Dynamic Disorder in Receptor-ligand Forced Dissociation Experiments

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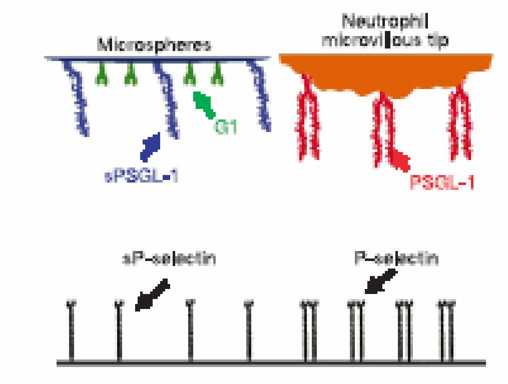
KITP, April 24, 2006

Dynamic Disorders in Force Experiments

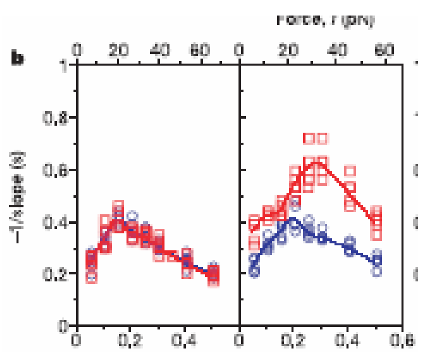
Outline:

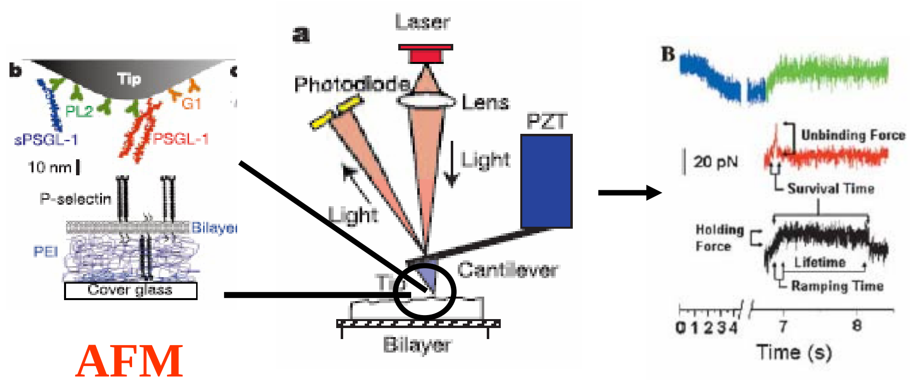
- Background;
- Bell rate model with dynamic disorder;
- Force modulating dynamic disorder;
- Conclusion.

