Anomalous diffusion in biomolecular systems by non-equilibrium statistical mechanics and computer simulations

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« Normal » diffusion

Fick's phenomenological approach

IV. *Ueber Diffusion; von Dr. Adolf Fick,*
Prosector in Zürich.

Die Hydrodiffusion durch Membranen dürfte billig nicht blofs als einer der Elementarfactoren des organischen Lebens sondern auch als ein an sich höchst interessanter physikalischer Vorgang weit mehr Aufmerksamkeit der Physiker in Anspruch nehmen als ihr bisher zu Theil geworden ist. Wir besitzen nämlich eigentlich erst vier Untersuchungen, von Brücke [1]), Jolly [2]), Ludwig [3]) und Cloetta [4]) über diesen Gegenstand, die seine Erkenntnifs um einen Schritt weiter gefördert haben. Vielleicht ist der Grund dieser spärlichen Bearbeitung zum Theil in der grofsen Schwierigkeit zu suchen, auf diesem Felde genaue quantitative Versuche anzustellen. Und in der That ist diese so grofs, dafs es mir trotz andauernder Bemühungen noch nicht hat gelingen wollen, den Streit der Theorien zu

1) Pogg. Ann. Bd. 58, S. 77.
2) Zeitschrift für rationelle Medicin, auch d. Ann. Bd. 78, S. 261.
3) Ibidem, auch d. Ann. Bd. 78, S. 307.
4) Diffusionsversuche durch Membranen mit zwei Salzen. Zürich 1851.

A. Fick, Annalen der Physik 170, 59 (1855).

$$\mathbf{j} = -D\nabla f \quad \text{and} \quad \partial_t f + \nabla\cdot\mathbf{j} = 0$$

$$\frac{\partial}{\partial t} f(\mathbf{r},t) = D\Delta f(\mathbf{r},t)$$

$$\sigma^2(t) := \frac{\int d^n r\, |\mathbf{r}|^2 f(\mathbf{r},t)}{\int d^n r\, f(\mathbf{r},t)} = 2nDt,$$

n : dimension

Einstein's statistical approach

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.

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

$$\frac{1}{\tau}\int_{-\infty}^{+\infty} \frac{\Delta^2}{2}\,\varphi(\Delta)\,d\Delta = D$$

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

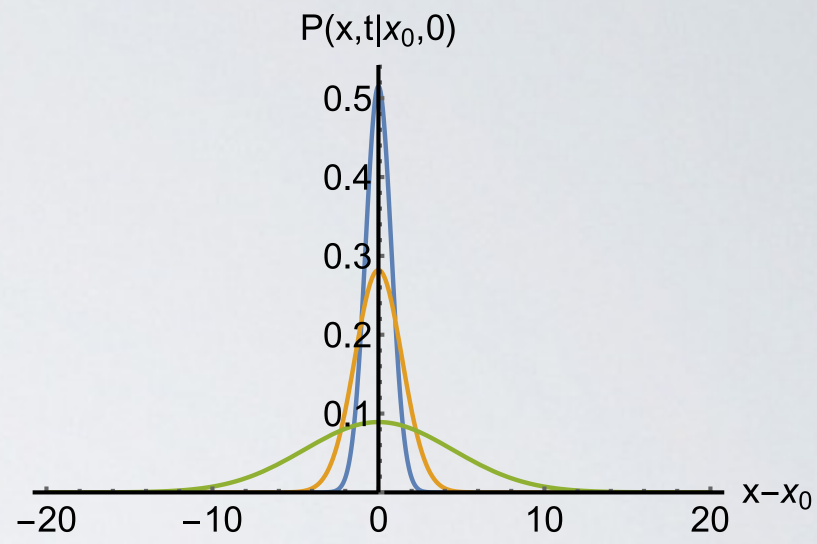
$$\lambda_x = \sqrt{\overline{x^2}} = \sqrt{2\,D\,t}.$$

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

Free diffusion as a stochastic (Wiener) process

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

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

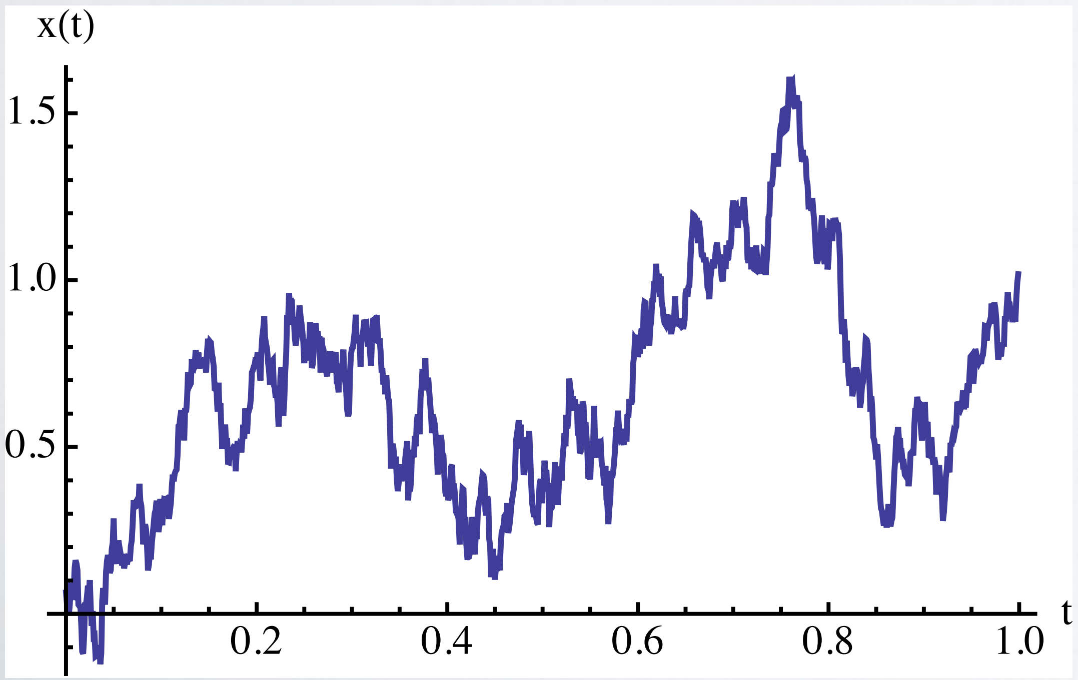


$$x(t_0+\Delta t) = x(t_0) + \xi$$

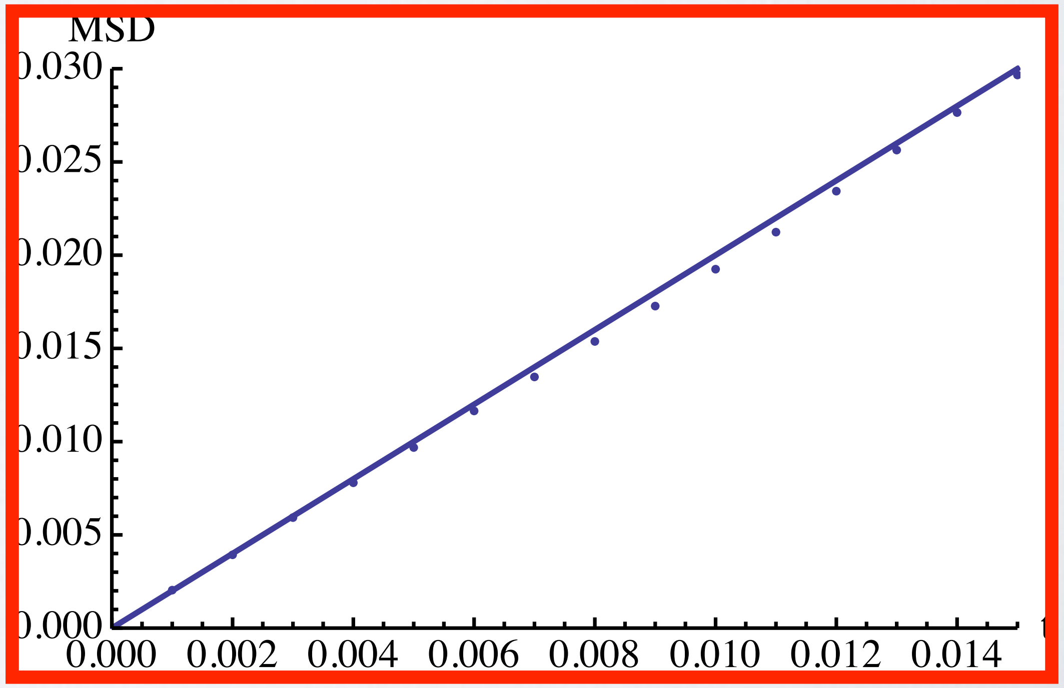
$$\overline{\xi} = 0$$
$$\overline{\xi^2} = 2D\Delta t$$

white noise

Trajectory



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



Anomalous diffusion in « crowded » media

ANOMALOUS DIFFUSION IN TRUE SOLUTION.

BY HERBERT FREUNDLICH AND DEODATA KRÜGER.

Received 30th April, 1935.

H. Freundlich and D. Krüger, Trans. Faraday Soc. 31, 906 (1935).

$$\sigma^2(t) := \frac{\int d^n r \, |\mathbf{r}|^2 f(\mathbf{r}, t)}{\int d^n r \, f(\mathbf{r}, t)}$$

Anomalous Diffusion of Acetone into Cellulose Acetate*

F. A. LONG, E. BAGLEY, AND J. WILKENS
Department of Chemistry, Cornell University, Ithaca, New York
(Received May 18, 1953)

F.A. Long, E. Bagley, and J. Wilkens,
The Journal of Chemical Physics 21, 1412 (1953).

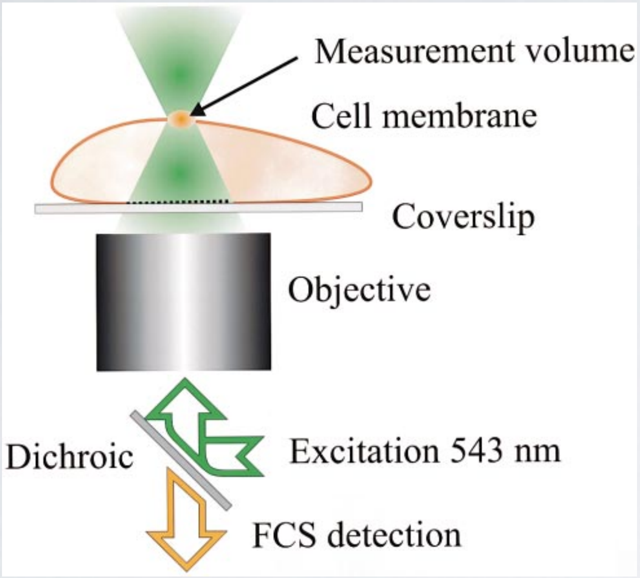
$$\sigma^2(t) \propto t^\alpha$$

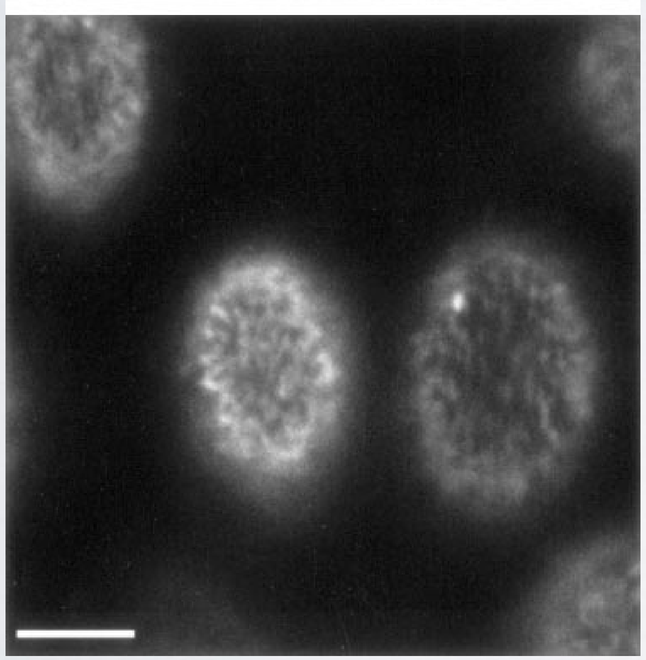
$$0 < \alpha < 1$$

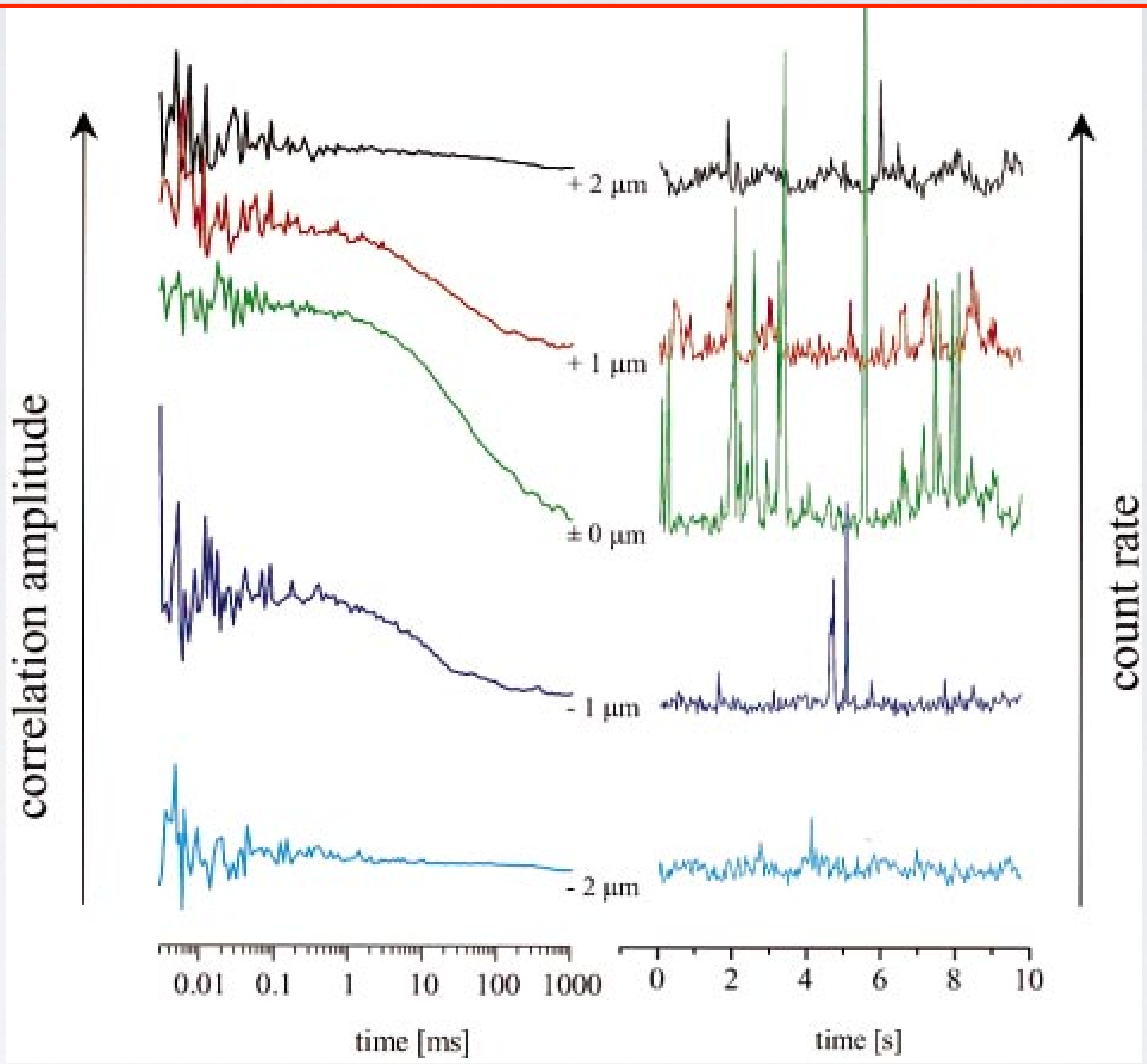
(subdiffusion)

Subdiffusion of lipids observed by FCS

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





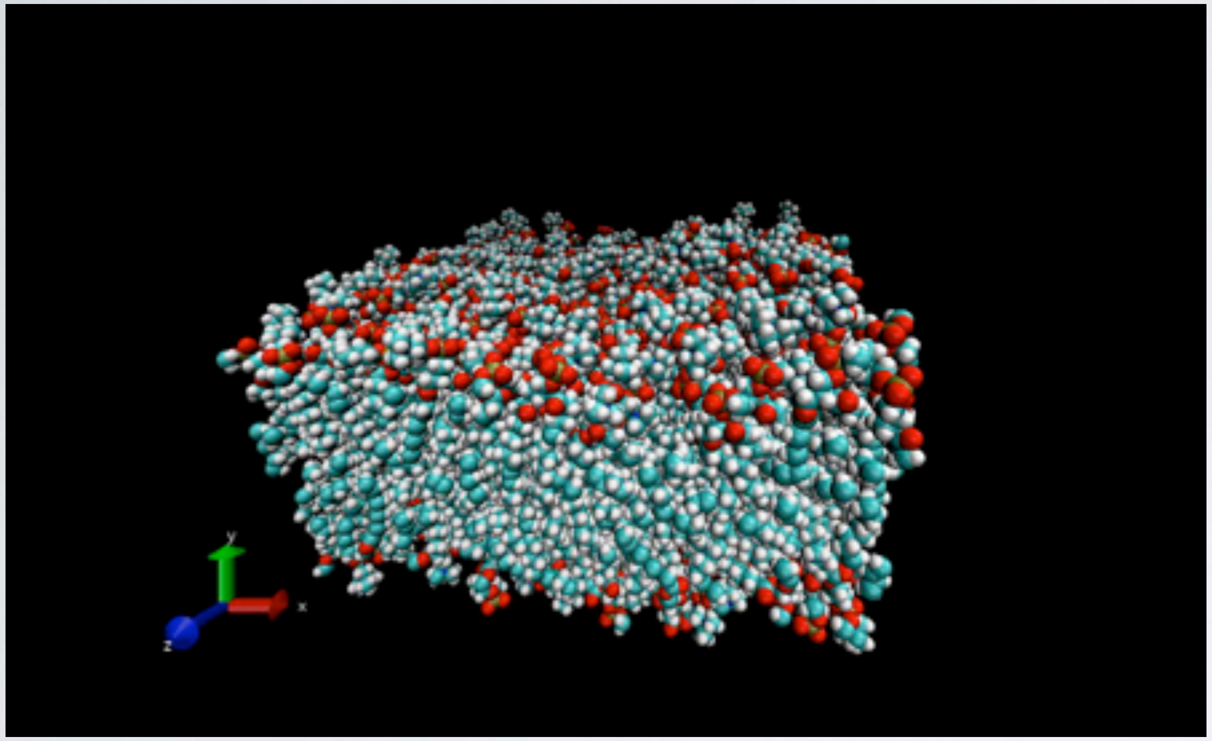


$$\sigma^2(t) \propto t^\alpha$$

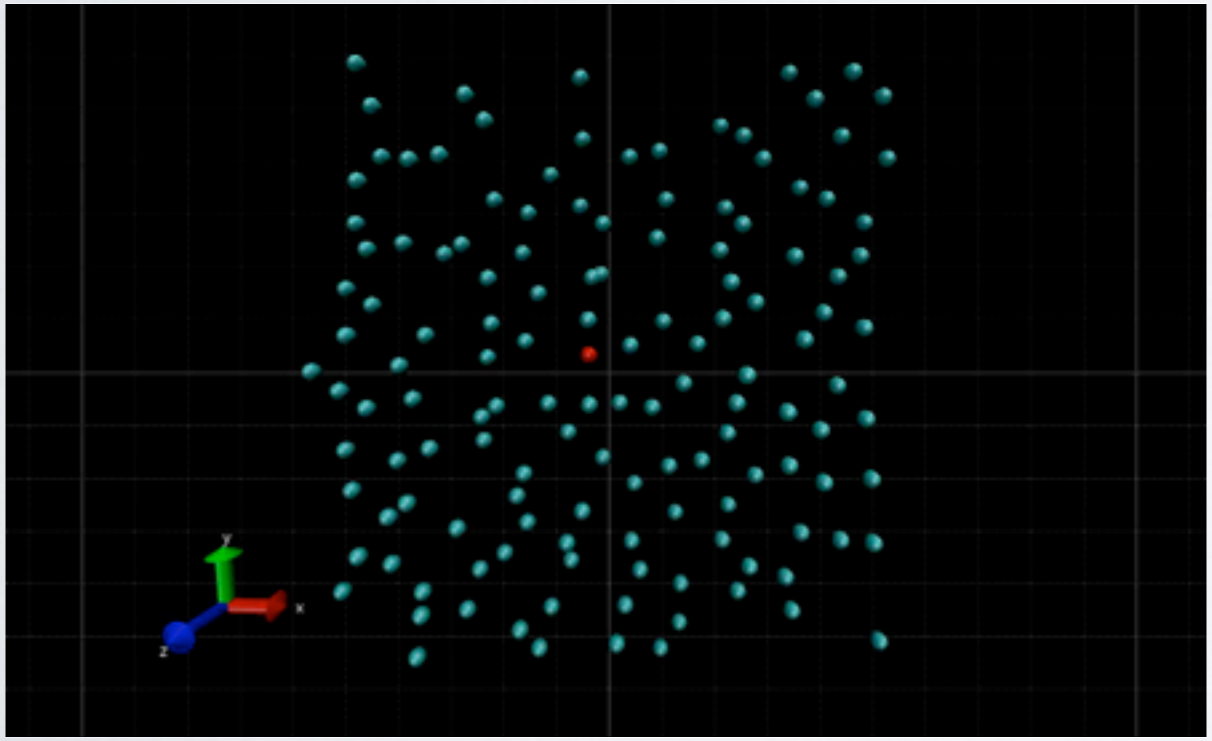
ms to s time scale

Subdiffusion of lipids observed by MD simulation

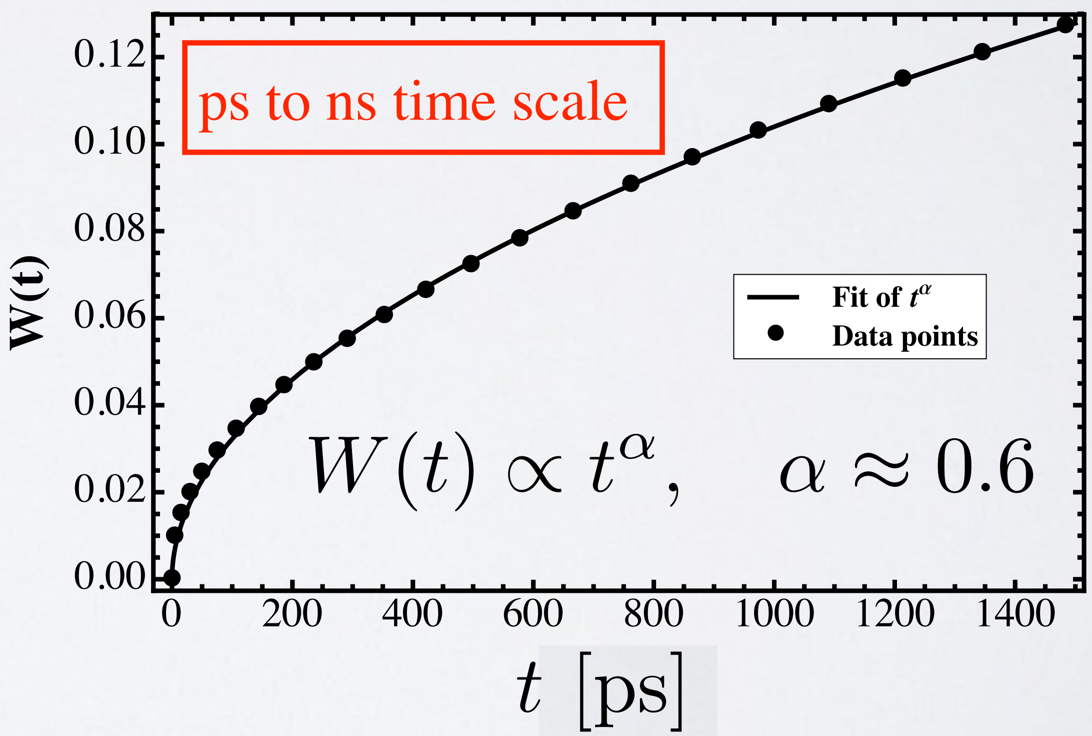
S. Stachura and G.R. Kneller, Mol Sim. 40, 245 (2013).



