Modeling Anomalous Transport in Biological Media

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Normal diffusion

5. ***Über die von der molekularkinetischen Theorie der Wärme geforderte Bewegung von in ruhenden Flüssigkeiten suspendierten Teilchen;***
von A. Einstein.

In dieser Arbeit soll gezeigt werden, daß nach der molekularkinetischen Theorie der Wärme in Flüssigkeiten suspendierte Körper von mikroskopisch sichtbarer Größe infolge der Molekularbewegung der Wärme Bewegungen von solcher Größe ausführen müssen, daß diese Bewegungen leicht mit dem Mikroskop nachgewiesen werden können. Es ist möglich, daß die hier zu behandelnden Bewegungen mit der sogenannten „Brownschen Molekularbewegung“ identisch sind; die mir erreichbaren Angaben über letztere sind jedoch so ungenau, daß ich mir hierüber kein Urteil bilden konnte.

A. Einstein, *Ann. Phys.*, vol. 322, no. 8, 1905.

f(x,t) is a concentration

$$f(x, t+\tau)\,dx = dx \cdot \int_{\Delta=-\infty}^{\Delta=+\infty} f(x+\Delta)\,\varphi(\Delta)\,d\Delta$$

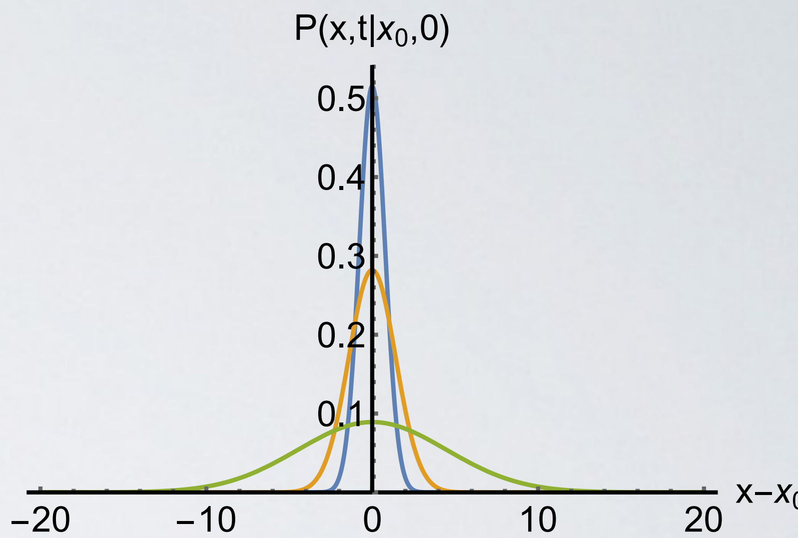
$$\frac{\partial f}{\partial t} = D\,\frac{\partial^2 f}{\partial x^2}.$$

$$f(x,t) = \frac{n}{\sqrt{4\pi D}}\,\frac{e^{-\frac{x^2}{4Dt}}}{\sqrt{t}}.$$

$$\lambda_x = \sqrt{\overline{x^2}} = \sqrt{2Dt}.$$

Free diffusion as a stochastic process

p(x,t|x₀,0) is a transition probability



$$\partial_t P(x,t|x_0,0) = D\frac{\partial^2}{\partial x^2}P(x,t|x_0,0)$$

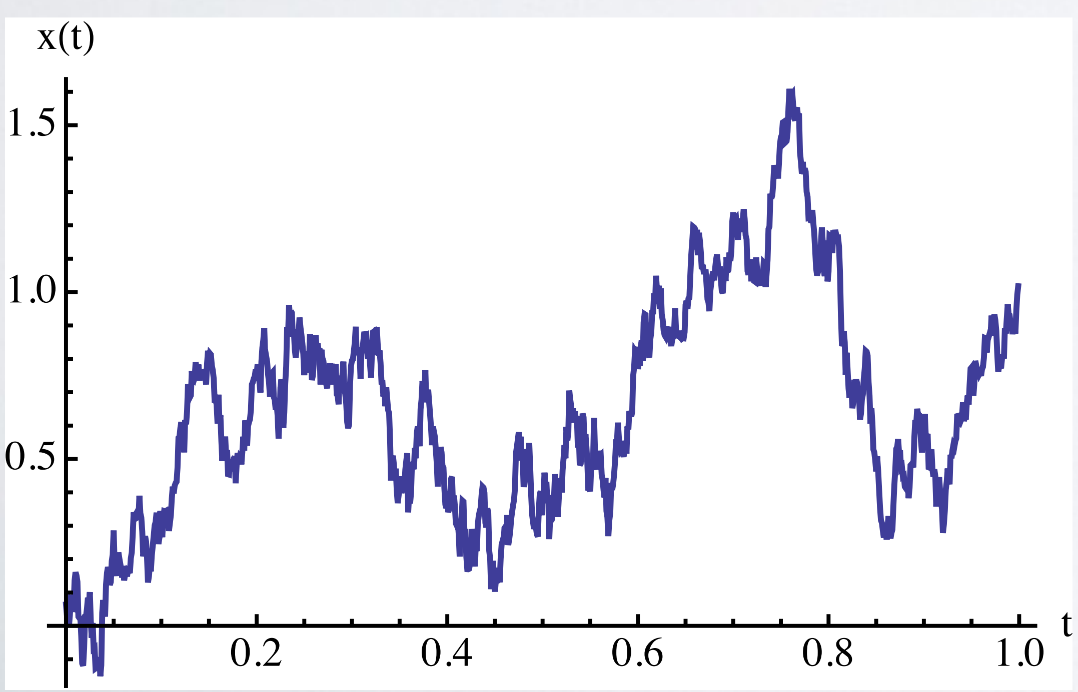
$$x(t_0+\Delta t) = x(t_0) + \xi$$

$$\overline{\xi} = 0$$

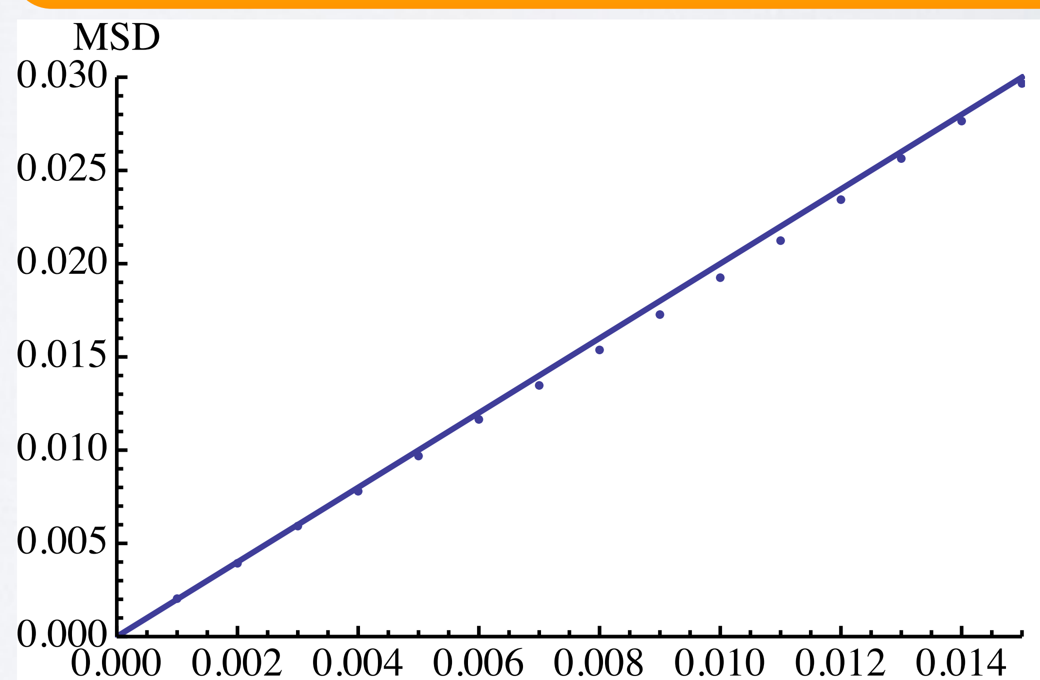
$$\overline{\xi^2} = 2D\Delta t$$

white noise

Trajectory

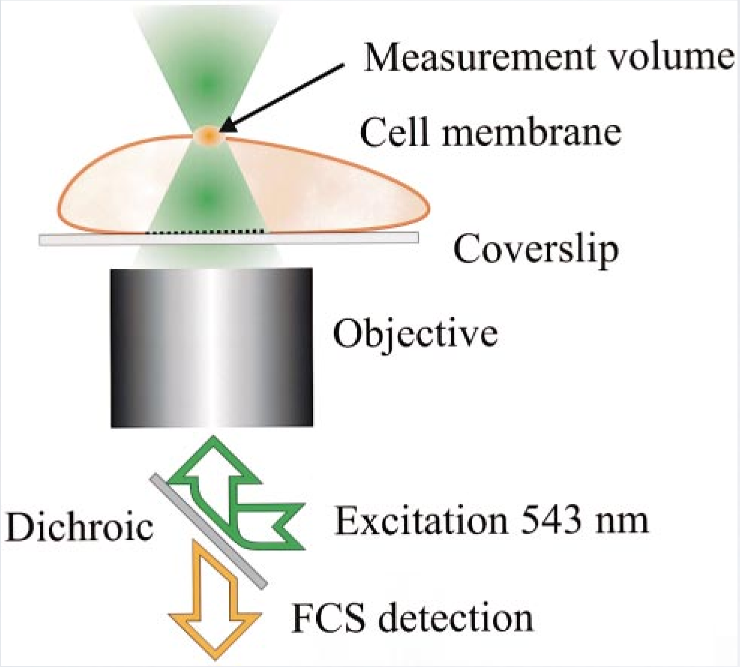


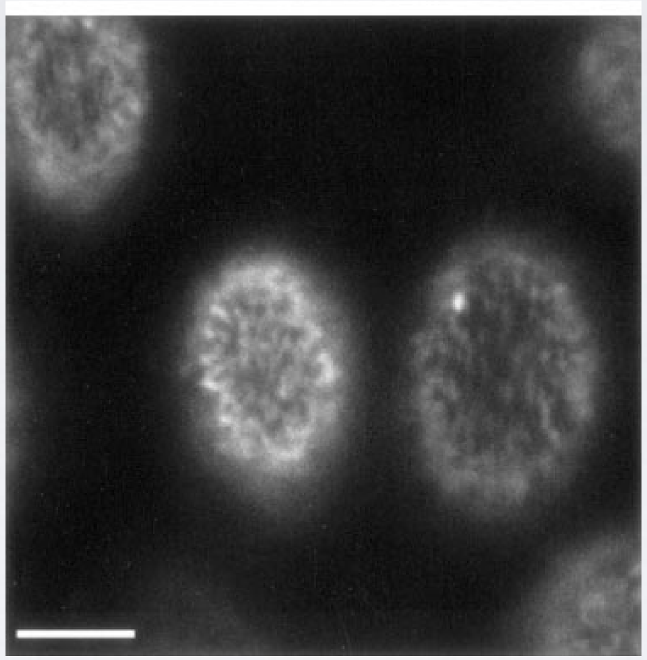
$$W(t) := \langle (x(t)-x(0))^2 \rangle = 2Dt$$

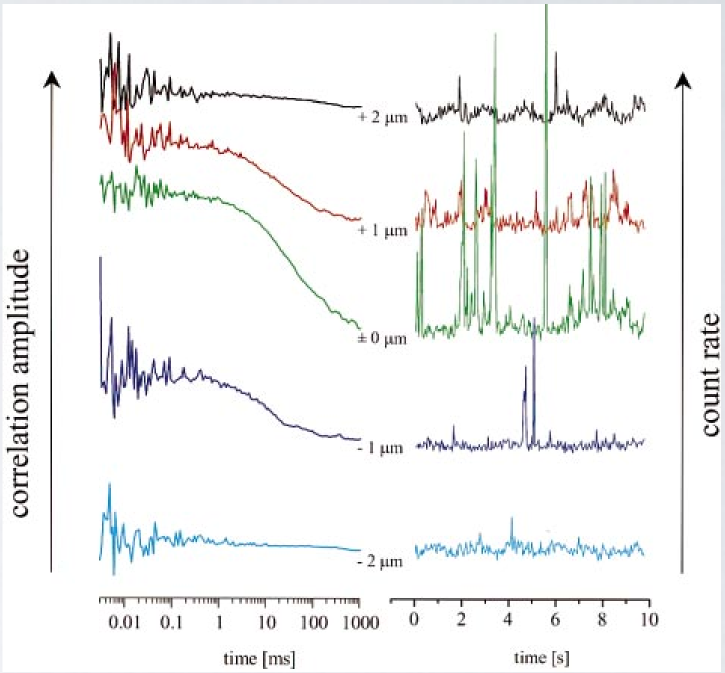


Subdiffusion of lipids observed by FCS

P. Schwille, J. Korlach, and W. Webb, Cytometry 36, 176 (1999).







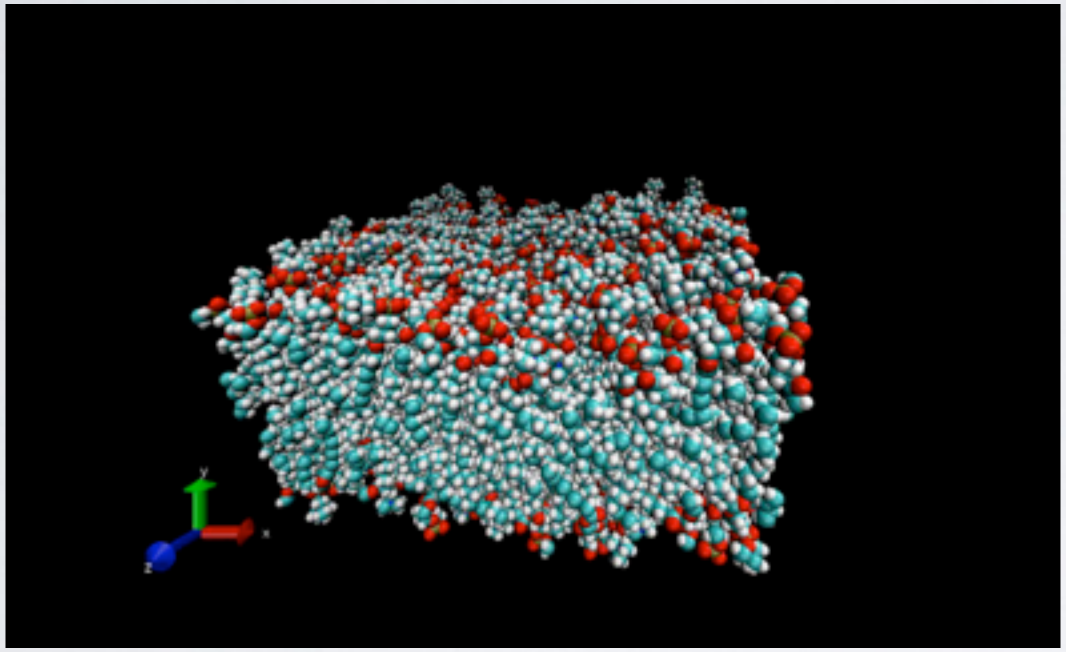
ms to s time scale

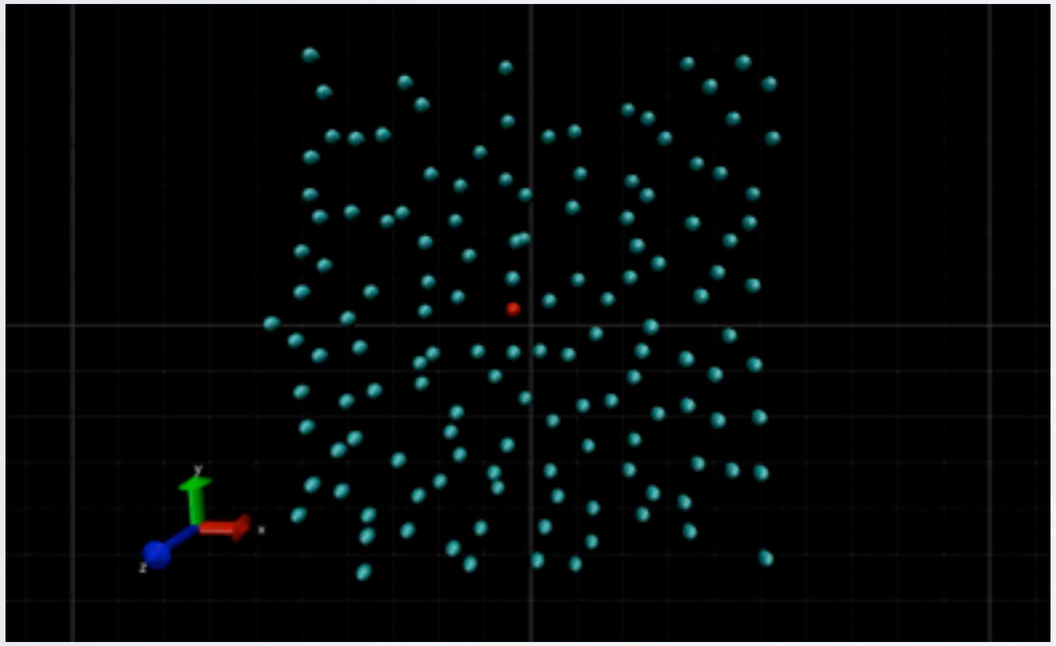
$$P_{anom}[\underline{r}', (t+\tau) | \underline{r}, t] = \frac{1}{(\pi \Gamma \tau^{\alpha})^{n/2}} e^{\frac{-(\underline{r}-\underline{r}')^2}{\Gamma \tau^{\alpha}}}$$

$$W(t) := 2 D_{\alpha} t^{\alpha} \qquad \alpha \approx 0.74$$

Subdiffusion of lipids observed by MD simulation

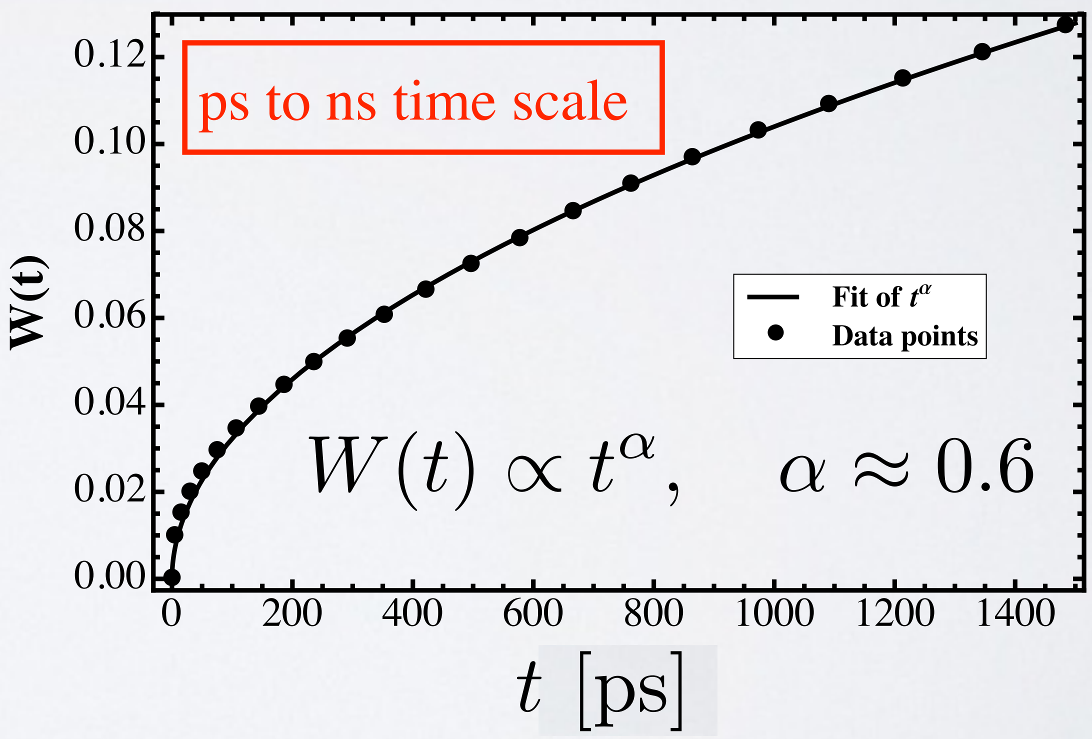
S. Stachura and G.R. Kneller, Mol Sim. 40, 245 (2013).