Forced dissociation experiments



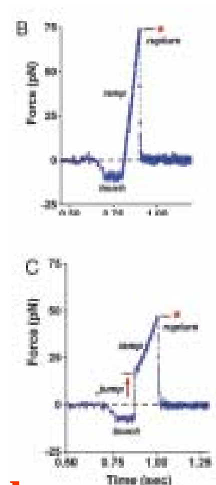
Flow Chamber





AFM

$$F(t)=f_0+r\ t$$



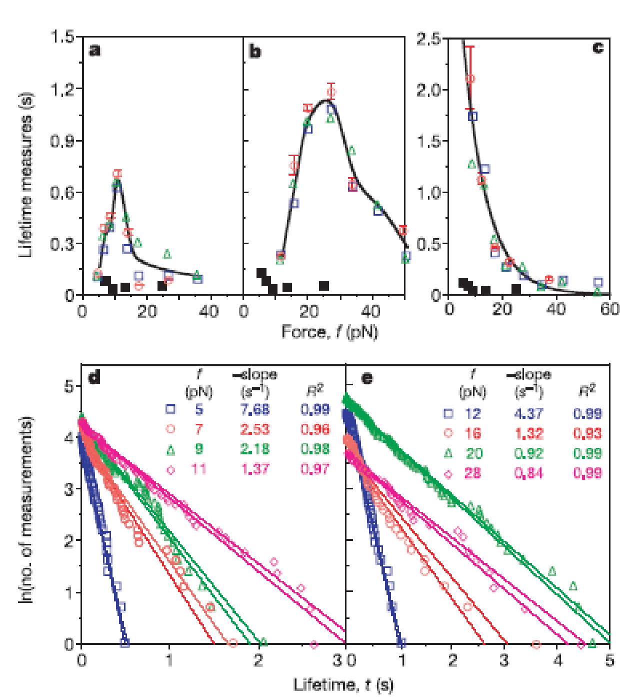
Steady-ramp

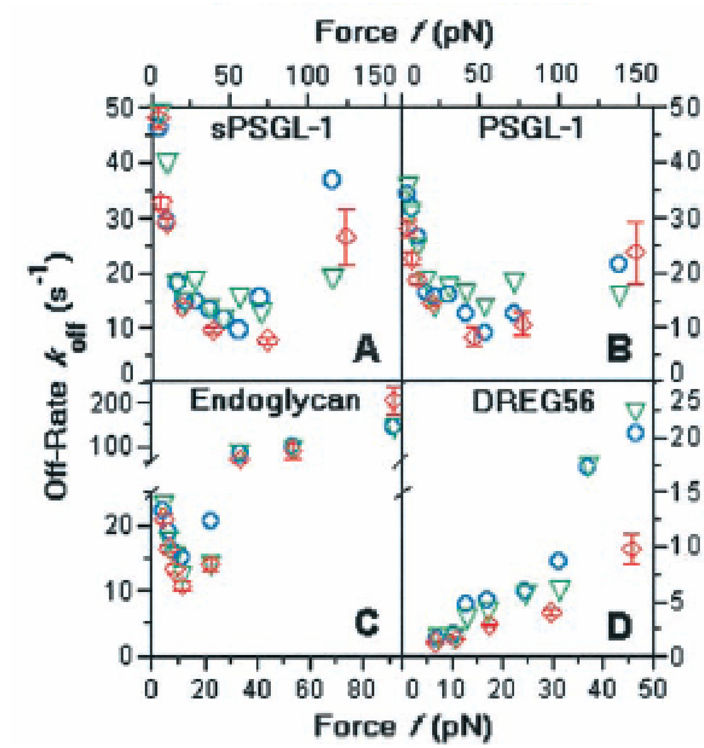
Jump-ramp

Biomembrane Force Probe

Catch-slip bond transitions

- Constant force mode





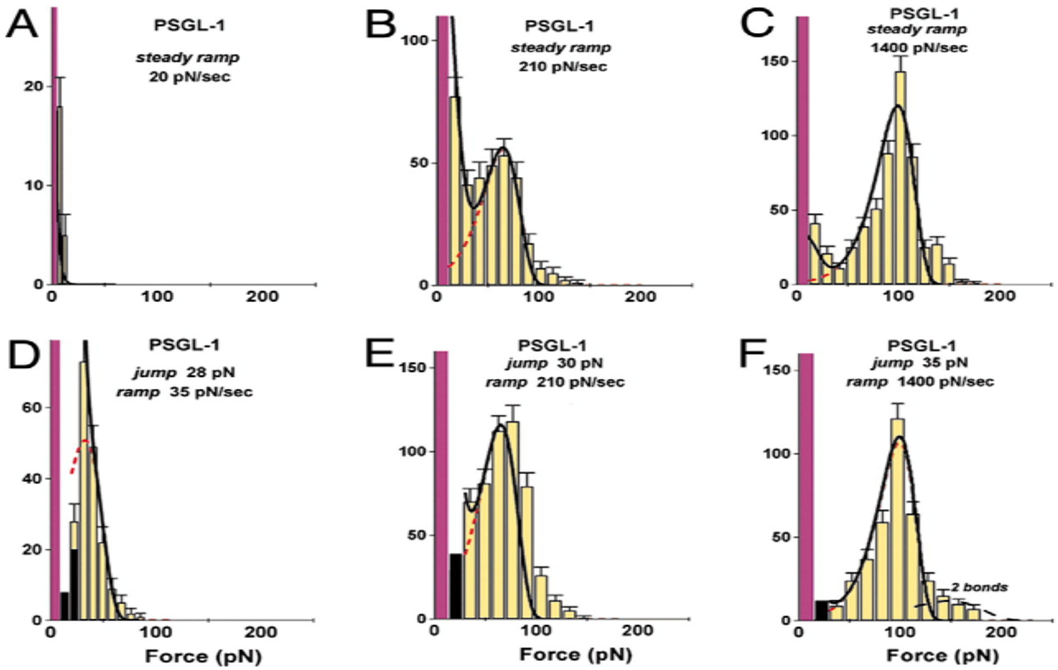
PSGL-1-P-selectin

PSGL-1-L-selectin

Marshall et al. Nature 2003

Sarangapani et al. JBC 2004

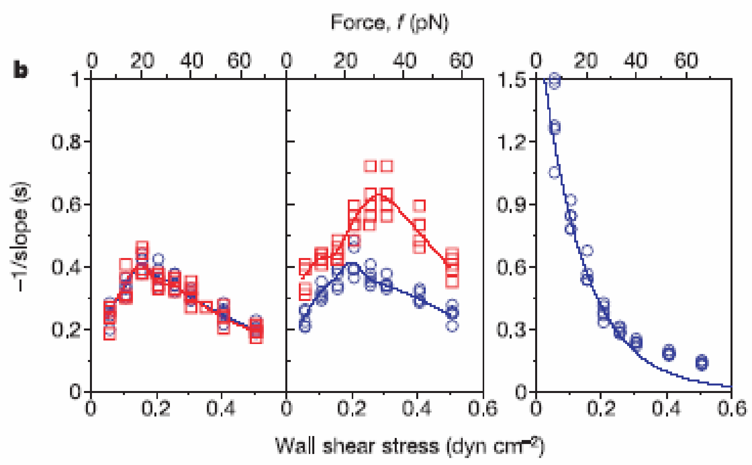
- Dynamic force mode:



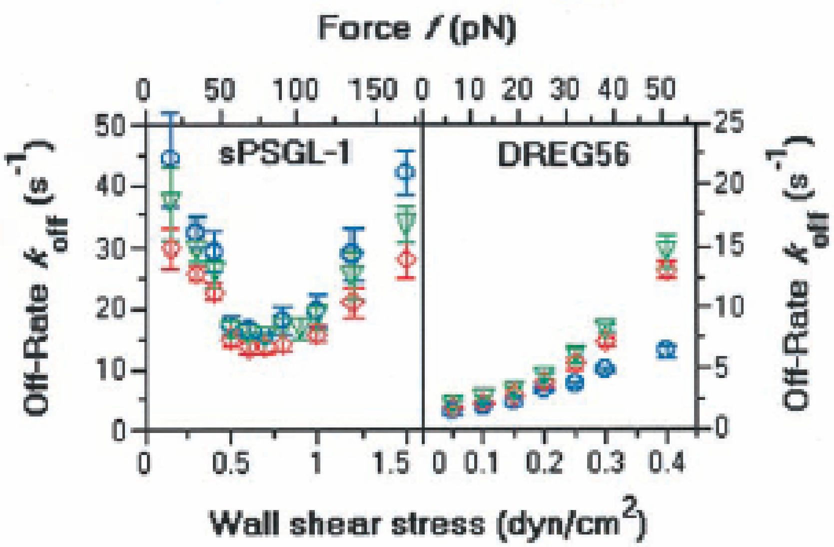
PSGL-1-P-selectin

Evans et al., PNAS 2004

- Flow chamber experiments:



PSGL-1-P-selectin



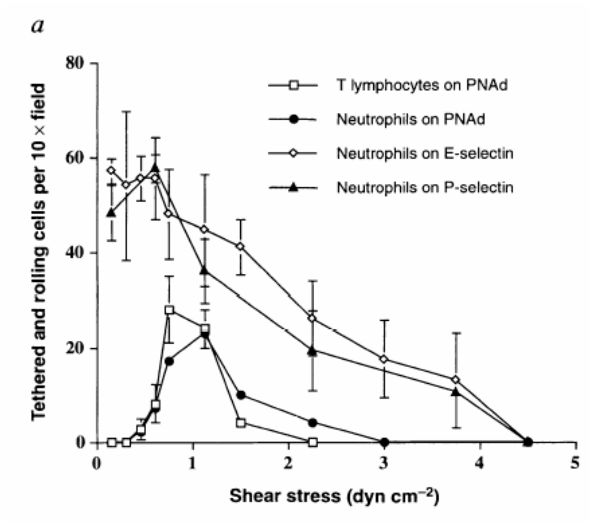
PSGL-1-L-selectin

Marshall et al. Nature 2003

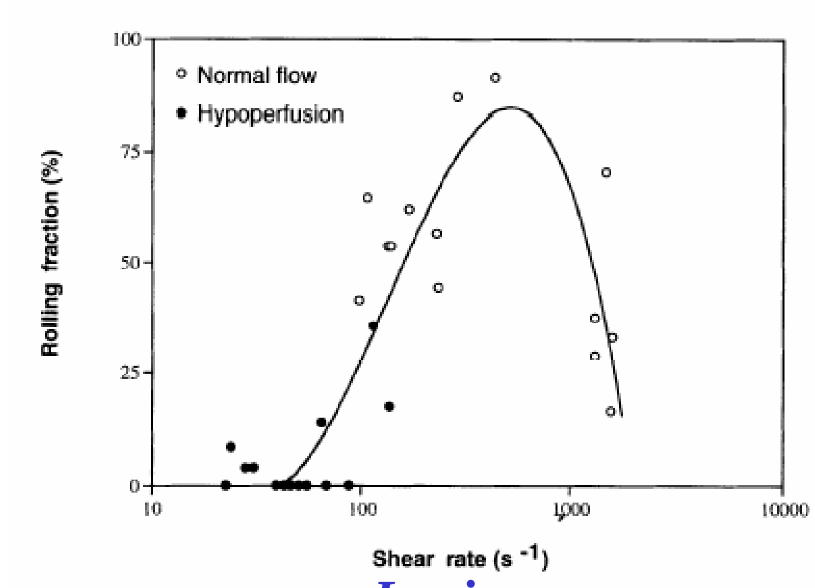
Sarangapani et al. JBC 2004

Important?

- The shear threshold phenomenon: the number of rolling leukocytes increasing and then decreasing while monotonically increasing wall shear stress.



