Physics & physiology of (anomalous) diffusion

— Potsdam/online, 1st October 2020 —

190+ years after Brown: Microscopical observations

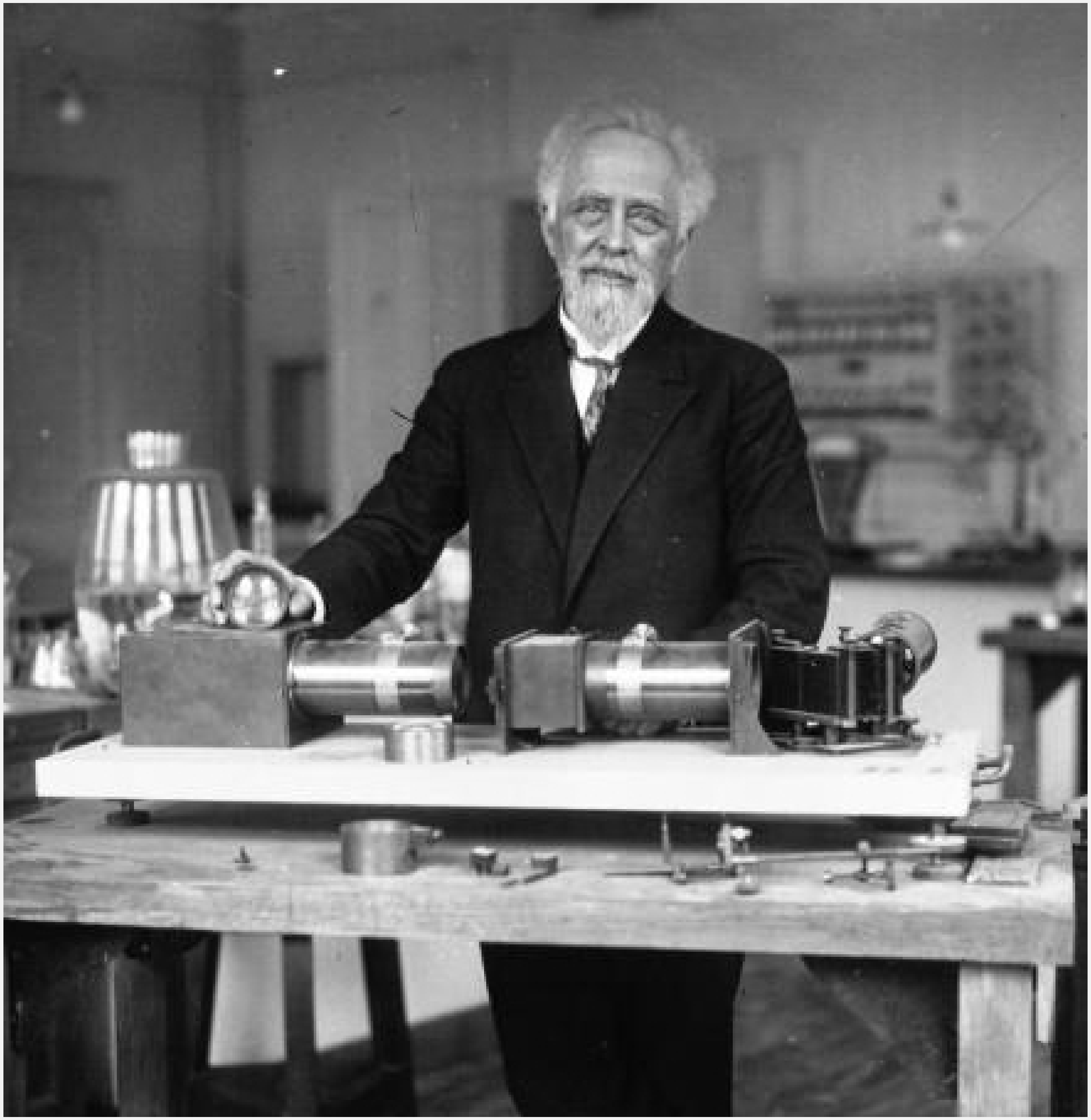
on the particles contained in the pollen of plants; and on the general existence of *active molecules* in organic and inorganic bodies

Grains of pollen, taken from Clarkia pulchella antherae fully grown but before bursting, were filled with particles or granules of unusually large size, varying from nearly 1/4000th to 1/5000th of an inch in length . . .

Rocks of all ages, including those in which organic remains have never been found, yielded the molecules in abundance. Their existence was ascertained in each of the constituent molecules of granite, a fragment of the Sphinx being one of the specimens examined.

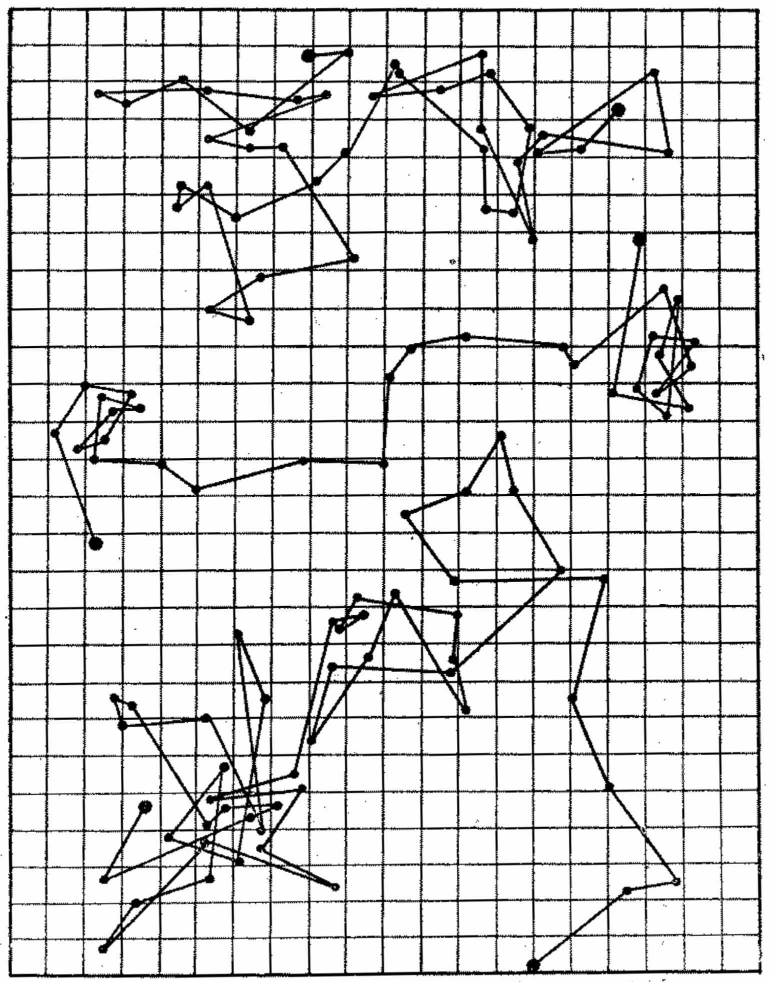
R Brown, Edinburgh new Philosophical Journal 358-371 (1828)

110+ years after Jean Perrin



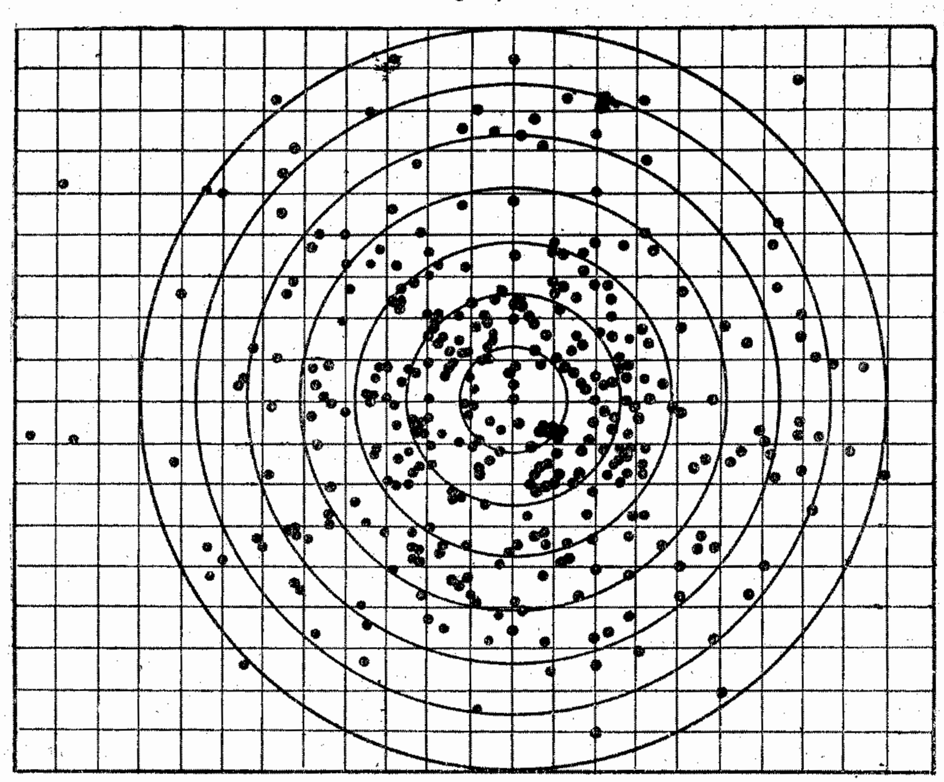
Brownian motion

Fig. 6.



Δt=30 sec

Fig. 7.



$$P(\mathbf{r},\Delta t) = \frac{1}{(4\pi K \Delta t)^{d/2}} \exp\left(-\frac{r^2}{4K\Delta t}\right)$$

Einstein-Smoluchowski relation ($\langle \mathbf{r}^2(t)\rangle = 2dKt$):

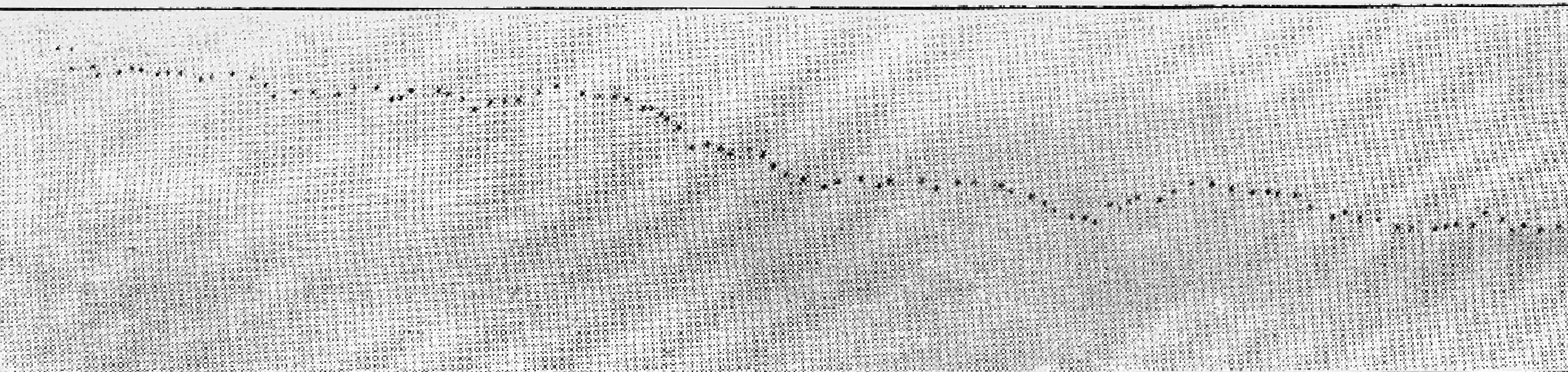
$$K = \frac{k_B T}{m\eta} = \frac{(R/N_A)T}{m\eta}$$

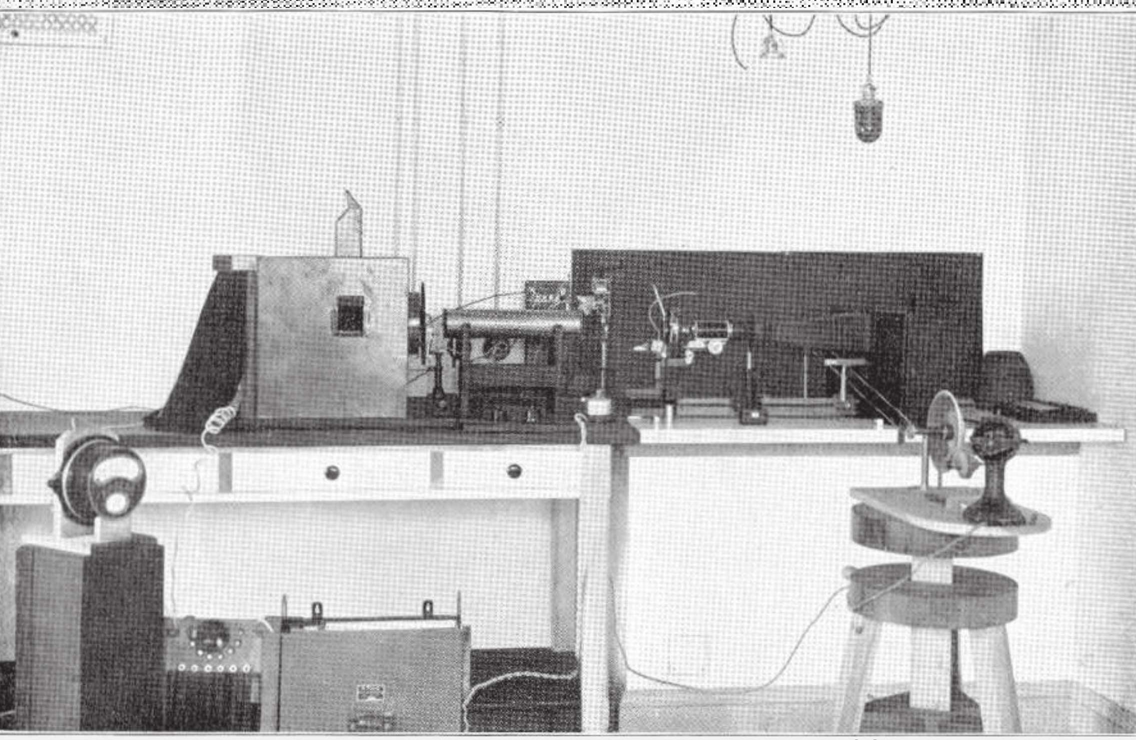
J Perrin, Comptes Rendus (Paris) 146 (1908) 967: $N_A = 70.5 \times 10^{22}$

Ivar Nordlund (1887-1918)

Verksam ved fysikalisk-kemiska institutionen vid Uppsala universitet. Arbetade även som amatörfotograf. Svåger till A Hamberg

Ivar Nordlund: 100+ years of SPT with time series analysis





I Nordlund, Z Physik (1914): $N_A = 5.91 \times 10^{23}$

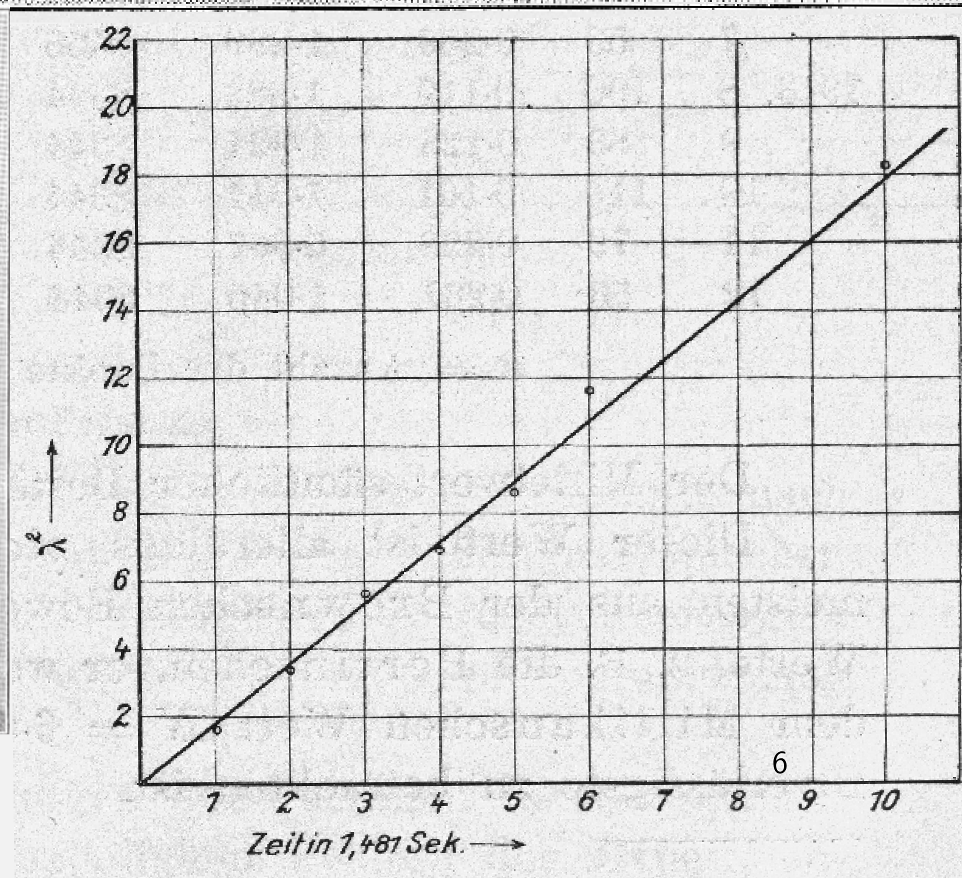
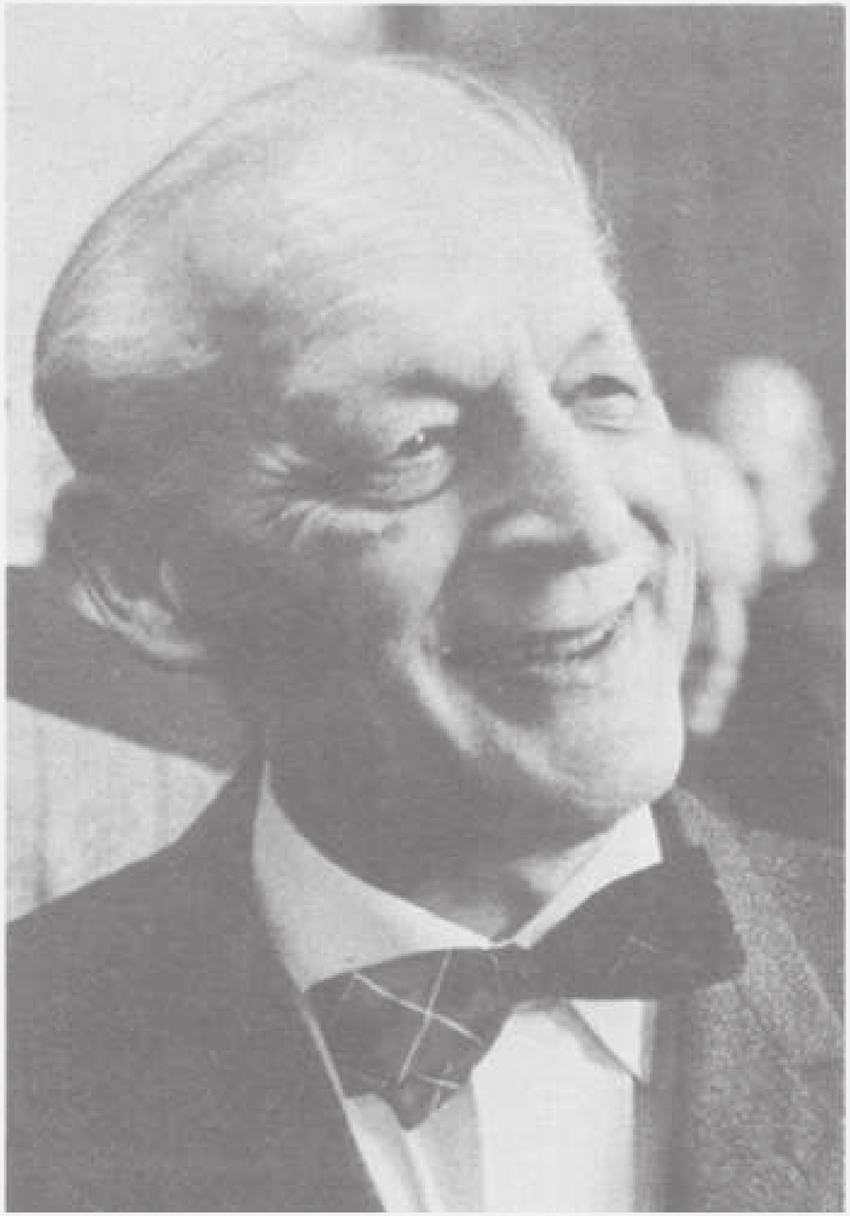


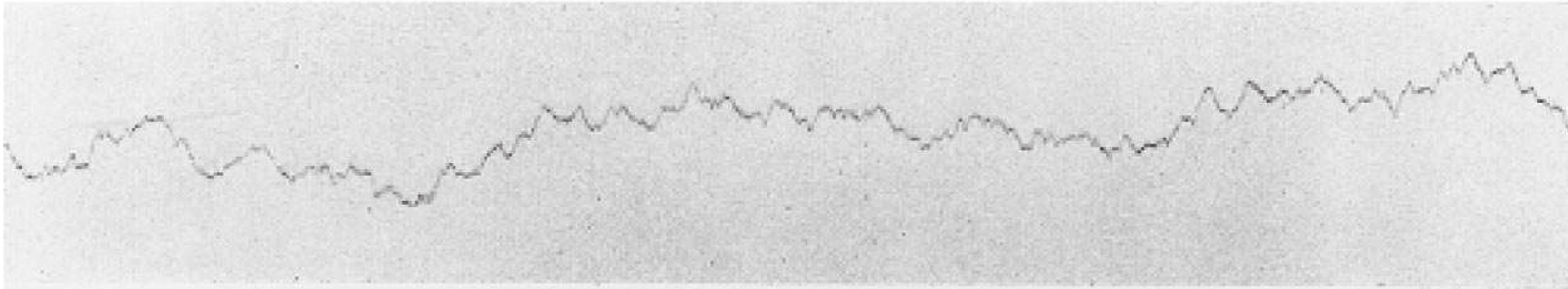
Fig. 11.