- 2x137 POPC molecules (10 nm × 10 nm in the XY-plane)
- 10471 water molecules (fully hydrated)
- OPLS force field
- T=310 K

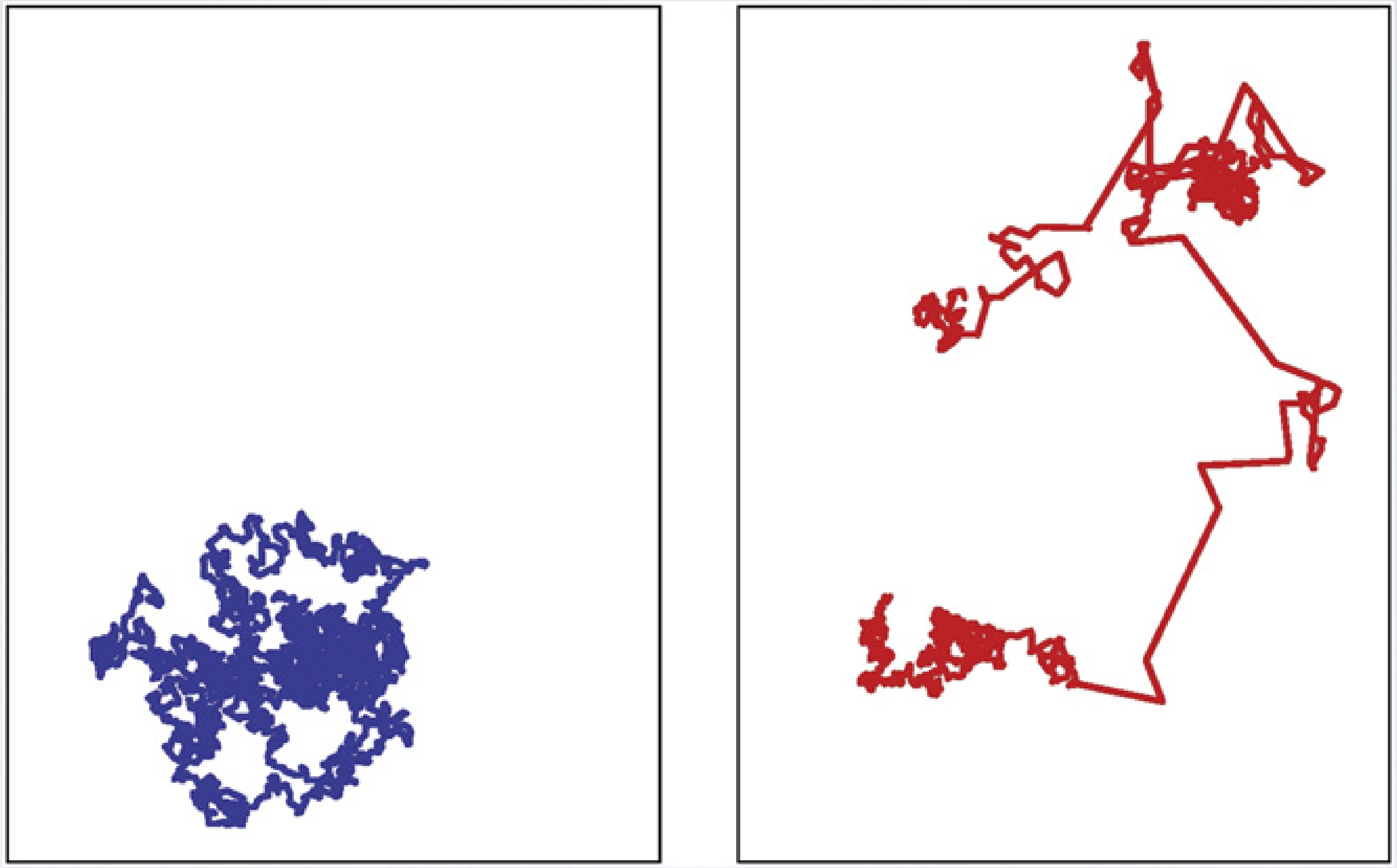
MSD for lateral diffusion



See also G.R. Kneller, K. Baczynski, and M. Pasenkiewicz-Gierula, J Chem Phys 135, 141105 (2011).
J.H. Jeon, H. Monne, M. Javanainen, and R. Metzler, Phys Rev Lett (2012).

Superdiffusion and chemotaxis of E. coli

F. Matthäus, M. Jagodič, and J. Dobnikar, Biophysical Journal 97, 946 (2009).



Normal diffusion of the E. coli, bacteria in absence of chemotaxis

Superdiffusion of the E. coli, bacteria in presence of chemotaxis

$$W(t) \propto t^{\alpha}, \quad 1 < \alpha < 2$$

Fractional diffusion equation

$$\partial_t P(\mathbf{x}, t|\mathbf{x}_0, 0) = {}_0\partial_t^{1-\alpha} \left\{ D_\alpha \frac{\partial^2}{\partial \mathbf{x}^2} \right\} P(\mathbf{x}, t|\mathbf{x}_0, 0) \quad (0 < \alpha < 2)$$

$${}_0\partial_t^{\rho} g(t) = \partial_t^{(-)n} \int_0^t dt' \, \frac{(t-t')^{\beta-1}}{\Gamma(\beta)} g(t').$$

Fractional Riemann-Liouville derivative of order ρ

Write $\rho = n - \beta$, where $n = 0, 1, 2, \ldots$, $\beta \geq 0$.

$$W(t) = 2D_\alpha t^\alpha$$

On *all* time scales!

See e.g. Metzler and Klafter. Phys Rep (2000) vol. 339 (1) pp. 1-77

Self-similarity of Brownian motion

Consider a self-similar stochastic processes[1]

$$c^{-H}Y(ct) =_d Y(t)$$

such that $Y(t) =_d t^H Y(1), \quad (t > 0,\ 0 < H < 1)$

Assume zero mean average and stationary increments:

$$\langle Y(t) \rangle = 0$$
$$\langle [Y(t) - Y(t-1)]^2 \rangle = \langle Y^2(1) \rangle = \sigma^2$$

[1] Kolmogoroff, A. Wienersche Spiralen und einige andere interessante Kurven im Hilbertsche Raum. C. R. (Dokl.) Acad. Sci. URSS 26 (n. Ser.), 115–118 (1940).

[2] J. Beran, *Statistics for Long-Memory Processes*. Chapman and Hall, 1994.

Then the MSD is

$$\langle [Y(t) - Y(s)]^2 \rangle = \sigma^2 (t-s)^{2H}, \quad 0 < s < t$$

and the covariance is

$$\langle Y(t) Y(s) \rangle = \frac{\sigma^2}{2} \left(t^{2H} - (t-s)^{2H} + s^{2H} \right)$$

Setting $D_H = \sigma^2/2$, one recognizes "normal diffusion" for $H = 1/2$, subdiffusion for $0 < H < 1/2$, and superdiffusion for $1/2 < H < 1$.

Limit of self-similarity

$$W(t) = 2\int_0^t dt'\,(t-t')c_{vv}(t')$$

Velocity autocorrelation function

$c_{vv}(t) = \langle \mathbf{v}(t)\cdot\mathbf{v}(0)\rangle$

$t \to 0$

$$W(t) \overset{t\to 0}{\sim} \langle \mathbf{v}^2\rangle t^2$$

Ballistic regime

Deterministic Generalized Langevin equation

$$\dot{\mathbf{v}}(t) = -\int_0^t dt'\,\kappa(t-t')\mathbf{v}(t') + \mathbf{f}^{(+)}(t)$$

$\langle \mathbf{v}(t)\cdot\mathbf{f}^{(+)}(t')\rangle = 0.$

$t \to \infty$

$$W(t) \overset{t\to\infty}{\sim} 2D_\alpha t^\alpha$$

Asymptotic regime

Asymptotic analysis of diffusion

Neuer Beweis und Verallgemeinerung der Tauberschen Sätze, welche die Laplacesche und Stieltjessche Transformation betreffen.

Von *J. Karamata* in Belgrad.

Journal für die Reine und Angewandte Mathematik (Crelle's Journal) **1931,** 27–39 (1931).

$$h(t) \overset{t\to\infty}{\sim} L(t)t^{\rho} \Leftrightarrow \hat{h}(s) \overset{s\to 0}{\sim} L(1/s)\frac{\Gamma(\rho+1)}{s^{\rho+1}} \quad (\rho > -1).$$

$\hat{h}(s) = \int_0^{\infty} dt\ \exp(-st)h(t) \quad (\Re\{s\} > 0)$ Laplace transform

$\lim_{t\to\infty} L(\lambda t)/L(t) = 1$, with $\lambda > 0$. Slowly growing function

What can be learned from diverging integrals?

Combining

1. Mathematics (α is given)

$$W(t) \overset{t\to\infty}{\sim} 2D_\alpha L(t)t^\alpha \longleftrightarrow \hat{W}(s) \overset{s\to 0}{\sim} 2D_\alpha L(1/s)\frac{\Gamma(\alpha+1)}{s^{\alpha+1}}.$$

$$\lim_{t\to\infty} L(t) = 1 \qquad \lim_{t\to\infty} t\frac{dL(t)}{dt} = 0$$

Special choice of L(t)

2. Physics

$$W(t) = 2\int_0^t d\tau\,(t-\tau)c_{vv}(\tau)$$

$$\frac{dc_{vv}(t)}{dt} = -\int_0^t d\tau\,\kappa(t-\tau)c_{vv}(\tau)$$

From the GLE

$$\hat{W}(s) = \frac{2\hat{c}_{vv}(s)}{s^2} = \frac{2\langle v^2\rangle}{s^2(s+\hat{\kappa}(s))}$$

Obtain asymptotic forms for Laplace transforms of VACF and memory function

Kneller, G. R. , J Chem Phys 134, 224106 (2011).

Generalized Kubo relation for D_α

Kneller, G. R., J Chem Phys 134, 224106 (2011).

$$\hat{c}_{vv}(s) \overset{s\to 0}{\sim} D_\alpha \Gamma(\alpha+1) L(1/s) s^{1-\alpha}.$$

$$D_\alpha = \lim_{s\to 0} s^{\alpha-1} \hat{c}_{vv}(s) / \Gamma(1+\alpha)$$

$$D_\alpha = \frac{1}{\Gamma(1+\alpha)} \int_0^\infty dt \; {}_0\partial_t^{\alpha-1} c_{vv}(t).$$

reduces to the normal Kubo relation for $\alpha = 1$

$$D = \int_0^\infty c_{vv}(t)$$

Generalized relaxation constant

$$\hat{\kappa}(s) \overset{s\to 0}{\sim} \frac{\langle \mathbf{v}^2 \rangle}{D_\alpha \Gamma(\alpha+1)} \frac{s^{\alpha-1}}{L(1/s)}$$

$$\eta_\alpha = \Gamma(1+\alpha) \lim_{s\to 0} s^{1-\alpha} \hat{\kappa}(s)$$

$$\eta_\alpha = \Gamma(1+\alpha) \int_0^\infty dt \; {}_0\partial_t^{1-\alpha} \kappa(t)$$

$$D_\alpha = \frac{\langle \mathbf{v}^2 \rangle}{\eta_\alpha}$$

Fluctuation-Dissipation theorem

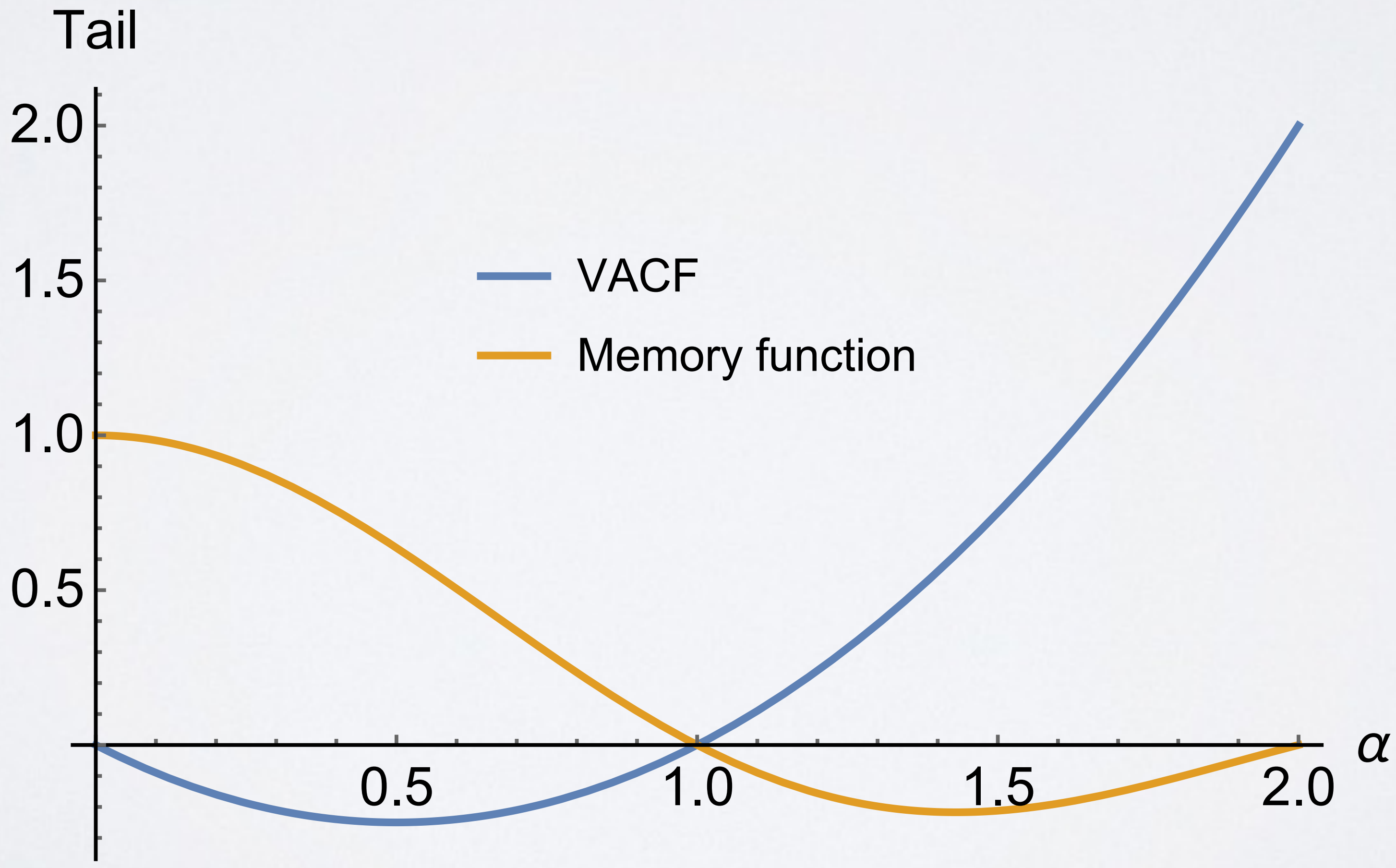
Kneller, G. R. , J Chem Phys 134, 224106 (2011).

Long time tails

$$\lim_{t\to\infty} L(t) = 1 \qquad \lim_{t\to\infty} t\frac{dL(t)}{dt} = 0$$

$$c_{vv}(t) \overset{t\to\infty}{\sim} D_\alpha \alpha(\alpha-1)L(t)t^{\alpha-2},$$ also sufficient for $1 < \alpha < 2$

$$\kappa(t) \overset{t\to\infty}{\sim} \frac{\langle \mathbf{v}^2\rangle}{D_\alpha}\frac{\sin(\pi\alpha)}{\pi\alpha}\frac{1}{L(t)}t^{-\alpha}.$$ also sufficient for $0 < \alpha < 1$



Interpretation of the memory function as a «cage»

$$\dot{\mathbf{v}}(t) = -\int_0^t dt'\,\kappa(t-t')\mathbf{v}(t') + \mathbf{f}^{(+)}(t)$$

$$\kappa(t) \equiv \Omega^2 \Rightarrow c_{vv}(t) = \langle v^2 \rangle \cos \Omega t$$

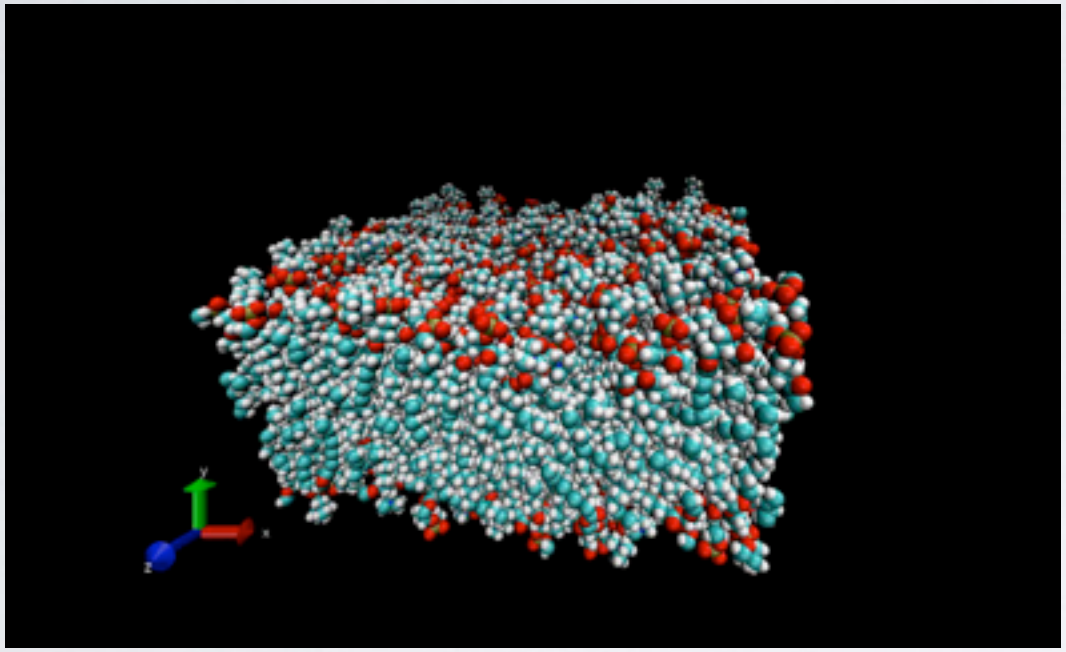
special choice of constant memory

oscillatory «rattling» motions in the «cage» of nearest neighbors

☛ The asymptotic decay of this cage determines the type of diffusion which is observed (normal, anomalous).