In vitro



In vivo

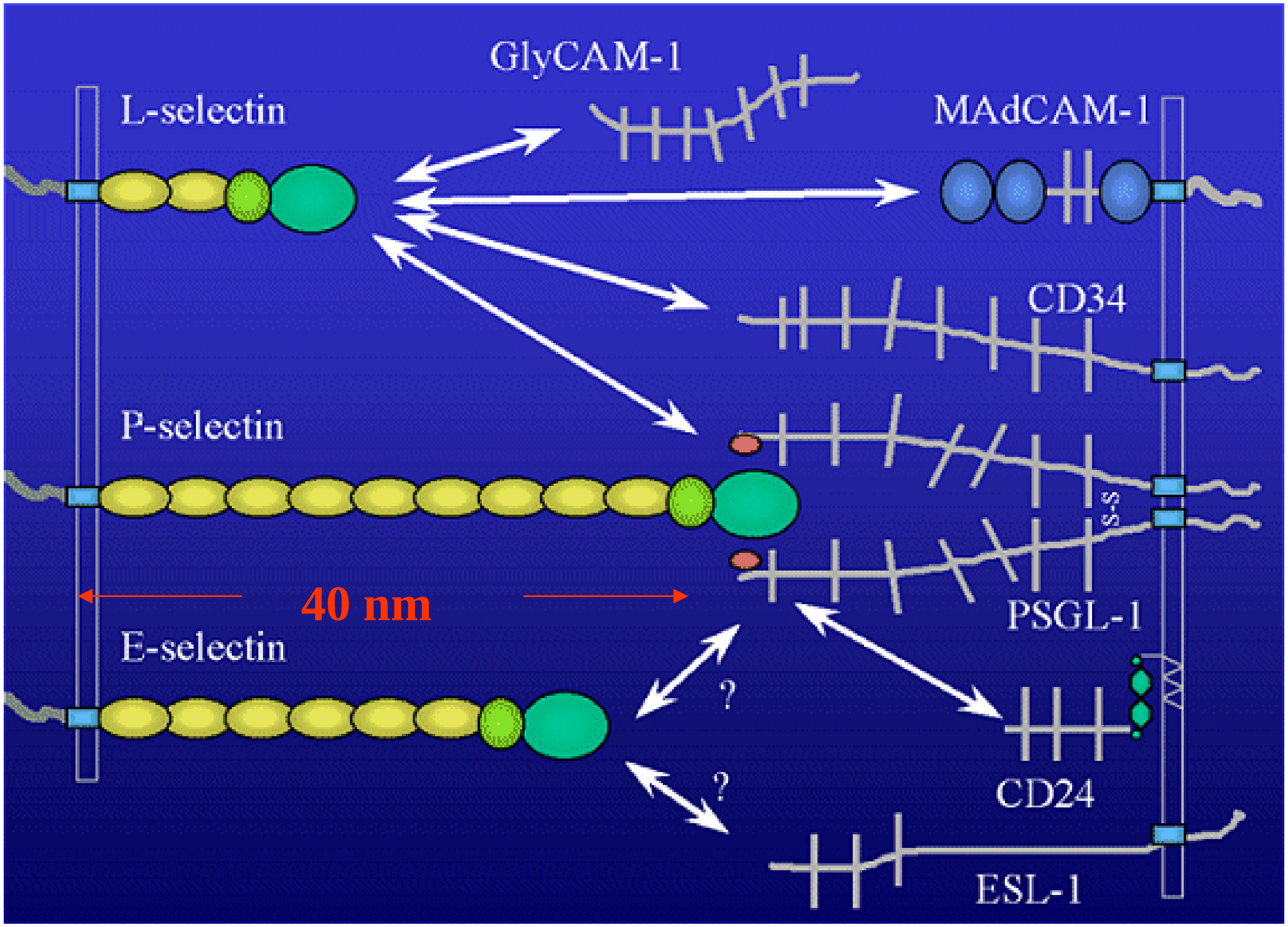
Finger et al., Nature 1996

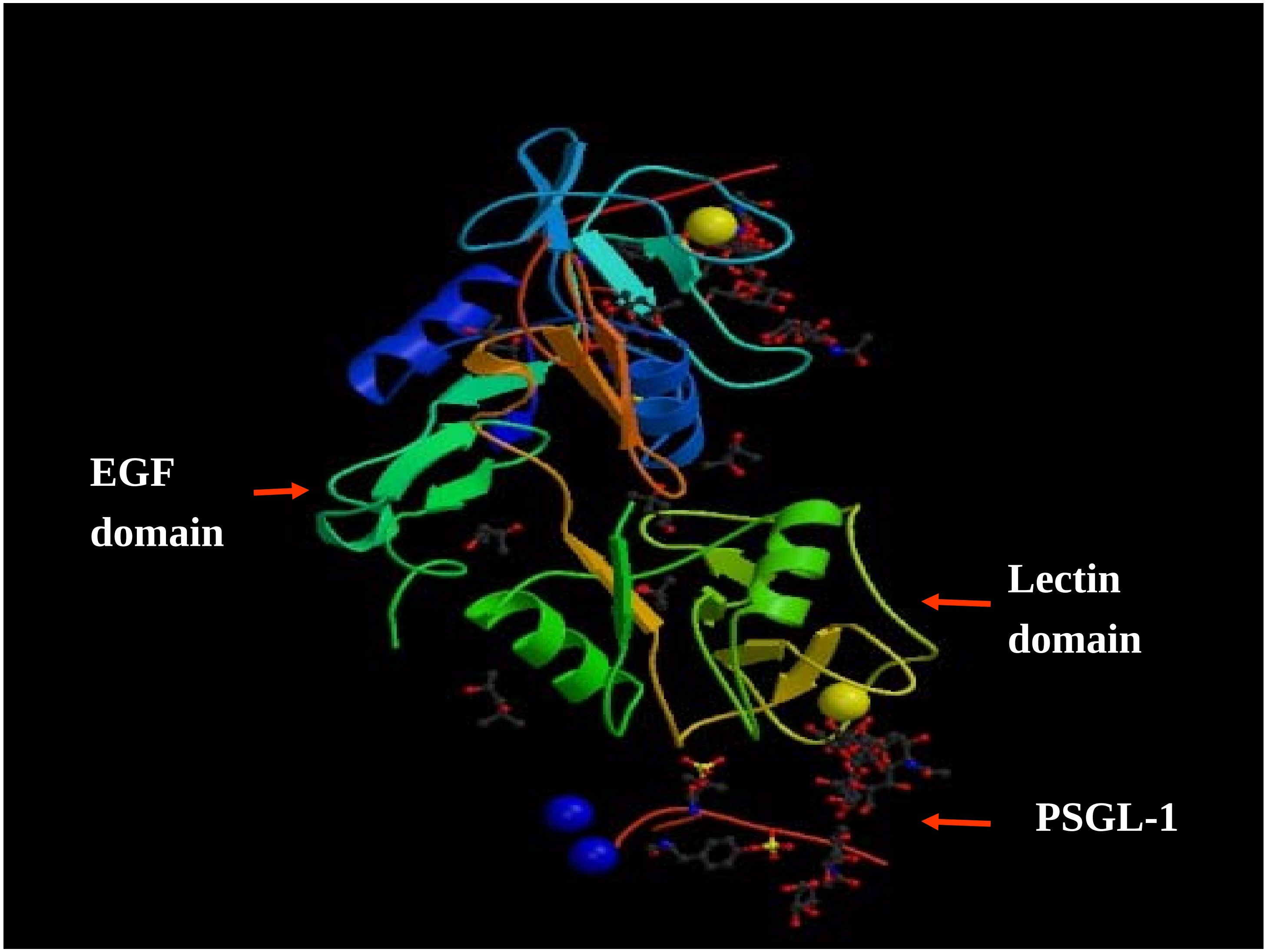
- FimH-mediated binding of type 1 fimbriated Escherichia coli to mannosylated glycoproteins, staphylococcus aureus binding to collagen, and GP-Ib-mediated platelet adhesion to von Willebrand factor are all enhanced by fluid flow.

- Irreversibility of specific biological adhesion: the work required to peel off a unit area of adhesion larger than the energy release from forming an area of adhesion.