Eugen Kappler (1905-1977)



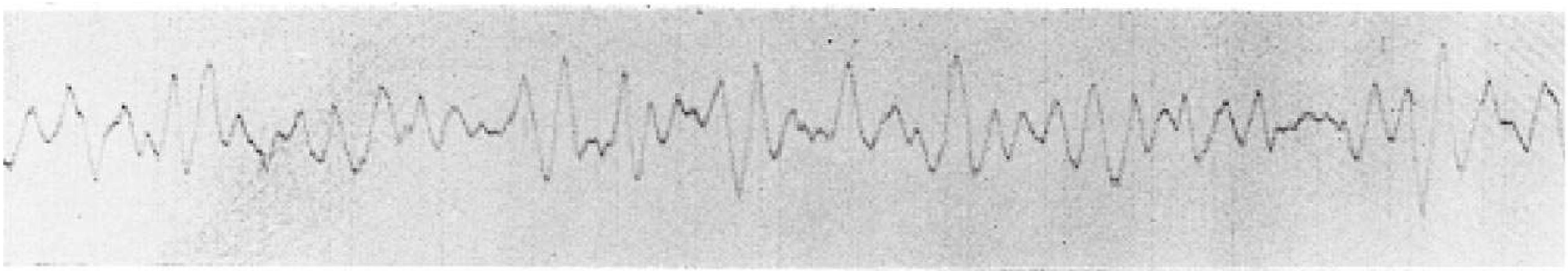
Obiturary by L Reimer, Physikalische Blätter Feb 1978 pp 86

Eugen Kappler: ultimate diffusion measurements



Registrieraufnahme der Brownschen Bewegung (natürliche Größe).
Direktionskraft $9{,}428 \cdot 10^{-9}$ abs. Einh. Trägheitsmoment: $1 \cdot 10^{-7}$ abs. Einh. Abstand Spiegel–Kamera: 72,1 cm.
Zeitmarke: 30 sec $dx = 1$ mm. a) Atmosphärendruck. Temperatur 13° C

Fig. 5a

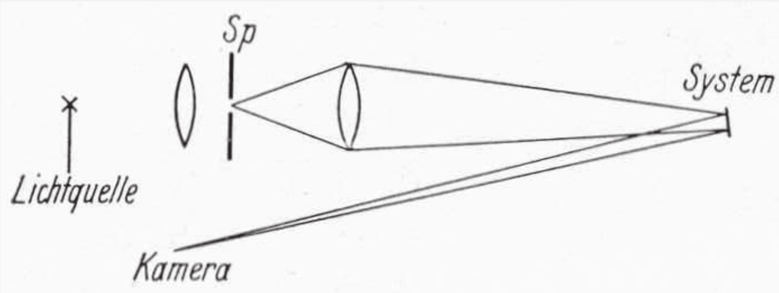


Registrieraufnahme der Brownschen Bewegung (natürliche Größe).
Direktionskraft $9{,}428 \cdot 10^{-9}$ abs. Einh. Trägheitsmoment $1 \cdot 10^{-7}$ abs. Einh. Abstand Spiegel–Kamera: 72,1 cm.
Zeitmarke: 30 sec $dx = 1$ mm. b) $1 \cdot 10^{-3}$ mm Hg. Temperatur 13° C

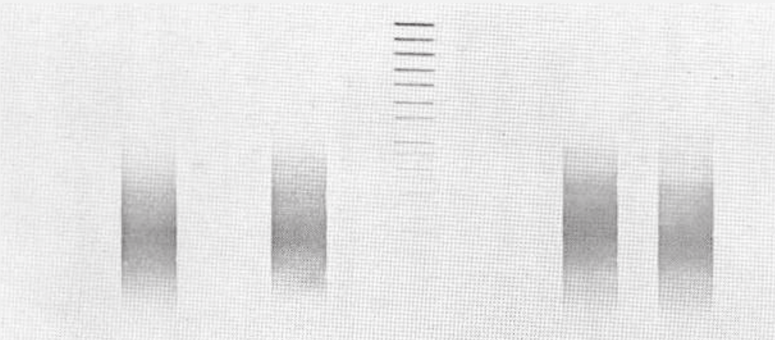
Fig. 5b

E Kappler, Ann d Physik (1931): $N_A = 60.59 \times 10^{22} \pm 1\%$

Kappler's diffusion measurements: mapping Boltzmann

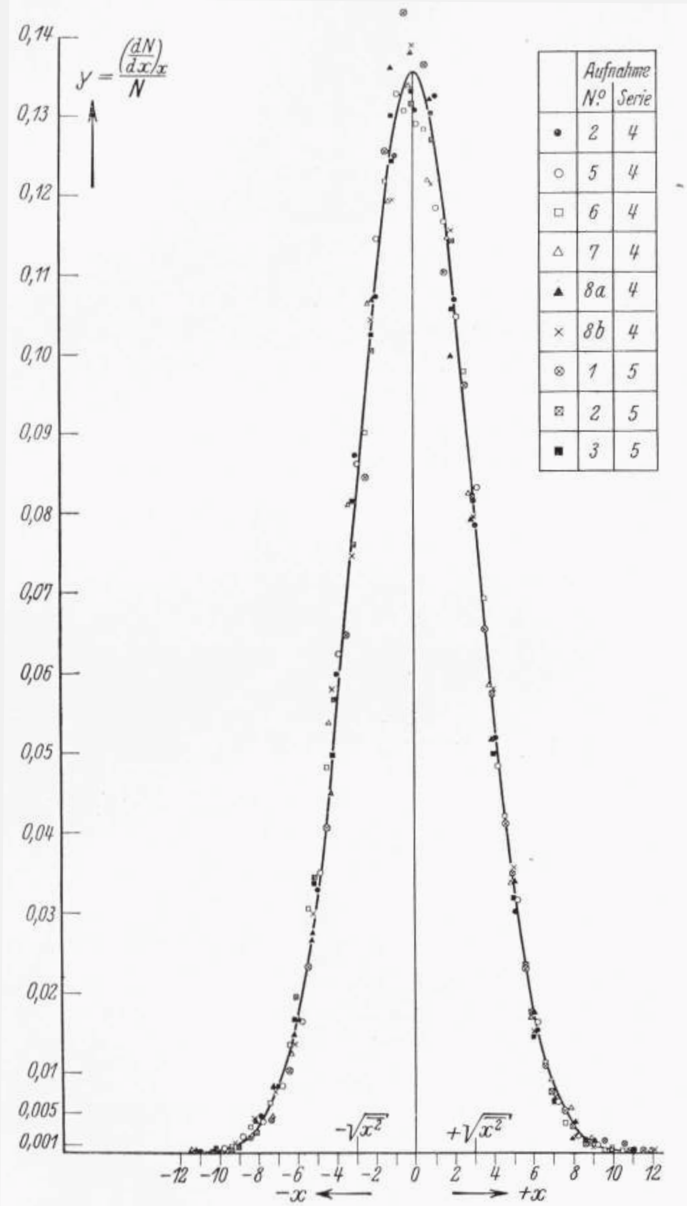


Schema der Meßanordnung
Fig. 1



Distribution @ fixed photographic plate

$$P_{\mathrm{eq}}(x) = \mathscr{N} \exp\left(-\frac{\theta x^2}{k_B T}\right)$$



E Kappler, Ann d Physik (1931): $N_A = 60.59 \times 10^{22} \pm 1\%$

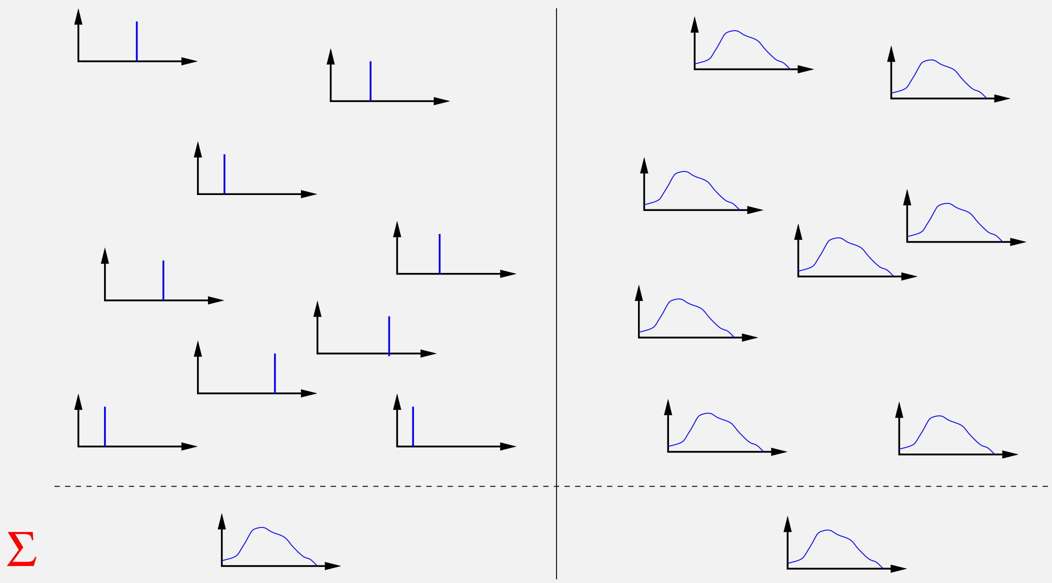
Fluxes, random walks, & fluctuating forces . . .

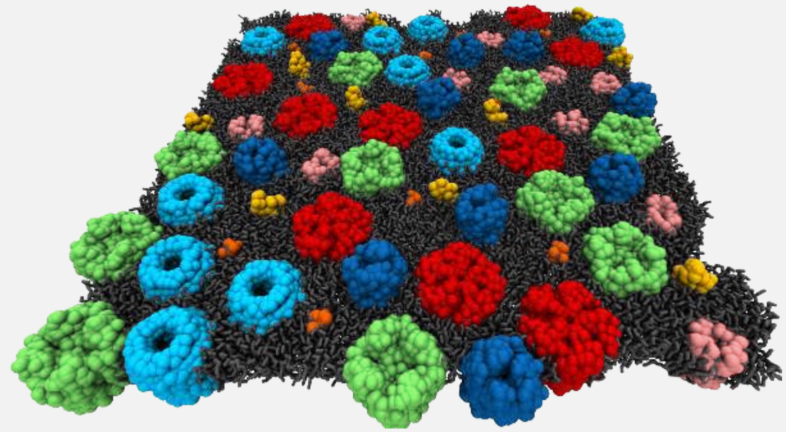
Paul Langevin (1872-1946)
Albert Einstein (1879-1955)

Marian Smoluchowski
(1872-1917)

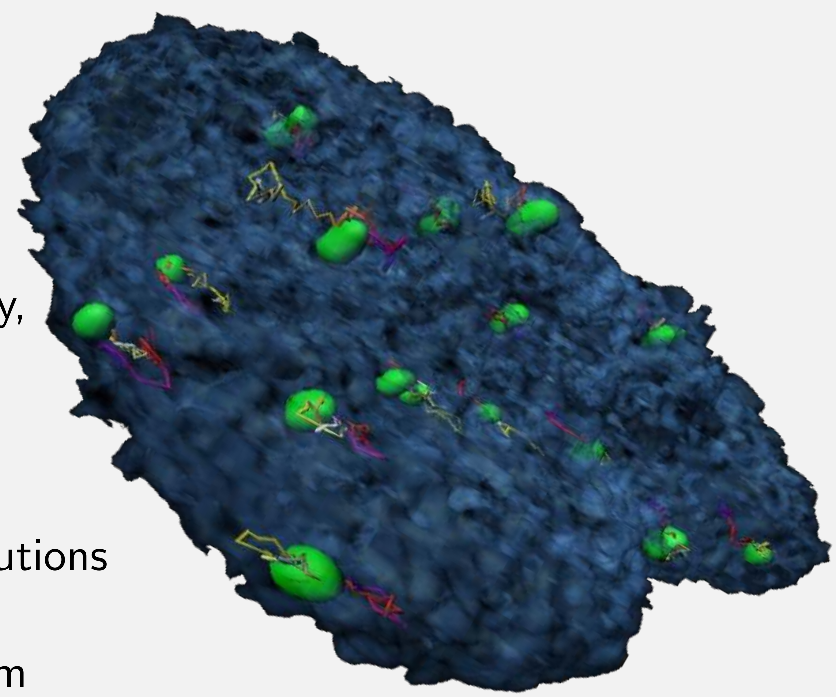
William Sutherland
(1859-1911)

Single molecular insight & information from fluctuations





Courtesy Matti Javanainen



Novel insights from single particle tracking (e.g., superresolution microscopy, supercomputing)

↷ New physics: anomalous diffusion, (non)ergodicity, ageing, heterogeneity, quenched environment & c.

↷ Fluctuations & their distributions often provide important information on the system:
– fluctuating first-passage times reflect broad distributions
– fluctuating finite-time single-particle observables
– fluctuating parameters reflect disorder in the system

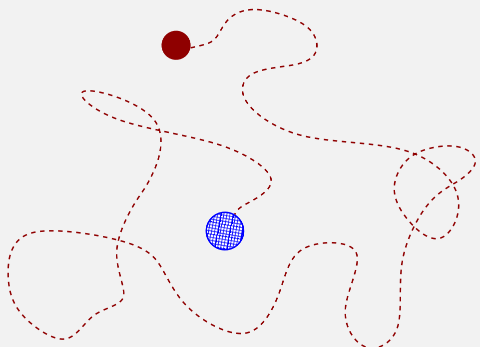
E Barkai, Y Garini & RM, Phys Today (2012)

Courtesy Yuval Garini

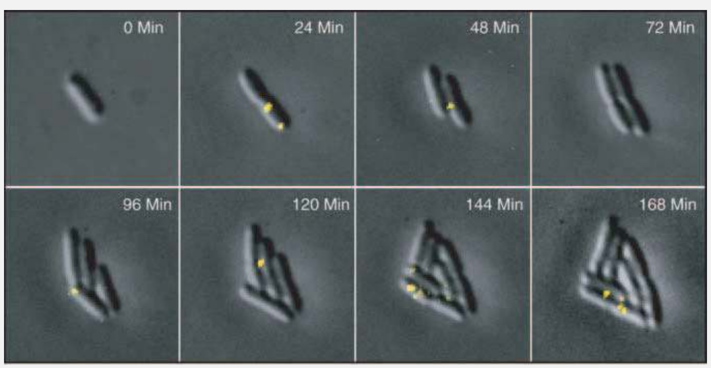
Case study I: fluctuations of molecular reaction times

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

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



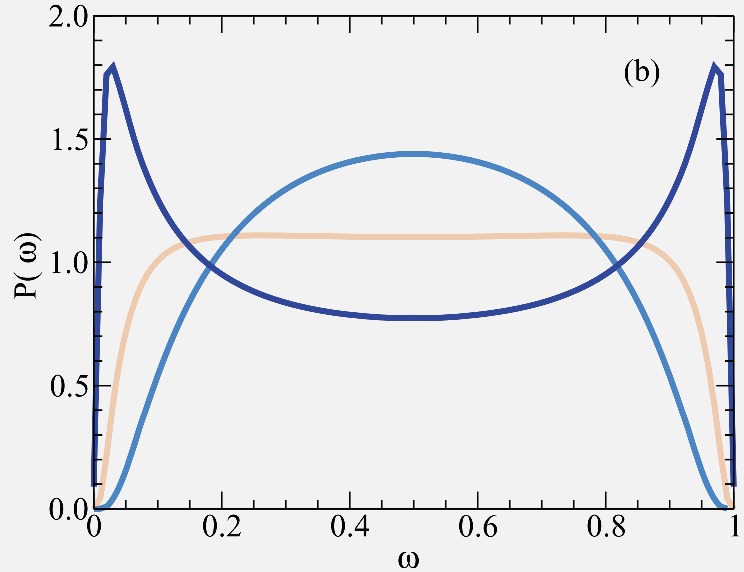
Yu et al, Science (2006)



Uniformity index for two independent first-passage times τ_1, τ_2:

$$\omega = \frac{\tau_1}{\tau_1 + \tau_2}$$

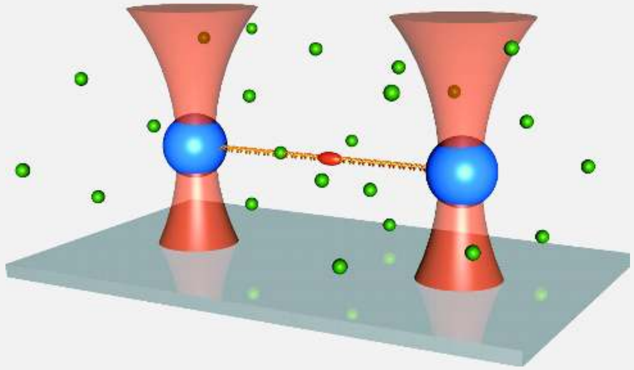
$\curvearrowright$ $\omega = 1/2$ means good reproducibility $\lightning$ many processes

