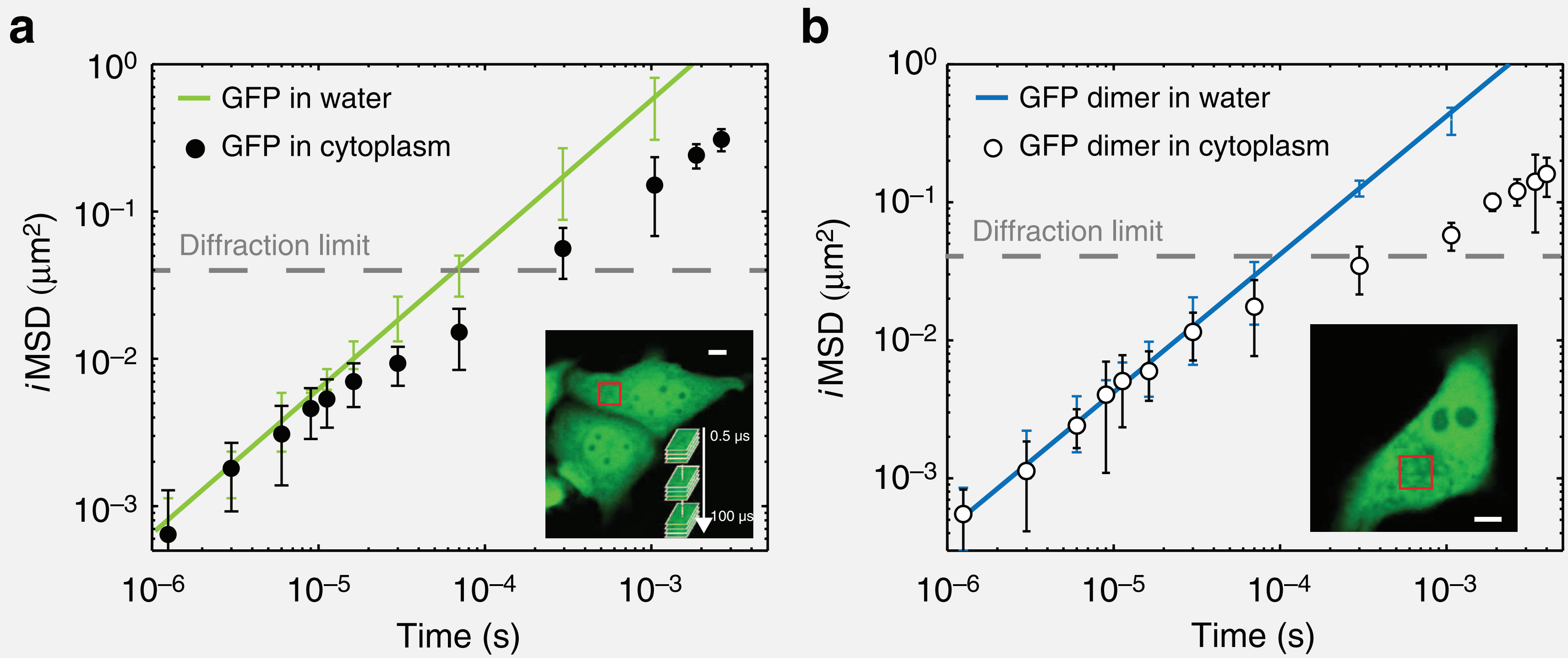
perfect reactivity $\kappa = \infty$



target size $\epsilon = 0.2$

D Grebenkov, RM & G Oshanin, NJP (2017); E-print (2018)

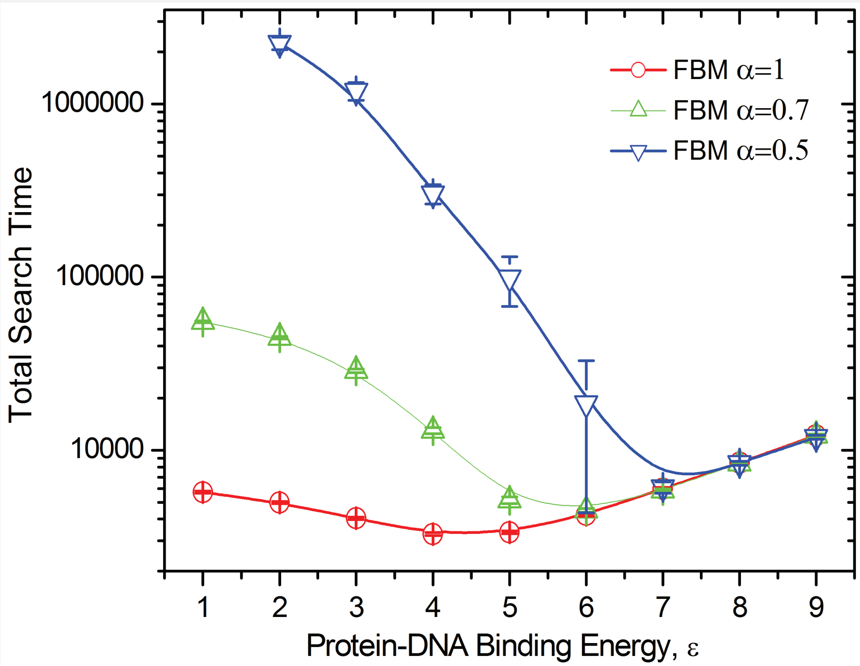
Anomalous diffusion of GFP in cell cytoplasm & nucleus

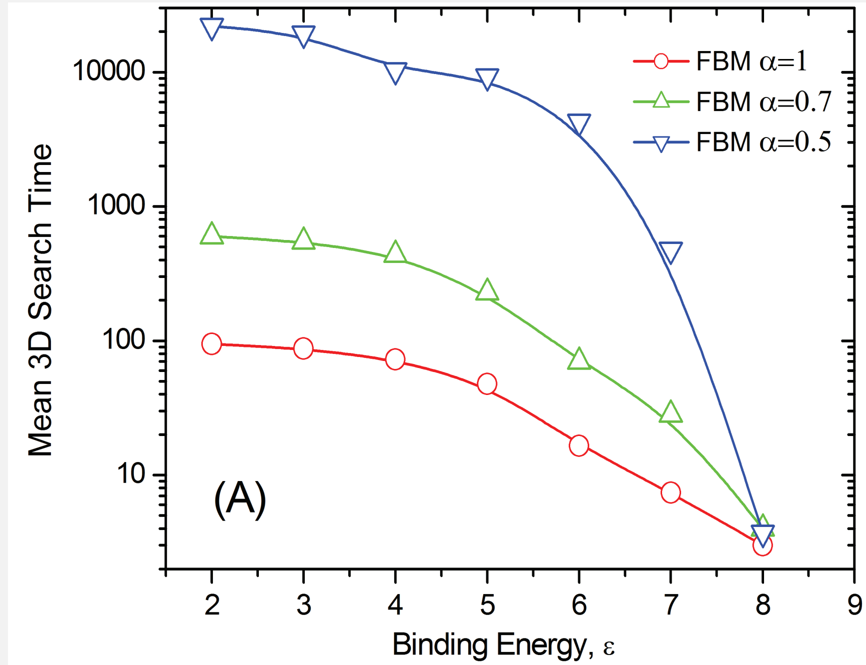


$\langle \mathbf{r}^2(t) \rangle \simeq K_\alpha t^\alpha$: Subdiffusion when $0 < \alpha < 1$

C di Renzo, V Piazza, E Gratton, F Beltram & F Cardarelli, Nat Comm (2014)

Anomalous facilitated diffusion





Many unknowns in the modelling:

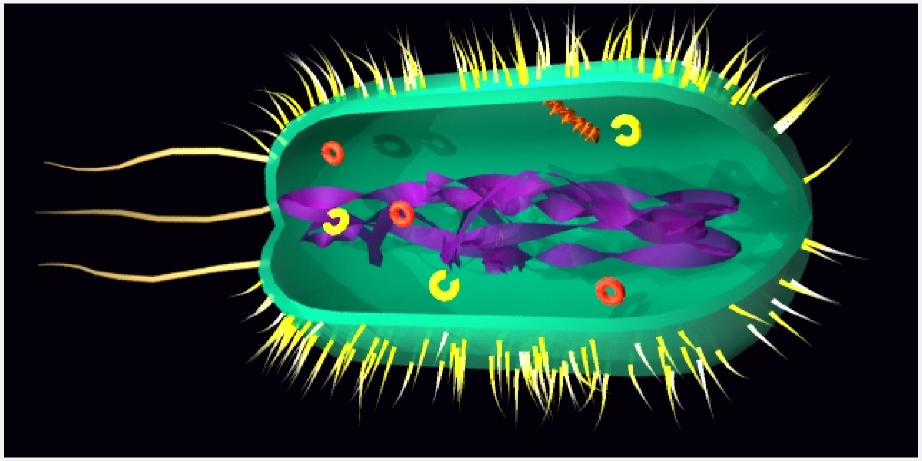
Physical mechanism of anomalous diffusion & cutoff time of anomalous motion?

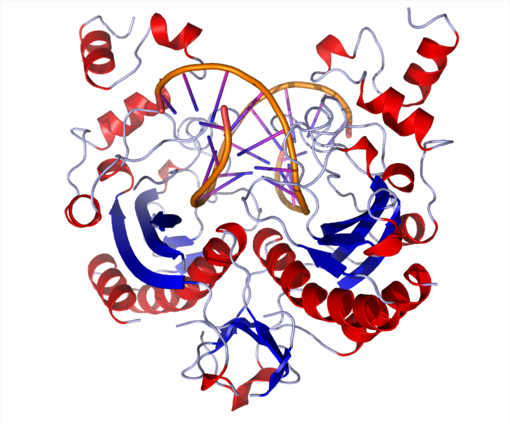
Effects of crowders with different sizes: see eg Shin et al, Soft Matter (2015) influencing immediate rebinding?

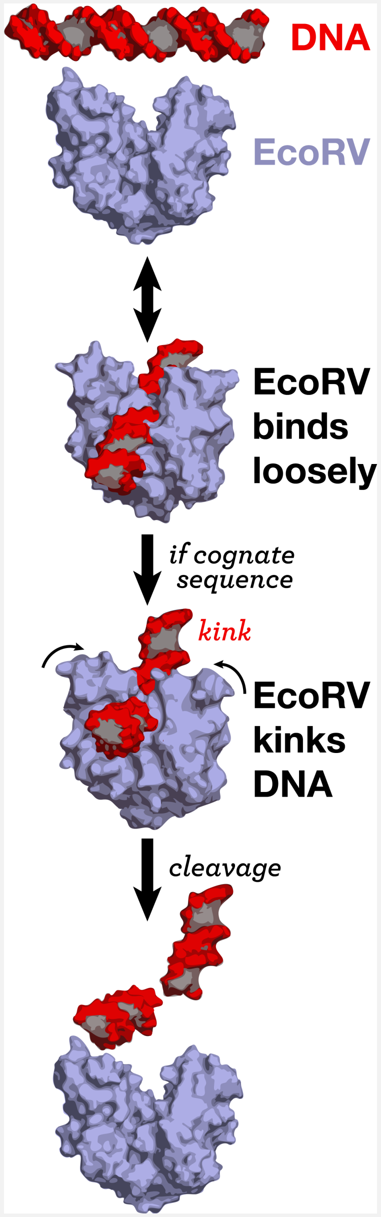
DNA conformations & dynamics due to crowding & active motion: Shin et al, NJP (2015), NJP (2016)

L Liu, AG Cherstvy & RM, JPC (2017)

Subdiffusion does not compromise cellular fitness

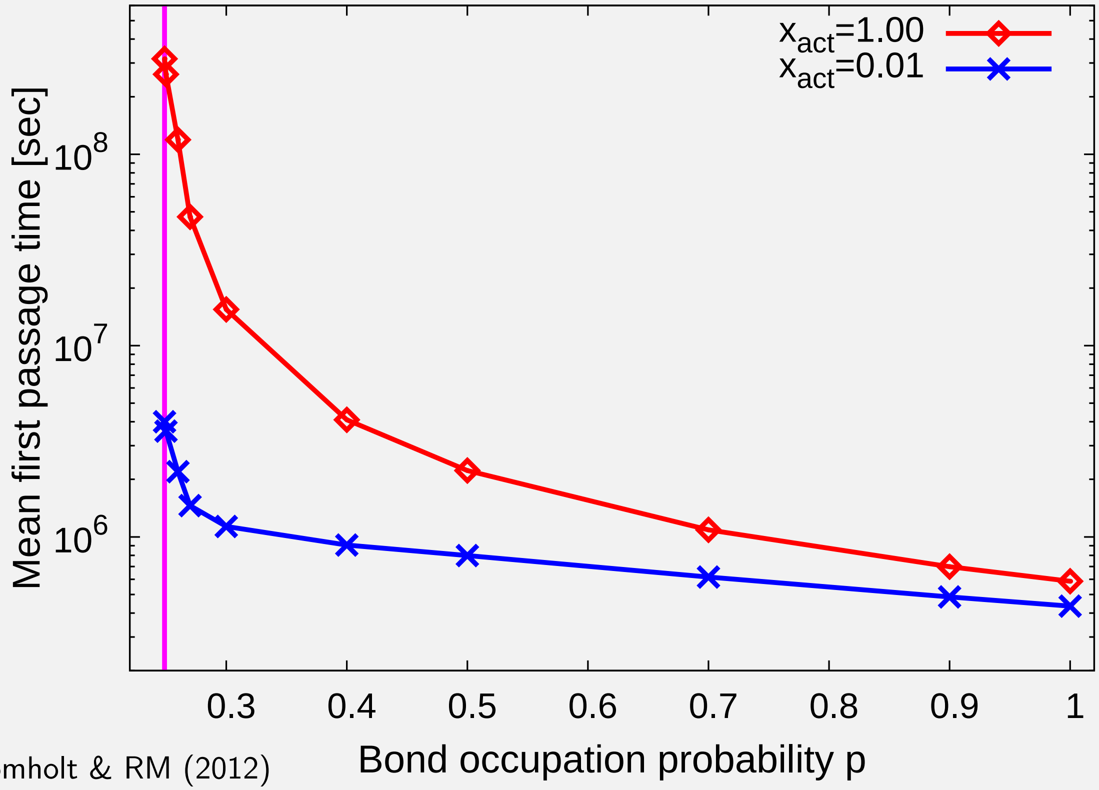






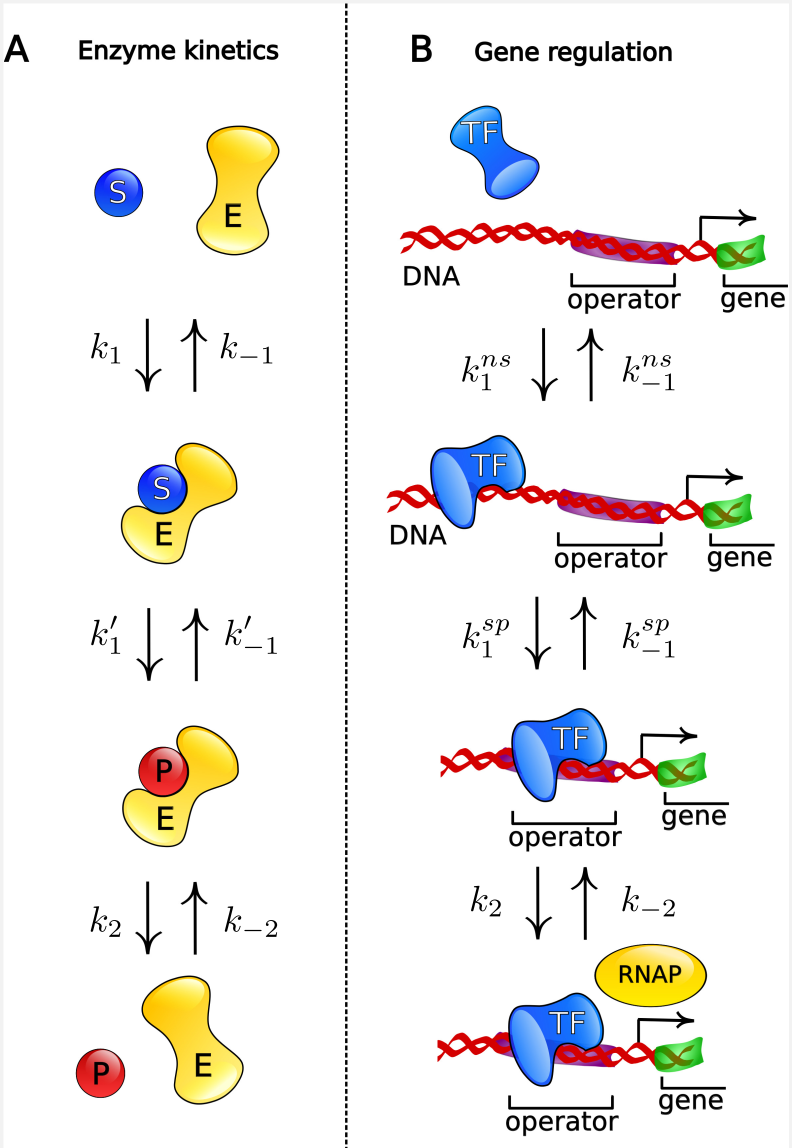
Restriction enzyme
EcoRV
Binding mode:
1% active
99% inactive

