Lecture 7: Two-state system, ion channels

Goal: Statistical mechanics modeling. Compute the probability of microstates, including applied forces.

- Two-state system
- Mechanosensitive ion channels

state variable $\sigma_i = \{0, 1\}$

two-state system + mechanics

PBOC Chapter 7.1.2, 11.5

Statistical mechanics for biophysics

Previously (Lecture 3):

Microstates: Canonical ensemble

Definition: a ***microstate*** is a microscopic arrangement of the constituents of a system

Example: Ligand binding to a receptor protein

$\sigma_i = \{0, 1\}$

unbound

bound

Lattice model

L ligands

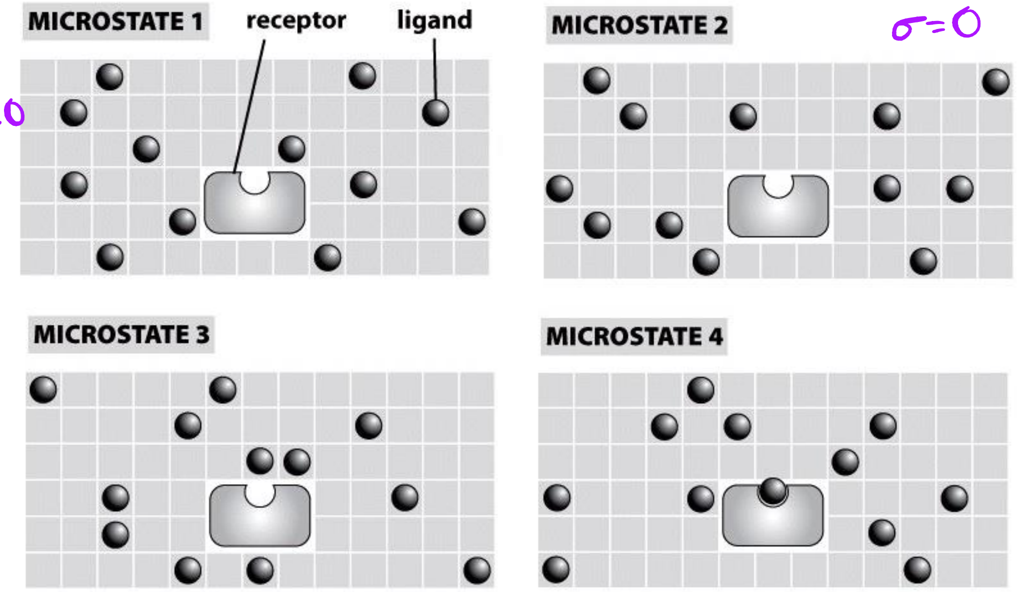
$\boldsymbol{\Omega}$ boxes

max. one ligand per box

energy ε_b of a bound ligand

energy ε_{sol} of a ligand in solution

$\sigma = 0$



$\sigma = 0$

$\sigma = 0$

$\sigma = 1$

Statistical mechanics for biophysics

Previously (Lecture 6):

Microstates: Canonical ensemble

Suppose a system can exist in states with energies E_i.
What is the probability of finding the system in a given state?

Boltzmann distribution, probability of finding the system in a microstate with energy E_i *(derivation, Section 6.1.3)*

$$p(E_i) = \frac{1}{Z} e^{-E_i/k_B T} \qquad (6.4)$$

Partition function, normalization factor so that $\sum_{i=1}^{N} p(E_i) = 1$

$$Z = \sum_{i=1}^{N} e^{-E_i/k_B T} \qquad (6.5)$$

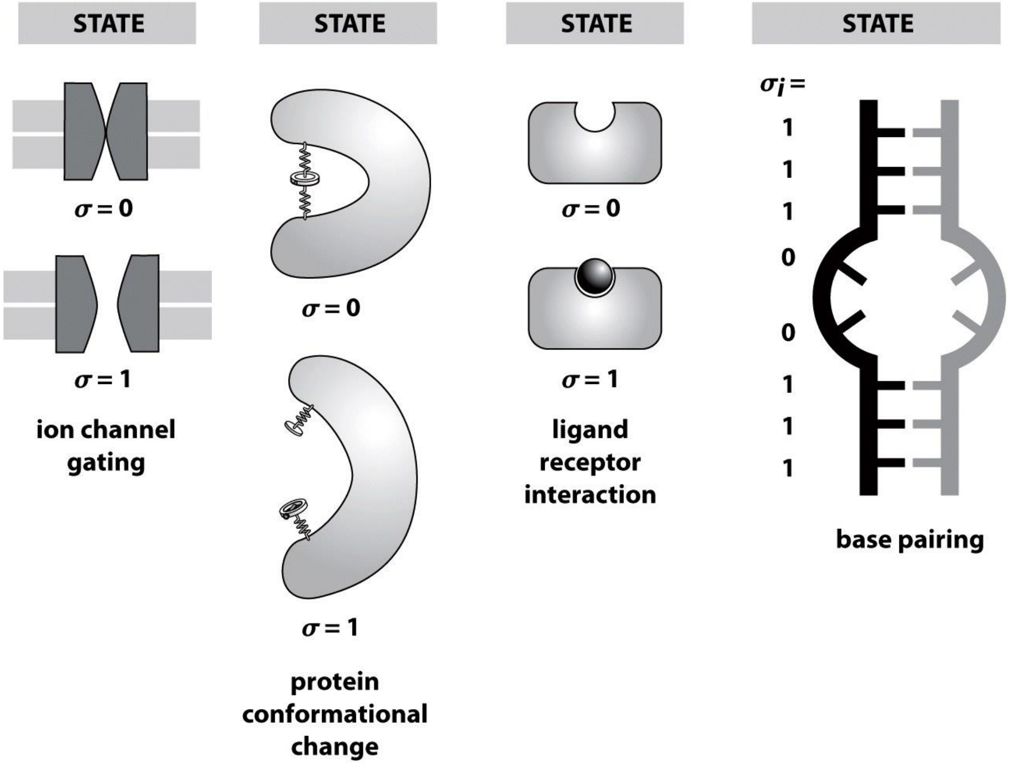
Two-state system

System takes on different states in time or as an ensemble:

