Fractional Gaussian Noise, Subdiffusion and Stochastic Networks in Biophysics

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Single-Molecule Experiments

- Statistics & probability experienced fundamental change in the past 20 years
- Biophysics & chemistry also witnessed dramatic progress: **single-molecule experiments**
- Using nanotechnology, scientists can study biological processes on a single-molecule basis (eg. enzymatic kinetics, protein/DNA dynamics)

"Seeing images of single atoms is a religious experience"

--- Richard Feynman

New Aspects for Scientific Discovery

- Can measure molecular properties ***individually***, instead of inferring from population statistics
- If the reaction/kinetic time is slow, ensemble experiments become almost impossible due to the ***difficulty of synchronization***
- Single-molecule trajectory provides detailed ***dynamic information***
- Understanding the dynamics of individual is essential to unlock their biofunctions

Statistical & Probabilistic Challenges

- Require new stochastic modeling

  Subdiffusion

  Enzymatic reaction

- Data are noisier, and efficient inference methodology is needed

Brownian diffusion

- Since Einstein's 1905 paper, the theory of Brownian diffusion has revolutionized not only natural sciences but also social sciences.

- Brownian motion described by Langevin equation

$$m\frac{dv_t}{dt} = -\zeta v_t + F(t)$$

where $F(t)$ is white noise process satisfying

$$E\{F(t)F(t')\} = \zeta k_B T \cdot \delta(t-t')$$

by **fluctuation-dissipation** theorem.

- Solution: Ornstein-Uhlenbeck process $v(t)$ Gaussian
- Displacement (location) $x(t) = \int_0^t v(s)ds$

$$E\{x(t)^2\} \sim 2\frac{k_B T}{\zeta} t, \text{ for large } t$$

--- Corner stone for statistical mechanics

Subdiffusion

- Brownian diffusion, however, cannot explain so called subdiffusion:

$$E\{x(t)^2\} \propto t^{\alpha}, \quad 0 < \alpha < 1$$

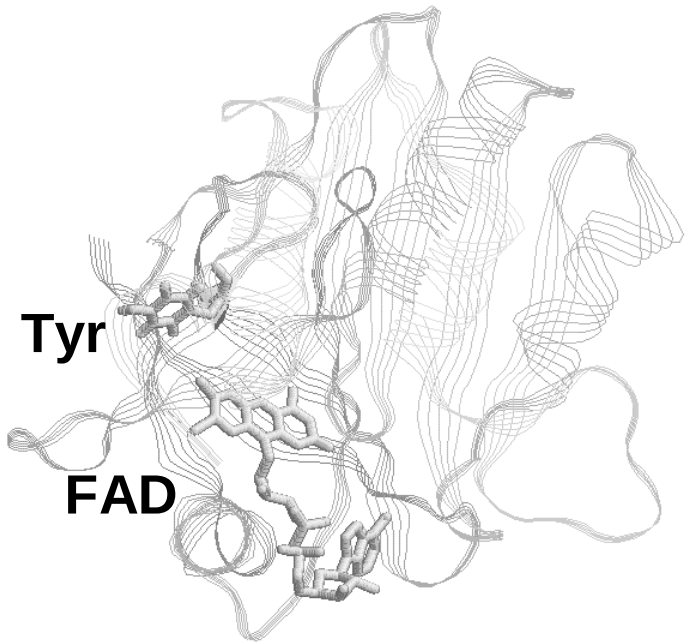
- Distance fluctuation within a single protein molecule (Yang *et al*. 2003, *Science*; Min *et al*. 2005, *Physical Review Letters*).

- Need tools beyond Langevin equation and BM.

Single-molecule fluorescence experiment on protein complex

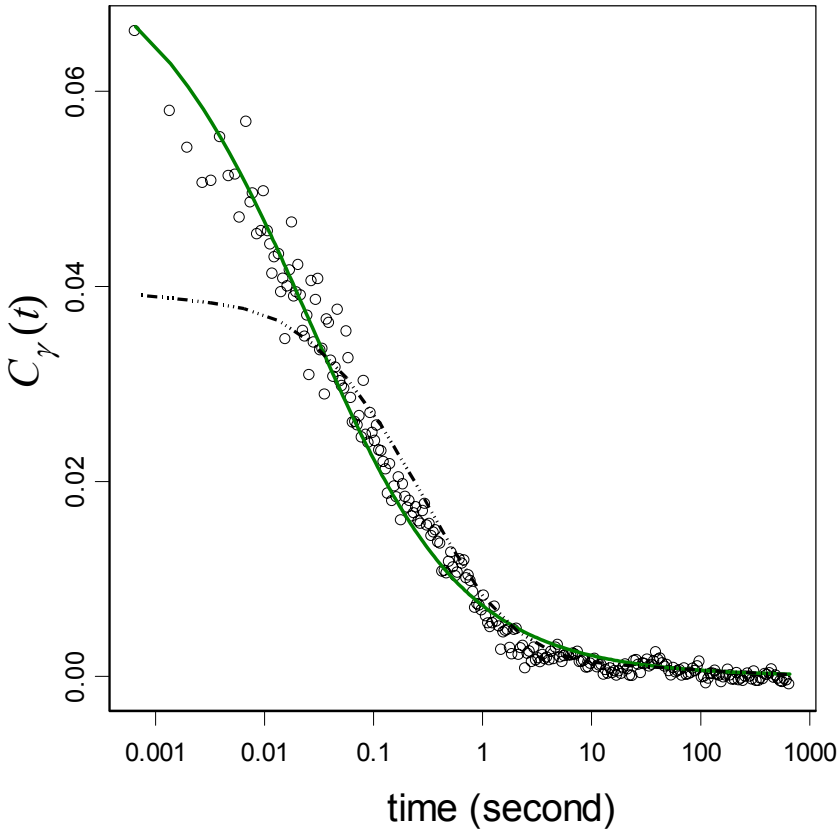
- Yang et al. (2003, *Science*) studied a protein-enzyme complex **Fre**, catalyzes the reduction of flavin
- Fre contains two substructures:
  a flavin adenine dinucleotide (FAD)
  and a tyrosine (Tyr).
- Fluorescence lifetime of FAD varies due to **distance fluctuation**
- Relationship between fluorescence lifetime and distance

$$\gamma^{-1}(t) = [k_0 e^{-\beta(X_{eq}+X_t)}]^{-1}$$



Autocorrelation function $E\{\Delta\gamma^{-1}(0)\,\Delta\gamma^{-1}(t)\}$

$$\Delta\gamma^{-1}(t) = \gamma^{-1}(t) - E\{\gamma^{-1}(t)\}$$



- Need tools beyond Langevin equation and BM.

- The model: Generalized Langevin equation with fractional Gaussian noise (GLE with fGn).

Generalized Langevin Equation with fGn

- Langevin equation $m\frac{dv_t}{dt} = -\zeta v_t + F(t)$
- Generalized Langevin equation $m\frac{dv_t}{dt} = -\zeta \int_{-\infty}^{t} v_u K(t-u)du + G_t,$
- **Fluctuation-dissipation theorem** links memory kernel $K(t)$ with fluctuating force $E\{G_t G_s\} = \zeta k_B T \cdot K(t-s)$

- Key question: How to introduce the noise structure?
- Understand the white noise: White noise is the derivative of the Wiener process $F_t = \frac{d}{dt} B_t$
- $B(t)$ is the unique process: (i) Gaussian, (ii) independent increment, (iii) stationary increment, (iv) self-similar

- Natural generalization: (i) Gaussian (ii) stationary increment (iii) self-similar.

- The **ONLY** candidate fBM $B^{(H)}(t)$, 0 < *H* < 1
  $E\{B_t^{(H)}\} = 0$, and covariance function
  $$E\{B_t^{(H)} B_s^{(H)}\} = (|t|^{2H} + |s|^{2H} - |t-s|^{2H})/2 \quad \text{for } t, s \geq 0.$$
  when *H* = 1/2, reduces to *B*(*t*).

- Fractional Gaussian noise $F^{(H)}(t) = \frac{dB_t^{(H)}}{dt}$:
  Gaussian & stationary.
- Memory kernel
  $$K_H(t) = E\{F^{(H)}(0)F^{(H)}(t)\}$$
  $$= H(2H-1)|t|^{2H-2}, \text{for } t \neq 0$$
- Spectral density
  $$\tilde{K}_H(\varpi) = \int_{-\infty}^{\infty} e^{it\varpi} K_H(t)dt = \Gamma(2H+1)\sin(H\pi)|\varpi|^{1-2H}$$

Toward subdiffusion

- Applying Fourier transform on

$$m\frac{dv_t}{dt} = -\zeta\int_{-\infty}^{t} v_u K_H(t-u)du + F_t^{(H)},$$

$v(t)$ Gaussian $E\{v(t)\} = 0$,

$$C(t) = E\{v(0)v(t)\} = \frac{1}{2\pi}\int_{-\infty}^{\infty} e^{it\varpi}\tilde{C}(\varpi)d\varpi$$

$$\tilde{C}(\varpi) = \frac{k_B T\zeta\tilde{K}_H(\varpi)}{\left|\zeta\tilde{K}_H^{+}(\varpi) - i\varpi m\right|^2}$$

- For displacement $X(t) = \int_0^t v(s)ds$

$$E\{X(t)^2\} = \int_0^t\int_0^t E\{v(s)v(u)\}du\,ds$$

$$E\{X(t)^2\} \sim \frac{k_B T}{\zeta}\frac{2\sin(2H\pi)}{\pi H(2H-1)(2H-2)}t^{2-2H} \propto t^{2-2H}$$

- $H > 1/2$ leads to subdiffusion!

Harmonic potential

- GLE: $m\frac{dv_t}{dt} = -\zeta\int_{-\infty}^{t} v_u K_H(t-u)du + F_t^{(H)}$,
- For external field $U(x)$, changes to

$$m\ddot{X}(t) = -\zeta\int_{-\infty}^{t} \dot{X}(u)K_H(t-u)du - U'(X_t) + F^{(H)}(t)$$

where $X(t) = \int_0^t v(s)ds$, $\ddot{X}(t) = \frac{dv(t)}{dt}$.

For harmonic potential $U(x) = \frac{1}{2}m\omega^2 x^2$

$$m\ddot{X}(t) = -\zeta\int_{-\infty}^{t} \dot{X}(u)K_H(t-u)du - m\omega^2 X(t) + F^{(H)}(t)$$

- Fourier method gives $E\{X(t)X(s)\}$, $E\{X(t)v(s)\}$

Overdamped condition

- Acceleration negligible, GLE reads

$$m\omega^2 X(t) = -\zeta\int_{-\infty}^{t} \dot{X}(u)K_H(t-u)du + F^{(H)}(t)$$

$$m\omega^2 X(t) = -\zeta \int_{-\infty}^{t} \dot{X}(u) K_H(t-u)du + F^{(H)}(t)$$

- Solution: $X(t)$ stationary Gaussian $E\{X(t)\}=0$

$$C_{xx}(t) = E\{X(0)X(t)\}$$

$$= \frac{k_B T}{m\omega^2} E_{2-2H}\left(-\frac{m\omega^2}{\zeta\Gamma(2H+1)} t^{2-2H}\right)$$

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

- For all H,

$$C_{xx}(0) = E\{X(0)X(0)\} = \frac{k_B T}{m\omega^2}$$

the **thermal equilibrium** value.

