Ctrl & Comp in Bio Sys - Westlake Univ., Fall 2025

Lecture 1: Order of Magnitude (OoM) reasoning in physics and biology

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1 Order of Magnitude(OoM) reasoning

The world is connected, and our "eye" to see such connections are orders of magnitude reasoning. Seemingly unrelated observations could be in fact deeply constraining each other. To practice this "vision", we explore some calculations below, with contexts gradually shifting from the macroscopic world we are more familiar with to the microscopic world of molecules and cells.

1.1 Hangzhou Exodus

To get a feeling for order of magnitude reasoning, let us start with an estimate for the following problem. Imagine Hangzhou is in a sudden crisis, so we need to evacuate the population of Hangzhou, what would be the best way to do it? By Car? Train? Airplane? Remember that Hangzhou has a population of about 10 million.

We probably want to leave Hangzhou fast. So let us consider the transportation method that is fastest for individuals.

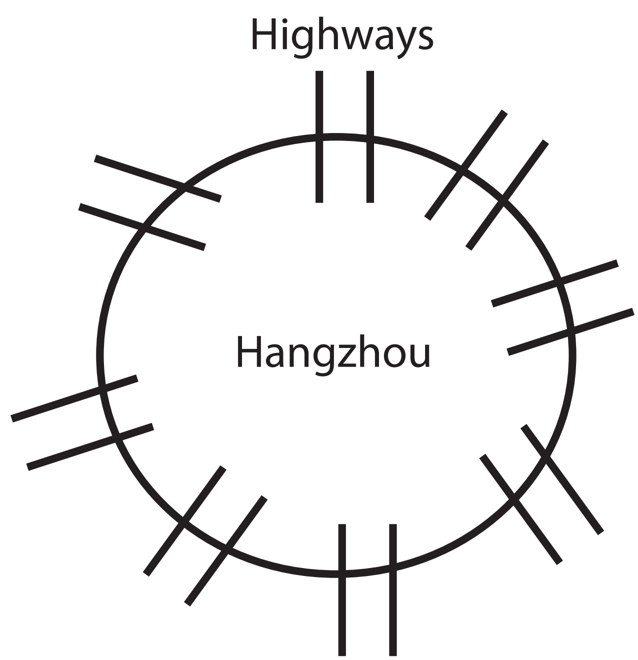
- By airplane:
  - We have 1 airport in Hangzhou
    Let's say under emergency we need $2\ \mathrm{min}$ for an airplane to leave airport.
    $$2\ \mathrm{min/airplane} \Longrightarrow 60 \times 24 \approx 10^3\ \mathrm{min/day}$$
    $$\Longrightarrow \approx 500\ \mathrm{airplane/day}$$

$$10^2 \text{ people/airplane} \Longrightarrow 5 \times 10^4 \text{ people/day}$$
$$\Longrightarrow 200 \text{ days}$$

200 days is too long for to escape from an apocalypse. Is there a method that can be faster than this? We observe that the key bottleneck of the airplane method is that we only have one airport in Hangzhou. The airplane itself is fast, but the number of runways is too low.

Given this, let us leave the estimate for trains as an exercise (we would guess it is too slow overall due to the same reason of bottleneck as the airplane method), and directly jump to escape by cars. Cars have many lanes on highways to travel, which may resolve the previous bottleneck.

Figure 1



- By cars
  - Let's say totally we have 10 highways to leave Hangzhou (Roughly check the map, see Fig 1)

    $4 \text{ lanes/way} \Longrightarrow 8 \text{ lanes total/way}$ (Emergency state: all lanes going out.)

    $\Longrightarrow \approx 10^2 \text{ lanes}$
  - Properties of cars

Speed	$v \approx 80 \text{ km/h} \approx 20 \text{ m/s}$
Distance between cars	$L \approx 40 \text{ m/car}$ (let's say we need 2s to react)
Capacity	$N = 4 \text{ people/car}$

$$\text{FLuxPerLane} = \frac{N \cdot v}{L} = \frac{4\ \text{people/car} \times 20\ \text{m/s}}{40\ \text{m/car}} \approx 2\ \text{people/s}$$

$\Longrightarrow 100\ \text{lanes} \times 2\ \text{people/(s} \cdot \text{lane)} \times 3600\ \text{s/hour} \times 24\ \text{h/day} \approx 2 \times 10^7\ \text{people/day}$
So roughly 1 day all people are evacuated.

