2025 Fall. CCBS. Lecture 1.

⓪. Course intro. ①. OoM reasoning. ②. Chemical Reaction Networks.

Sibling class: Frontiers in SynBio. chenlab.org/page/teaching. 15:10 - 17:45.
Zibo Chen. E10-211.

⓪. This course is about understanding and analyzing biology from physics / $\boxed{\text{systems}}$ perspectives, and introducing the tools to do so.
industry.

- At the end. you should be able to reason about any biological problem you're interested in.
- The "hats", or "tools", we introduce are <u>non-traditional</u>. and <u>in-depth</u>. (at least a bit.). <u>Exciting!</u>

Topics that now I look back. what I would like to learn about early on

e.g. OoM esti, stat physics, Control / adaptation / dynamics. Dimensions.
computation, holistic analysis / reaction order,
optimization, proteome allocation / growth.
Stochastic analysis.

— Adaptation machines / Computation machines. / ???
biomechanics.
to be discovered

(so many topics. so ...)

- Fast paced. — 11 weeks. 1 HW per week.

Format: students present soln to prev week's HW.

Score: 20% Attendence. 40% just to hand in homeworks.
30% for presentation. 10%. note scribe

- Possibly final exam. — how you'd improve this course
what would be your syllabus.

① . O.o.M reasoning.

- The world is connected. Observations that seem totally unrelated could in fact be deeply constrained.

  e.g. Solar eclipse and size of earth....

- Our "eye" to see these connections is Reasoning.

  especially. Order of Magnitude estimates.

  The point : numbers can say a lot.

  Be fast. not details. 1, few, 10.

  OoM. are robust. Details are fragile.

- Practice this vision through examples below.

  From macroscopic. (our life) to microscopic. (molecules & cells).

(1.1). Hangzhou Exodus.

- If we need to evacuate all people in Hangzhou

  How to do it? What's the best way?.

  By car? Train? Airplane?

- By airplane. 1 plane / 2min. $\Rightarrow$. $60\times24 \approx 60\times25 \simeq 1500$. min per day.

  $\Rightarrow$. 700 planes / day.

  300 people / plane $\Rightarrow$ 2×10^5 people / day.

  杭州 ~ 47万人

  10^7 people in HZ $\Rightarrow$ 50 days.

  (Reason? Bottleneck — # airport = 1. 1 plane takeoff at the same time.)

- By car. What's the bottle neck? # highways / lanes.

- Roughly 10 main highways. (look at map).

  "双向四车道" 4 lanes each direction is typical.

  Emergency state: all lanes going out.

  $\Rightarrow$ ~10 lanes / highway. $\Rightarrow$ 100 lanes total.

- Driving at $\underbrace{80\ \text{km/h}}_{}$ (V). 4 people / car (N). 40 meters apart (L).

  $\Rightarrow \frac{1}{3.6} \approx 20$ m/s $\longrightarrow$ 2 second to react. ("3秒间隔法").

So. per lane. Flux of people $= \frac{N \cdot V}{L} = \frac{\#\text{people/car} \cdot \text{speed}}{\#\text{cars / length}} = $ # people/time. Flux of people.

$= \frac{4 \cdot 20\ \text{m/s}}{20\ \text{m}} = 2$ people/second. for each lane.

$\Rightarrow \underset{p/s}{2} \times \underset{s/day}{\underbrace{3600}_{3\times10^3} \times \underbrace{24}_{3\times10}} \approx 2\times10^5$ people / day

$\Rightarrow$ 100 lanes gives 2×10^7 people / day.

So. roughly 1 day all people are evacuated!

- Could it be that # cars is not enough? (new bottleneck?)

  Could be. but.... does it matter?

  $\text{Flux} = \frac{NV}{L} = \frac{N}{\tau}$. τ = time to react to guarantee safety. which is fixed

  e.g. we walk 1 m/s. need 2 m distance between people.

So, we could just WALK ON HIGHWAYS to evacuate.