- For H = 1/2, recovers the Brownian diffusion result

$$C_{xx}(t) = E\{X(0)X(t)\} = \frac{k_B T}{m\omega^2} e^{-2\frac{m\omega^2}{\zeta}t}$$

The Hamiltonian for GLE with fGn

- GLE with fGn can be derived from the interaction between a particle and a harmonic oscillator heat bath.
- Start from system Hamiltonian ⇨ $H_s = \frac{1}{2}mv^2 + \frac{1}{2}m\omega^2 x^2$

  $= \frac{p^2}{2m} + \frac{1}{2}m\omega^2 x^2, \qquad p = mv$

  and the heat bath Hamiltonian

  ⇨ $H_B = \sum_j \left(\frac{p_j^2}{2m_b} + \frac{1}{2}m_b\omega_j^2 (q_j - \frac{\gamma_j}{\omega_j^2}x)^2 \right)$

  where m_b the media molecule mass, ω_j individual frequency, and γ_j coupling strength of jth oscillator.
- Equation of motion for $H_s + H_B$

$$\frac{dx}{dt} = \frac{\partial}{\partial p}(H_s + H_B), \quad \frac{dp}{dt} = -\frac{\partial}{\partial x}(H_s + H_B)$$

$$\frac{dq_j}{dt} = \frac{\partial}{\partial p_j}(H_s + H_B), \quad \frac{dp_j}{dt} = -\frac{\partial}{\partial q_j}(H_s + H_B)$$

- Solve it. Leads to (i) GLE

$$m\ddot{X}(t) = -\zeta \int_{-\infty}^{t} \dot{X}(u)K(t-u)du - m\omega^2 X(t) + F(t)$$

where

$$K(t) = m_b \sum_j \frac{\gamma_j^2}{\omega_j^2} \cos\omega_j t = m_b \int \frac{\gamma^2(\varpi)}{\varpi^2} \cos(\varpi t) g(\varpi) d\varpi$$

$$F(t) = \sum_j m_b \gamma_j (q_j(0) - \frac{\gamma_j}{\omega_j^2} x(0)) \cos(\omega_j t) + \sum_j \frac{\gamma_j}{\omega_j} p_j(0) \sin(\omega_j t)$$

and (ii) the fluctuation-dissipation theorem

$$E\{F_t F_s\} = k_B T \zeta \cdot K(t-s)$$

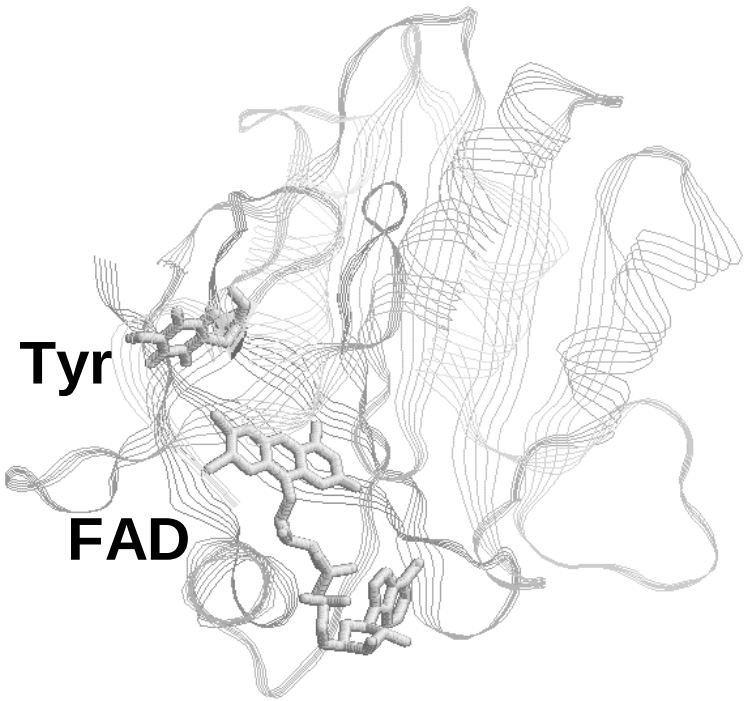
- Furthermore, if we take

$$\gamma^2(\varpi)g(\varpi) = \frac{1}{\pi}\Gamma(2H+1)\sin(H\pi)|\varpi|^{3-2H}$$

$$K(t) = H(2H-1)t^{2H-2}$$

⇨ fGn memory kernel

Back to experiment



Fluorescence lifetime of FAD depends on the distance between FAD and Tyr

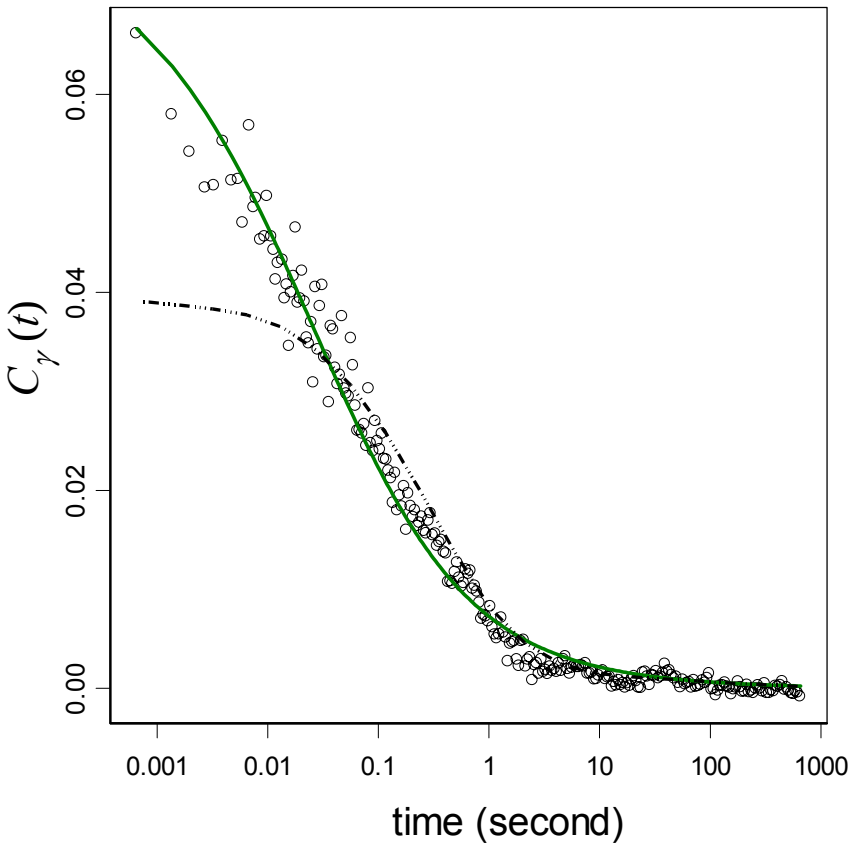
$$\gamma^{-1}(t) = [k_0 e^{-\beta(X_{eq}+X_t)}]^{-1}$$

⇨ Model $X(t)$ by GLE with fGn under harmonic potential

easy calculation of lifetime autocorrelation

$$Cov\{\gamma^{-1}(0),\ \gamma^{-1}(t)\} = k_0^2 e^{2\beta X_{eq}+\beta^2 C_{xx}(0)}(e^{\beta^2 C_{xx}(t)} - 1)$$

Fitting experimental autocorrelation



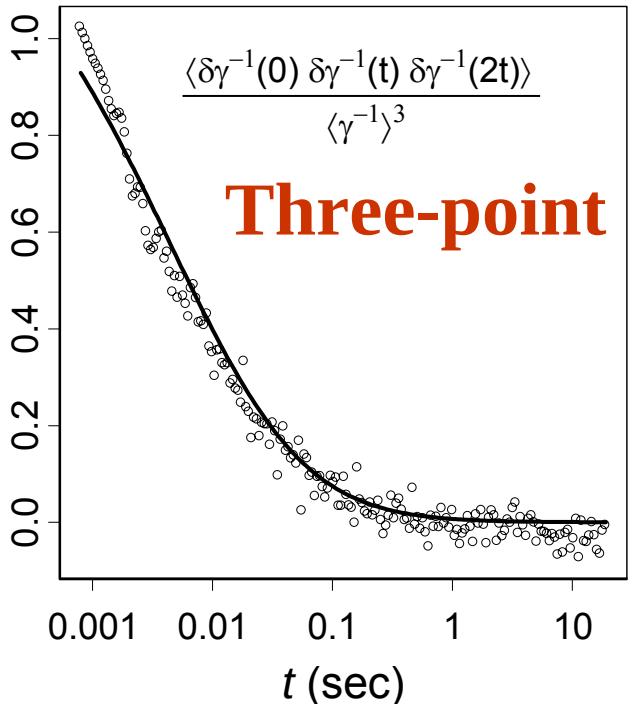
$$H \qquad \frac{\zeta}{m\omega^2} \qquad \frac{k_B T}{m\omega^2}\beta^2$$

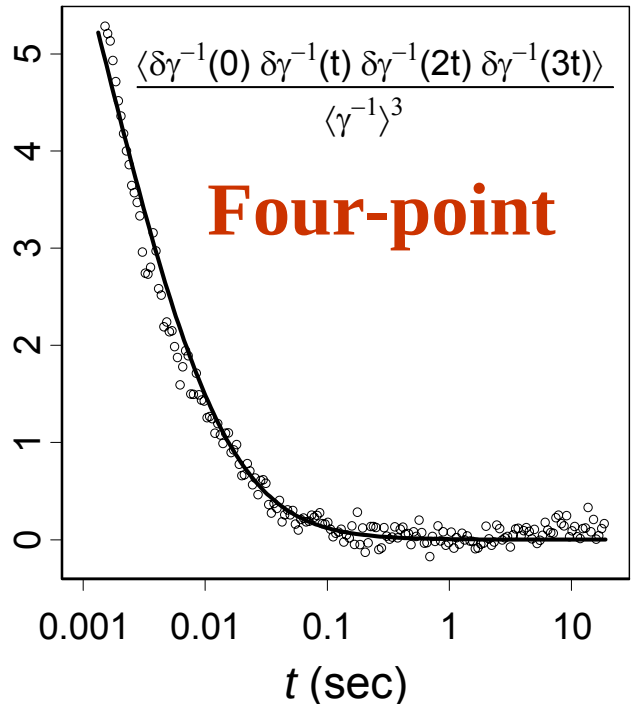
0.74 0.40 0.81

Kou and Xie, *Phys. Rev. Lett.*, **93**, 180603 (2004).

