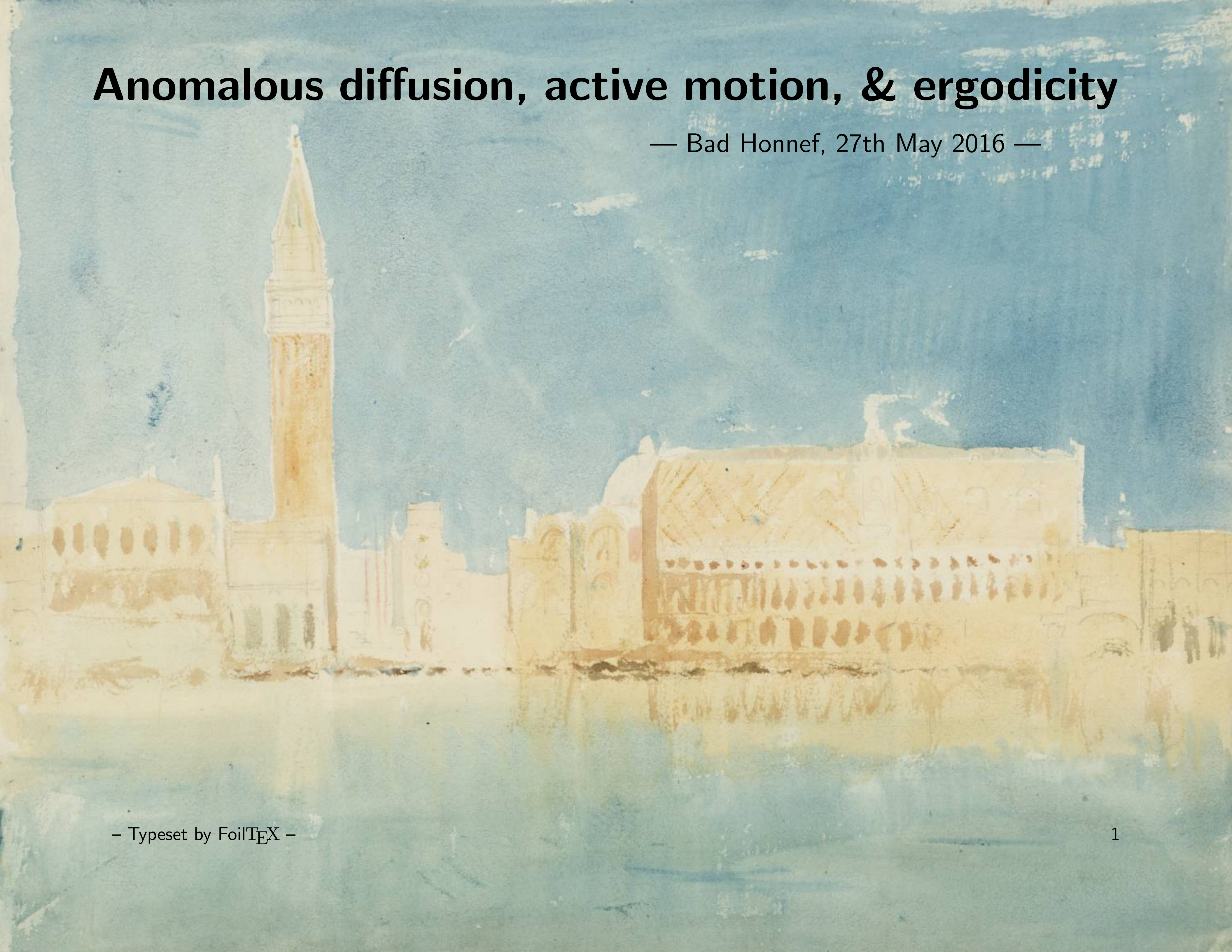
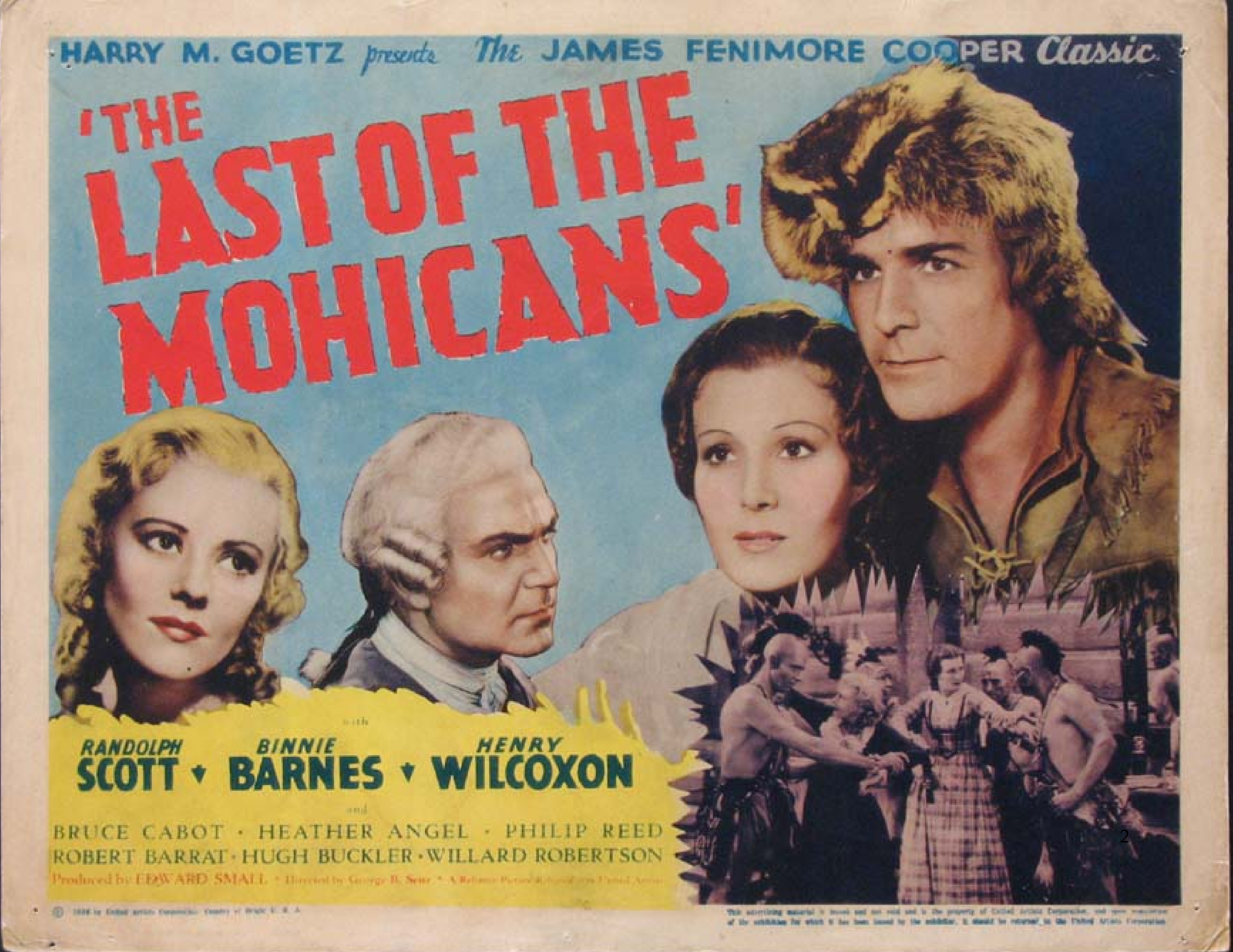


Anomalous diffusion, active motion, & ergodicity

— Bad Honnef, 27th May 2016 —



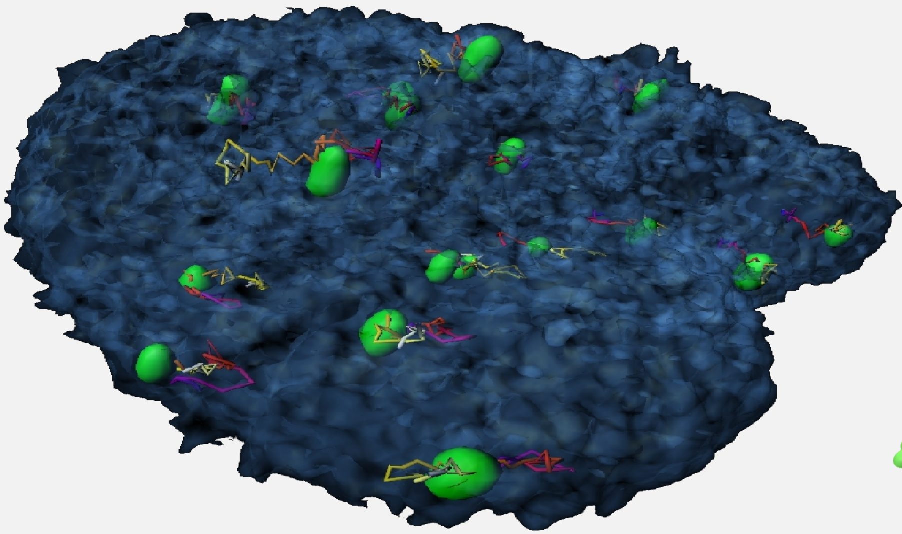
HARRY M. GOETZ presents The JAMES FENIMORE COOPER Classic
'THE LAST OF THE MOHICANS'
with
RANDOLPH SCOTT • BINNIE BARNES • HENRY WILCOXON
and
BRUCE CABOT • HEATHER ANGEL • PHILIP REED
ROBERT BARRAT • HUGH BUCKLER • WILLARD ROBERTSON
Produced by EDWARD SMALL

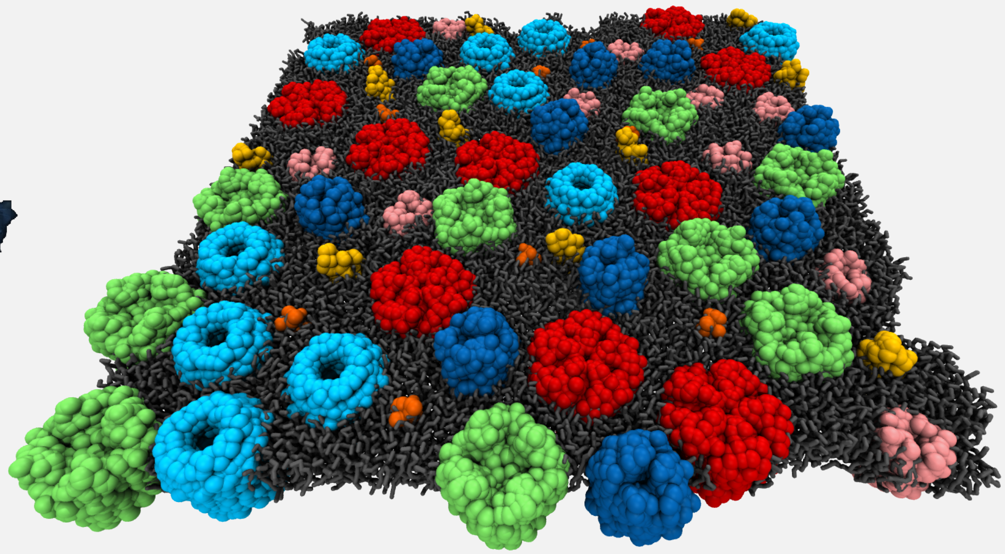
Single particle tracking provides unprecedented insight

Superresolution microscopy & supercomputing provide time series $\mathbf{r}(t)$

$\curvearrowright$ insight into the dynamics of complex systems such as living cells

$\curvearrowright$ need for quantitative understanding & new physical concepts (non-ergodic & ageing dynamics)





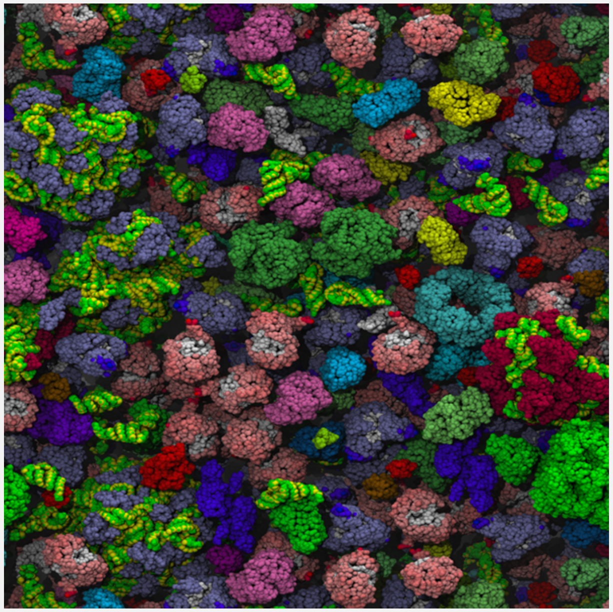
Courtesy Yuval Garini

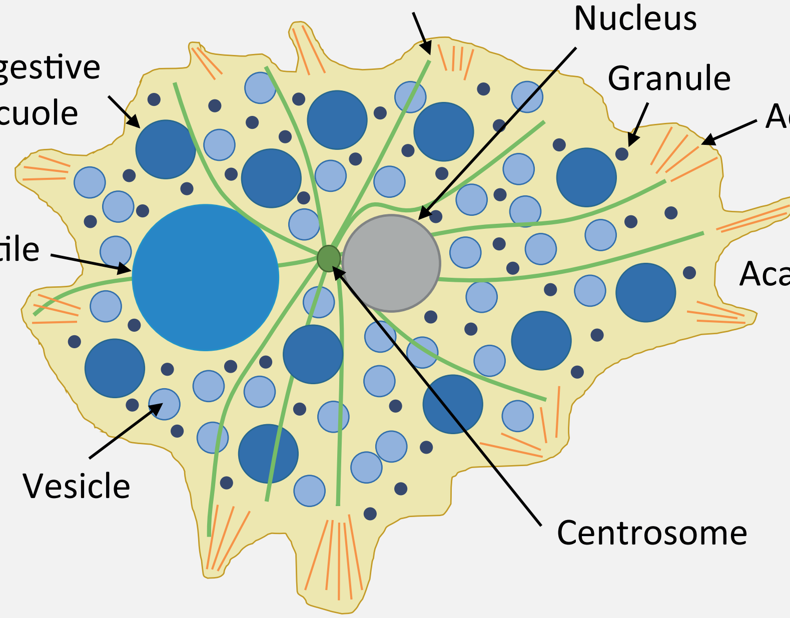
Courtesy Matti Javanainen

Superdense & supercrowded enrivonments in living cells

Superdense [I Golding & EC Cox, PRL (2007)] ↗

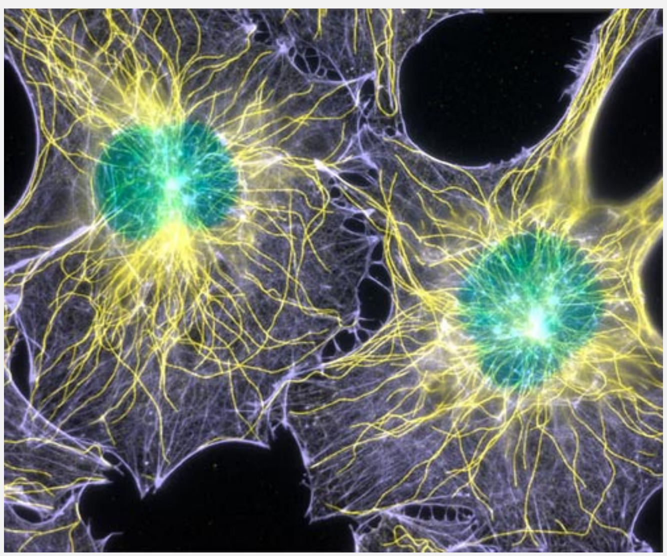
SR McGuffee & AH Elcock, PLoS CB (2010)