State variable $\sigma_i = \{0,1\}$

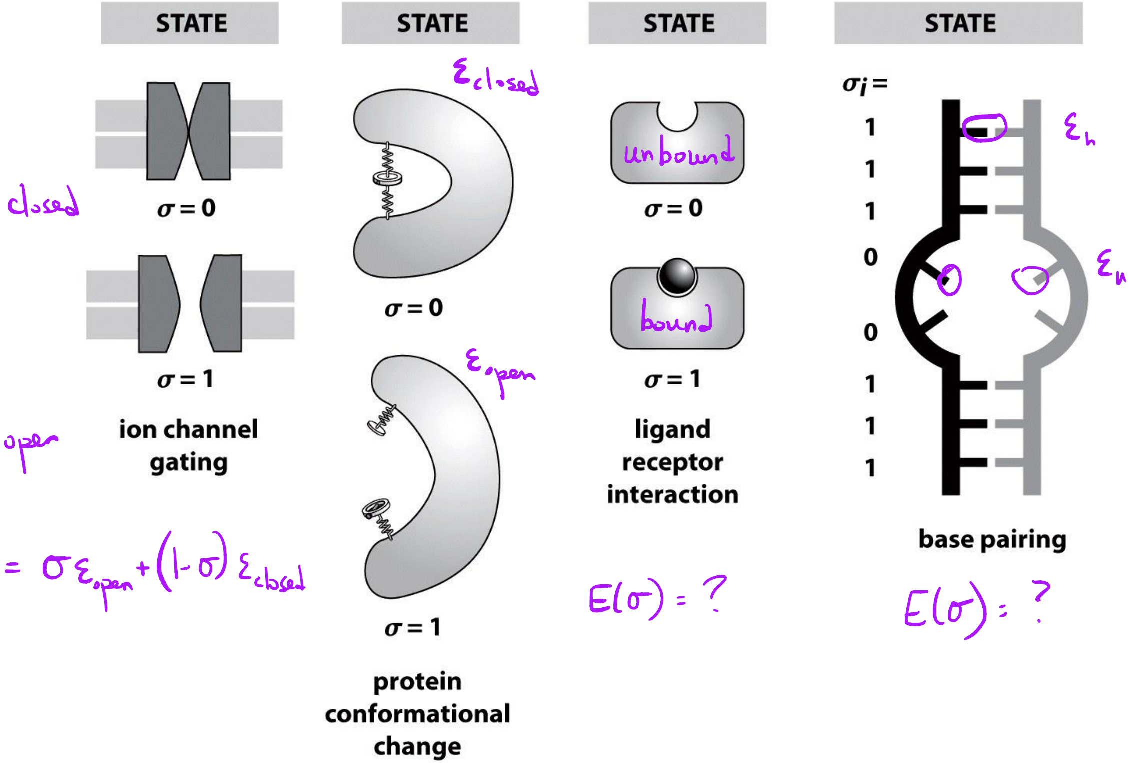
Note: We have chosen this convention; other choices for σ are possible by adjusting $E(\sigma)$

State variables, σ



Two-state system

State variables, σ



$E(\sigma) = \sigma \varepsilon_{open} + (1-\sigma)\varepsilon_{closed}$

$E(\sigma) = ?$

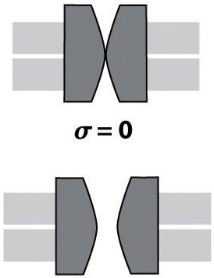
$E(\sigma) = ?$

Two-state system

State variables, σ

STATE

closed



$\sigma = 0$

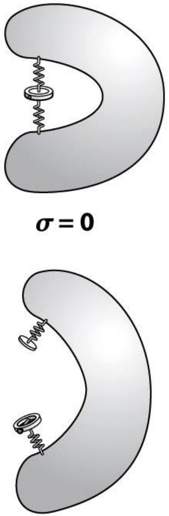
$\sigma = 1$

open

ion channel gating

$E(\sigma) = \sigma \varepsilon_{open} + (1-\sigma)\varepsilon_{closed}$

STATE

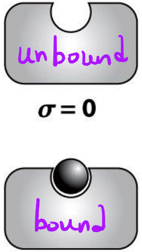


$\sigma = 0$

$\sigma = 1$

protein conformational change

STATE

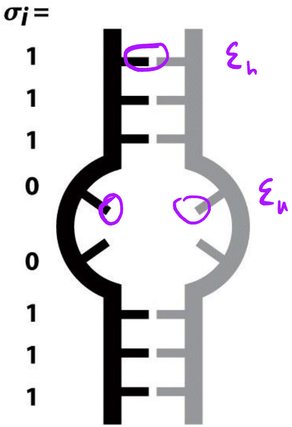


$\sigma = 0$

$\sigma = 1$

ligand receptor interaction

STATE



base pairing

$$E(\sigma) = \sum_i \sigma_i \varepsilon_h + \sum_i (1-\sigma_i)\varepsilon_u$$

$$E(\sigma) = L\varepsilon_{sol}(1-\sigma) + ((L-1)\varepsilon_{sol} + \varepsilon_b)\sigma$$

