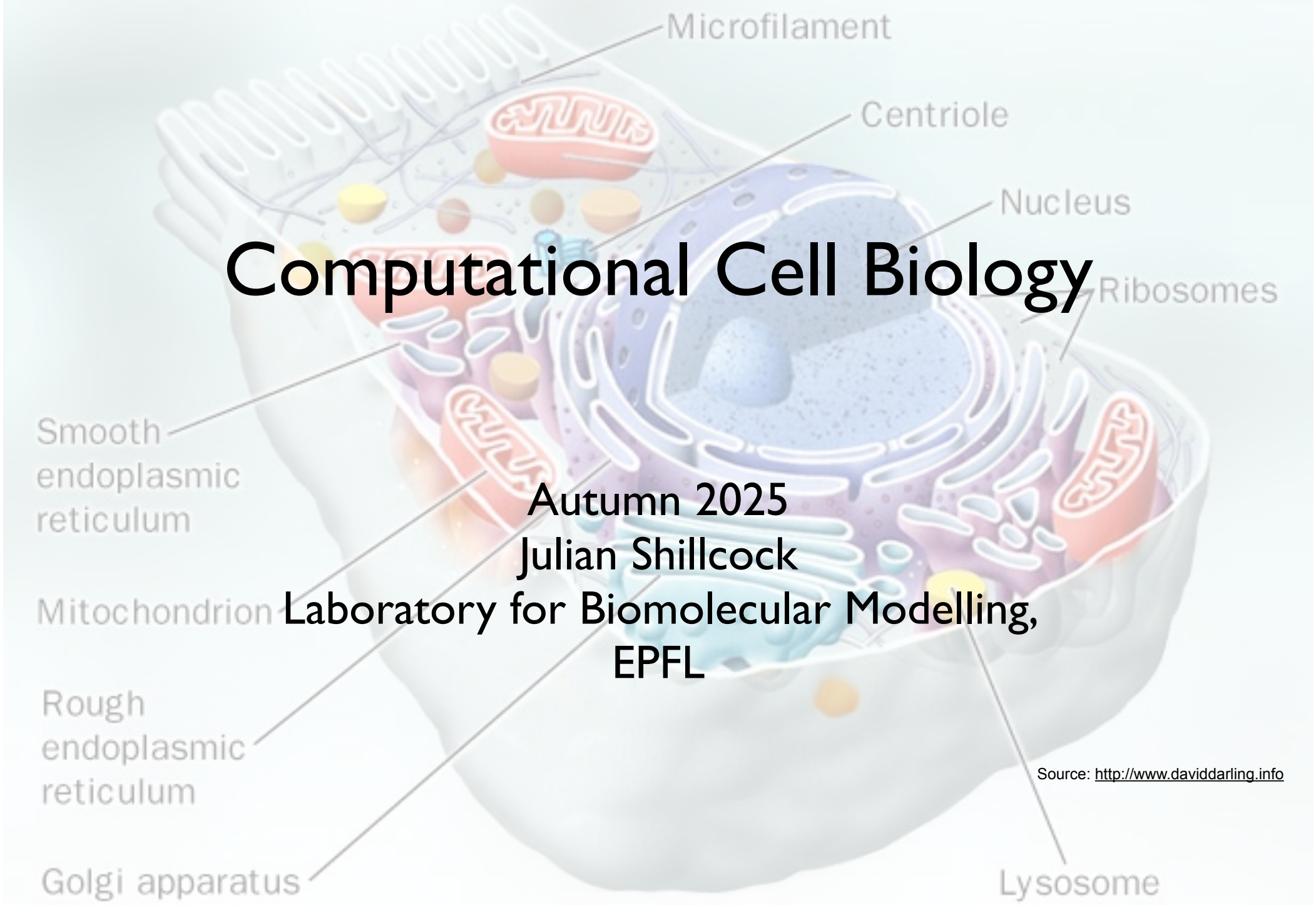


Computational Cell Biology

Autumn 2025

Julian Shillcock
Laboratory for Biomolecular Modelling,
EPFL

Source: http://www.daviddarling.info

Core Concepts

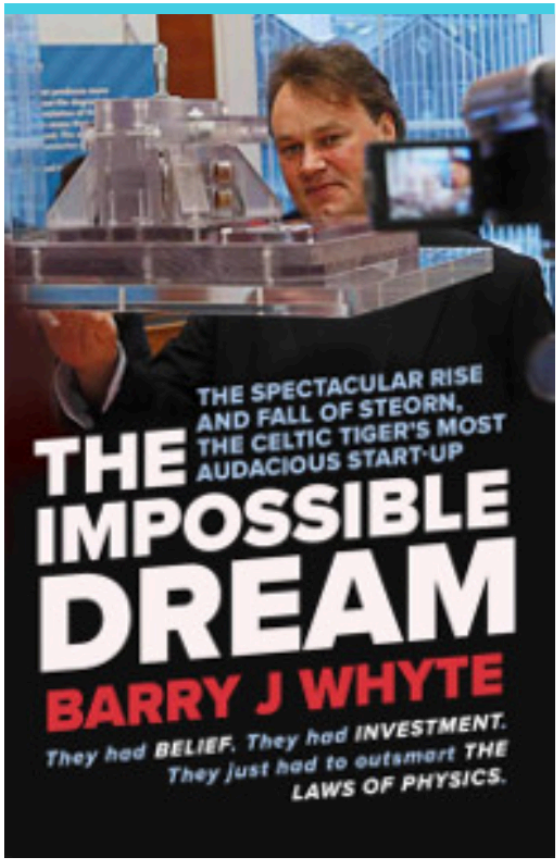
Reversibility is important to a cell as it minimises energy dissipated

All natural processes are irreversible (*but some still try to invent perpetual motion machines…Steorn 2009*)

A cell uses phase transitions to make large changes with minimum energy consumption: a small change in a parameter can create a huge change in the state of a system

Driving force comes from the surroundings, i.e, equipartition theorem… again! I*f you poke a system you change a few d.o.f* but if you change the temperature you change all of them

1 Claim something impossible
2 Fail
3 Write a book about it…. get rich



The Impossible Dream: book brings new account of Steorn's journey

May 18, 2020 Michael Ferrier

Irish Business Post journalist Barry J Whyte, who wrote several articles covering Steorn over the years, has published a book detailing the whole saga. The Impossible Dream: The spectacular rise and fall of Steorn, one of the Celtic Tiger's most audacious start-ups is available now through Amazon for Kindle, and will be released on paperback in September. I […]

Quote of the day:

They had belief. They had investment. They just had to outsmart the Laws of Physics

http://dispatchesfromthefuture.com

Why does this scam still work?

Surely everyone has heard about conservation of energy?

Thermodynamics is unlike other theories in physics - it's an extrapolation from experience not a fundamental theory.

There might always an exception … cue magnetic fields, gyroscopes, …

Compare: Quantum electrodynamics

Spectral lines in atoms… Rutherford's experiment of firing He ions at Au foil and some bounced back… nucleus and electrons

electrons … TVs …

Schrodinger equation describes behaviour of atoms and molecules and (so far) all its predictions have been demonstrated

Thermodynamics claims to describe every physical process
but we cannot check every process, maybe it doesn't apply *here?*

In case you think scientists are immune to this …

LETTERS

A charge-driven molecular water pump

XIAOJING GONG[1,2], JINGYUAN LI[3], HANGJUN LU[1,2,4], RONGZHENG WAN[1], JICHEN LI[5], JUN HU[1,6]* AND HAIPING FANG[1]*

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Published online: 21 October 2007; doi:10.1038/nnano.2007.320

https://www.nature.com/articles/nnano.2007.320

They claimed to use MD simulations to show that water could be spontaneously pumped through a C-nanotube in a membrane without any energy input

Static charges cannot drive a continuous flow of water molecules through a carbon nanotube