Mutant enzyme
Binding mode:
100% active



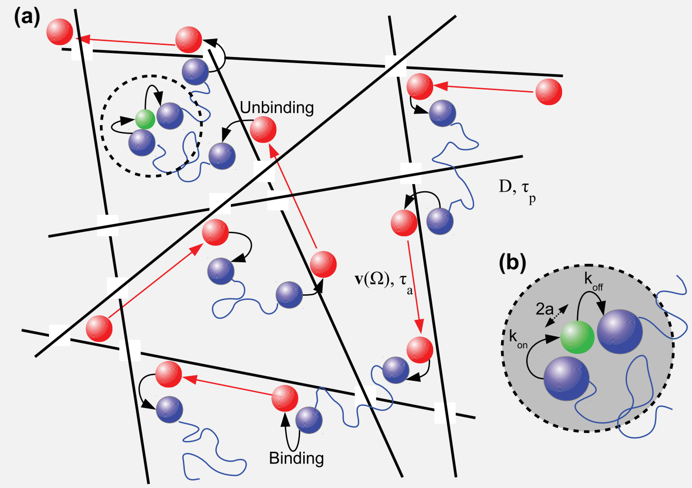
L Esmaeili Sereshki, MA Lomholt & RM (2012)

Low-# Michaelis-Menten

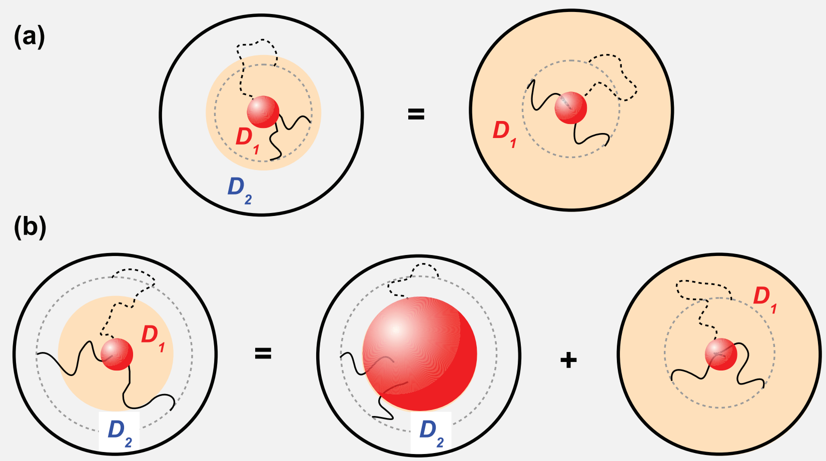


O Pulkkinen & RM, Sci Rep (2015)

Active sensing limit



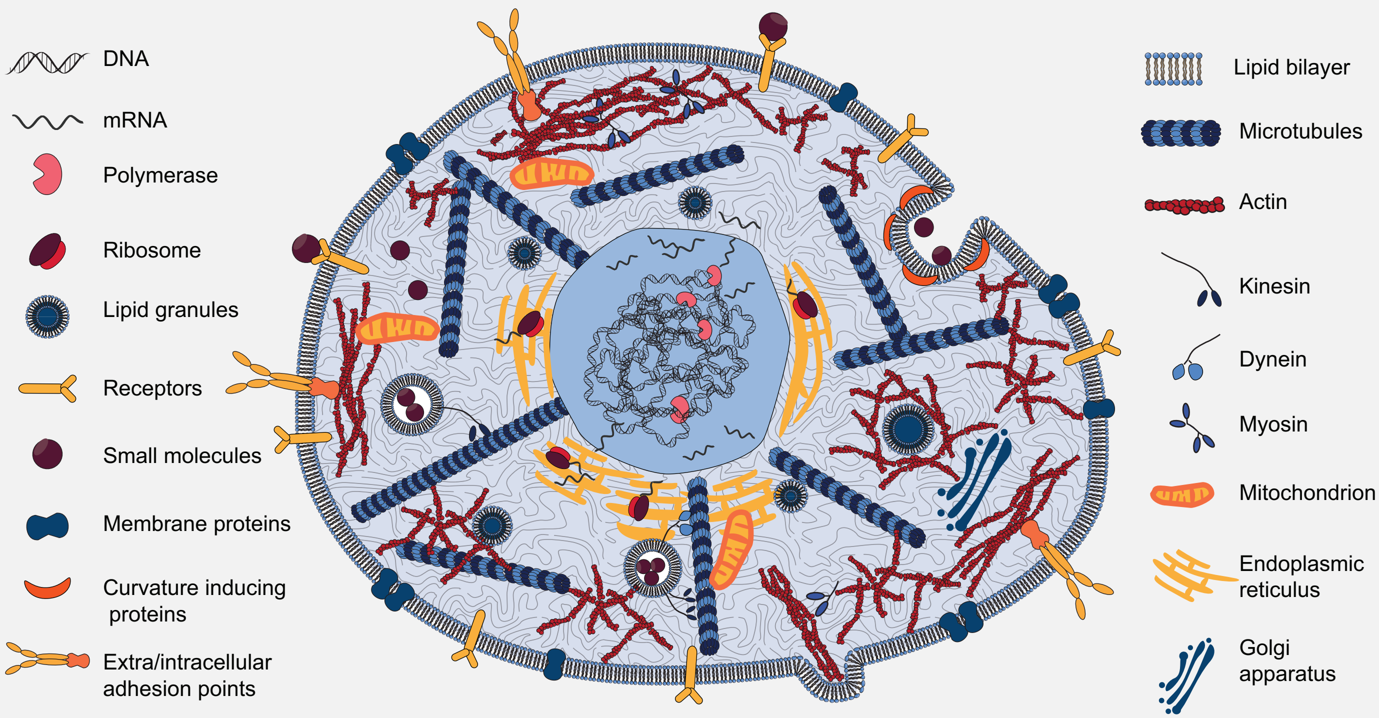
Heterogeneous FPT



New time scale in FP PDF!

A Godec & RM, PRE(R) & PRE (2015), Sci Rep (2016)

Gene regulation in eukaryotic cells

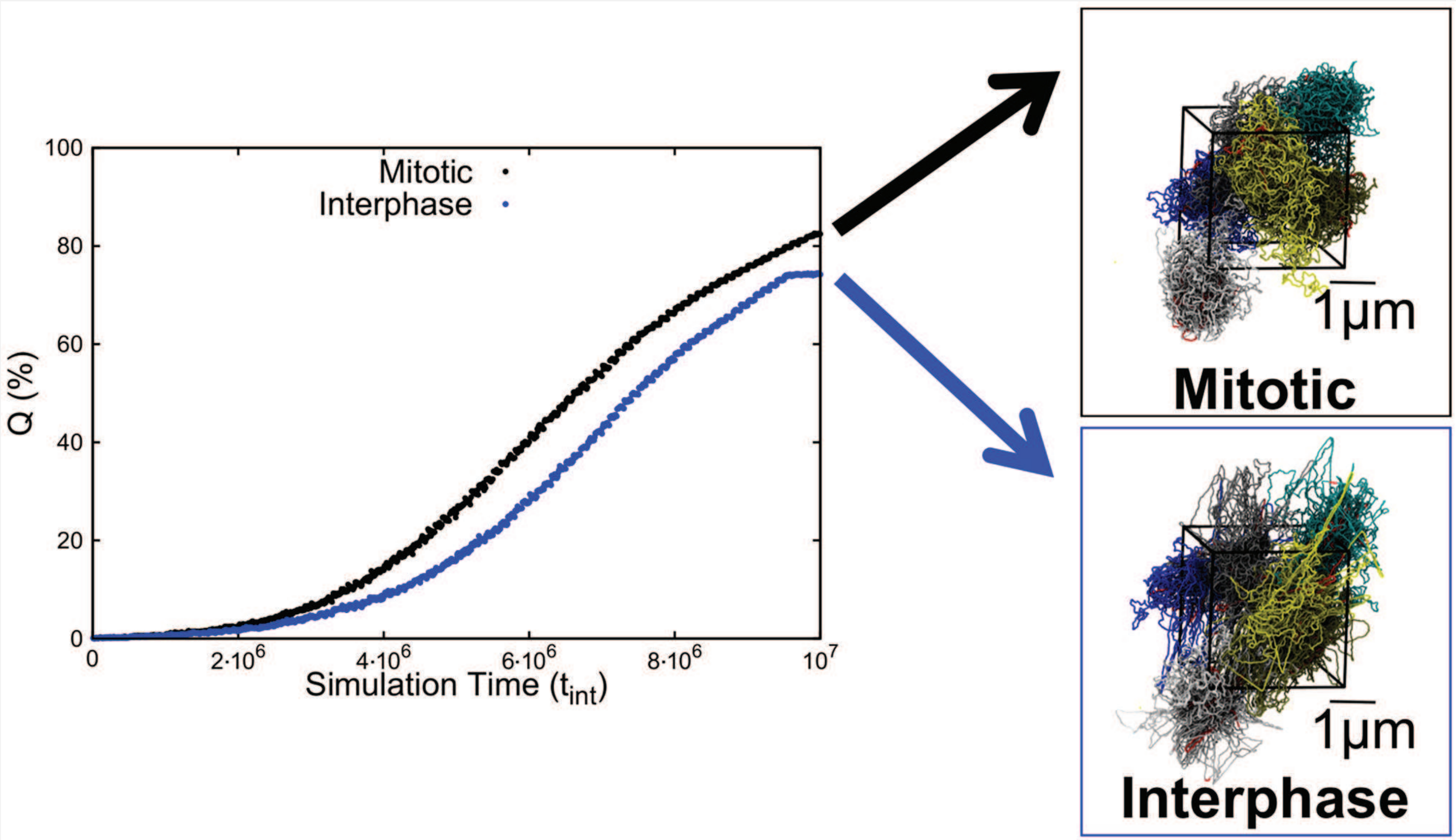


Exchange versus nucleic membrane, chromosomal dynamics & packaging

Active motion: motor transport, drag, or swirling (cytoplasmic streaming), see, e.g., Seisenberger et al, Science (2001) or Reverey et al, Sci Rep (2015)

K. Nørregaard, RM, C. Ritter, K. Berg-Sørensen & L. Oddershede, Chem Rev (2017)

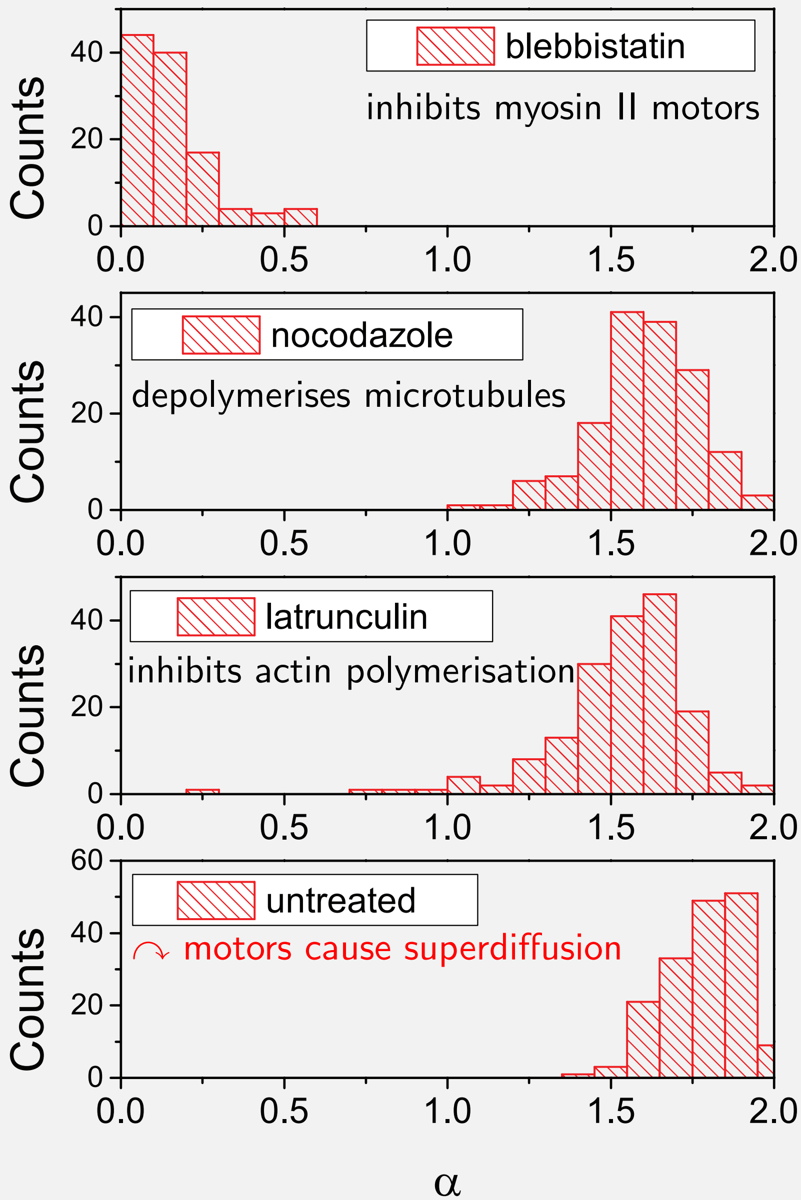
Colocalisation still exists in the nucleus

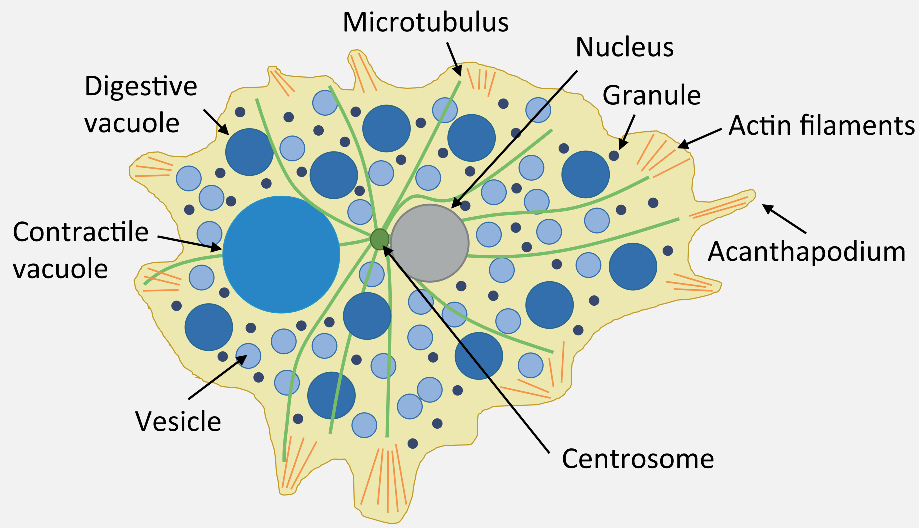


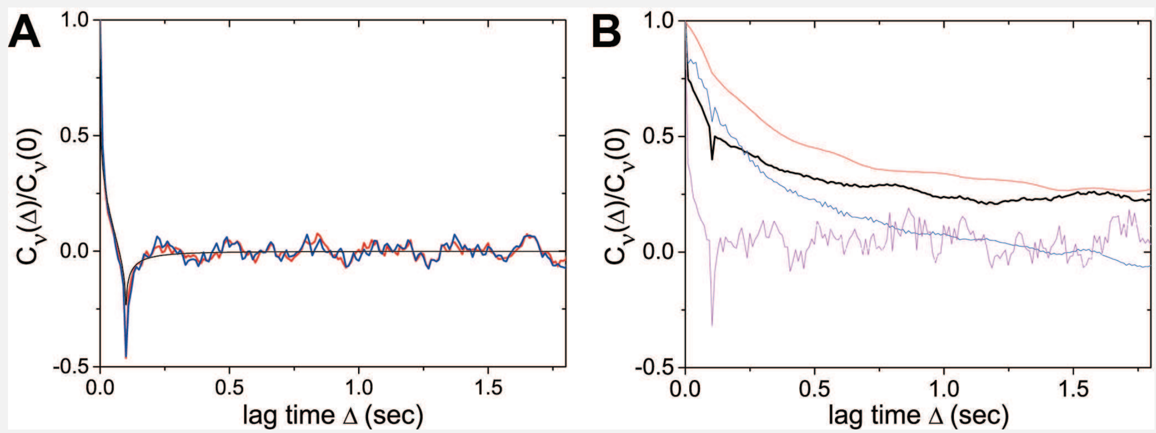
Increase of percentage Q of coregulated pairs of genes in chromosome 19 which colocalise during the MD protocol. Red (???) highlighted regions designate chromosome regions involved in the coregulatory network

M Di Stefano, A Rosa, V Belcastro, D di Bernardo, & C Micheletti, PLoS Comp Biol (2013)

