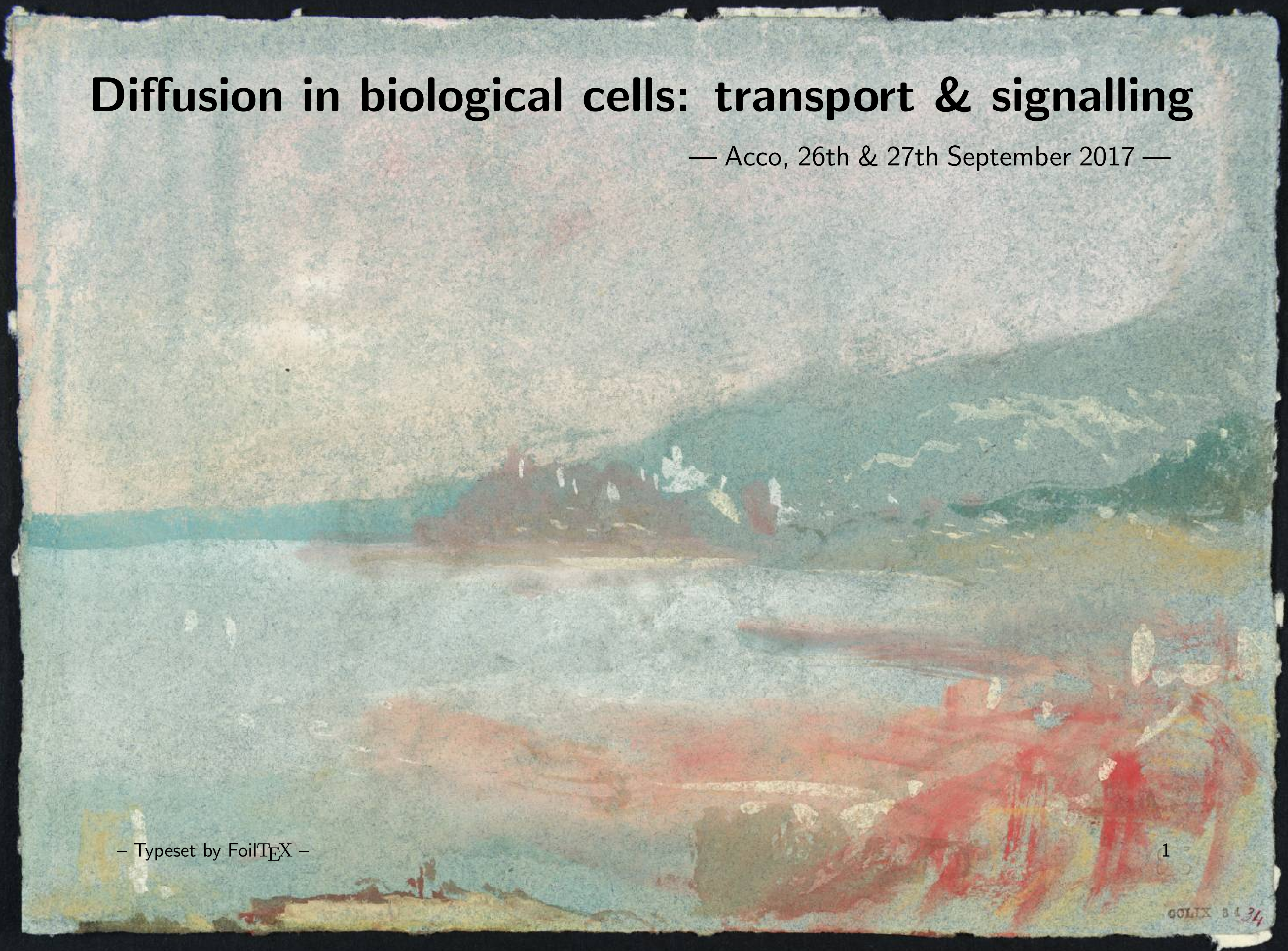
Diffusion in biological cells: transport & signalling

— Acco, 26th & 27th September 2017 —



Agenda

I Some facts on DNA

II Central dogma of molecular biology

III Basics of gene regulation

IIII Facilitated diffusion model

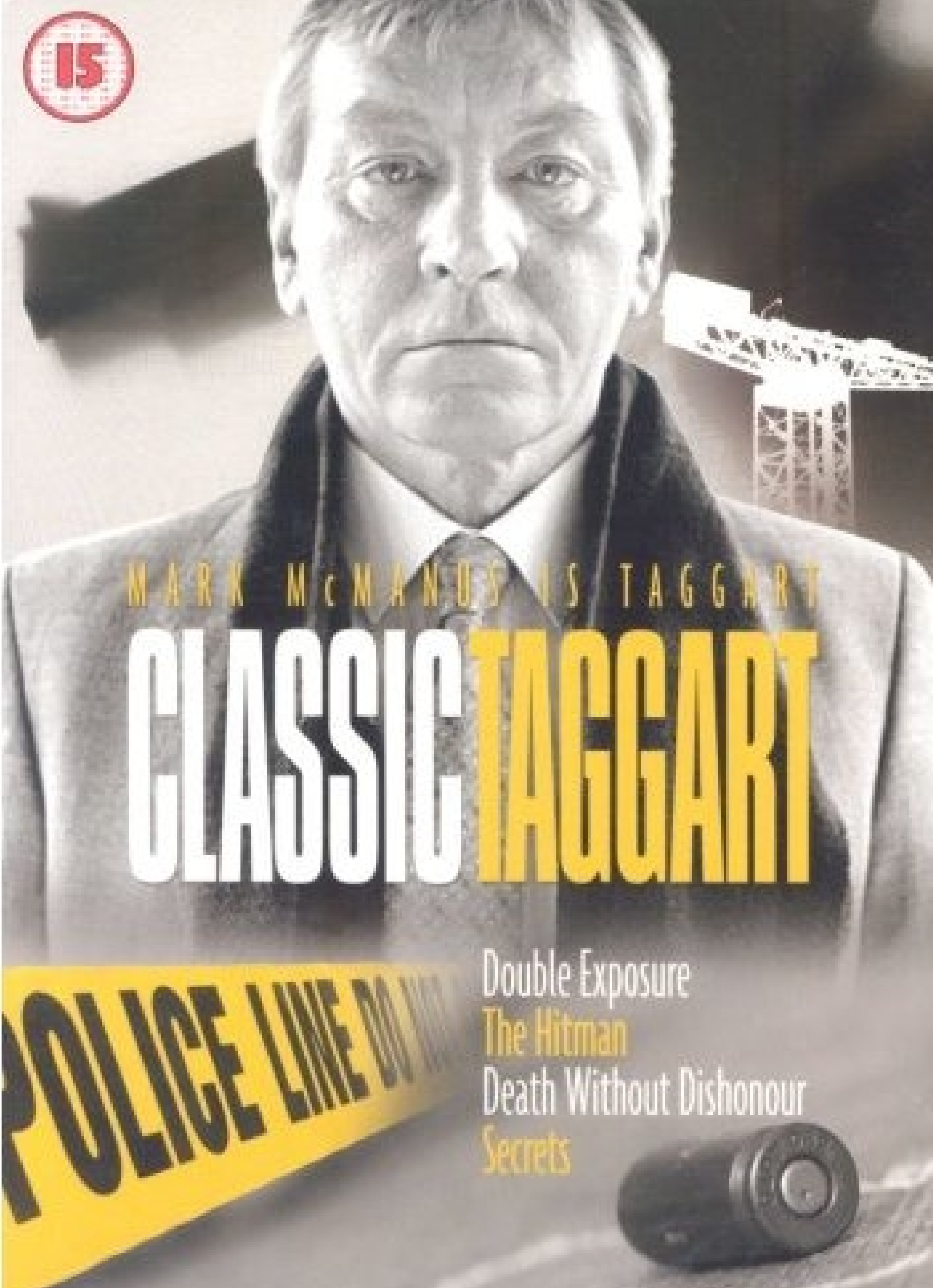
𝍸 Macromolecular crowding

𝍸I Anomalous diffusion

𝍸II First passage problem

𝍸III Few-encounter limit

Whodunnit…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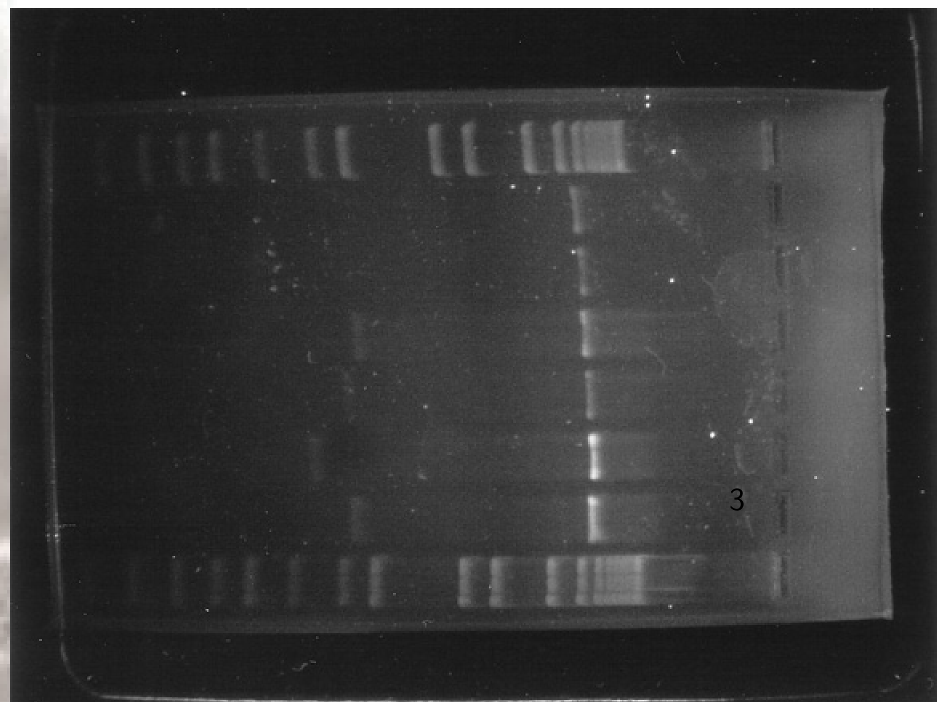
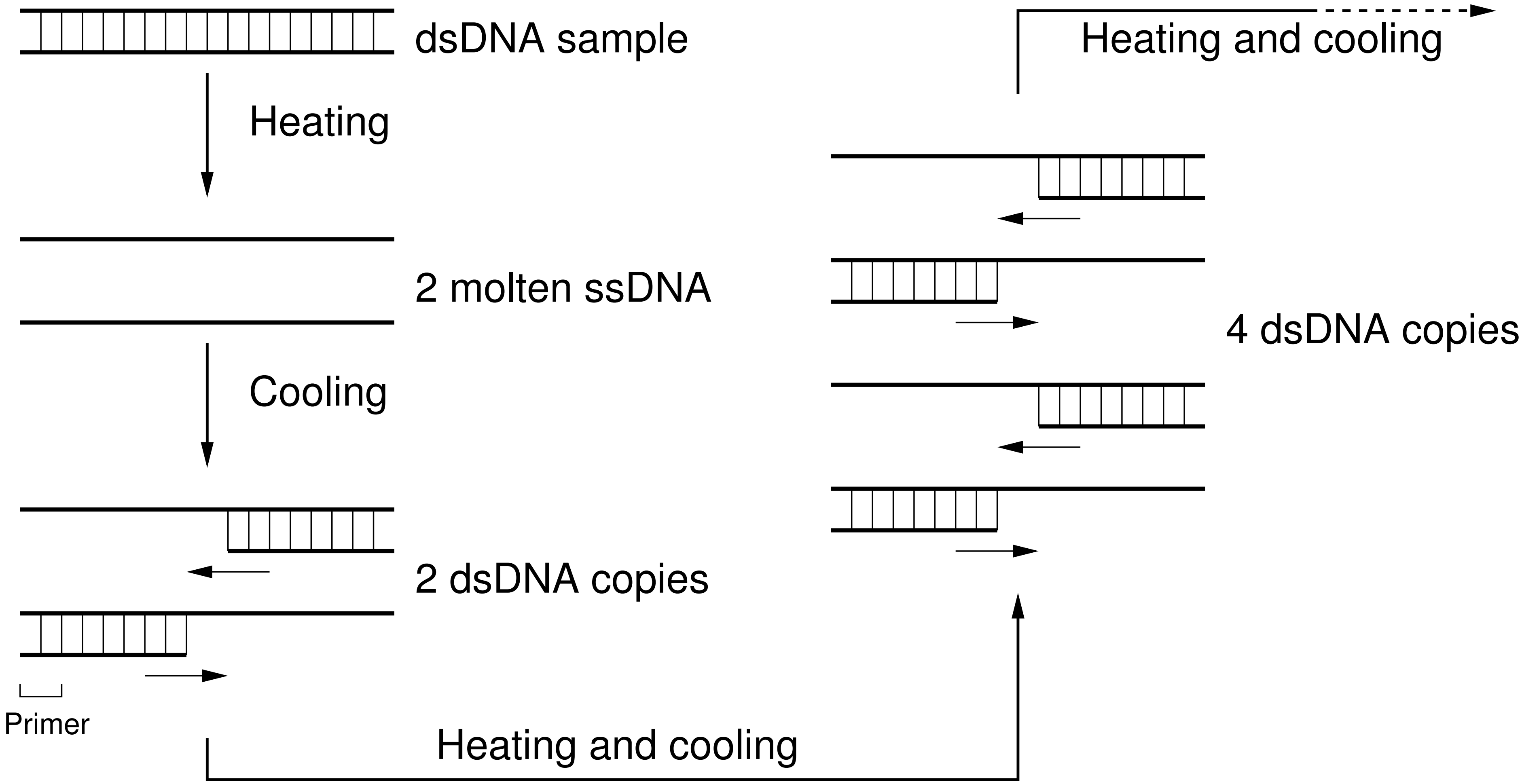
MARK McMANUS IS TAGGART
CLASSIC TAGGART
POLICE LINE DO
Double Exposure
The Hitman
Death Without Dishonour
Secrets

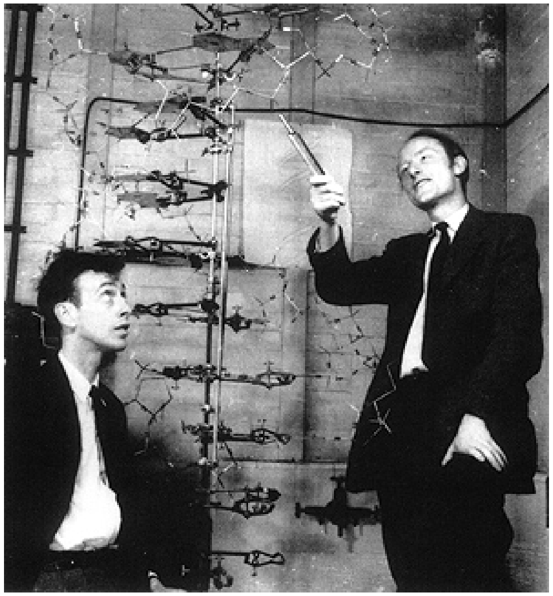

CSI: DNA LABORATORY
CSI:

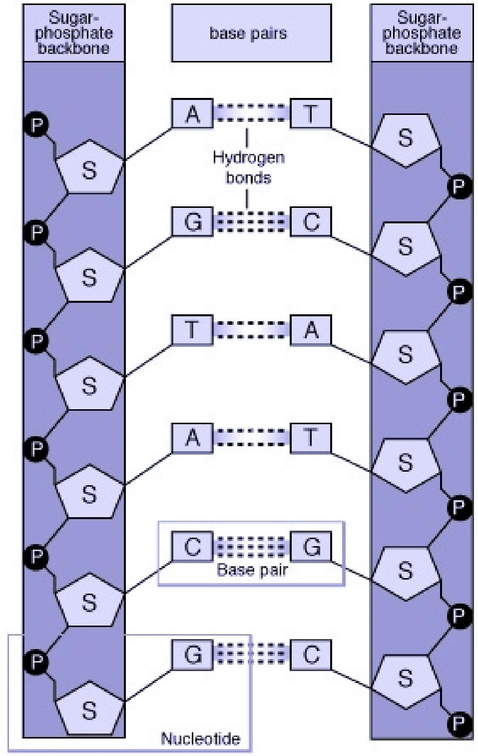


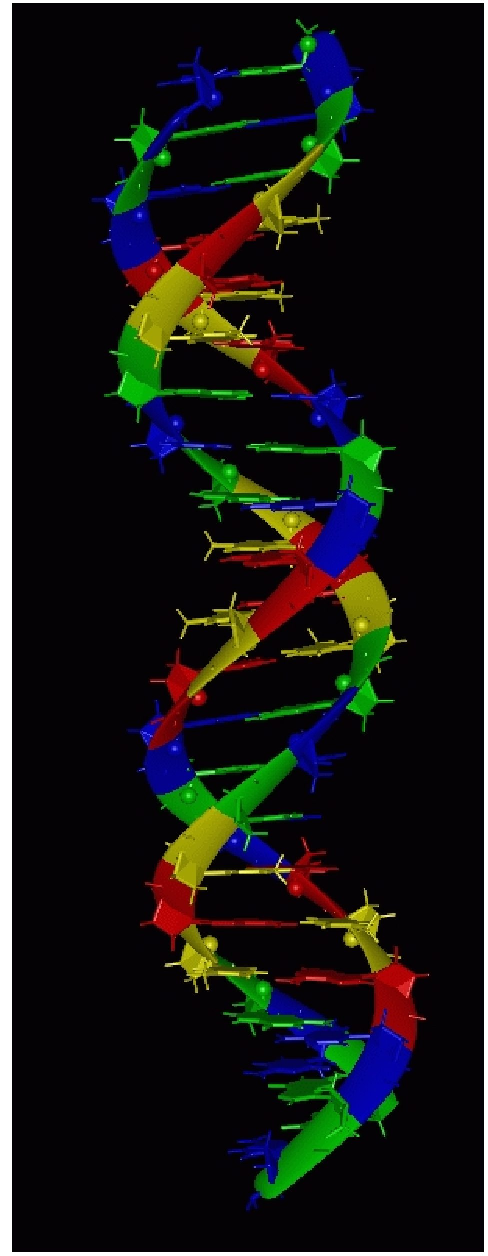
Polymerase chain reaction



Chief character: DeoxyriboNucleic Acid







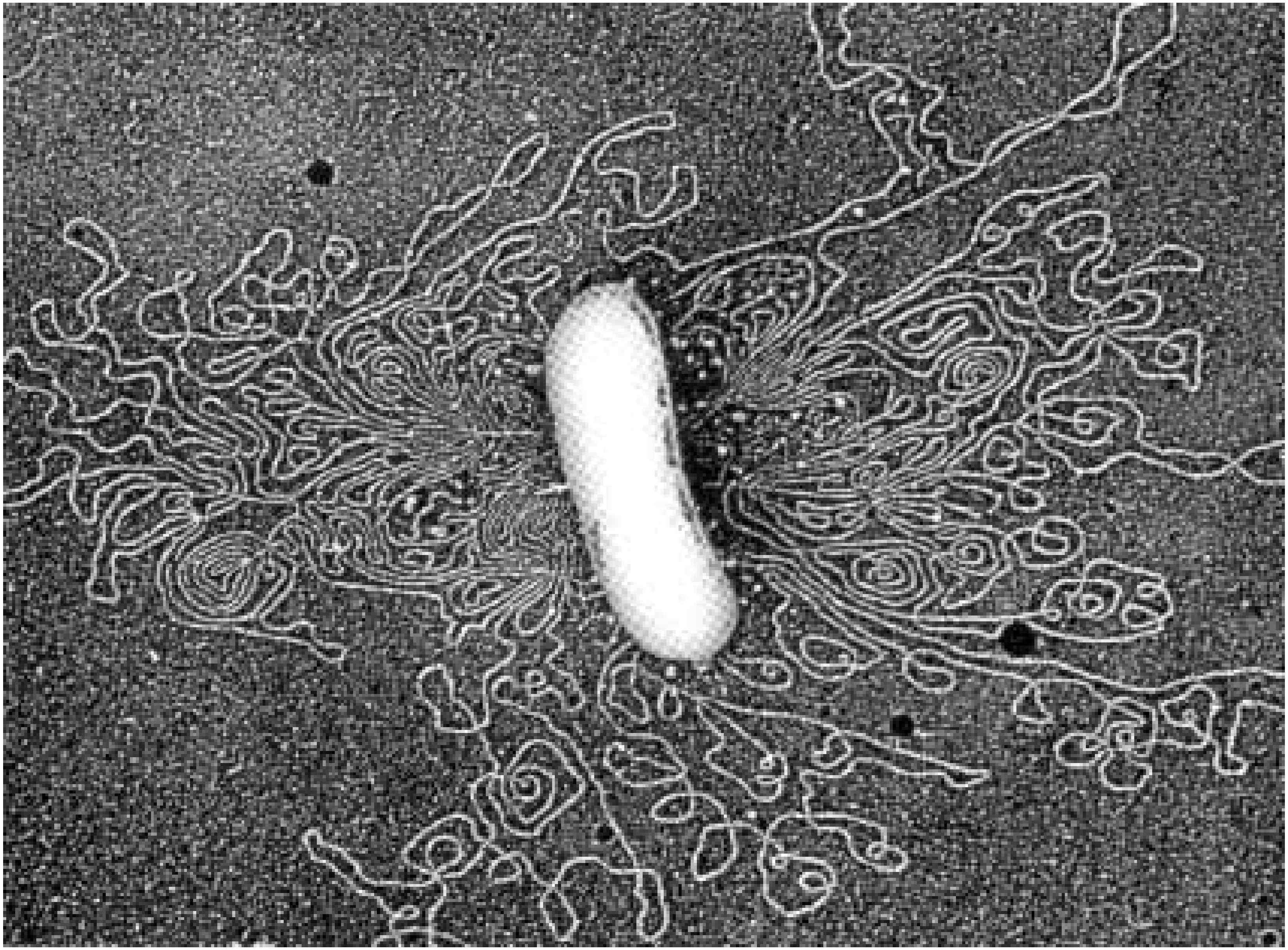
$d \simeq 2\text{nm}$

$\Delta_{\text{bp}-\text{bp}} \simeq 3.5\text{Å}$

$\ell_p(\text{dsDNA}) \simeq 50\text{nm}$

$\ell_p(\text{ssDNA}) \simeq 1\text{nm}$

ϕ29-phage	6μm
E.coli	3mm
Human cell	2m
Sth Amer lungfish	35m



Persistence length

Flexible rod:

$$\ell_p = \frac{\pi \mathsf{Y} \left(R^4 - R_i^4\right)}{4 k_B T} \;\therefore\; \text{Young's modulus } \mathsf{Y}$$

Spaghetti $\varnothing = 2$mm, Y $= 10^9$erg/cm^3, $T = 300$K; $k_B = 1.38 \times 10^{-16}$erg/K:

$$\ell_p \approx 2 \times 10^{18}\text{cm} = 2 \times 10^{13}\text{km} \approx 2 \text{ ly}$$

or 1/2 distance to Proxima centauri

Spaghetti of $\varnothing = 2$nm:

$$\ell_p \approx 20\text{nm}$$

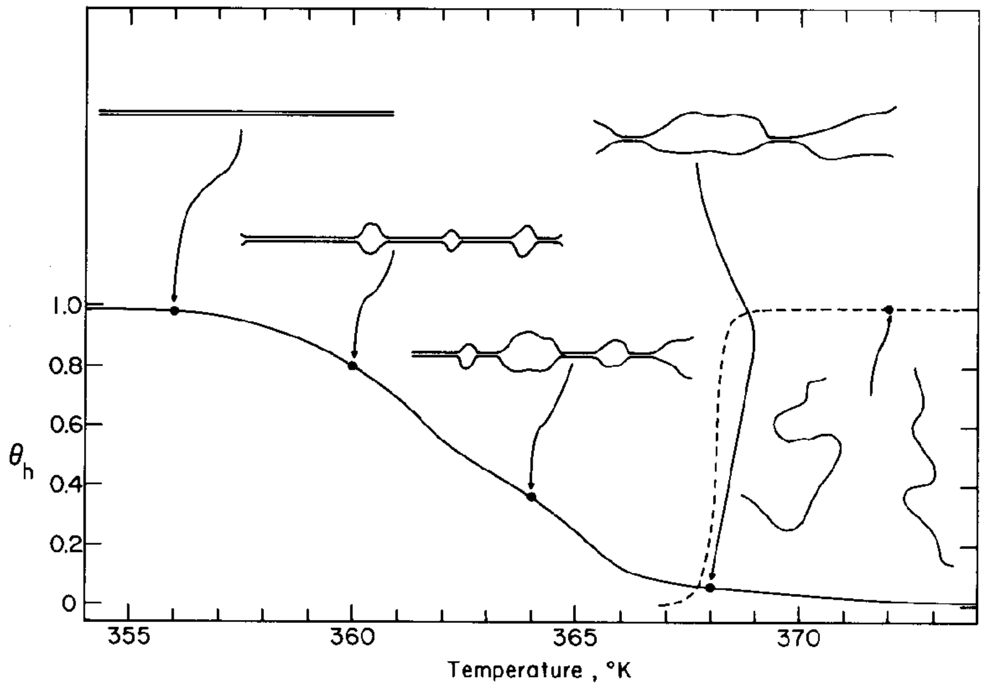
Double-stranded DNA:

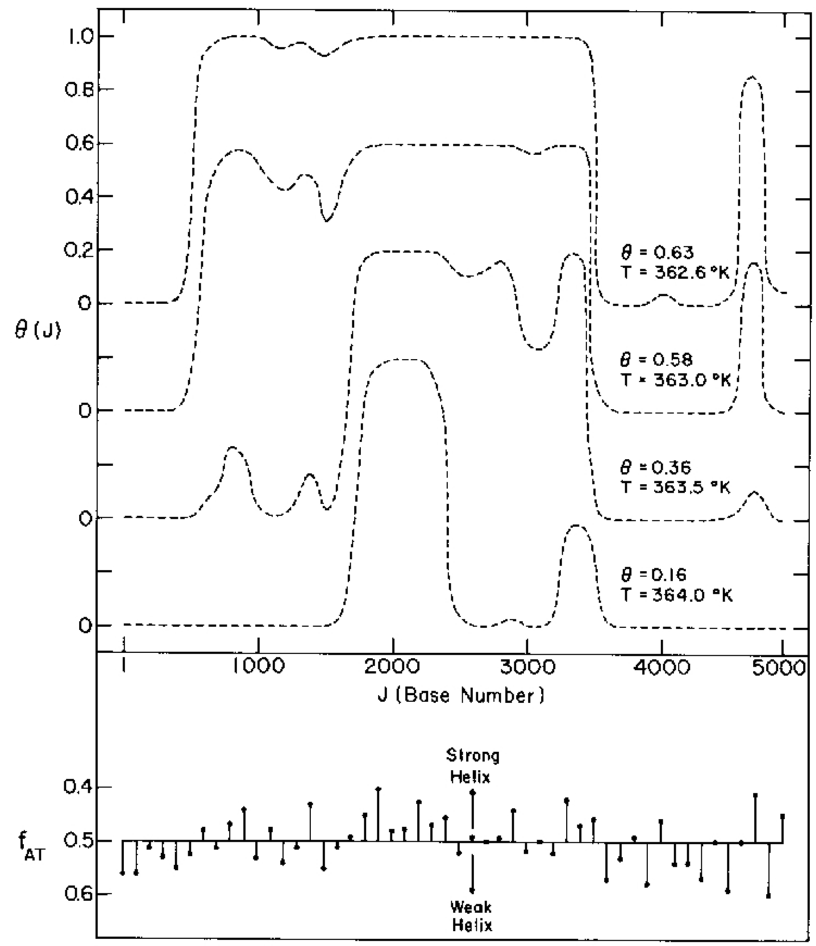
$$\ell_p \approx 53\text{nm}$$

DNA melting

DNA melting in bulk solution (UV absorption)

Thermal melting profile:



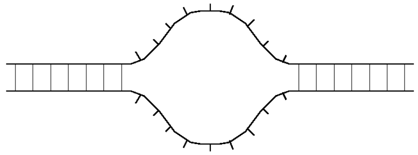


Poland & Scheraga, *Theory of helix-coil transitions*; Wartell & Benight, Phys Rep (1987); Richard & Guttmann, J Stat Phys (2004)

DNA stability landscape

Partition factor for bubble of m broken bps:

$$\mathscr{Z}(m) = \sigma_0 u^m (1+m)^{-c}$$



$$u = \exp\left(\beta[\Delta G_{ij} + \mathfrak{T}\theta_0]\right) \therefore \theta_0 = \frac{2\pi}{10.35}$$

·AA·/·TT· $\Delta G = -8.45\frac{\text{kcal}}{\text{mol}} + \underbrace{24.86\frac{\text{cal}}{\text{mol}\cdot\text{K}}T}_{7.72\text{kcal/mol@37°C}}$

·AA·/·TT· $T_m \approx 68°\text{C} \wedge$ ·GG·/·CC· $T_m \approx 102°\text{C}$

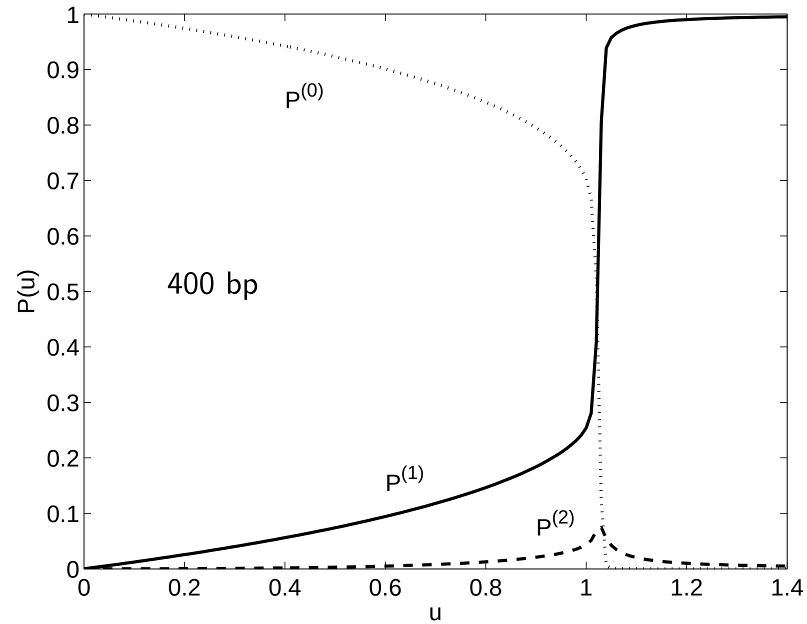
·TA·/·AT· $\Delta G = 0.1 k_B T \wedge$ ·GC·/·CG· $\Delta G = -3.9 k_B T$

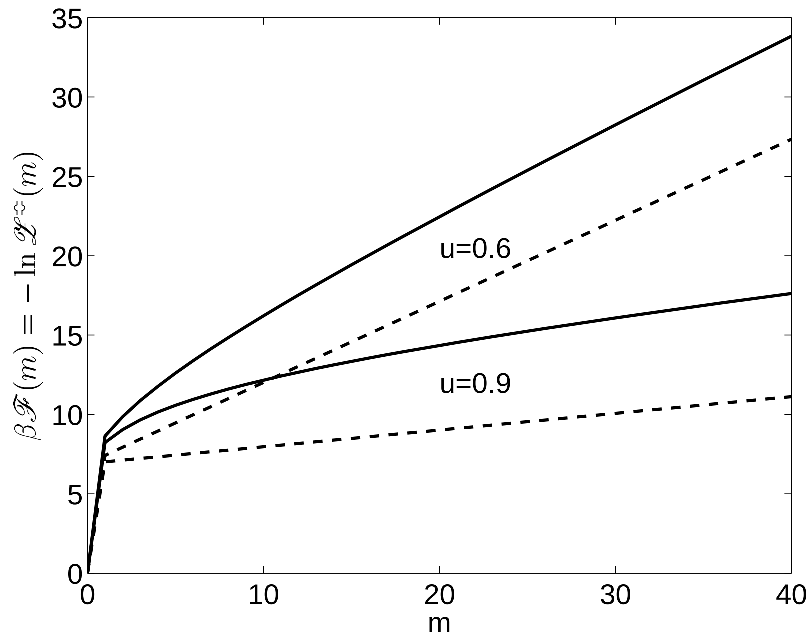
Loop initiation: $\sigma_0 \simeq 10^{-3\ldots-5} \triangleq 7\ldots12 k_B T$

Loop closure exponent: $c \approx 1.76$ (1)

Zipping rate: $k^{-1} \simeq 20\ldots100\,\mu\text{sec}$

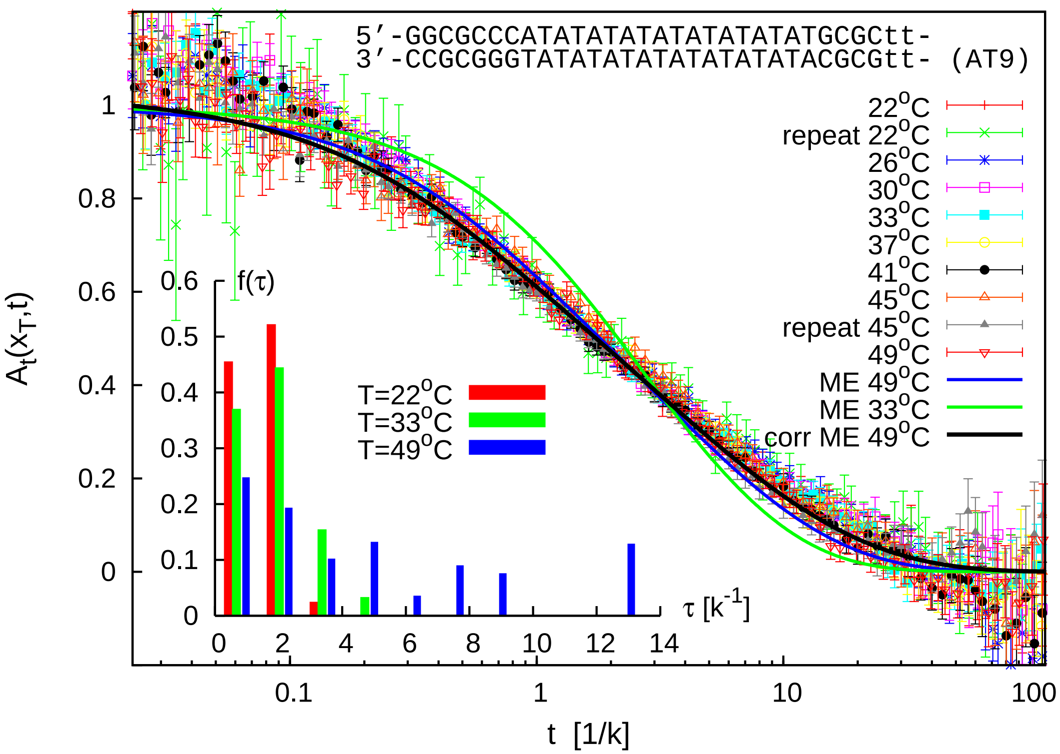
Bubble lifetime: $\tau_{\text{bubble}} \simeq 1\,\text{msec}$

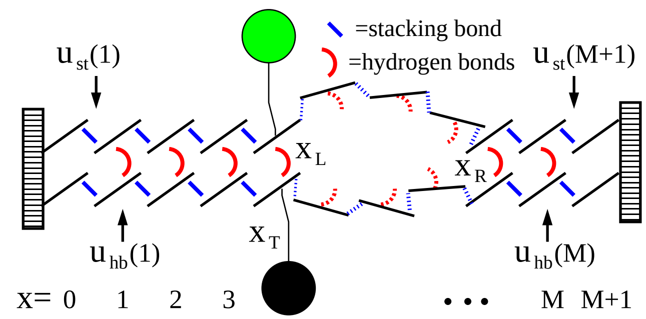




Poland & Scheraga, *Theory of helix-coil transitions*; Krueger et al, Biophys J (2006)

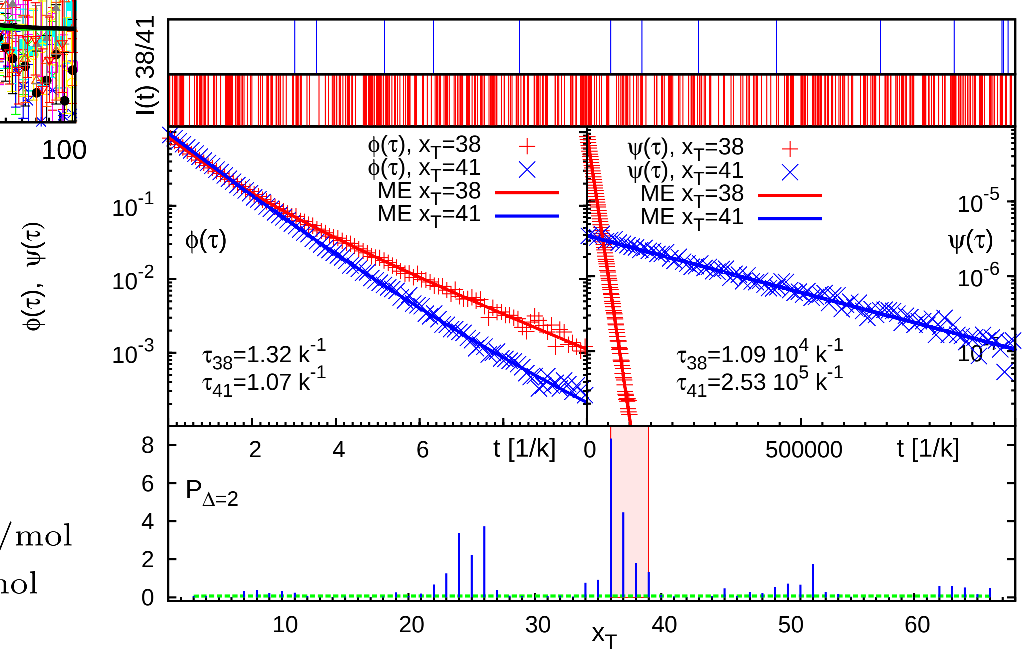
DNA-breathing may assist transcription initiation