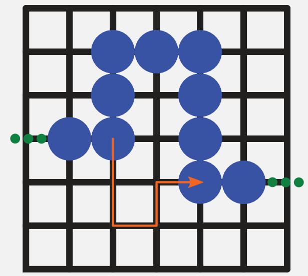


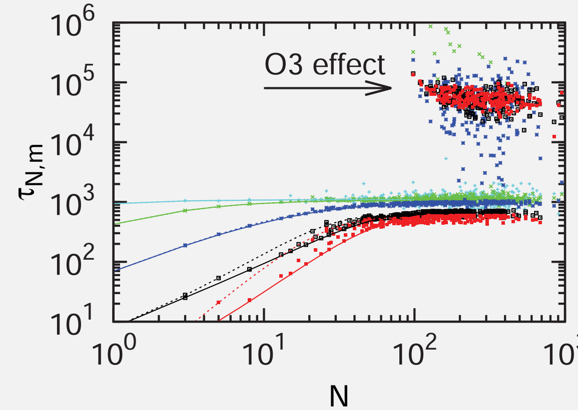
M v Smoluchowski, Physikal Zeitschr (1916)

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

TF target location, TF localisation & rapid search







B vd Broek . . . RM & G Wuite, PNAS (2008)
MA Lomholt . . . G Wuite & RM, PNAS (2009)

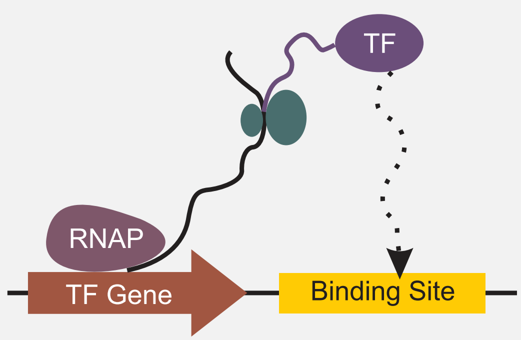
M Bauer & RM, PLoS ONE (2013)

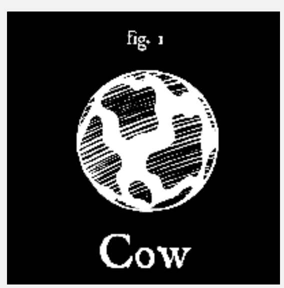
M Bauer . . . & RM, Sci Rep (2015)

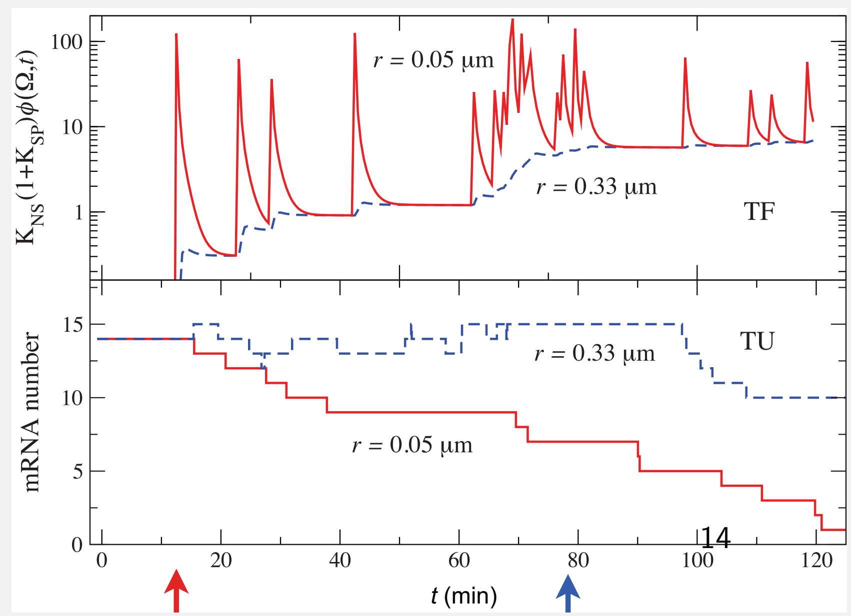
Képès et al: TF targets are typically located next to or at regular distances from the TF gene $\rightarrow$ TF gene-target pairs close in 3D [J Mol Biol (2004)]

Kuhlman & Cox: • TF distribution highly heterogeneous • TF gene influences distribution: localisation of TF near TF gene [Mol Syst Biol (2012)]

Kolesov et al: target gene of *local* TFs is significantly close to TF gene $\rightsquigarrow$ rapid search hypothesis [PNAS (2007)]







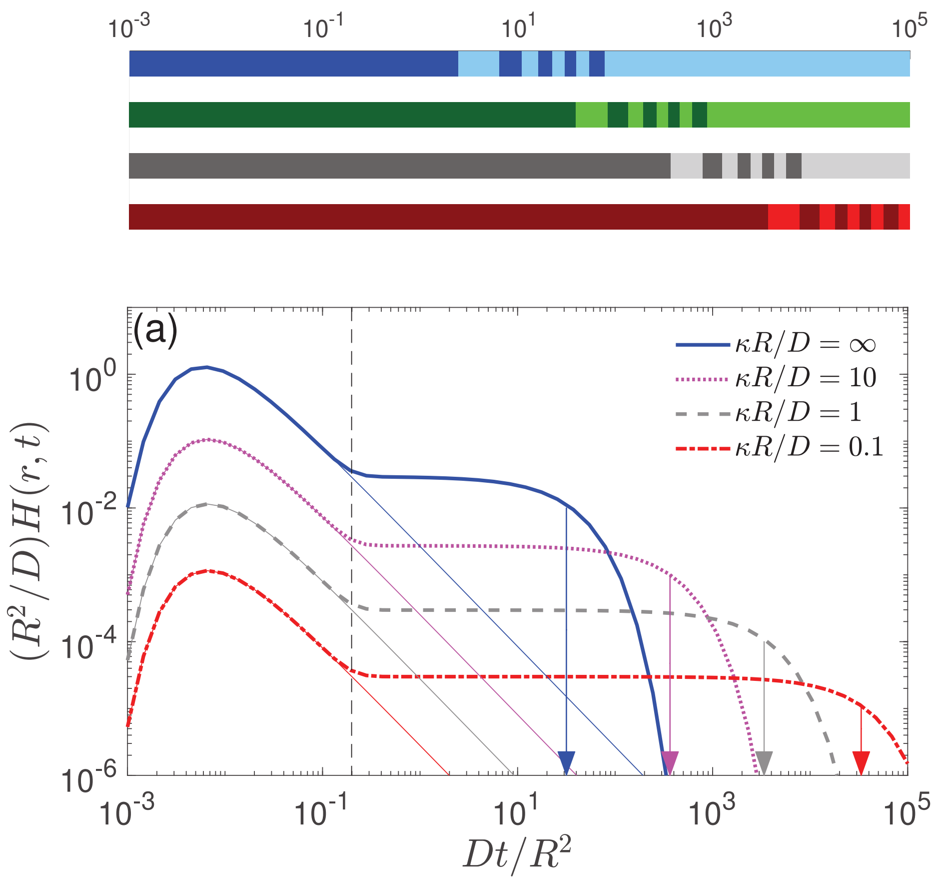
O Pulkkinen & RM, PRL (2013): TF-target gene distance matters $\rightarrow$

Strongly defocused (fluctuating) reaction times

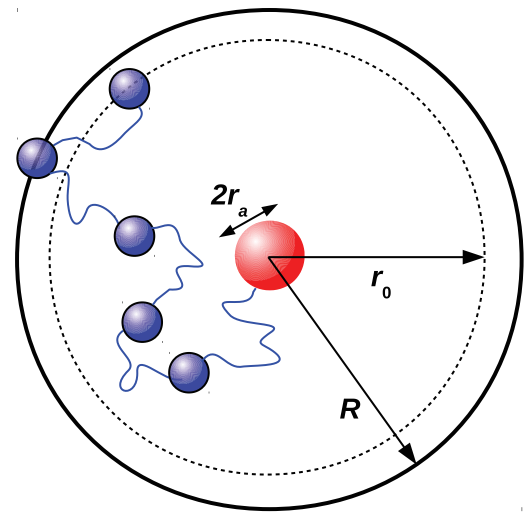
Geometry control: direct trajectories independent of outer boundary

Reaction control: finite reactivity requires multiple collisions

Full first passage time density:



Direct vs indirect trajectories:



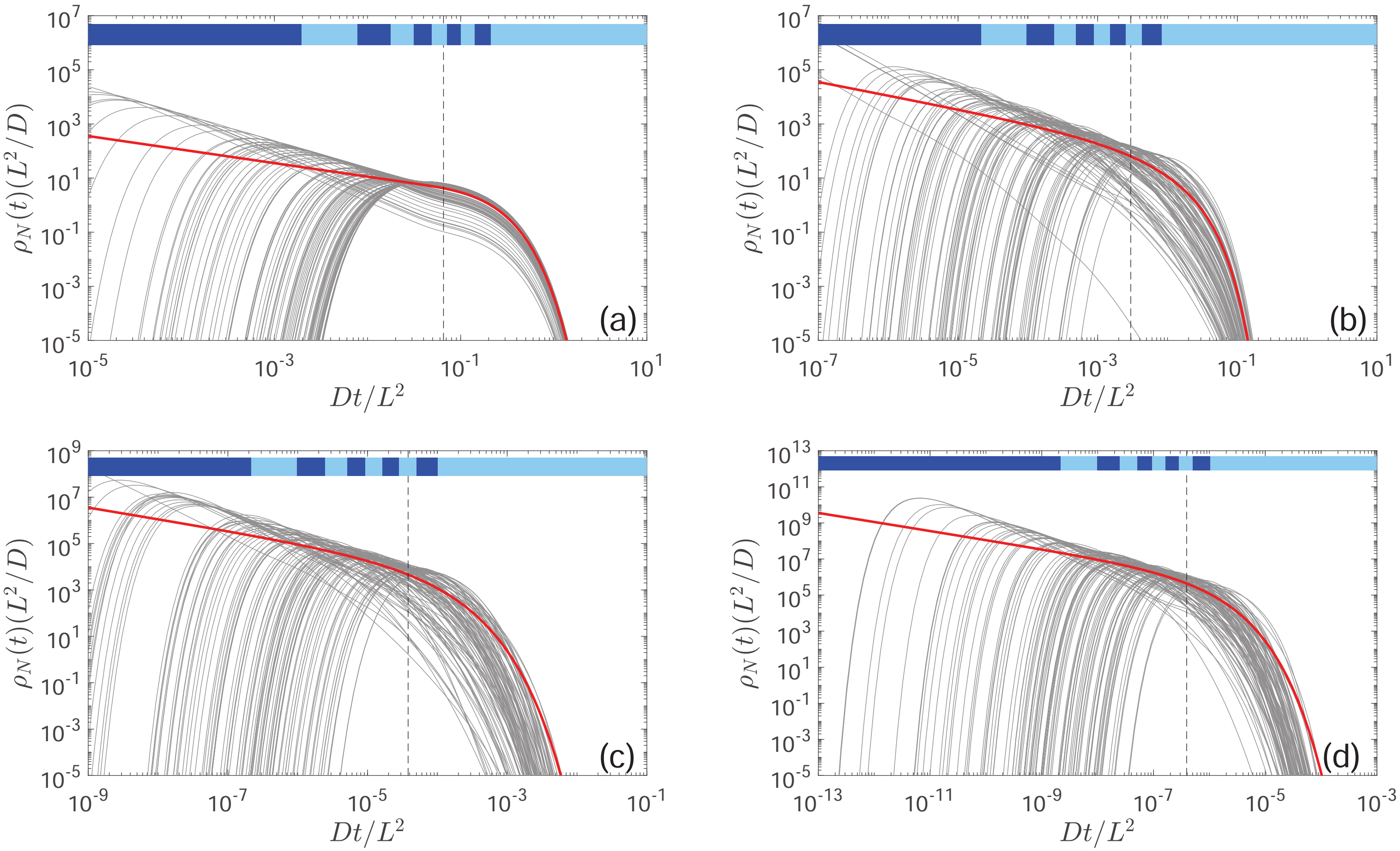
$$\langle t \rangle = \frac{(r_0 - r_a)(2R^3 - r_0 r_a[r_0 + r_a])}{6Dr_0 r_a} + \frac{R^3 - r_a^3}{3\kappa r_a}$$

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

Reaction/search speedup for N "molecules" in parallel

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

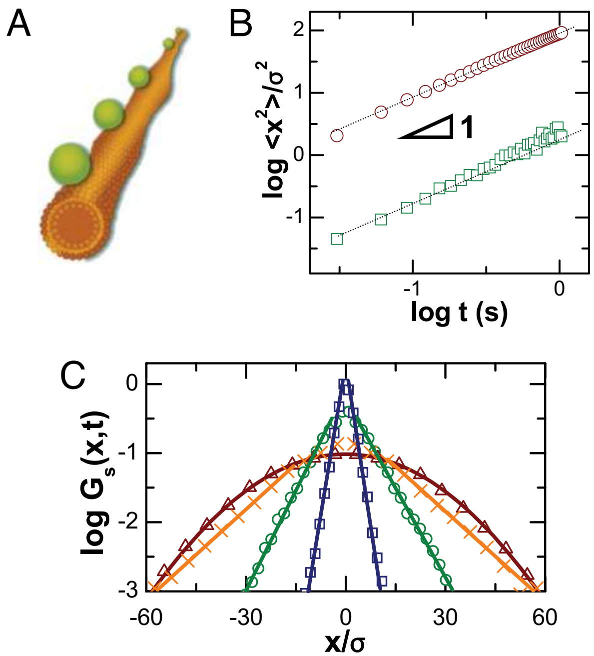
Uniformly distributed initial conditions: $\langle t \rangle \simeq \begin{cases} 1/N^2, & \text{perfect reactivity} \\ 1/N, & \text{partial reactivity} \end{cases}$



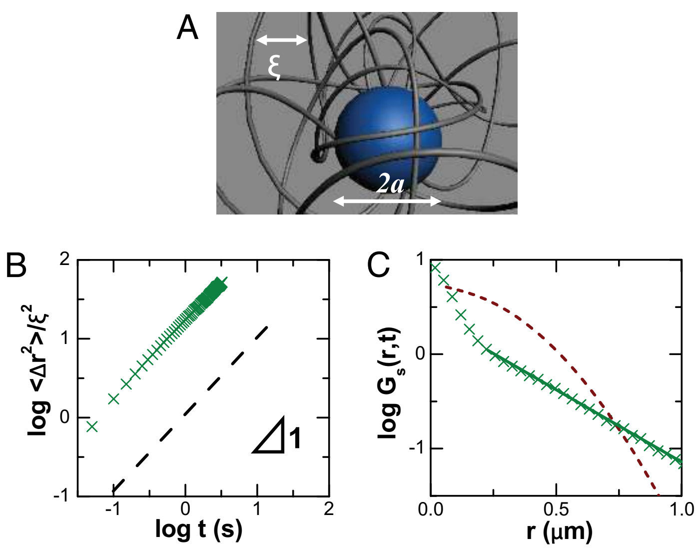
Grey lines: 100 random initial positions

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

Case study II: fluctuating diffusivity & non-Gaussianity

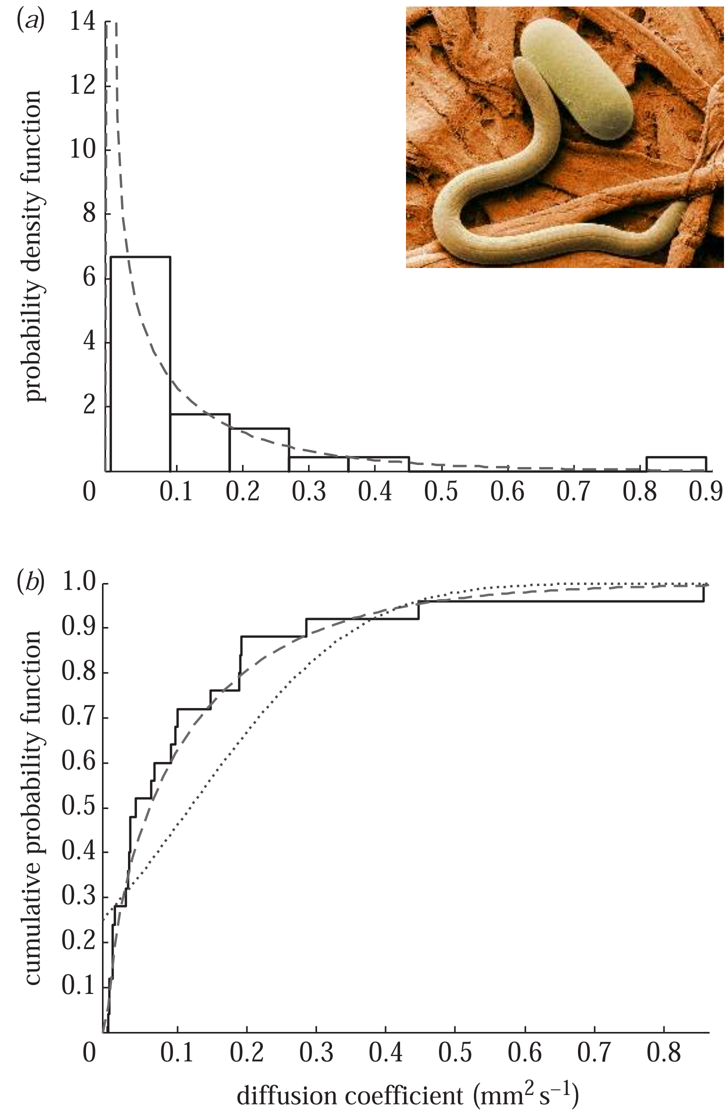


Colloidal beads on nanotubes



Nanospheres in entangled actin

Motion of *Phasmarhabditis* nematodes



Wang et al, PNAS (2009); Nature Mat (2012)

S Hapca, JW Crawford & IM Young, Interface (2009)

Fickian, non-Gaussian diffusion with diffusing diffusivity

B Wang, J Kuo, SC Bae & S Granick, Nat Mat (2012): $\langle x^2(t)\rangle = 2K_1 t$, yet $P(x,t)$ non-Gaussian. Superstatistical approach $P(x,t) = \int_0^\infty G(x,t|D)p(D)dD$

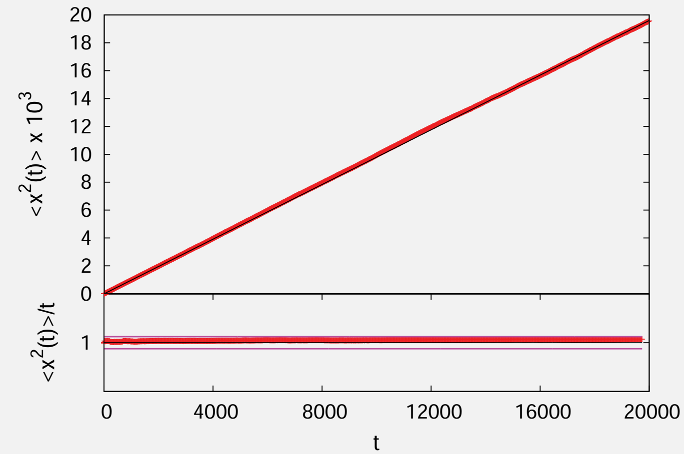
[C Beck & EDB Cohen, Physica A (2003); C Beck Prog Theor Phys Suppl (2006)]

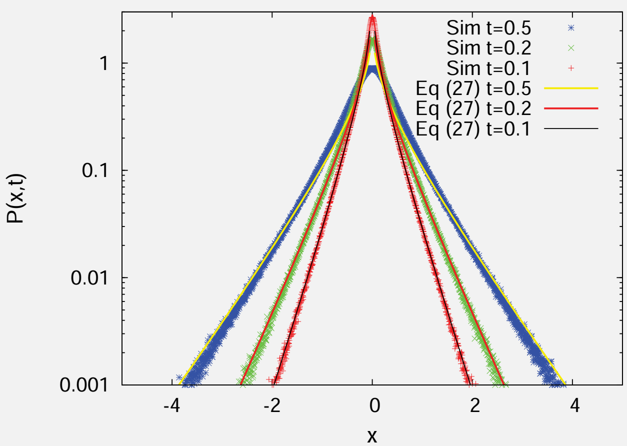
MV Chubinsky & G Slater, PRL (2014): diffusing diffusivity