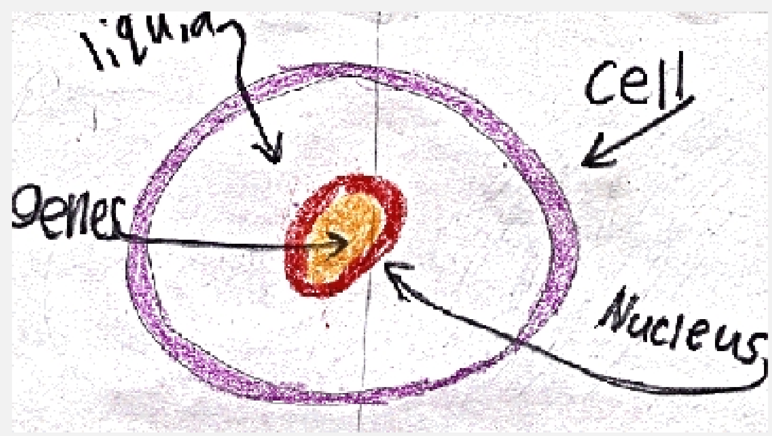




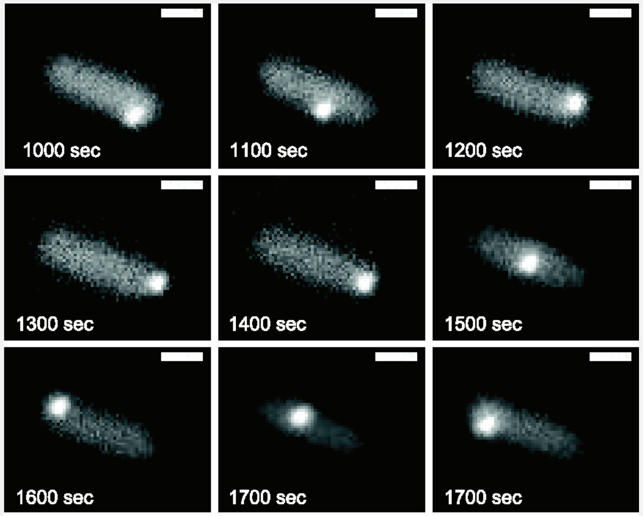
Supercrowded [JF Reverey, JH Jeon, H Bao, M Leippe, RM & C Selhuber-Unkel, Sci Rep (2015)]

NIH web *Inside the cell*

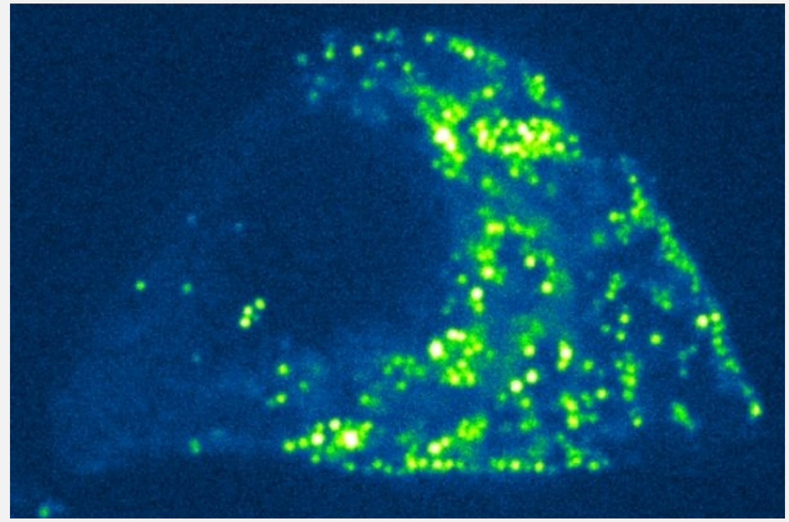




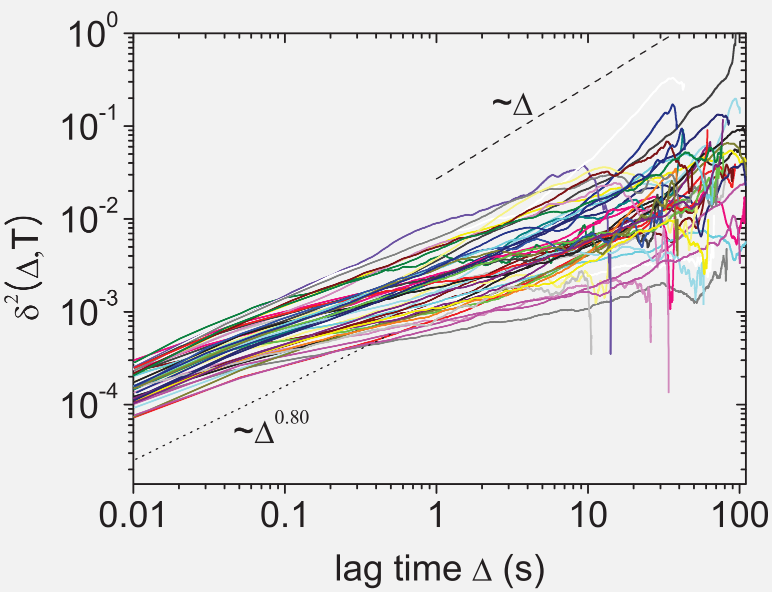
In vivo anomalous diffusion of submicron tracers



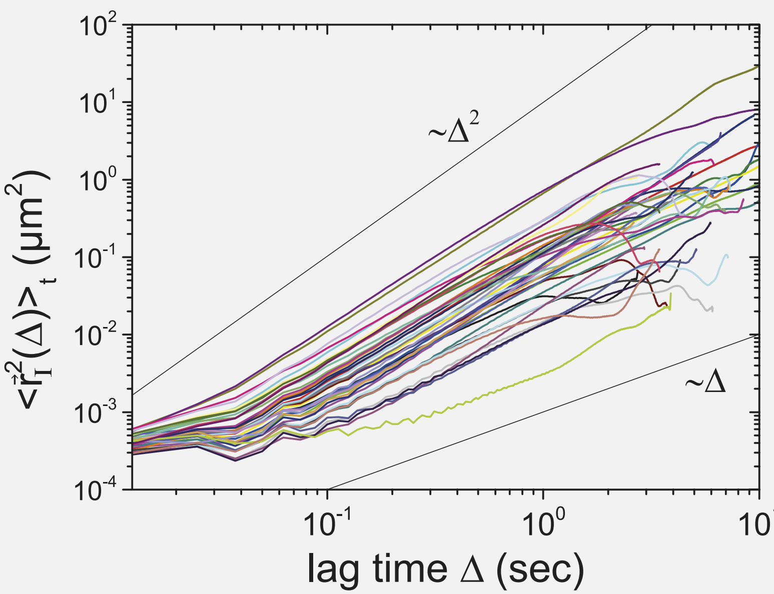
I Golding & EC Cox, PRL (2006)



SMA Tabei et al, PNAS (2013)

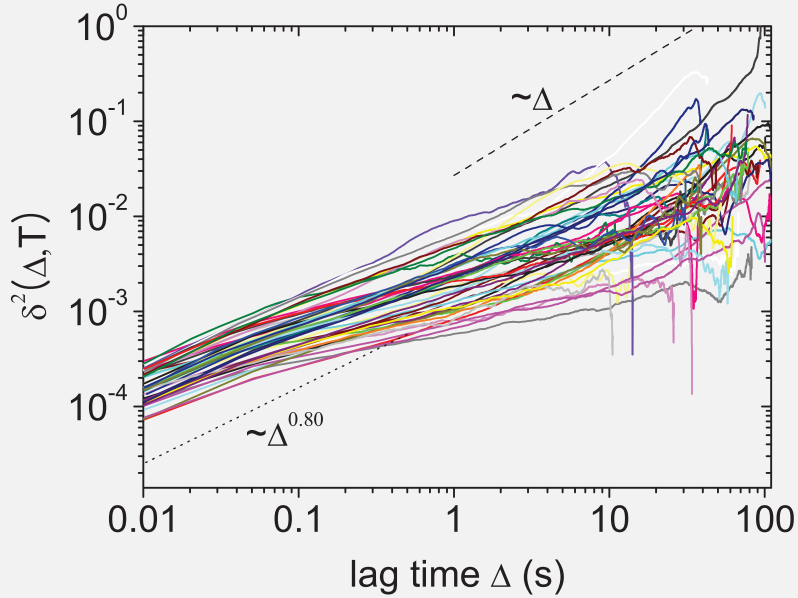


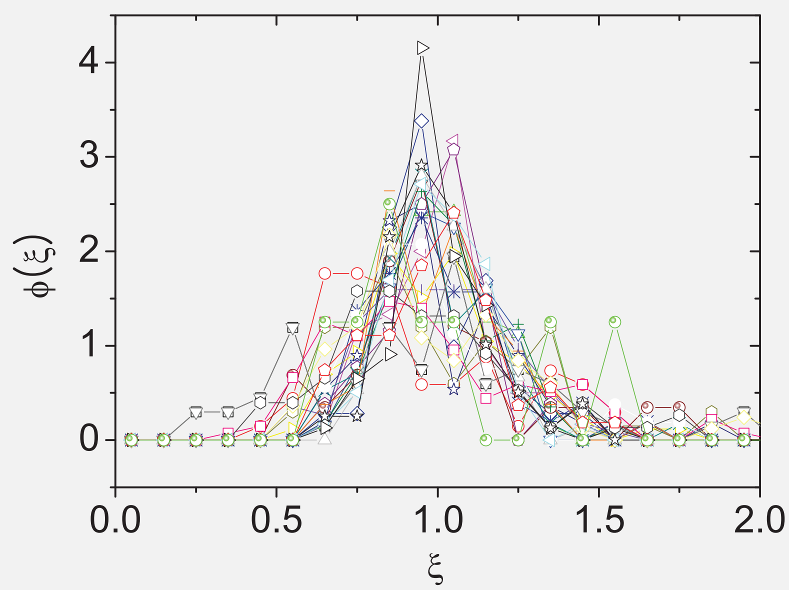
JH Jeon, . . . LB Oddershede & RM, PRL (2011)

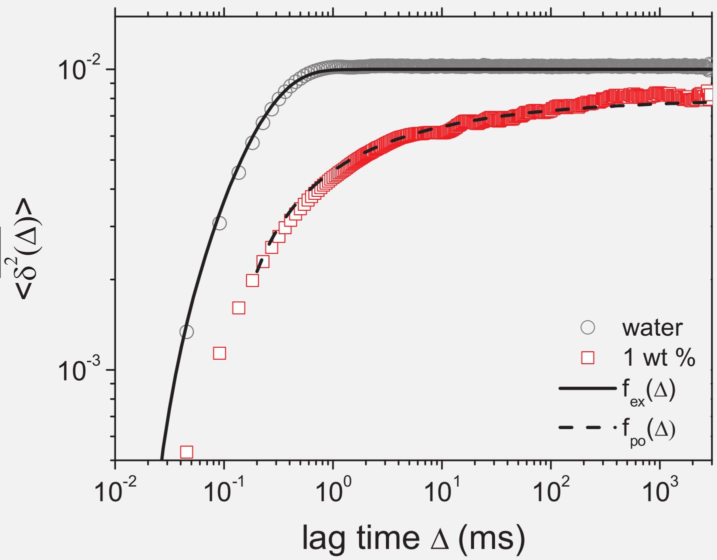


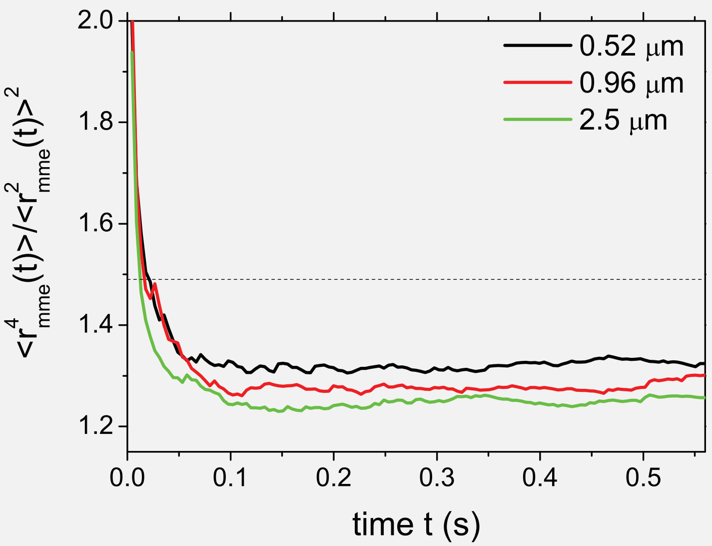
J Reverey, . . . RM & C Selhuber-Unkel, Sci Rep (2015)

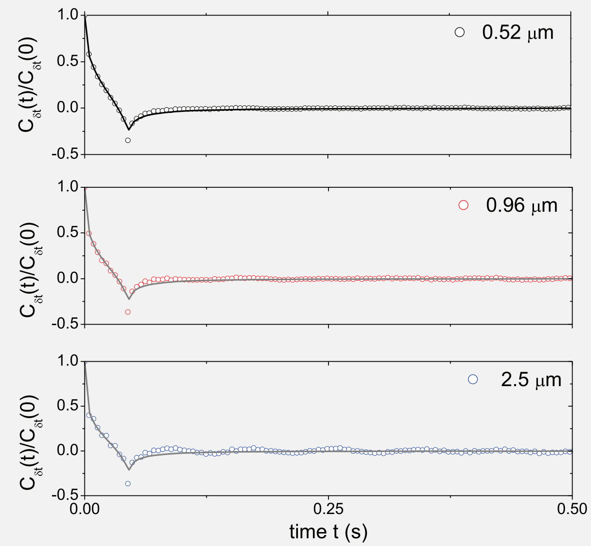
Passive motion of submicron tracers is viscoelastic