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



MSD for lateral diffusion

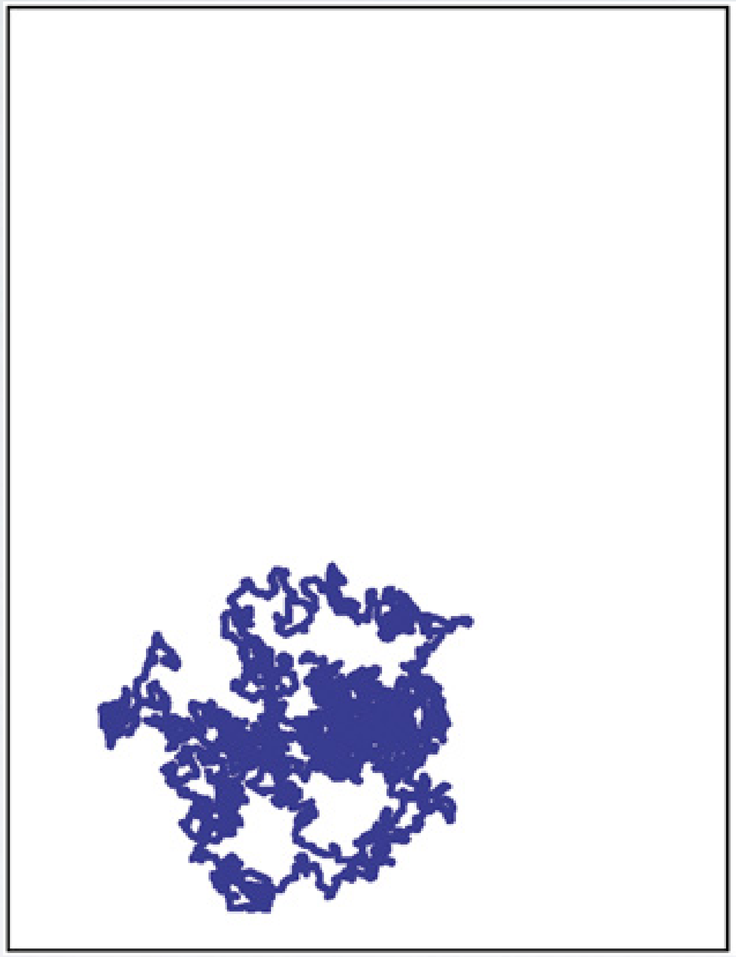


See also

E. Flenner, J. Das, M. Rheinstädter, and I. Kosztin, Phys Rev E 79, 11907 (2009).
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/Fokker Planck equation

W. Wyss, Journal of Mathematical Physics 27, 2782 (1986).
R. Metzler, E. Barkai, and J. Klafter, Phys Rev Lett 82, 3563 (1999).

$$\frac{\partial}{\partial t} p(\mathbf{r}, t|\mathbf{r}_0, 0) = \partial_t^{1-\alpha} D_\alpha \Delta p(\mathbf{r}, t|\mathbf{r}_0, 0)$$

$$\partial_t^{1-\alpha} g(t) = \frac{d}{dt} \int_0^t d\tau \, \frac{(t-\tau)^{\alpha-1}}{\Gamma(\alpha)} g(\tau)$$ Fractional derivative

$$\Rightarrow \quad W(t) = \frac{2nD_\alpha t^\alpha}{\Gamma(1+\alpha)}.$$

Modeling protein dynamics

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

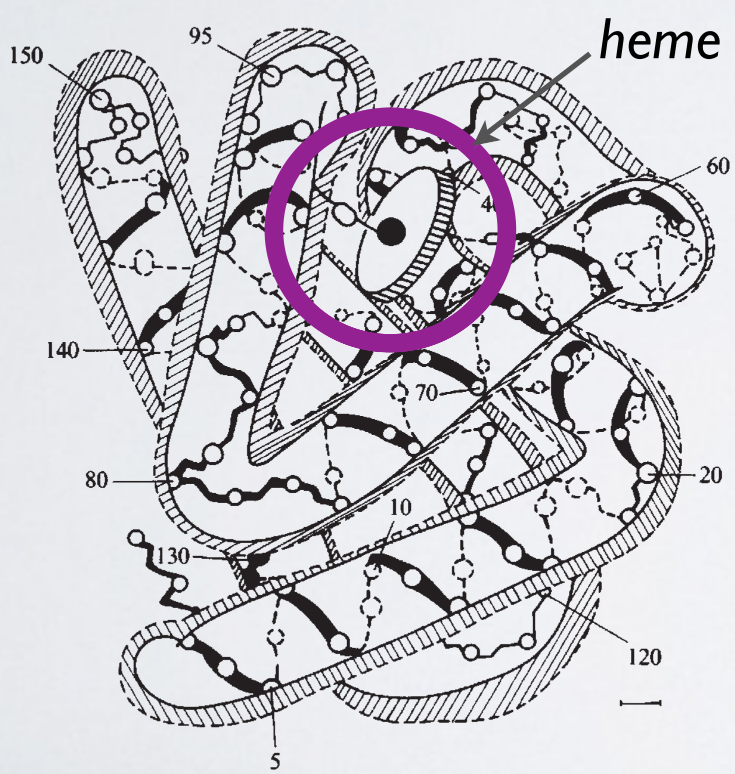
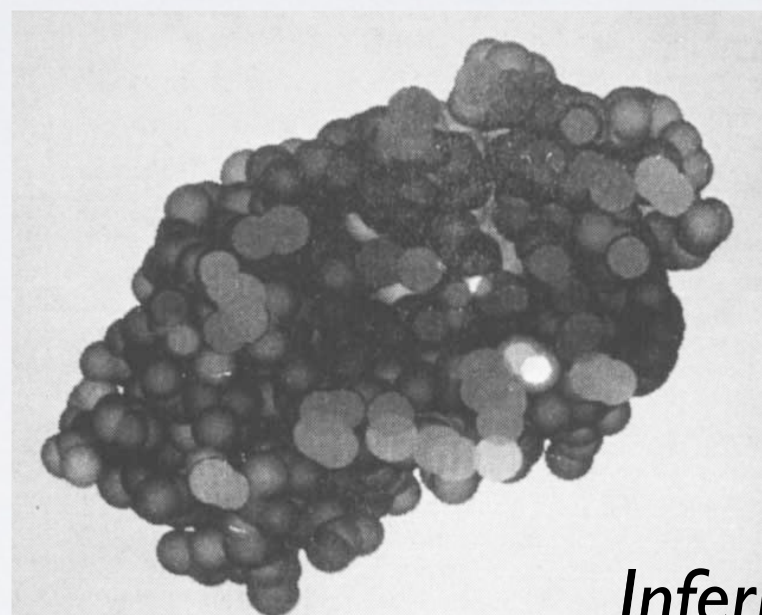
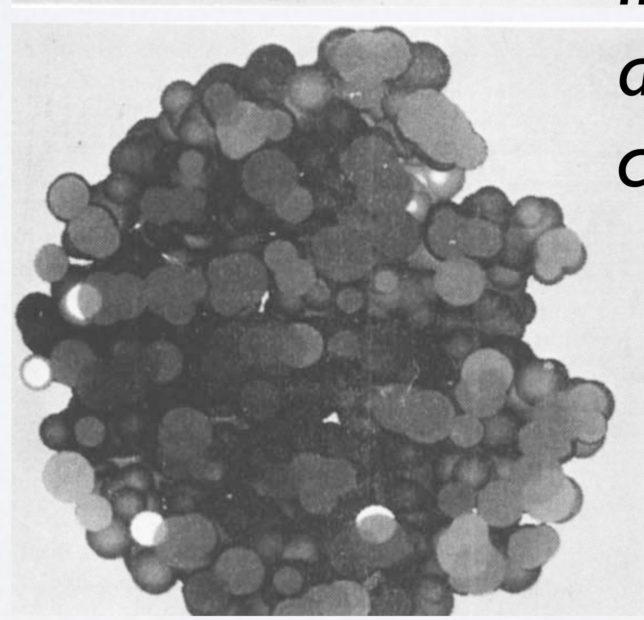


Fig. 3 Backbone (main chain) structure of myoglobin. The solid lines indicate the static structure as given in ref. 37. Circles denote the C^{α} carbons; some residue numbers are given. The shaded area gives the region reached by conformational substates with a 99% probability. Scale bar, 2 Å.





Inferring atomic motional amplitudes from crystallographic B-factors

Conformational substates in a protein: Structure and dynamics of metmyoglobin at 80 K

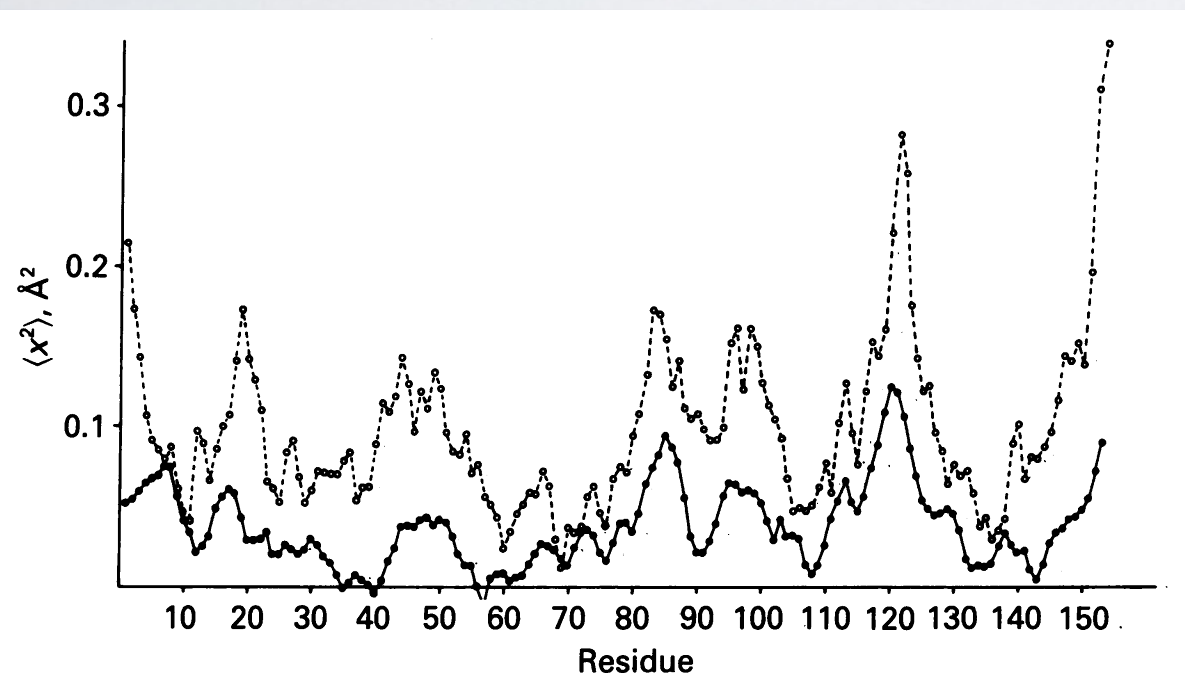
(low-temperature crystallography/Mössbauer absorption/Debye–Waller factor/intramolecular motion/lattice disorder)

H. Hartmann*, F. Parak*§, W. Steigemann*, G. A. Petsko†, D. Ringe Ponzi†, and H. Frauenfelder‡

Proc. Natl. Acad. Sci. USA
Vol. 79, pp. 4967–4971, August 1982
Biophysics

Protein dynamical transition

Average position fluctuations per residue from ***crystallography*** *at 80 K and 300 K*



Position fluctuation of the Fe atom from ***Mössbauer spectroscopy***

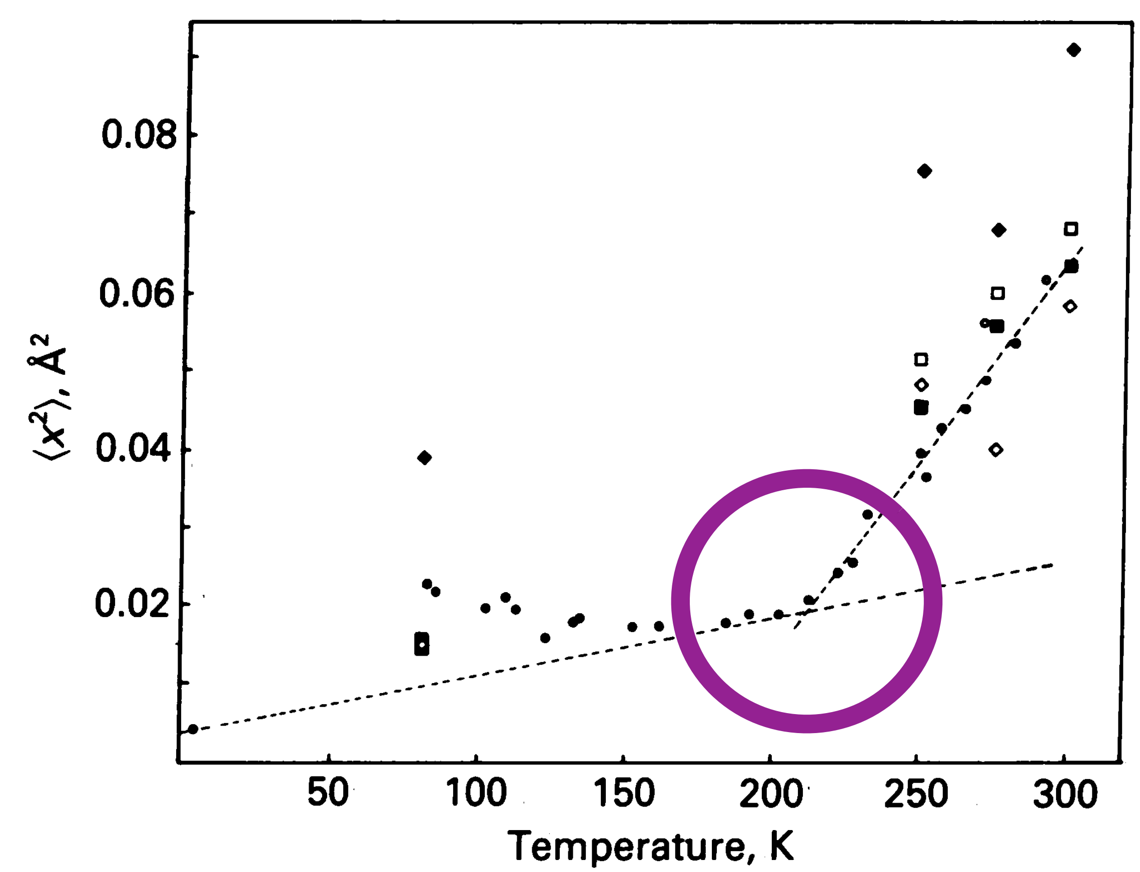


Fig. 3. Temperature dependence of $\langle x^2 \rangle$ values. ●, Fe measured by Mössbauer spectroscopy (13); ■, Fe determined by x-ray analysis; ◆, histidine-93(F8); ◇, histidine-64(E7).

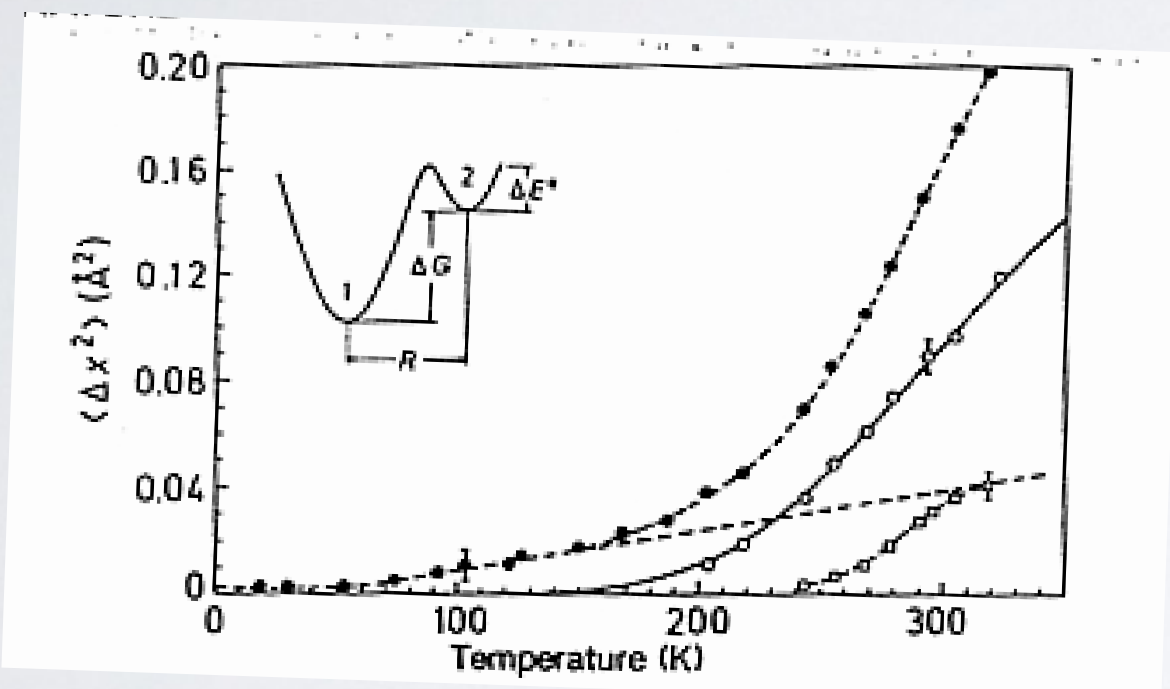
Dynamical transition of myoglobin revealed by inelastic neutron scattering

Wolfgang Doster*, Stephen Cusack† & Winfried Petry‡

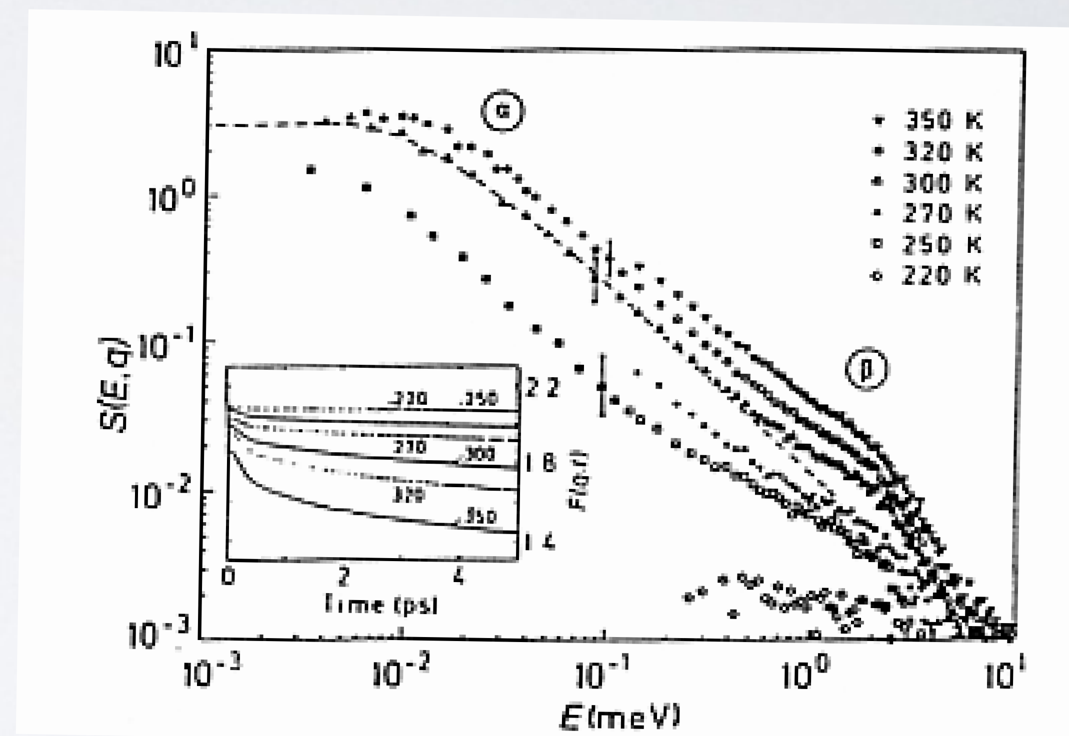
NATURE VOL. 337 23 FEBRUARY 1989

Dynamical transition by neutron scattering

Elastic scattering



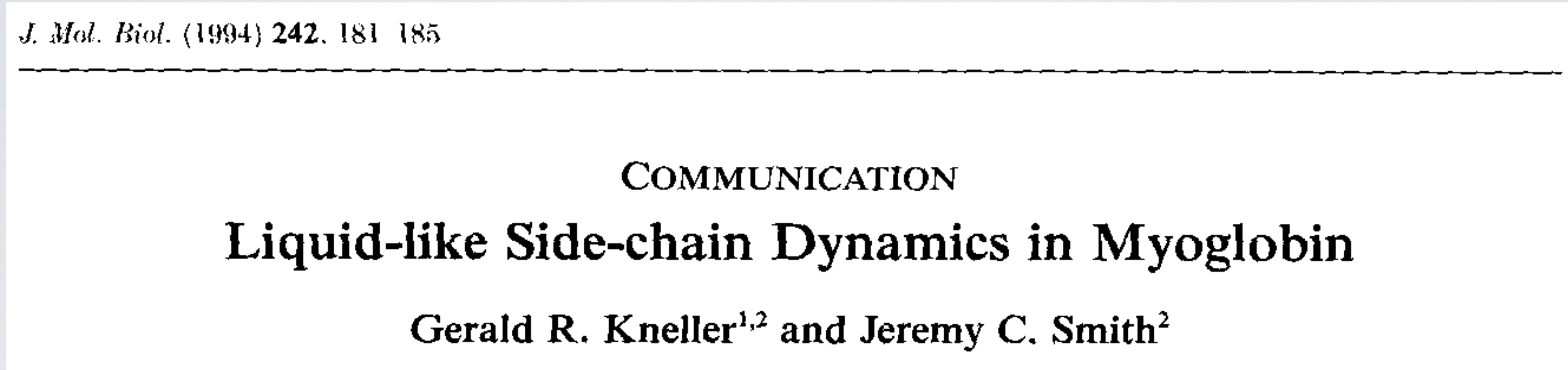
Quasielastic scattering



Position fluctuation averaged over <u>all</u> (hydrogen) atoms

Onset of diffusive motions on the picosecond time scale

Simulated motions in myoglobin


J. Mol. Biol. (1994) **242**, 181–185

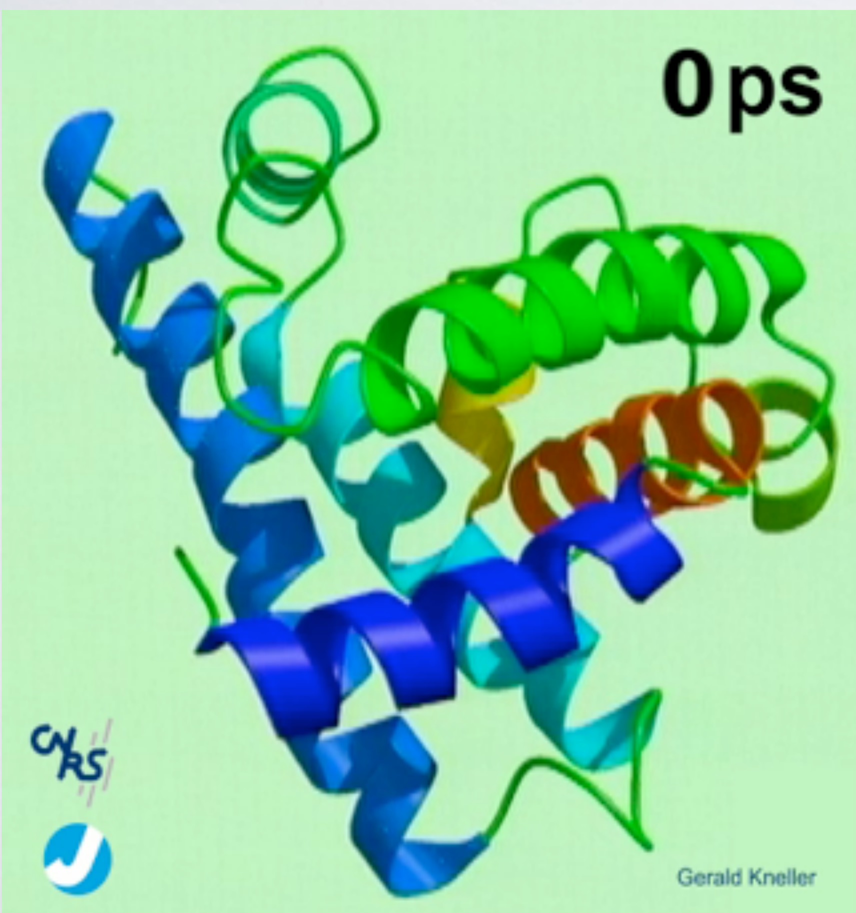
COMMUNICATION

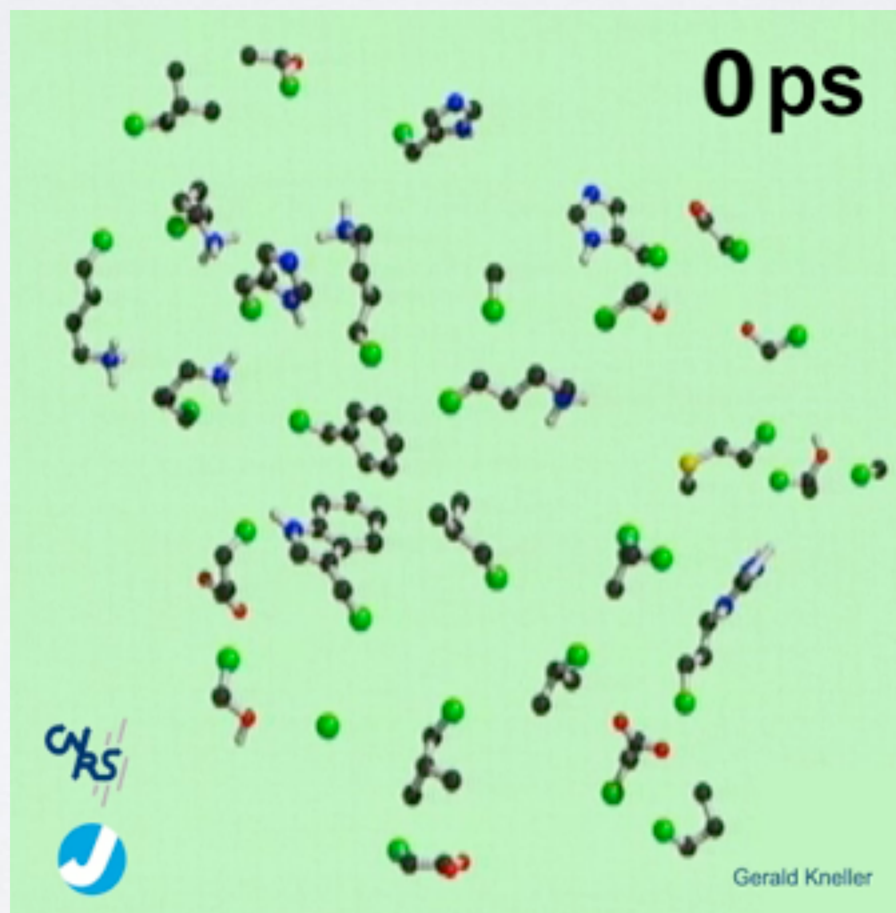
Liquid-like Side-chain Dynamics in Myoglobin