Visualizing the cage effect in a POPC bilayer

S. Stachura and G.R. Kneller, Mol Sim. 40, 245 (2013).



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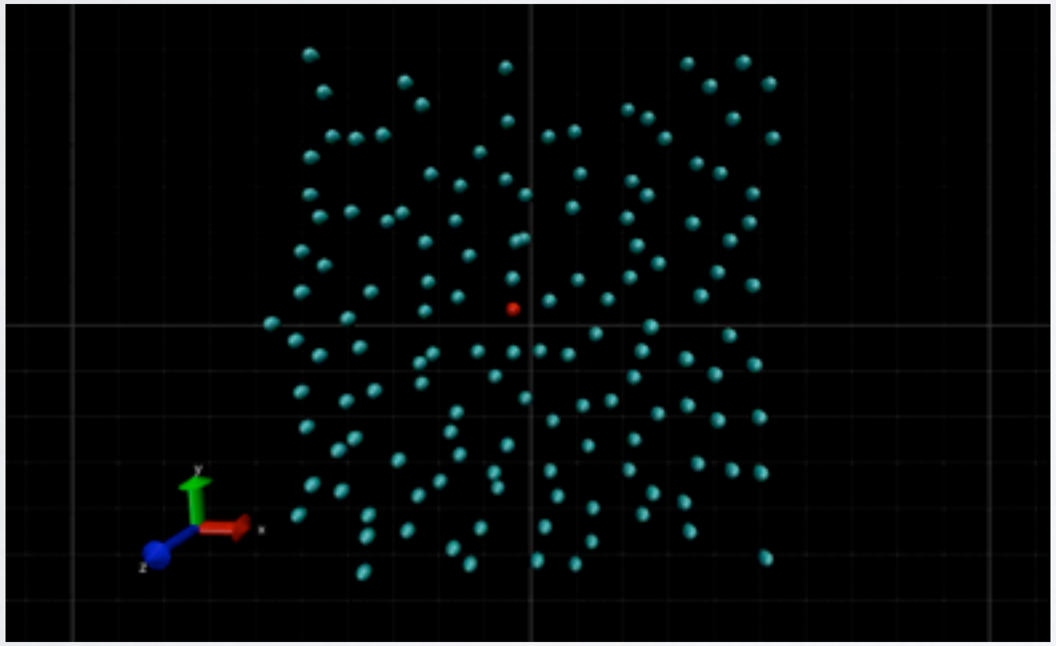
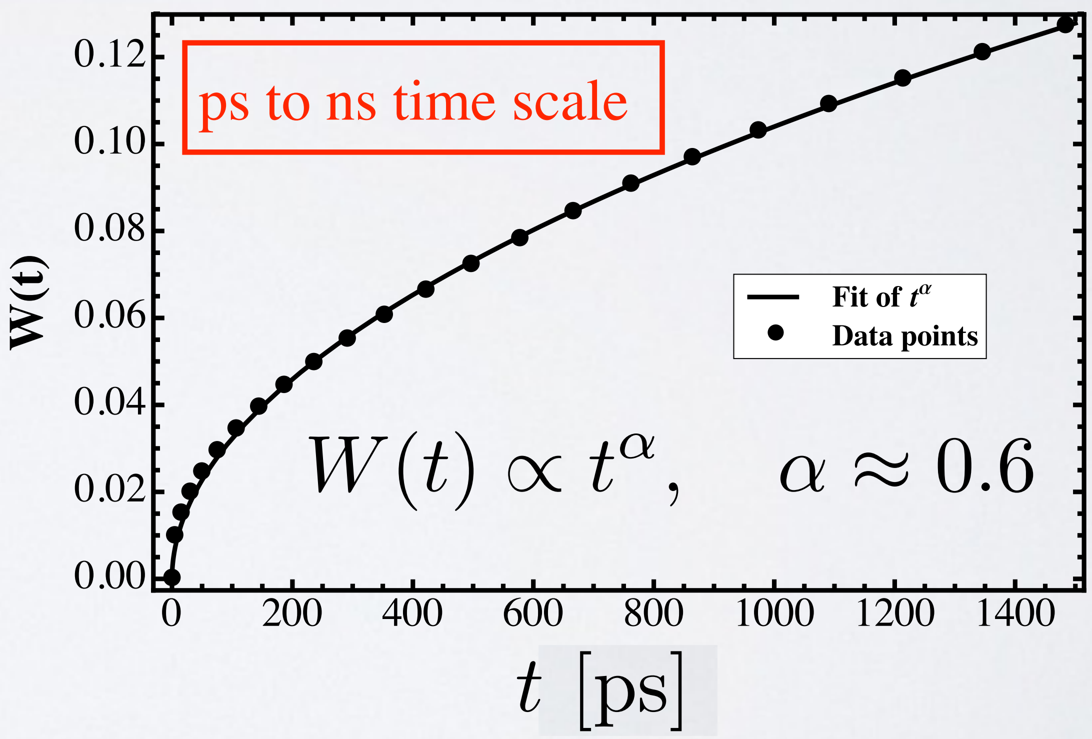


MSD for lateral diffusion



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J.H. Jeon, H. Monne, M. Javanainen, and R. Metzler, Phys Rev Lett (2012).

Van Hove correlation function and the „cage" of nearest neighbours

- The pair Distribution Function (PDF), g(r), is proportional to the probability of finding a particle between distances „r+dr", from a tagged central particle in a liquid.
- Time-dependent PDFs (van Hove PDFs), $G_D(r,t)$, display the dynamic structure in a liquid.

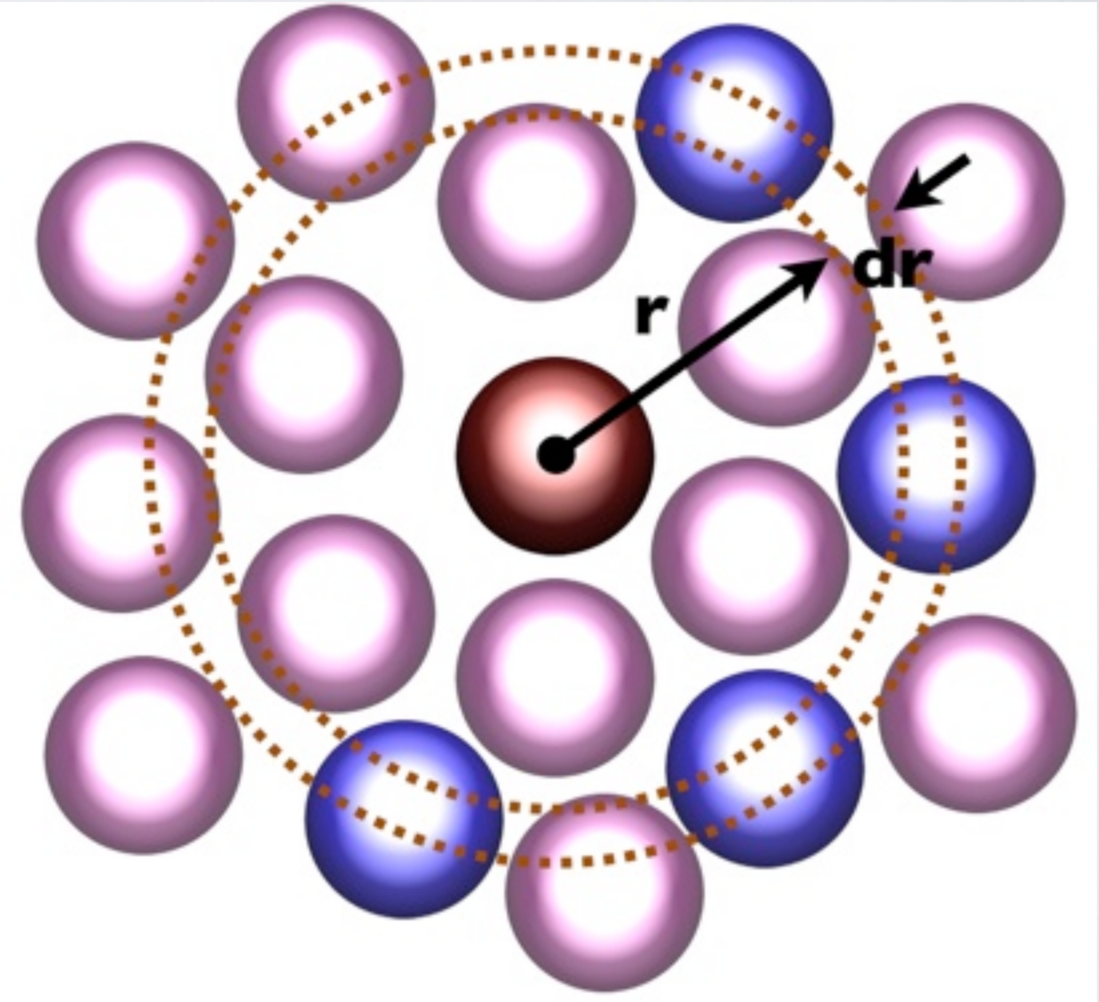
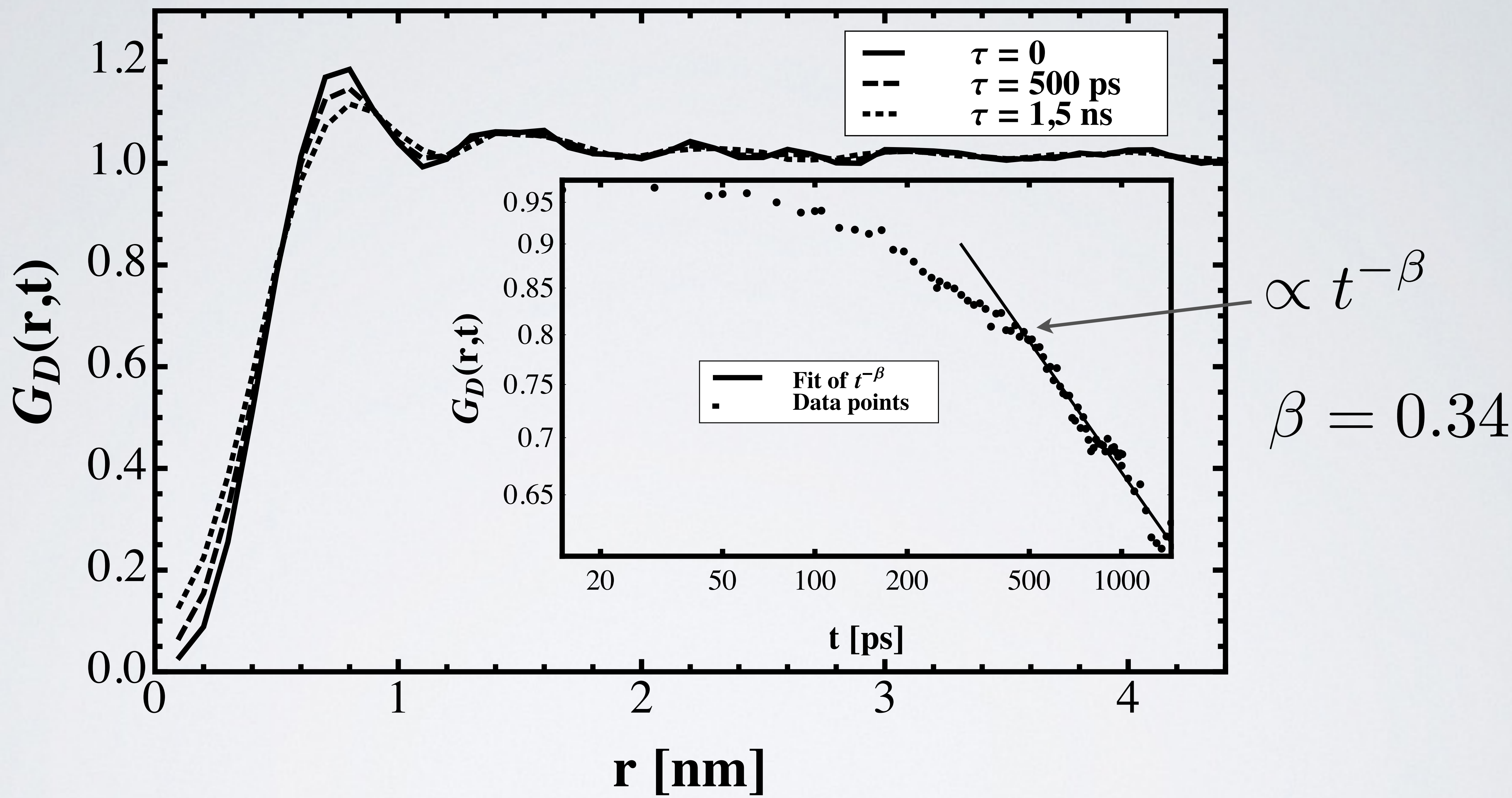


Image: "The structure of the cytoplasm" from Molecular Biology of the Cell. Adapted from D.S. Goodsell, Trends Biochem. Sci. 16:203-206, 1991.

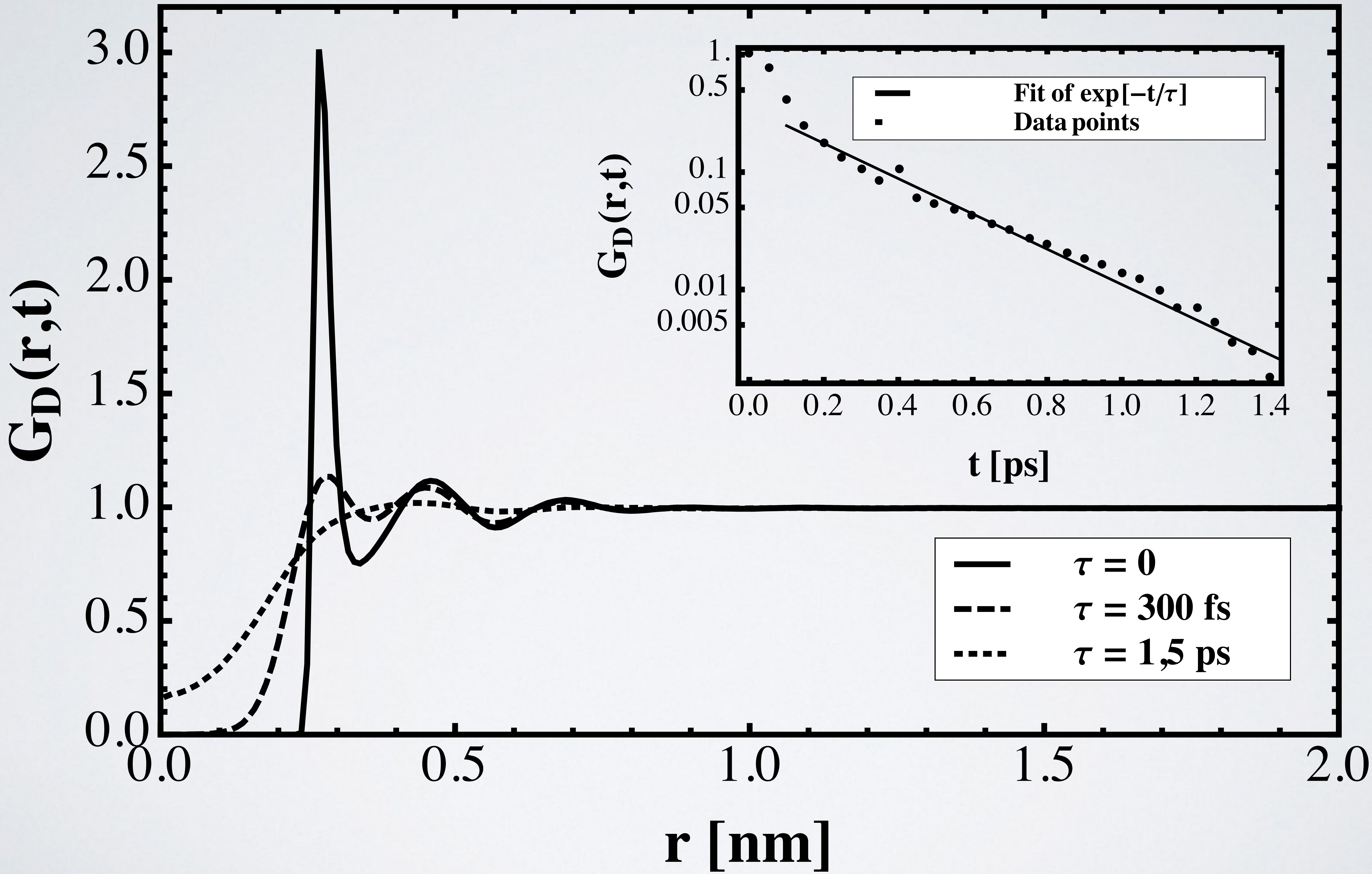
- (Van Hove) PDFs can be obtained from scattering experiments (neutron scttering, inelastic X-ray scattering)

Time-dependent pair correlation function for POPC

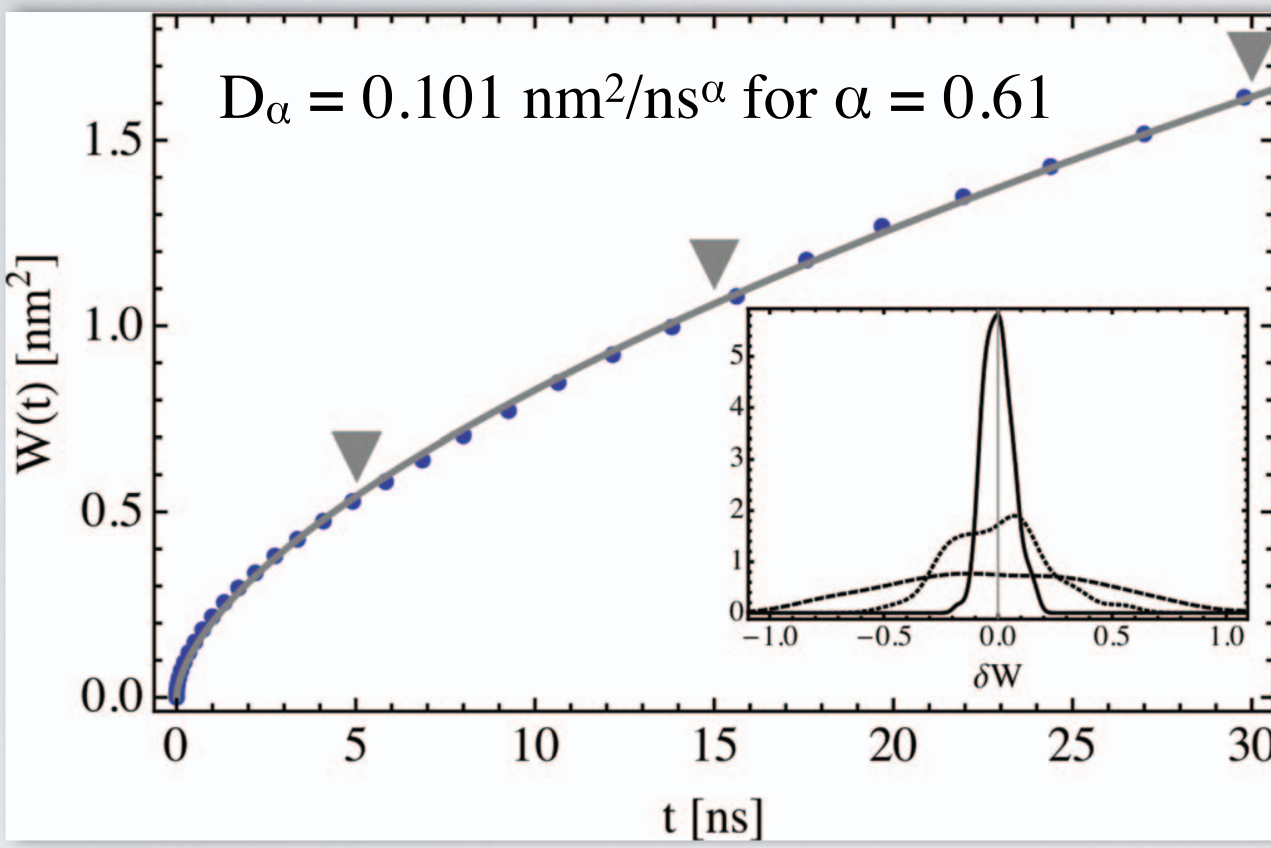


Time-dependent Pair Correlation Function G_d(r,t) of POPC lipids (CM) for three time slices : t=0 (thick line), t=500 ps (dashed line) and for t=1.5 ns (dotted line). **Inset:** Log-log plot for the decay of Gd(r,t) as a function of time for r =0.8 nm.

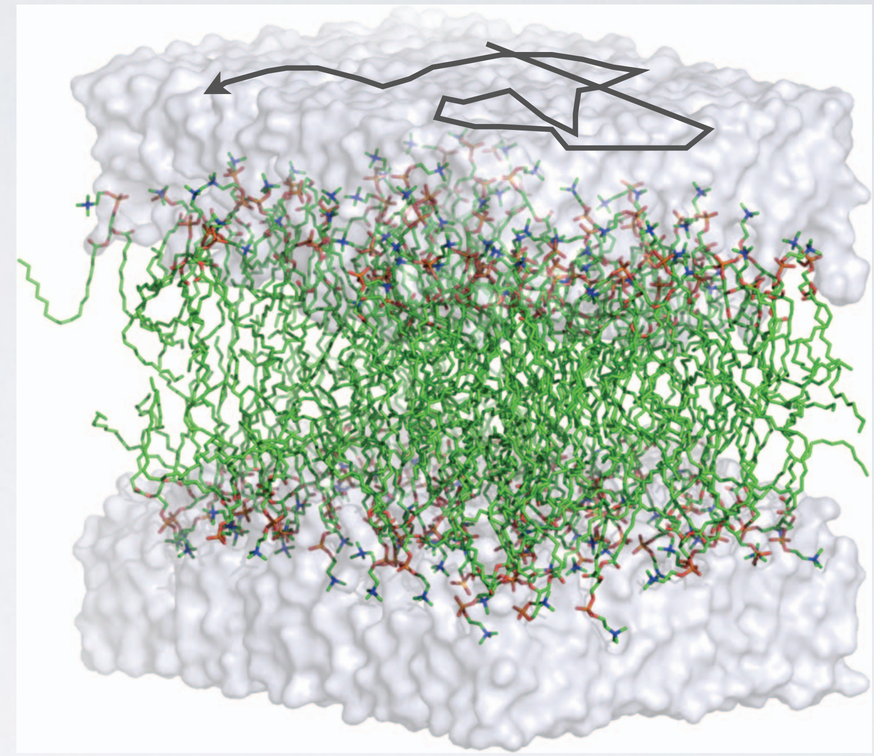
Bulk water for comparison....