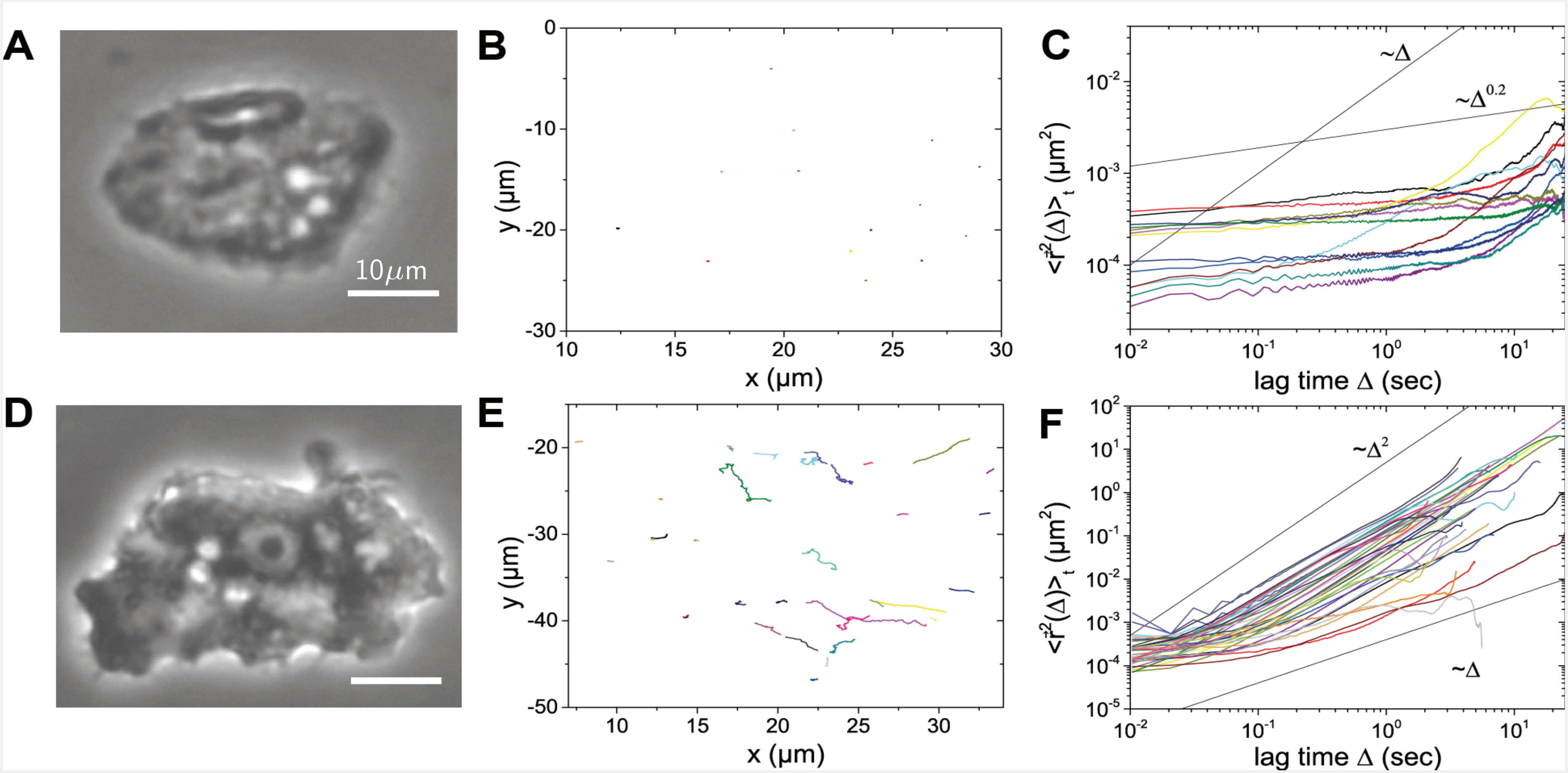






JH Jeon, . . . L Oddershede & RM, PRL (2011); JH Jeon, N Leijnse, L Oddershede & RM, NJP (2013)

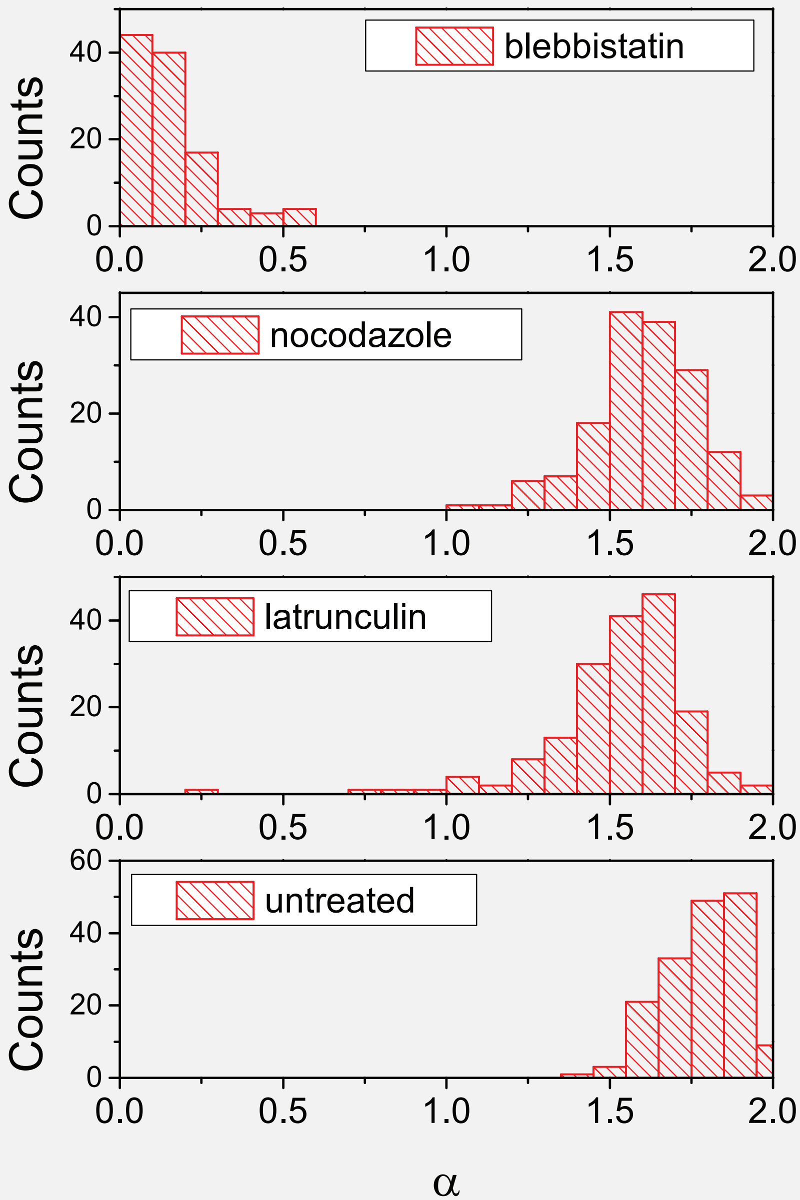
Superdiffusion in living Acanthamoeba castellani



Blebbistatin treated cells: A-C right after treatment; D-F 1 h after treatment

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

Superdiffusion in living Acanthamoeba castellani



inhibits myosin II motors

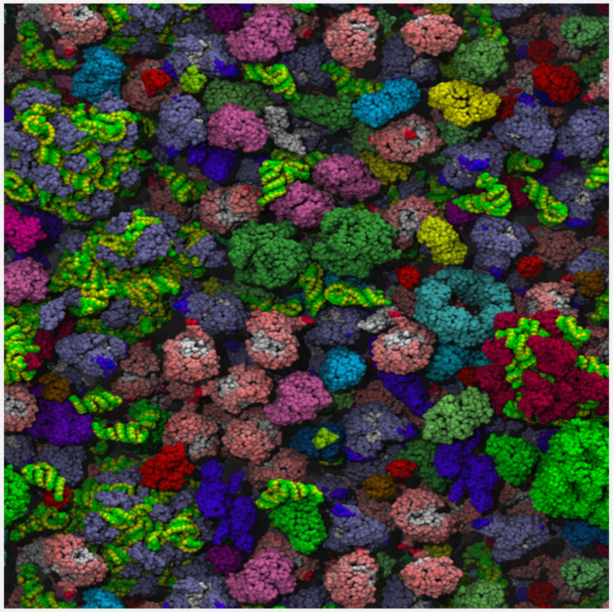
depolymerises microtubules

inhibits actin polymerisation

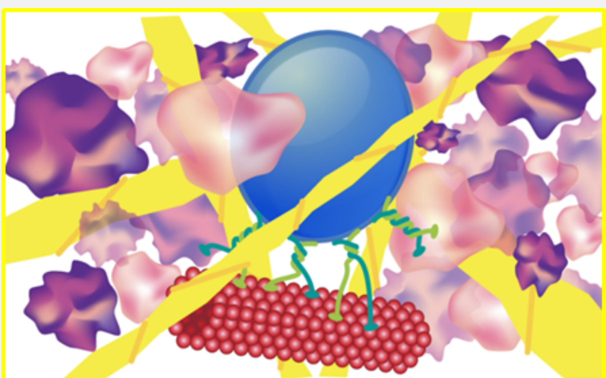
↷ motors cause superdiffusion

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

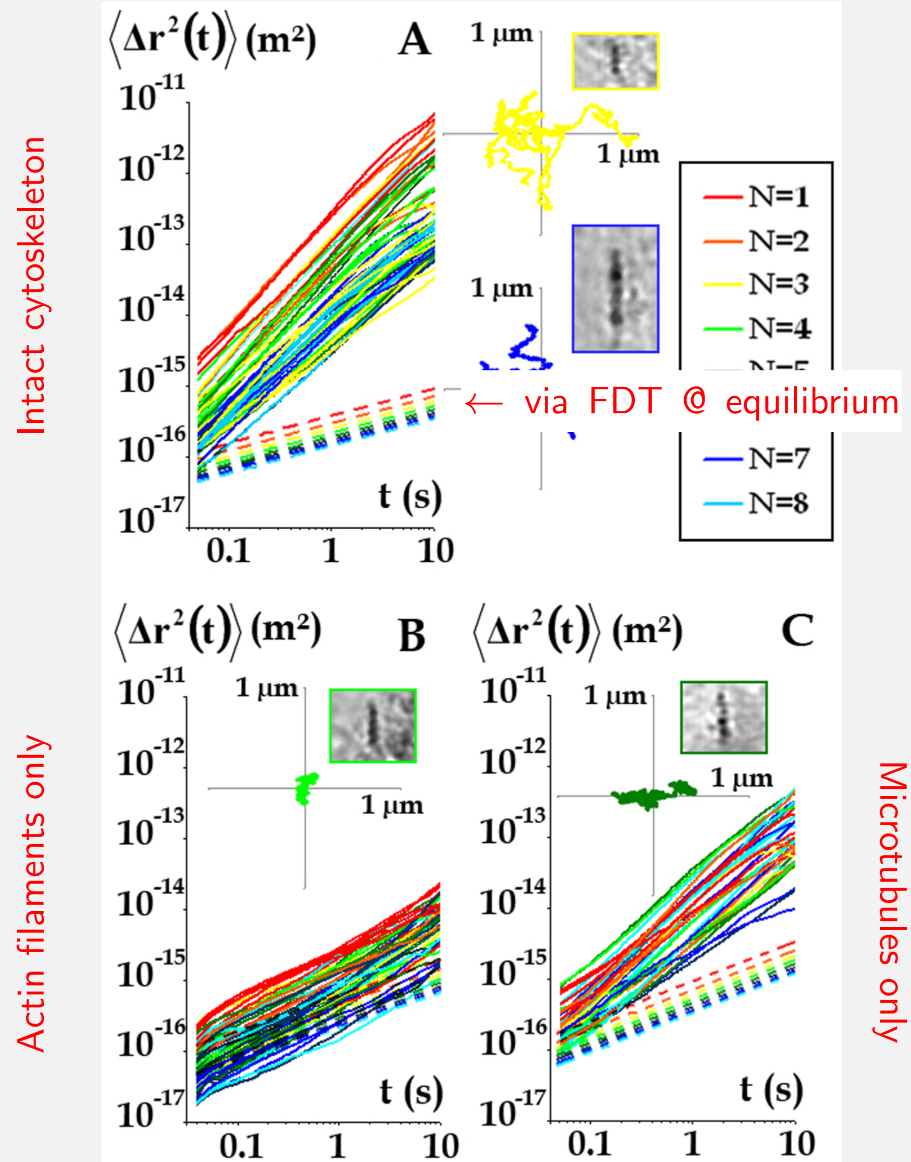
Molecular motor transport in living biological cells



SR McGuffee & AH Elcock, PLoS Comp Biol (2010)



Courtesy S Granick



D Robert, TH Nguyen, F Gallet & C Wilhelm, PLoS Comp Biol (2010)

Molecular motor transport in living biological cells

Experimentally established:

Passive subdiffusion

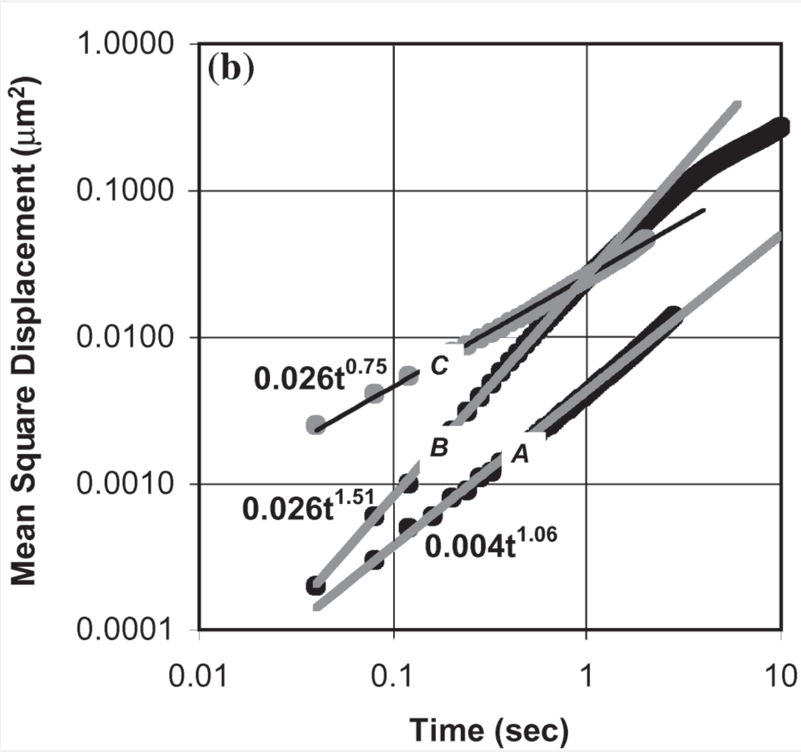
$$\langle \delta \mathbf{r}^2(t) \rangle = \langle \mathbf{r}(\mathbf{t})^2 \rangle - \langle \mathbf{r}(t) \rangle^2 \simeq t^\alpha$$

with $0 < \alpha < 1$

Active superdiffusion

$$\langle \delta \mathbf{r}^2(t) \rangle = \simeq t^\beta, \quad 1 < \beta < 2$$

Exponents are connected: $\beta = 2\alpha$



A: blebbistatin—no microtubules

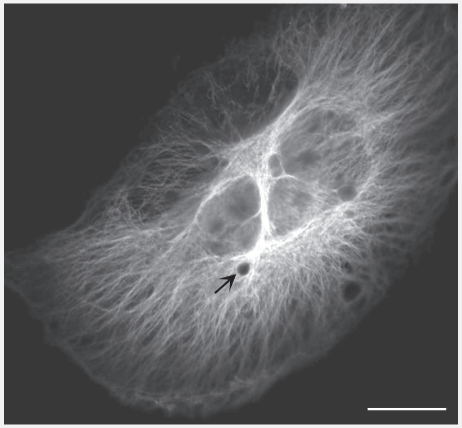
B: motor transport

C: Passive lipid granule motion

A Caspi, R Granek & M Elbaum, PRL (2000)