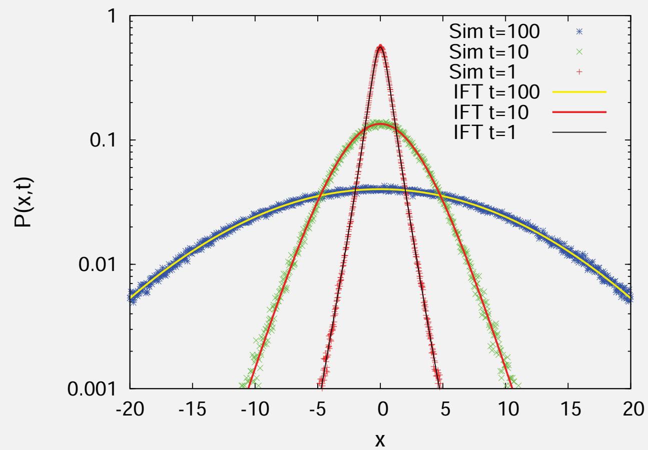
[see also R Jain & KL Sebastian, JPC B (2016)]

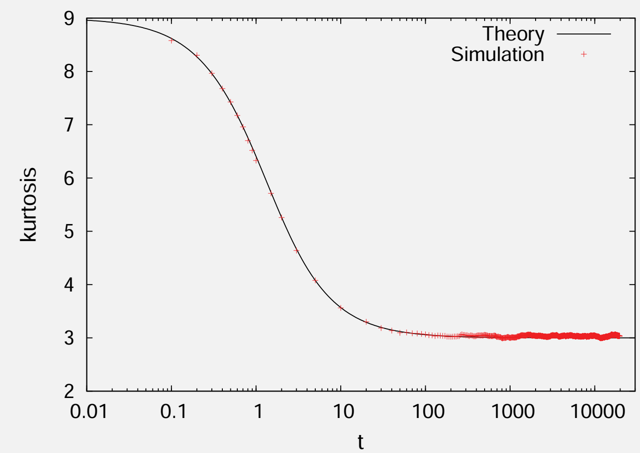
Our minimal model for diffusing diffusivity:

$$\dot{x}(t) = \sqrt{2D(t)}\xi(t)$$
$$D(t) = y^2(t)$$
$$\dot{y}(t) = -\tau^{-1}y + \sigma\eta(t)$$



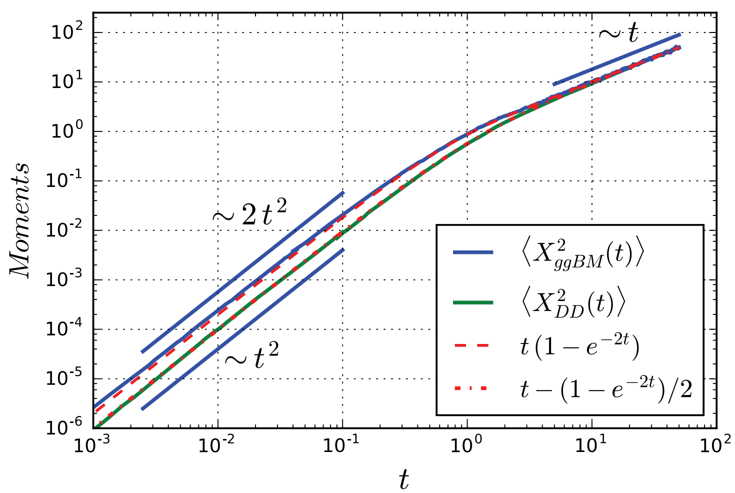


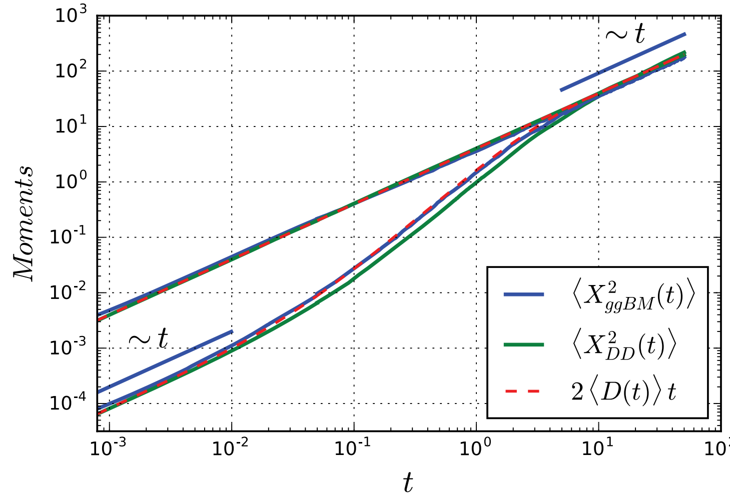




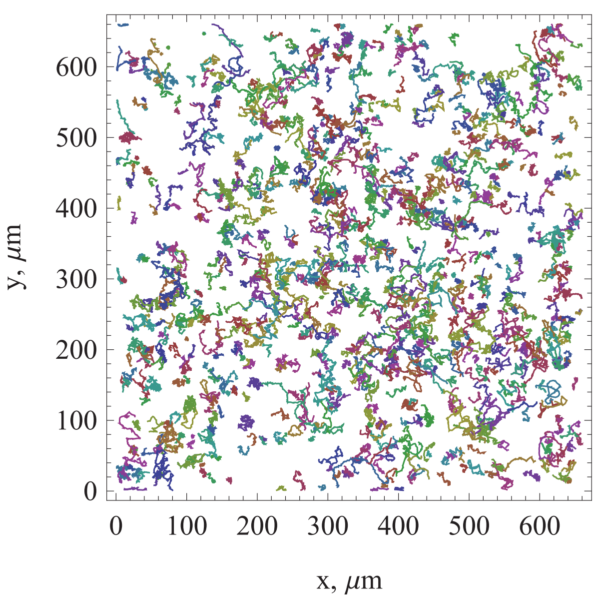
AV Chechkin, F Seno, RM & IM Sokolov, PRX (2017); generalised $\gamma(D)$: V Sposini, AV Chechkin, G Pagnini, F Seno & RM, NJP (2018)

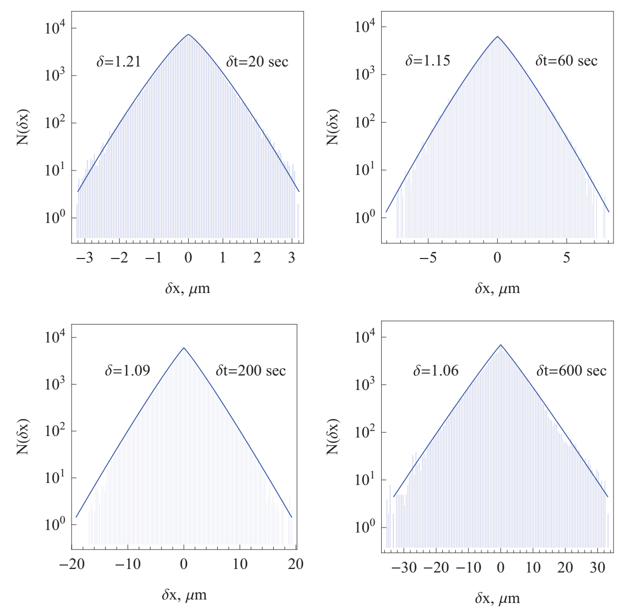
Non-equilibrium initial conditions for $D(t)$ dynamics





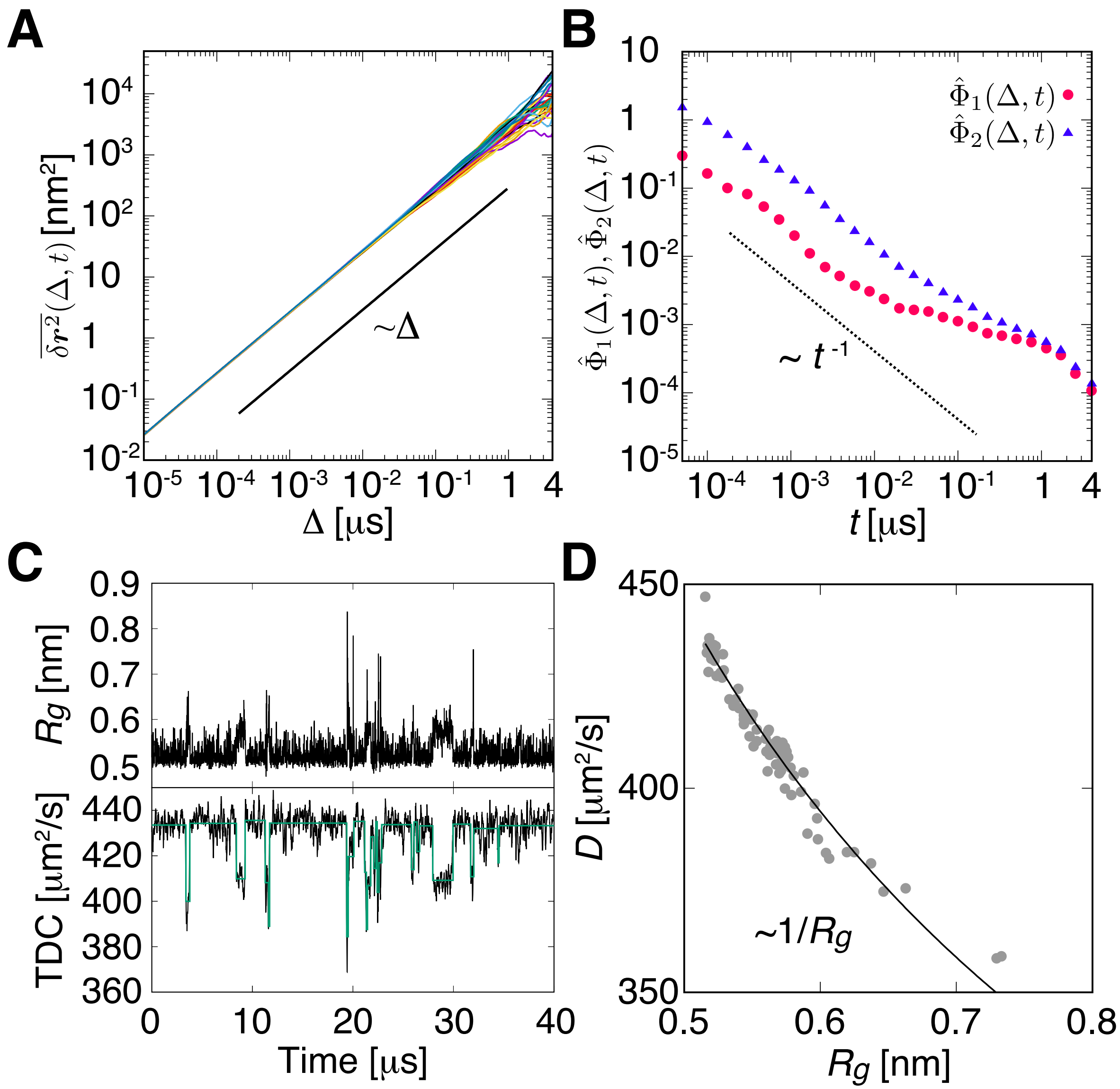
Increasing non-Gaussianity in moving amoeba cells

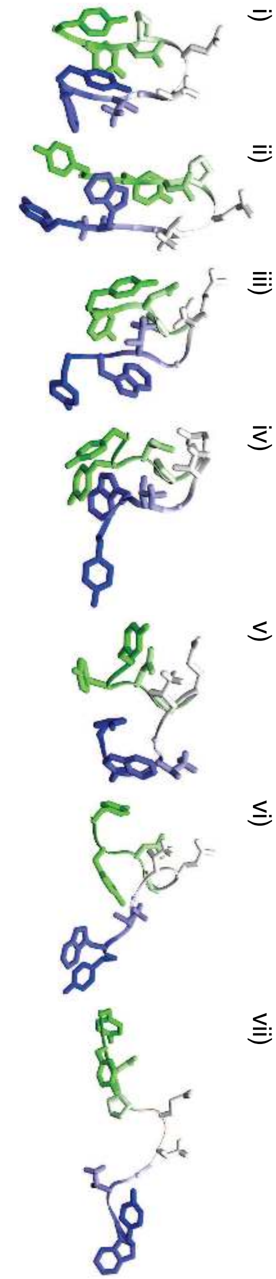




V Sposini, AV Chechkin, G Pagnini, F Seno & RM, NJP (2018); AG Cherstvy, O Nagel, C Beta & RM, PCCP (2018)

Instantaneous diffusivity of shape-fluctuating proteins

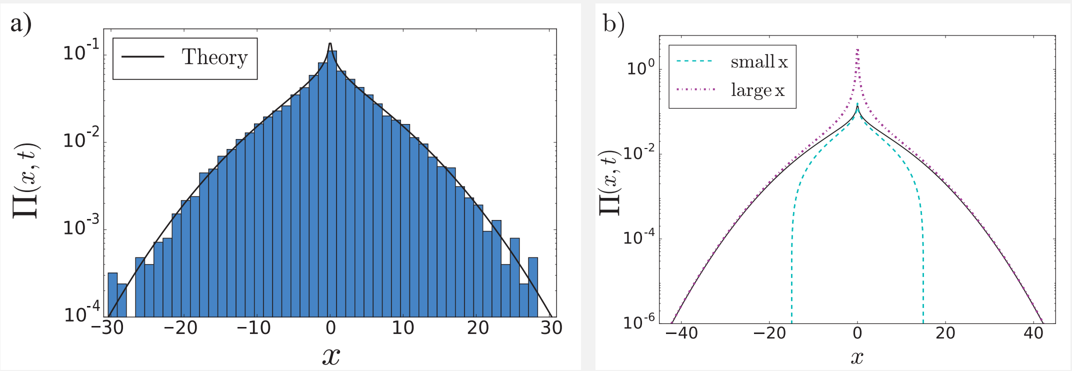


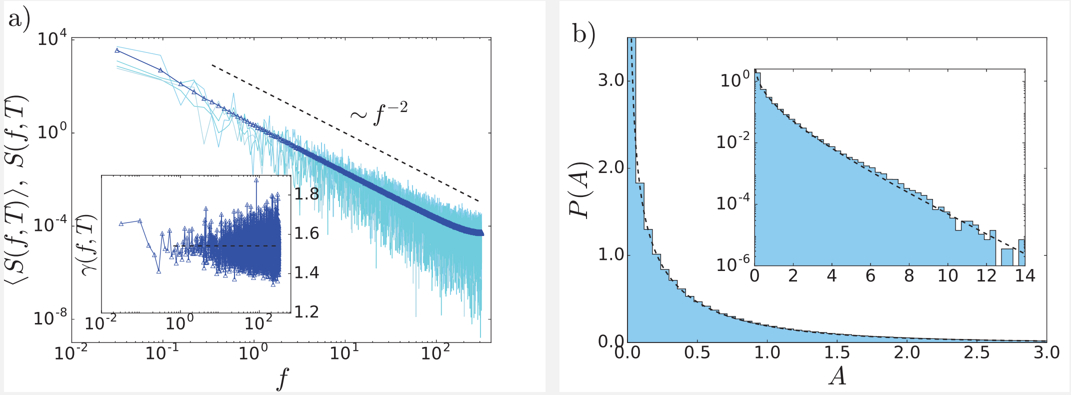


E Yamamoto, T Akimoto, A Mitsutake & RM, E-print (2020)

Other random-diffusivity models

1. Extreme value statistic of tails for small # jumps [E Barkai & S Burov, PRL (2020)]
2. Multimerisation of tracer [M Hidalgo-Soria & E Barkai, PRE (2020)]
3. Two-state model (2 Gaussians!) [A Sabri, X Xu, D Krapf & M Weiss, PRL (2020)]
4. Compartmenalisation model with partial reflectivity [J Ślęzak & S Burov, E-print (2020)]
5. Jump processes & functionals of Brownian motion [V Sposini, D Grebenkov, RM, G Oshanin & F Seno, NJP (2020)]





$$\dot{x}_t = \sqrt{2D_0\Psi_t}\xi_t \quad \therefore$$

Rectified BM: $\Psi_t\Theta(B_t)$:

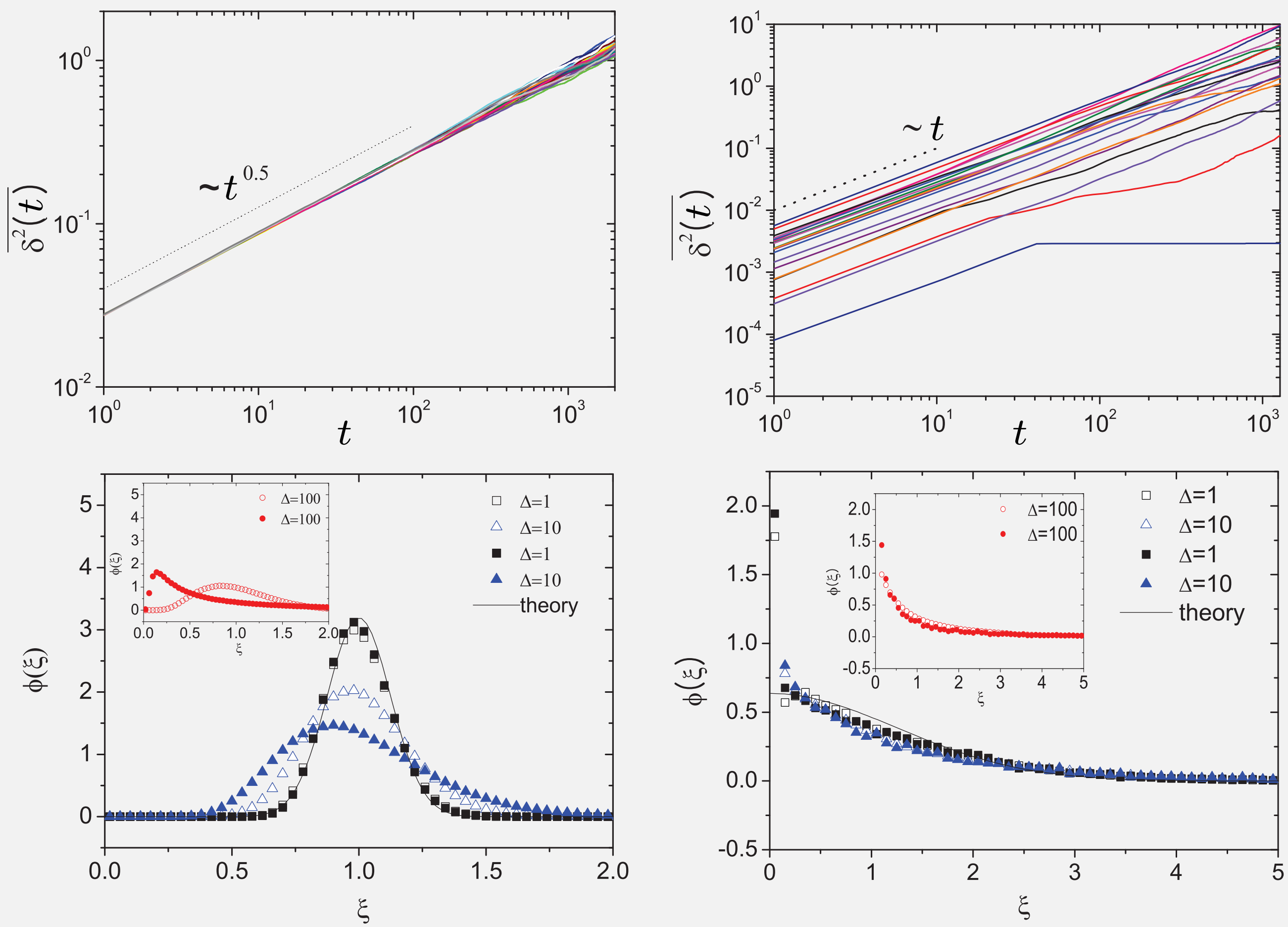
$$P(x,t) = \frac{\exp(-x^2/[8D_0t])}{2\sqrt{\pi^3 D_0 t}} \times K_0\left(\frac{x^2}{8D_0t}\right)$$