Above we see the importance of scaling.

1.2 Jump Height in Animals | How would jump height change with animal size?

- A student jumps. — additional height they can reach.

  ≈ 40 cm Athlete $\rightarrow$ maybe 60 cm.

- Energy. Animals jump by unleashing energy stored in muscles.

$$E_g = Mgh = E_m \} \text{ energy stored in muscles.}$$

- $E_m \propto L^3$. Muscle takes up volume. (a fraction.) L is length scale of animal.

  $\Rightarrow E_m \propto L^3 \propto M f_m$. f_m is volume fraction of muscles.

  (ρ is omitted — water.)

  $\Rightarrow E_g = Mgh = E_m \propto M f_m$.

  $\Rightarrow$ $\underline{h \propto M^0 f_m}$. Jump height is indep of mass or volume or size!

  (as long as it's the same muscle mechanism.)

- Rat : 50 cm.

  Flea : 25 cm. $M = 10^{-3}$ g

  Cats : 100 cm.

- What about jump speed?

  $\frac{1}{2}\cancel{m}v^2 = \cancel{m}gh$. h is const. so. v is const.

  $v \propto h \propto M^0$ fn.

- What about amount of time to ~~release~~ energy / take the jump?

Time to jump. is ~~moving through~~ your own body length.

(exert force by muscle.)

$$\tau \propto \frac{L}{v}.$$

So. smaller animals ~~need to~~ release energy much faster.

$\Rightarrow$. Could this be limited by muscle mechanisms?

half length contracted in 0.1 seconds. for fast muscles.

Human. $v \sim 3$ m/s. $\frac{L}{v} \sim 0.3$ seconds. ($L \sim 1$m).

This is > 0.1 seconds. so fast enough.

Cat. $v \sim$ same. $L \sim 0.3$ m. pushing the limit.

Flea. $L \sim 2$ mm. $\Rightarrow$. $\frac{L}{v} \sim 0.6$ ms. !

Too fast for muscles..

$\Rightarrow$. Store energy in shells...

(optional)

- Is air resistance an issue for fleas?

Drag. $F_d \sim \frac{1}{2} C_D \overset{\text{air density.}}{\rho_a} \underset{\text{velocity?}}{v^2} \underset{\text{area.}}{L^2}$. $C_D \sim 1$ coeff. of drag.

Stopping length. $\sim l$.

Kinetic energy loss is $F_d l \sim \frac{1}{2}\rho_a v^2 L^2 l$.

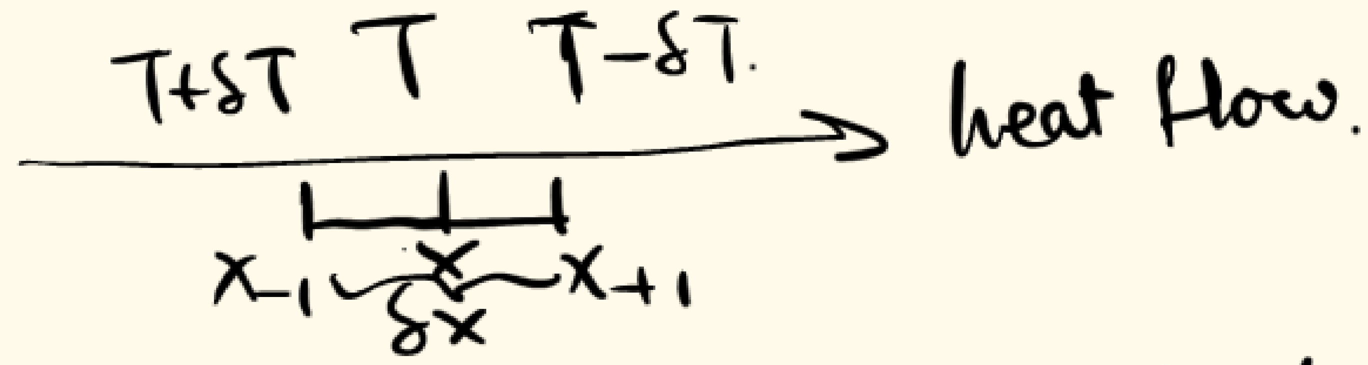
(Compare with total energy.) $= \frac{1}{2}mv^2 = \frac{1}{2}\rho_w L^3 v^2$.