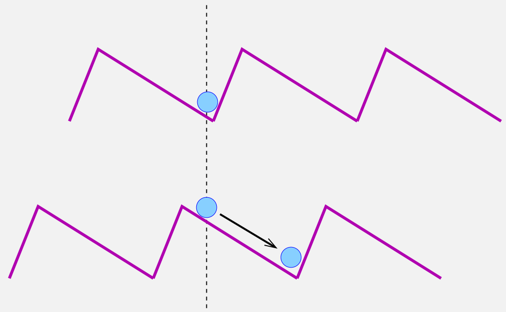
Viscoelastic medium with complex modulus (microrheology):

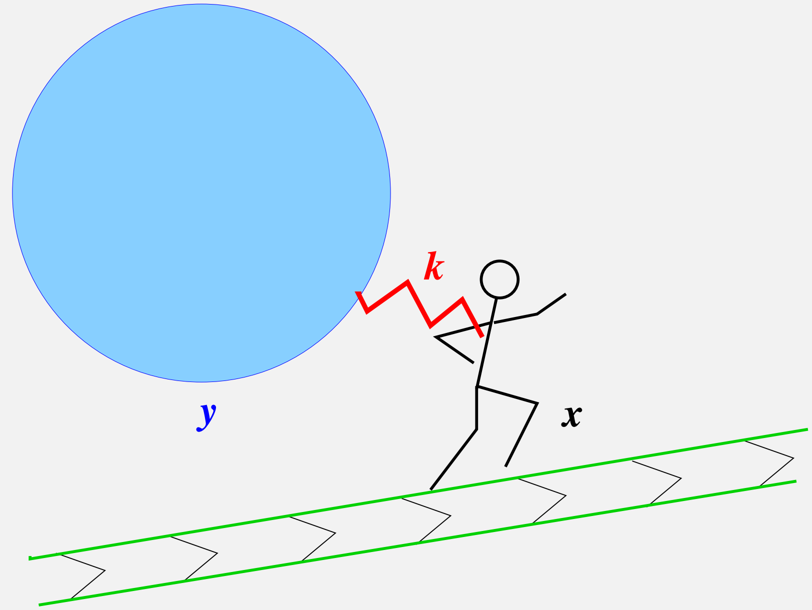
$$G^*(\omega) \simeq (i\omega)^\alpha$$



Molecular motor in crowded viscoelastic environment

x: motor position
y: cargo position
k: spring constant
U: 2-state ratchet
$\zeta(t)$: ratchet config
f_0: external load
$\xi(t), \xi_c(t)$: fGn
$\eta_c(t) \simeq \eta_\alpha / t^\alpha$





Equations of motion:

$$\int_0^t \eta_c(t-t')\dot{y}(t')dt' = -k(y-x) + \xi_c(t)$$

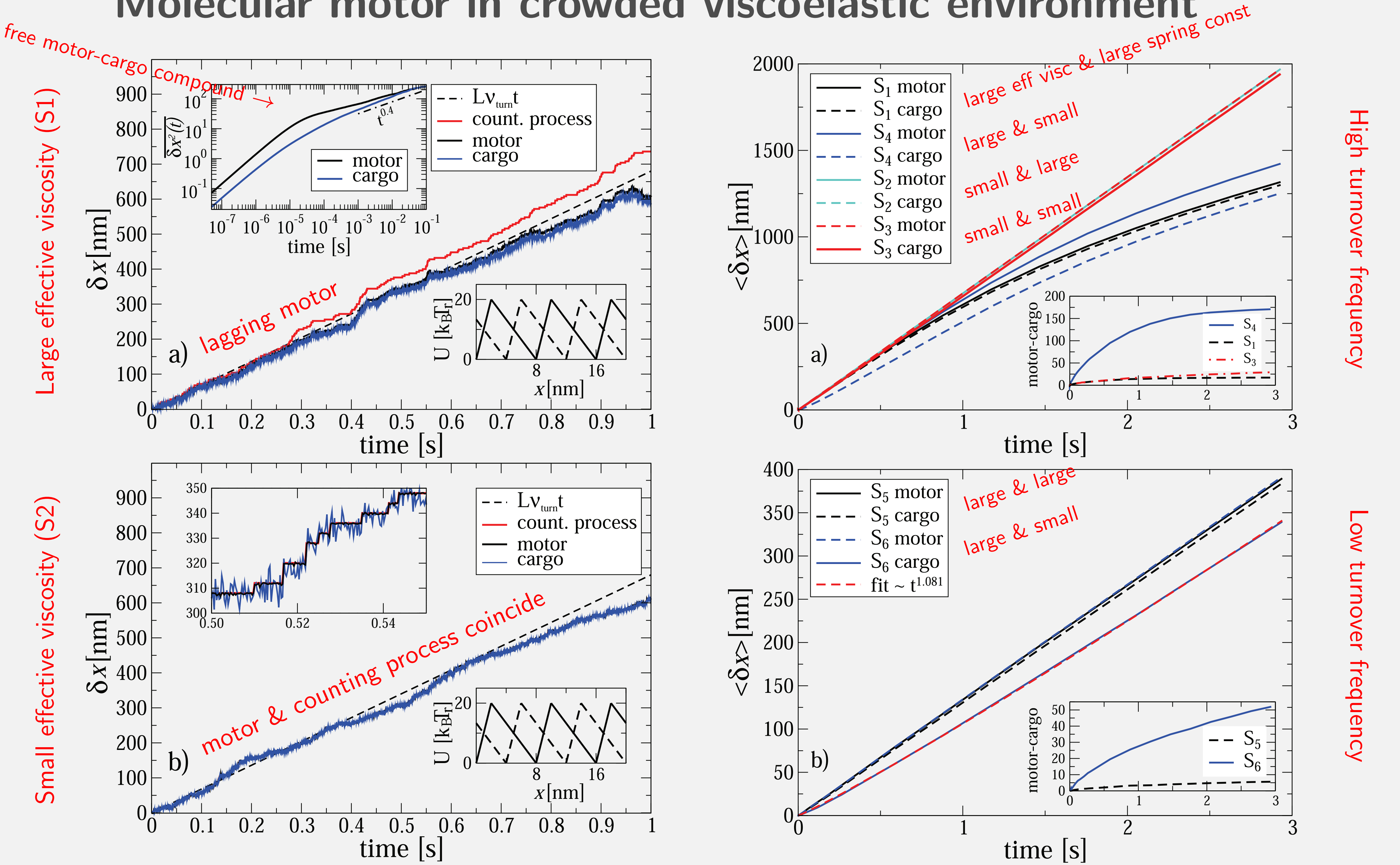
$$\int_0^t \eta(t-t')\dot{x}(t')dt' = k(y-x) - \frac{\partial}{\partial x}U(x,\zeta(t)) - f_0 + \xi(t)$$

Free cargo motion ($D_c = k_B T/\eta_c$ & $D_\alpha = k_B T/\eta_\alpha$):

$$\langle y^2(t)\rangle = 2D_c t E_{1-\alpha,2}\left(-\left[\frac{t}{\tau_{\rm in}}\right]^{1-\alpha}\right) \simeq \begin{cases} 2D_c t, & t \ll \tau_{\rm in} \\ 2D_\alpha t^\alpha/\Gamma(1+\alpha), & t \gg \tau_{\rm in} \end{cases}$$

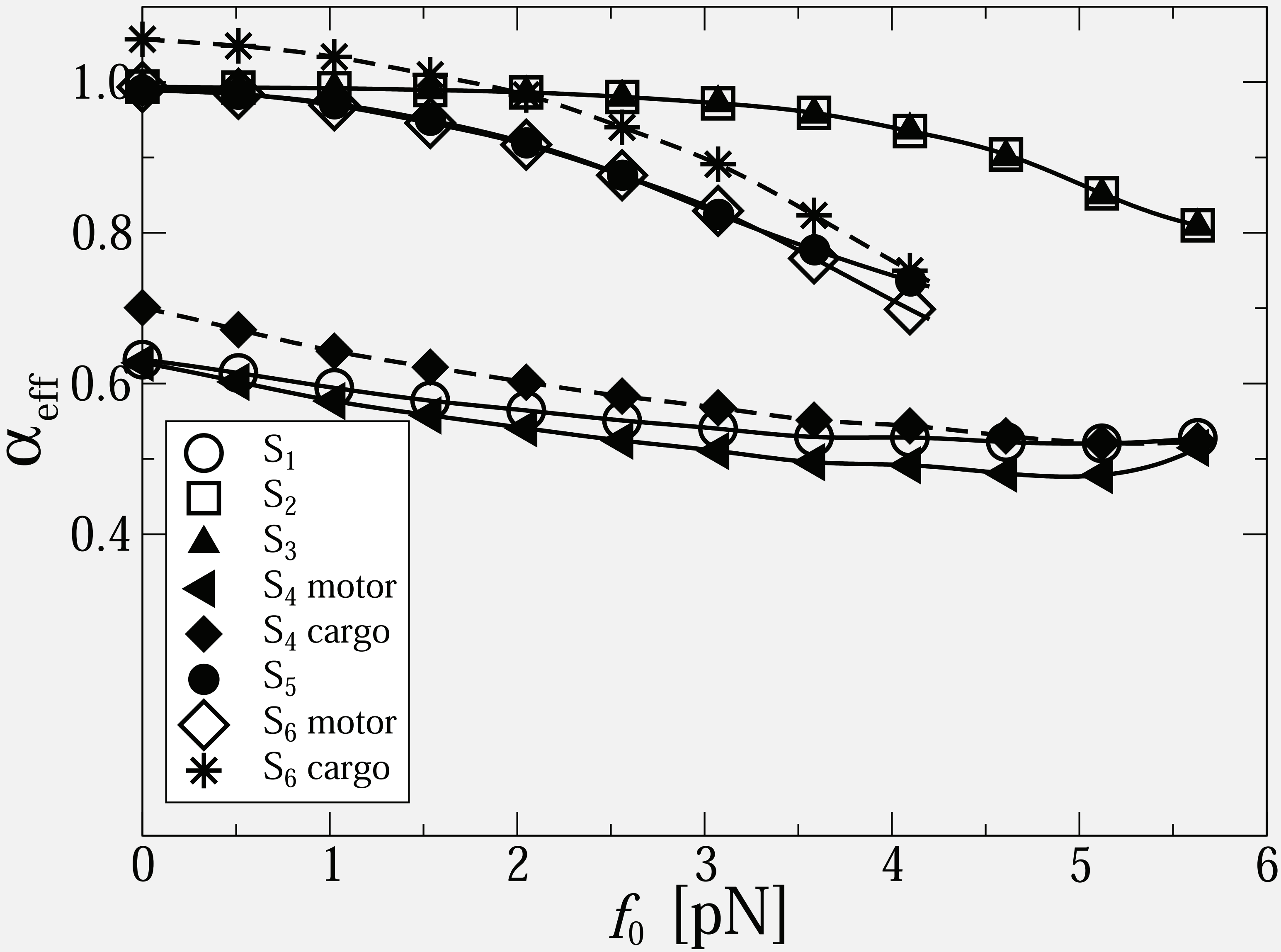
I Goychuk, VO Kharchenko & RM, PLoS ONE (2014); PCCP (2014)

Molecular motor in crowded viscoelastic environment

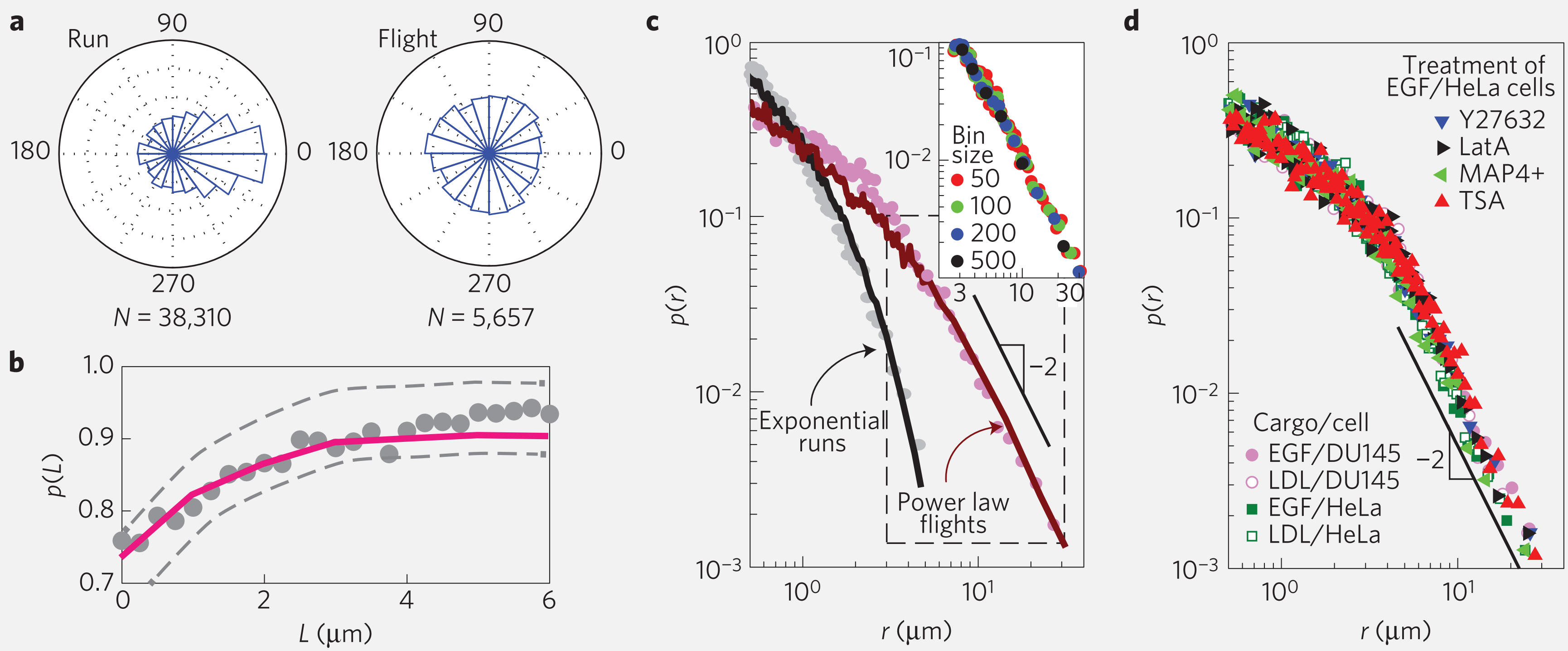


I Goychuk, VO Kharchenko & RM, PLoS ONE (2014); PCCP (2014)

Molecular motor in crowded viscoelastic environment



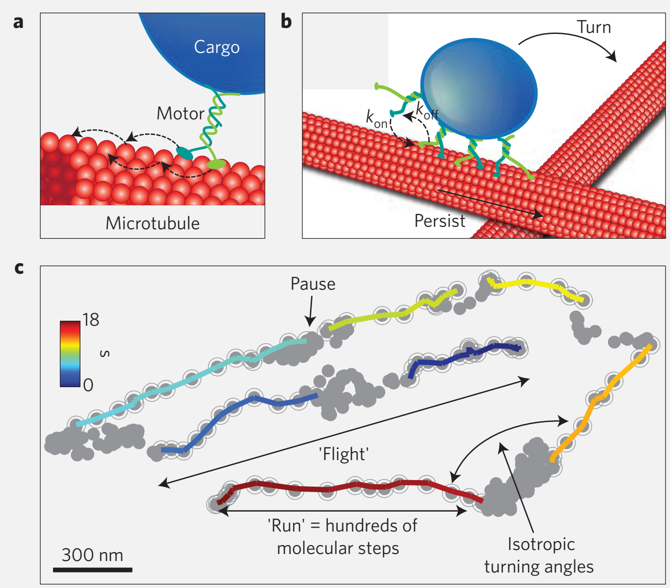
Lévy walks of molecular motors in living cells