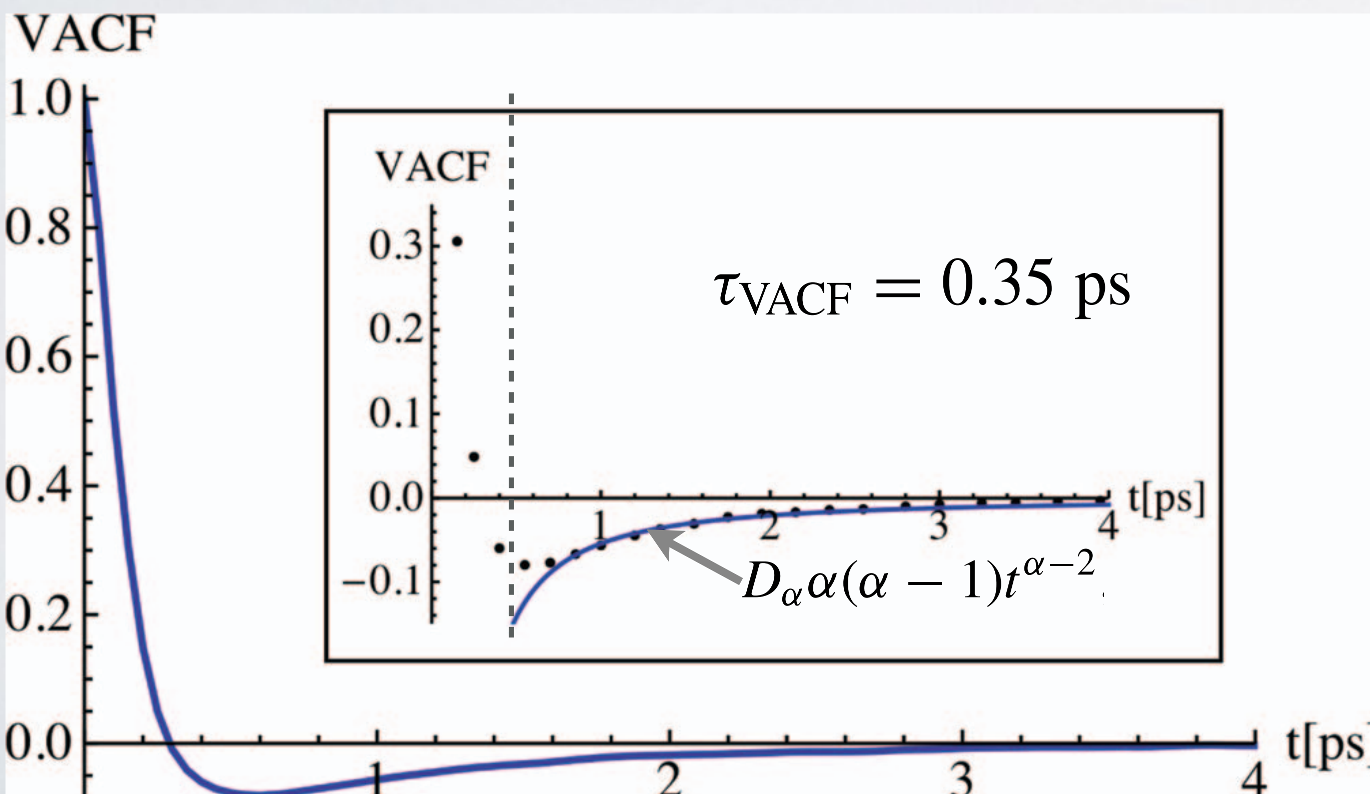


VACF relaxation time scale



Simulated DOPC system





$$\tau_{\text{VACF}} = \left(\frac{D_\alpha \Gamma(1+\alpha)}{\langle v^2 \rangle} \right)^{1/(2-\alpha)}$$

$$D_\alpha = \frac{\langle v^2 \rangle \tau_{\text{VACF}}^{2-\alpha}}{\Gamma(1+\alpha)}$$

G. R. Kneller, K. Baczynski, and M. Pasenkiewicz-Gierula. *J. Chem. Phys.*, 135(14):141105, 2011.

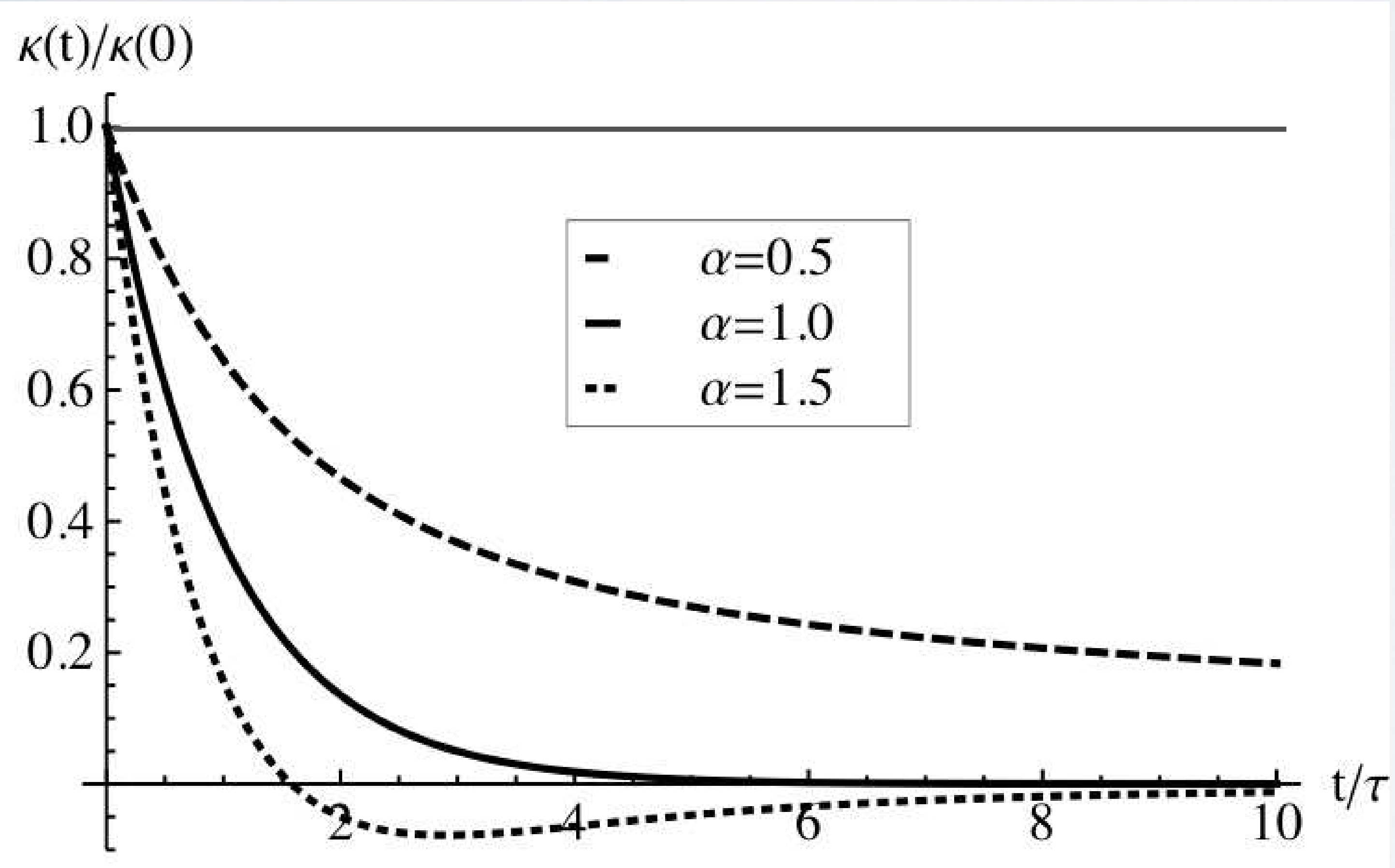
Simple model for anomalous diffusion

model memory function

$$\kappa_f(t) = \Omega^2 M(\alpha, 1, -t/\tau)$$

Kummer function

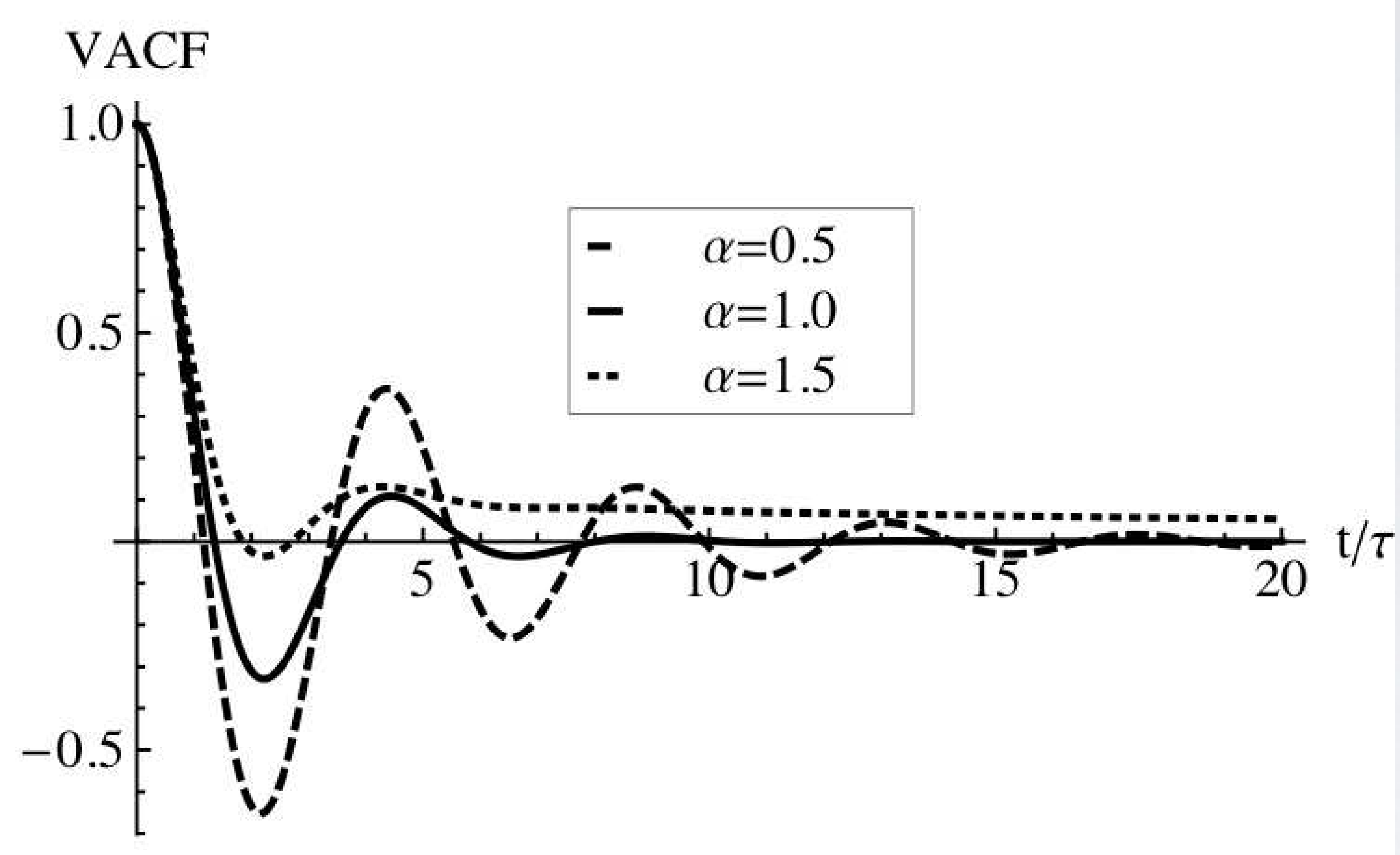
$$\hat{\kappa}_f(s) = \Omega^2 \left\{ \frac{\tau^\alpha}{s^{1-\alpha}} \frac{1}{(s\tau + 1)^\alpha} \right\}$$

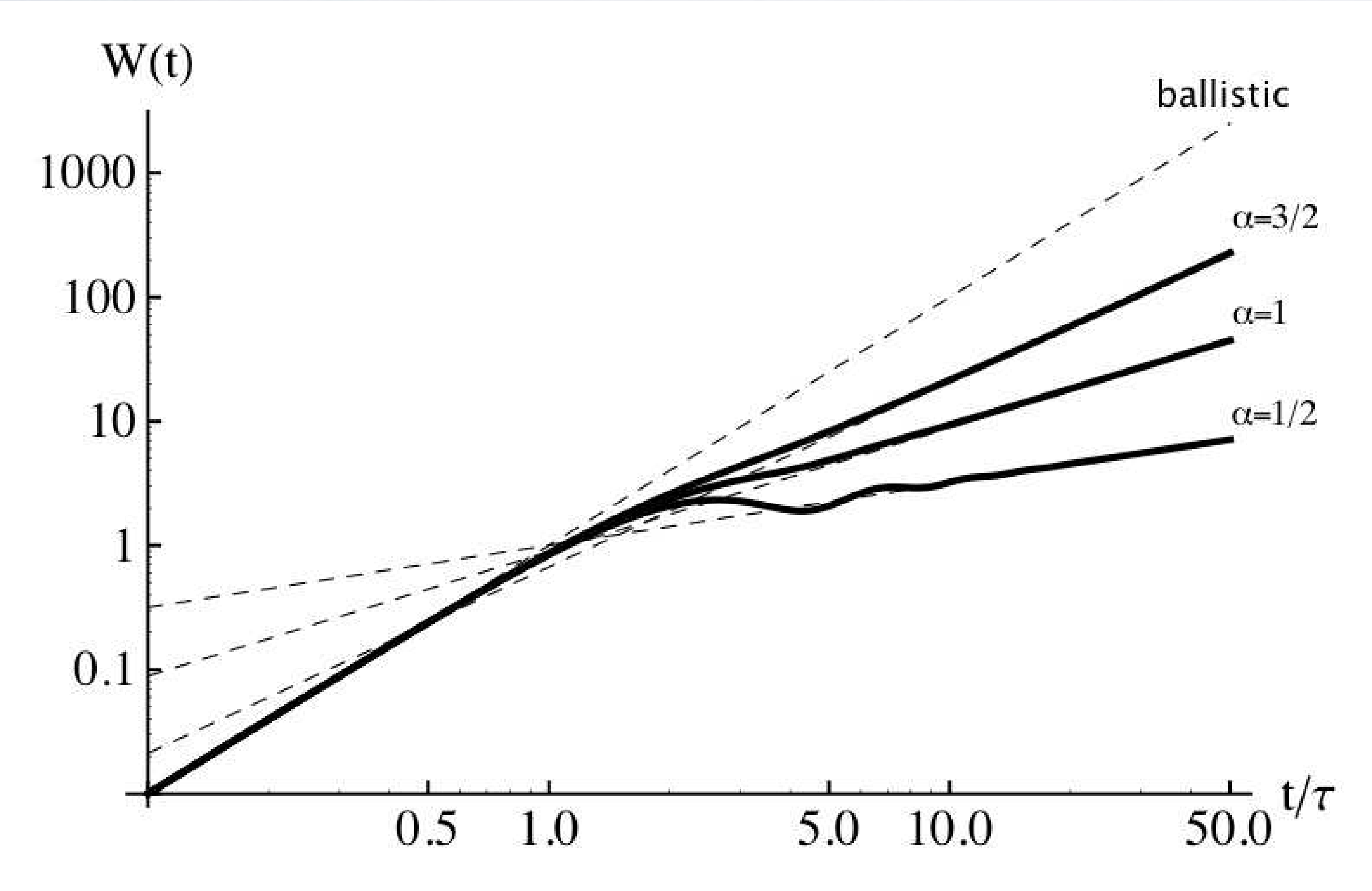


asymptotic form

$$\kappa_f(t) \overset{t\to\infty}{\sim} \begin{cases} \Omega^2 \frac{(t/\tau)^{-\alpha}}{\Gamma(1-\alpha)}, & \alpha \neq 1, \\ \Omega^2 \exp(-t/\tau), & \alpha = 1. \end{cases}$$

G. Kneller, *J. Chem. Phys.*, vol. 134, p. 224106, 2011.





$$D_\alpha = \frac{\langle \mathbf{v}^2 \rangle}{\Gamma(1+\alpha)\Omega^2 \tau^\alpha}$$

Anomalous Brownian motion as an asymptotic model

- Consider a tagged particle in a liquid whose MSD grows as $W(t) \sim t^\alpha$

- Scale its memory function according to

$$\kappa(t) \to \lambda\kappa(t)$$

where $\lambda \to 0$. This corresponds to increasing its mass according to $m \to m/\lambda$.