$\Rightarrow \ l \sim \frac{\rho_w}{\rho_a} L \sim 10^3 L.$

So. if the flea jumps 10^3 times its own body length.

then air resistance becomes important....

(1.3). Heat diffusion.



- Heat flux. $J = -K \nabla T$. K is thermal conductivity.

  $\nabla T \approx \frac{\delta T}{\delta x}$ is gradient of temp.

Heat capacity per volume. c_v.

is heat added per change in temperature.

So. $\Delta E \sim c_v \delta T$. for change in E per volume

when T change by δT.

- Temperature changing in time.

Conservation of energy: at x. change temperature by δT.

in δt time.

then. $\delta x \, c_v \, \delta T = \left(J(x_{-1}) - J(x_{+1}) \right) \delta t$

$= K \left(\nabla T(x_{+1}) - \nabla T(x_{-1}) \right) \delta t$

$$\Rightarrow \frac{\delta T}{\delta t} = \frac{K}{c_v} \frac{\nabla T(x_{+1}) - \nabla T(x_{-1})}{\delta x}$$

$$\Rightarrow \frac{dT}{dt} = k \nabla^2 T. \qquad k = \frac{K}{c_v} \text{ is heat diffusivity.}$$

Heat equation.

Non-dimensionalize: $u = \frac{T}{T_0}$. $x = L\hat{x}$. $t = \tau \hat{t}$.

$$\Rightarrow \frac{du}{d\hat{t}} = \frac{k\tau}{L^2} \nabla^2 u$$

Or. intuitively, to get a typical scaling.

get rid of partial derivatives (for variation in a unit time / length / etc.)

to have $\frac{\partial T}{\partial t} = k \frac{\partial^2 T}{\partial x^2}$

$\Rightarrow \frac{T}{t} \approx k \frac{T}{x^2}$.

$\Rightarrow$. $kt \approx x^2$.

$$\boxed{t \approx \frac{x^2}{k}}$$

- How long to heat up a potato?

From experience. ~ 10 min. $L \sim 10$ cm.

$\Rightarrow$. $k \approx \frac{x^2}{t} \approx \frac{1 \times 10^{-3} m^2}{600 \text{ s}} \approx 1.5 \times 10^{-6} m^2/s$

Now we have k. we can heat up anything!

- Cool down the moon. since its ~~birth~~.

$L = 2500 km = 2 \times 10^6$ m.

$t \approx \frac{x^2}{k} \sim \frac{4 \times 10^{12} m^2}{1.5 \times 10^{-6} m^2/s} \sim 3 \times 10^{18}$ s

$(3600 \times 24 \sim 10^5$ s/day $\Rightarrow 3 \times 10^7$ s/yr$)$

$\Rightarrow$. $t \sim 1 \times 10^{10}$ yr.

Solar system age : 4.6 billion yrs. 5×10^9 yrs.

So. not fully cooled but pretty much.