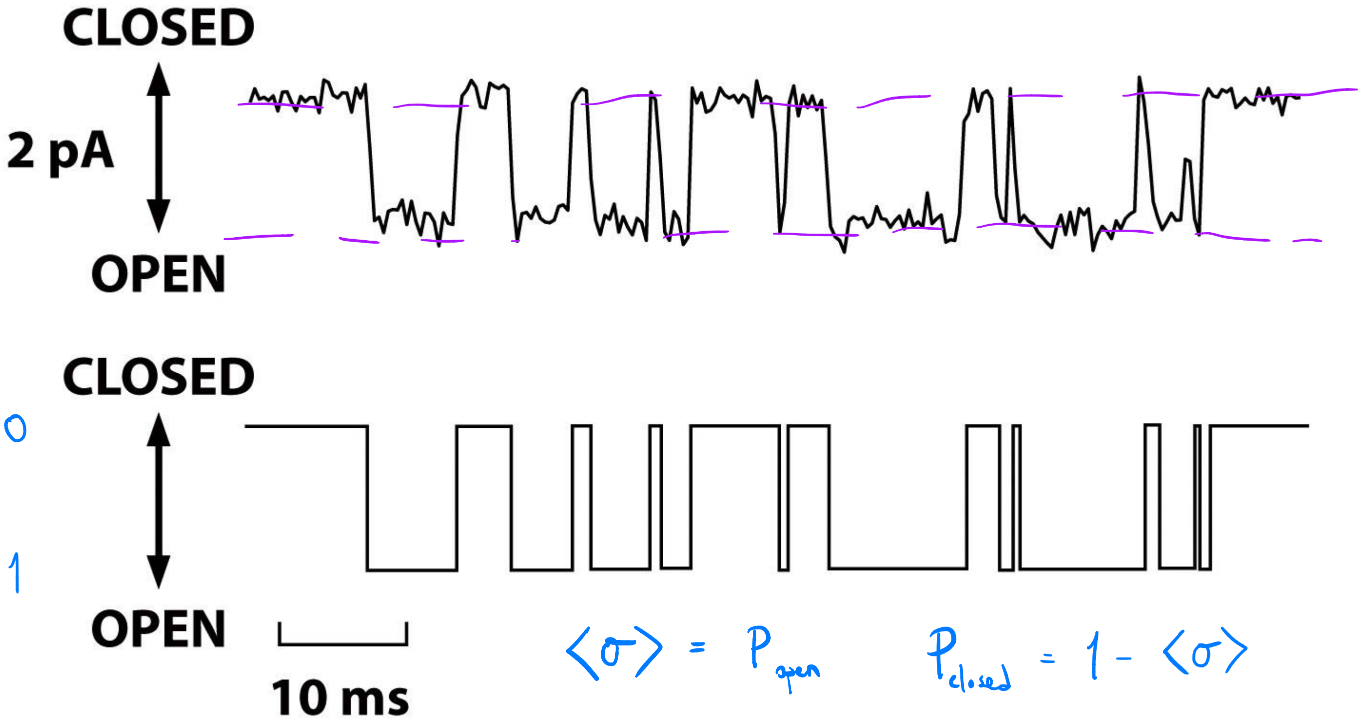
$$= \varepsilon_{sol}(L-\sigma) + \varepsilon_b \sigma$$

Two-state system

Ion channel gating

$E(\sigma) = \sigma \varepsilon_{open} + (1-\sigma)\,\varepsilon_{closed}$

Experiment: rapid transitions between two states



current

$I = 0$ pA

$I \approx -2$ pA

Model: $\sigma = 0$

$\sigma = 1$

$\langle \sigma \rangle = P_{open}$ $\quad P_{closed} = 1 - \langle \sigma \rangle$

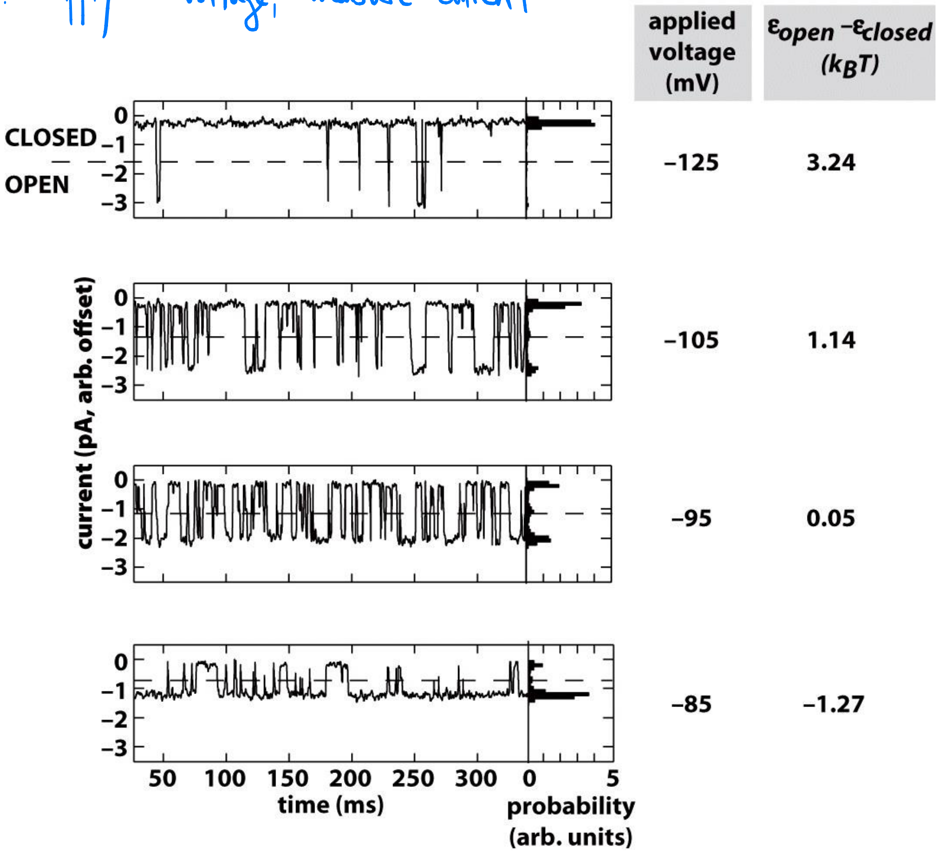
Two-state system

Ion channel gating

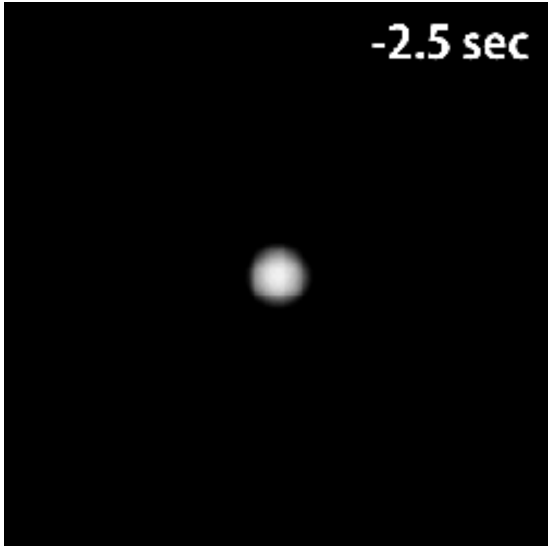
Experiment: Apply a voltage, measure current