T7 phage promoter: TATA @ bps 36-39, TSS @ bp 40

```
     1                   20
     |                   |
5'-aTGACCAGTTGAAGGACTGGAAGTAATACGACTC
   AGTATAGGGACAATGCTTAAGGTCGCTCTCTAGGAg-3'
     |  |                            |
    38 41                           68
```



$\Delta G_{\text{TATA}} = -9.2\text{kcal/mol} \vee \Delta G_{\text{rand}} = -11.9\text{kcal/mol}$

TATA-binding protein: $\Delta G_{\text{TATA-bind}} = -10.5\text{kcal/mol}$

RNA polymerase: $\Delta G_{\text{polymerase}} = -11.5\text{kcal/mol}$

T Ambjörnsson, SK Banik, O Krichevsky & RM, PRL (2006); Biophys J (2007); HC Fogedby & RM, PRL (2007)

DNA bubble dynamics as quantum Coulomb problem

Continuum form of the Poland-Scheraga free energy:

$$\mathscr{F} = \gamma_0 + \gamma_1 \left(1 - \frac{T}{T_m}\right) x + c \ln x$$

Langevin equation for bubble breathing

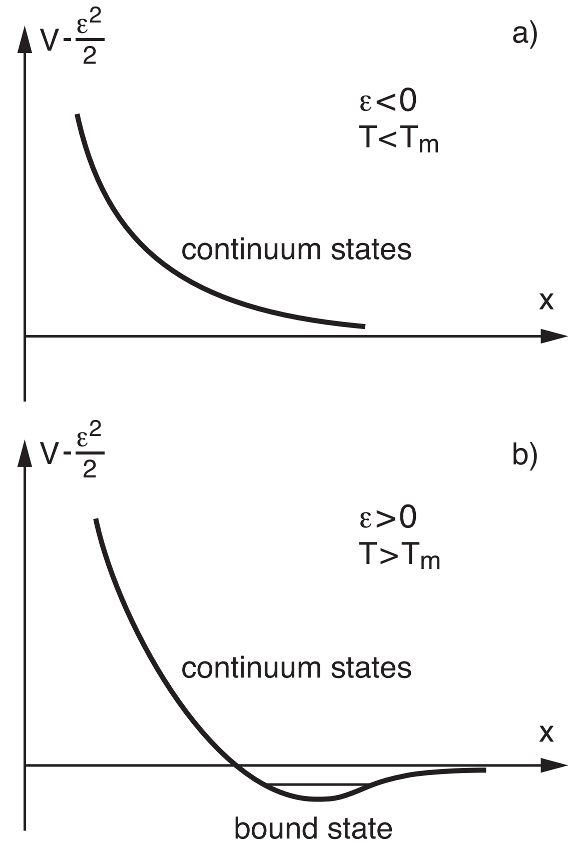
$$\frac{dx}{dt} = -D\frac{d\mathscr{F}}{dx} + \xi(t), \;\; \langle \xi(t)\xi(t')\rangle = 2Dk_BT\delta(t-t')$$

Fokker-Planck equation ($\mu = c/2k_BT$):

$$\frac{\partial P}{\partial t} = \frac{\partial}{\partial x}\left(\frac{\mu}{x} - \underbrace{\frac{\gamma_1}{2k_BT}\left[\frac{T}{T_m} - 1\right]}_{\epsilon}\right) P + \frac{1}{2}\frac{\partial^2 P}{\partial x^2}$$

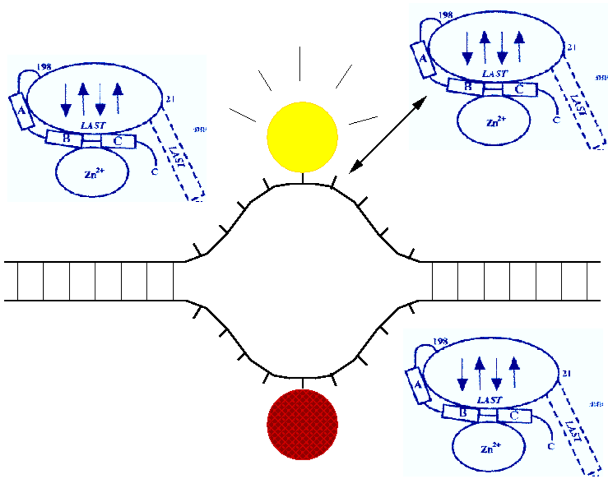
With $P = e^{\epsilon x} x^{-\mu} \tilde{P}$, obtain imaginary time Schrödinger Eq:

$$-\frac{\partial \tilde{P}}{\partial t} = -\frac{1}{2}\frac{\partial^2 \tilde{P}}{\partial x^2} + \left(\frac{\mu(\mu+1)}{2x^2} - \frac{\mu\epsilon}{x} + \frac{\epsilon^2}{2}\right)\tilde{P}$$



HC Fogedby & RM, Phys Rev Lett (2007), Phys Rev E (2007)

DNA and single-stranded DNA binding proteins (SSBs):



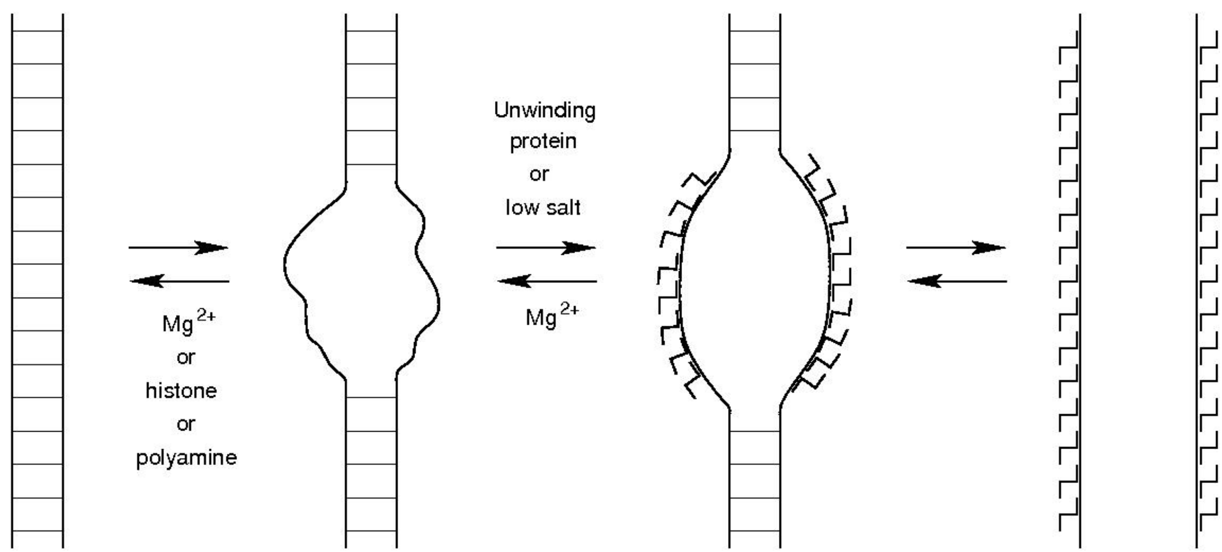
Binding strength $\kappa = c_0 K^{\mathrm{eq}}$

Equilibrium constant K^{eq}

SSB-concentration c_0

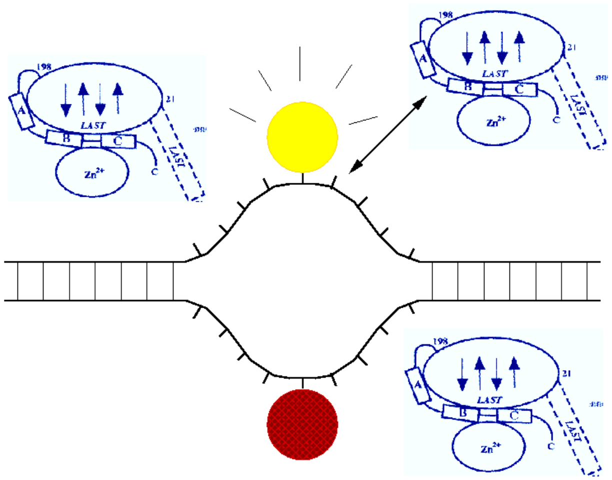
SSB-size λ in units of bp

Classical view
SSB-induced
denaturation:



Kornberg, *DNA synthesis* (1974); R Karpel, IUBMB Life (2002)

DNA and single-stranded DNA binding proteins (SSBs):



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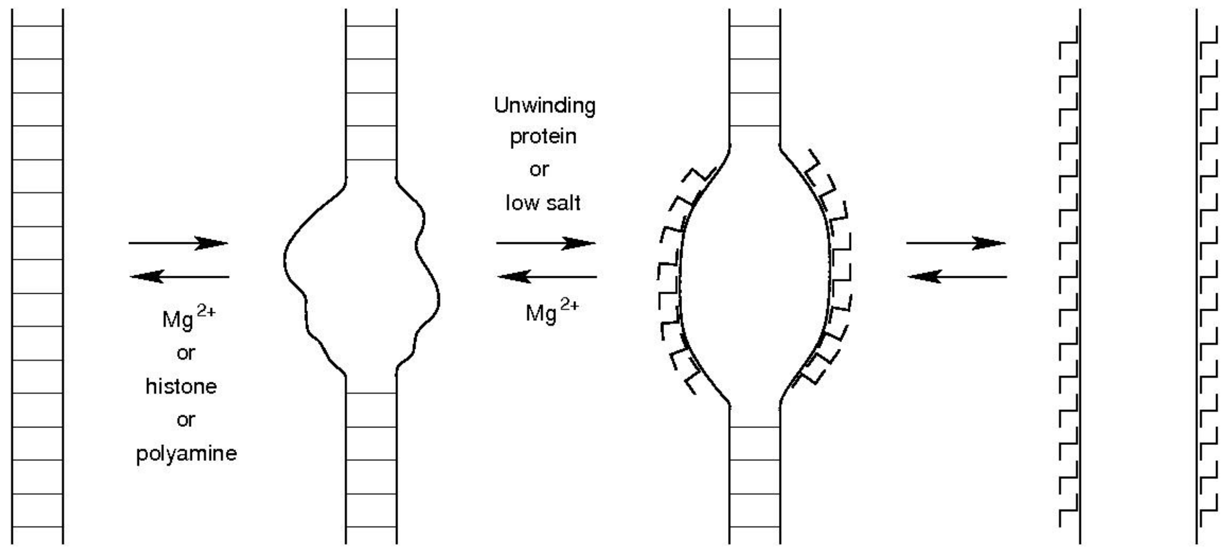

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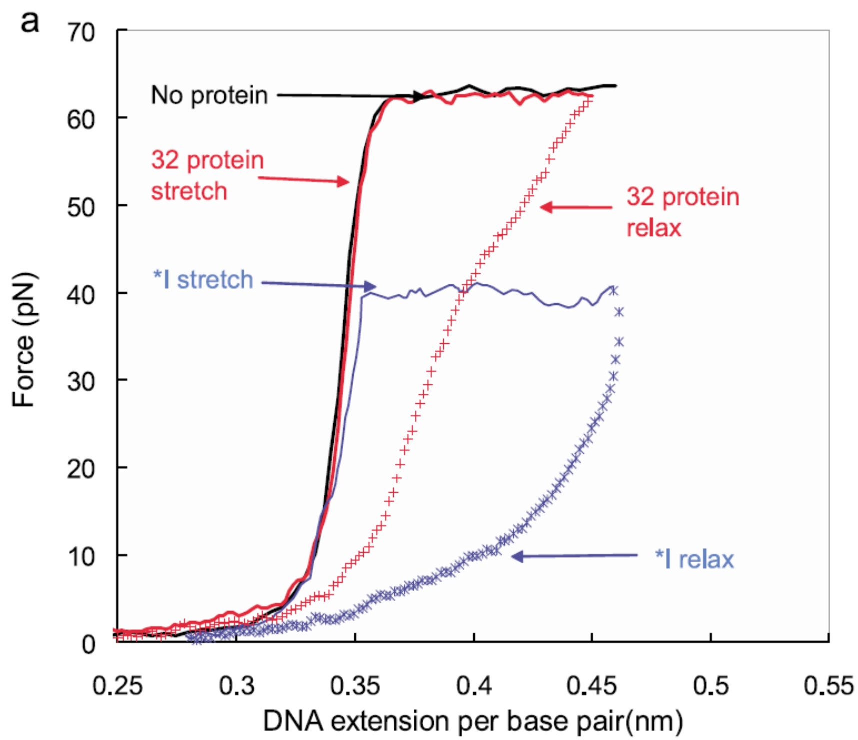
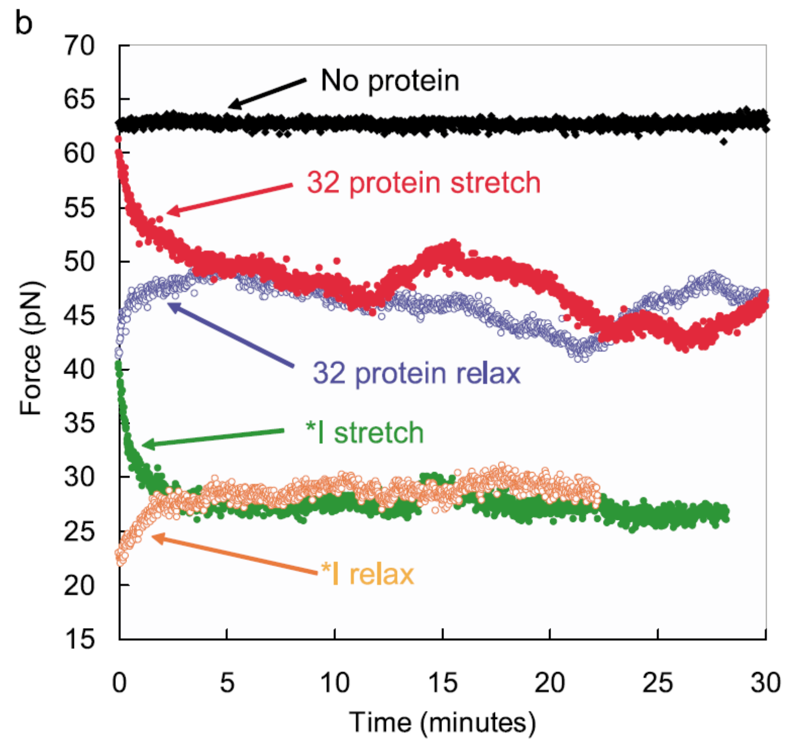
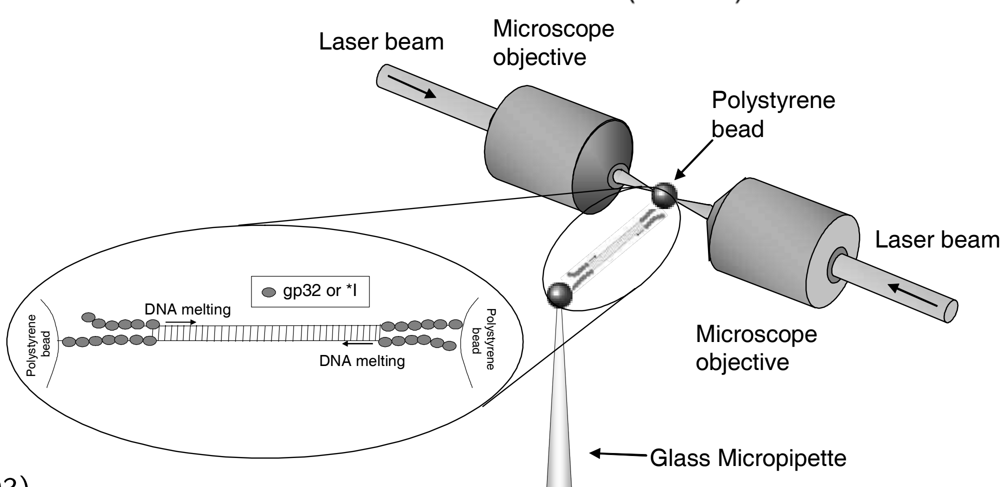
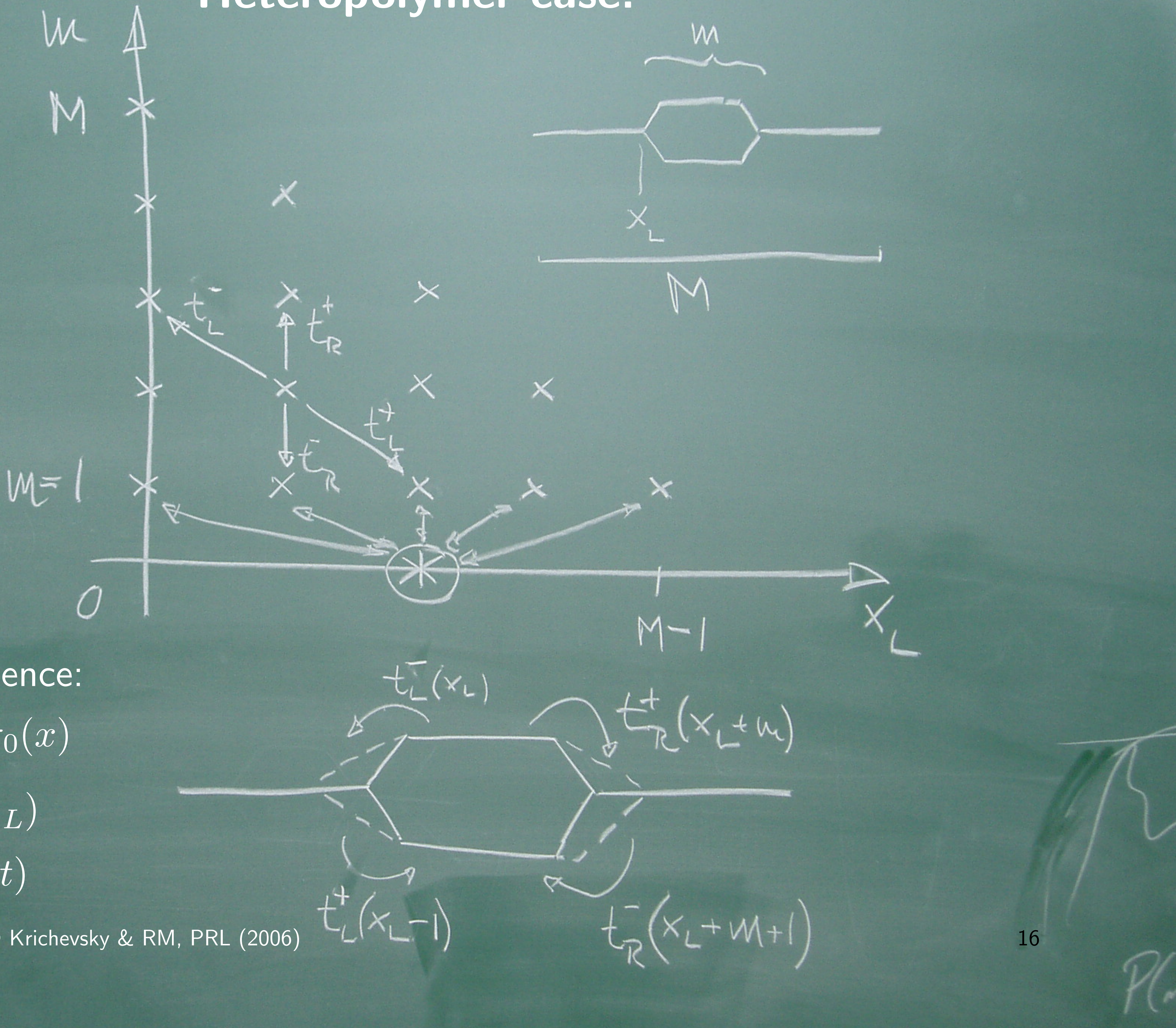






K Pant, RL Karpel, MC Williams, J Mol Biol (2003)

Heteropolymer case:



Sequence dependence:

$u, \sigma_0 \to u(x), \sigma_0(x)$

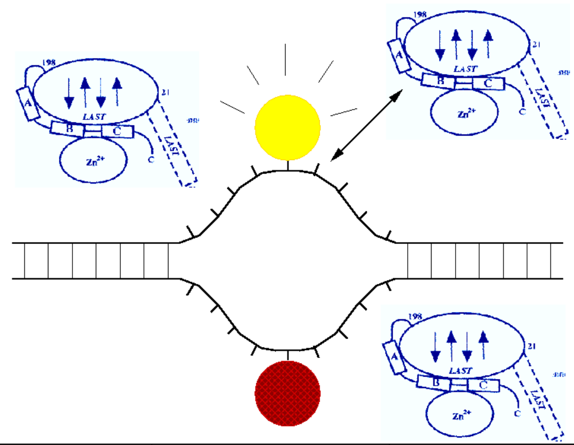
$\mathsf{t}^{\pm} \to \mathsf{t}^{\pm}_{R/L}(x_{R/L})$

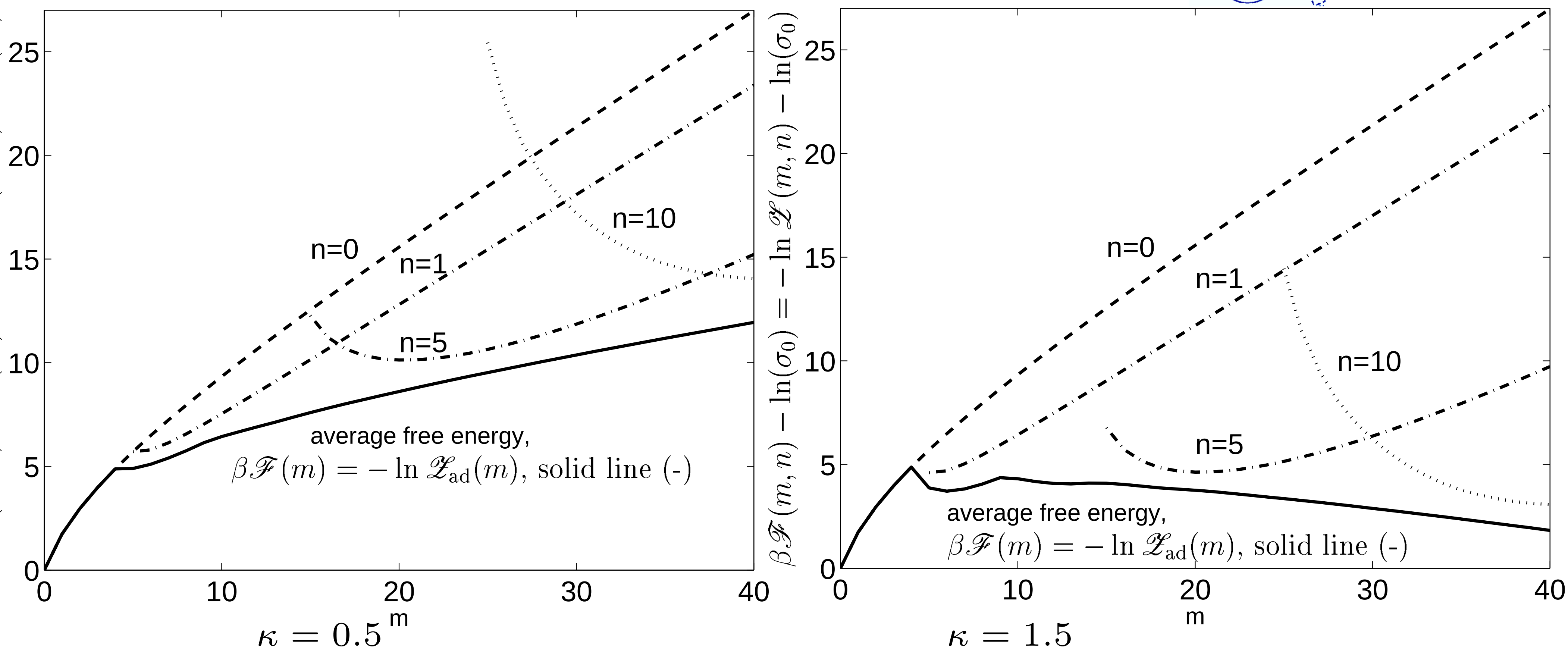
$P \to P(m, x_L, t)$

T Ambjörnsson, SK Banik, O Krichevsky & RM, PRL (2006)

Breathing bubbles and ssDNA binding proteins (SSBs)

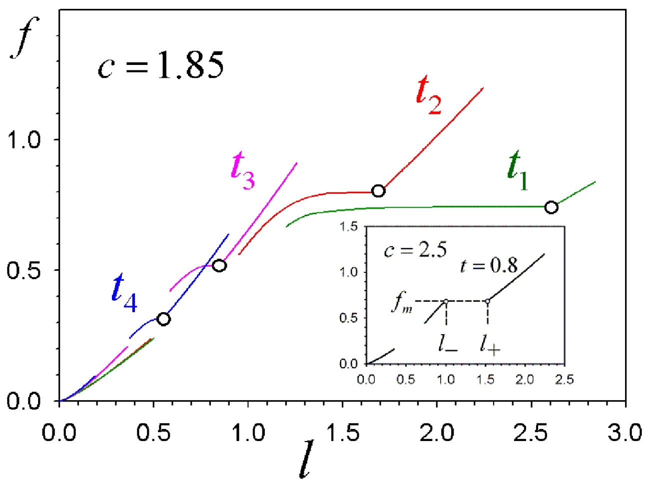
$$\frac{\partial}{\partial t}P(m,n,t) = \mathscr{M}(m,n)P(m,n,t)$$

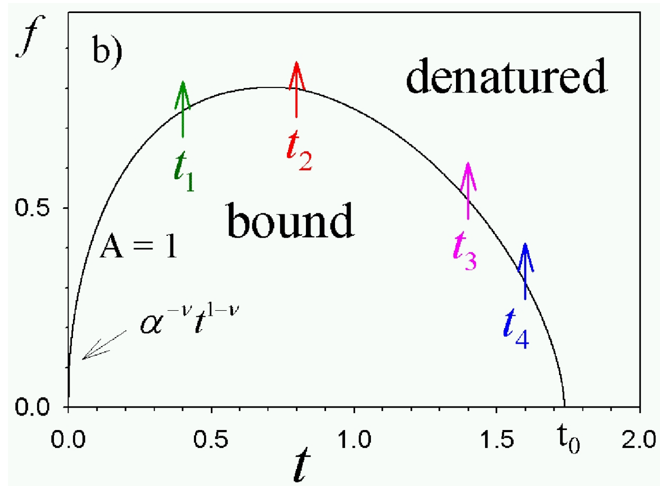


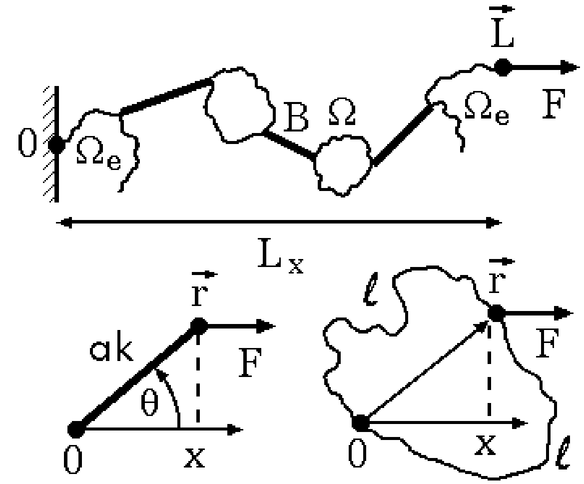


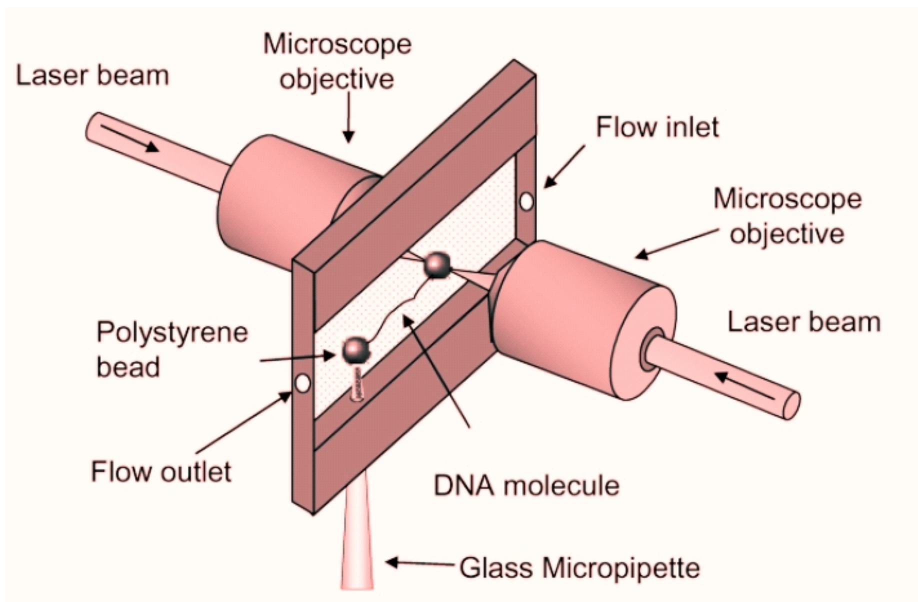
T Ambjörnsson & RM, PRE Rapid Comm (2005)

Stretching denaturation transition of DNA









@ $F > 0$ new critical exponent:

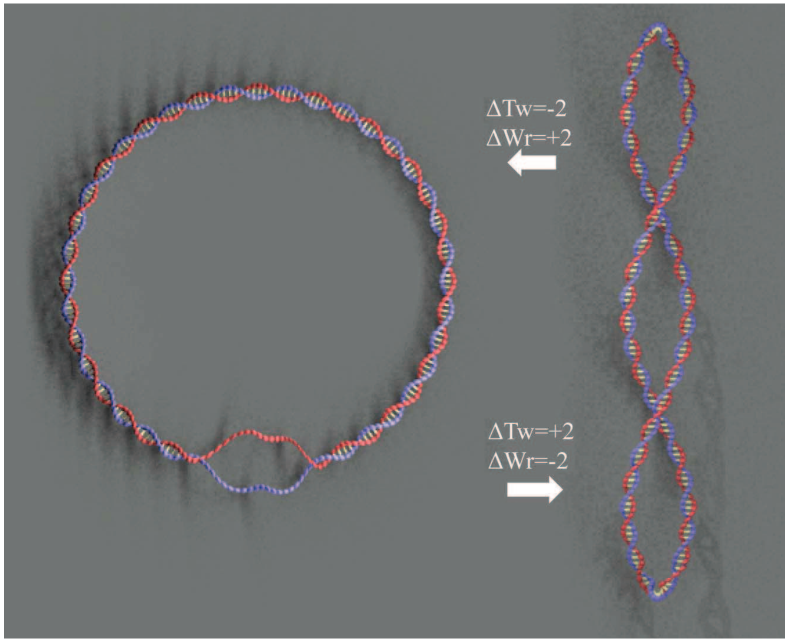
$c = 4\nu - 1/2 \approx 1.85$

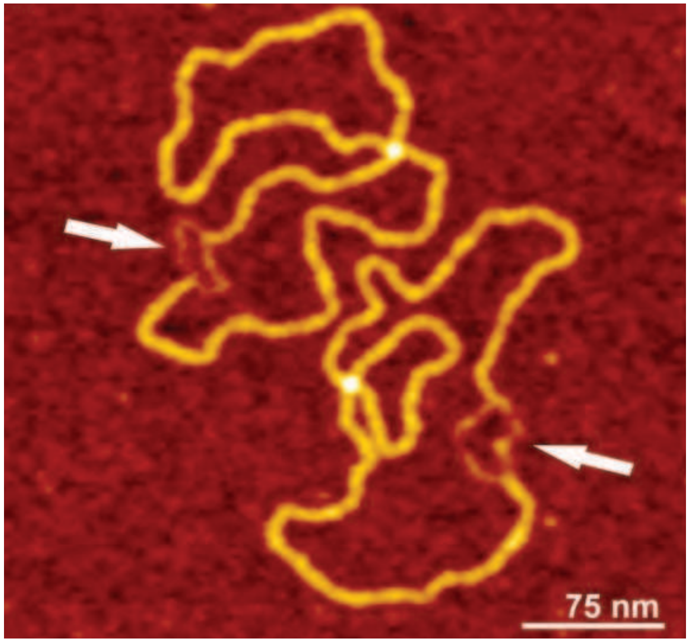
$(c = 3\nu \approx 1.76 \text{ @ } F = 0)$

Melting temperature: $T_m = T_m(F)$

A Hanke, MG Ochoa & RM, PRL (2008)

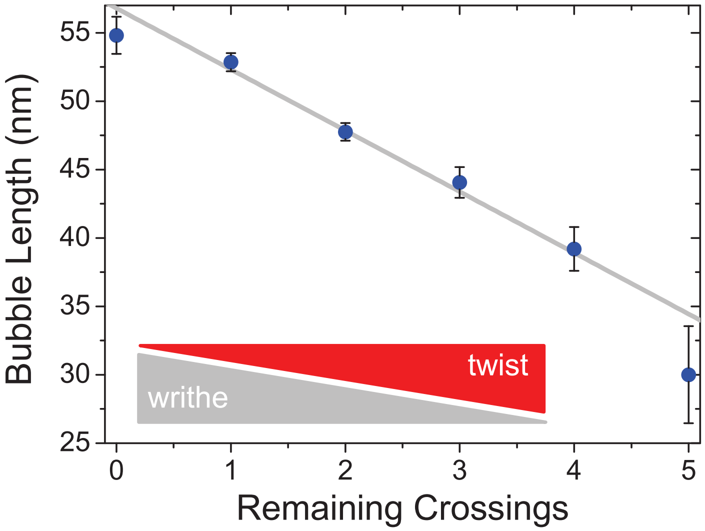
Quantifying undertwist-induced bubble formation