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

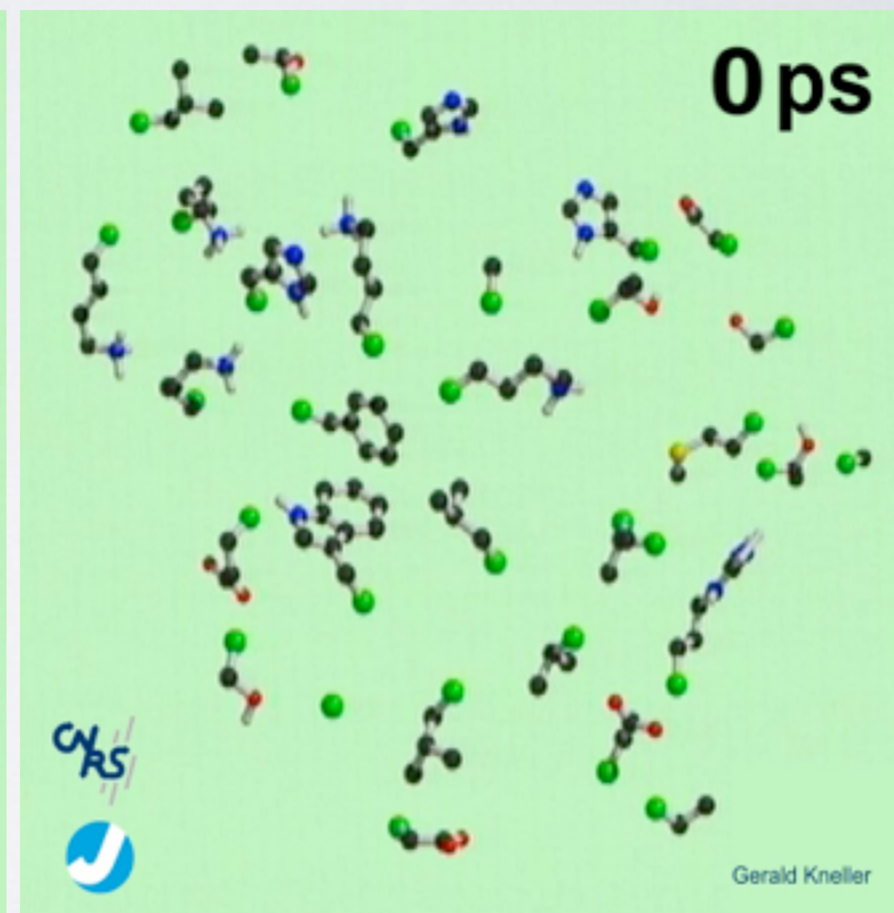
Backbone

The "side-chain liquid"



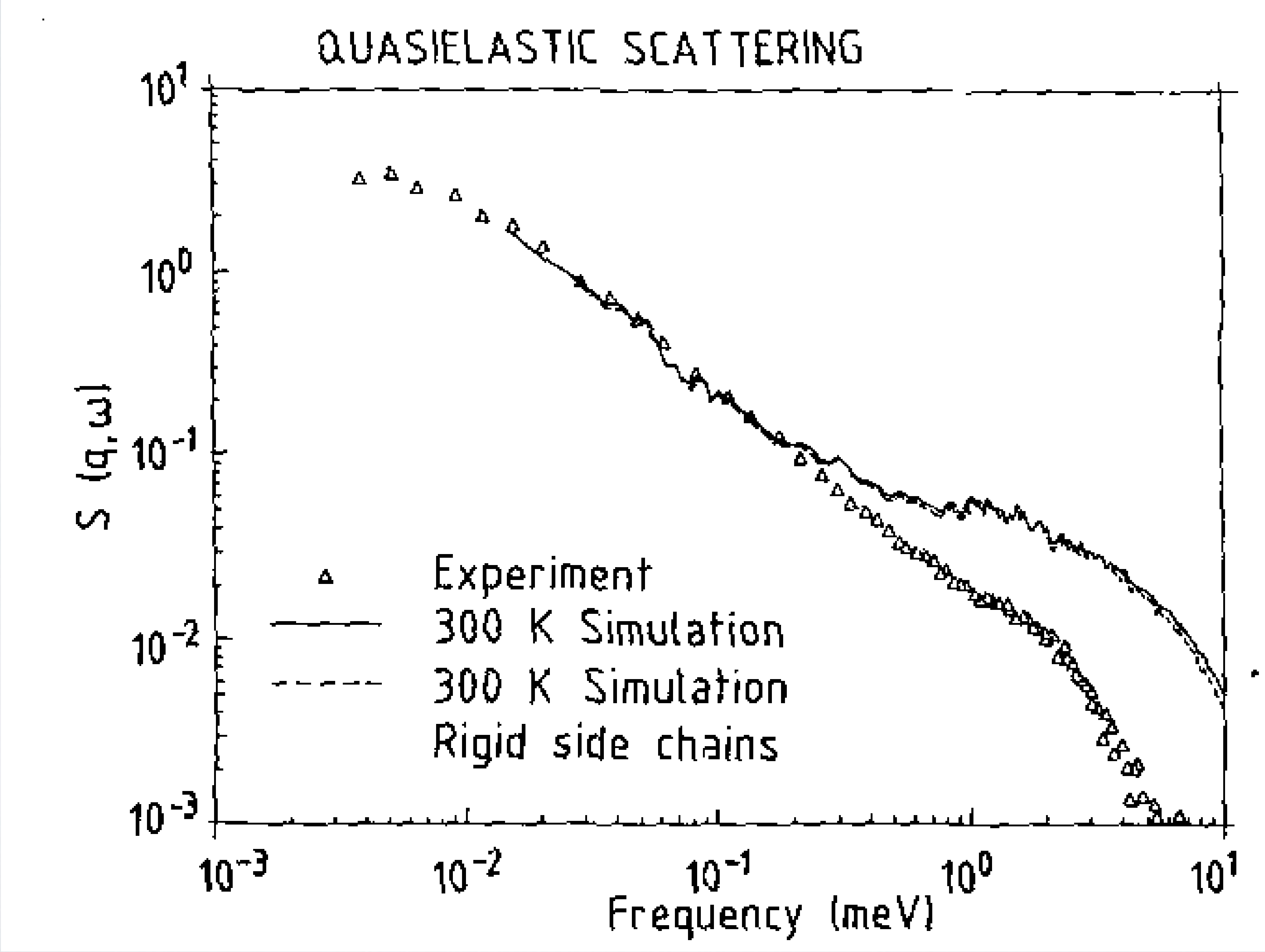


flexible



rigid

Rigid side-chain diffusion produces quasielastic scattering

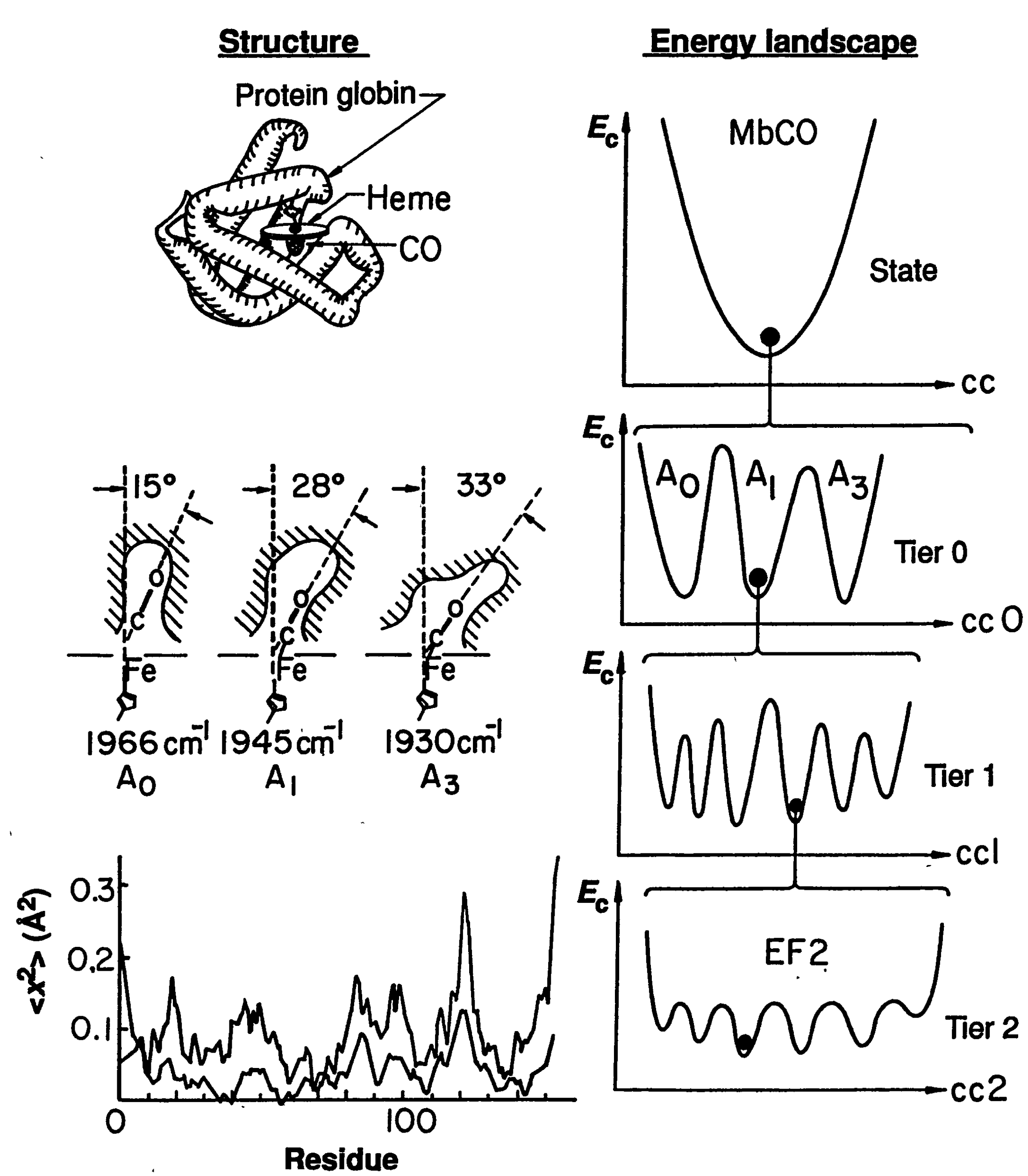


The Energy Landscapes and Motions of Proteins

Hans Frauenfelder, Stephen G. Sligar, Peter G. Wolynes

SCIENCE, VOL. 254

Conformational substates



Non-exponential rebinding kinetics of CO

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

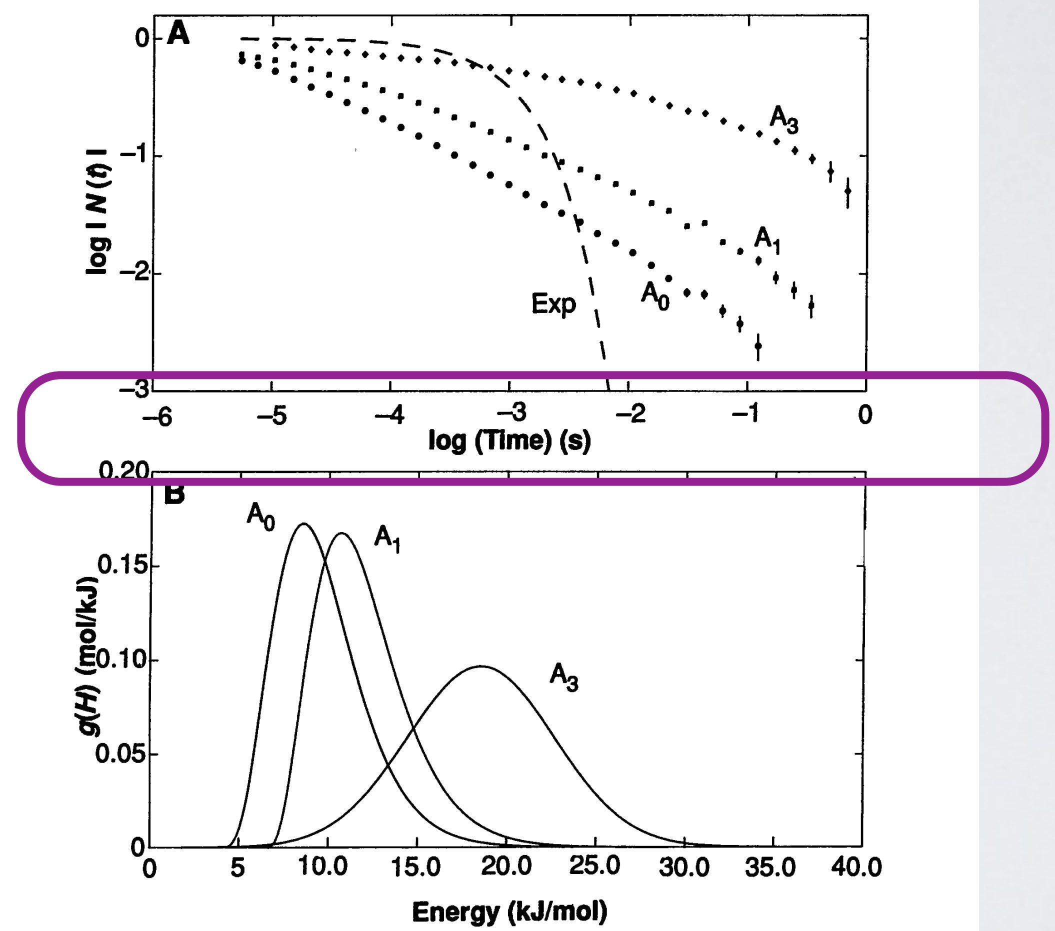


Fig. 2. Rebinding of CO to Mb after photodissociation, measured separately for the substates of tier 0 at pH 5.7. (**A**) $N(t)$ is the fraction of proteins that have not rebound a CO at the time t after photodissociation. All three substates (A_0, A_1, and A_3) rebind nonexponentially in time. (**B**)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

Protein dynamics is self-similar multiscale dynamics

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

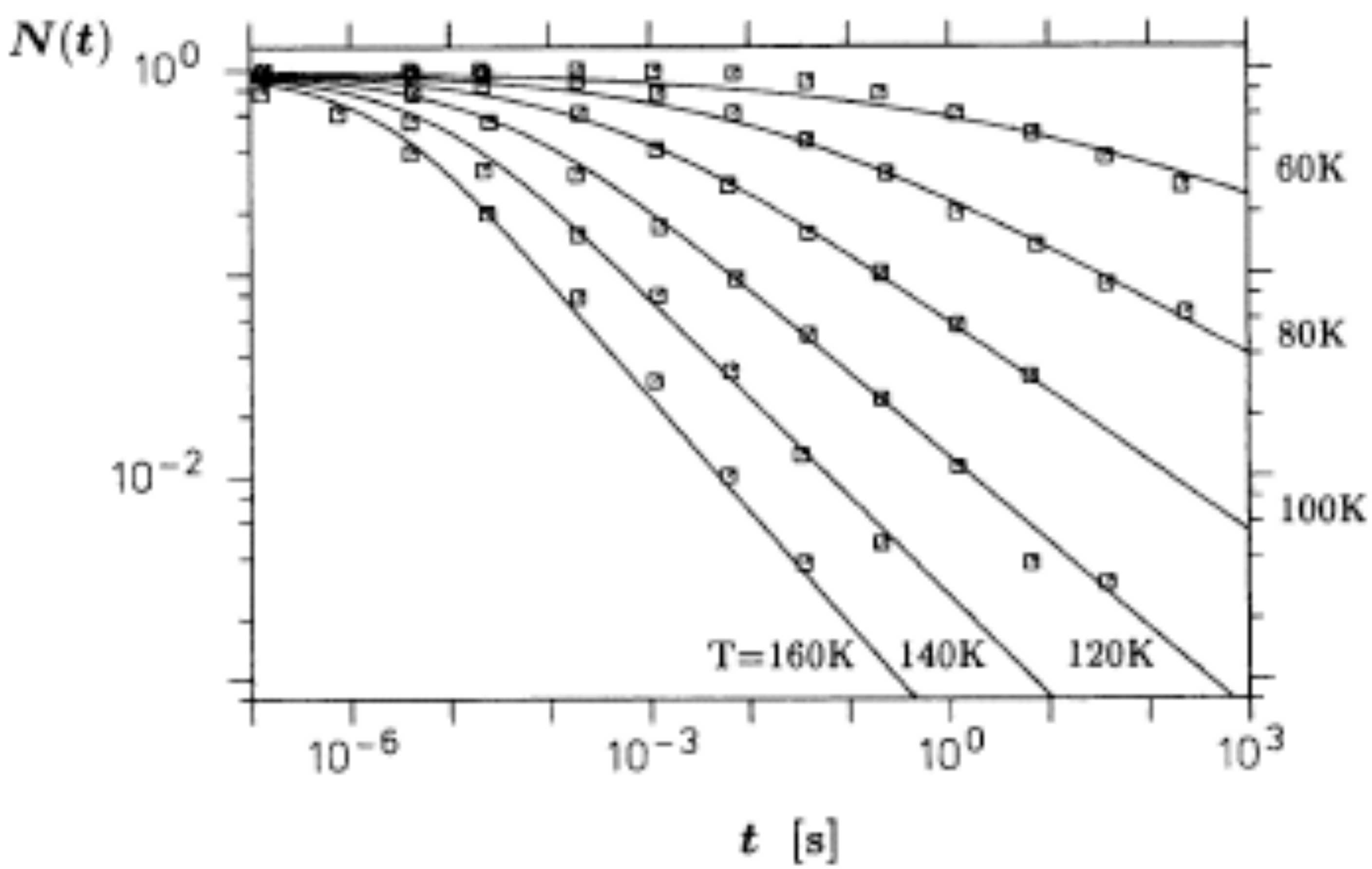


FIGURE 2 Three-parameter model Eq. 32 for rebinding of CO to Mb after photo dissociation. The parameters are $\tau_m = 8.4 \times 10^{-10}$s, $\alpha = 3.5 \times 10^{-3}\ K^{-1}$ and $k = 130$, the data points are from Austin et al. (1975).

