Take-Home Message

Thermodynamics works everywhere

TD relates observables in experiments and between experiments and simulations

Equipartition theorem drives self-assembly in bulk and in membranes

Universality of Thermodynamics

The law that entropy always increases, holds, I think, the supreme position among the laws of Nature. If someone points out to you that your pet theory of the universe is in disagreement with Maxwell's equations — then so much the worse for Maxwell's equations. If it is found to be contradicted by observation — well, these experimentalists do bungle things sometimes. But if your theory is found to be against the second law of thermodynamics I can give you no hope; there is nothing for it but to collapse in deepest humiliation.

A. Eddington

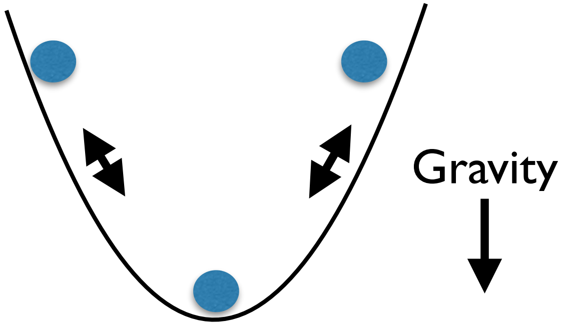
Classical mechanics

Classical mechanics studies the motion of objects in the world, it finds relations between external mechanical coordinates (x_i, v_i, f_i) and time that determine the **KE and PE** that are consistent with Newton's laws.

In classical mechanics, mechanical energy (or work) is conserved

But mechanical systems are observed to minimise their energy - why?

e.g., a ball rolls up and down a slope, but eventually stops at the bottom



Energy is lost due to friction, air resistance, sound, etc.

If there were no losses, the ball would oscillate forever.

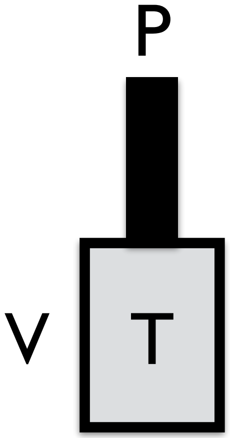
The motion of macroscopic objects (e.g., billiard balls) is usually unaffected by temperature

Q. What is the diffusion constant of a billiard ball? (η_{air} = 18 µPa.sec)
Q. How does its energy of motion compare to the thermal energy (1/2 k_BT)?

Classical thermodynamics

Classical thermodynamics studies the interior of a system using macroscopic coordinates (P, V, T) that determine the ***Internal Energy*** of the system, and finds relations among these coordinates that are consistent with the laws of thermodynamics.

It is a generalisation from every-day experience (involving heat, work, temperature, etc) to an ideal system that deals only with special states of a system called ***Equilibrium States.***



It is an experimental result that equilibrium states of a system can be described with just a few experimental properties (*thermodynamic coordinates*),

e.g., a gas needs N, P, V, T not 10^{23} molecular coordinates.

Unlike classical mechanics, no energy is lost in thermodynamics - it just gets passed between different degrees of freedom

Q. Given a fixed mass of gas, with no chemical reactions, in a box of constant volume at constant temperature, how can its pressure be changed without altering V or T?

Q. If we arbitrarily change P, V, T **adiabatically** and return to the initial state, is the system's internal energy the same as before?

CM and TD are idealisations

Just as classical mechanics involves ideal objects (point particles, frictionless pulleys, rigid bodies, no air resistance, etc) so thermodynamics involves ideal processes:

- Frictionless pistons
- Infinitely-slow motion (quasi-static process)
- Infinitesimal temperature and pressure differences
- Heat reservoirs unaffected by any gain or loss of heat
- No turbulence or gradients in fluids, or inelastic deformations in solids
- Reversible processes

Whether or not these concepts apply to a system has to be determined by experiment. But when they are at least approximately true, we have a powerful means of predicting the behaviour of the system.

Not all idealisations are equivalent: we can imagine an adiabatic wall that prevents all heat transfer across it.

Q. Why cannot we imagine a wall that prevents the gravitational force crossing it?

Role of thermodynamics in cell biology?

Thermodynamics is concerned with understanding the properties of matter in so far as they are affected by changes of temperature.

Cells are isothermal - so what is the need for thermodynamics?

- TD gives relations between observable, macroscopic coordinates (P, V, T) that provide insight into experiments (cp point mass in classical mechanics)
- TD connects theory/simulations with experiments (often the only connection!)
- Many processes in a cell are near equilibrium because leaving eq. is energetically expensive
- Concepts of TD are applicable to cellular processes even if they are not *in* equilibrium but *near* equilibrium

Thermodynamics makes predictions

The usefulness of thermodynamics arises from its universality:

- all *dilute* gases obey the same ideal gas law: $PV = NRT$
- small particles suspended in water exhibit continual, random motion *independent* of their nature (Brownian motion)
- polymer properties are *independent* of monomer details (random walk)
- entropy dominates the shape fluctuations of the plasma membrane and vesicles because the membrane bending energy is small
- phase behaviour of mixtures of polymeric fluids depends on their physical chemical properties (we can often *ignore* atomic details):

concentration
molecular weight and shape
attraction / repulsion of monomers

And when it is applicable, it is immensely powerful in predicting how a system behaves. If we can map a cellular function onto a thermodynamic model, we can predict a lot about it.

Self-assembly is a consequence of Equipartition Thm.

- Self-assembled structures form because they minimise a system's free energy by **phase separating** rather than staying mixed
- The cell uses self-assembly because it's **free**
- It's free because of the Equipartition Theorem

The total energy of a molecular system is continually redistributed among all its atoms and molecules by random thermal motion; this allows the system to eventually discover its state of lowest free energy.