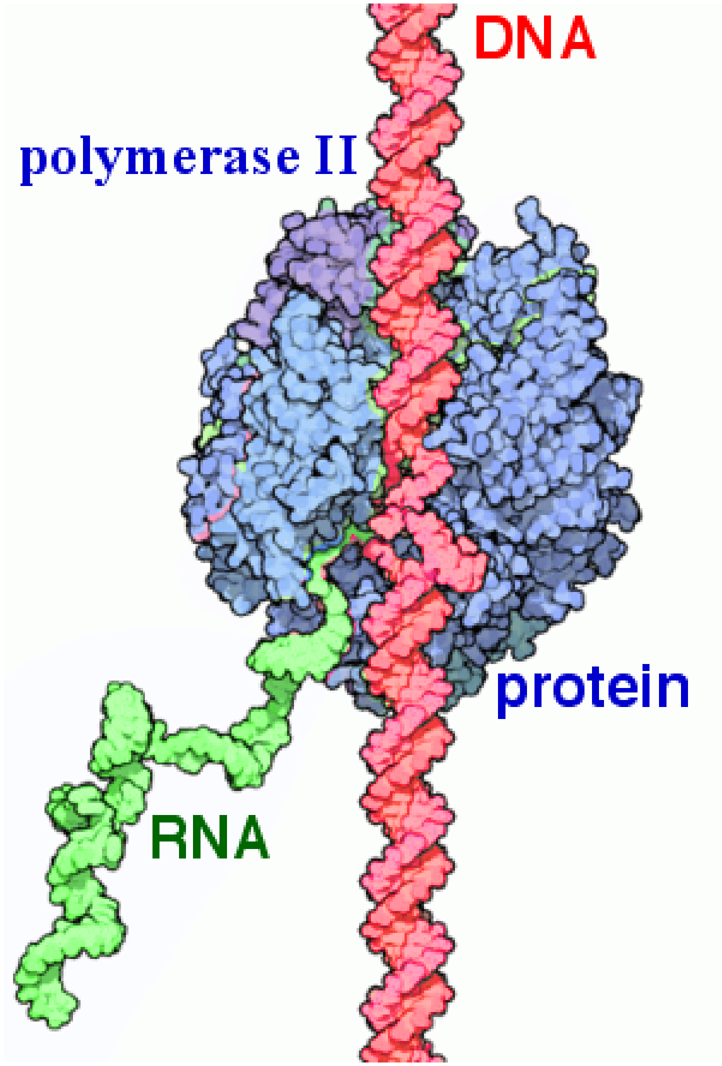
DNA superhelical density:

$$\sigma = \frac{\mathrm{Lk} - \mathrm{Lk}_0}{\mathrm{Lk}_0} \approx -0.06$$

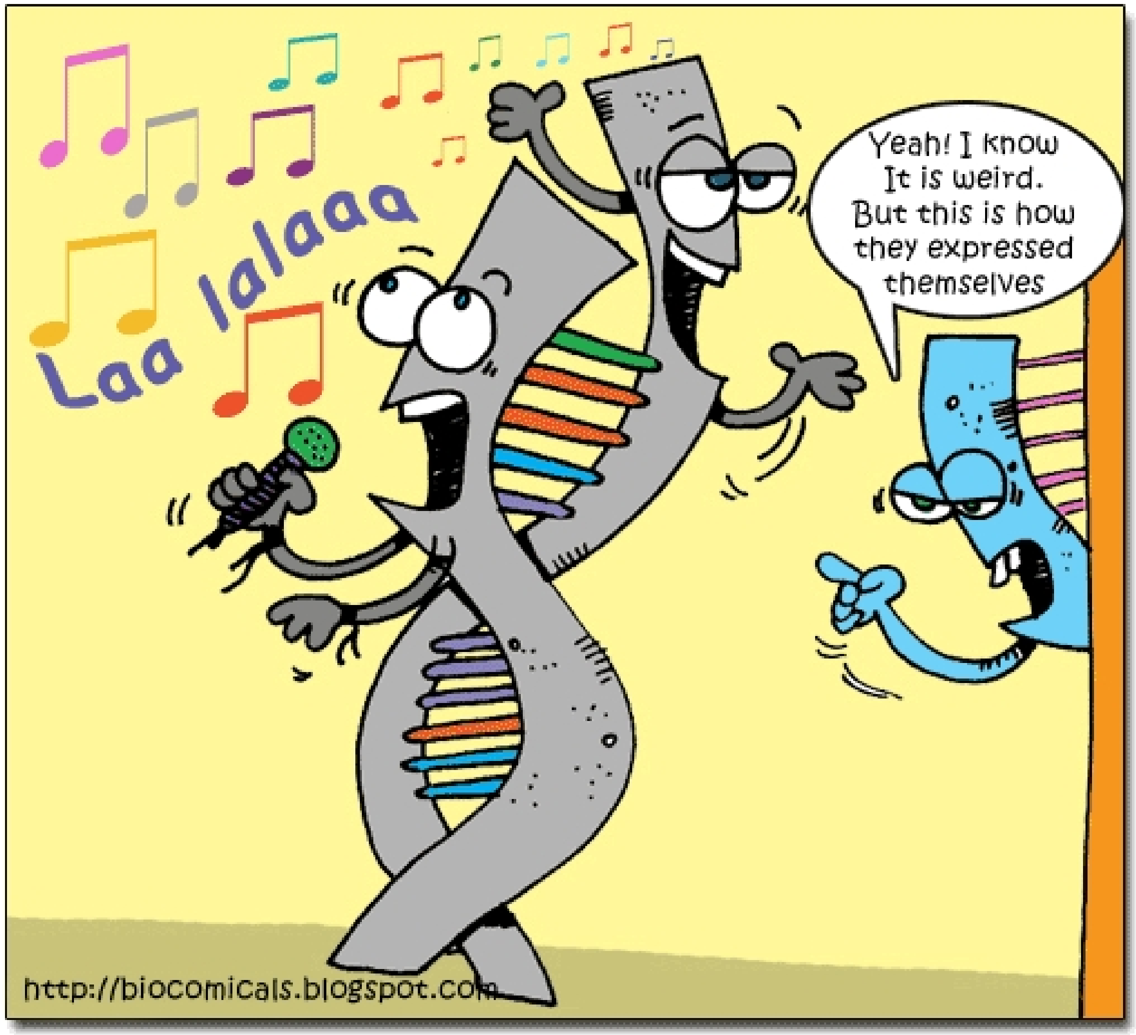


J-H Jeon, J Adamczik, G Dietler & RM, PRL (2010); J Adamczik, J-H Jeon, RM & G Dietler, Soft Matter (2012)

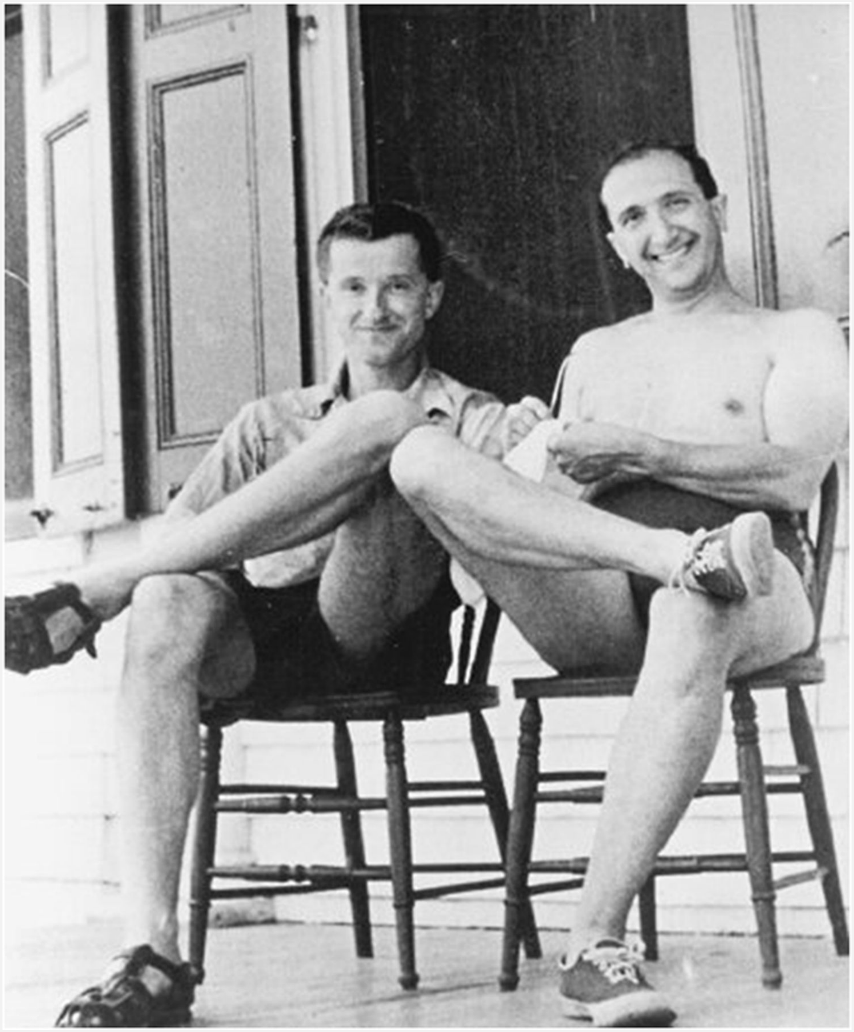
Polymerase action



Gene expression: producing proteins from genetic code



Luria-Delbrück experiment (1943)



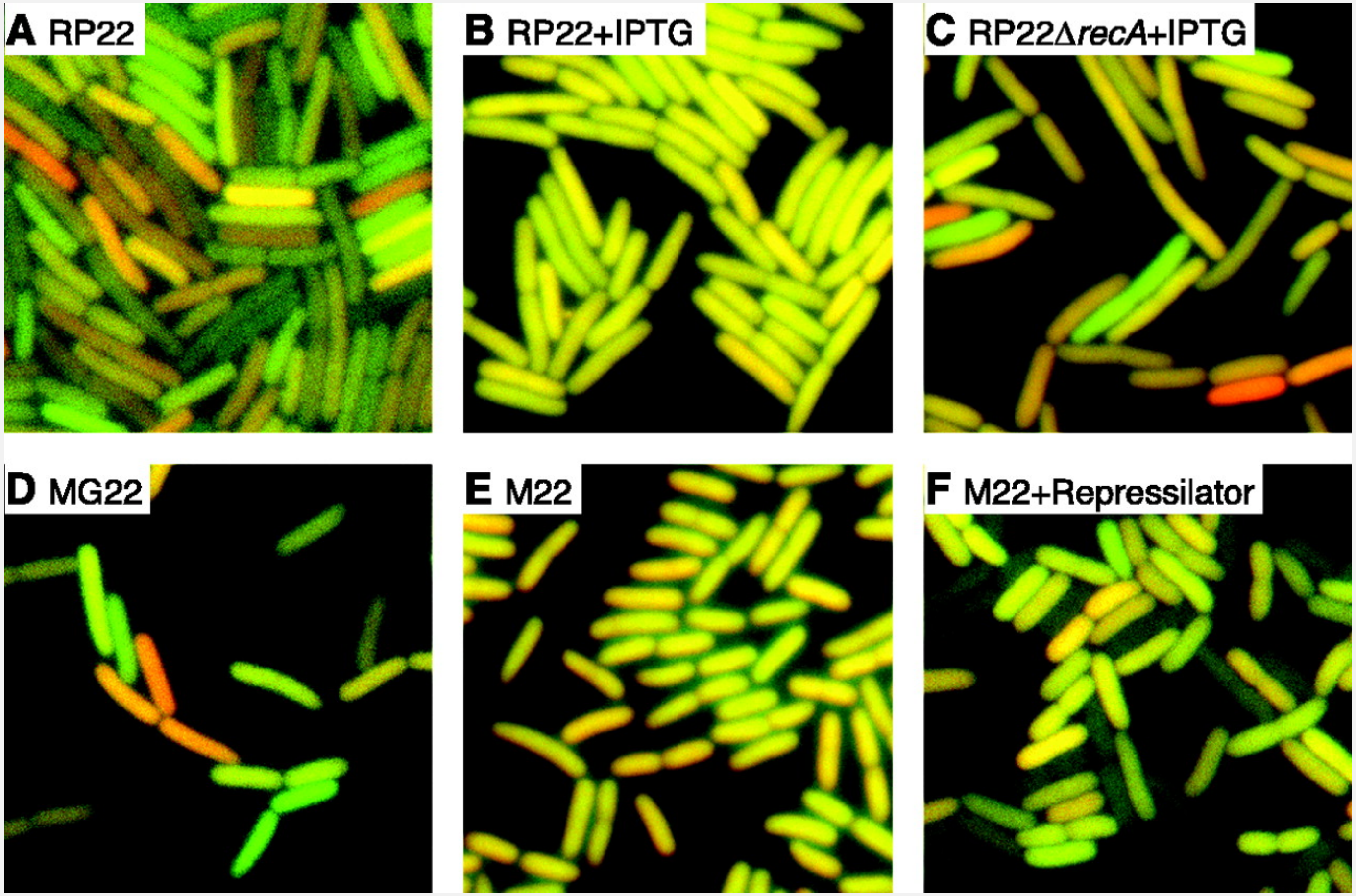
The Luria-Delbrück experiment or Fluctuation Test demonstrates that in bacteria mutations against a specific viral infection arise *randomly over time*, and are not induced by exposure to the virus itself. Those bacteria with the appropriately mutated genes will survive and proliferate the resistance.

Max Delbrück and Salvador Luria (Nobel Prize, 1969)

SE Luria & M Delbrück, Genetics (1943)

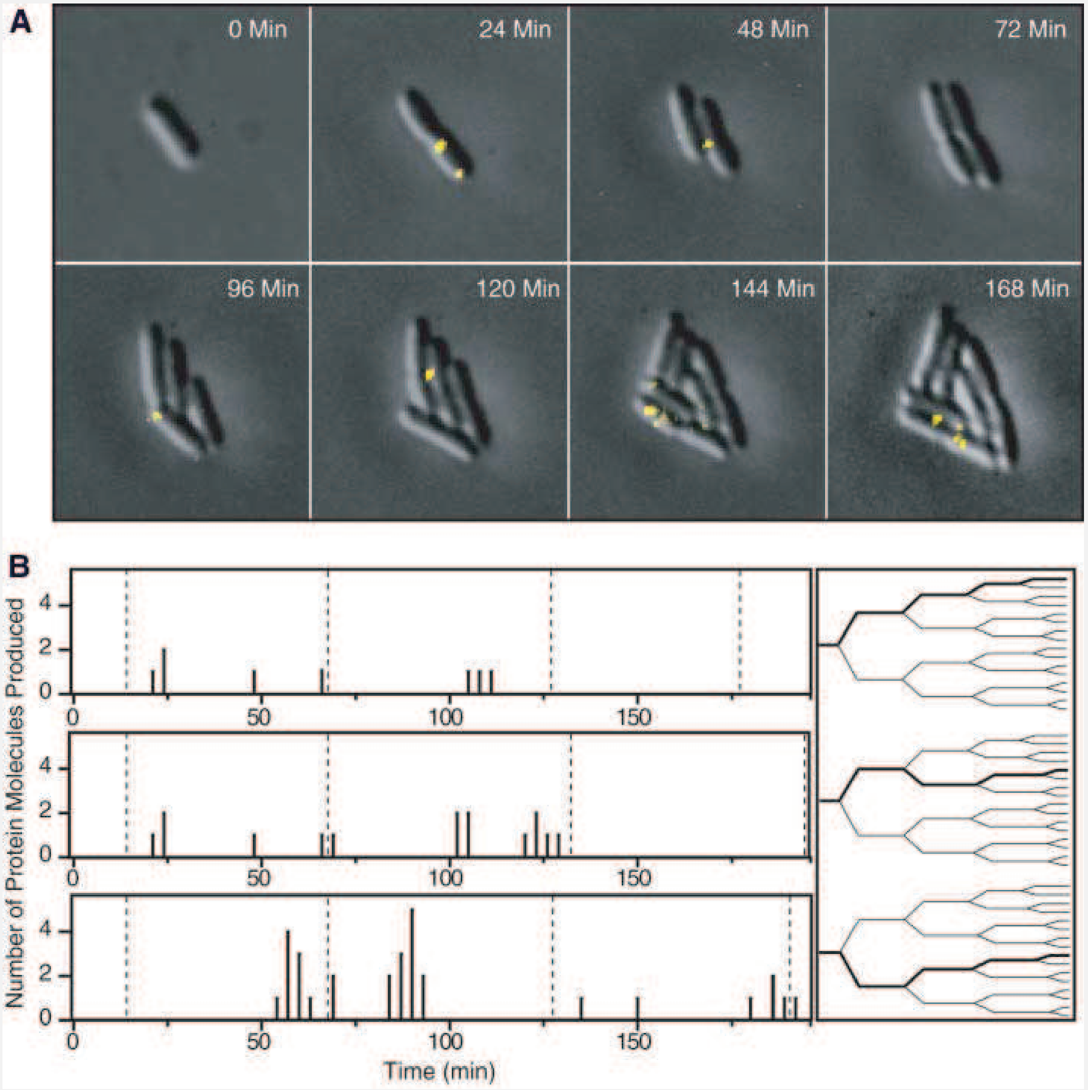
Gene regulation is intrinsically stochastic

Phenotypic difference in a single cell line:



Elowitz et al, Science (2002)

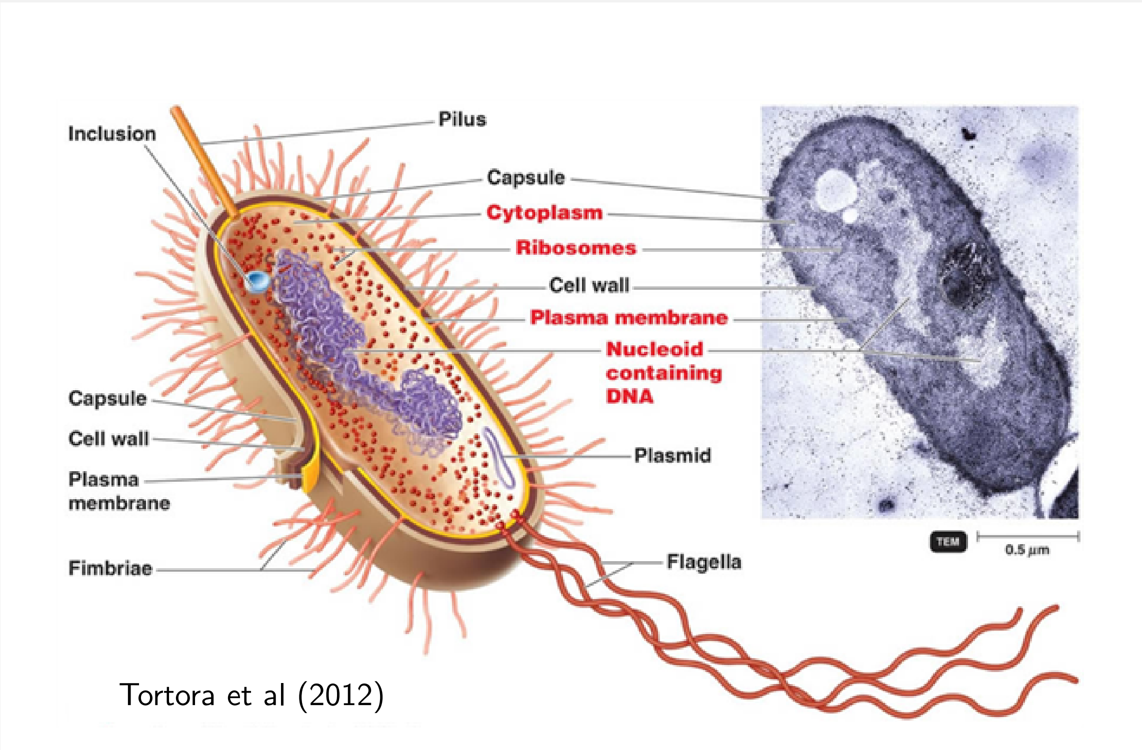
Gene expression one molecule at a time



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

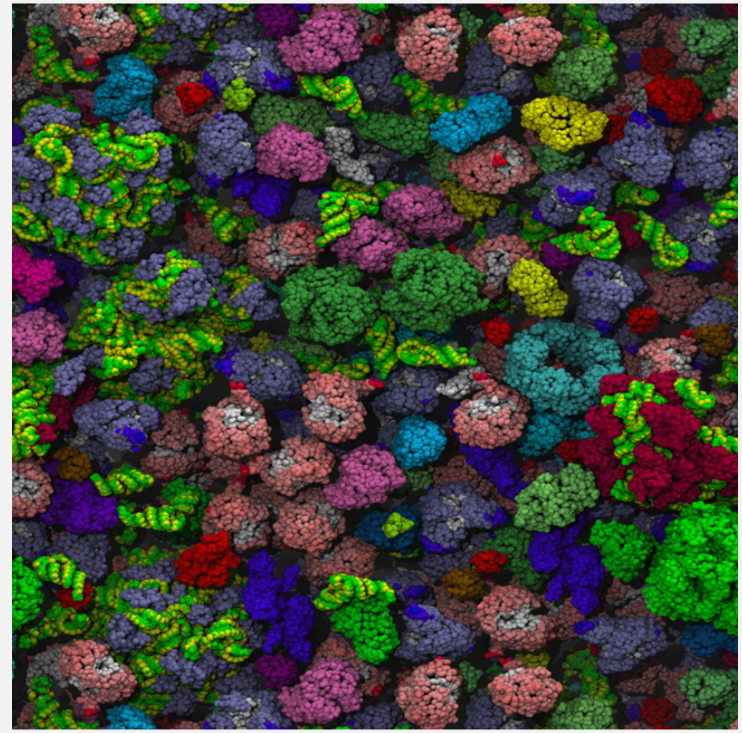
Yu et al, Science (2006); I Golding et al, Cell (2005)

Main protagonist: bacteria cells such as E.coli



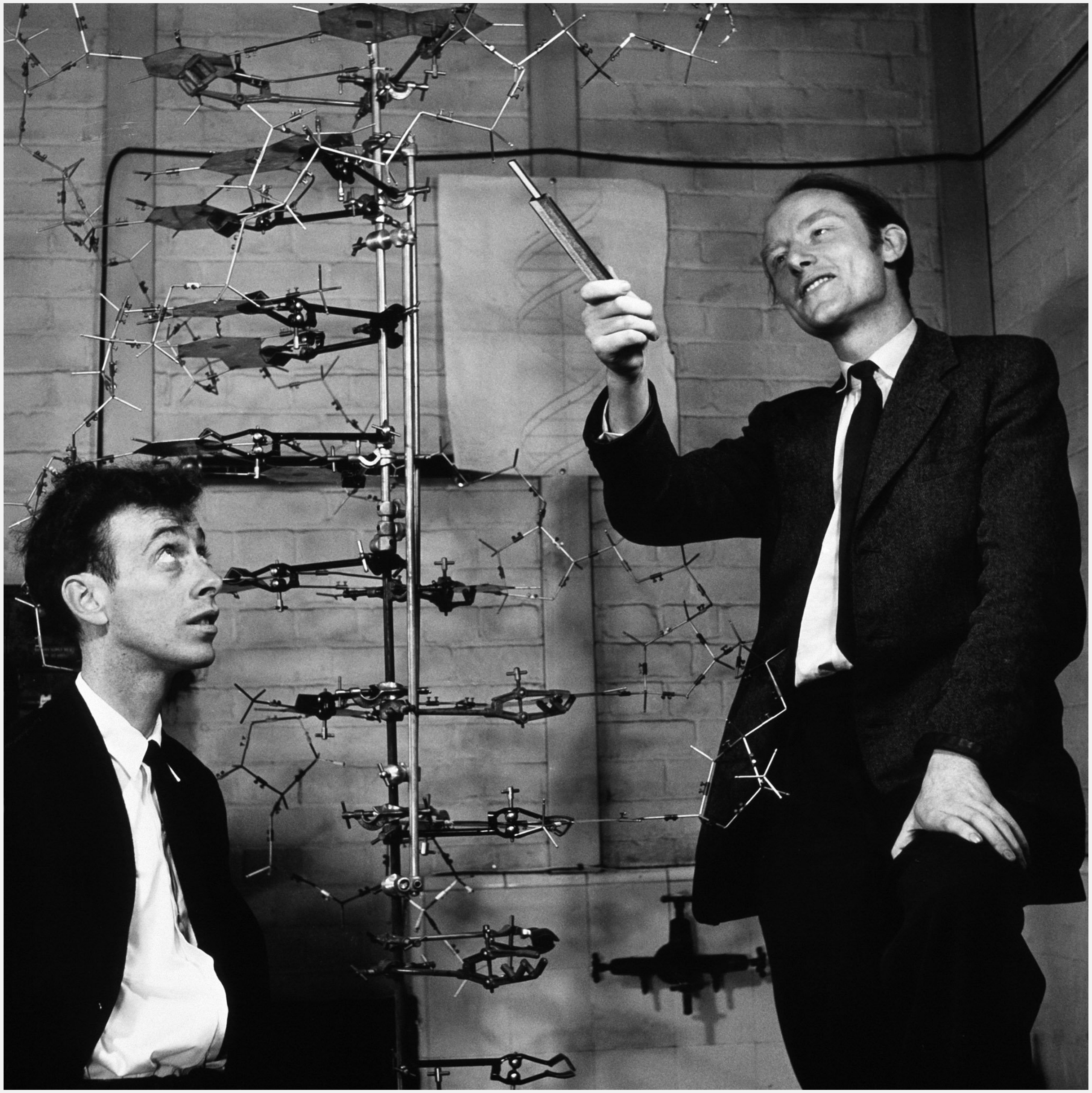
Tortora et al (2012)

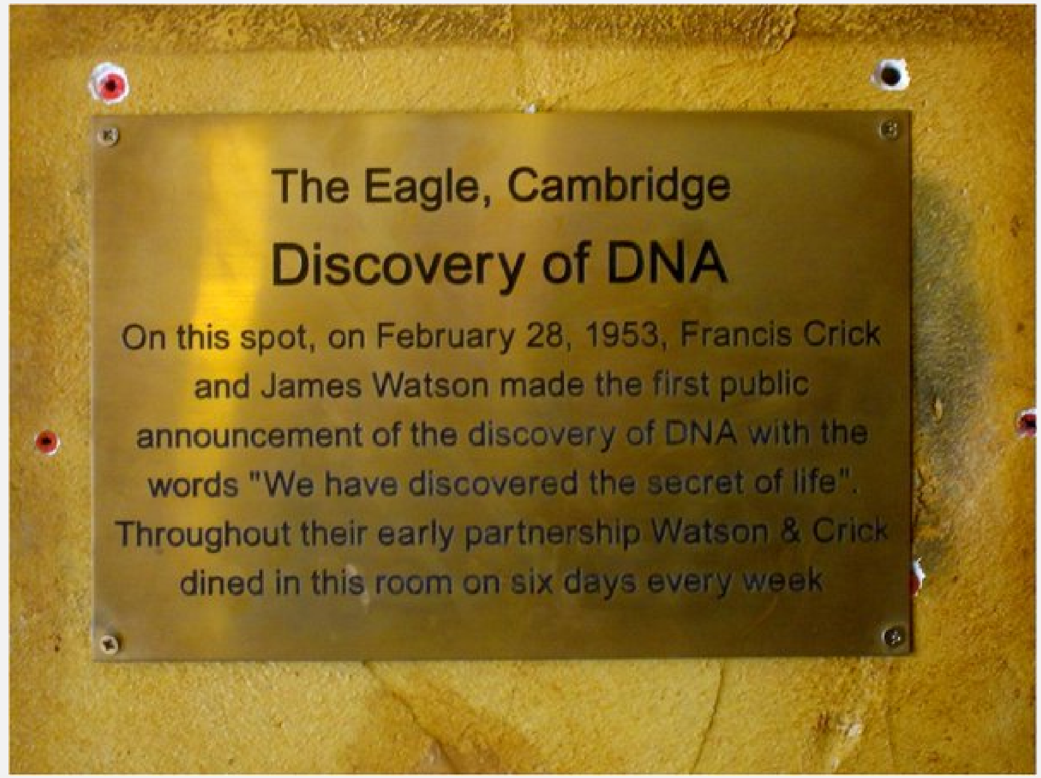
McGuffee & Elcock, PLoS Comp Biol (2010)



(∃ also cells with fully delocalised chromatin)

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.

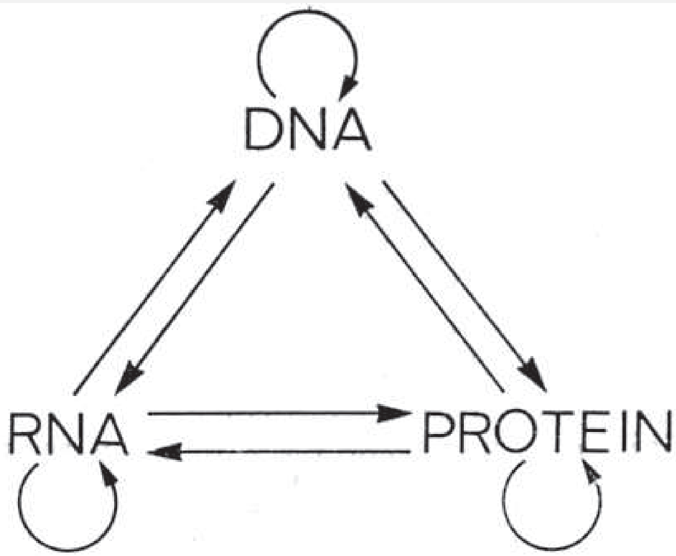


Fig. 1. The arrows show all the possible simple transfers between the three families of polymers. They represent the directional flow of detailed sequence information.

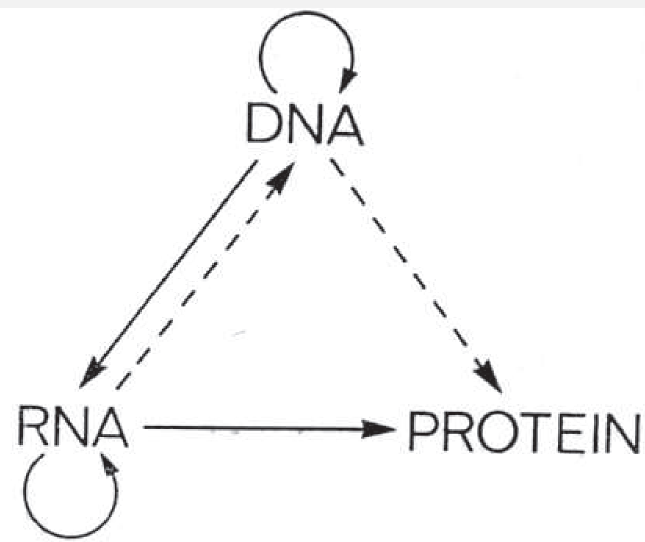
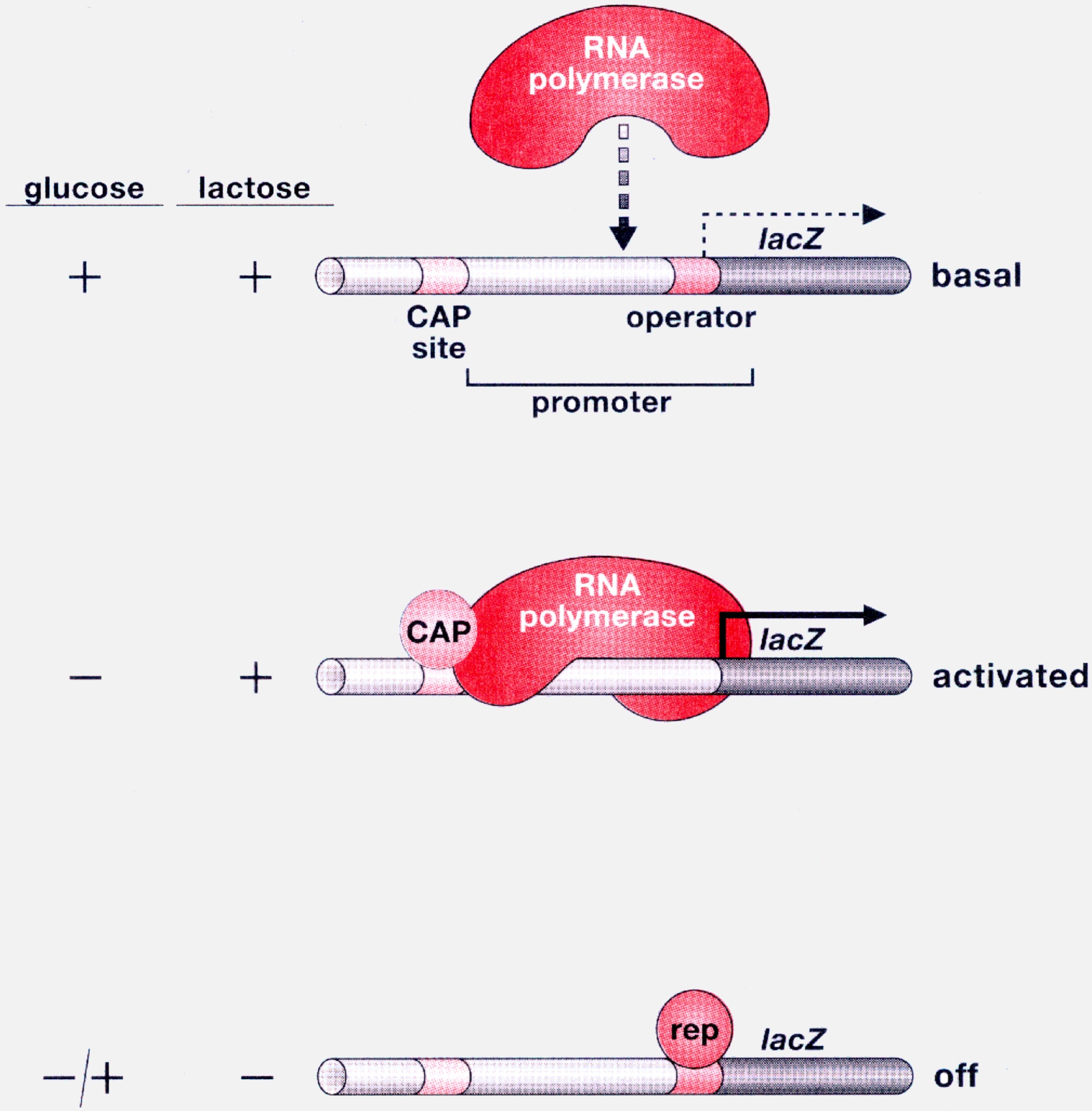


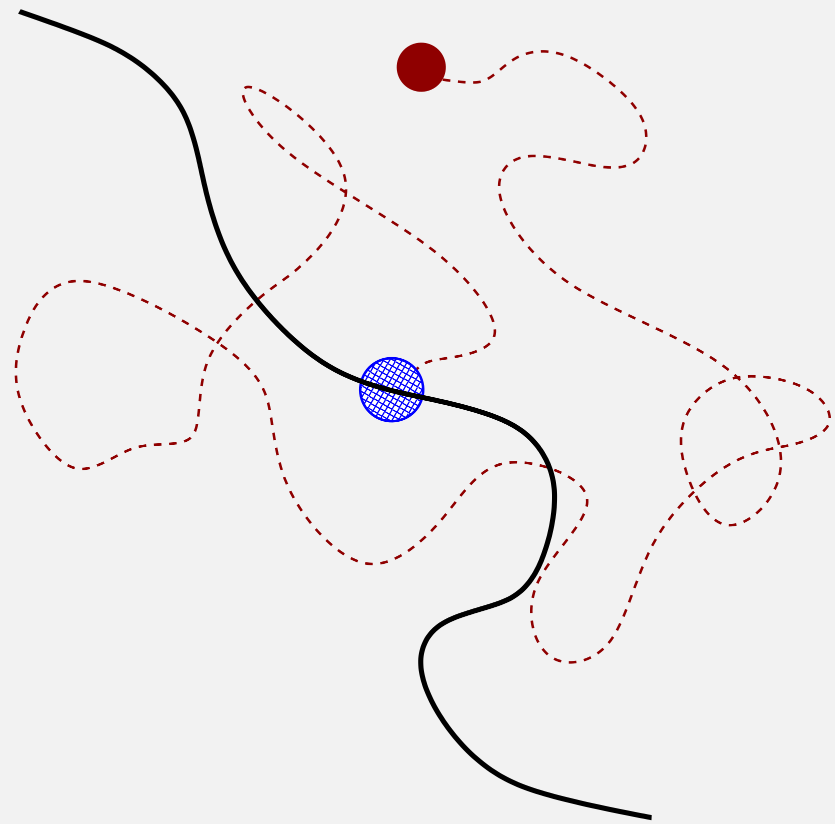
Fig. 2. The arrows show the situation as it seemed in 1958. Solid arrows represent probable transfers, dotted arrows possible transfers. The absent arrows (compare Fig. 1) represent the impossible transfers postulated by the central dogma. They are the three possible arrows starting from protein.

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

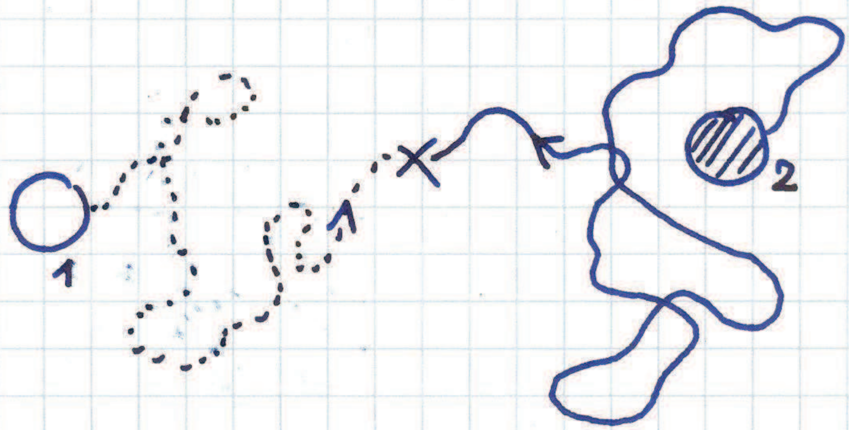
$$k_{\mathrm{on}} \approx \frac{10^{10}}{(\mathrm{mol}/l) \times \mathrm{sec}}$$

$\rightarrow$ Facilitated diffusion picture

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

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?

