ANOMALOUS DIFFUSION PROCESSES IN MEMBRANE TRANSPORT AND PROTEIN DYNAMICS: PHYSICAL INSIGHTS FROM A MATHEMATICAL THEOREM

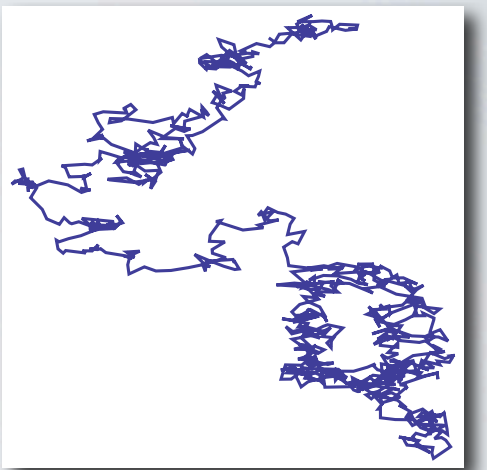
Gerald Kneller
Centre de Biophysique Moléculaire, CNRS Orléans
Université d'Orléans
Synchrotron Soleil, St Aubin

Outline

- Introduction: «Normal» diffusion and Brownian motion
- Asymptotic analysis of free anomalous diffusion, application to diffusion in membranes
- Anomalous, internal protein dynamics, examples from simulation and experiment
- Conclusions

Sub- and superdiffusion

$$W(t) = \left\langle [x(t) - x(0)]^2 \right\rangle \overset{t\to\infty}{\to} 2D_\alpha t^\alpha$$



$0 < \alpha < 1$: **sub**diffusion
(diffusion of molecules in membranes)

$\alpha = 1$: **normal** diffusion
(diffusion of molecules in liquids)

$1 < \alpha < 2$: **super**diffusion
(target-site search by DNA-binding proteins)

Diffusion and Brownian motion - the «classical» treatment...

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.

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

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

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

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

Diffusion and the Wiener process

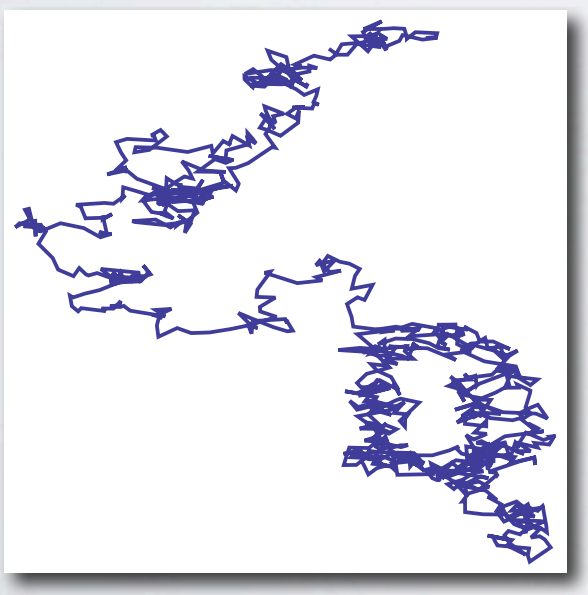
$$\partial_t P(x,t|x_0,0) = D\frac{\partial^2}{\partial x^2} P(x,t|x_0,0)$$

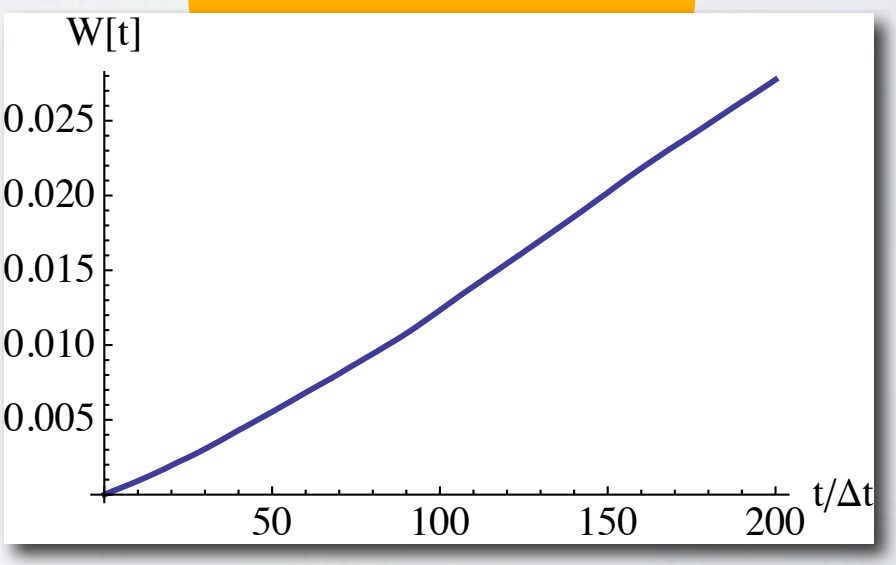
$$\boxed{x(t_0+\Delta t) = x(t_0) + \xi}$$

$$\boxed{\begin{aligned}\overline{\xi} &= 0 \\ \overline{\xi^2} &= 2D\Delta t\end{aligned}}$$

white noise

$$W(t) = 2Dt$$





Langevin's approach to diffusion

P. Langevin, *C. Rendus Acad. Sci. Paris*, vol. 146, pp. 530–533, 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.

$$m\frac{d^2x}{dt^2} = -6\pi\mu a\frac{dx}{dt} + X.$$

$$\overline{\Delta_x^2} = \overline{x^2} - \overline{x_0^2} = \frac{RT}{N}\frac{1}{3\pi\mu a}\tau;$$

Diffusion in velocity space - Rayleigh process

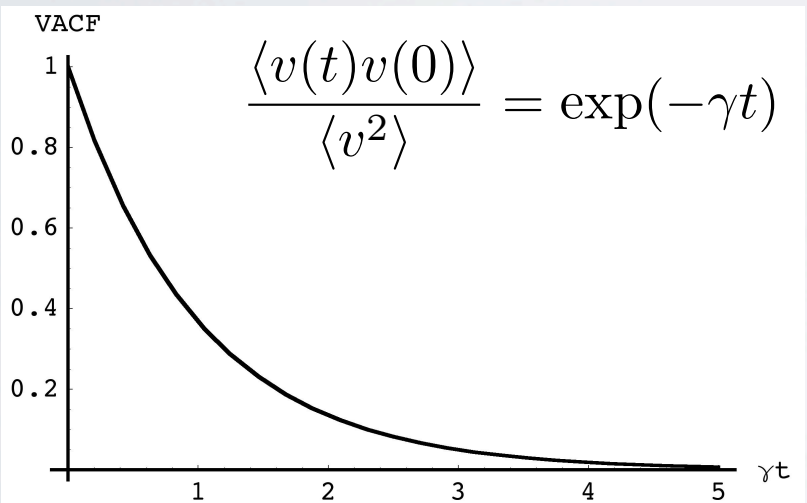
$$\frac{\partial P}{\partial t} = \gamma \frac{\partial}{\partial v}\left\{vP\right\} + \gamma \frac{k_B T}{M}\frac{\partial^2 P}{\partial v^2}$$

$$P \equiv P(v,t|v_0,0)$$

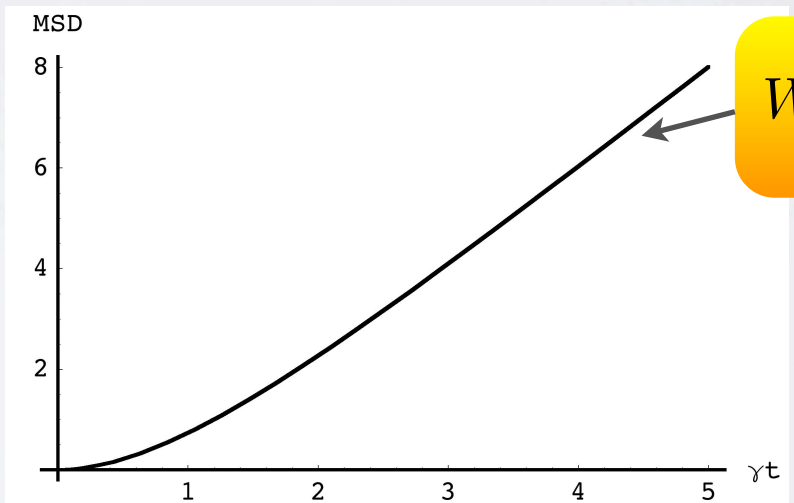
$$v(t_0+\Delta t) = v(t_0) - \Delta t \gamma v(t_0) + \xi$$

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

$$\overline{\xi^2} = 2\gamma \frac{k_B T}{M}\Delta t$$



$$\frac{\langle v(t)v(0)\rangle}{\langle v^2\rangle} = \exp(-\gamma t)$$



$$W(t) \approx 2\frac{k_B T}{M\gamma}t$$

FIGURE I.3. The normalised VACF $\psi(t)$ of a Brownian particle and the corresponding MSD.

Anomalous diffusion by *fractional* diffusion equations

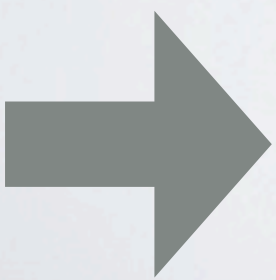
$$\partial_t P(x,t) + \frac{\partial J(x,t)}{\partial x} = 0$$

$$J(x,t) = -D\frac{\partial P(x,t)}{\partial x}$$

Normal free diffusion: Instantaneous response to a gradient in *P(x,t)*

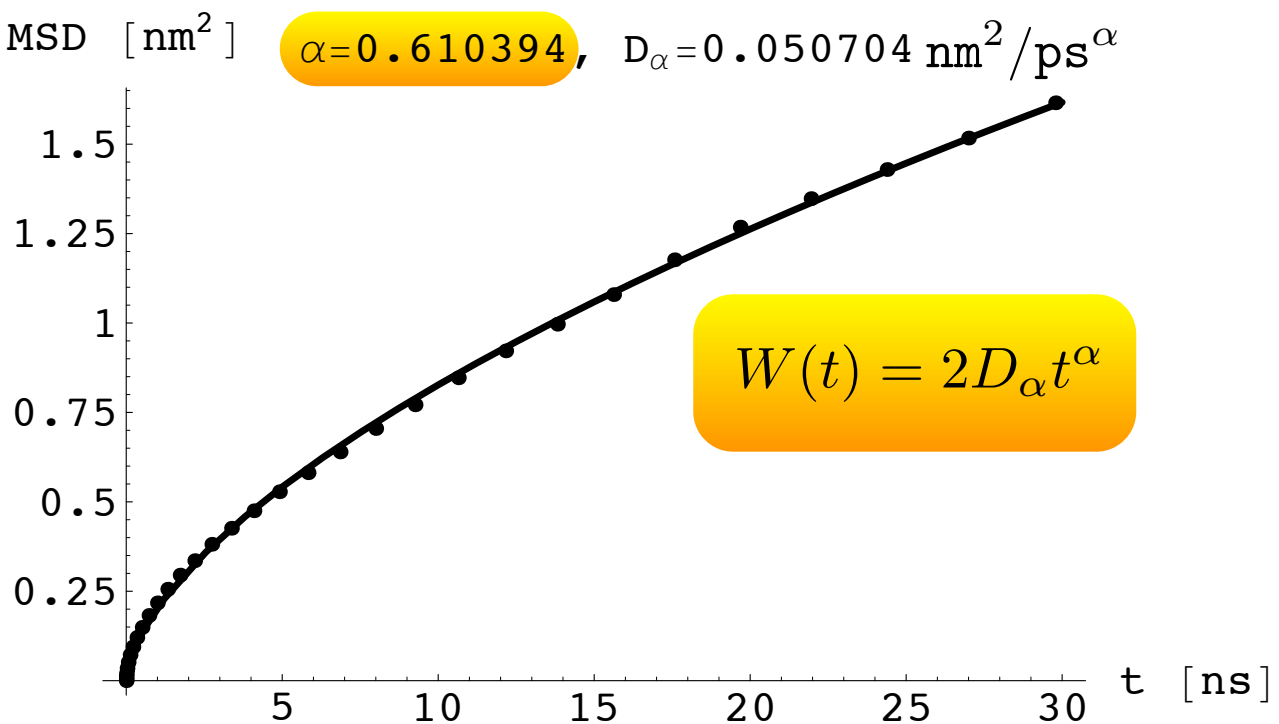
$$J(x,t) = -D_\alpha \frac{d}{dt}\int_0^t dt' \, \frac{(t-t')^{\alpha-1}}{\Gamma(\alpha)} \frac{\partial P(x,t')}{\partial x}$$

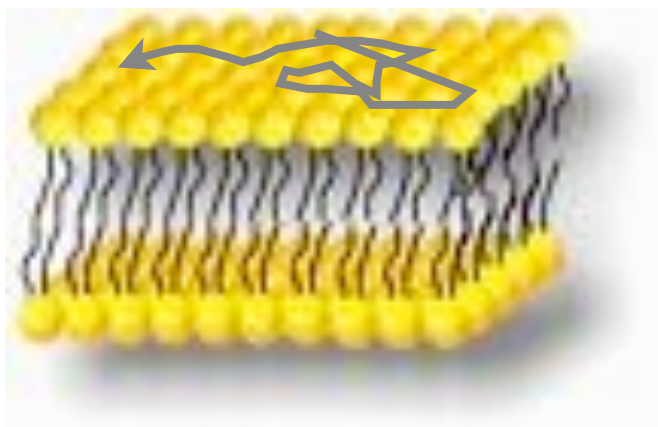
Anomalous free diffusion: Retarded response to a gradient in *P(x,t)*, representing *memory effects*.

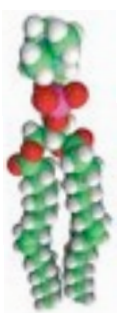


$$W(t) = 2D_\alpha t^\alpha$$

Lateral diffusion of molecules in a DOPC membrane







DOPC molecule

MD data from MP Pasenkiewicz-Gierula, Krakow University

Develop a physical picture of normal and anomalous diffusion, which is based considerations for the *asymptotic* behavior of the mean square displacement and on the (exact) Generalized Langevin Equation.

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

The *memory function*, $\kappa(t)$, and the «projected acceleration», $f^+(t)$, are described on the basis of classical Hamiltonian mechanics of the *full* system.

The physical interpretation of a memory function is that of a «cage».

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

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).

Infer the asymptotic form for the memory function and the VACF from the asymptotic form of the MSD (0<α<2)

$$W(t) \overset{t\to\infty}{\approx} L(t)t^{\alpha} \longleftrightarrow \hat{W}(s) \overset{s\to 0}{\approx} \frac{L(1/s)}{s^{\alpha+1}}$$

Tauberian theorem

$$\lim_{t\to\infty} \frac{L(\lambda t)}{L(t)} = 1 \qquad \hat{W}(s) = \int_0^\infty dt\, \exp(-st) W(t)$$

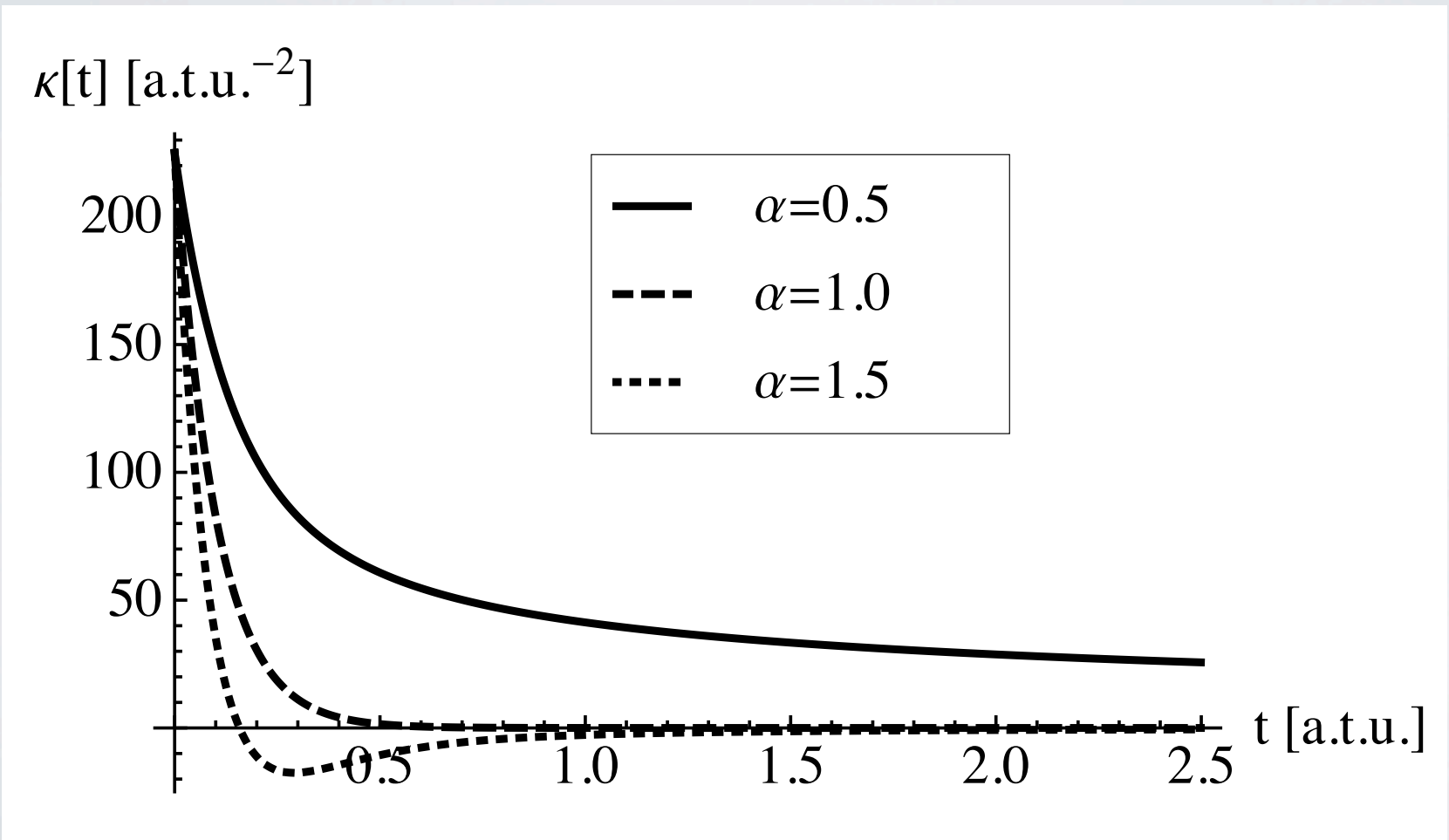
Use $L(t) \equiv 2D_\alpha$ and $\hat{W}(s) = \dfrac{2\hat{c}_{vv}(s)}{s^2} = \dfrac{2\langle v^2\rangle}{s^2(s+\hat{\kappa}(s))}$