We will cover lipid membrane self-assembly in a later lecture

Membrane-bound compartments self-assemble from dispersed lipids because of the hydrophobic effect, but there are other forces between other molecules that can stabilise large aggregates or compartments, and can assemble domains in membranes, e.g., protein clustering.

Indirect forces

Indirect forces originate in Coulomb's law (electrostatics) but depend on the temperature, and usually involve many weak interactions supporting each other rather than one dominant strong interaction.

This makes them hard to calculate, and almost impossible to guess their functional form or even their sign.

Importantly: indirect forces can be "free", i.e., they arise from the thermodynamics of the environment at room temperature and not on the atomic structure of the interacting molecules (cp. polymer not depending on monomer identity).

Entropic forces

Today

hydrophobic effect of oily chains in water

depletion (molecular crowding)

fluctuation-induced forces

Membrane-mediated forces

curvature

composition

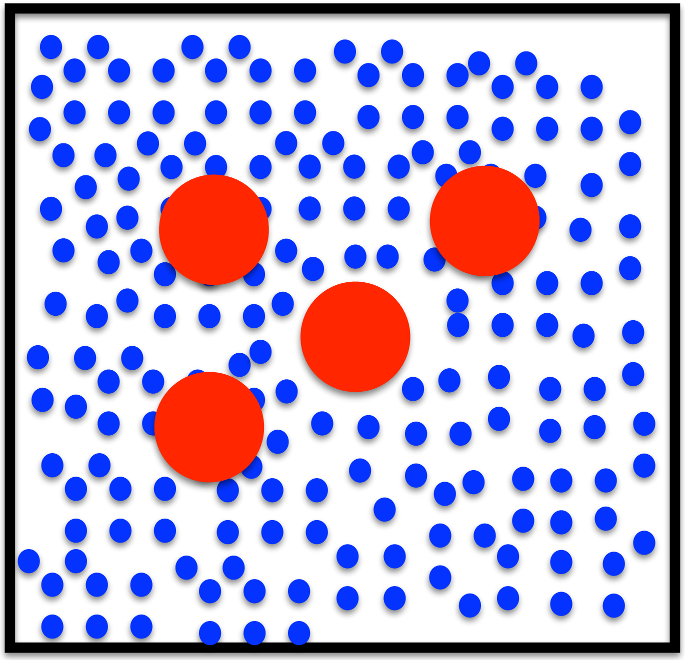
thickness mismatch

Depletion forces

Depletion forces arise when some entities reduce the freedom to move (or fluctuate) of others.

Large solute particles (red) exclude the smaller solvent molecules (blue) from around them.

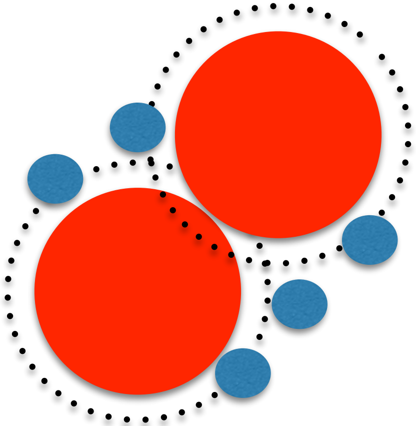
If the red ones cluster, some volume is freed up, and there is more space for the solvent to move around, hence the entropy increases.



Not to scale

Depletion forces don't only arise in bulk solvent, they also arise within membranes (see later).

They are independent of the type of entity (atom, molecule, nanoparticle, membrane) and only require the molecules to be *mobile* and *repulsive* at short range (steric or hard-core repulsion).