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

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

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 $M^{-1}\,sec^{-1}$, $[D_i] = cm^2/sec$

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

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

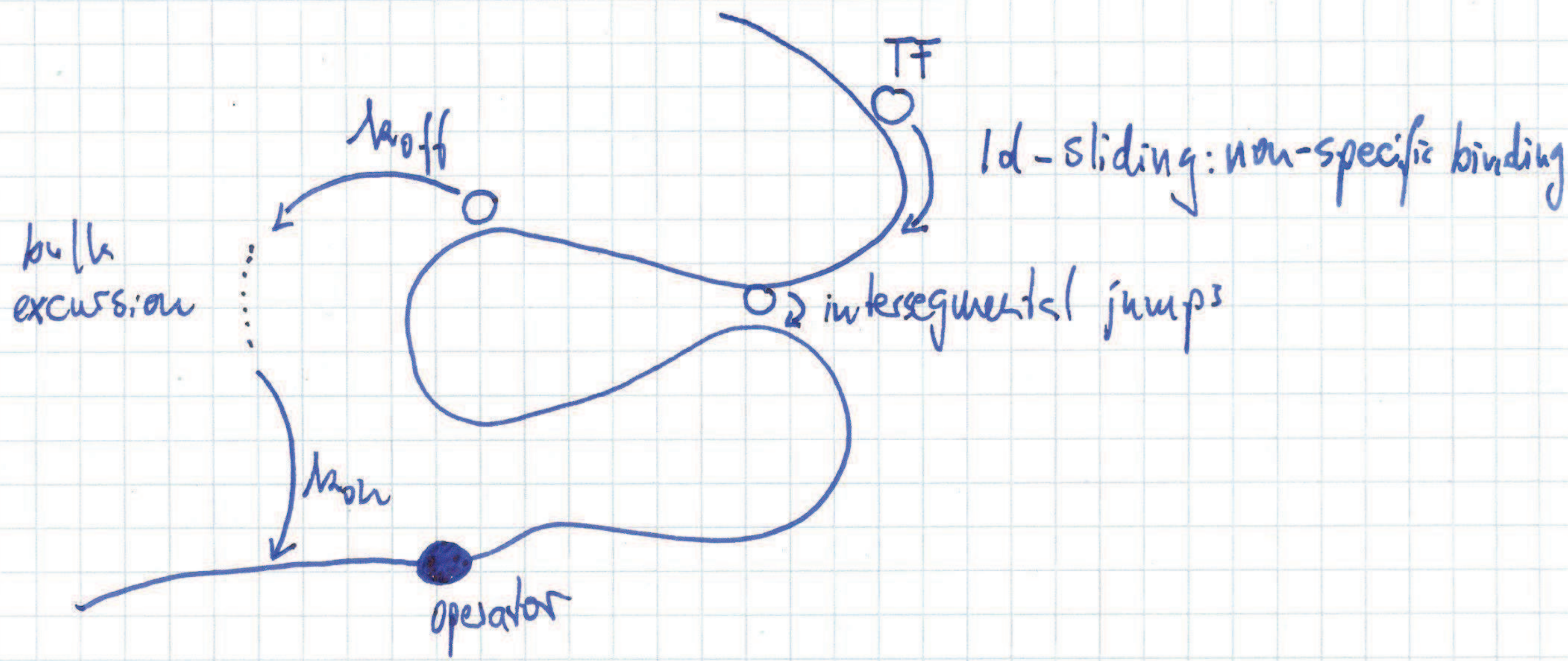
$\kappa \approx 0.05$ ($\approx 1/5$ of TF surface represents active site, $\approx 1/4$ of cylindrical DNA surface interacts with TF)

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

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

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

Adam & Delbrück (1968): idea of facilitated diffusion
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 ∃ a high probability, that the TF lands on a previously unexplored part of the DNA

disadvantage sliding: oversampling ⇒ needs to be limited by k_{off}

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

⇒ <u>optimisation of TF-search by facilitated diffusion!</u>

∃ many different approaches to calculate k_a 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 $k_{on} = \frac{j_{st}}{n_{bulk}}$

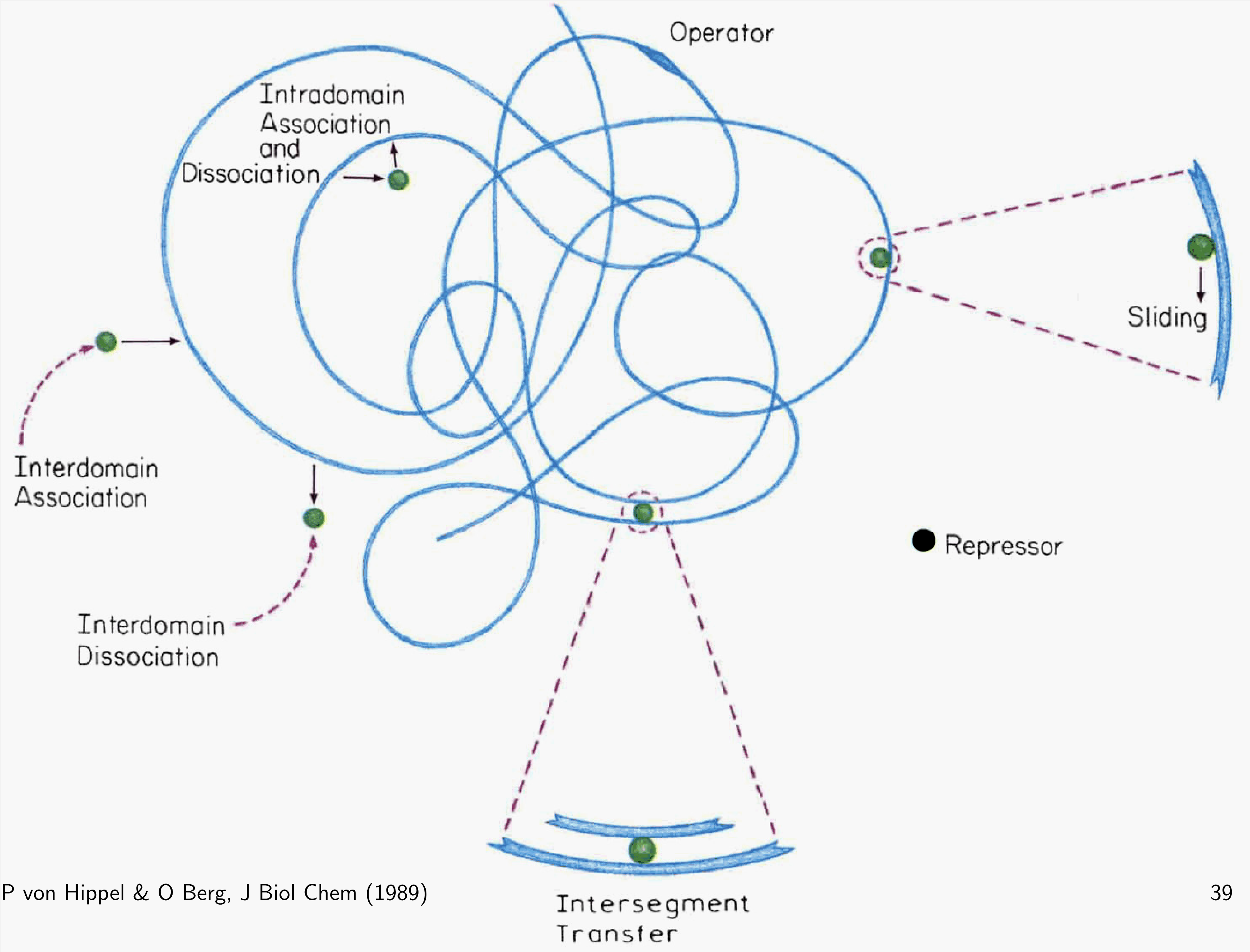
For a cylindrical DNA:

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

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

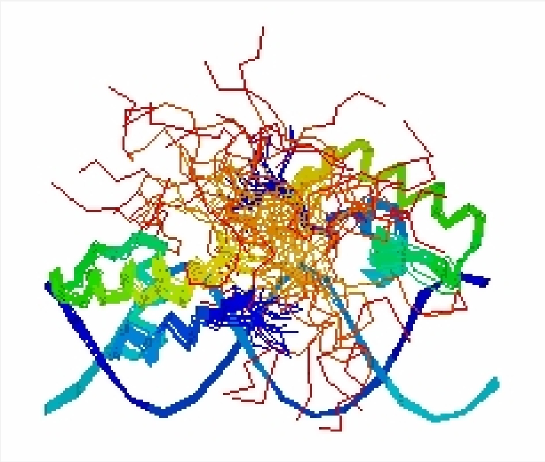
effective sliding length: ℓ_{sl} corrected by immediate rebinding events

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



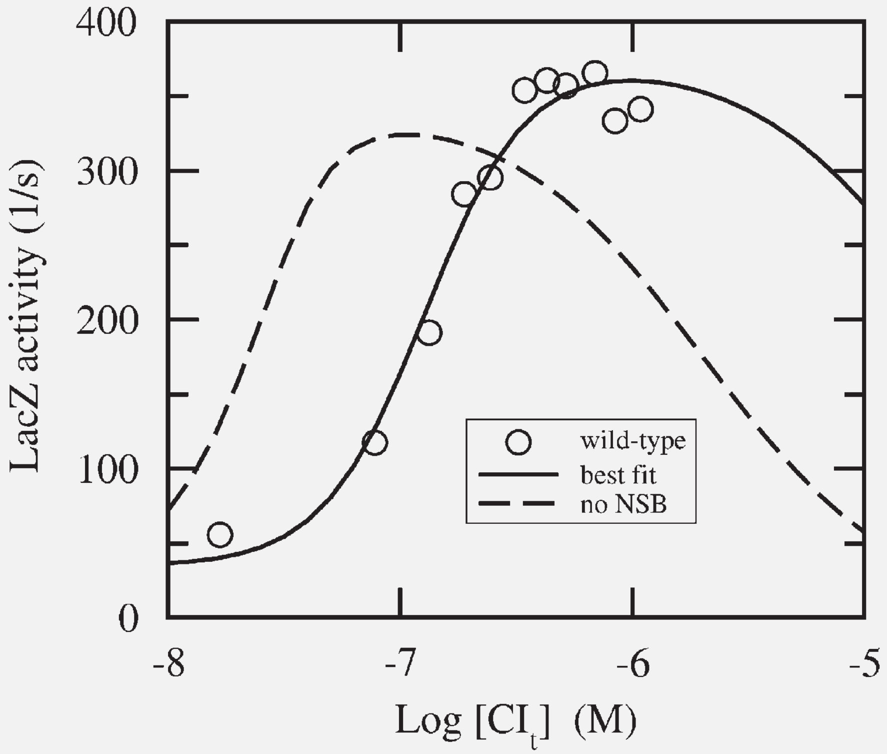
Lac repressor, nonspecific binding

Lac repressor, specific binding

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

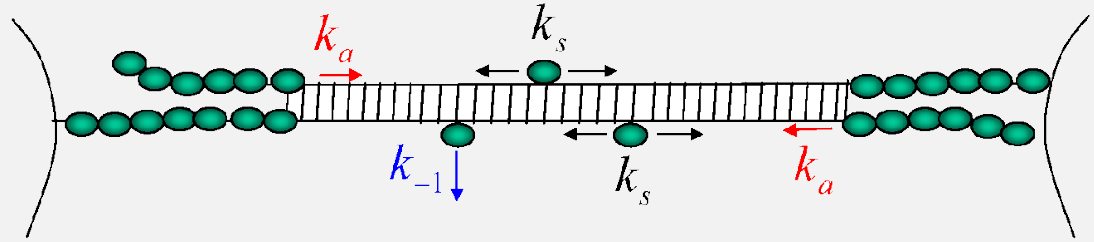
$$\Delta G_{\mathrm{NSB}}(\mathrm{CI}) = -4.1 \pm 0.9\,\mathrm{kcal/mol},$$

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



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

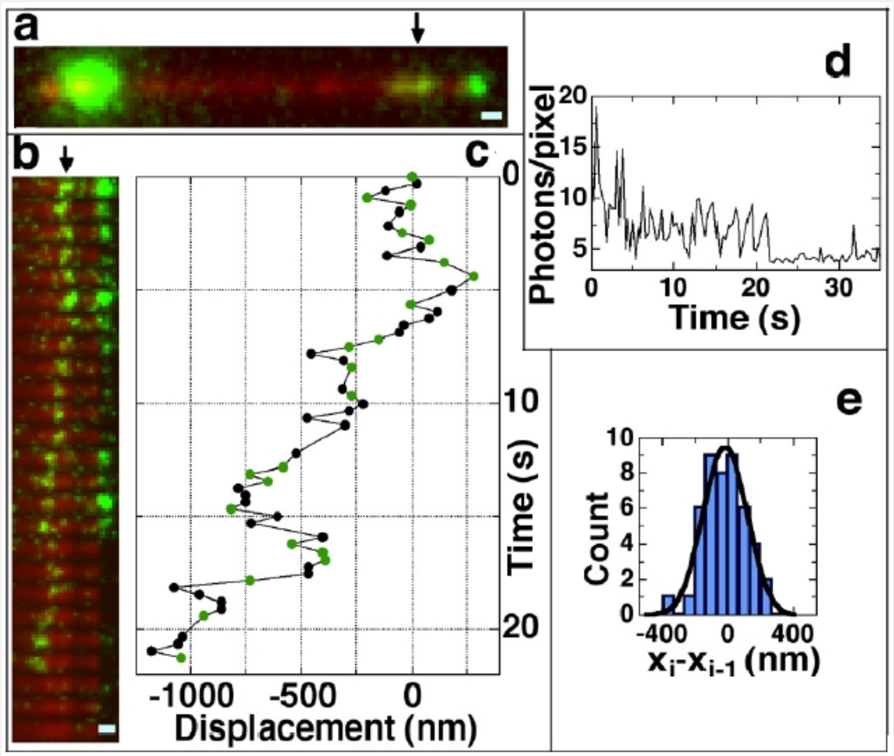
Proof of 1D search mode

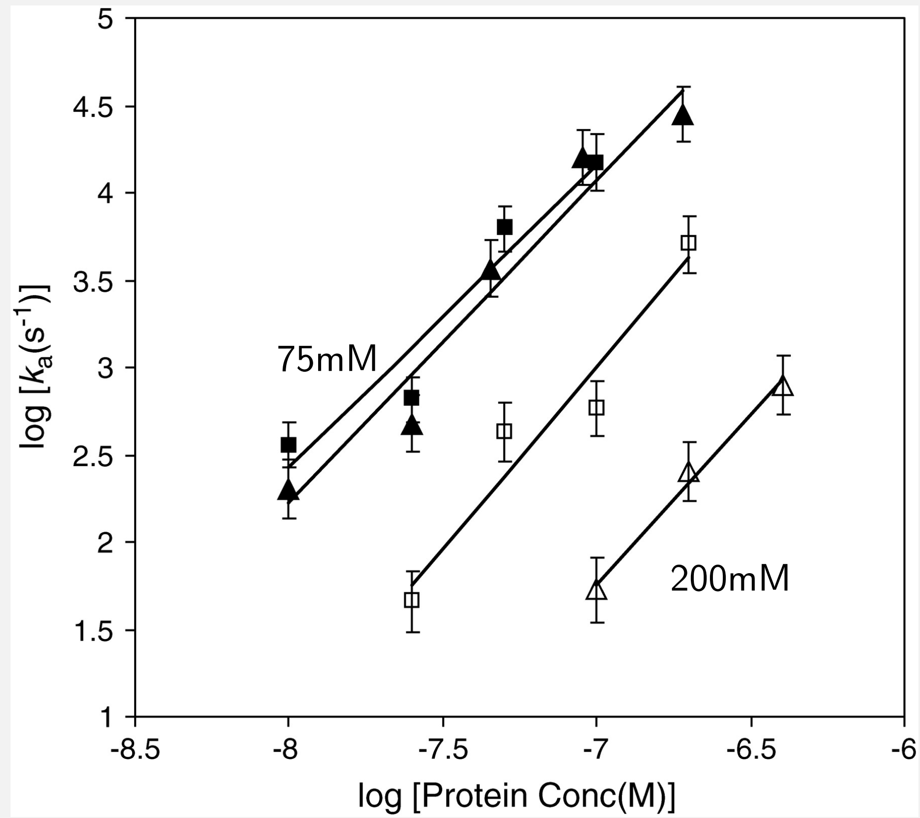


McGhee & von Hippel isotherm

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

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





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

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

Calculating facilitated diffusion (our version)

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

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)

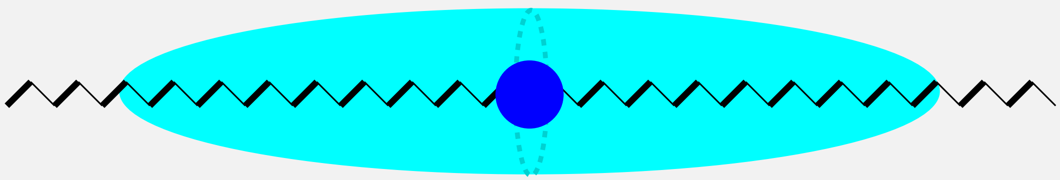
The antenna effect

Target search rate for cylindrical DNA model:

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

Sliding length:

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

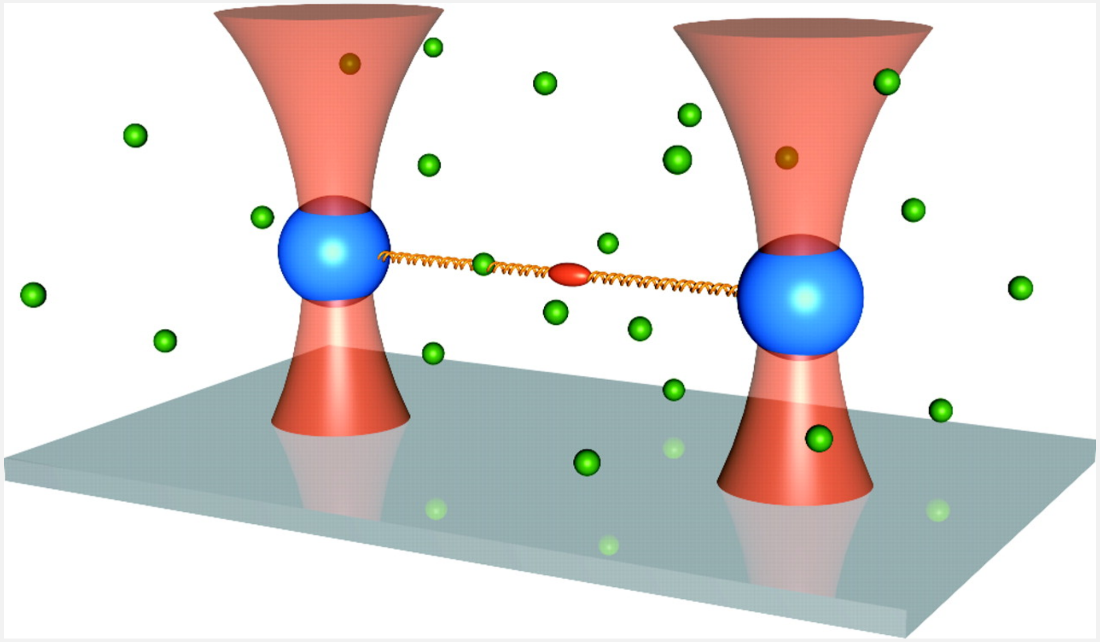


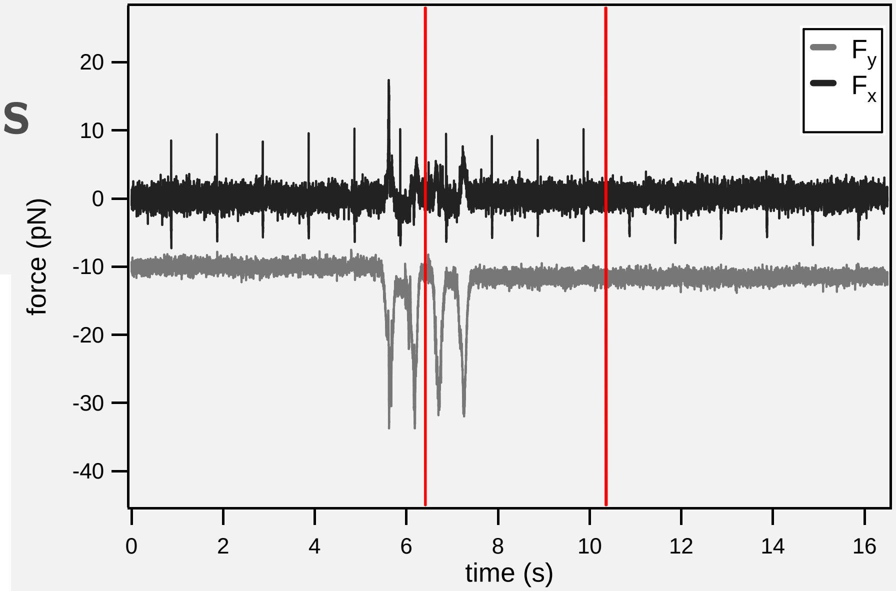
Effective sliding length:

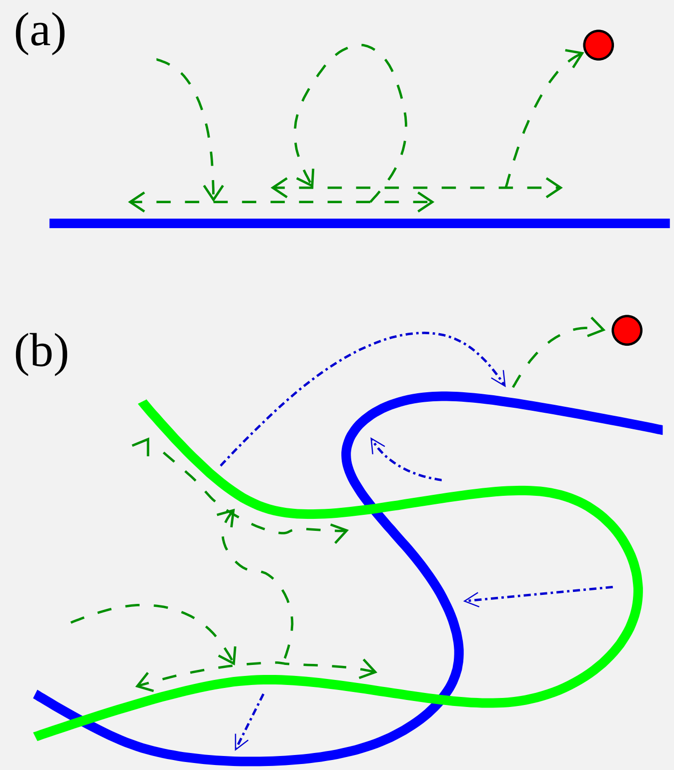
$$\ell_{\mathrm{sl}}^{\mathrm{eff}} = \sqrt{\frac{k_{\mathrm{on}}}{2\pi D_{3d}}} \times \ell_{\mathrm{sl}}$$

microhop correction: $\sqrt{\frac{k_{\mathrm{on}}}{2\pi D_{3d}}}$

The rôle of DNA conformations







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

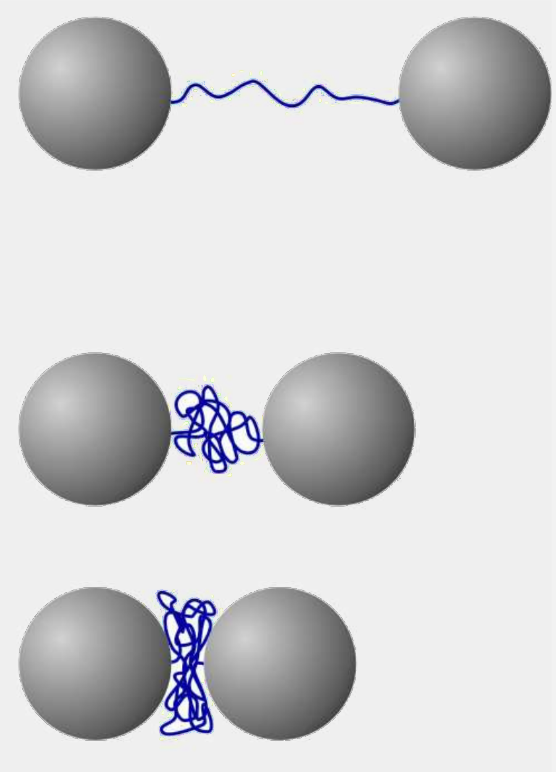
[comp λ DNA 48.5kbp]

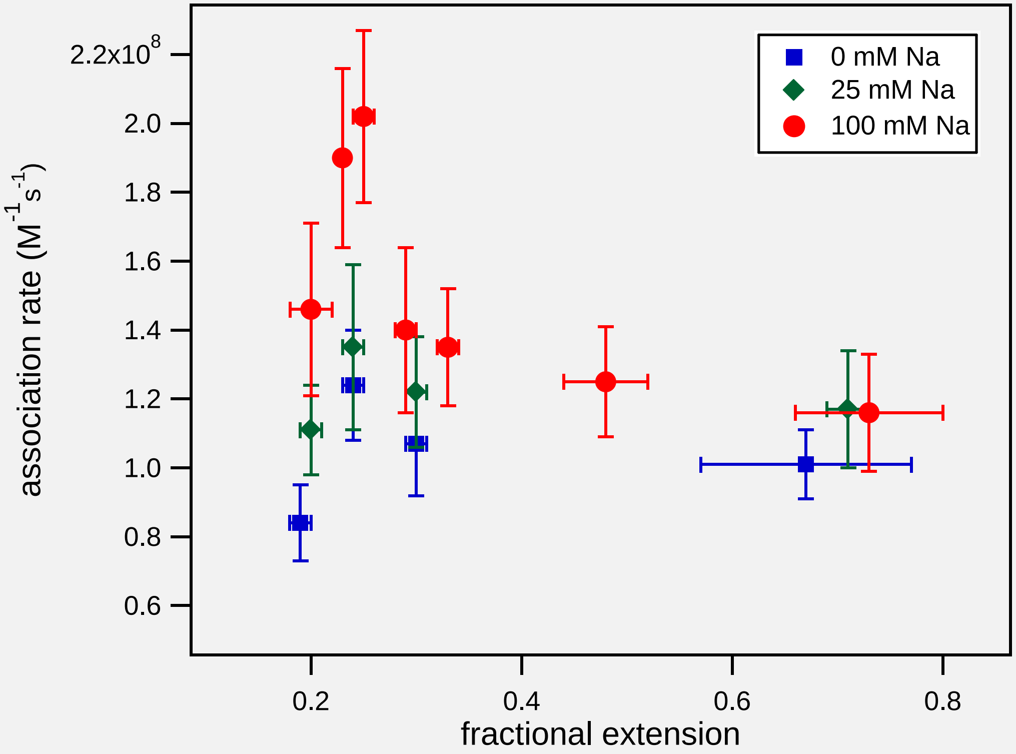
B van den Broek, MA Lomholt, S-M Kalisch, RM & GJL Wuite, PNAS (2008)

More compact DNA conformations speed up the search

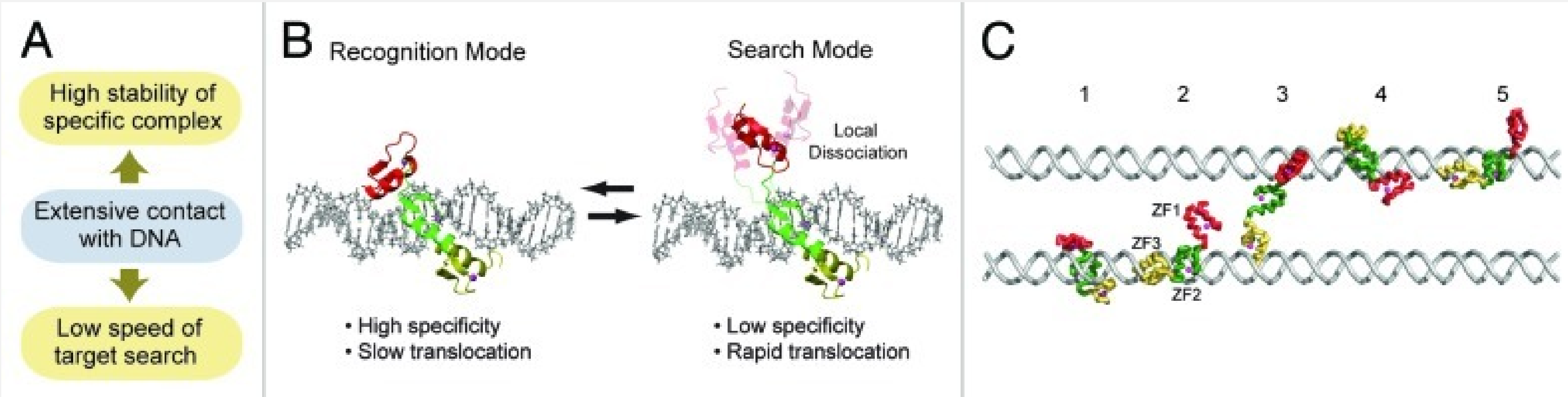
[NaCl]	$k_{\text{on}}^{\text{straight}}$ [Ms]	$l_{\text{sl}}^{\text{eff}}$ [bp]	$1/\sqrt{l_{\text{DNA}}}$ [bp]	ℓ_p [bp]	R_{theory}	R_{measured}
0 mM	0.8×10^8	195	518	188	1.18	1.3 ± 0.2
25 mM	1.0×10^8	250	485	175	1.23	1.1 ± 0.2
100 mM	1.0×10^8	250	150	159	1.67	1.7 ± 0.3
150 mM	0.9×10^9	15.5	120	153	1.15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

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





Speed-stability paradox in TF search along DNA



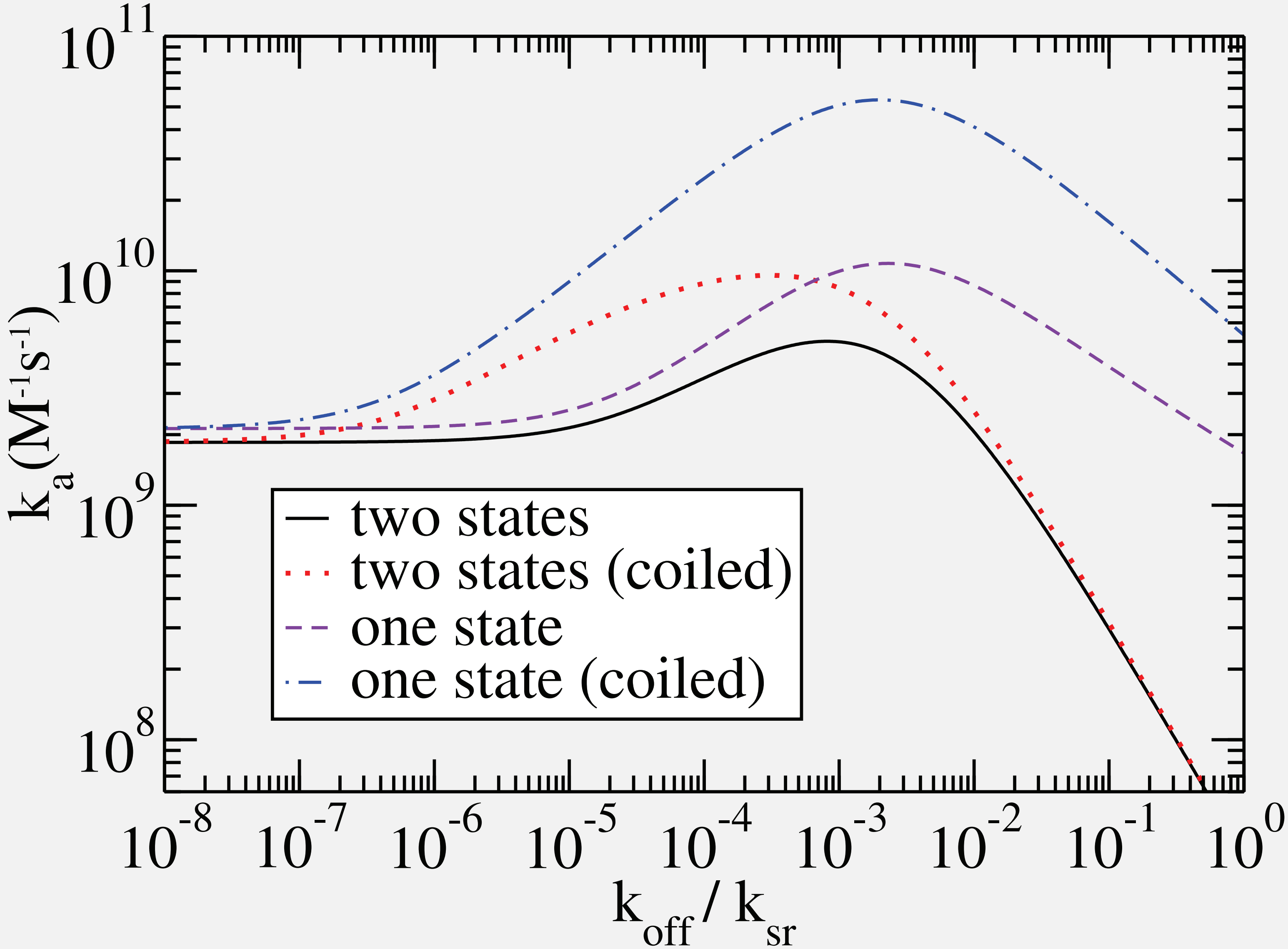
From simulations:

B: Search & recognition modes for a zinc finger protein

C: Intersegmental transfer of the protein

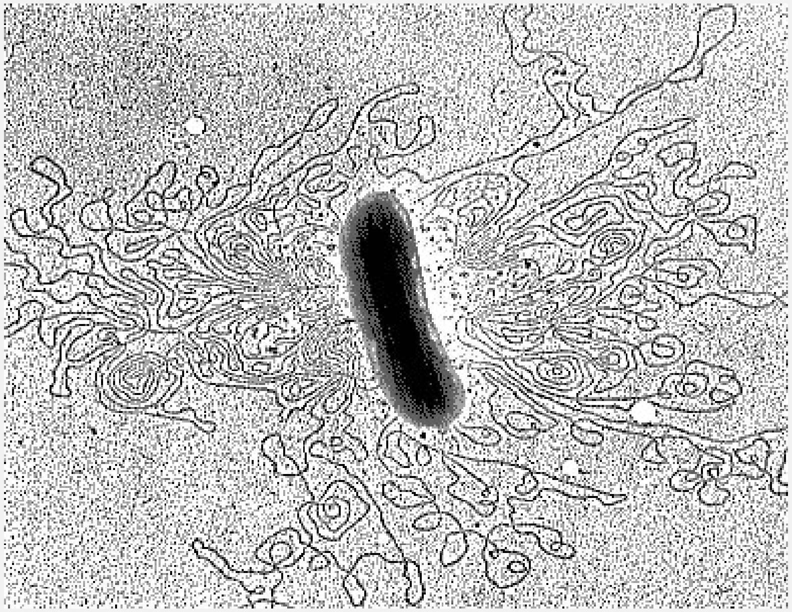
M Slutsky & L Mirny, Biophys J (2004); J Iwahara & Y Levy, Transcription (2013)

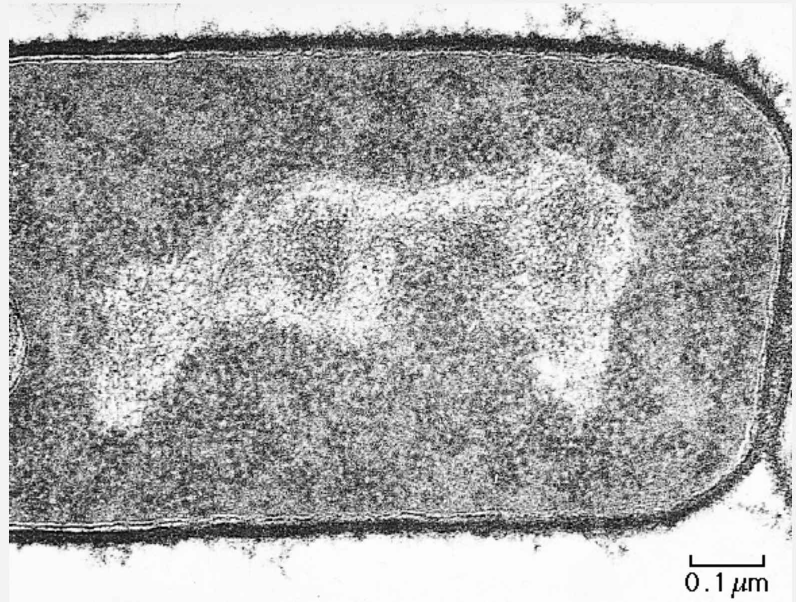
Facilitated diffusion: rate with search & recognition states

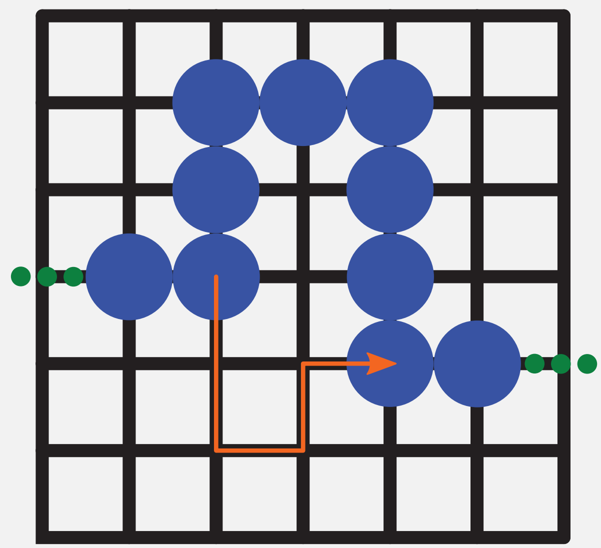


M Bauer & RM, Biophys J (2012)