Superdiffusion in living Acanthamoeba castellani





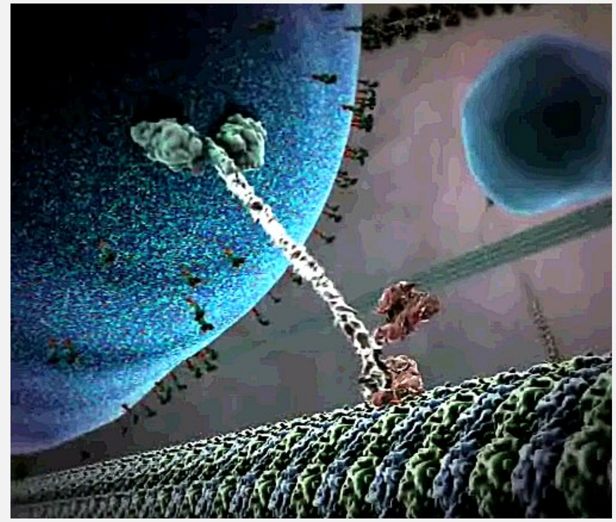


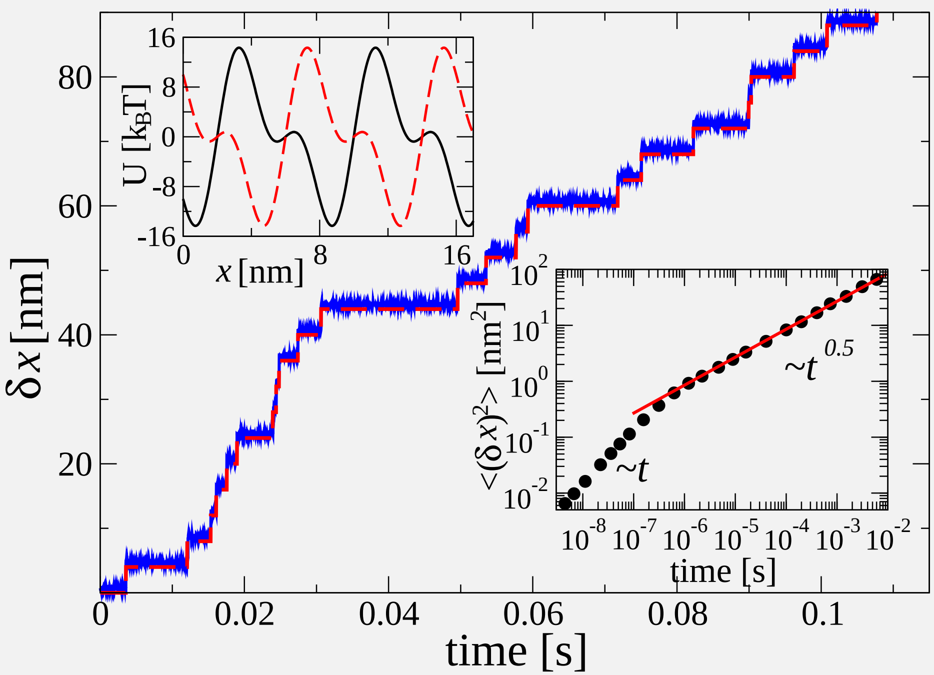
JF Reverey, J-H Jeon, H Bao, M Leippe, RM & C Selhuber-Unkel, Sci Rep (2015)

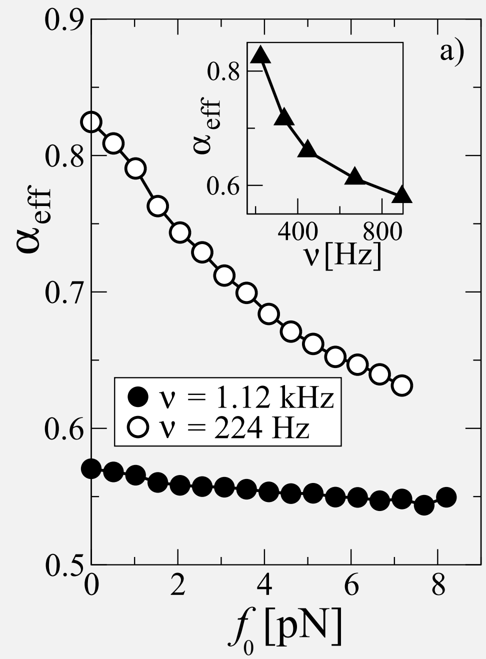
Molecular motor dynamics

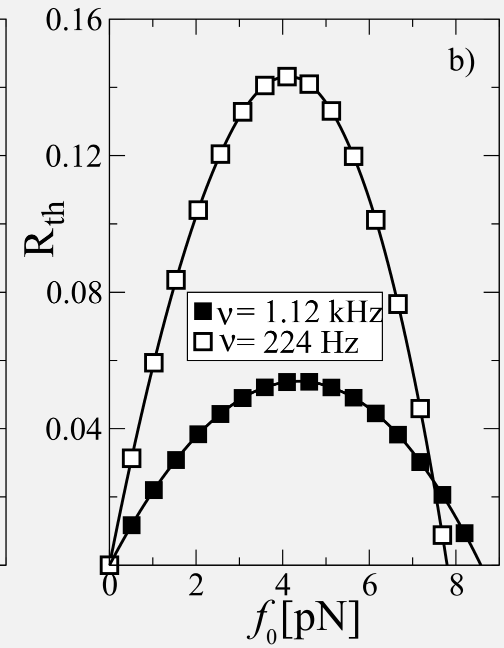
A large cargo subdiffuses freely & causes anomalous transport by the motor in the viscoelastic, crowded liquid of cells:

$$\langle x(t)\rangle \simeq t^{\alpha} \quad \Leftrightarrow \quad \langle \Delta x^2(t)\rangle \simeq t^{2\alpha}$$



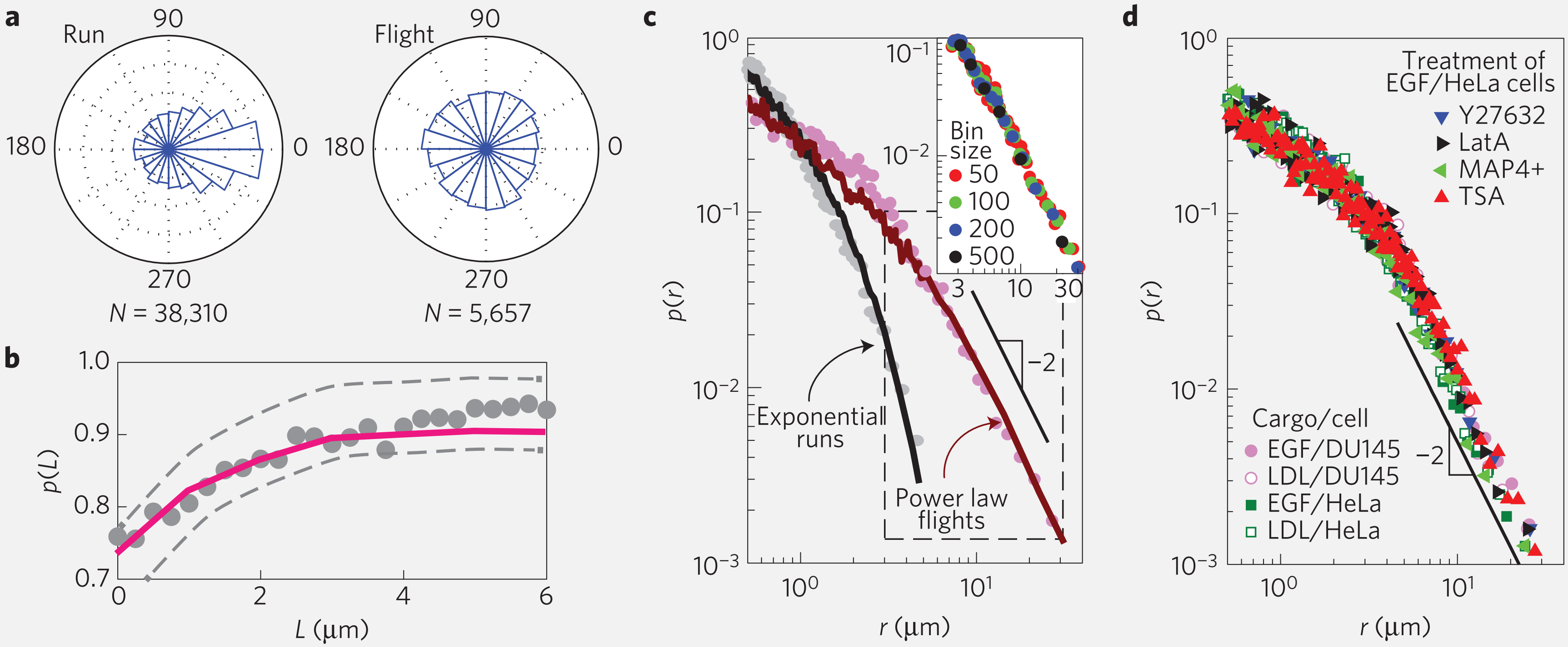






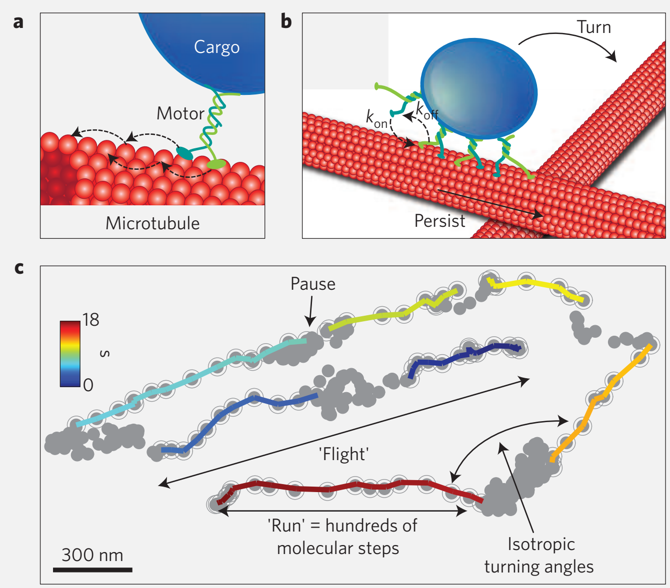
D Robert, T-H Nguyen, F Gallet & C Wilhelm, PLoS ONE (2010); I Goychuk, V Kharchenko & RM, PLoS ONE (2014), PCCP (2014)

Lévy walks of molecular motors in living cells



Run: motor motion on microtubule for $1/k_{\text{off}}$

Flight: consecutive runs persisting in direction

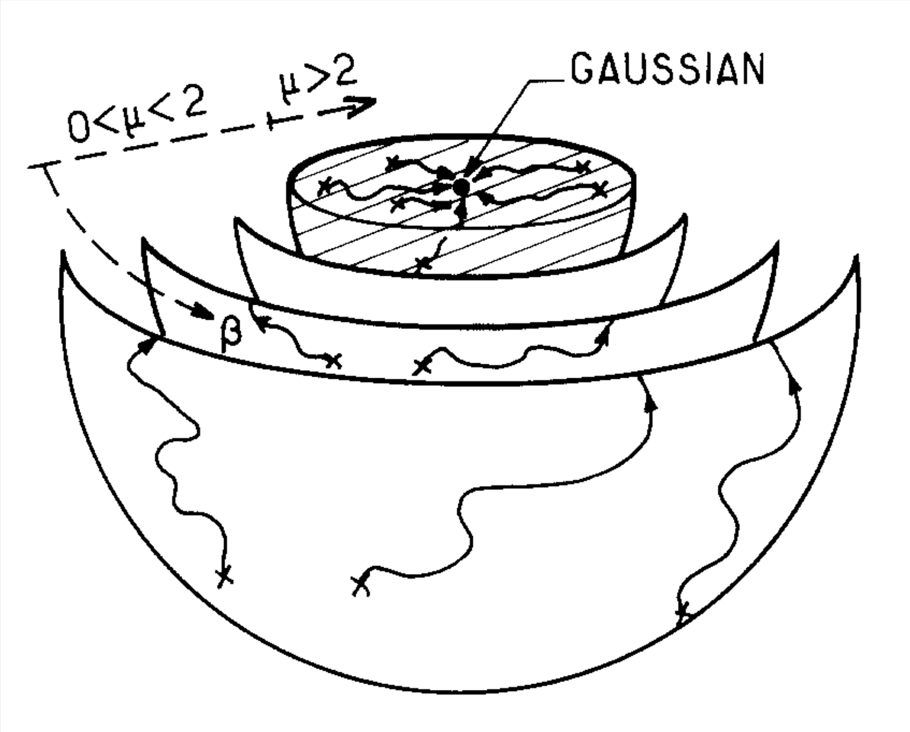


K Chen, B Wang & S Granick, Nat Mat (2015)

Lévy foraging: on the watchout for sparse targets

Rôle of the Central Limit Theorem (de Moivre, 1733)

$$F(X) \simeq \frac{1}{|X|^\mu}$$



JP Bouchaud & A Georges, Phys Rep (1991)

If the distribution of the sum $Y_n = \sum_{i=1}^{n} X_n$ of i.i.d. random variables X_n converges to some distribution P for $n \to \infty$, P is stable. If the variance of Y_n is finite, P is Gaussian (Gnedenko-Kolmogorov GCLT).

$$f_{\alpha,\beta}(x) = \frac{1}{\pi}\mathrm{Re}\int_0^\infty \exp\left(-\mathrm{i}xz - z^\alpha \exp\left\{\mathrm{i}\frac{\pi\beta}{2}\right\}\right) \iff f_{\alpha,\beta}(x) \simeq \frac{1}{|x|^{1+\alpha}}\ (0 < \alpha < 2)$$

Examples: Gauß distribution ($\alpha = 2$), Cauchy/Lorentz distribution ($\alpha = 1$)

The Lévy flight model

Ingredients: Poisson waiting time and Lévy jump length distribution:

$$\psi(t) = \tau^{-1} \exp\left(-t/\tau\right) \quad \lambda(x) = \mathsf{L}_\alpha(x,\sigma) \sim \sigma^\alpha / |x|^{1+\alpha}$$

Fractional diffusion equation:

$$\frac{\partial}{\partial t} P(x,t) = K^\alpha \frac{\partial^\alpha}{\partial |x|^\alpha} P(x,t) \quad \therefore \quad K^\alpha = \frac{\sigma^\alpha}{\tau}$$

Fractional derivative:

$$\frac{\partial^\alpha}{\partial |x|^\alpha} P(x,t) \equiv \kappa^{-1} \frac{\partial^2}{\partial x^2} \int_{-\infty}^{\infty} \frac{P(x',t)}{|x-x'|^{\alpha-1}} \therefore \kappa \equiv 2\Gamma(2-\alpha) \left| \cos \frac{\pi\alpha}{2} \right|$$

$$\Leftrightarrow \mathscr{F}\{\partial^\alpha P(x,t)/\partial |x|^\alpha\} = -|k|^\alpha P(k,t)$$

Solution in Fourier space:

$$P(k,t) = \exp\left(-K^\alpha |k|^\alpha t\right) \qquad \rightsquigarrow \qquad P(x,t) \simeq \frac{K^\alpha t}{|x|^{1+\alpha}}$$

RM & J Klafter, Phys Rep (2000); JPA (2004)

Lévy foraging hypothesis: to avoid oversampling

Shlesinger & Klafter (1986): Lévy flights as efficient search mechanism

Lévy foraging hypothesis: *Superdiffusive motion governed by fat-tailed propagators optimise encounter rates under specific (but common) circumstances: hence some species must have evolved mechanisms that exploit these properties* [. . .].

Lévy flight (Mandelbrot): $\psi(t) = \tau^{-1} \exp(-t/\tau) \wedge$

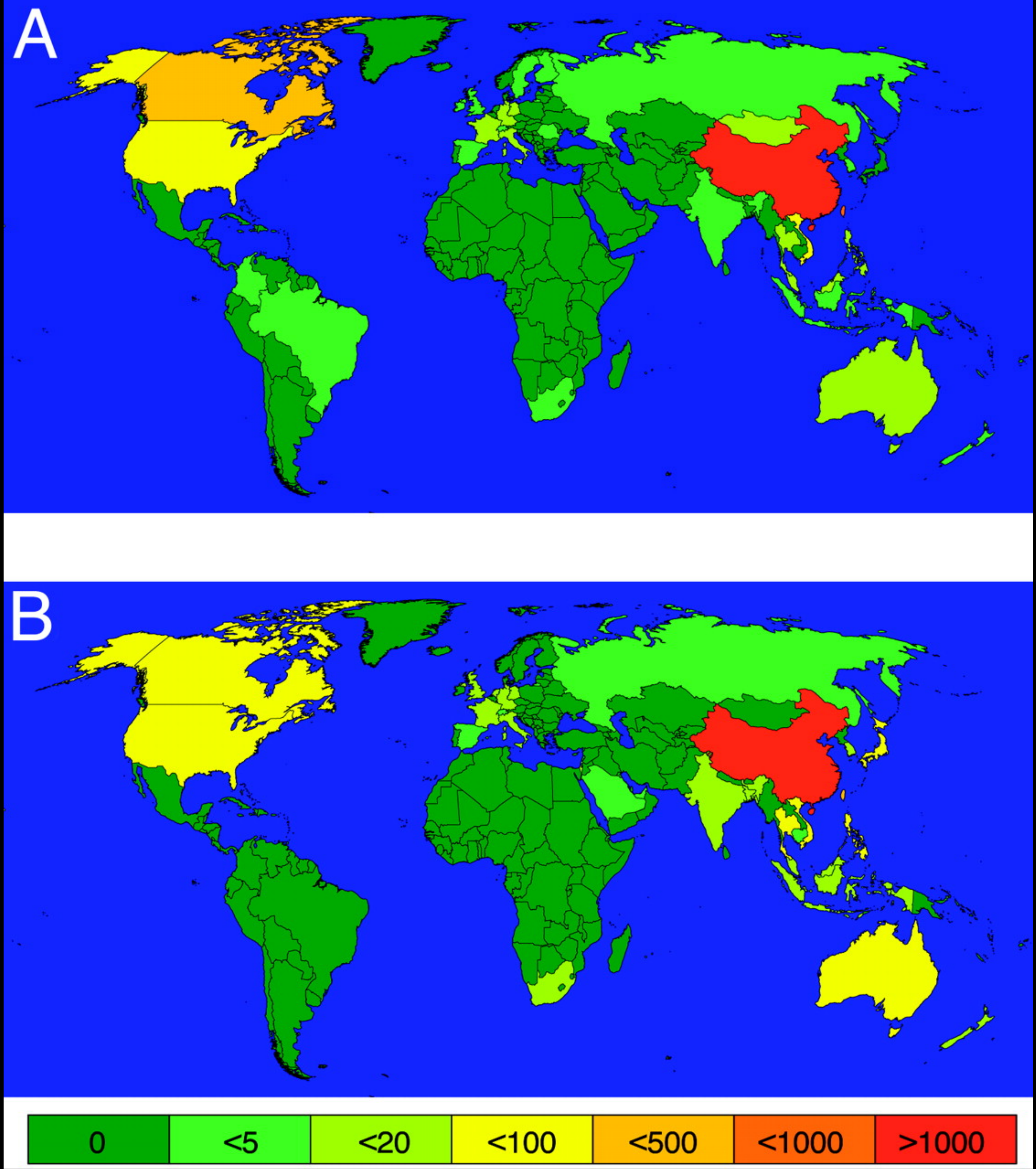
$$\lambda(x) \simeq |x|^{-1-\alpha}, \quad 0 < \alpha < 2 \quad \curvearrowright \quad \langle x^2(t) \rangle \to \infty$$