Roughly 1 day to evacuate all people in Hangzhou, which is very nice indeed! However, we assumed the only bottleneck is the number of lanes and ignored other possible constraints. Could new limiting factors come into play? For example, we assumed there are enough cars in Hangzhou, and every person can get into a car. Could the actual number of cars be limiting? What if people drive slower or faster than the speed we assumed?

To reason about these problems, let us investigate the real bottleneck of the cars method. We notice that the flux of people per lane is dependent on both the speed of driving and the distance between cars, and the latter is limited by our time to react, τ. But τ is the same due to fundamental human reflex, which cannot be drastically reduced. So this is the actual bottleneck. Let us rewrite our calculation in terms of τ.

- Could it be that number of Cars is not enough?
  (A new bottom neck? Could be, but does it matter?)
  Let τ be the time to react to guarantee safety.And <u>τ is fixed</u> as we are all human.
  $$\text{Flux} = \frac{Nv}{L} = \frac{N}{\tau} \quad \left(\tau = \frac{L}{v}\right)$$
  $\Longrightarrow \text{Car} = \text{Walking}$
  e.g. we walk $1\ \text{m/s}$, need $2\ \text{m}$ distance between people.
  So, we could just <u>WALK ON HIGHWAYS</u> to evacuate.

The Hangzhou exodus example shows how the dimensions of key quantities dictate the solution to a problem. Next, let us consider another problem that further demonstrates this dimensional reasoning, and how it can be used to extend our intuition from the macroscopic world we are familiar with to other scales.

1.2 Dimensional reasoning: jump height in animals

Many animals can jump while across different sizes, we humans can jump, cats can jump, fleas can jump. We may be wondering if there is some relationship between jump heights and animal sizes?

- Example: A student can jump:
  $30\ \text{cm}$ for Karla; Maybe $60\ \text{cm}$ for a professional athlete.
  (There is no change of orders of magnitude within humans.)

- To infer the relationship, let's analyze from the energy:

$$
\begin{aligned}
E_g = mgh = E_m &\quad (E_g: \text{ gravitational potential energy})\\
m \propto L^3 &\quad (m \propto \text{Volume} \propto \text{Length}^3)\\
E_m \propto L^3 f_m &\quad (f_m: \text{ volume fraction of muscle})\\
\implies h \propto L^0 f_m &
\end{aligned}
$$

Jump height is <u>independent</u> of mass/volume/size.

The above result is saying, the height an animal can jump has nothing to do with its mass, volume or size, the only thing that matters is f_m, the muscle fraction, as long as the animal still uses the same muscle mechanism to jump. And this is roughly true:

- Rat : 50 cm
  Flea : 25 cm
  Cats : 100 cm (Roughly same order of magnitude)

The next question is time, as we have the same h, we got the same speed leaving the ground.

$$\frac{1}{2}mv^2 = mgh \implies v \text{ is constant as } h \text{ is constant}$$

So humans, rats, fleas and cats all share roughly the same speed when leaving the ground. Imagine fleas leaving the ground 3 meters per second! This is like thousands of body lengths per second, which scales to human would be kilometers per second!

If we observe Karla's jumping action carefully, we can find this jump takes her about 0.5 s from stretching the leg to leaving the ground. This duration is reasonable for muscles since she has about 0.5 m to release the muscle energy. But what about other animals?

- Time cost to release the energy in the muscle

  The time τ is proportional to the height one can use to speed up. Thus

$$\tau \propto \frac{L}{v} \quad (\tau: \text{ time to release energy})$$

Human:	$v \approx 3 \text{ m/s} \implies \frac{L}{v} = \frac{1 \text{ m}}{3 \text{ m/s}} \approx 0.3 \text{ s}$
Cat:	$v \approx 3 \text{ m/s} \implies \frac{L}{v} = \frac{0.2 \text{ m}}{3 \text{ m/s}} \approx 0.1 \text{ s}$
Flea:	$v \approx 3 \text{ m/s} \implies \frac{L}{v} = \frac{2 \text{ mm}}{3 \text{ m/s}} \approx 1 \text{ ms}$!!