From the GLE

$$\partial_t \psi(t) = -\int_0^\infty d\tau\, \kappa(t-\tau)\psi(\tau) \longleftrightarrow \psi(t) = \frac{1}{2\pi i}\oint ds\, \frac{\exp(st)}{s+\hat{\kappa}(s)}$$

For the scaled memory function one gets

$$\psi_\lambda(t) = \frac{1}{2\pi i}\oint ds\, \frac{\exp(st)}{s+\lambda\hat{\kappa}(s)}$$

$$= \frac{1}{2\pi i}\oint ds\, \frac{\exp(s\lambda t)}{s+\hat{\kappa}(\lambda s)}$$

Here

$$\hat{\kappa}(s) \overset{s\to 0}{\sim} \frac{\langle v^2\rangle}{D_\alpha \Gamma(\alpha+1)} s^{\alpha-1}$$

Infinitely repeated scaling

$$\psi_\lambda(t) \overset{\lambda\to 0}{\sim} \frac{1}{2\pi i}\oint du\, \frac{\exp\left(\lambda^{1/(2-\alpha)} u[t/\tau_{\mathrm{VACF}}]\right)}{u+u^{\alpha-1}}$$

$$= E_{2-\alpha}\left(-\lambda[t/\tau_{\mathrm{VACF}}]^{2-\alpha}\right)$$

VACF of an anomalous Rayleigh particle

Mittag-Leffler function

$$E_\alpha(z) = \sum_{n=0}^\infty \frac{z^n}{\Gamma(1+n\alpha)}$$

$$\tau_{\mathrm{VACF}} = \left(\frac{D_\alpha \Gamma(1+\alpha)}{\langle v^2\rangle}\right)^{1/(2-\alpha)}$$

Fractional OU process in velocity space

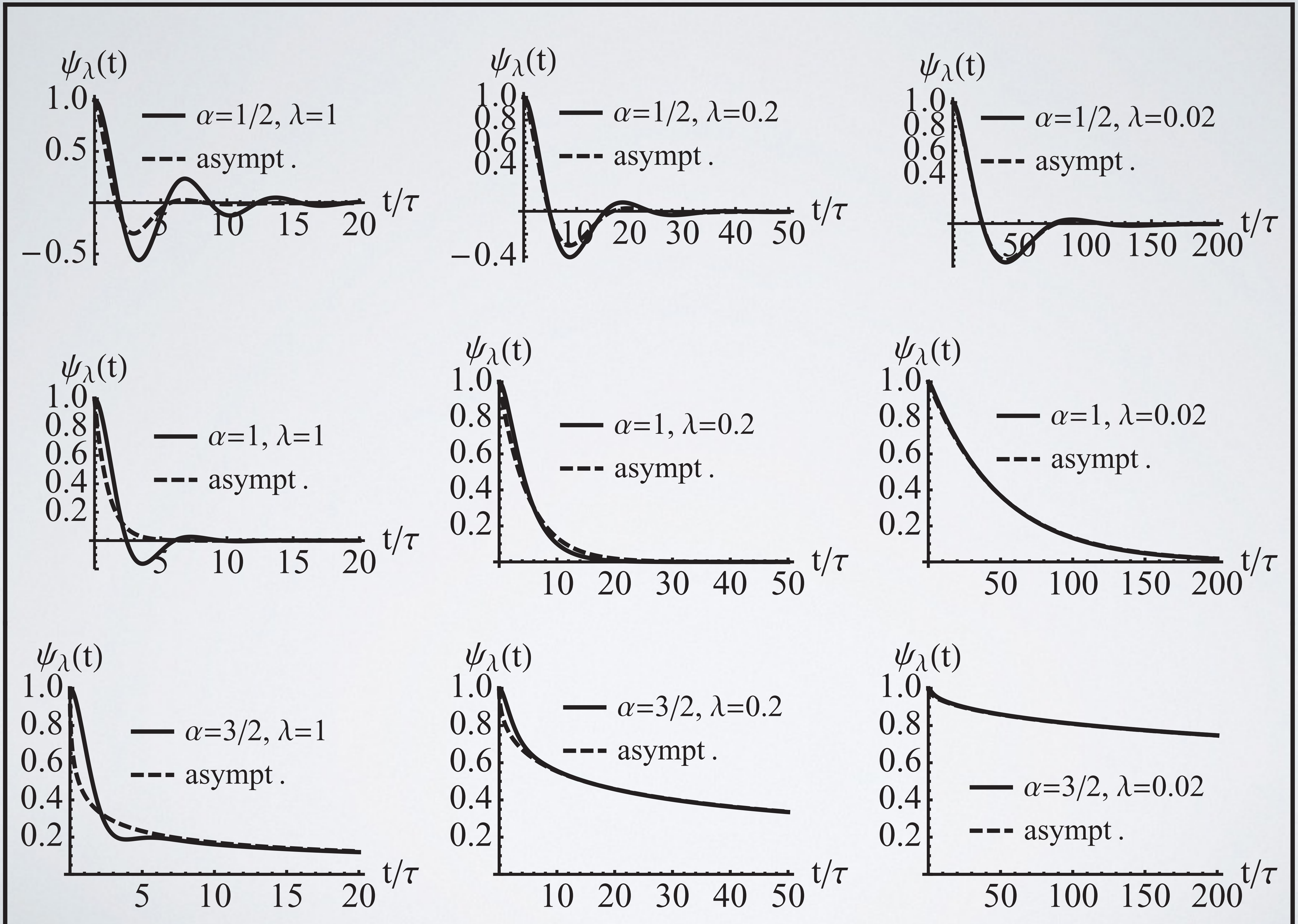
$$\partial_t p(v,t|v_0,0) = \eta_{2-\alpha}\, {}_0\partial_t^{\alpha-1} \left\{ \frac{\partial}{\partial v} v + \frac{k_B T}{m} \frac{\partial^2}{\partial v^2} \right\} p(v,t|v_0,0).$$

VACF of an « anomalous Rayleigh particle »

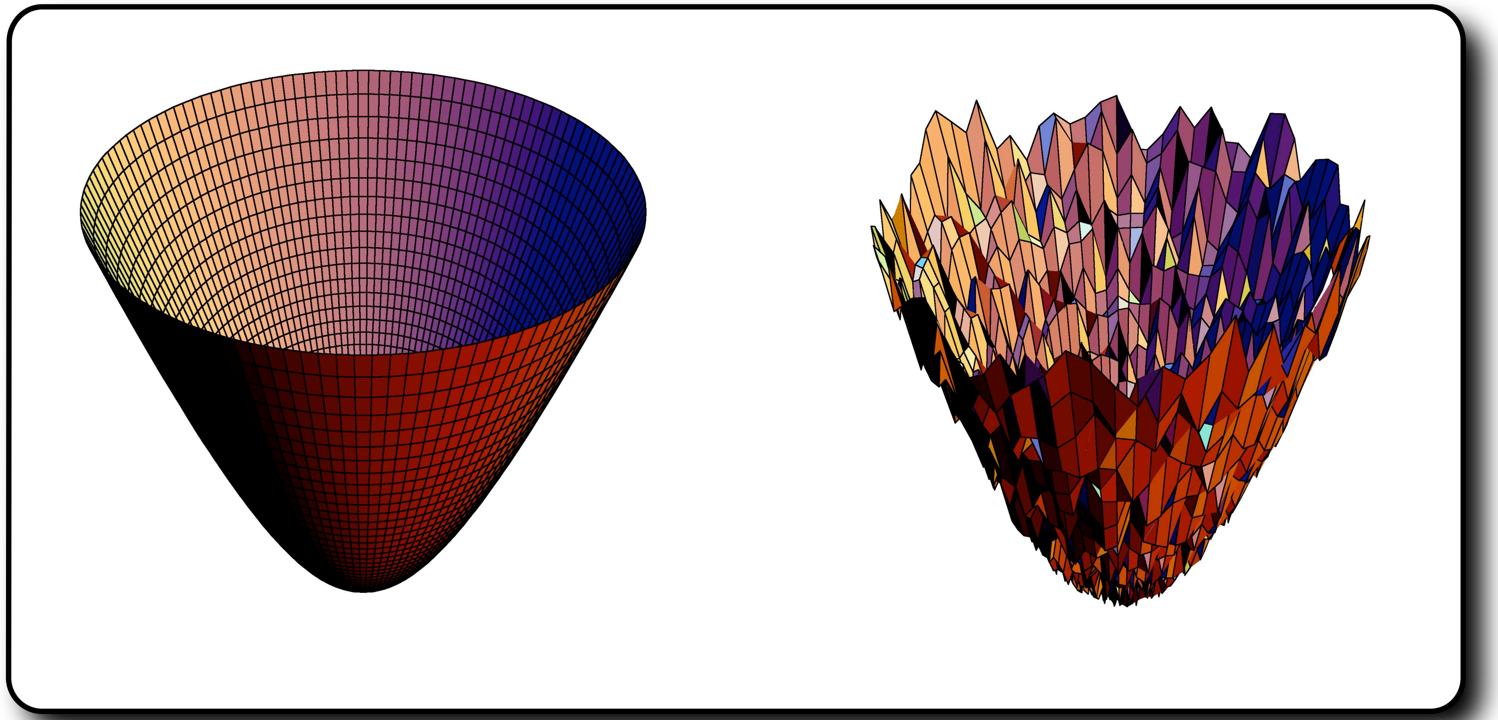
$$\psi(t) = \frac{k_B T}{m} \int\int dv dv_0\, v v_0 p(v,t|v_0,0) p_{eq}(v_0)$$

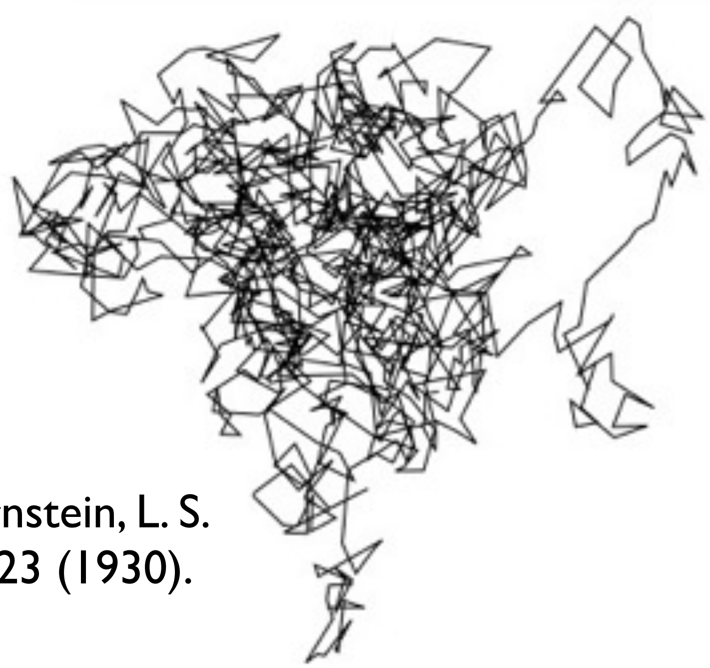
$$= E_{2-\alpha}(-[t/\tau_{\mathrm{VACF}}]^{2-\alpha}])$$

Example for the analytical example shown before ($\tau \equiv \tau_{VACF}$)



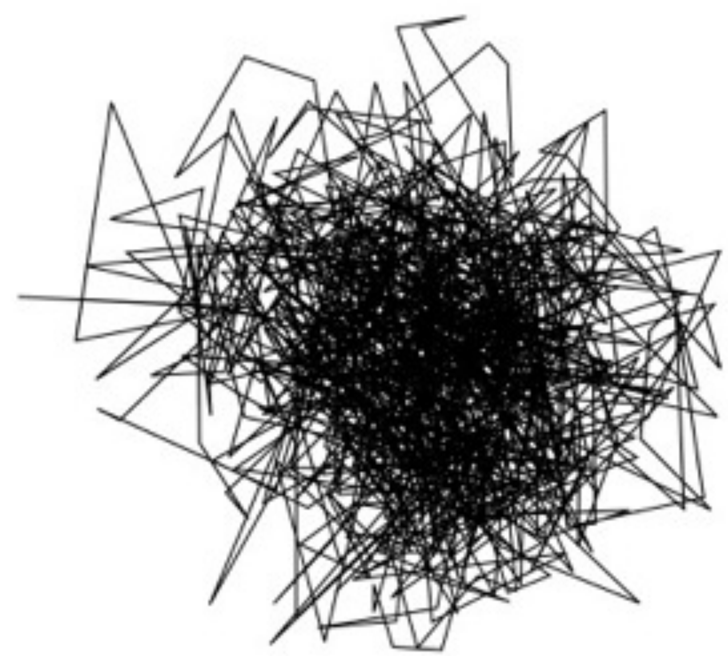
Anomalous diffusion in a harmonic well - a model for atomic motions in proteins





Uhlenbeck, G. E. & Ornstein, L. S. Physical Review 36, 823 (1930).

Ornstein-Uhlenbeck process



1. Shao, Y. Physica D: Nonlinear Phenomena 83, 461–477 (1995).
2. Metzler, R. & Klafter, J. Phys Rep 339, 1–77 (2000).

Fractional Ornstein-Uhlenbeck process

Nature Vol. 280 16 August 1979

Temperature-dependent X-ray diffraction as a probe of protein structural dynamics

Hans Frauenfelder, Gregory A. Petsko* & Demetrius Tsernoglou
Department of Physics, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801
and
Department of Biochemistry, Wayne State University School of Medicine, Detroit, Michigan 48201

proteins have *dynamic* structures

Myoglobin

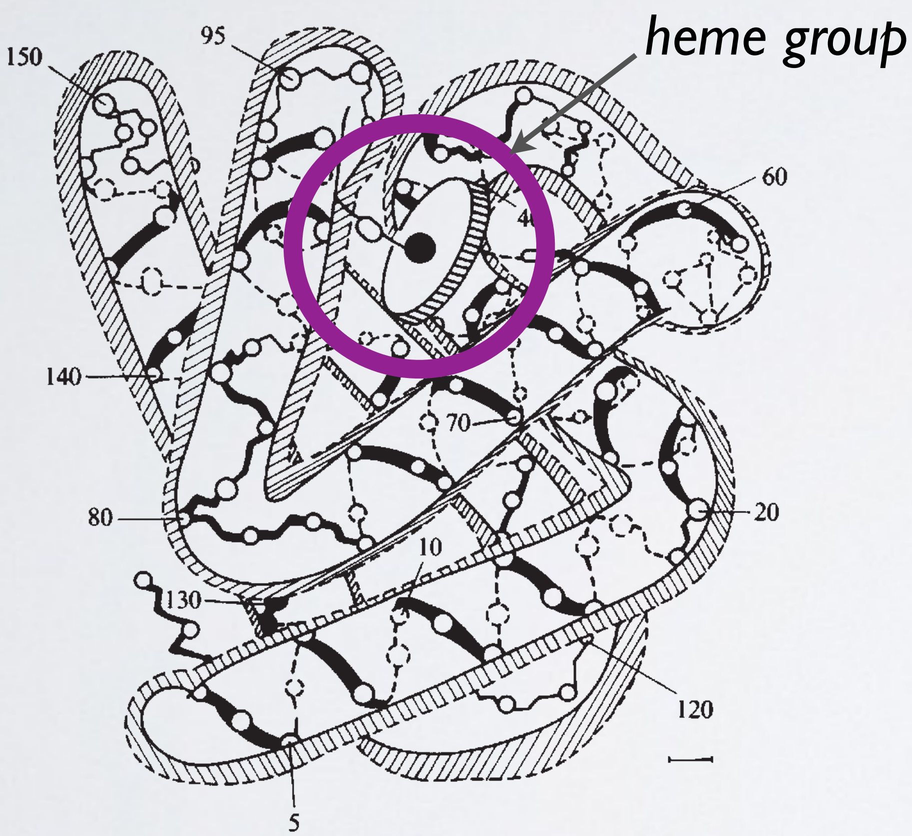
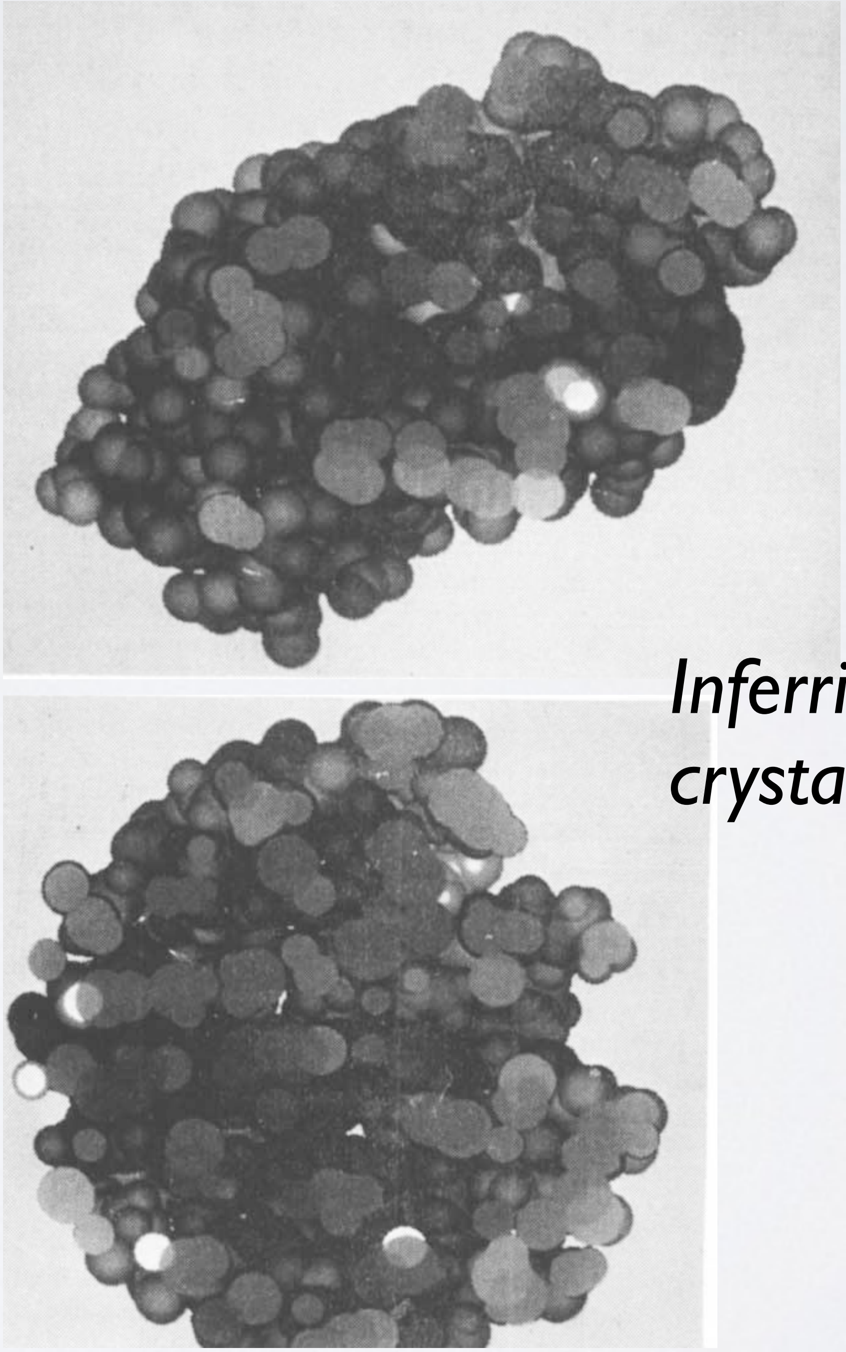


Fig. 3 Backbone (main chain) structure of myoglobin. The solid lines indicate the static structure as given in ref. 37. Circles denote the C^{α} carbons; some residue numbers are given. The shaded area gives the region reached by conformational substates with a 99% probability. Scale bar, 2 Å.