Lévy walk (Shlesinger, Klafter & Wong, JSP, 1982): spatiotemporal coupling

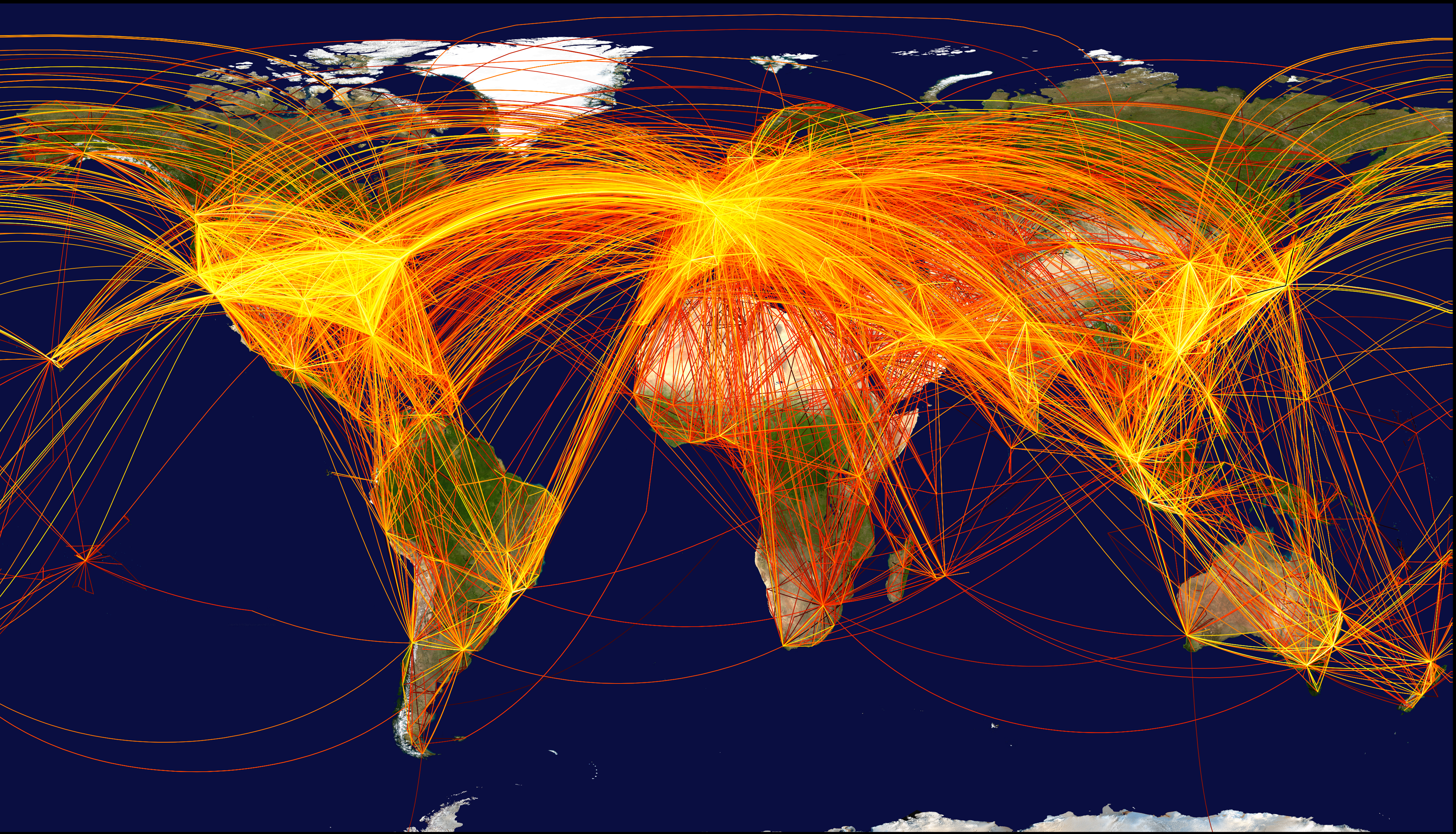
$$\psi(x,t) = \lambda(x)\delta(x - |v|t) \quad \curvearrowright \quad \langle x^2(t) \rangle \simeq t^{3-\alpha}$$

Viswanathan GE, da Luz MGE, Raposo EP, Stanley HE, The physics of foraging (CUP, 2011)

Map copyright © Philip's, a division of Octopus Publishing Group Ltd.
Source: *Philip's Atlas of World History*.


A
B
0
<5
<20
<100
<500
<1000
>1000

Non-locality due to long-distance travel

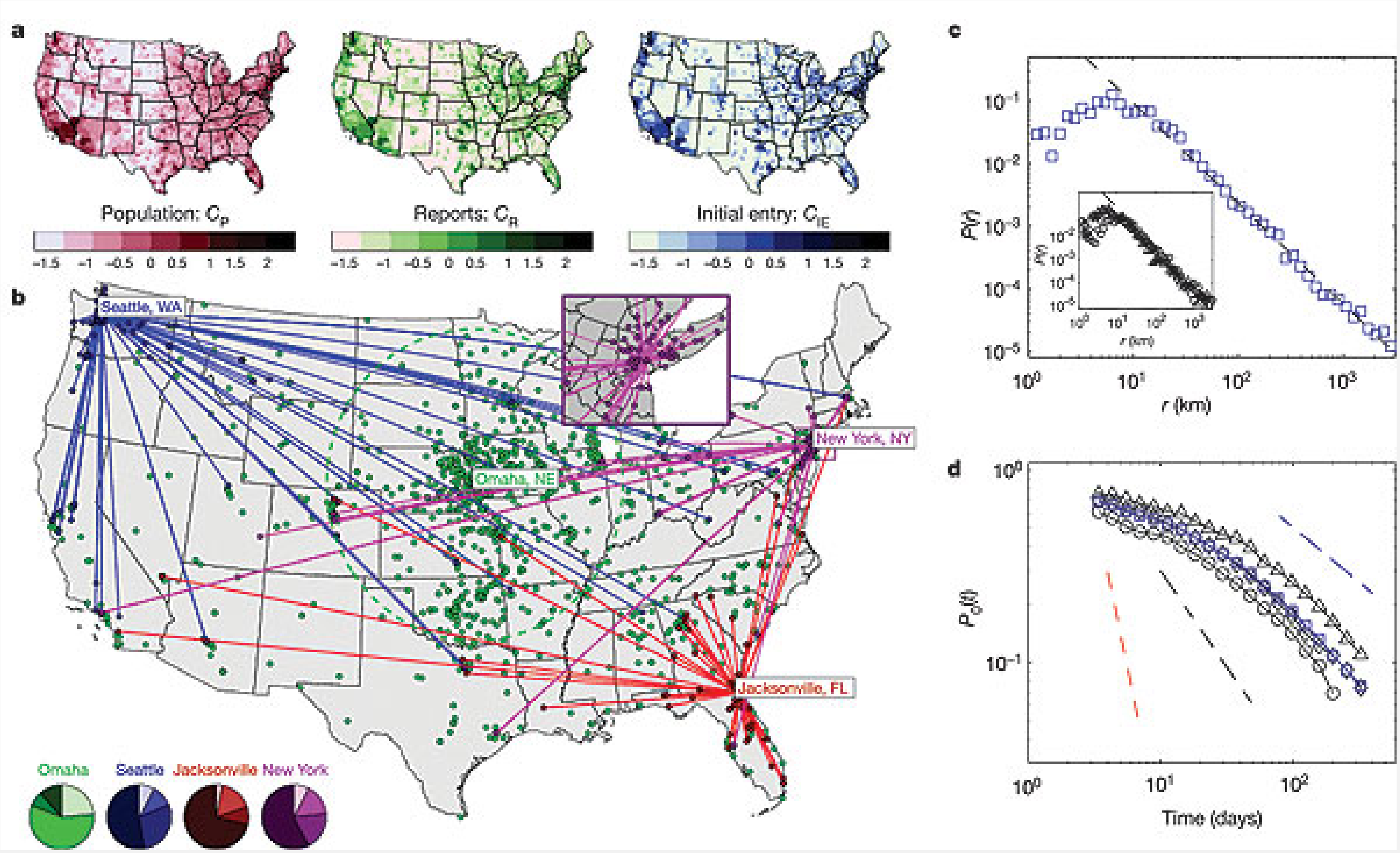


Courtesy, D Brockmann


SEE WHERE I HAVE BEEN
TRACK WHERE I GO NEXT
www.WHERESGEORGE.com
THE UNITED STATES OF AMERICA
IN GOD WE TRUST
ONE
ANNUIT COEPTIS
MDCCLXXVI
NOVUS ORDO SECLORUM
THE GREAT SEAL
OF THE UNITED STATES
ONE DOLLAR
FEDERAL RESERVE NOTE
THE UNITED STATES OF AMERICA
THIS NOTE IS LEGAL TENDER
FOR ALL DEBTS, PUBLIC AND PRIVATE
D 49824621 F
WASHINGTON, D.C.
TRACK THIS BILL
WHERESGEORGE.COM
WOOSTER
OHIO
SERIES
2006
Treasurer of the United States.
Secretary of the Treasury.
WASHINGTON
ONE DOLLAR
THIS IS A REGISTERED BILL

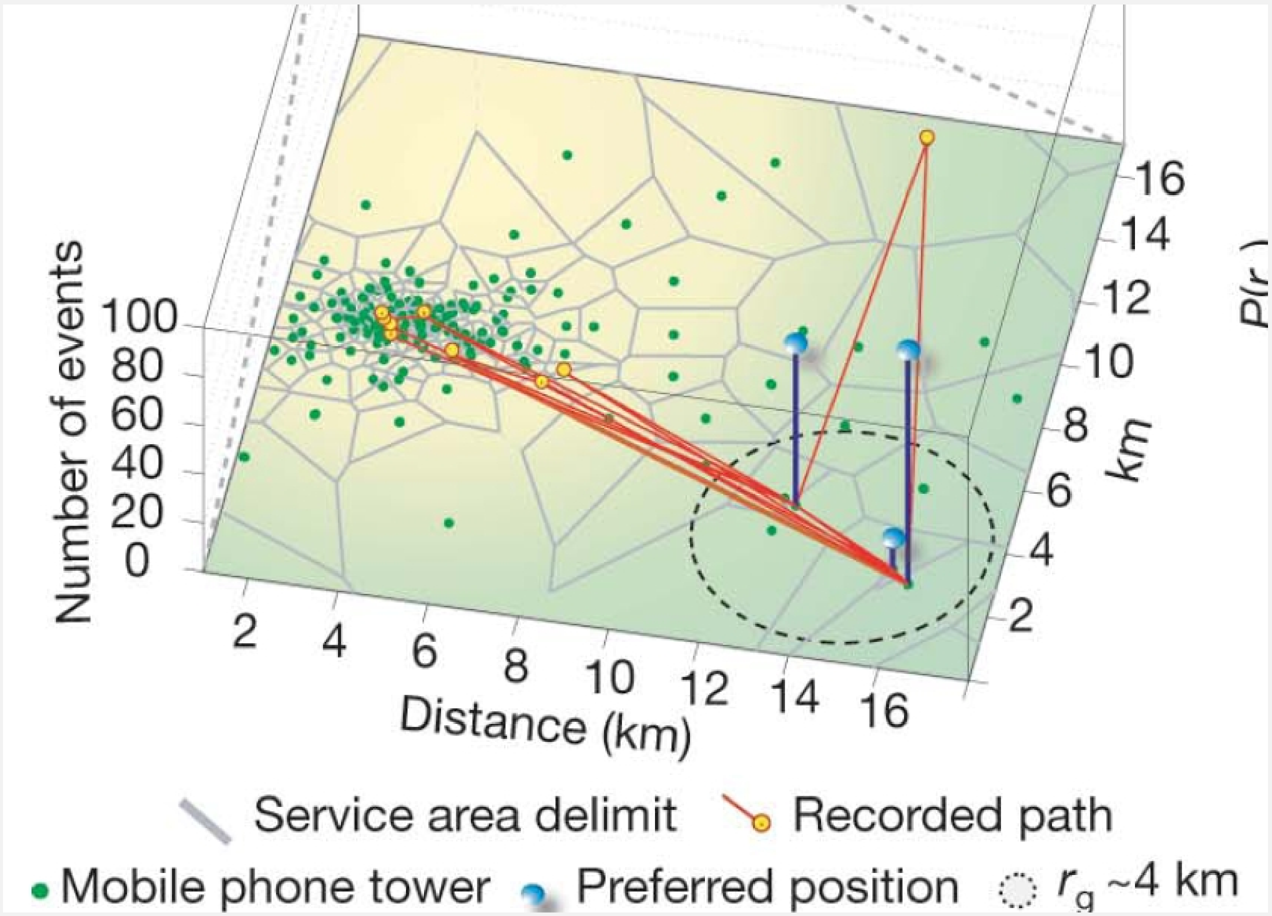
D Brockmann, Physics World (2010)

Human movement behaviour: money sticks



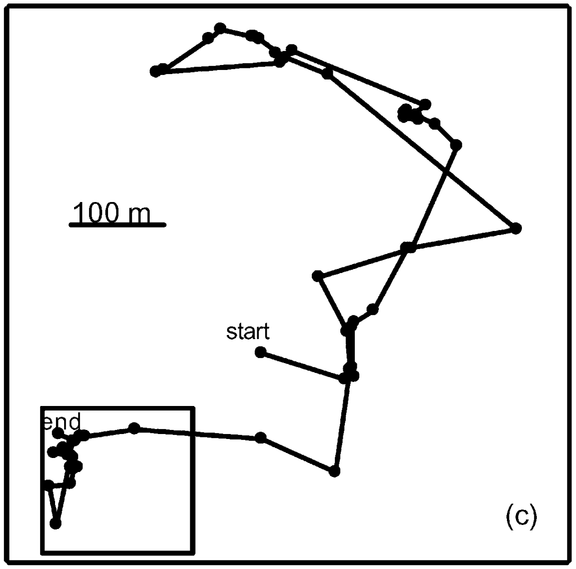
D Brockmann, L Hufnagl, T Geisel, Nature 439, 462 (2006)

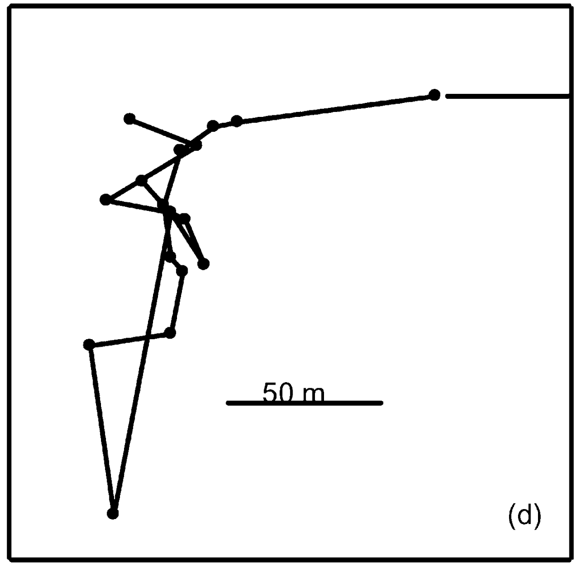
Single human motion patterns: mobile phone tracking

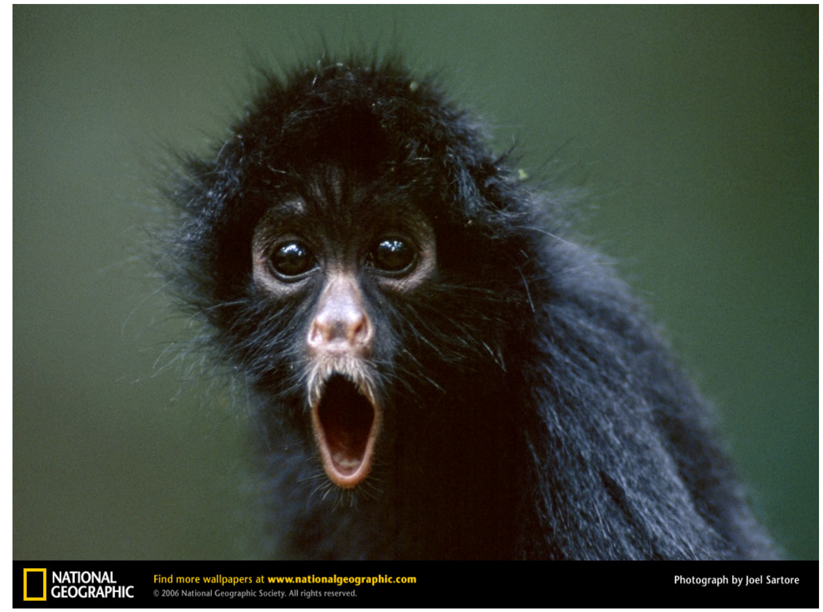


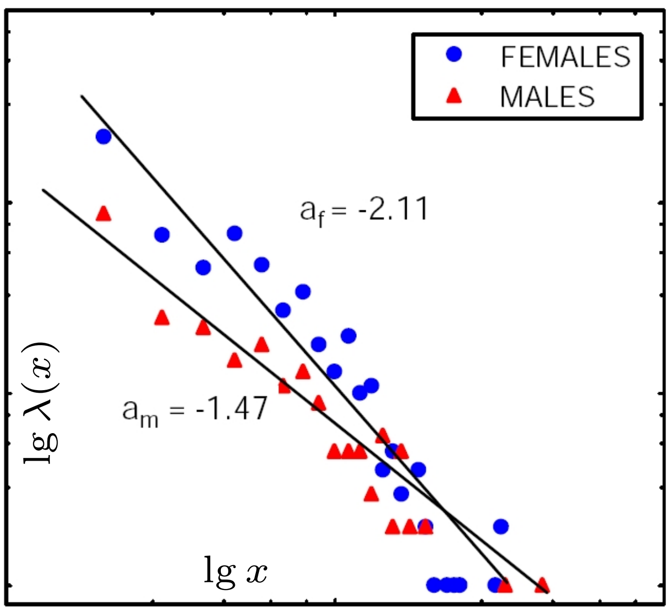
MC González, CA Hidalgo & A-L Barabási, Nature (2008)