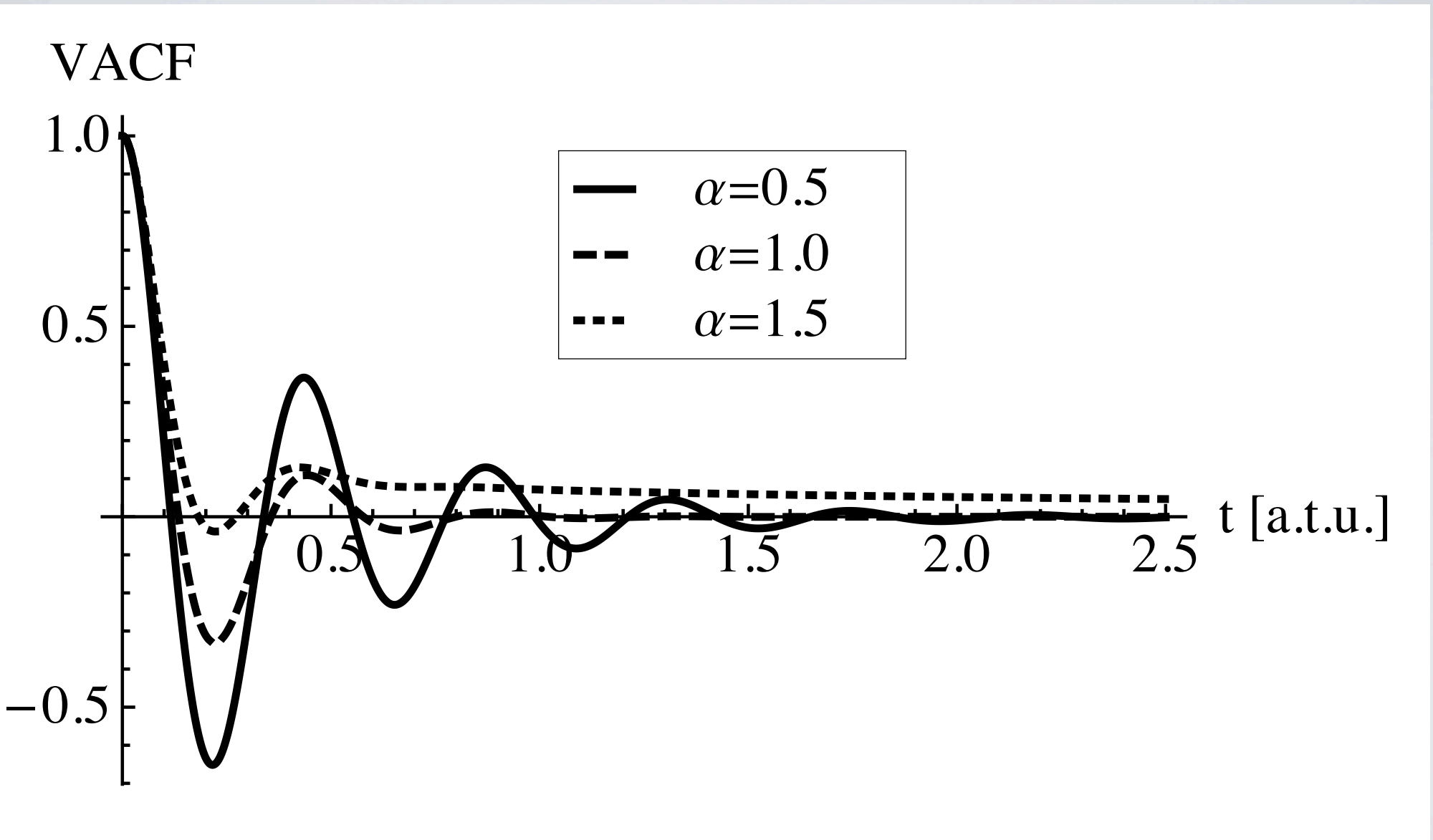
$$\kappa(t) \overset{t\gg\tau}{\approx} \Omega^2 C_\alpha \frac{(t/\tau)^{-\alpha}}{\Gamma(1-\alpha)}$$

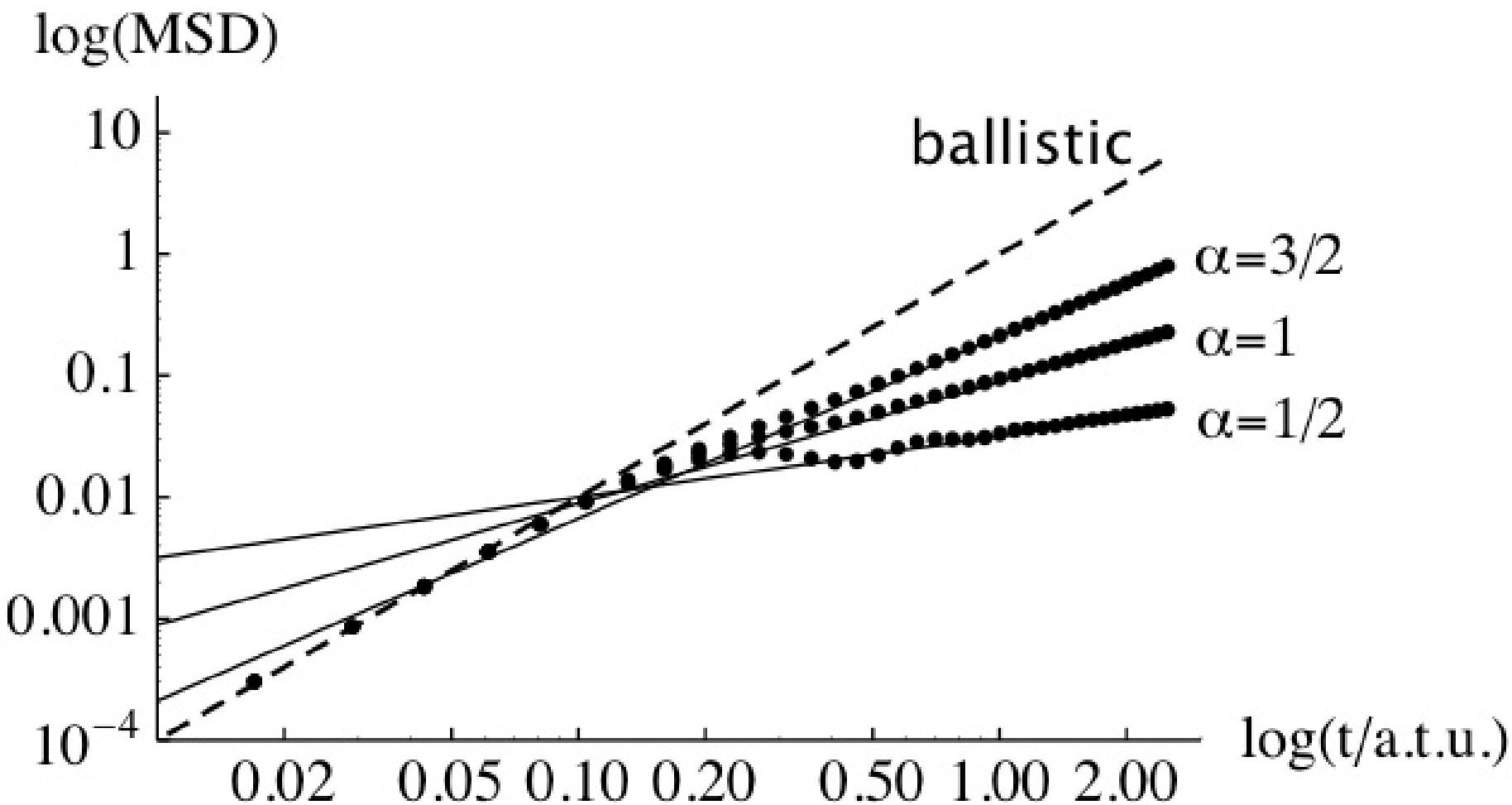
$$c_{vv}(t) \overset{t\gg\tau}{\approx} \alpha(\alpha-1) D_\alpha t^{\alpha-2}$$

Numerical example

Model memory function $\kappa(t) \overset{t\to\infty}{=} \begin{cases} \Omega^2 \dfrac{(t/\tau)^{-\alpha}}{\Gamma(1-\alpha)} & \text{if} \quad \alpha \neq 1 \\ \Omega^2 \exp(-t/\tau) & \text{if} \quad \alpha = 1 \end{cases}$




VACF
1.0
0.5
−0.5
0.5
1.0
1.5
2.0
2.5
t [a.t.u.]
α=0.5
α=1.0
α=1.5


log(MSD)
10
1
0.1
0.01
0.001
10^{-4}
ballistic
α=3/2
α=1
α=1/2
0.02
0.05
0.10
0.20
0.50
1.00
2.00
log(t/a.t.u.)

A model for DOPC

$$\kappa(t) = \Theta(t)\Omega^2 M(a, b, -t/\tau)$$

Model for the memory function

Kummer's function: $M(a, b, z) = \sum_{n=0}^{\infty} \frac{(a)_n}{(b)_n} \frac{z^n}{n!}$ $\qquad M(a, a, z) = \exp(z)$

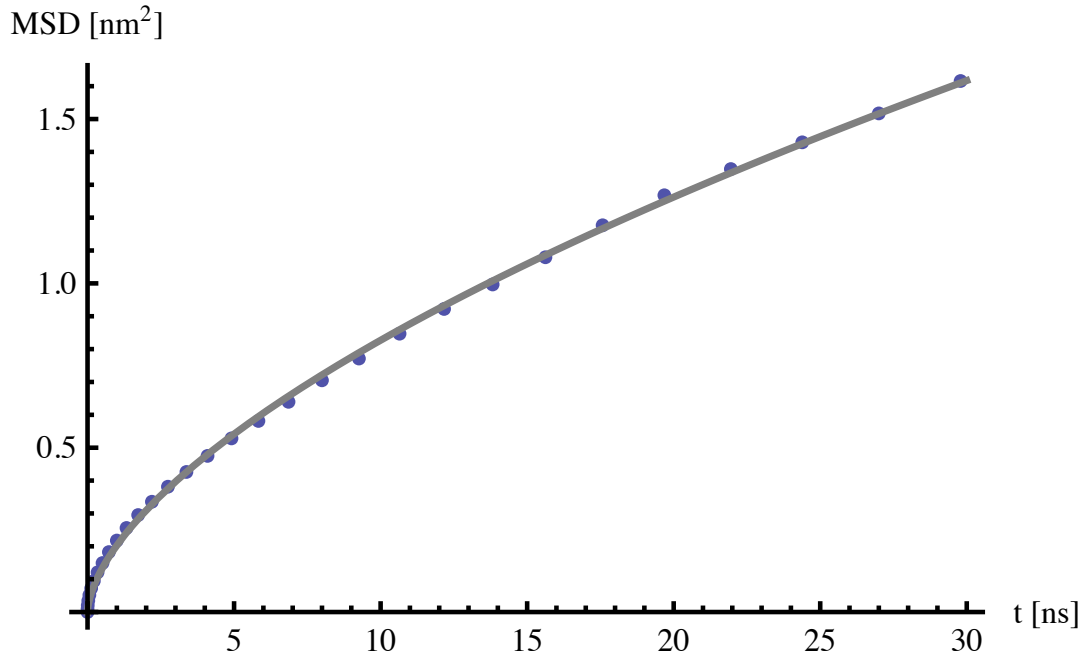
$$\kappa(t) \overset{t\to\infty}{\approx} \Omega^2 \frac{\Gamma(b)}{\Gamma(b-a)} (t/\tau)^{-a} \quad \text{if } a \neq b$$

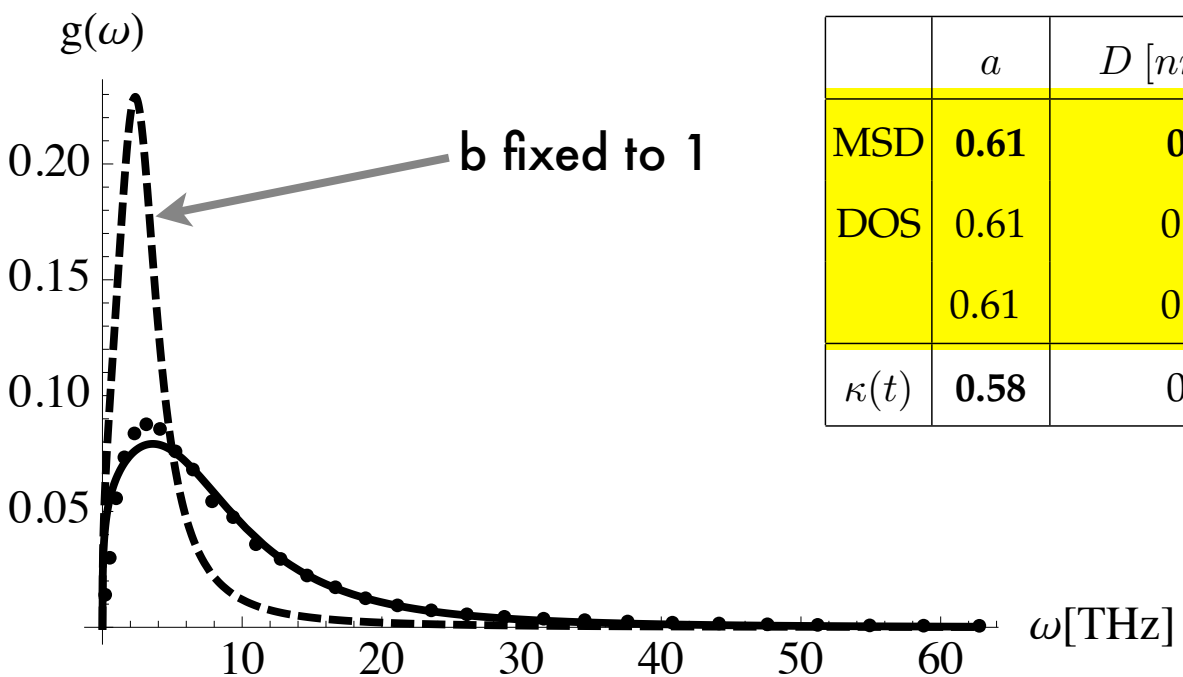
$$c_{vv}(t) = \langle v^2 \rangle \int_0^{\infty} d\omega\, g(\omega) \cos(\omega t)$$

VACF

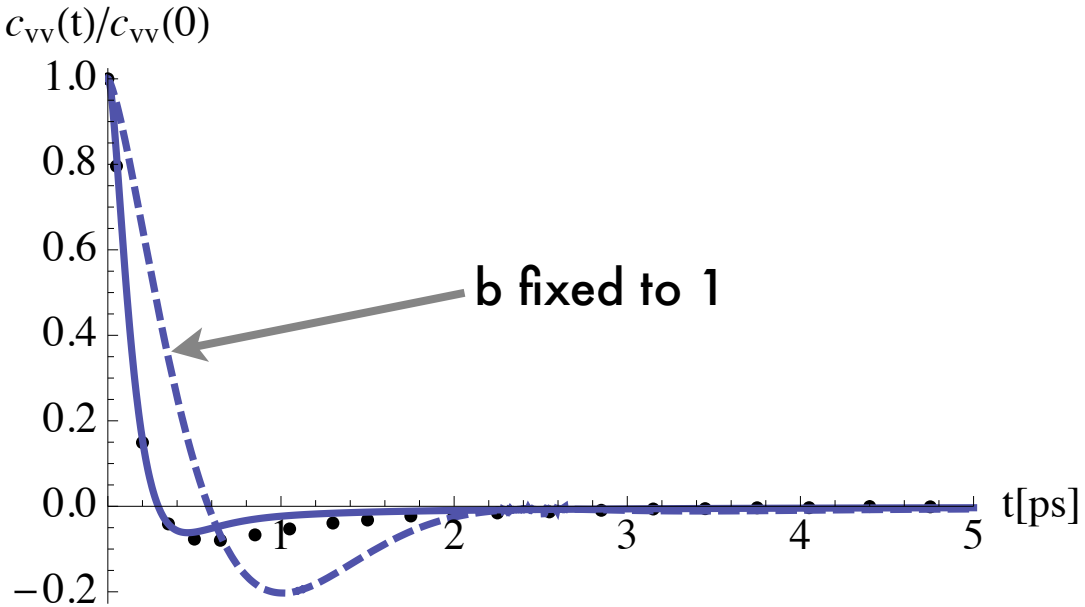
$$g(\omega) = \Re \left\{ \frac{1}{i\omega + \frac{\Omega^2}{i\omega}\, {}_{(2)}F_{(1)}(1, a, b, -1/[i\omega\tau])} \right\}$$

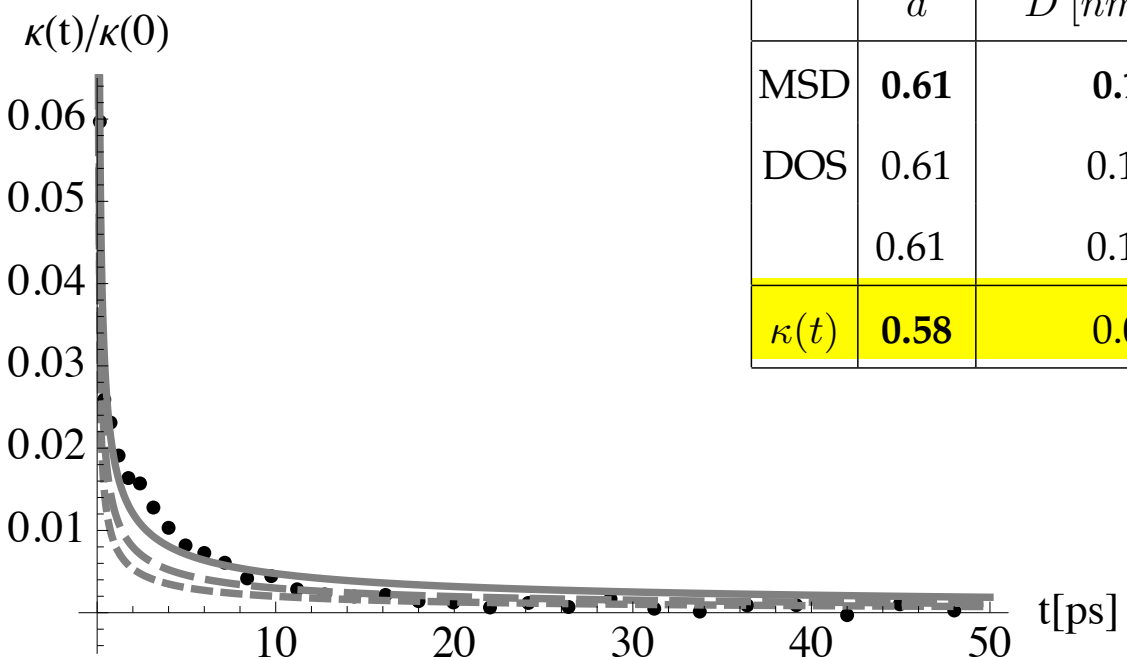
DOS





	a	$D\ [nm^2/ns^a]$	b	$\tau\ [ps]$	$\Omega\ [1/ps]$
MSD	**0.61**	**0.101**			
DOS	0.61	0.101	**0.66**	**0.029**	**15.34**
	0.61	0.101	1.00	**0.0028**	**26.03**
$\kappa(t)$	**0.58**	0.039	**0.70**	**0.021**	15.91