Case study III: Fluctuations of time-averaged MSD & PSD

Amplitude fluctuations of TAMSD encoded in: $\xi = \dfrac{\overline{\delta^2(t)}}{\left\langle\overline{\delta^2(t)}\right\rangle}, \quad \left\langle\overline{\delta^2(t)}\right\rangle = \dfrac{1}{N}\sum_{i=1}^{N}\overline{\delta_i^2(t)}$

$\mathrm{EB} = \langle\xi^2\rangle - 1$. For Brownian motion $\mathrm{EB} \sim 4t/(3T)$, & $\lim_{T\to\infty}\phi(\xi) = \delta(\xi - 1)$

Fractional Brownian motion



Continuous time random walk
(Fractional Fokker-Planck equations)

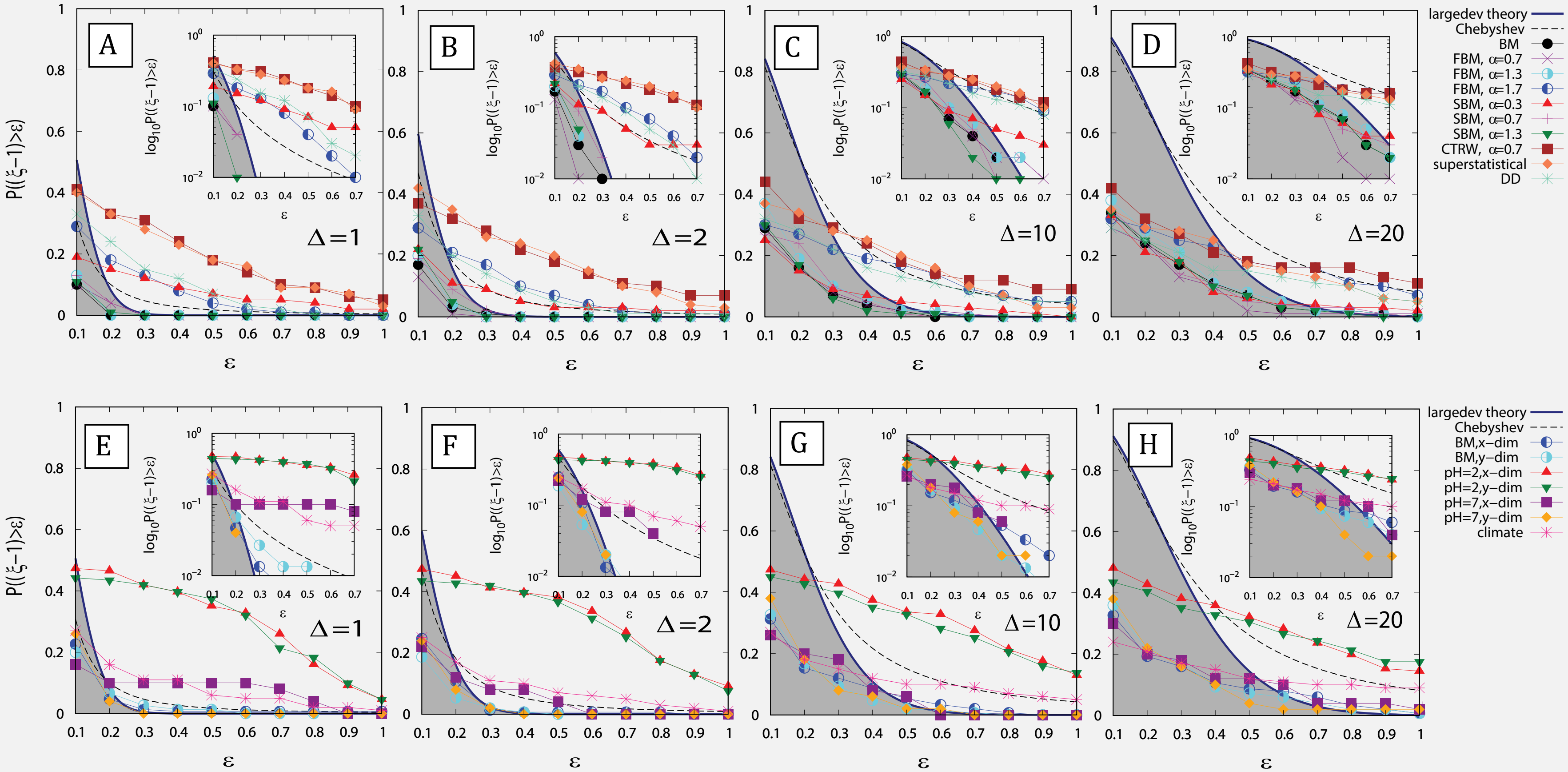
Large-deviation statistics for TAMSD

Chebyshev's inequality for Brownian motion $X(1), X(2), \ldots, X(N)$, given deviation ε:

$$P\Big((\xi-1)\geq\varepsilon\Big)\leq\frac{4\Delta}{4\Delta+3N\varepsilon^2},\quad \xi=\frac{\overline{\delta^2(\Delta)}}{\langle\overline{\delta^2(\Delta)}\rangle},\quad \langle\xi\rangle=1$$

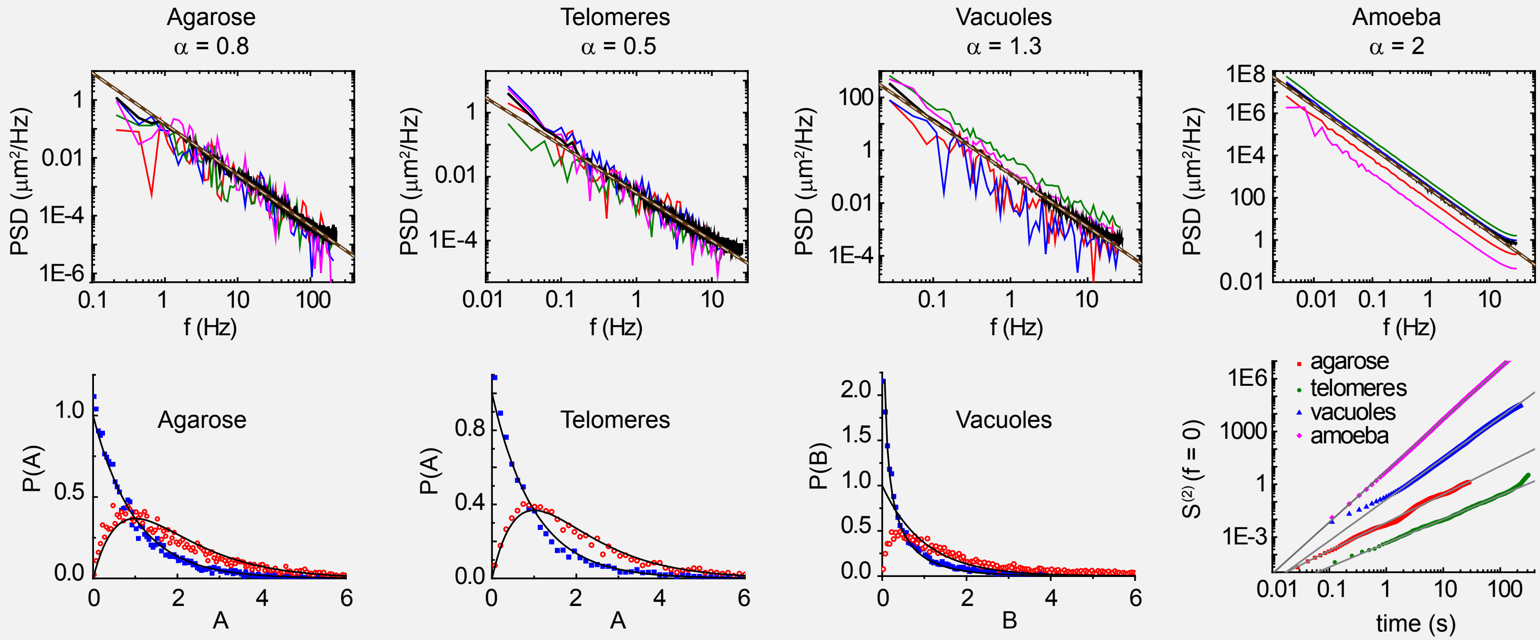
Large-deviation result:

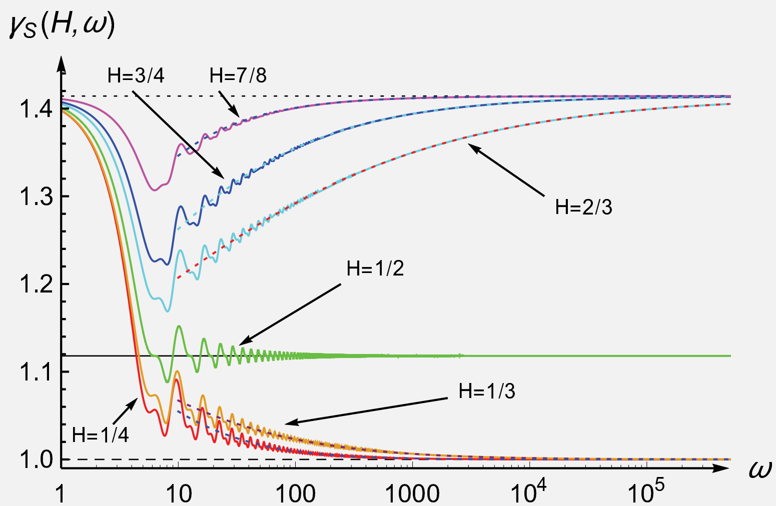
$$P\Big((\xi-1)\geq\varepsilon\Big)\leq\exp\Big(-a\mathcal{H}(b)\Big),\quad \mathcal{H}(b)=1+b-\sqrt{1+2b};\quad a,b=f(\Delta,\ldots)$$



S Thapa, A Wyłomańska, G Sikora, CE Wagner, D Krapf, H Kantz, AV Chechkin & RM, E-print (2020)

Power spectral density of a single FBM trajectory



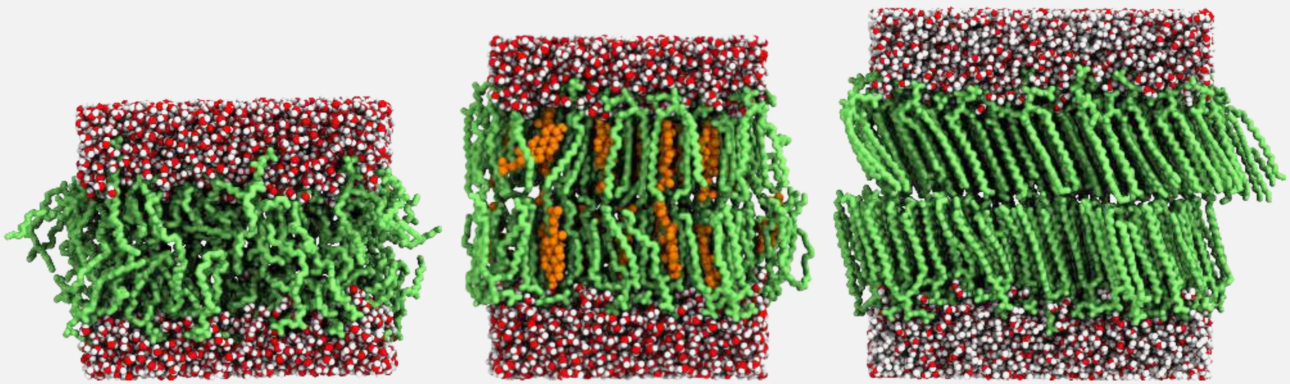


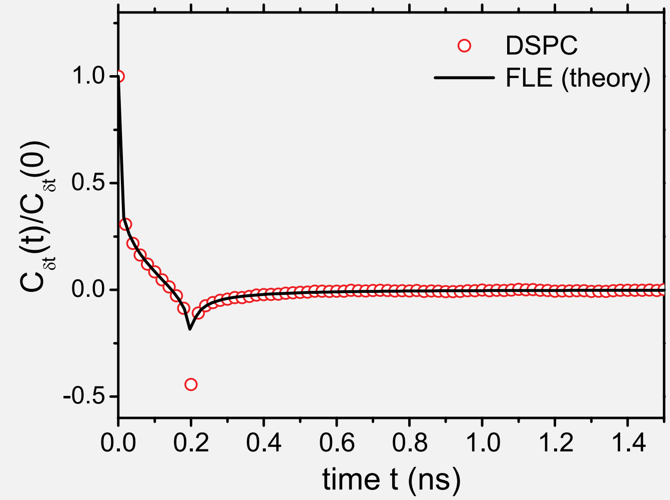
$$S(f,T) = \frac{1}{T}\left|\int_0^T \exp(ift)X_t dt\right|^2$$

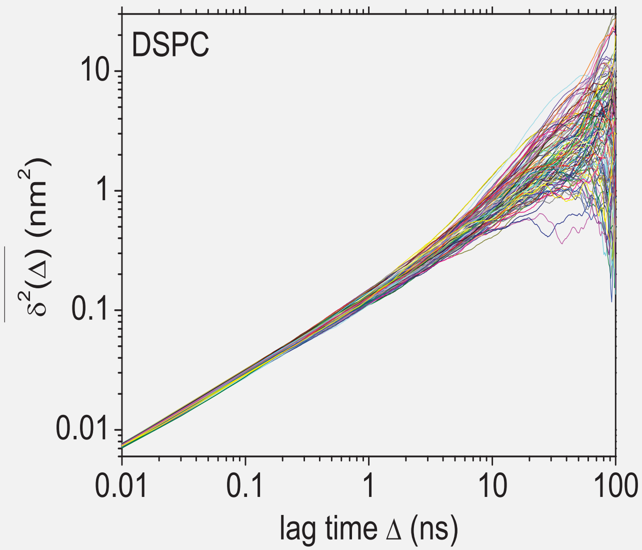
$$\gamma = \frac{\left(\langle S_T^2(f)\rangle - \langle S_T(f)\rangle^2\right)^{1/2}}{\langle S_T(f)\rangle}$$

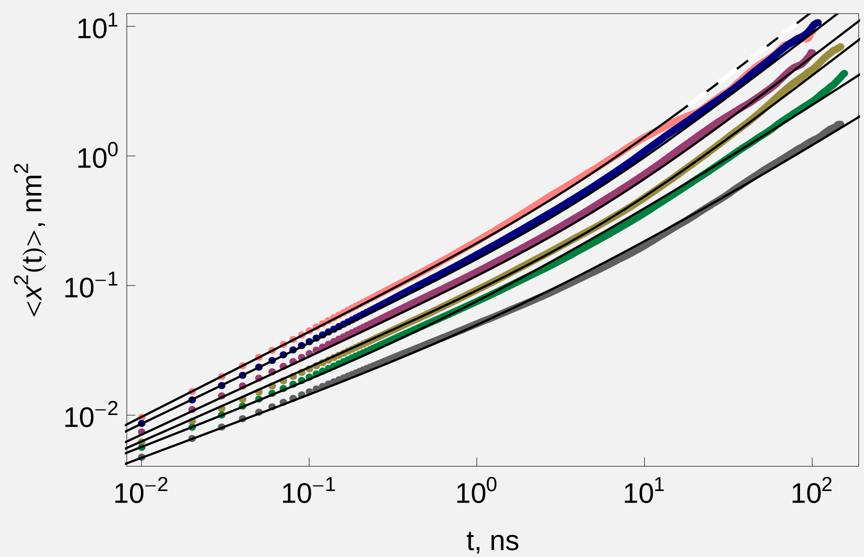
D Krapf, N Lukat, E Marinari, RM, G Oshanin, C Selhuber-Unkel, A Squarcini, L Stadler, M Weiss & X Xu, PRX (2019)

Case study IV: single lipid motion in bilayer membranes









Pure bilayer:

$t^{2/3} \longrightarrow t^1$

/w cholesterol/gel:

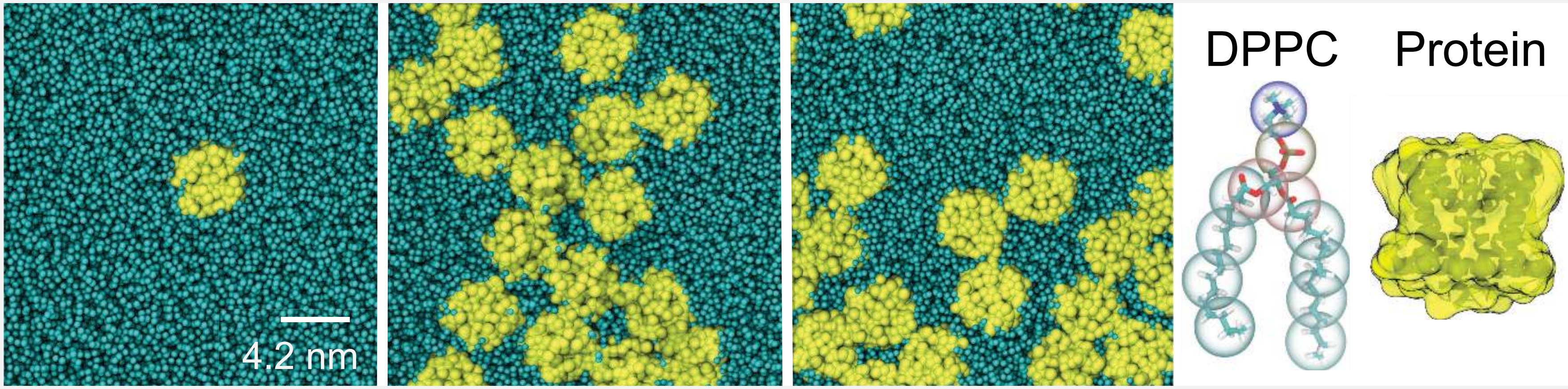
$t^{\alpha} \longrightarrow t^{\alpha'>\alpha}$