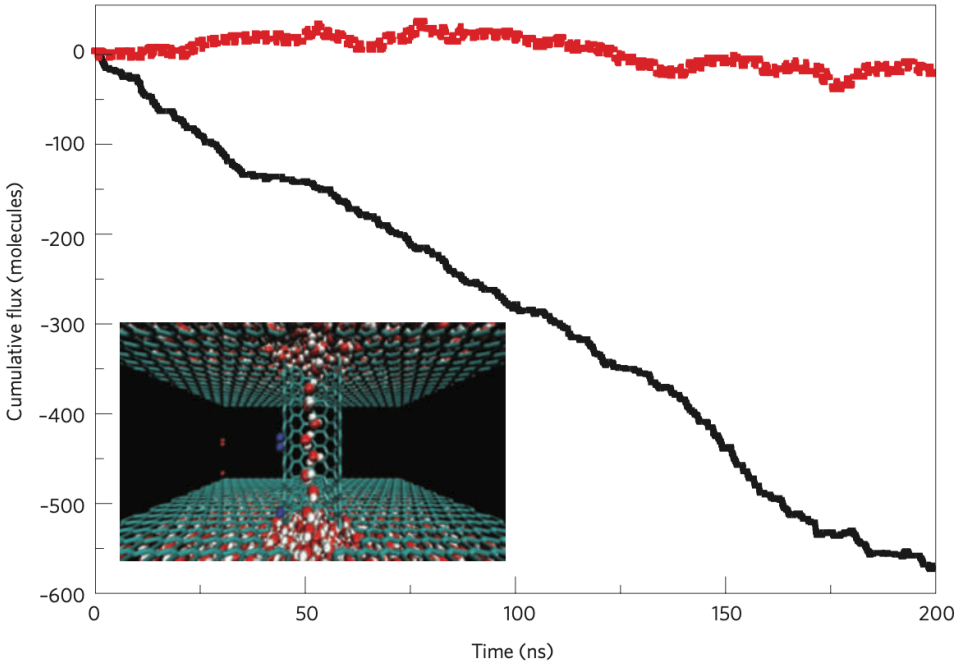


Figure 1 | Cumulative flux of water molecules as a function of time for two different MD simulations of the system shown in the inset. The inset shows a carbon nanotube connecting two reservoirs of

https://www.nature.com/articles/nnano.2010.152

It was a mistake in Gong et al.'s MD simulations, but there is no indication on Nature's site that it's wrong — and it is still being cited.

How to cite: *Angew. Chem. Int. Ed.* **2025**, *64*, e202502267
doi.org/10.1002/anie.202502267

Water

Enhanced Water Permeation in Positively Charged Water Channels: Insights into the Molecular Mechanism

Yinglan Wang, Jun-Li Hou, and Wenning Wang**

from the introduction:

channels.[7g] Early research also highlighted that single-walled carbon nanotube (SWNT) with positioned positive charges can function as effective water pumps.[7d] Analysis of

2nd Law of Thermodynamics

2nd Law says that entropy always increases: it restricts the direction of spontaneous physical changes so that heat always flows from higher to lower temperatures.

Note. There is no guarantee that a simulation will do the same. Force calculations and RNGs can be deceptively well behaved and wrong.

1st law — Whatever can happen given the system's energy/constraints **will** happen

2nd law — Whatever can happen in the most ways is what we **observe**

Kelvin-Planck: "It is impossible to devise an engine which, working in a cycle, shall produce no effect other than the extraction of heat from a reservoir and the performance of an equal amount of mechanical work."

Clausius: "It is impossible to devise an engine which, working in a cycle, shall produce no effect other than the transfer of heat from a colder to a hotter body."

What is Free Energy?

An **isolated** system has a constant internal energy (that's what *isolated* means!)

What happens if a system is not isolated?

It is found experimentally that there is still a quantity related to the internal energy that is minimised in equilibrium - **Free Energy** - whose definition depends on the boundary. There are as many types of free energy as there are boundary conditions on a system.

