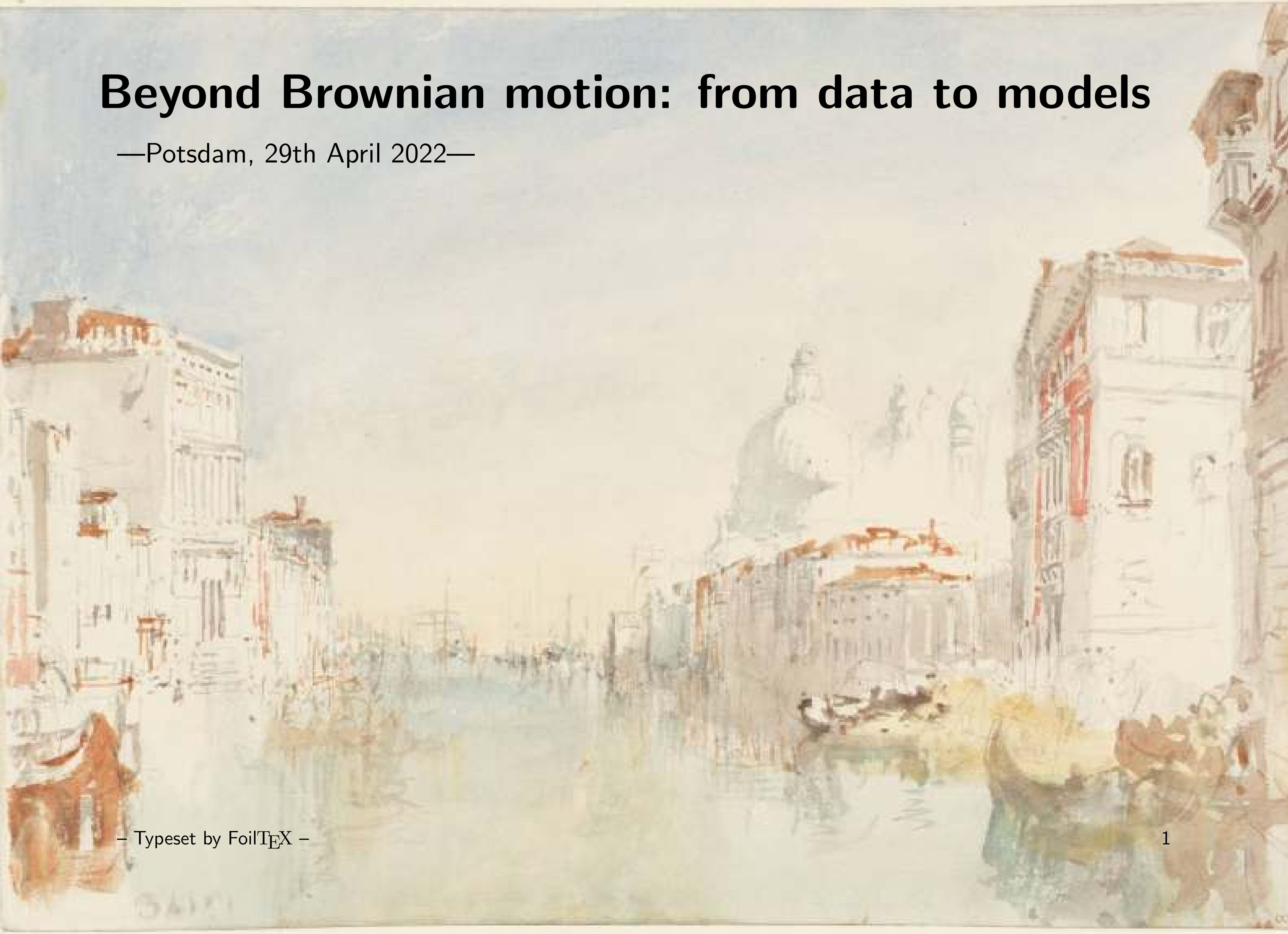


Beyond Brownian motion: from data to models

—Potsdam, 29th April 2022—

THE

PHILOSOPHICAL MAGAZINE

AND

ANNALS OF PHILOSOPHY.

[NEW SERIES.]

SEPTEMBER 1828.

XXVII. *A brief Account of Microscopical Observations made in the Months of June, July, and August, 1827, on the Particles contained in the Pollen of Plants; and on the general Existence of active Molecules in Organic and Inorganic Bodies.* By ROBERT BROWN, *F.R.S., Hon. M.R.S.E. & R.I. Acad., V.P.L.S., Corresponding Member of the Royal Institutes of France and of the Netherlands, &c. &c.*

[We have been favoured by the Author with permission to insert the following paper, which has just been printed for private distribution.—ED.]

My inquiry on this point was commenced in June 1827, and the first plant examined proved in some respects remarkably well adapted to the object in view.

This plant was *Clarckia pulchella*, of which the grains of pollen, taken from antheræ full grown, but before bursting, were filled with particles or granules of unusually large size, varying from nearly $\frac{1}{4000}$th to about $\frac{1}{3000}$th of an inch in length, and of a figure between cylindrical and oblong, perhaps slightly flattened, and having rounded and equal extremities. While examining the form of these particles immersed in water, I observed many of them very evidently in motion; their motion consisting not only of a change of place in the fluid, manifested by alterations in their relative positions, but also not unfrequently of a change of form in the particle itself; a contraction or curvature taking place repeatedly about the middle of one side, accompanied by a corresponding swelling or convexity on the opposite side of the particle. In a few instances the particle was seen to turn on its longer axis. These motions were such as to satisfy me, after frequently repeated observation, that they arose neither from currents in the fluid, nor from its gradual evaporation, but belonged to the particle itself.

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 minerals of granite, a fragment of the Sphinx being one of the specimens examined.

Fluxes, random walks, & fluctuating forces: $\langle \mathbf{r}^2(t)\rangle \propto Kt$

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

Marian Smoluchowski
(1872-1917)

William Sutherland
(1859-1911)

Einstein's conditions on Brownian motion

Paul Lévy [Processus stochastiques & mouvement brownien (1965)]: ≪The stochastic process, that we will call linear Brownian motion, is a schematisation that well represents the properties of real Brownian motion, observable on a sufficiently small but not infinitely small scale, and which assumes that the same properties exist across the scales.≫

Einstein's postulate: a stochastic process describes normal diffusion if

(i) $\exists$ finite correlation time beyond which displacements are independent

(ii) displacements are identically distributed

(iii) displacements have a finite second moment

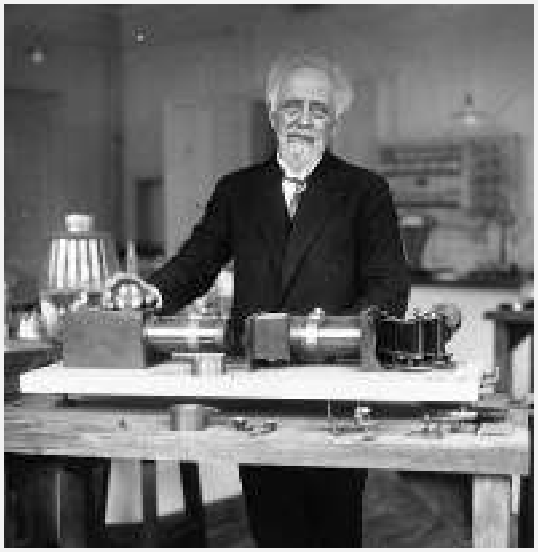
Main characteristics: linear mean squared displacement & Gaussian probability density

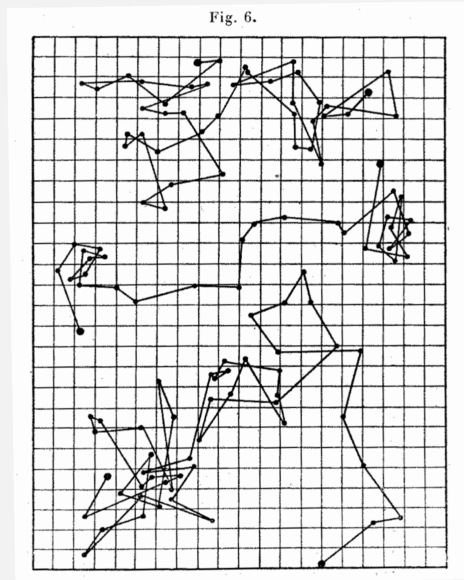
$$\langle \mathbf{r}^2(t)\rangle = 2dK_1 t, \quad P(\mathbf{r},t) = (4\pi K_1 t)^{-d/2} \exp\left(-\frac{\mathbf{r}^2}{4K_1 t}\right)$$

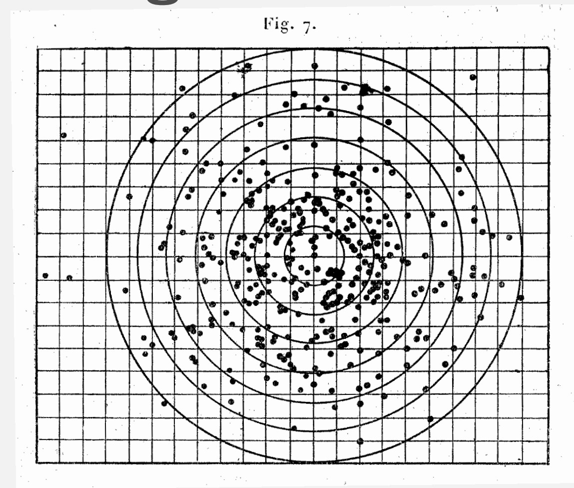
Violation of these conditions leads to anomalous diffusion with MSD $\langle \mathbf{r}^2(t)\rangle \simeq K_\alpha t^\alpha$ and/or non-Gaussian PDF

N van Kampen, Stochastic processes in physics & chemistry

Les atomes: Brownian motion and Avogadro's number

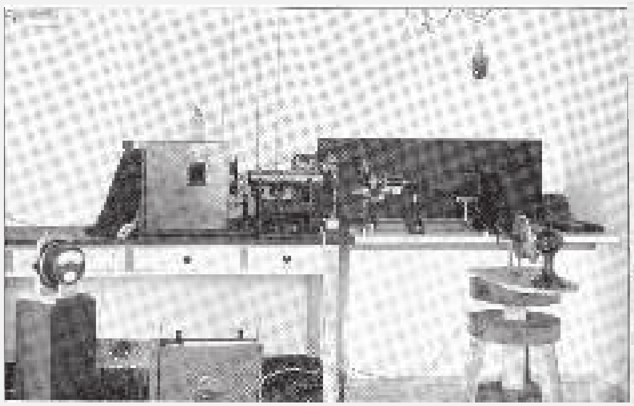


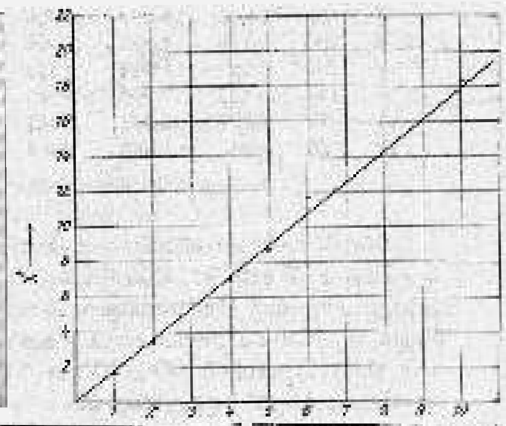




Δt=30 sec

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





J Perrin, Comptes Rendus (Paris) 146 (1908) 967: $N_A = 70.5 \times 10^{22}$; I Nordlund, Z Physik (1914): $N_A = 5.91 \times 10^{23}$

Brownian motion & random walks applied . . .

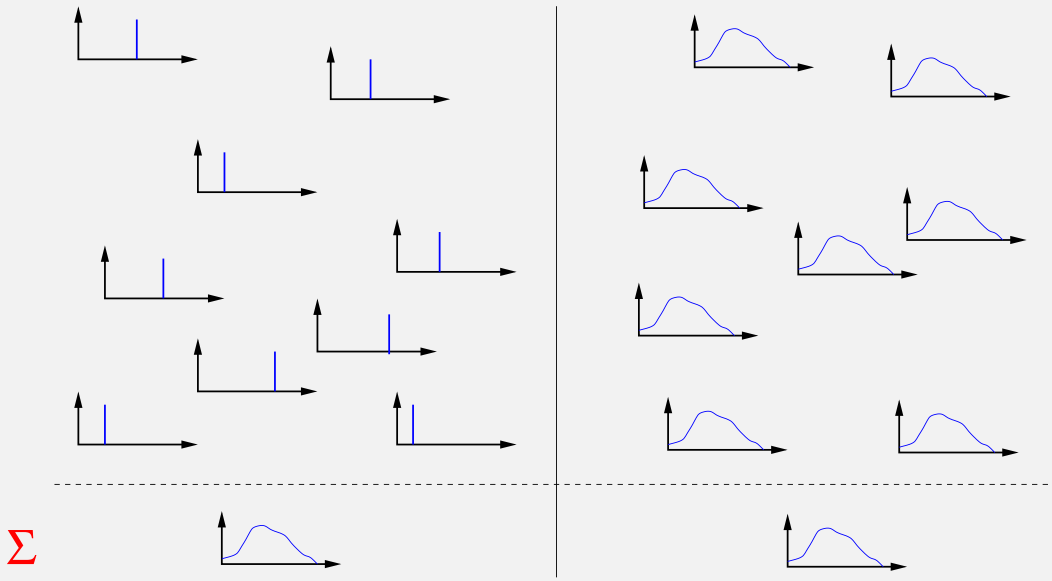
Louis Bachelier, 1900:
Brownian motion of
financial markets

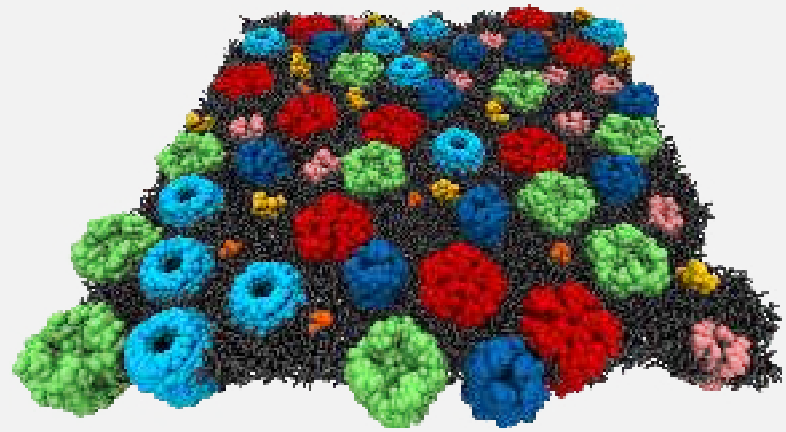
Karl Pearson, 1905:
Spreading of mosquitoes
in rain forests

Marian v Smoluchowski, 1916:
Molecular reaction kinetics

Elliott Montroll, 1943:
Manhattan project,
chain reaction of
neutrons

Single molecular insight & information from fluctuations





Courtesy Matti Javanainen

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

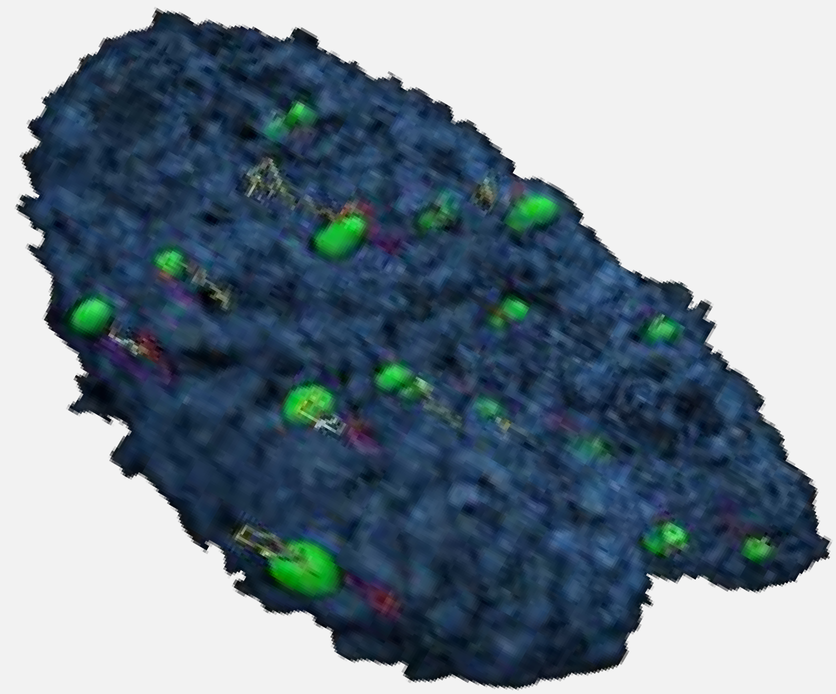
↷ Anomalous diffusion:

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

(non)ergodicity, ageing, quenched/annealed disorder

↷ Non-Gaussian displacement PDFs

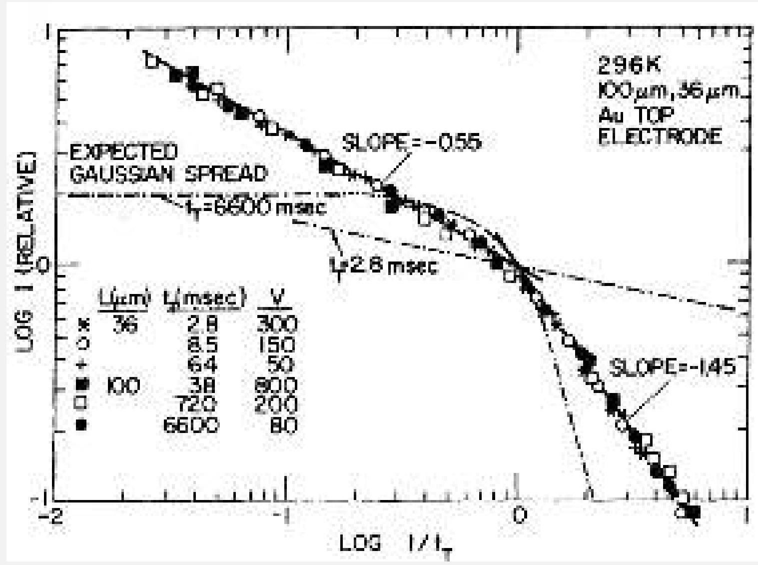
↷ Strong trajectory-trajectory fluctuations

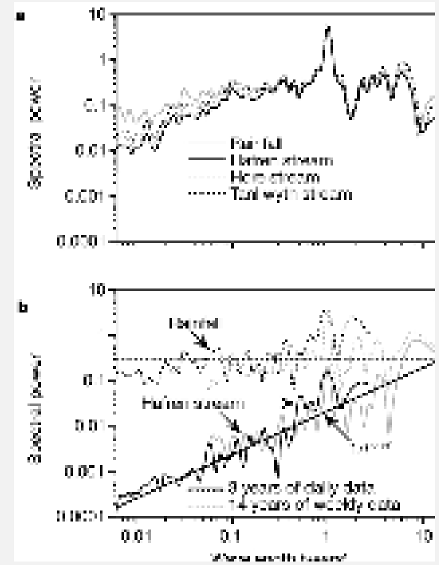


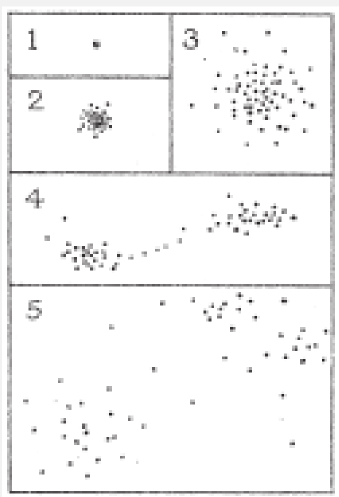
Courtesy Yuval Garini

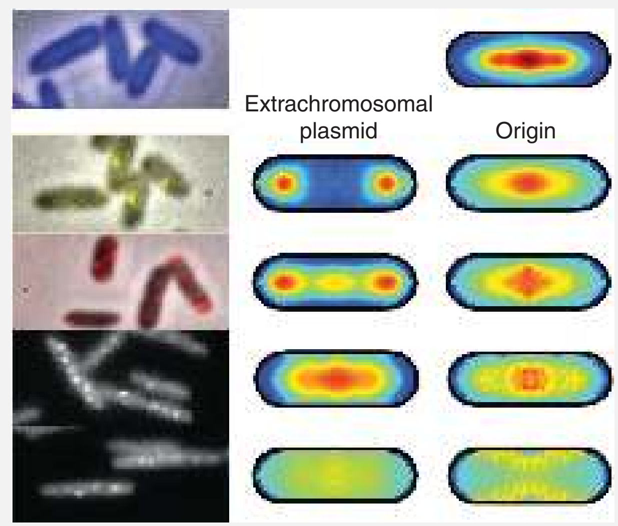
E Barkai, Y Garini & RM, Phys Today (2012)

