Physical factors that elicit a response

- Fluid dynamic shear stress (> 0.5 Pa)
- Cyclic strain of cell substrate (> 1%)
- Osmotic stress
- Compression in a 3D matrix
- Normal stress (> 500 Pa)
- Mechanical perturbations via tethered microbeads (> 1 nN)
Forces applied at one point in the cell, are transmitted via the cytoskeletal network.

Fibroblast with fluorescent mitochondria forced by a magnetic bead. D. Ingber, P. LeDuc
Mechanotransduction: Current theories


- Direct mechanical effects on the nuclear membrane, DNA, and gene expression (Ingber)

- Stretch-activated ion channels (Gullinsgrud, 2003, 2004)

- Glycocalyx deformation coupling to the cortical cytoskeleton (Weinbaum, 2003)


- Constrained autocrine signaling (Tschumperlin, et al., 2004)
Early events in mechanotransduction: 1) Protein activation progresses in a wave from the site of bead forcing (Wang et al., 2005)

- Response of a membrane-targeted Src reporter.

- Phosphorylation of a domain taken from a c-Src substrate, P130cas, leads to a conformational change that reduces FRET.

- A wave of activation propagates away from the site of forcing at a speed of ~18 nm/s

Neither mechanism -- of force transduction or propagation of activation wave -- are understood
Stretch-activated ion channels constitute one method of mechanotransduction.

SEM of the stereocilia on the surface of a single hair cell (Hudspeth)

Tension in the tip link activates a stretch-activated ion channel, leading to intracellular calcium ion fluctuations.
Leukocyte rolling and transient adhesion

http://labs.idi.harvard.edu/springer/pages/multimedia

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Shear Stress = 2 dynes/cm²

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http://cbr.med.harvard.edu/investigators/springer/lab/lab_goodies/ROLLVIVO.MOV
Leucocyte adhesion/arrest and transmigration

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1D Energy Landscape with Two States: Perturbed by extrinsic force

Transition State $T$
(intermediate that must be crossed going from A to B, or B to A; also called activated state of $G_0^0$)

Change in $G_B$ of $\Delta G_B = F \Delta \chi$, or $G_B = G_B^0 - F(\chi_B - \chi_A)$

Linear perturbation $F \Delta \chi$ or “tilting” of energy landscape about pivot point at state A

$G^0(\chi, F = 0)$

$G(\chi, F > 0)$

$G_A^0 = \text{free energy of state A, in absence of constant applied force}$

$G_A^0 = G_A^0 - F(\chi_A - \chi_A) = G_A^0$

$G_B = \text{free energy of state B, in presence of constant applied force}$

$G_B = G_B^0 - F(\chi_B - \chi_A)$

$\Delta G_A^0 = \text{activation energy that must be overcome to get from state A to transition state T under no F, and } = G_T^0 - G_A^0$

$p_A^0 = \text{probability of being in state A in absence of constant F, given by Boltzmann distbn } = 1/Z \exp(-G_A^0/k_B T)$ \text{ where Z is partition funct.}$

$k_{eq}^0 = \text{equilibrium constant in absence of F; dimensionless ratio of probabilities of being in state B to state A,}$

defined as $p_B^0/p_A^0 = \exp(G_B^0 - G_A^0)/k_B T = \exp[-(G_B^0 - G_A^0)/k_B T] = -\Delta G_{AB}^0/k_B T$

$k_{eq} = \text{equilibrium constant in presence of F; dimensionless ratio of probabilities of being in state B to state A,}$

defined as $p_B/p_A = \exp[-(G_B - G_A)/k_B T] = \exp[-(\Delta G_{AB}^0 - F(\chi_B - \chi_A))/k_B T] = K_{eq}^0 \exp\{+[F(\chi_B - \chi_A)]/k_B T\}$

$k_{12}^0 = \text{transition rate from A to B governed by the activation energy barrier moving from A to B, in absence of constant F, in [1/sec]}$

$k_{12} = \text{transition rate from A to B in the presence of constant F, in [1/sec]}$

$k_{21} = \text{C exp}\{-[\Delta G_A^0 - F(\chi_T - \chi_A)]\} = k_{12}^0 \exp\{+[F(\chi_T - \chi_A)]\}$. Note $k_{21} = C \exp\{-[\Delta G_B^0 - F(\chi_T - \chi_B)]\} = k_{21}^0 \exp\{+[F(\chi_T - \chi_B)]\}$
State probabilities, rate constants and transition times

\[ k_+ = C \exp \left[ - \frac{(G_a - G_1) - F(x_a - x_1)}{k_B T} \right] \]
Essential equations

\[
\frac{p_2}{p_1} = K_{eq} = \frac{k_+}{k_-} = \exp \left[ -\frac{(G_2 - G_1) - F(x_2 - x_1)}{k_B T} \right]
\]

\[
k_+ = C \exp \left[ -\frac{(G_a - G_1) - F(x_a - x_1)}{k_B T} \right]
\]

\[
k_- = C \exp \left[ -\frac{(G_a - G_2) - F(x_a - x_2)}{k_B T} \right]
\]
Measured energy landscape for PrP at $F = 9.1$ pN

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