Higher order autocorrelation functions

$$\delta\gamma^{-1}(t) := \gamma^{-1}(t) - \langle\gamma^{-1}(t)\rangle$$





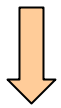
Same parameters:

H	$\frac{\zeta}{m\omega^2}$	$\frac{k_B T}{m\omega^2}\beta^2$
0.74	0.40	0.81

A prediction for three-point autocorrelation

- GLE with fGn predicts time symmetry

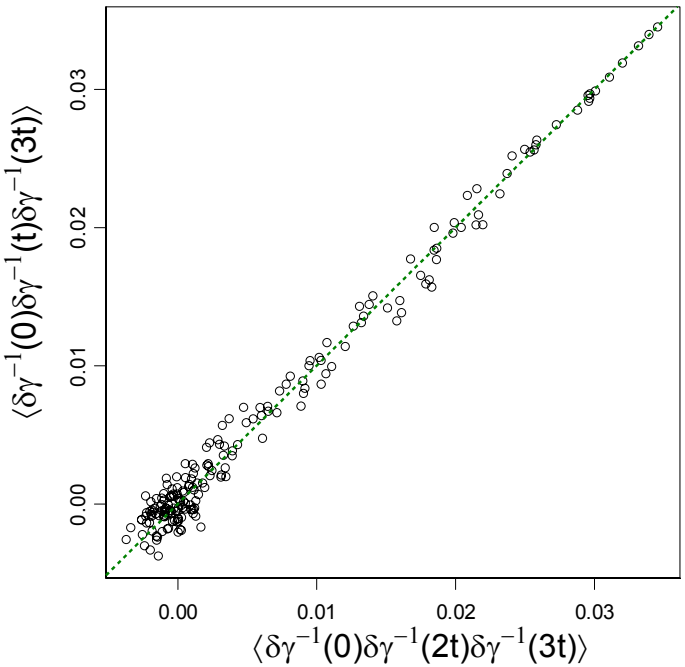
$$E\{\delta\gamma(0)^{-1}\,\delta\gamma(t_1)^{-1}\,\delta\gamma(t_1+t_2)^{-1}\}$$
$$= E\{\delta\gamma(0)^{-1}\,\delta\gamma(t_2)^{-1}\,\delta\gamma(t_1+t_2)^{-1}\}$$



- In particular

$$E\{\delta\gamma^{-1}(0)\,\delta\gamma^{-1}(t)\,\delta\gamma^{-1}(3t)\}$$
$$= E\{\delta\gamma^{-1}(0)\,\delta\gamma^{-1}(2t)\,\delta\gamma^{-1}(3t)\}\ \text{for all}\ t$$

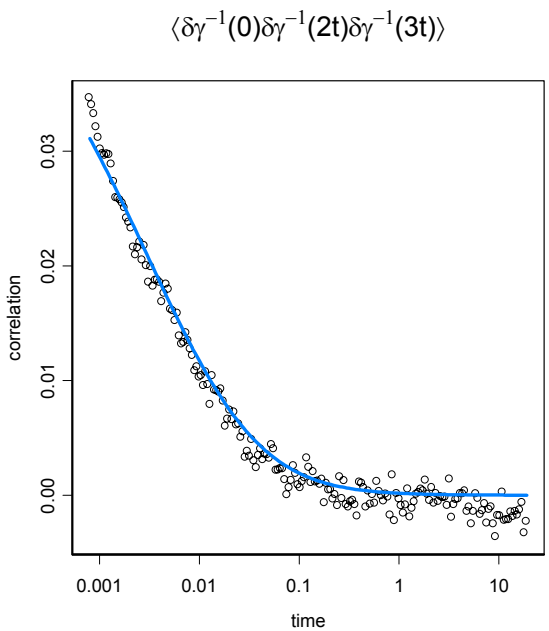
- Check with experiments:

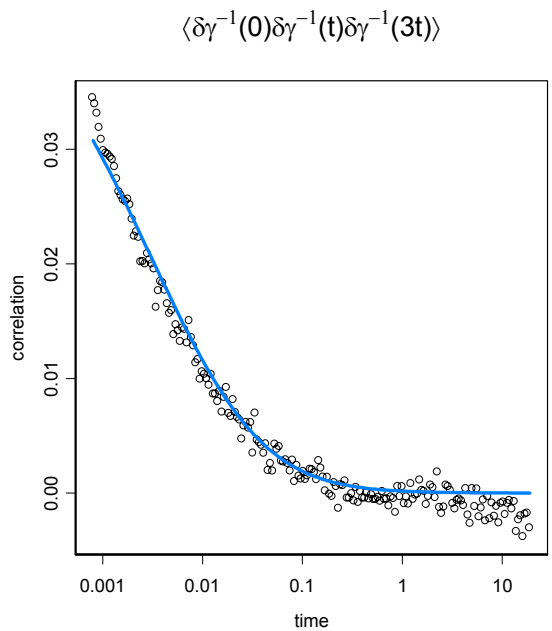


$$E\{\delta\gamma^{-1}(0)\,\delta\gamma^{-1}(t)\,\delta\gamma^{-1}(3t)\}$$

versus

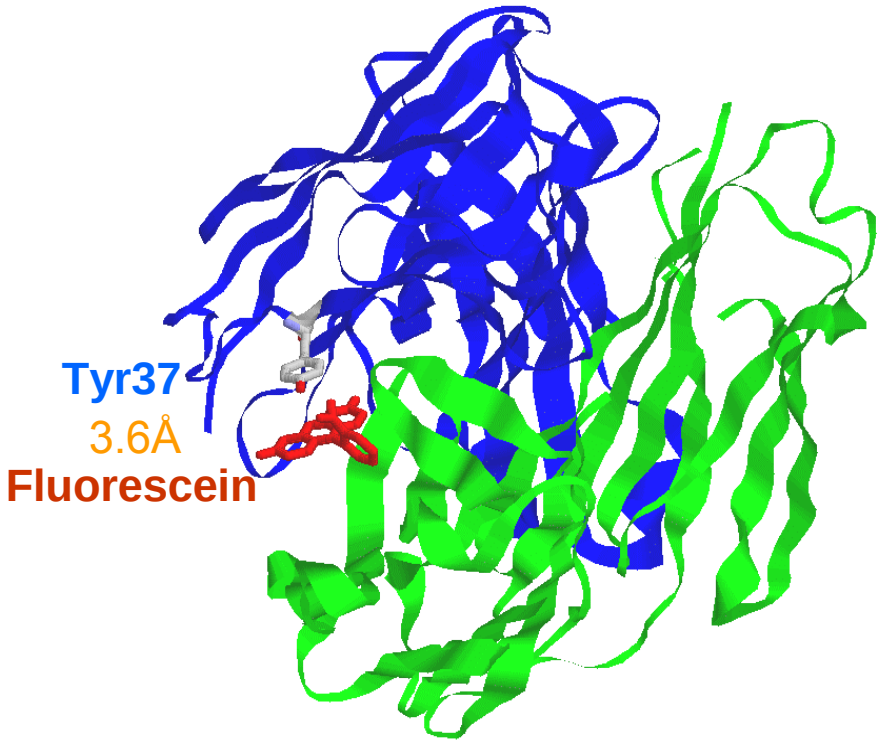
$$E\{\delta\gamma^{-1}(0)\,\delta\gamma^{-1}(2t)\,\delta\gamma^{-1}(3t)\}$$





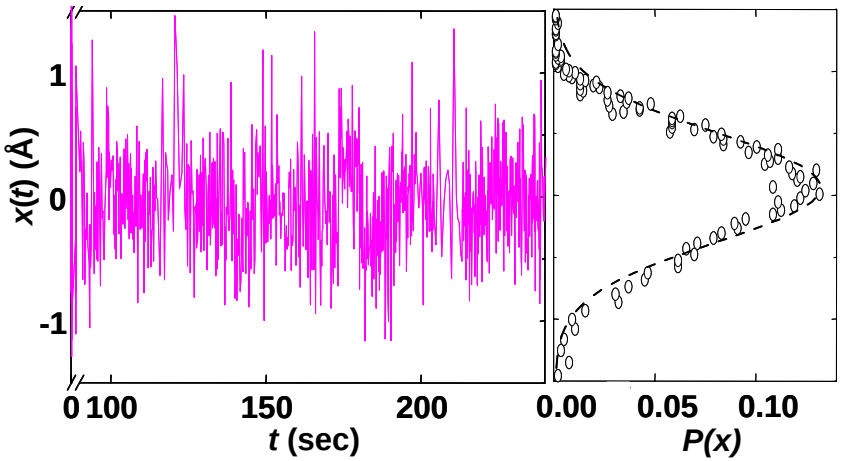
Another system

A protein complex formed between fluorescein (FL) and monoclonal anti-fluorescein (anti-FL)



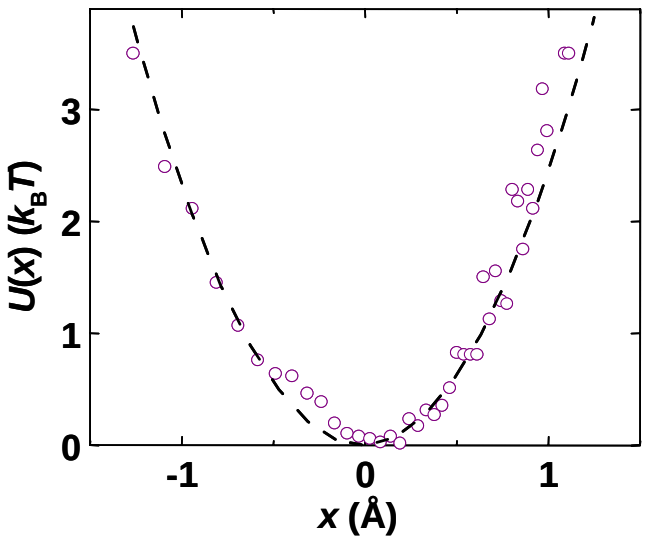
Min, *et al*. *Phys. Rev. Lett.* **94**, 198302 (2005).

- Obtain distance fluctuation from $\gamma^{-1}(t) = [k_0 e^{-\beta(X_{eq}+X_t)}]^{-1}$

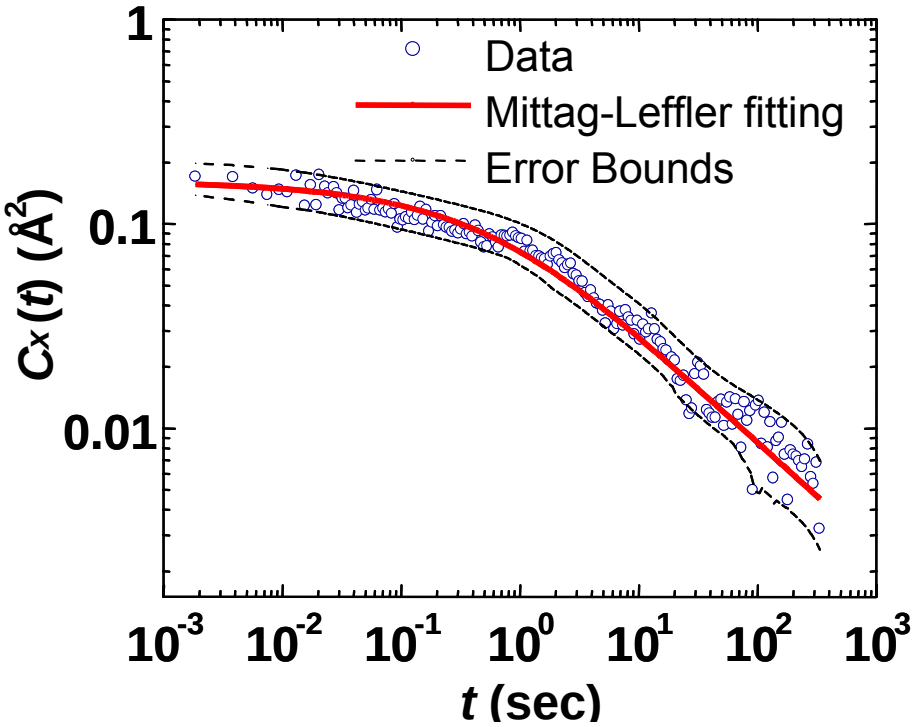


- Since $P(x) \propto \exp(-U(x)/k_B T)$

  Potential function $\hat{U}(x) = -k_B T \ln \hat{P}(x)$



Autocorrelation of distance fluctuation



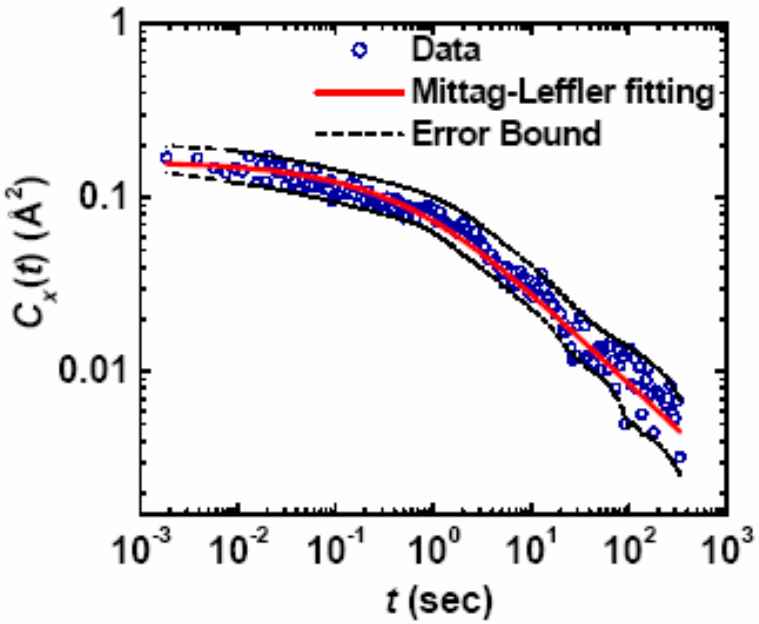
$$m\omega^2 x(t) = -\zeta \int_{-\infty}^{t} \dot{x}(u) K(t-u)\,du + F(t)$$