Typical ensemble measurements

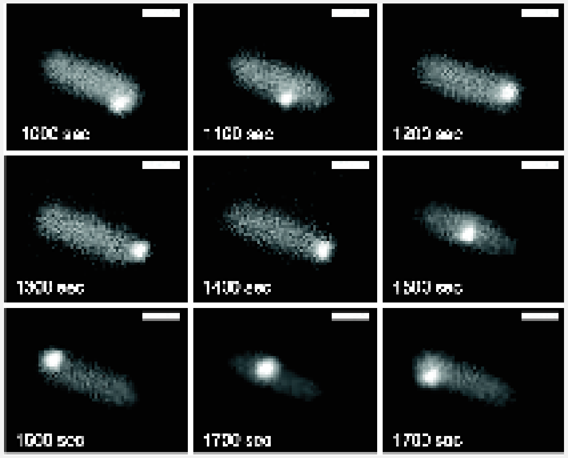


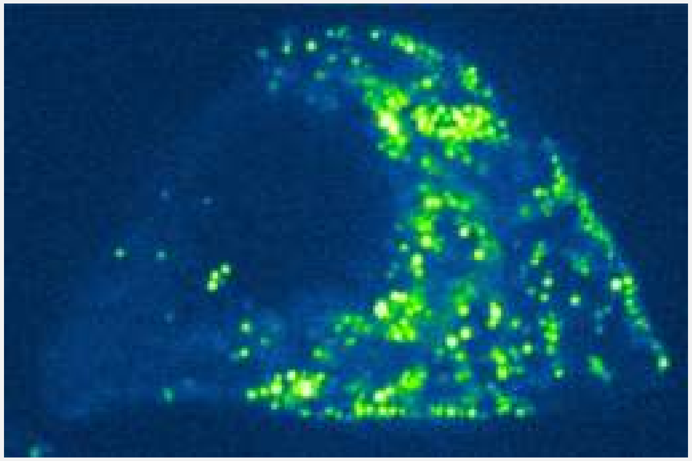


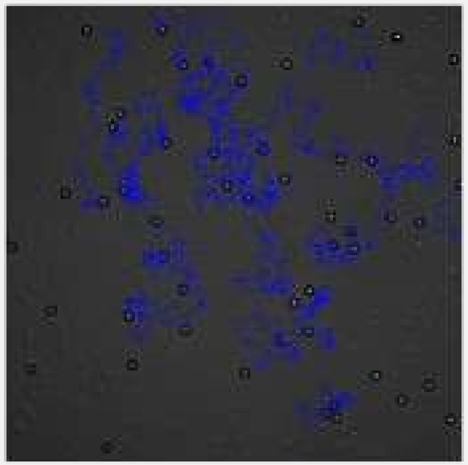

Figs. 1–5.

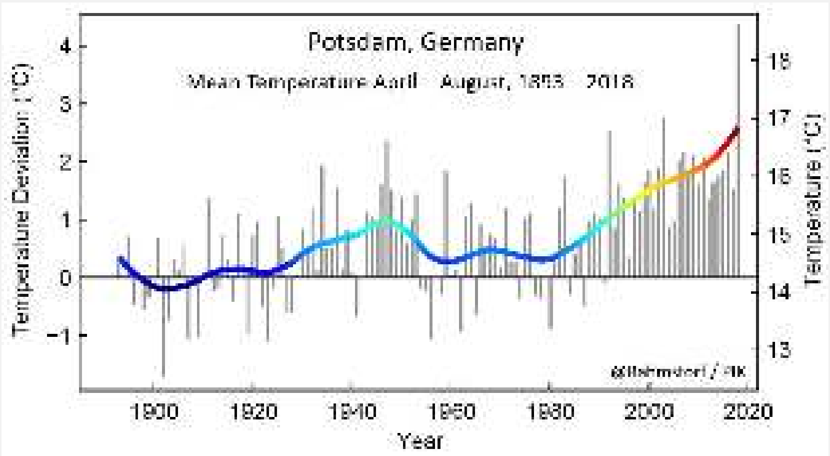


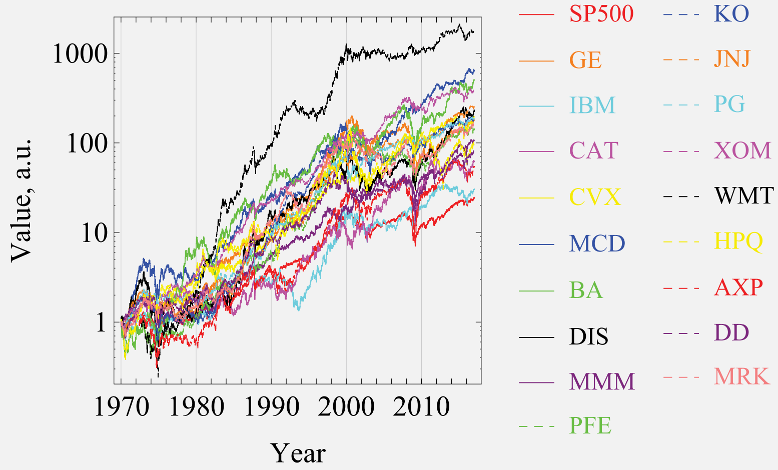
Typical single particle tracking (in lack of alternative)

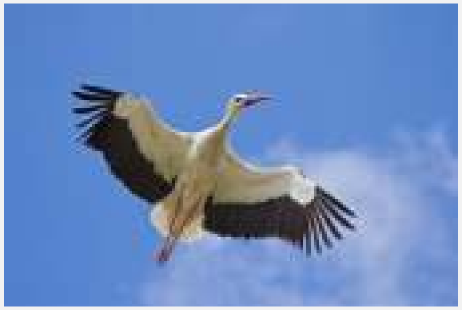








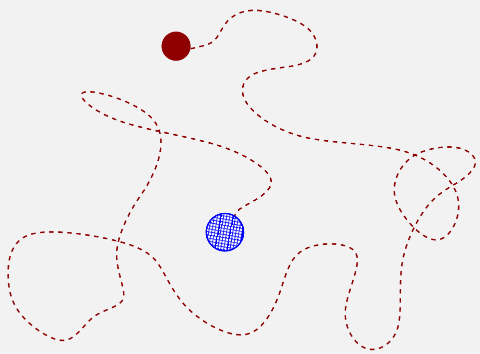


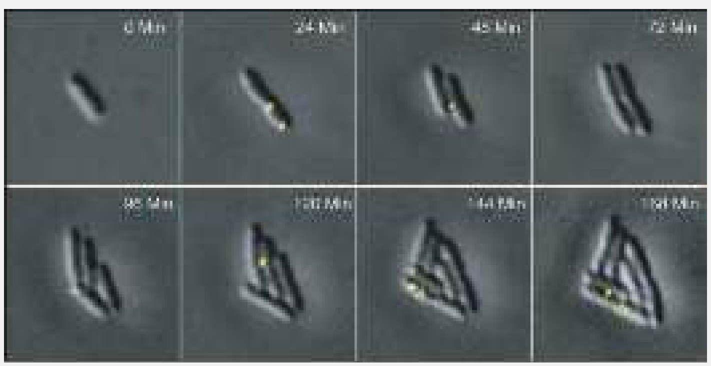


Molecular reaction times: macro vs micro

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

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

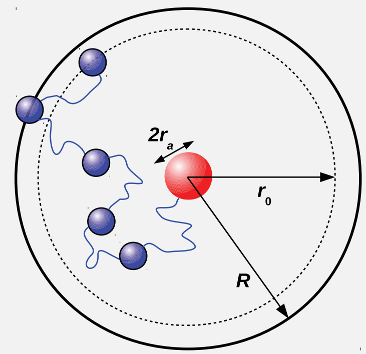


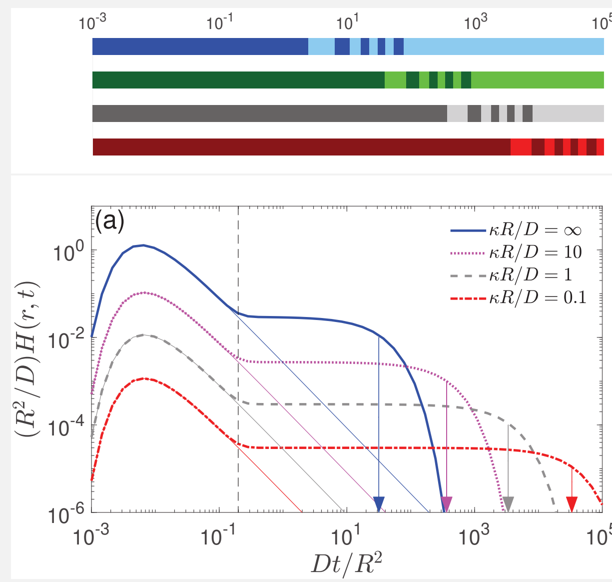


Yu et al, Science (2006)

Strong defocusing of reaction times

Geometry- vs reaction-control

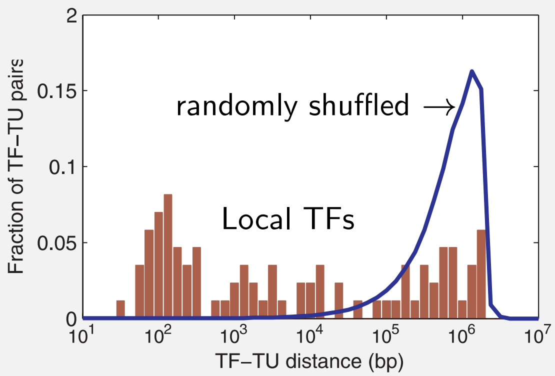


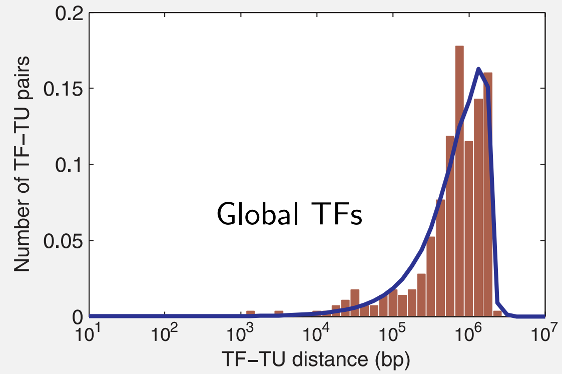


M v Smoluchowski, Physikal Zeitschr (1916)

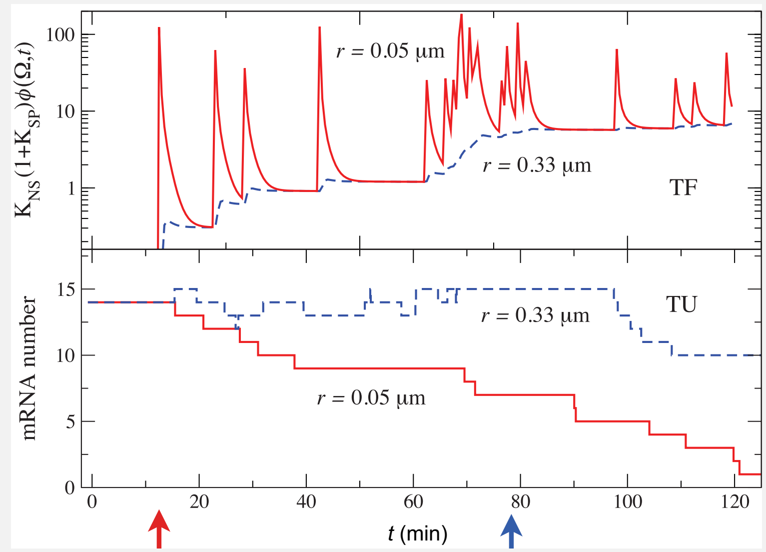
A Godec & RM, PRX (2016); D Grebenkov, RM & G Oshanin (2018-)

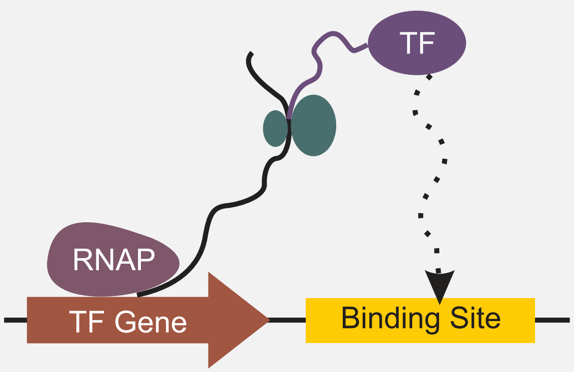
Rapid search hypothesis & why distance matters in 1μm cells

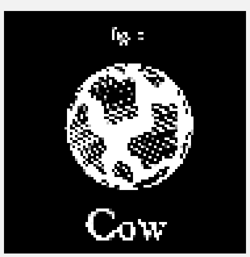


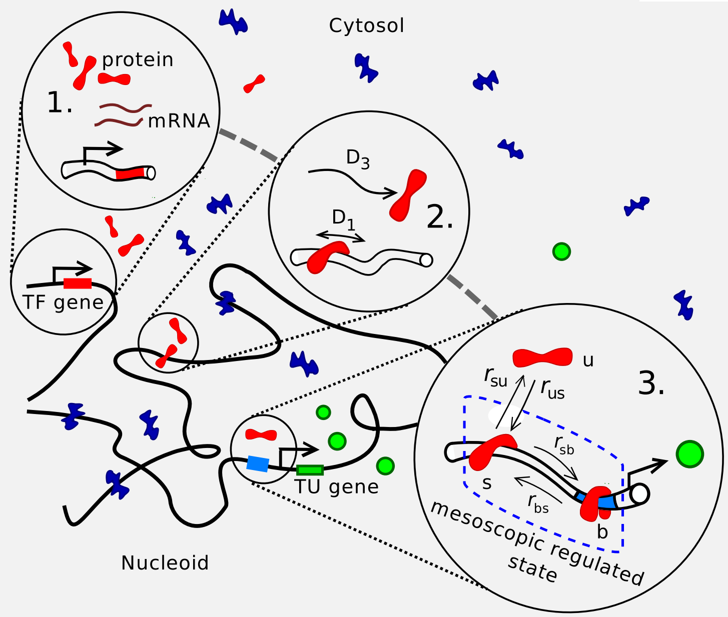


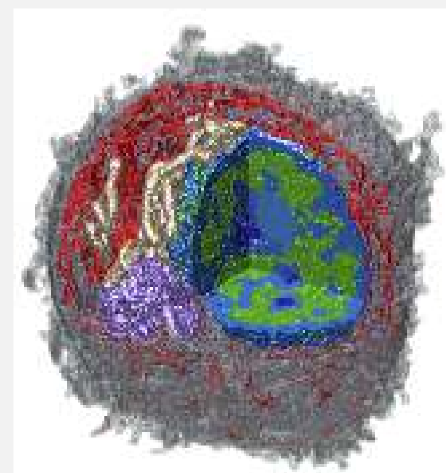
TF-TU gene-gene distance [G Kolesov . . . LA Mirny, PNAS (2007)]







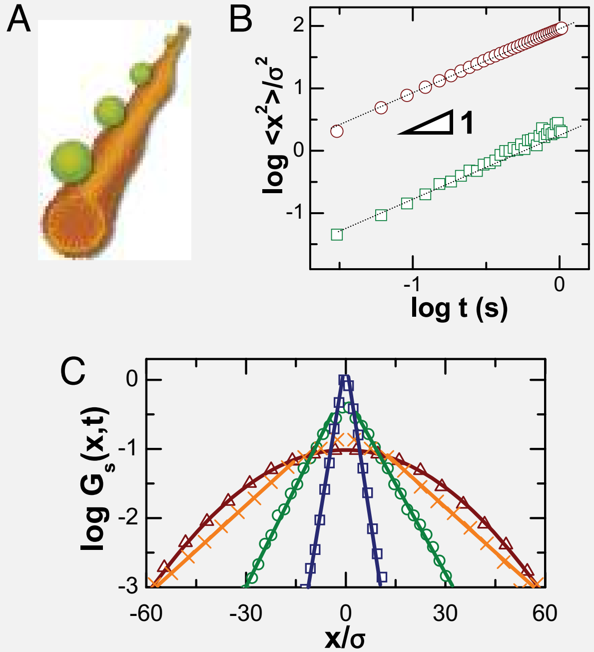




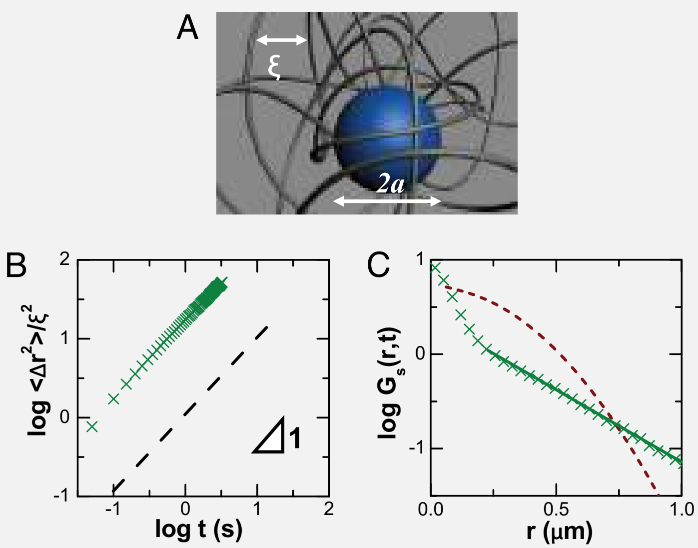
O Pulkkinen & RM, PRL (2013)

J Ma . . . SA Isaacson, PLoS Comp Biol (2020)