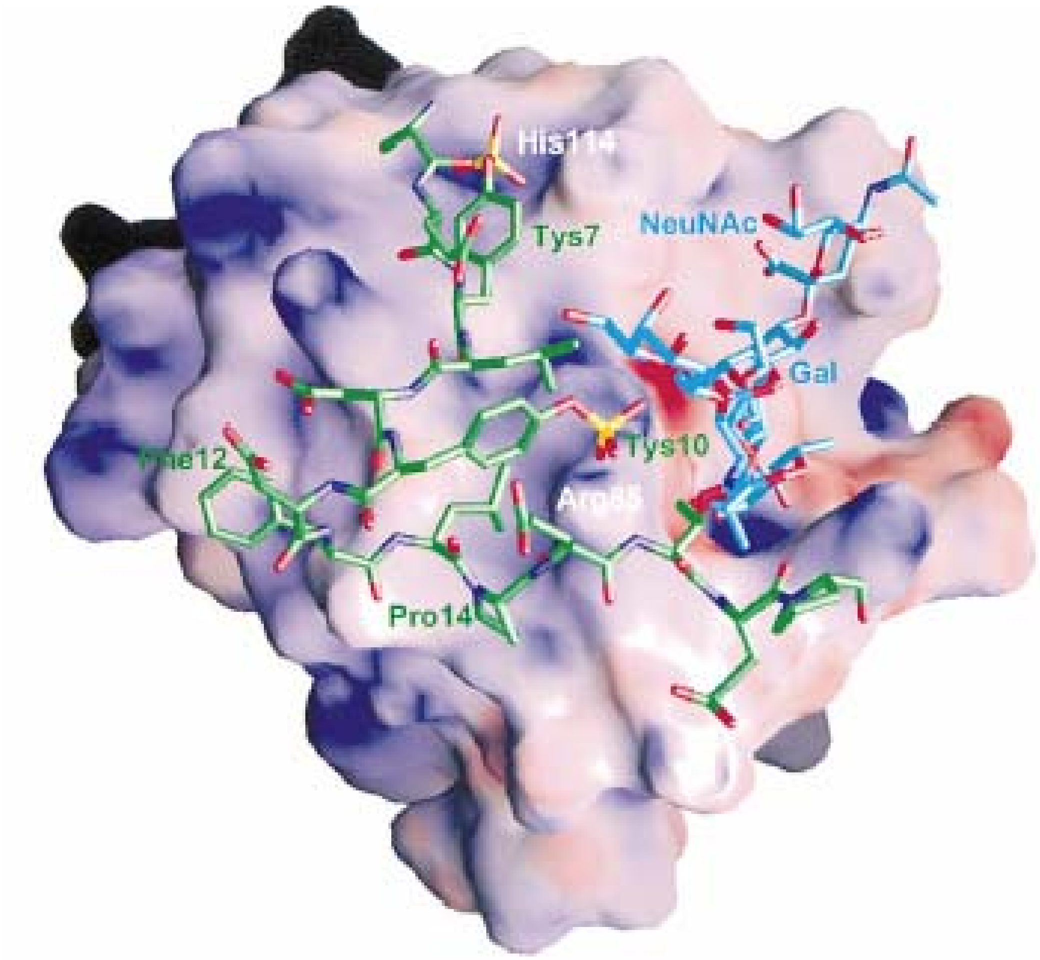
Thomas et al., Cell 2002

Evans, Blood cells 1993


GlyCAM-1
L-selectin
MAdCAM-1
CD34
P-selectin
S-S
40 nm
PSGL-1
E-selectin
?
?
CD24
ESL-1



Somers et al., Cell 2000



Electrostatic Potential surface representation

Forced dissociation rates models

- Bell, G.I., Science (1978)

$$k_{\mathrm{off}}(f) = k^0_{\mathrm{off}} \exp(f\xi / k_{\mathrm{B}}T)$$

- **Dembo, M.D**., Proc. R. Soc. Lond. B (1988)

$$k_{\mathrm{off}}(f) = k^0_{\mathrm{off}} \exp[(1-\kappa_{ts}/\kappa) f^2 / 2\kappa k_{\mathrm{B}}T]$$

- Evans, E. and Ritchie. K., Biphys. J. (1997)

$$k_{\mathrm{off}}(f) = \alpha[f/(k_{\mathrm{B}}T/\xi)]^{\beta}$$

Kramers reaction rate theory

- Forced dissociation rate constant

$$k_{\text{off}}(f) = \frac{D}{l_{\text{c}} l_{\text{ts}}} \exp\left[-E_{\text{b}}(f)/k_{\text{B}}T\right]$$

where $D/l_{\text{c}}l_{\text{ts}}$ is the attempt frequency, the two length scales: $l_{\text{c}} = \int dx \exp[-\Delta E_{\text{c}}(x)/k_{\text{B}}T]$ and

$$l_{\text{ts}} = \int dx \exp[\Delta E_{\text{ts}}(x)/k_{\text{B}}T],$$

and $E_{\text{b}}(f)$ is the barrier height on applied force.

$$E_{\text{b}}(f) = E_{\text{b}}(0) - fx$$

- For local harmonic approximations,

$$l_{\text{c}} \approx (2\pi k_B T/\kappa_{\text{c}})^{1/2} \text{ and } l_{\text{ts}} \approx (2\pi k_B T/\kappa_{\text{ts}})^{1/2}$$

Evans and Ritchie, BJ 1997

A typical rate process with

DYNAMIC DISORDER?

What's dynamic disorder?

- An important issue in nonequilibrium statistical mechanism
- Reaction rate depending on several stochastic control variables, e.g., energy barrier height
- Induced by environmental change, global molecular conformational changes or local conformational changes at the active site
- Popular concept in single molecule enzymology

Zwanzig, Acc.Chem. Res 1990

Xie et al. JCP A 1999

Why dynamic disorder?

- The interface between PSGL-1 ligand and P-selectin reported to be broad and shallow

- Energy barriers and/or projection distance in Bell expression might be stochastic variables

- Possible biological function of the physical effect

Dynamic Disorders in Force Experiments

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Gaussian Stochastic rate model

- Irreversible forced dissociation process

  Binding state $\xrightarrow{k_{\text{off}}(t, f)}$ Unbinding state,

  where $k_{\text{off}}(t, f)$ is time-dependent and

  satisfies Bell expression,

$$k_{\text{off}}(t, f) = k_0 e^{-\beta[\Delta G^+(t) - f x^+(t)]}$$

- The survival probability $P(t)$ of the binding state assumed to have first order decay rate equation, then $P(t) = \left\langle \exp\left(-\int_0^t k_{\text{off}}(\tau, f)\, d\tau \right) \right\rangle$

$$\approx \exp\left[-\int_0^t \langle k_{\text{off}}(\tau, f) \rangle\, d\tau + \text{higher order terms} \right]$$

- The simplest statistical assumptions required
  - a stationary process
  - finite time correlation functions.
  - Gaus

$$\langle \Delta G^{\ddagger}(t) \rangle = \Delta G_0^{\ddagger}$$
$$\langle x^{\ddagger}(t) \rangle = x_0^{\ddagger}$$
$$\langle x^{\ddagger}(t) x^{\ddagger}(0) \rangle - \langle x^{\ddagger}(0) \rangle^2 = K_x(t)$$
$$\langle \Delta G^{\ddagger}(t) \Delta G^{\ddagger}(0) \rangle - \langle \Delta G^{\ddagger}(0) \rangle^2 = K_g(t)$$
$$\langle \Delta G^{\ddagger}(t) x^{\ddagger}(0) \rangle - \langle \Delta G^{\ddagger}(0) \rangle \langle x^{\ddagger}(0) \rangle = K_{gx}(t).$$

- Forced dissociation rate with dynamic disorder

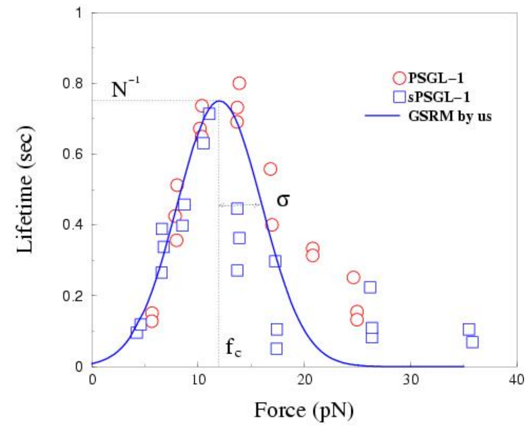
$$\langle k_{\text{off}}(f)\rangle = k_0 \exp\left[-\beta\Delta G_0^{\ddagger} + \frac{\beta^2}{2}K_g - \frac{(x_0^{\ddagger} - \beta K_{gx})^2}{2K_x}\right] \times \exp\left[\frac{\beta^2 K_x}{2}\left(f - \frac{\beta K_{gx} - x_0^{\ddagger}}{\beta K_x}\right)^2\right],$$

- Four cases:
  - $K_g = K_x = K_{gx} = 0$ the Bell expression
  - $K_x = K_{gx} = 0$ the intrinsic rate $k_0 \exp(-\beta\Delta G^{+} + \beta^2 K_g / 2)$
  - $K_g = K_{gx} = 0$ the mean rate $k_0 \exp(-\beta\Delta G^{+}) \exp\left(\beta x^{+}_0 f + \beta^2 K_x f^2 / 2\right)$
  - If $x_e^{+} \equiv \beta K_{gx} - x_0^{+} > 0$ then mean rate has Gaussian form with mean value $f_c = x_e^{+} / \beta K_x$