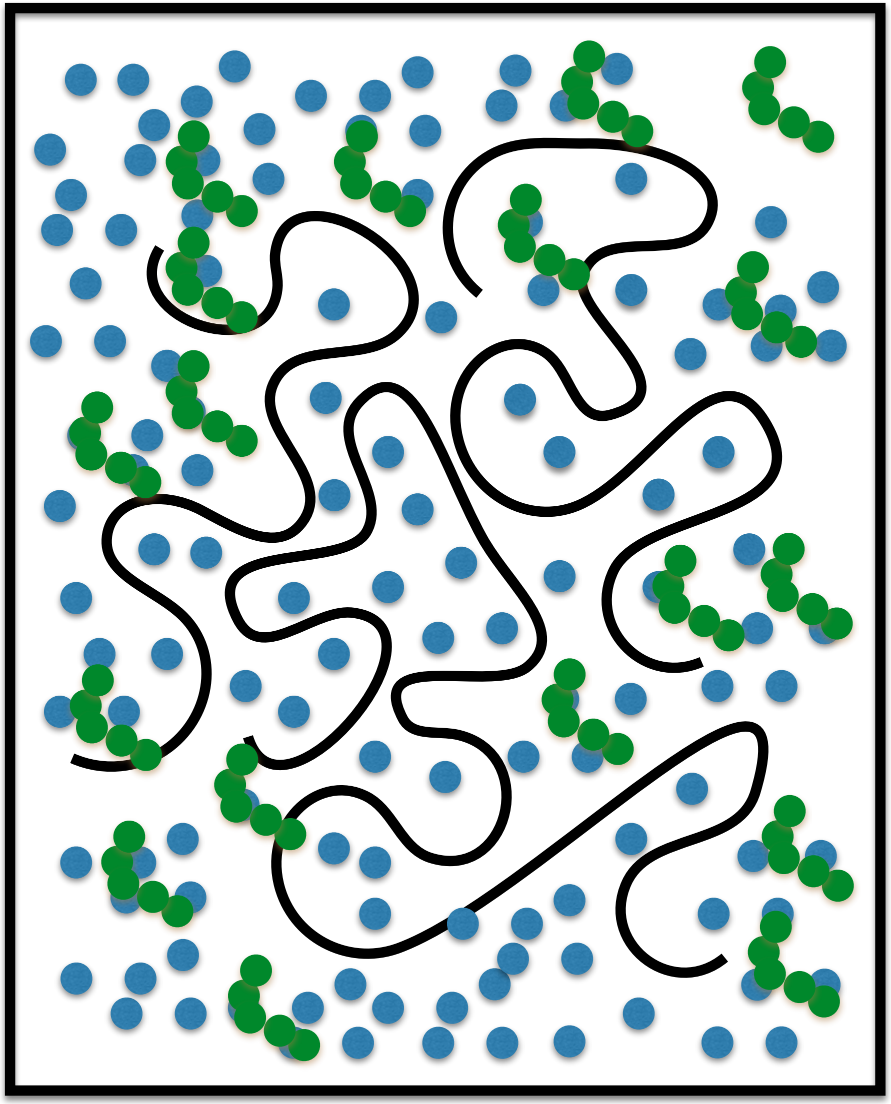


Molecular crowding

Consider a dilute solution of long polymers in water in the presence of concentrated short polymers.

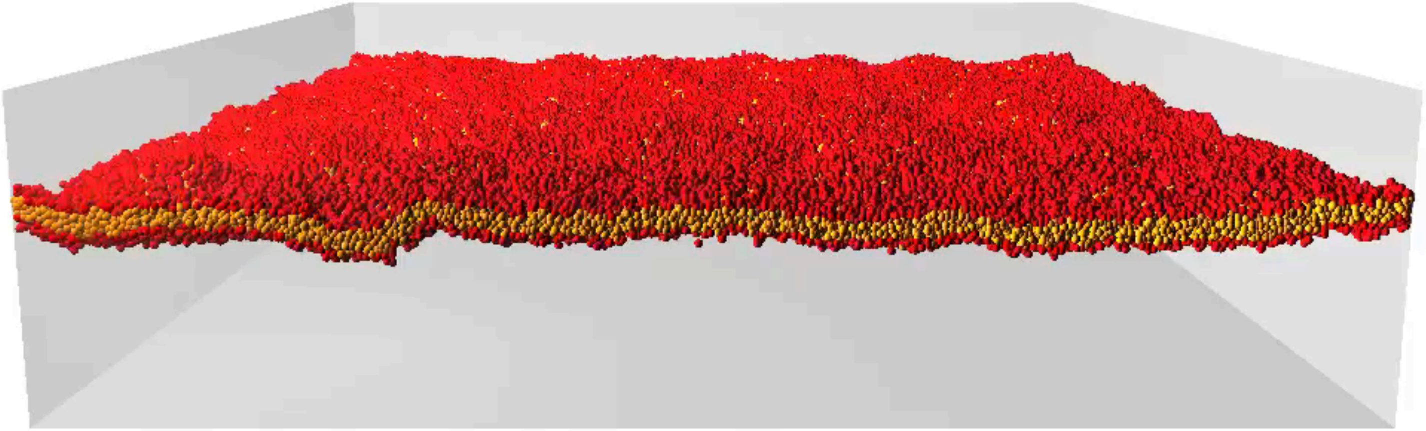
If the two polymer types are sterically repulsive, the long ones restrict the motion and shape fluctuations of the short ones.

This leads to a force on the long ones that squeezes them into an aggregate to maximise the entropy of the short ones.



Membrane fluctuation force

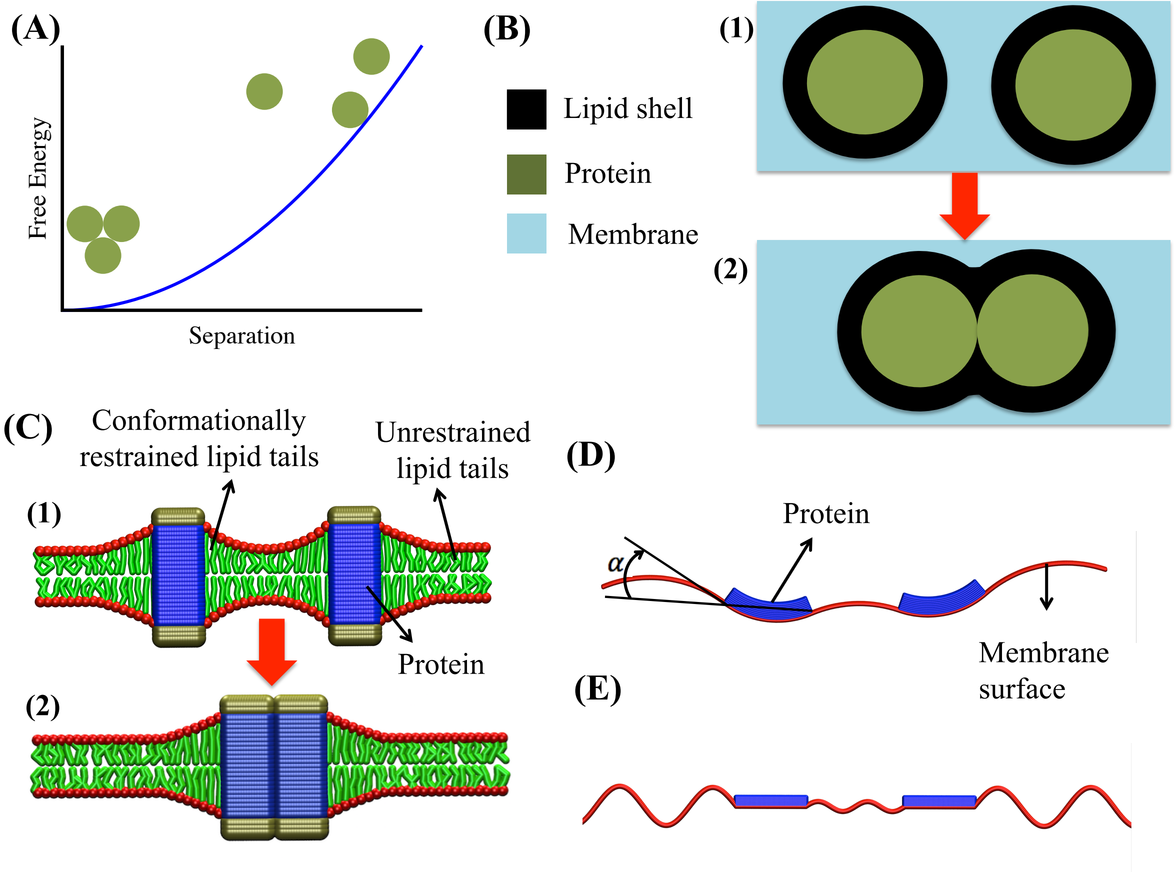
The thermal fluctuations of a lipid membrane give rise to a repulsive force on an object or material that approaches and suppresses its fluctuations: this would lower its entropy and therefore is opposed.