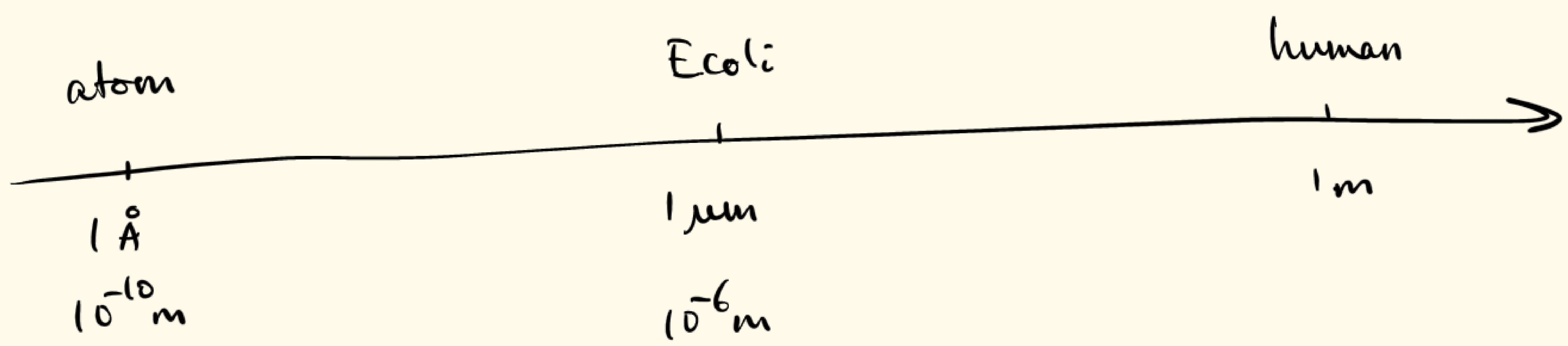
Reality: Moon is fully cooled down. Molten core at beginning speeds up.

(2) OoM reasoning in biology.

- In addition. OoM in biology is often very helpful to give a "null hypothesis", "null model". before we spend much time doing literature reading, detailed simulations, or even experiments...

(2.1). Molecules in cells.

- References: Cell biology by the numbers.
  Snapshot: Timescales in biology



- E.coli is our standard reference for the microscopic world.
  Yeast, 5μm. Mammalian. 20μm ((10μm roughly).

• Volume? $1\,\mu m^3 = 10^{-18} m^3 = 10^{-15} L = \underline{1\ fL}$.

So. 1μL of bacteria ⇒ 10^9 cells

1 mL of bacterial culture at saturation ⇒ pellet is 1μL.

10^{-3} of volume are cells — dilute solution. (much less dense than the class room!)

• Mass? Water density. 1g/mL. ⇒. $10^{-18} m^3 \cdot \frac{1g}{10^{-6} m^3} = 10^{-12} g$
$= \underline{1\ pg}$

How many proteins in a cell?.

— What's a typical protein?

— What's a typical amino acid?

Glucose. 3×10^2 Dalton. $\Rightarrow$. roughly 3×10^2 atoms $\Rightarrow$ Size is $L^3 = 300\ \mathring{A}^3$
$C_6H_{12}O_6$ (nucleotides) (Å) $\Rightarrow$. $L \sim 5\ \mathring{A} = 0.5\,nm$

Amino acid. 10^2 Dalton. a bit lighter.

$N-C-CO_2 \approx 50$
R. $+ \approx 50$

(Average: Smallest. ≈ 60, largest. ≈ 700) (Average in log). Geometric mean. $\sqrt{10^4} = 100$.

How many a.a. in a protein? ~ 300.

(lower bound: 50. upper bound: 5×10^3 $\Rightarrow$. $\sqrt{2\times10^5} \sim \frac{10^3}{2} \sim 500$.)

$\Rightarrow$. 30 kDa/protein.

$\Rightarrow$. # proteins/cell $= \frac{1\,pg}{30\,kDa/protein} \cdot \frac{6\times10^{23}\,Da}{g} = 2\times10^{-12+23-5}$

$\boxed{= 2\times10^6 \text{ proteins/cell.}}$

(if all protein.)

- Concentration?

  # molecules in a cell per protein?

  10^3 genes. $\Rightarrow$ typically 10^3 molecules for each protein.

  1 molecule/cell $\Rightarrow$. $\frac{1}{1\,\mu m^3} \frac{L}{mol} M = \frac{1}{10^{-18}\,m^3} \frac{10^{-3}\,m^3}{6\times10^{23}} M \sim 10^{-9}\,M = \boxed{1\,nM}$

  $\Rightarrow$. Protein typical conc. $1\,\mu M$.