In vivo bacterial gene regulation: E.coli



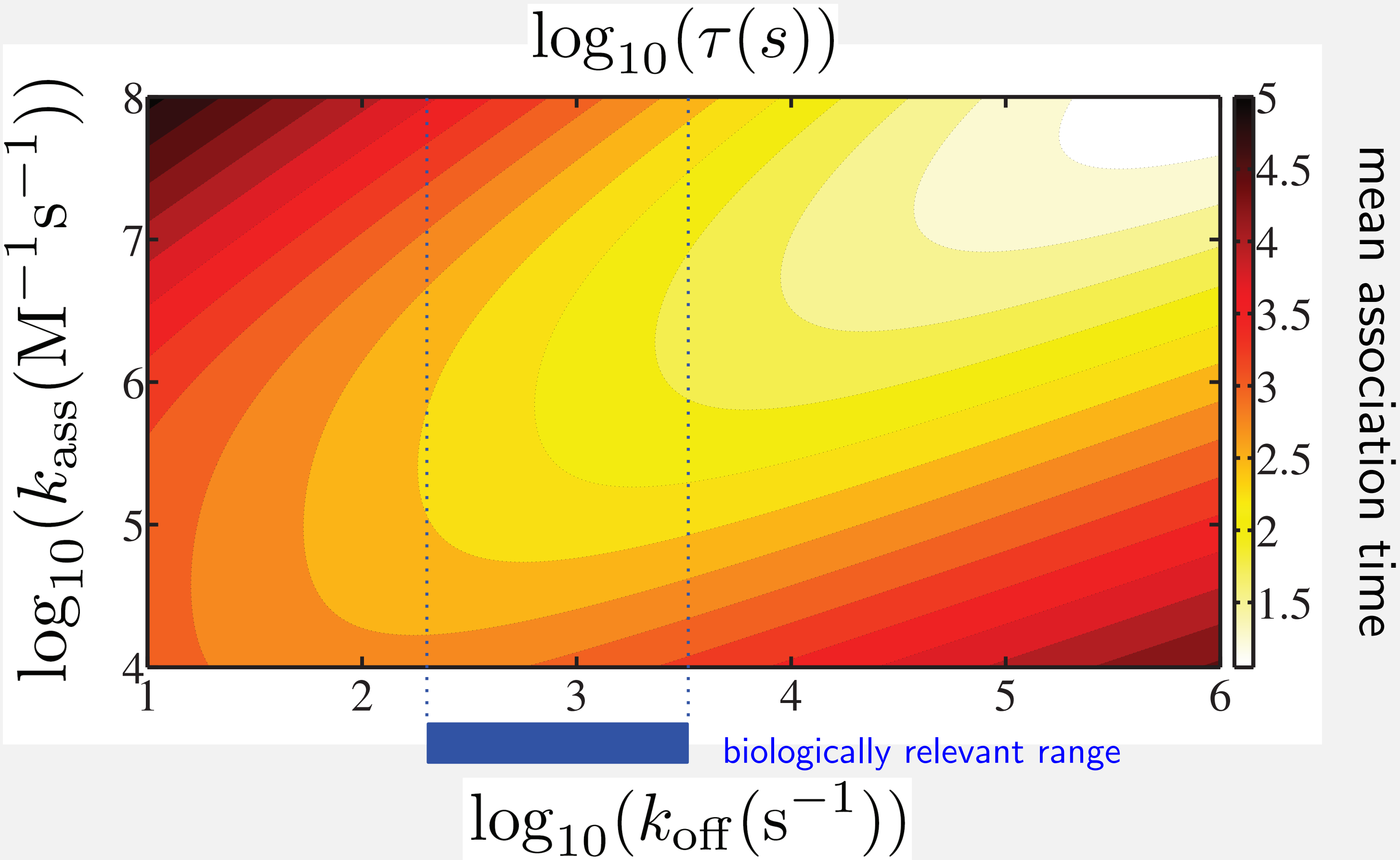




Chromosome is approx a SAW

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

In vivo gene regulation consistent with facilitated diffusion



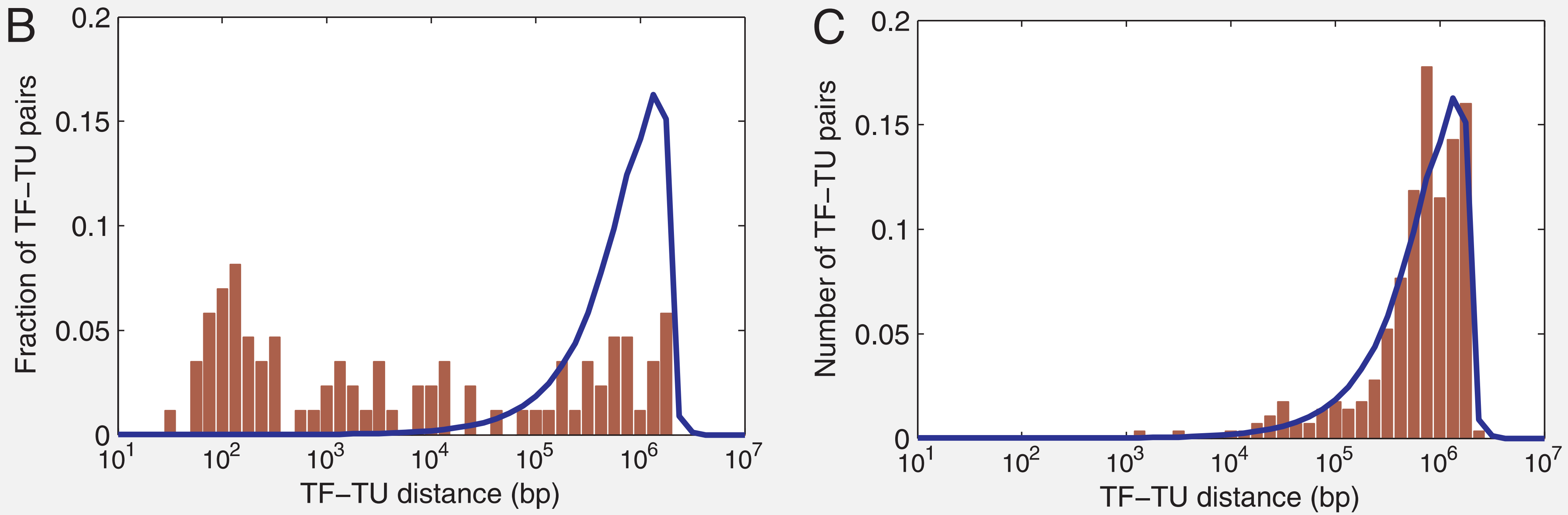
@ optimum the target association time is $\tau \approx 311$sec (no fit parameter)

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

TF regulation effects gene proximity

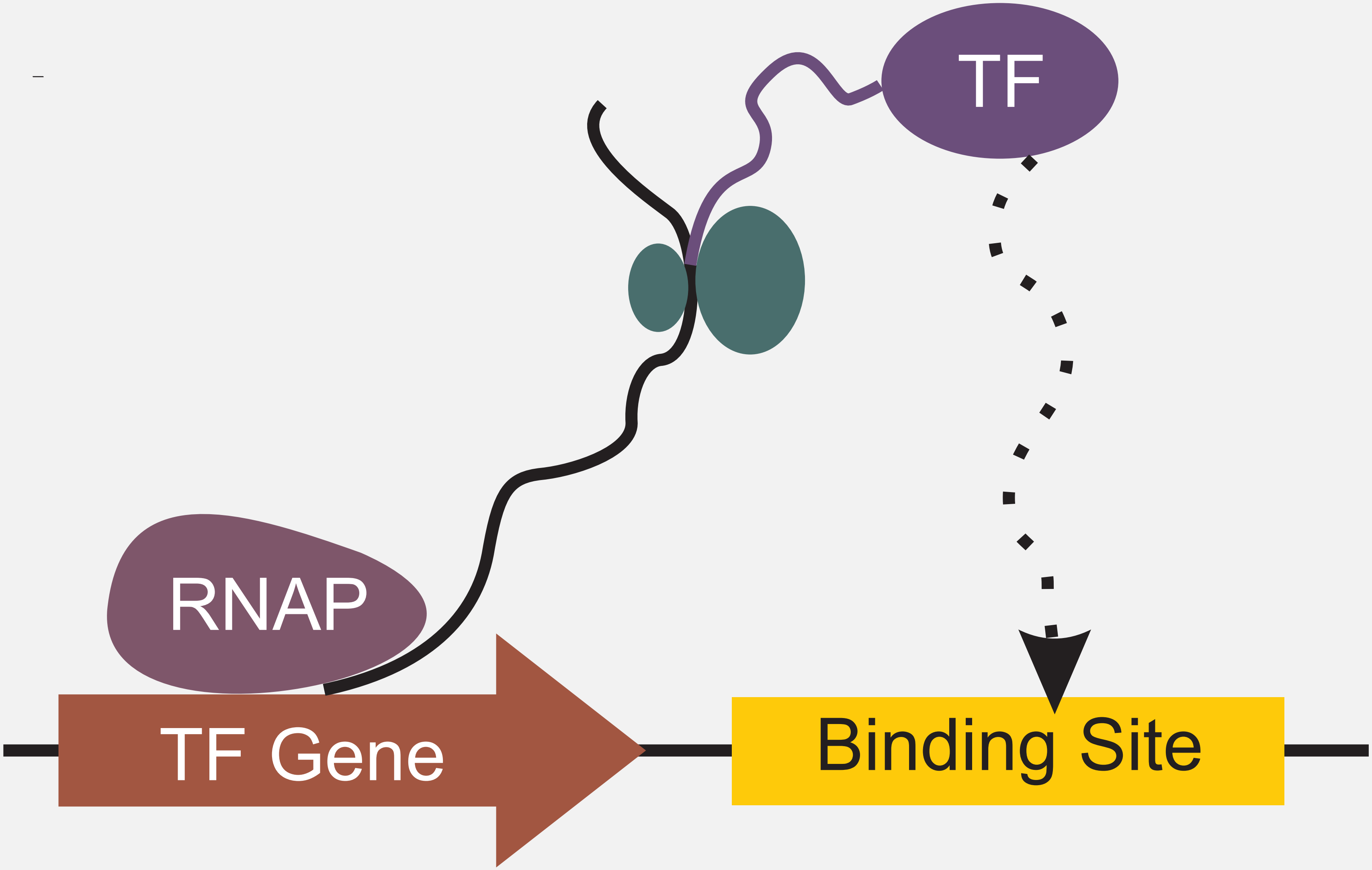
Does distance between genes interacting via TFs matter?

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

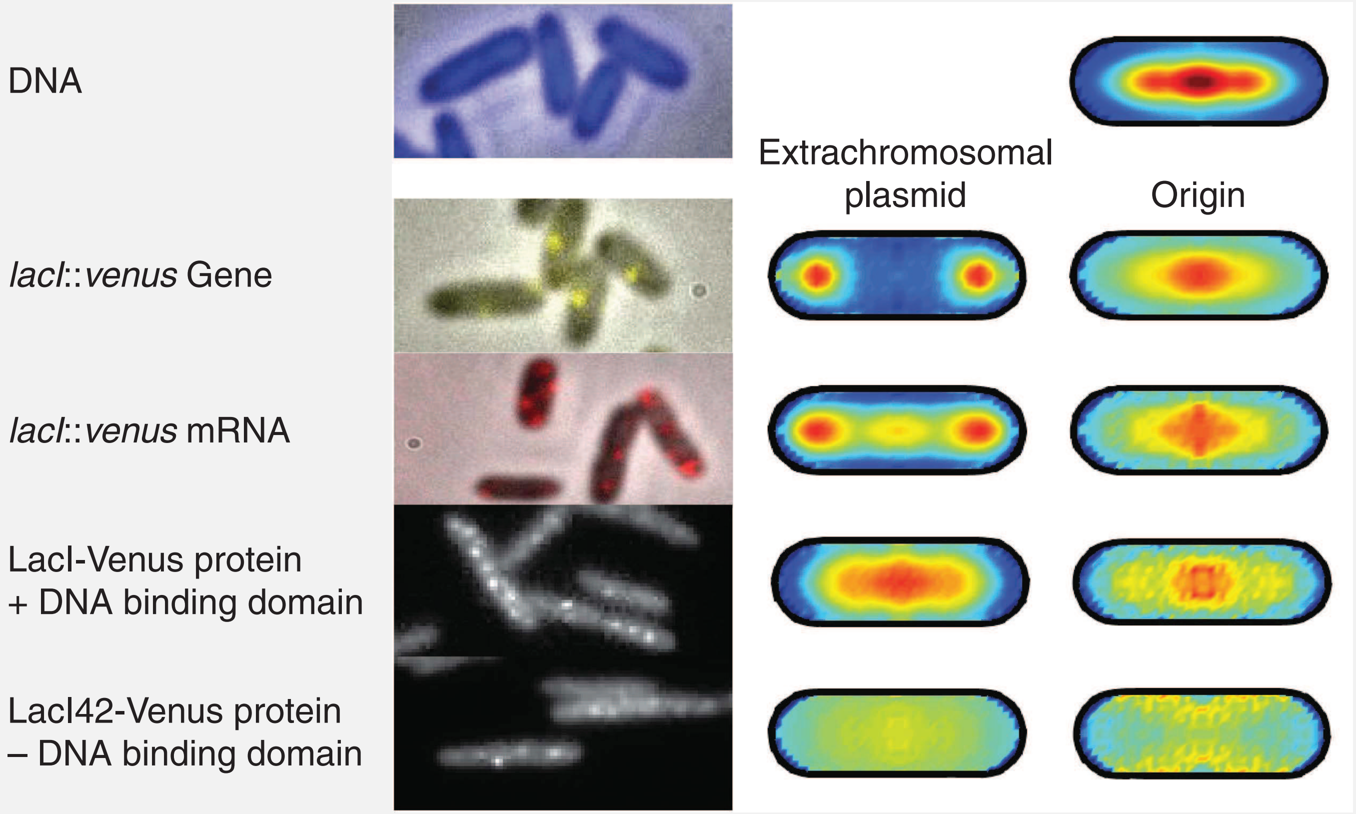


Kolesov et al, PNAS (2007)

Spatial aspects: do gene locations matter?

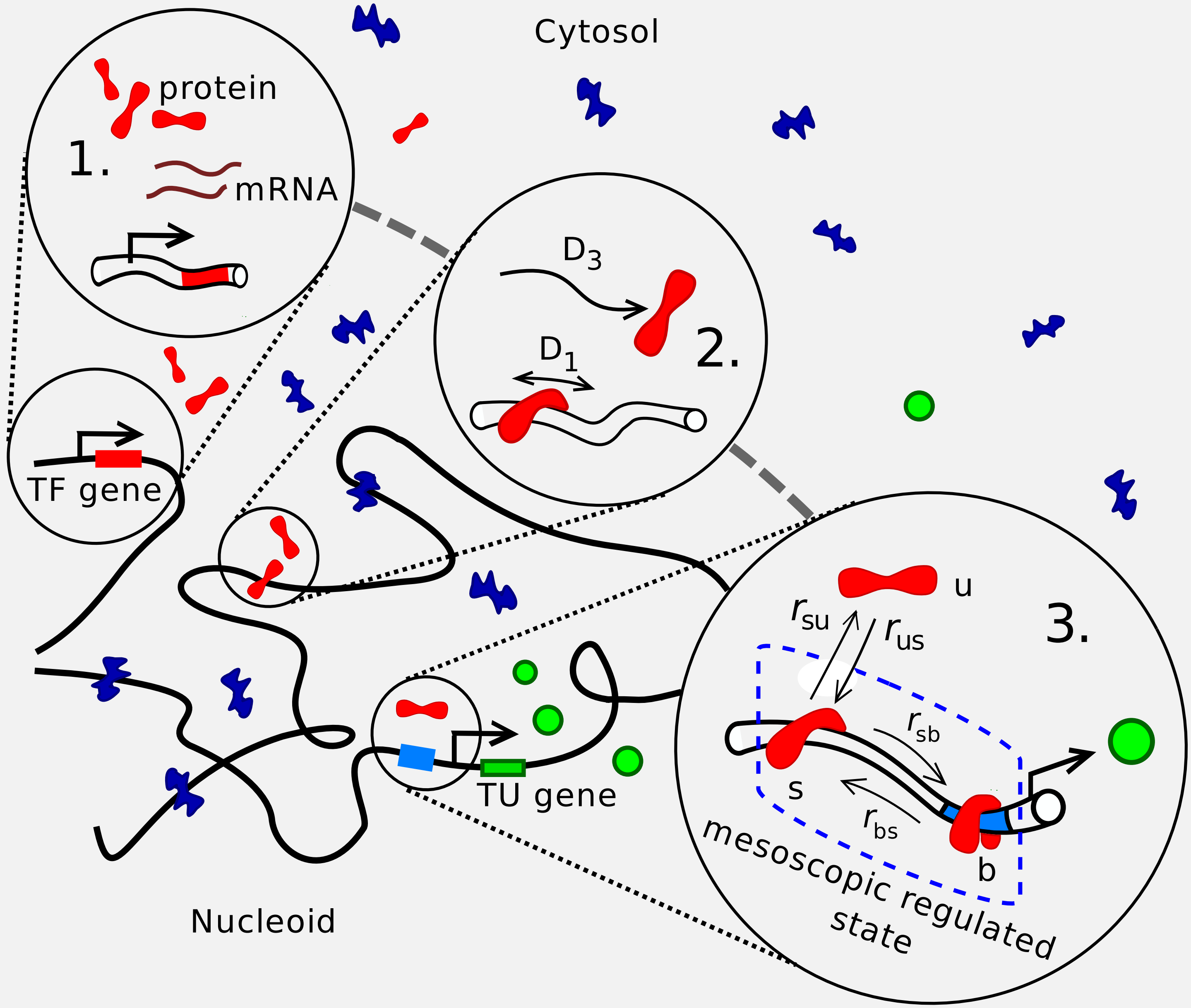
Képès: TF targets are typically located next to or at regular distances from the TF gene $\rightarrow$ TF gene-target pairs close in 3D

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



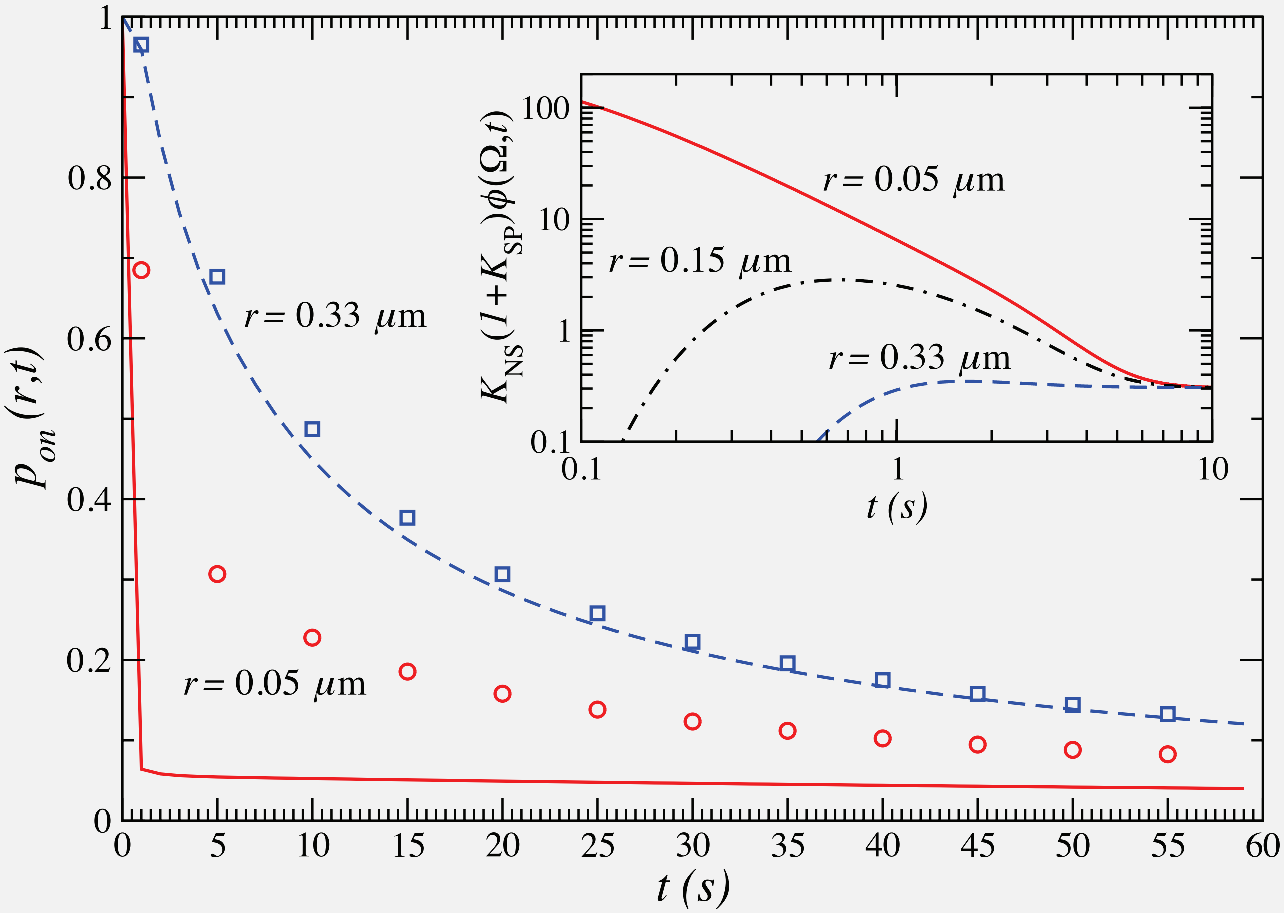
Kepes et al, J Mol Biol (2004); Kuhlman & Cox, Mol Syst Biol (2012)

Transient intracellular signalling is diffusion controlled



O Pulkkinen & RM, PRL (2013)

Result 1: transient response to repression



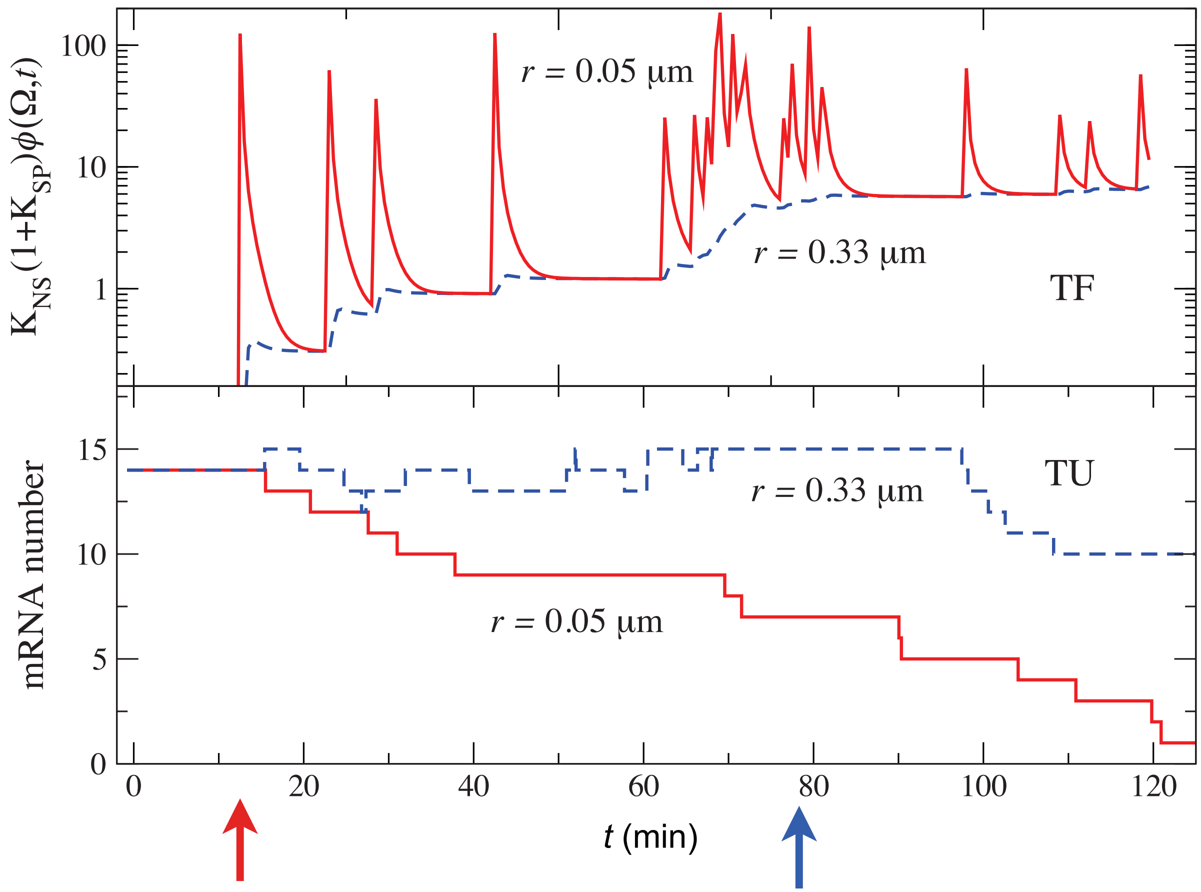
Mean field approximation (full & dashed lines):

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

O Pulkkinen & RM, PRL (2013)

Result 2: time dependence of gene response

Sample paths from MC simulations:



TF density at the target operator

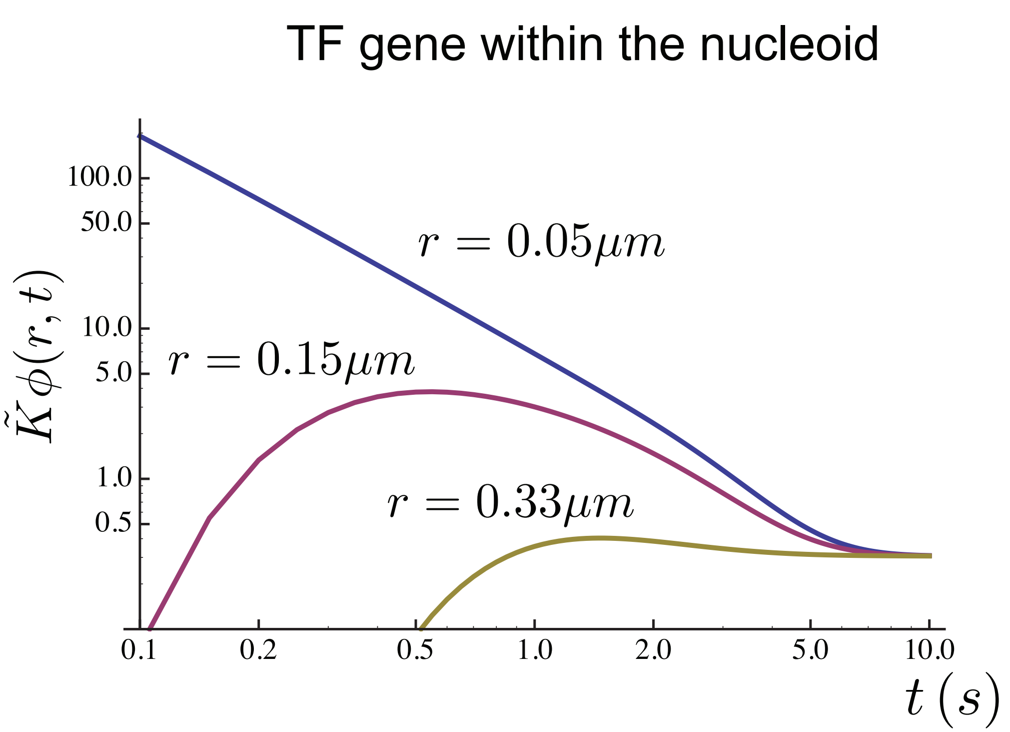
Target expression

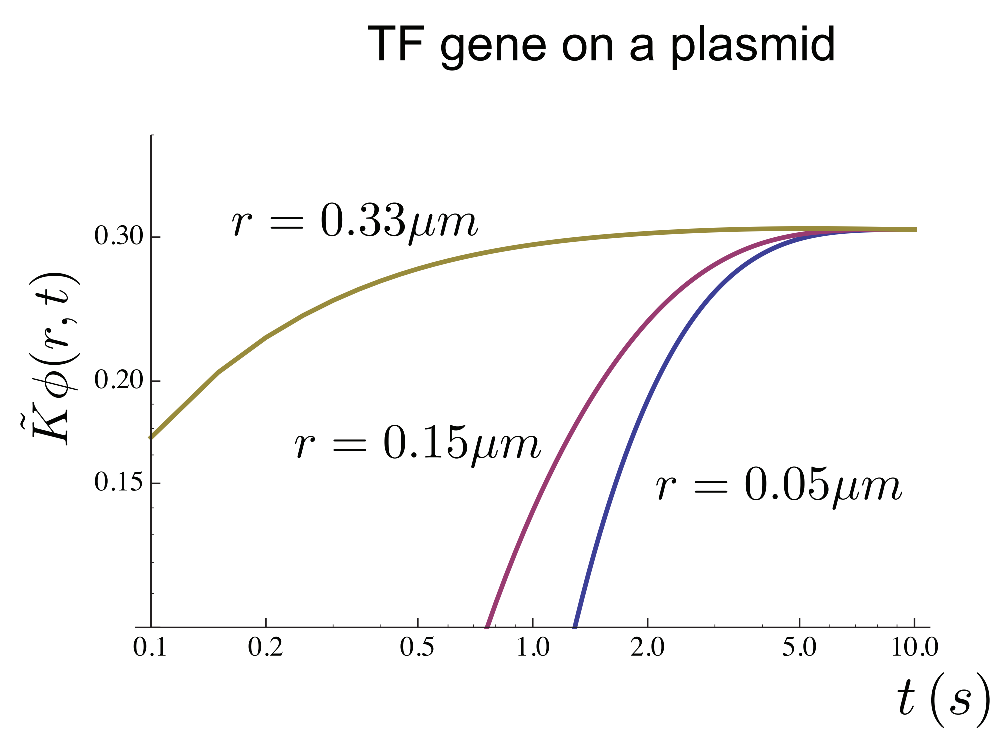
First repressor binding at r = 0.05 µm

First repressor binding at r = 0.33 µm

O Pulkkinen & RM, PRL (2013)

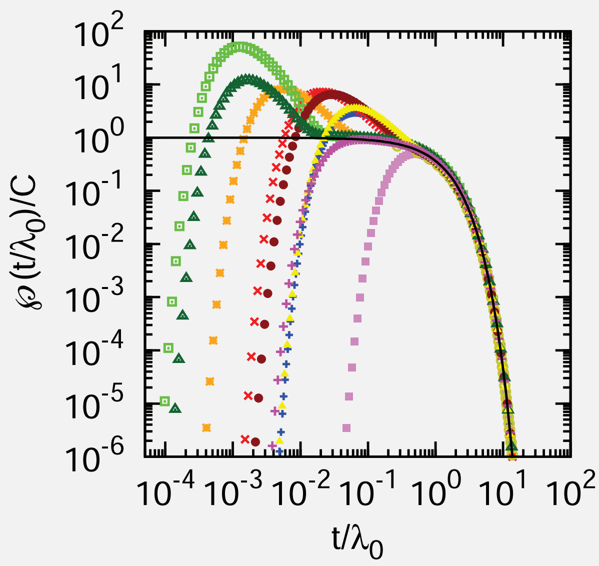
Result 3: gene location matters

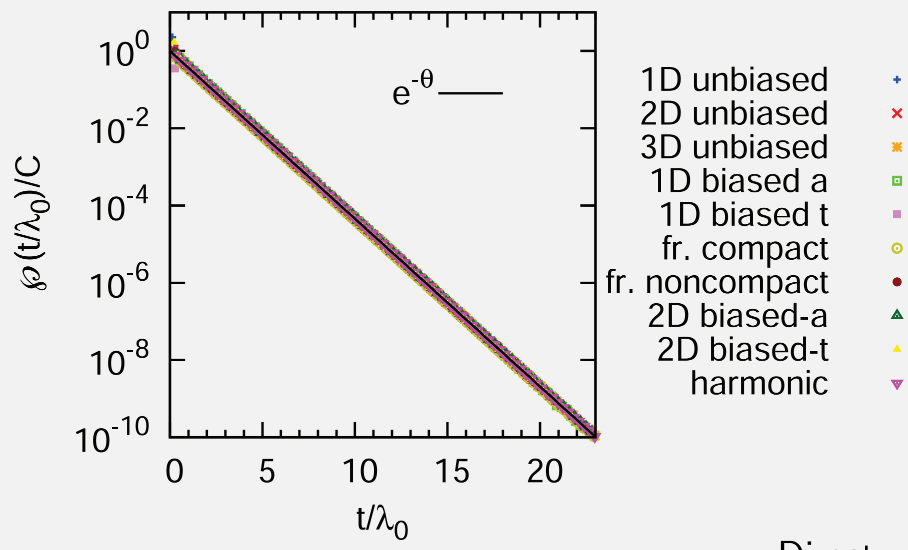


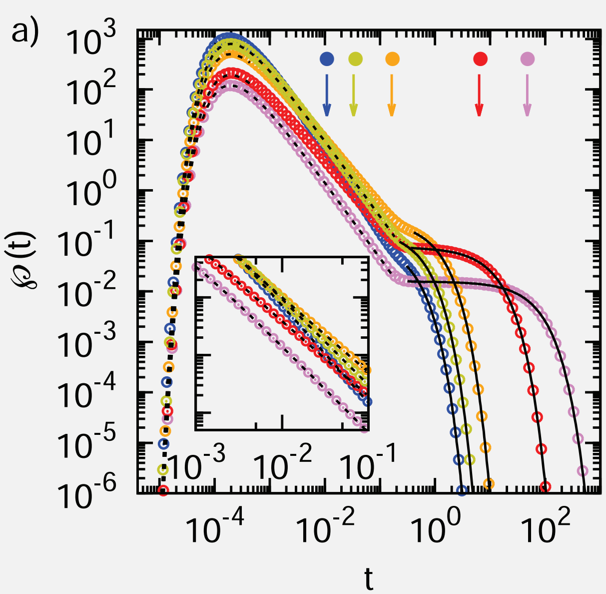


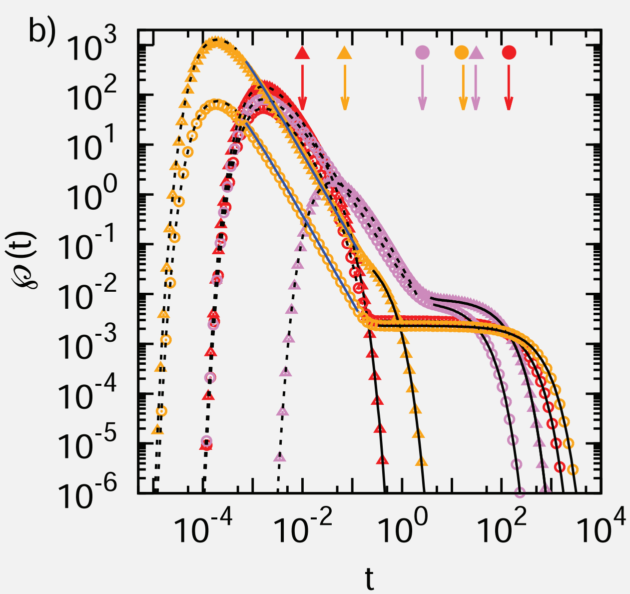
O Pulkkinen & RM, PRL (2013)

Universal proximity effect in few encounter limit

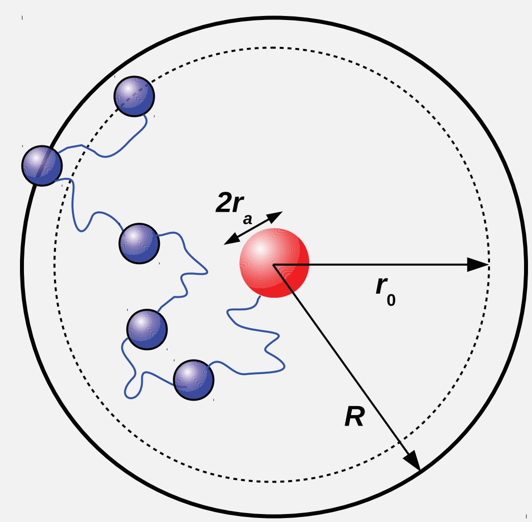






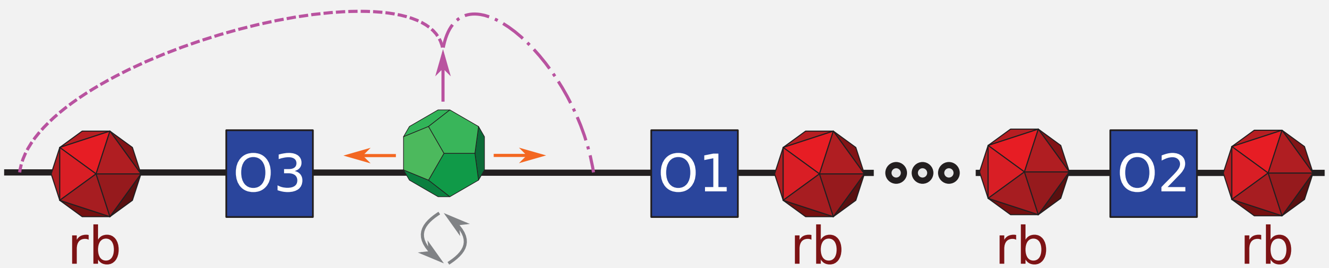


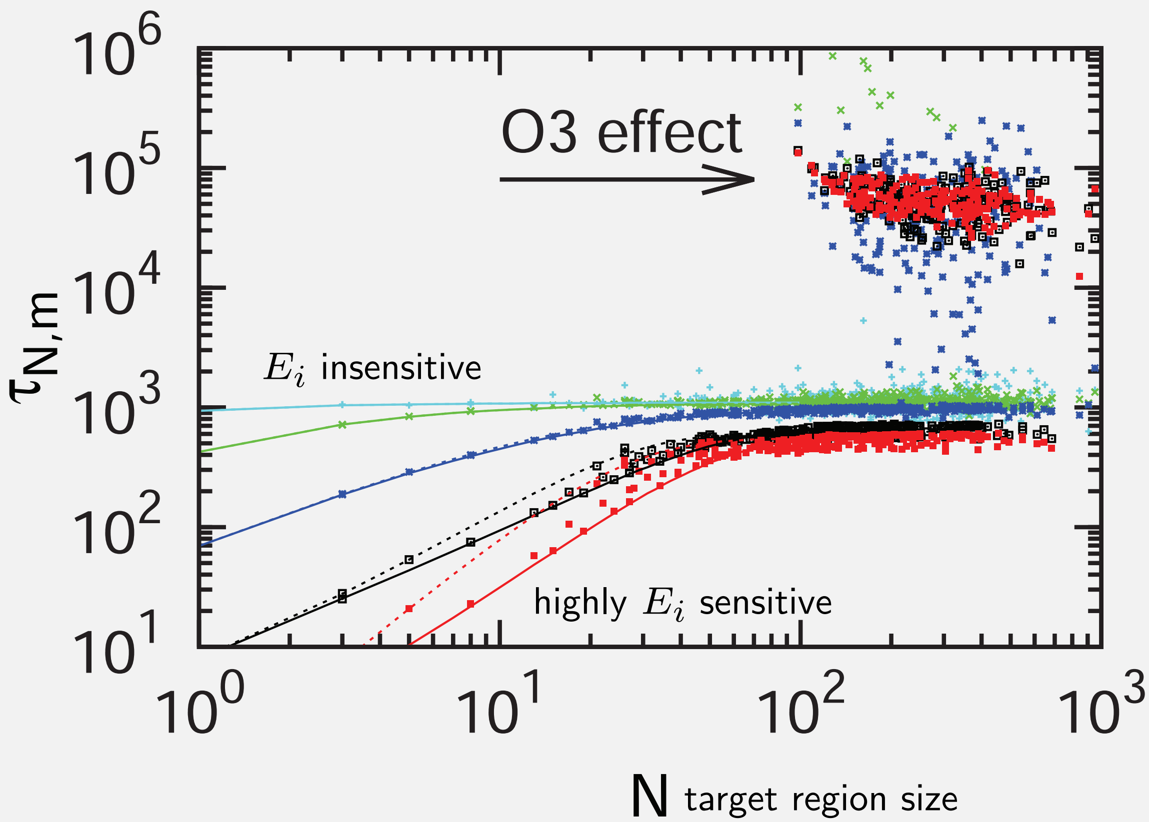
Direct vs indirect trajs:



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

Sequence (binding energy) effects on target search time



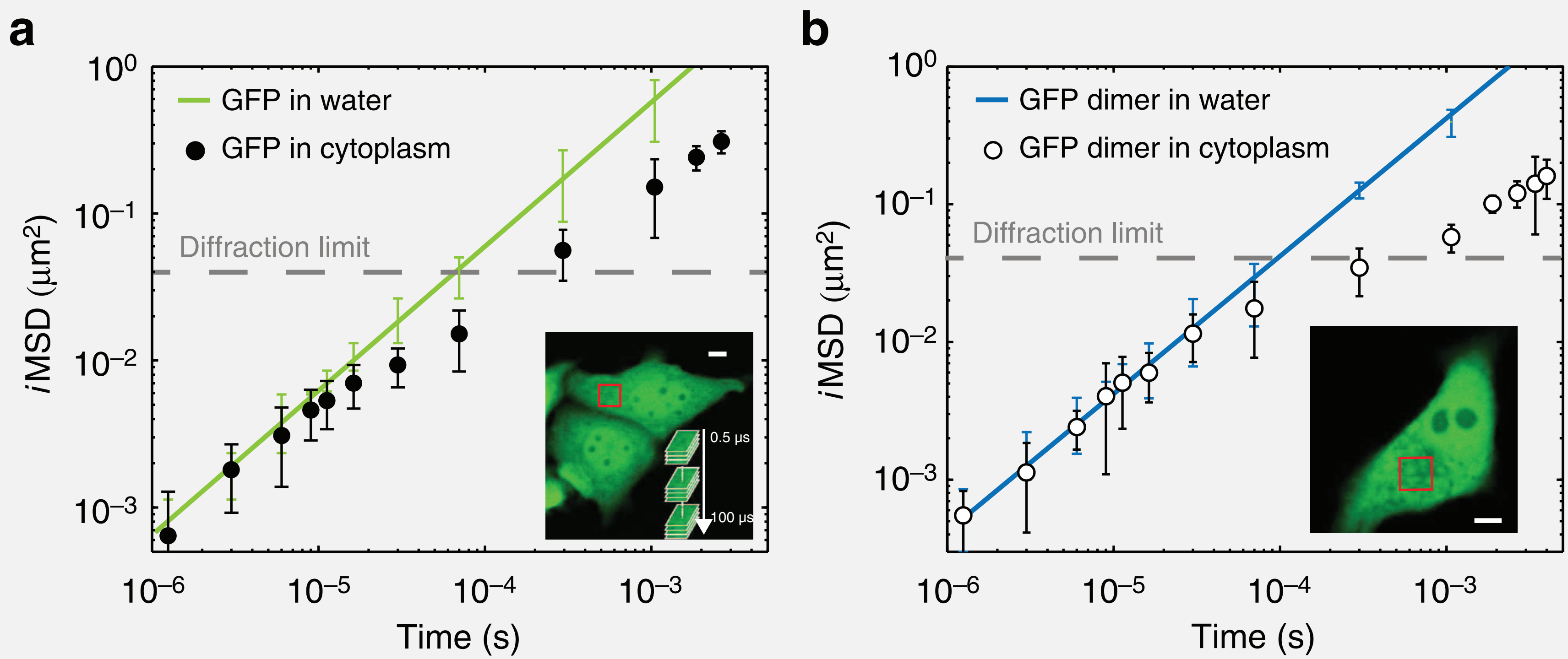


full line: centred target

dashed line: target @ boundary

M Bauer & RM, Sci Rep (2015)

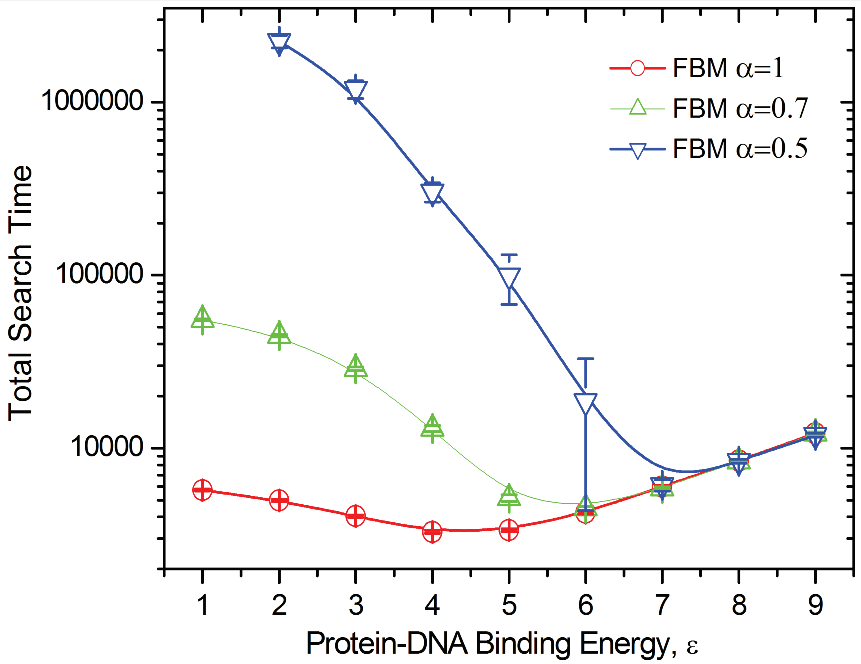
Anomalous diffusion of GFP in cell cytoplasm & nucleus

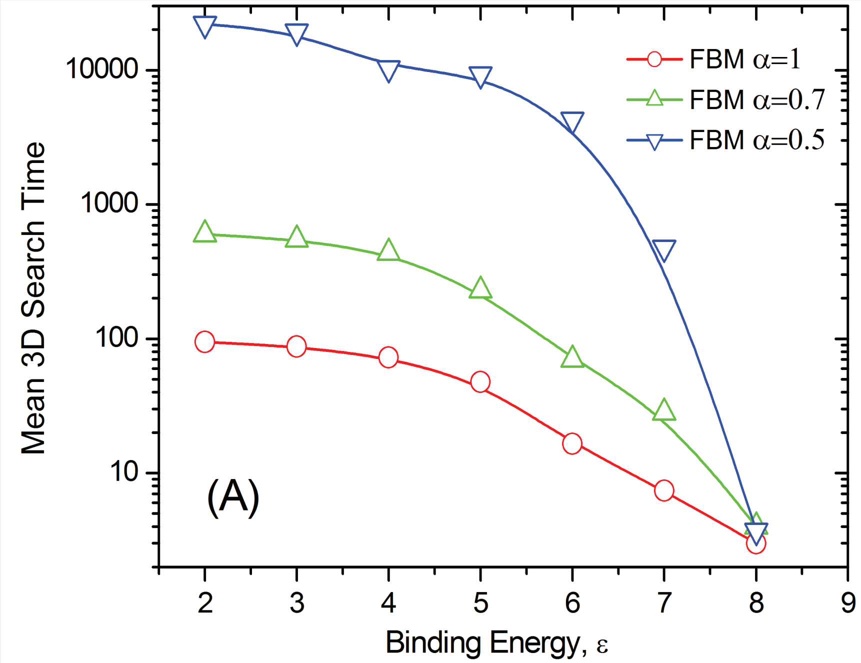


$$\langle \mathbf{r}^2(t) \rangle \simeq K_\alpha t^\alpha : \text{ Subdiffusion when } 0 < \alpha < 1$$

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

Anomalous facilitated diffusion





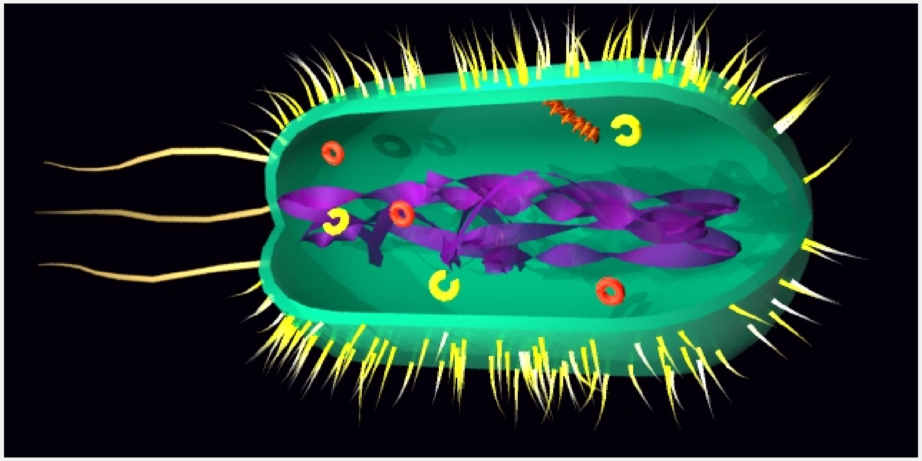
Many unknowns in the modelling:

Physical mechanism of & cutoff time of anomalous motion?

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

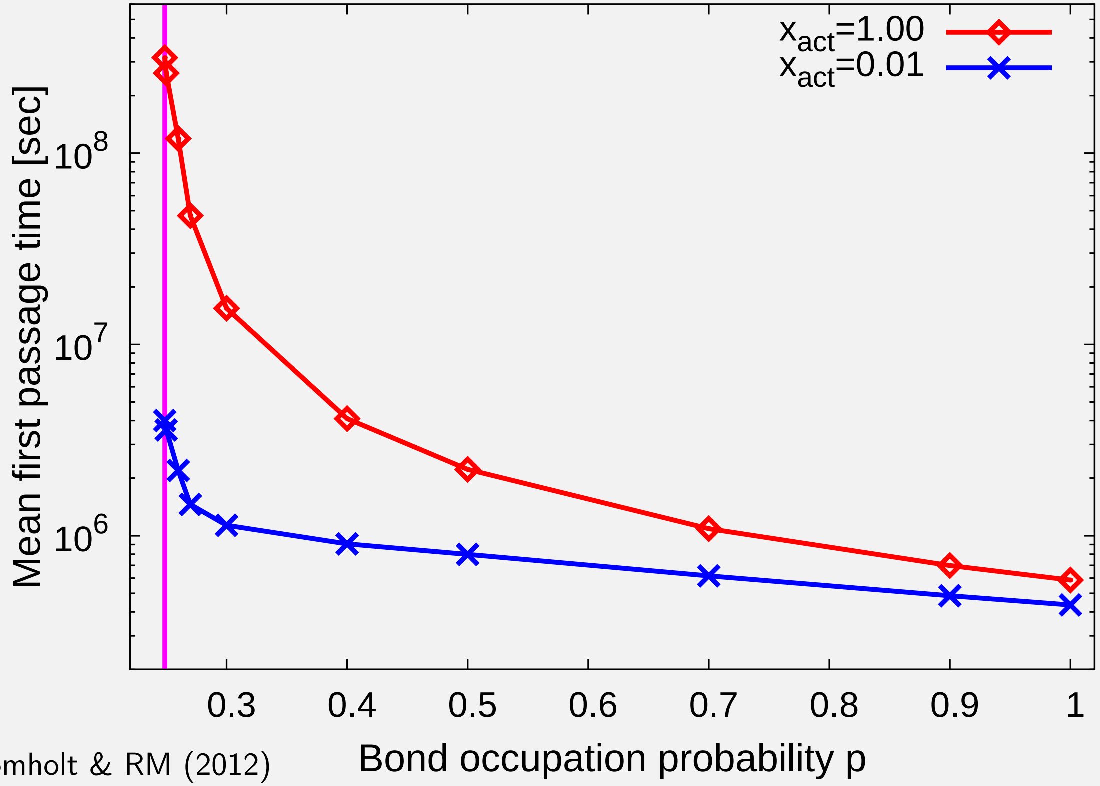
L Liu, AG Cherstvy & RM, JPC (2017)

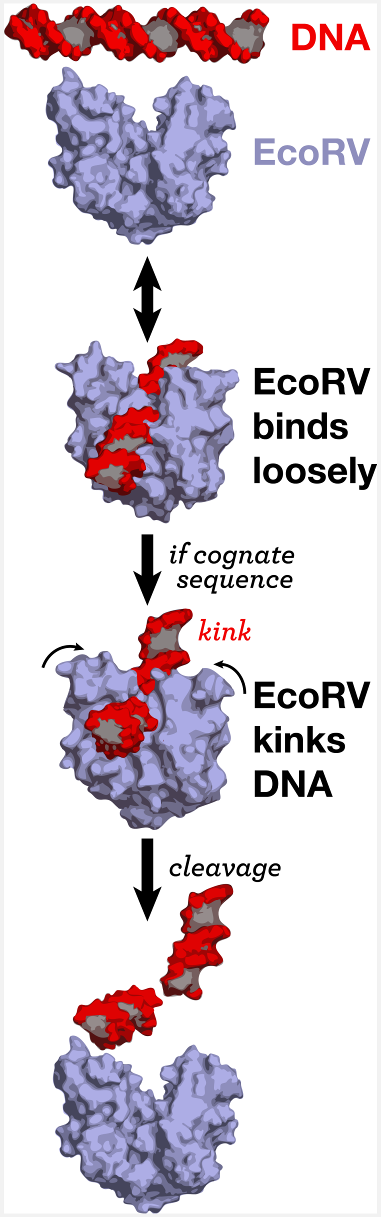
Subdiffusion does not compromise cellular fitness



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

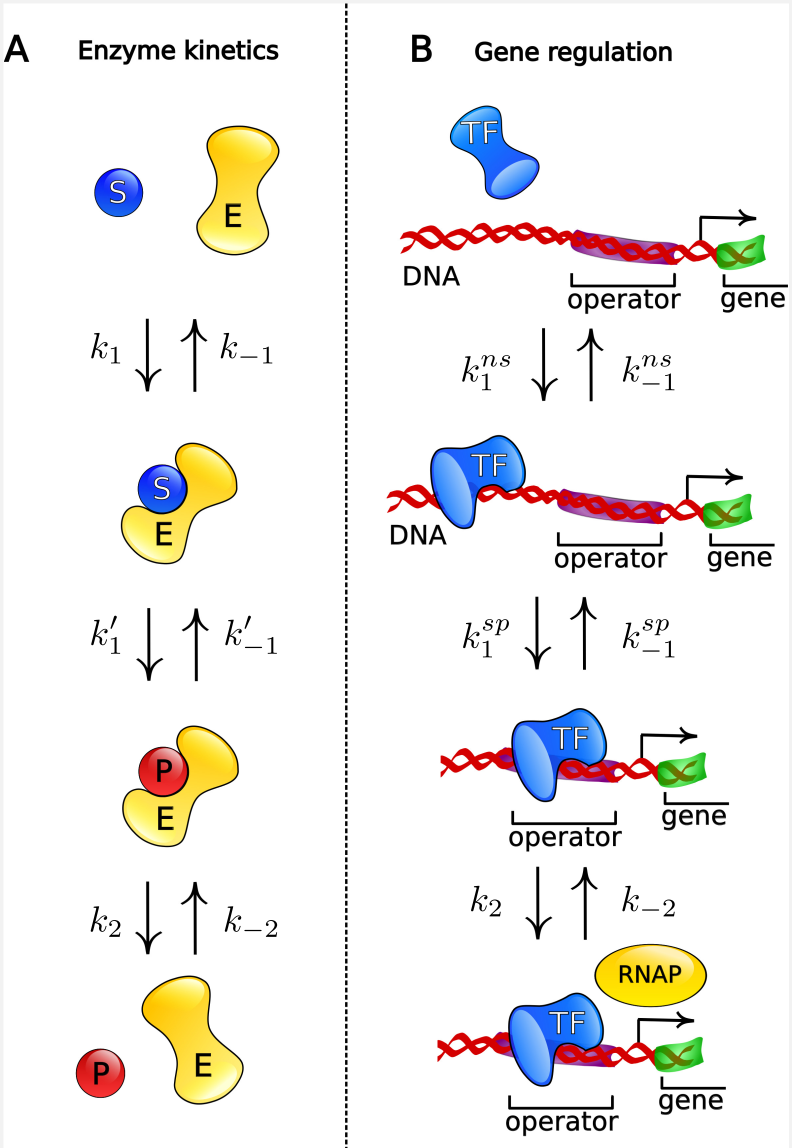
Mutant enzyme
Binding mode:
100% active





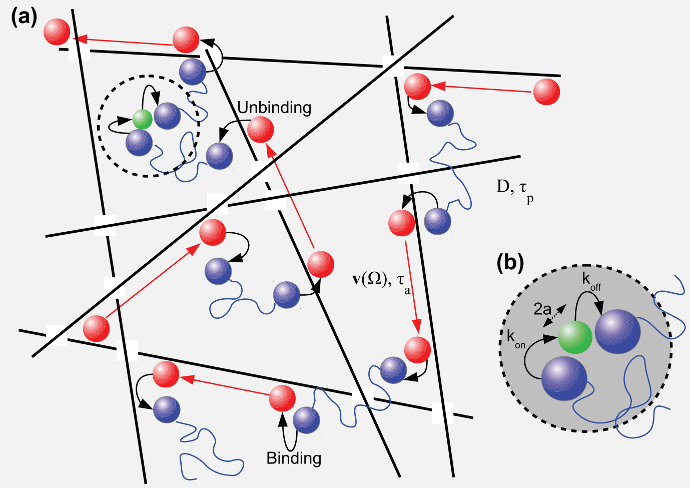
L Esmaeili Sereshki, MA Lomholt & RM (2012)

Low-# Michaelis-Menten

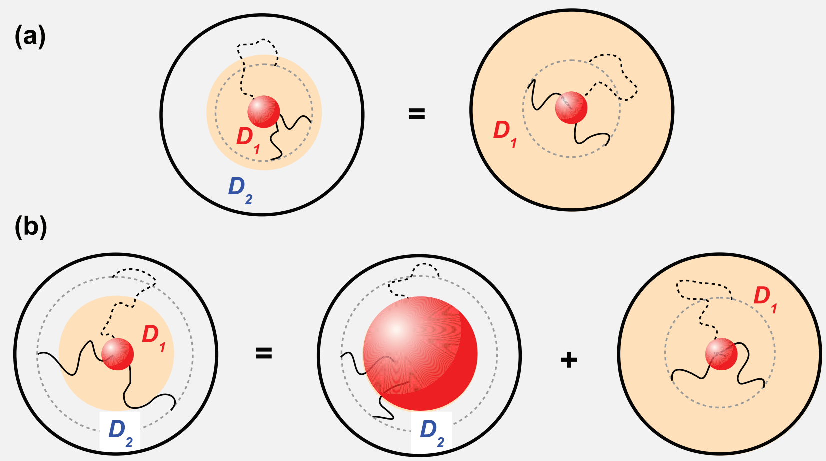


O Pulkkinen & RM, Sci Rep (2015)

Active sensing limit



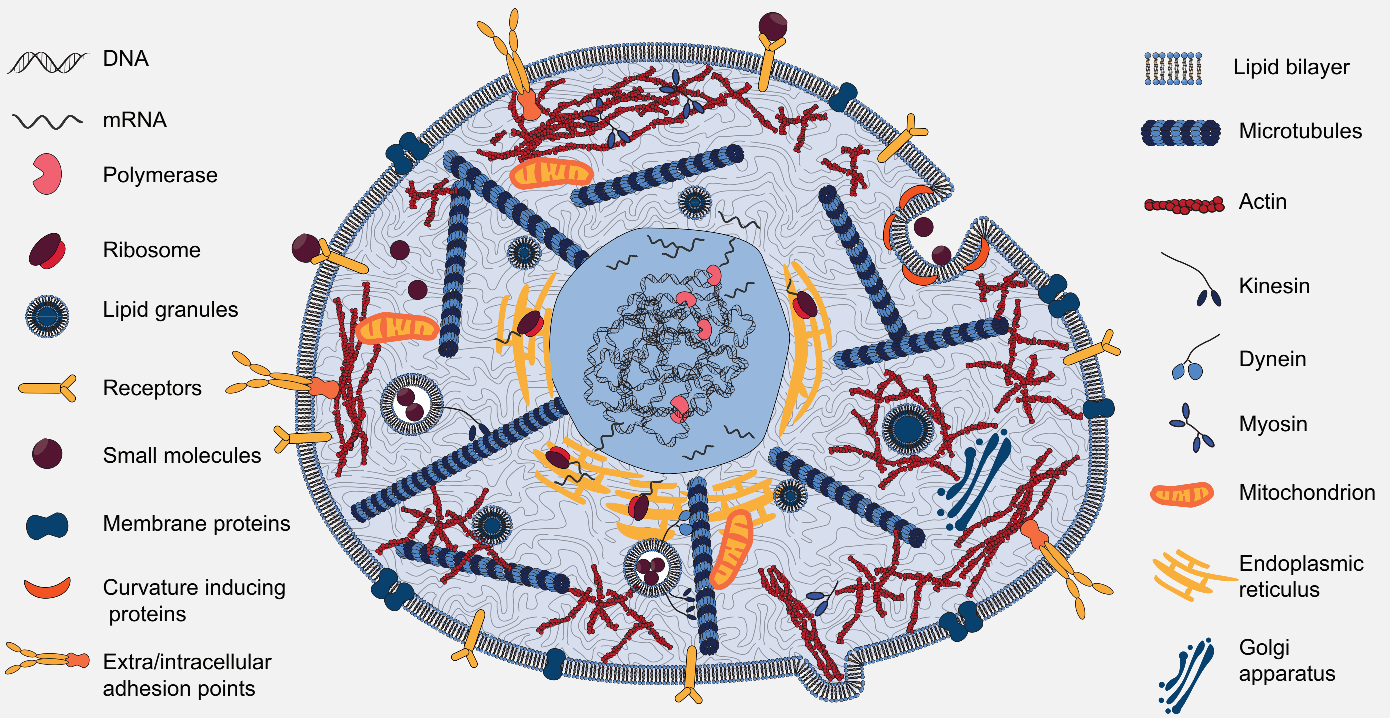
Heterogeneous FPT



New time scale in FP PDF!

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

Gene regulation in eukaryotic cells

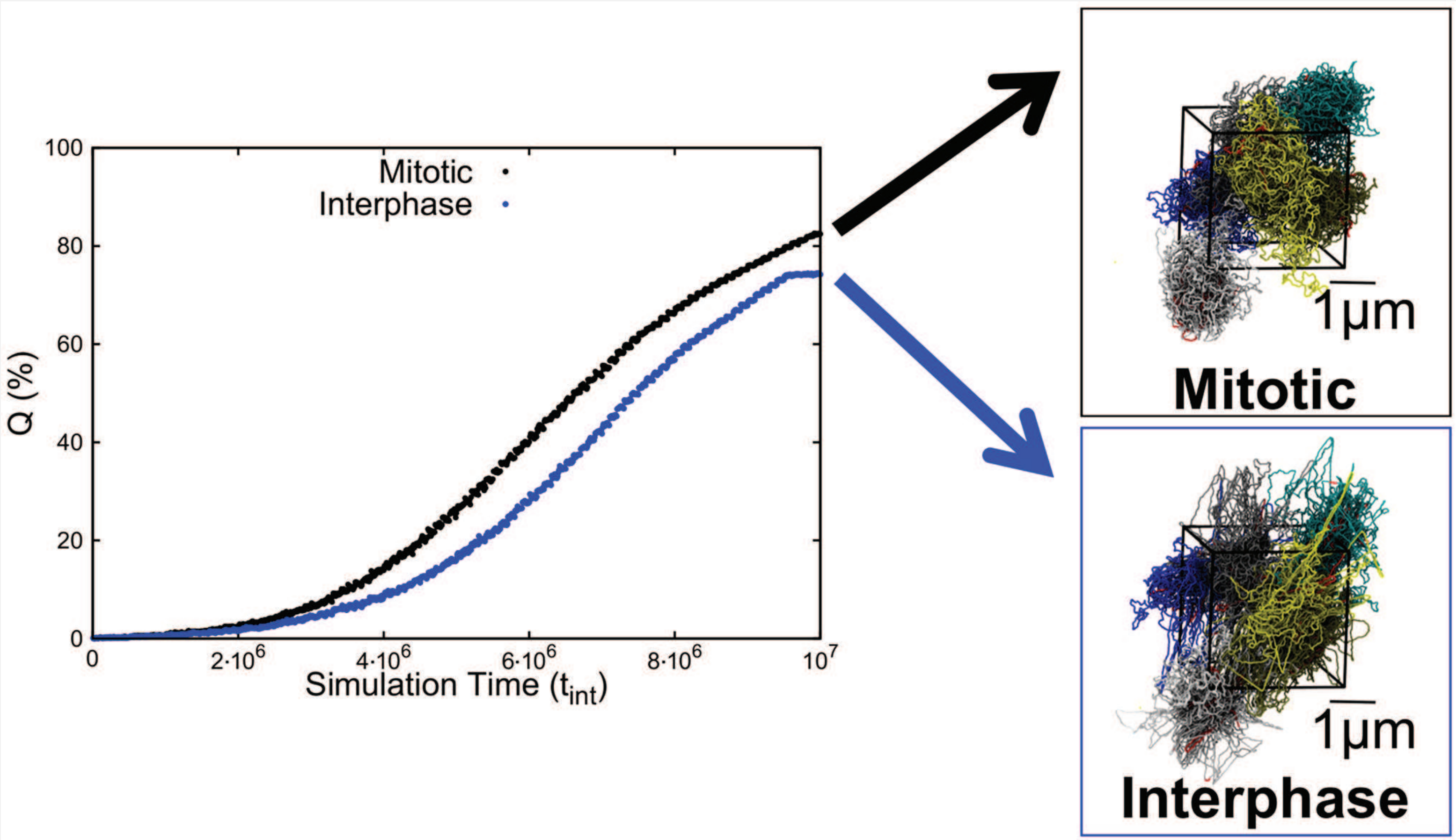


Exchange versus nucleic membrane, chromosomal dynamics & packaging

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)

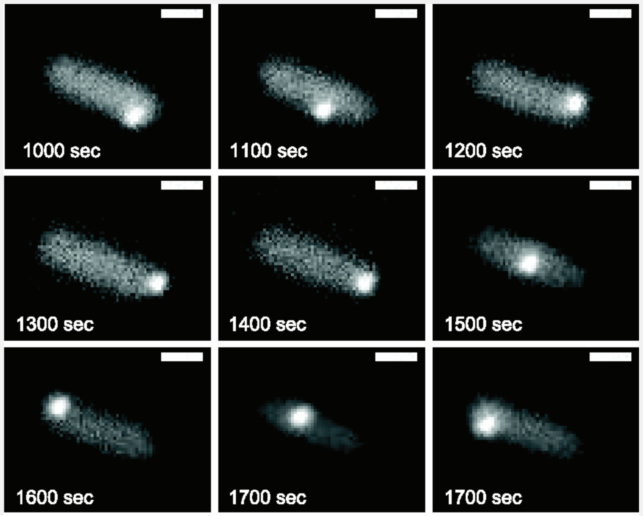
Colocalisation still exists in the nucleus



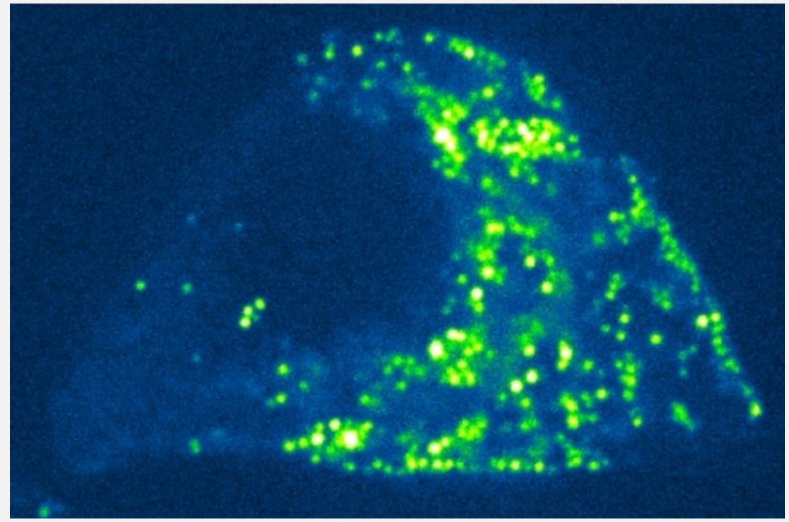
Increase of percentage Q of coregulated pairs of genes in chromosome 19 which colocalise during the MD protocol. Red (???) highlighted regions designate chromosome regions involved in the coregulatory network

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

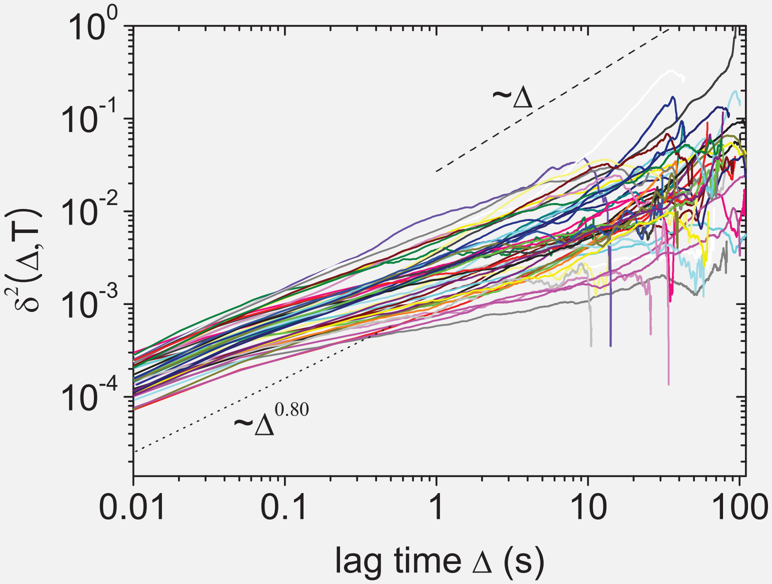
In vivo anomalous diffusion of submicron tracers



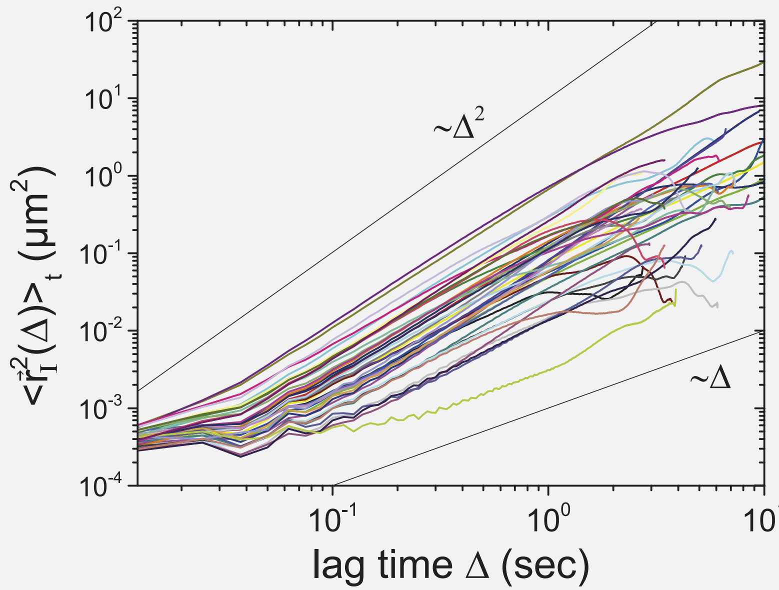
I Golding & EC Cox, PRL (2006)



SMA Tabei et al, PNAS (2013)

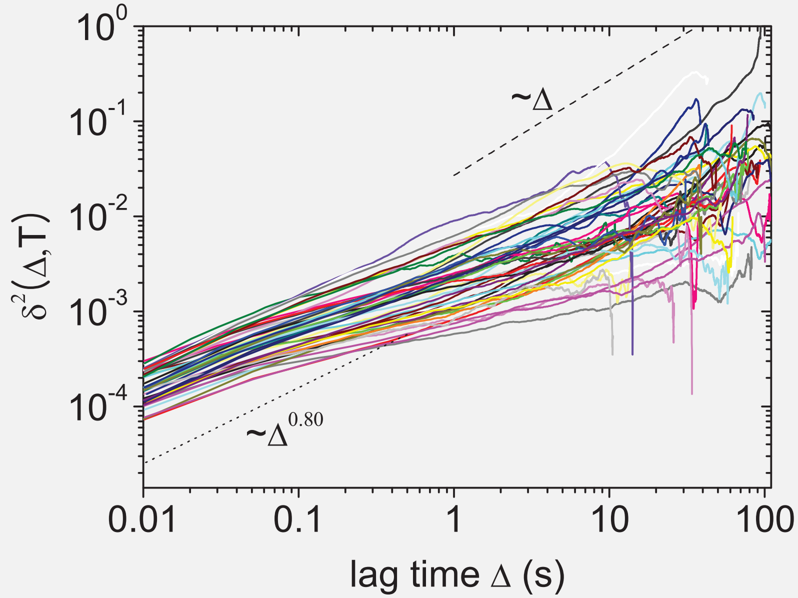


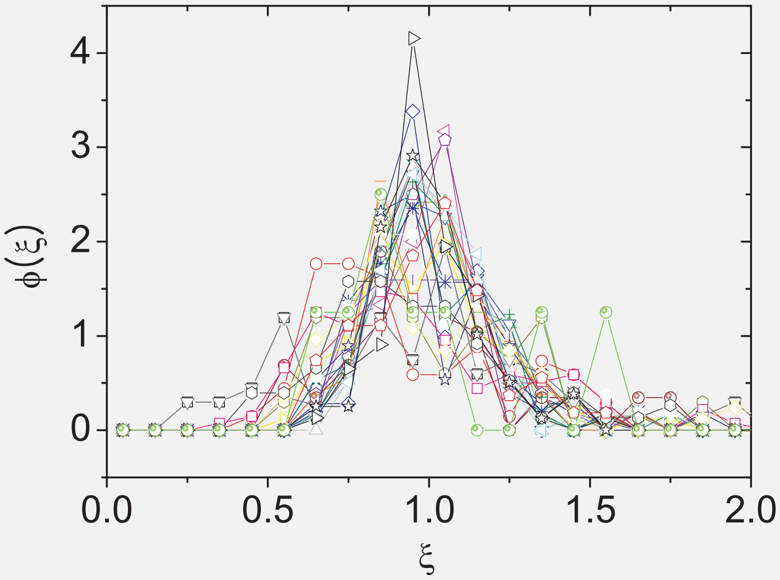
JH Jeon, . . . LB Oddershede & RM, PRL (2011)