Can a membrane exert forces on nearby or adsorbed objects?

Indirect forces: membrane-mediated

Unlike bare forces, membrane-mediated forces arise when two (or more) proteins/nanoparticles adsorb to/embed in a membrane and perturb its state.



Johannes et al. TCB 2018

A) All operate by lowering the total free energy of membrane+proteins

B) Capillary force/line tension

C) Depletion force

D) Curvature force

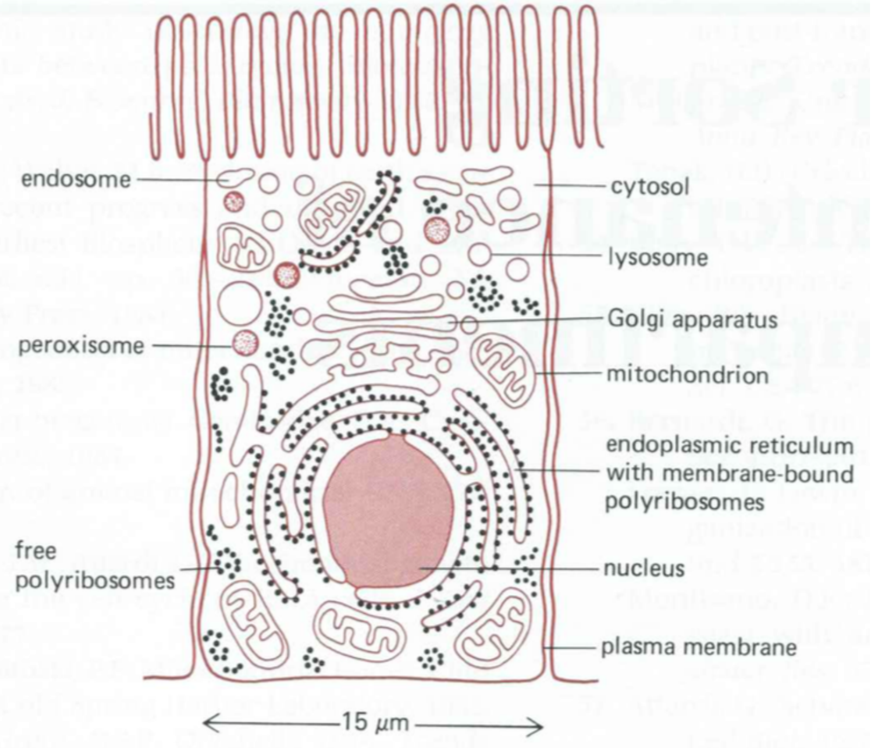
E) Fluctuation-induced force
(Lecture 12)

Indirect forces create compartments

Compartments allow spatial localisation of function: reactions can be kept apart, acidic environment in one place, neutral in another, gradients can form:

- Nucleus - separates transcription from translation
- Rough ER - ribosomes synthesize proteins
- Smooth ER - lipid synthesis
- Golgi - sorting proteins for destination
- Mitochondria - e^- transport, H^+ gradient
- Endosome - imports material into cell

Alberts and Bray, Fig. 8.1



and compartments come for free if you make the right molecules (lipids, proteins) and rely on the equipartition theorem.