Inferring atomic motions from crystallgraphic B-factors

The Energy Landscapes and Motions of Proteins

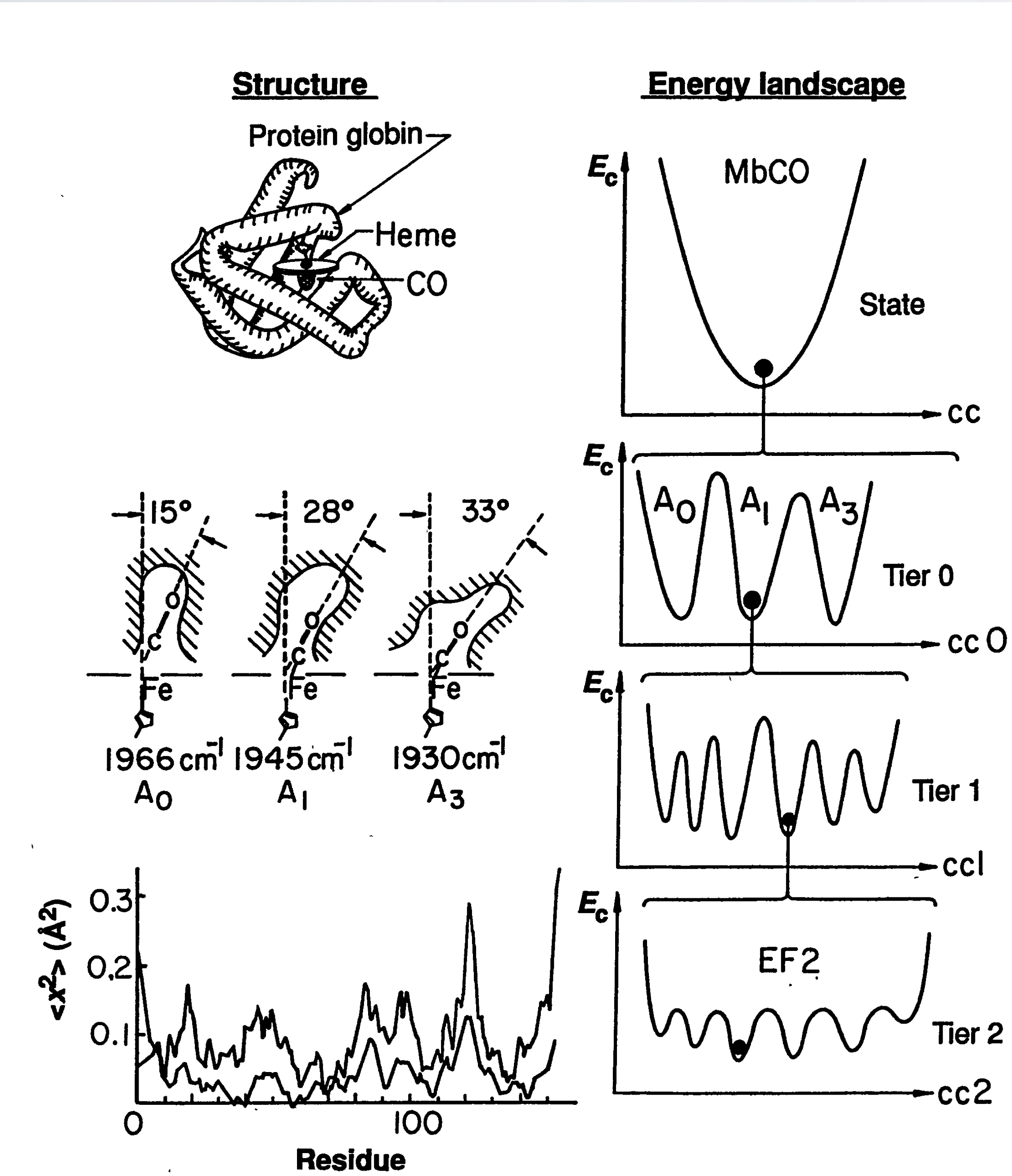
SCIENCE, VOL. 254

HANS FRAUENFELDER, STEPHEN G. SLIGAR, PETER G. WOLYNES

Conformational substates

Non-exponential rebinding kinetics of CO

$$N(t) = \int dH\, g(H) \exp[-k(H)t]$$



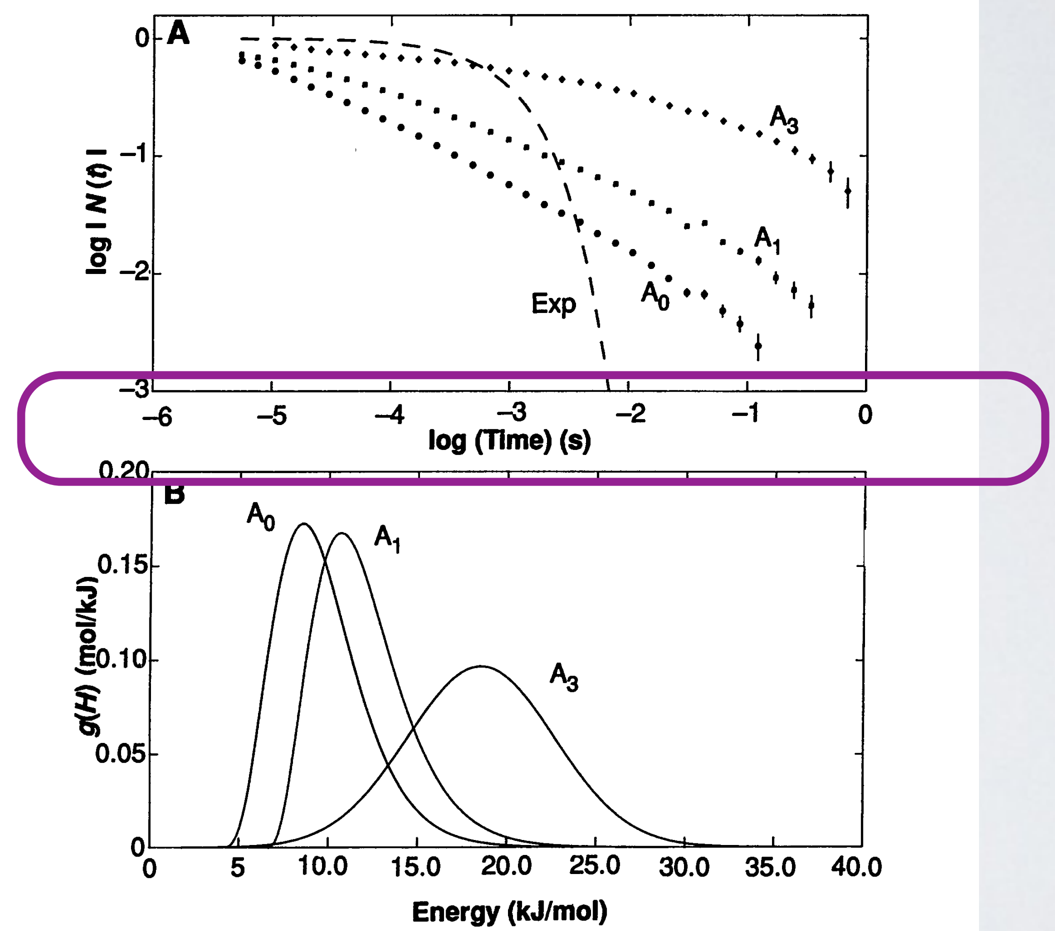


Fig. 2. Rebinding of CO to Mb after photodissociation, measured separately for the substates of tier 0 at pH 5.7. (**A**) $N(t)$ is the fraction of proteins that have not rebound a CO at the time t after photodissociation. All three substates (A_0, A_1, and A_3) rebind nonexponentially in time. (**B**) The activation enthalpy spectra, defined through Eq. 1.

Fractional kinetics of CO-rebinding to Mb

46 Biophysical Journal Volume 68 January 1995 46–53

A Fractional Calculus Approach to Self-Similar Protein Dynamics

Walter G. Glöckle and Theo F. Nonnenmacher
Department of Mathematical Physics, University of Ulm, D-89069 Ulm, Germany

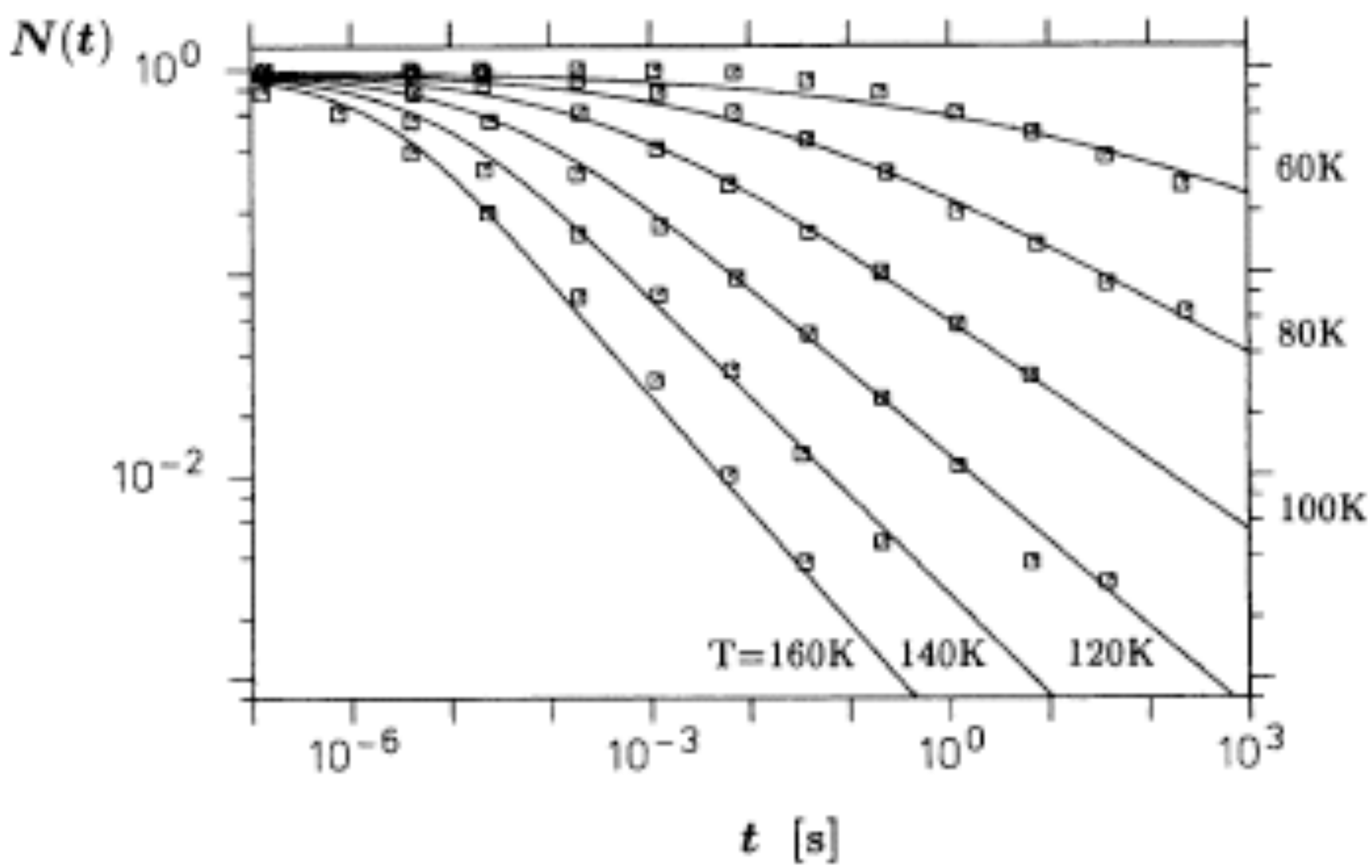


FIGURE 2 Three-parameter model Eq. 32 for rebinding of CO to Mb after photo dissociation. The parameters are $\tau_m = 8.4 \times 10^{-10}$s, $\alpha = 3.5 \times 10^{-3}\ K^{-1}$ and $k = 130$, the data points are from Austin et al. (1975).

$$N(t) = N(0)E_\alpha(-[t/\tau]^\alpha)$$

Simulated motions in myoglobin

J. Mol. Biol. (1994) **242**, 181–185

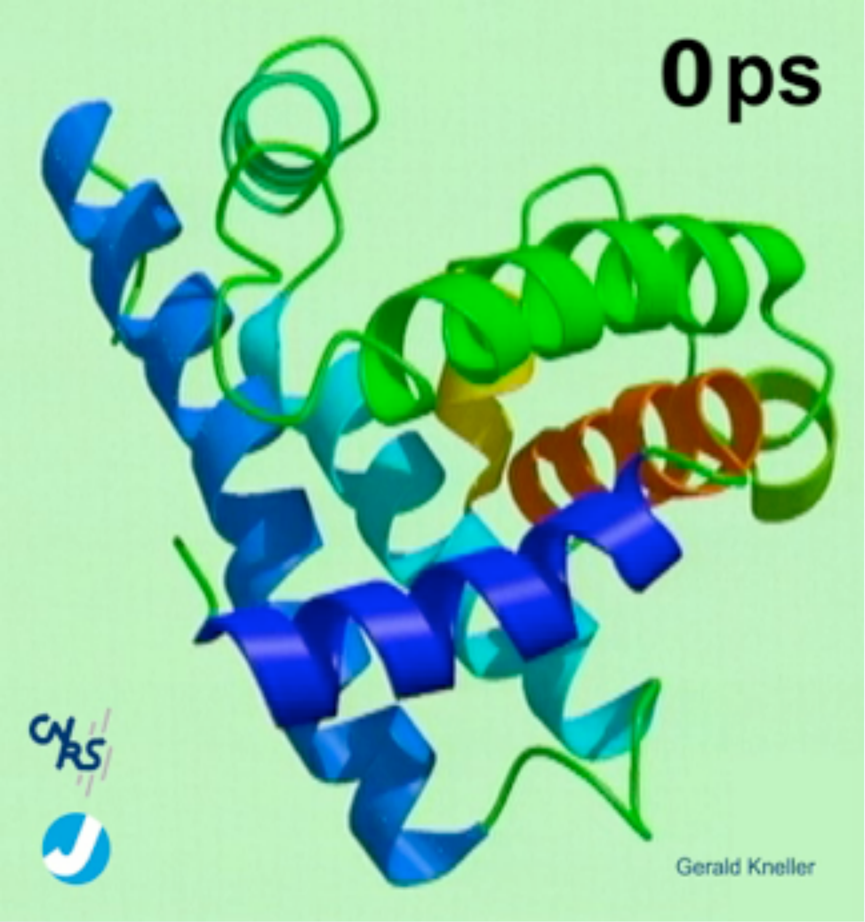
COMMUNICATION

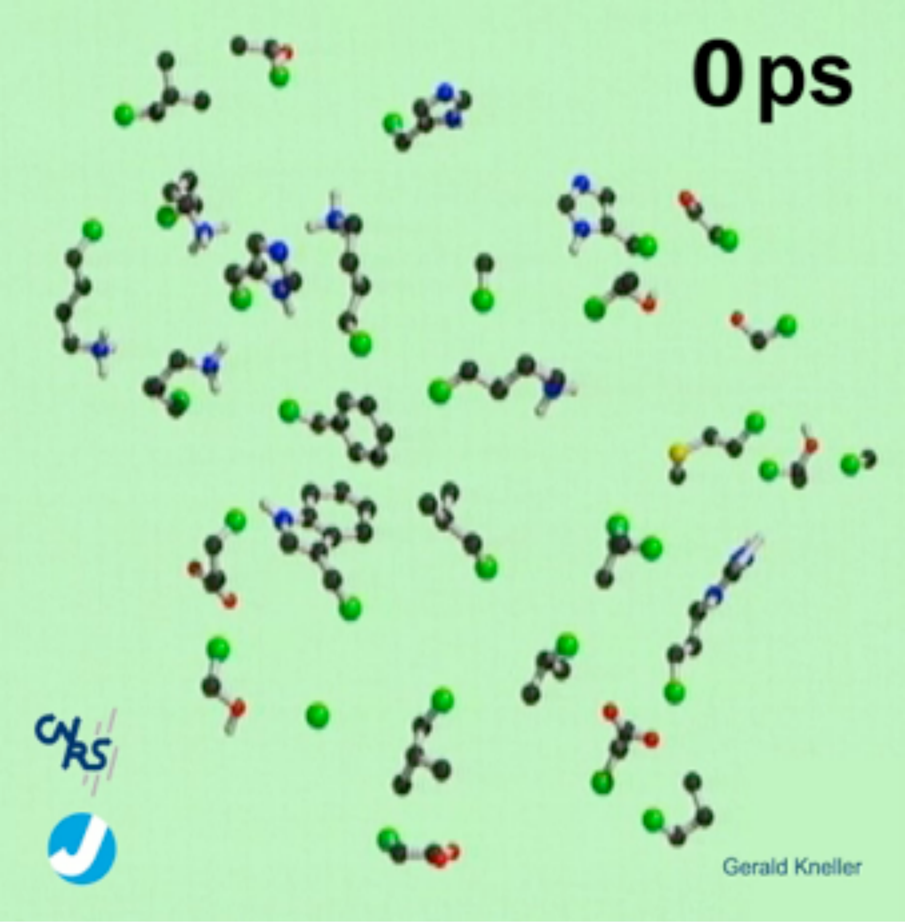
Liquid-like Side-chain Dynamics in Myoglobin

Gerald R. Kneller[1,2] and Jeremy C. Smith[2]

Backbone

The "side-chain liquid"





flexible

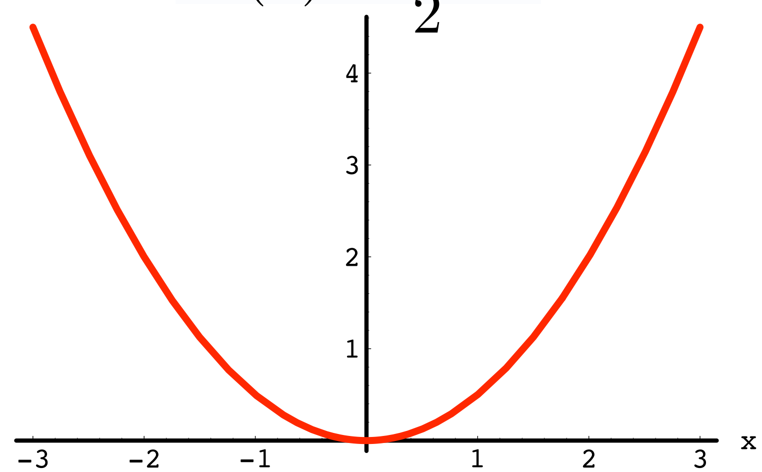
rigid

Fractional Smuluchowski equation

$$\partial_t P(\mathbf{x}, t|\mathbf{x}_0, 0) = {}_0\partial_t^{1-\alpha} \left\{ D_\alpha \frac{\partial}{\partial \mathbf{x}} \cdot \left(\frac{\partial}{\partial \mathbf{x}} + \frac{1}{k_B T} \frac{\partial U(\mathbf{x})}{\partial \mathbf{x}} \right) \right\} P(\mathbf{x}, t|\mathbf{x}_0, 0)$$

OU process in position space

$$U(x) = \frac{1}{2} K x^2$$



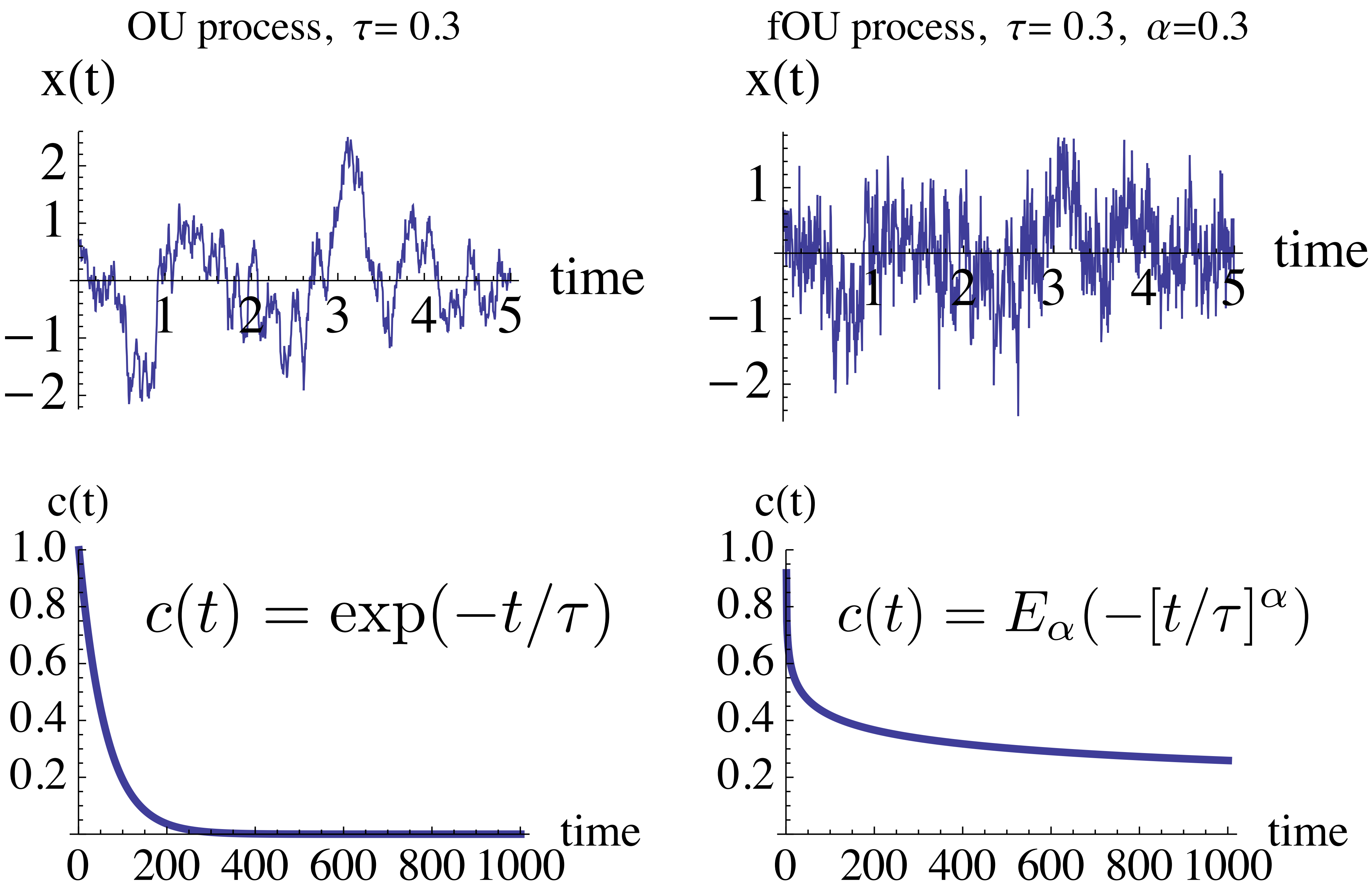
$$c_{xx}(t) = \langle \mathbf{x}^2 \rangle E_\alpha(-[t/\tau]^\alpha)$$