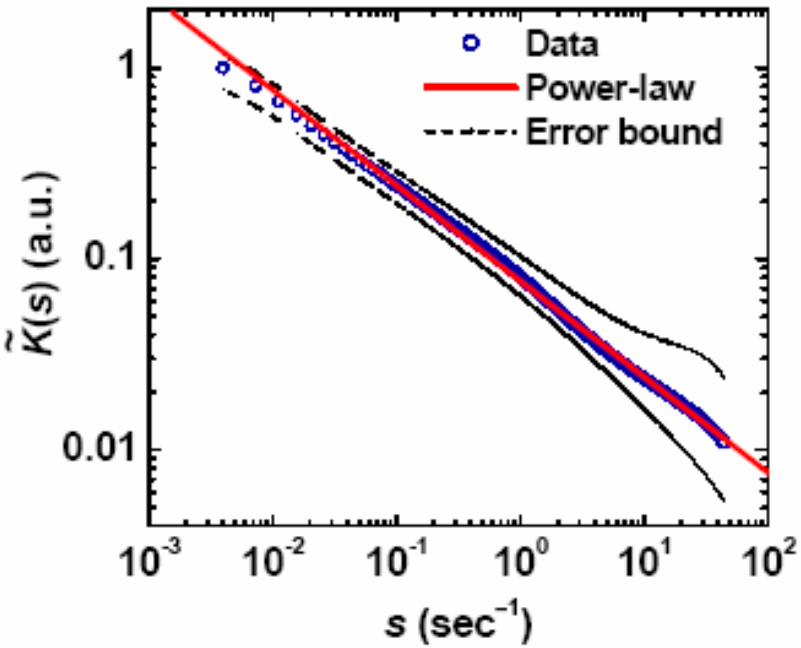
one-to-one correspondence

$$\tilde{K}(s) = \frac{m\omega^2}{\zeta} \frac{\tilde{C}_x(s)}{C_x(0) - s\tilde{C}_x(s)}$$

Experimental Memory kernel

$$\tilde{K}(s) = \frac{m\omega^2}{\zeta} \frac{\tilde{C}_x(s)}{C_x(0) - s\tilde{C}_x(s)}$$





$$K(t) \propto t^{-\alpha-1} = t^{-0.51 \pm 0.07}$$

Brief Recap

- Propose Generalized Langevin Equation with fGn to explain subdiffusion
- Explains the observed conformational dynamics
- One set of parameters fits all
- Key model assumptions verified from experiments

Michaelis-Menten Mechnism

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} ES \xrightarrow{k_2} E^0 + P, \qquad E^0 \xrightarrow{k_3} E$$

$$\frac{d[E]}{dt} = -k_1[E][S] + k_{-1}[ES]$$

$$\frac{d[ES]}{dt} = k_1[E][S] - (k_{-1} + k_2)[ES]$$

$$\frac{d[E^0]}{dt} = \frac{d[P]}{dt} = k_2[ES]$$

⇩

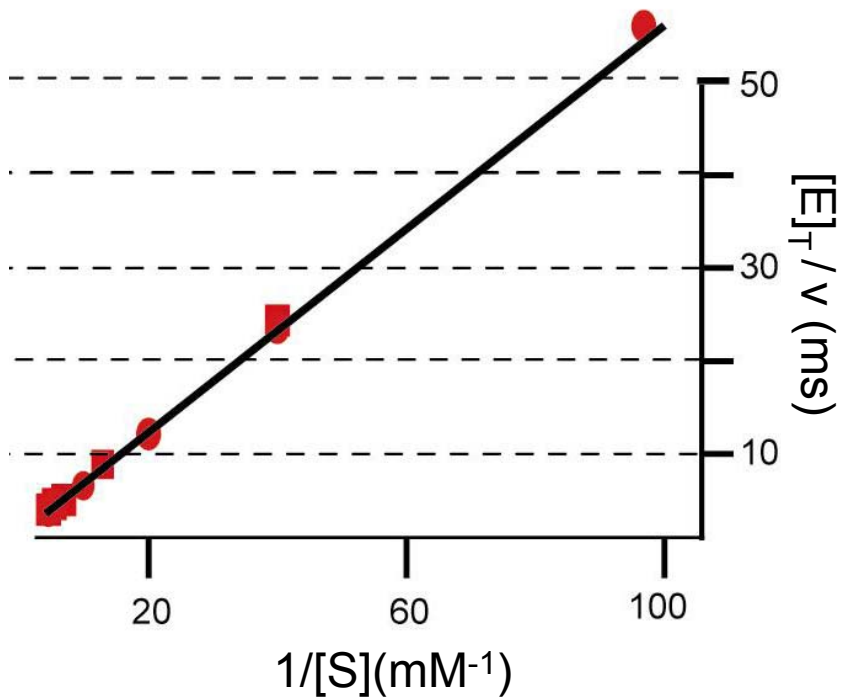
Classical Michaelis-Menten equation

$$v = \frac{v_{\max}[S]}{[S] + K_M},$$

$$v_{\max} = k_2([E] + [ES])$$

$$K_M = (k_{-1} + k_2)/k_1$$

Lineweaver-Burke plot



Single-molecule case

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} ES \xrightarrow{k_2} E^0 + P$$

$$\frac{dP_E(t)}{dt} = -k_1[S]P_E(t) + k_{-1}P_{ES}(t)$$

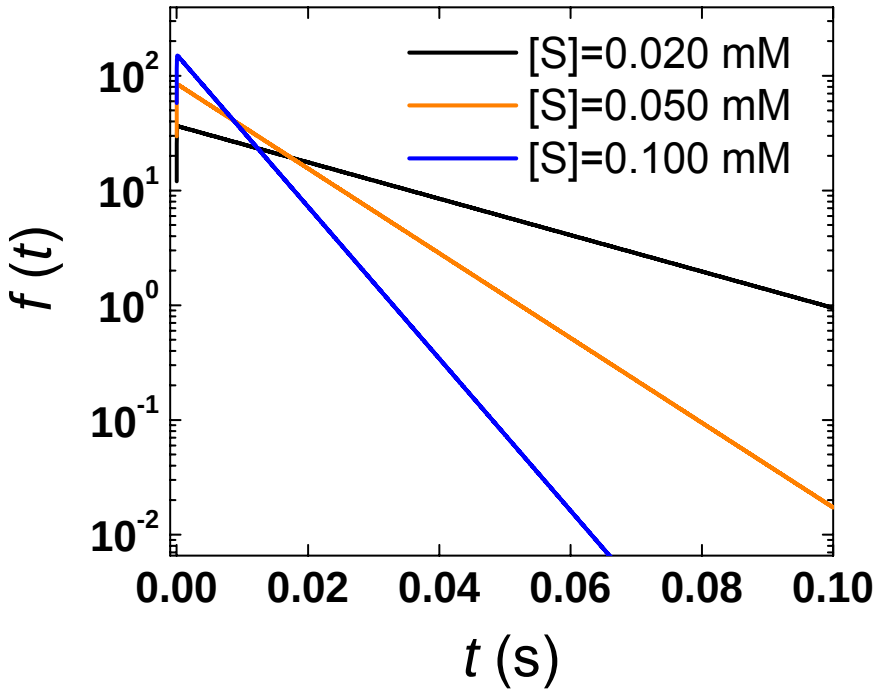
$$\frac{dP_{ES}(t)}{dt} = k_1[S]P_E(t) - (k_{-1} + k_2)P_{ES}(t)$$

$$\frac{dP_{E^0}(t)}{dt} = k_2 P_{ES}(t)$$

⇒ Turnover time distribution

$$f(t) = \frac{k_1 k_2 [S]}{2A}\left[\exp(A+B)t - \exp(B-A)t\right]$$

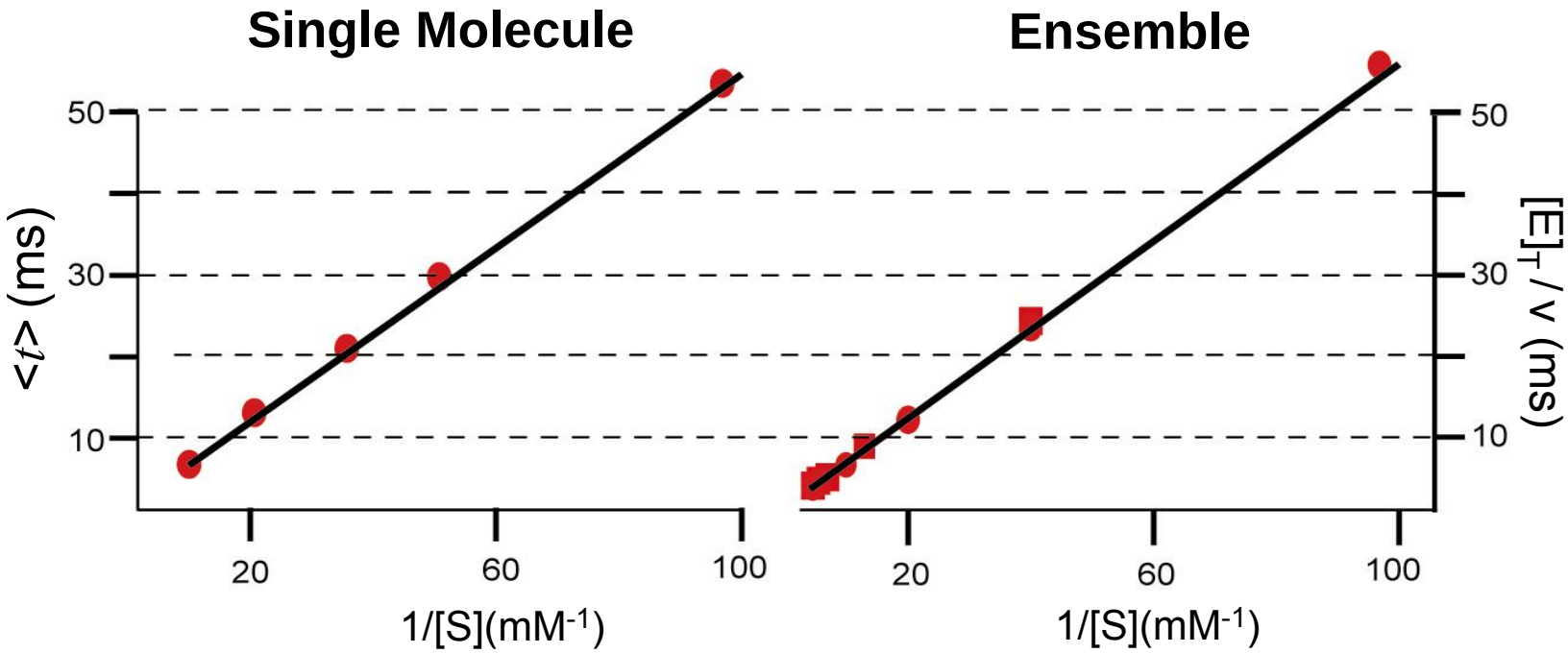
$$A = \sqrt{B^2 - k_1 k_2 [S]},\ B = -(k_1[S] + k_{-1} + k_2)/2$$