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MSD	**0.61**	**0.101**			
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	0.61	0.101	1.00	**0.0028**	**26.03**
$\kappa(t)$	**0.58**	0.039	**0.70**	**0.021**	15.91

Anomalous diffusive motions in proteins seen in experiments and simulations

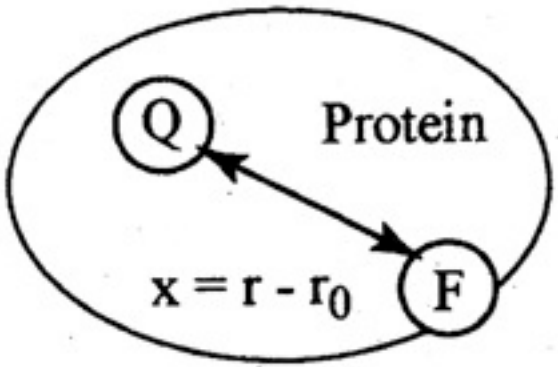
Fluorescence correlation spectroscopy

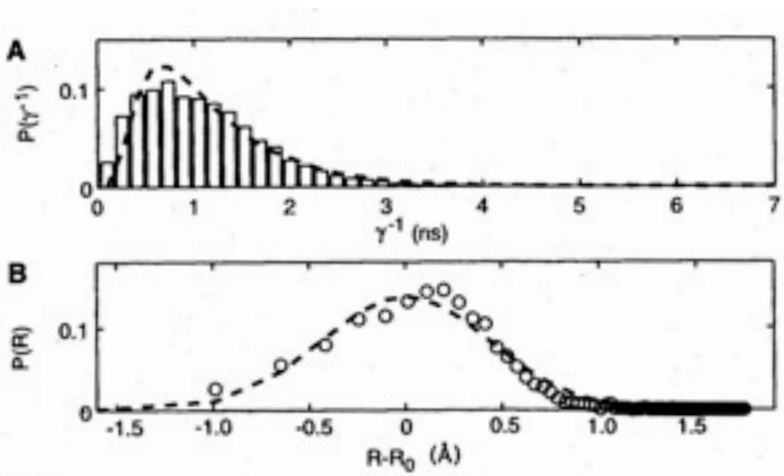
Protein Conformational Dynamics Probed by Single-Molecule Electron Transfer

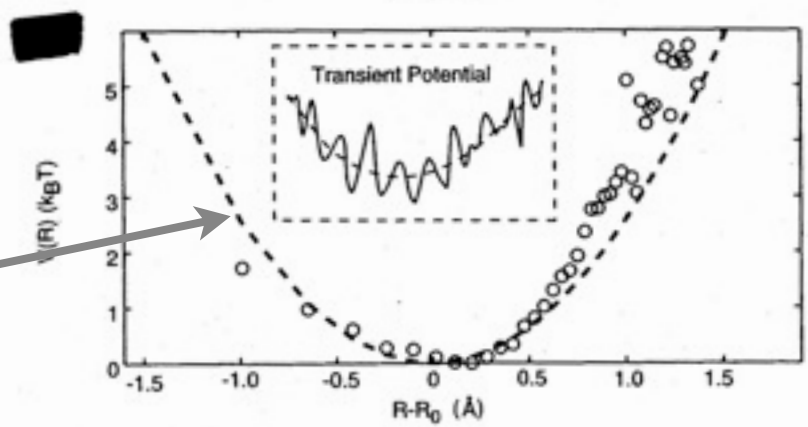
Haw Yang,[1]* Guobin Luo,[1] Pallop Karnchanaphanurach,[1] Tai-Man Louie,[2] Ivan Rech,[3] Sergio Cova,[3] Luying Xun,[2] X. Sunney Xie[1]†

Electron transfer is used as a probe for angstrom-scale structural changes in single protein molecules. In a flavin reductase, the fluorescence of flavin is quenched by a nearby tyrosine residue by means of photo-induced electron transfer. By probing the fluorescence lifetime of the single flavin on a photon-by-photon basis, we were able to observe the variation of flavin-tyrosine distance over time. We could then determine the potential of mean force between the flavin and the tyrosine, and a correlation analysis revealed conformational fluctuation at multiple time scales spanning from hundreds of microseconds to seconds. This phenomenon suggests the existence of multiple interconverting conformers related to the fluctuating catalytic reactivity.

10 OCTOBER 2003 VOL 302 SCIENCE www.sciencemag.org



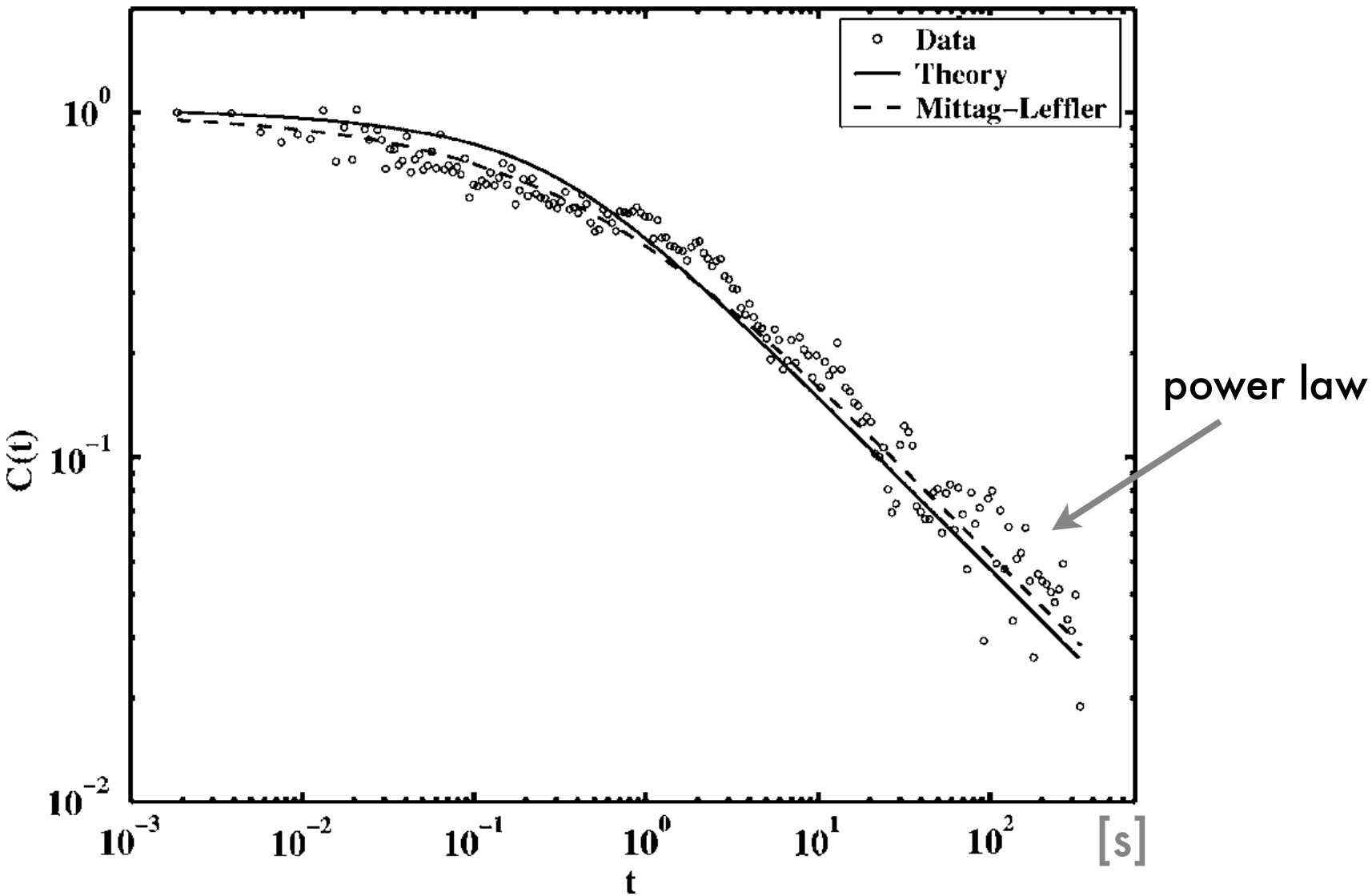




$$V(R) = \frac{1}{2}K(R - R_0)^2$$

$$K \approx 2N/m$$

Non-exponential position correlation function



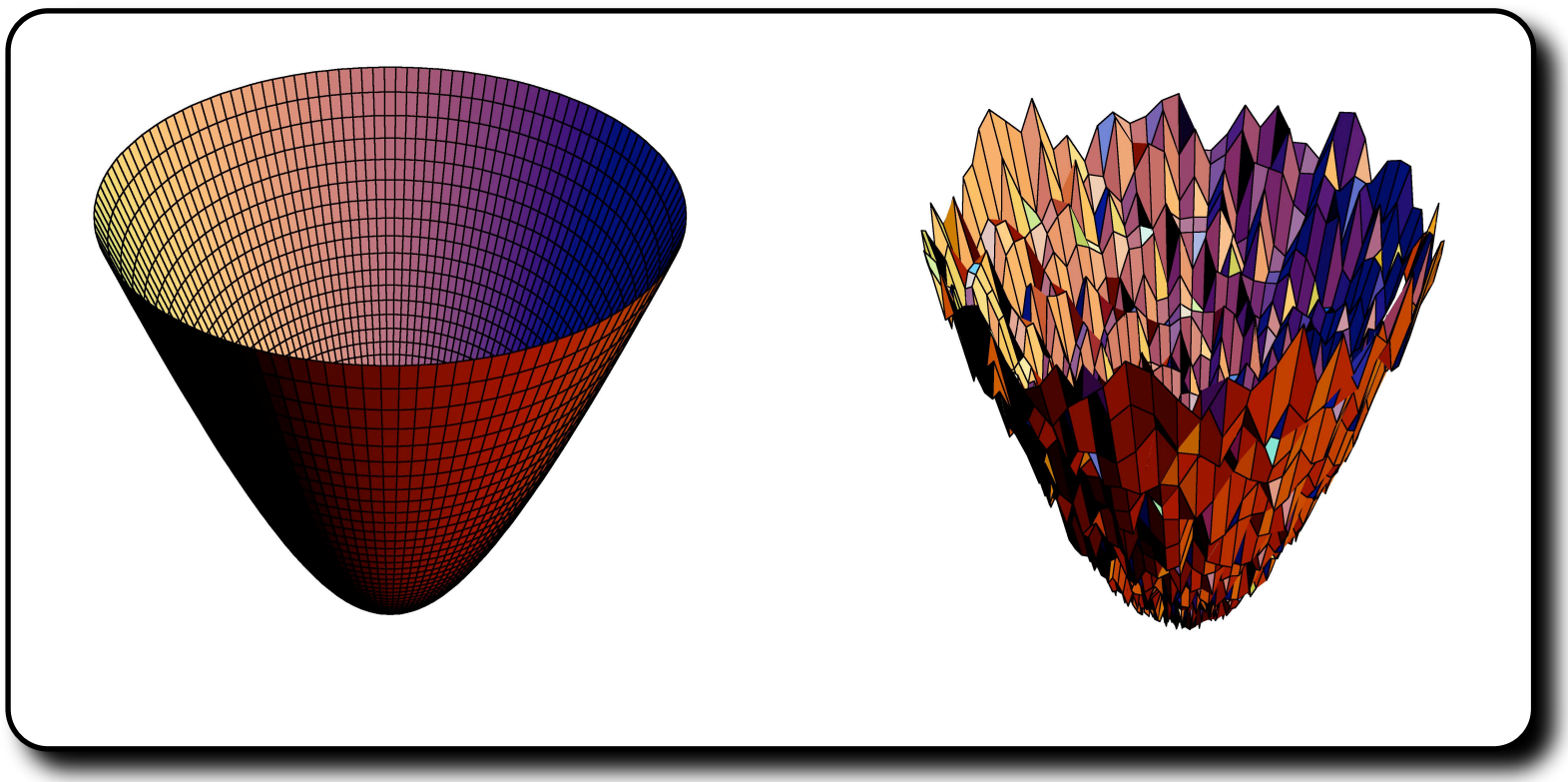
power law

P. Debnath, M. Wei, S. Xie, and B.J. Cherayil. *J. Chem. Phys.*, 123:204903, 2005.

Fractional Brownian dynamics

Diffusion in a smooth harmonic potential : Ornstein-Uhlenbeck process [1]

Diffusion in a "rugged" harmonic potential : Fractional Ornstein-Uhlenbeck process [2]



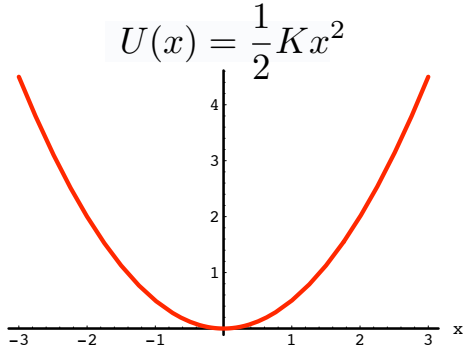
[1] M.C. Wang and G.E. Uhlenbeck. On the theory of Brownian motion II. Phys. Rev., 93(1):249–262, 1945.

[2] R. Metzler and J. Klafter. The random walk's guide to anomalous diffusion: A fractional dynamics approach. *Phys. Rep.*, 339:1–77, 2000.

Anomalous diffusion in a harmonic potential (fractional Ornstein-Uhlenbeck process)

- **Diffusion equation**

$$\frac{\partial P(x,t)}{\partial t} + \frac{\partial J(x,t)}{\partial x} = 0$$



$$F(x) = -\frac{\partial U}{\partial x}$$

$$J(x,t) = -D\frac{P(x,t)}{\partial x} + \frac{D}{k_B T}F(x)P(x,t)$$

- **Fractional diffusion equation**

$$\frac{\partial P(x,t)}{\partial t} + \frac{\partial \tilde{J}(x,t)}{\partial x} = 0$$

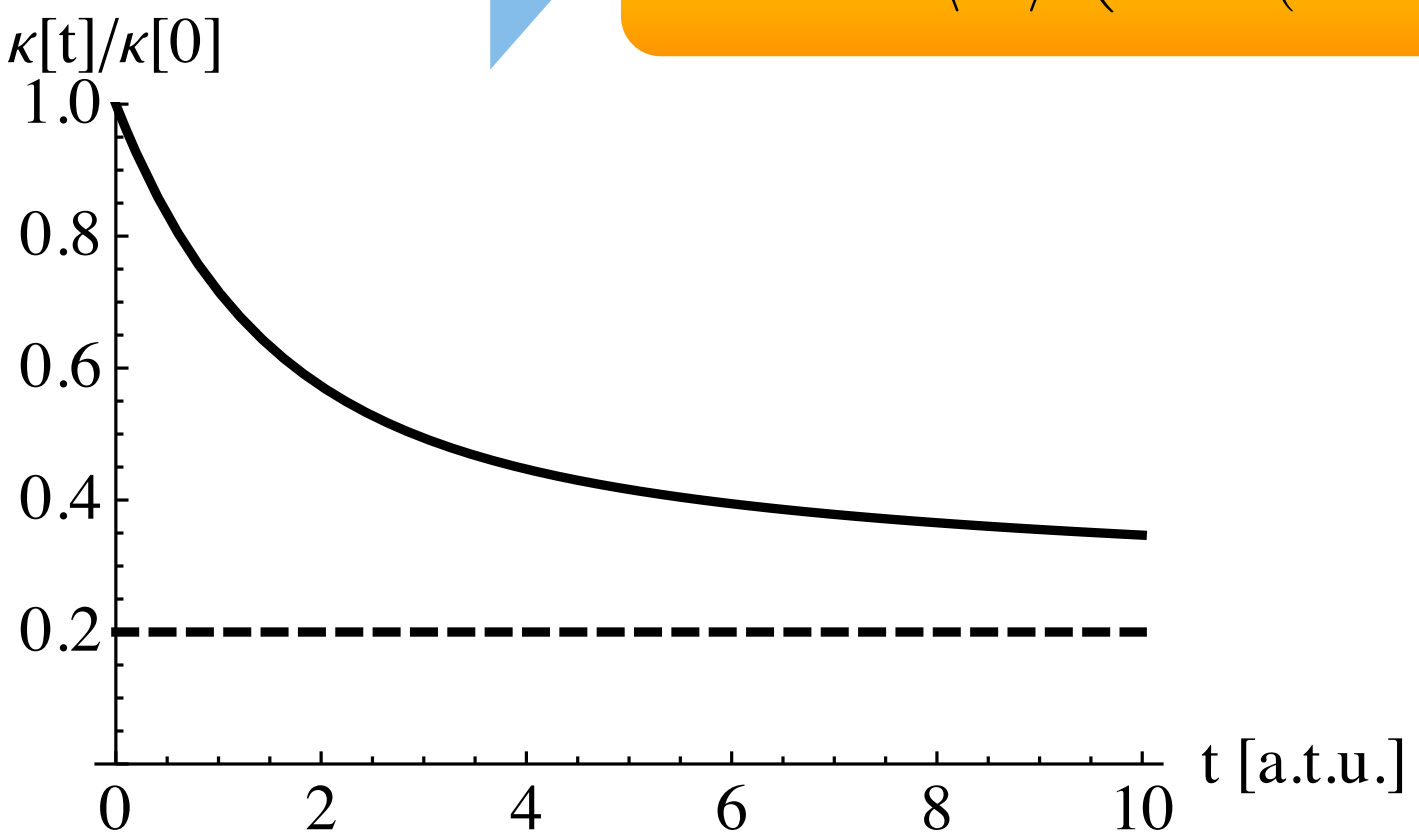
memory effects through fractional derivative

$$\tilde{J}(x,t) = \tilde{\tau}^{1-\alpha}\frac{d}{dt}\int_0^t d\tau\,\frac{(t-\tau)^{\alpha-1}}{\Gamma(\alpha)}J(x,\tau)$$

Referring to the cage model....