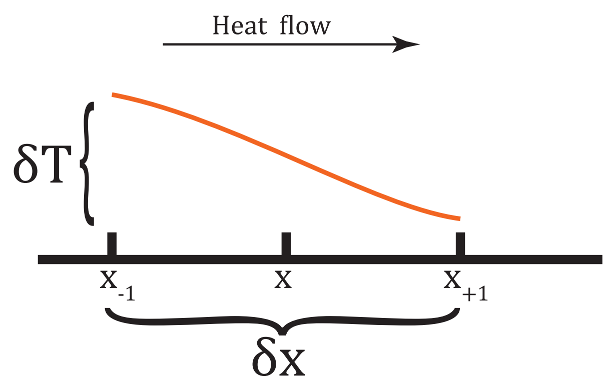
Even fast muscles need about 0.1 s to contract its half length, 1 ms is far too short. The truth is fleas choose to store energy in the bending of their shells to go beyond this limitation on the the speed of release due to muscle mechanisms.

From rough calculations, we could use scaling to go from numbers we are familiar with and scale up to what is very different scales animals are doing.

For the next example, let's heat up everything, to see what intuition that heating up potatoes can bring us. If we know how long to heat up a potato, can we assume how long to cool down the moon?

1.3 Scaling: heating potatoes, and the moon

Figure 2



Firstly we need to link together the time and the heat change, to find how item's size can involve this process. For simplicity, let's consider a rod 2, with a temperature gradient along its length, decreasing from left to right.

- Heat diffusion on rod
  From intuitive, heat flux should be proportional to the local gradient of temperature,this gives:

$$J = -K\nabla T \qquad (J:\ \text{Flux of the heat})$$
$$\nabla T \approx \frac{\delta T}{\delta x} \quad (\nabla T:\ \text{Gradient of Temperature })$$

  And also, the neat change of temperature is reflected by the stored energy.

$$\Delta E \approx C_V \delta T \quad (C_V:\ \text{Heat capacity per Volume, with unit: Heat}/T)$$
$$\text{(Change in } E \text{ per volume taken } T \text{ change by } \delta T\text{)}$$

To derive how temperature changes over time, we will apply the principle of energy conservation. Consider a small segment of the rod with length δx, The net heat flux (the heat flowing in minus the heat flowing out) results in a change in the segment's internal energy. This energy balance leads to the following relationship:

- Temperature changing in time
  From conservation of energy: at x change temperature by δT in δt time then
  $$\delta x C_v \delta T = (J_{x_{-1}} - J_{x_{+1}})\delta t = K(\nabla T_{x_{+1}} - \nabla T_{x_{-1}})\delta t$$
  $$\Longrightarrow \frac{\delta T}{\delta t} = \frac{K}{C_V} \cdot \frac{\nabla T_{x_{+1}} - \nabla T_{x_{-1}}}{\delta x}$$
  $$\Longrightarrow \frac{\partial T}{\partial t} = \kappa \nabla^2 T \qquad (\kappa = \frac{K}{C_V} \text{ is heat diffusivity})$$

Now we have the partial derivative equation to describe how T changed with time, that says the temperature's change rate on one site is proportional to the temperature's Hessian on this site. The object's size's effect on the temperature change time is embedded within this Hessian. To get the atypical scaling, we can simply remove the partial derivatives. (We can derive the scaling just from variation in a unit time/length/etc).

- Thus we have
  $$\frac{\partial T}{\partial t} = \kappa \frac{\partial^2 T}{\partial x^x}$$
  $$\Longrightarrow \frac{T}{t} \approx \kappa \frac{T}{x^2}$$
  $$\Longrightarrow t \approx \frac{x^2}{\kappa}$$

So the time grows with size's square. To cool down the moon, now we need another parameter κ, we don't know yet but we can estimate from heating up potatoes.

- Hong long to heat up a potato?
  From experience, about 10 min is need to heat up a potato of size10 cm
  $\Longrightarrow \kappa \approx \frac{x^2}{t} \approx \frac{1\times10^{-2}\ \mathrm{m}^2}{600\ \mathrm{s}} \approx 1.5 \times 10^{-5}\ \mathrm{m}^2/\mathrm{s}$
  Now we get the number of κ, finally we can turn our view to moon!