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

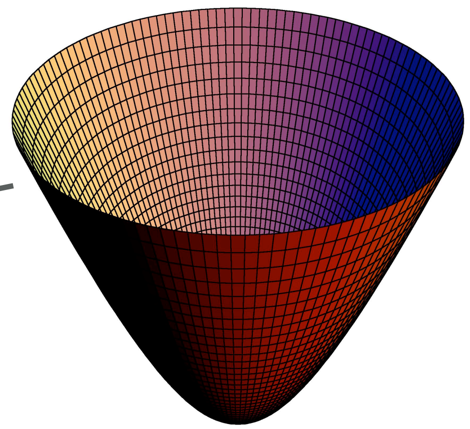
Mittag-Leffler function

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

Fractional Ornstein-Uhlenbeck process: A model for atomic motions in proteins

$$\frac{\partial}{\partial t} p(\mathbf{u}, t|\mathbf{u}_0, 0) = \partial_t^{1-\beta} \mathcal{L}\, p(\mathbf{u}, t|\mathbf{u}_0, 0), \quad 0 < \beta \leq 1$$

$$V(\mathbf{u}) = \frac{K}{2}|\mathbf{u}|^2$$



$$\mathcal{L} = D_\beta \frac{\partial}{\partial \mathbf{u}} \cdot \left\{ \frac{\partial}{\partial \mathbf{u}} + \frac{K\mathbf{u}}{k_B T} \right\}$$

$$c_{uu}(t) = \langle |\mathbf{u}|^2 \rangle E_\beta(-[t/\tau]^\beta)$$

Mittag-Leffler function

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

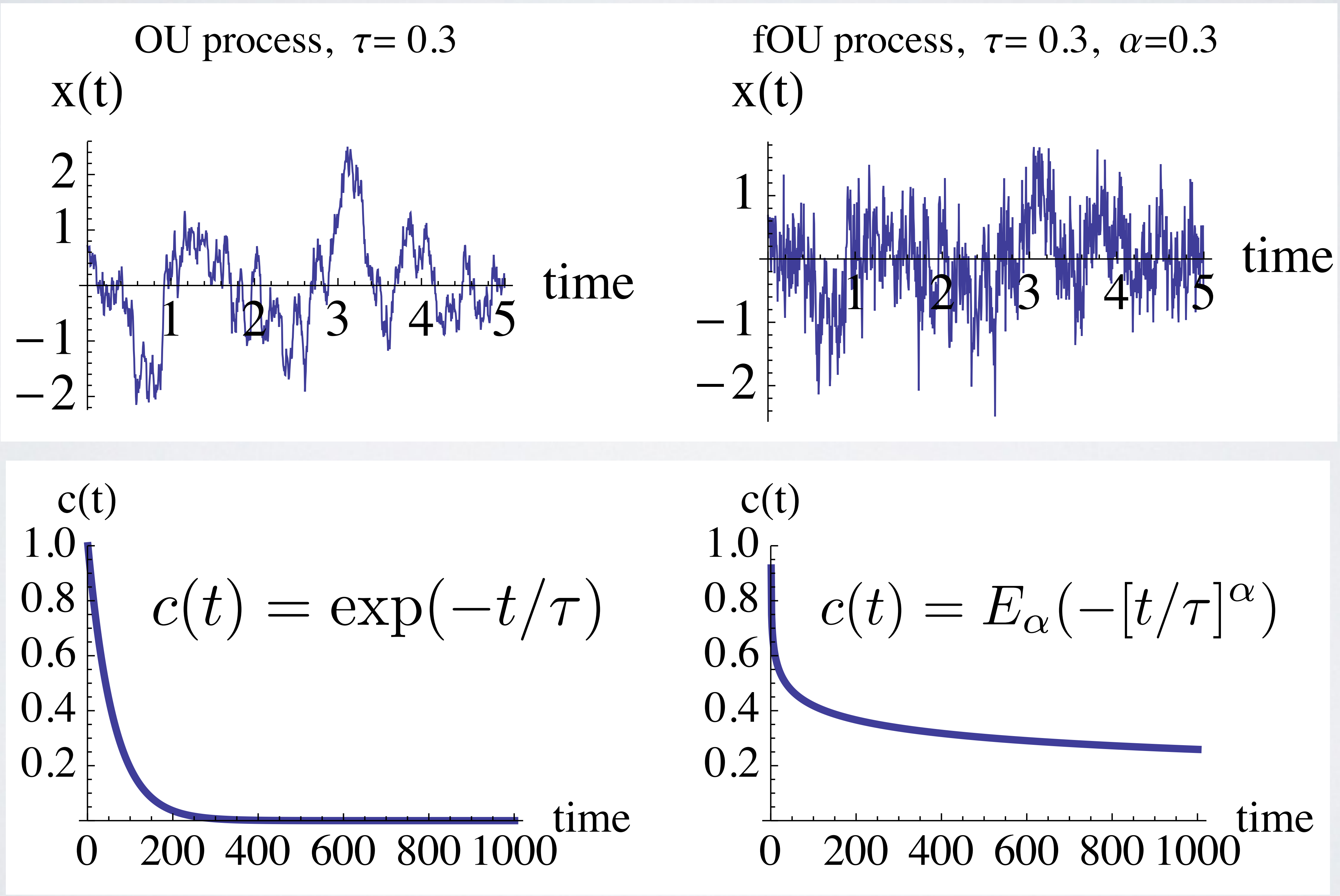
$$W(t) = 2\langle |\mathbf{u}|^2 \rangle \left(1 - E_\beta(-[t/\tau]^\beta)\right)$$

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

Y. Shao, Physica D: Nonlinear Phenomena 83, 461 (1995).

R. Metzler and J. Klafter, Phys Rep 339, 1 (2000).

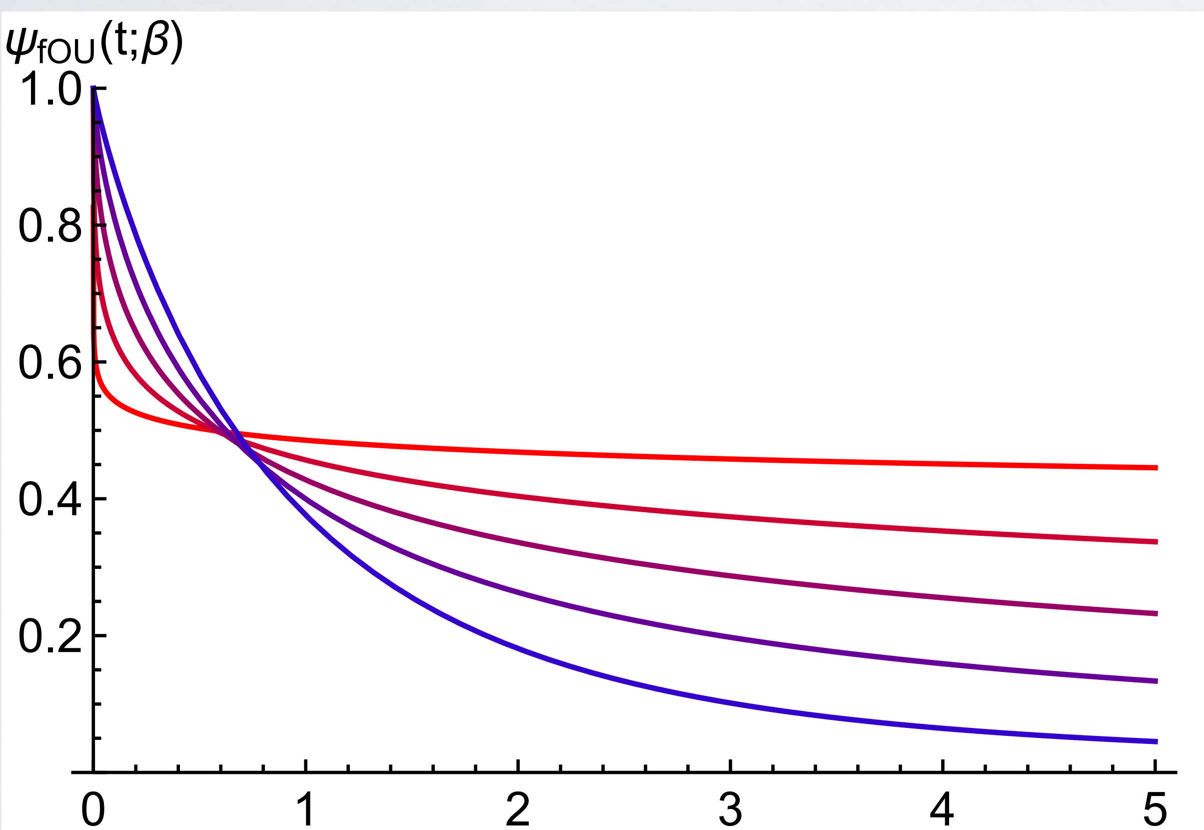
Time series and autocorrelation functions



Multiscale relaxation with the fOU model

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

$$p_{\mathrm{fOU}}(\lambda;\beta) = \frac{\sin(\pi\beta)}{\lambda\left(\lambda^{-\beta} + \lambda^{\beta} + 2\cos(\pi\beta)\right)}$$



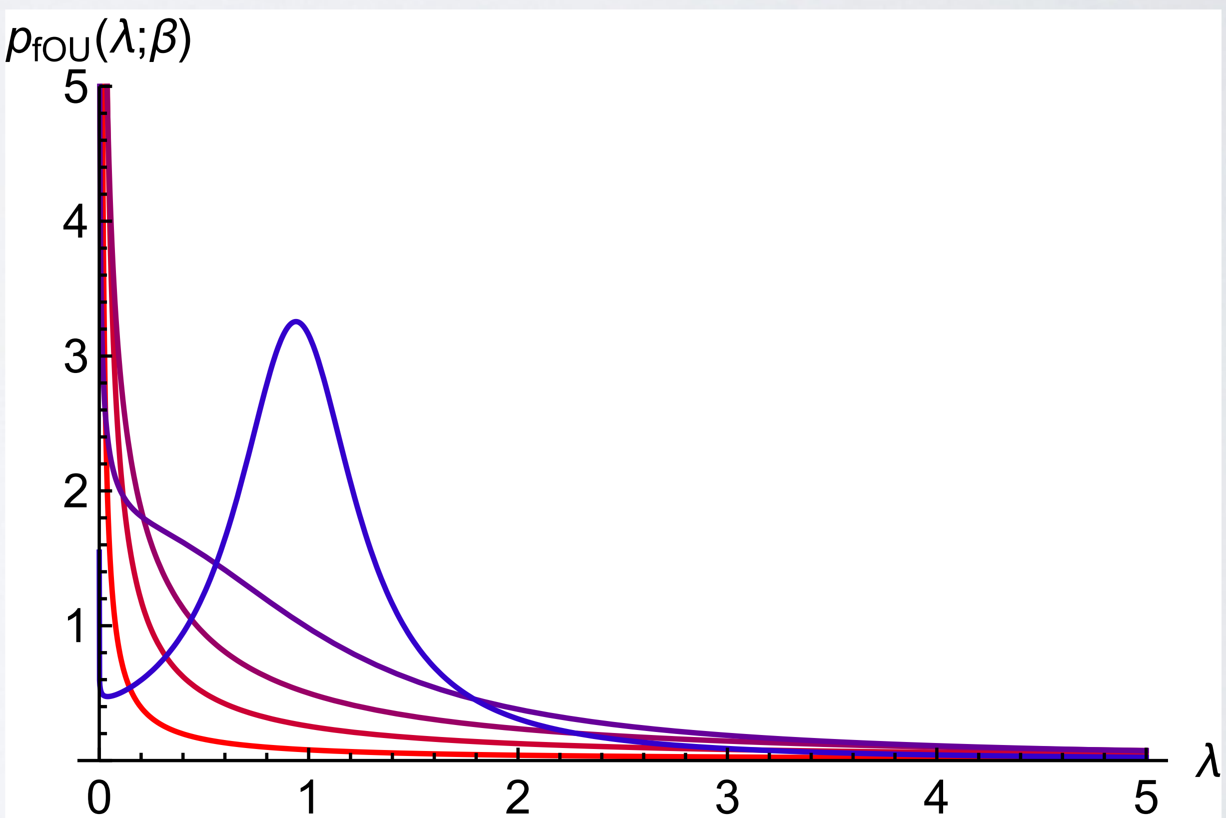
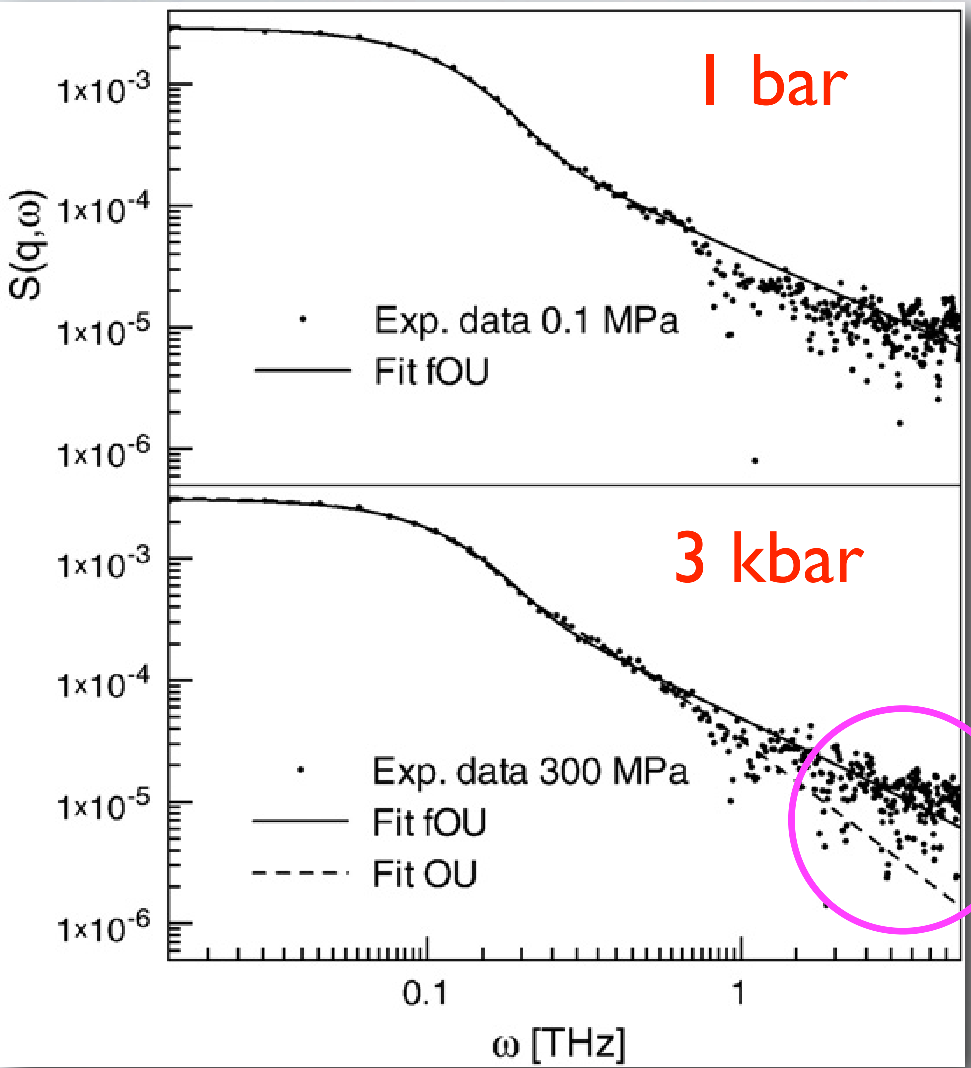


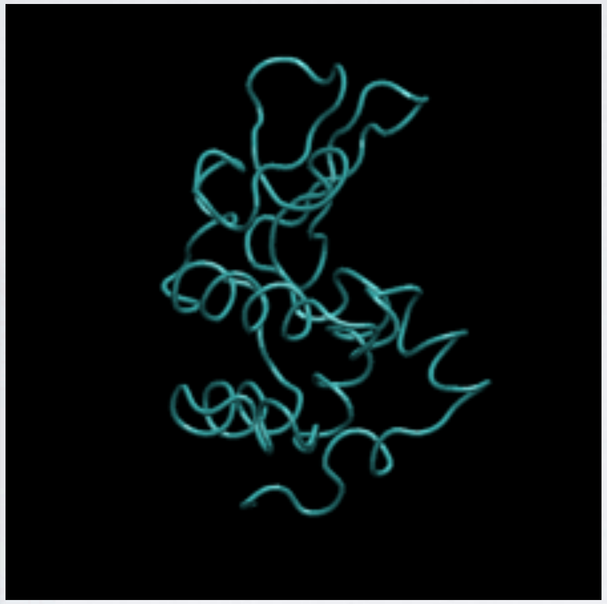
Fig. 1. **Left:** Normalized DACF $\psi_{\mathrm{fOU}}(t;\beta)$ for $\beta = 0.1, 0.3, \ldots, 0.9$ (red to blue). **Right:** Corresponding relaxation spectra $p_{\mathrm{fOU}}(\lambda;\beta)$.

Application 1: Lysozyme under hydrostatic pressure

Neutron scattering

QENS dynamic structure factor

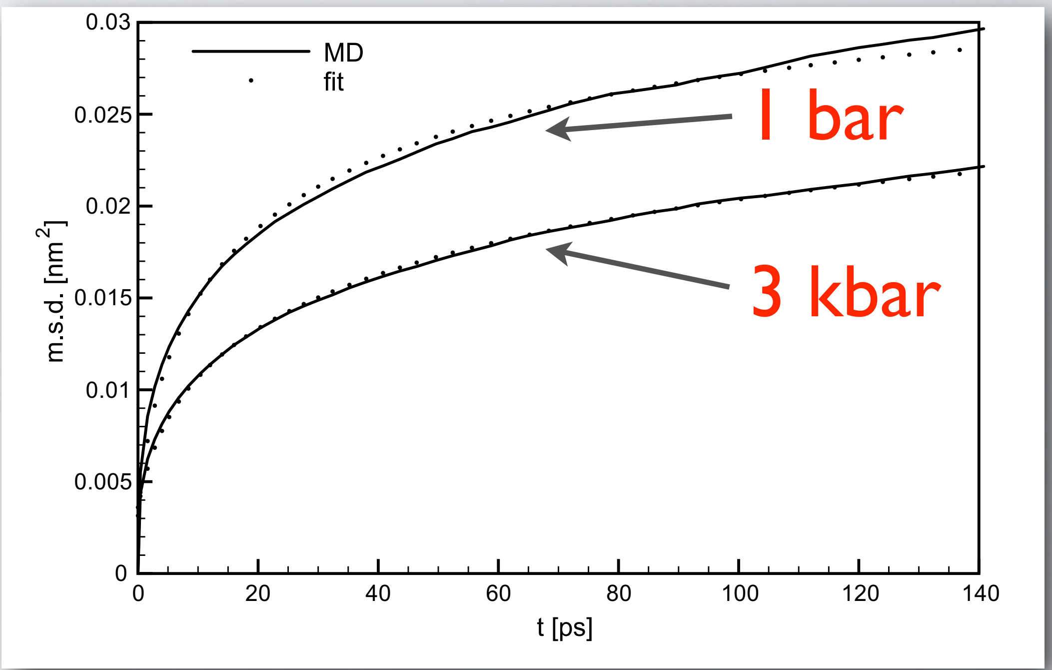




Lysozyme

MD simulation

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

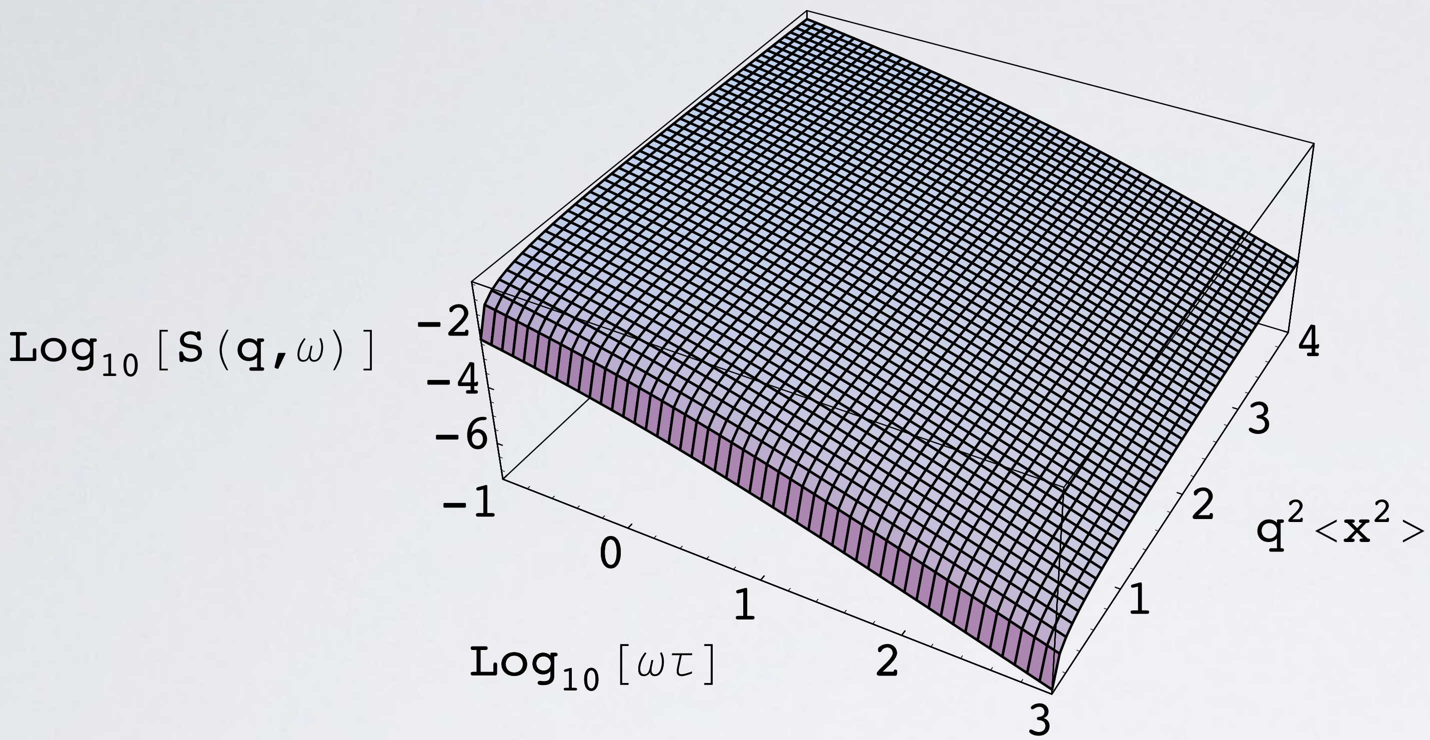


From MD simulation

	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

- Kneller, Phys Chem Chem Phys 7, 2641 (2005).
- 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.

Neutron scattering and fOU model



Parameters:

- Scale parameter τ $(\tau_{\alpha,n} = n^{-1/\alpha}\tau,\ n = 1, 2, 3\ldots)$
- Form parameter α
- Mean position fluctuation $\langle x^2 \rangle$

$$S(q,\omega) = \exp(-q^2\langle x^2\rangle)\left\{\delta(\omega) + \sum_{n=1}^{\infty}\frac{q^{2n}\langle x^2\rangle^n}{n!}\frac{1}{2\pi}L_\alpha(\omega;\tau_{\alpha,n})\right\}$$

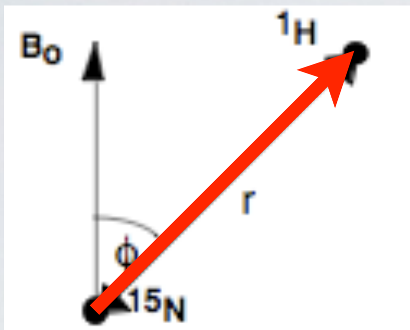
$$L_\alpha(\omega;\tau) = \frac{2\tau\sin(\alpha\pi/2)}{|\omega\tau|\left(|\omega\tau|^\alpha + 2\cos(\alpha\pi/2) + |\omega\tau|^{-\alpha}\right)}, \qquad 0 < \alpha \le 1$$

G. Kneller, *Physical Chemistry Chemical Physics*, vol. 7, pp. 2641 – 2655, 2005.

Application 2: Protein dynamics and NMR

- Calandrini, Abergel, Kneller, J. *Chem. Phys.*, vol. 128, p. 145102, 2008.
- Calandrini, Abergel, Kneller, *J. Chem. Phys.*, vol. 133, p. 145101, 2010.

Relaxation $^{15}N - {}^{1}H$



$$C_{ii}(t) = \langle P_2(\boldsymbol{\mu}_i(t) \cdot \boldsymbol{\mu}_i(0)) \rangle,$$

$$c_{ii}(t) = C_{ii,R}(t) C_{ii,I}(t)$$

Global rotation   **Internal dynamics**

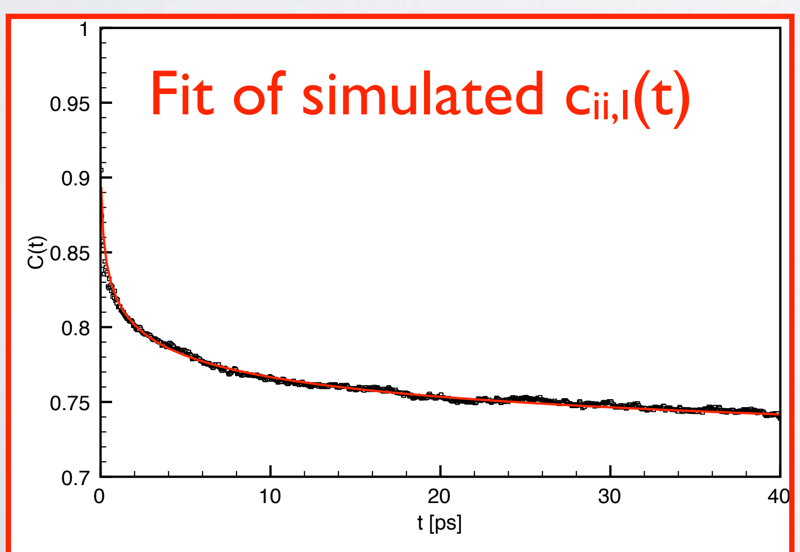
Relaxation rates

$$R_{1i} = d^2(3J_{ii}(\omega_N) + J_{ii}(\omega_{H-N}) + 6J_{ii}(\omega_{H+N})) + 2c^2 J_{ii}(\omega_N),$$

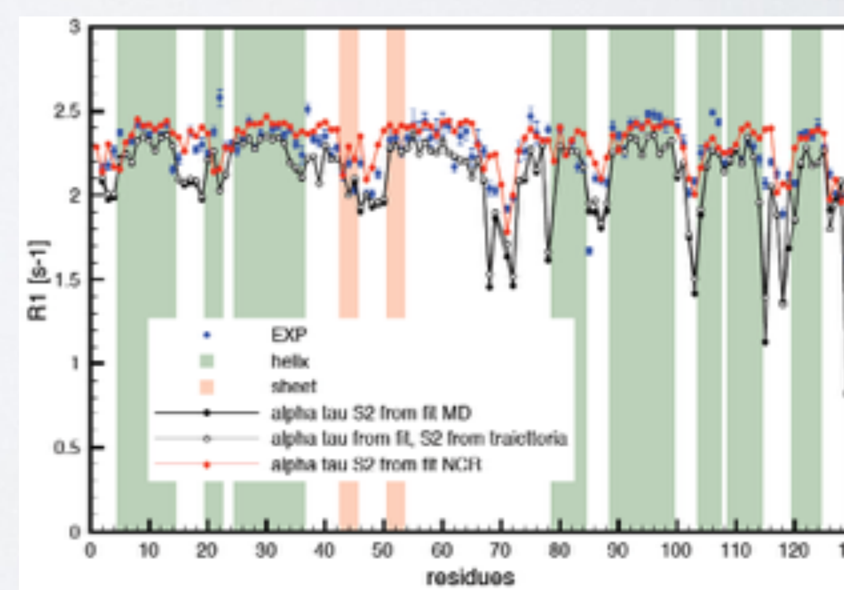
$$R_{2i} = d^2\left(2J_{ii}(0) + \frac{3}{2}J_{ii}(\omega_N) + \frac{1}{2}J_{ii}(\omega_{H-N}) + 3J_{ii}(\omega_H) + 3J_{ii}(\omega_{H+N})\right) + c^2\left(\frac{4}{3}J_{ii}(0) + J_{ii}(\omega_N)\right).$$