High voltage: mostly closed

Low voltage: mostly open



Two-state system

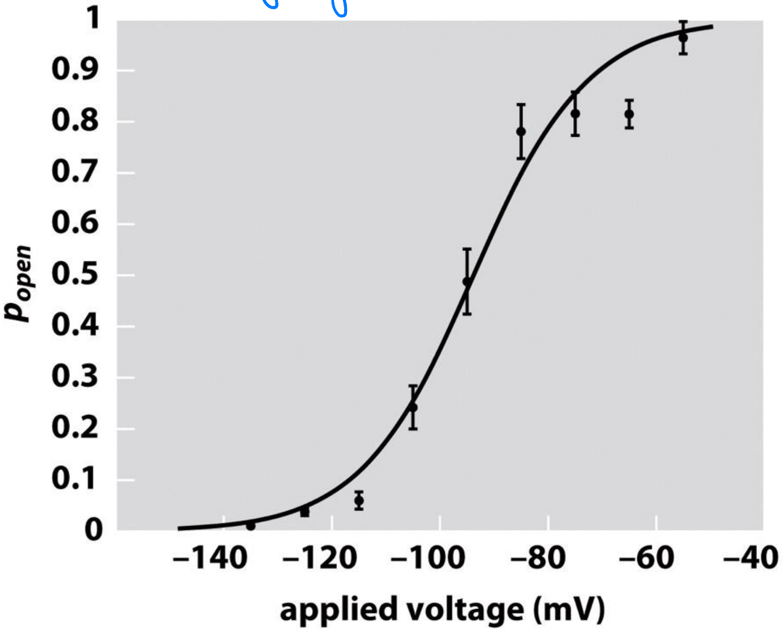


ATP-induced structural changes

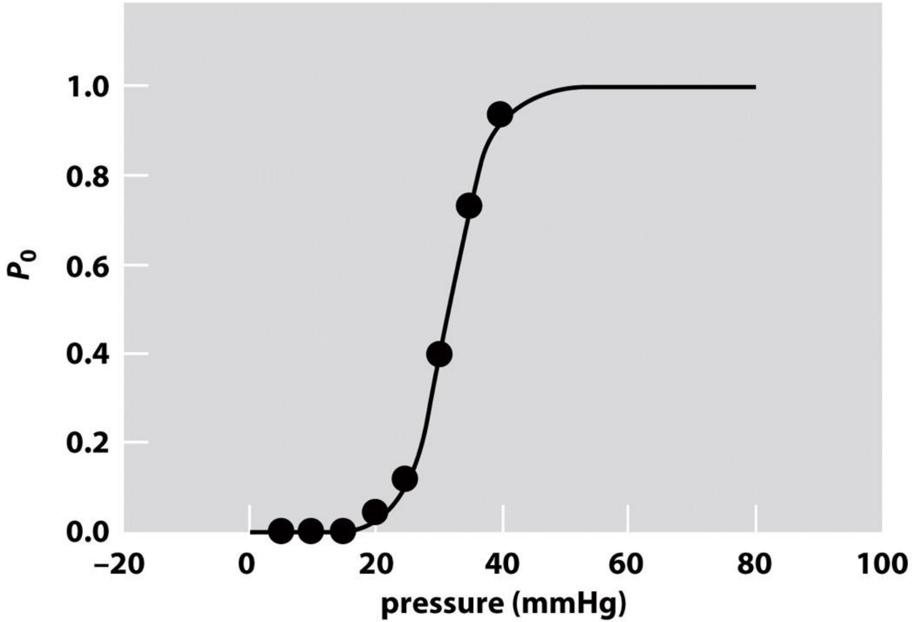
Two-state system

Ion channel gating

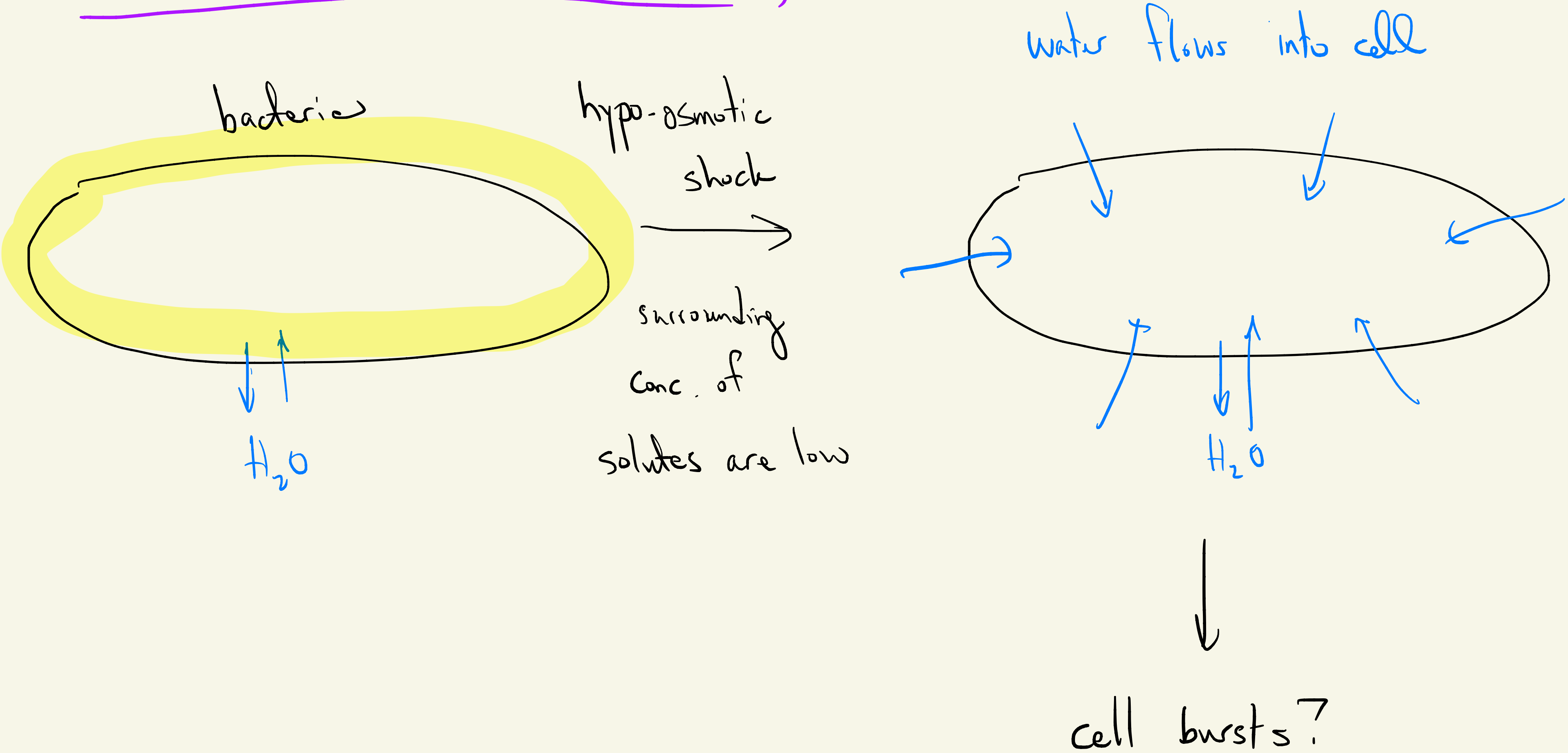
voltage-gated ion channel (like in neurons)