Review of classical thermodynamics

There are two approaches to thermodynamics:

Macroscopic:

no assumptions about the structure of matter
few coordinates needed (P, V, T, …)
usually suggested by our senses
measurable
sufficiently large compared to molecules that it is continuous

Experiments

Microscopic:

assumes matter is made up of molecules
many quantities (~10^{23} position + velocity) must be specified
quantities not suggested by senses
not measurable
comparable to molecular size

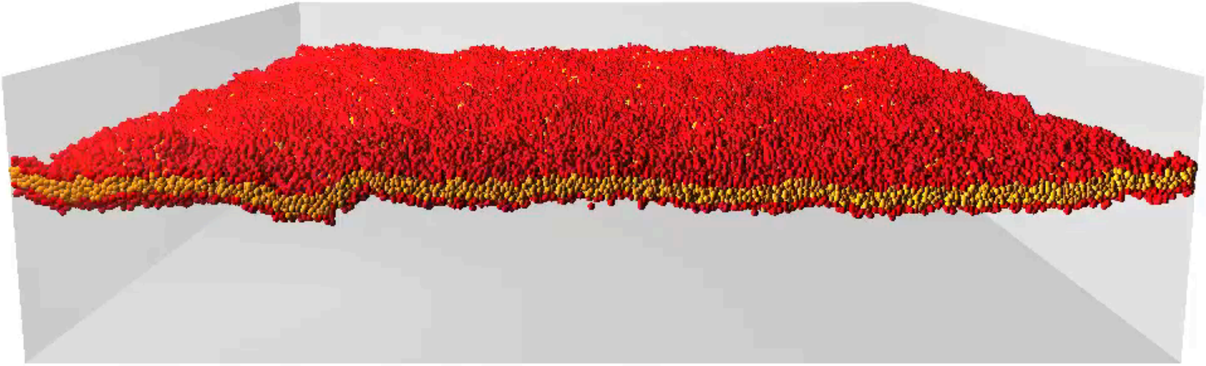
Simulations

Microscopic thermodynamics connects simulations to experiments

Q. How do we know these are the same?

Q. What measurments could we do to prove it?

J. Ipsen, MEMPHYS, SDU



Microscopic thermodynamics

Whereas macroscopic thermodynamics deals only with observable coordinates and properties (P, V, T, etc), microscopic thermodynamics regards a system as composed of molecules in distinct states:

A macrostate is a specification of a few macroscopic coordinates: N, P, V, T, …

A microstate is a specification of all 10^{23} x(t) and v(t) coordinates of the molecules

The molecules are assumed to obey some microscopic force law (either Newton's laws or Quantum Mechanics) that determines their motion, and the observable properties are obtained by averaging them over all accessible states of the system.

Statistical mechanics finds links between the macrostates observed in experiments and the (unobservable) microstates of the system by counting how many microstates make up each macrostate and averaging observables appropriately.

Computer simulations are a way of performing this averaging automatically - they generate a chain of microstates that yield macroscopic observables by averaging their values over all accessible states.

A brief history of thermodynamics

Thermodynamics started as a practical question: **how to get work from heat**

1774 James Watt invented the first steam-engine (Comment on efficiency)
(except for Newcomen, 1712, Savery 1698, others, and Heron of Alexandria, 1st Century)

1790 Count Rumford (Benjamin Thompson) bored a cylinder under water and after 2 hours the water boiled: "bystanders were astonished to see water boil in the absence of a fire" *

1823 Sadi Carnot wrote "Réflexions sur la puissance motrice de feu"
(he thought heat was a substance, and a hot body contained a lot of it and a cold body little, but he still managed to get correct conclusions)

1839 Séguin showed that heat is energy
1842 Meyer calculated the conversion factor of work into heat

~1849 Joule wrote down the 1st Law of Thermodynamics (Energy is conserved)

~ 1850s Clausius and Kelvin independently wrote down the 2nd Law of Thermodynamics
(Heat flows spontaneously only from a hot body to a cold body)

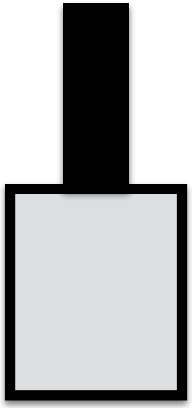
* Entropy and Low Temperature Physics, J. S. Dugdale
Hutchinson University Press, London, 1966

Phase

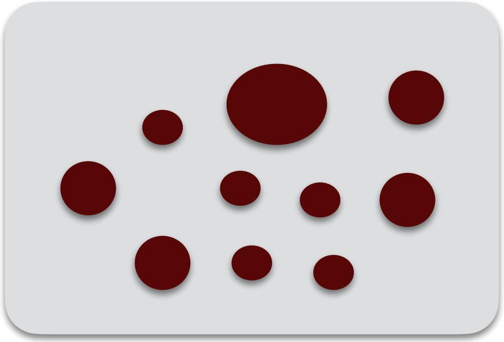
“ A ***phase*** is an homogeneous region of matter bounded by surfaces across which its properties change discontinuously (e.g., solid, liquid or gas) “

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

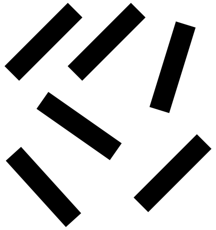
Water



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

Equilibrium

A phase of a substance is in ***thermodynamic equilibrium*** if there are no spontaneous changes in its state.

Thermodynamic equilibrium = Mechanical + Chemical + Thermal equilibrium

Mechanical equilibrium = no unbalanced forces in a system nor across its boundaries

Chemical equilibrium = no chemical reactions, diffusion nor flow “

Thermal equilibrium = no spontaneous changes when in contact with a heat reservoir at the same temperature

If a system *can* make spontaneous changes *it will*, and will stop only when no more spontaneous changes can occur. They are driven by the tendency of the system to incessantly move through its phase space because its energy is continually being redistributed (equipartition theorem).

Once all macroscopic changes have ceased, the system is in equilibrium, and can be described using a few macroscopic coordinates (e.g., pressure, volume, temperature, …)

Equilibrium does not mean static

Equilibrium does not mean static: it means *observable* properties do not change with time.

What doesn't change in the following examples?