Brownian yet non-Gaussian diffusion in soft & bio-matter



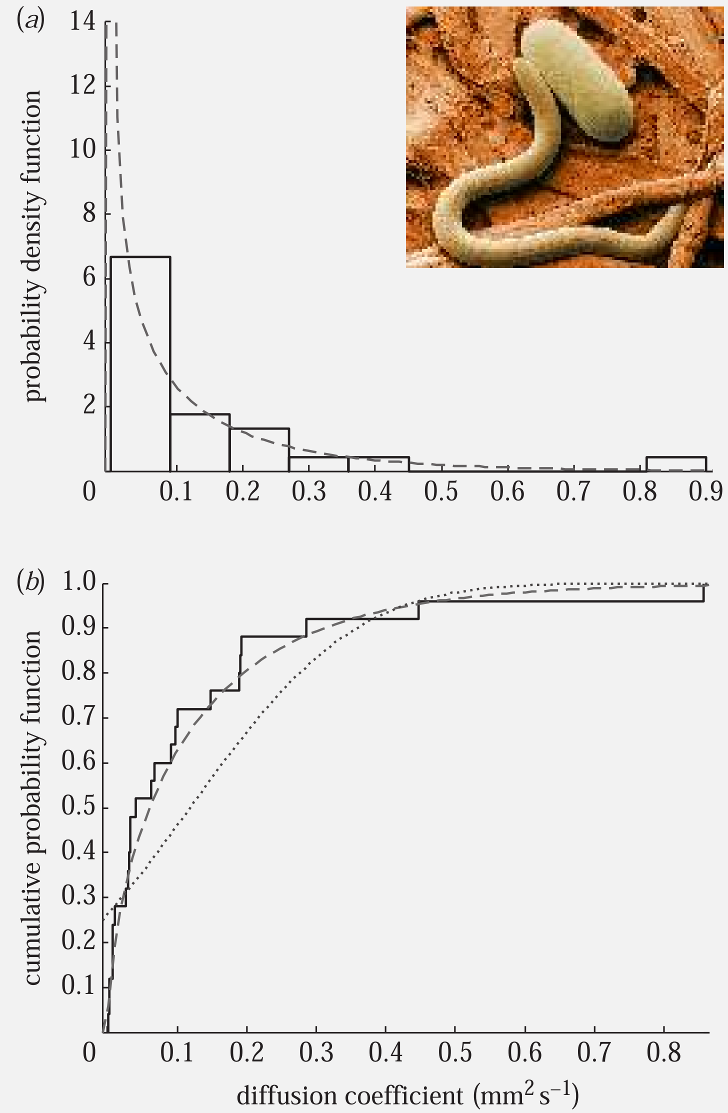
Colloidal beads on nanotubes



Nanospheres in entangled actin

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

Motion of *Phasmarhabditis* nematodes



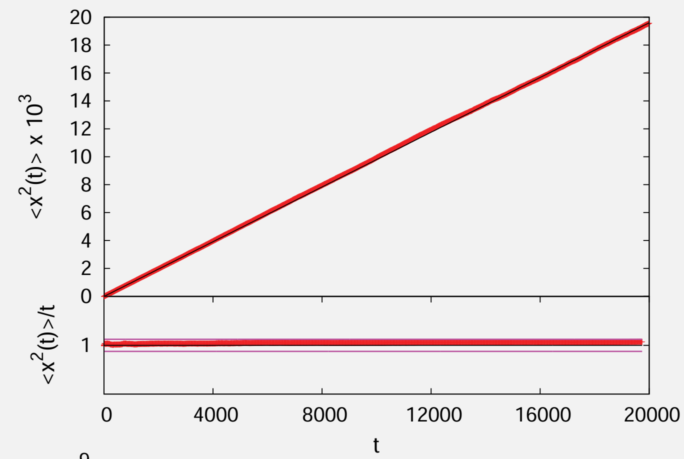
S Hapca, JW Crawford & IM Young, Interface (2009)

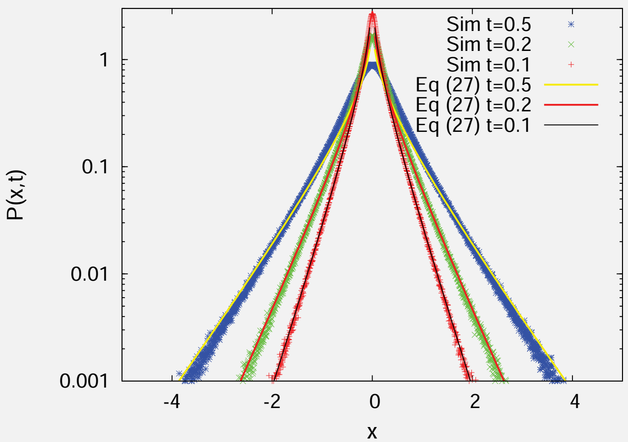
Fickian, non-Gaussian diffusion with diffusing diffusivity

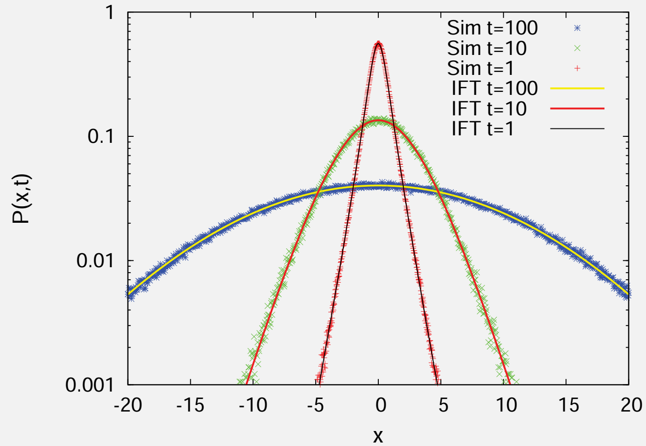
MV Chubinsky & G Slater, PRL (2014): diffusing diffusivity
[see also R Jain & KL Sebastian, JPC B (2016)]

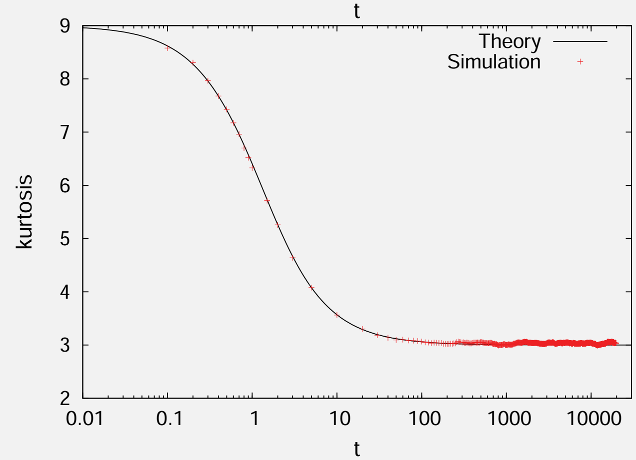
Our minimal model for diffusing diffusivity:

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



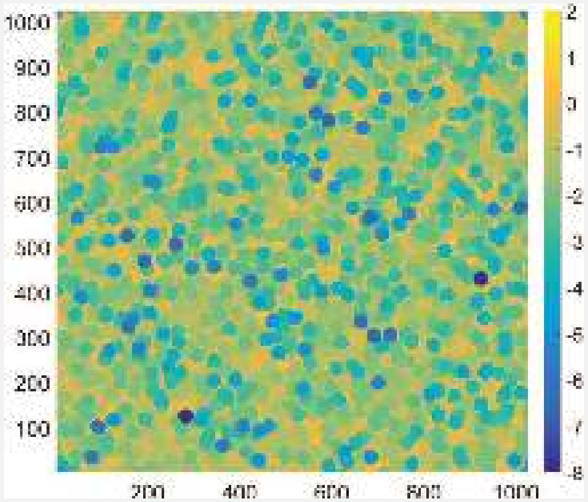
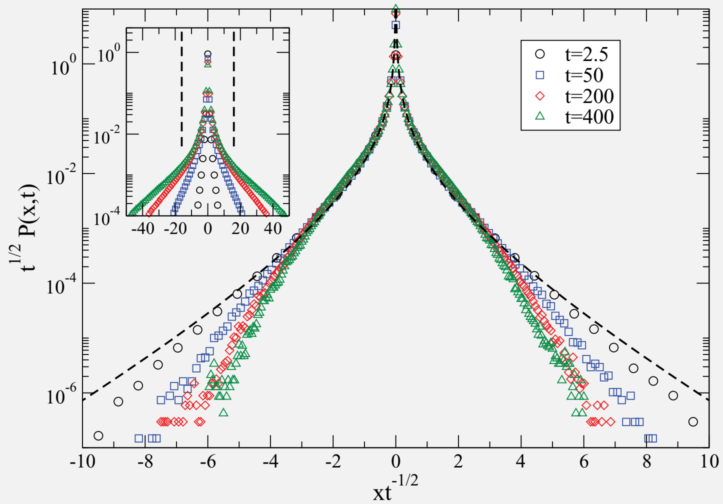






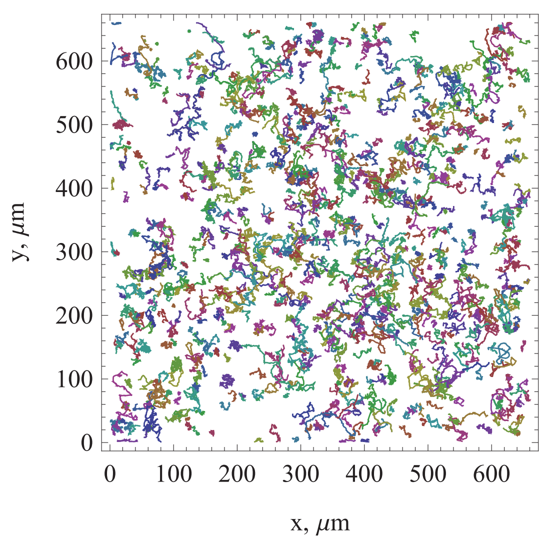
Generalised γ distribution & non-equilibrium diffusivity initial conditions: V Sposini, AV Chechkin, G Pagnini, F Seno & RM, NJP (2018)

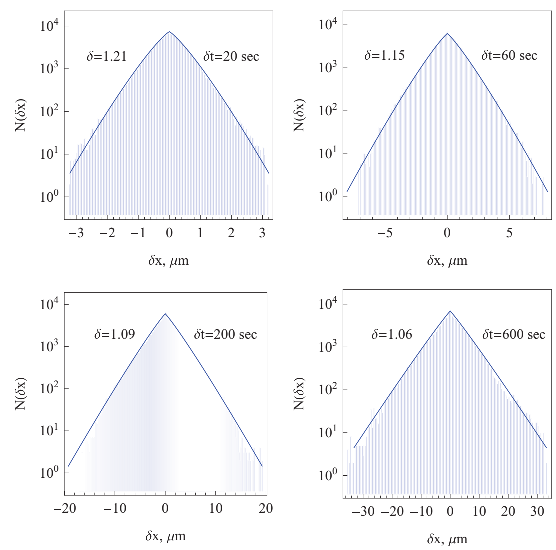
Non-Gaussian diffusion in quenched landscape models

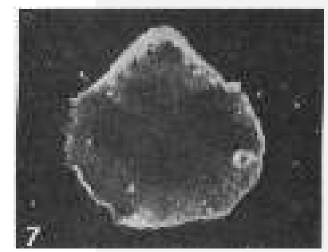



L Luo & M Yi, PRE (2018,2019); see also EB Postnikov, A Chechkin & IM Sokolov, NJP (2020)

Increasing non-Gaussianity in moving amoeba cells





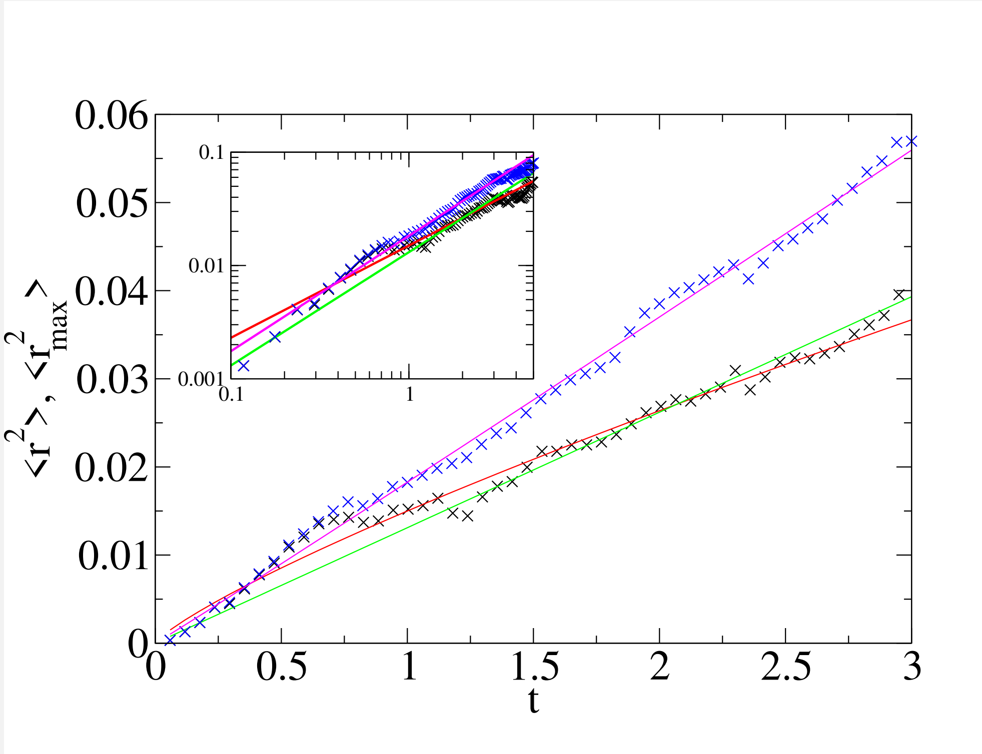


AG Cherstvy, O Nagel, C Beta & RM, PCCP (2018)

Fitting power-laws: Is it really anomalous?

Coefficient of variation is smaller for MME PDF than for regular PDF:

$$\gamma = \frac{\sqrt{\langle \mathbf{r}^2(t)\rangle - \langle \mathbf{r}(t)\rangle^2}}{\langle \mathbf{r}(t)\rangle} \rightsquigarrow \frac{\gamma(\text{MSD})}{\gamma(\text{MME})} = 1.61 \text{ (1D)},\ 1.44 \text{ (2D)},\ 1.34 \text{ (3D)}$$



Analysis of an experimental set of 67 trajectories, the longest consisting of 210 points, for quantum dots freely diffusing in a solvent. MSD (black $\times$), fitted by a power law with exponents $\alpha = 0.81$ (red line). We also show a fit with fixed exponent $\alpha = 1$ (green line, expected behavior for Brownian motion). MME (blue $\times$), fitted by a power law (red line, $\alpha = 1.02$). Time is in seconds, distances are in μm^2. Inset: double-logarithmic plot of the same data.

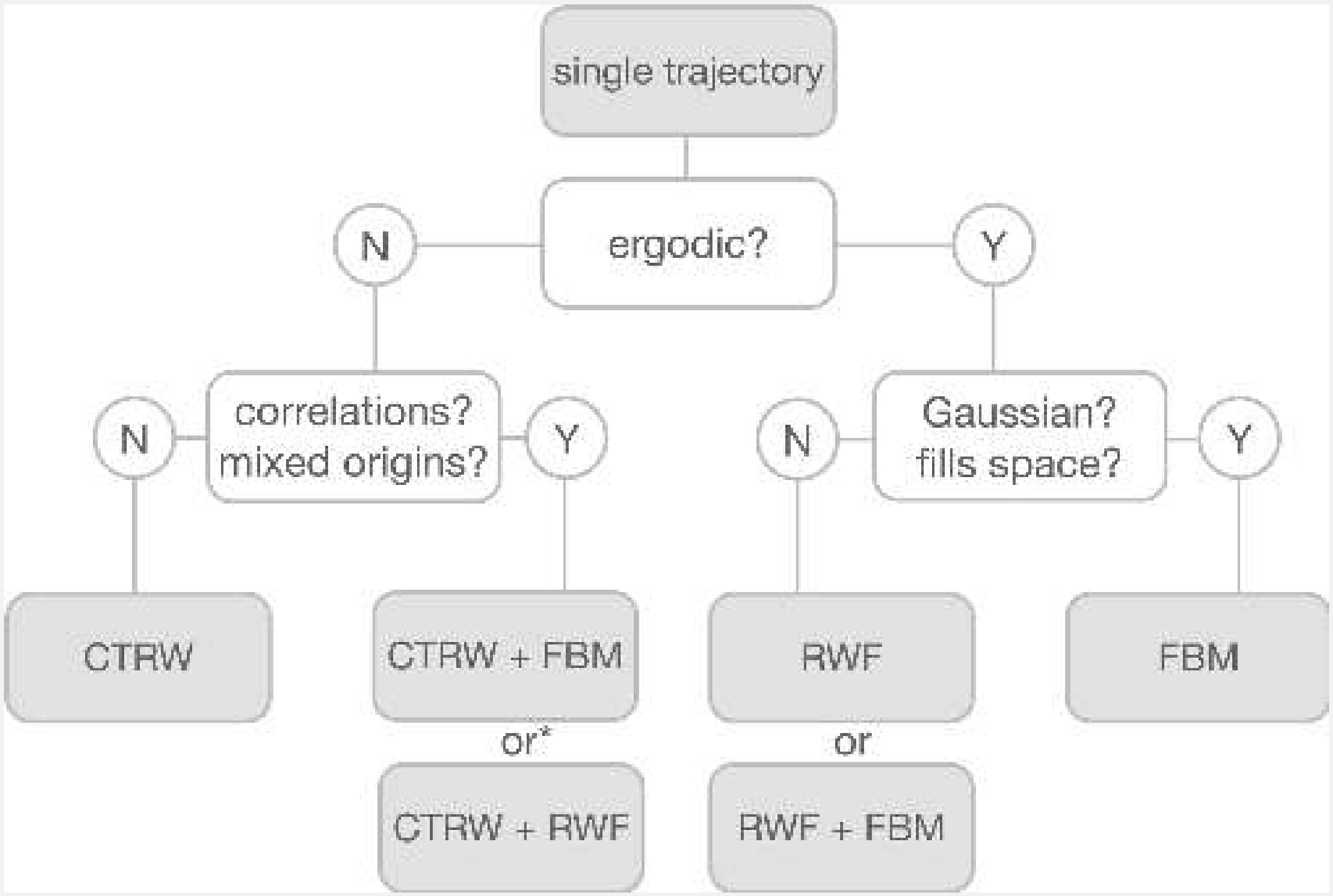
V Tejedor, O Bénichou, R Voituriez, R Jungmann, F Simmel, C Selhuber-Unkel, L Oddershede, BPJ (2010)

Complementary statistical observables enable decision trees

Central limit theorem (law of large numbers): emergence of “universal” Gaussian

Anomalous diffusion: universality broken, different processes effect $\langle \mathbf{r}^2(t)\rangle \simeq K_\alpha t^\alpha$

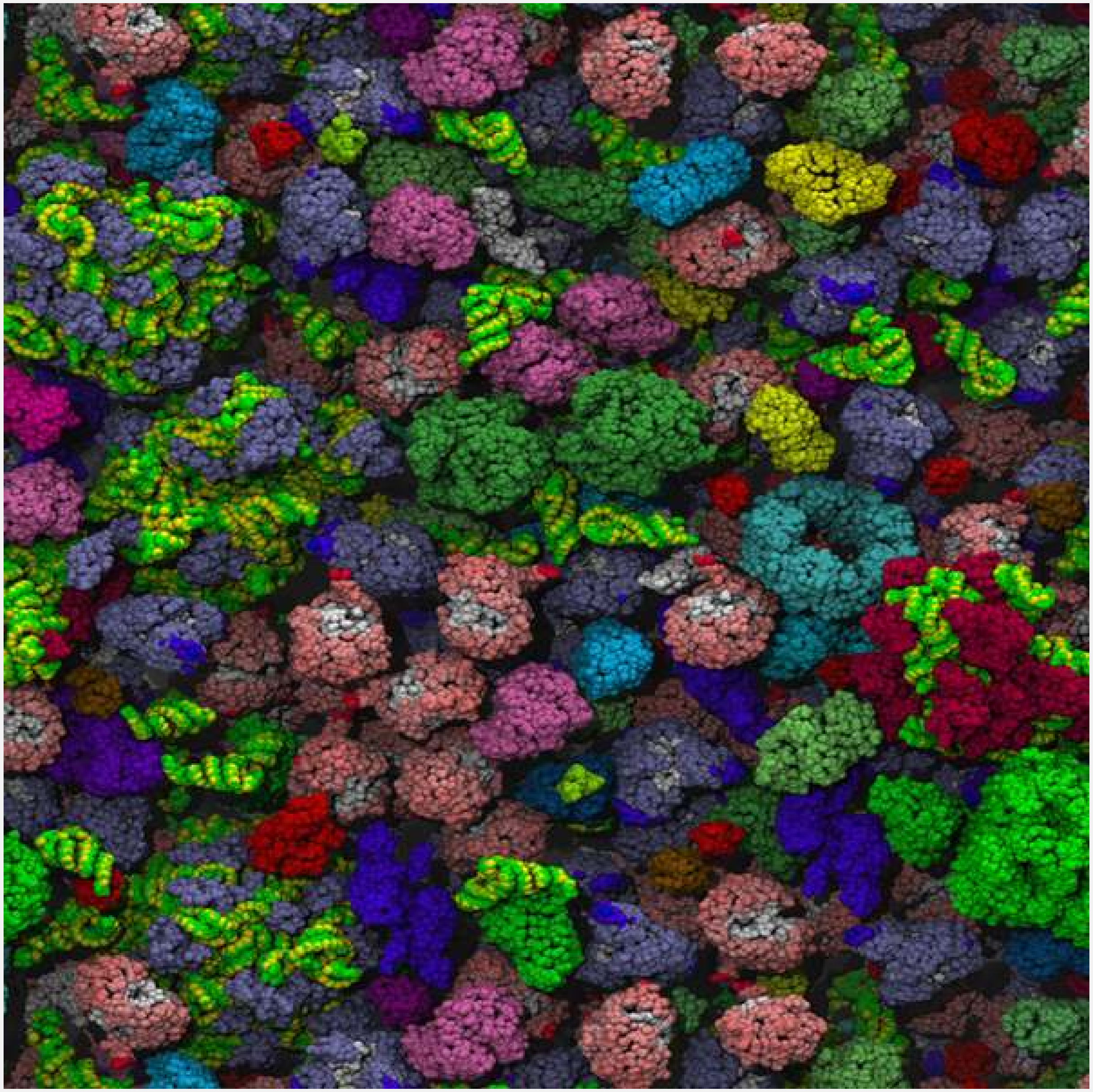
Physics from data? $\curvearrowright$ First-passage/reactions, parameter extraction . . .