- Cool down the moon since its birth.
  $$L = 2000\ \mathrm{km} = 2 \times 10^6\ \mathrm{m}$$
  $$t \approx \frac{x^2}{\kappa} = \frac{4 \times 10^{12}\ \mathrm{m}^2}{1.5 \times 10^{-5}\ \mathrm{m}^2/\mathrm{s}} \approx 3 \times 10^{17} \mathrm{s}$$
  $$(3600\ \mathrm{s} \times 24\ \mathrm{h} \times 365\ \mathrm{day} \Longrightarrow 3 \times 10^7\ \mathrm{s/year})$$
  $$\Longrightarrow t \approx 1 \times 10^{10} years$$

The solar system is approximately: 4.6 billion years $\approx 5 \times 10^9$ years. Our calculation suggests the Moon is not yet fully cooled, but very close. In reality, the Moon is considered fully cooled. This is because, early in its history, its molten core greatly accelerated the cooling process through convection, which is a much more efficient method of heat transfer than conduction alone.

Through these examples, we've seen how order of magnitude reasoning reveals profound connections. These cases demonstrate that by identifying the core physical constraints and understanding how they scale, we can make powerful predictions across vastly different domains.

Now let's dive into the biology world to see what surprise the order of magnitude reasoning can bring us.

1.4 OoM in biology: molecules in cells

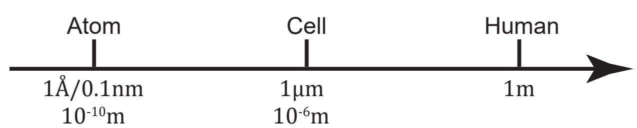
1.4.1 Order of Magnitude(OoM) reasoning in biology

- In biology world, OoM is often very helpful to give a "Null hypothesis","Null model", predicting what should occur based only on fundamental physical or chemical principles, before we spend much time doing literature reading, detailed simulations, or even experiments.

Like physics, in biology world,we often care about some quantities. At the single-item level, we care about properties like length, volume, weight, speed, position... At the population level, quantities like number and concentration etc. become important. Let's start with some of these basic properties of different molecules within cells.

1.4.2 Molecules in cells

- References: cell biology by the numbers. Also, "Snapshot: characteristic rates and timescales in cell biology". s



- Length scale of different cells
  E.coli $1\ \mu m$
  Yeast $5\ \mu m$
  Mammalian $20\ \mu m$($10\ \mu m$ roughly)

To make the following analysis more specific, let's take E.coli as our standard reference for the microscopic world.

- E.coli
  - Volume of E.coli:
    $1\ \mu m^2 = 1 \times 10^{-18}\ m^3 = 1 \times 10^{-15} L = 1\ fL$ (f : femto)
    $1\ \mu L\ (\texttt{of bacteria}) \Longrightarrow 1 \times 10^9$cells
    As $1\ mL$ of bacterial culture at saturation $\Longrightarrow$ pellet is $1\ \mu L$

So for $1\ \mathrm{mL}$ of culture media, the E.coli cells are actually takes only 10^{-3} of the volume which is even less dense than our classroom.

– Mass (of proteins? metabolites?):

Glucose/Nucleotide:	$3 \times 10^2\ \mathrm{Da} \Longrightarrow \mathrm{Size}: (3 \times 10^2)^{\frac{1}{3}} \approx 6\ \text{Å}$
Amino acid(a.a):	$10^2\ \mathrm{Da}$(a bit lighter (from about $60 \sim 200\ \mathrm{Da}$))

The a.a.'s average MW is $10^2\ \mathrm{Da}$ is because we calculate average in log, $\sqrt{60 \times 200} \approx 100$. Further this is because the order of magnitude changes under log space.