- Gas molecules move in an isolated box: the pressure does not change
- Rigid liquid crystal molecules (or TMV) move and rotate in dilute solution: density and orientational distributions
- Chemical reaction A + B <—> C + D: concentrations [A], [B], [C], [D]
- ATP molecules diffuse throughout the cytoplasm: local concentration of [ATP]
- A folded protein fluctuates about its lowest energy folded state: mean shape
- An intrinsically-disorderd protein explores its (large!) conformational ensemble (recall the DPD polymer being stretched): the ensemble doesn't change

What motions are consistent with equilibrium?

A) A system may have **characteristic** motions in equilibrium that are the most important ones for a certain biological process:

e.g., gas molecules diffuse in a box, polymer conformational fluctuations, membrane shape fluctuations

These motions are what a good model should represent, which is why many polymers can be modelled as phantom chains, and membranes can be modelled as fluctuating elastic sheets ignoring lipid diffusion within them.

B) A system may exhibit some motions that **equilibrate rapidly** compared to other slower motions of interest:

e.g., ATP diffuses to all parts of the cytosol much faster than a motile cell crawls, so we can treat the ATP concentration as uniform in a model of cell crawling.

C) Unbalanced forces, accelerations, turbulence, flows, unbalanced chemical reactions, temperature gradients, are **not** consistent with equilibrium

Role of thermodynamics in cell biology?

Thermodynamics is concerned with understanding the properties of matter in so far as they are affected by changes of temperature.

- Temperature drives diffusion ($D = k_B T/6\pi\eta a$, η = viscosity, a = sphere radius)
- Cells maintain gradients of ions, molecules: gradients relax by diffusion
- Some gradients relax faster than others (pressure, salt concentration, etc), once they have, they may be considered in equilibrium compared to slower processes of interest
- New properties appear (entropy, diffusion) that are typically unimportant on macroscopic scales.
- Concepts of *work* and *heat* take on new roles
- Adiabatic means "happens fast enough that no heat transfer occurs during process"
- Thermodynamics gives us relations between measurable quantities, a framework for understanding changes and distinguishing between fast and slow processes that allow us to focus on the relevant dynamics for the problem at hand (separation of scales)

Equation of state

Can P, V, T for a gas in a box in equilibrium take any values independently of each other?

Experimentally, it is found that the macroscopic thermodynamic coordinates of a system *in equilibrium* satisfy a relation (***equation of state***) although we may not be able to write it down:

$$f(P, V, T) = 0$$

- Classical thermodynamics cannot predict the equation of state of a system
- It must be determined from experiment or a microscopic model of a system
- It depends on the intermolecular forces, molecular shape, phase of the material (crystal, liquid, gas, etc), composition, macroscopic shape (long thin wire versus planar oil film), magnetic field, etc.
- But just knowing it exists gives us a lot of information and relationships

Difference between a model and reality: experimentally, a gas must have an equation of state, i.e., there must be a relation between P, V, T in equilibrium, but there are more than 60 equations describing gas/liquid-vapour/liquid regions and none of them work everywhere.

Mathematical aside in Partial Differential Calculus

If a relation exists among three coordinates - $f(x, y, z) = 0$ - then we can write x as a function of y, z and y as a function of x, z, or z as a function of x, y.

$$dx = \left(\partial x/\partial y \right)_z dy + \left(\partial x/\partial z \right)_y dz$$

$$dy = \left(\partial y/\partial x \right)_z dx + \left(\partial y/\partial z \right)_x dz$$

$$dz = \left(\partial z/\partial x \right)_y dx + \left(\partial z/\partial y \right)_x dy$$

We then get:

$$\left(\partial x/\partial y \right)_z = 1 / \left(\partial y/\partial x \right)_z$$

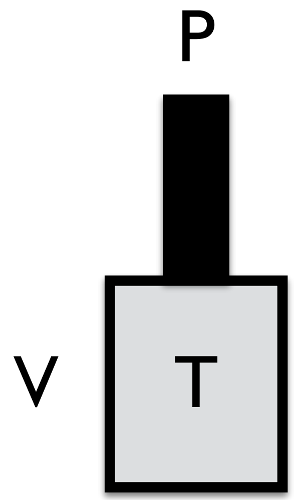
and

$$\left(\partial x/\partial y \right)_z \left(\partial y/\partial z \right)_x \left(\partial z/\partial x \right)_y = -1$$

Classical thermodynamics is largely the application of relations like this to the internal energy of a system and its equation of state.

Ideal gas equation of state

An ideal gas is defined by the two equations:



$$PV = NRT$$

$$U = U(T)$$

VdW gas is defined by:

$$\left(P + aN^2/V^2 \right)\left(V - Nb \right) = Nk_BT$$

Nb is effectively the reduction in available volume due to the size of the N gas molecules

aN^2/V^2 is the extra pressure that must be added to compensate for inter-molecular attraction that tends to make them clump and reduce the pressure on the walls

When we think of a gas, it is tempting to think of an ideal gas: but it is not clear if this is accurate in a given experiment. In cellular structures like membranes, protein/lipid aggregates, ribosomes, etc. crowding, attractions, etc, we have to develop new intuition about the thermodynamic behaviour of the material.

Exercise: calculation of isothermal compressibility

Recall from the DPD lecture that the a_{WW} conservative parameter was set from the compressibility of water.

$$K_T = -1/V\ (\partial V/\partial P)_T$$

What are the units of P, V and K_T?