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

Flight: consecutive runs persisting in direction

↷ search optimisation



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

Ultraweak ergodicity breaking of Lévy walks

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

Time averaged MSD

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

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

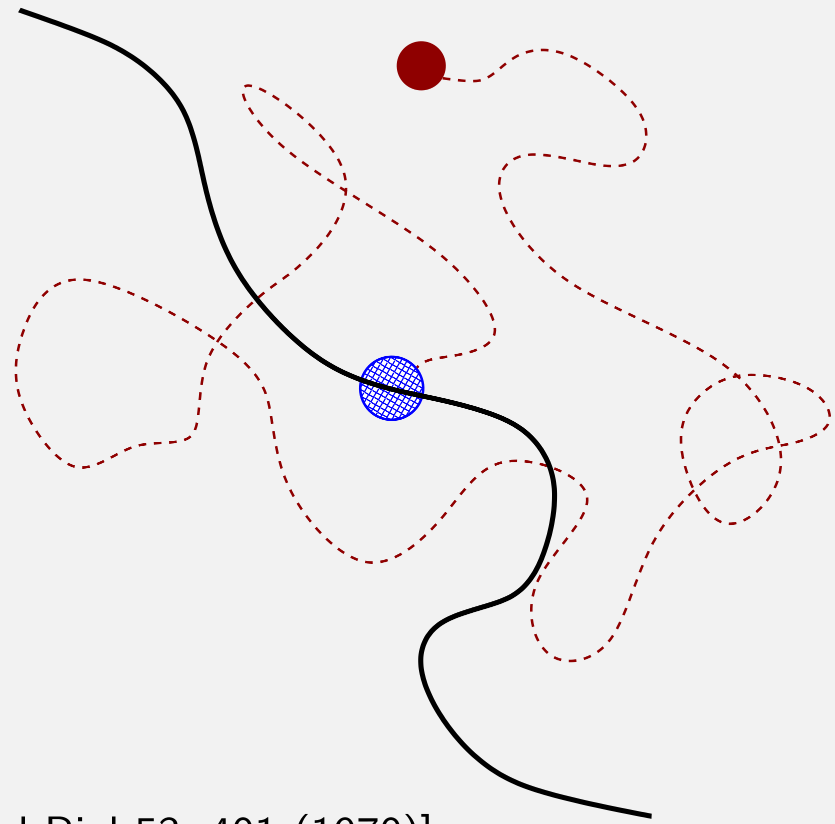
Linear response for constant external force f $(0<\alpha<2)$:

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

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

Single particle tracking on macroscopic scales

Smoluchowski search picture: a centenary



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 $\varnothing_{\mathrm{TF}} \approx 5\text{nm}$):

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

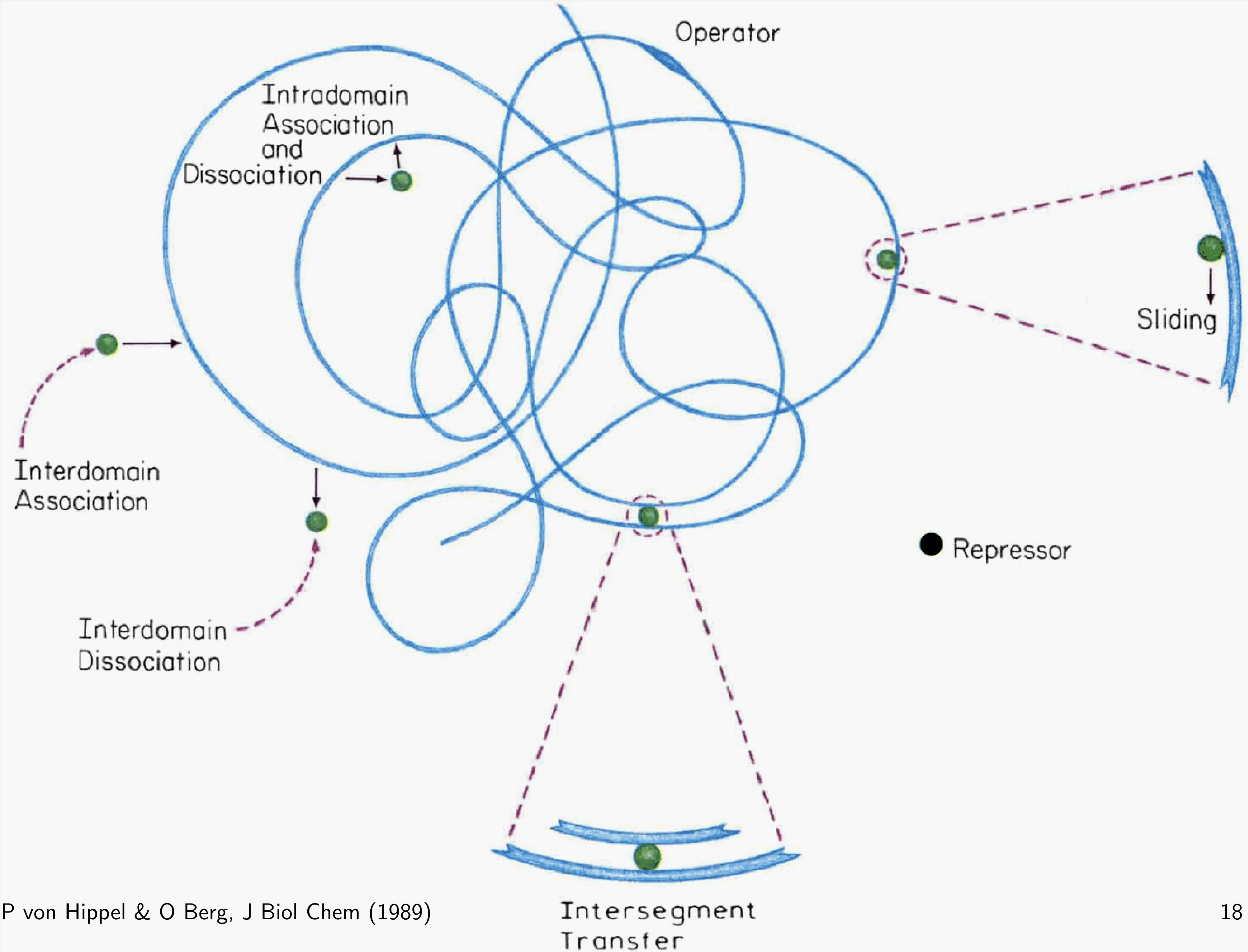
Lac repressor [AD Riggs, S Bourgeois, M Cohn, J Mol Biol 53, 401 (1970)]:

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

$\rightarrow$ Facilitated diffusion picture

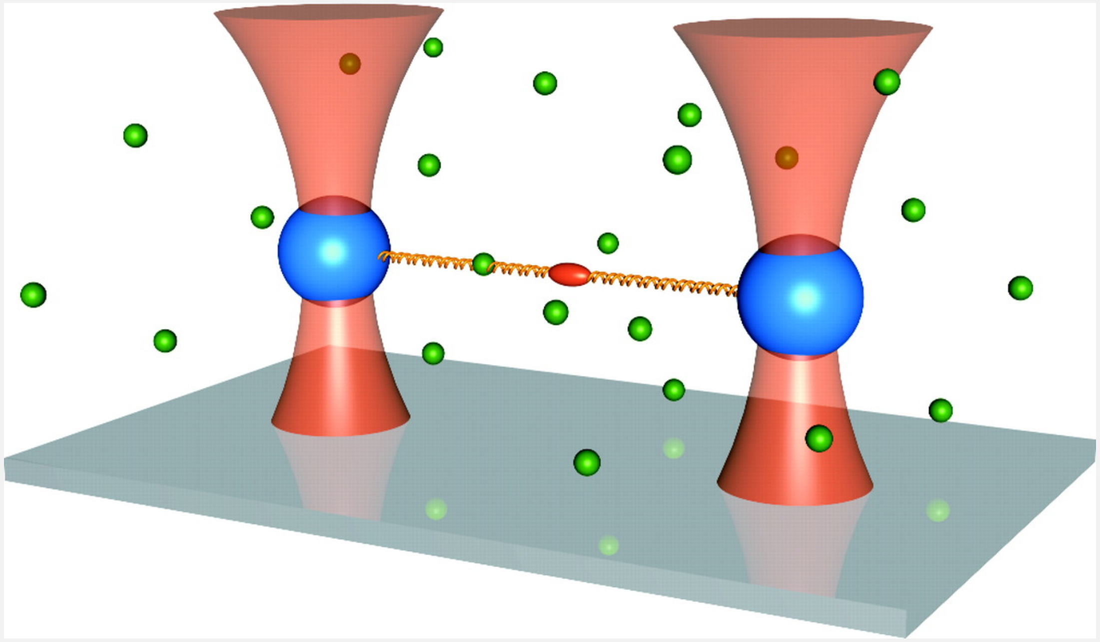
M v Smoluchowski, Physikal. Zeitschr. (1916); P von Hippel and O Berg, J Biol Chem (1989)

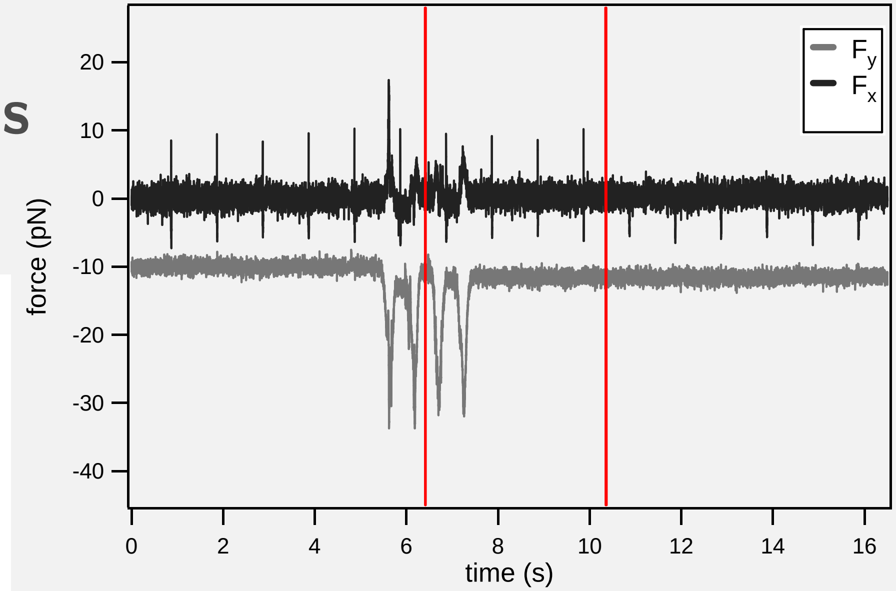
Facilitated diffusion: the Berg-von Hippel model

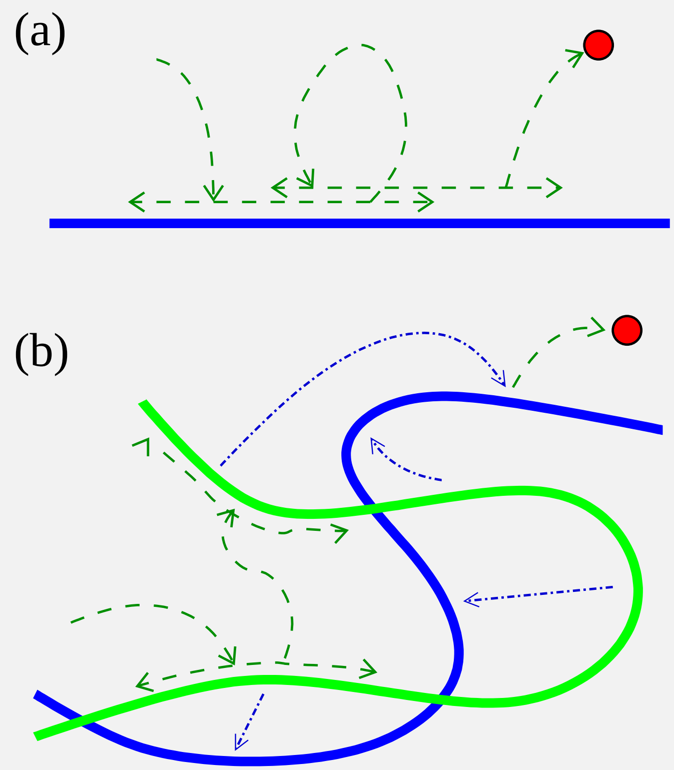


P von Hippel & O Berg, J Biol Chem (1989)

The rôle of DNA conformations







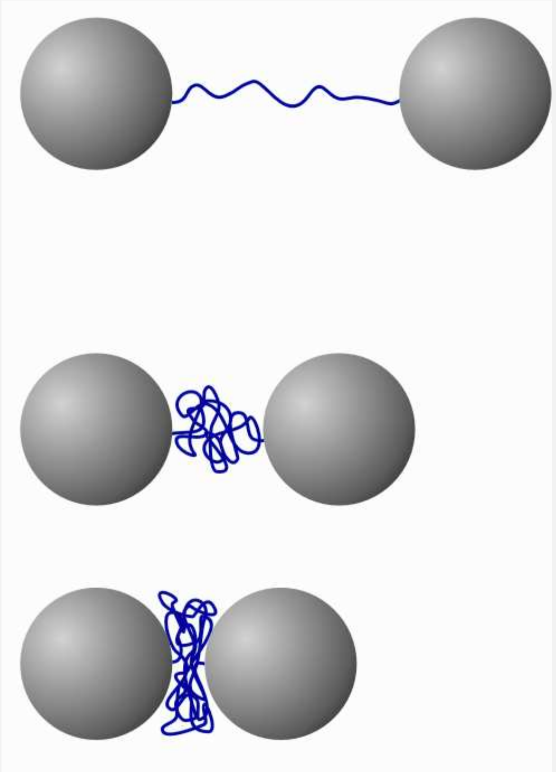
pCco5 plasmid DNA: 6538bp $\approx 2.2\mu$m $\approx 45\ell_p$