Free energy is *stored energy* that we can extract from a system, e.g., a compressed spring or gas, chemical changes in a battery.

Free energies

Consider a system of N particles in various kinds of "box" (e.g., simulation box):

Isolated system: U = Internal energy: N, V, U are constant

Isothermal system: F = U - TS = Helmholtz free energy: N, V, T are constant

Isothermal, isobaric system: G = U + PV - TS = Gibbs free energy: N, P, T are constant

Open system with a fixed, diathermal wall: Ω = U - TS + μN = Grand potential:

Chemical potential μ, V, T are constant

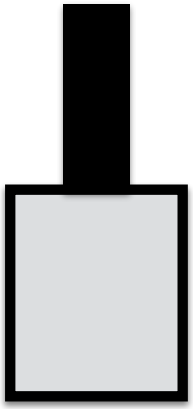
In any problem, the recipe is to identify the boundary conditions, construct an appropriate free energy, minimise it, and that gives the equilibrium state. If, as a result of changing a parameter like T, the system takes up a new phase, we have a phase transition.

Phases and phase transitions

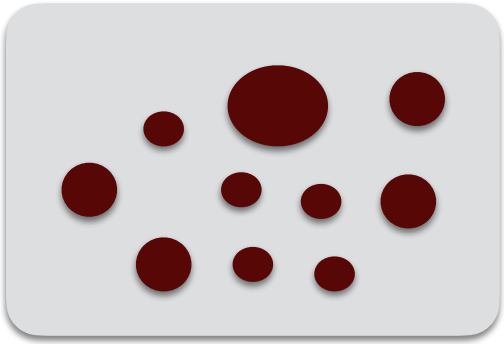
" A ***phase*** is an homogeneous region of matter bounded by surfaces across which its properties change discontinuously (e.g., solid, liquid or gas) "

" An ***equilibrium phase*** has no internal gradients nor between it and its surroundings "

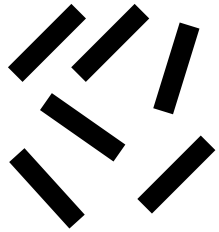
Water



Gas in isolated box with a piston



Solution of micelles



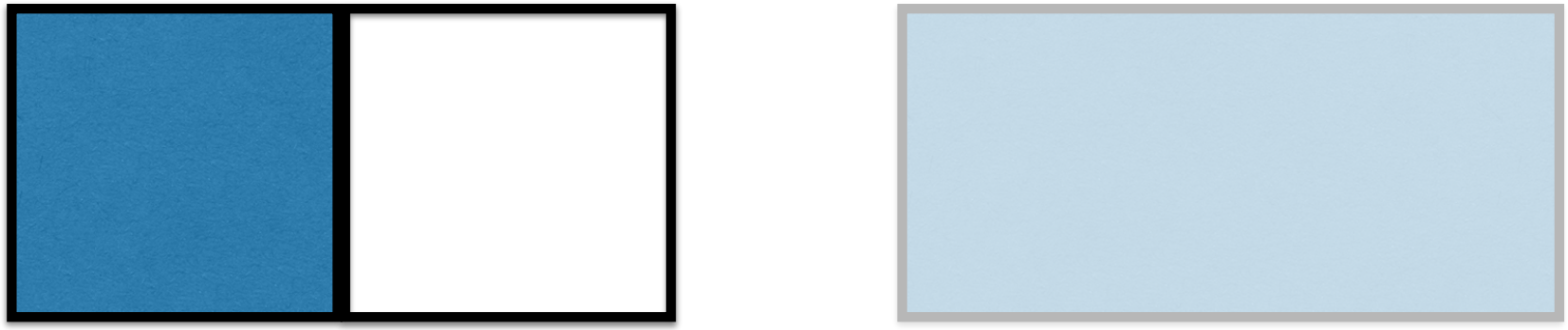
Rodlike liq. crys. / TMV in solution

"Homogeneous" contains an **implicit** average over a region of space, e.g., micelles in water.
NB. Molecular shape may or may not be relevant depending on concentration, cp. ideal gas.