⇩

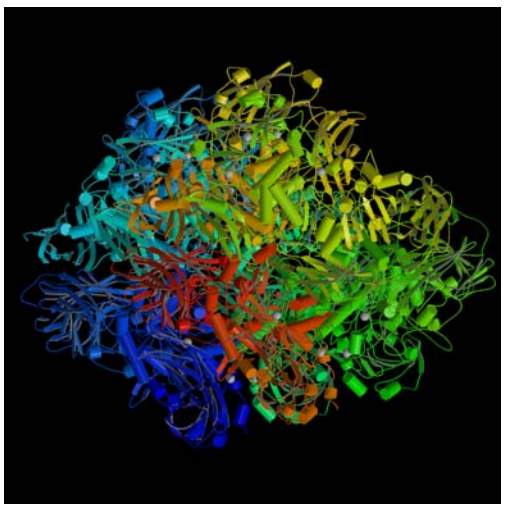
Reaction rate:

$$v = \frac{1}{E(T)} = \frac{k_2[S]}{[S] + K_M}$$: Still obey the hyperbolic form



English *et al*., Nature Chem. Biol., 2, 87 (2006)

β-galactosidase



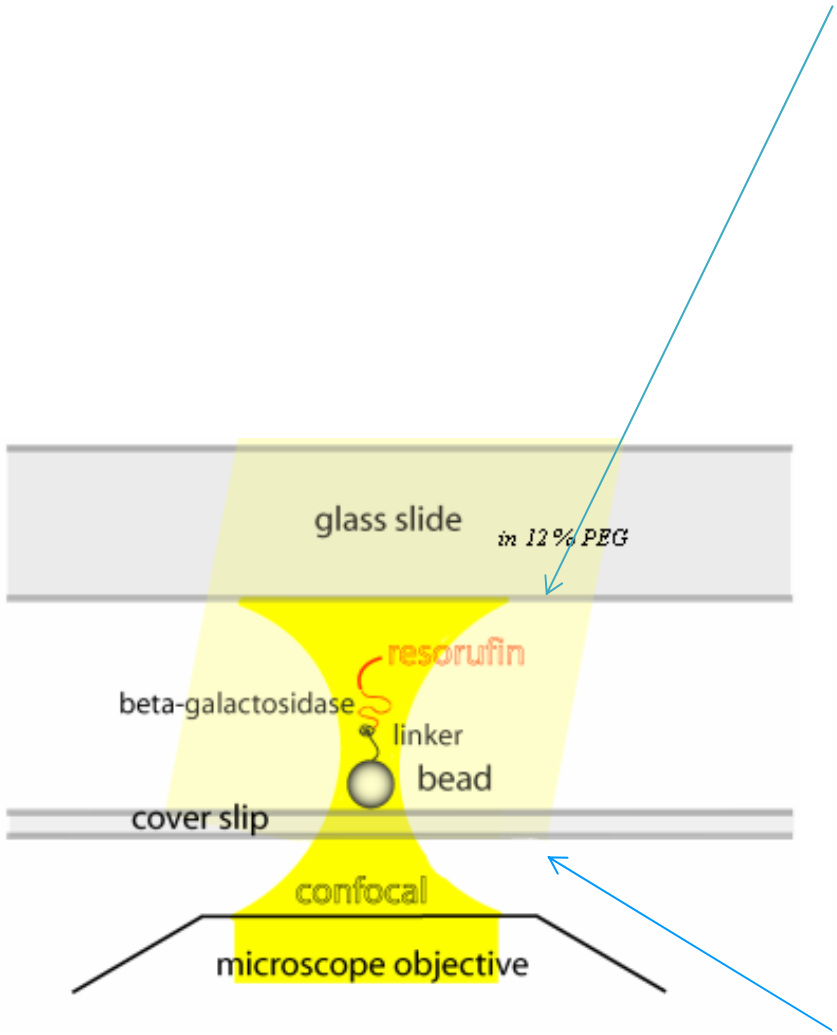
E. coli ß-gal catalyzes Hydrolysis of Lactose

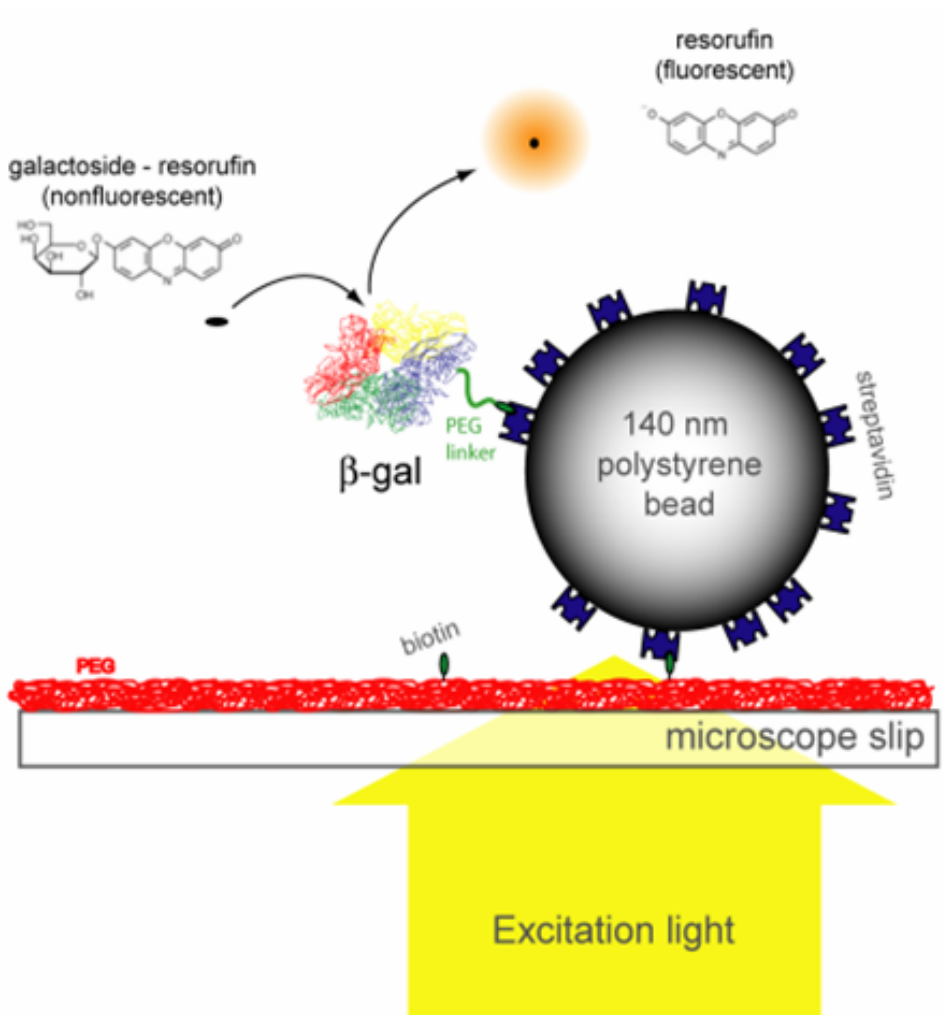
The experiment uses **photogenic** substrate

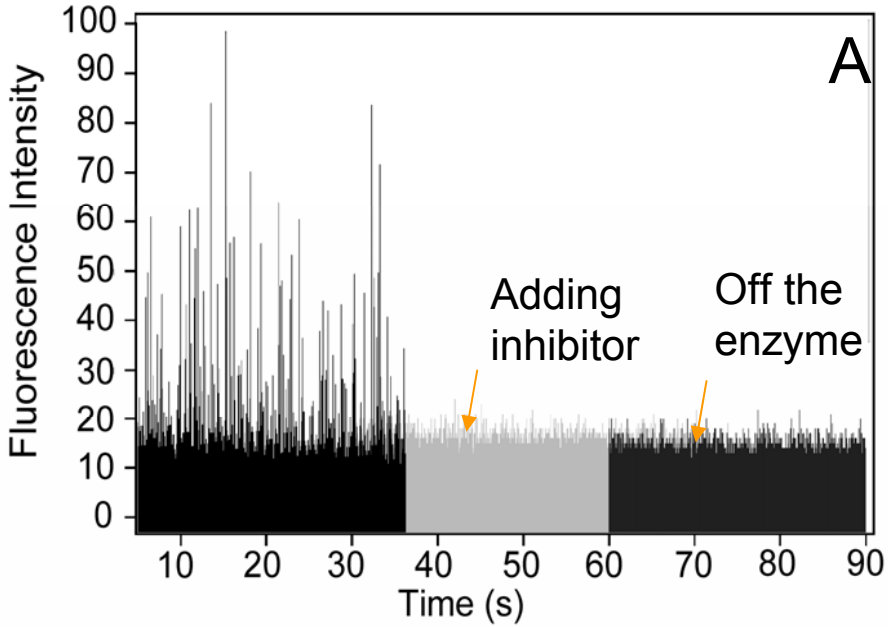
$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_2} E^0 + P$$

Single Molecule Turnover Experiment of ß-galactosidase

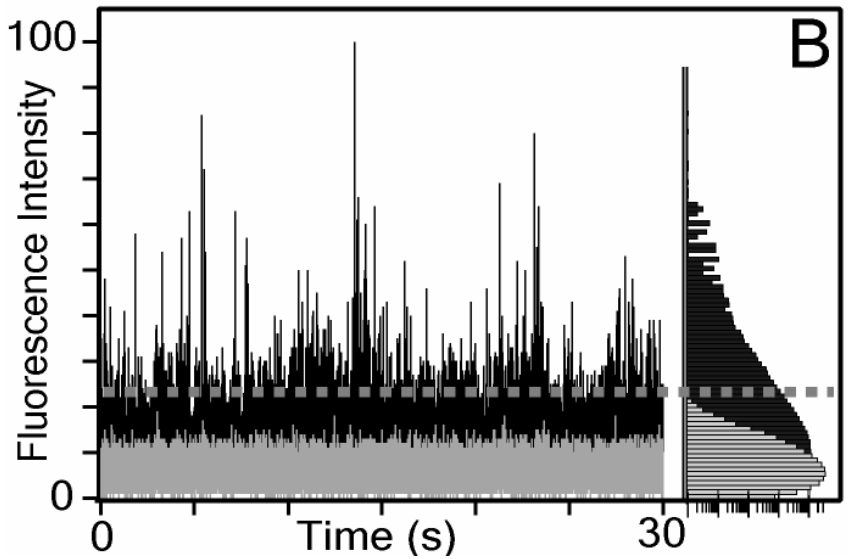
Each enzymatic turnover creates a fluorescent burst