Y Meroz & IM Sokolov, Phys Rep (2015)

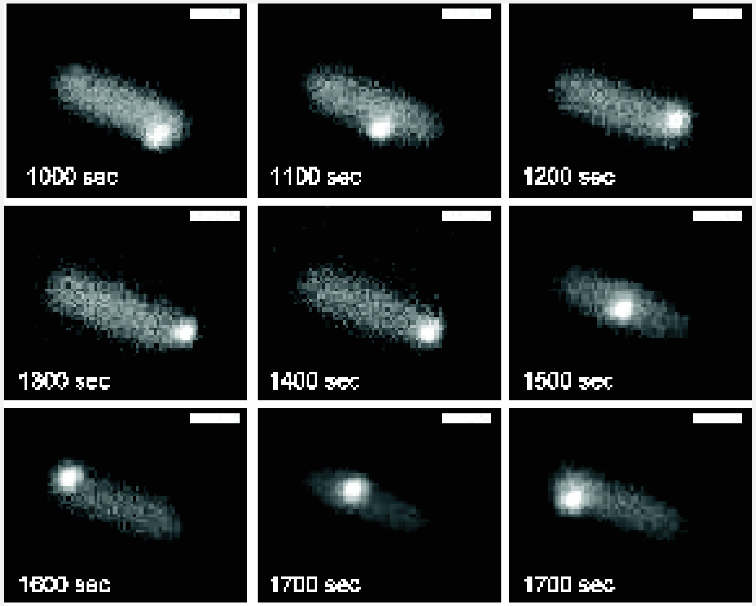

1 QUEEN'S PARK

Macromolecular crowding in living cells

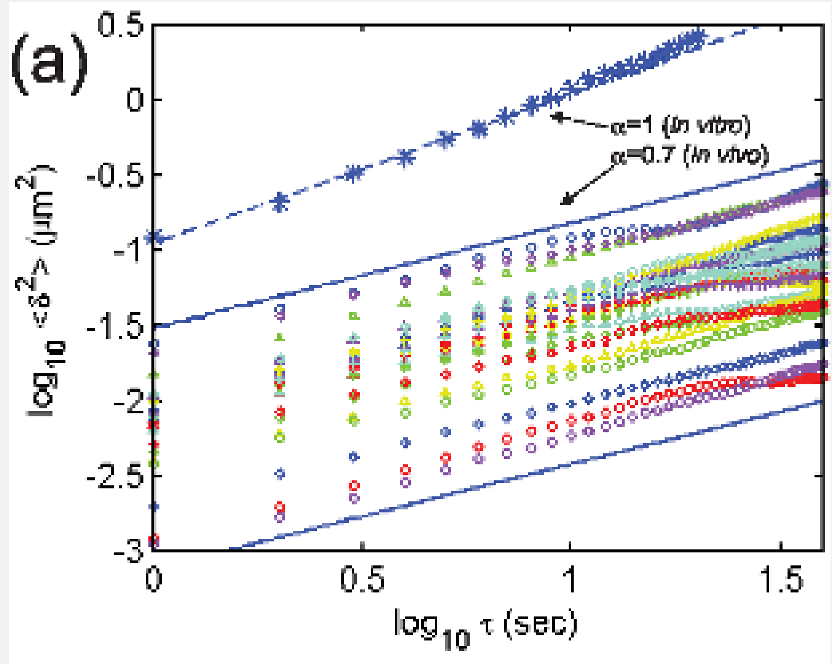


SR McGuffee & AH Elcock, PLoS Comp Biol (2010)

Crowding in cells effects anomalous diffusion

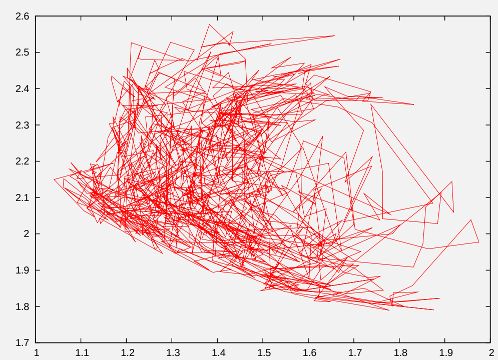


labelled mRNA motion in *E.coli*



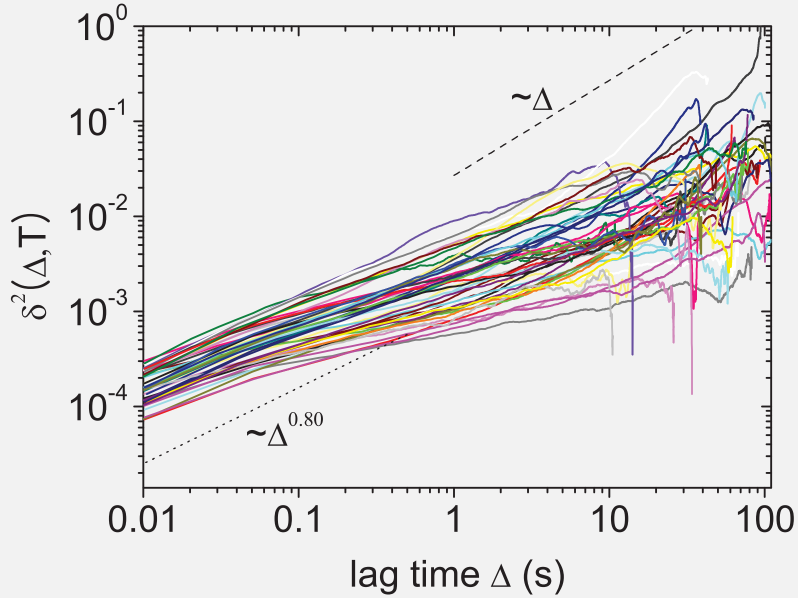
$$\text{Subdiffusion: } \overline{\delta^2(\tau)} \simeq K_\alpha \tau^\alpha, \qquad 0 < \alpha < 1, \qquad [K_\alpha] = \mathrm{cm}^2/\mathrm{sec}^\alpha$$

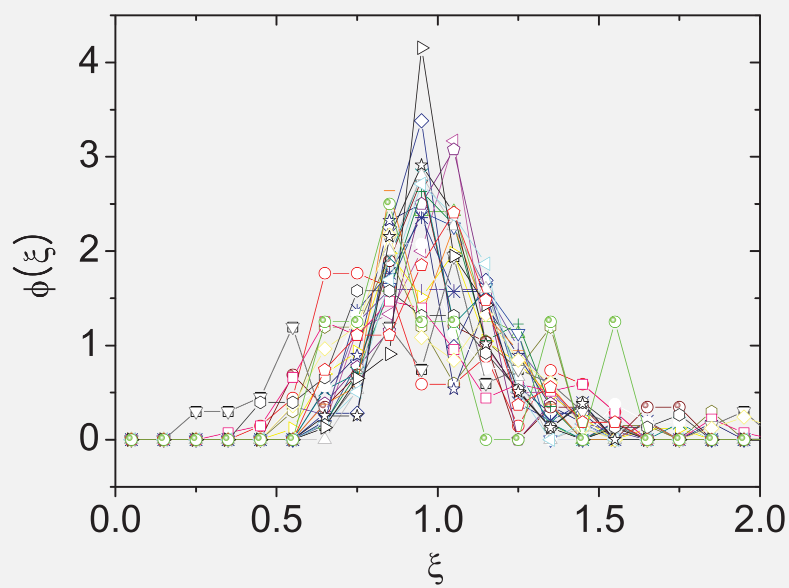
- Spatial inhomogeneity
- Short time series
- Dynamic origin



I Golding & EC Cox, PRL (2006)

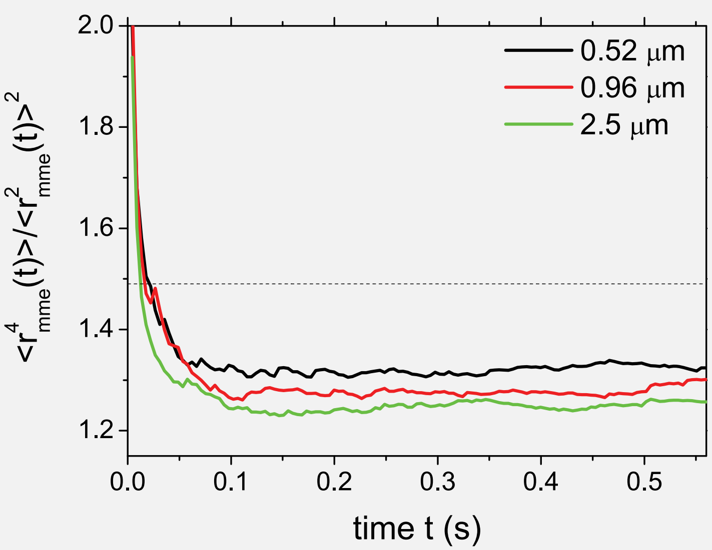
Passive motion of submicron tracers in cells is viscoelastic

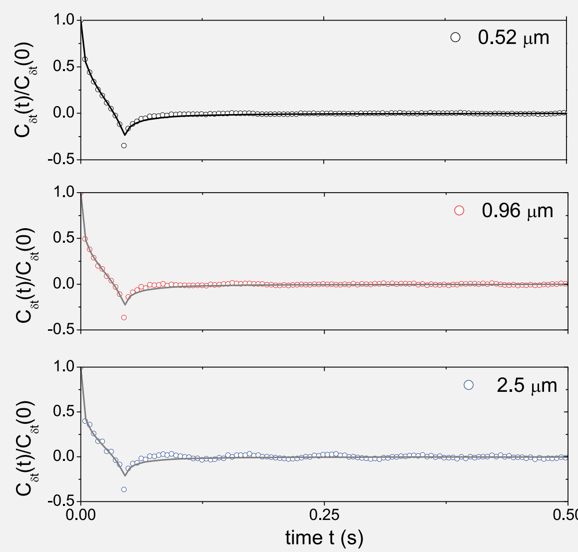


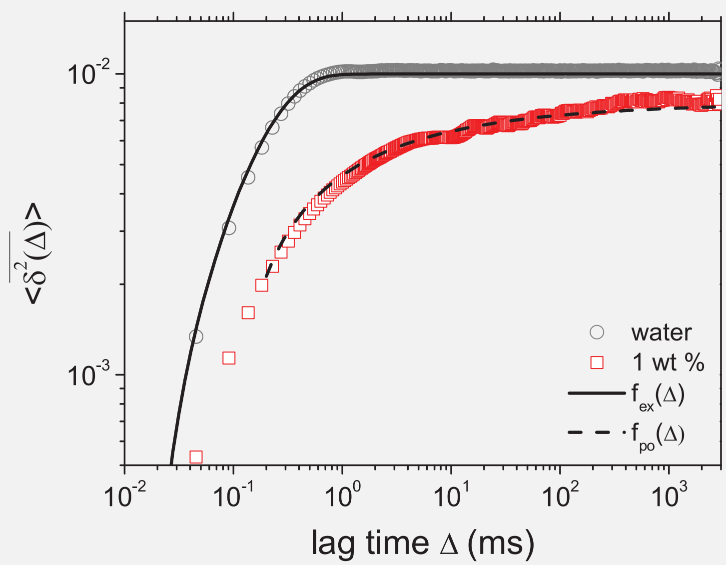


Lipid granules in living yeast cells ←

Tracer beads in wormlike micellar solution ⟶



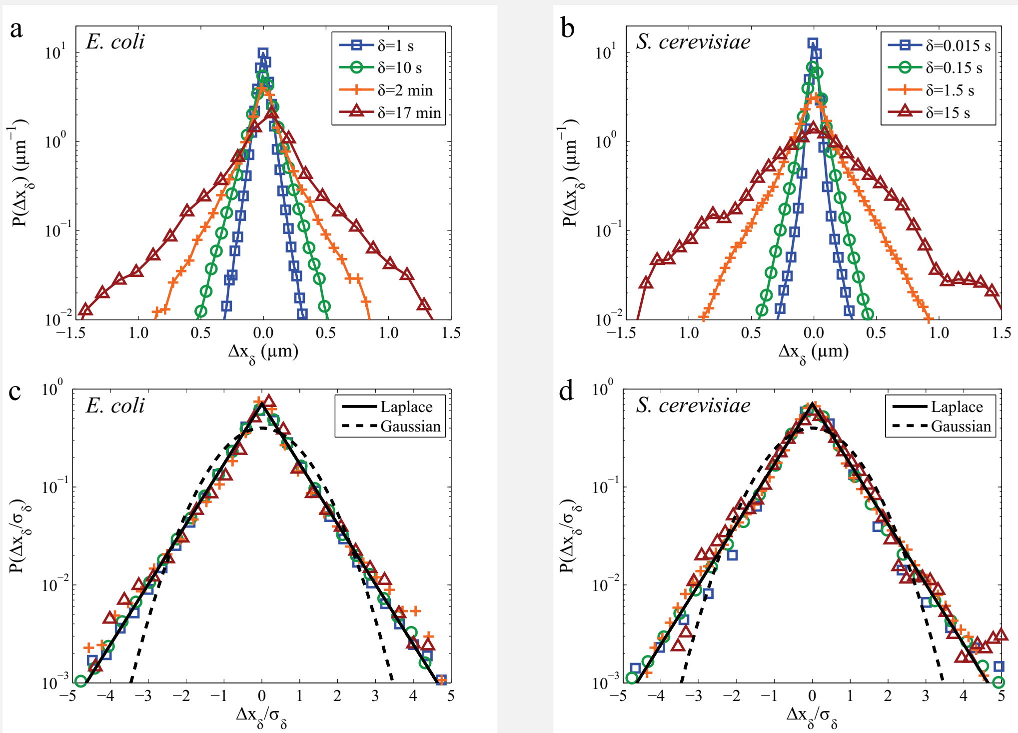


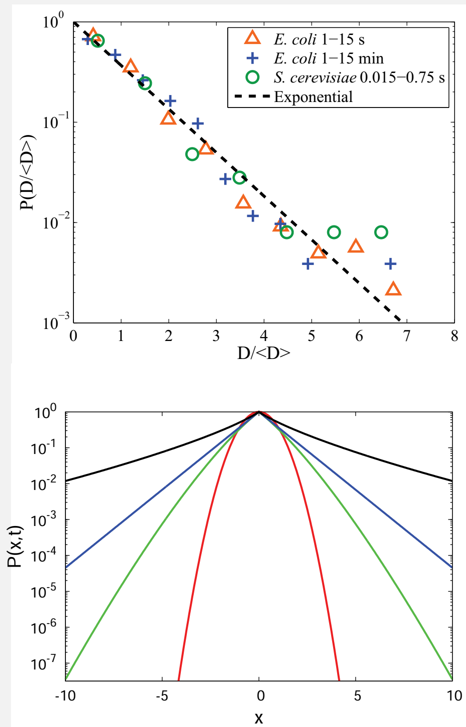


JH Jeon, . . . L Oddershede & RM, PRL (2011); JH Jeon, N Leijnse, L Oddershede & RM, NJP (2013)

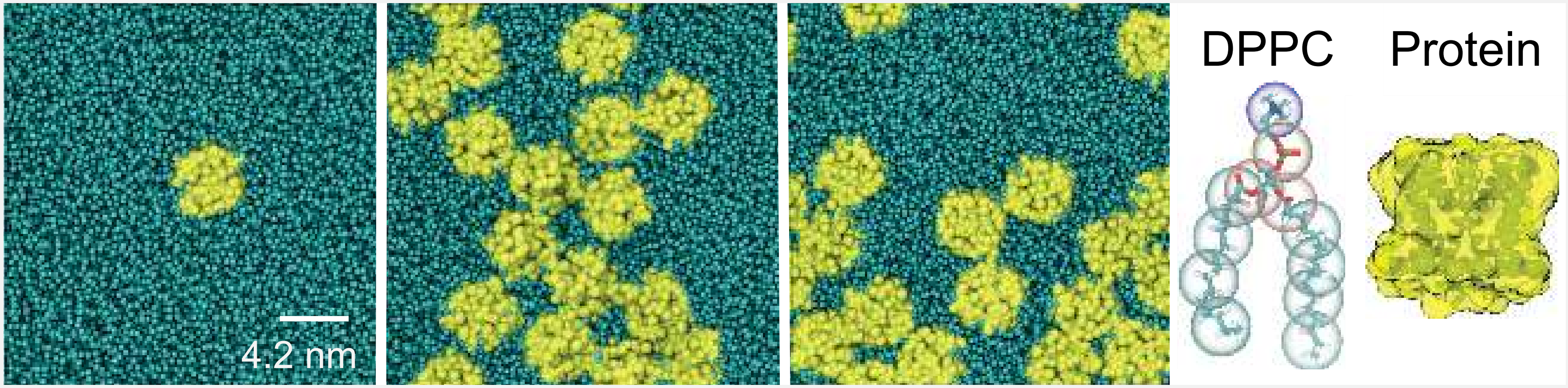
Non-Gaussian diffusion in viscoelastic systems

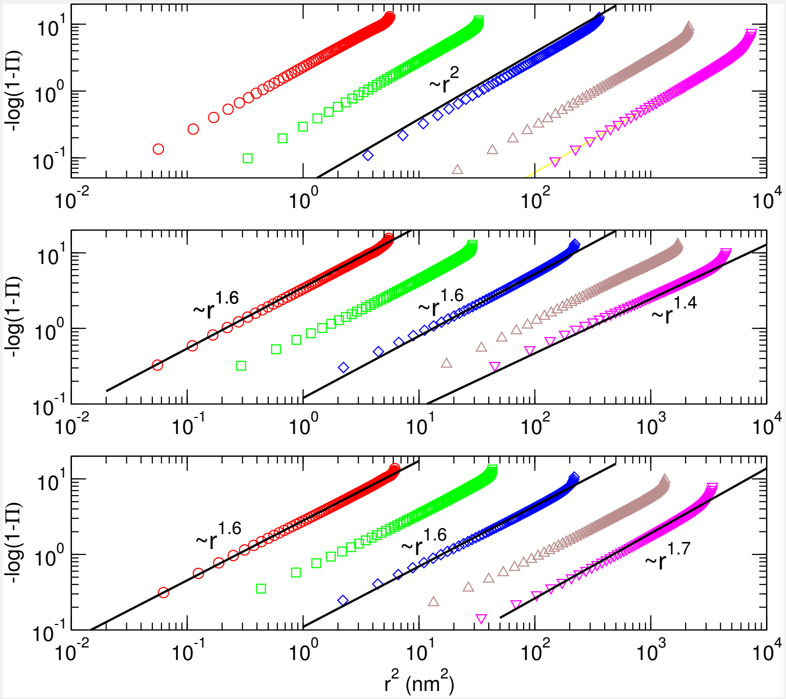
So far consensus: submicron tracer motion in cytoplasm is FBM-like, i.e., Gaussian
RNA-protein particles in E.coli & S.cerevisiae perform exponential anomalous diffusion:





Crowding in membranes: non-Gaussian lipid/protein diffusion

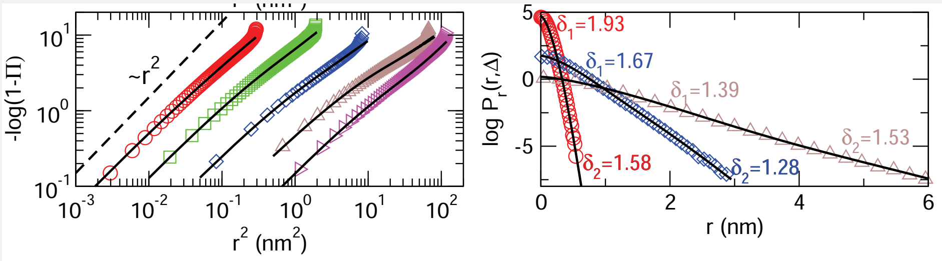




Dilute membrane: $P(r,t)$ Gauss

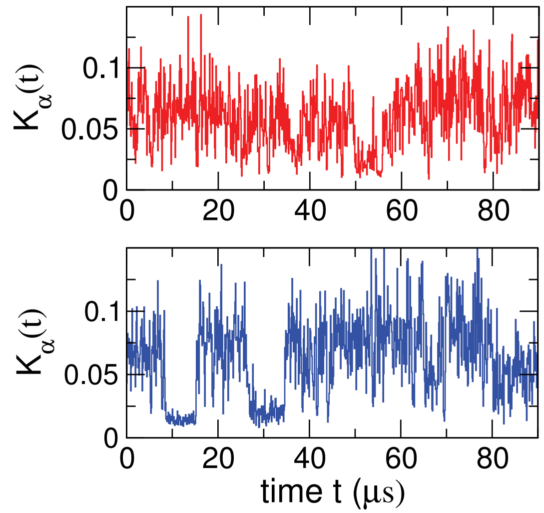
Crowded membrane ($\delta \approx 1.3 \ldots 1.7$):

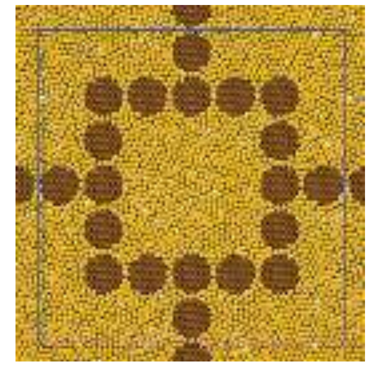
$$P(r,t) \propto \exp\left(-\left[\frac{r}{ct^{\alpha/2}}\right]^{\delta}\right)$$

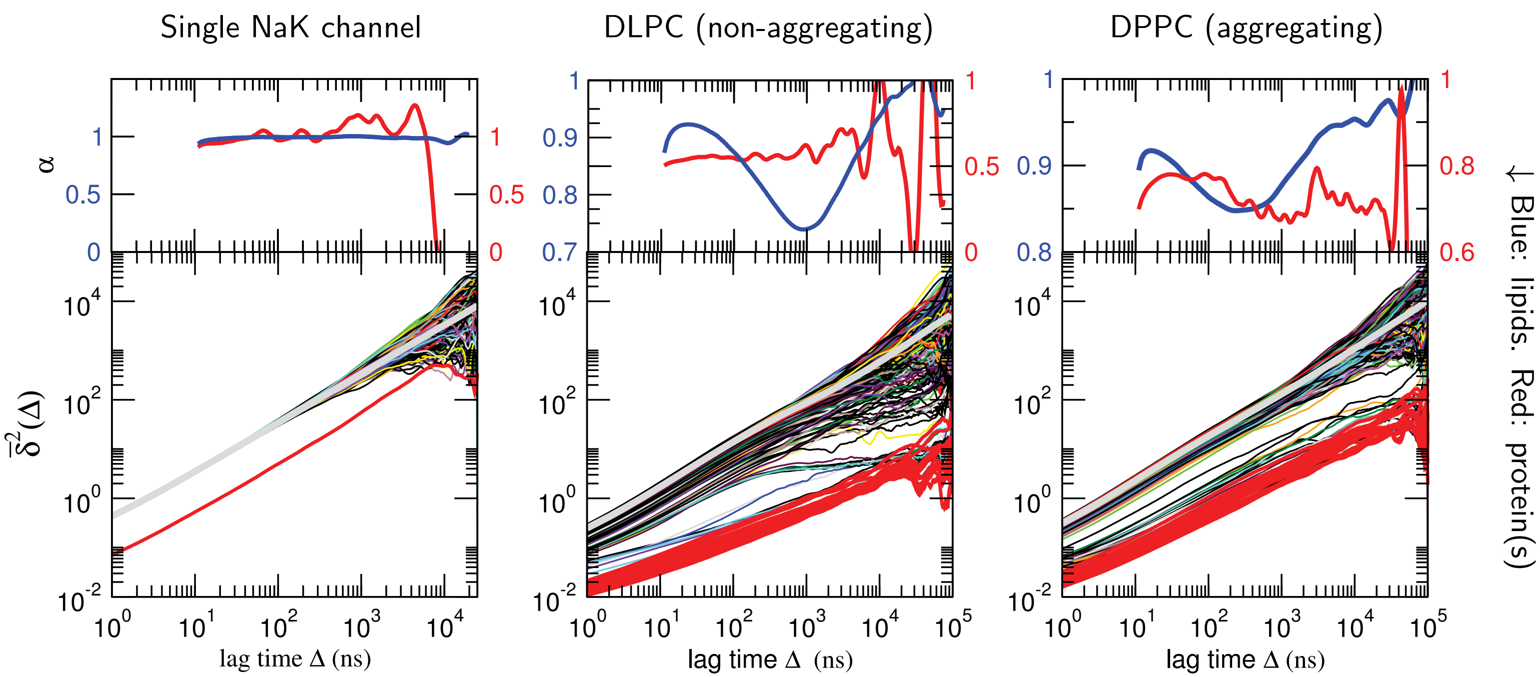


J-H Jeon, M Javanainen, H Martinez-Seara, RM & I Vattulainen, PRX (2016); compare Faraday Disc (2013)

Intermittent lipid diffusion in protein-crowded membranes

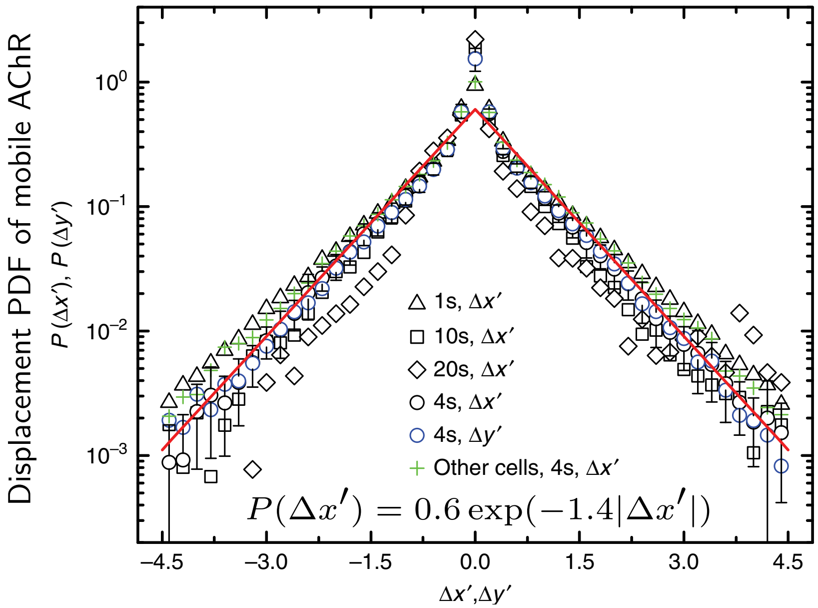


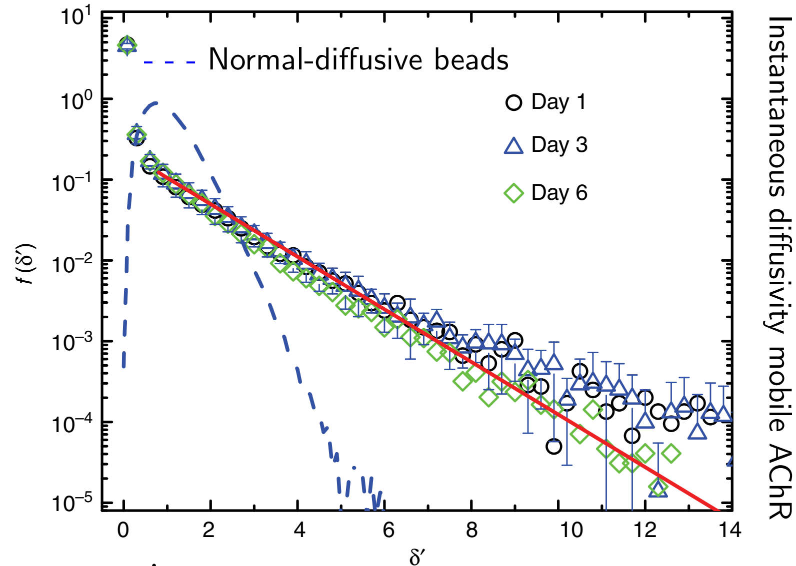




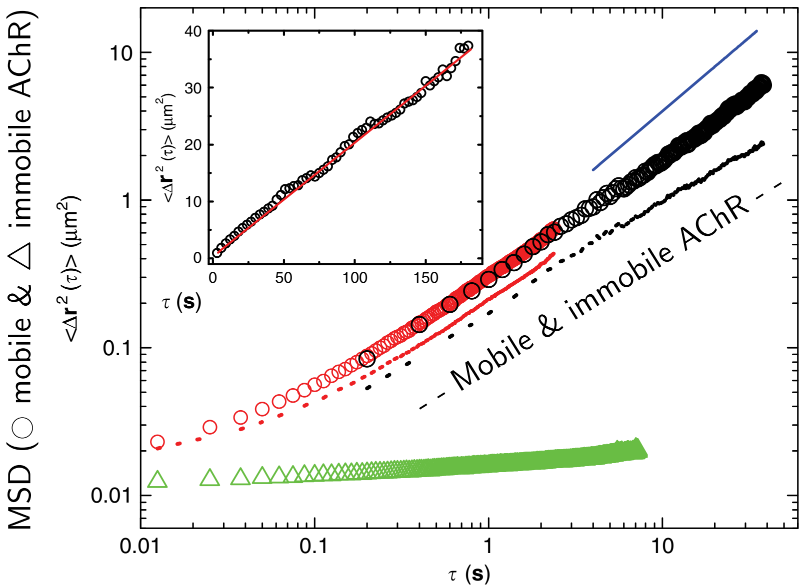
J-H Jeon, M Javanainen, H Martinez-Seara, RM & I Vattulainen, PRX (2016); compare Faraday Disc (2013)

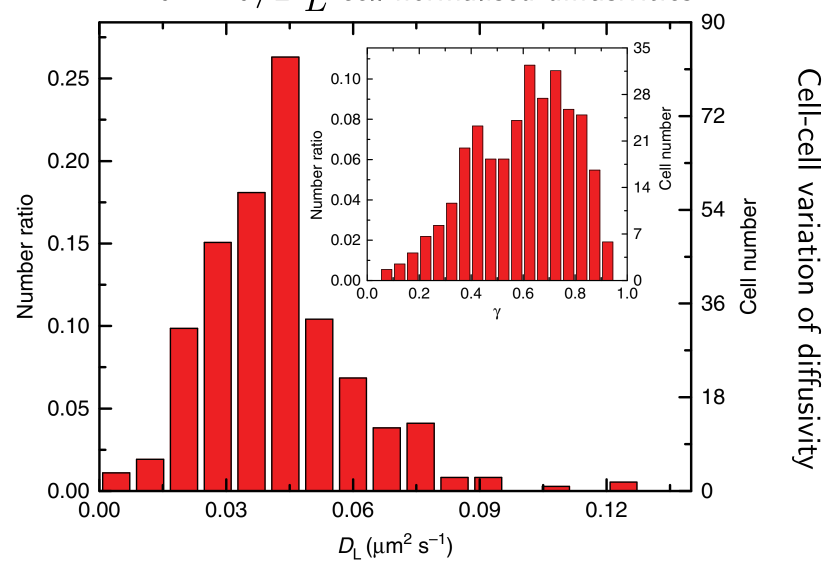
Non-Gaussianity of acetylcholine receptors in Xenopus cells





$\delta' = \delta/D_L$ cell-normalised diffusivities

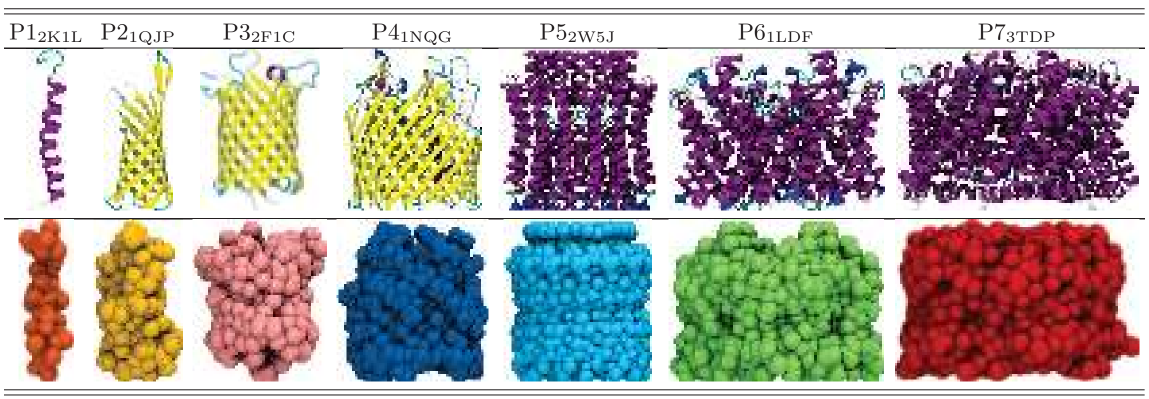


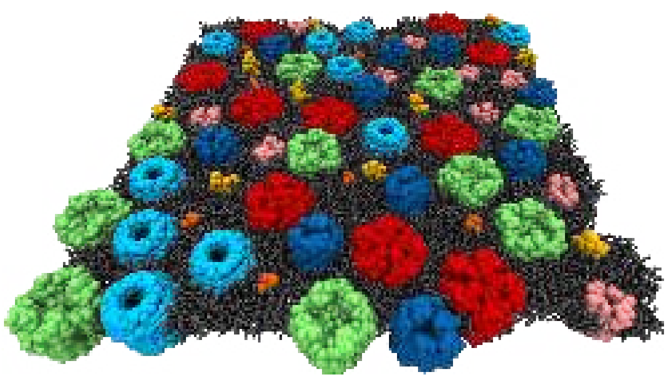


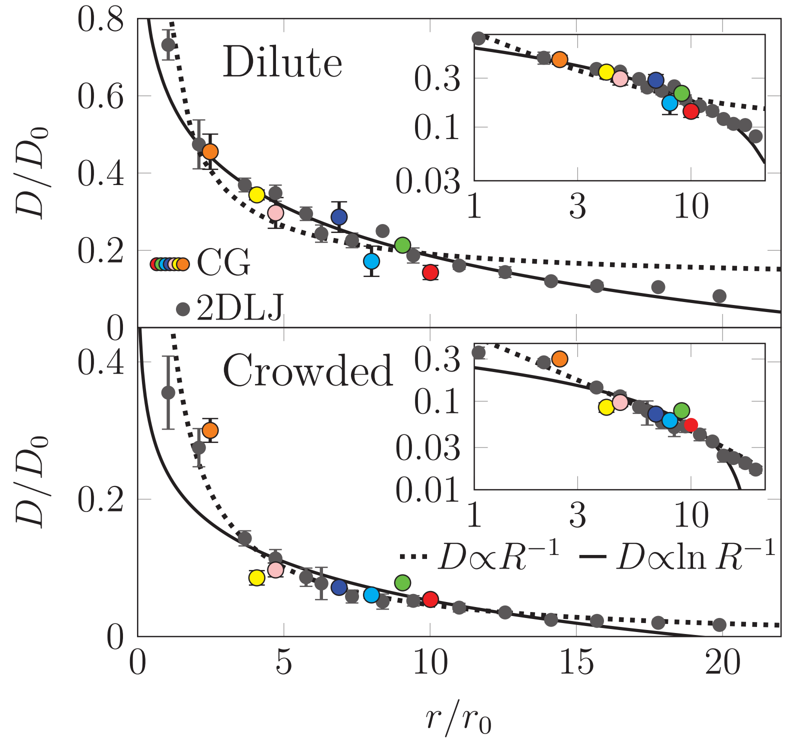
D_L from $\langle \mathbf{r}^2(\tau) \rangle = 2D_L\tau$

W He, H Song, Y Su, L Geng, BJ Ackerson, HB Peng & P Tong, Nat Comm (2016)

Diffusion of proteins in crowded lipid bilayer membranes







Dilute system: Saffman-Delbrück law

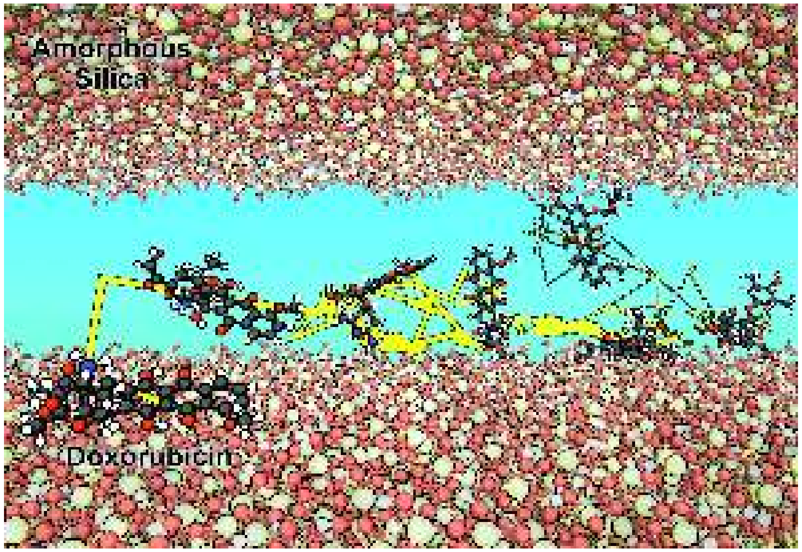
$$D(R) \simeq \log(1/R)$$

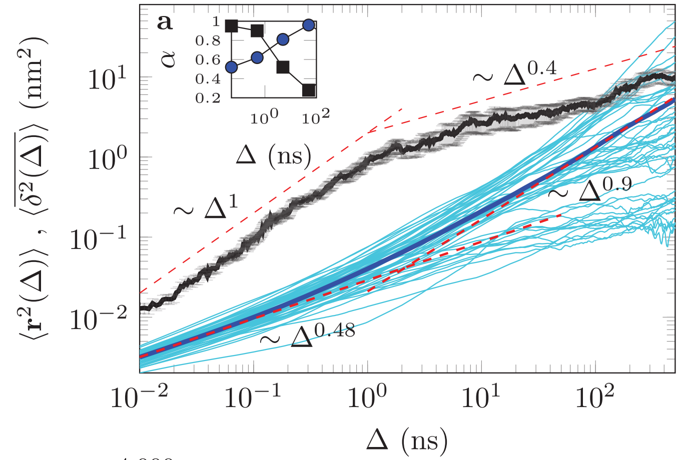
Crowded membrane & 2DLJ discs:

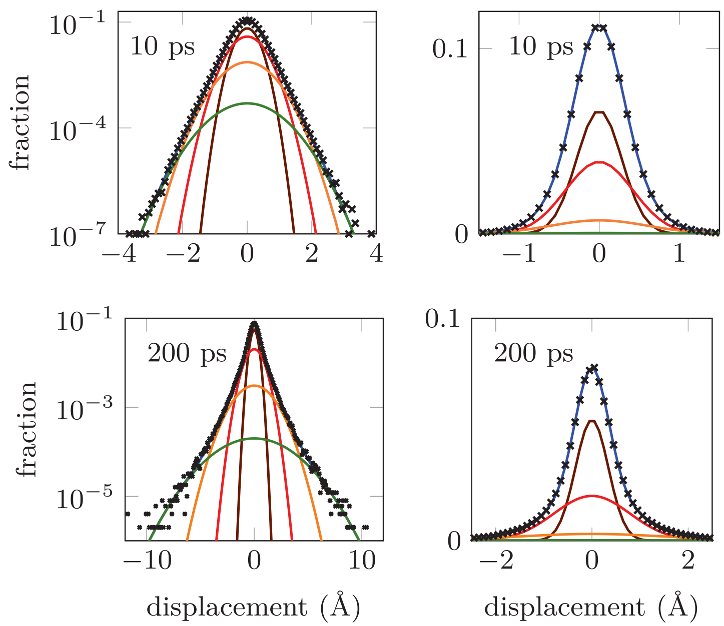
$$D(R) \simeq 1/R$$

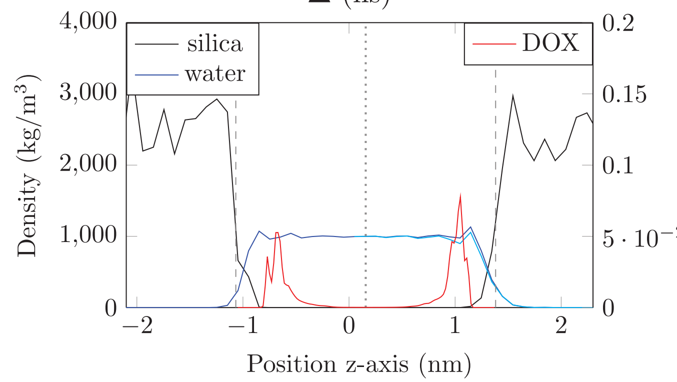
M Javanainen, H Seara Monne, RM & I Vattulainen, JPC Lett (2017)

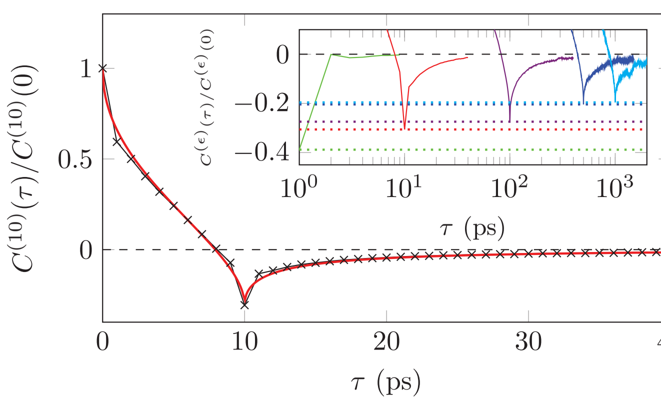
Doxorubicin drug molecule diffusion in silica nanochannels



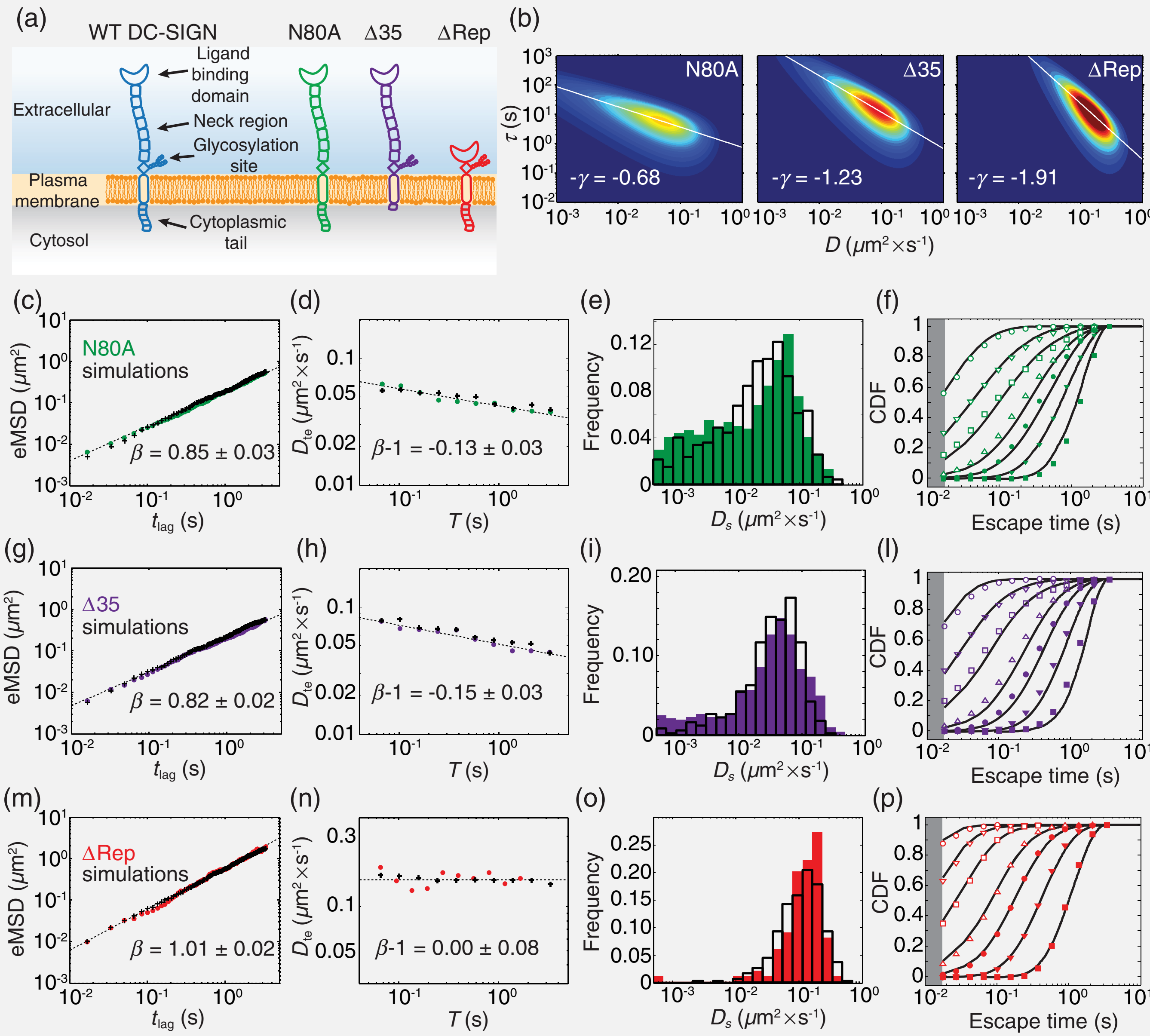






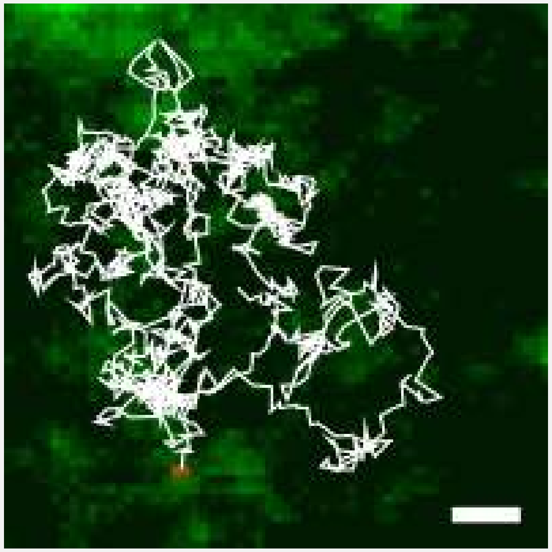


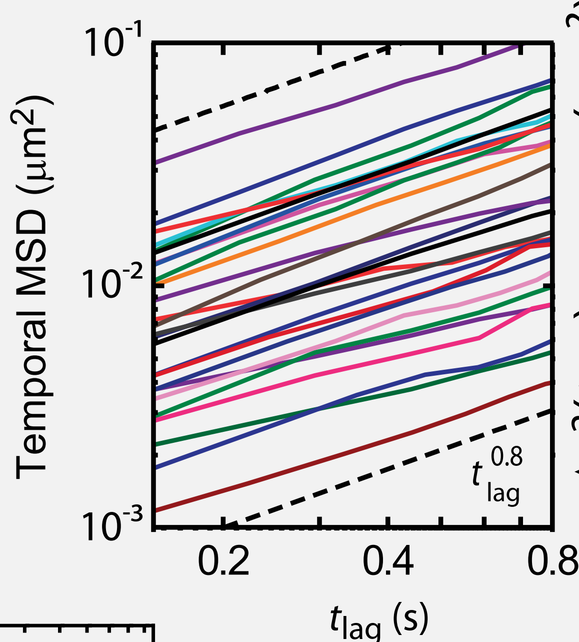
Ageing in the motion of membrane embedded proteins

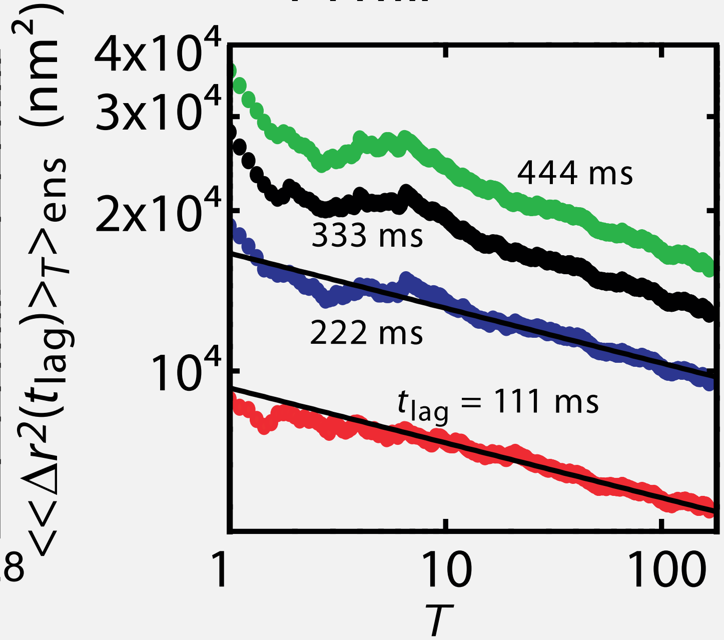


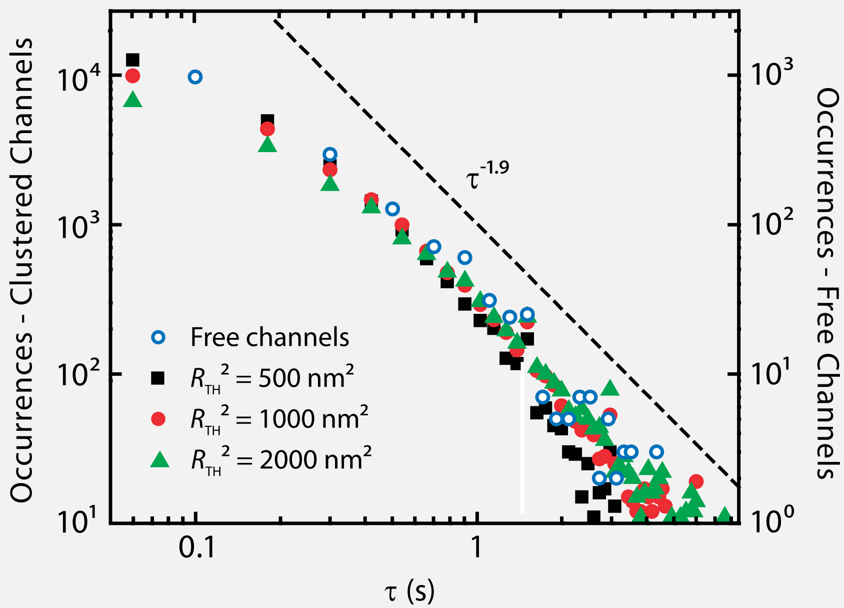
C Manzo . . . M Garcia Parajo, PRX (2015)

CTRW-like motion of Ka channels in plasma membrane









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

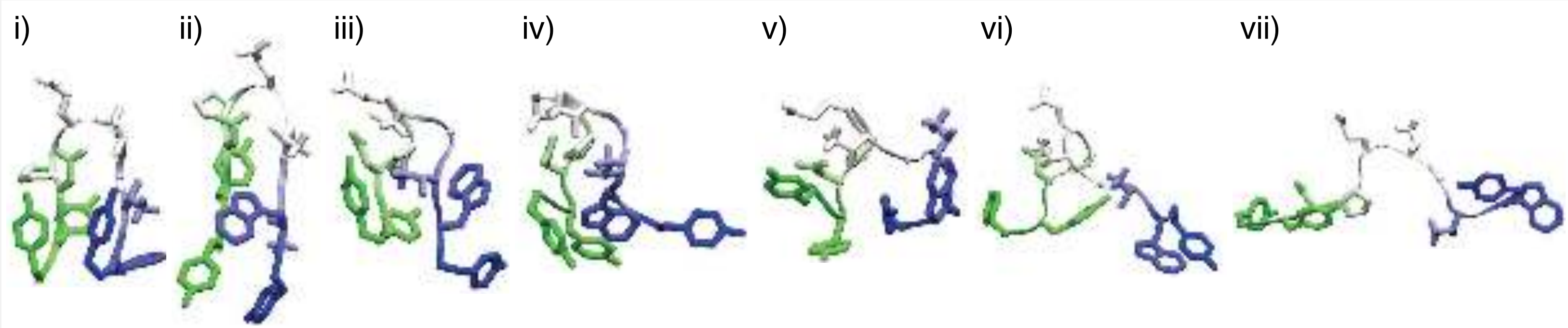
$\overline{\delta^2(\Delta)}$ apparently random

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

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

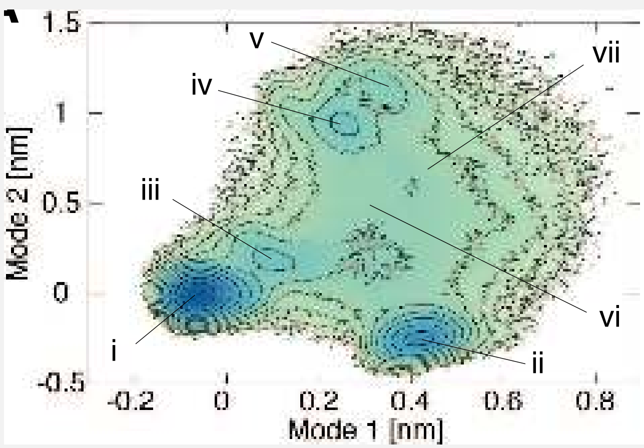
AV Weigel, B Simon, MM Tamkun & D Krapf, PNAS (2011); theory: Y He, S Burov, RM & E Barkai, PRL (2008)

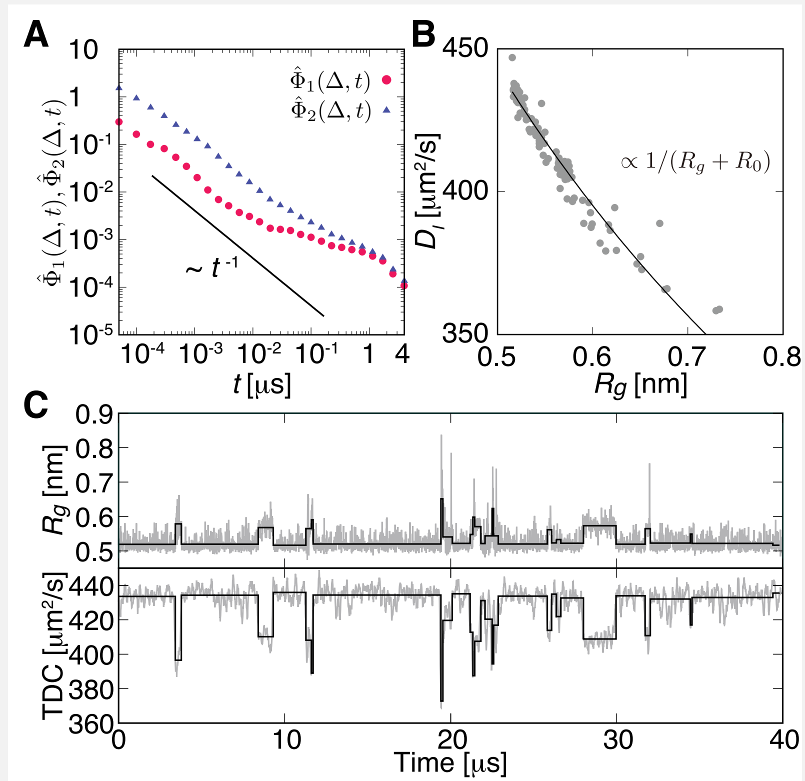
Instantaneous diffusivity of shape-fluctuating proteins



Instantaneous Einstein-Stokes-type relation (for different pressure & temperature):

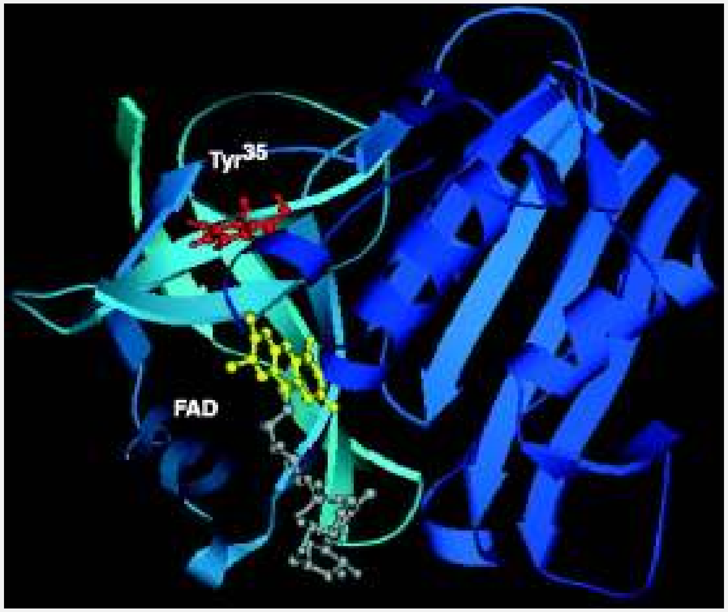
$$D \propto \frac{1}{R_g + R_0}, \quad R_0 \approx 0.3\text{nm}$$

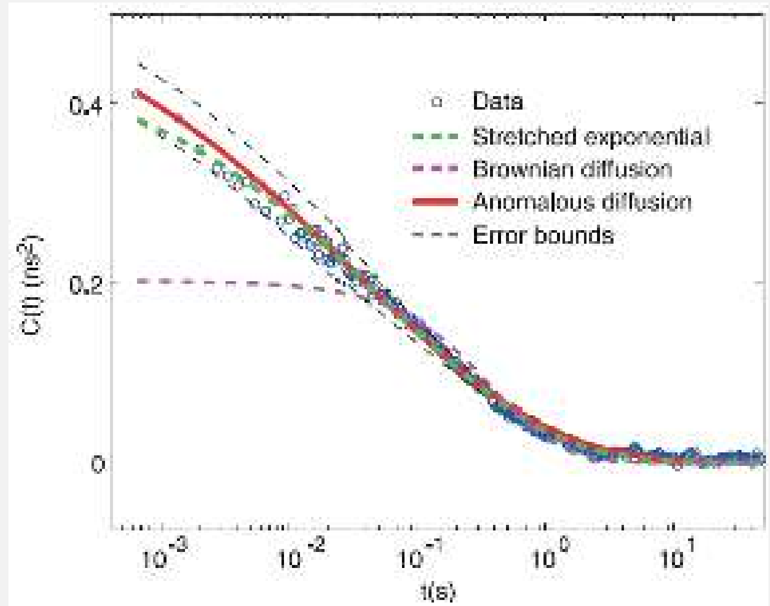


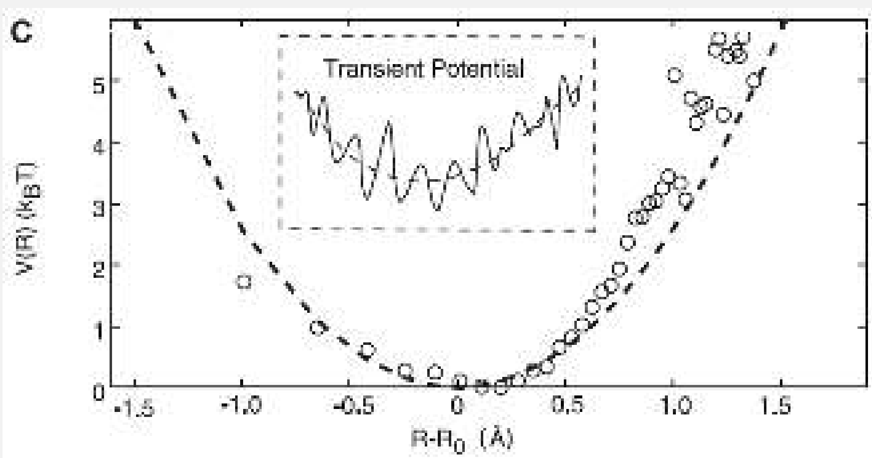


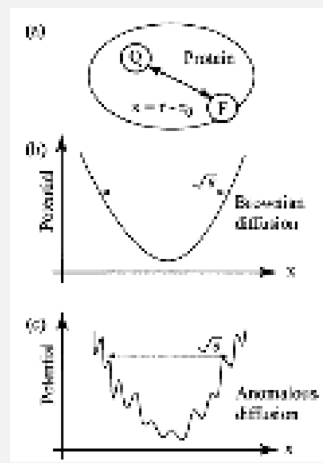
E Yamamoto, T Akimoto, A Mitsutake & RM, PRL (2021)