Model $$c_{ii,I}(t) = S_{ii}^2 + (1 - S_{ii}^2) E_\alpha(-[t/\tau]^\alpha)$$

Prediction of Expérimental data (R1, R2, …)



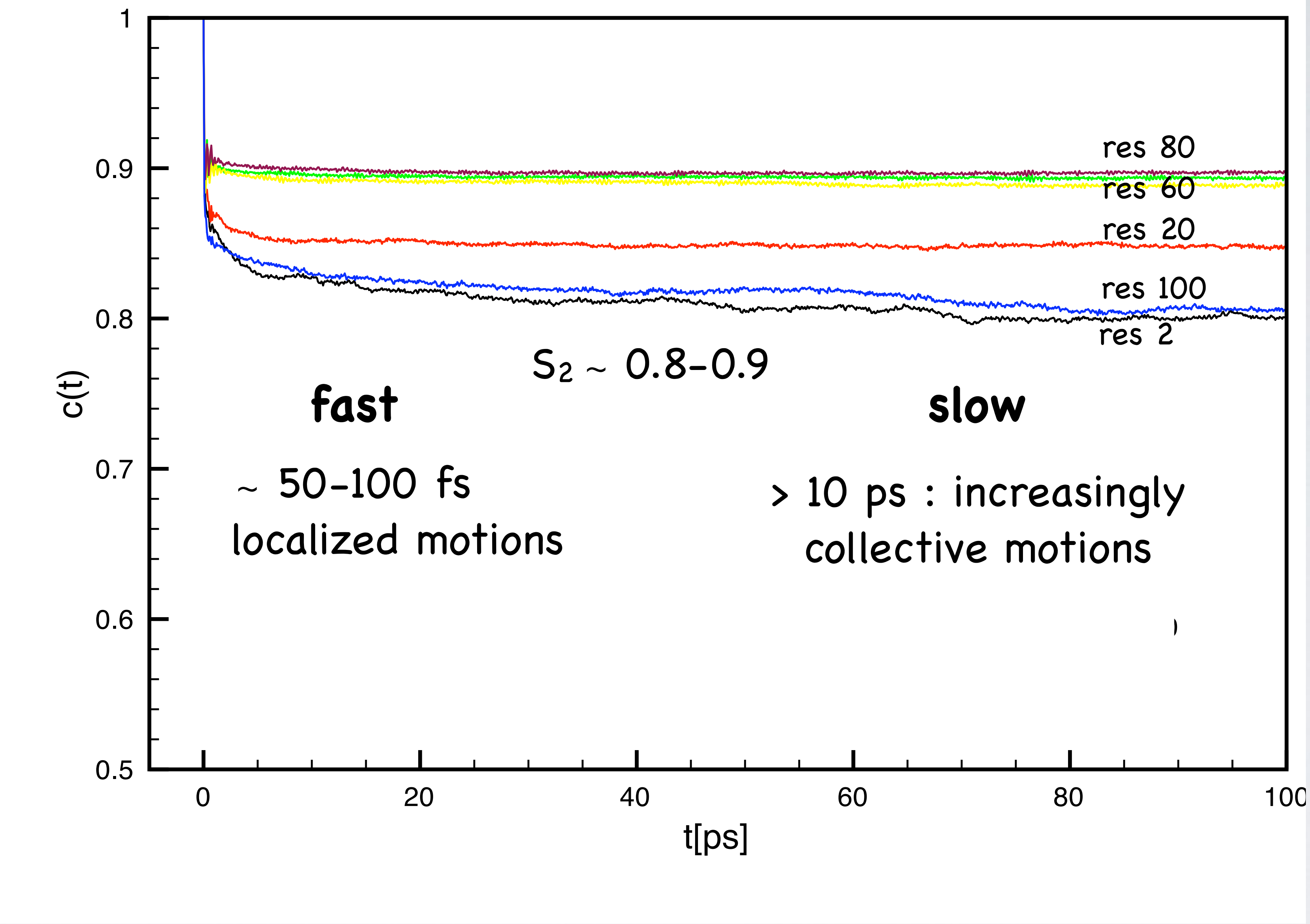
$$J(\omega) = \int_{-\infty}^{+\infty} dt\, \cos(\omega t) C(t)$$



N-H reorientational correlations in the peptide planes of calbindin seen by MD simulation

lysozyme

res 104



trajectory 1 ns

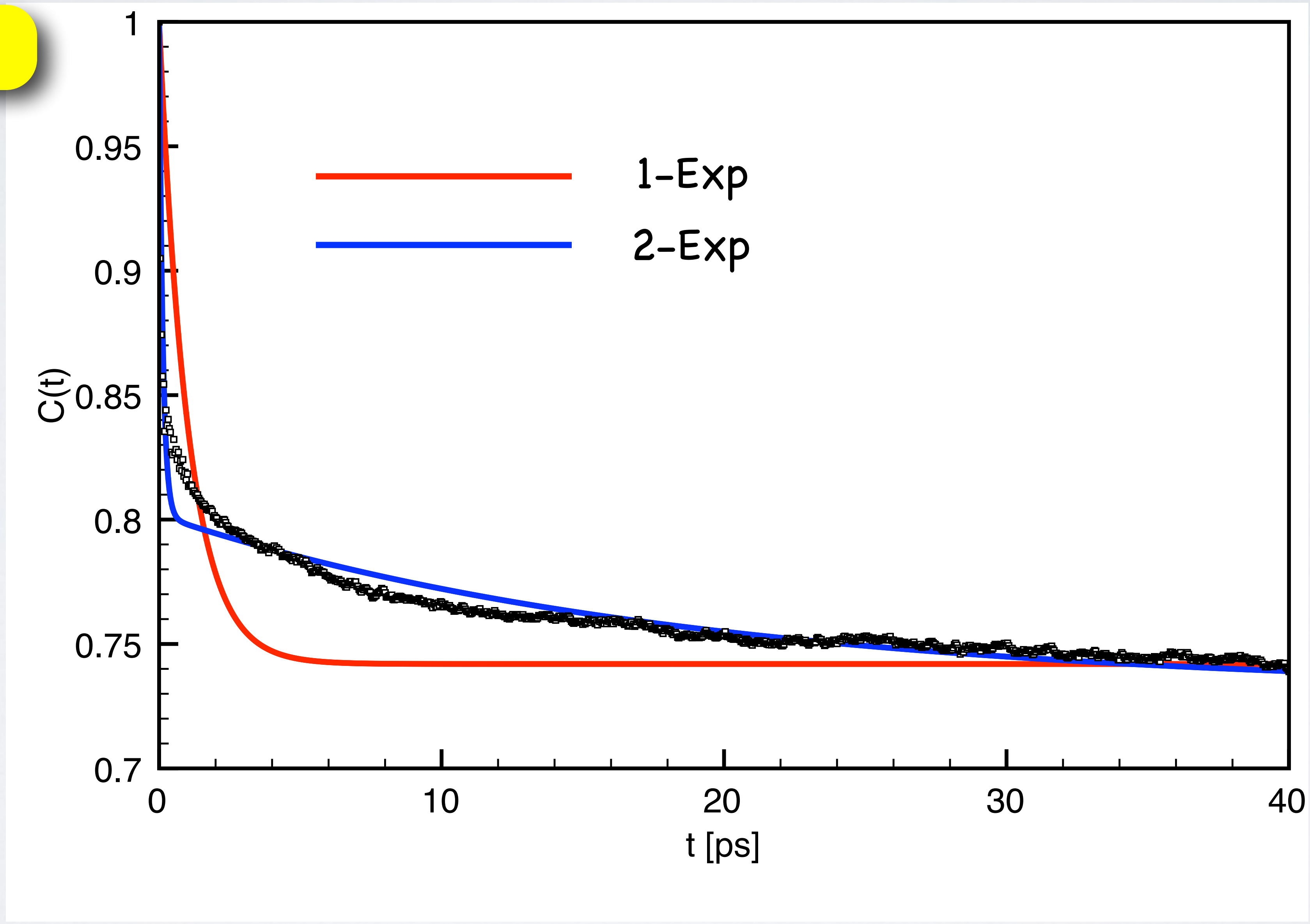
Δ t=40 fs

V. Calandrini, G.R. Kneller, manuscript in preparation

try fits with 1 & 2 exponentials ("model free", Liparo-Szabo)

lysozyme

res 104

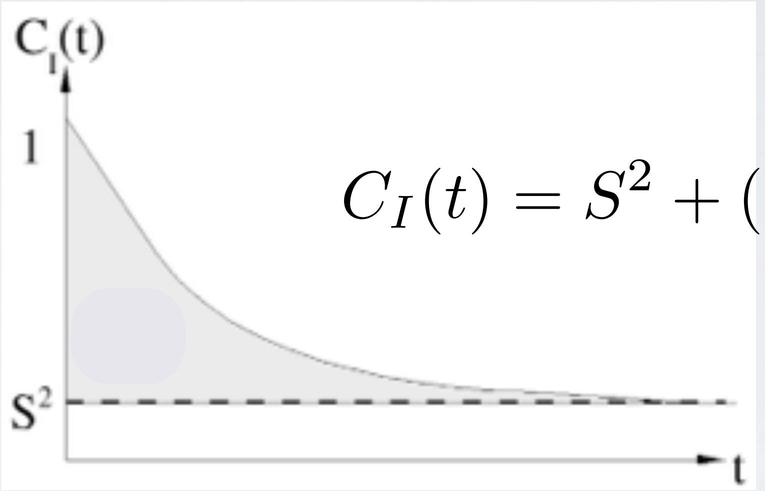


Estimating correlation times in NMR

$$c_{ii}(t) = C_{ii,R}(t) C_{ii,I}(t)$$

global rotation — internal dynamics

$$C_R(t) = \exp(-[t/\tau_0])$$



$$C_I(t) = S^2 + (1 - S^2) E_\alpha \left(-[t/\tau]^\alpha\right)$$

$$\tau_{tot} = \int_0^\infty dt\, c(t) = J(0)$$

$$\tau_{tot} = S^2 \tau_0 + (1 - S^2) \frac{\tau (\tau/\tau_0)^{\alpha - 1}}{1 + (\tau/\tau_0)^\alpha}$$

$$\tau_{I,\mathrm{eff}}$$

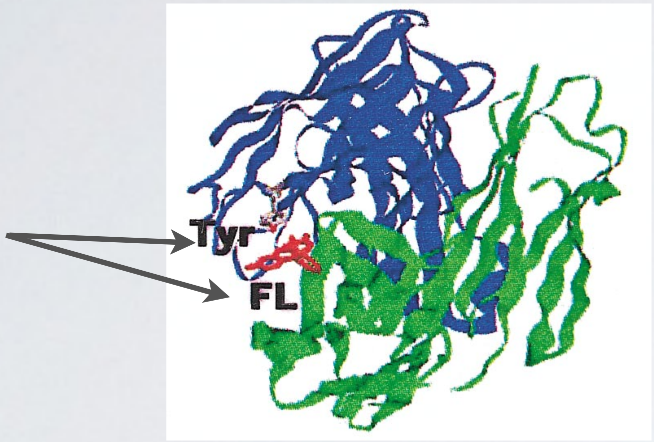
$$\tau \le \tau_{I,\mathrm{eff}} \le \tau_0$$

$\alpha = 1$ — $\alpha = 0$

The form of $C_I(t)$ matters !

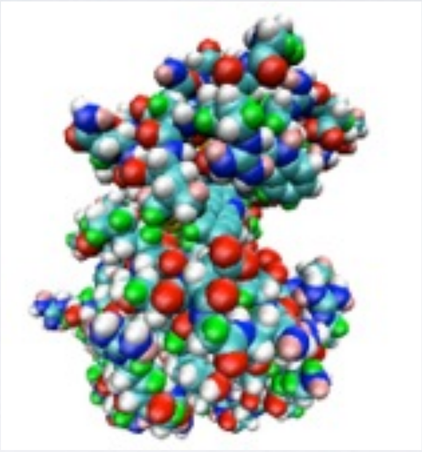
Self-similar protein dynamics

*The phenomenon of **self-similarity** on the time scale can be modeled by **stochastic processes with long-time memory**.*



FL/Anti-FL complex

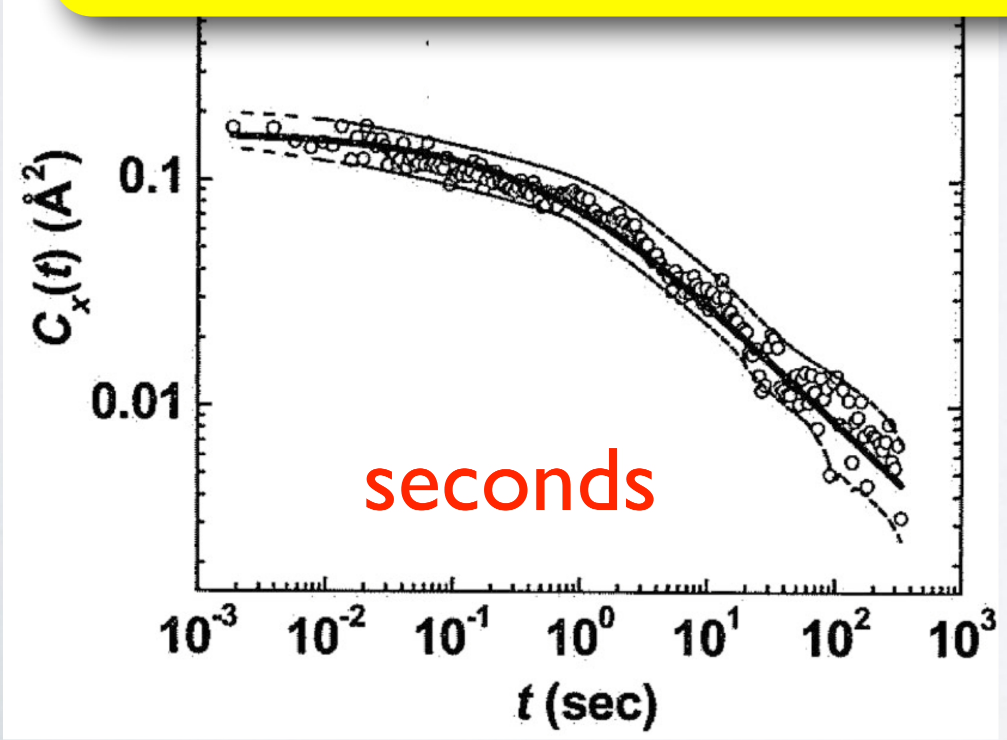
Min et al. PRL 94, 1983021



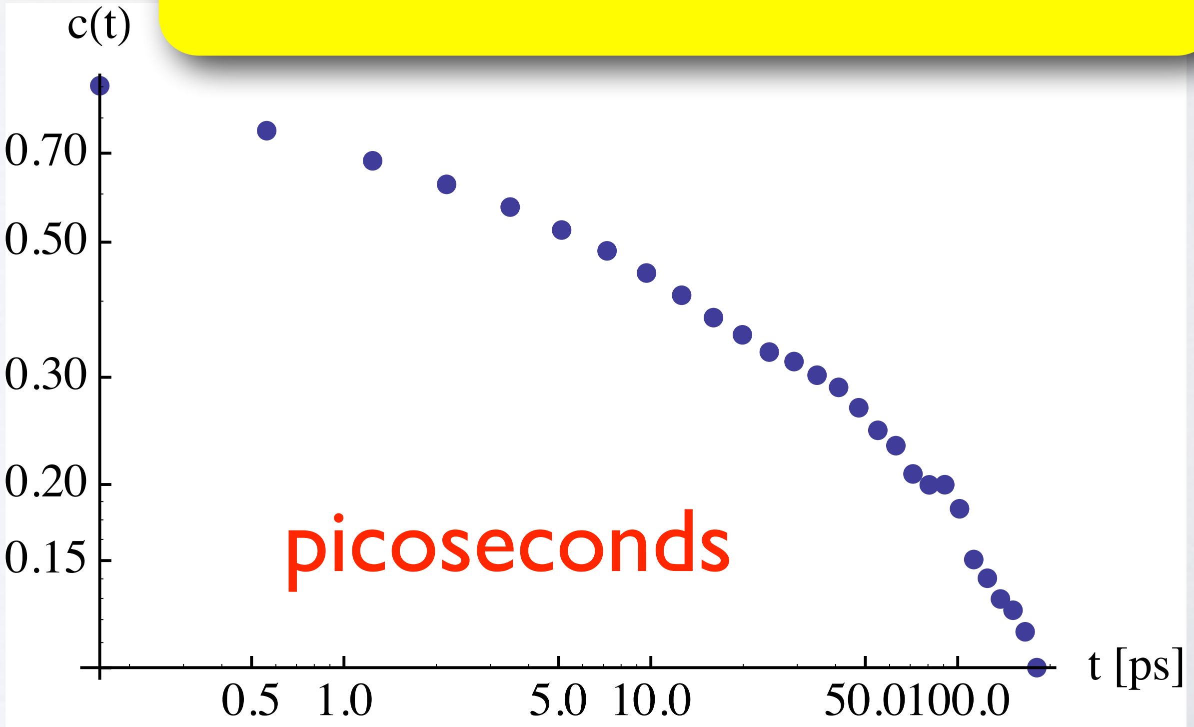
Lysozyme

G.R. Kneller,et al J Chem Phys 136, 191101 (2012).

Distance autocorrelation by single molecule fluorescence spectrocopy



position-autocorrelation functions by MD simulation



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.

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

The moments of the relaxation reate spectrum diverge.

Modeling diffusion in velocity space

$$x(t) - x(0) = \int_0^t dx(\tau) \overset{v(t)=\dot{x}(t)}{=} \int_0^t d\tau v(\tau)$$

$$\Rightarrow \quad \underbrace{\langle (x(t) - x(0))^2 \rangle}_{W(t)} = 2 \int_0^t d\tau \, (t - \tau) \, \underbrace{\langle v(\tau) v(0) \rangle}_{c_{vv}(\tau)}$$

MSDs are computed via velocity autocorrelation functions (VACFs).

Distinguish

- Ballistic regime ($t \to 0$): $W(t) \overset{t \to 0}{\sim} \langle |\mathbf{v}|^2 \rangle t^2$
- Asymptotic regime ($t \to \infty$): $W(t) \overset{t \to \infty}{\sim} \dfrac{2nD_\alpha t^\alpha}{\Gamma(1+\alpha)}$

Langevin's stochastic equation of motion

P. Langevin, C. Rendus Acad. Sci. Paris 146, 530 (1908).

PHYSIQUE. — *Sur la théorie du mouvement brownien.* Note de M. **P. Langevin**, présentée par M. Mascart.

I. Le très grand intérêt théorique présenté par les phénomènes de mouvement brownien a été signalé par M. Gouy (¹) : on doit à ce physicien d'avoir formulé nettement l'hypothèse qui voit dans ce mouvement continuel des particules en suspension dans un fluide un écho de l'agitation thermique moléculaire, et de l'avoir justifiée expérimentalement, au moins de manière qualitative, en montrant la parfaite permanence du mouvement brownien et son indifférence aux actions extérieures lorsque celles-ci ne modifient pas la température du milieu.

Une vérification quantitative de la théorie a été rendue possible par M. Einstein (²), qui a donné récemment une formule permettant de prévoir quel est, au bout d'un temps donné τ, le carré moyen $\overline{\Delta_x^2}$ du déplacement Δ_x d'une particule sphérique dans une direction donnée x par suite du mouvement brownien dans un liquide, en fonction du rayon a de la particule, de la viscosité μ du liquide et de la température absolue T. Cette formule est

$$\overline{\Delta_x^2} = \frac{\mathrm{RT}}{\mathrm{N}}\,\frac{1}{3\pi\mu a}\,\tau, \tag{1}$$

où R est la constante des gaz parfaits relative à une molécule-gramme et N

(¹) Gouy, *Journ. de Phys.*, 2ᵉ série, t. VII, 1888, p. 561; *Comptes rendus*, t. CIX, 1889, p. 102.
(²) A. Einstein, *Ann. d. Physik*, 4ᵉ série, t. XVII, 1905, p. 549; *Ann. d. Physik*, 4ᵉ série, t. XIX, 1906, p. 371.

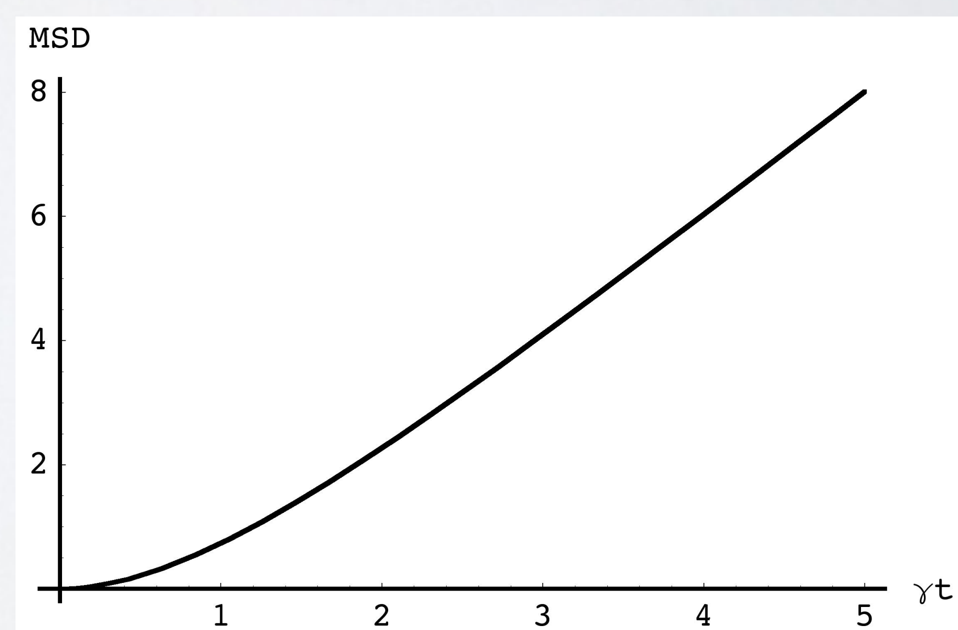
$$\dot{\mathbf{v}} + \gamma \mathbf{v} = \mathbf{f}_s(t)$$

white noise

$$c_{vv}(t) = \frac{3k_BT}{m}\exp(-\gamma t)$$

Asymptotic form of the MSD

$$W(t) \overset{t\gg 1/\gamma}{\sim} 6\underbrace{\frac{k_BT}{m\gamma}}_{D}\,t$$



VACF of an (anomalous) Rayleigh particle:

E. Barkai and R. Silbey, J Phys Chem B 104, 3866 (2000).

Consider a (f)OU process in velocity space

$$\frac{\partial}{\partial t} p(\mathbf{v}, t|\mathbf{v}_0, 0) = \partial_t^{1-\rho} \mathcal{L}_v \, p(\mathbf{v}, t|\mathbf{v}_0, 0), \qquad 0 < \rho < 2.$$

$$\mathcal{L}_v = \eta_\rho \left\{ \frac{\partial}{\partial \mathbf{v}} \cdot \mathbf{v} + \frac{k_B T}{m} \frac{\partial}{\partial \mathbf{v}} \cdot \frac{\partial}{\partial \mathbf{v}} \right\}$$

$$c_{vv}(t) = \langle |\mathbf{v}|^2 \rangle E_\rho(-[t/\tau_v]^\rho). \qquad \tau_v = (1/\eta_\rho)^{1/\rho}$$

$$W(t) \overset{t \gg \tau_v}{\sim} \frac{2\langle |\mathbf{v}|^2 \rangle \tau_v^\rho}{\Gamma(3-\rho)} t^{2-\rho}. \qquad D_\alpha = \frac{\langle |\mathbf{v}|^2 \rangle}{n} \eta_{2-\alpha}^{-1}$$

$$\rho = 2 - \alpha, \quad \text{with} \quad 0 < \alpha < 2$$

Generalized (deterministic) Langevin Equation

[1] R. Zwanzig. Statistical mechanics of irreversibility, pages 106–141. Lectures in Theoretical Physics. Wiley-Interscience, New York, 1961.
[2] R. Zwanzig. Nonequilibrium statistical mechanics. Oxford University Press, 2001.

$$\frac{d\mathbf{v}(t)}{dt} = -\int_0^t d\tau\, \kappa(t-\tau)\mathbf{v}(\tau) + f^{(+)}(t)$$

$$\langle \mathbf{v}(0)\cdot \mathbf{f}^{(+)}(t)\rangle = 0$$

$$\kappa(t) = \langle \mathbf{f}^{(+)}(0)\cdot \mathbf{f}^{(+)}(t)\rangle$$

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

The GLE is a deterministic equation of motion for a « tagged » particle. The external force $f^{(+)}(t)$ can be expressed in terms of the Liouville operator for the whole system and a projection operator on the selected dynamical variable (here v).