Mittag-Leffler function

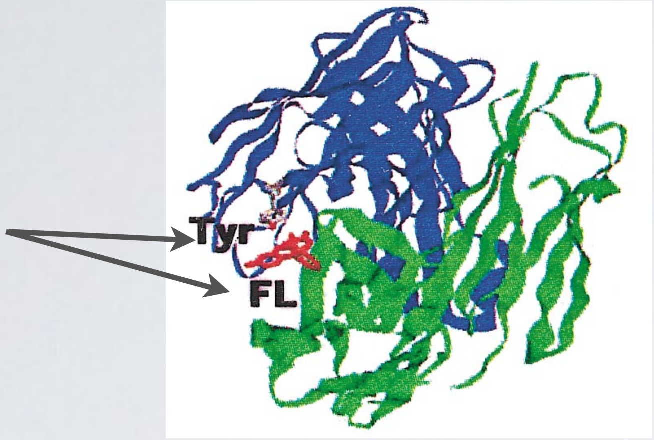
$$E_\alpha(z) = \sum_{n=0}^{\infty} \frac{z^n}{\Gamma(1 + n\alpha)}$$

$$W(t) = 2(\langle \mathbf{x}^2 \rangle - \langle \mathbf{x} \rangle^2)(1 - E_\alpha(-[t/\tau]^\alpha))$$

Time series and autocorrelation functions

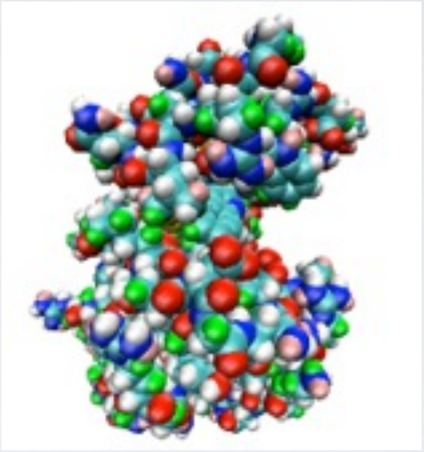


Self-similar internal protein dynamics



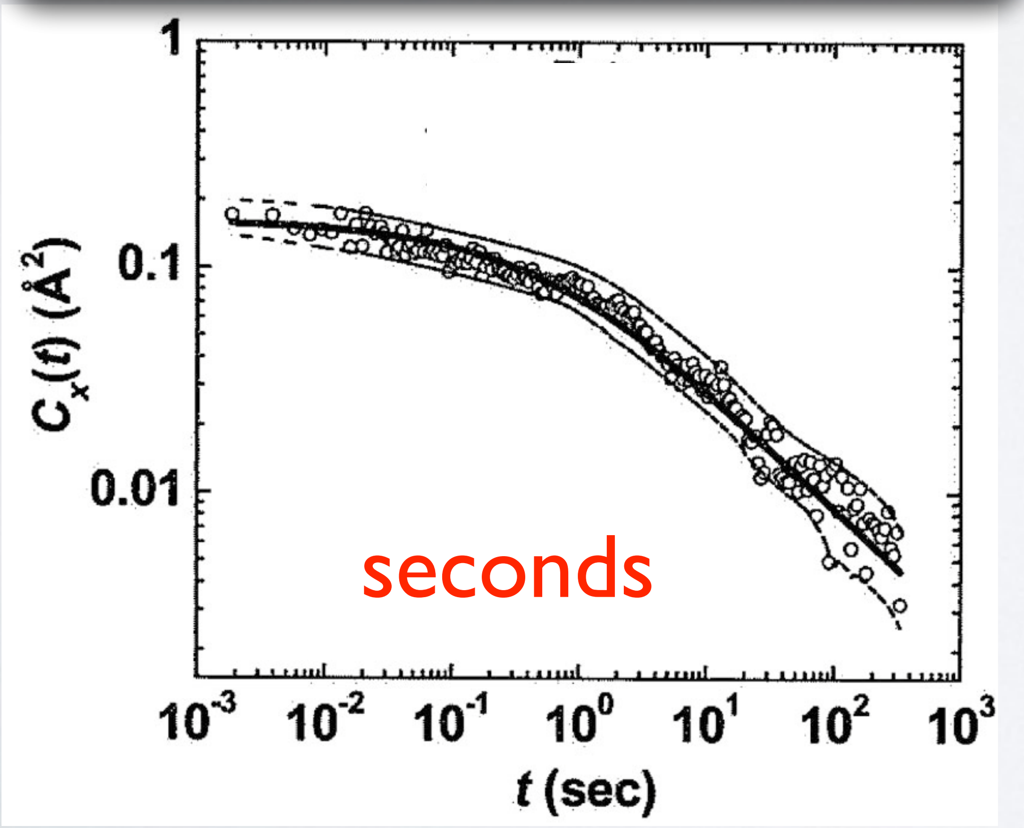
FL/Anti-FL complex

Min et al. PRL 94, 198302

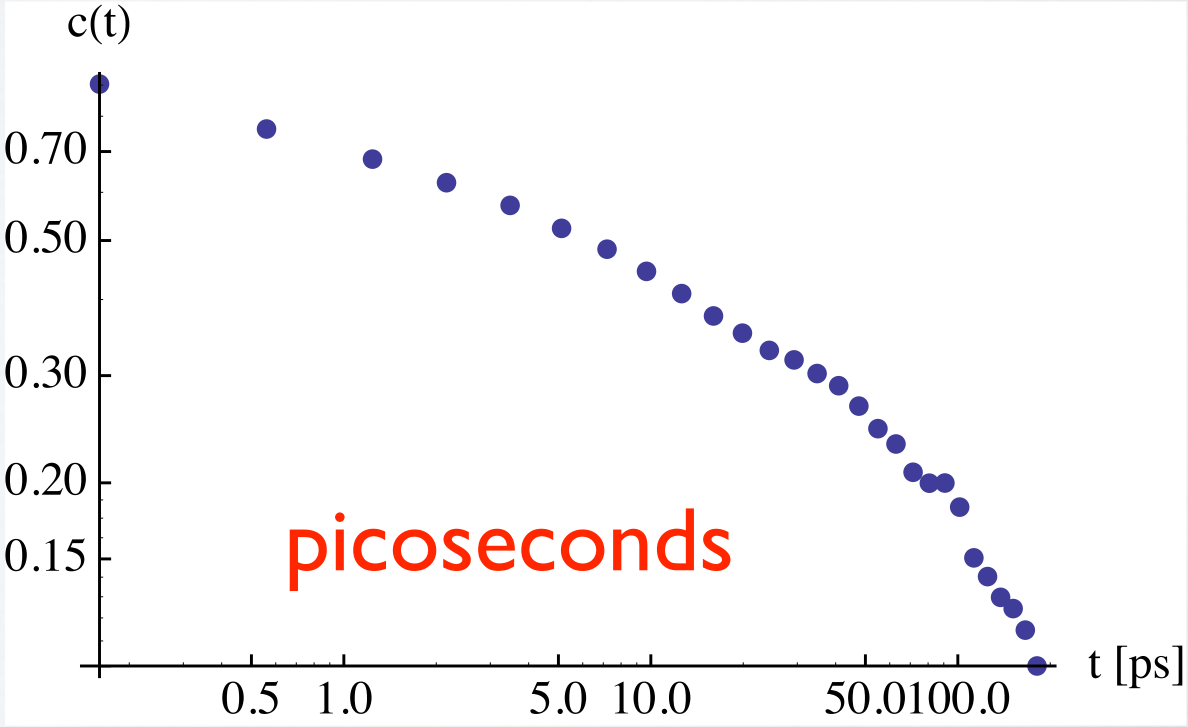


Lysozyme

Distance autocorrelation by single moleculefluorescence spectrocopy



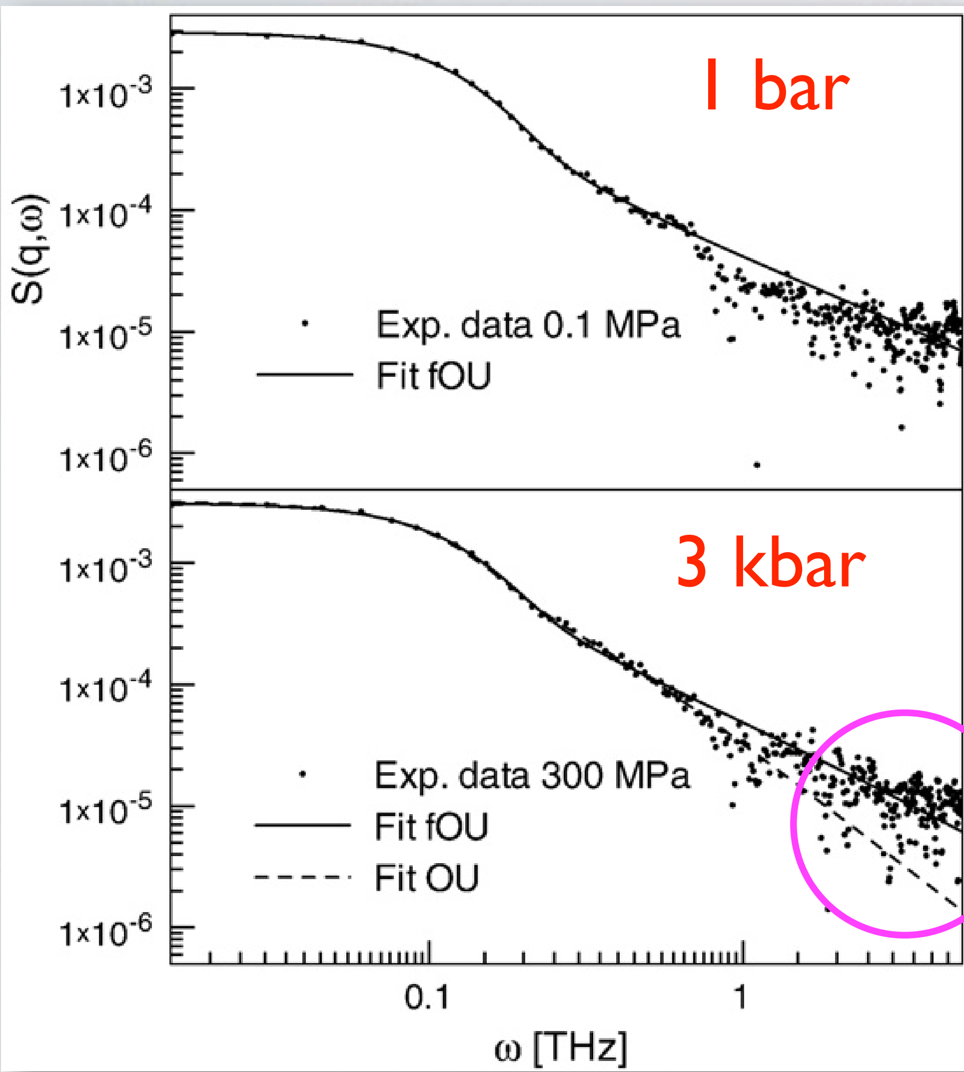
position auto-correlation function from MD

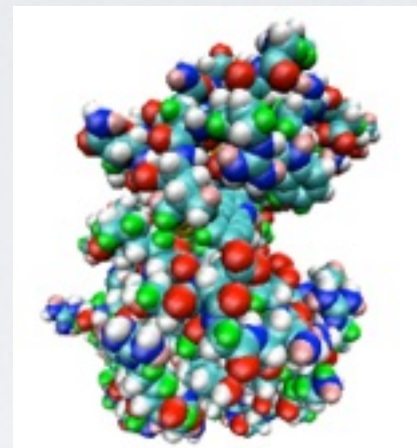


Lysozyme under hydrostatic pressure

Neutron scattering

QENS dynamic structure factor

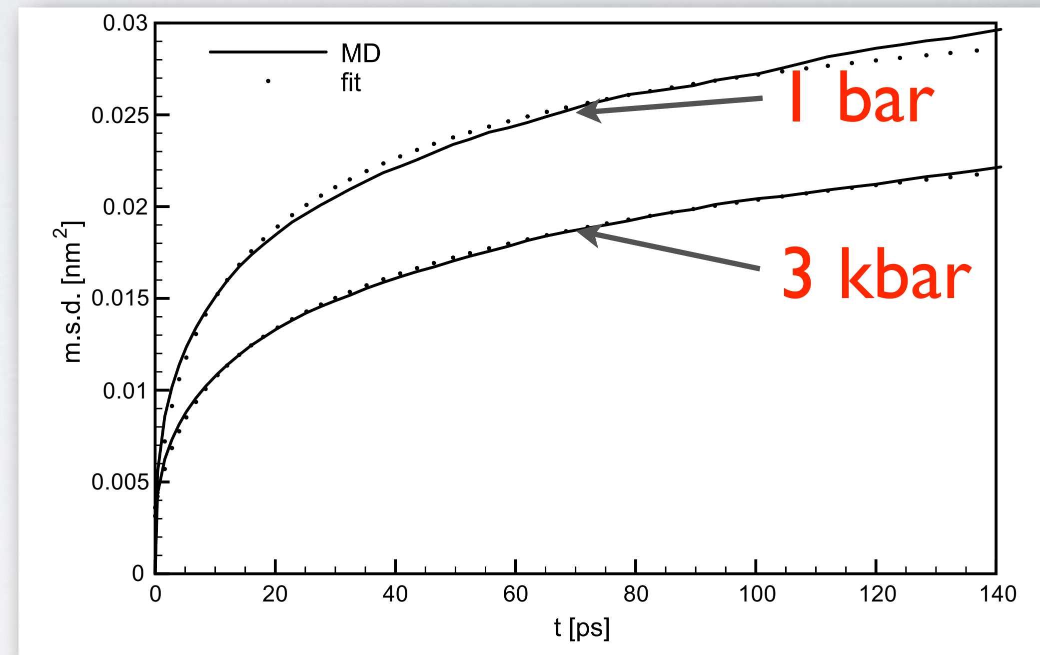




Lysozyme

MD simulation

Mean square displacement <[x(t)-x(0)]²> of the H atoms in lysozyme MD simulation



From MD simulation

	0.1 MPa			300 MPa		
	$\langle x^2 \rangle$ (nm^2)	α	τ (ps)	$\langle x^2 \rangle$ (nm^2)	α	τ (ps)
MSD	6.17×10^{-3}	0.54	31.75	4.74×10^{-3}	0.54	39.08

- Calandrini, Kneller, *J. Chem. Phys.*, vol. 128, no. 6, p. 065102, 2008.
- Calandrini et al,, *Chem. Phys.*, vol. 345, pp. 289–297, 2008.
- Kneller, Calandrini, *Biochimica et Biophysica Acta*, vol. 1804, pp. 56–62, 2010.

Limit of fractional Brownian dynamics

The model correlation functions have the experimentally observed power law decay, but they are not analytic and thus unphysical at t=0.

$$\left.\frac{d^n c(t)}{dt^n}\right|_{t=0} = (-1)^n \infty$$

Asymptotic analysis

$$W(t) \overset{t\to\infty}{\sim} 2D_0 L(t), \quad \text{with} \quad D_0 = \langle(\mathbf{x} - \langle\mathbf{x}\rangle)^2\rangle$$

$$c_{vv}(t) \overset{t\to\infty}{\sim} D_\alpha \alpha(\alpha-1) L(t) t^{\alpha-2},$$

$$\kappa(t) \overset{t\to\infty}{\sim} \frac{\langle\mathbf{v}^2\rangle}{D_\alpha} \frac{\sin(\pi\alpha)}{\pi\alpha} \frac{1}{L(t)} t^{-\alpha}.$$

α=0

$$c_{vv}(t) \overset{t\to\infty}{\sim} 0,$$

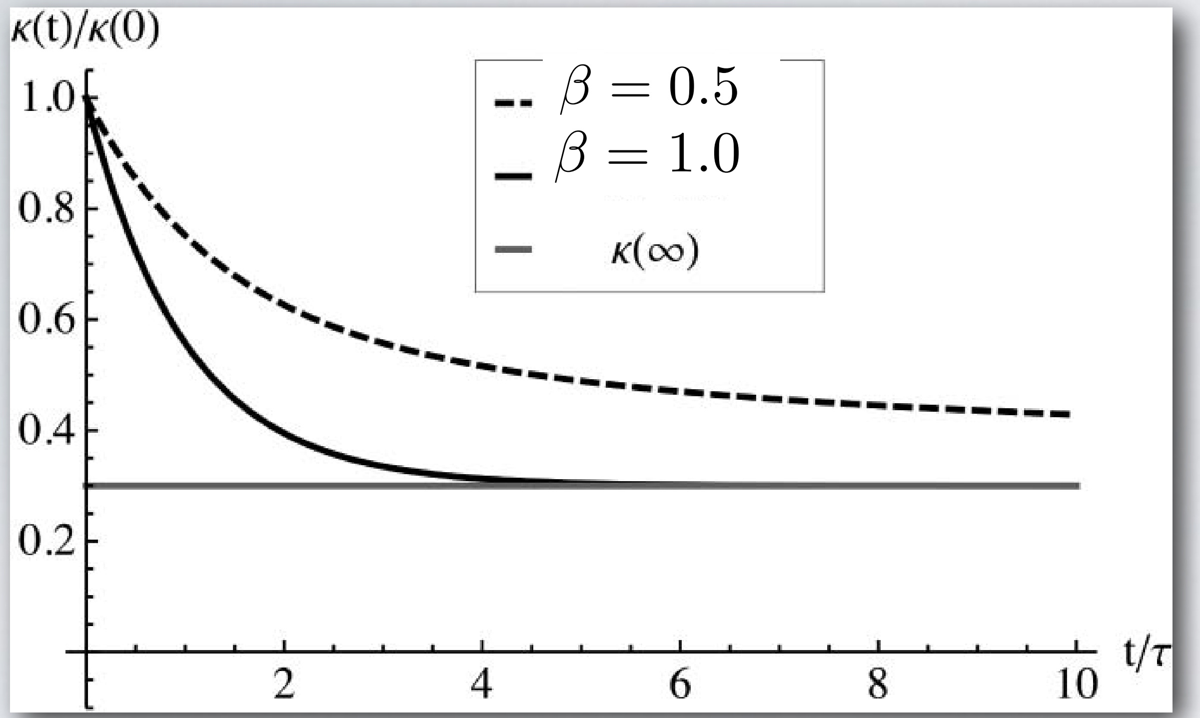
No long time tail

$$\kappa(t) \overset{t\to\infty}{\sim} \frac{\langle\mathbf{v}^2\rangle}{D_0} \frac{1}{L(t)}$$

The memory function tends to a plateau value if L tends to 1

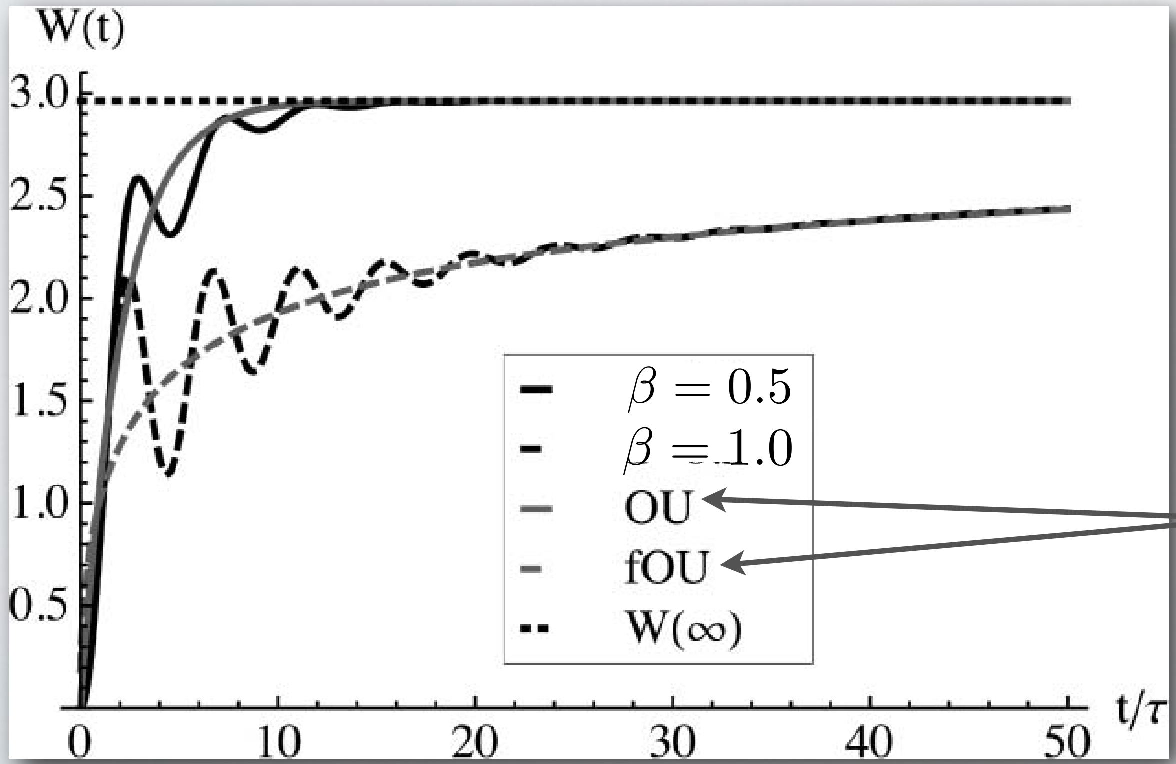
« Constant cage »