Now we need how many a.a. in a protein to calculate the MW of proteins

– How many a.a. in a protein?

$$\begin{cases} \text{lower bound} & 50\ \text{a.a.} \\ \text{upper bound} & 5 \times 10^3\ \text{a.a.} \end{cases} \Longrightarrow \sqrt{2 \times 10^5} \approx 300\ \text{a.a.}$$

$\Longrightarrow \approx 300\ \text{a.a./protein} \Longrightarrow MW = 30\ \mathrm{kDa/mol}$

$$\Longrightarrow \text{Num of protein per cell} = \frac{1\ \mathrm{pg}}{30\ \mathrm{kDa/mol}} \cdot \frac{6 \times 10^{23}\ \mathrm{Da}}{\mathrm{mol}} \approx 2 \times 10^7$$

The above result gives us a theoretical upper bound of the number of proteins within one e.coli, as we assume all molecules within one e.coli is protein. While commonly, for one type of protein, this number is from $10^3 \sim 10^4$

– Concentration:
What is the concentration of one molecule per cell?
$1\ \text{molecule/cell} \Longrightarrow \frac{1}{1 \times 10^{-15}\ \mathrm{L}} \frac{\mathrm{mol}}{6 \times 10^{23}} \approx 10^{-9}\ \mathrm{M} = 1\ \mathrm{nM}$

Metabolites	$10^6 \sim 10^7\ /\text{cell} \Longrightarrow 1 \sim 10\ \mathrm{mM}$
Protein	$10^3 \sim 10^4\ /\text{cell} \Longrightarrow 1 \sim 10\ \mu\mathrm{M}$

– Volume of Genome, protein
Genome: E.coli got $5\ \mathrm{Million}$ base pairs
If we first calculate about length:

$$5 \times 10^6\ \mathrm{bp} \times 0.3\ \mathrm{nm/bp} \approx 1 \times 10^6\ \mathrm{nm} = 10^3\ \mu\mathrm{m}$$

This result indicate that the genome are so long that it needs to be folded at least $1,000$ times to put into E.coli. But what about its volume?
Now we calculate its volume:

$$3 \times 10^2\ \text{Å}^3/\mathrm{bp} \cdot 5 \times 10^7\ \mathrm{bp} = 300 \cdot (1 \times 10^{-4}\ \mu\mathrm{m})^3 \cdot 5 \times 10^7 \approx 1.5 \times 10^{-2}\ \mu\mathrm{m}^2$$

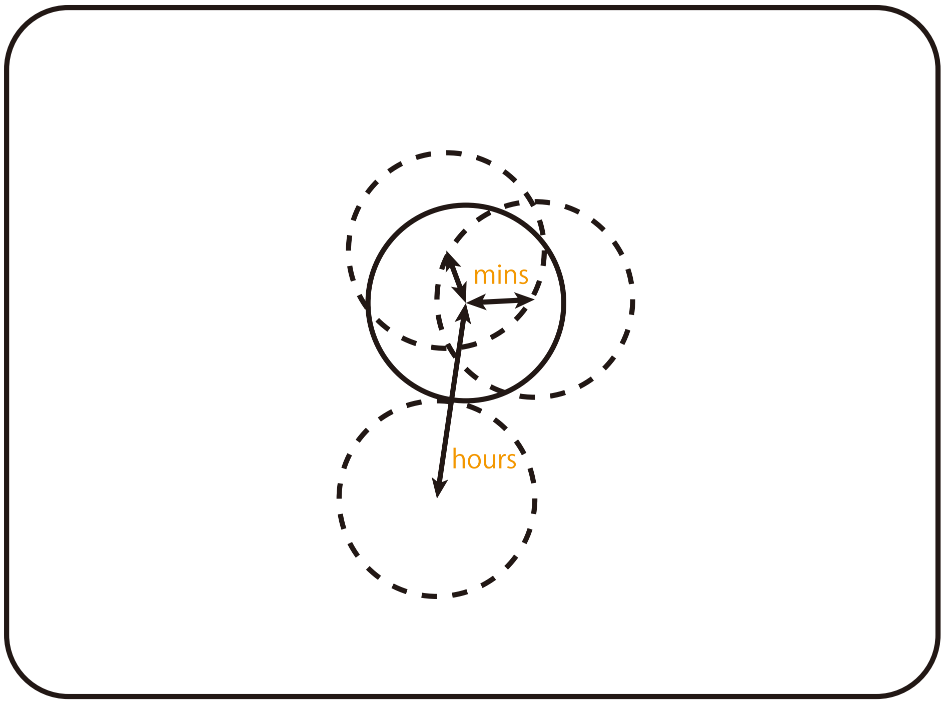
So while long, Genome only take $\sim 1\%$of volume of a cell.
What about protein's volume? Roughly one e.coli have about 10^7 proteins, thus:

$$300 \text{ a.a} \times 100 \text{ Å}^3 \times 10^7 \approx 0.3 \text{ µm}^3 \Longrightarrow 20 - 40\% \text{ of the cell}$$

So unlike genome, proteins are crowded!