Mori-Zwanzig model for the memory function

$$\dot{\kappa}_n(t) + \Omega_n \kappa_n(t) + \int_0^t d\tau\, \kappa_{n+1}(t-\tau)\kappa_n(\tau) = 0$$

$$\hat{\kappa}_1(s) = \cfrac{\kappa_1(0)}{s + \Omega_1 + \cfrac{\kappa_2(0)}{s + \Omega_2 + \dots \cfrac{\kappa_M(0)}{s + \Omega_M}}}.$$

Continued fraction

$$\hat{c}_{vv}(s) = \frac{c_{vv}(0)}{s + \Omega + \hat{\kappa}_1(s)}$$

☛ Model with M+1 poles

c_{vv}(t) is multi-exponential

MSD for multi-exponential VACFs

Using the Laplace transform $\hat{f}(s) = \int_0^t dt \, \exp(-st) f(t)$

$$W(t) = 2\int_0^\infty d\tau \, (t-\tau) c_{vv}(\tau) \Leftrightarrow \hat{W}(s) = \frac{2\hat{c}_{vv}(s)}{s^2}$$

If $\hat{c}_{vv}(s)$ is a rational function, with poles s_k such that $\Re\{s_k\} < 0$, and if $\hat{c}_{vv}(0)$ is finite, $\hat{W}(s)$ has a pole of second order at $s = 0$ and it follows from the residue theorem

$$W(t) = \lim_{s\to 0} \frac{d}{ds} \{\exp(st)\hat{c}_{vv}(s)\} + \text{ exponentially decaying terms.}$$

Therefore $\boxed{W(t) \overset{t\to\infty}{\sim} 2Dt}$ where $D = \hat{c}_{vv}(0) = \int_0^\infty c_{vv}(t)$.

Can such considerations be generalized ?

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)

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

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

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).

$$\hat{c}_{vv}(s) \overset{s\rightarrow 0}{\sim} nD_\alpha L(1/s)s^{1-\alpha}$$

$$D_\alpha = \lim_{s\rightarrow 0} \frac{s^{\alpha-1}\hat{c}_{vv}(s)}{n}.$$

$$D_\alpha = \frac{1}{n}\int_0^\infty dt\, \partial_t^{\alpha-1} c_{vv}(t)$$

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

$$D = \frac{1}{n}\int_0^\infty dt\, c_{vv}(t)$$

Generalized relaxation constant

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

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

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

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

Fluctuation-Dissipation theorem

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

Referring to Kubo

JOURNAL OF THE PHYSICAL SOCIETY OF JAPAN Vol. 12, No. 6, JUNE, 1957

Statistical-Mechanical Theory of Irreversible Processes. I.

General Theory and Simple Applications to Magnetic and Conduction Problems

By Ryogo KUBO

Department of Physics, University of Tokyo

(Received March 2, 1957)

Here transport coefficients are derived on the basis of linear response theory.

Long-time tails

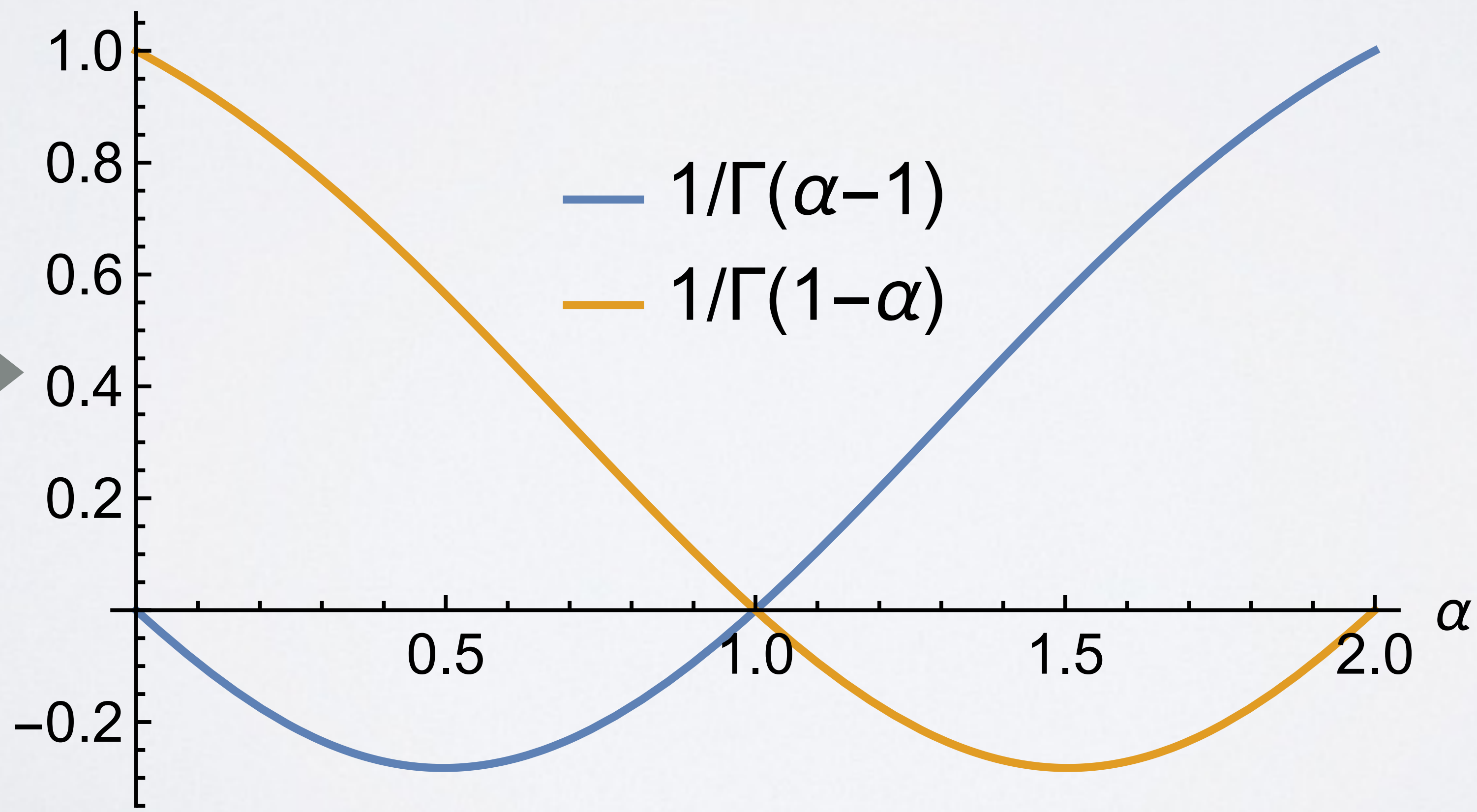
$$\lim_{t\to\infty} L(t) = 1 \qquad \lim_{t\to\infty} t\frac{dL(t)}{dt} = 0$$

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

also sufficient for $1 < \alpha < 2$

$$\kappa(t) \overset{t\to\infty}{\sim} \frac{t^{-\alpha}\left\langle |\mathbf{v}|^2 \right\rangle}{n\Gamma(1-\alpha) D_\alpha L(t)}.$$

also sufficient for $0 < \alpha < 1$



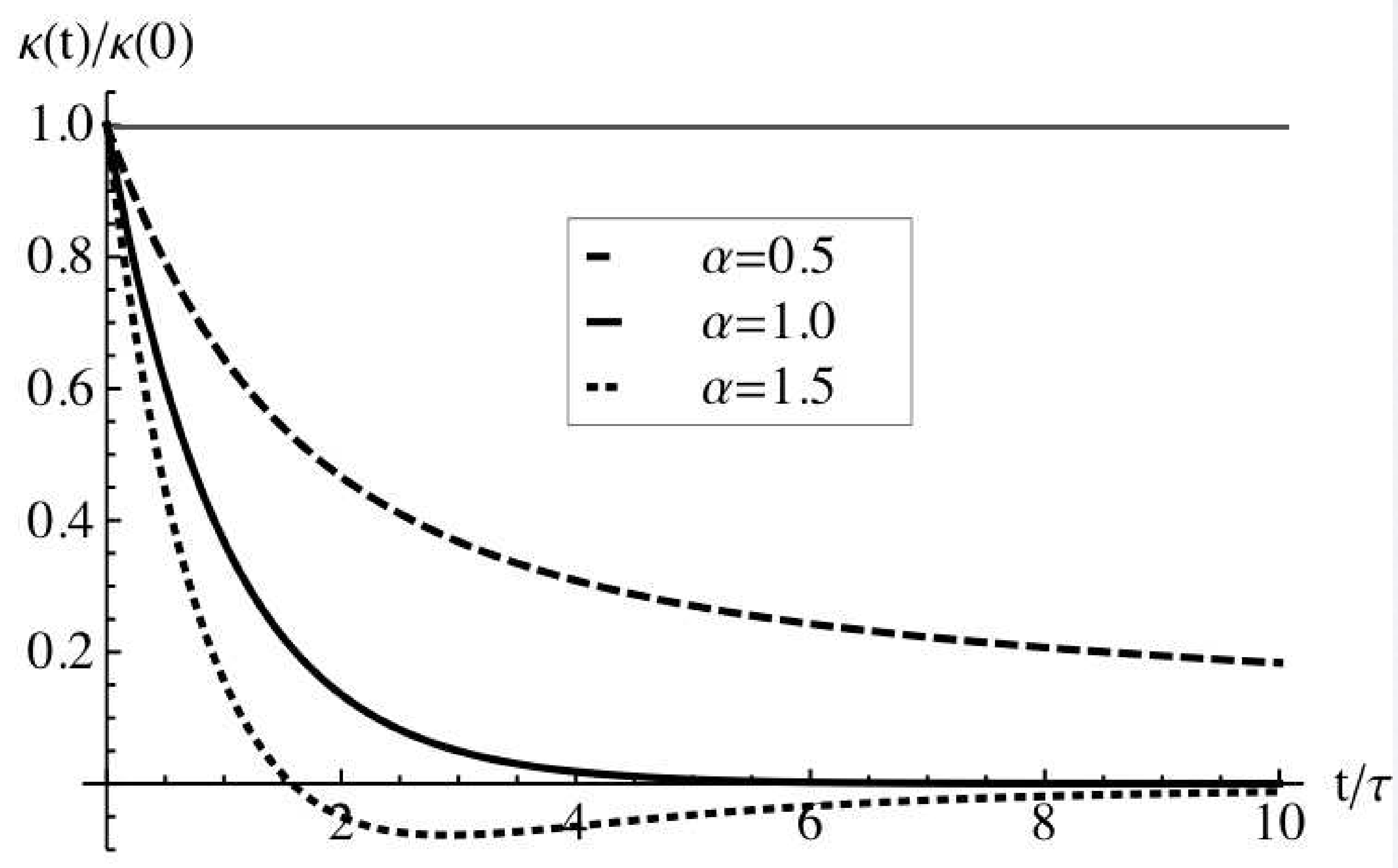
Simple model for anomalous diffusion

Model memory function

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

Kummer function

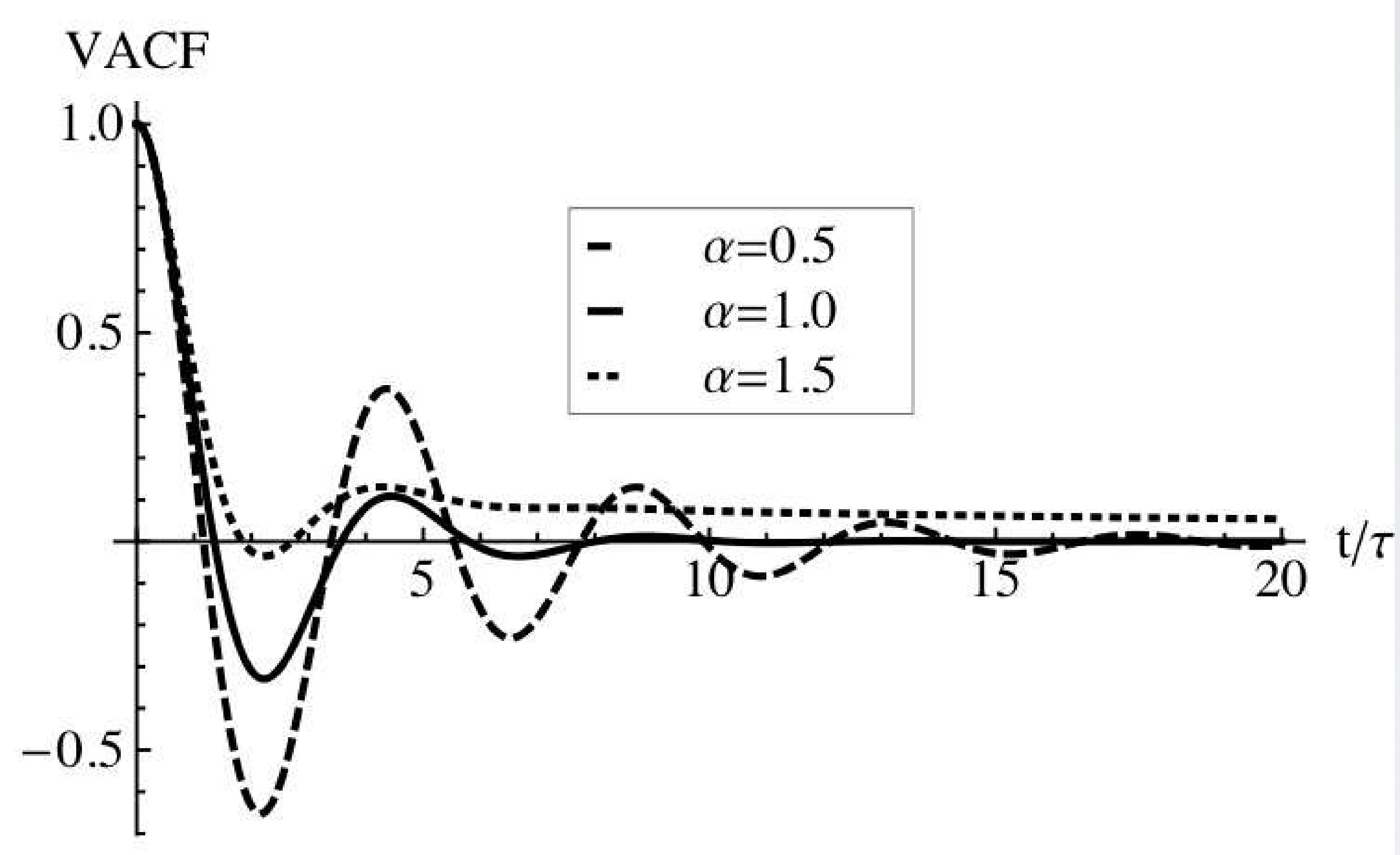
$$\hat{\kappa}_f(s) = \Omega^2 \left\{ \frac{\tau^\alpha}{s^{1-\alpha}} \frac{1}{(s\tau+1)^\alpha} \right\}$$

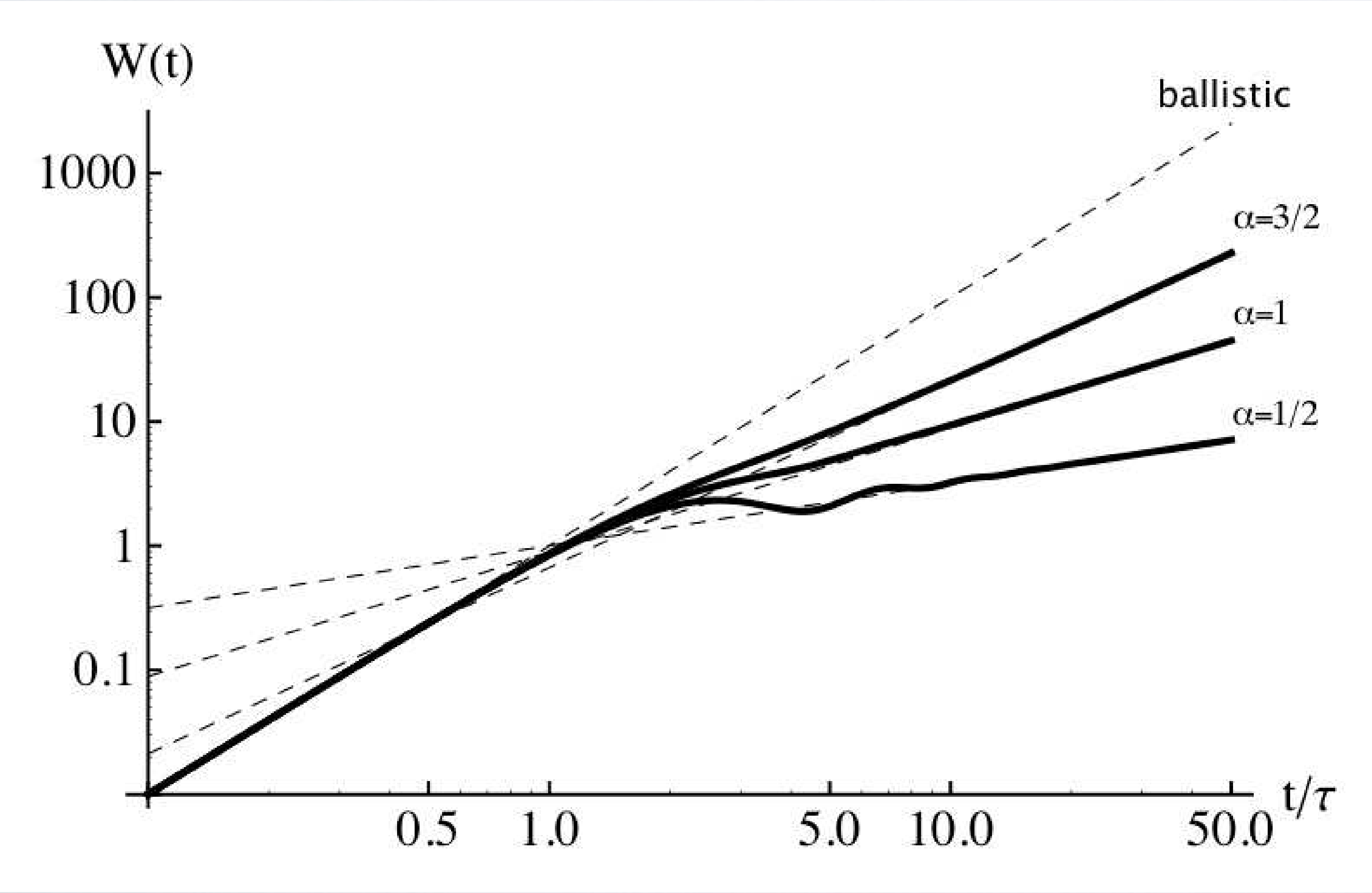


asymptotic form

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

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

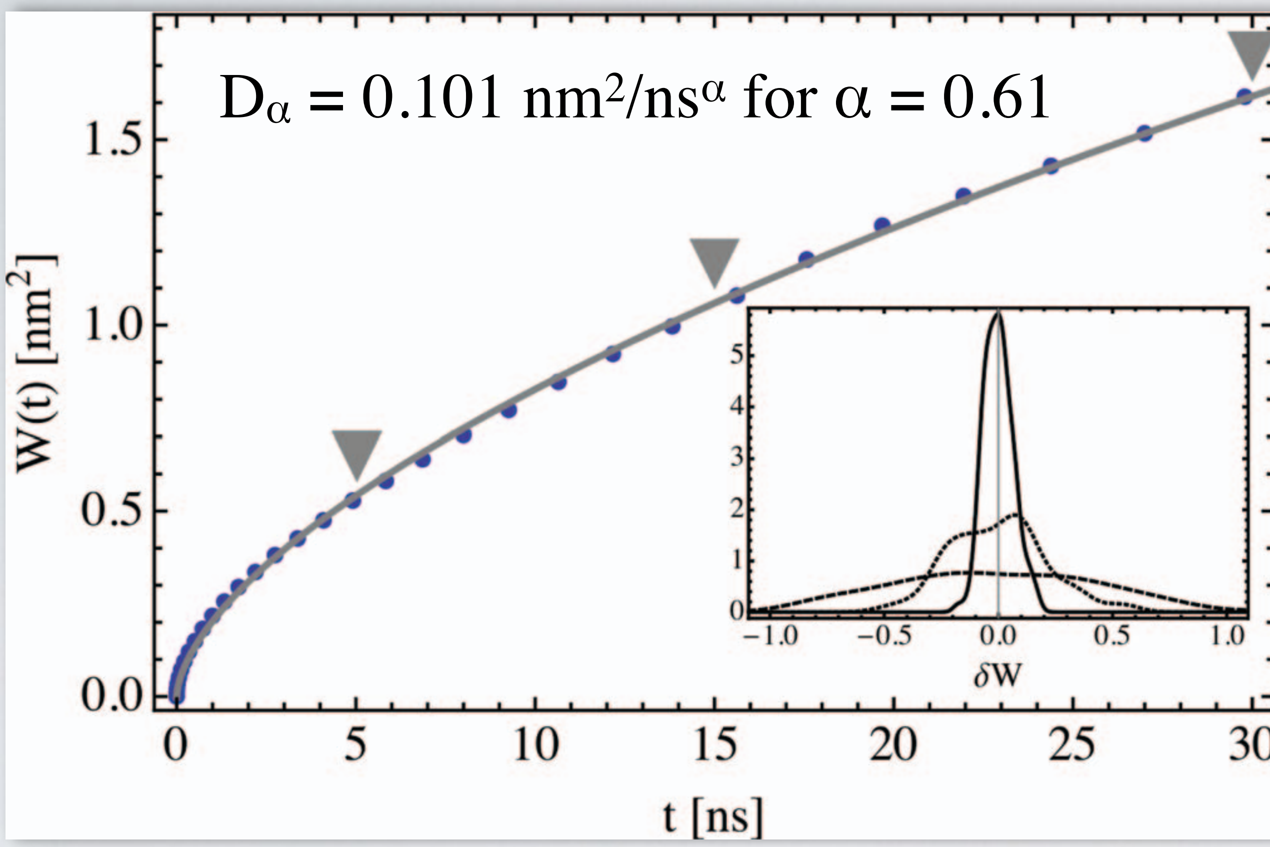




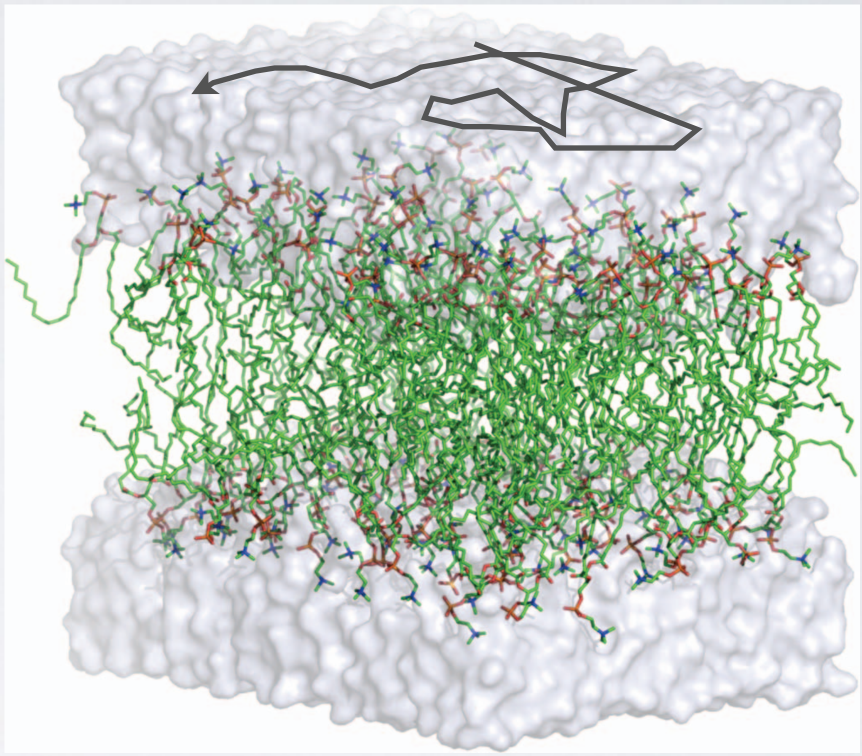
$$D_\alpha = \frac{\langle |\mathbf{v}|^2 \rangle}{n\Omega^2 \tau^\alpha}$$