A) What is the compressibility of an ideal gas? (Do this derivation)

$$PV = NRT$$

B) What is the dimensionless compressibility of a DPD fluid (Do this derivation)

$$P = \rho k_B T + \alpha\, a_{WW}\, \rho^2 \qquad \alpha = 0.1 \text{ (Groot and Warren 1997)}$$

C) What is the compressibility of a a Van der Waals gas? (Optional derivation)

$$(P + aN^2/V^2)(V - Nb) = Nk_BT$$

Deriving the DPD conservative force for water

$K = -1/V\ dV/dp\ = -\ 1/V\ (1\ /\ (dp/d\rho\ .\ d\rho/dV)\ ),$

given $V = N/\rho$

$K = -1/V.\ -N/\rho^2\ \ d/d\rho\ (\ \rho kT + \alpha\ a_{WW}\ \rho^2\ )$

$= 1/\rho\ (\ kT + 2\ \alpha\ a_{WW}\ \rho\ )$

$\rho KkT\ = 1\ /\ (\ 1 + 2\ \beta\ \alpha\ a_{WW}\ \rho) = 1/16$

so $\beta a\ a_{WW}\ \rho = 7.5$

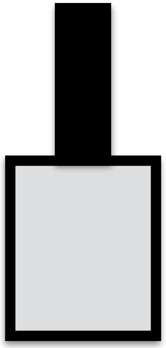
And $\alpha = 0.1$ from Groot and Warren 1997, so

$\beta a_{WW}\ \rho = 75$, and choosing density $\rho = 3$, gives $\beta a_{WW} = 25$

Ensemble

A thermodynamic ***ensemble*** is a specification of the constraints on a phase.

There are as many ensembles as there are combinations of constraints: constant mass, volume, pressure, temperature, area, surface tension, length, force, etc.



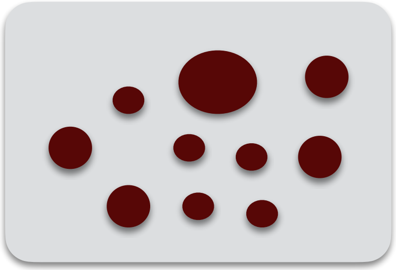
Gas in a box with a piston clamped at constant volume and diathermal walls: N, V, T

Most common ensembles for fluid systems are:

Microcanonical - N, V, E are constant

Canonical - N, V, T

Grand Canonical - μ, V, T



Solution of micelles: V, T, N_{lipid} (not number of micelles!)

Types of Process

How does a system move from one state to another?

An ***adiabatic process*** is one that takes place without any heat transfer (Q = 0)

- this does not mean that the system is isolated: the process could occur much faster than heat can be transported across its boundaries. This is relevant for cells. If a process is adiabatic it doesn't matter how the work is done, no energy is lost so the system ends up in the same state regardless of the path.

An ***isothermal process*** is one that takes place at constant temperature

- this does not mean that no heat is transferred: a heat gain could be exactly balanced by the performance of work or vice versa.

Other types of process exist (isobaric, isochoric, etc) or ones in which several variables change simultaneously.

Work

"If a system is caused to change from an initial state to a final state by adiabatic means only, the work done is the same for **ALL** adiabatic paths connecting the two states."

Work can take many forms depending on the type of system (all have units of energy and involve the product of an **intensive** variable and an **extensive** variable):

- -P.dV for a gas subject to an applied pressure p
- f.dL for a polymer whose length is changed by an amount dL by an applied force f
- σ.dA for a thin liquid film whose area is increased by an amount dA against surface tension

An ***intensive coordinate*** is one that is independent of the mass or volume of the system, .e.g, pressure, temperature, magnetic field, etc.

An ***extensive coordinate*** is one that is proportional to the mass or volume, e.g., volume, magnetisation, length of a wire, etc.

Internal Energy

Whenever a quantity depends only on the initial and final states, an important conclusion follows:

there is a function of the thermodynamic coordinates - the **Internal Energy U** - whose value at the final state minus its value at the initial state is equal to the adiabatic work done.

$$U = -W$$

The sign is chosen so that if a system *does* work, W is positive and its internal energy decreases, e.g., if a gas under pressure p expands by an amount dV (> 0), then $W = p\,dV$, and U decreases.

Internal energy is a function of the thermodynamic coordinates - U(T, V), U(T, P) U(P, V) - and is similar to the *potential energy* of a mechanical system that is a function of its external mechanical coordinates.

cp. Potential energy of a body in a gravitational field (or a charge in an E field) depends only on its position, and the change in PE is equal to the work done on the body independently of the path it follows.

1st Law of Thermodynamics

"When a system whose surroundings are at a different temperature, and on which work may be done, undergoes a process, the energy transferred by non-mechanical means, equal to the difference between the internal energy change and the work done is called Heat."

1st Law of Thermodynamics

$$Q = U - (-W)$$

or

$$U = Q - W$$

1st law means more than just energy is conserved:

- it asserts the existence of an **internal energy function U** whose value at the final state minus its value at the initial state equals the adiabatic work done in going from the initial to the final state (when $Q = 0$) or $Q - W$ if not
- energy is conserved when heat is included
- heat is energy in transit by virtue of a temperature difference

Reversible Process

Thermodynamics assumes frictionless pistons, perfectly adiabatic walls, no energy loss, etc, and a ***reversible process*** is an idealisation of a physical change. All natural processes are irreversible.

A reversible process -

is ***quasi-static*** - so all changes proceed infinitely slowly
has ***no dissipative effects*** - no friction, heat loss, hysteresis or inelastic effects, etc.

When a system undergoes a reversible process both the **system** and its **surroundings** can be brought back to their original state without any extra work being done or heat being transferred: everything is exactly as it was before the change.

Question. Why does the Krebs cycle have so many steps?

In order to keep the energy changes (heat released) small so that the system remains **close to equilibrium** as it passes through all its stages. If all the heat were released in a single, complex chemical reaction it would be very inefficient.