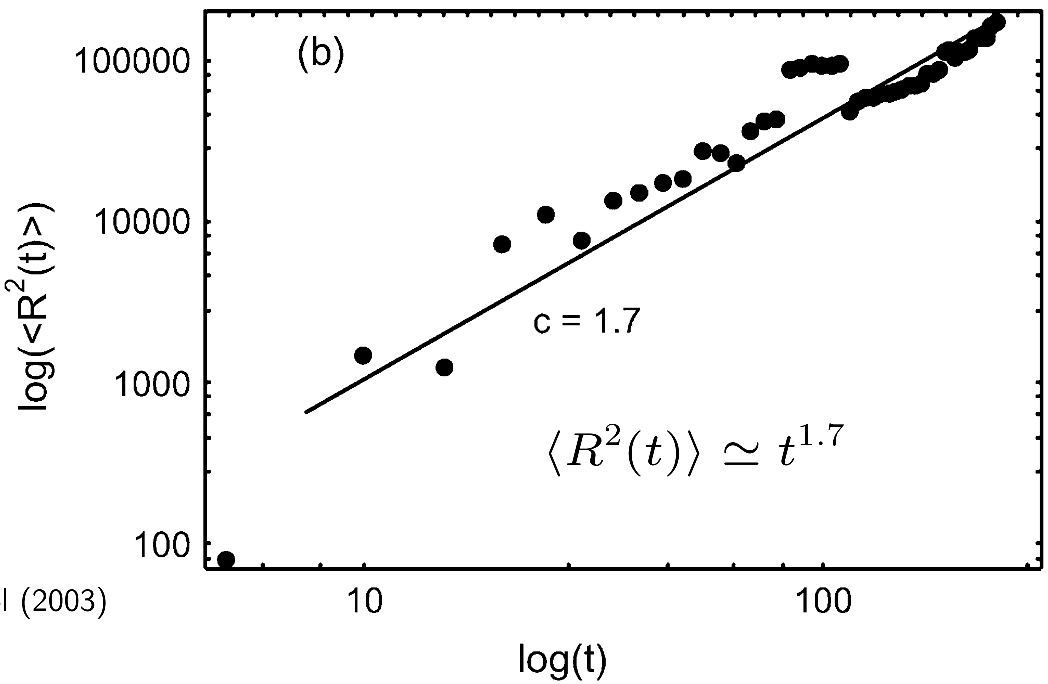
The jumps of the spider monkeys





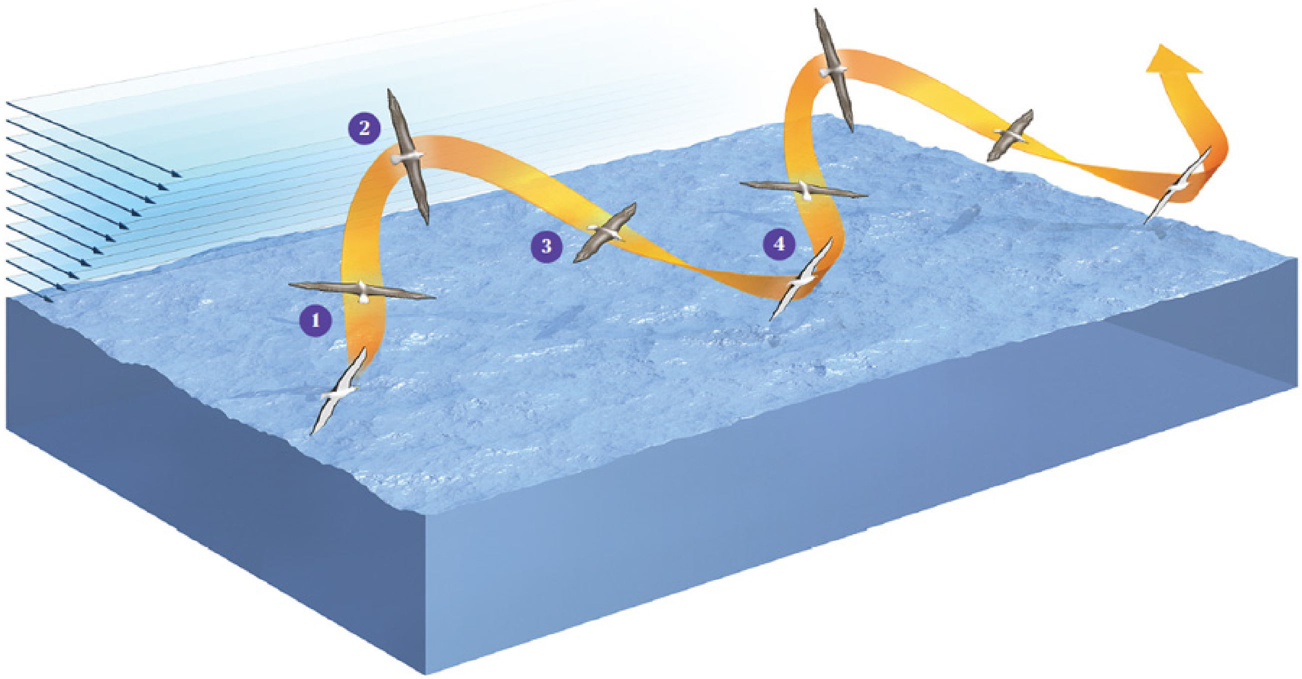






Ramos-Fernandez et al, Behav Ecol Sociobiol (2003)

The good old albatross story: some do it



Dynamic soaring (unflapping flight)

Shear wind field >30 km/h:

[1] bird climbs into wind

[2] turns to leeward

[3] descends

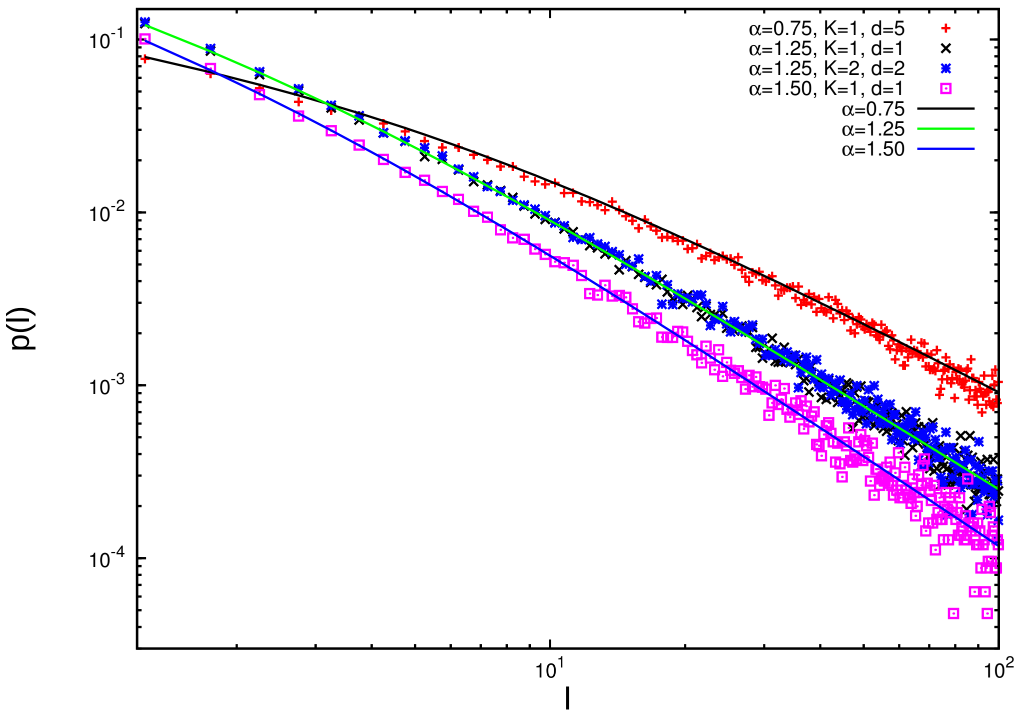
[4] again turns into wind

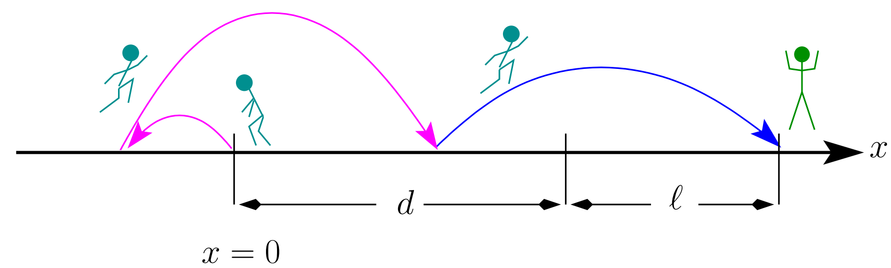
Viswanathan et al, Nature (1996, 1999): Lévy flight of albatross

Edwards et al, Nature (2007): flawed data analysis

Humphries et al, PNAS (2012): single birds indeed Lévy fly

Overshooting the target: leapovers





$$\lambda(x) \simeq |x|^{-\alpha-1}$$

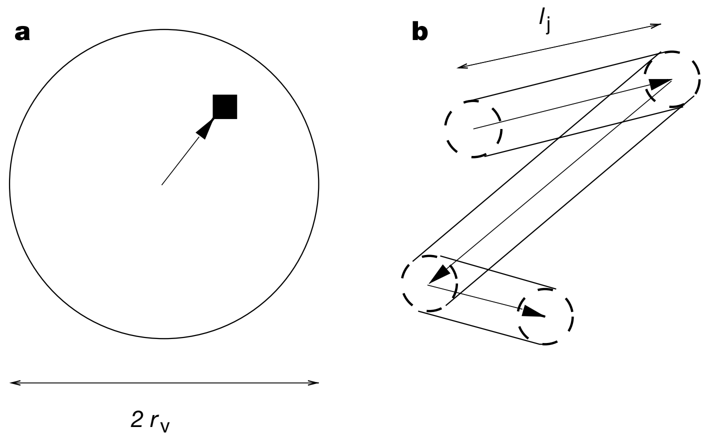
$$\wp_{\mathrm{fa}}(\tau) \simeq x_0^{\alpha-1} \times t^{1/\alpha-1}$$

$$\wp_{\mathrm{fp}}(\tau) \sim \frac{d^{\alpha/2}}{\alpha\sqrt{\pi K^{(\alpha)}}\Gamma(\alpha/2)}\tau^{-3/2}$$ First passage: Sparre Andersen universality

$$\wp_l(\ell) = \frac{\sin(\pi\alpha/2)}{\pi}\frac{d^{\alpha/2}}{\ell^{\alpha/2}(d+\ell)} \curvearrowright \langle\ell\rangle \to \infty \ \forall\alpha$$ Leapover length

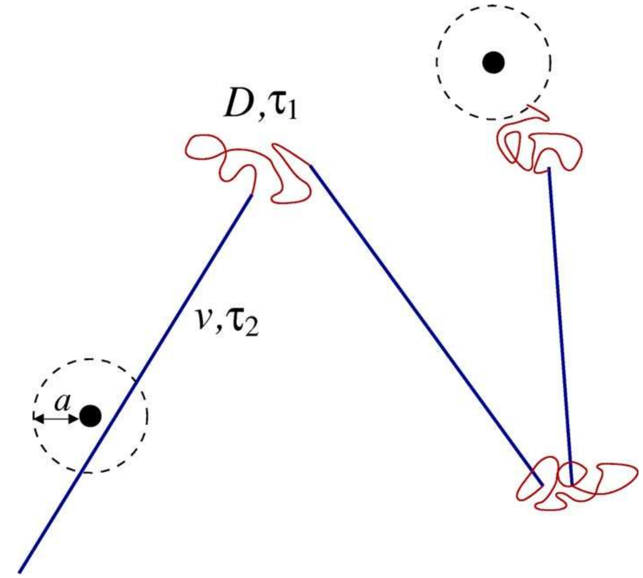
T Koren, MA Lomholt, AV Chechkin, J Klafter & RM, PRL (2007); AV Chechkin, RM, VY Gonchar & LV Tanatarov, JPA (2003)

Getting around the leapover problem



Lévy search with radius of vision r_v

GM Viswanathan, SV Buldyrev, S Havlin, MGE da Luz, EP Raposo & HE Stanley, Nature (1999)

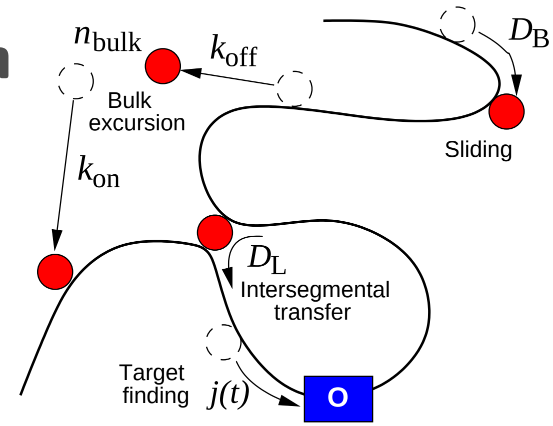


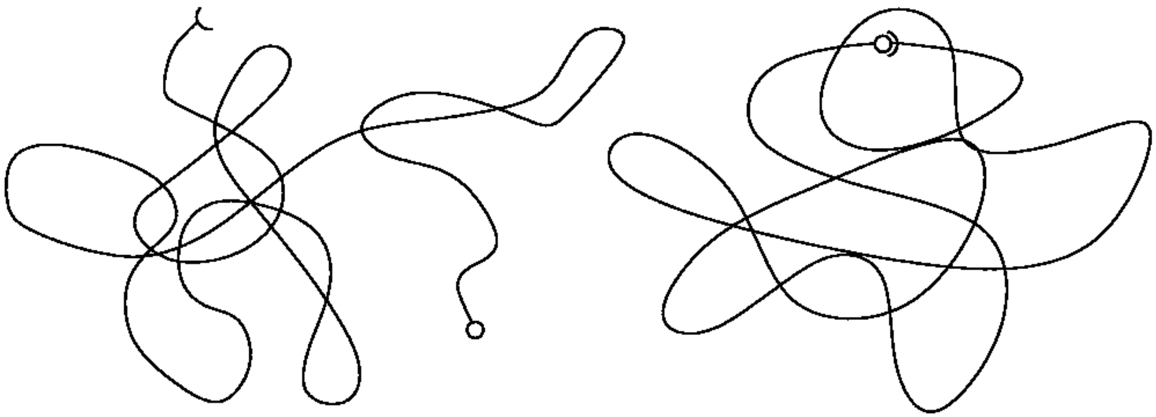
Intermittent search: Lévy less sensitive to changing environment: plasticity

MA Lomholt, T Koren, RM & J Klafter, PNAS (2008)

Both models: Cauchy distribution $\lambda(x) \sim |x|^{-2}$ optimises search for rare targets

Naturally intermittent: facilitated diffusion



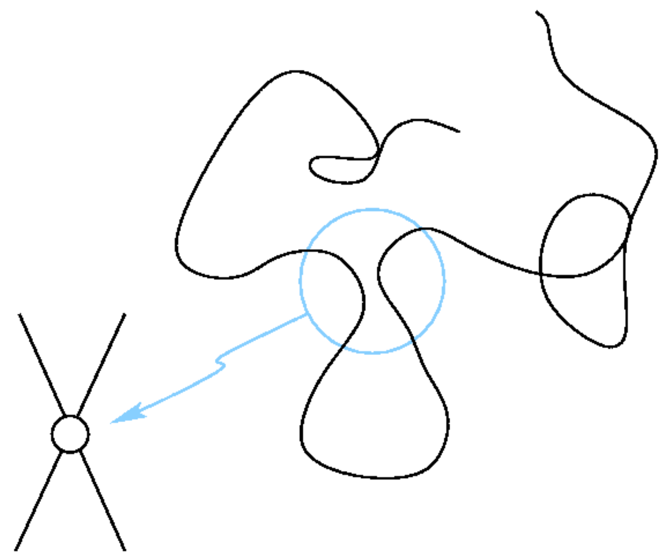


Cyclization is returning random walk ($t \div \ell$):