There are distinct types of bounding surface (or wall):

Adiabatic = neither heat nor matter transport across the surface
Diathermal = heat transport but not matter
Open = heat and matter transport

Entropy



Experimentally, an isolated system (constant N, V, E) has a constant internal energy and, in equilibrium, no further spontaneous changes occur.

When a gas in an isolated box (adiabatic walls) is allowed to expand, it fills available space.

Why does it expand?

It is overwhelmingly likely that the random thermal motion of the molecules drives them to occupy the newly-available volume. Energy is transferred between all the dof of the system until no further spontaneous changes occur, this state has the maximum ***entropy***.

What has this got to do with cells?

Entropic spring

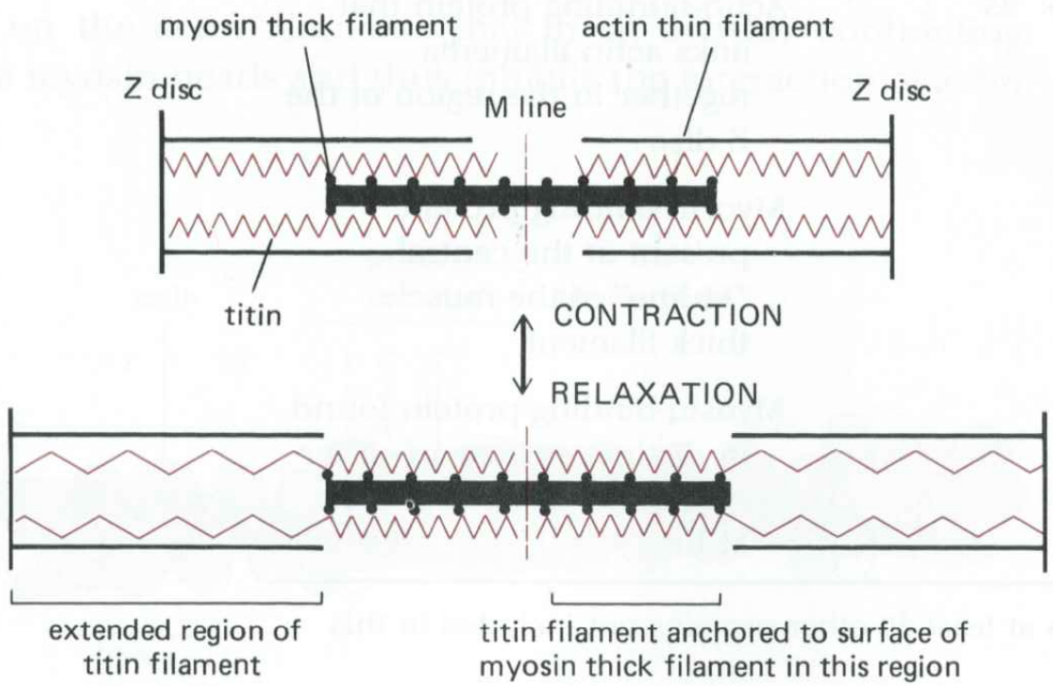


Fig.. 11-21 Mol. Biol. Cell, B Alberts et al.

" Many biological molecules have a defined mechanical function. For these molecules, their resistance to unfolding in response to an applied mechanical force is of critical physiological importance. Titin is the protein responsible for passive elasticity in skeletal muscle, where it functions as a molecular spring… "

C. Bustamente et al., Ann. Rev. Biochem. 73:705-748 (2004)

Titin is the largest protein in the human body, 3 MDa, , 40,000 residues, and 10% of muscle mass.