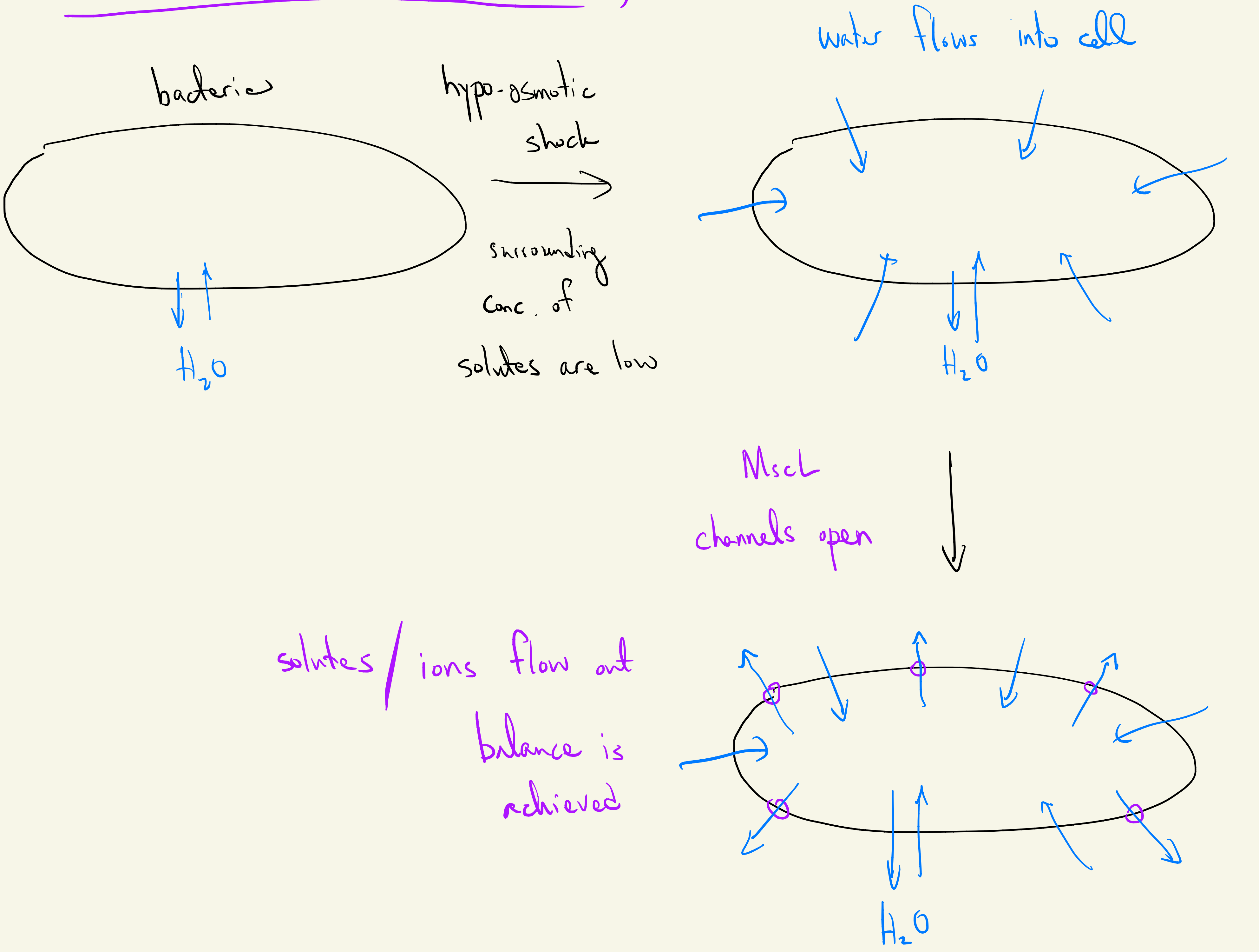
mechanosensitive ion channel (like in bacteria)



Mechanosensitive Ion Channels (MscL)



Mechanosensitive Ion Channels (MscL)

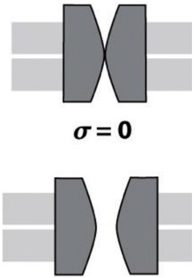


Two-state system

$E(\sigma) = \sigma\,\varepsilon_{open} + (1-\sigma)\,\varepsilon_{cl}$

Ion channel gating

Calculate P_{open} in presence of membrane tension, τ energy/area



	STATE	Energy	Weight
closed	$\sigma = 0$	ε_{closed}	$e^{-\beta\varepsilon_{closed}}$
open	$\sigma = 1$	$\varepsilon_{open} - \underbrace{\tau\Delta A}_{\text{change in channel area when it opens}}$	$e^{-\beta(\varepsilon_{open} - \tau\Delta A)}$

ion channel gating

Channel opening relieves membrane tension by reducing membrane area

$$P_{open} = \frac{e^{-\beta(\varepsilon_{open} - \tau\Delta A)}}{e^{-\beta\varepsilon_{closed}} + e^{-\beta(\varepsilon_{open} - \tau\Delta A)}} = \langle\sigma\rangle$$