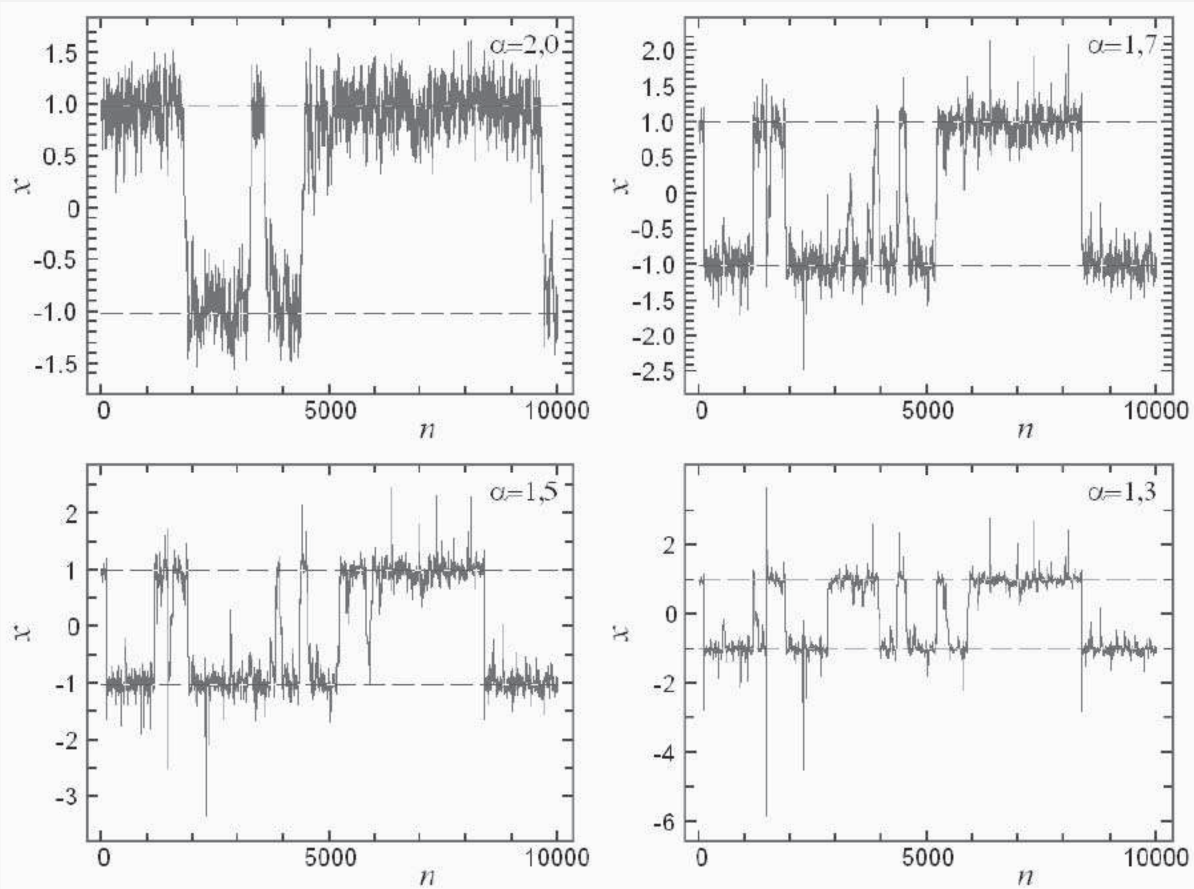
$$p(\ell) \sim \begin{cases} \ell^{-d/2} & \text{phantom chain} \\ \ell^{-d\nu-(\gamma-1)} & \text{SAW, } \nu \approx \frac{3}{5},\ \gamma \approx \frac{7}{6} \end{cases}$$

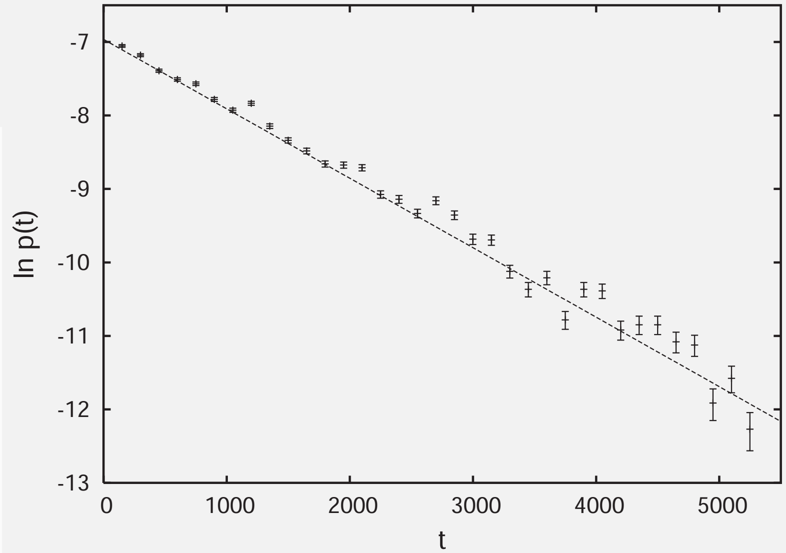
Probability for contact is more restrictive:

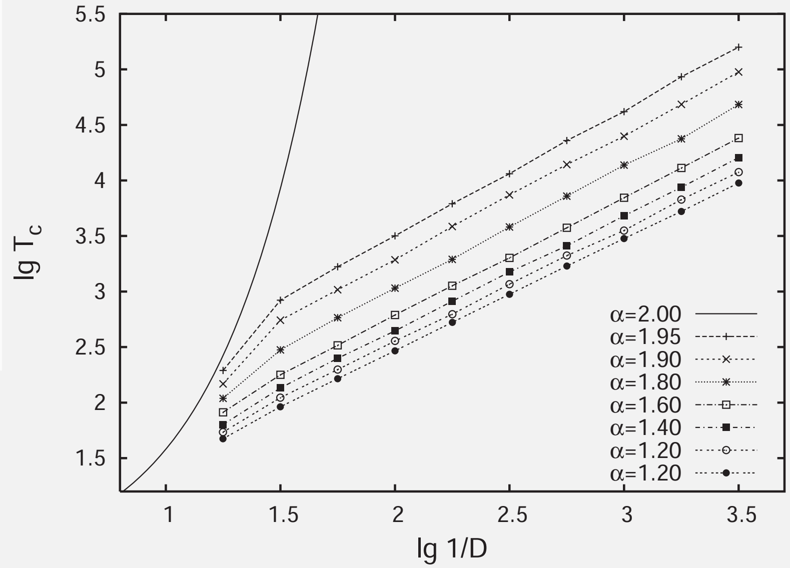
$$p(\ell) \sim \ell^{-d\nu+\sigma_4} \sim \ell^{-1-1.2} \curvearrowright \langle \ell^2 \rangle \to \infty$$



Barrier crossing of Lévy flights



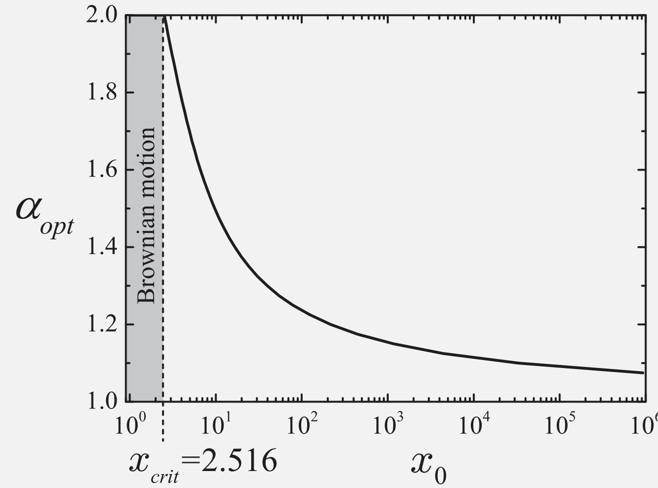




AV Chechkin, VYu Gonchar, J Klafter & RM, Europhys Lett 2005

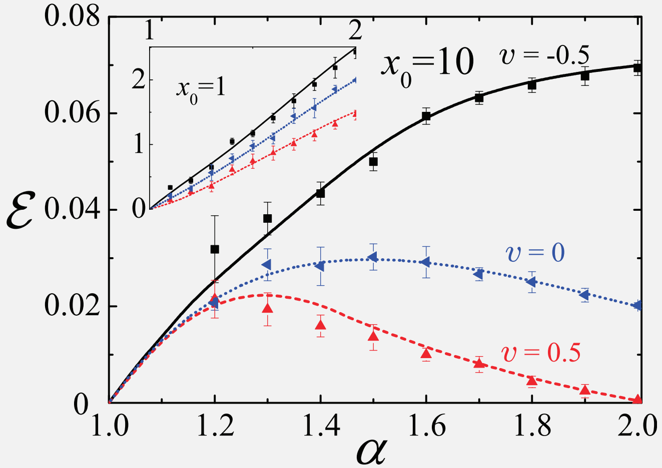
Lévy flights do not always optimise random search

$$\frac{\partial P(x,t)}{\partial t} = \frac{\partial^\alpha P(x,t)}{\partial |x|^\alpha} - v\frac{\partial P(x,t)}{\partial x} - \wp_{\mathrm{fa}}(t)\delta(x), \quad 1 < \alpha < 2$$

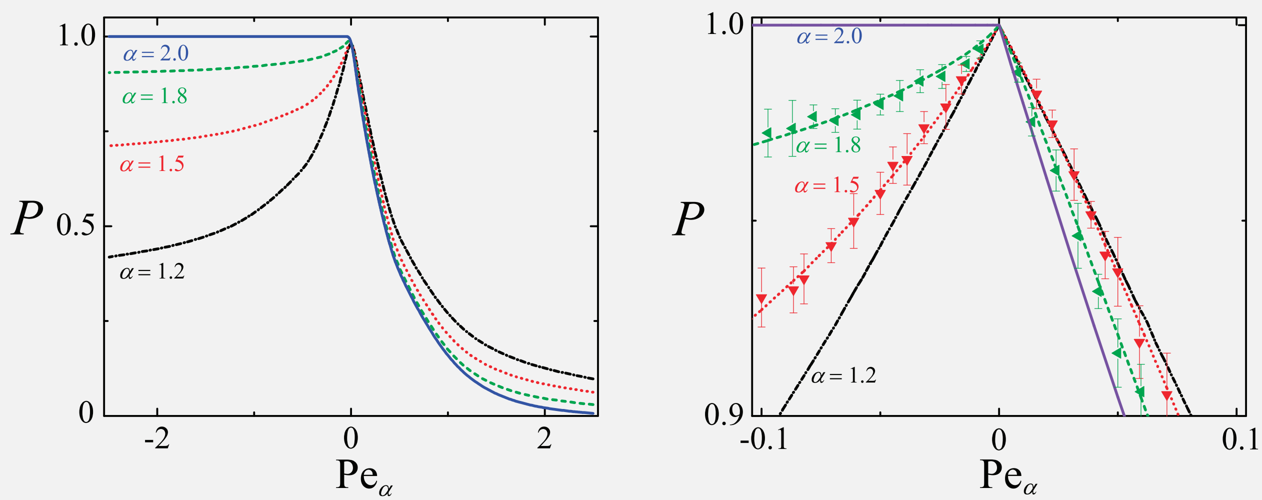


Search efficiency

$$\mathscr{E} = \left\langle \frac{1}{t} \right\rangle = \int_0^\infty \wp(s)ds$$



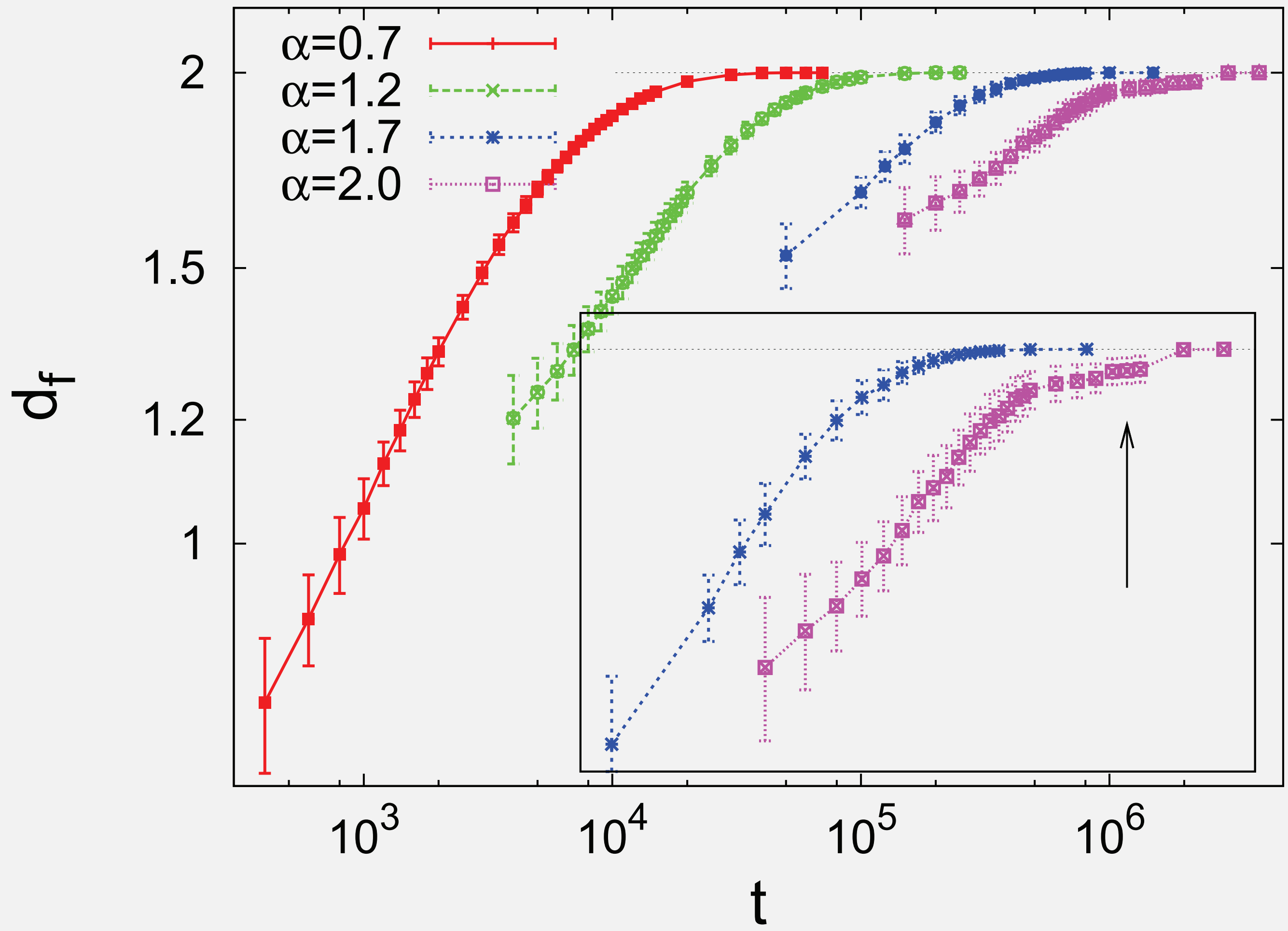
Search reliability $P = 1 - \mathscr{S}(\infty)$



VV Palyulin, AV Chechkin & R Metzler, PNAS (2014), JSTAT (2014)

Area coverage of Lévy flights

LFs with jump length distribution $\lambda(x) \simeq \sigma^{\mu}/|x|^{1+\mu}$



M Vahabi, J Schulz & RM, PRE (2013)

Ultraweak ergodicity breaking of Lévy walks & flights

$$\langle x^2(t)\rangle \sim \frac{2(\alpha-1)}{(3-\alpha)(2-\alpha)}t^{3-\alpha} \sim (\alpha-1)\overline{\delta^2(t)},\quad 1<\alpha<2$$

Time averaged MSD

$$\overline{\delta^2(\Delta)} = \frac{1}{T-\Delta}\int_0^{T-\Delta}\Big(x(t+\Delta)-x(t)\Big)^2 dt$$

$$\overline{\delta^2(\Delta)} \sim 2\left(\frac{(1+\Delta)^{3-\alpha}-1}{(3-\alpha)(2-\alpha)} - \frac{\Delta}{2-\alpha}\right) + \left(\frac{\alpha-1}{3}\left[\frac{\Delta}{T}\right]^3 - \alpha\left[\frac{\Delta}{T}\right]^2\right)T^{3-\alpha}$$

Linear response for constant external force f $(0<\alpha<2)$:

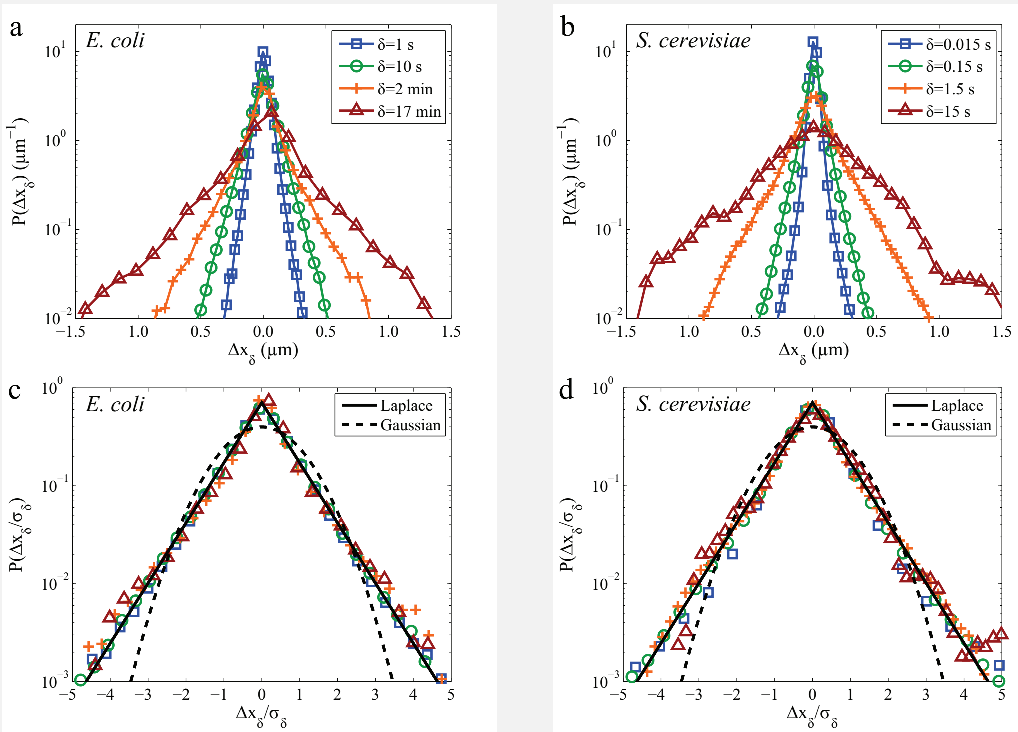
$$\langle x(t)\rangle \sim \beta f\begin{cases}\frac{1}{2}t^2, & 0<\alpha<1\\ \frac{1}{2-\alpha}t^{3-\alpha}, & 1<\alpha<2\end{cases} \qquad \langle x(t)\rangle = \frac{1}{2}\beta f\langle x^2(t)\rangle$$

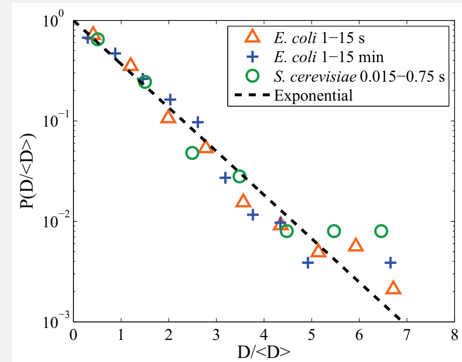
A Godec & RM, PRL (2013), PRE (2013); D Froemberg & E Barkai, PRE (2013), EPJE (2013)

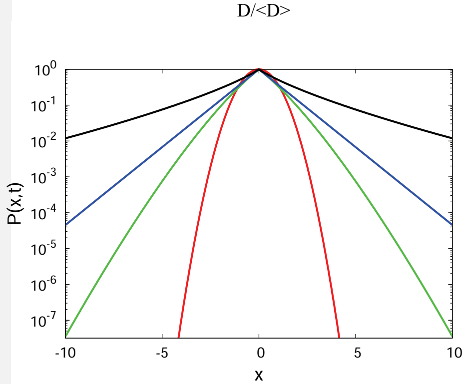
Abb. 140. Erlegter Albatroß mit 2,80 Meter Spannweite.
In der Mitte Kapitänlt. Siburg und Oberlt. Löwisch.

Non-Gaussian diffusion in viscoelastic systems

So far consensus: submicron tracer motion in cytoplasm is FBM-like, i.e., Gaussian
RNA-protein particles in E.coli & S.cerevisiae perform exponential anomalous diffusion:







TJ Lampo, S Stylianidou, MP Backlund, PA Wiggins & AJ Spakowitz, BPJ (2017); N&V: RM, BPJ (2017)

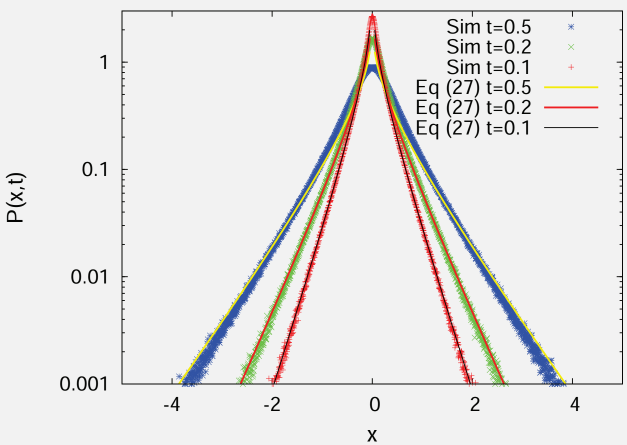
Non-Gaussian diffusion with diffusing diffusivity

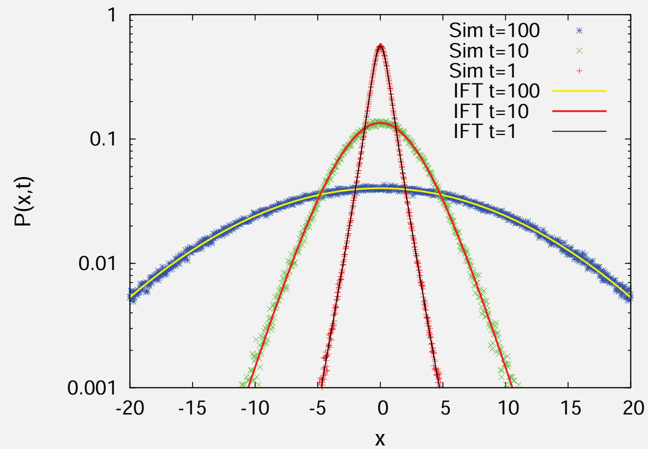
B Wang, J Kuo, SC Bae & S Granick, Nat Mat (2012): superstatistical approach $P(x,t) = \int_0^\infty G(x,t)p(D)dD$

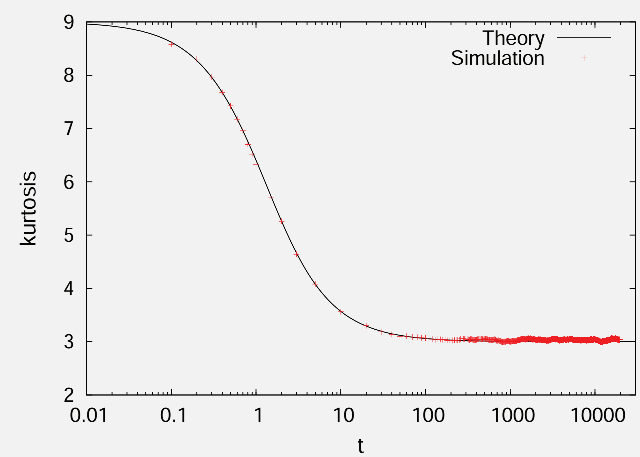
MV Chubinsky & G Slater, PRL (2014); R Jain & KL Sebastian, JPC B (2016): diffusing diffusivity

Our minimal model for diffusing diffusivity with Fickian $\langle x(t)\rangle = 2D_{\text{eff}}t$:

$$\dot{x}(t) = \sqrt{2D(t)}\xi(t)$$
$$D(t) = y^2(t)$$
$$\dot{y}(t) = -y + \eta(t)$$

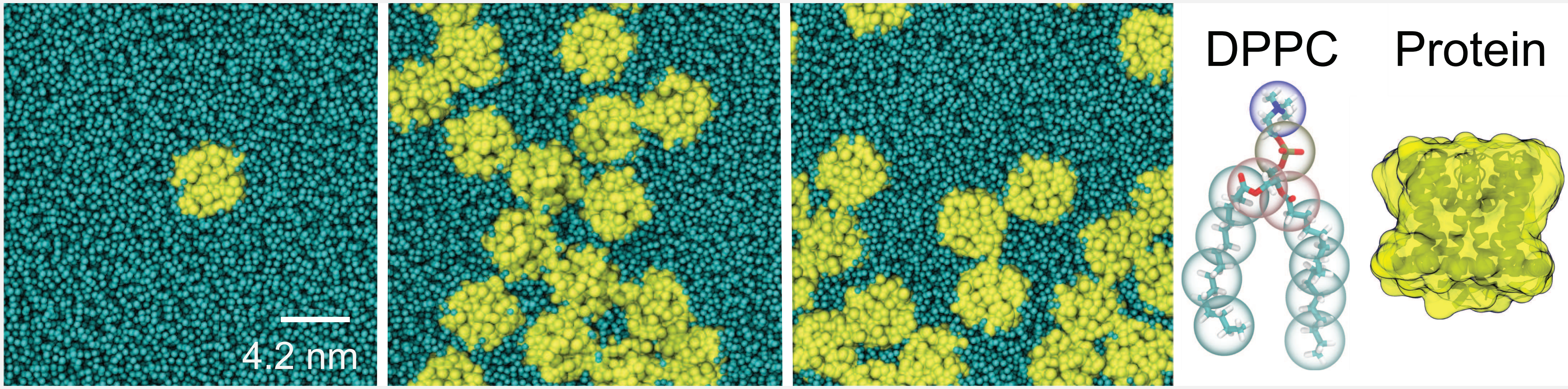


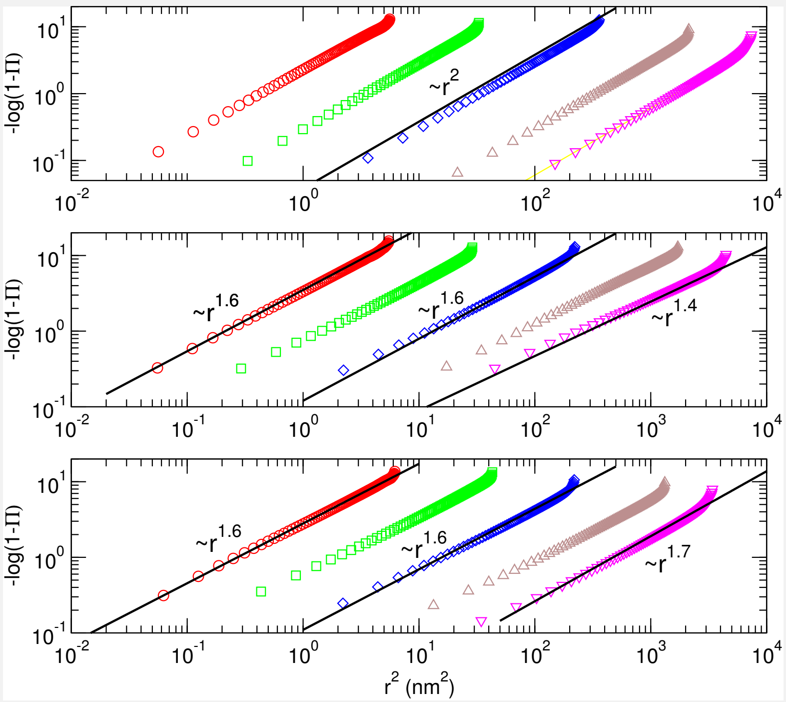




AV Chechkin, F Seno, RM & IM Sokolov, PRX (2017)

Crowding in membranes: non-Gaussian lipid/protein diffusion

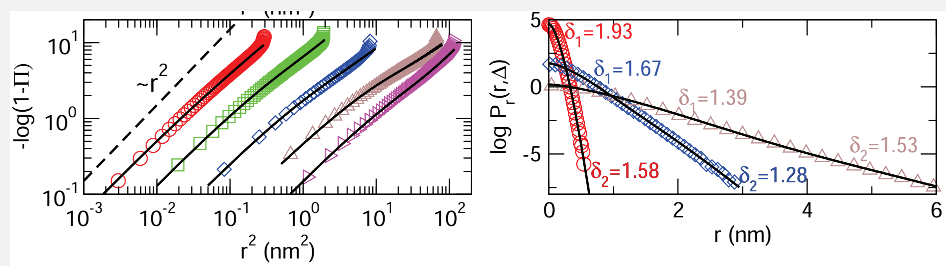




Dilute membrane: $P(r,t)$ Gauss

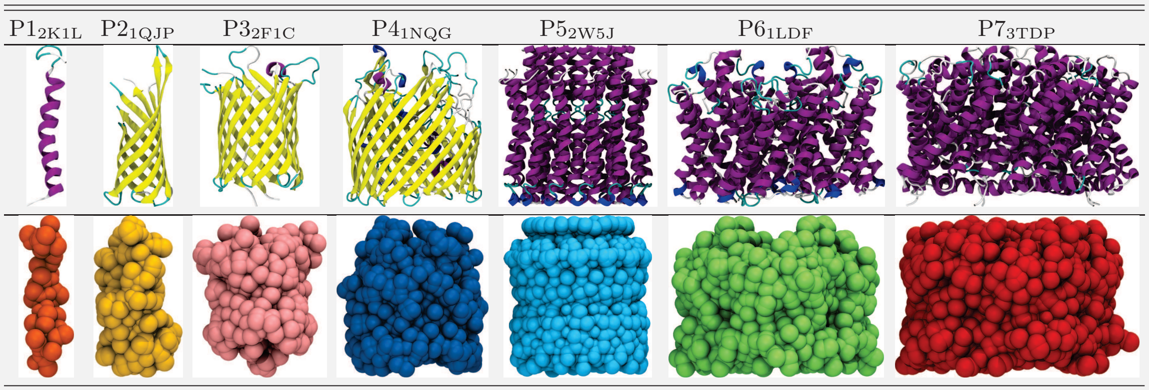
Crowded membrane ($\delta \approx 1.3 \ldots 1.7$):

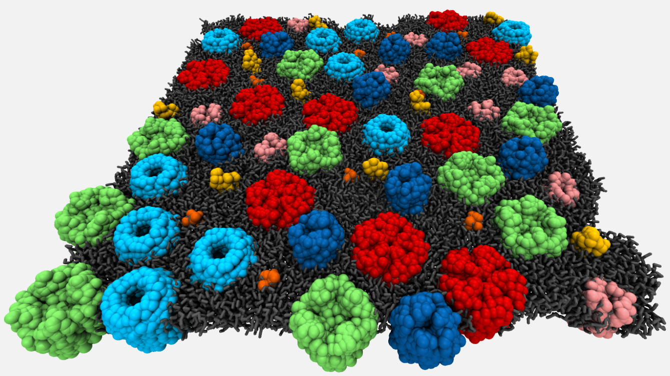
$$P(r,t) \propto \exp\left(-\left[\frac{r}{ct^{\alpha/2}}\right]^{\delta}\right)$$

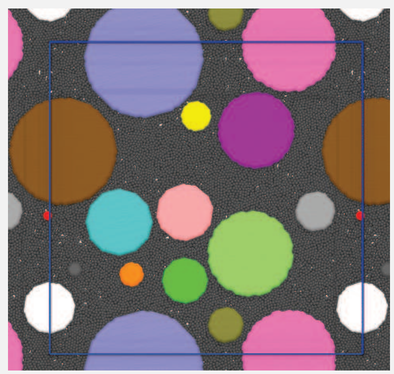


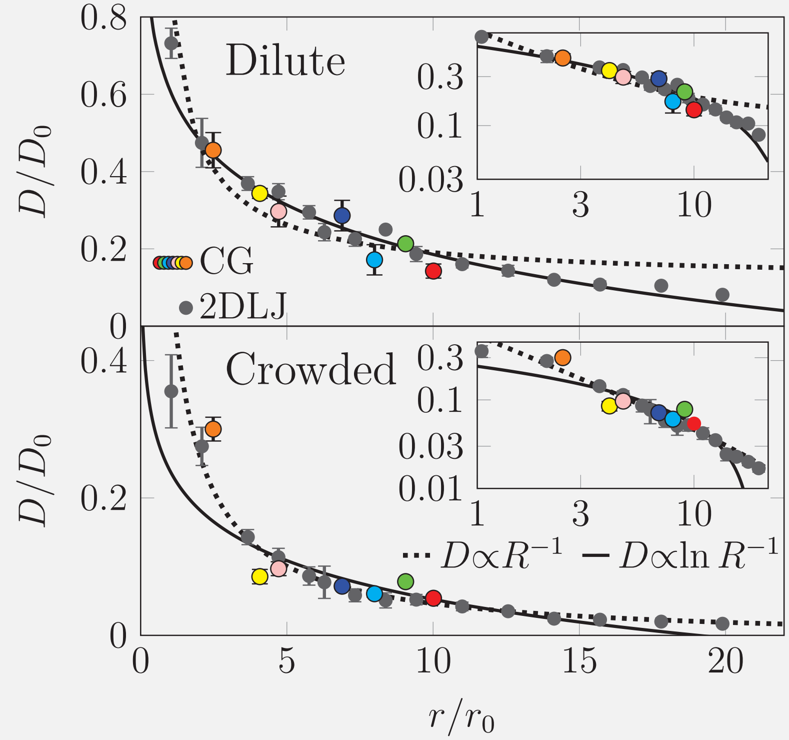
J-H Jeon, M Javanainen, H Martinez-Seara, RM & I Vattulainen, PRX (2016)