- Comparison with the experimental data

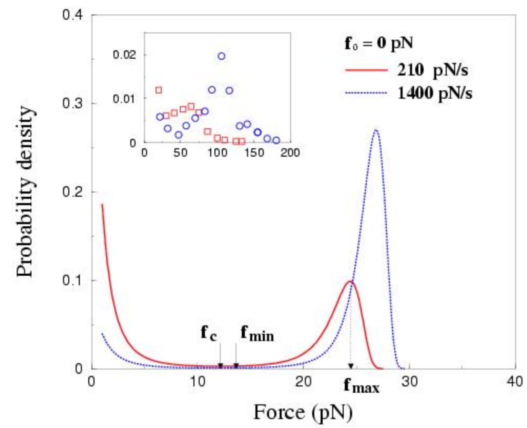
  - Constant force mode

$$\bar{t}(f) = N^{-1}\exp\left[-\frac{(f-f_c)^2}{2\sigma^2}\right]$$
$$= \left\{k_0^d \exp\left[-\frac{x_e^{\ddagger 2}}{2K_x}\right]\right\}^{-1}$$
$$\times \exp\left[-\left(f-\frac{x_e^{\ddagger}}{\beta K_x}\right)^2 /2(\beta^{-2}K_x^{-1})\right]$$



  - Dynamic force mode

$$P(f,f_0) = \frac{N}{r}\exp\left[\frac{(f-f_c)^2}{2\sigma^2} - \frac{N}{r}\int_{f_0}^{f} df' e^{\frac{(f'-f_c)^2}{2\sigma^2}}\right]$$



Bell rate model with dynamic disorder

- Energy surface depends on the forced dissociation reaction coordinate and conformational coordinate, and the latter perpendicular to the former; for each conformation *x* there is a dissociation rate obeying the Bell expression.
- Diffusic

$$\frac{\partial p(x,t)}{\partial t} = D\frac{\partial^2 p}{\partial x^2} + \frac{D}{k_B T}\frac{\partial}{\partial x}\left(p\frac{\partial V}{\partial x}\right) - k_{\text{off}}(x,f)p$$

force

Agmon and Hopfield, JCP 1983

- Slow and rapid diffusion limits:
  - $D \to 0,\ p(x,t) = p(x,0)\exp[-k_{\mathrm{off}}(x, f)t]$
  - $D \to \infty,\ \ p(x,t) = p(x,0)\exp[-t\int k_{\mathrm{off}}(x', f)\, p^{eq}(x')dx']$

  where $p^{eq} \propto \exp[-V(x)/k_{\mathrm{B}}T]$
- Observation the survival probability $Q(t)$ then
  - $D \to 0,\ \mathrm{Q}(t) = \int p(x,0)\exp[-k_{\mathrm{off}}(x, f)t]dx$
  - $D \to \infty,\ \ \mathrm{Q}(t) = \exp[-t\int k_{\mathrm{off}}(x', f)\, p^{eq}(x')dx'] = \exp[-t\langle k_{\mathrm{off}}\rangle]$
- Numerical and perturbation approaches for intermediate diffusions

- Given a bound diffusion under a harmonic potential, projection distance and barrier height linear functions of the conformational coordinate, i.e.,

$$V(x) = \frac{k_x}{2} x^2, \qquad \begin{aligned} \Delta G^\ddagger(x) &= \Delta G_0^\ddagger + k_g x, \\ \xi^\ddagger(x) &= \xi_0^\ddagger + k_\xi x. \end{aligned}$$

then in $D \to \infty$ limit

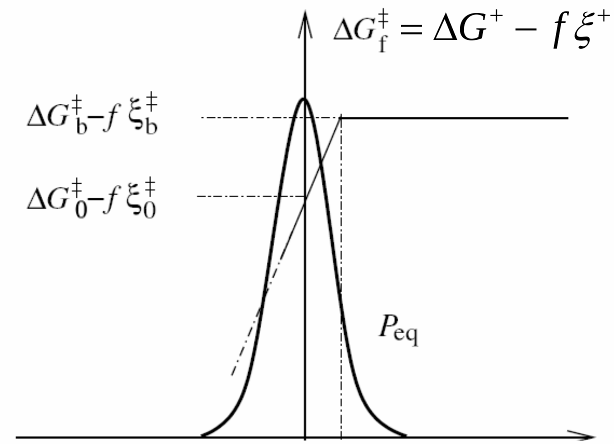
$$\langle k_{\text{off}} \rangle = k_0 \exp\left[-\beta \Delta G_0^\ddagger + \frac{\beta^2}{2} K_g - \frac{(\xi_0^\ddagger - \beta K_{g\xi})^2}{2K_x}\right] \times \exp\left[\frac{\beta^2 K_\xi}{2}\left(f - \frac{\beta K_{g\xi} - \xi_0^\ddagger}{\beta K_\xi}\right)^2\right],$$

where

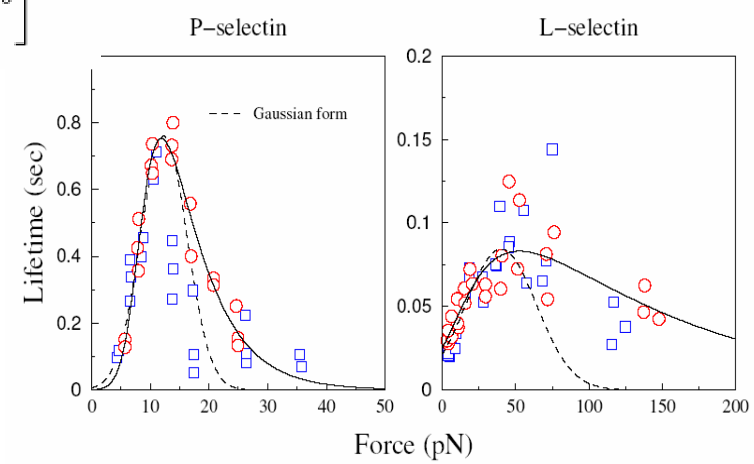
$$K_\xi = \frac{k_\xi^2}{\beta k_x}, \; K_g = \frac{k_g^2}{\beta k_x}, \; K_{g\xi} = \frac{k_\xi k_g}{\beta k_x}.$$

- Comparison with the experimental data

$$\langle k_{\rm off}\rangle = \frac{k_0}{2}\exp\left[-\beta\Delta G_0^\ddagger + \frac{\beta k_g^2}{2k_x} - \frac{\beta k_x}{2k_\xi^2}\left(\frac{k_\xi k_g}{k_x}-\xi_0^\ddagger\right)^2\right] \times \exp\left[\frac{\beta k_\xi^2}{2k_x}\left(f - \frac{k_g k_\xi/k_x - \xi_0^\ddagger}{k_\xi^2/k_x}\right)^2\right] \times \mathrm{erfc}\left[-\sqrt{\frac{\beta k_x}{2}}\left(x_b + \frac{k_g}{k_x} - \frac{k_\xi}{k_x}f\right)\right] + \frac{k_0}{2}\exp\left[-\beta\Delta G_b^\ddagger + \beta f\xi_b^\ddagger\right] \times \mathrm{erfc}\left[\sqrt{\frac{\beta k_x}{2}}\,x_b\right]$$



where $\mathrm{erfc}(x) = \frac{2}{\sqrt{\pi}}\int_x^\infty e^{-x^2}\,dx.$



- Dynamic force mode:
  - In $D \to \infty$ limit

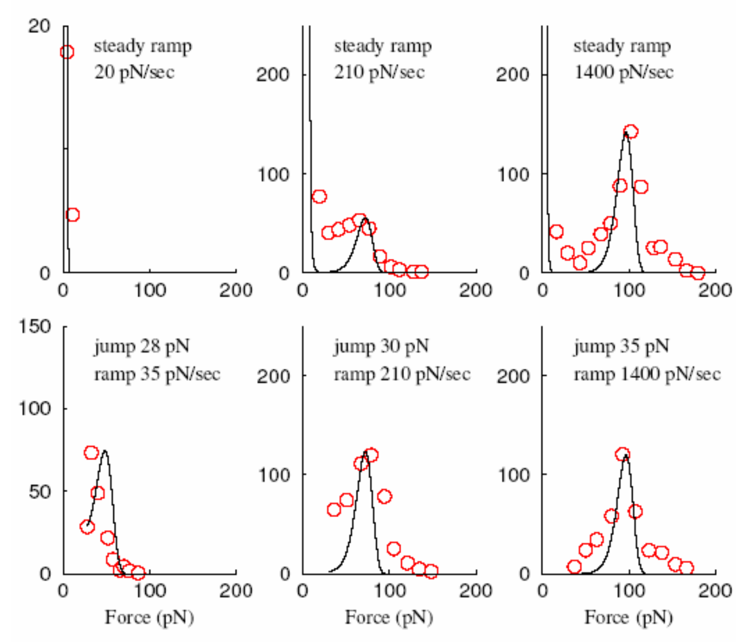
$$Q(t) = \exp[-\int_0^t \langle k_{\text{off}}(f_t)\rangle dt]$$