From above data and calculation we have built some sense of this micro-world, and static. But what about dynamics?

1.4.3 Rates in cells — Diffusion(How molecules move in cells)



Let's first get some sense of how diffusion happens for this microscopic world.

From our calculations for the heat diffusion case, we know the diffusion behavior has the following scaling relating τ, the duration, and x, the distance the diffusion behavior can reach.

- Diffusion scaling:
  $\frac{1}{\tau} = \frac{D}{x^2}$

The diffusion effect was first studied by Robert Brown, 1827. He put a pollen under water and observed under a microscope, and found the pollen jiggling without any apparent force. And now we can make his experiment as a reference to start up. Let's estimate the diffusion coefficient for pollen first.

- Infer the parameter for pollen.

How big is a pollen particle? From our daily experience, while we can see the granules that contains lots of pollen particles, we cannot observe individual pollen particles directly by naked eye. However, Brown can observe a pollen particle under a microscope, a microscope in the 1800s so not a very large magnification. So we could estimate that a pollen particle should be around the size of an eukaryotic cell which can be easily observed under the microscope, so ~ $10\ \mu m$.

Some observation is that: When pollen jiggles under microscope, we can see the jiggles in seconds, so the movement should be roughly $\sim 1\ \mu m$ on seconds timescale. But most movements cancel out.

To move a significant distance, around one body length $10\ \mu m$, requires much longer, since we do not see the pollen particles significantly move within minutes of observations. Therefore, $10\ \mu m$ movement requires about $1\ h$, so D can be estimated as $D = \frac{x^2}{\tau} = \frac{(10\ \mu m)^2}{3600\ s} \approx 3 \times 10^{-3}\ \mu m^{-2}/s$.

Pollen provides a good beginning for us to scale down to proteins, so the key question is, how does D change when the particle size decreases? From our intuition, the smaller the particle, the faster it shall move. In other words, D is negatively correlated with L which denotes the particle size. We can guess $D \propto L^{-1}$, and it turns out to be true.

Why? Diffusion is balance between thermal force (water hitting on pollen) and drag in viscous(low Re,"skin friction drag")

$$\begin{cases} \text{Force} \propto L^2 \\ \text{Friction} \propto L\nu \end{cases} \qquad \text{(two forces are balanced)}$$

$$D = \mu K_B T \propto \mu \propto \frac{\nu}{F} \propto \frac{\nu}{L\nu} \propto L^{-1}$$

Now let's go from pollen to proteins

- Diffusion rate of protein
  Protein size: $(300)^{\frac{1}{3}} \approx 1\ nm$
  $\frac{D_{protein}}{D_{Pollen}} \propto \frac{L_{pollen}}{L_{protein}} = \frac{10\ \mu m}{1\ nm} = 1 \times 10^4 \Longrightarrow D_{protein} = 100\ \mu m^2/s$
  With the diffusion rate, now we can calculate how long it takes for a protein to move across different cells just by passive diffusion.

- Time for a protein to diffusion in different cell

E.coli:	$1\ \mu m$	$t \approx \frac{x^2}{D} = \frac{(1\ \mu m)^2}{100\ \mu m^2/s} = 1 \times 10^{-2}\ s$
Mammalian:	$10\ \mu m$	$t \approx \frac{x^2}{D} \approx \frac{(10\ \mu m)^2}{100\ \mu m^2/s} = 1\ s$
Eggs	$100\ \mu m$	$t \approx \frac{x^2}{D} \approx \frac{(100\ \mu m)^2}{100\ \mu m^2/s} = 100\ s$
Axon:	$1\ m$	$t \approx \frac{x^2}{D} \approx \frac{(1\times10^6\ \mu m)^2}{100\ \mu m^2/s} = 10^{10}\ s \approx 3 \times 10^2$ years

Thus we see for long cells like neurons, transferring proteins by passive diffusion becomes inefficient as $t \propto x^2$. This suggests that more efficient protein transport mechanisms must exist for these cells.