Geometry-induced violation of Saffman-Delbrück relation









Dilute system: Saffman-Delbrück law

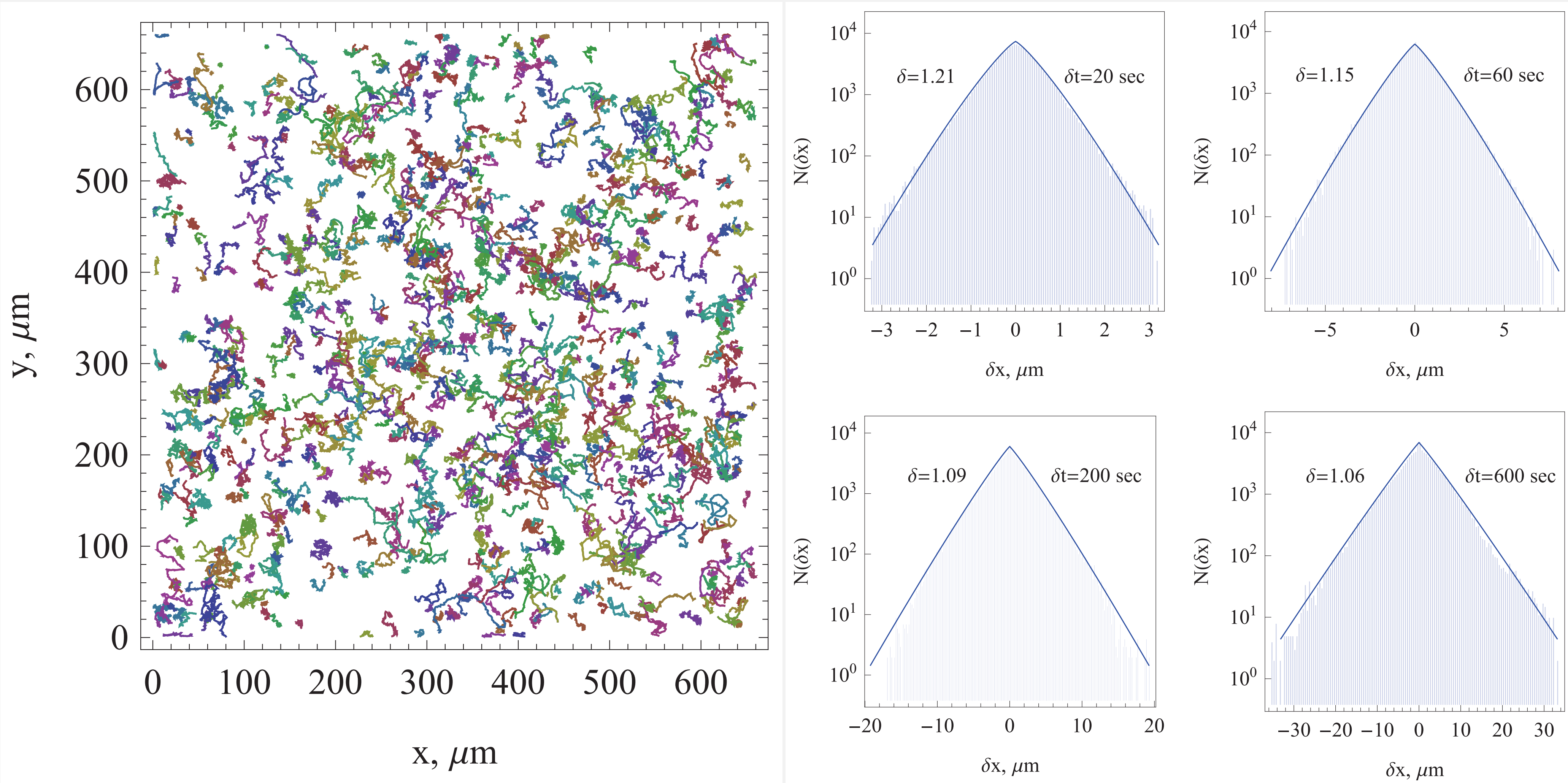
$$D(R) \simeq \log(1/R)$$

Crowded membrane & 2DLJ discs:

$$D(R) \simeq 1/R$$

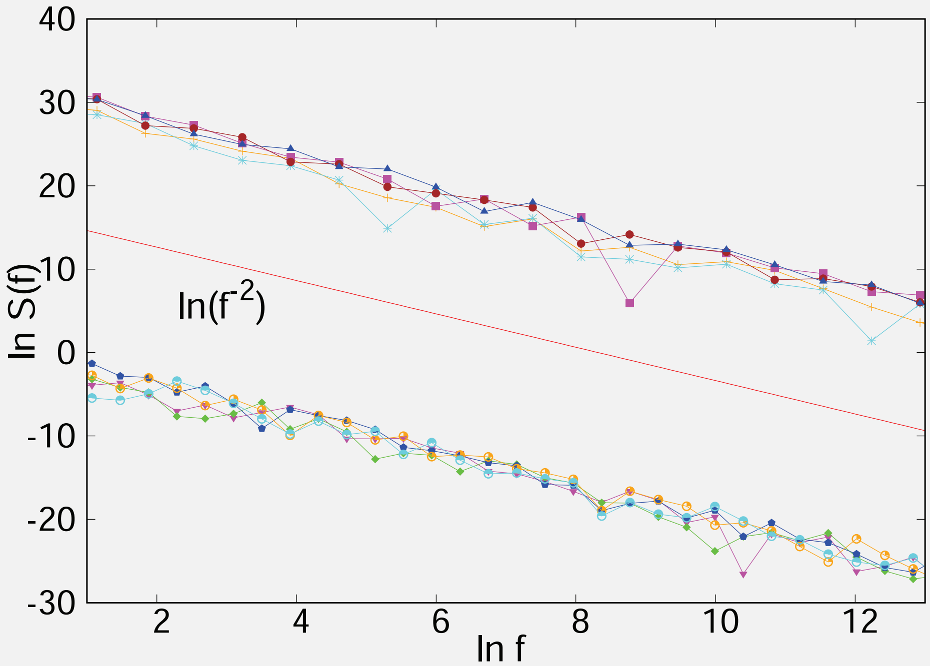
M Javanainen, H Seara Monne, RM & I Vattulainen, JPC Lett (2017)

Non-Gaussian diffusion of Dictyostelium cells

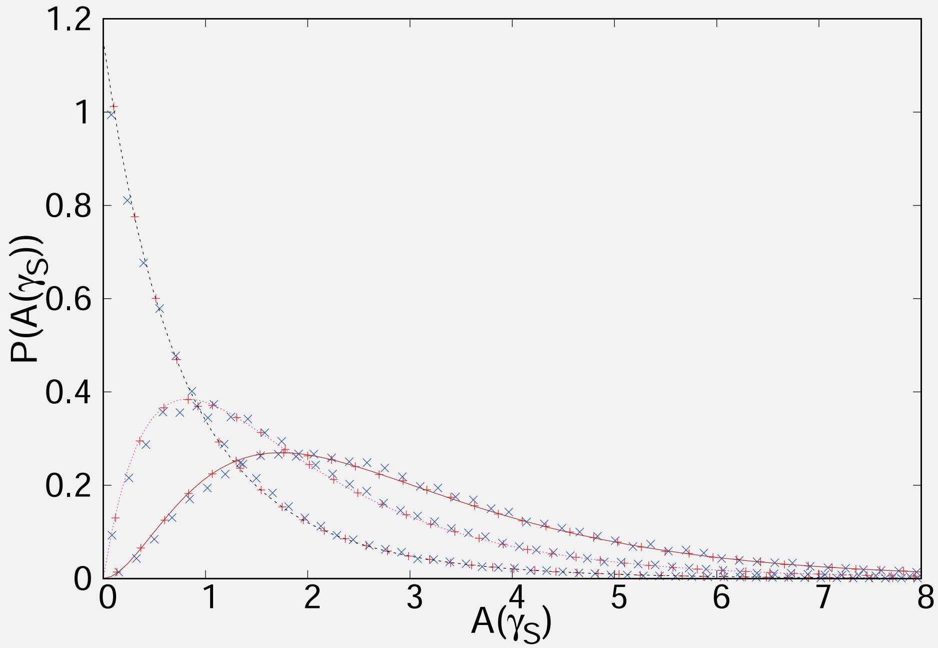


AG Cherstvy, O Nagel, C Beta & RM (2018)

Power spectral density of a single Brownian trajectory



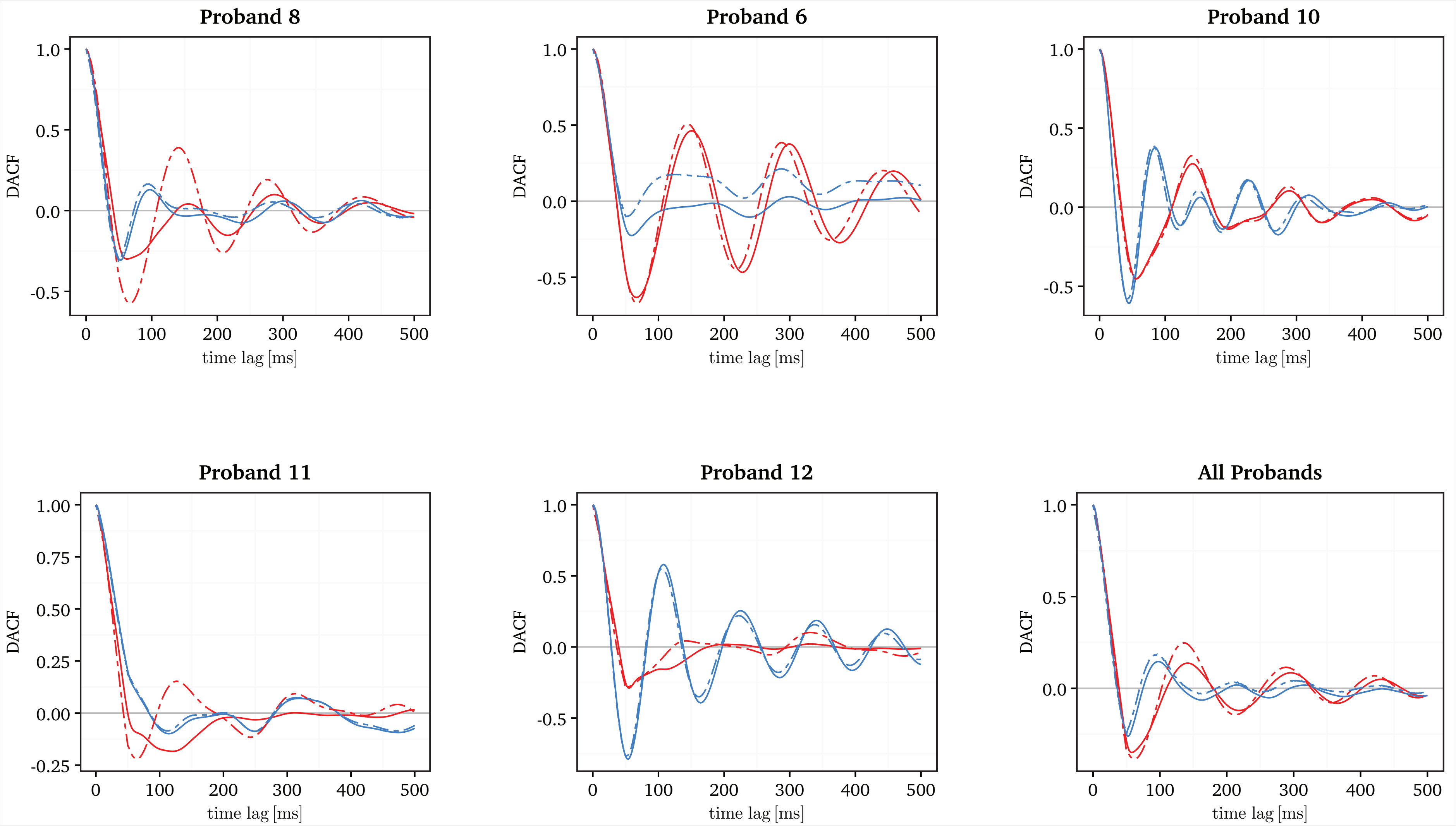
Power spectrum /w conserved slope



Amplitude distribution for various d

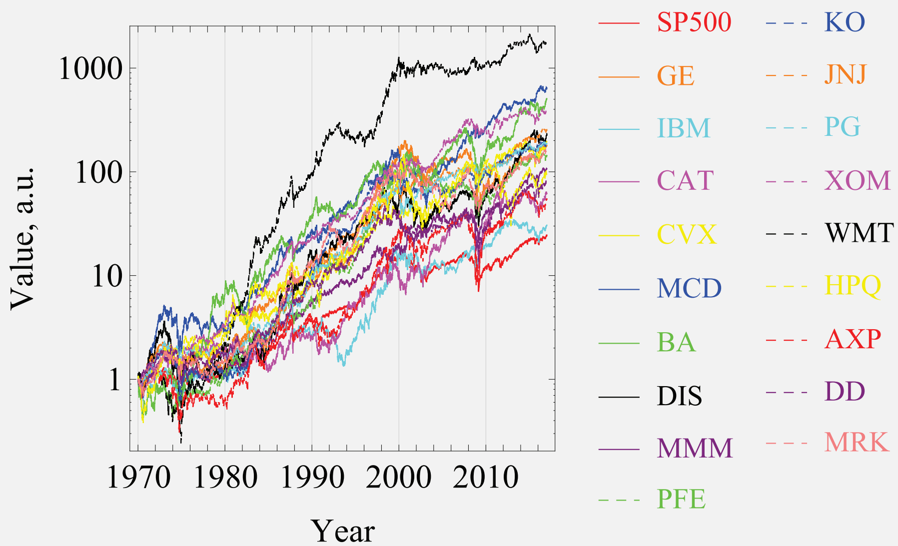
D Krapf, E Marinari, RM, G Oshanin, A Squarcini & X Xu, NJP (2018)

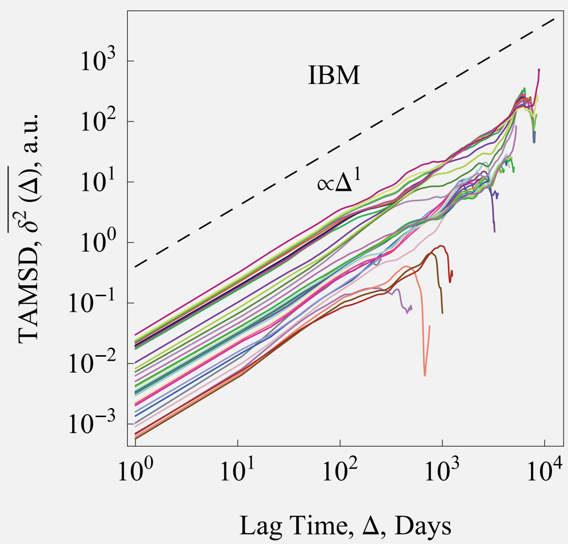
Stochasticity of fixational eye movements

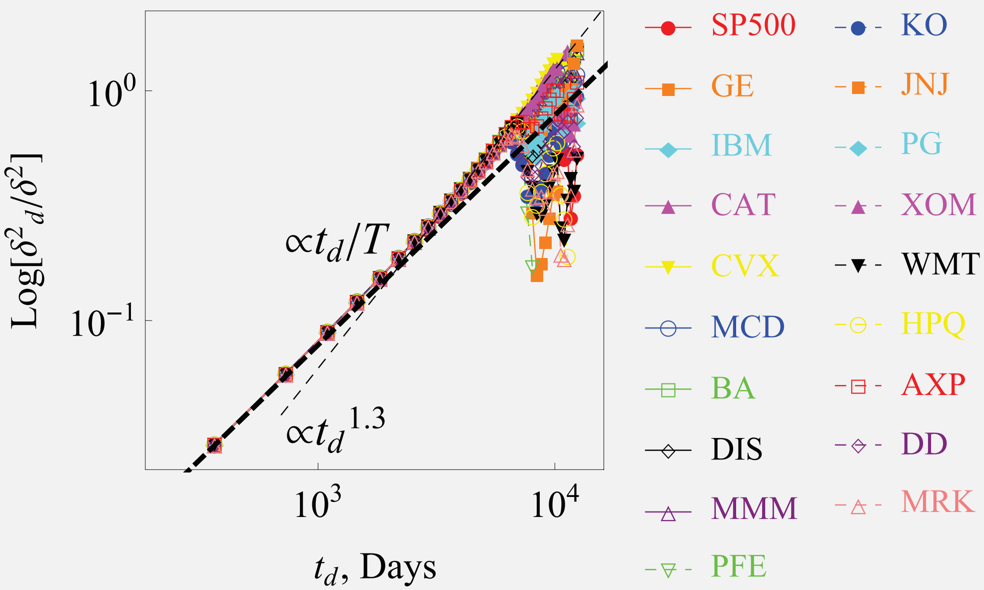


CJJ Herrmann, RM & R Engbert, Sci Rep (2017)

Time averages & ageing in financial market time series







$$dX(t) = \mu X(t)dt + \sigma X(t)dW(t)$$

$$\overline{\delta_d^2(\Delta)} = \frac{\int_{t_d}^{T-\Delta}[X(t+\Delta)-X(t)]^2\,dt}{T-t_d-\Delta} \sim \frac{\Delta}{T-t_d}X_0^2\left(e^{\sigma^2 T}-e^{\sigma^2 t_d}\right)$$

$$\log\left[\left\langle\overline{\delta_d^2(\Delta,t_d)}\right\rangle \Big/ \left\langle\overline{\delta^2(\Delta)}\right\rangle\right] \sim t_d/T$$

AG Cherstvy, D Vinod, E Aghion, AV Chechkin & RM, NJP (2017)

Journal of Physics A's new Biological Modelling section

Journal of Physics A
Mathematical and Theoretical

Biological Modelling

For anything interesting too mathematical for Biophys J, Phys Biol, or J Theoret Biol, or not general enough for PRL or NJP ...

Suggestions for topical reviews & special issues are welcome

Summary

I Gene expression based on stochastic binding of TFs; facilitated diffusion model verified in vitro for certain TFs. Speed-stability paradox

II Facilitated diffusion model also applies to in vivo gene regulation

III Distance matters: conformation of DNA in facilitated diffusion & gene-gene distance for TF-TU regulation—support for rapid search hypothesis

IIII (Transient) anomalous diffusion of TFs in vivo

IIIII Anomalous diffusion models: RM & al, PCCP (2014)

Anomalous diffusion in membranes: RM & al, BBA Biomembranes (2016)

Single molecule manipulation & tracking: C Nørregaard et al, Chem Rev (2017)

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