  - The probability density of the dissociation force

$$P(f, f_0) = \frac{\langle k_{\text{off}}(f)\rangle}{r} \exp\left[-\frac{1}{r}\int_{f_0}^{f} \langle k_{\text{off}}(f')\rangle df'\right]$$

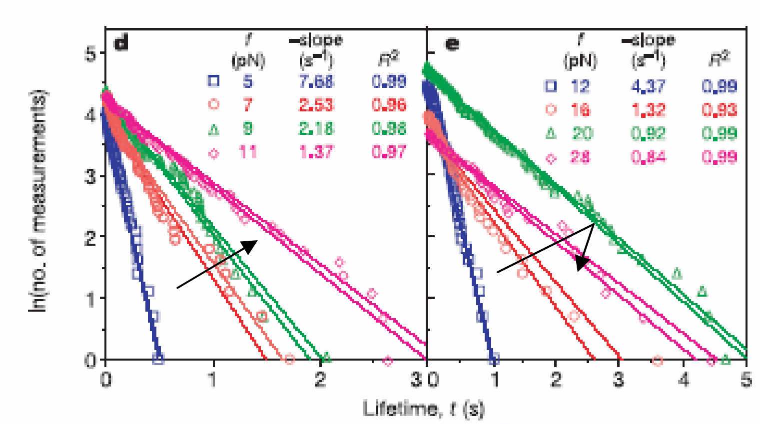
  - Equivalent dimeric bonds assumption,

$$P_d(f, f_0) = P(f/2, f_0/2)^2$$

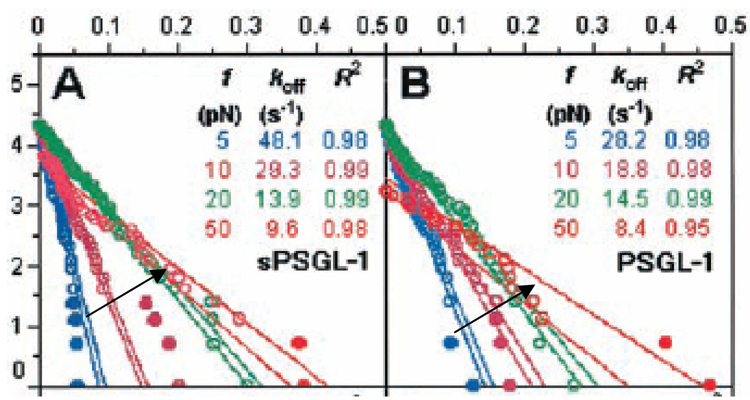


PSGL-1-P-selectin

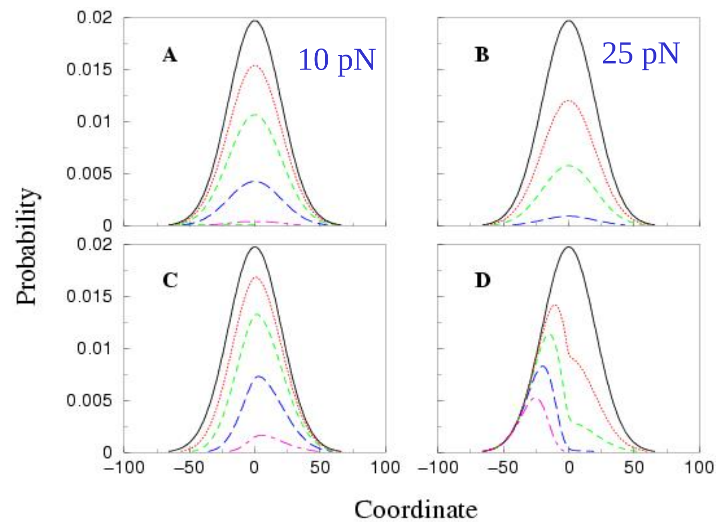
- Intermediate diffusion coefficients

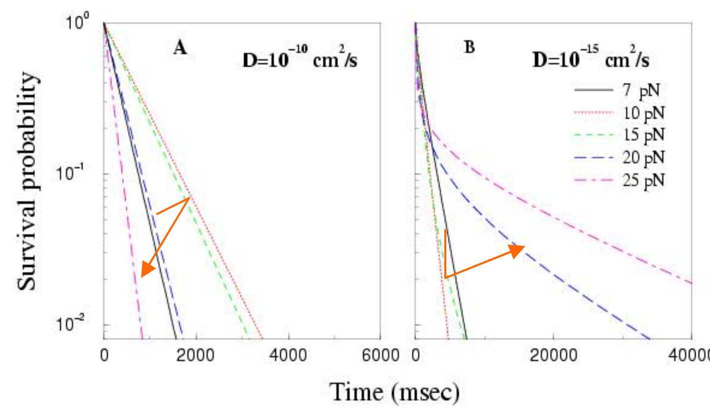


PSGL-1-P-selectin



PSGL-1-L-selectin



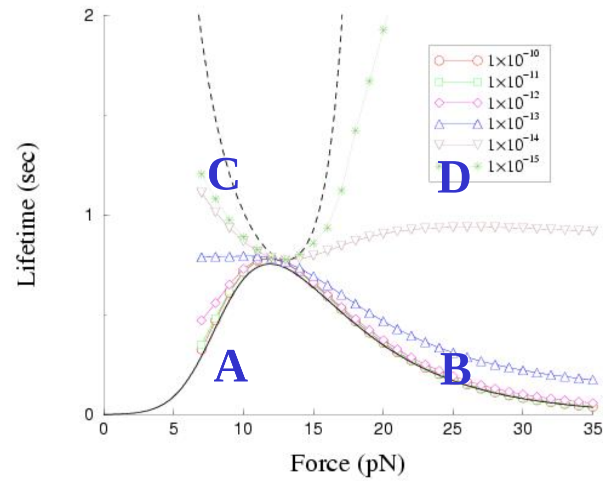


- Nondiffusion limit $D \to 0$,
  - For the linear functions

$$\langle\tau\rangle(f) \;=\; k_0^{-1}\exp\left[\beta\Delta G_0^{\ddagger} + \frac{\beta}{2}\frac{k_g^2}{k_x} - \frac{\beta k_x}{2k_\xi^2}\left(\frac{k_g k_\xi}{k_x} + \xi_0^{\ddagger}\right)^2\right] \times \exp\left[\frac{\beta k_\xi^2}{2k_x}\left(f - \frac{k_g k_\xi/k_x + \xi_0^{\ddagger}}{k_\xi^2/k_x}\right)^2\right],$$

  - For the piecewise functions

$$\langle\tau\rangle(f) \;=\; \frac{k_0^{-1}}{2}\exp\left[\beta\Delta G_0^{\ddagger} + \frac{\beta}{2}\frac{k_g^2}{k_x} - \frac{\beta k_x}{2k_\xi^2}\left(\frac{k_g k_\xi}{k_x} + \xi_0^{\ddagger}\right)^2\right] \times \exp\left[\frac{\beta k_\xi^2}{2k_x}\left(f - \frac{k_g k_\xi/k_x + \xi_0^{\ddagger}}{k_\xi^2/k_x}\right)^2\right] \times \operatorname{erfc}\left[-\sqrt{\frac{\beta k_x}{2}}\left(x_b - \frac{k_g}{k_x} + \frac{k_\xi}{k_x}f\right)\right] + \frac{k_0^{-1}}{2}\exp\left[\beta\Delta G_0^{\ddagger} - \beta f \xi_b^{\ddagger}\right]\operatorname{erfc}\left[\sqrt{\frac{\beta k_x}{2}}x_b\right],$$