$$W(t) \overset{t\to\infty}{\approx} 2\langle x^2\rangle \left(1 - \frac{[t/\tau]^{-\alpha}}{\Gamma(1-\alpha)}\right)$$

$$\kappa(t) \overset{t\to\infty}{\approx} \frac{\langle v^2\rangle}{\langle x^2\rangle} \left(1 + \frac{[t/\tau]^{-\alpha}}{\Gamma(1-\alpha)}\right)$$

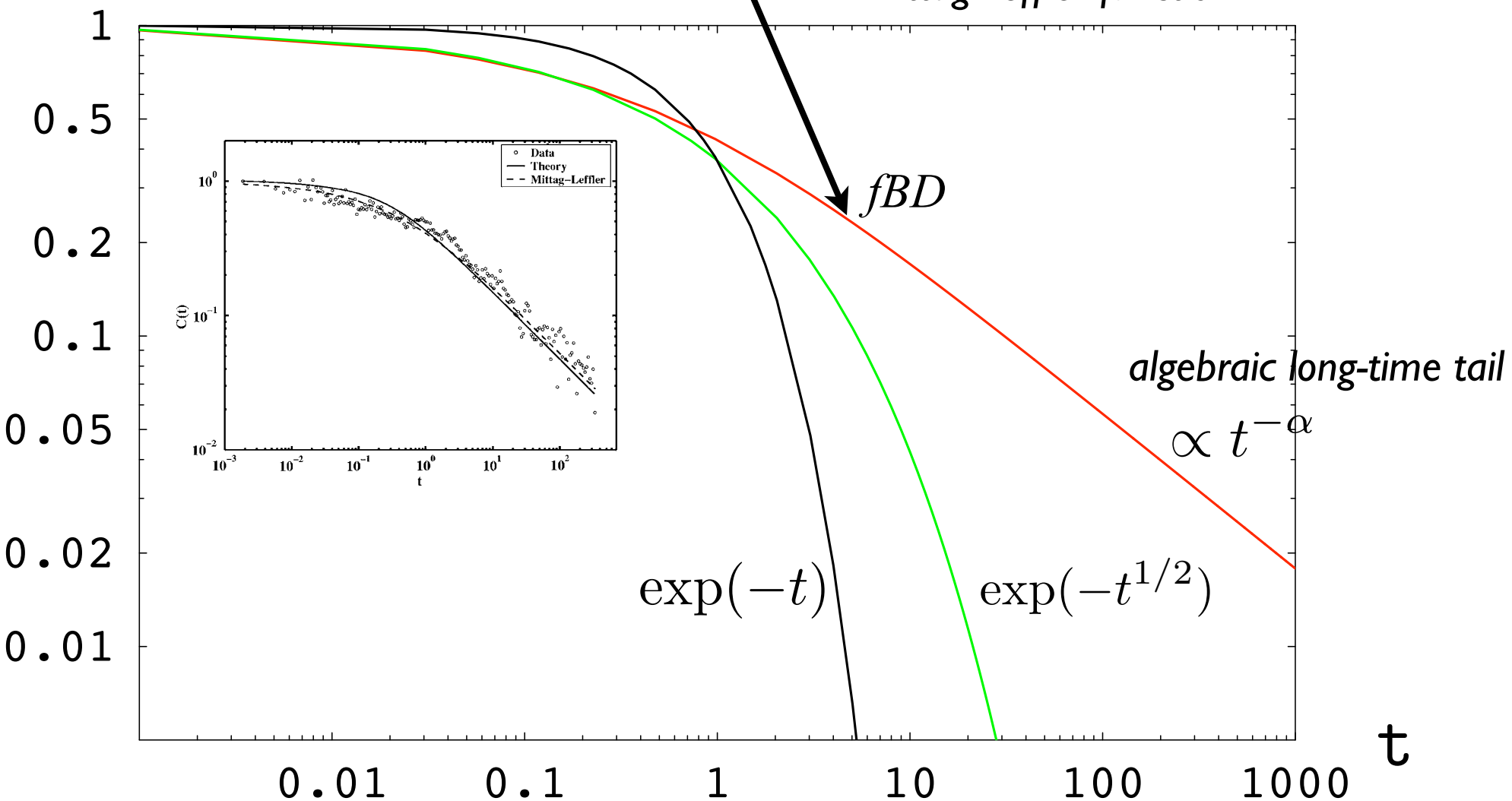


Model correlation function (α=0.5)

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

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

Mittag-Leffler function



Fractional reaction kinetics

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

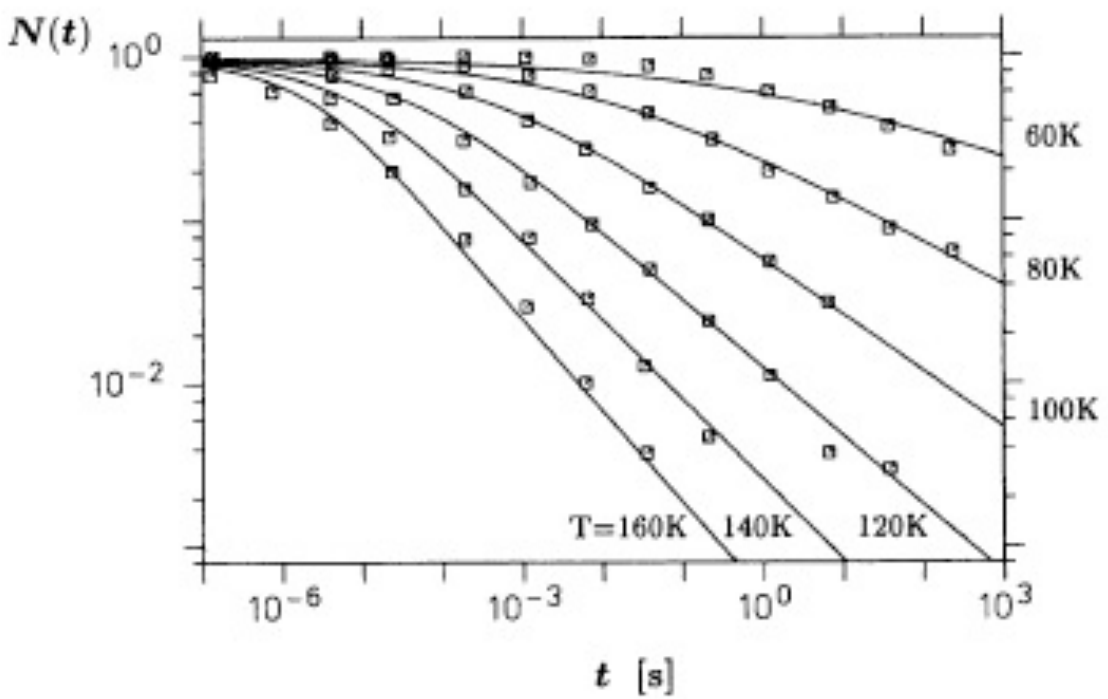
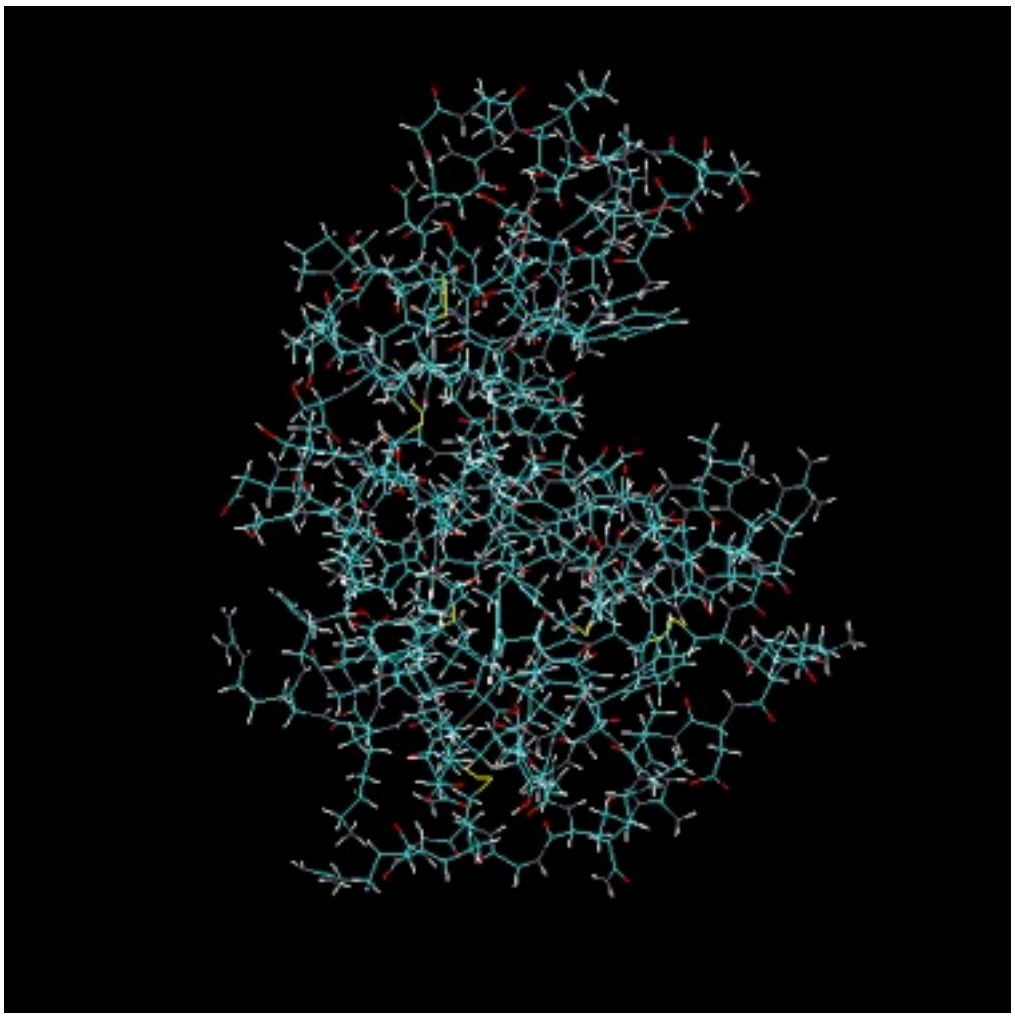


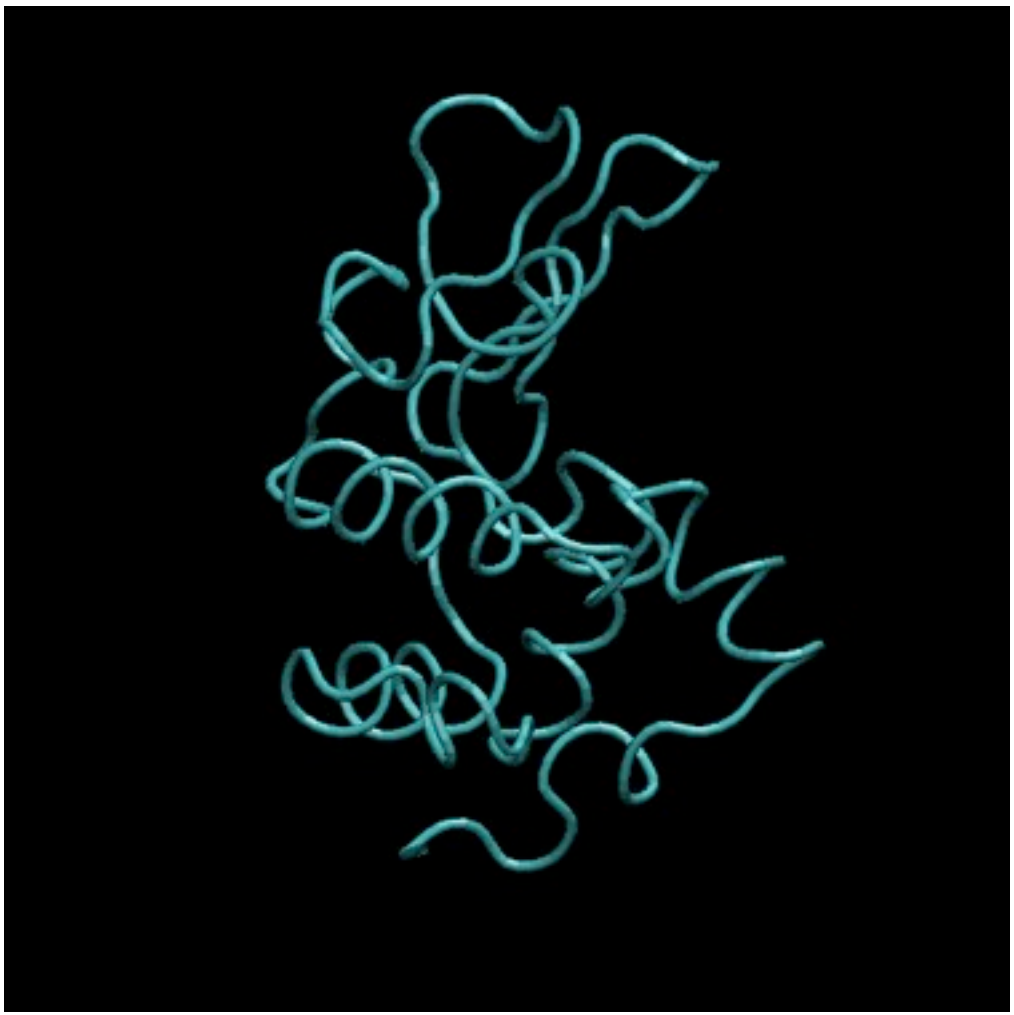
FIGURE 2 Three-parameter model Eq. 32 for rebinding of CO to Mb after photo dissociation. The parameters are $\tau_m = 8.4 \times 10^{-10}$s, $\alpha = 3.5 \times 10^{-3}\ K^{-1}$ and $k = 130$, the data points are from Austin et al. (1975).

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

Molecular dynamics simulations

Lysozyme

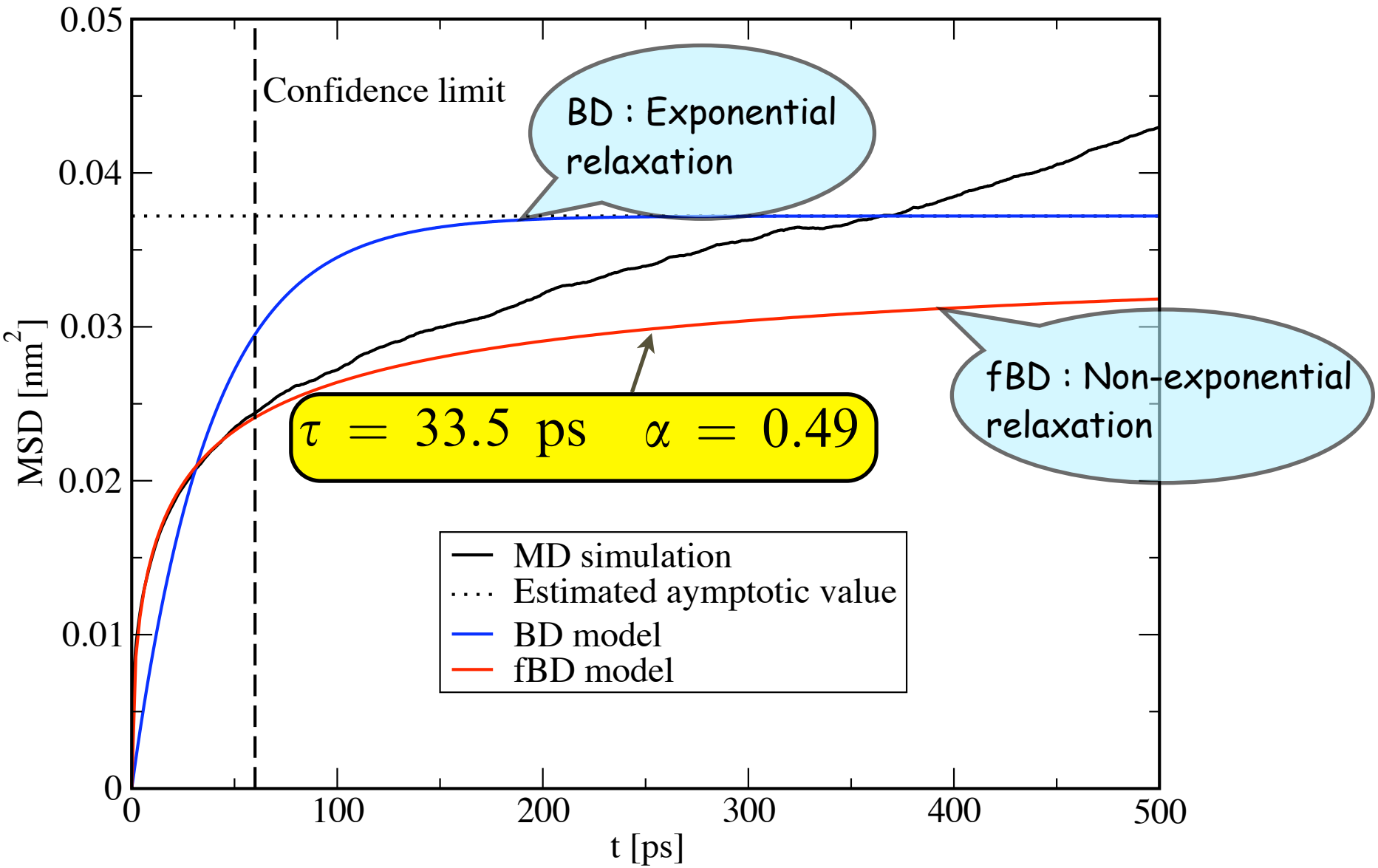




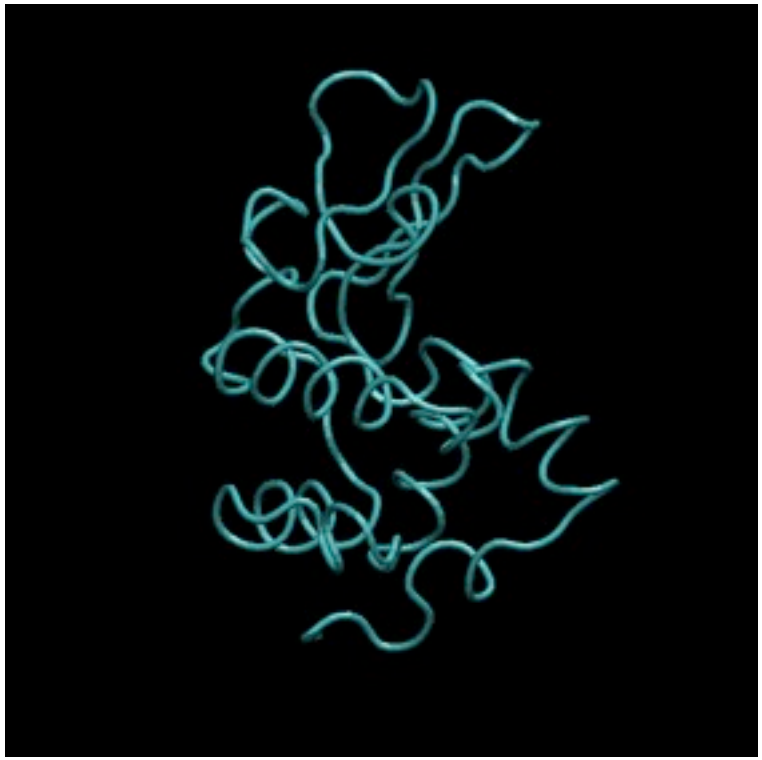
all atoms

main chain

Mean square displacement from MD



Collective motions



- Study collective motions

$$\psi(\mathbf{q},t)=\langle \delta\rho(\mathbf{q},t)\,\delta\rho(-\mathbf{q},0)\rangle$$