Protein conformational dynamics

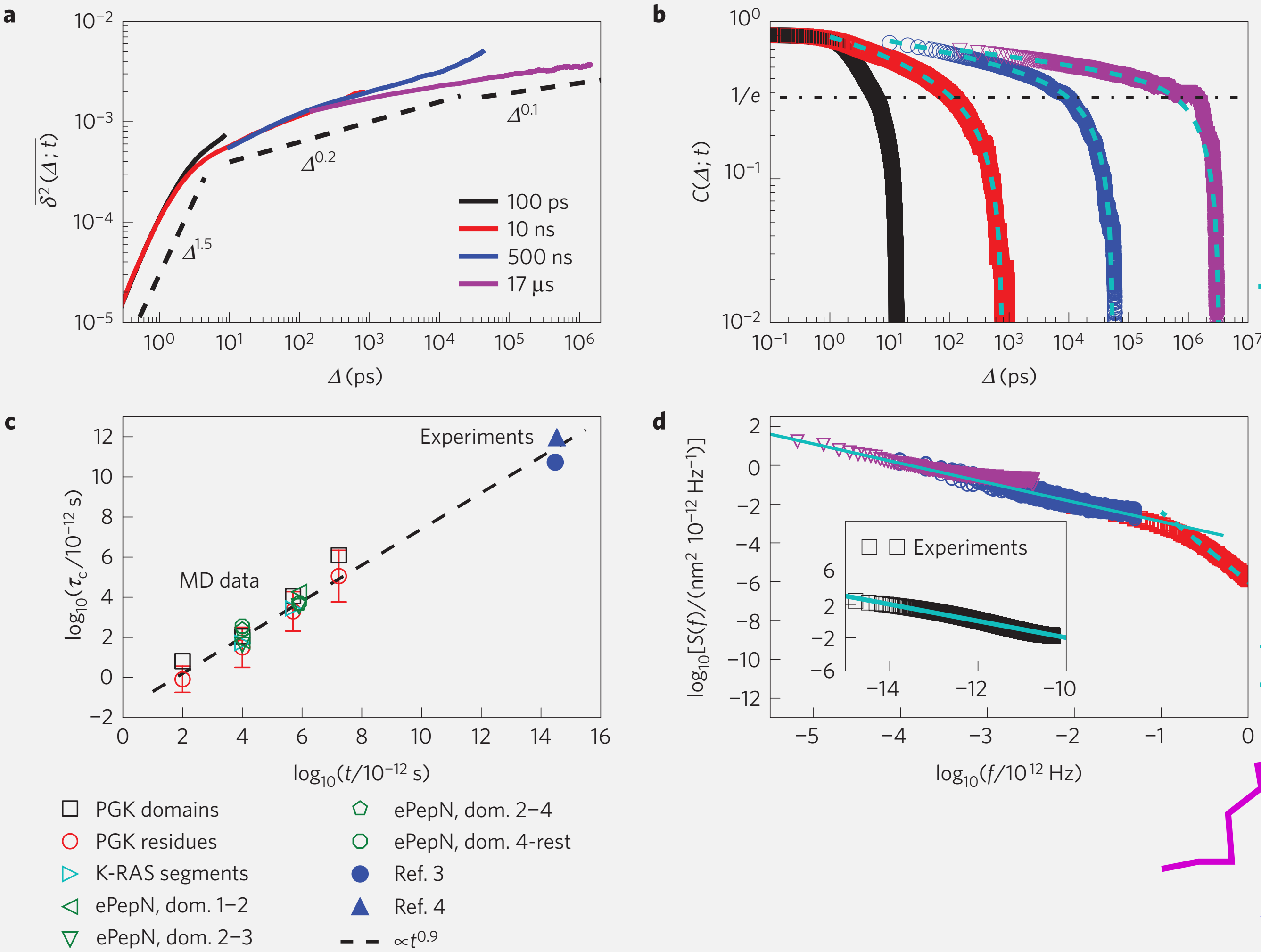


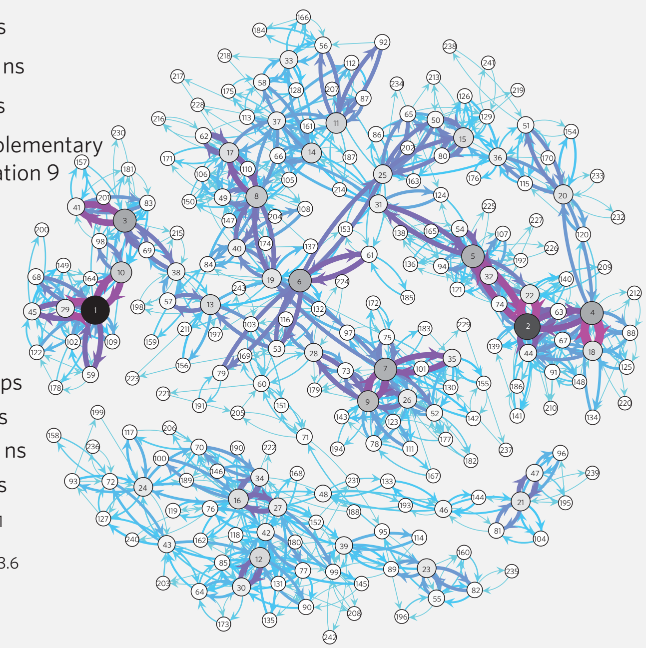


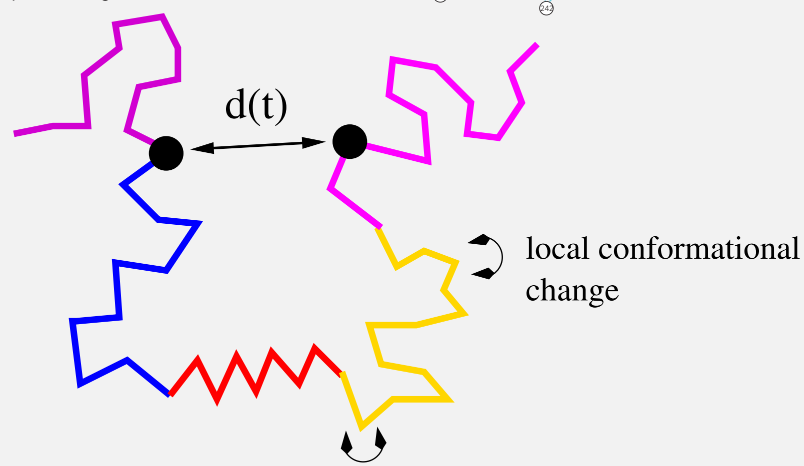




Self-similar internal protein dynamics: 13 decades of ageing

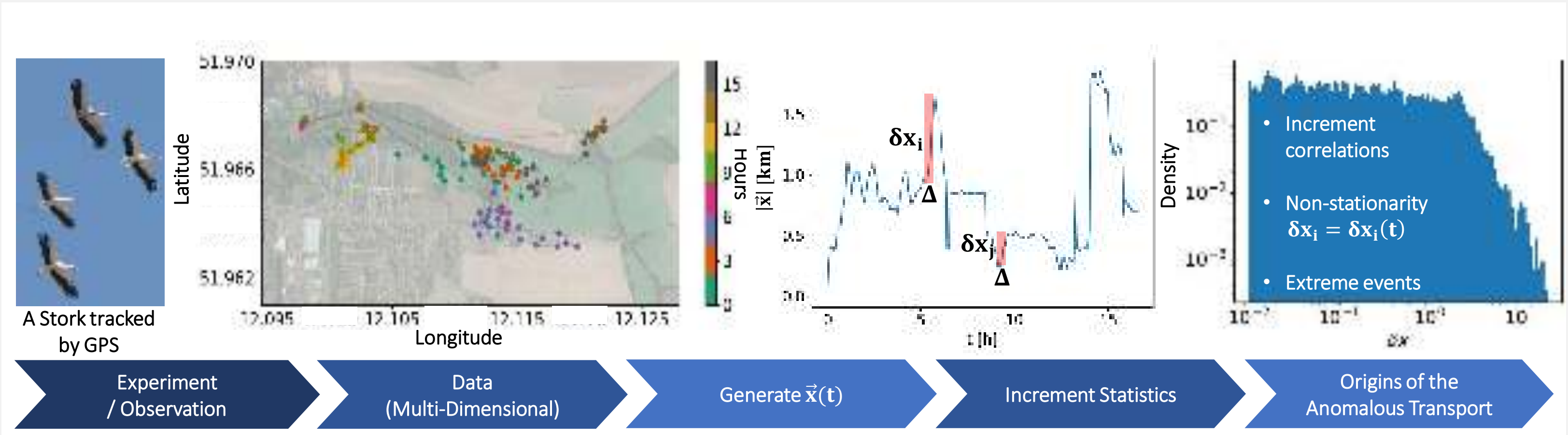






X Hu, L Hong, MD Smith, T Neusius, X Cheng & JC Smith, Nature Phys (2016); N&V RM Nature Phys (2016)

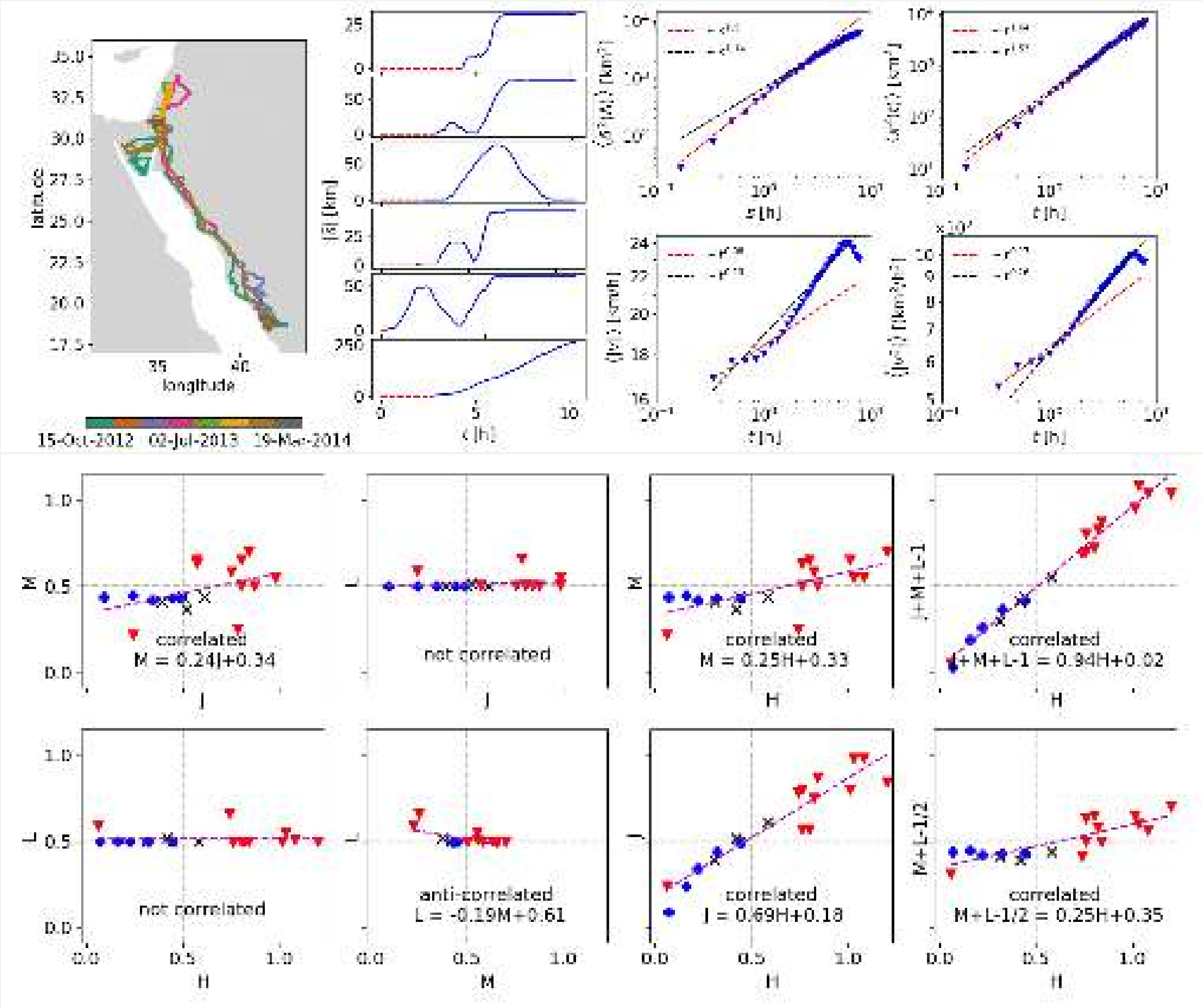
Scaling analysis of anomalous diffusion



- **Moses**
  - M<1/2: Process slowing down/ Statistical aging
  - M=1/2: No effect of non-stationarity
  - M>1/2: Process is accelerating with time
- **Noah**
  - L=1/2: No effect from extreme events
  - L>1/2: Rare extreme events
- **Joseph**
  - J<1/2: Anti-correlations
  - J=1/2: No effect of temporal correlations
  - J>1/2: Positive, long-ranged correlations

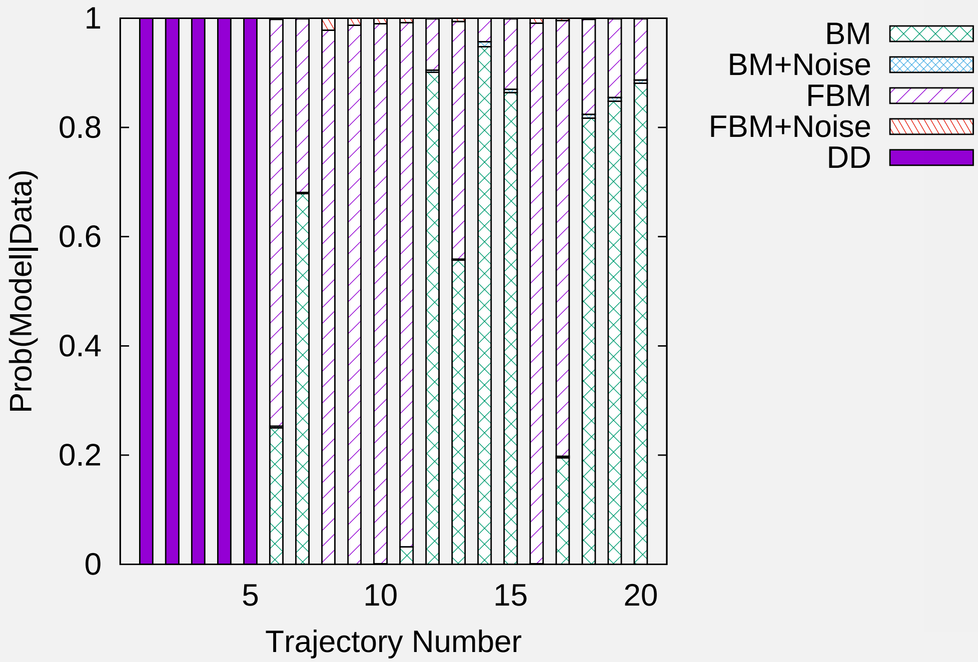
data set	ensemble size	regime	J	L	M	H measured	H prediction	$\frac{\lvert H_p - H\rvert}{H}$
Rhodamine 100%	174	$50 < t < 1500$ ms	0.50	0.50	0.41	0.38 ± 0.02	0.42 ± 0.04	10%
Rhodamine 90%	298	$50 < t < 1500$ ms	0.38	0.50	0.42	0.28 ± 0.02	0.30 ± 0.03	7%
Rhodamine 85%	239	$50 < t < 1500$ ms	0.34	0.50	0.40	0.22 ± 0.02	0.24 ± 0.05	9%
Rhodamine 75%	258	$50 < t < 1500$ ms	0.22	0.51	0.44	0.18 ± 0.02	0.18 ± 0.01	$>$1%
Rhodamine 30%	436	$50 < t < 1500$ ms	0.09	0.50	0.44	0.07 ± 0.02	0.04 ± 0.03	**
Tracers in	200	$0.1 < t < 5$ s	0.39	0.50	0.41	0.31 ± 0.01	0.30 ± 0.02	3%
treated cells		$5 < t < 50$ s	0.50	0.50	0.44	0.44 ± 0.01	0.44 ± 0.01	$<$1%
Tracers in	1000	$0.1 < t < 2$ s	0.39	0.50	0.44	0.31 ± 0.01	0.33 ± 0.02	6%
untreated cells		$2 < t < 8$ s	0.60	0.50	0.47	0.55 ± 0.01	0.57 ± 0.01	4%
Amoeba	1142	$1 < t < 6$ min	0.61	0.50	0.44	0.58 ± 0.01	0.55 ± 0.03	5%
		$10 < t < 100$ min	0.52	0.52	0.37	0.42 ± 0.02	0.40 ± 0.02	5%
Harvester ants	67	$10 < t < 100$ s	0.88	0.50	0.57	0.92 ± 0.12	0.95 ± 0.08	3%
		$100 < t < 400$ s	0.59	0.51	0.35	0.47 ± 0.03	0.45 ± 0.03	4%
Commuting kite	107	$0.1 < t < 3$ min	0.87	0.50	0.49	0.84 ± 0.02	0.86 ± 0.02	2%
		$3 < t < 12$ min	0.80	0.50	0.50	0.76 ± 0.01	0.80 ± 0.02	5%
Searching kite	587	$0.5 < t < 20$ min	0.24	0.59	0.22	0.06 ± 0.02	0.06 ± 0.01	$<$1%
Stork (Jun-Jul)	455	$0.2 < t < 2$ h	0.46	0.88	-0.24	*	0.10 ± 0.03	–
		$2 < t < 10$ h	0.18	0.50	0.48	*	0.16 ± 0.08	–
Stork (Aug-Sep)	394	$0.2 < t < 2$ h	0.98	0.55	0.55	1.20 ± 0.03	1.08 ± 0.02	10%
		$2 < t < 10$ h	0.84	0.50	0.70	1.03 ± 0.01	1.04 ± 0.06	1%
Stork (Oct-Jan)	854	$0.2 < t < 2$ h	0.78	0.66	0.25	0.74 ± 0.02	0.68 ± 0.03	8%
		$2 < t < 10$ h	0.57	0.50	0.65	0.80 ± 0.02	0.73 ± 0.10	9%
Stork (Mar-Apr)	391	$0.2 < t < 2$ h	0.98	0.51	0.55	1.08 ± 0.02	1.04 ± 0.02	4%
		$2 < t < 10$ h	0.80	0.50	0.65	1.01 ± 0.01	0.95 ± 0.07	6%
Vulture	444	$0.1 < t < 2$ h	0.75	0.50	0.58	0.82 ± 0.02	0.84 ± 0.02	1%
		$2 < t < 5.5$ h	0.57	0.50	0.63	0.76 ± 0.02	0.70 ± 0.04	9%