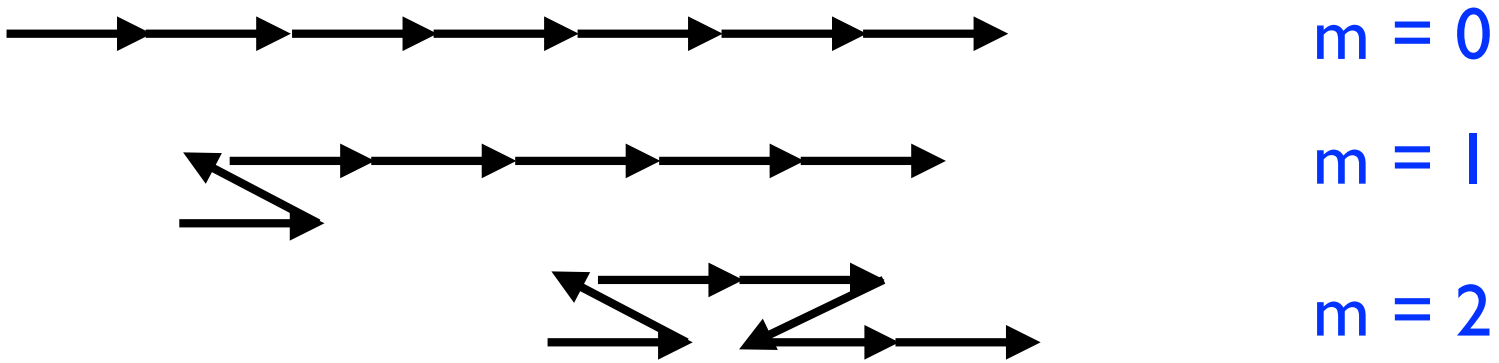
What is an entropic spring?

A 1d polymeric molecule whose resistance to an applied force depends on its length and whose conformations are accessible to thermal excitation.

Collapse transition of entropic spring

A polymeric molecule will stretch and shrink as its monomers fluctuate in space due to thermal motion. In equilibrium, deviations from the mean end-to-end length will cost free energy.

Consider a 1d polymer of N identical monomers (= bonds) in which each bond can only point to the right (+X) or left (-X) independently of all others with no energy cost.

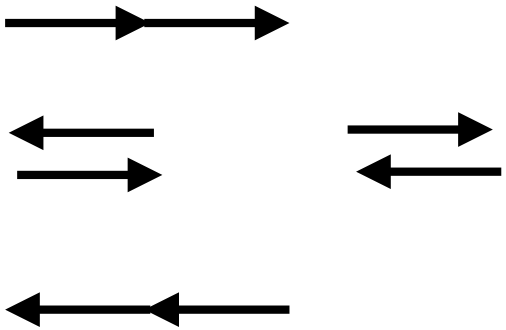


If there are m left-pointing bonds out of N bonds, there are $\Omega(m, N) = N! / m! (N-m)!$ conformations. The free energy of the chain is $F = E - TS$, but $E = 0$, and entropy is:

$$S(m, N) = k_B \ln(N! / m! (N-m)!)$$

What is the most likely conformation?

Think - Pair - Share calculation, 5 mins



N = 2, m = 0

N = 2, m = 1

N = 2, m = 2

1) Draw all possible configurations for N = 3, and verify the formula for $\Omega(m, N) = N! / m! (N-m)!$

2) How many configurations are there for N = 10?

3) How many for N = 100?

NB. Use Stirling's approximation: $\ln N! \sim N \ln N - N$

Blackboard calculation

We have

$$F = -TS = - k_B \ln(N! / m! (N-m)!)$$

Now assume that N, m are both >> 1 and bond flips are completely random.

The polymer contour length is: $L_0 = N a$

It's actual length with m flips: $L = (N - 2 M) a$

$x = L/L_0 = (N-2M)/N = 1 - 2M/N$

$N = L_0/a$

$M = (L_0 - L)/2a$

Calculate the free energy F of the polymer in terms of the variable $x = L/L_0$?