Density fluctuation $\delta\rho(\mathbf{q},t)=\rho(\mathbf{q},t)-\langle\rho(\mathbf{q},t)\rangle$

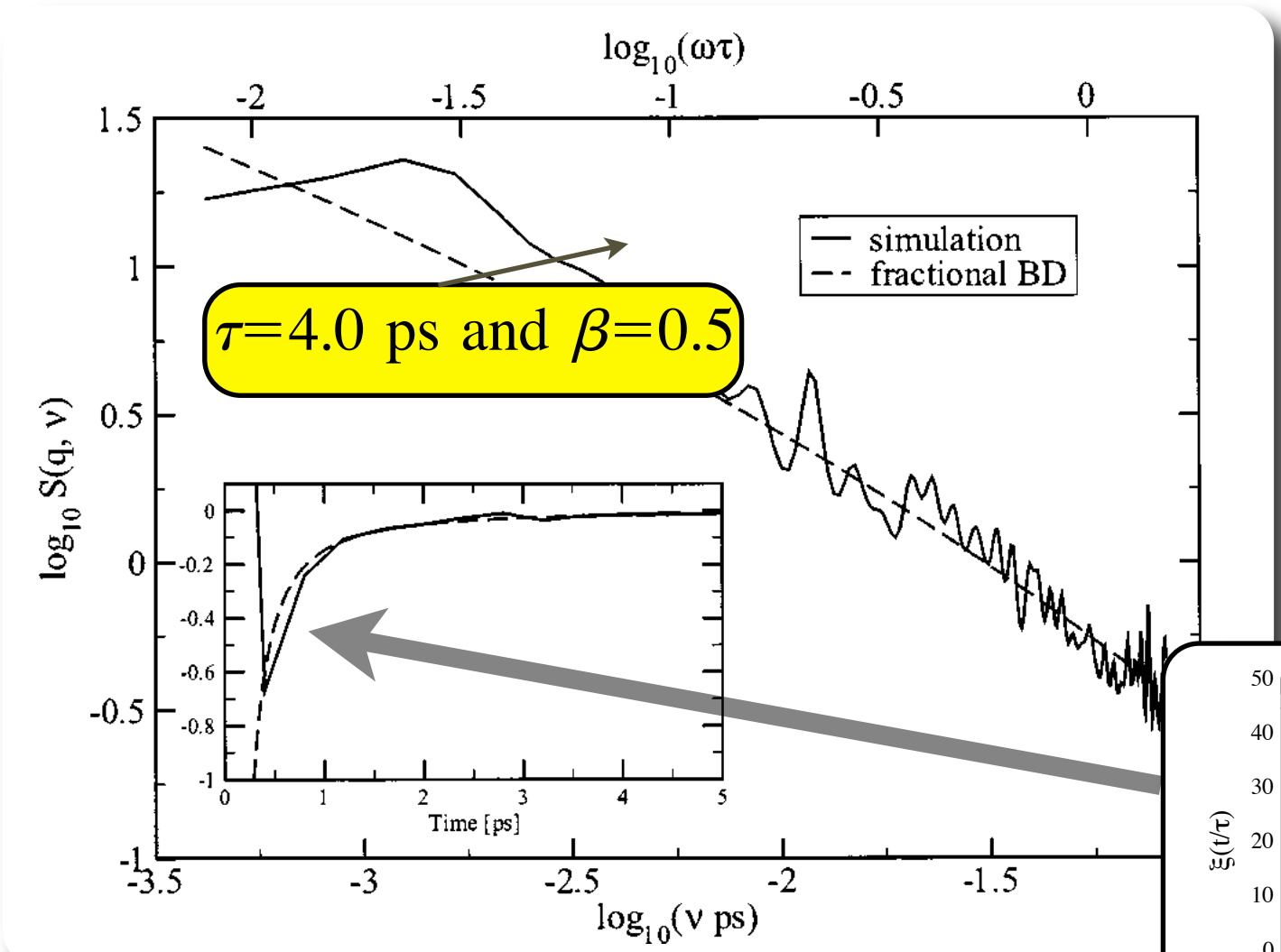
Density $\rho(\mathbf{q},t)=\sum_{\alpha}\exp(i\mathbf{q}.\mathbf{R}_{\alpha}(t))$

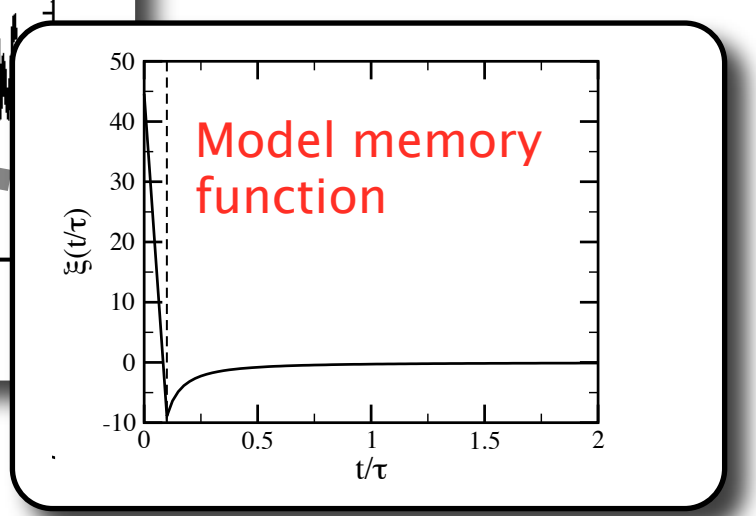
- Compute memory function [1]

$$\frac{d}{dt}\psi(\mathbf{q},t)=-\int_0^t d\tau\,\xi(\mathbf{q},t-\tau)\,\psi(\mathbf{q},\tau)$$

[1] G.R. Kneller and K. Hinsen. *J. Chem. Phys.*, 115(24):11097–11105, 2001.

Simulation versus model



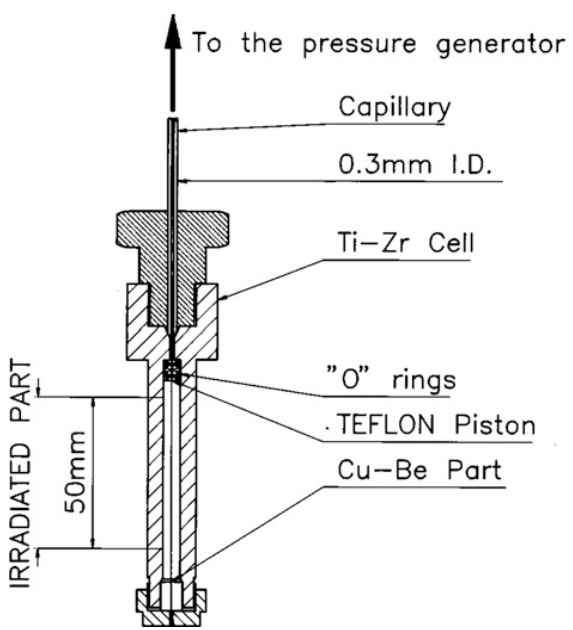


[1] G. Kneller and K. Hinsen, *J .Chem. Phys.*, **121**(20) 10278–10283, 2004.

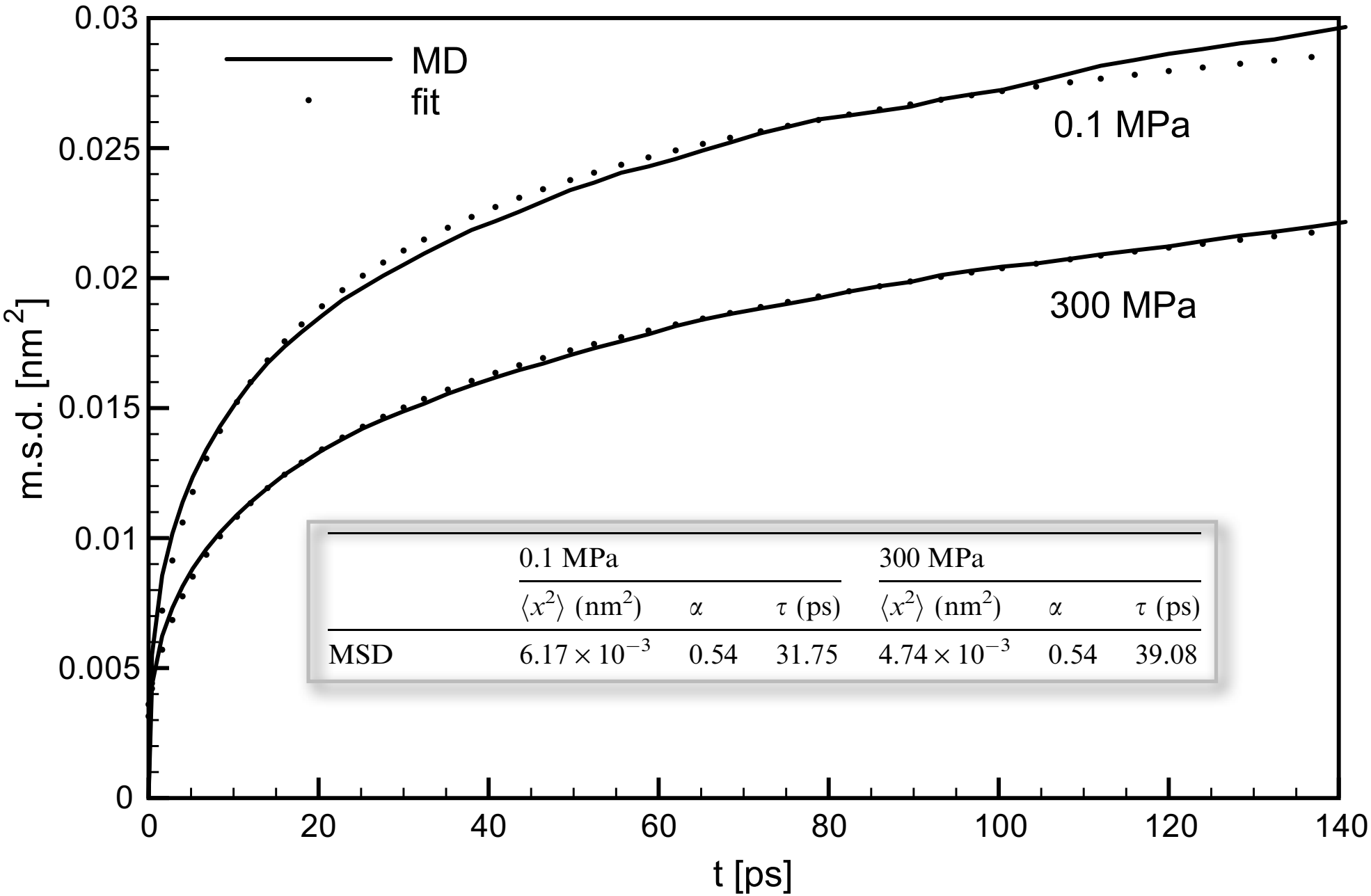
Fractional BD and protein dynamics under pressure : neutron scattering & MD

Quantify the influence of non-denaturing pressure on the internal dynamics of proteins in terms of fOU parameters

Titanium-zirconium pressure cell (b_{coh} = 0)



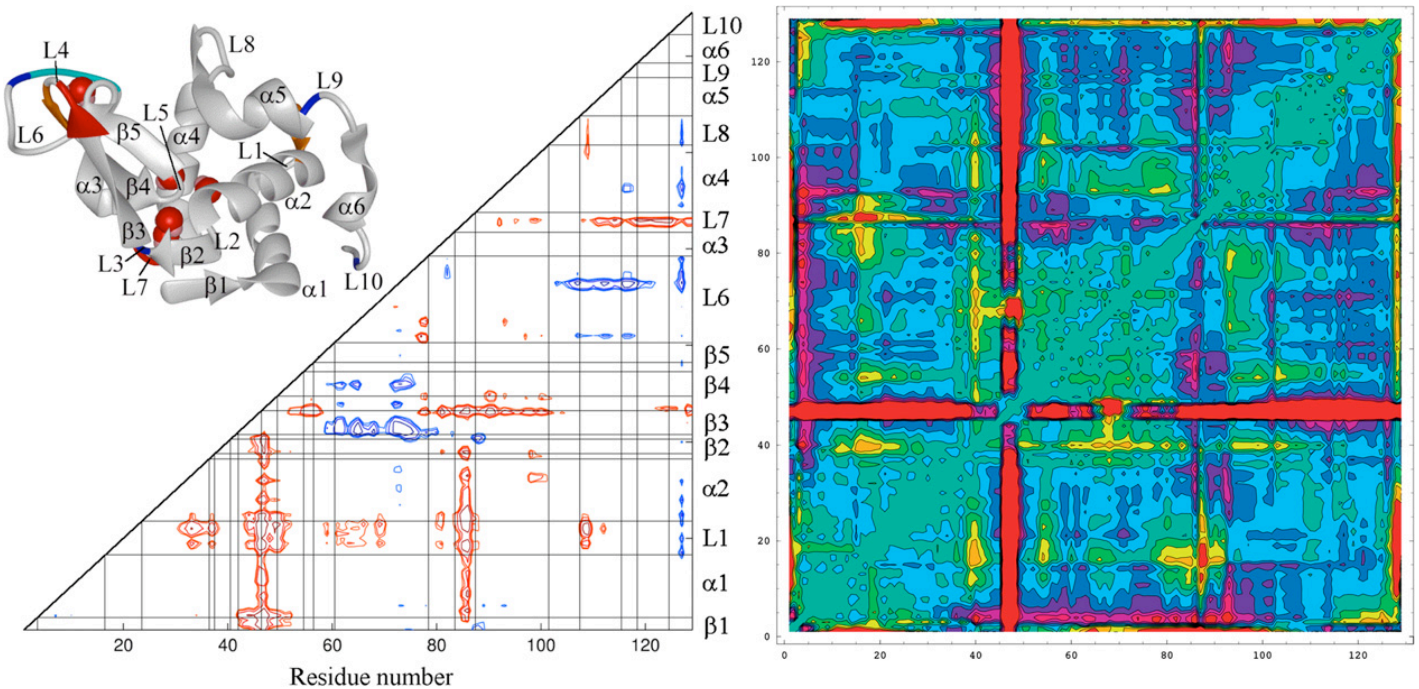
MD - time-dependent mean square displacement



	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

V. Calandrini, V. Hamon, K. Hinsen, P. Calligari, M.-C. Bellissent-Funel, and G.R. Kneller. *Chem. Phys.*, 345:289–297, 2008.

Changement of volume & structure



NMR[1]

Simulation[2]

Compression:

$$\frac{\Delta V_{exp}}{V_{exp}} = -2\%$$

$$\frac{\Delta V_{MD}}{V_{MD}} = -2.25\%$$

[1] M. Refaee, T. Tezuka, K. Akasaka, and M.P. Williamson. *J. Mol. Biol.*, 327:857–865, 2003.

[2] V. Hamon, P. Calligari, K. Hinsen, and G.R. Kneller. *Journal of Non-Crystalline solids*, 352:4417–4423, 2006.

Neutron scattering - ns time scale

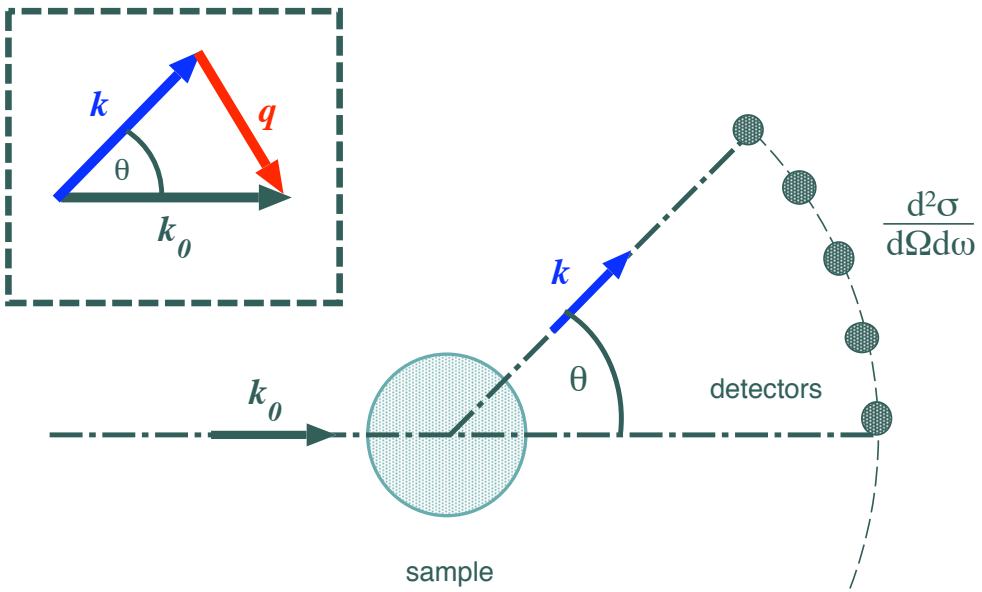


FIGURE IV.5. Schematic view of a neutron scattering experiment.