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- Optimal binding of P-selectin critically dependents on the relative orientations of its ligand
- Negative projection distance physically counterintuitive
- Diffusi ant force

$$\frac{\partial p(x,t)}{\partial t} = D\frac{\partial^2 p}{\partial x^2} + \frac{D}{k_B T}\frac{\partial}{\partial x}\left(p\frac{\partial V_{f_\perp}}{\partial x}\right) - k_{\text{off}}(x, f_\parallel)p$$

where $V_{f_\perp} = V(x) - f_\perp x,\ f_\perp = f\sin\theta,$

and $f_{//} = f\cos\theta \geq 0.$

- Bell-like forced dissociations:
  - Given a bound diffusion under harmonic potential and barrier height to be linear function of coordinate, i.e.,

$$V(x) = k_x x^2/2, \quad \Delta G(x) = \Delta G_0^{+} + k_g x$$

In larger *D* limit

$$\langle k_{\text{off}} \rangle \approx k_0 \exp\left[-\beta \Delta G_0^{\ddagger} + \frac{\beta k_g^2}{2k_x}\right] \exp[\beta d^{\ddagger} f].$$

where

$$d^{+} = \xi^{+} \cos\theta - \frac{k_g}{k_x} \sin\theta$$

  - $d^{\ddagger} =/>/<0$ corresponding ideal/slip/catch bonds

- Dembo-like forced dissociations:
  - Given a bound diffusion under harmonic potential and barrier height, i.e.,

    $$\Delta G^{\ddagger}(x) = \Delta G_1^{\ddagger} + k_g(x - x_1)^2/2,$$

    Under larger *D* limit

    $$\langle k_{\mathrm{off}} \rangle \approx k_0 \left(\frac{k_x}{k_x + k_g}\right)^{\frac{1}{2}} \exp\left[-\beta \Delta G_1^{\ddagger} + \beta \xi^{\ddagger} f_{\parallel}\right] \times \exp\left[-\frac{\beta k_g (f_{\perp} - k_x(x_1 - x_0))^2}{2k_x(k_x + k_g)}\right]$$

  - A slip to catch transition occurs if force increases over $D^{\ddagger} k_x (k_x + k_g)/2k_g \sin^2\theta$

    $D^{\ddagger} = \xi^{\ddagger}\cos\theta + 2k_g(x_1 - x_0)\sin\theta/(k_x + k_g)$, where

- Comparison with the experiments

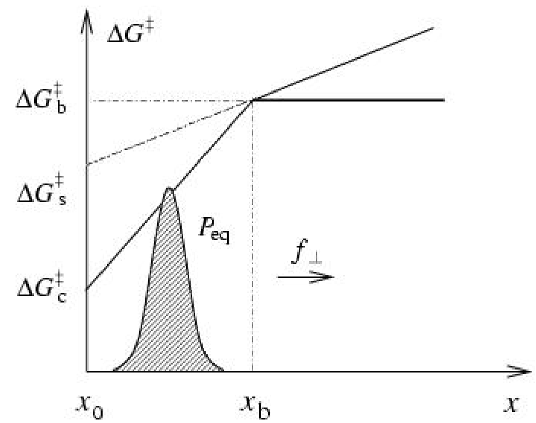
$$\Delta G^\ddagger(x) = \begin{cases} \Delta G_c^\ddagger(x) = \Delta G_b^\ddagger + k_c(x - x_b), & x \le x_b \\ \Delta G_s^\ddagger(x) = \Delta G_b^\ddagger + k_s(x - x_b), & x > x_b \end{cases}$$

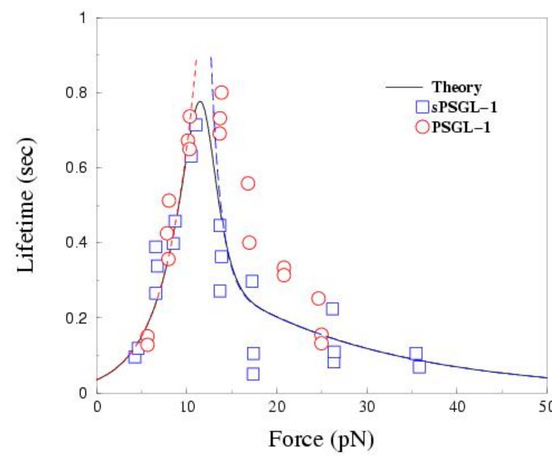
$$\langle k_{\text{off}} \rangle \approx \frac{k_0^c}{2} \exp\left[\frac{\beta k_c^2}{2k_x}\right] \exp\left[-\beta d_c^\ddagger f\right] \times \text{erfc}\left[-\left(\Delta + \frac{k_c}{k_x}\right)\sqrt{\frac{\beta k_x}{2}} + f\sqrt{\frac{\beta}{2k_x}}\sin\theta\right] + \frac{k_0^s}{2} \exp\left[\frac{\beta k_s^2}{2k_x}\right] \exp\left[\beta d_s^\ddagger f\right] \times \text{erfc}\left[\left(\Delta + \frac{k_s}{k_x}\right)\sqrt{\frac{\beta k_x}{2}} - f\sqrt{\frac{\beta}{2k_x}}\sin\theta\right]$$

$$k_0^c = k_0 \exp[-\beta \Delta G_c^\ddagger(x_0)],$$
$$k_0^s = k_0 \exp[-\beta \Delta G_s^\ddagger(x_0)].$$

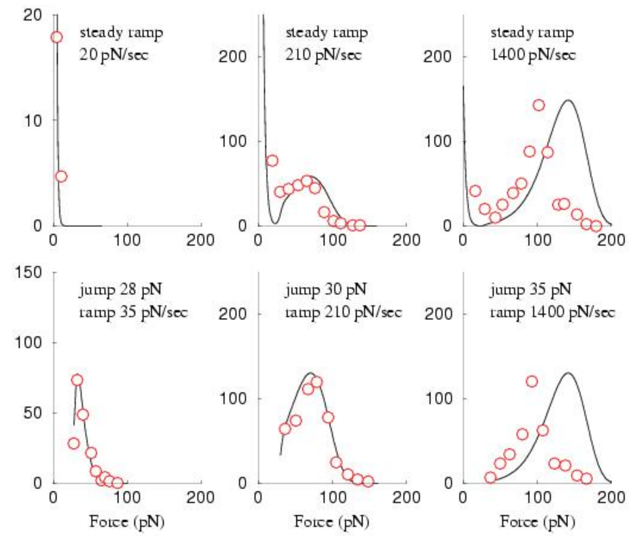
	d_c nm	d_s nm	k_0^c sec^{-1}	k_0^s sec^{-1}
Experiment (24)		0.14		0.2
Dynamic disorder by us	1.2	0.22	23.2	1.68

Hanley et al., JBC 2003





- For dynamic force mode:



  - $P_d(f, f_0) = P(f/2, f_0/2)^2$ and

$$P(f, f_0) = \frac{\langle k_{off}(f)\rangle}{r}\exp\left[-\frac{1}{r}\int_{f_0}^{f}\langle k_{off}(f')\rangle df'\right]$$

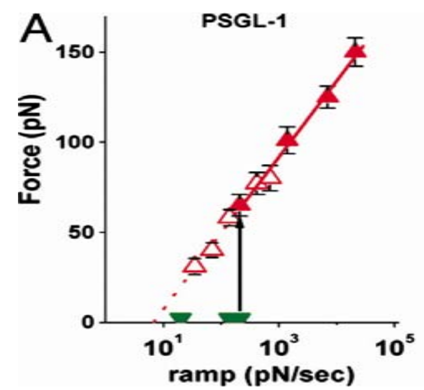
  - Minimum and maximum

$$\frac{d\langle k_{off}(f)\rangle}{df} = \langle k_{off}(f)\rangle^2$$

then

$$f_{min} = f_c + \langle k_{off}(f_c)\rangle^2 \Big/ r\frac{d^2}{df^2}\langle k_{off}(f_c)\rangle \propto 1/r$$

$$f_{max} \approx \frac{1}{\beta d_s}\ln\frac{\beta r d_s}{k_0\exp\left[-\beta\Delta G_s(x_0) + \beta d_s^2 k_s/2\right]} \propto \ln r$$