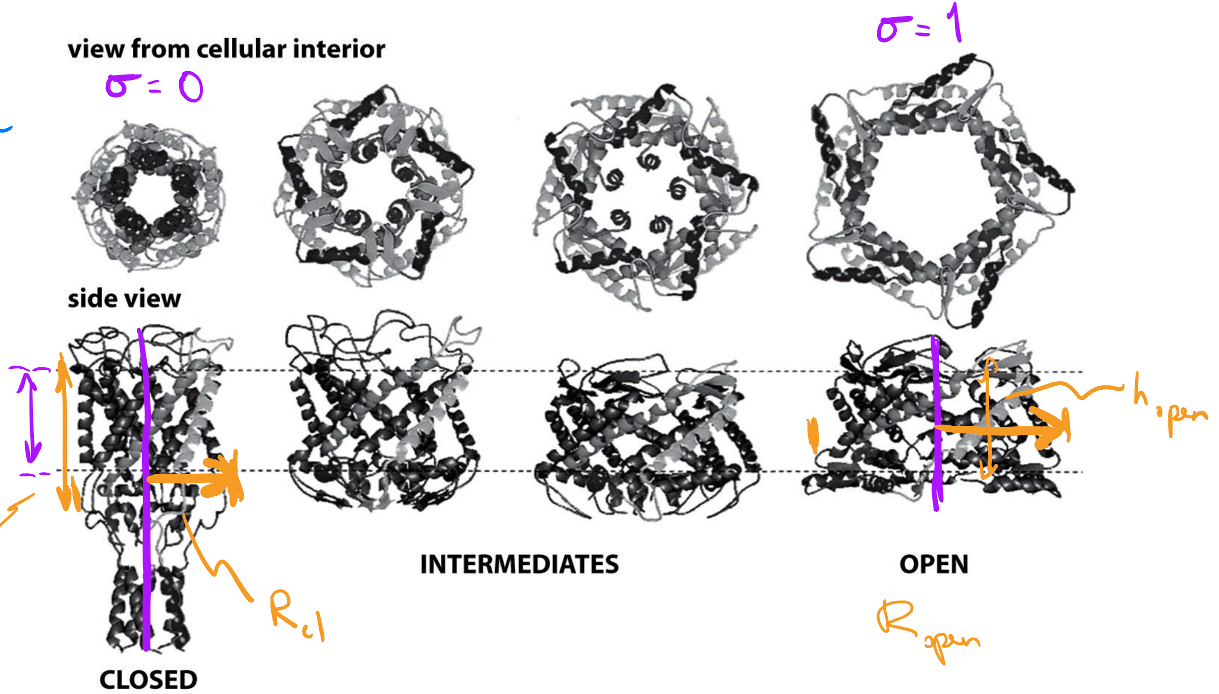
The active membrane

PB.C 11.5

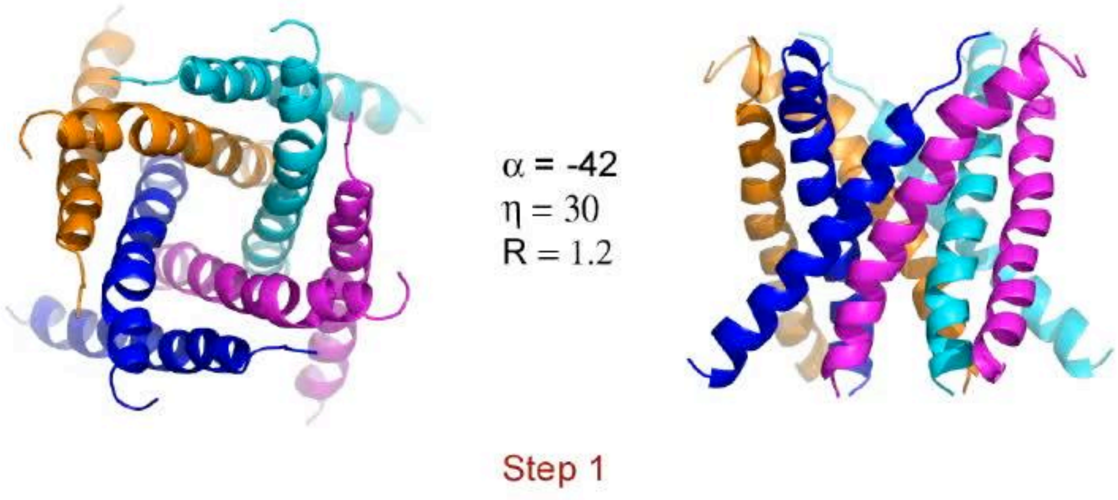
Mechanosensitive Ion Channels and Membrane Elasticity

bacterial mechanosensitive ion channel MscL

membrane thickness, w.