A car is inefficient because temperature and pressure gradients waste energy in heat loss.

Exact and Inexact Differentials

For infinitely small changes, we can replace the macroscopic quantities, U, Q, W by infinitesimal quantities, dU, dQ, and dW.

$$dU = dQ - dW$$

dU is the differential of an actual function - the internal energy U - so it can be expanded as Taylor series in its coordinates - P,V,T:

$$dU(T, V) = (\partial U/\partial T)_V \, dT + (\partial U/\partial V)_T \, dV$$

It is an ***exact*** differential. (Question: why only 2 arguments and not all 3 of p, V, T?)

But dW and dQ are NOT differentials of any functions there are NO functions W(P, V, T) and Q(P, V, T) of the TD coordinates, and dW and dQ are **inexact differentials**.

The performance of work and the flow of heat are simply methods by which the internal energy of a system can be changed. The internal energy **cannot** be separated into a thermal and mechanical part.

Summary

Cellular world is different from the ours, but thermodynamics is the same.

TD answers questions: 1) what can a system possibly do, 2) what is it most likely to do?

- **1st Law -** Only processes that conserve energy are observed, and systems in equilibrium have an internal energy that depends only on their macroscopic coordinates (if E increases in a sim. you have a problem; if you pump E into a sim. where does it go?)

- **2nd Law -** Of processes that conserve energy, which ones occur? (Heat never spontaneously flows up a temperature gradient)

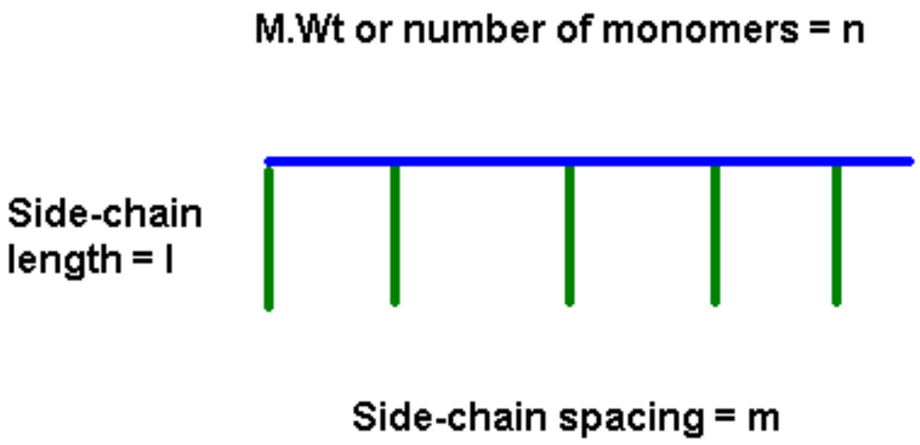
- TD provides *the* quantitative link between simulations and experiments: in experiments we want to change 1 parameter and observe effects, we cannot do this if other properties are changing as well: diff. calculus gives the rules relating such changes.

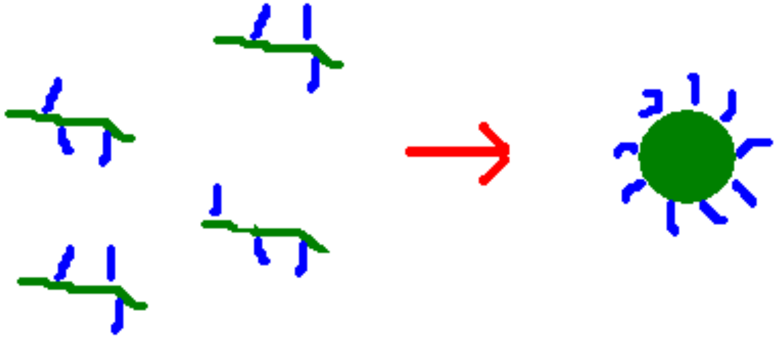
- Leaving equilibrium is energetically expensive so cells tend to stay close to equilibrium and equilibrium thermodynamics can relate observations

Break / Exercise

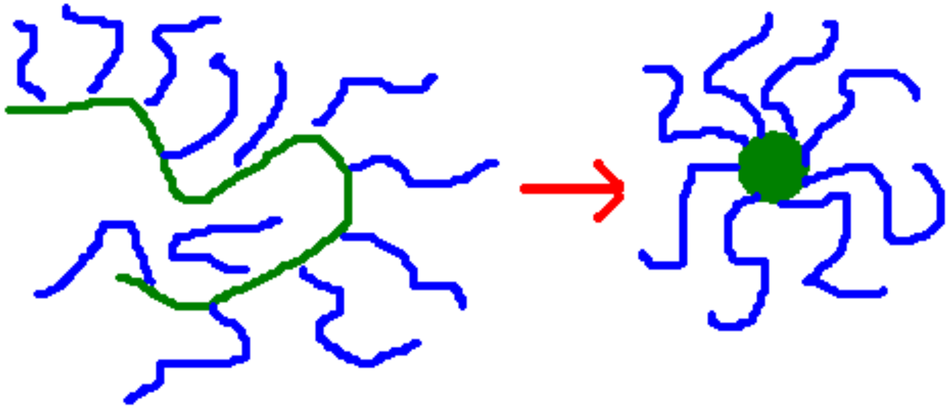
- Comb polymers and micelle formation
- Project ideas

What molecular details might influence comb polymer aggregation?





Molecular structure and nature of backbone/sidechains, e.g., hydrophilic or hydrophobic



Side-chain / backbone entropy vs. energy