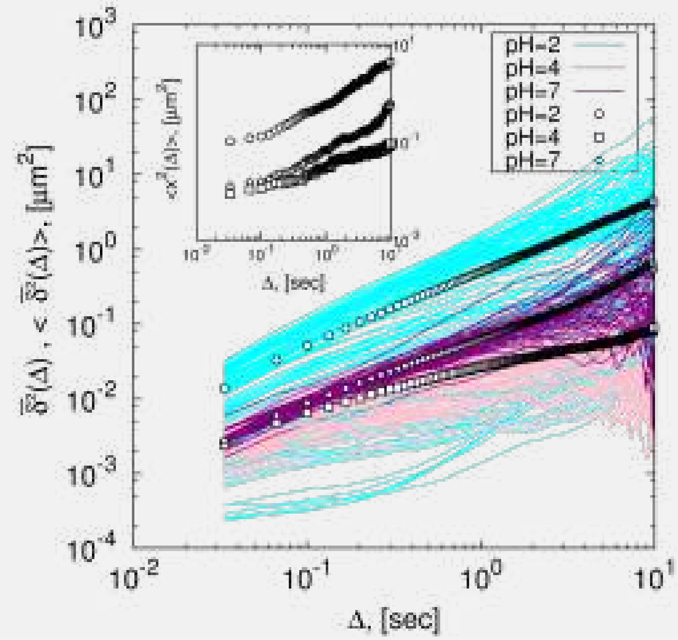
Scaling analysis of anomalous diffusion

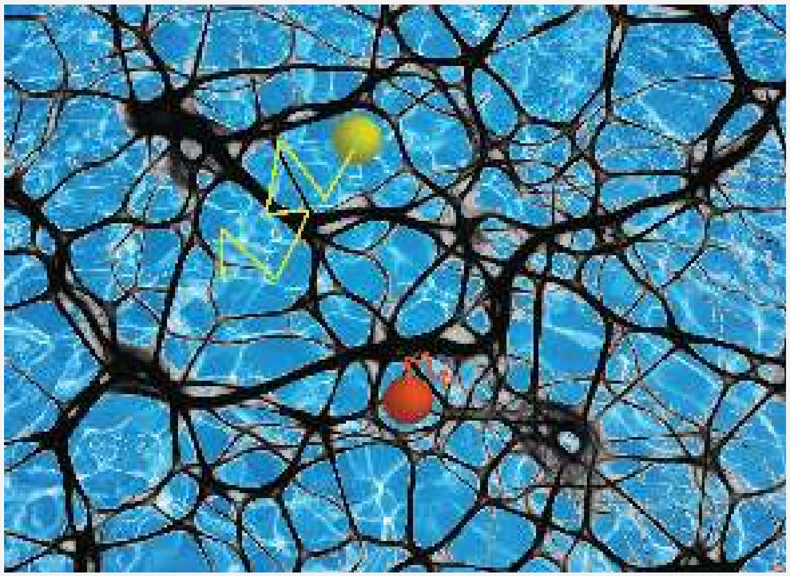


O Vilk, E Aghion, T Avgar, C Beta, O Nagel, M Weiss, A Sabri, D Krapf, R Sarfati, DK Schwartz, R Metzler, R Nathan, M Assaf (2022)

Maximum likelihood Bayesian data analyses







Nested sampling à la Skilling

Objective model selection

Parameter estimation

S Thapa, AG Cherstvy & RM, PCCP (2018); AG Cherstvy, S Thapa, CE Wagner & RM, Soft Matter (2019)

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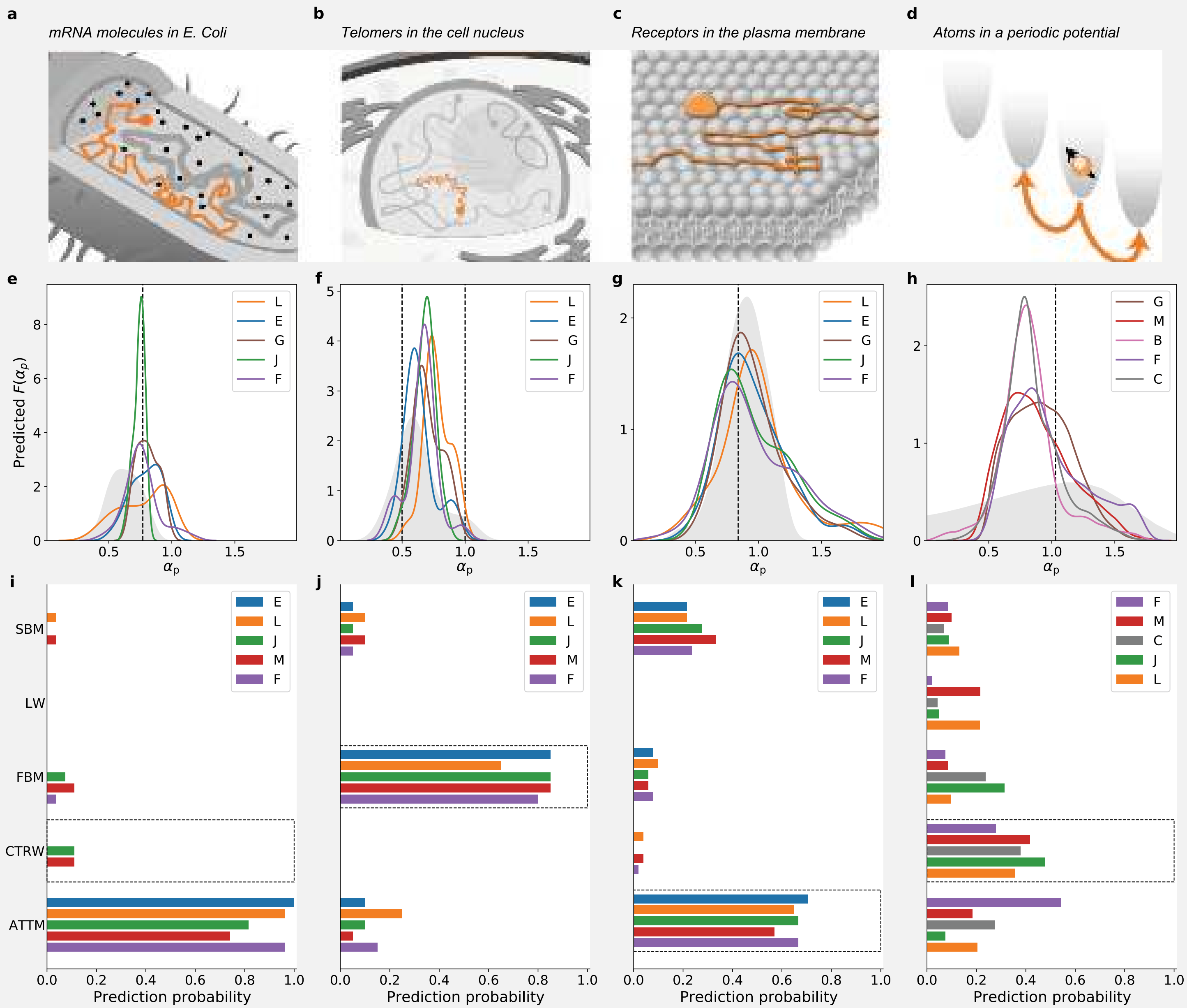
Objective comparison of methods to decode anomalous diffusion

Gorka Muñoz-Gil [1], Giovanni Volpe [2]✉, Miguel Angel Garcia-March [3], Erez Aghion [4], Aykut Argun [2], Chang Beom Hong [5], Tom Bland [6], Stefano Bo [4], J. Alberto Conejero [3], Nicolás Firbas [3], Òscar Garibo i Orts [3], Alessia Gentili [7], Zihan Huang [8], Jae-Hyung Jeon [5], Hélène Kabbech [9], Yeongjin Kim [5], Patrycja Kowalek [10], Diego Krapf [11], Hanna Loch-Olszewska [10], Michael A. Lomholt [12], Jean-Baptiste Masson [13], Philipp G. Meyer [4], Seongyu Park [5], Borja Requena [1], Ihor Smal [9], Taegeun Song [5,14,15], Janusz Szwabiński [10], Samudrajit Thapa [16,17,18], Hippolyte Verdier [13], Giorgio Volpe [7], Artur Widera [19], Maciej Lewenstein [1,20], Ralf Metzler [16] & Carlo Manzo [1,21]✉

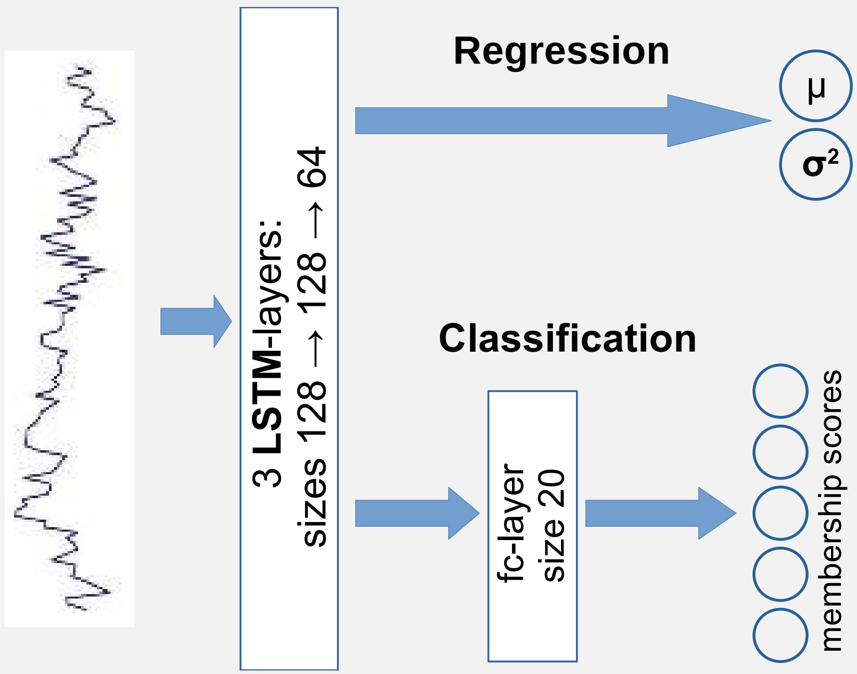
The ANomalous DIffusion challenge

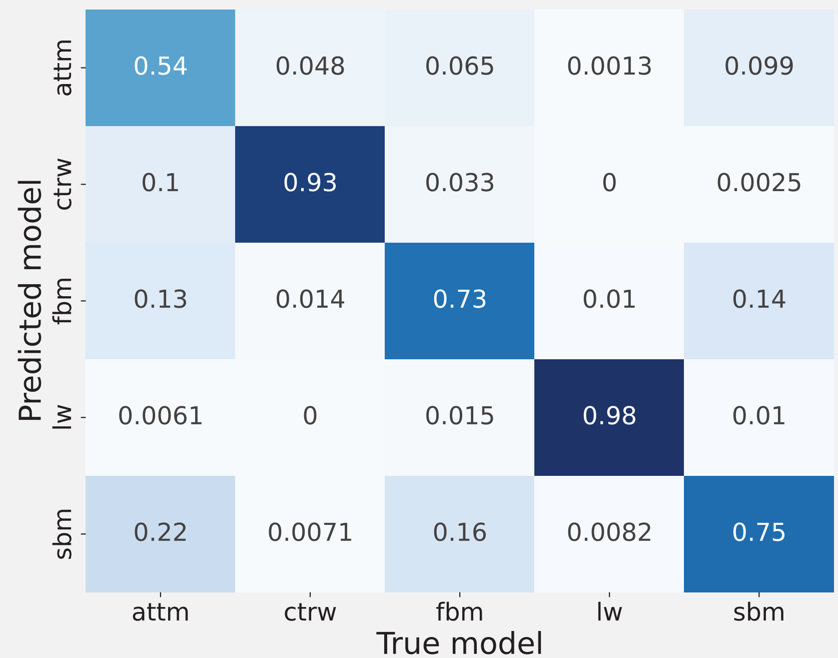


G Muñoz-Gil et al., Nat Commun (2021)

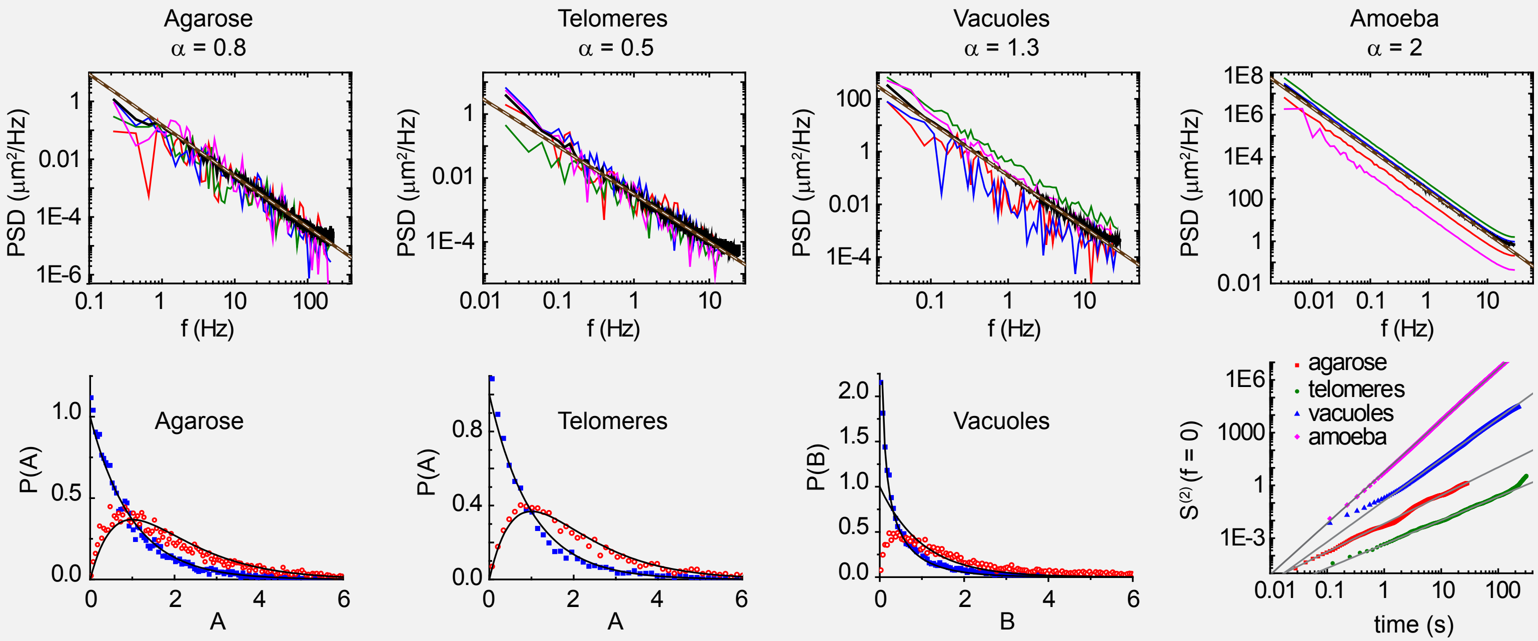
Bayesian-weighted deep learning model selection

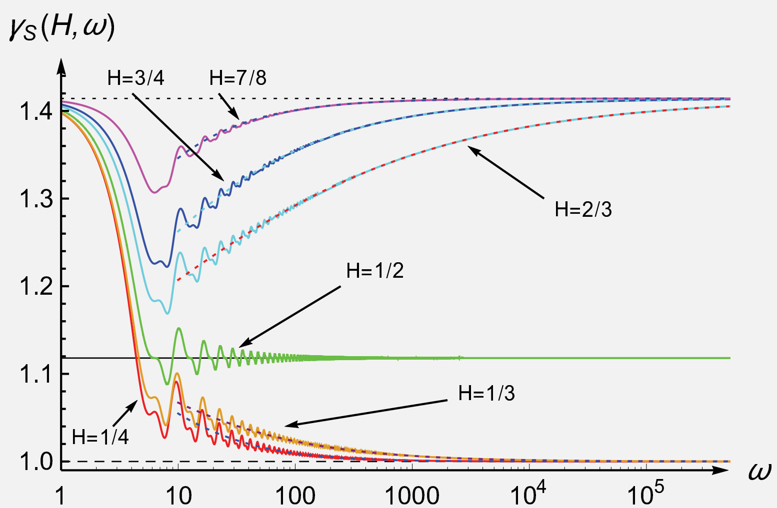
Long **S**hort-**T**erm **M**emory approach (recurrent neural network architecture)





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)

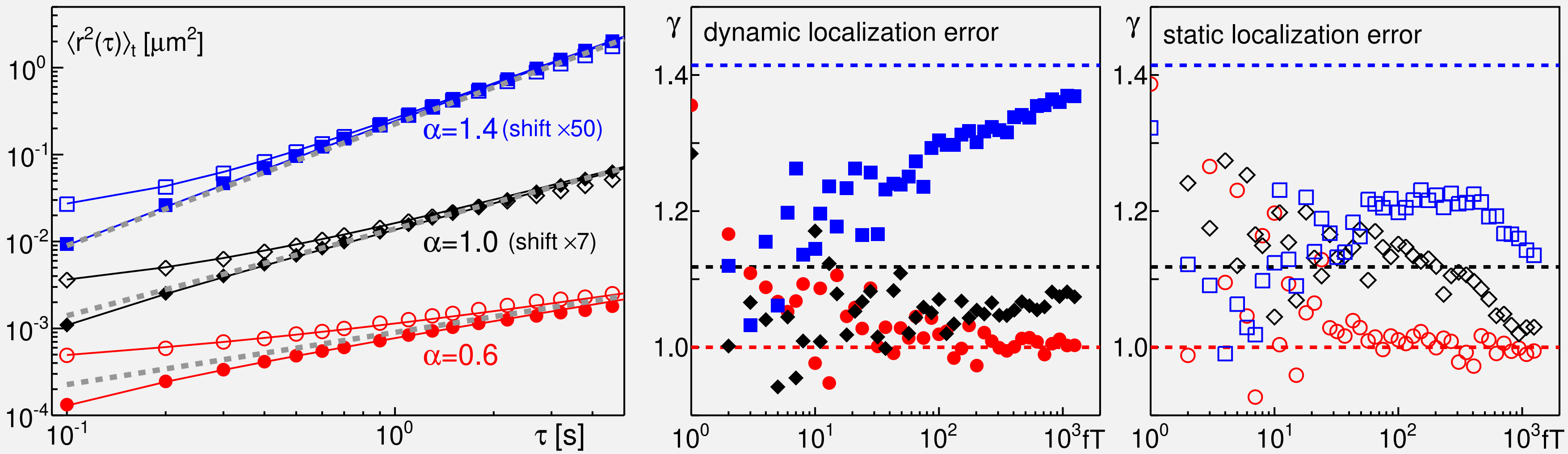
Robust criterion for anomalous diffusion

Two sources of noise: static (finite photon count, additive OU) & dynamic (finite measurement time). Static noise effect on γ:

$$H < 1/2: \qquad \gamma_Y^2(f,T) \sim 1; \qquad \sigma_e = 0 : 1$$

$$H = 1/2: \qquad \gamma_Y^2(f,T) \sim 1 + \frac{1}{4}\left(1 + \frac{\sigma_e^2}{2u^2 D} f^2\right)^{-2}; \qquad \sigma_e = 0 : \frac{\sqrt{5}}{2}$$

$$H > 1/2: \qquad \gamma_Y^2(f,T) \sim 1 + \left(1 + \frac{\sigma_e^2}{u^2 D} T^{1-2H} f^2\right)^{-2}; \qquad \sigma_e = 0 : \sqrt{2}$$



V Sposini, D Krapf, E Marinari, R Sunyer, F Ritort, F Taheri, C Selhuber-Unkel, R Benelly, M Weiss, RM & G Oshanin (2022)

$\sum$ummary

- I Diffusive spreading is a ubiquitous mode of transportation in Nature that comes for free

- II Inhomogeneity of environment and/or tracers cause pronouncedly non-Gaussian distributions

- III Disorder effects anomalous diffusion: non-universality $\rightsquigarrow$ different physical models. Need to know process

- IIII Measurement errors need to be known & taken into consideration

- 𝍸 Objective data analysis methods aid in identification of models & parameters: Bayesian-maximum likelihood, deep learning, & their combinations

For slides or questions: write to rmetzler@uni-potsdam.de

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Aljaz Godec (MPIBC Göttingen)
Denis Grebenkov (École Polytechnique)
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