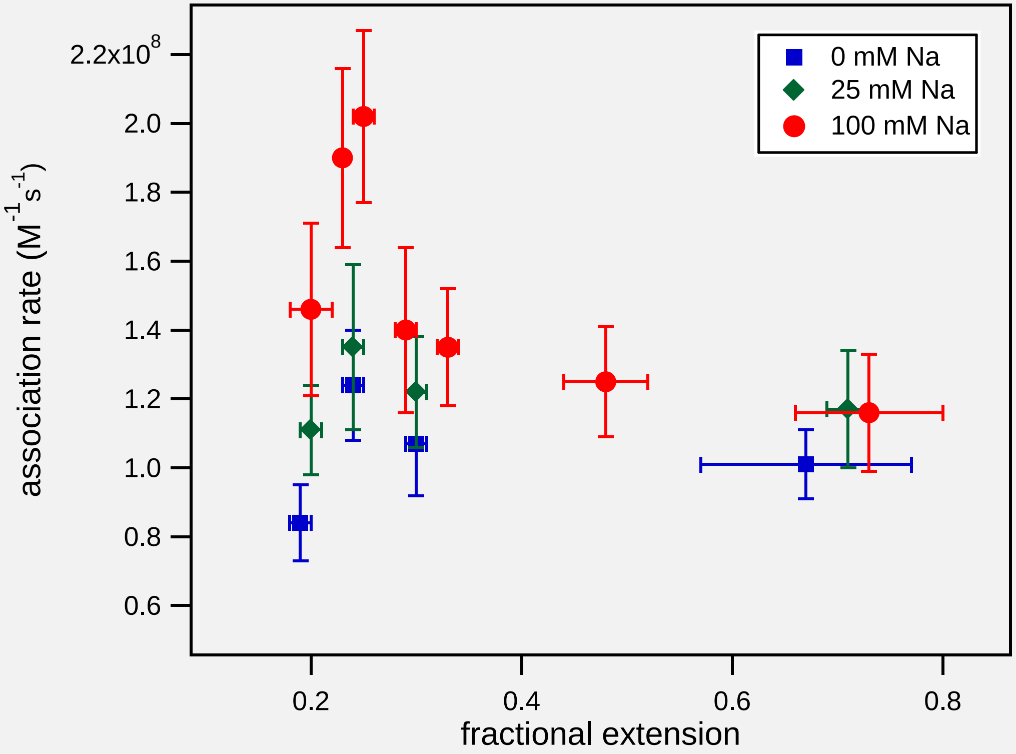
[comp λ DNA 48.5kbp]

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

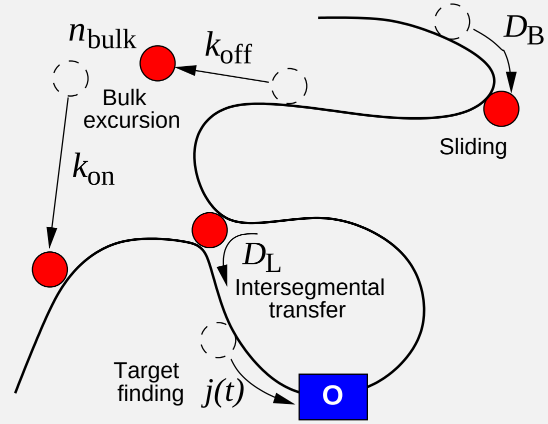
$R = k_{\text{on}}^{\text{max}}/k_{\text{on}}^{\text{straight}}$: enhancement ratio of attachment rates @ max and straight configuration)

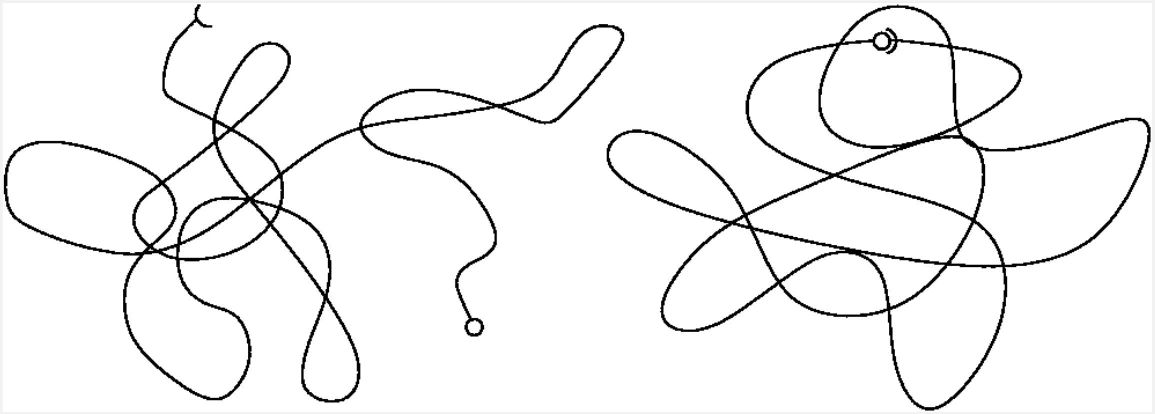




MA Lomholt, B van den Broek, S-M Kalisch, GJL Wuite & RM, PNAS (2009)

Length stored in a polymer loop



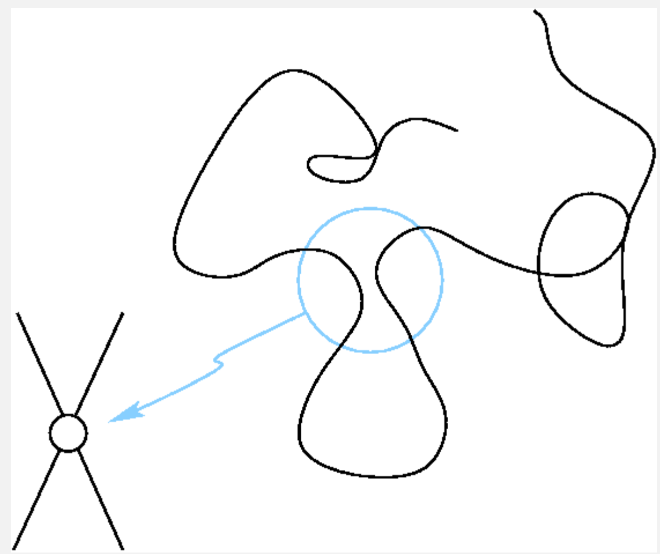


Cyclization is returning random walk ($t \div \ell$):

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

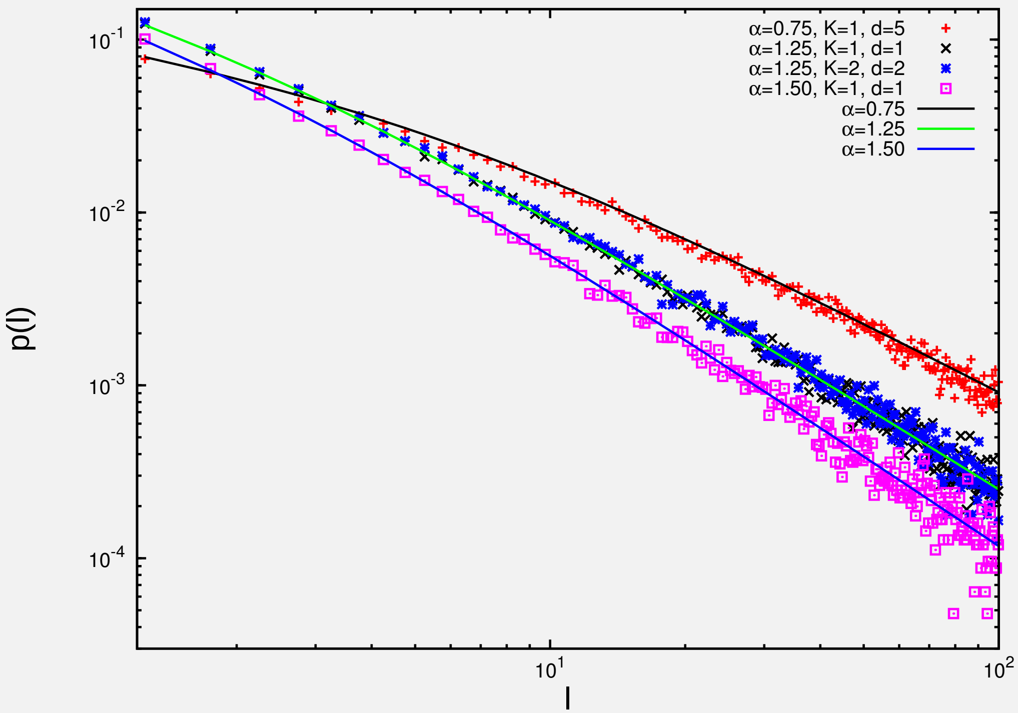
Probability for contact is more restrictive:

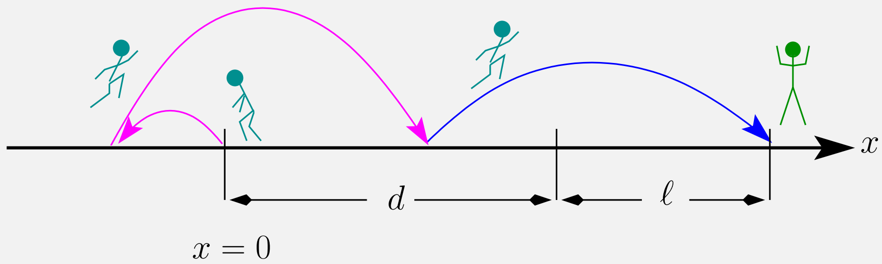
$$p(\ell) \sim \ell^{-d\nu+\sigma_4} \sim \ell^{-1-1.2} \quad \curvearrowright \langle \ell^2 \rangle \to \infty$$



J des Cloizeaux & G Jannink, Polymers in Solution (1990); B Duplantier, J Stat Phys (1989); Exptl ν: F Valle et al, PRL (2005)

Overshooting the target: Leapovers





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

$$\wp_{\mathrm{fp}}(\tau) \sim \frac{d^{\alpha/2}}{\alpha\sqrt{\pi K^{(\alpha)}}\Gamma(\alpha/2)}\tau^{-3/2}$$ 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)

Optimal target search *in vitro*

Lévy flight comp /w $\lambda(x) \simeq |x|^{-1-\alpha} \therefore \alpha = 1.2$ (3D SAW) $\wedge\ \alpha = 0.5$ (3D RW):

$$\frac{\partial}{\partial t}n(x,t) = \left(D_{\mathrm{B}}\frac{\partial^2}{\partial x^2} + D_{\mathrm{L}}\frac{\partial^\alpha}{\partial|x|^\alpha} - k_{\mathrm{off}}\right)n(x,t) + k_{\mathrm{on}}n_{\mathrm{bulk}} - j(t)\delta(x)$$

Relevant time scales: unbinding: k_{off}^{-1}

turnover between diffusion mechanisms:

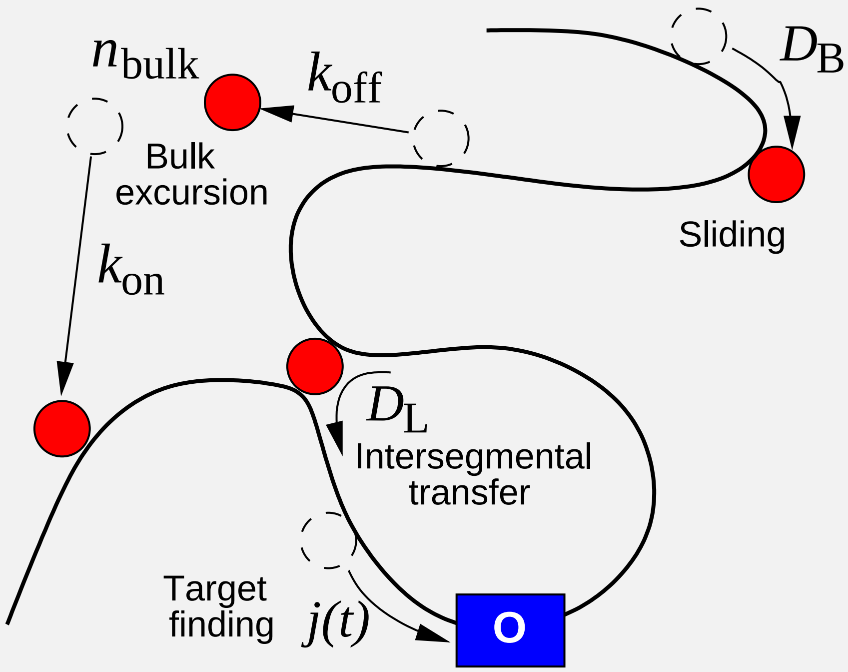
$\tau_{\mathrm{BL}} \equiv \left(D_{\mathrm{B}}^\alpha/D_{\mathrm{L}}^2\right)^{1/(2-\alpha)}$ diffusion

Number of absorbed particles:

$$J(t) = \int_0^t j(t')dt'$$

Survival of target site (N =protein number):

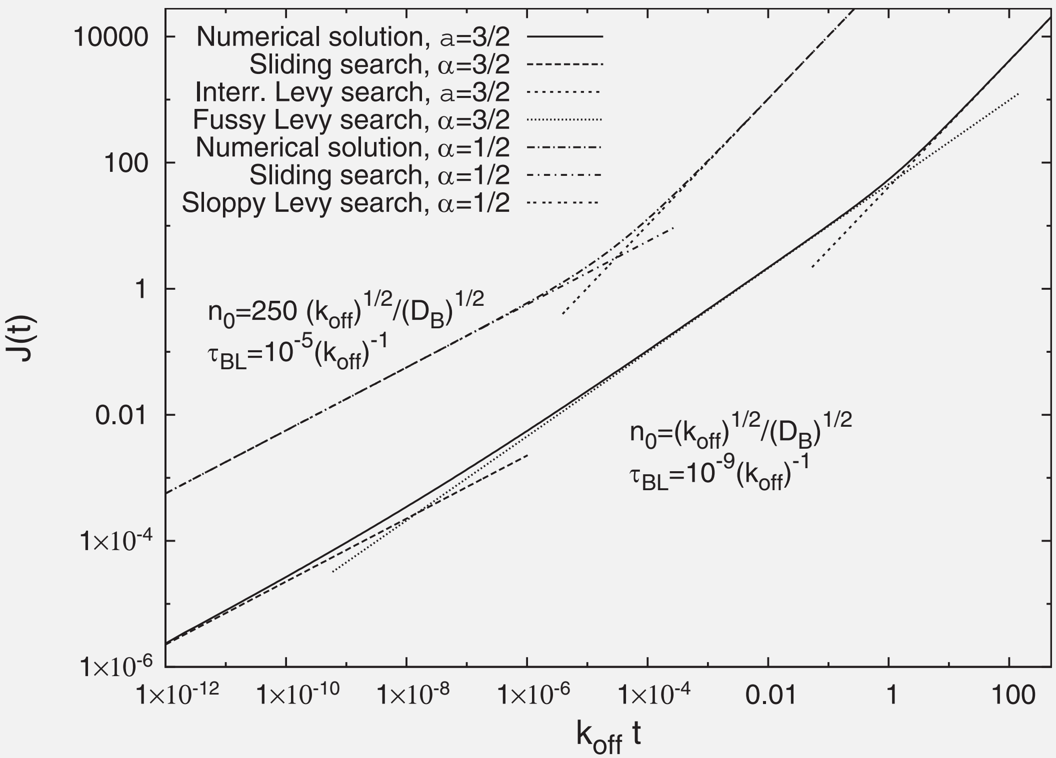
$$\begin{aligned} P_{\mathrm{surv}}(t) &= (1 - J(t)/N)^N \\ &\to \exp\{-J(t)\} \end{aligned}$$