Explore the structure and the dynamics of condensed matter at the atomic scale (nm,ns)

$$\frac{d^2\sigma}{d\Omega d\omega} = \frac{k}{k_0} S(\mathbf{q},\omega)$$

$$S(\mathbf{q},\omega) = \frac{1}{2\pi}\int_{-\infty}^{+\infty} dt\ \exp(-i\omega t) I(\mathbf{q},t)$$

$$\boxed{I_{coh}(\mathbf{q},t) = \langle \rho^*_{coh}(\mathbf{q},0)\rho_{coh}(\mathbf{q},t)\rangle}$$

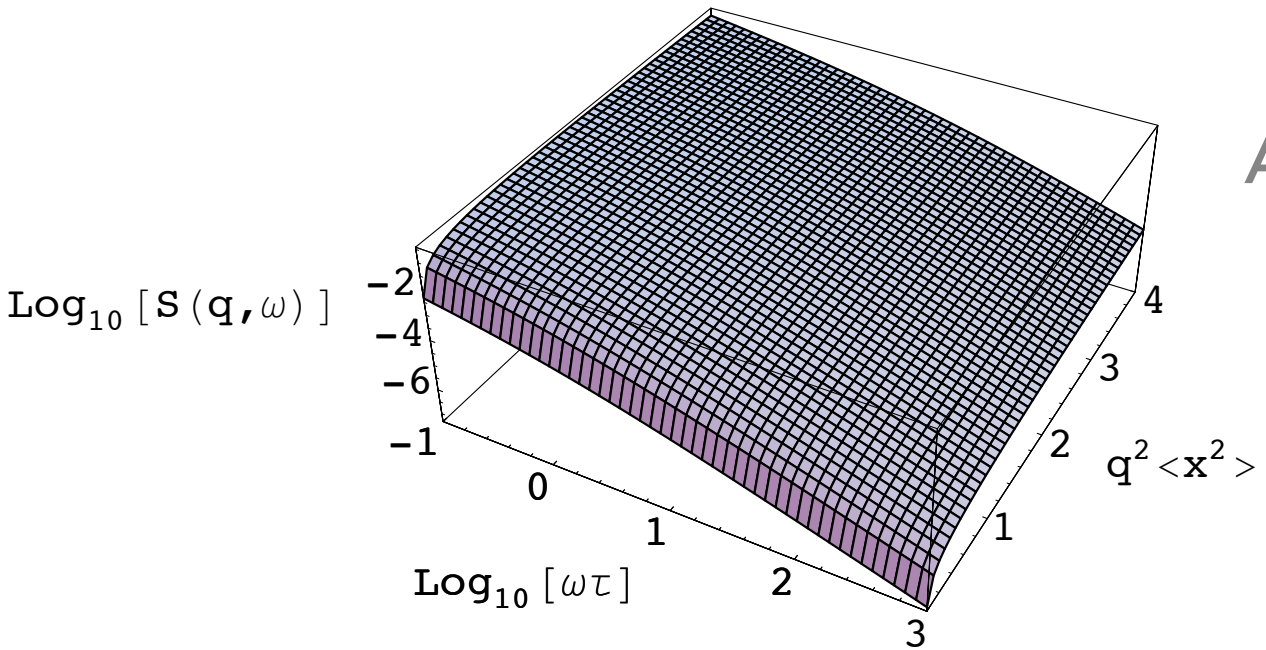
$$\rho_{coh}(\mathbf{q},t) = \frac{1}{\sqrt{N}}\sum_{\alpha=1}^{N} b_{\alpha,coh}\exp(-i\mathbf{q}^T\cdot\mathbf{R}_\alpha(t))$$

Structure and collective dynamics

$$\boxed{I_{inc}(\mathbf{q},t) = \frac{1}{N}\sum_{\alpha=1}^{N}|b_{\alpha,inc}|^2\langle\rho^*_\alpha(\mathbf{q},0)\rho_\alpha(\mathbf{q},t)\rangle}$$

Single particle dynamics

Neutron scattering and fBD model



Anomalous diffusion in a harmonic potential

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

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

$$\tau_{\alpha,n} = \lambda_{\alpha,n}^{-(1/\alpha)}, \quad n \neq 0 \qquad \lambda_{\alpha,n} := \tilde{\tau}^{1-\alpha}\lambda_n \qquad \lambda_n = n\eta$$

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

Analyzing QENS data....

Account for translational diffusion and instrumental resolution

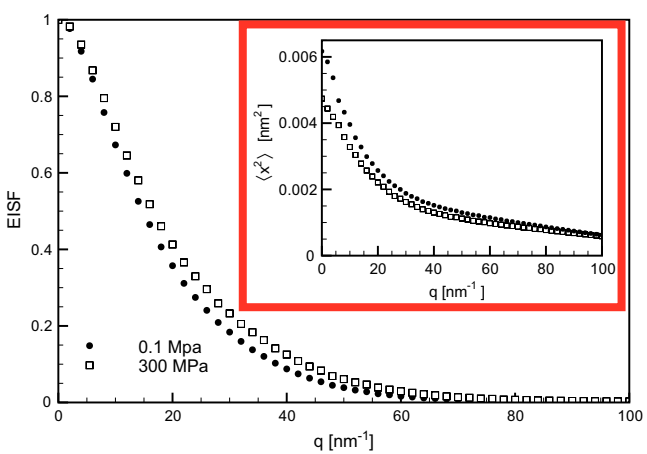
$$S_{\mathrm{m}}(q,t) = (S * l * r)(\omega)$$

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

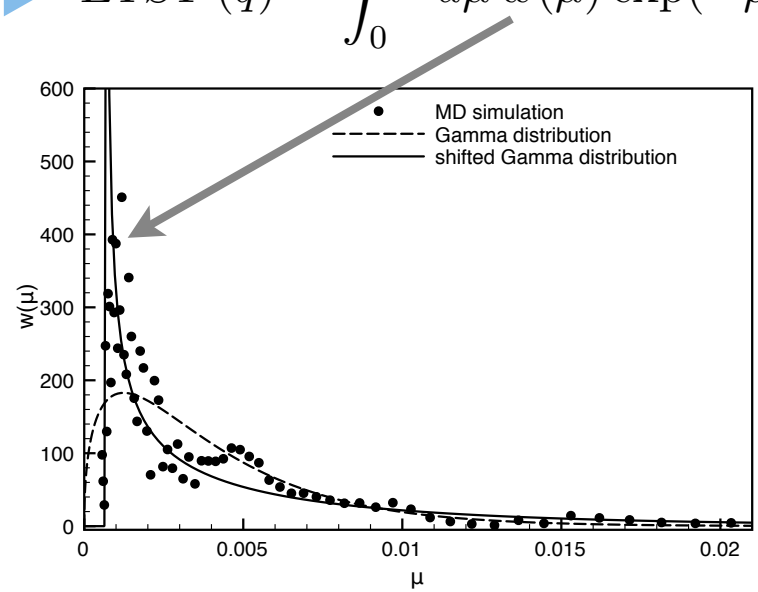
Model dynamic structure factor

Take into account the non-gaussian form of the EISF

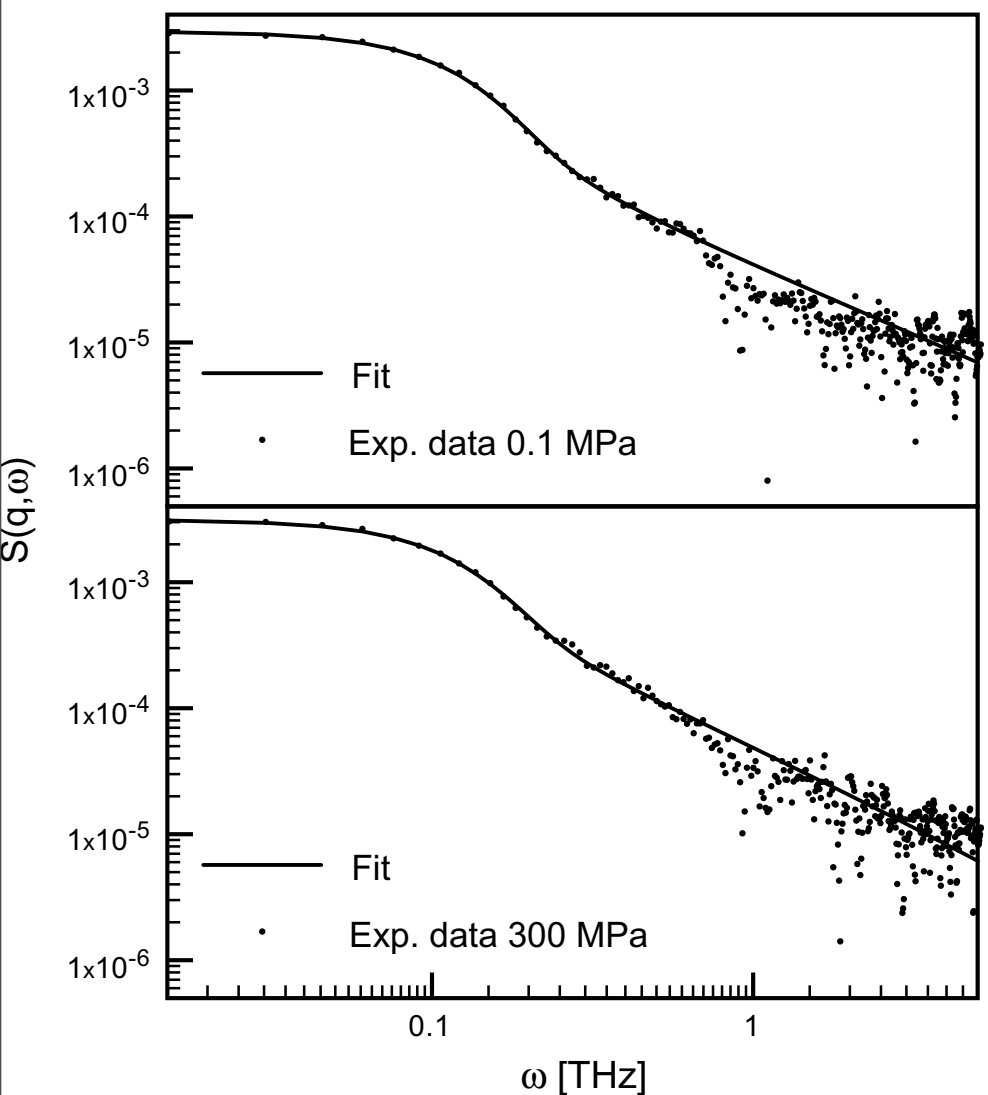
$$EISF(q) \approx \exp(-q^2\langle x^2\rangle(q)) \quad \Longleftrightarrow \quad EISF(q) = \int_0^{\infty} d\mu\, w(\mu) \exp(-\mu q^2)$$



V. Calandrini, *et al*. *Chem. Phys.*, 345:289–297, 2008.



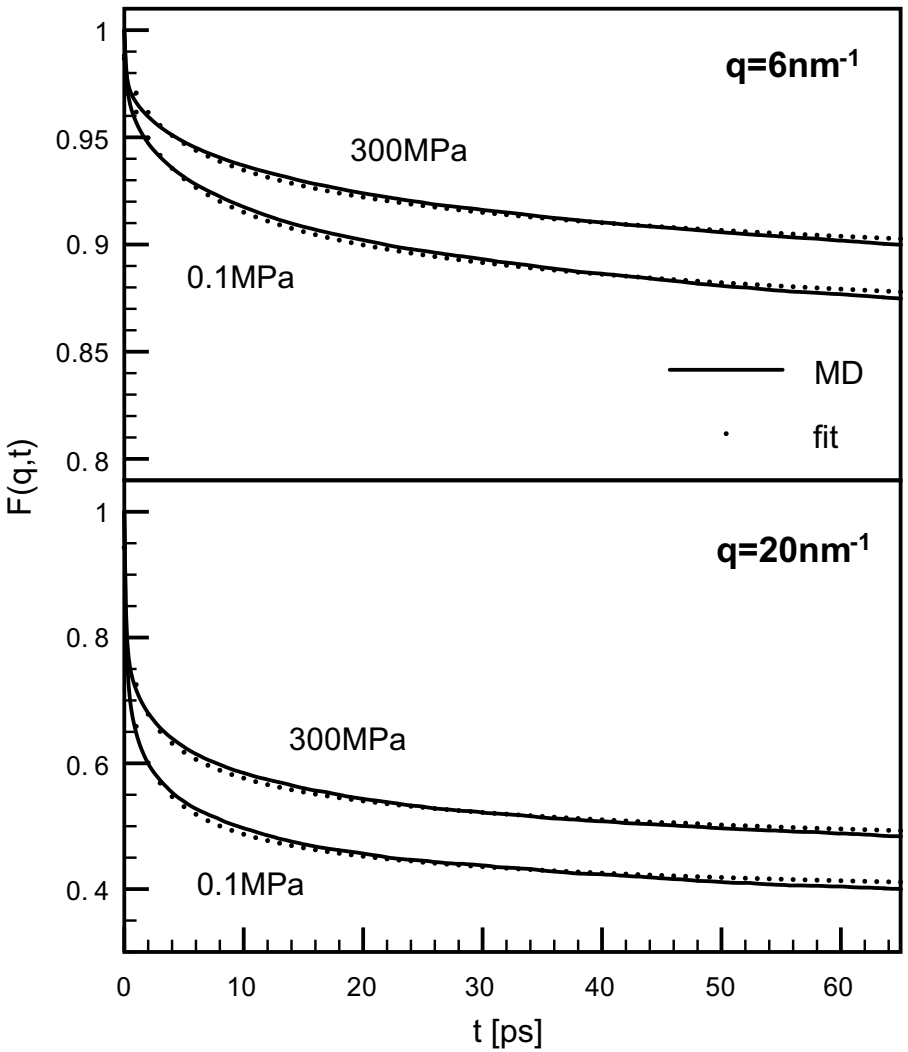
[1] G. Kneller and K. Hinsen, *J .Chem. Phys. 2009*, in press

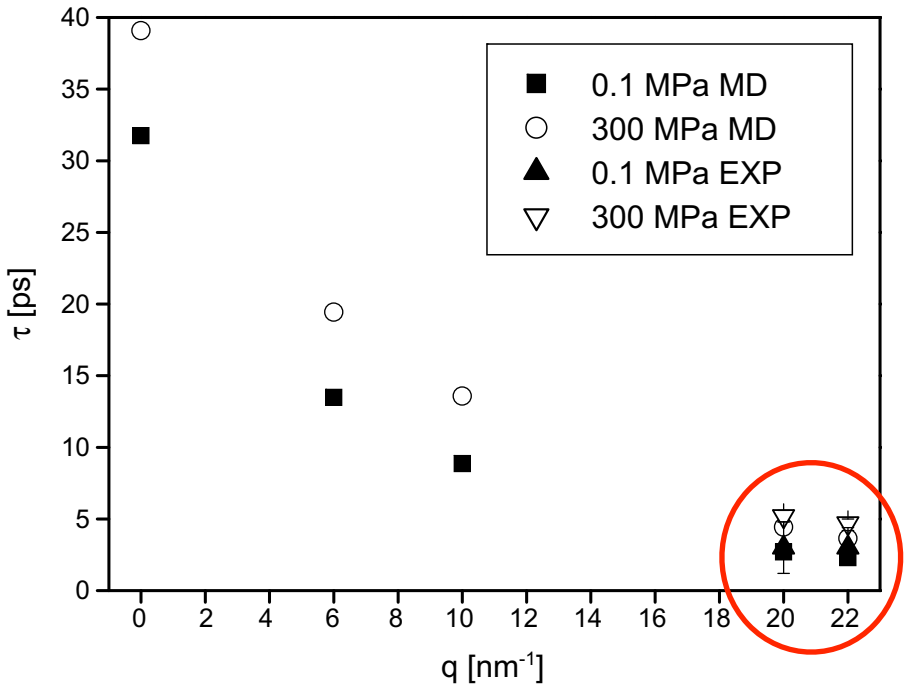


		$S_{inc}(20\ nm^{-1},\omega)$	$S_{inc}(22\ nm^{-1},\omega)$
0.1 MPa	$\langle x^2\rangle$ (nm^2)	2.57×10^{-3}	2.41×10^{-3}
	α	0.35(2)	0.40(2)
	τ (ps)	3(2)	3(1)
	$\overline{D}$ (nm^2 ps^{-1})	$0.53(3)\times10^{-4}$	
300 MPa	$\langle x^2\rangle$ (nm^2)	2.21×10^{-3}	2.08×10^{-3}
	α	0.52(1)	0.55(1)
	τ (ps)	5.2(2)	4.7(3)
	$\overline{D}$ (nm^2 ps^{-1})	$0.50(3)\times10^{-4}$	

V. Calandrini, *et al*. *Chem*. *Phys*., 345:289–297, 2008.

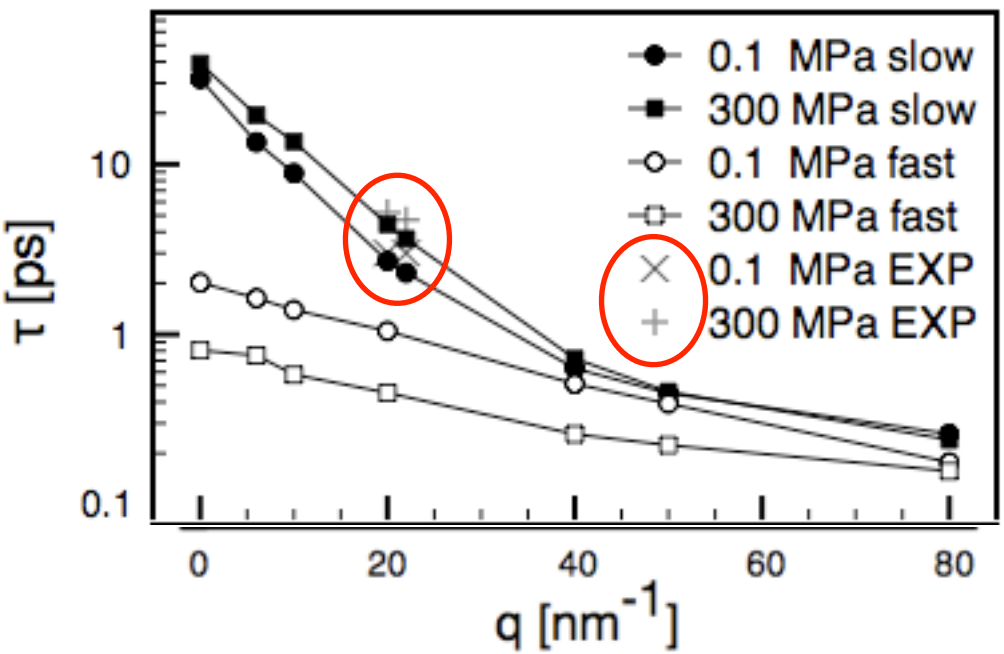
Simulated intermediate scattering function





$$I(q,t) = \exp(-q^2\langle x^2\rangle)\sum_{n=0}^{\infty}\frac{q^{2n}\langle x^2\rangle^n}{n!}E_\alpha(-[t/\tau_n]^\alpha)$$

A more detailed analysis of fast (20 ps) and slow protein dynamics (1 ns)



slow dynamical regime ➡ slowing down

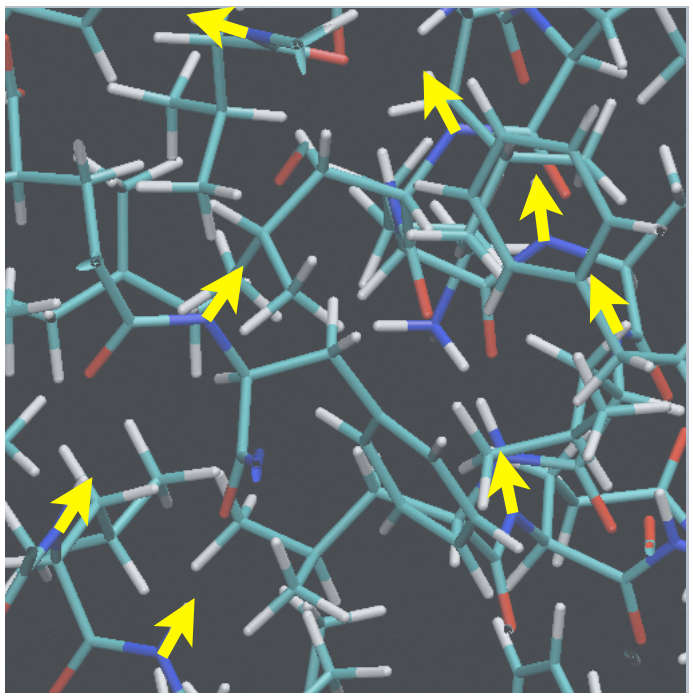
large scale motions are particularly concerned. The effect disappears for motions localized within a radius of about 1.5 ° A.

fast dynamical regime ➡ acceleration

The effect progressively decreases with increasing localization of the observed motions.