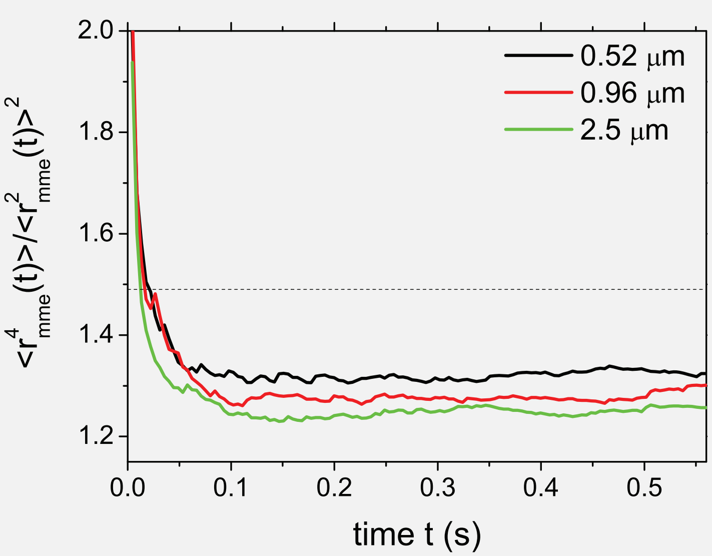


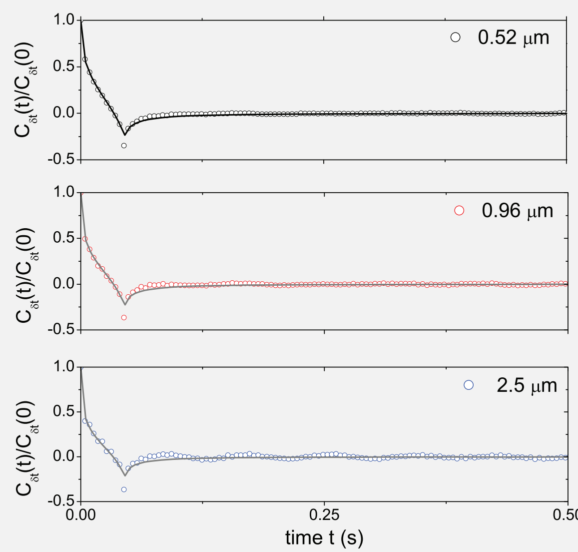
J Reverey, . . . RM & C Selhuber-Unkel, Sci Rep (2015)

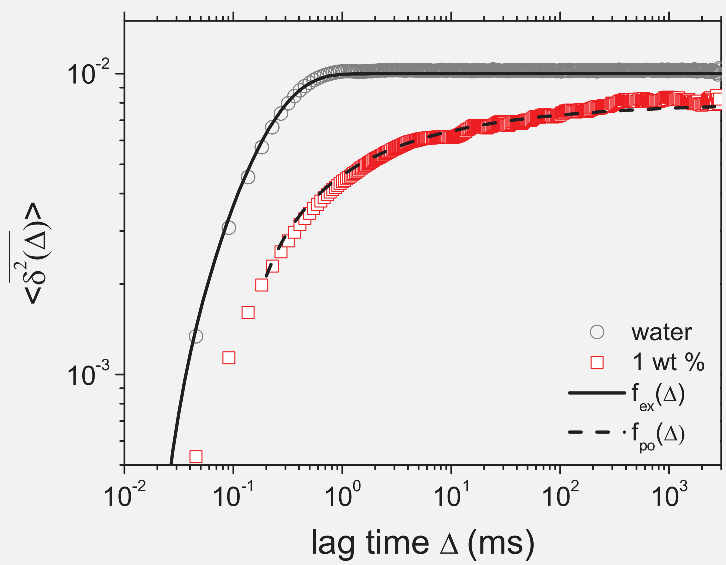
Passive motion of submicron tracers is viscoelastic





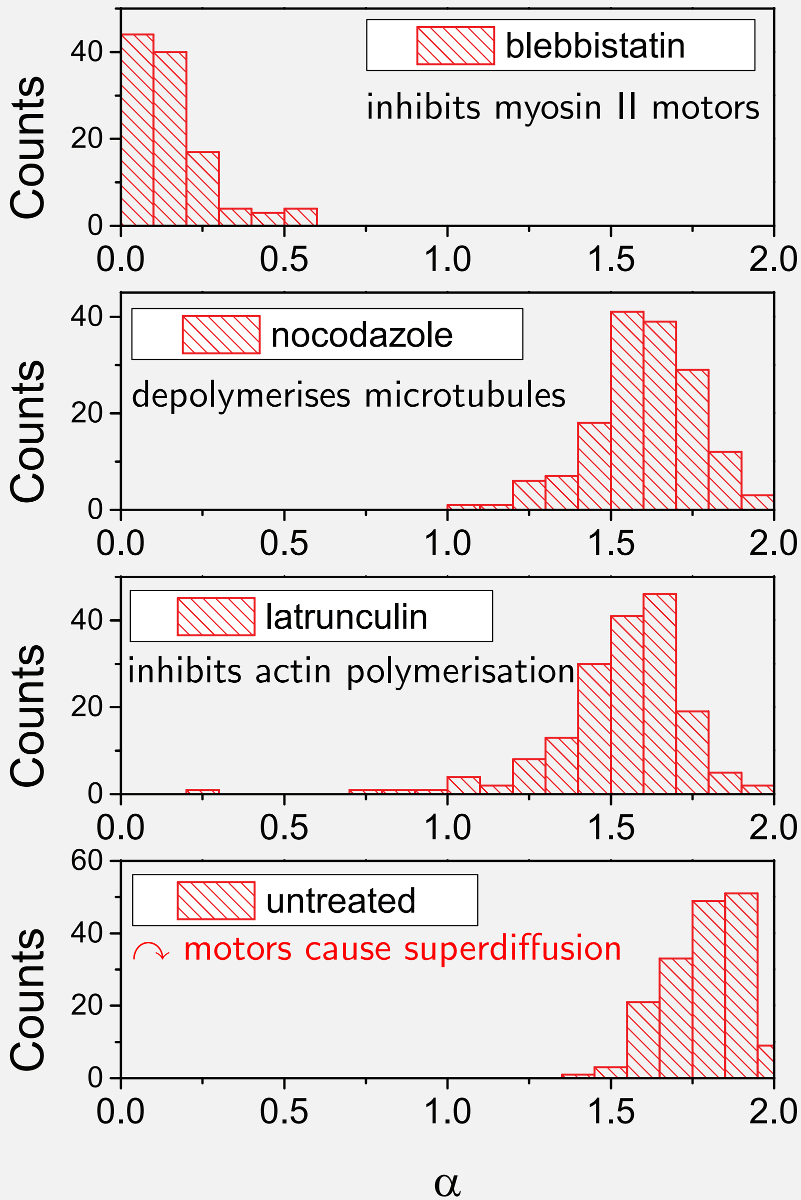


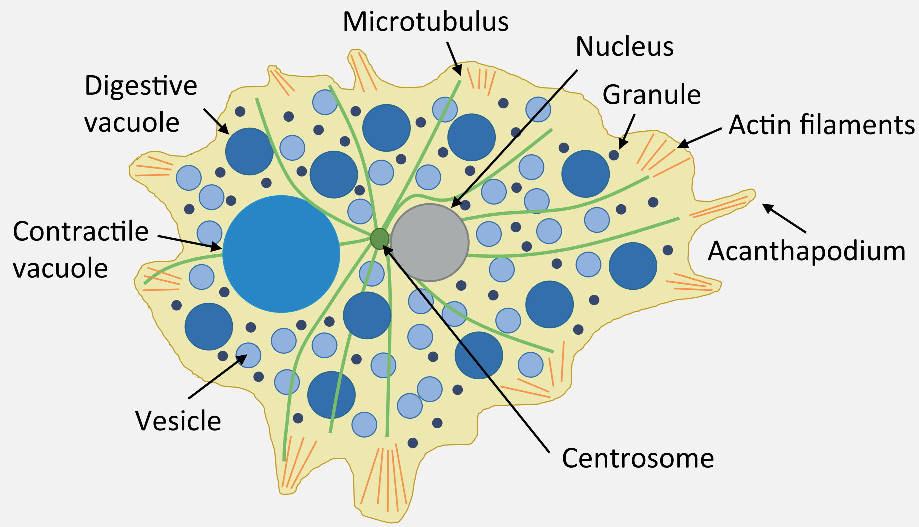


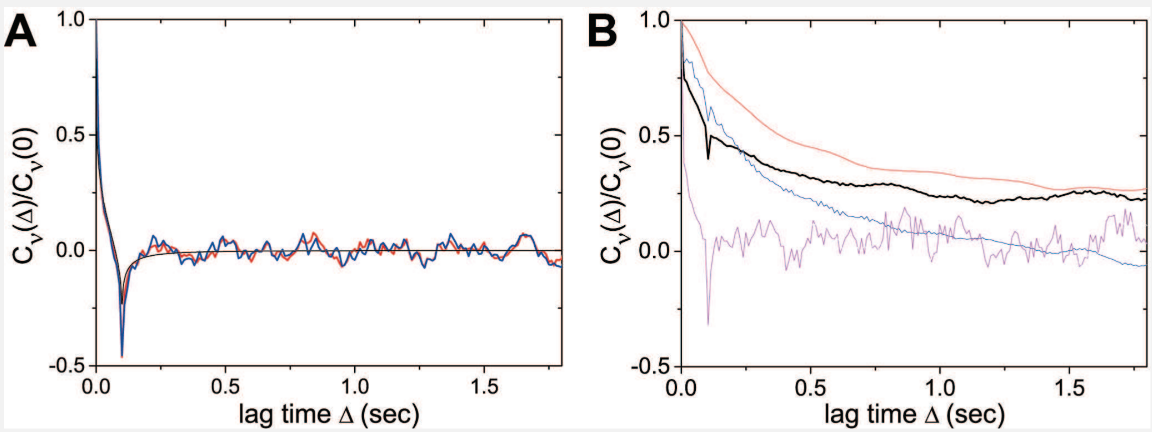


JH Jeon, . . . L Oddershede & RM, PRL (2011); JH Jeon, N Leijnse, L Oddershede & RM, NJP (2013)

Superdiffusion in living Acanthamoeba castellani





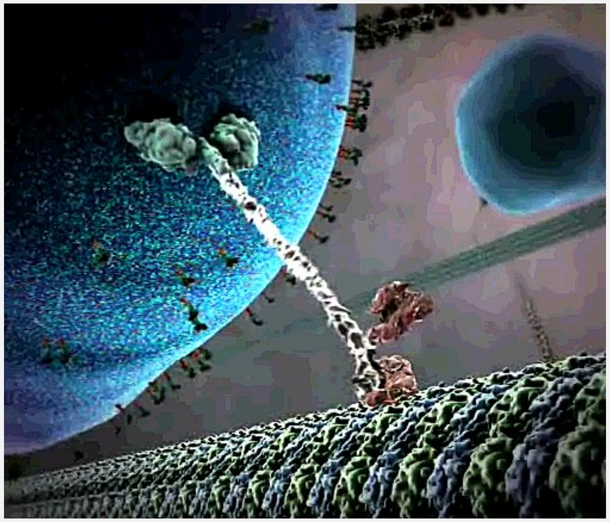


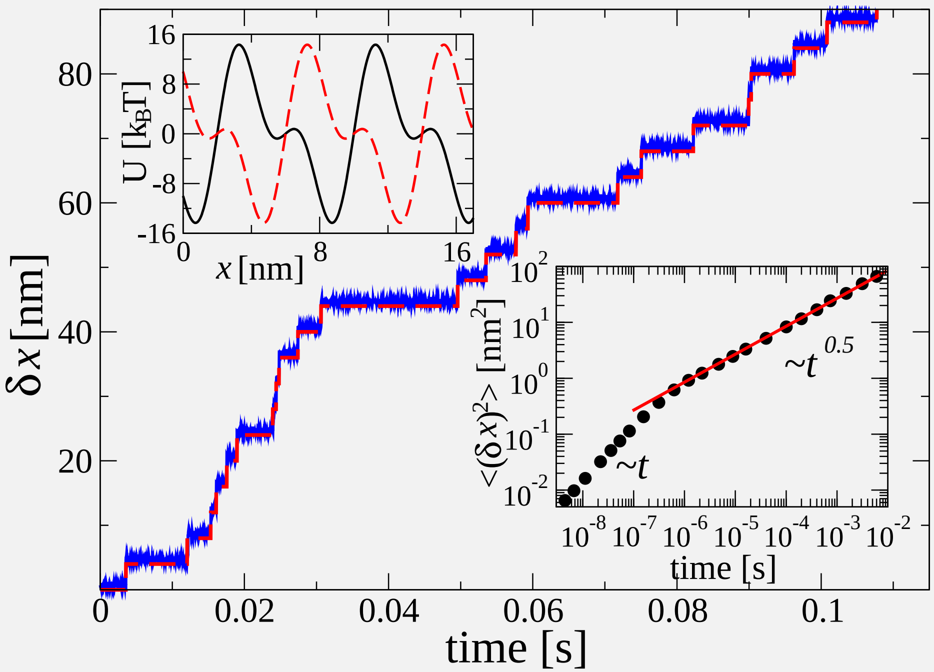
JF Reverey, J-H Jeon, H Bao, M Leippe, RM & C Selhuber-Unkel, Sci Rep (2015)

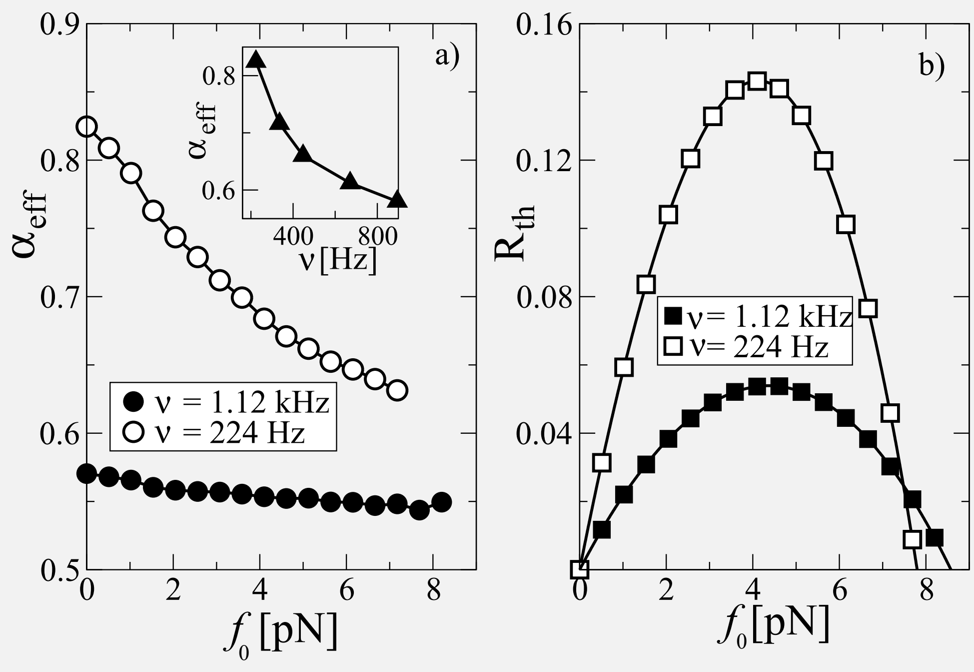
Molecular motor dynamics

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

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

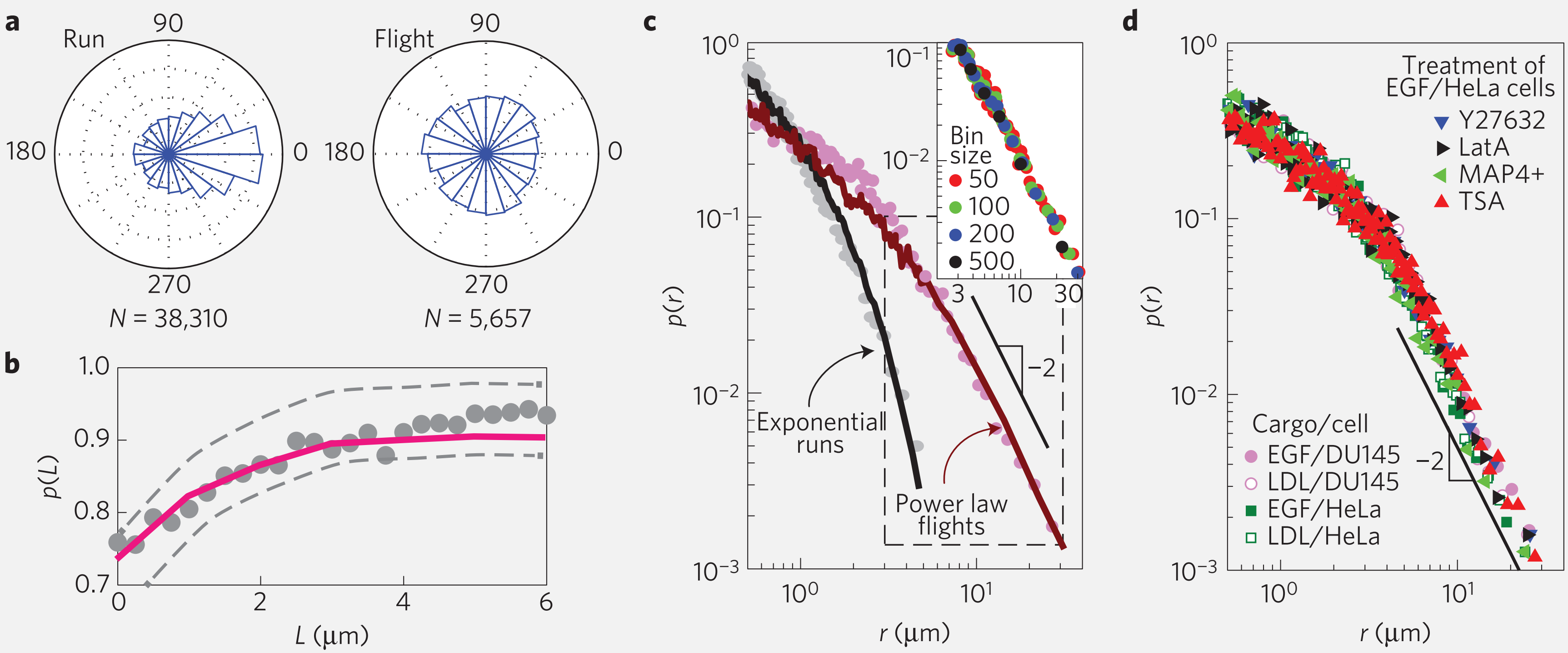






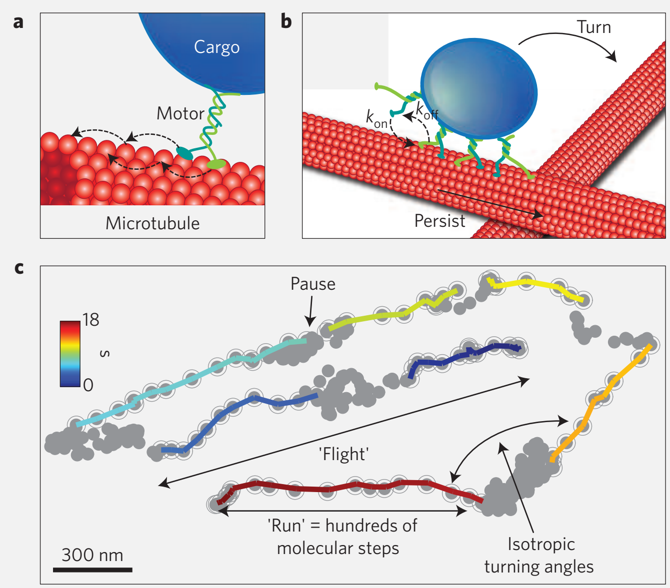
D Robert, T-H Nguyen, F Gallet & C Wilhelm, PLoS ONE (2010); I Goychuk, V Kharchenko & RM, PLoS ONE (2014), PCCP (2014)

Lévy walks of molecular motors in living cells



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

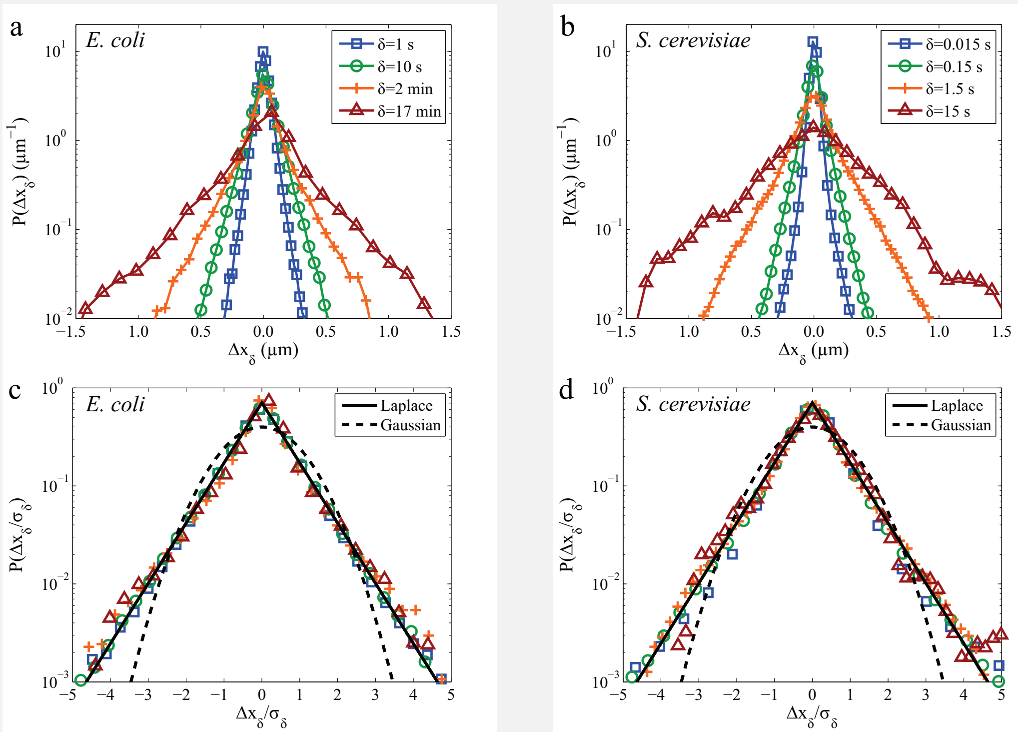
Flight: consecutive runs persisting in direction

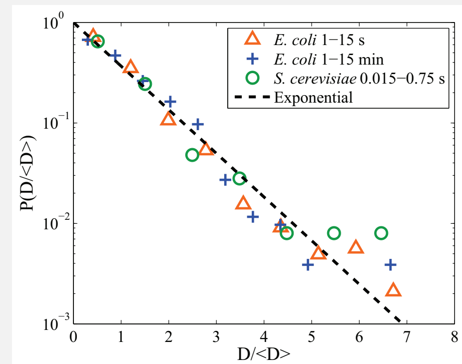


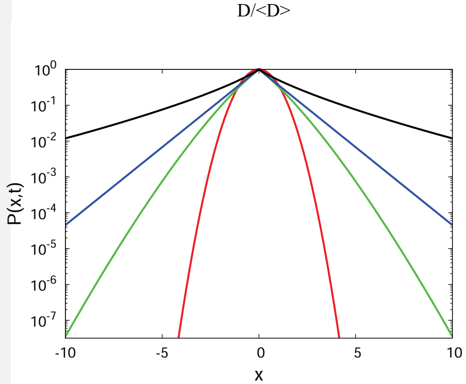
K Chen, B Wang & S Granick, Nat Mat (2015)

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 $P(x,t)=\int_0^\infty G(x,t)p(D)dD$

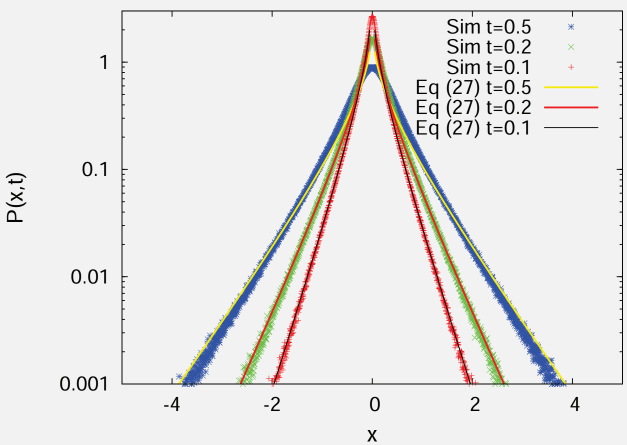
MV Chubinsky & G Slater, PRL (2014); R Jain & KL Sebastian, JPC B (2016): diffusing diffusivity

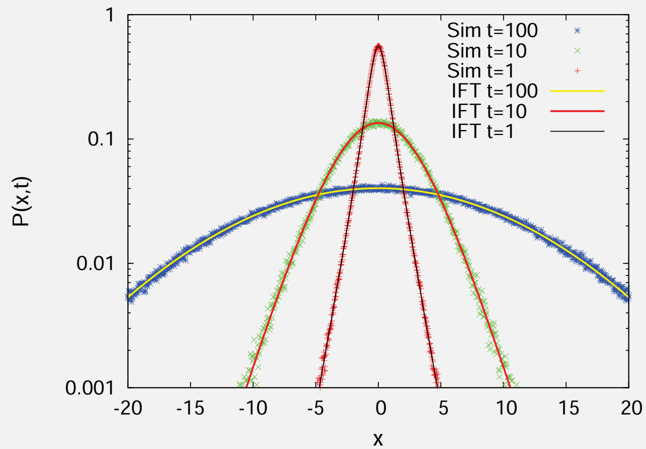
Our minimal model for diffusing diffusivity with Fickian $\langle x(t)\rangle = 2D_{\text{eff}}t$:

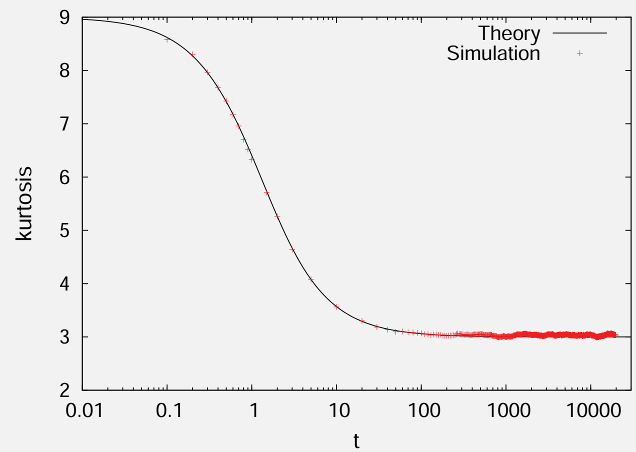
$$\dot{x}(t)=\sqrt{2D(t)}\xi(t)$$

$$D(t)=y^2(t)$$

$$\dot{y}(t)=-y+\eta(t)$$

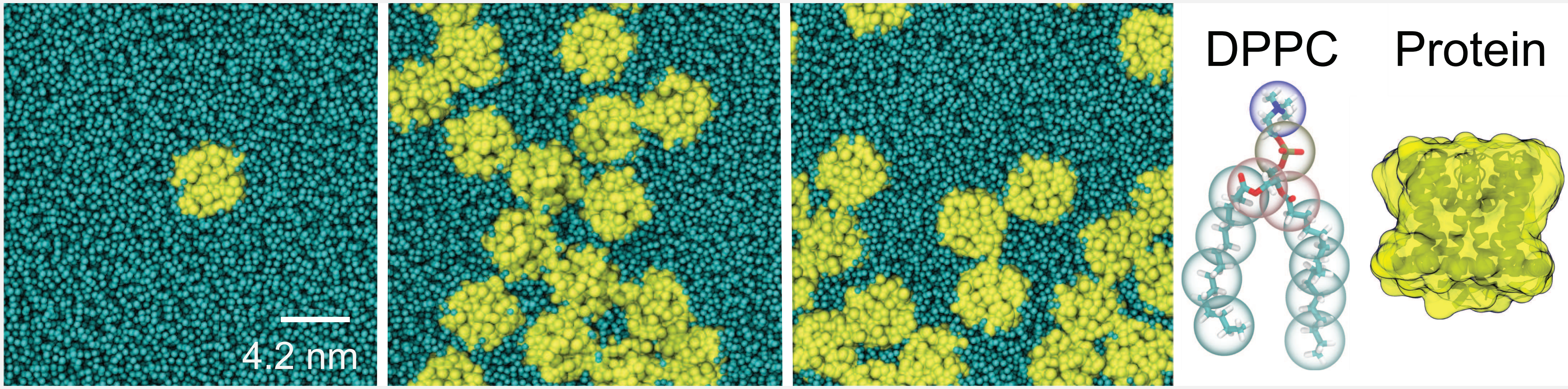


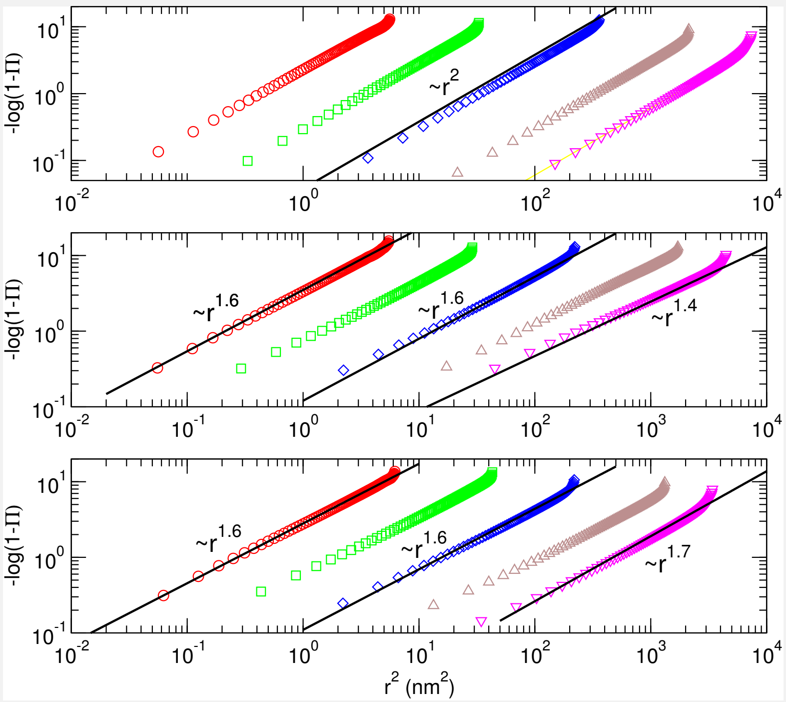




AV Chechkin, F Seno, RM & IM Sokolov, PRX (2017)

Crowding in membranes: non-Gaussian lipid/protein diffusion

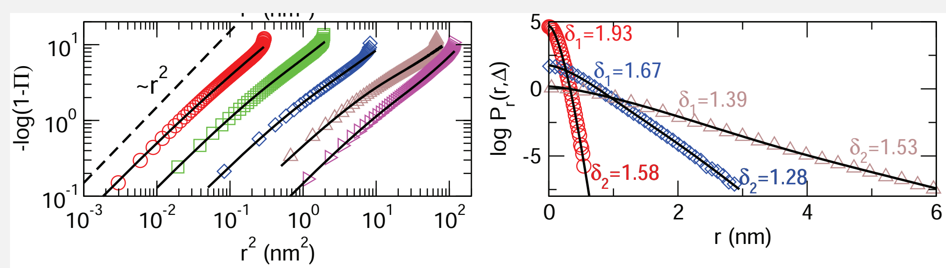




Dilute membrane: $P(r,t)$ Gauss

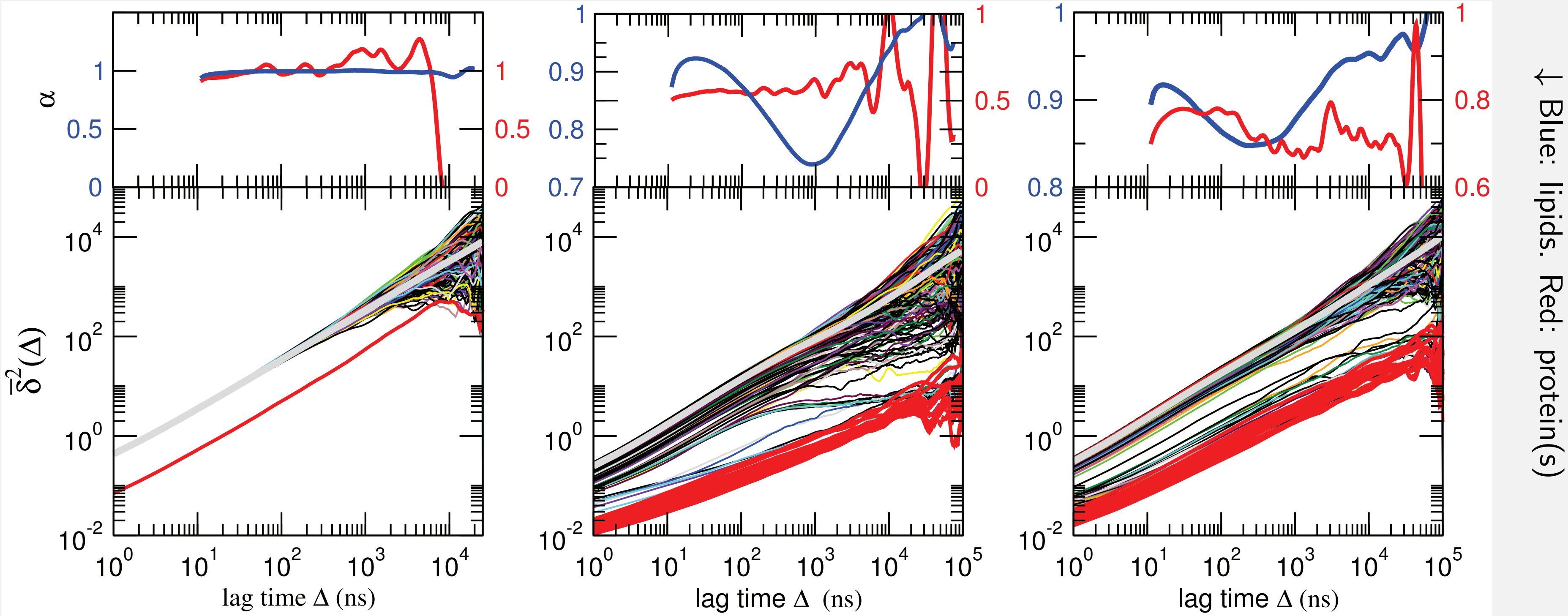
Crowded membrane ($\delta \approx 1.3 \ldots 1.7$):

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



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

Crowding in membranes increases dynamic heterogeneity



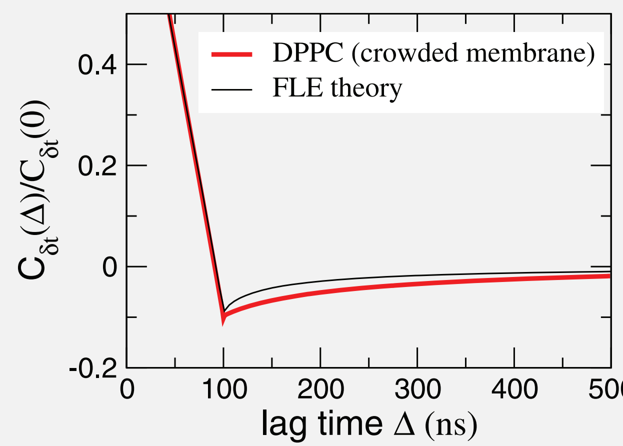
Single NaK channel

DLPC (non-aggregating)

DPPC (aggregating)

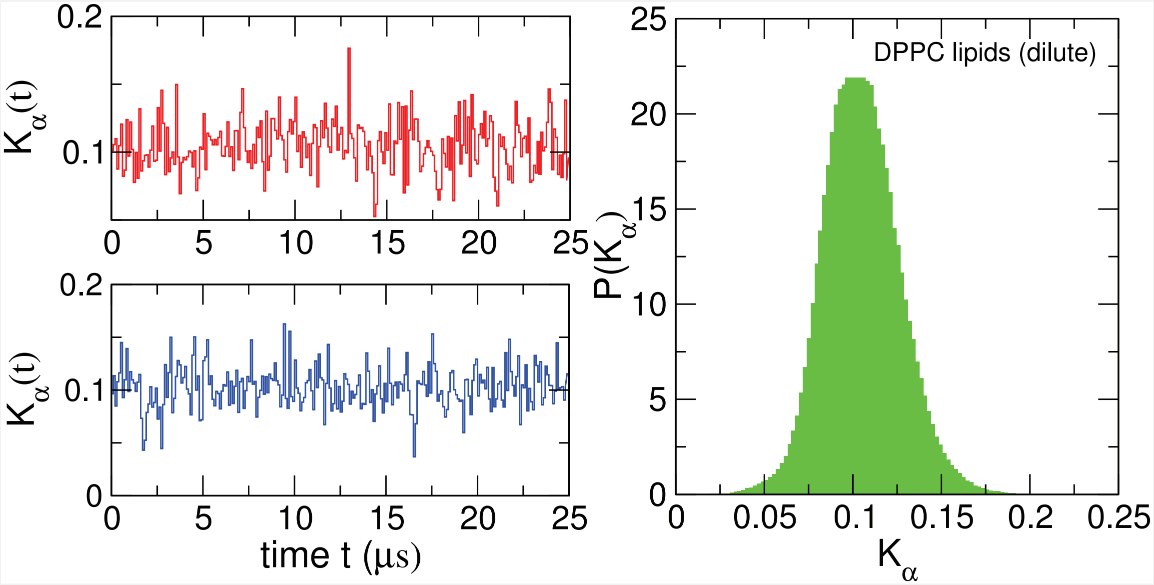
Lipids & proteins behave quite differently