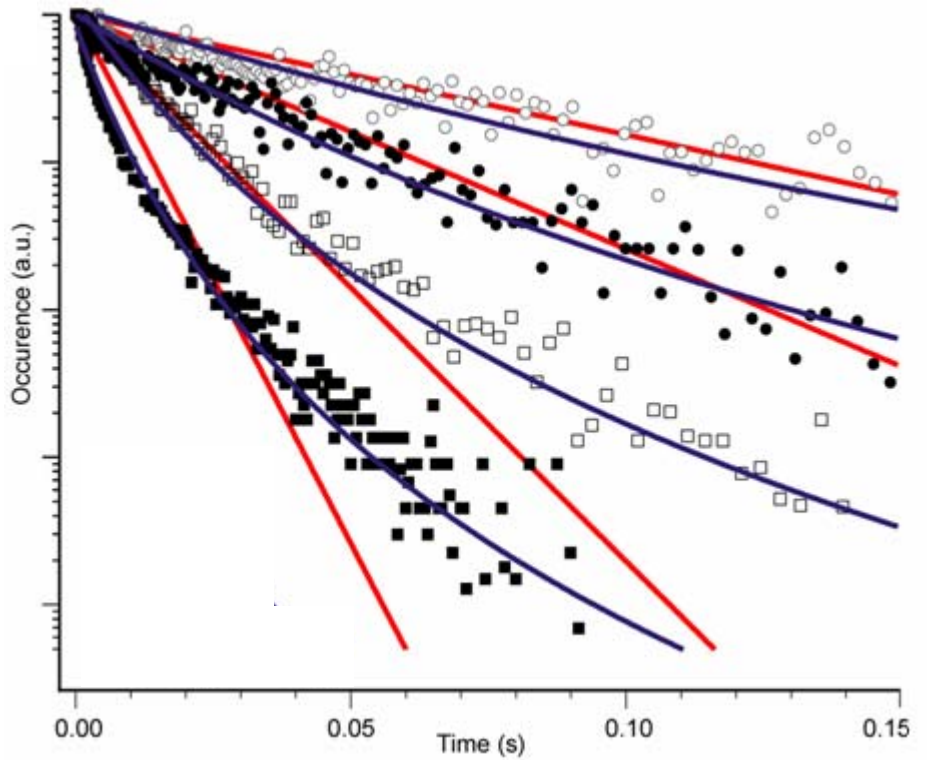


Low Substrate Concentration 20μM



High Substrate Concentration 100μM

Multi-exponential Distributions of Turnover Times



[S]=10 μM

[S]=20 μM

[S]=50 μM

[S]=100 μM

- Skewed decay at high substrate concentration
- Single exponential decay at low substrate concentration

Memory between successive turnover times

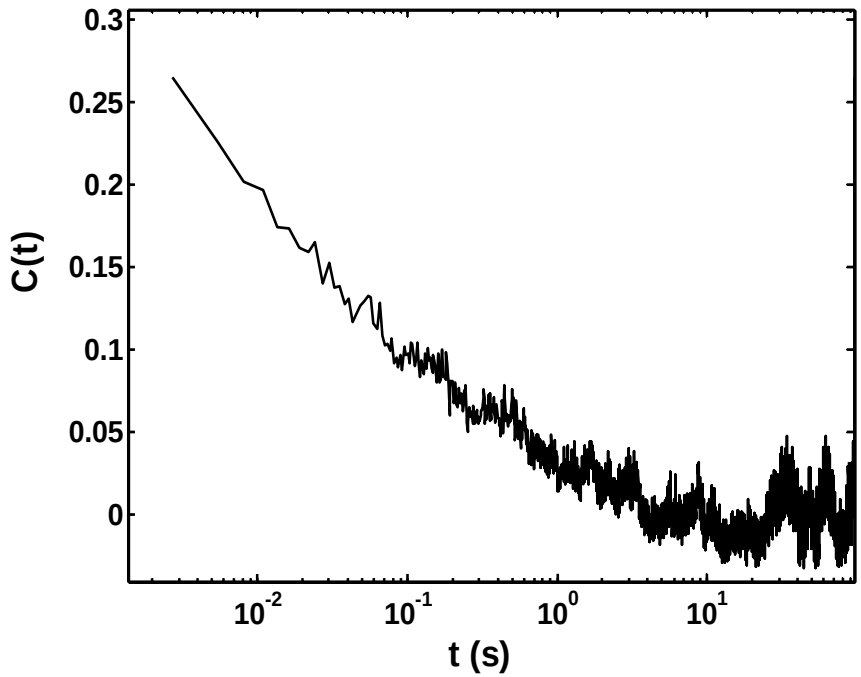
- Under Michaelis-Menten Mechnism

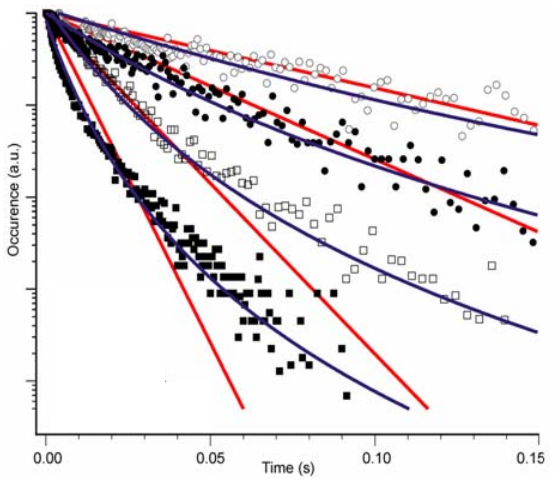
$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} ES \xrightarrow{k_2} E^0 + P$$

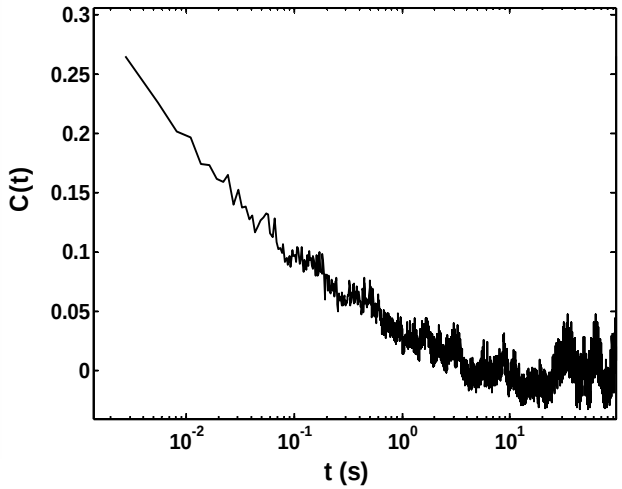
three-state continuous-time **Markov** chain

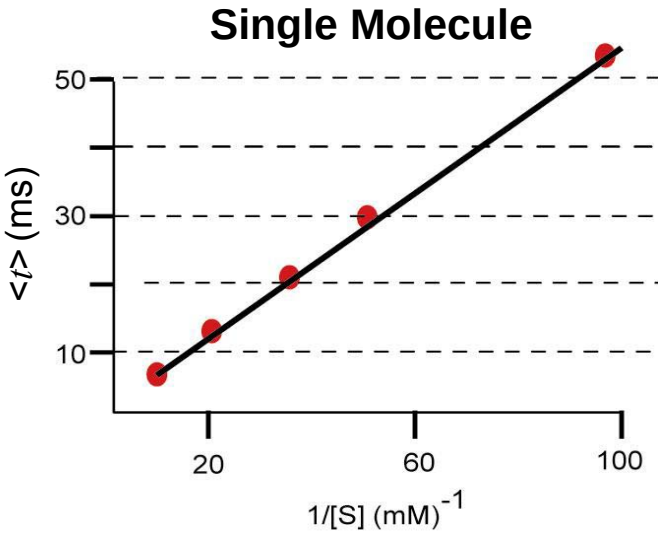
- Successive turnover times should have **NO** correlation

Experimental data




Occurence (a.u.)
0.00
0.05
Time (s)
0.10
0.15


C(t)
0.3
0.25
0.2
0.15
0.1
0.05
0
10^{-2}
10^{-1}
10^{0}
10^{1}
t (s)


Single Molecule
50
30
10
<t> (ms)
20
60
100
1/[S] (mM)$^{-1}$

✗ ✗ ✓ ?

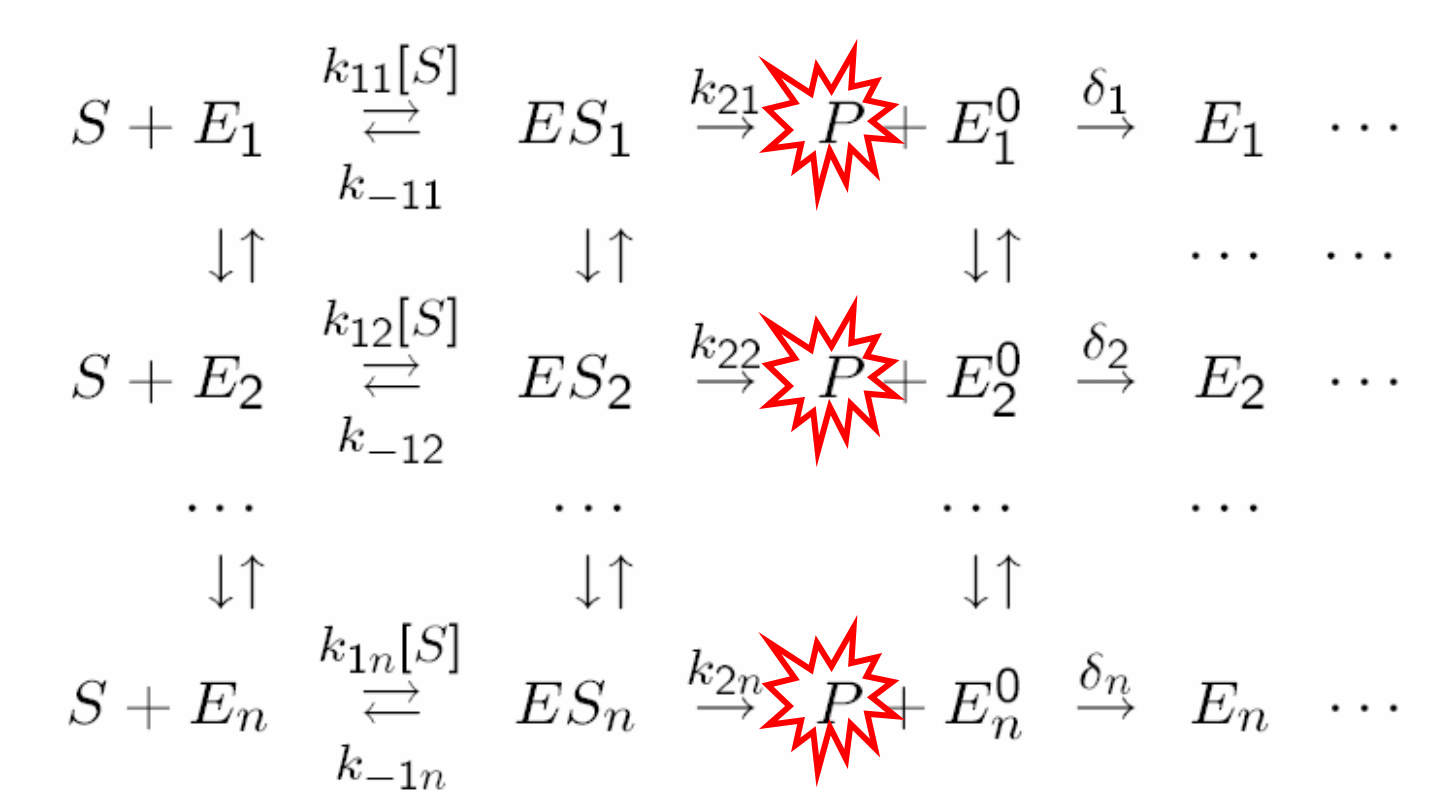
Dynamic disorder – the fluctuation of enzyme

- An enzyme is a **dynamic** entity with constant spontaneous conformation fluctuation

- Conformation **fluctuation** occurs on a board range of time scales

- Different conformation could have **different** enzymatic reaction rate constants.