The active membrane

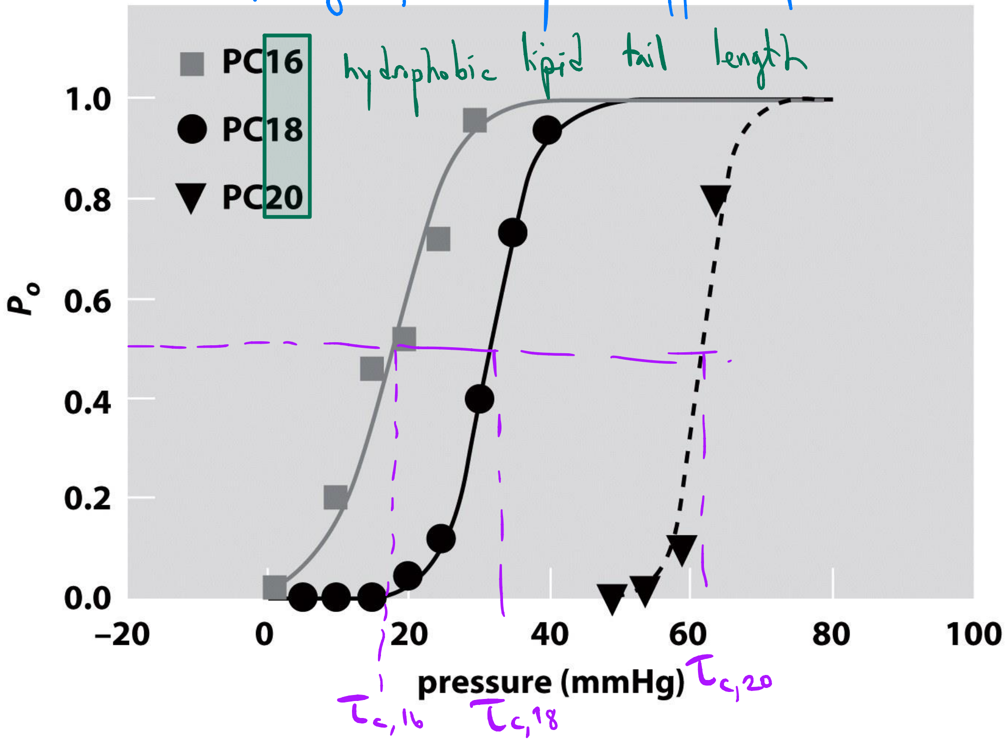


The crystal structure of tetrameric SaMscL

The active membrane

Mechanosensitive Ion Channels and Membrane Elasticity

opening probability vs. applied pressure



short tails → lower pressure required to open

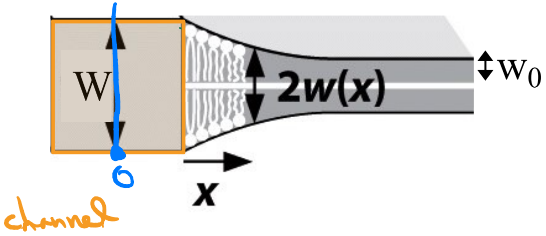
long tails → higher pressure required to open

hydrophobic matching + mechanics

- critical tension, τ_c, at which channels are equally likely to be open or closed

The active membrane

Energetic cost to change membrane thickness



$$u(x) = w(x) - w_0$$

Question: How will this change free energy, T_c?

Channel has radius R

PBoC 11.5

One-dimensional solution for MscL

Connecting elastic energy minimization to two-state system.

What do we know about u(x)?

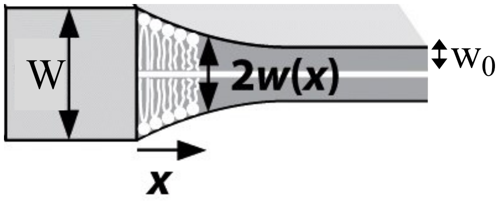
B.C.
$$\begin{cases} u(R) = \frac{W}{2} - w_0 \\ u'(R) = 0 \\ u(\infty) = 0 \\ u'(\infty) = 0 \end{cases}$$

u(x) minimizes free energy, subject to B.C.

The active membrane

One-dimensional solution for MscL

elastic energy from hydrophobic inclusion



$$u(x) = w(x) - w_0$$

$$G_h[u(x)] = \underbrace{\frac{K_b}{2}\int_R^{\infty}\left(\frac{d^2u}{dx^2}\right)^2 dx}_{\substack{\text{bending energy}\\(11.7)}} + \underbrace{\frac{K_t}{2w_0^2}\int_R^{\infty} u(x)^2 dx}_{\substack{\text{thickness energy}\\(11.8)}}. \qquad (11.35)$$

1D energy/length

minimize free energy:

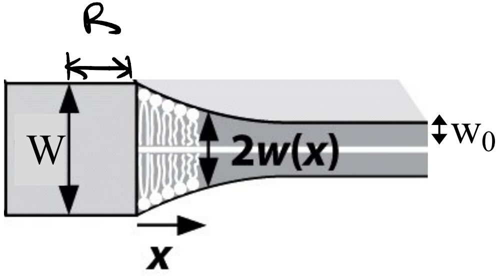
- functional derivative (5.7 Appendix)
- derive equilibrium equation (11.40-11.43)
- identify physical solutions u(x) (11.44-11.51)
- apply BC, substitute back into free energy (11.51-57)

$$G_h = \frac{K_t U^2}{\sqrt{2}\lambda w_0^2}. \qquad (11.57)$$

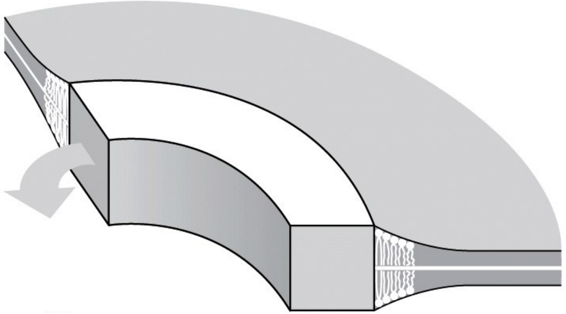
where λ is the decay length of the deformation, $U = \frac{W}{2} - w_0$ is hydrophobic mismatch between protein & membrane

The active membrane

Two-dimensional solution for MscL



$u(x) = w(x) - w_0$



$$G_h = \frac{K_t U^2}{\sqrt{2}\lambda w_0^2}. \quad \text{(1D elastic energy)} \qquad (11.57)$$

use cylindrical symmetry to calculate total energy (11.58-59)

$$\begin{aligned} G_{\mathrm{MscL}} &= G_h + G_{\mathrm{tension}} \\ &= \underbrace{G_0}_{\text{offset}} + \underbrace{\frac{K_t U^2}{\sqrt{2} w_0^2 \lambda}}_{\substack{\text{energy/length} \\ \text{"line tension"}}} \overset{KU^2}{} \underbrace{2\pi R}_{\text{circumference}} - \underbrace{\tau \pi R^2}_{\text{loading device}} \end{aligned} \quad .(11.58)$$

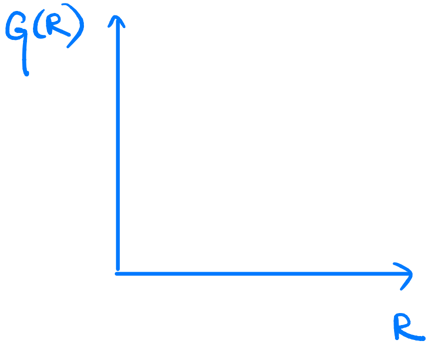
where λ represents the decay length, and $U = \dfrac{W}{2} - w_0$

The active membrane

One-dimensional solution for MscL

- Sketch the free energy as a function of channel radius.
- Find the critical tension, defined as the tension at which the free energies of open and closed states are equal. τ_c