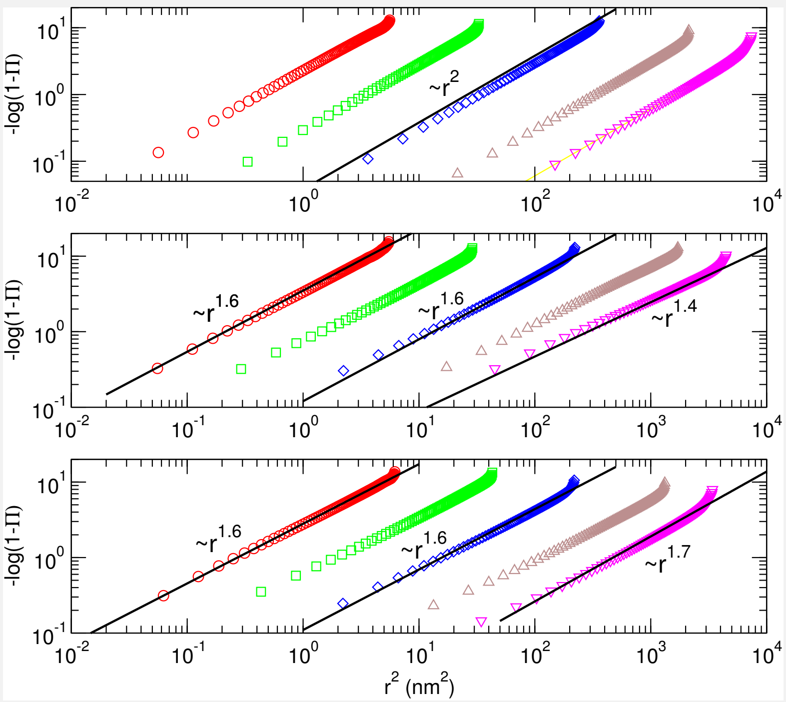
Tempered GLE

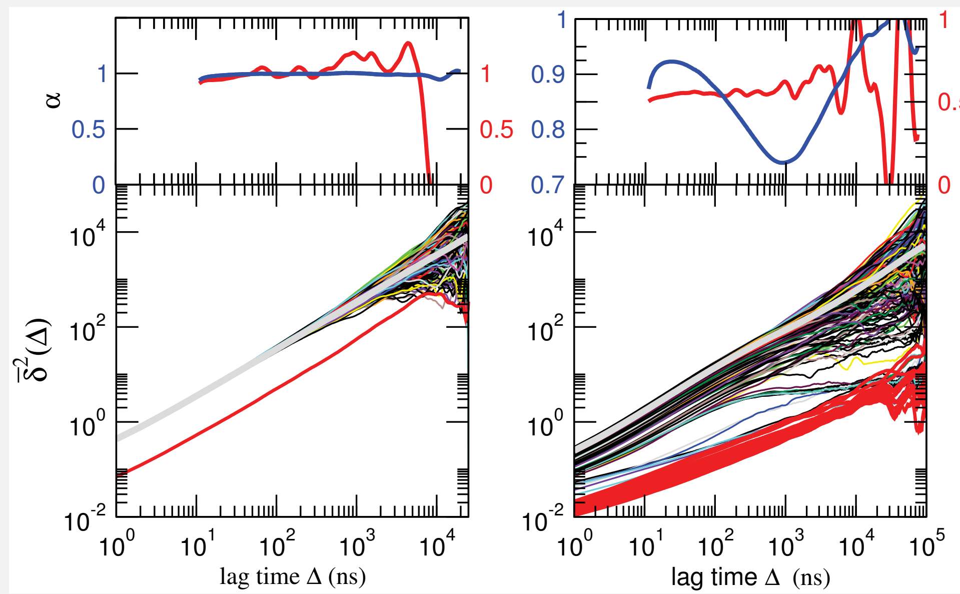
D Molina-Garcia, T Sandev, H Safdari, G Pagnini, AV Chechkin & RM, NJP (2018)

J-H Jeon, H Martinez-Seara Monne, M Javanainen & RM, PRL (2012)

Crowding in membranes: non-Gaussian lipid/protein diffusion

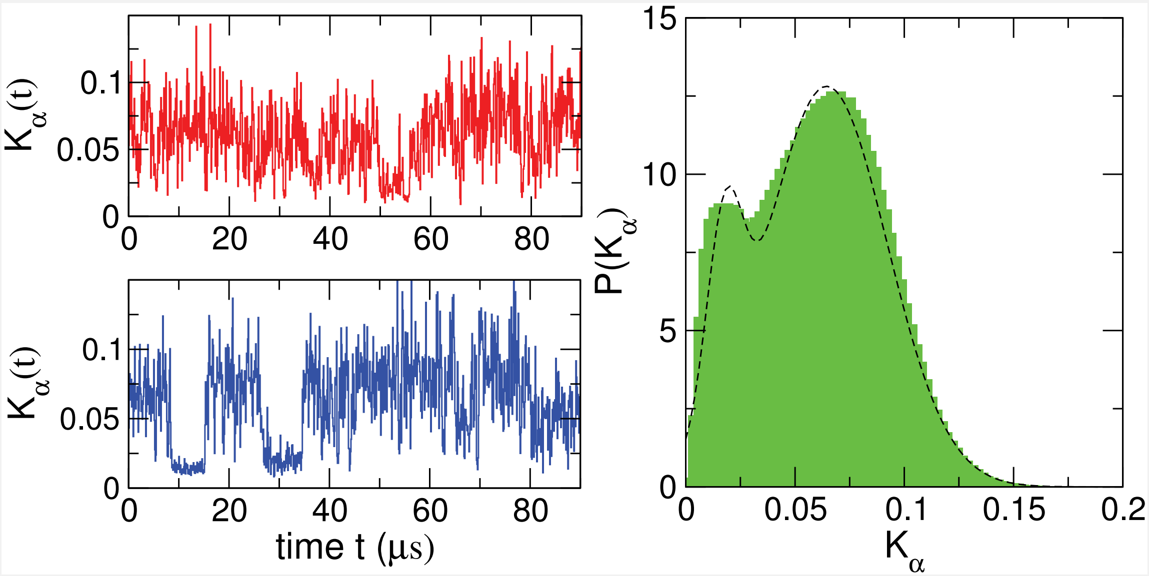


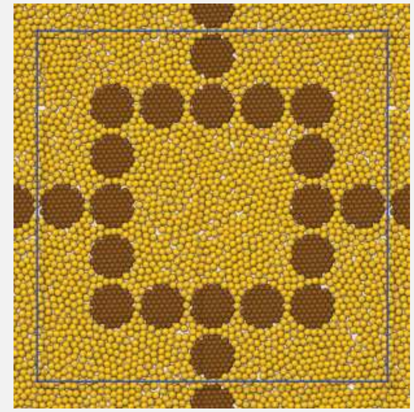




J-H Jeon, M Javanainen, H Martinez-Seara, RM & I Vattulainen, PRX (2016); see also Faraday Disc (2013)

Crowding in membranes increases dynamic heterogeneity



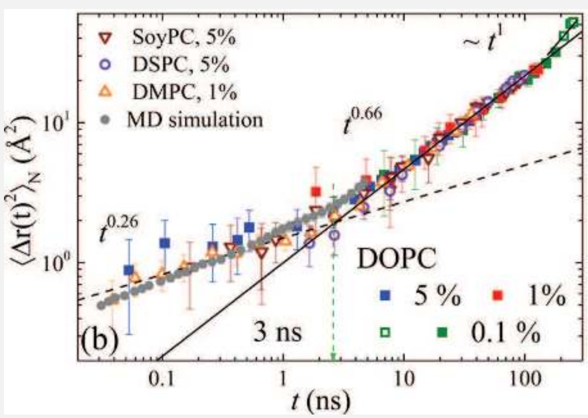


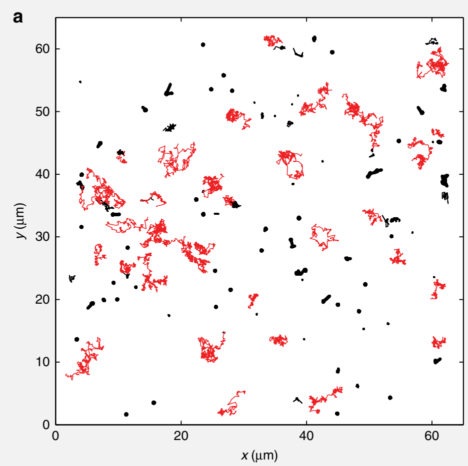
2D "blocked" argon

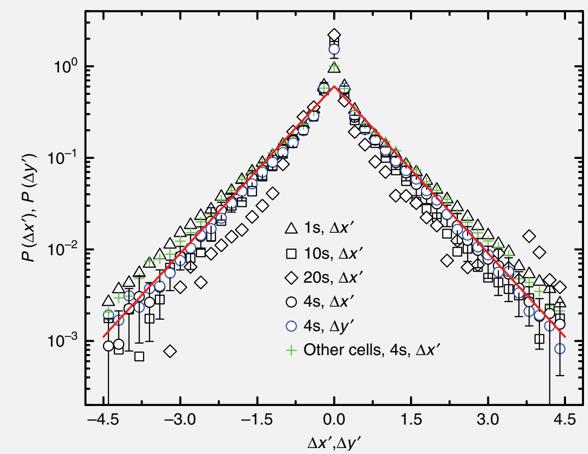
J-H Jeon, M Javanainen, H Seara Monne, RM & I Vattulainen, PRX (2016)

Experiments reveal crossovers & non-Gaussianity

S Gupta . . . GJ Schneider, JPC Lett (2018)

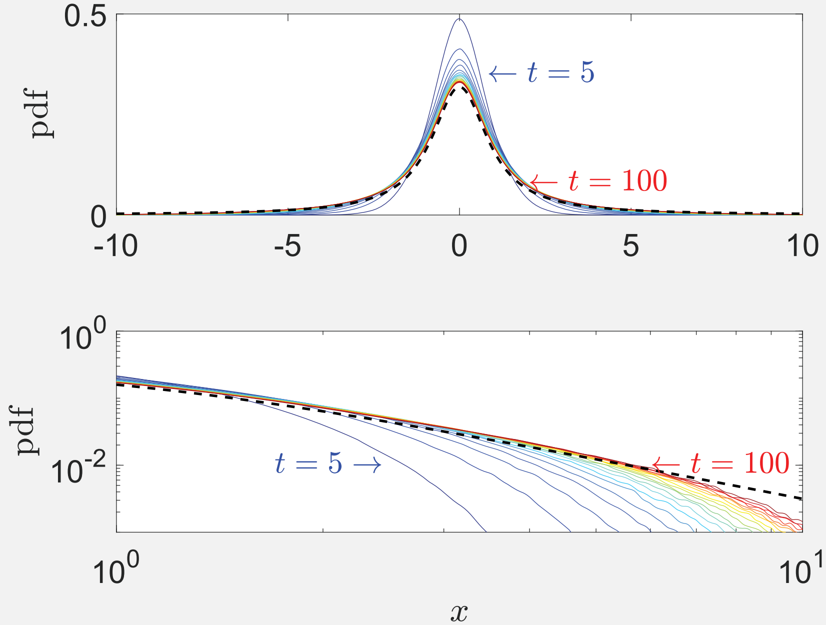


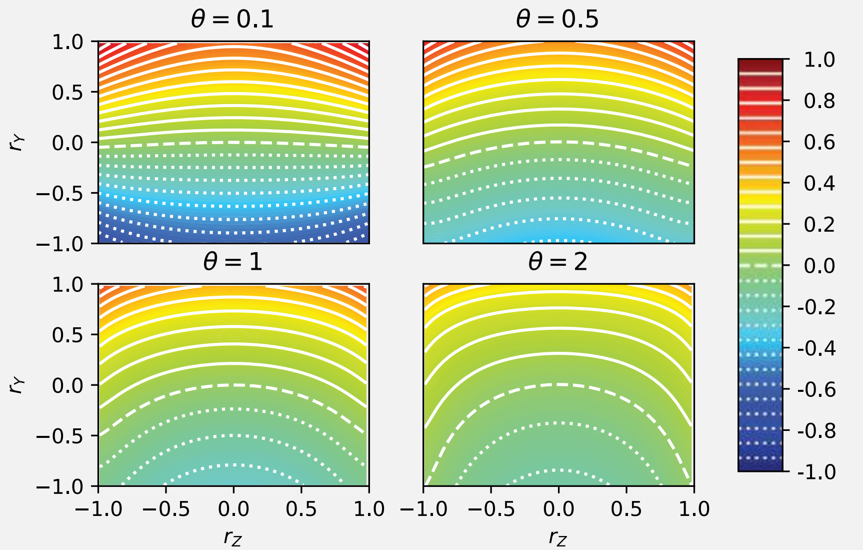




W He . . . P Tong, Nat Comm (2016)

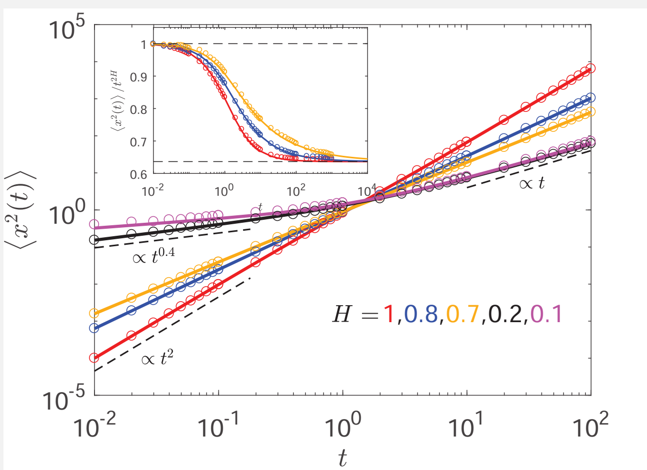
Non-Gaussian dynamics in the presence of correlated noise

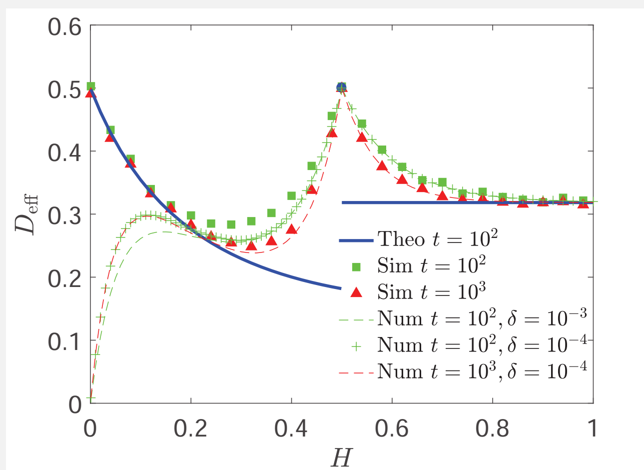


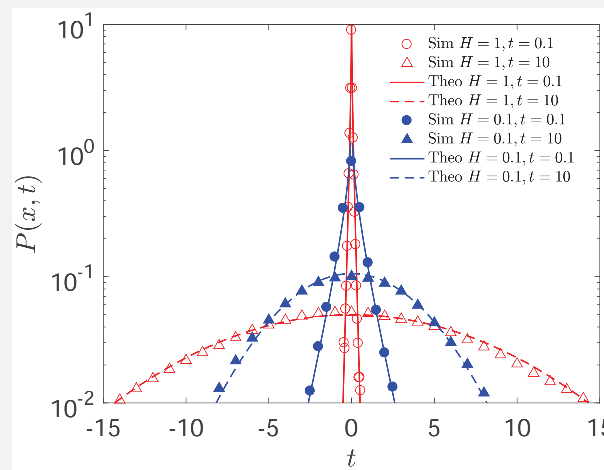


Codiffererence detects non-Gaussianity & non-ergodicity

Viscoelastic diffusing-diffusivity model

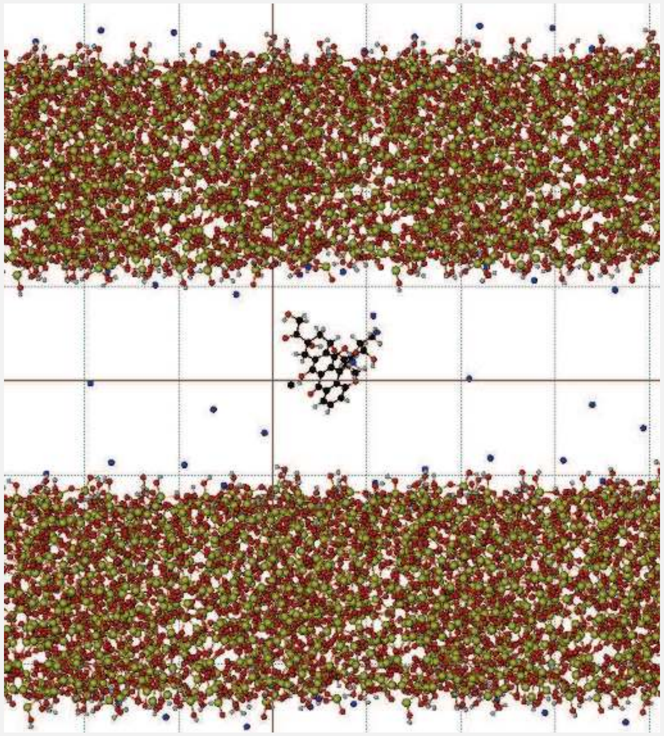


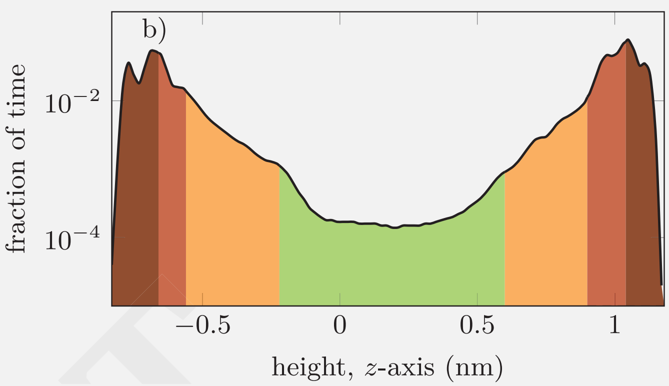


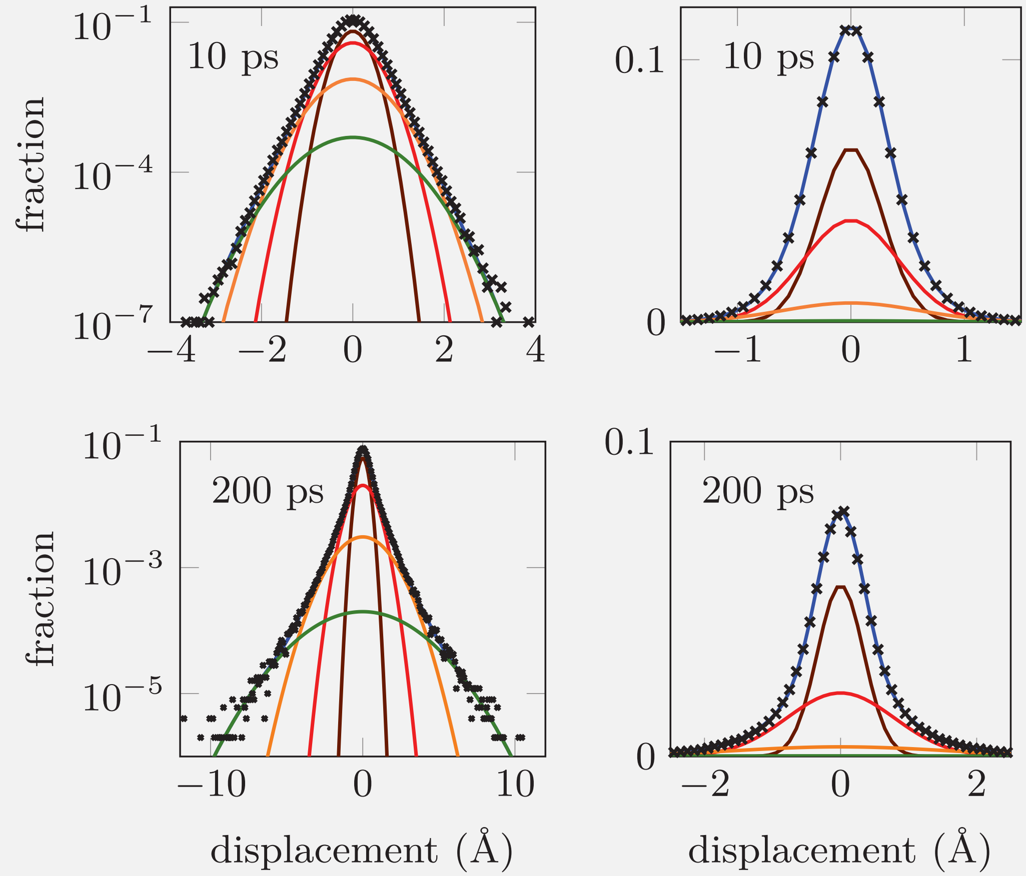


J Ślęzak, M Magdziarz & RM, NJP (2018), NJP (2019); W Wang, AV Chechkin, F Seno, IM Sokolov & RM, NJP (2020)