Dynamic disorder – the fluctuation of enzyme

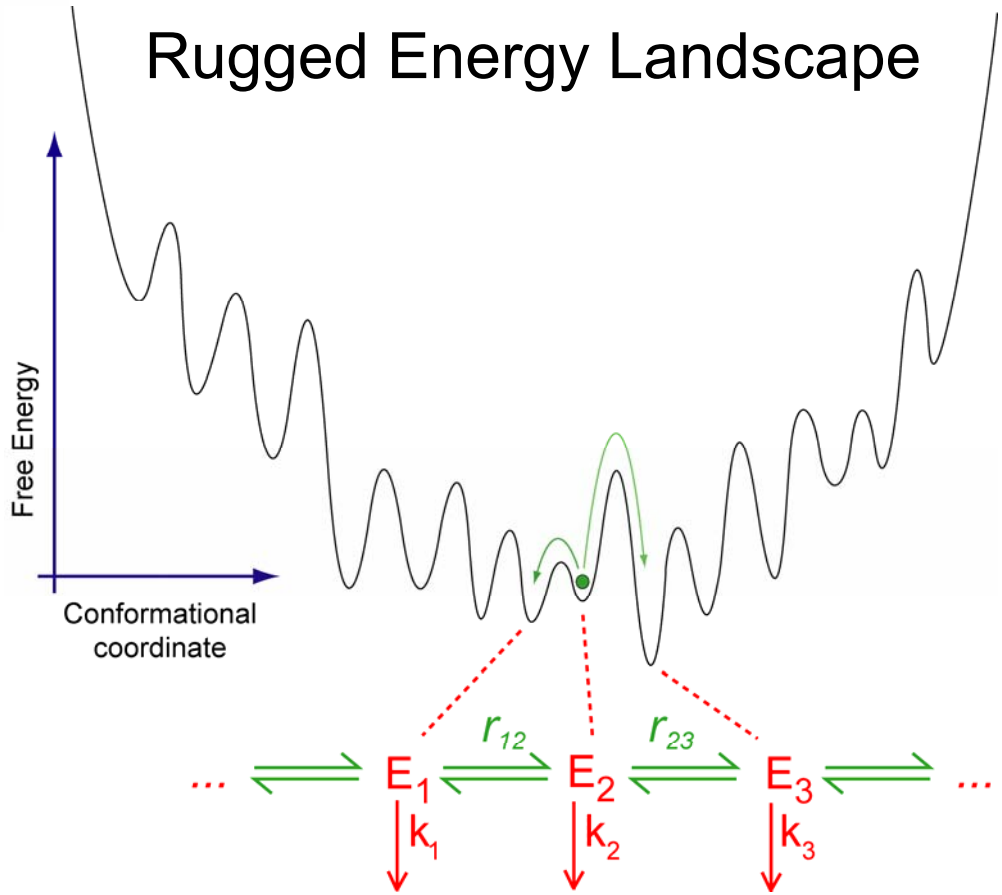


All the E_1, E_2, … are experimentally indistinguishable

Kou *et al.*, *J. Phys. Chem.* B, 109, 19068 (2005)

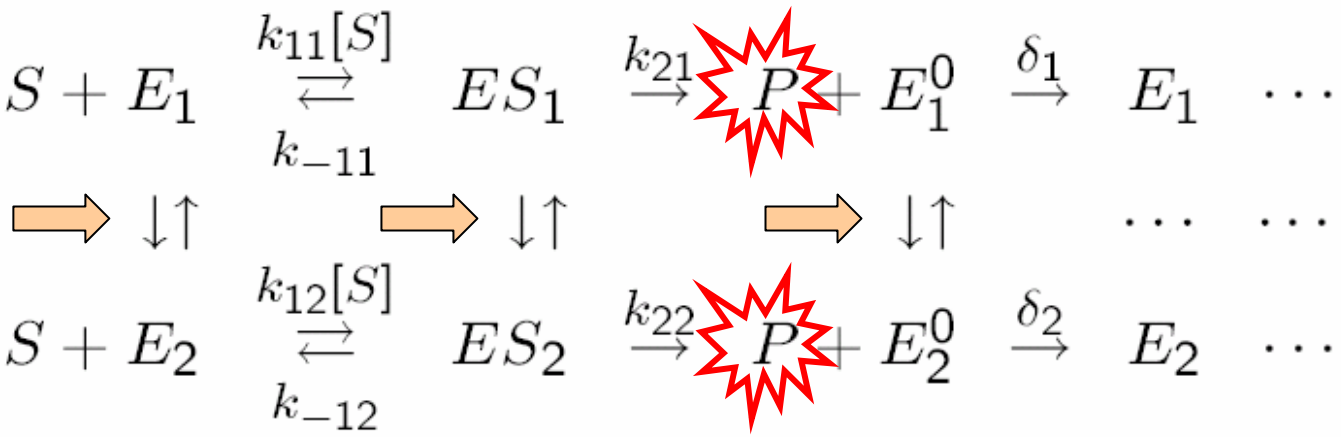
Dynamic disorder – the fluctuation of enzyme

$$
\begin{array}{ccccccc}
S+E_1 & \underset{k_{-11}}{\overset{k_{11}[S]}{\rightleftarrows}} & ES_1 & \overset{k_{21}}{\rightarrow} & P+E_1^0 & \overset{\delta_1}{\rightarrow} & E_1 \quad \cdots \\
\downarrow\uparrow & & \downarrow\uparrow & & \downarrow\uparrow & & \cdots \quad \cdots \\
S+E_2 & \underset{k_{-12}}{\overset{k_{12}[S]}{\rightleftarrows}} & ES_2 & \overset{k_{22}}{\rightarrow} & P+E_2^0 & \overset{\delta_2}{\rightarrow} & E_2 \quad \cdots \\
\cdots & & \cdots & & \cdots & & \cdots \\
\downarrow\uparrow & & \downarrow\uparrow & & \downarrow\uparrow & & \\
S+E_n & \underset{k_{-1n}}{\overset{k_{1n}[S]}{\rightleftarrows}} & ES_n & \overset{k_{2n}}{\rightarrow} & P+E_n^0 & \overset{\delta_n}{\rightarrow} & E_n \quad .
\end{array}
$$



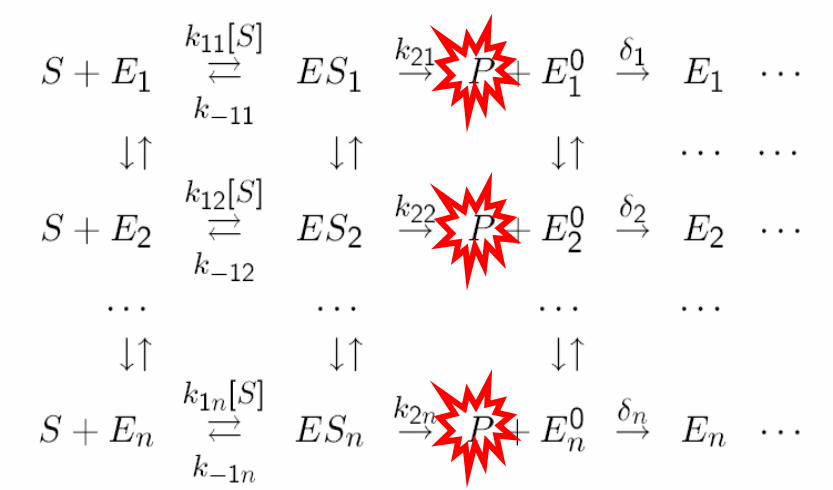
Explain the memory

If parallel transition rates are small



Transitions will stay in one channel for a quite while before going to the next

Naturally give rise to the strong correlation



Turnover time:
first passage time

Can be solved via Laplace transform and matrix analysis

Under various conditions

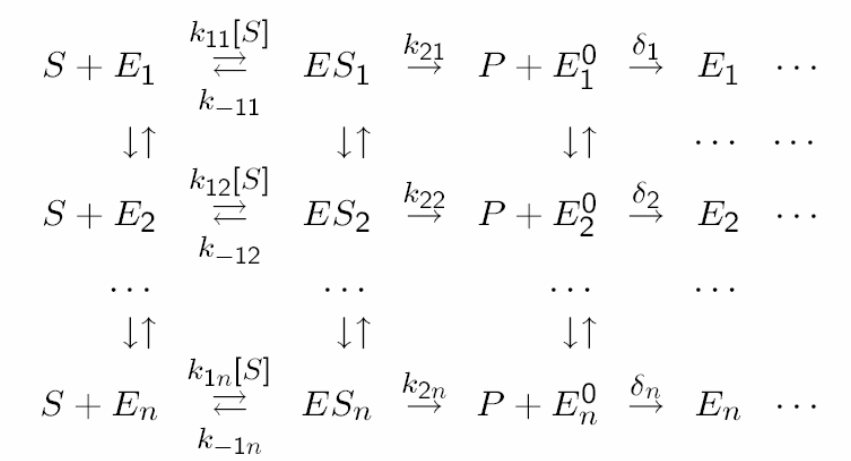
Single Molecule Michaelis-Menten Equation

$$v = \frac{1}{E(T)} = \frac{\gamma_2[S]}{[S] + C_M}$$

$$\gamma_2 = \left[\int_0^\infty \frac{p(k_2)}{k_2} dk_2 \right]^{-1}$$

$$C_M = \frac{\gamma_2 + k_{-1}}{k_1}$$

Weighted harmonic mean



Reaction rate

$$v = \frac{1}{E(T)} = \frac{\gamma_2[S]}{[S]+C_M}$$

If one of the following conditions holds:

(a) slow interconversion between E_i

(b) slow interconversion between ES_i

} Quasi static

(c) fast interconversion between E_i

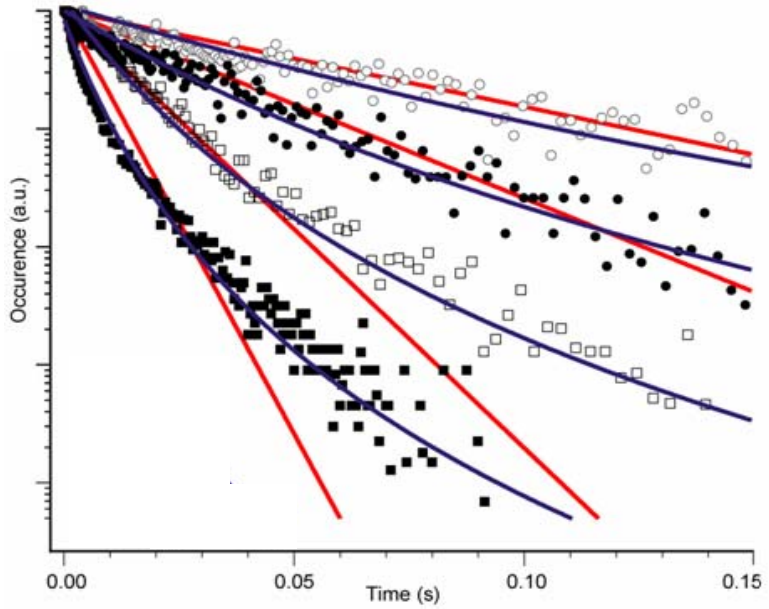
(d) fast interconversion between ES_i

(e) $k_{-1i} >> k_{2i}$ Quasi equilibrium

(f) k_{2i}/k_{-1i} = const Conformational equilibrium

Model fitting

$$
\begin{array}{ccccccc}
S + E_1 & \underset{k_{-11}}{\overset{k_{11}[S]}{\rightleftarrows}} & ES_1 & \overset{k_{21}}{\rightarrow} & P + E_1^0 & \overset{\delta_1}{\rightarrow} & E_1 \\
\downarrow\uparrow & & \downarrow\uparrow & & \downarrow\uparrow & & \cdots \\
S + E_2 & \underset{k_{-12}}{\overset{k_{12}[S]}{\rightleftarrows}} & ES_2 & \overset{k_{22}}{\rightarrow} & P + E_2^0 & \overset{\delta_2}{\rightarrow} & E_2 \\
\cdots & & \cdots & & \cdots & & \cdots \\
\downarrow\uparrow & & \downarrow\uparrow & & \downarrow\uparrow & & \\
S + E_n & \underset{k_{-1n}}{\overset{k_{1n}[S]}{\rightleftarrows}} & ES_n & \overset{k_{2n}}{\rightarrow} & P + E_n^0 & \overset{\delta_n}{\rightarrow} & E_n
\end{array}
$$



[S]=10 μM

[S]=20 μM

[S]=50 μM

[S]=100μM

- Skewed decay at high substrate concentration
- Single exponential decay at low concentration

$$k_{11} = k_{12} = \ldots = k_{1n} = k_1$$

$$k_{-11} = k_{-12} = \ldots = k_{-1n} = k_{-1}$$

Turnover Time distribution for fluctuating enzymes

$$
\begin{array}{ccccccc}
S+E_1 & \underset{k_{-11}}{\overset{k_{11}[S]}{\rightleftarrows}} & ES_1 & \overset{k_{21}}{\rightarrow} & P+E_1^0 & \overset{\delta_1}{\rightarrow} & E_1 \quad \cdots \\
\downarrow\uparrow & & \downarrow\uparrow & & \downarrow\uparrow & & \cdots \quad \cdots \\
S+E_2 & \underset{k_{-12}}{\overset{k_{12}[S]}{\rightleftarrows}} & ES_2 & \overset{k_{22}}{\rightarrow} & P+E_2^0 & \overset{\delta_2}{\rightarrow} & E_2 \quad \cdots \\
\cdots & & \cdots & & \cdots & & \cdots \\
\downarrow\uparrow & & \downarrow\uparrow & & \downarrow\uparrow & & \\
S+E_n & \underset{k_{-1n}}{\overset{k_{1n}[S]}{\rightleftarrows}} & ES_n & \overset{k_{2n}}{\rightarrow} & P+E_n^0 & \overset{\delta_n}{\rightarrow} & E_n \quad \cdots
\end{array}
$$

Quasi Static Limit:

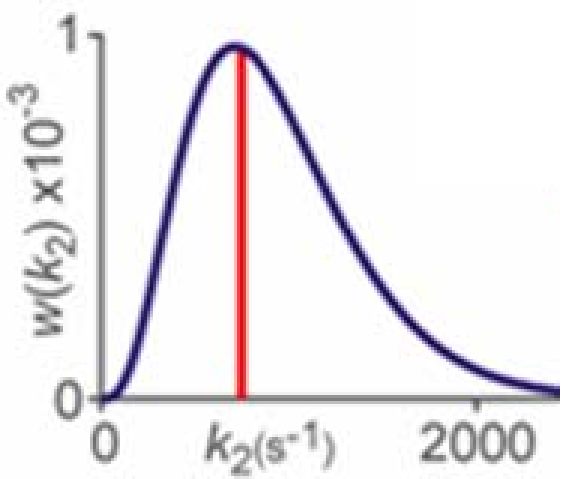
$$f(t) = \int_0^\infty dk_2 w(k_2) \frac{k_1 k_2 [S]}{2A} \left[\exp(A+B)t - \exp(B-A)t \right]$$

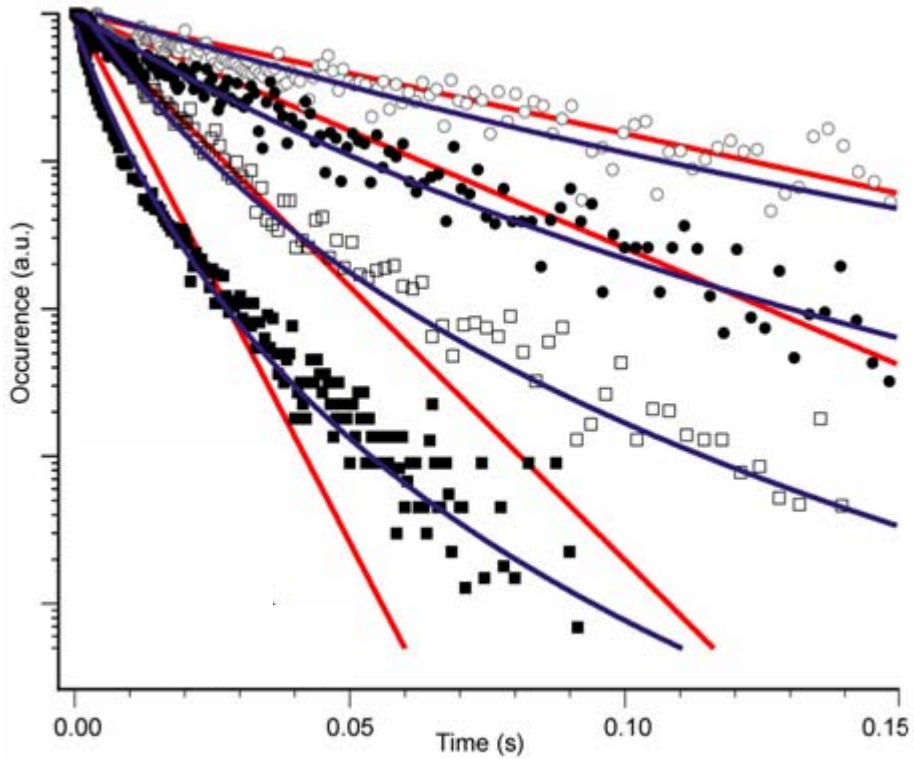
$$A = \sqrt{B^2 - k_1 k_2 [S]},\ B = -(k_1[S] + k_{-1} + k_2)/2$$

Multi-exponential Distributions of Turnover Times

Gamma Distribution

$$w(k_2) = \frac{1}{b^a \Gamma(a)} k_2^{a-1} \exp(-k_2 / b)$$





[S]=10 μM

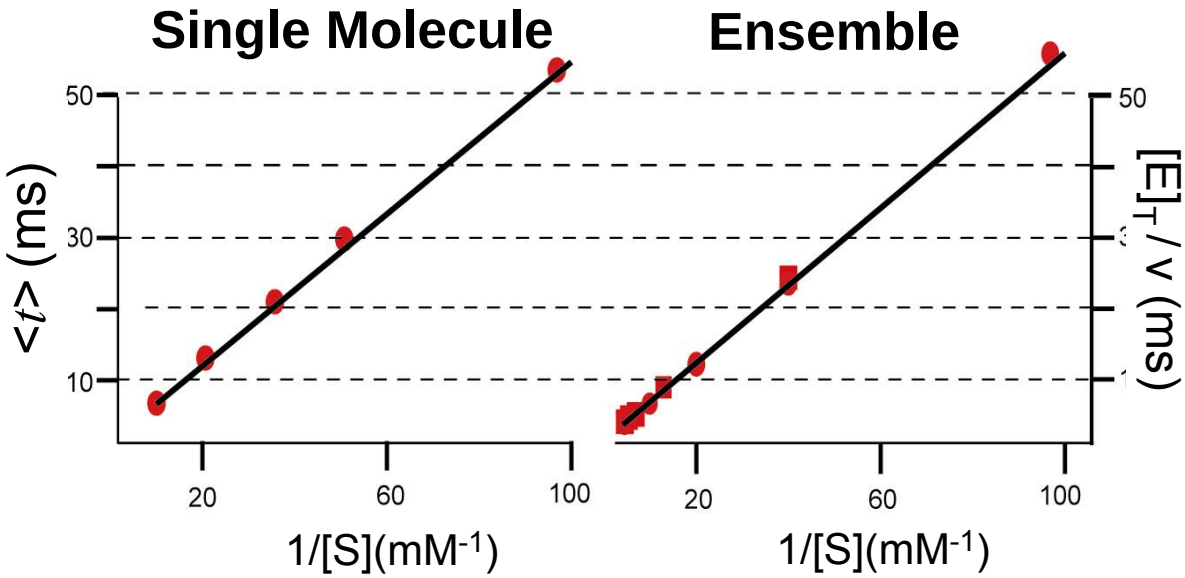
[S]=20 μM

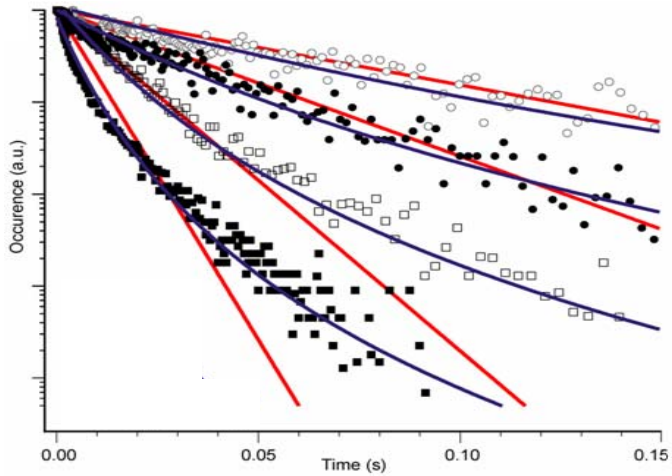
[S]=50 μM

[S]=100 μM

$k_1 = 5 \times 10^7\ \mathrm{M^{-1}s^{-1}}$ $\quad k_{-1} = 1.83 \times 10^4\ \mathrm{s^{-1}}$

$a = 4.2,\ b = 224\ \mathrm{s^{-1}}$





Consequences:

(a) Single Molecule reconciled with ensemble study

(b) Dynamic disorder might be masked in ensemble studies!

(c) The apparent k_2 and K_M of the Michaelis-Menten equation are complex functions of the k_2 and K_M of a large distribution of conformers, different from their conventional interpretations.

Summary

- Michaelis-Menten with dynamic disorder
  - Introduce a stochastic network model
  - Explains experimental puzzle
  - Derive single-molecule Michaelis-Menten equation
  - Dynamic disorder might be masked in ensemble studies!

- Generalized Langevin Equation with fGn
  - Explains the observed conformational dynamics
  - One set of parameters fits all
  - Prediction confirmed by experimental data
  - Each model assumption verified from experiments

Summary (Continued)

- The connection
  - Simple underlying picture behind both
  - An enzyme is a dynamic entity with conformational fluctuation on a board range of time scales.
  - The interconverting conformations have different enzymatic reaction rate constants.

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