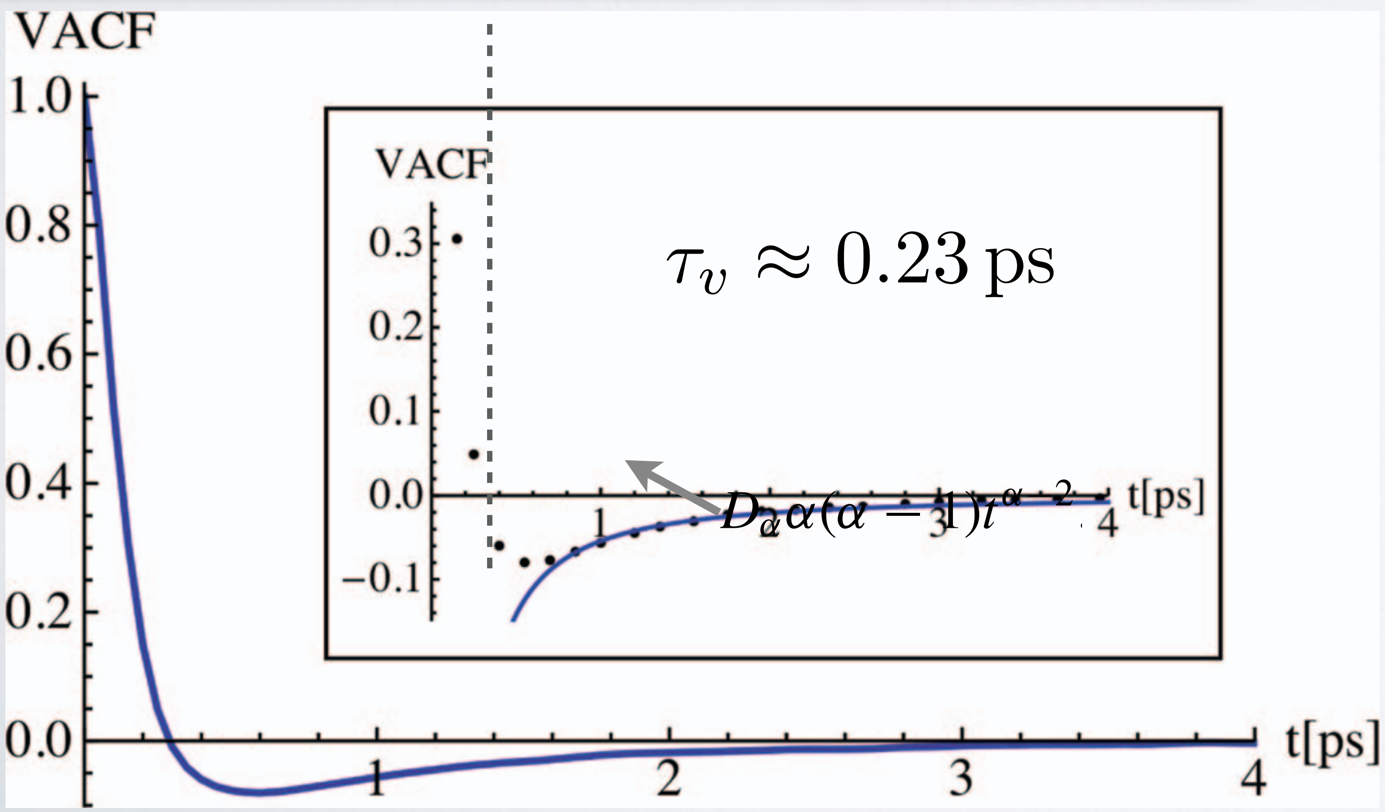
Lateral CM-VACF for a « real » lipid molecule

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



Simulated DOPC system





$$\tau_v = \left(\frac{nD_\alpha}{\langle|\mathbf{v}|^2\rangle}\right)^{1/(2-\alpha)}.$$

Anomalous Brownian motion and time scale separation

G.R. Kneller, J Chem Phys 141, 041105 (2014).

G.R. Kneller and G. Sutmann, J Chem Phys 120, 1667 (2004).

- 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

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

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

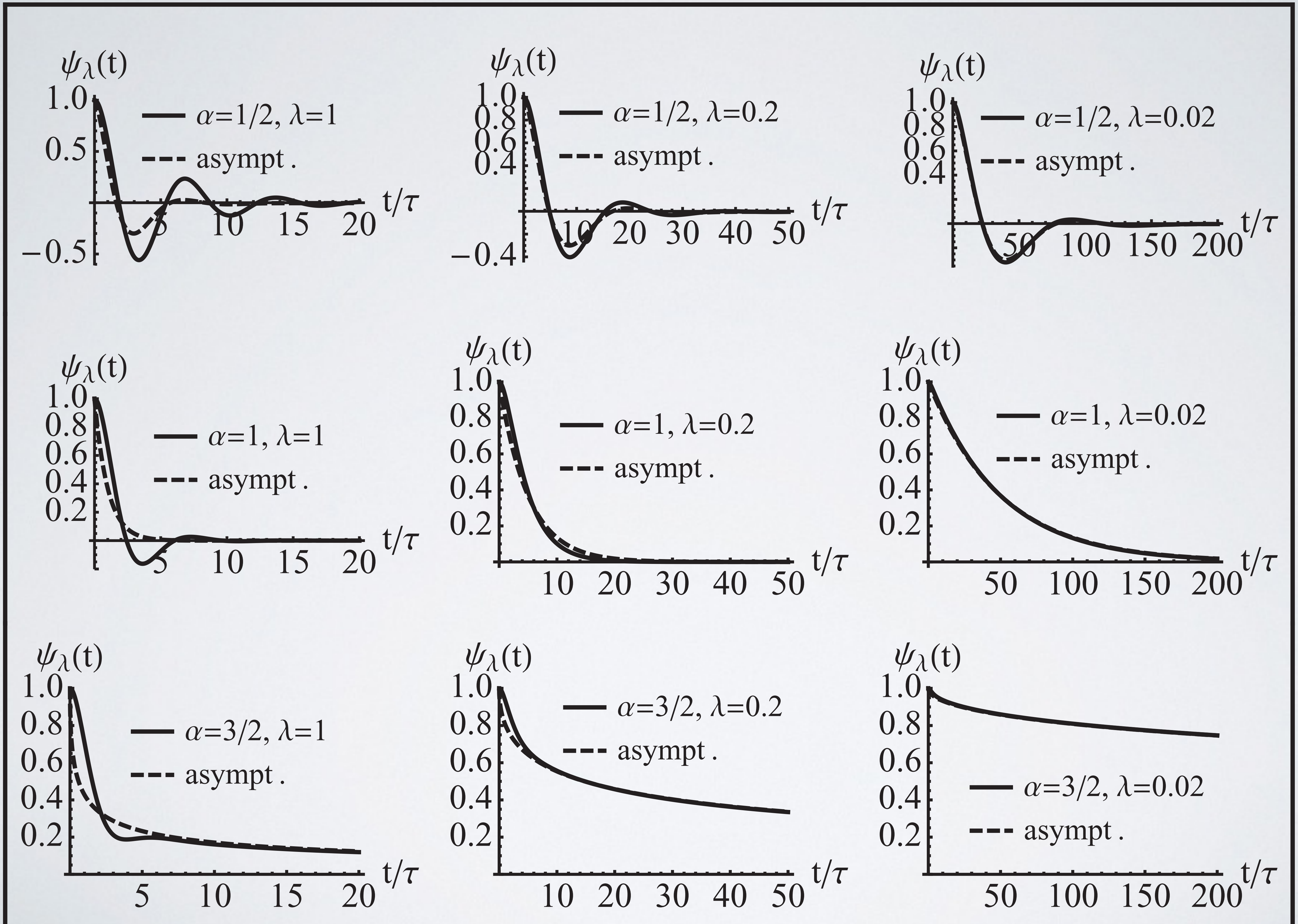
VACF of an anomalous Rayleigh particle

Mittag-Leffler function

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

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

Example for the analytical example shown before ($\tau \equiv \tau_v$)



Confined diffusion

The slowly growing function L(t) defines the asymptotic approach of the MSD to its plateau value.

$$W(t) \overset{t\to\infty}{\sim} 2nD_0 L(t).$$

The « diffusion constant » is the mean-square position fluctuation (MSPF).

$$D_0 = \frac{1}{n}\langle|\mathbf{u}|^2\rangle$$

The memory function approaches a plateau value, too.

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

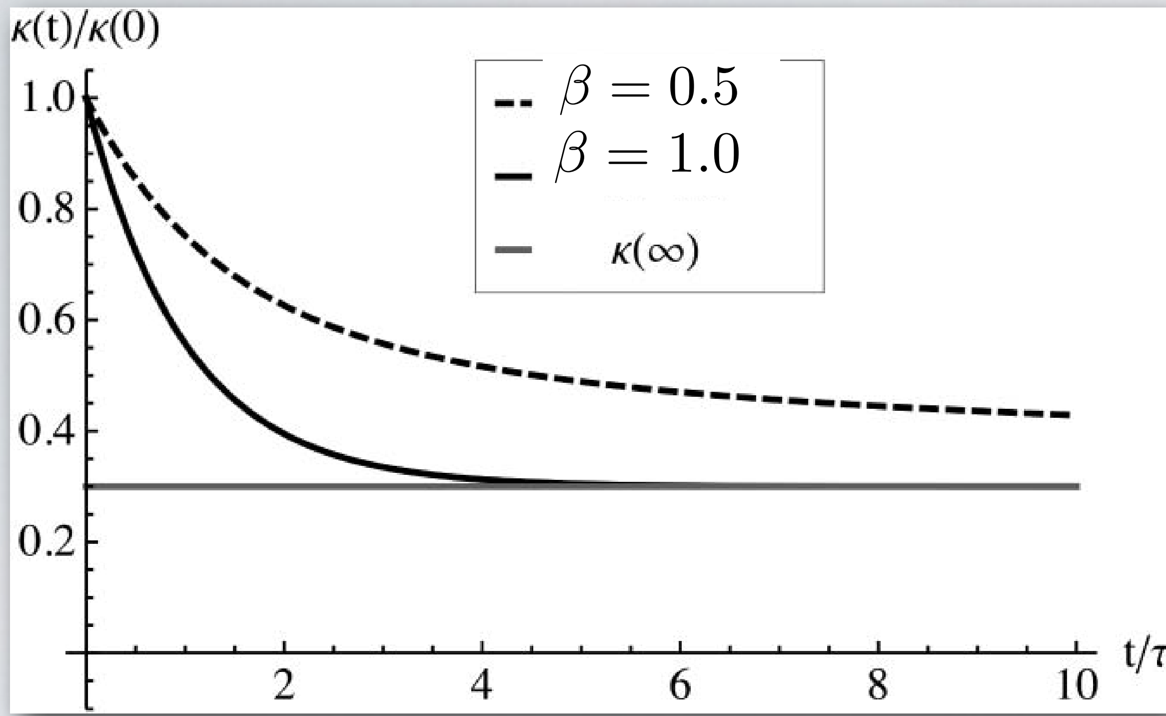
The condition for anomalous diffusion is that

$$\tau_c = \int_0^\infty dt\, \frac{\kappa(t)-\kappa(\infty)}{\kappa(0)-\kappa(\infty)}$$ diverges

$$\frac{1}{L(t)} - 1 \overset{t\to\infty}{\sim} C\, t^{-\beta}$$

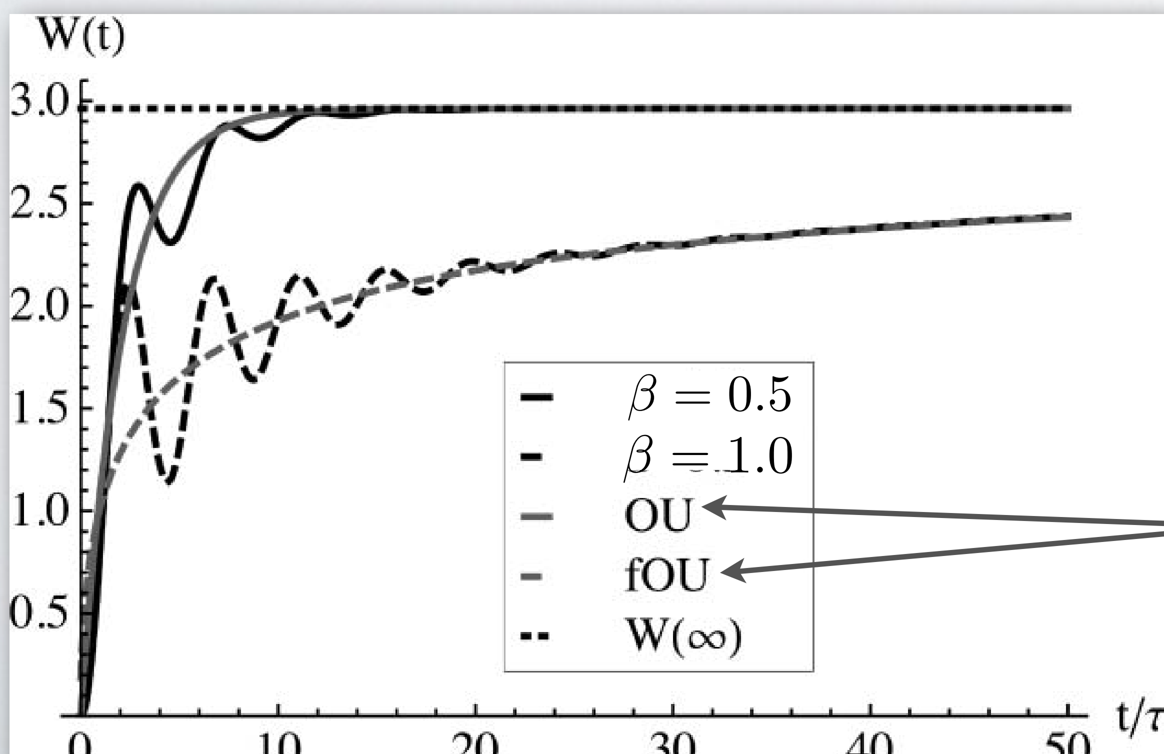
$$0 < \beta \leq 1$$

Illustration



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

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

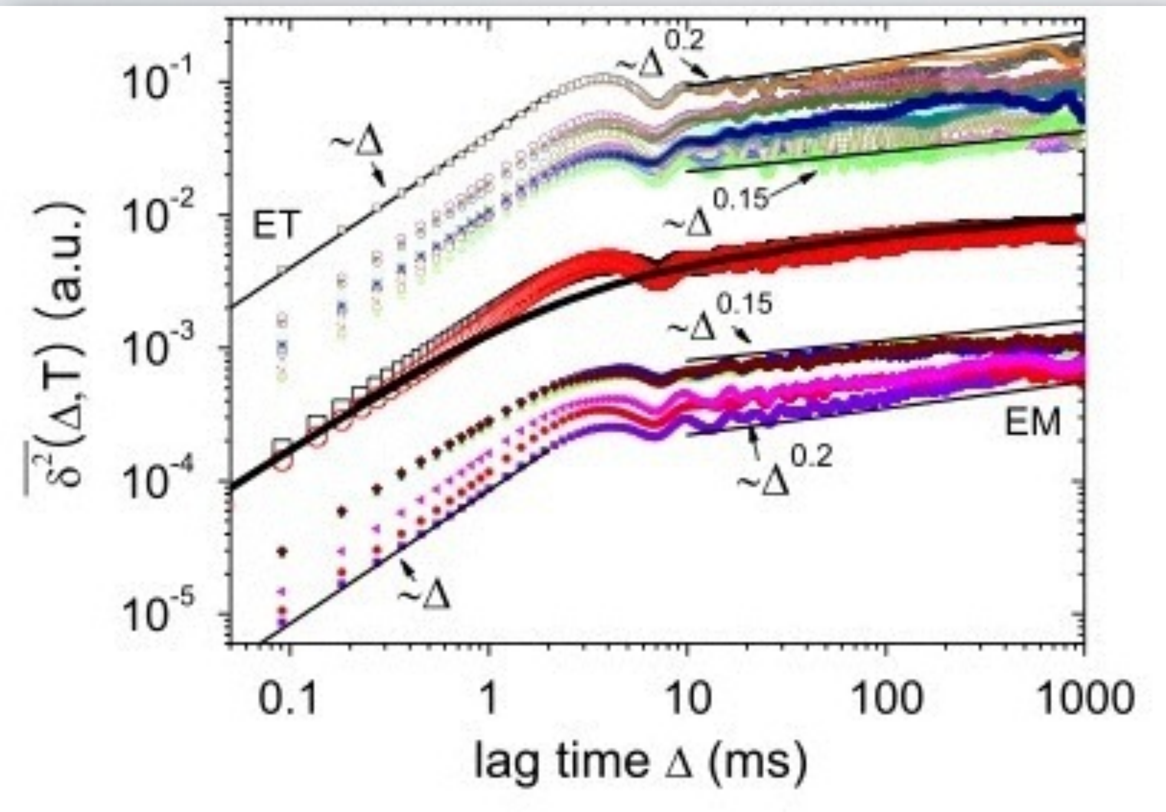


GLE versus fractional brownian motion

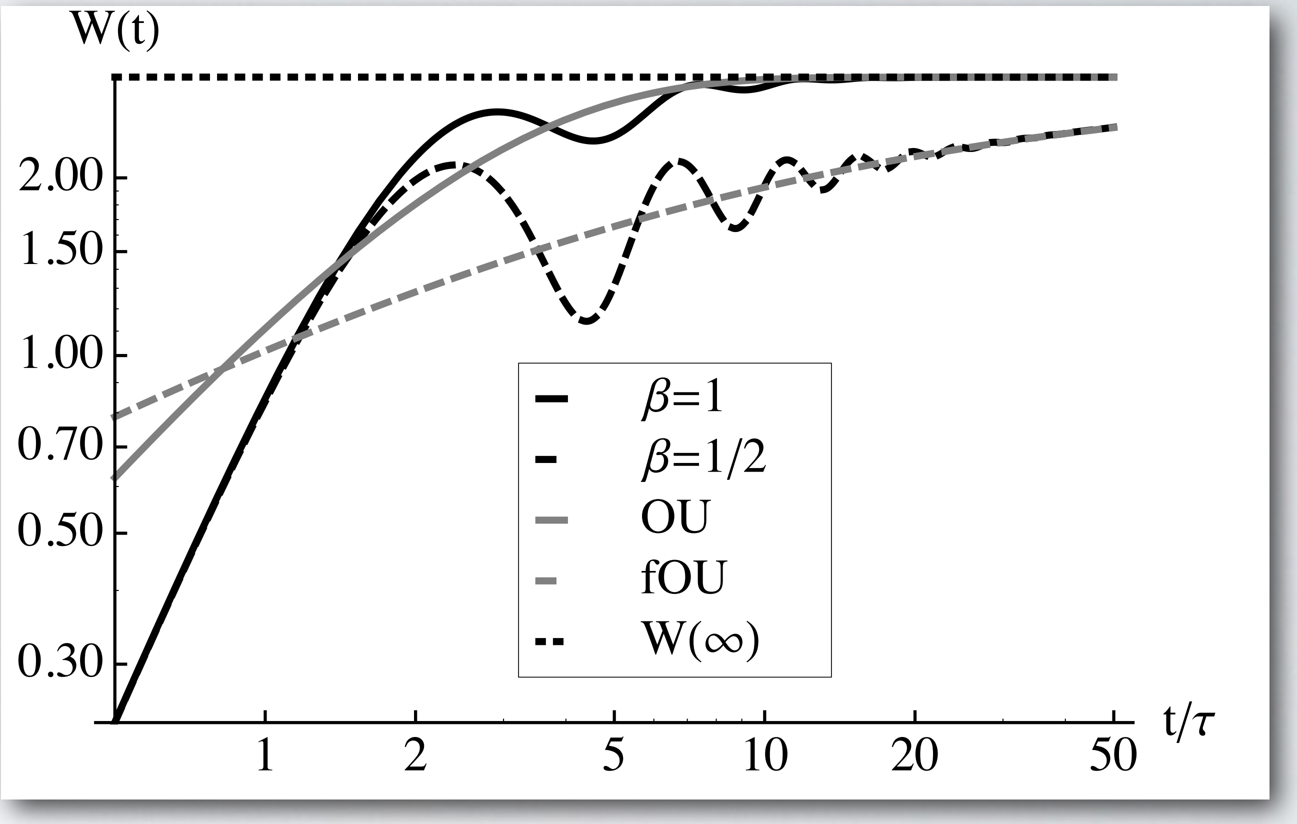
$$W_{(\mathrm{f})\mathrm{OU}}(t) = 2\langle \mathbf{u}^2 \rangle (1 - E_b(-[t/t_0]^b)), \quad 0 < b \leq 1,$$

Protein dynamics in optical tweezers

Jeon et al. PRL 106, 048103 (2011)



Simple analytical model



Systematic construction of relaxation rate spectra

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

$$c_{uu}(t) = \langle |\mathbf{u}|^2 \rangle \psi(t)$$

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

$$\hat{\psi}(s) = \int_0^\infty d\mu \, \frac{p(\mu)}{s+\mu},$$

$$p(\lambda) = \frac{1}{\pi} \lim_{\epsilon \to 0} \Im\{\hat{\psi}(-\lambda - i\epsilon)\}.$$