Collapse of an entropic spring

The entropic spring's free energy as a function of its end-to-end length is:

$$F(L/L_0) = k_B T.(L_0/2a) f(L/L_0)$$

where $f(x) = (1 - x) \ln(1 - x) + (1 + x) \ln(1 + x) - 2 \ln 2$

and L = end-to-end length of the polymer, L_0 = maximum length of polymer (all bonds parallel). It exerts a force on its two ends that increases as $x = L/L_0$ moves away from 0. And it has a minimum at x = 0 or L = 0. Hence, the chain **collapses** to zero length in the absence of an applied tension.

(Graph f(x) what curve does it remind you of?)

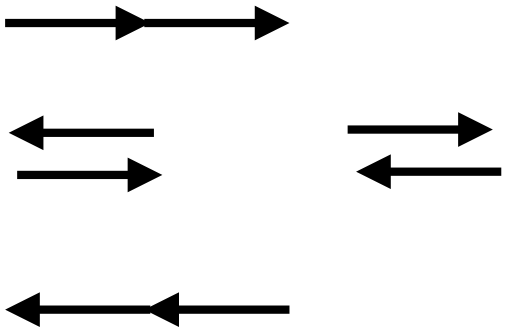
Note.

1) Free energy increases with temperature, i.e., it is an *entropic spring*, with spring constant ~ $k_B T/a$
2) Free energy increases with polymer contour length L_0
3) Free energy is **maximised** for fully stretched chain ($L = +/- L_0$)

The most likely conformation **minimises** the free energy w.r.t. length, and gives the force exerted by the polymer (the force-extension curve):

$$\text{Force} = - dF(L/L_0)/dL = -dF(x)/dx \, . \, dx/dL = (k_B T/2a) \, . \ln((1 - x)/(1 + x))$$

Think - Pair - Share, 5 mins



N = 2, m = 0

N = 2, m = 1

N = 2, m = 2

$F(L/L_0) = k_B T.(L_0/a).f(L/L_0)$

where $f(x) = 1/2((1 - x).\ln(1 - x) + (1 + x).\ln(1 + x) - 2.\ln 2)$

1) How would you modify the free energy to include pulling both ends of the spring with a constant force?
2) What unrealistic assumption have we made about the random bond flips?
3) How could we fix the problem in 2?

Relation of entropic spring to phantom chain

What is the mean-square end-to-end length of the entropic spring in equilibrium?

Starting from: $F(x) = k_B T.(L_0/a)((1 - x).\ln(1 - x) + (1 + x).\ln(1 + x) - 2.\ln 2)$

where $x = L/L0$, and using: $\ln(1 + x) \sim x - x^2/2 + x^3/3 + \ldots$

We get

$$F(x) \sim k_B T.(L_0 / 2a)(x^2 - 2 \ln 2)$$

Ignoring the constant term, we use the Equipartition theorem to get

$< F / k_B T > = (L_0 / 2a) < x^2 > = 1/2$

or $< x^2 > = a / L_0$, but $x = L/L_0$ and $L_0 = Na$, so

$$< L^2 > = Na^2$$

and the entropic spring has the same end-to-end length dependence on its contour length (N) as a phantom chain.

Summary

Phase transitions are reversible *macroscopic* changes driven by *microscopic* interactions (equipartition thm. provides energy for the change to all molecules simultaneously)

Entropic spring is a mean field theory of phase transitions - it ignores connectivity - but gives reasonable prediction

Small changes in a control parameter (temp., conc., etc) can have huge effects (water-ice)

Cells use phase transitions to organise their biochemistry, e.g., organelle membranes, intrinsically-disordered proteins

Break

10 mins.

Free books in AAB 021

just come by and take them

Exercise

1) Projects

part of the project is to estimate what you are able to simulate, and what questions you can answer in the time available

take into account the time required to run the simulations, system size, # of parameters to vary, # of simulations

work in groups

creativity in the project is more important than getting very precise results IF you can state the sources of error

do include your thoughts and comments about what you have done, what you could improve, etc.

2) Any problems running simulations on helvetios?