V. Calandrini and G.R. Kneller. *J. Chem. Phys.*, 128(6):065102, 2008.

Simulating the protein dynamics seen by NMR spectroscopy



Express NMR relaxation rates/NOEs in terms of the Fourier spectrum of the N-H reorientational time correlation function

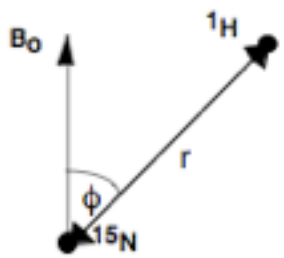
$$
\begin{aligned}
R_{2\,i} &= d^2\left(2J_{ii}(0) + \tfrac{3}{2}J_{ii}(\omega_{\mathrm{N}}) + \tfrac{1}{2}J_{ii}(\omega_{\mathrm{H}} - \omega_{\mathrm{N}}) + 3J_{ii}(\omega_{\mathrm{H}}) + 3J_{ii}(\omega_{\mathrm{H}} + \omega_{\mathrm{N}})\right) \\
&\quad + c^2\left(\tfrac{4}{3}J_{ii}(0) + J_{ii}(\omega_{\mathrm{N}})\right) \\
R_{1\,i} &= d^2\Big(3J_{ii}(\omega_{\mathrm{N}}) + J_{ii}(\omega_{\mathrm{H}} - \omega_{\mathrm{N}}) + 6J_{ii}(\omega_{\mathrm{H}} + \omega_{\mathrm{N}})\Big) + 2c^2 J_{ii}(\omega_{\mathrm{N}}) \\
\eta_{\mathrm{NH}\,i} &= 1 + \tfrac{\gamma_H}{\gamma_N}\tfrac{d^2}{R_1}\left(6J_{ii}(\omega_{\mathrm{H}} + \omega_{\mathrm{N}}) - J_{ii}(\omega_{\mathrm{H}} - \omega_{\mathrm{N}})\right)
\end{aligned}
$$

$$
d^2 = \frac{\mu_0^2\hbar^2}{16\pi^2}\frac{(\gamma_H\gamma_N)^2}{10r_{\mathrm{NH}}^6} \quad \text{and} \quad c^2 = \frac{(\gamma_N B_0 \Delta\sigma_N)^2}{15}.
$$

$$
J_{ii}(\omega) = \int_0^\infty dt\ \cos\omega t\, c_{ii}(t)
$$

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

global rotation — internal dynamics

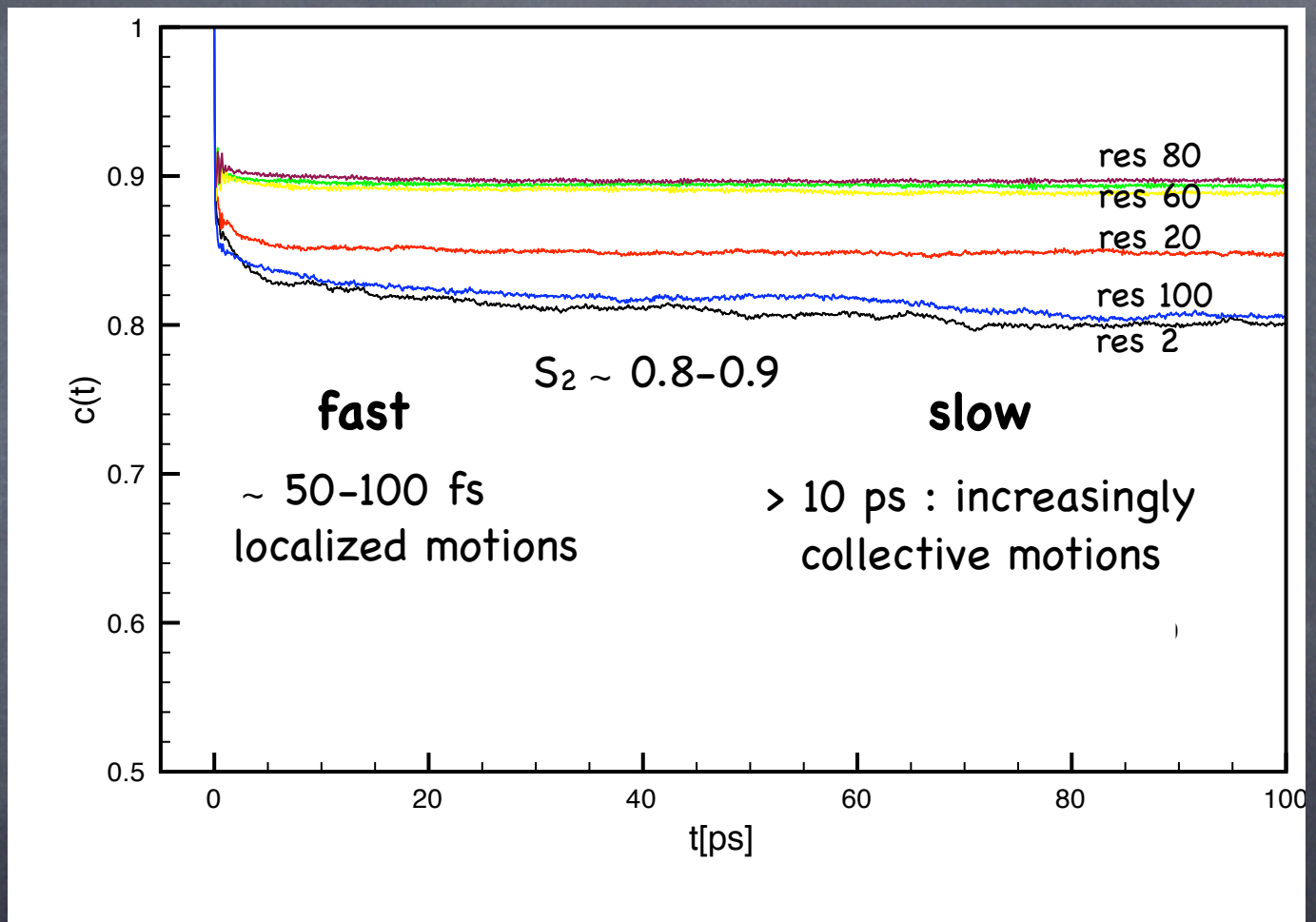


$$
C(t) = \frac{4\pi}{5}\sum_{m=-2}^{2}(-1)^m\langle Y_{2,-m}(\theta(0),\phi(0))Y_{2,m}(\theta(t),\phi(t))\rangle
$$

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

lysozyme

res 104



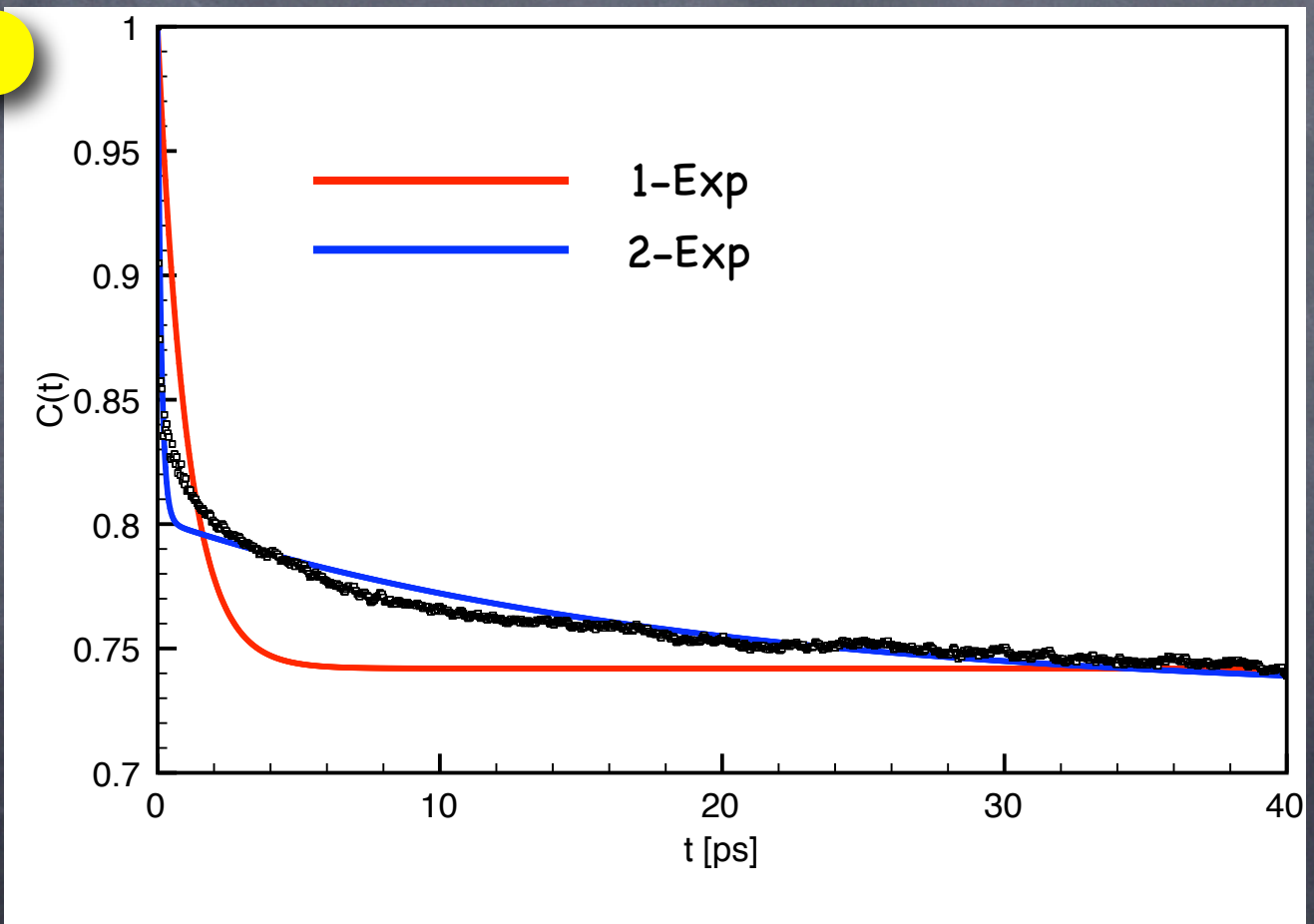
trajectory 1 ns
Δt=40 fs

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

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

lysozyme

res 104

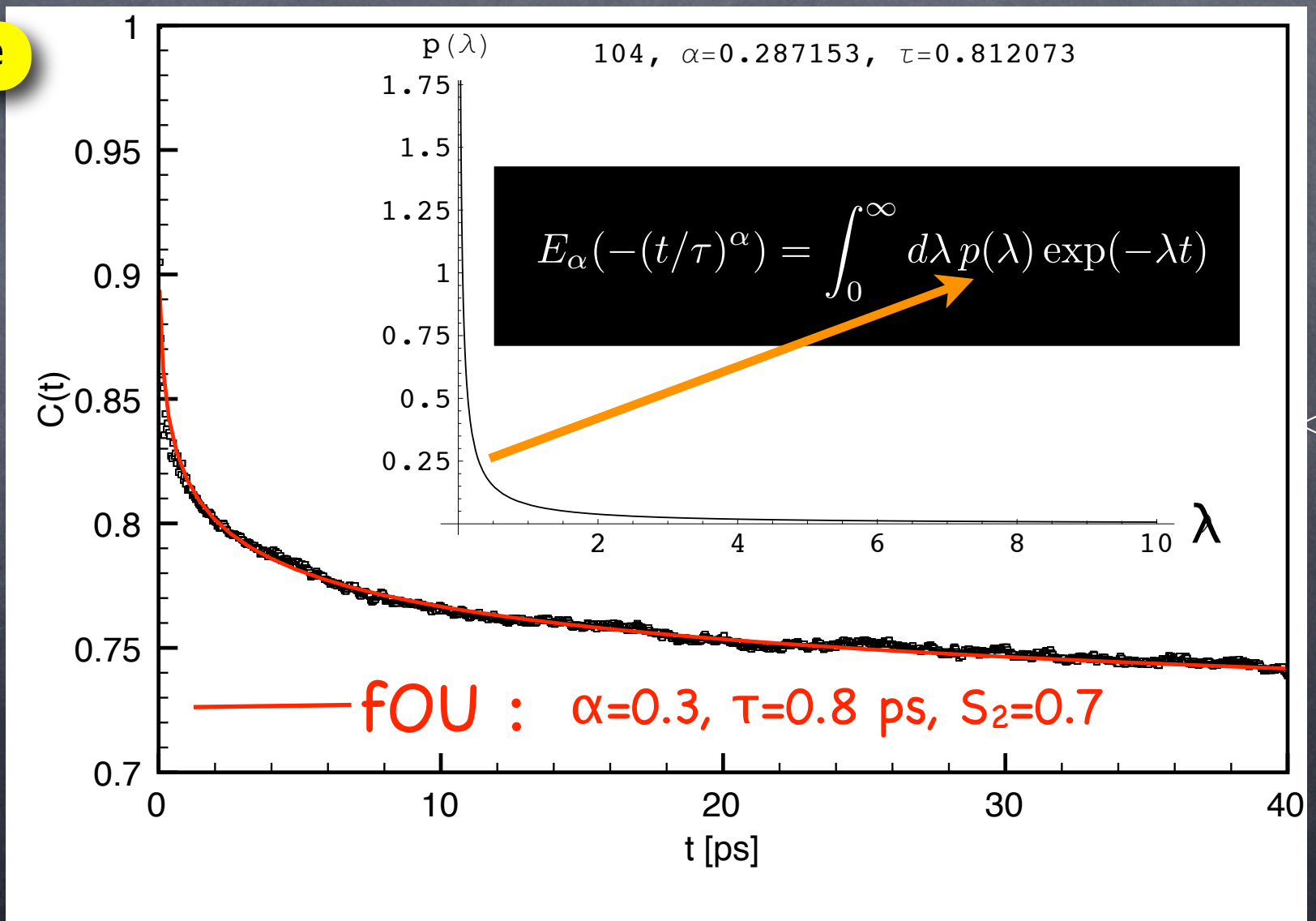


Rotational fractional Brownian dynamics

$$C_{ii}^{I}(t) = S_{ii}^{2} + (1 - S_{ii}^{2}) E_{\alpha}(-[t/\tau]^{\alpha}) \qquad E_{\alpha}(z) = \sum_{k=0}^{\infty} \frac{z^{k}}{\Gamma(1+\alpha k)},$$

lysozyme

res 104



< 1

Again Redfield's theory

$$
\begin{aligned}
R_{2\,i} &= d^2\left(2J_{ii}(0) + \tfrac{3}{2}J_{ii}(\omega_{\mathrm{N}}) + \tfrac{1}{2}J_{ii}(\omega_{\mathrm{H}} - \omega_{\mathrm{N}}) + 3J_{ii}(\omega_{\mathrm{H}}) + 3J_{ii}(\omega_{\mathrm{H}} + \omega_{\mathrm{N}})\right) \\
&\quad + c^2\left(\tfrac{4}{3}J_{ii}(0) + J_{ii}(\omega_{\mathrm{N}})\right) \\
R_{1\,i} &= d^2\Big(3J_{ii}(\omega_{\mathrm{N}}) + J_{ii}(\omega_{\mathrm{H}} - \omega_{\mathrm{N}}) + 6J_{ii}(\omega_{\mathrm{H}} + \omega_{\mathrm{N}})\Big) + 2c^2 J_{ii}(\omega_{\mathrm{N}}) \\
\eta_{\mathrm{NH}\,i} &= 1 + \tfrac{\gamma_H}{\gamma_N}\tfrac{d^2}{R_1}\left(6J_{ii}(\omega_{\mathrm{H}} + \omega_{\mathrm{N}}) - J_{ii}(\omega_{\mathrm{H}} - \omega_{\mathrm{N}})\right)
\end{aligned}
$$

$$
d^2 = \frac{\mu_0^2\hbar^2}{16\pi^2}\frac{(\gamma_H\gamma_N)^2}{10r_{\mathrm{NH}}^6} \quad \text{and} \quad c^2 = \frac{(\gamma_N B_0 \Delta\sigma_N)^2}{15}.
$$