  Metabolites? 1 mM.

- Genome? E. coli 5 Mbp.

  Length. 5×10^7 bp $\times 0.3$ nm $\Rightarrow$ 10^6 nm $\sim 10^3\,\mu m$.

  Volume? $0.3\,nm \times 1\,nm^2 \times 5\times10^7$ bp $\sim 10^7\,nm^3 \sim 10^{-2}\,\mu m^3$. 1% of cell vol.

- Protein volume? $300\,a.a. \times 10^2\ \mathring{A}^3 = 3\times10^4\times10^{-3} = 30\,nm^3$/protein.

  $\Rightarrow$. $2\times10^6 \times 30\,nm^3 \sim 6\times10^7\,nm^3 \sim 6\times10^{-2}\,\mu m^3$. 70% of cell vol.

  So. on the brink of filling up. It's super crowded!

2.2. Rates in cells. — Diffusion. (how molecules move in cells).

— Diffusion rates. $\frac{1}{\tau} = \frac{D}{x^2}$.

— Diffusion was first studied by Robert Brown, 1827.

Pollen jiggles in water, observed under microscope.

Pollen. can't see its granules by naked eye. can see under microscope.

so. like an Eukaryote cell. $\sim 1.0\,\mu m$

Jiggles under microscope  $\sim 1\mu m$ movement on seconds timescale.

$\Rightarrow D \sim 1\,\mu m^2/min$

$\sim 10^{-2}\,\mu m^2/s$.

But most movements cancel out. About $1\mu m$ net displacement on minutes timescale

— Go from Pollen to proteins.

D scales with particle size. L^{-1} (larger is slower)

(why? Diffusion is balance between thermal force (water hitting on pollen)

and drag in viscous (low Re.) $D = \frac{\text{velocity}}{\text{force}} \underbrace{k_B T}_{\text{thermal energy scale}}$.

= skin friction drag".

Force balance from drag. $F_{drag} \propto rv$

$\Rightarrow \mu = \frac{v}{F_{drag}} \propto \frac{1}{r}$. $\Rightarrow D \propto \frac{1}{r}$.

stress $\propto \frac{v}{r}$ (gradient).

force = stress · area $\propto vr$.

Protein size. $(300\,\text{Å})^{1/3} \sim 5\,\text{Å} \sim 1\,nm$.

$$\frac{D_{protein}}{D_{pollen}} \sim \left(\frac{L_{pollen}}{L_{protein}}\right) \Rightarrow \boxed{D_{protein} \sim \left(\frac{10\,\mu m}{1\,nm}\right) D_{pollen}}$$

(in water.)

$\sim 10^4 \cdot 10^{-2}\,\mu m^2/s$

$\sim \boxed{100\,\mu m^2/s}$

- Is diffusion fast enough for molecules in cells to be well-mixed?

  - Large molecules have decreased D in cells. because of crowding. (esp. bacteria).

    ($D_{cyto} < D_{water}$).

    But still. we can estimate. (say slow down by ~10 fold.)

    If > 30,100 kDa. $D \to 0$. e.g. chromosome.

  - Time to mix proteins in cells?

$$\tau \sim \frac{x^2}{D} \sim \frac{1\mu m^2}{10 \text{ to } 100\,\mu m^2/s} \sim 0.01 \text{ to } 0.1\ s.$$

  - Time to mix metabolites in cells?

    D is 10 fold larger for metabolites than proteins.

    (1Å vs 1nm). $\Rightarrow$ $\tau \sim 1ms$.

  - How big a cell would make diffusion too slow?

    Proteins, cell ~ 10μm. $\Rightarrow$ $\tau \sim 1$ to $10 s$

    cell ~ 100μm $\Rightarrow$ $\tau \sim 100$ to $10^3 s$

    e.g. axon ~1cm. too slow. (min to hours).

    frog egg ~ 1mm