Simple model



$$\kappa_c(t) = \Omega^2\left\{r + (1-r)M(\beta, 1, -t/\tau)\right\}$$

$$\kappa_c(t) - \kappa_c(\infty) \overset{t\to\infty}{\sim} \begin{cases} \Omega^2(1-r)\frac{(t/\tau)^{-\beta}}{\Gamma(1-\beta)}, & 0<\beta<1, \\ \Omega^2(1-r)\exp(-t/\tau), & \beta = 1. \end{cases}$$

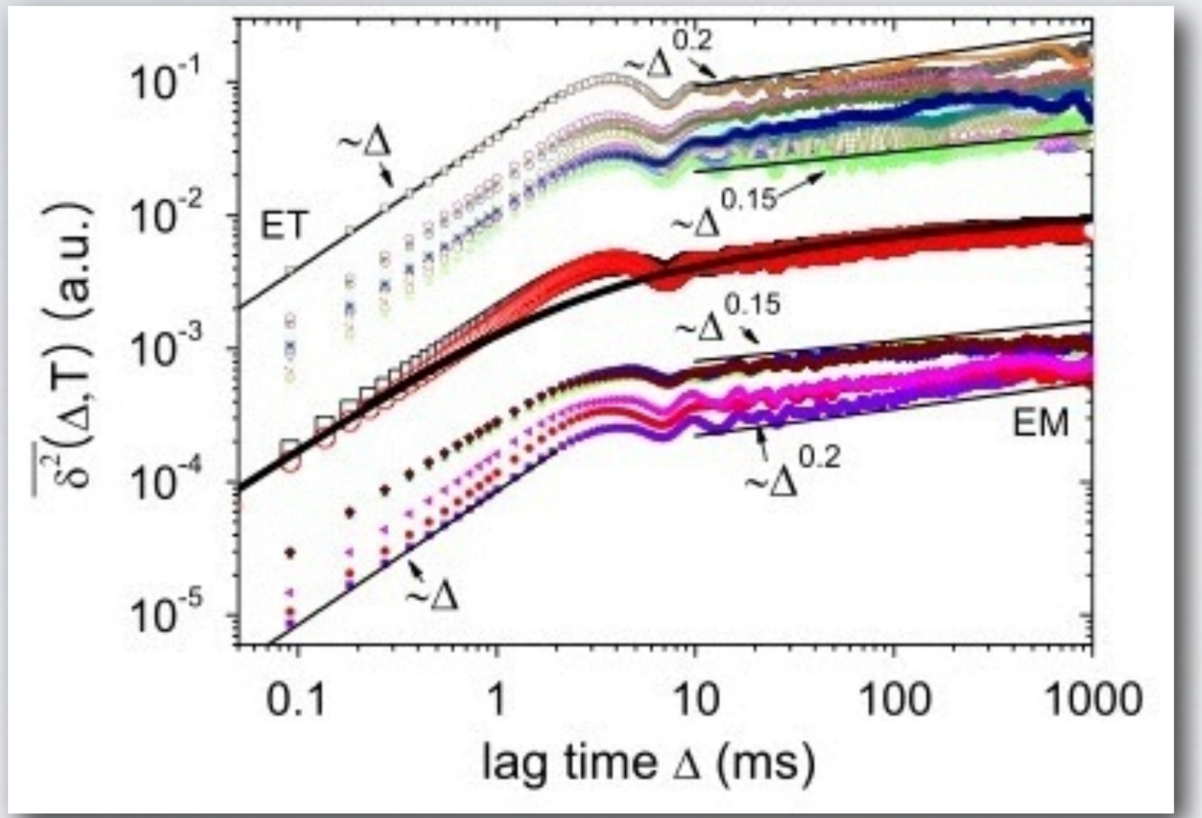


GLE versus fractional brownian motion

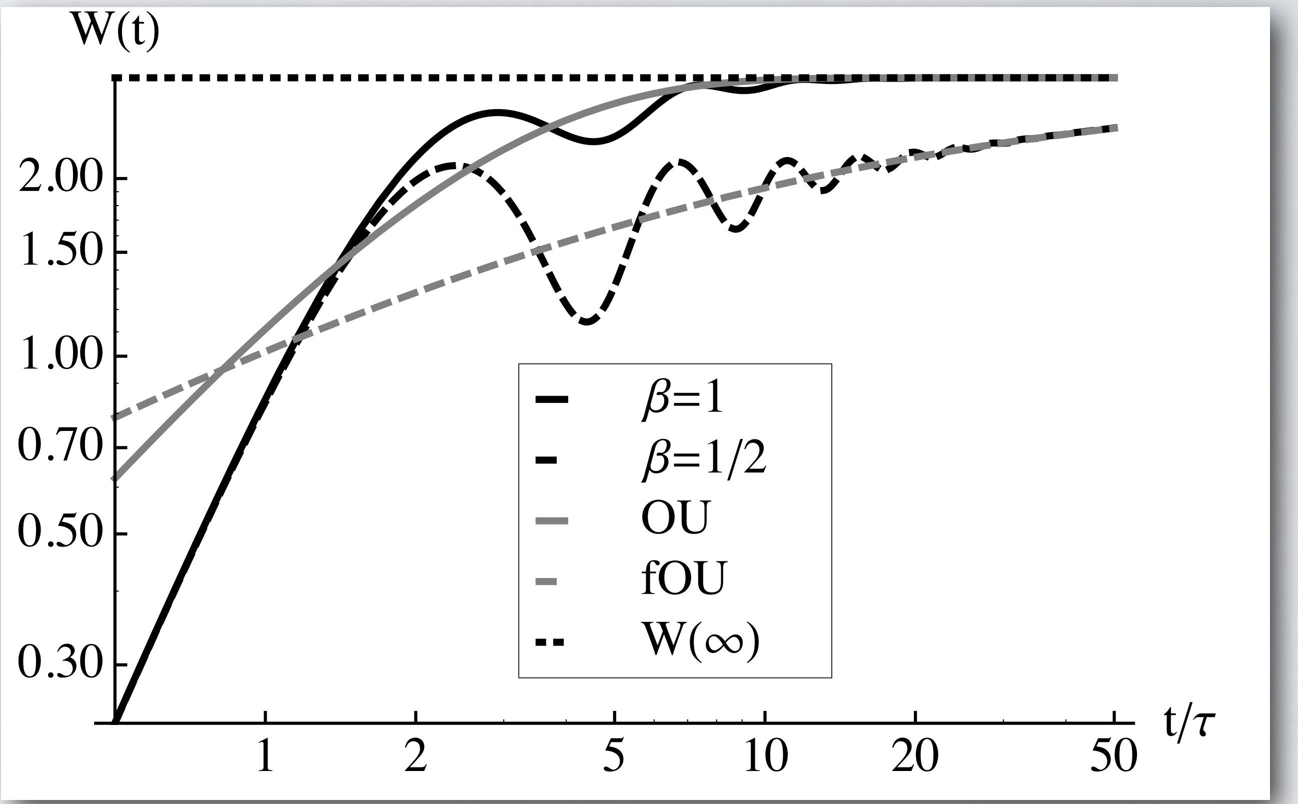
$$W_{\mathrm{(f)OU}}(t) = 2\langle \mathbf{u}^2\rangle(1 - E_b(-[t/t_0]^b)), \quad 0 < b \le 1,$$

Protein dynamics in optical tweezers

Jeon et al. PRL 106, 048103 (2011)



Simple analytical model



Coarse-grained model for protein dynamics

G.R. Kneller, K. Hinsen, and P. Calligari, J Chem Phys 136, 191101 (2012).

1. Multiscale relaxation model for the VACF of the C_α-atoms

$$\psi(t) = \int_0^\infty d\lambda\, p(\lambda) \exp(-\lambda t).$$

2. Assume that $\psi(t) \stackrel{t\to\infty}{\sim} t^{-\beta} \quad 0 < \beta < 1$

$$\Rightarrow \quad p(\lambda;\beta) = f(\lambda) \frac{\sin(\pi\beta)}{\pi} \frac{\Gamma(1-\beta)}{\lambda^{1-\beta}}$$

$\lim_{\lambda\to 0} f(\lambda) = C$, where C is a normalization constant

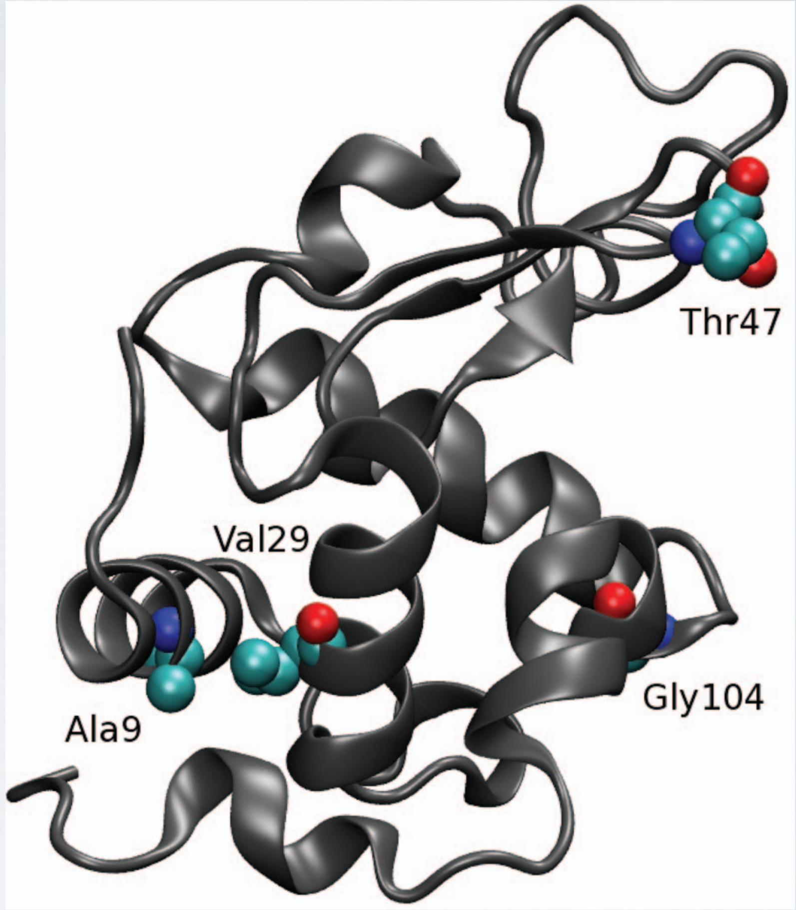


FIG. 1. Four selected residues in the lysozyme molecule.

3. Assume that all moments of p(λ) exist $\Rightarrow$ $f(\lambda) = C \exp(-\beta\lambda).$

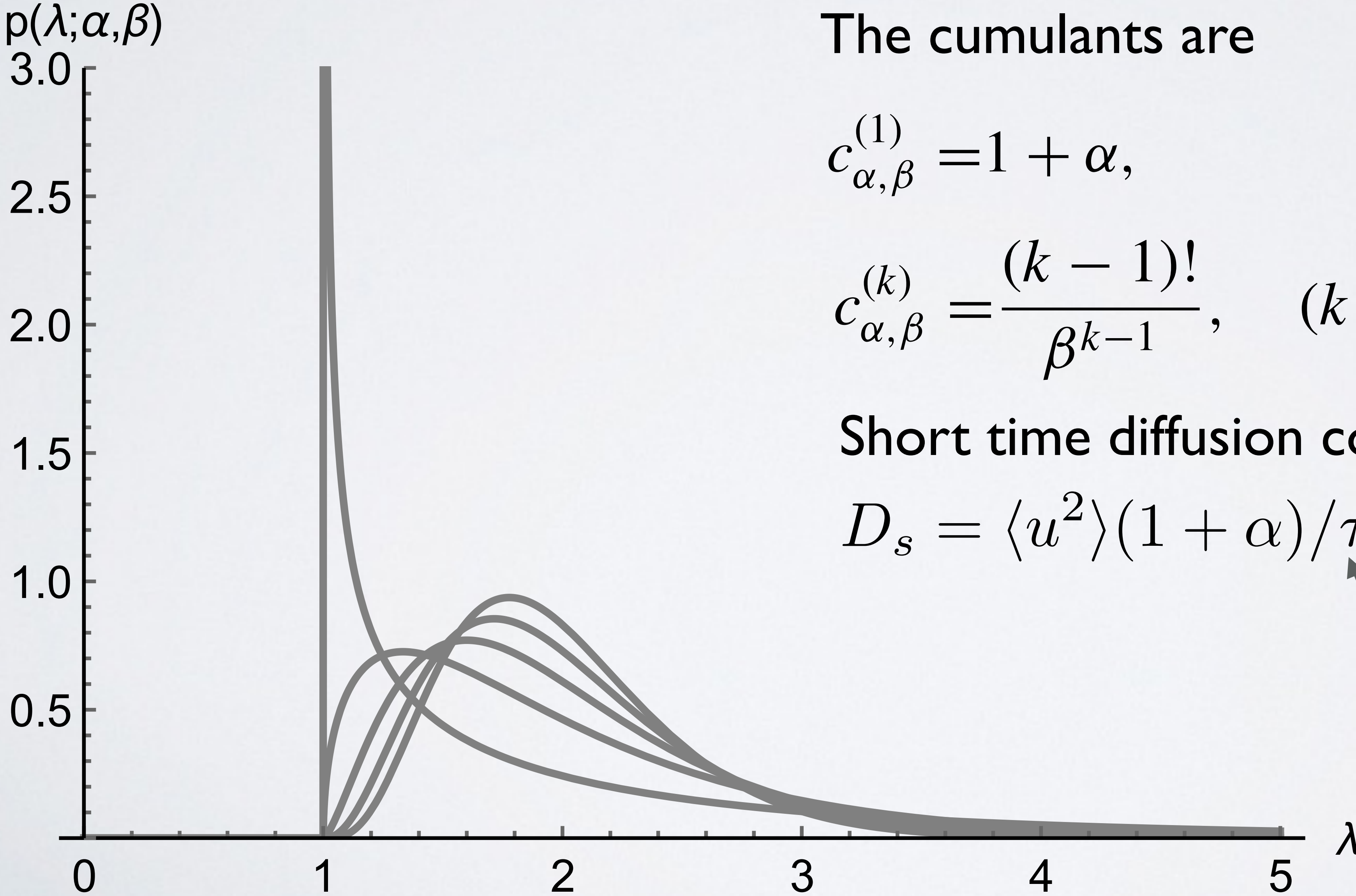
$$\Rightarrow \quad \psi(t;\beta) = \frac{1}{(1 + t/\beta)^\beta}$$

Refine the model - introduce a cutoff for λ

$$p(\lambda;\alpha,\beta) = \theta(\lambda-\alpha)p(\lambda-\alpha;\beta)$$

$$p(\lambda;\beta) = \frac{\lambda^{\beta-1}\beta^{\beta}\exp(-\beta\lambda)}{\Gamma(\beta)}$$

$$\psi(t;\alpha,\beta) = \frac{\exp(-\alpha t)}{(1+t/\beta)^{\beta}}.$$



The cumulants are

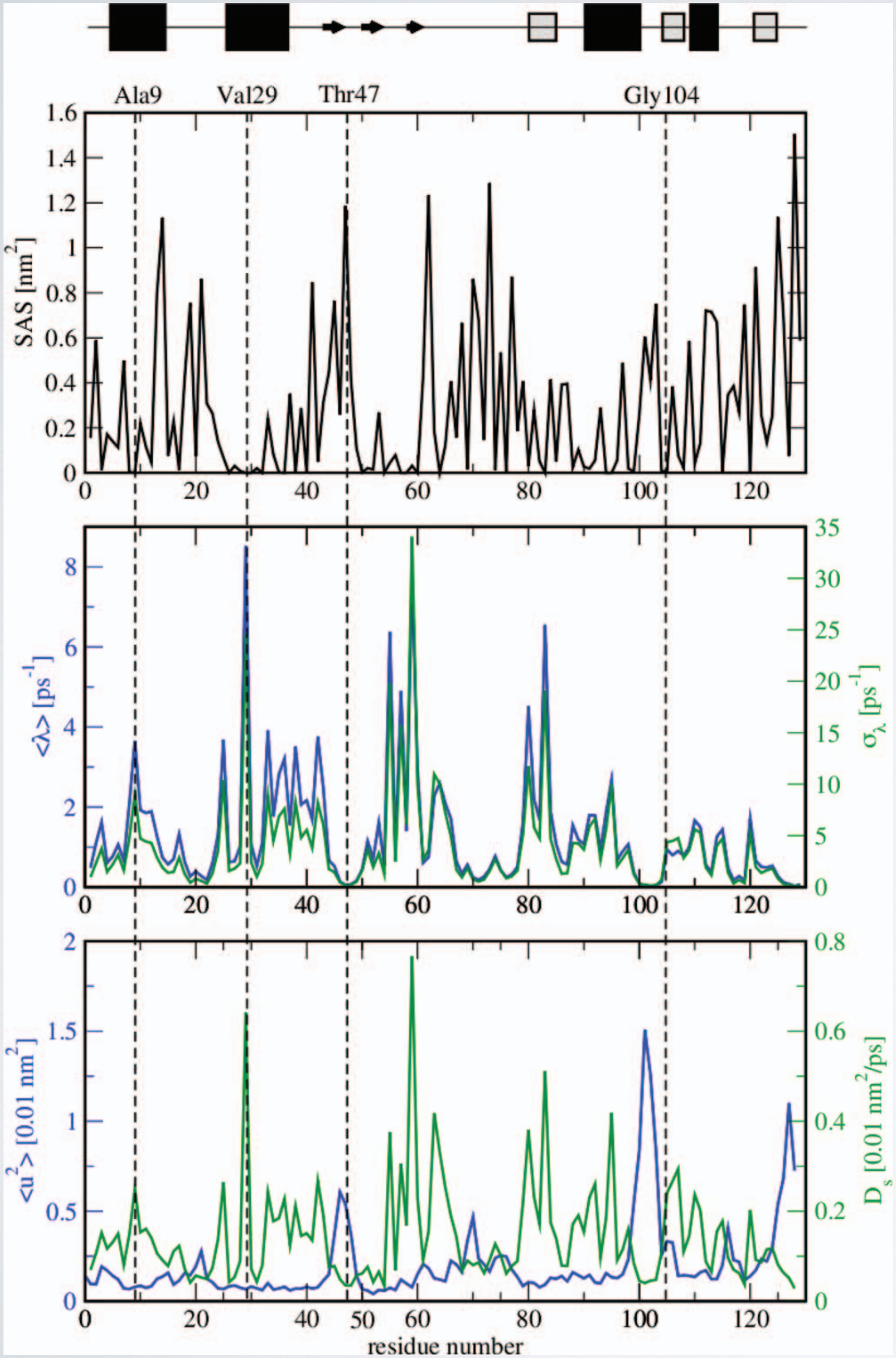
$$c^{(1)}_{\alpha,\beta} = 1+\alpha,$$

$$c^{(k)}_{\alpha,\beta} = \frac{(k-1)!}{\beta^{k-1}}, \quad (k=2,3,\ldots).$$

Short time diffusion coefficient

$$D_s = \langle u^2\rangle(1+\alpha)/\tau$$

time scale



Helices (black) and beta-sheets (grey).

Solvent-accessible surfaces.

Mean relaxation rates, $\bar{\lambda}$, and corresponding spreads (green).

Mean square position fluctuations, $\langle \mathbf{u}^2 \rangle$, and short-time diffusion coefficients, D_s (green).

CONCLUSIONS

- The combination of physical models (GLE) and **asymptotic analysis yields** insight into the origin anomalous diffusion : The decay of the local cage of neighbors represented by a memory function defines the type of diffusion.
- Free and confined diffusion can be handled
- Develop simple models to interpolate between the (known) short time and the long time regime of time correlation functions.

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