Compute experimental quantities from MD simulation

A. Abragam, Principles of Nuclear Magnetism (Clarendon Press, Oxford, 1961)

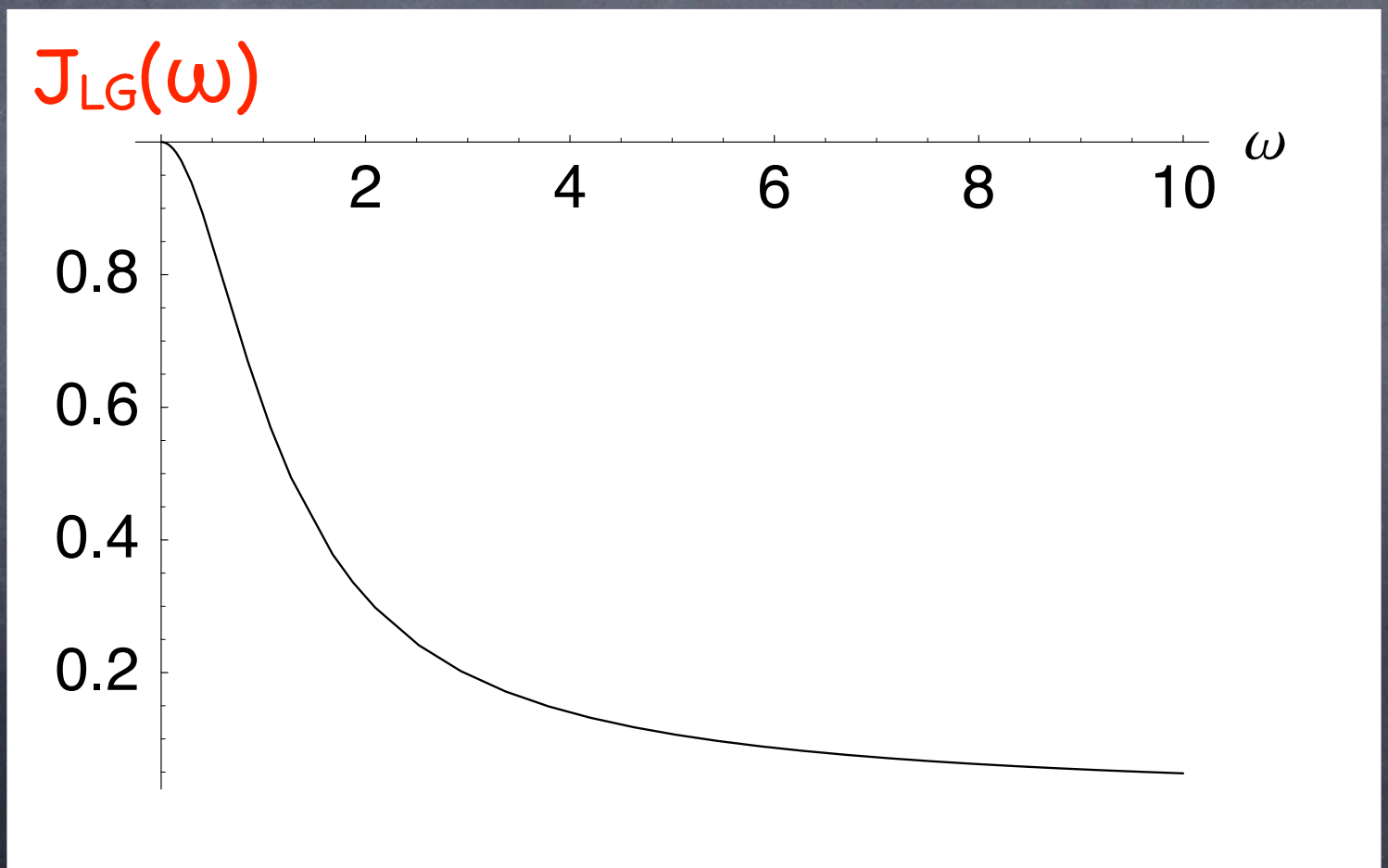
analytical expression for $J(\omega) = FT[C_0(t)C_I(t)]$

$$C_0(t) = \exp(-t/\tau_0)$$

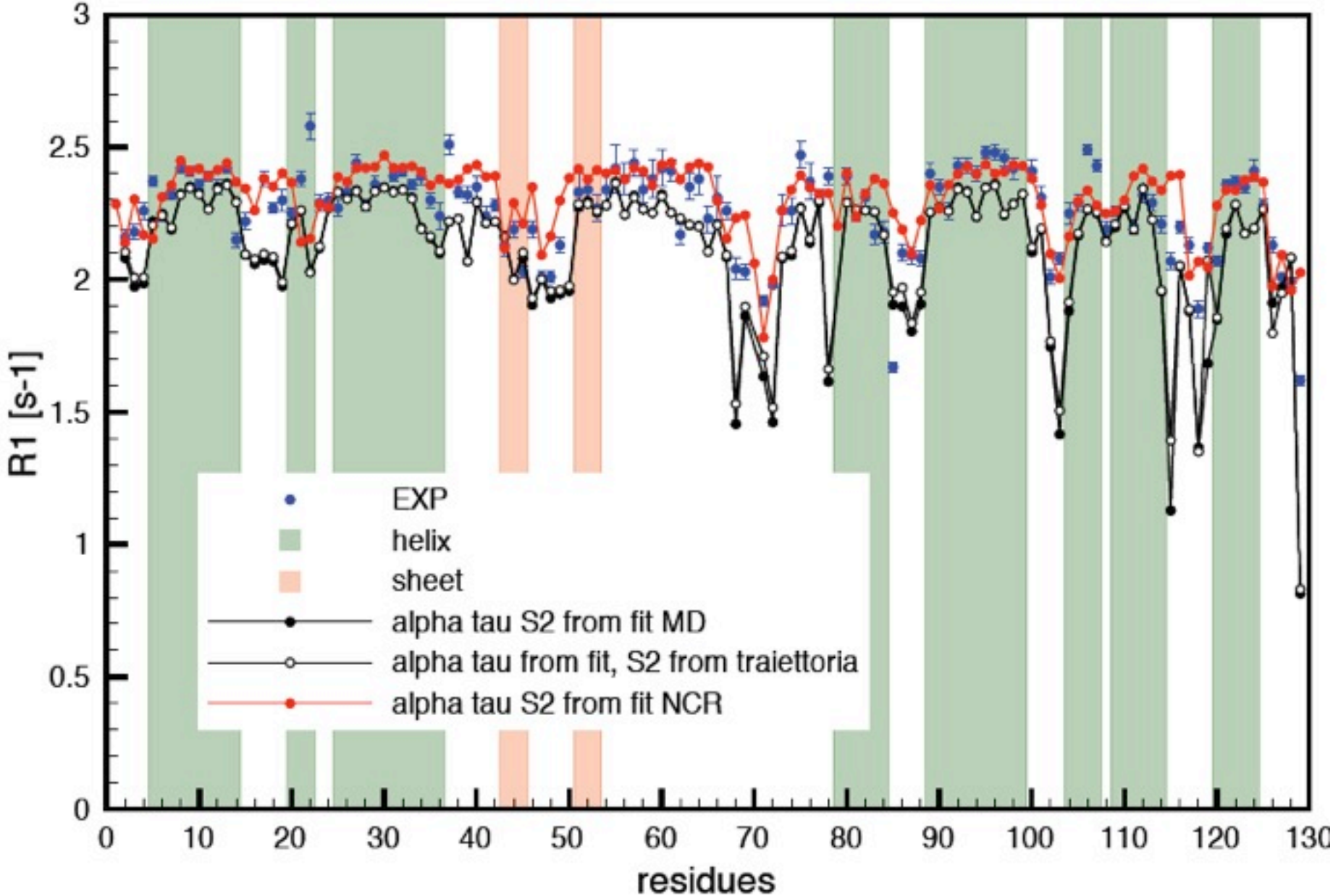
$$J(\omega) = \frac{2S^2\tau_0}{1+(\omega\tau_0)^2} + (1-S^2)\frac{2}{a}\frac{(a\tau)^\alpha \cos\beta + \cos[\beta(1-\alpha)]}{(a\tau)^\alpha + (a\tau)^{-\alpha} + 2\cos\beta\alpha}$$

$$a = \sqrt{\omega^2 + (1/\tau_0)^2}, \quad \beta = \arg(1/\tau_0 + i\omega),$$

$J_{LG}(\omega)$

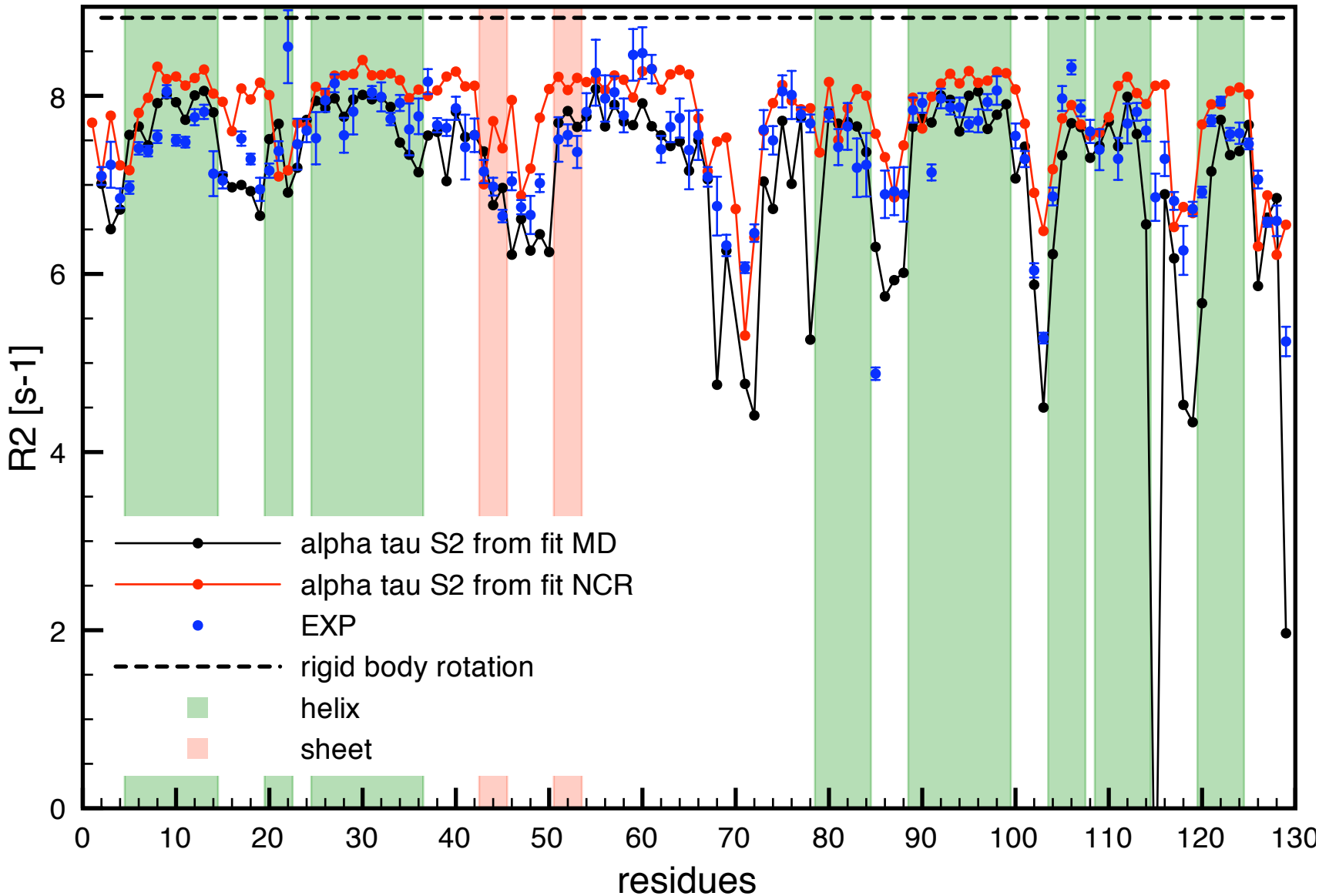


R1 [s^{-1}]

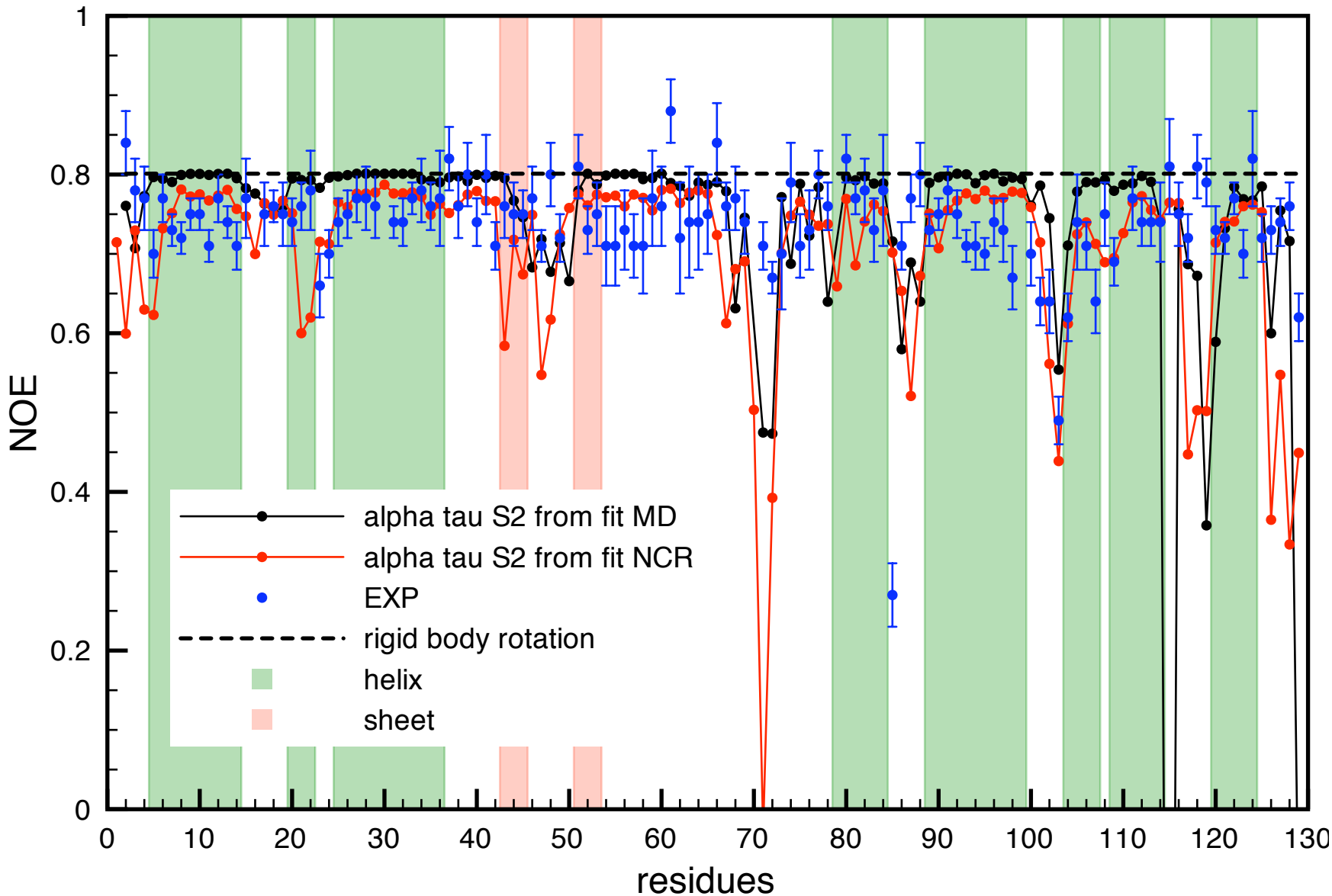


V. Calandrini, D. Abergel, and G. R. Kneller, *J. Chem. Phys.*, vol. 133, p. 145101, 2010.
(Experimental data from : M. Buck *et al*. *Biochemistry*, 34(12):4041–4055, 1995.)

R2 [s^{-1}]


R2 [s-1]
0
2
4
6
8
0
10
20
30
40
50
60
70
80
90
100
110
120
130
residues
alpha tau S2 from fit MD
alpha tau S2 from fit NCR
EXP
rigid body rotation
helix
sheet

NOEs


NOE
residues
alpha tau S2 from fit MD
alpha tau S2 from fit NCR
EXP
rigid body rotation
helix
sheet
0
0.2
0.4
0.6
0.8
1
0
10
20
30
40
50
60
70
80
90
100
110
120
130

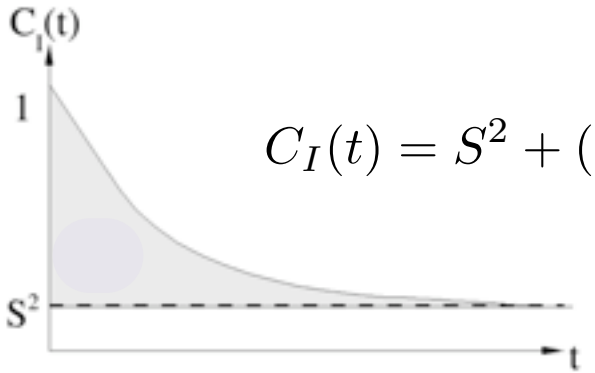
Estimating correlation times in NMR

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

global rotation — internal dynamics

$$J_{ii}(0) \equiv \int_0^\infty C(t)\,dt = S_{ii}^2\tau_0 + (1-S_{ii}^2)\frac{\tau_i(\frac{\tau_i}{\tau_0})^{\alpha_i-1}}{1+(\frac{\tau_i}{\tau_0})_i^\alpha}$$

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



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

$$\tau_{tot} = \int_0^\infty dt\, c(t) = J(0) \quad \Rightarrow \quad \tau_{tot} = S^2\tau_0 + (1-S^2)\frac{\tau(\tau/\tau_0)^{\alpha-1}}{1+(\tau/\tau_0)^\alpha}$$

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

$$\tau \leq \tau_{I,\text{eff}} \leq \tau_0$$

$\alpha = 1$ $\qquad$ $\alpha = 0$

The form of $C_I(t)$ matters !

Conclusions

- Anomalous free diffusion can be understood on the basis of a memory function-based «cage» model which fits well the MSDs observed for diffusing molecules in membranes.The long-time tails of the VACF and its memory function can be predicted from the asymptotic behavior of the MSD.

- Fractional Brownian Dynamics is robust model for the description of experimental and simulation data on internal protein dynamics. A physical picture can be provided on the basis of the cage model.

Merci à

- Konrad Hinsen, CBM Orléans/SOLEIL
- Vania Calandrini, CBM Orléans/SOLEIL
- Paolo Calligari, CBM Orléans/SOLEIL
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- Marie-Claire Bellissent-Funel, CEA Saclay
- Marta-Pasenkiewicz-Gierula, Univ. Krakow

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Software

Aller au niveau supérieur

Numerical methods are of little use without ready-to-use and tested implementations. Our policy is to make all methods developped in the group freely available to the scientific community.

MMTK — Par Konrad Hinsen — Dernière modification 13/02/2007 18:28

The Molecular Modelling Toolkit is a library which contains a wide range of algorithms that are used in molecular simulations and modelling. It is particularly useful for data analysis and visualization, but also contains standard techniques such as energy minimization and Molecular Dynamics. All our recently developped techniques for biomolecules have been implemented in MMTK.

nMOLDYN — Par Gerald Kneller — Dernière modification 14/02/2007 09:28

nMOLDYN is an interactive analysis program for Molecular Dynamics simulations. It is especially designed for the computation and decomposition of neutron scattering spectra, but also computes other quantities.

DomainFinder — Par Konrad Hinsen — Dernière modification 13/02/2007 18:29

DomainFinder is an interactive program to analyze collective motions in large proteins, either by comparing two experimental structure, or by applying an efficient normal mode technique to a single structure. Proteins up to a few thousand residues can be treated on a desktop computer in a few minutes.

ScrewFit — Par Paolo Calligari — Dernière modification 16/02/2007 18:22

ScrewFit is a program for the characterization of protein secondary structures. It provides an efficient description of structural