Stieltjes transform pair

This is the general form of p(λ):

$$p(\lambda) = f(\lambda) \frac{\sin(\pi\beta)}{\pi} \frac{\Gamma(1-\beta)}{\lambda^{1-\beta}} \quad (0 < \beta < 1).$$

$$\lim_{\lambda \to 0} f(\lambda) = \text{const.}$$

A special choice for f(λ)

$$f(\lambda) = \exp(-\beta\lambda)$$

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

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

$$\lim_{\beta\to\infty} \psi(t;\beta) = \exp(-t)$$

$$\lim_{\beta\to\infty} p(\lambda;\beta) = \delta(\lambda-1)$$

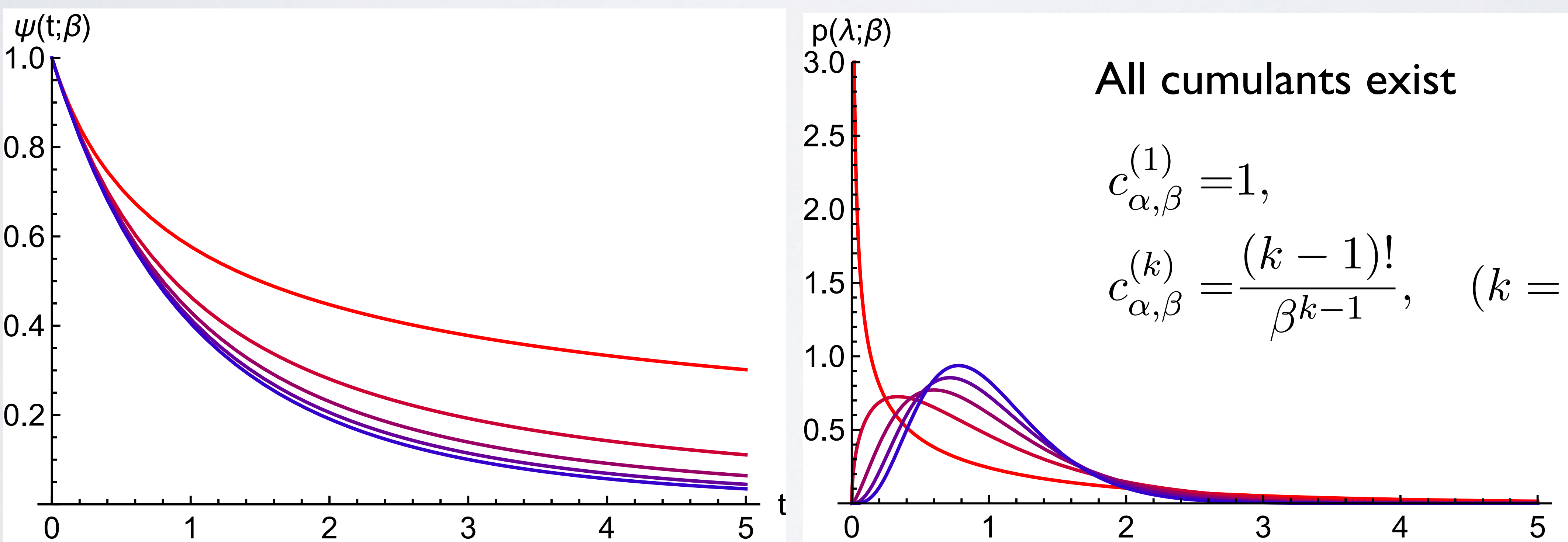
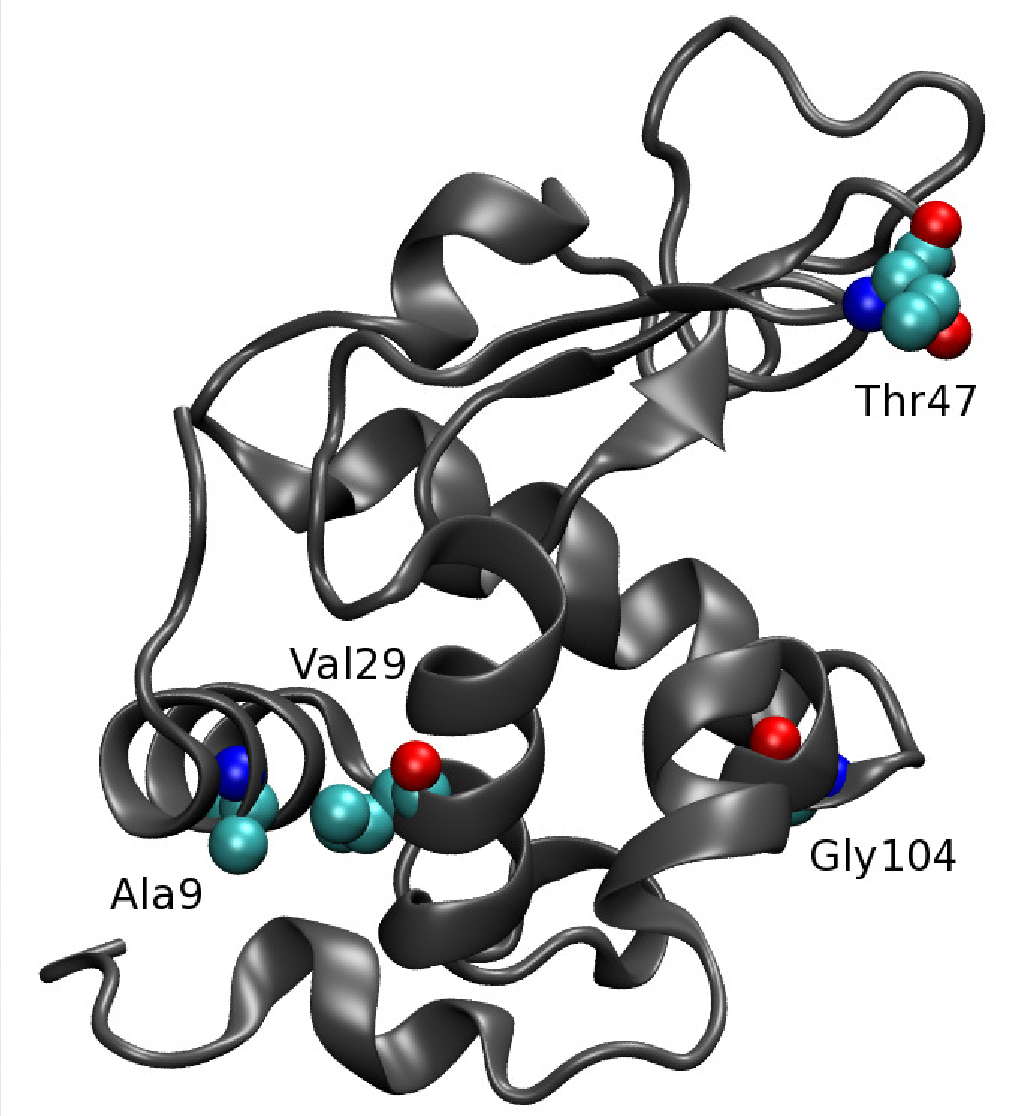
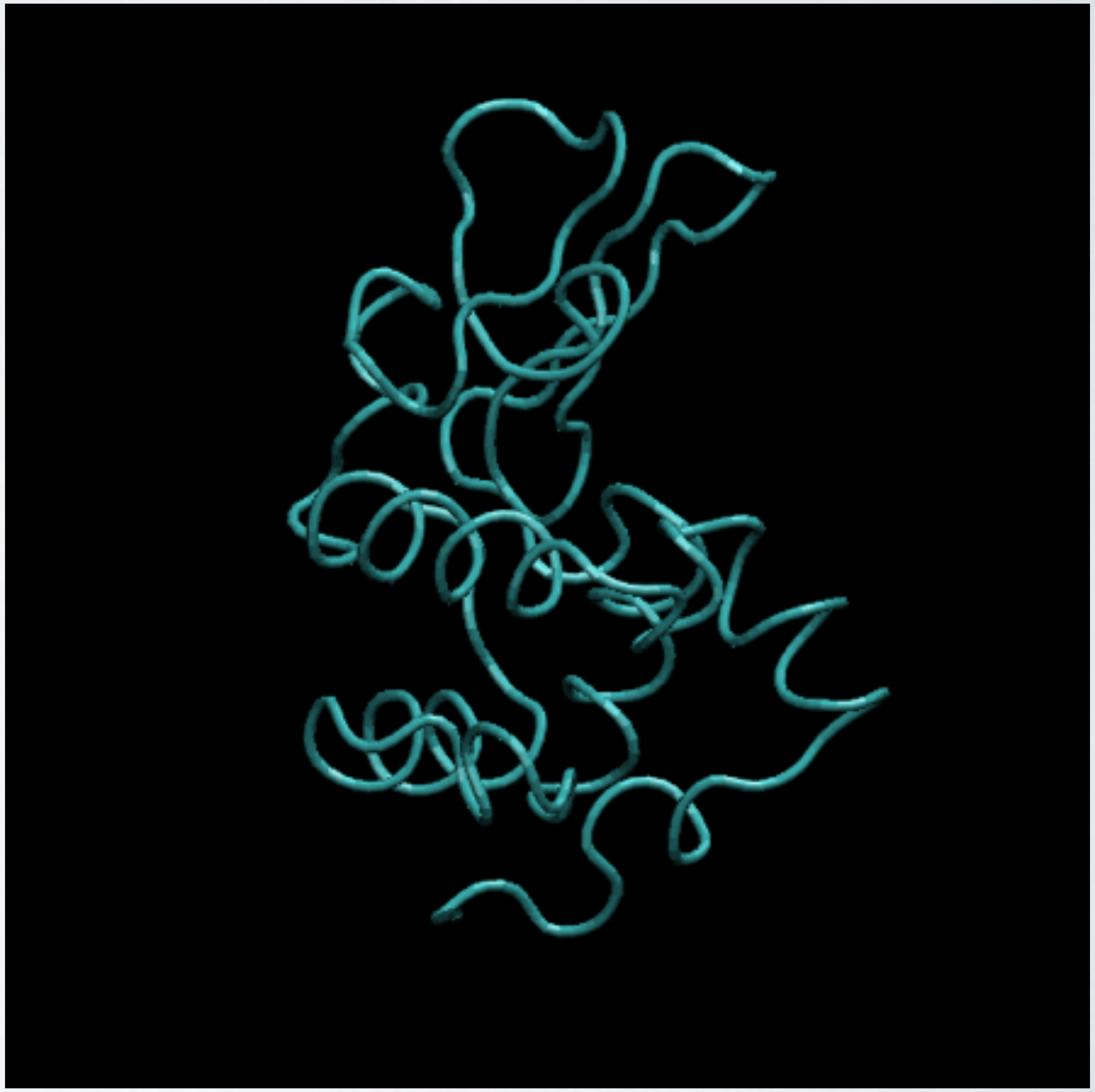


Fig. 8. **Left:** Normalized DACF $\psi(t;\beta)$ for $\beta = 0.5, 1.5, \ldots, 4.5$ (red to blue). **Right:** Corresponding relaxation spectra $p(\lambda;\beta)$.

Backbone relaxation dynamics in proteins

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



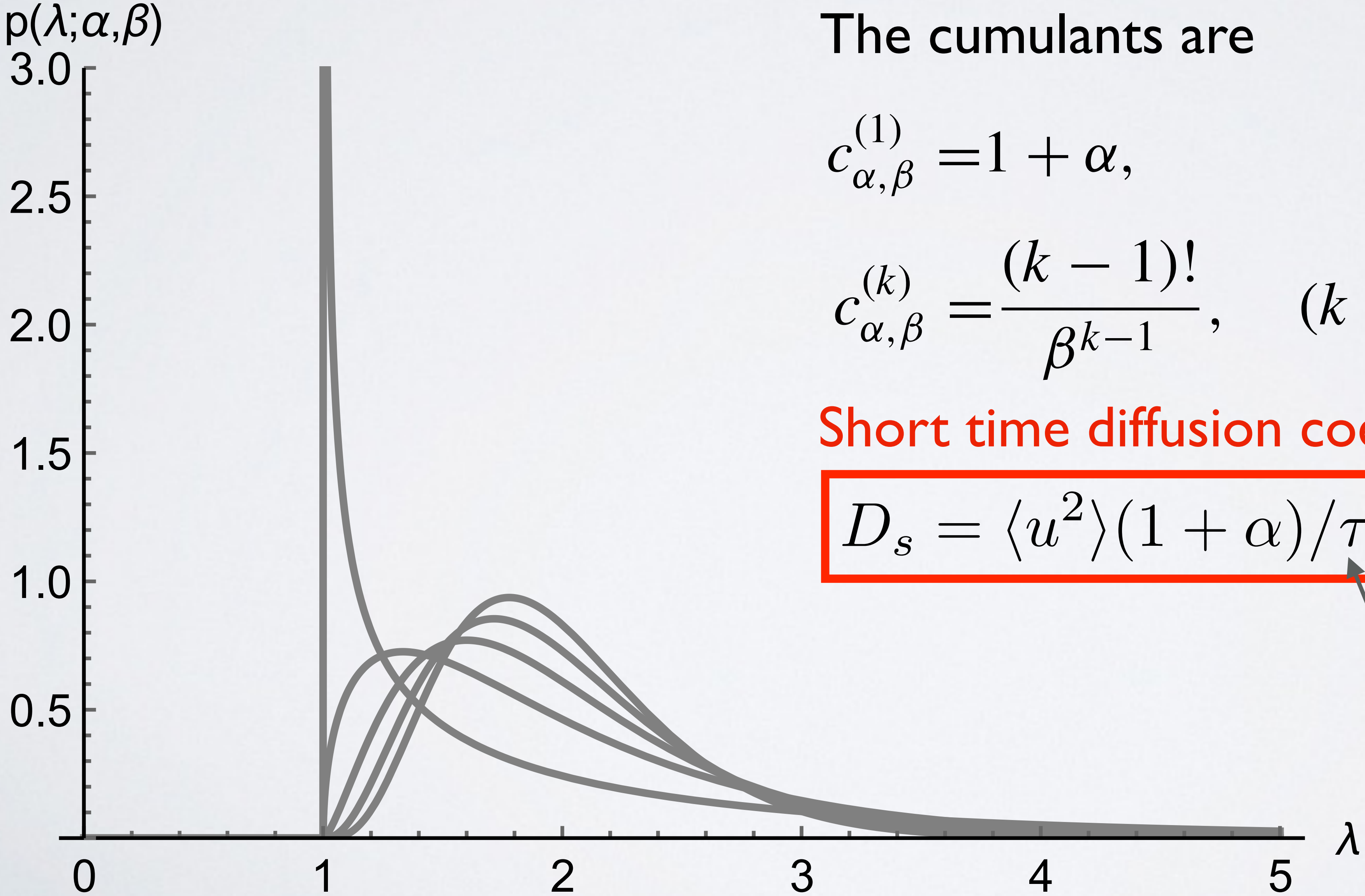


Refined relaxation model - introduce a cutoff for λ

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

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

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



The cumulants are

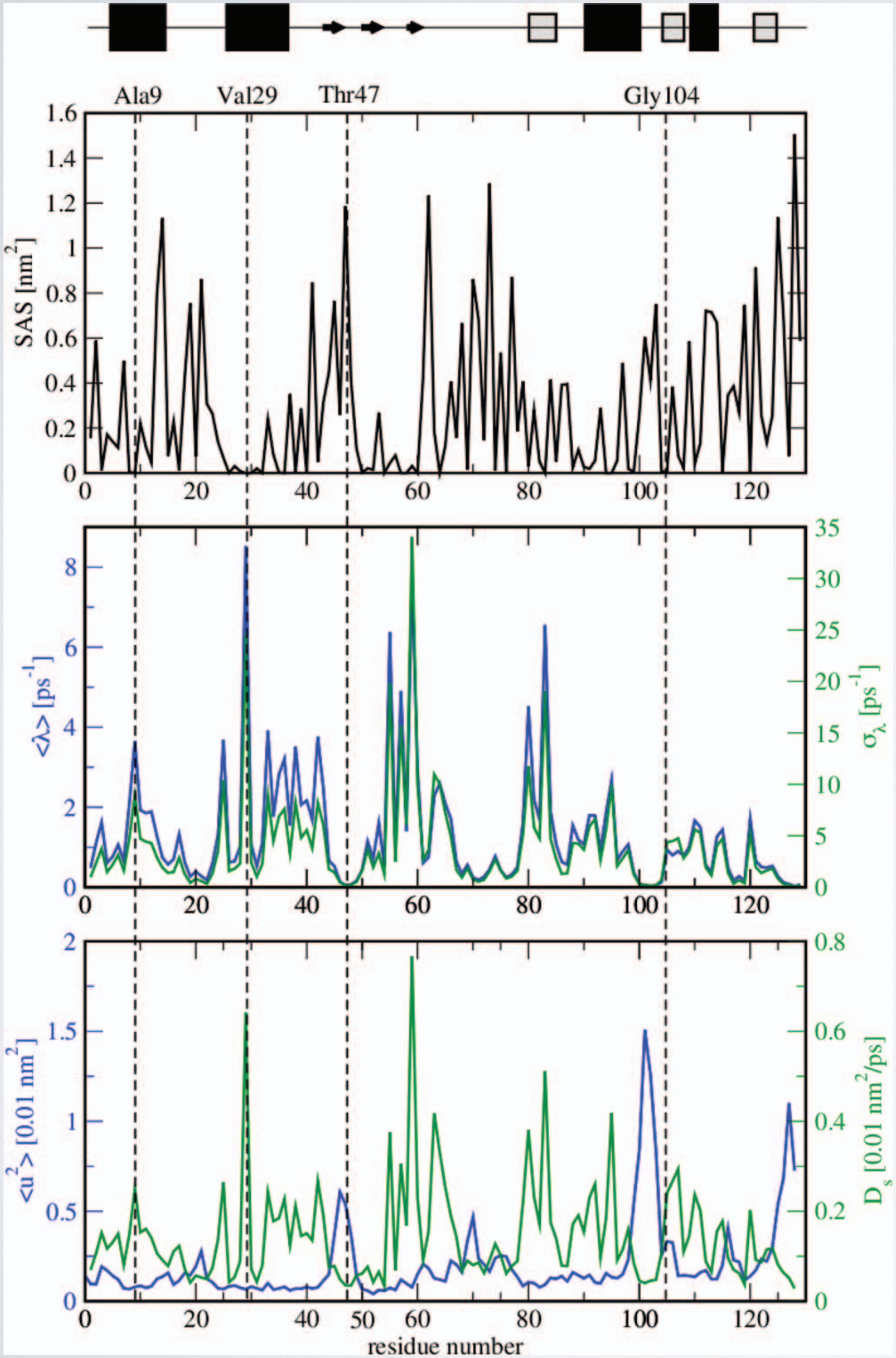
$$c^{(1)}_{\alpha,\beta} = 1+\alpha,$$

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

Short time diffusion coefficient

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

time scale



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

Solvent-accessible surfaces.

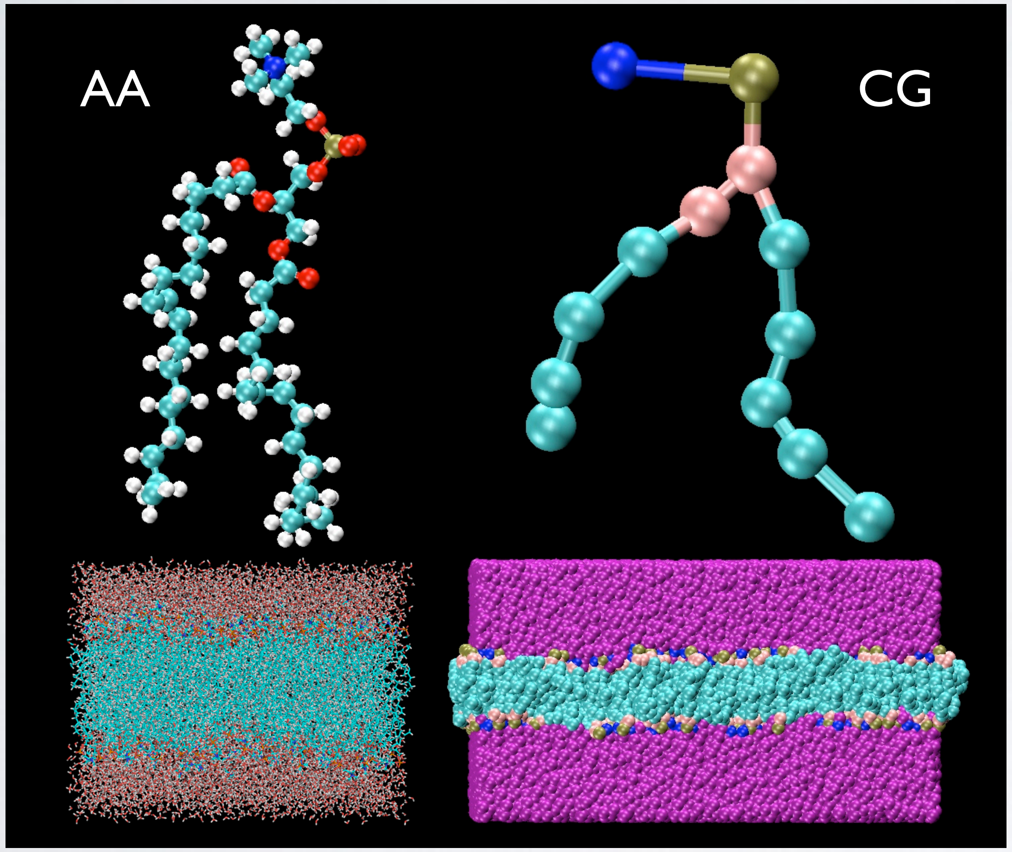
Mean relaxation rates, $\bar{\lambda}$, and corresponding spreads (green).

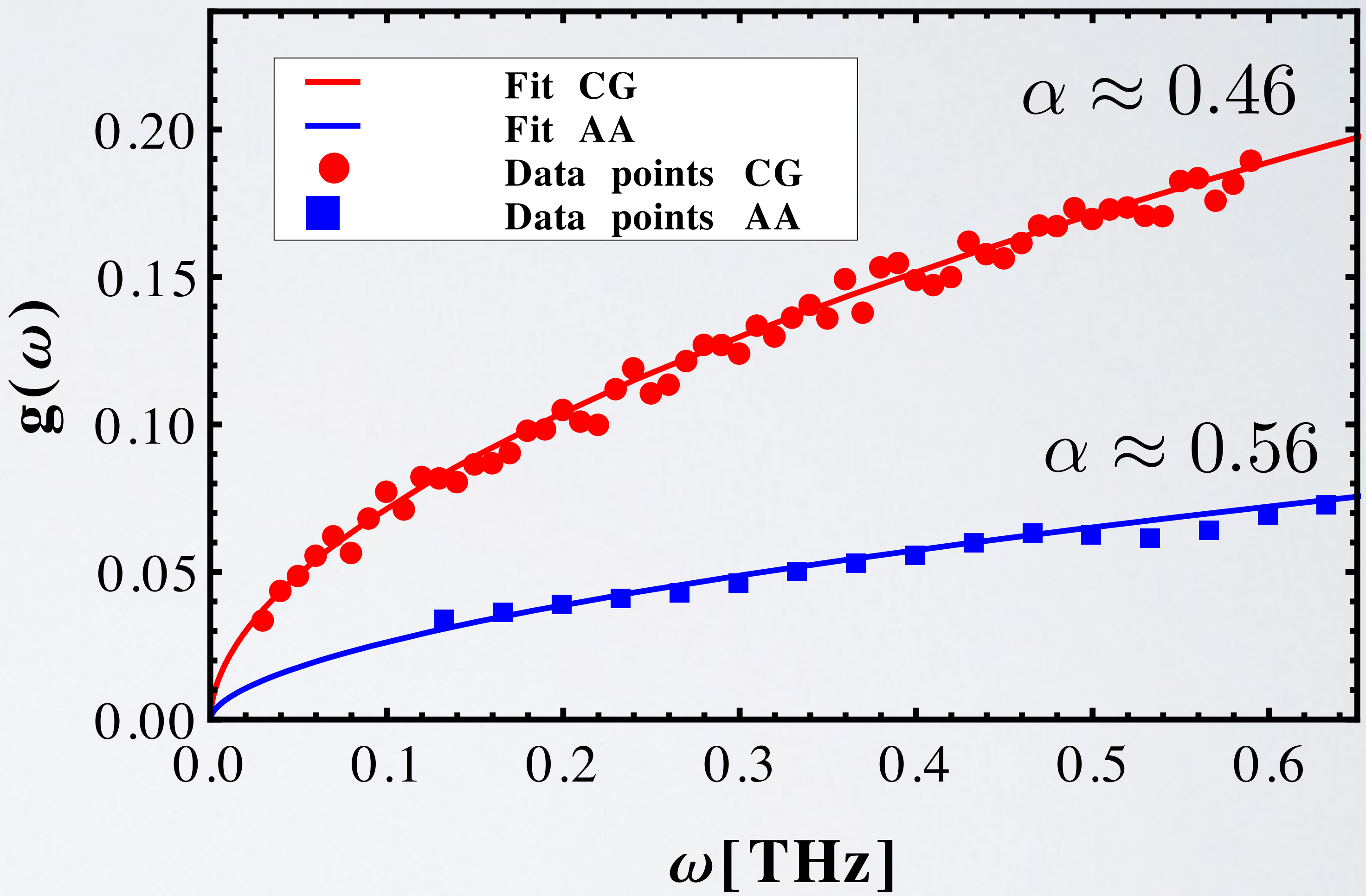
Mean square position fluctuations, $\langle \mathbf{u}^2 \rangle$, and short-time diffusion coefficients, D_s (green).

Anomalous diffusion in frequency space

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

Compare the DOS for POPC simulations with an all-atom (OPLS) and a coarse-grained (MARTINI) force field:





$$g(\omega) = \int_0^\infty dt\ \cos(\omega t) c_{vv}(t) \overset{\omega \ll 1/\tau_v}{\sim} n D_\alpha\, \omega^{1-\alpha} \sin\left(\frac{\pi\alpha}{2}\right)$$

CONCLUSIONS

- The combination of physical models (GLE) and **asymptotic analysis** allows for a rigorous definition of transport coefficients and yields insight into the diffusion process in terms of « caging effects ».
  - Free and confined diffusion can be handled
  - Relaxation spectra can be constructed systematically
  - Yields the asymptotic form for tha DOS at low frequencies
  - Compatible with quantum description
- Develop simple models to interpolate between the (known) short time and the long time regime of time correlation functions

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http://dirac.cnrs-orleans.fr/sputnik/home/

Fractional Smoluchowski equation

$$\frac{\partial}{\partial t} p(\mathbf{r}, t|\mathbf{r}_0, 0) = \partial_t^{1-\rho} \mathcal{L} p(\mathbf{r}, t|\mathbf{r}_0, 0)$$

$$\mathcal{L} = D_\rho \frac{\partial}{\partial \mathbf{r}} \cdot \left\{ \frac{\partial}{\partial \mathbf{r}} + \frac{1}{k_B T} \frac{\partial V(\mathbf{r})}{\partial \mathbf{r}} \right\}$$

1. **Free anomalous diffusion.** Here $V = 0$, $\rho \equiv \alpha$, $\boxed{0 \leq \alpha < 2}$
2. **Confined anomalous diffusion.** Here $V \neq 0$, $\rho \equiv \beta$, and $\boxed{\alpha = 0}$

MSD for confined (anomalous) diffusion (α=0)

$$\lim_{t \to \infty} W(t) = 2\langle |\mathbf{u}|^2 \rangle.$$

MSD tends to a plateau

$\mathbf{u}(t) = \mathbf{r}(t) - \langle \mathbf{r} \rangle$

$$W(t) = 2\{c_{uu}(0) - c_{uu}(t)\}$$

The diffusion is determined by the relaxation of $c_{uu}(t) = \langle \mathbf{u}(t) \cdot \mathbf{u}(0) \rangle$