Doxorubicin drug molecule diffusion in silica nanochannels



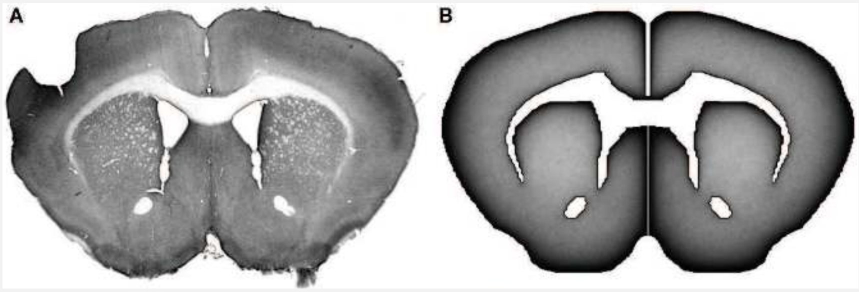


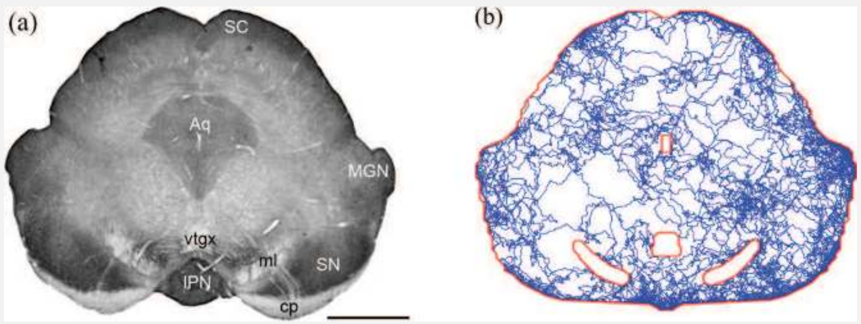


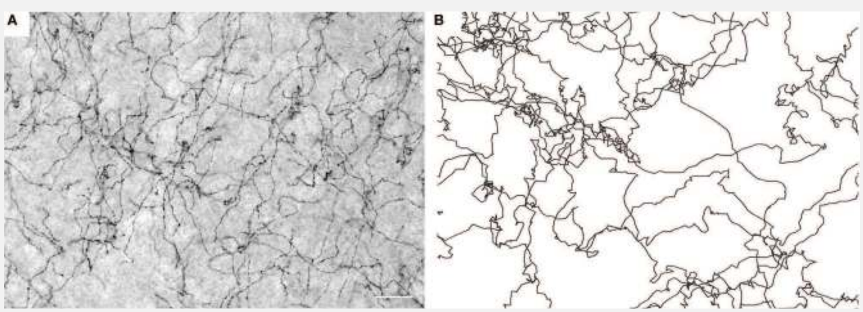
Dynamics is non-Gaussian, ageing, & anticorrelated

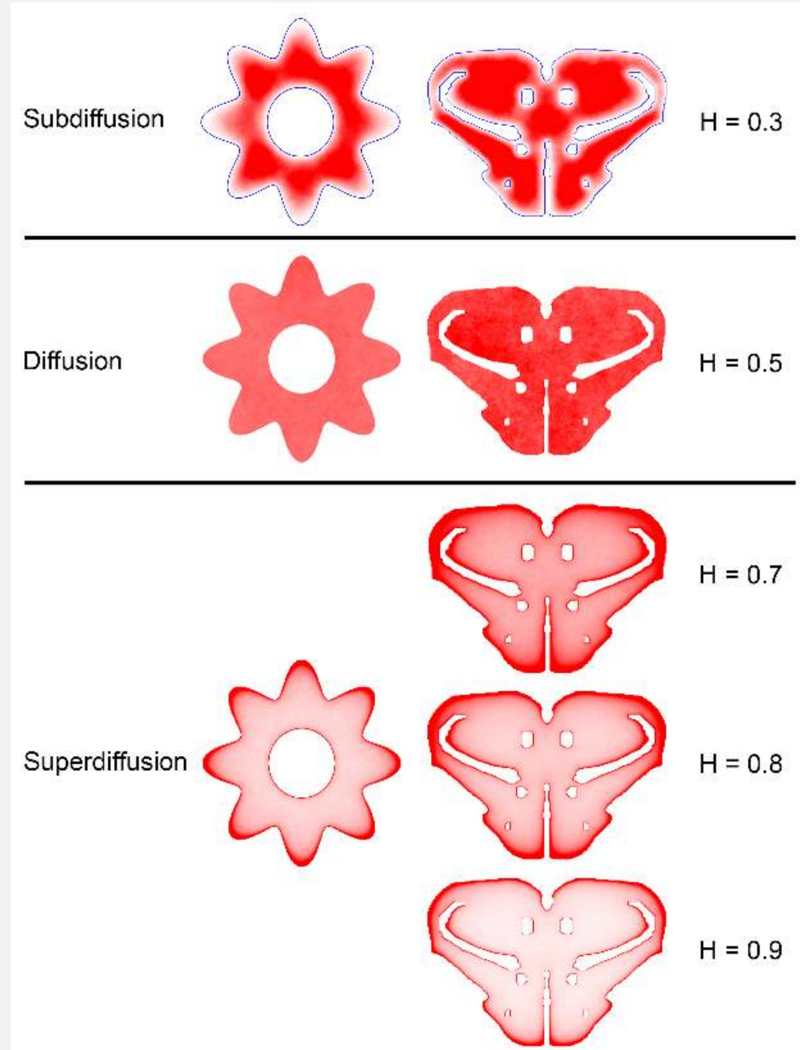
Brain serotonergic axons as FBM paths

Correlated fluctuations effect non-flat profile



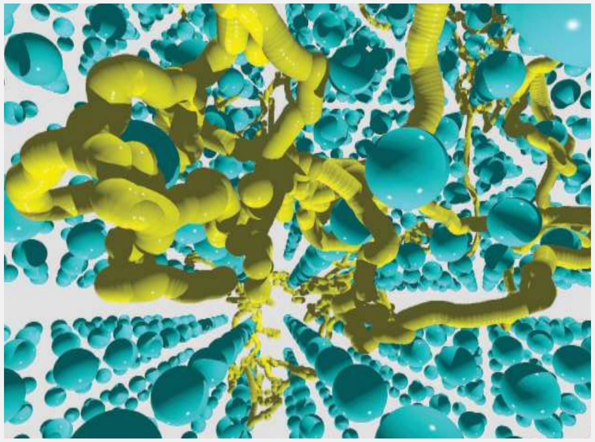




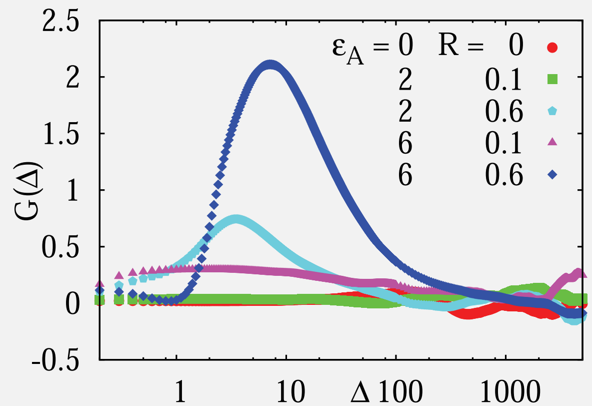


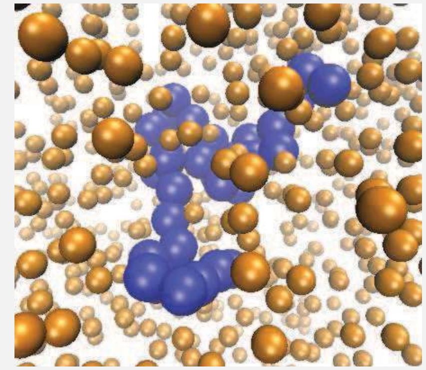
S Janušonis, N Detering, RM & T Vojta, Front Comp Neurosc (2020); T Guggenberger, T Vojta & RM, NJP (2019)

Non-Gaussianity & anomalous diffusion in crowding

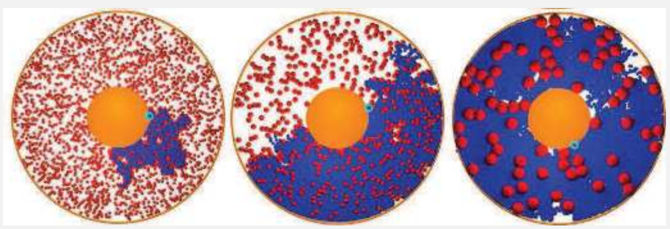


S Ghosh, AG Cherstvy & RM, PCCP (2015)

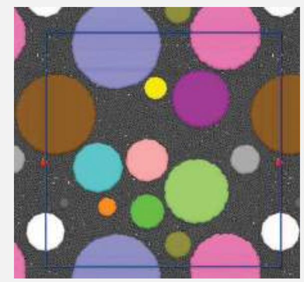


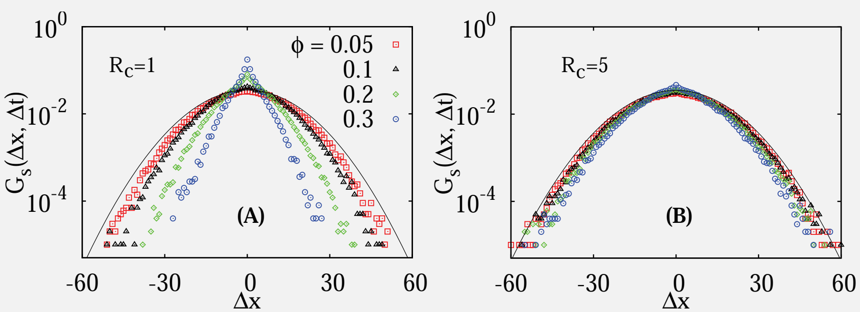


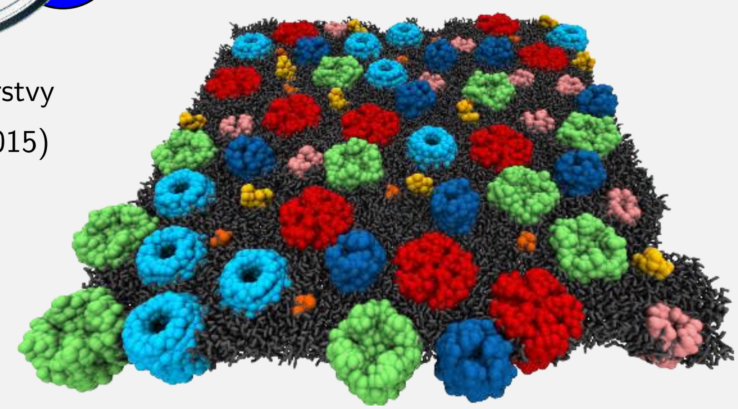
J Shin, AG Cherstvy WK Kim & RM, PCCP (2015)



J Shin, AG Cherstvy & RM, NJP (2015)



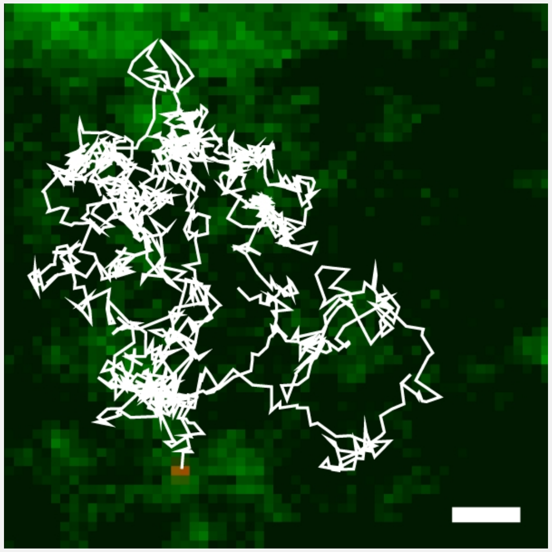


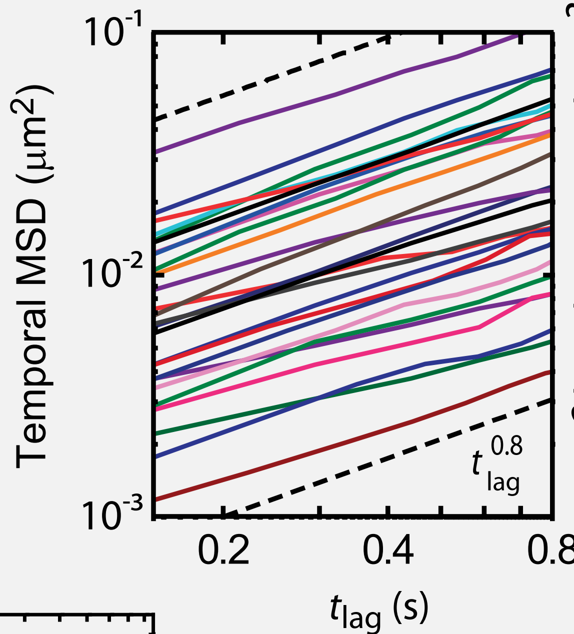


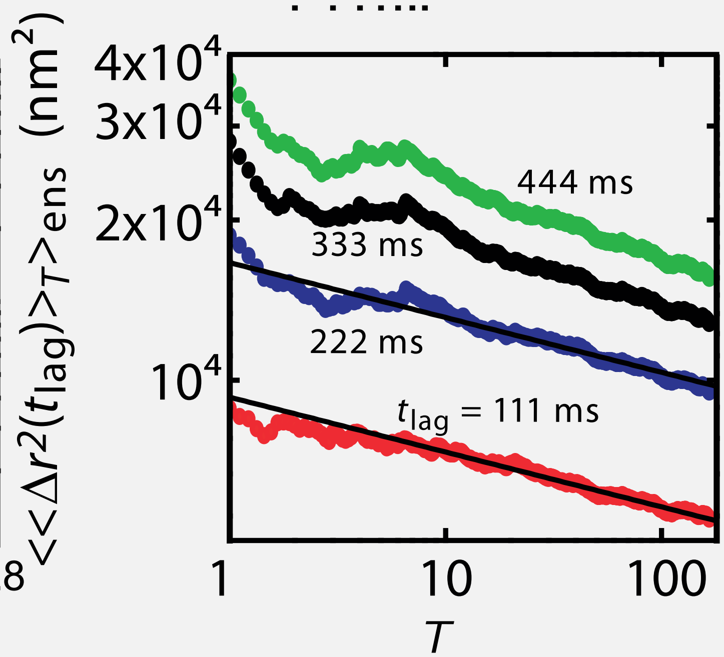
S Ghosh, AG Cherstvy, D Grebenkov & RM, NJP (2016)

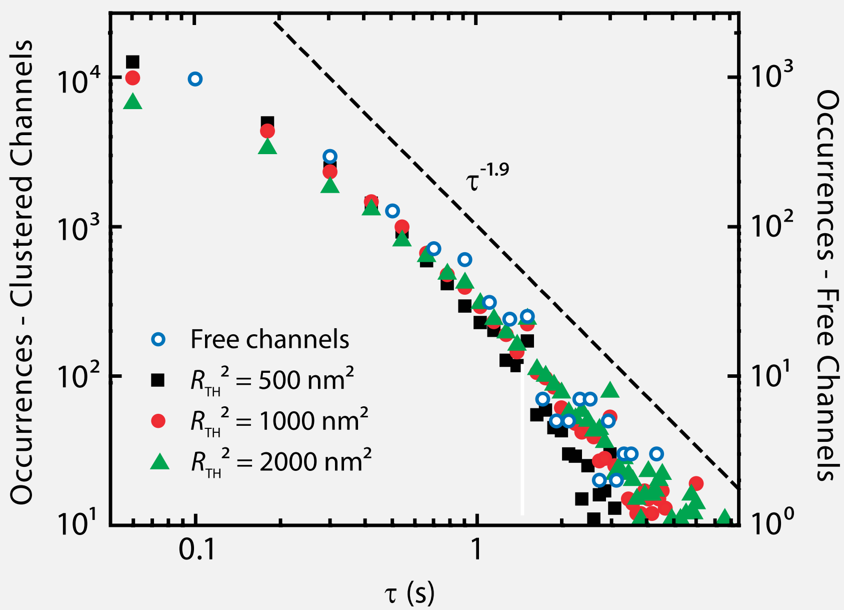
M Javanainen, H Seara, RM & I Vattulainen, JPC Lett (2017)

Case study V: trapping of Ka channels in plasma membrane









$\psi(\tau) \simeq \tau^{-1-\alpha}$ scale free

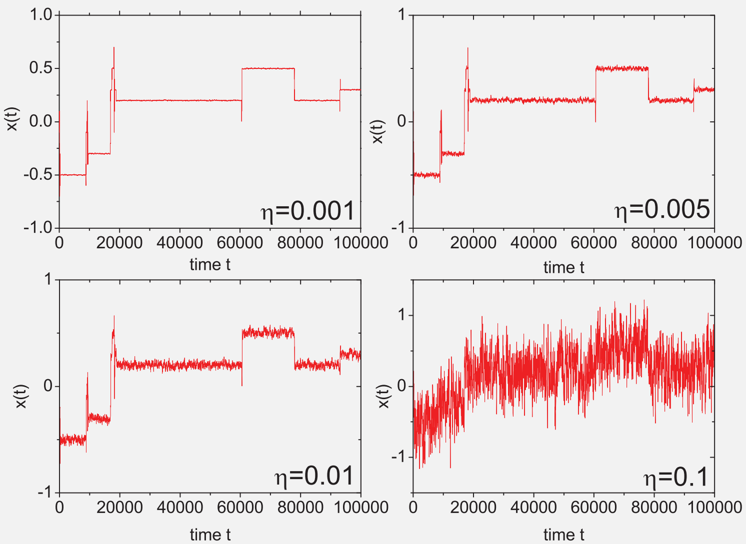
$\overline{\delta^2(t)}$ apparently random

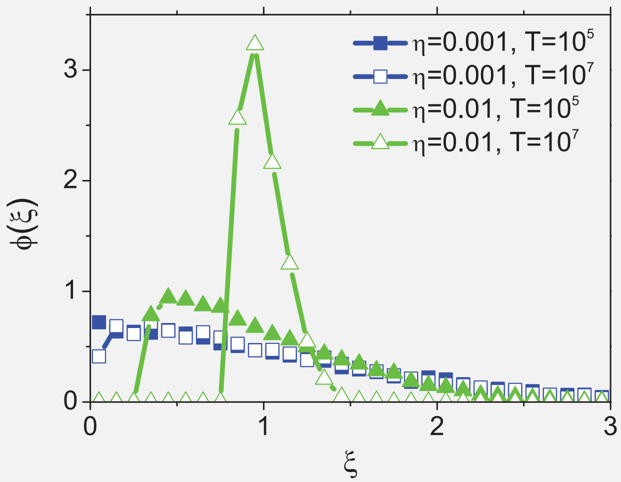
$$t/T^{1-\alpha} \simeq \overline{\delta^2(t)} \neq \langle \mathbf{r}^2(t) \rangle \simeq t^\alpha$$

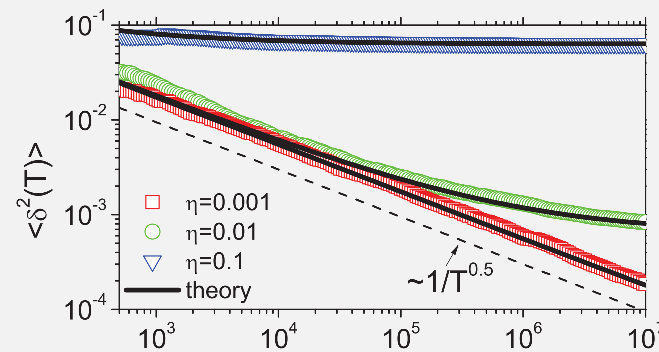
$$P(\mathbf{r}, t) \simeq \exp\left(-\beta r^{1/[1-\alpha/2]}\right)$$