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

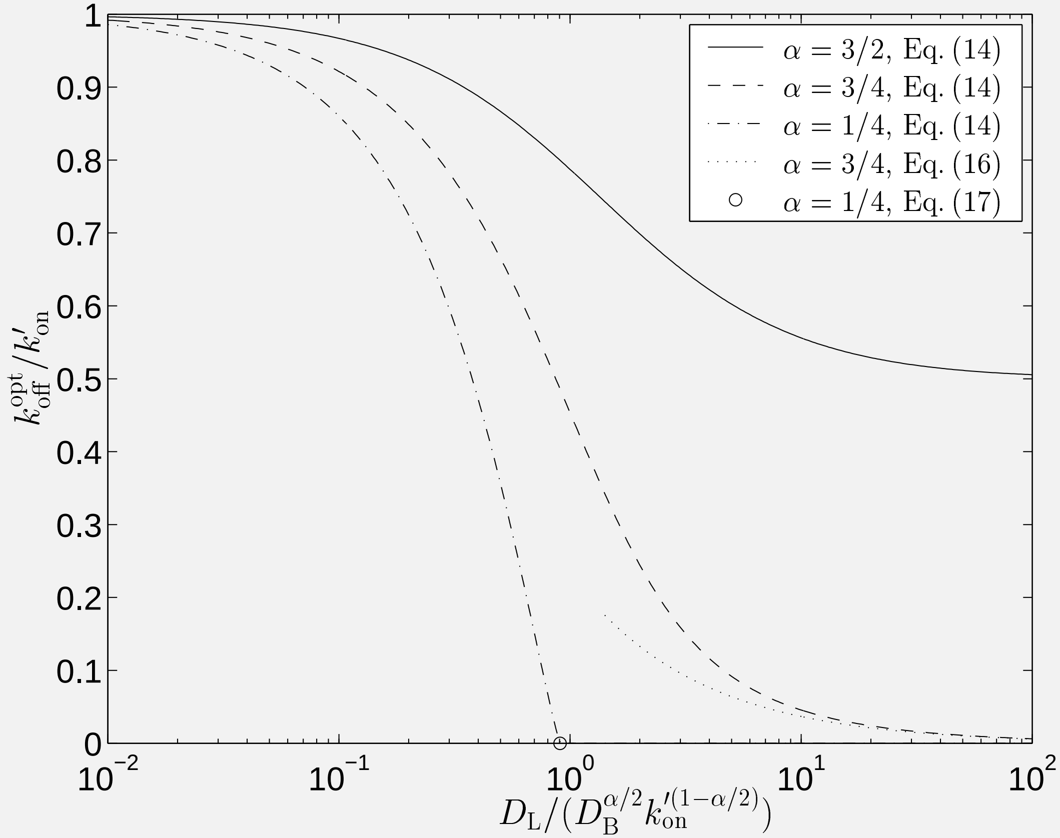
Optimal target search *in vitro*

Regime	$0 < \alpha < 1$	$1 < \alpha < 2$	$J \sim (t/\tau_i)^{\gamma_i}$
$t \ll \{\tau_{\rm BL}, k_{\rm off}^{-1}\}$	Sliding	Sliding	$\gamma_1 = 1/2$
$\tau_{\rm BL} \ll t \ll k_{\rm off}^{-1}$	Sloppy Lévy	Fussy Lévy	$\gamma_3 = 1 \,\vert\, \gamma_2 = \alpha^{-1}$
$\tau_{\rm BL} \ll k_{\rm off}^{-1} \ll t$	Sloppy Lévy	Int. Lévy	$\gamma_3 = 1 \,\vert\, \gamma_4 = 1$
$\{t, \tau_{\rm BL}\} \gg k_{\rm off}^{-1}$	Int. Sliding	Int. Sliding	$\gamma_5 = 1$



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

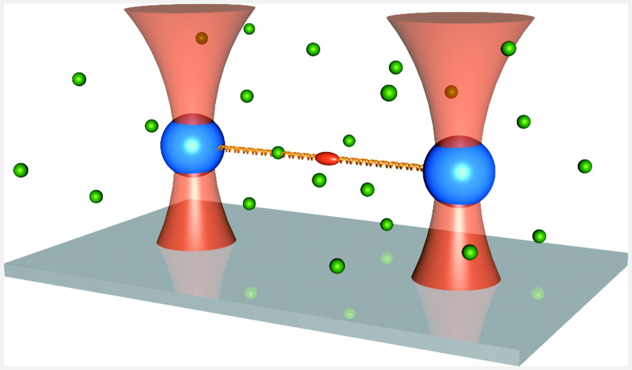
Relative time spent in bulk



Frequency of intersegmental transfer events

Regime	$1 < \alpha < 2$	$0 < \alpha < 1$
$D_{\mathrm{L}} \to 0$	$k_{\mathrm{off}}^{\mathrm{opt}} = k'_{\mathrm{on}}$	
$D_{\mathrm{L}} \to \infty$	$k_{\mathrm{off}}^{\mathrm{opt}} = (\alpha - 1)k'_{\mathrm{on}}$	$k_{\mathrm{off}}^{\mathrm{opt}} \to 0,\ D_{\mathrm{L}} \to \infty$, $1/2 < \alpha < 1$ $k_{\mathrm{off}}^{\mathrm{opt}} = 0,\ D_{\mathrm{L}} < \infty$, $0 < \alpha < 1/2$

Spatiotemporal gene regulation by diffusing regulatory proteins

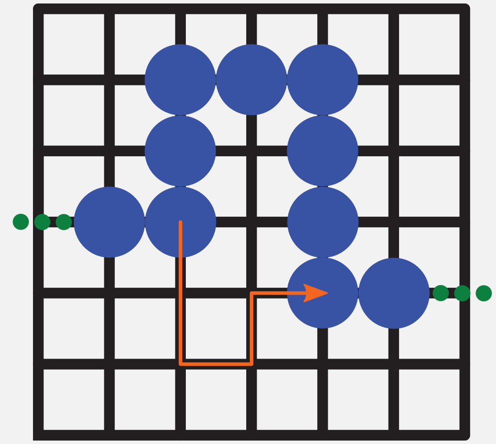


⟵ **DNA conformations**

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

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

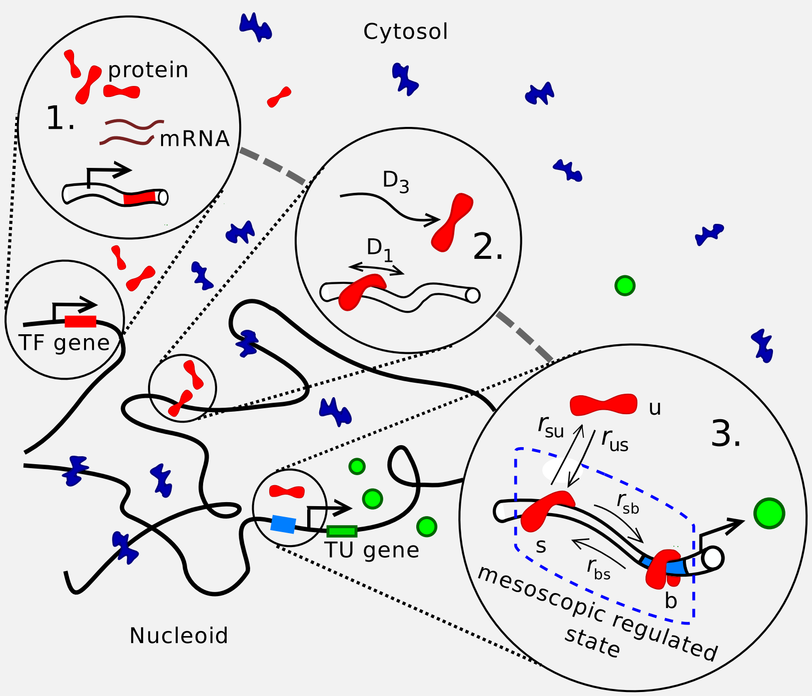
In vivo facilitated diffusion ⟶



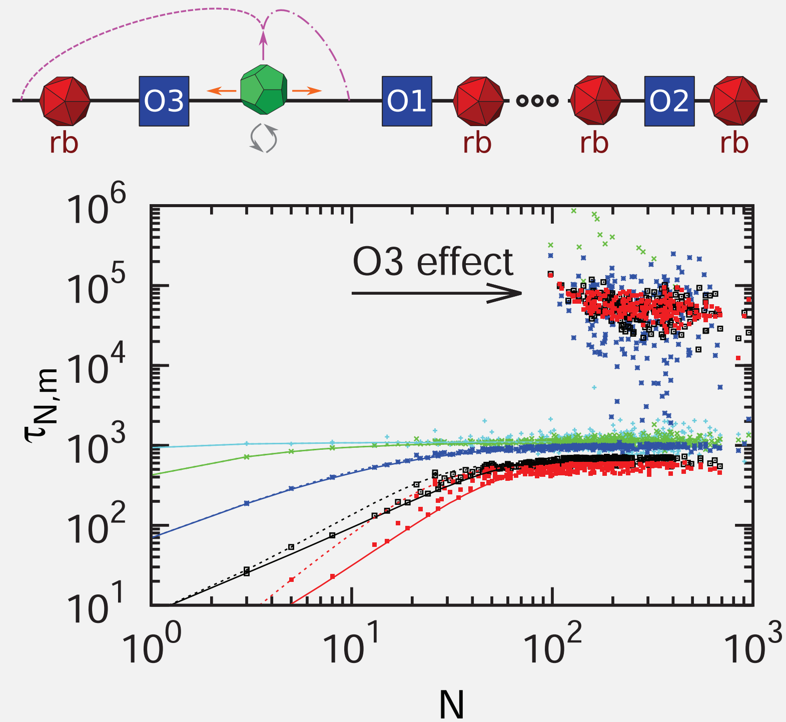
M Bauer & RM, PLoS ONE (2013)

Gene-gene talk: distance matters

O Pulkkinen & RM, PRL (2013)



Real sequence effects



M Bauer & RM, Sci Rep (2015)

Membranes can be supercrowded

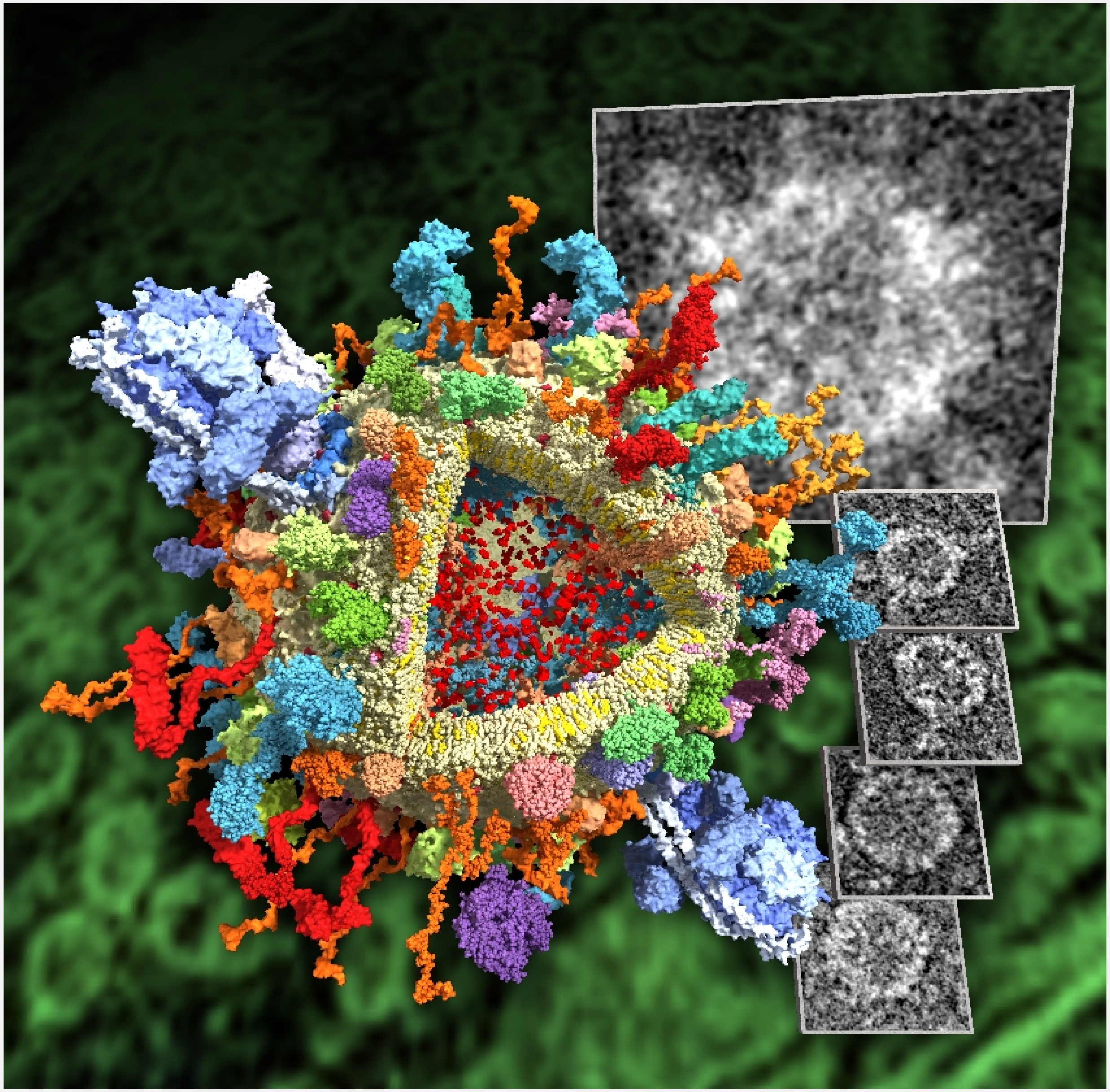
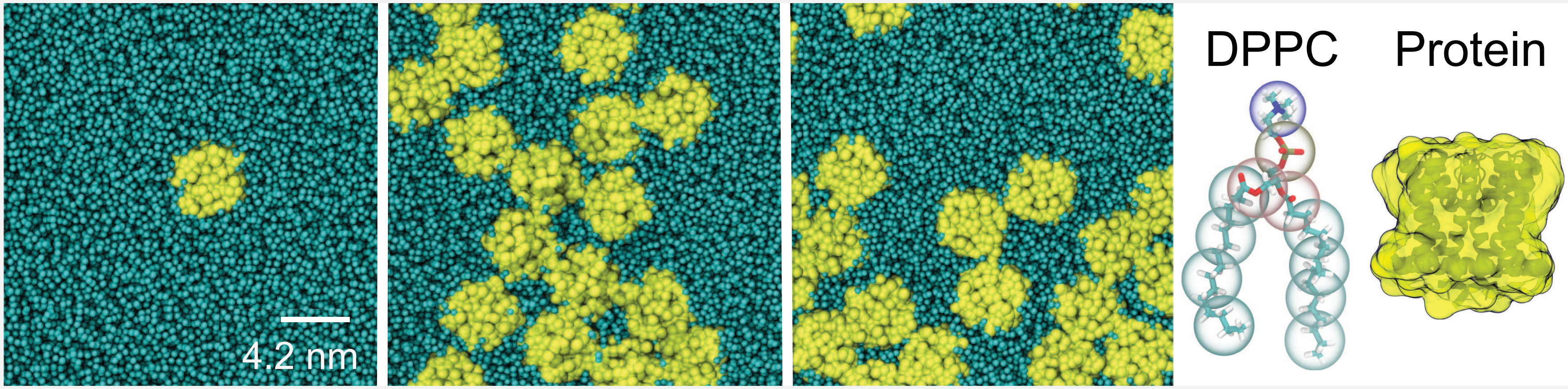
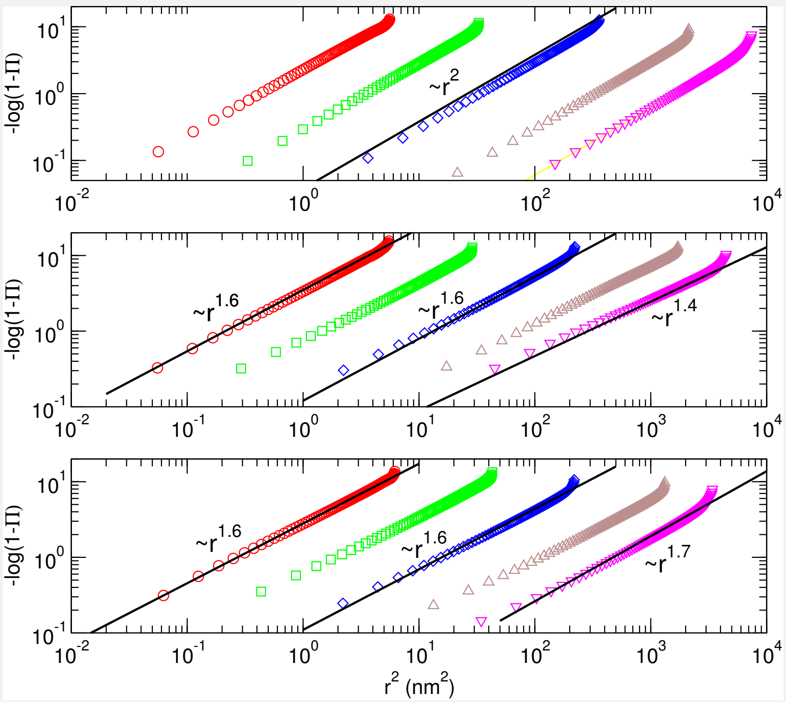