Increment correlation no longer simple FBM ⟶



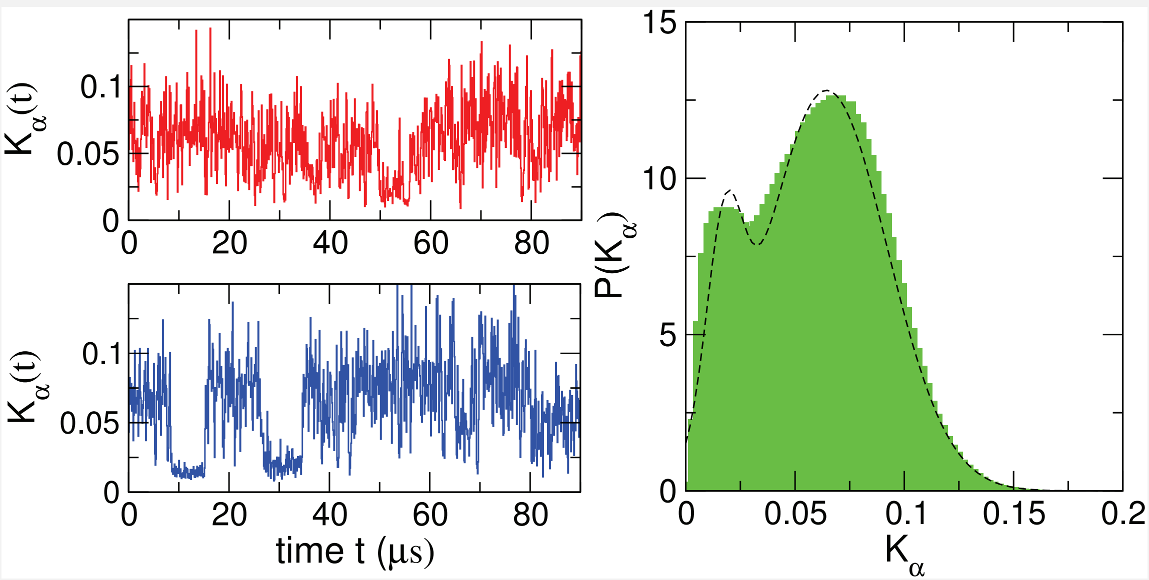
J-H Jeon, M Javanainen, H Martinez-Seara, RM & I Vattulainen, PRX (2016)

Crowding in membranes increases dynamic heterogeneity



Diffusivity(t) for two lipids

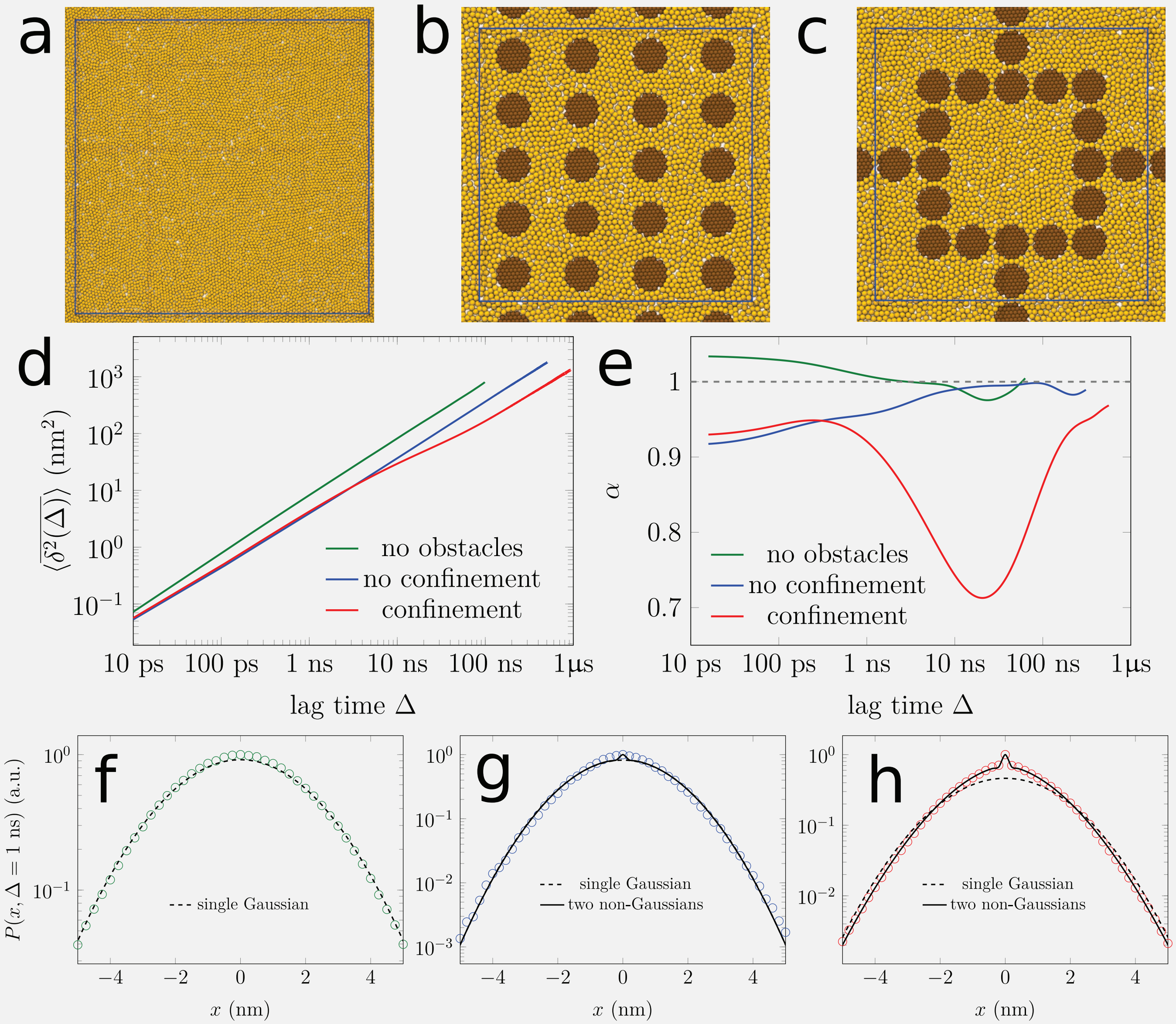
Lipid diffusivity, dilute membrane



Lipid diffusivity, crowded membrane

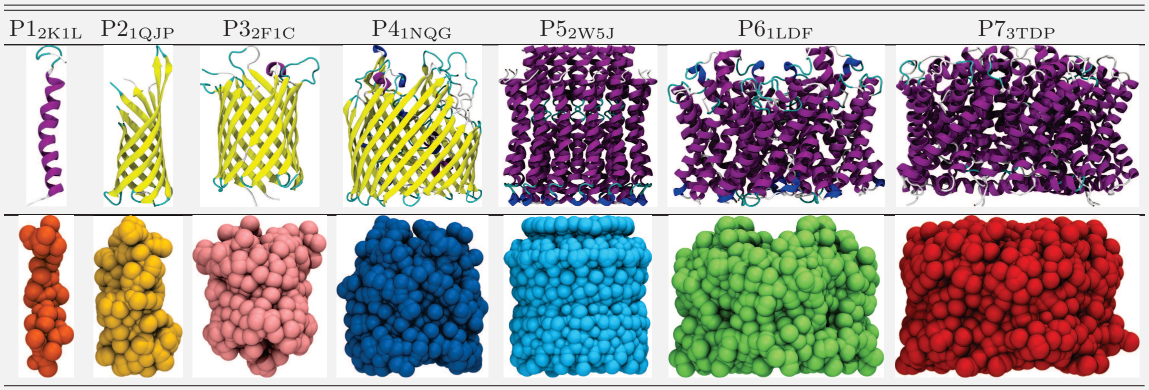
J-H Jeon, M Javanainen, H Martinez-Seara, RM & I Vattulainen, PRX (2016)

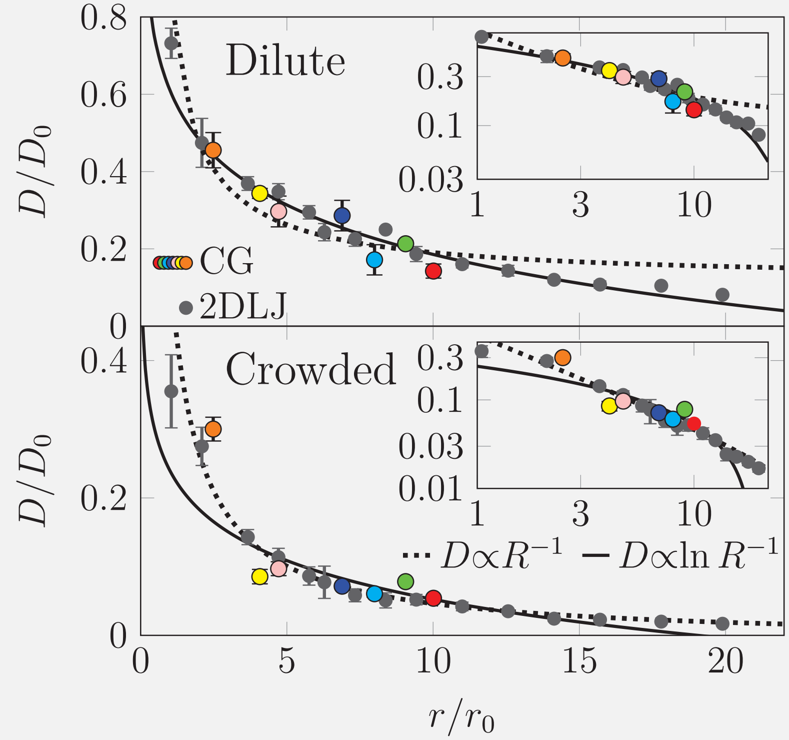
Confinement in argon system shows geometric origin

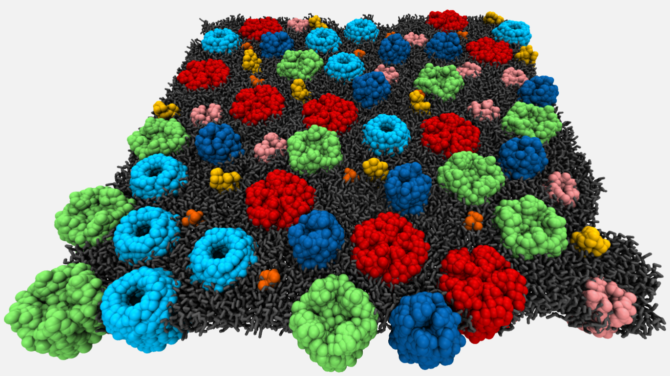


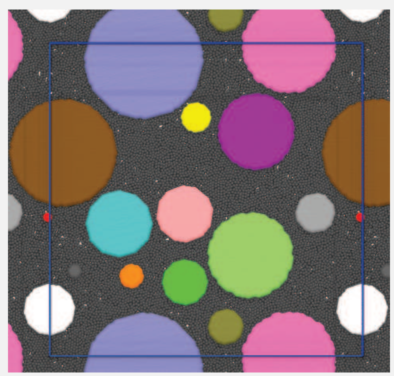
J-H Jeon, M Javanainen, H Seara Monne, RM & I Vattulainen, PRX (2016)

Geometry-induced violation of Saffman-Delbrück relation









Dilute system: Saffman-Delbrück law

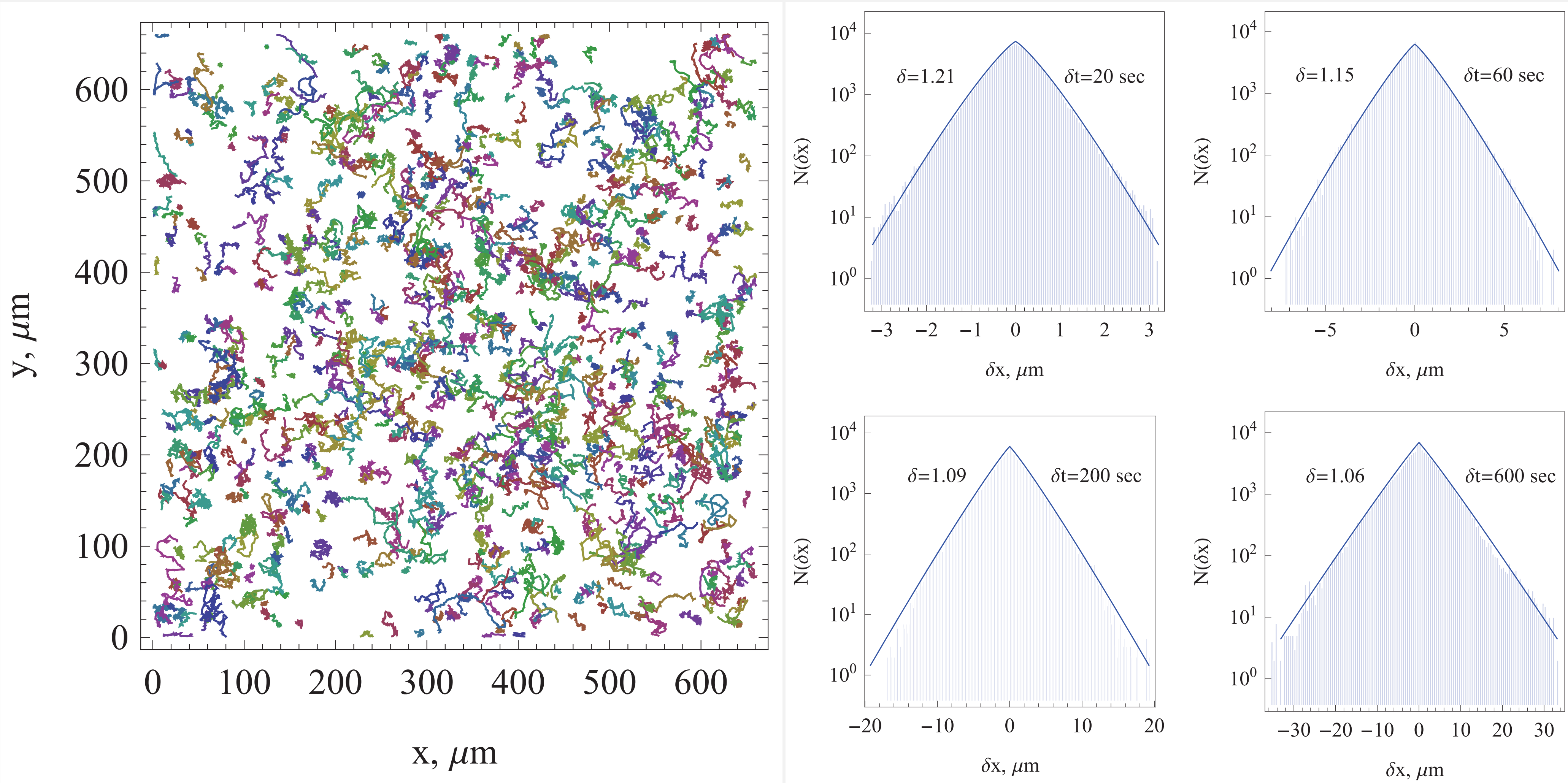
$$D(R) \simeq \log(1/R)$$

Crowded membrane & 2DLJ discs:

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

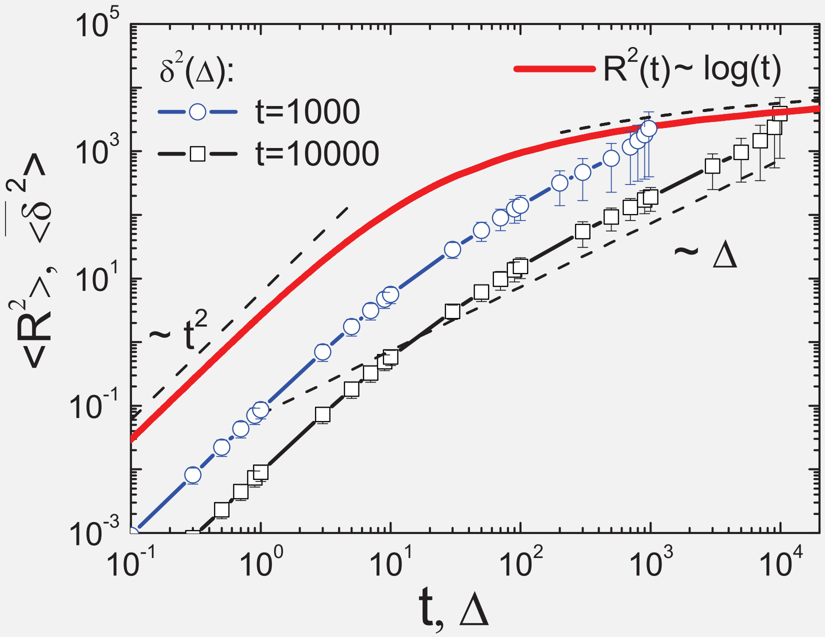
M Javanainen, H Seara Monne, RM & I Vattulainen, JPC Lett (2017)

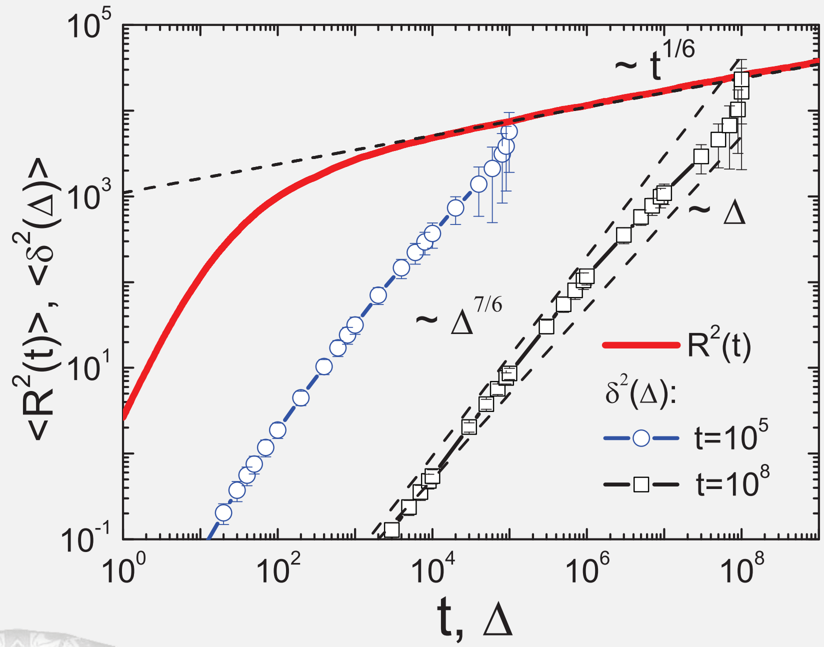
Non-Gaussian diffusion of Dictyostelium cells



AG Cherstvy, O Nagel, C Beta & RM (2017)

WEB in granular gas & SBM as mean field theory





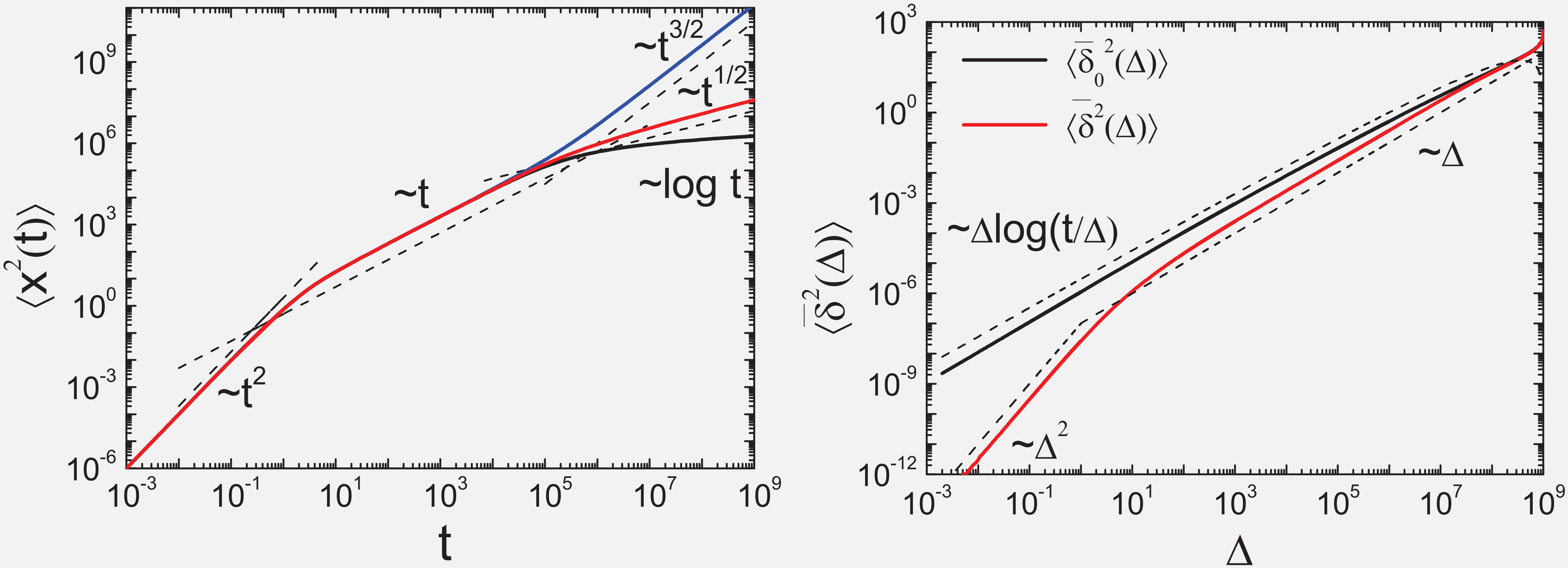
Haff's law: $\mathscr{T}(t)=\mathscr{T}_0/(1+t/\tau_0)^2$

$$\langle\mathbf{r}^2(t)\rangle\sim 6D_0\tau_0\log(1+t/\tau_0)$$

$$\left\langle\overline{\delta^2(\Delta)}\right\rangle\sim 6D_0\tau_0\Delta/T$$

A Bodrova, AV Chechkin, AG Cherstvy & RM, NJP (2015); PCCP (2015)

Non-existence of the overdamped limit in slow SBM

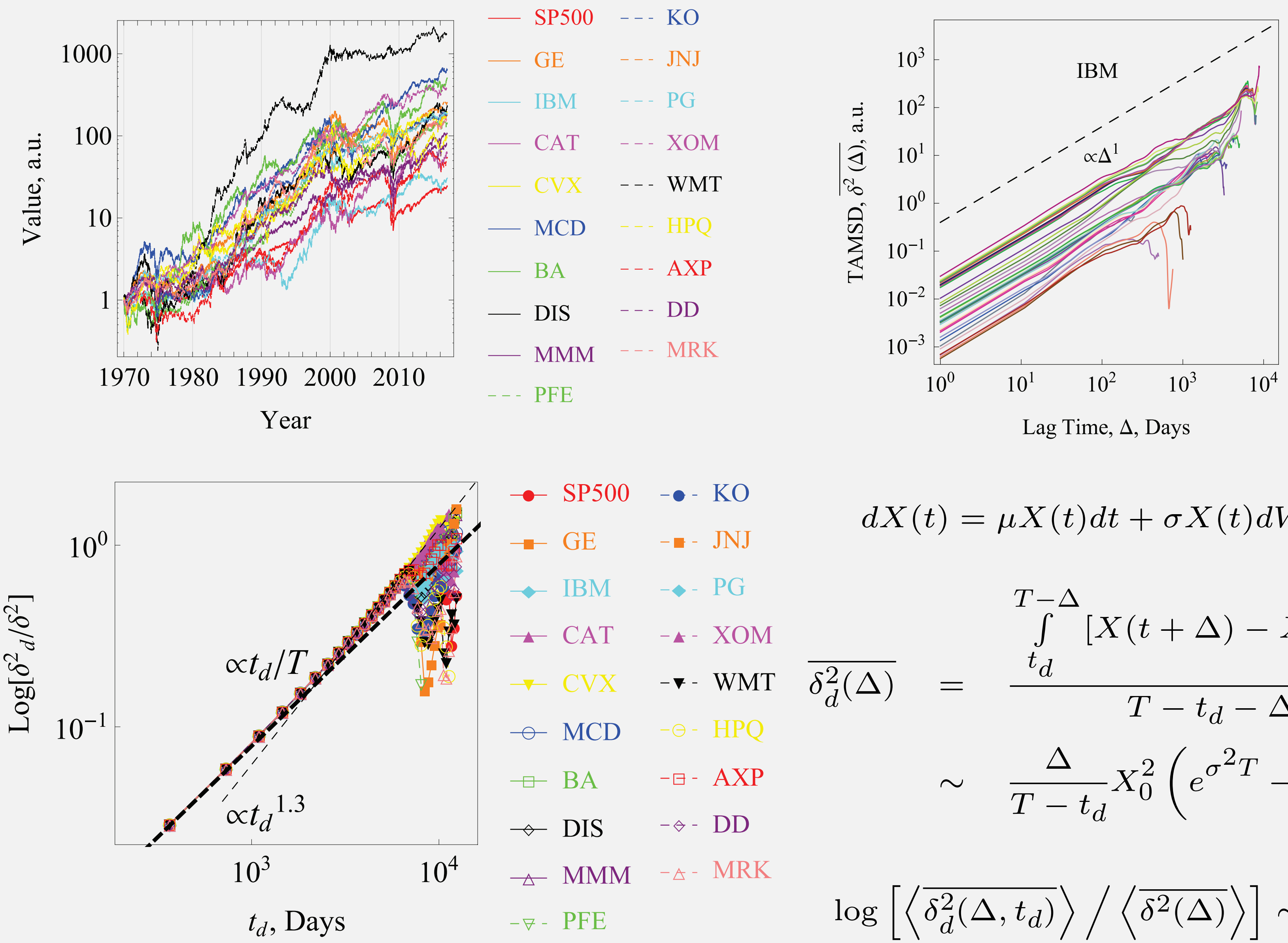


Crossover from ballistic to overdamped motion no longer defined by time scale of inverse friction. For small α & ultraslow the SBM overdamped limit is never fulfilled

Ageing case: [H Safdari, A Bodrova, AV Chechkin, AG Cherstvy & RM, PRE (2017)]

A Bodrova, AV Chechkin, AG Cherstvy, H Safdari, IM Sokolov & RM, Sci Rep (2016)

Time averages & ageing in financial market time series



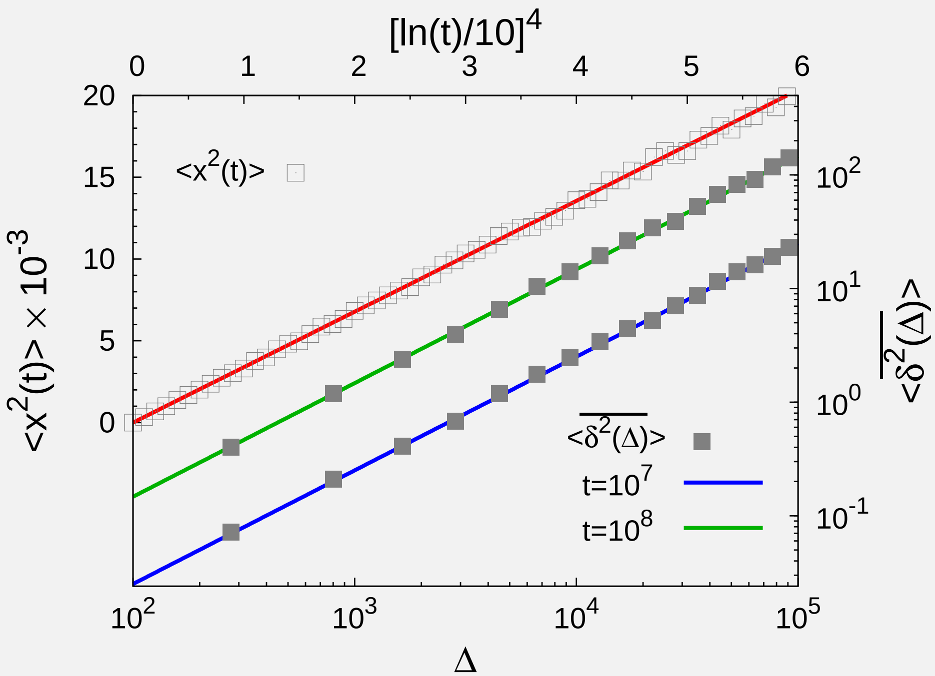
$$dX(t) = \mu X(t)dt + \sigma X(t)dW(t)$$

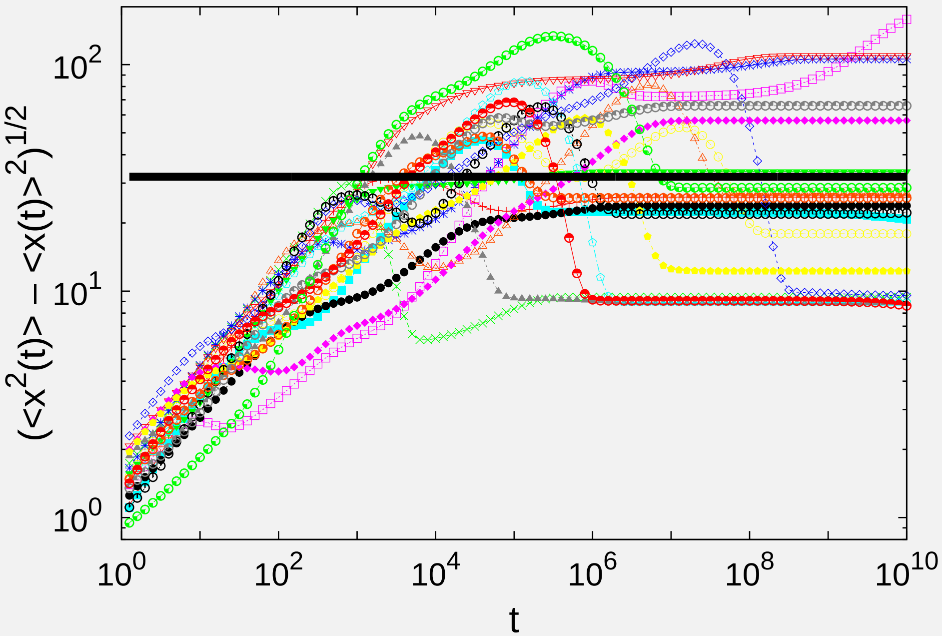
$$\overline{\delta_d^2(\Delta)} = \frac{\int_{t_d}^{T-\Delta} [X(t+\Delta) - X(t)]^2 \, dt}{T - t_d - \Delta} \sim \frac{\Delta}{T - t_d} X_0^2 \left(e^{\sigma^2 T} - e^{\sigma^2 t_d} \right)$$

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

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

Logarithmic evolution: Sinai diffusion & mean field CTRW





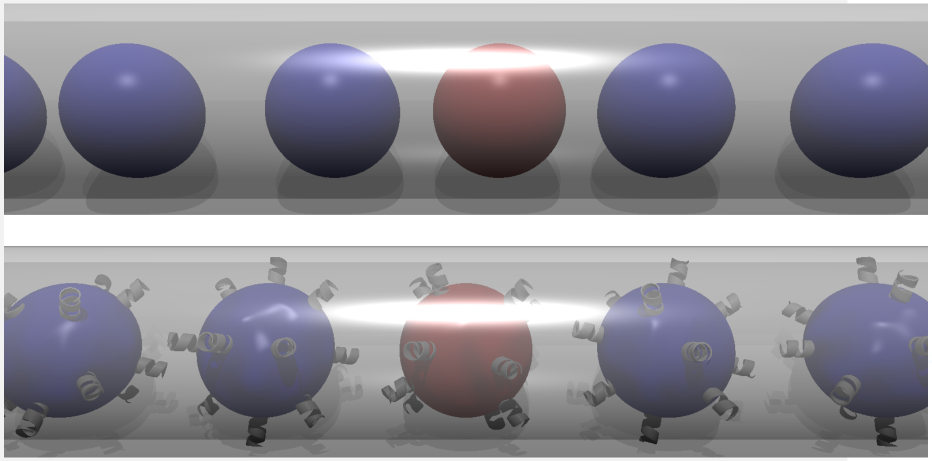
$$\left\langle \widetilde{x^2(t)} \right\rangle \simeq \log^4(t) \ \& \ \left\langle \overline{\widetilde{\delta^2(\Delta)}} \right\rangle \simeq \log^4(T)\frac{\Delta}{T}$$

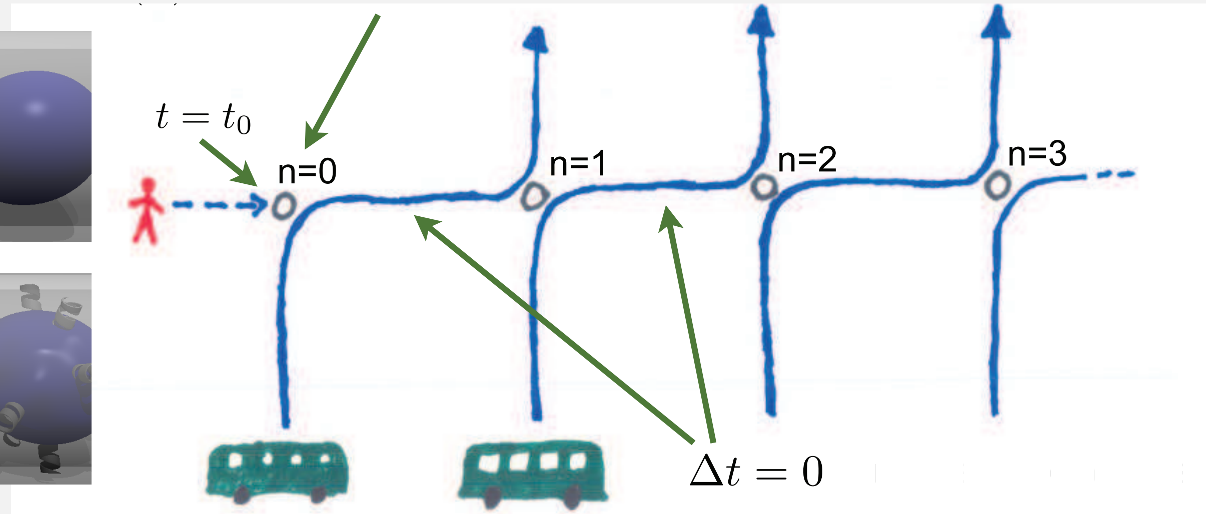
Mean field approach (comp ultraslow maps):

$$\psi(t) \simeq \frac{1}{t\log^4 t}$$

AV Chechkin, H Kantz, A Godec, RM & E Barkai, JPA (2014)

Ultraslow dynamics in ageing many-particle systems



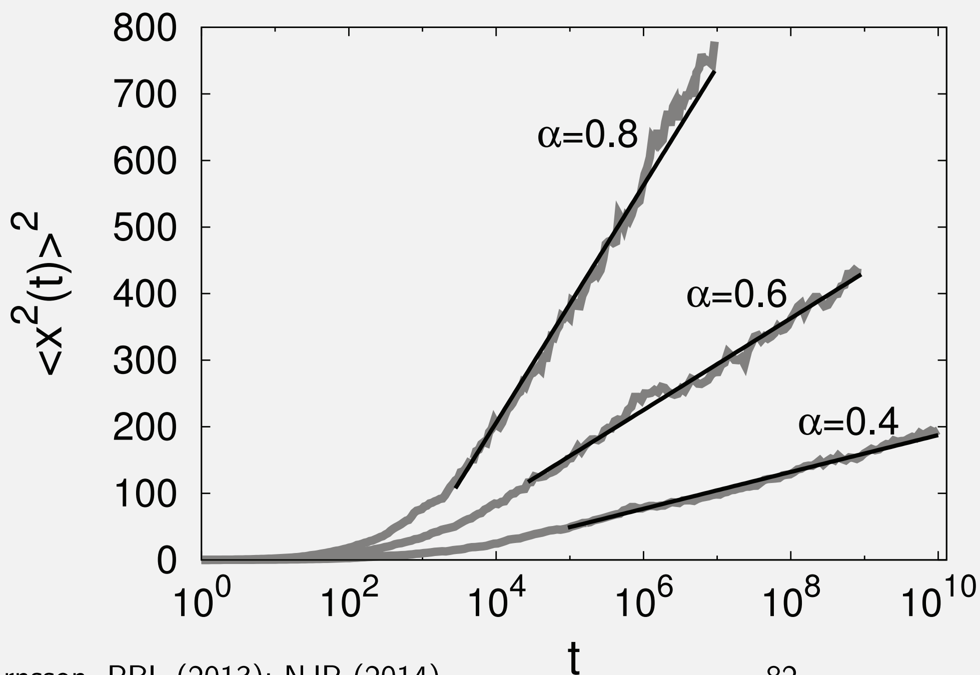


Brownian particles: Harris' law $\langle x^2(t)\rangle \simeq t^{1/2}$

Functionalised particles moving /w $\psi(t) \simeq t^{-1-\alpha}$
$\curvearrowright$ scaling argument: $n \to \log t$:

$$\left\langle x^2(t)\right\rangle \simeq \log^{1/2}\left(\frac{t}{t_0}\right)$$

WEB: $\overline{\delta^2(\Delta)} \simeq (\Delta/T)\log^{1/2} T$



[LP Sanders,] MA Lomholt, L Lizana, [K Fogelmark,] RM & T Ambjörnsson, PRL (2013); NJP (2014)

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

1. Gene expression based on stochastic binding of TFs; facilitated diffusion model verified in vitro for certain TFs. Speed-stability paradox
2. Facilitated diffusion model also applies to in vivo gene regulation
3. Distance matters I: conformation of DNA in facilitated diffusion
4. Distance matters II: gene-gene distance for TF-TU regulation—support for rapid search hypothesis
5. Sequence and auxiliary operator effects
6. (Transient) anomalous diffusion of TFs in vivo

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Christine Selhuber (U Kiel), Kirstine Berg-Sørensen (DTU)

Lene Oddershede (NBI Københavns U)

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