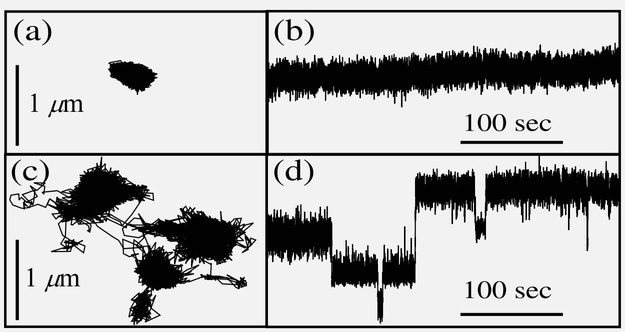
AV Weigel, B Simon, MM Tamkun & D Krapf, PNAS (2011); theory: Y He, S Burov, RM & E Barkai, PRL (2008)

Sumperimposed fluctuations in real systems

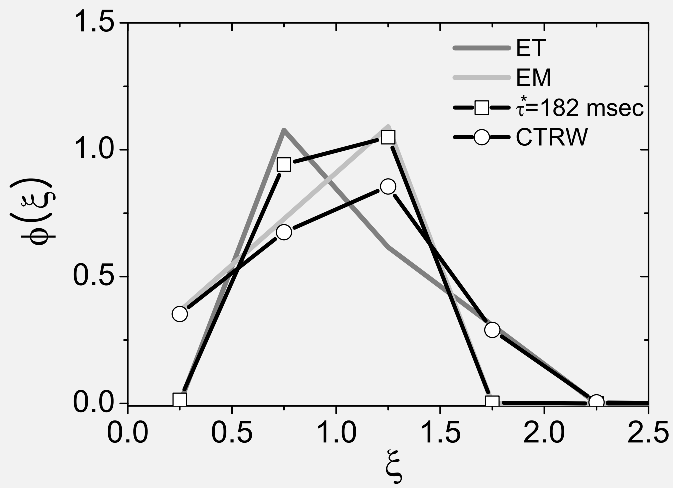


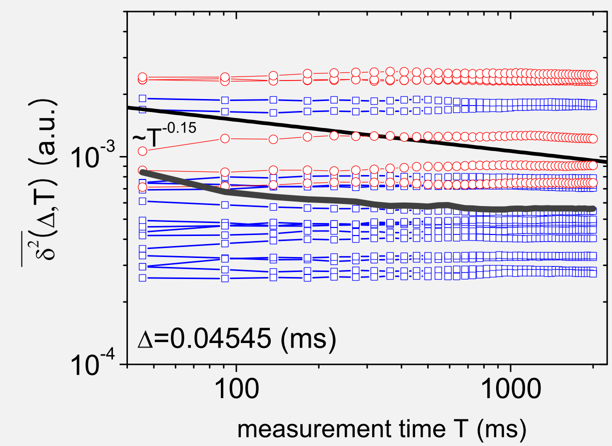






IY Wong . . . DA Weitz, PRL (2004)

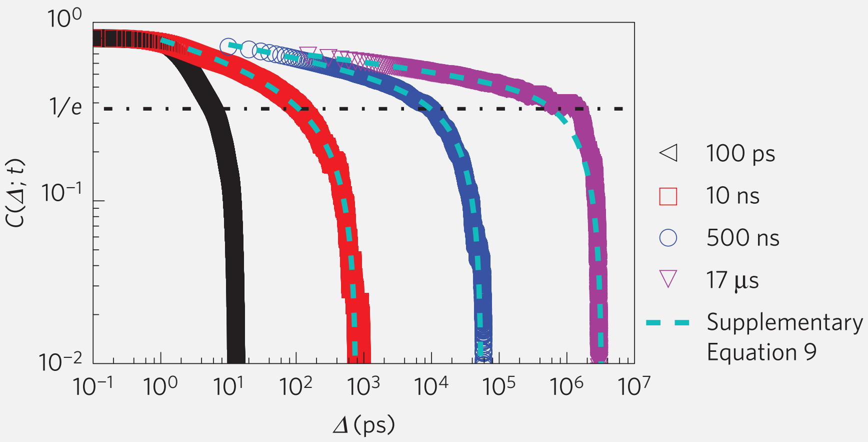


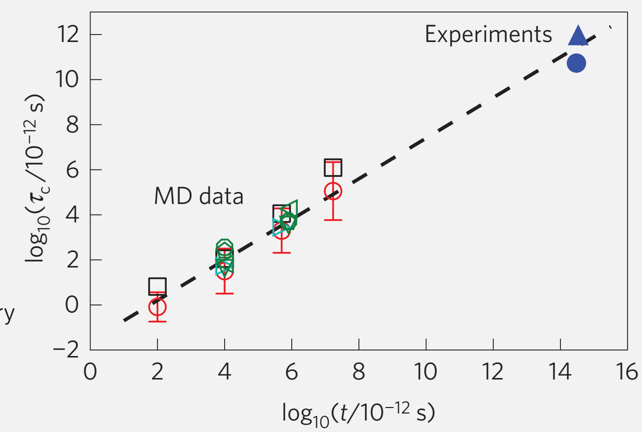


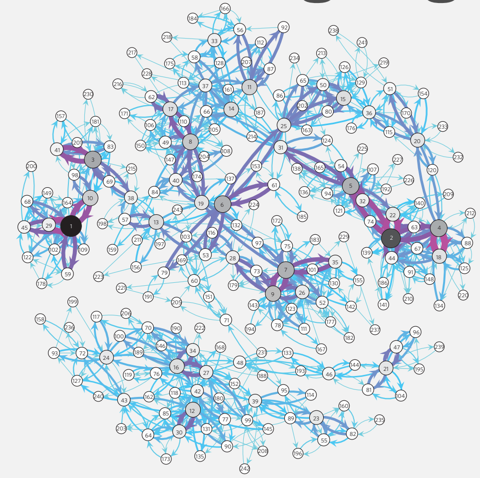
JH Jeon . . . K Berg-Sørensen, L Oddershede & RM, PRL (2011)

JH Jeon, E Barkai & RM, JCP (2013)

Self-similar internal protein dynamics: 13 decades of ageing



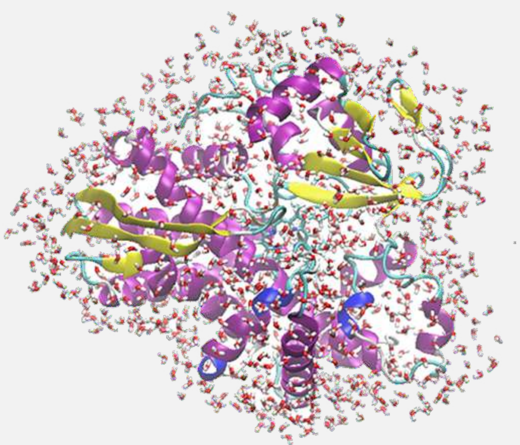




X Hu, L Hong, MD Smith, T Neusius, X Cheng & JC Smith, Nature Phys (2016); News & Views: RM, Nature Phys (2016)

Ageing renewal theory: J Schulz, E Barkai & RM, PRL (2013), PRX (2014)

Intermittent localisation of surface water on proteins



Bulk water:

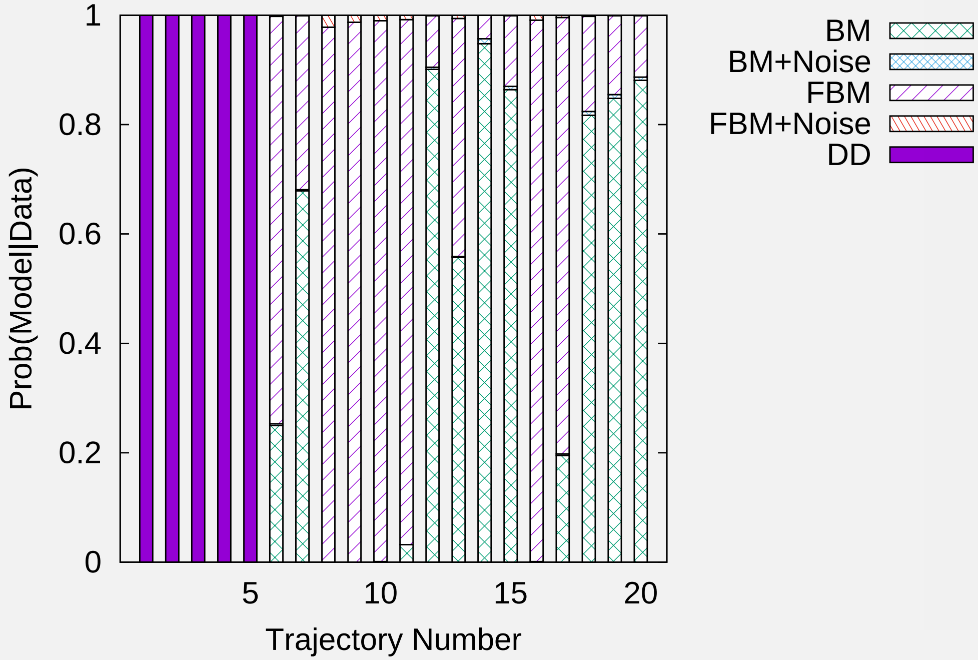
$\alpha = 1$

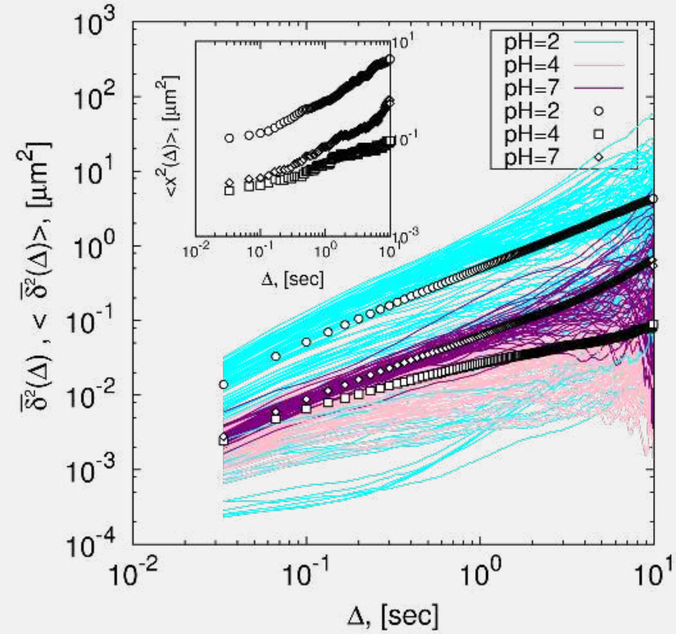
Hydration water:

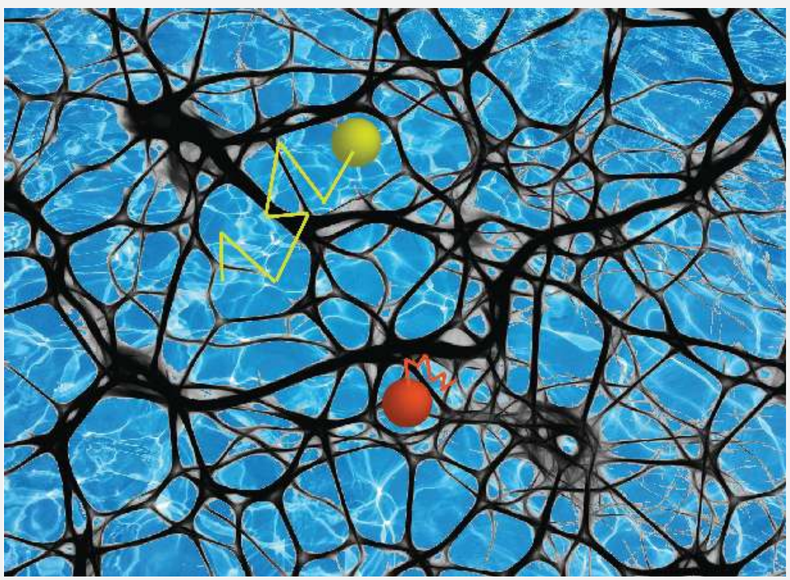
$\alpha \approx 0.8$

P Tan, Y Liang, Q Xu, E Mamontov, J Li, X Xing & L Hong, Phys Rev Lett (2018); see also RM, Viewpoint Phys (2018)

Maximum likelihood Bayesian data analyses



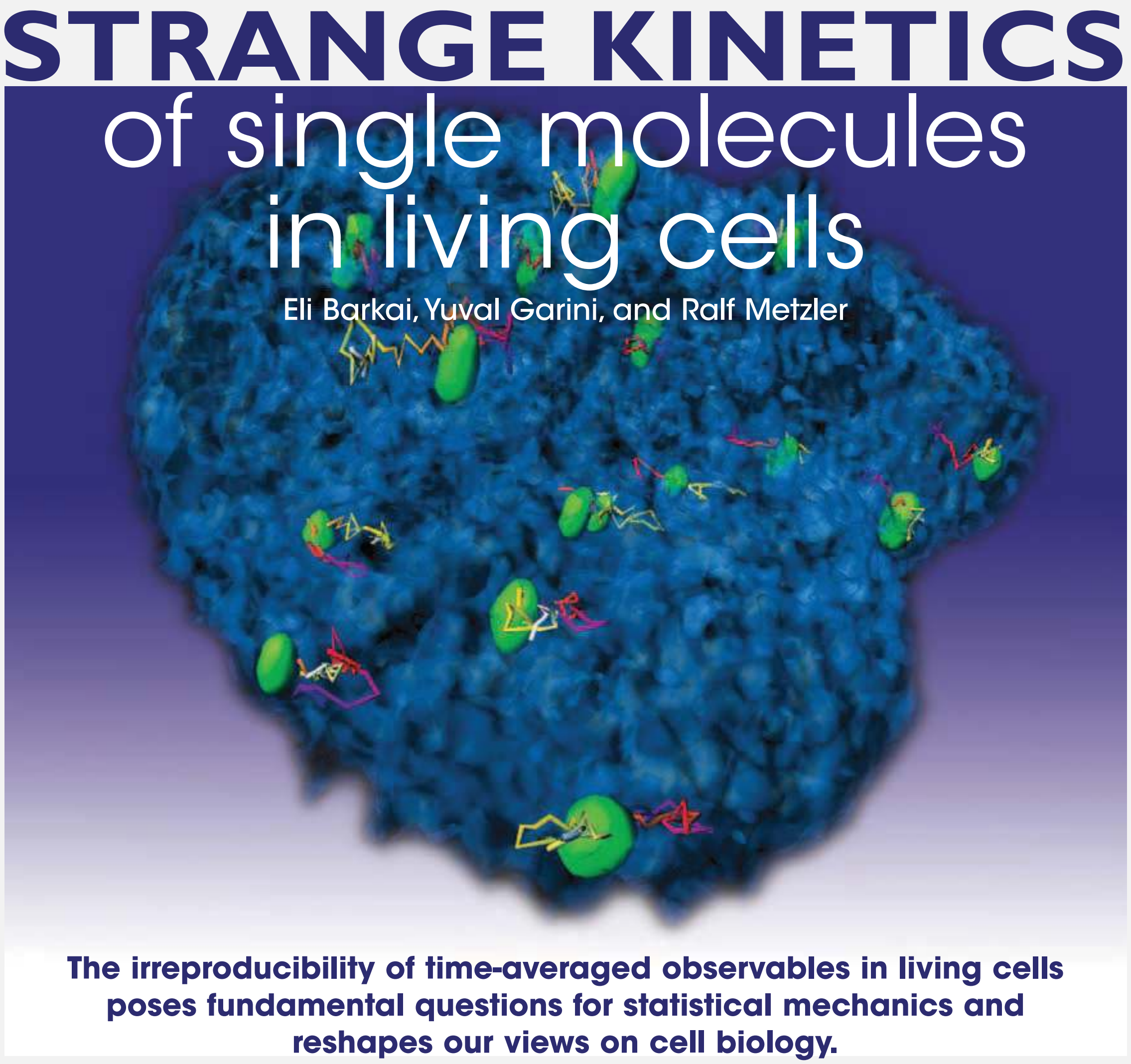


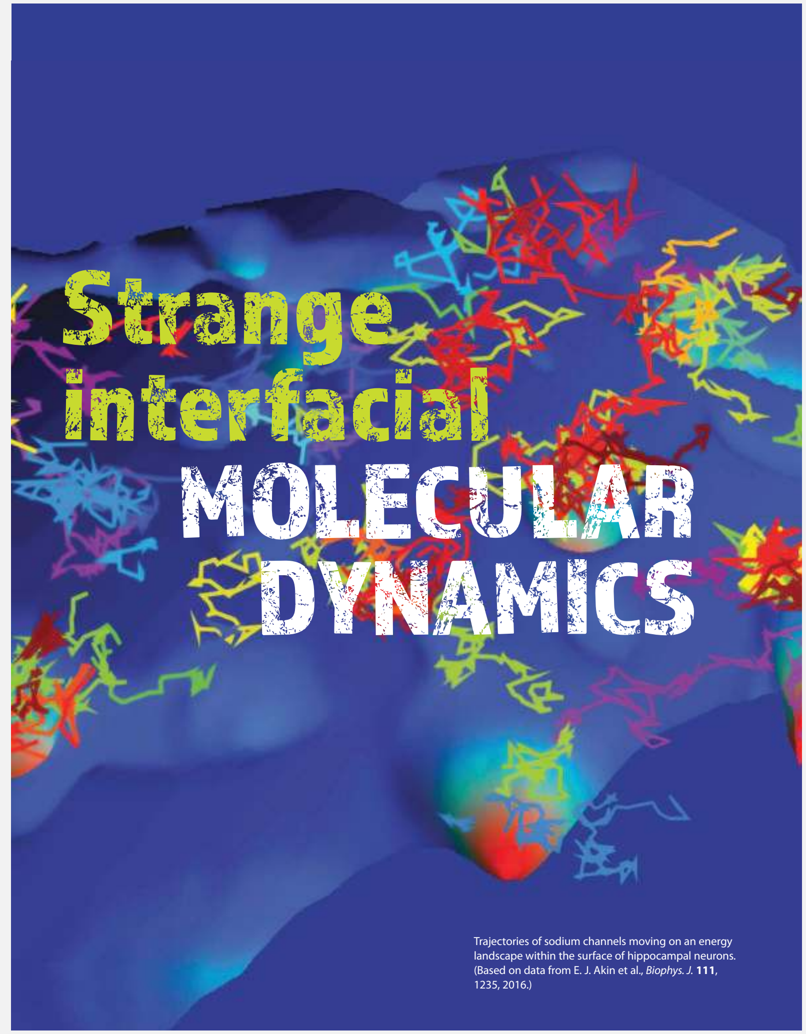


Nested sampling à la Skilling

Objective model selection

Parameter estimation





E Barkai, Y Garini & RM, Phys Today (2012); D Krapf & RM, Phys Today (2019)

∑ummary

- Don’t (always) average: learn from fluctuations
- Strong fluctuations in reaction times
- Fluctuations of diffusivities: Brownian yet non-Gaussian fluctuations
- Fluctuations of single-trajectory TAMSDs and power spectra
- Ageing CTRW: fluctuations are asymptotic
- Physics$\leftrightarrow$ARIMA time series analysis: J Ślęzak, K Burnecki & RM, NJP (2019)
- Bayes/max likelihood model determination

- Membrane dynamics: RM, JH Jeon & AG Cherstvy, Biochimica et Biophysica Acta - Biomembranes **1858**, 2451 (2016)
- Single molecule experiments: C Nørregaard, RM, CM Ritter, K Berg-Sørensen & LB Oddershede, Chem Rev **117**, 4342 (2017)
- Anomalous diffusion models: RM, JH Jeon, AG Cherstvy & E Barkai, Phys Chem Chem Phys **16**, 24128 (2014)

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