Figure courtesy Helmut Grubmüller

Crowding in membranes: non-Gaussian lipid/protein diffusion

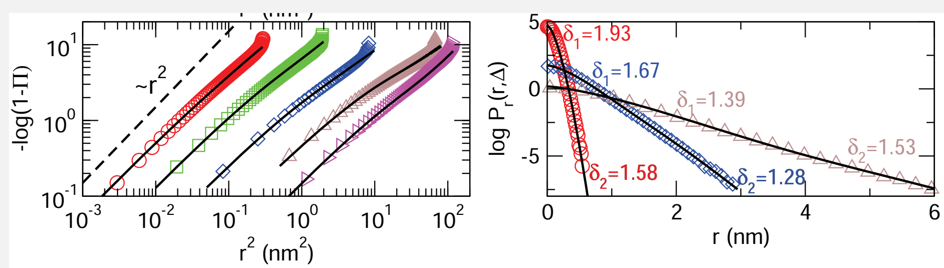




Dilute membrane: $P(r,t)$ Gauss

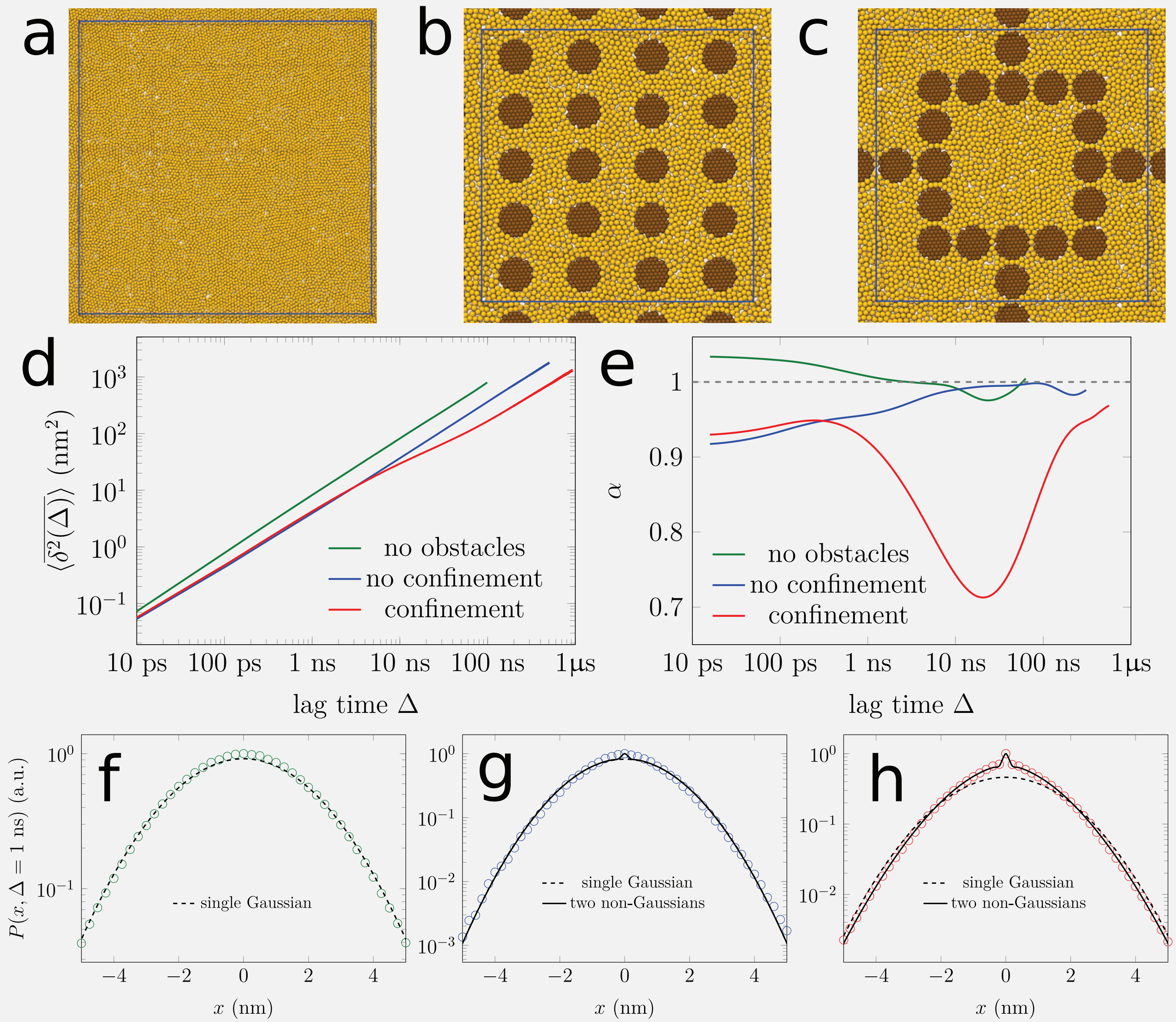
Crowded membrane ($\delta \approx 1.3 \ldots 1.7$):

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



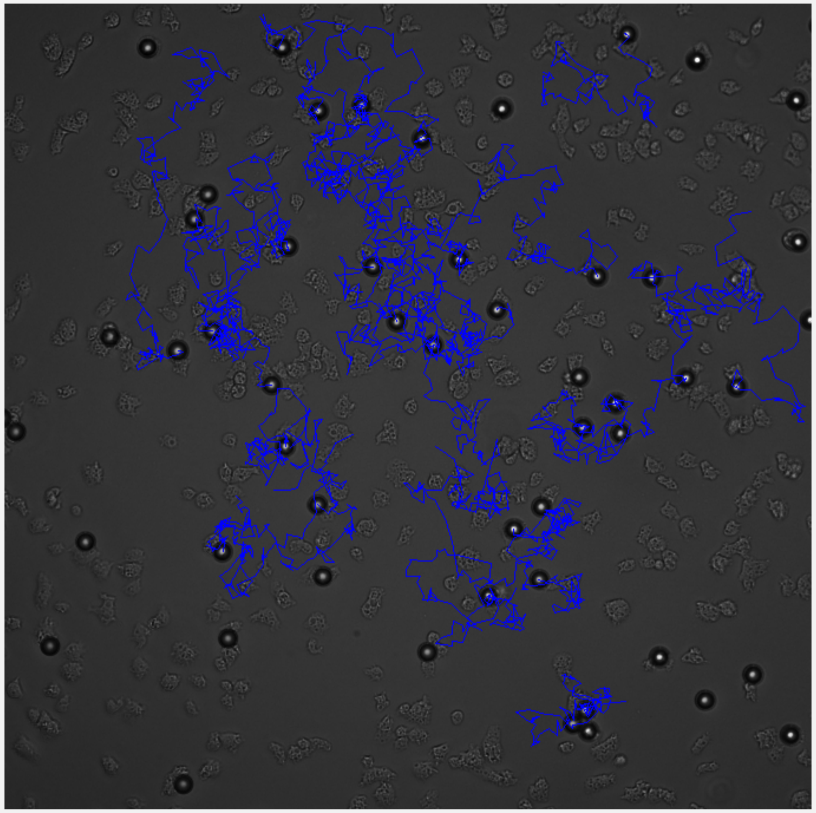
J-H Jeon, M Javanainen, H Martinez-Seara, RM & I Vattulainen, PRX (2016)

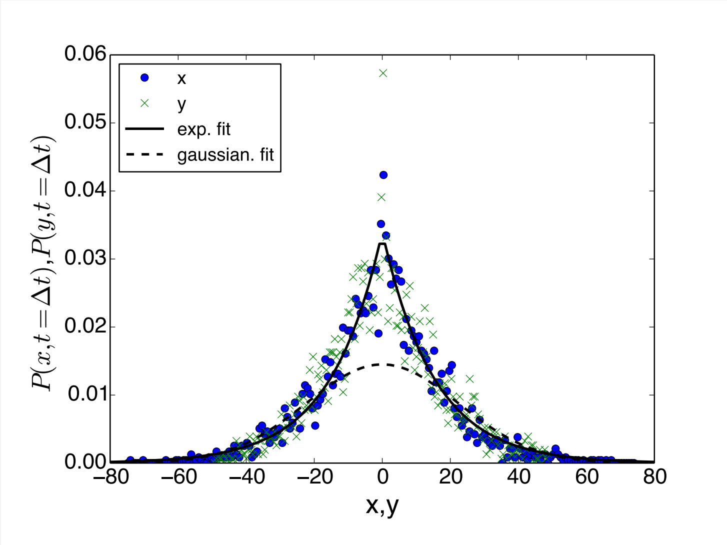
Crowding in membranes: confinement in argon system

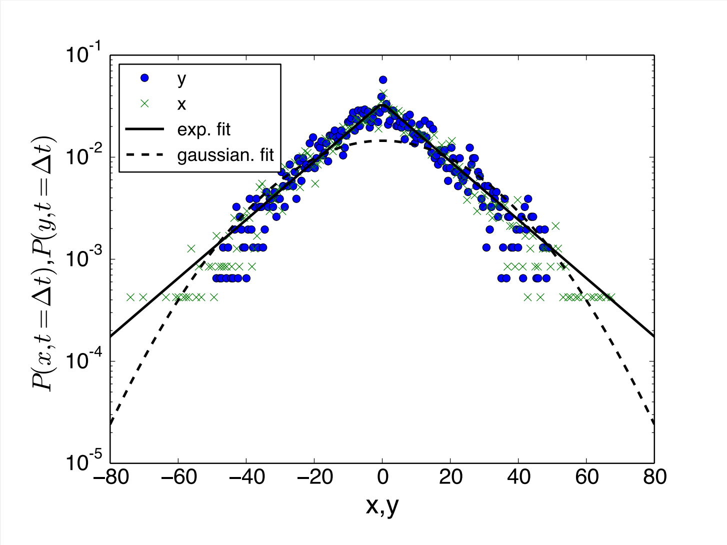


J-H Jeon, M Javanainen, H Seara Monne, I Vattulainen & RM, PRX (2016)

Brownian but not Gaussian diffusion of eukaryotic cells







B Wang, J Kuo, SC Bae & S Granick, Nat Mat (2012). Data: C Beta, UP

Journal of Physics A's new Biological Modelling section

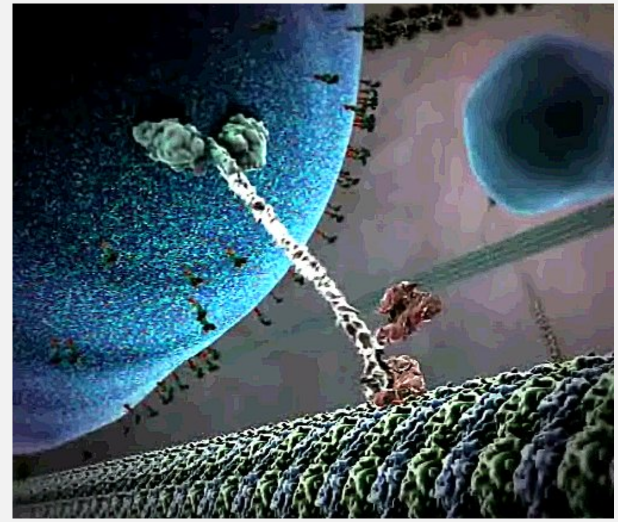
Journal of Physics A
Mathematical and Theoretical

Biological Modelling

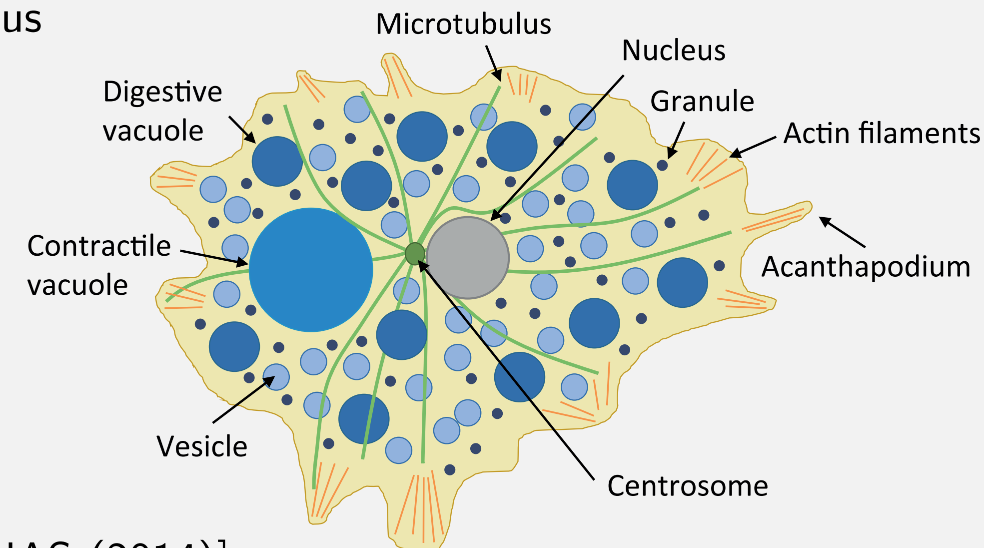
For anything interesting too mathematical for Biophys J, Phys Biol, or J Theoret Biol, or not general enough for PRL or NJP . . .

Suggestions for topical reviews & special issues are welcome

∑ummary



- Cells are crowded (superdense/supercrowded)
- Passive motion of tracers: subdiffusion
- Superdiffusion due to active motion and/or cytoplasmic flow
- Motor-cargo transport: normal or anomalous
- Lévy flights as approximate model in facilitated diffusion
- Optimisation of search process by non-local transfer mechanism
- More on Lévy intermittent search on Vladimir Palyulin's poster [also VV Palyulin, AV Chechkin & RM, PNAS (2014)]



RM, JH Jeon, AG Cherstvy & E Barkai, PCCP (2014); RM, JH Jeon & AG Cherstvy, BBA Biomembranes (2016)

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