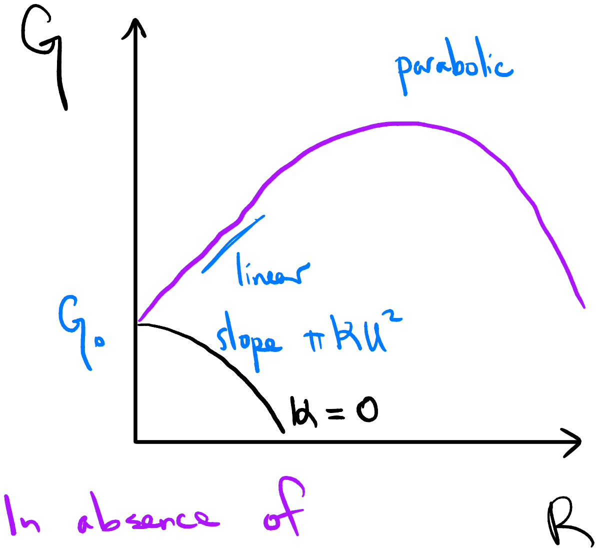
$$G(R) = G_0 + \underbrace{\pi K u^2 R}_{\text{membrane deformation}} - \underbrace{\tau \pi R^2}_{\text{tension (applied force)}}$$



τ_c, given R_{open} and R_{closed}

The active membrane

One-dimensional solution for MscL



In absence of membrane bending term, channel should always be <u>open</u>.

$$G(R) = G_0 + \pi K u^2 R - \tau \pi R^2$$

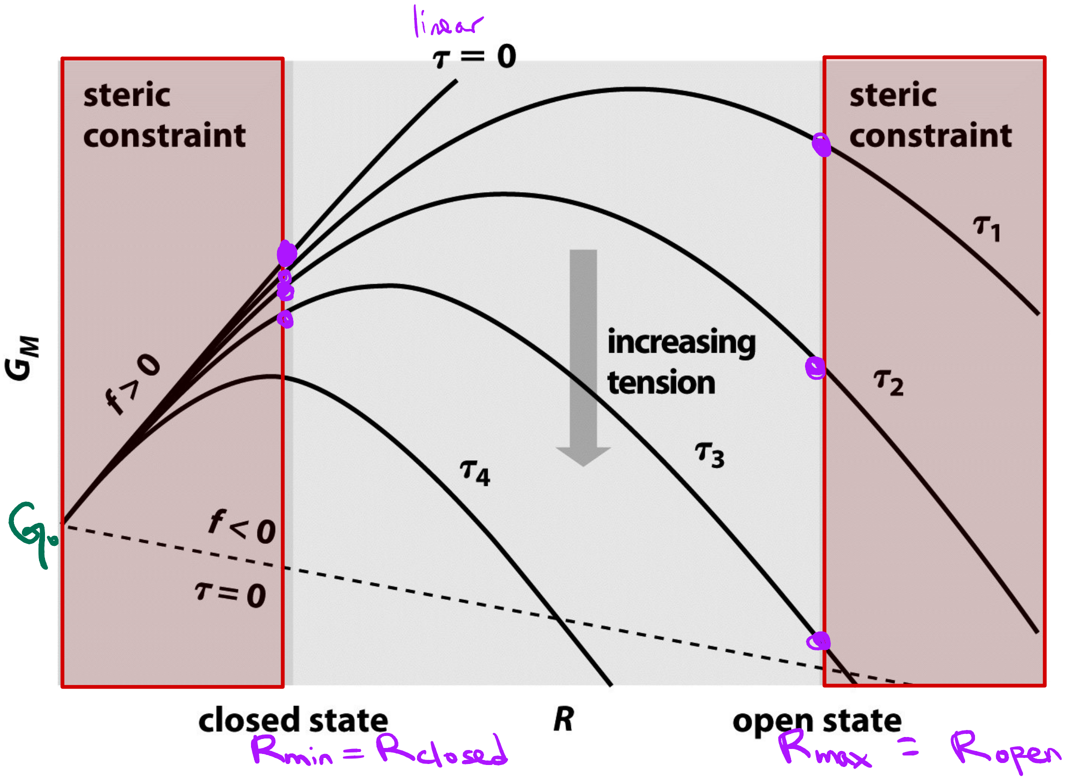
at $\tau = \tau_c$, $G(R_{open}) = G(R_{closed})$

$$\Rightarrow \quad K u^2 R_{open} - \tau_c R_{open}^2 = K u^2 R_{closed} - \tau_c R_{closed}^2$$

$$\tau_c = \frac{K u^2}{R_{cl} + R_{open}}$$

The active membrane

One-dimensional solution for MscL



As tension increases, transition from linear to parabolic occurs at smaller R

• stable radius

f: effective line tension

$$= \frac{K_t u^2}{\sqrt{2}\, w_0^2 \lambda}$$

The active membrane

One-dimensional solution for MscL

	Theory		Experiment	
n	τ_{crit} ($k_BT/\text{Å}^2$)	$\Delta G(\tau = 0)$ (k_BT)	$P_{1/2}$ (mmHg)	$\Delta G(\tau = 0)$ (k_BT)
16	$2.3 \cdot 10^{-3}$	5	24 ± 2	4
18	$5.2 \cdot 10^{-3}$	11.5	42 ± 5	9.4
20	$9.3 \cdot 10^{-3}$	20.4	72 ± 8	23.5

need pipette radius to compare

good agreement

$P = \tau / A$

scaling is in good agreement

Lecture 7: Two-state system, ion channels

Summary

- Two state systems: Can write the energy $E(\sigma)$ where σ is a state variable.
- Ion channels: open or closed state. Different energies → distinct probabilities.

  Energies change depending on external parameters, gating mechanisms.
- Mechanosensitive ion channels: Account for membrane deformation due to hydrophobic mismatch.

  Two local minima in free energy, corresponding to open & closed states.

Lecture 8: Diffusive dynamics

Goal: Role of Brownian motion in living systems. Compute the time to travel a distance, model diffusion in gradient.

- Brownian motion
- Concentration fields and diffusive dynamics

PBOC Chapter 13.1, 13.2.1-13.2.3

The active membrane

Mechanosensitive Ion Channels and Membrane Elasticity