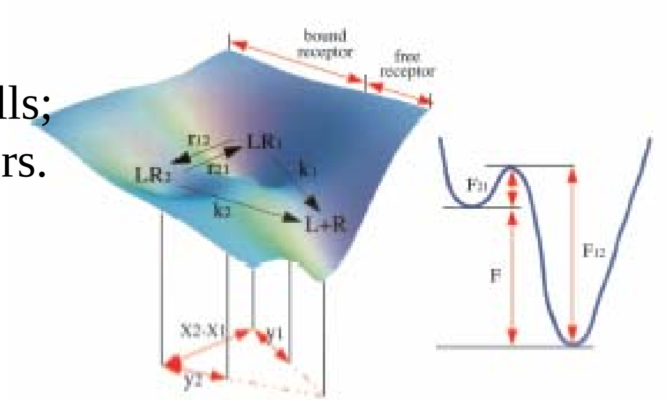


Dynamic Disorders in Force Experiments

Outline:

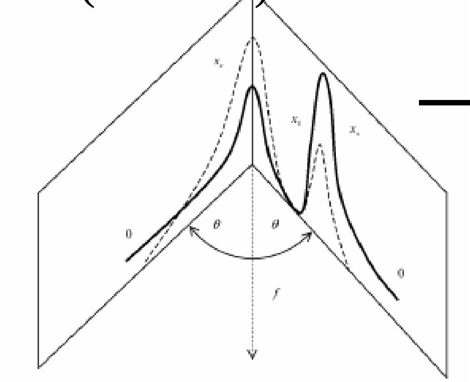
- ✓ Background;
- ✓ Bell rate model with dynamic disorder;
- ✓ Force modulating dynamic disorder;
- ❑ Conclusion.

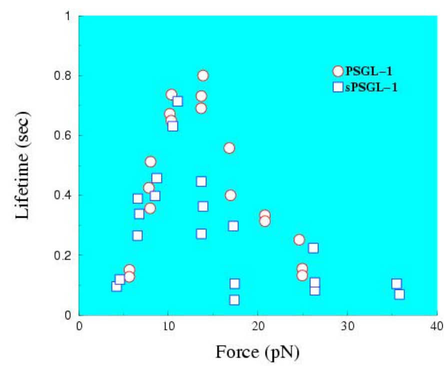
Two path ways;
Two energy wells;
Seven parameters.
By Thirumalai
(PNAS 2005)

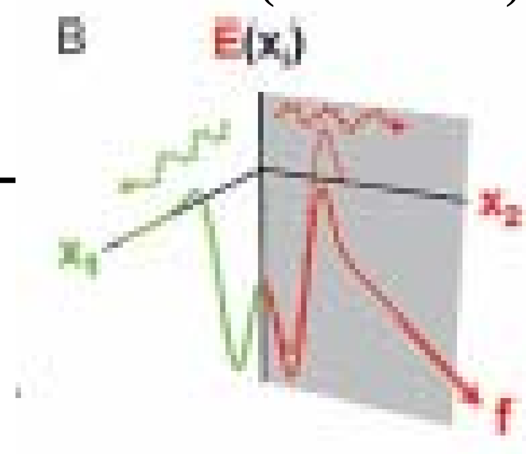


Two path ways;
Two energy wells;
five parameters;
Rapid equilibrium;
By Evans
(PNAS 2004)

Two path ways;
one energy well;
four parameters;
Catch bond;
By Thomas (BJ 2005)







Dynamic disorder in the dissociation rate

- Related to the chemical kinetic models

  - Defining $\Delta x = x_{i+1} - x_i$, $\bar{D} = D\Delta x^2$, $p_i = p(x_i, t)\Delta x$
  Master equation:

$$\frac{\partial p_i}{\partial t} = p_{i-1}k(i|i-1) + p_{i+1}k(i|i+1) - p_i\left[k(i-1|i) + k(i+1|i)\right] - k_i p_i$$

$$k(i|j) = \bar{D}\exp\left[-\frac{V_f(x_i) - V_f(x_j)}{2k_B T}\right].$$

  - The Simplest two-state case

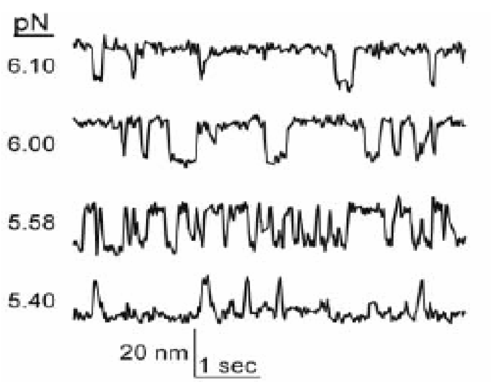
$$\begin{cases} \dfrac{dp_1}{dt} = p_2 k(1|2) - p_1 k(2|1) - k_1 p_1 \\ \dfrac{dp_2}{dt} = p_1 k(2|1) - p_2 k(1|2) - k_2 p_2 \end{cases}$$

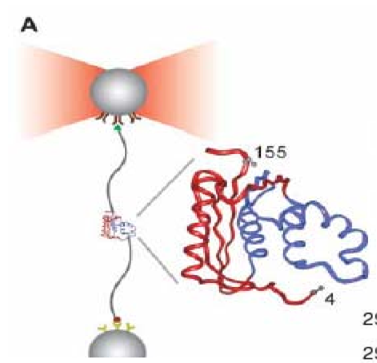
then $\frac{dQ}{dt} = -\frac{k_1 R + k_2\exp(\beta f\Delta x)}{R + \exp(\beta f\Delta x)}Q$ and $R = \exp\left[\frac{V_i(x_2) - V_i(x_1)}{k_B T}\right]$

Evans et al., PNAS 2004

- Dynamic disorder in forced folding/unfolding experiments?

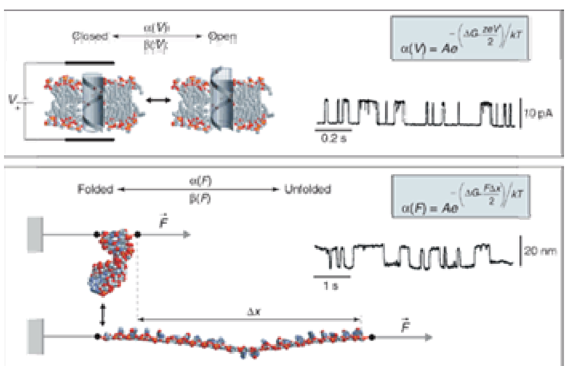
RNAse H

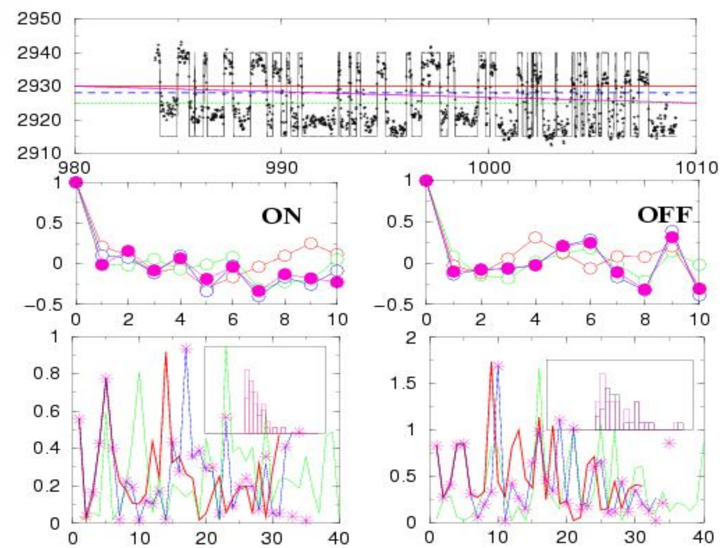




$$C(m) = \frac{\langle \Delta\tau(0)\Delta\tau(m)\rangle}{\langle \Delta\tau^2 \rangle}$$

In the absence of rate fluctuation, $C(0)$=1, 0 for m > 0.





Cecconi, et al. Science 2005

Liphardt et al. Science 2001

Lu et al., Science 1999

- Possible problems
  - General analytical solutions for diffusion-reaction equations
  - Forced dissociation/association reversible processes
  - Multiple receptor-ligand bonds
  - Irreversibility of specific biological adhesion phenomenon
  - Model of rolling leukocytes with catch bonds