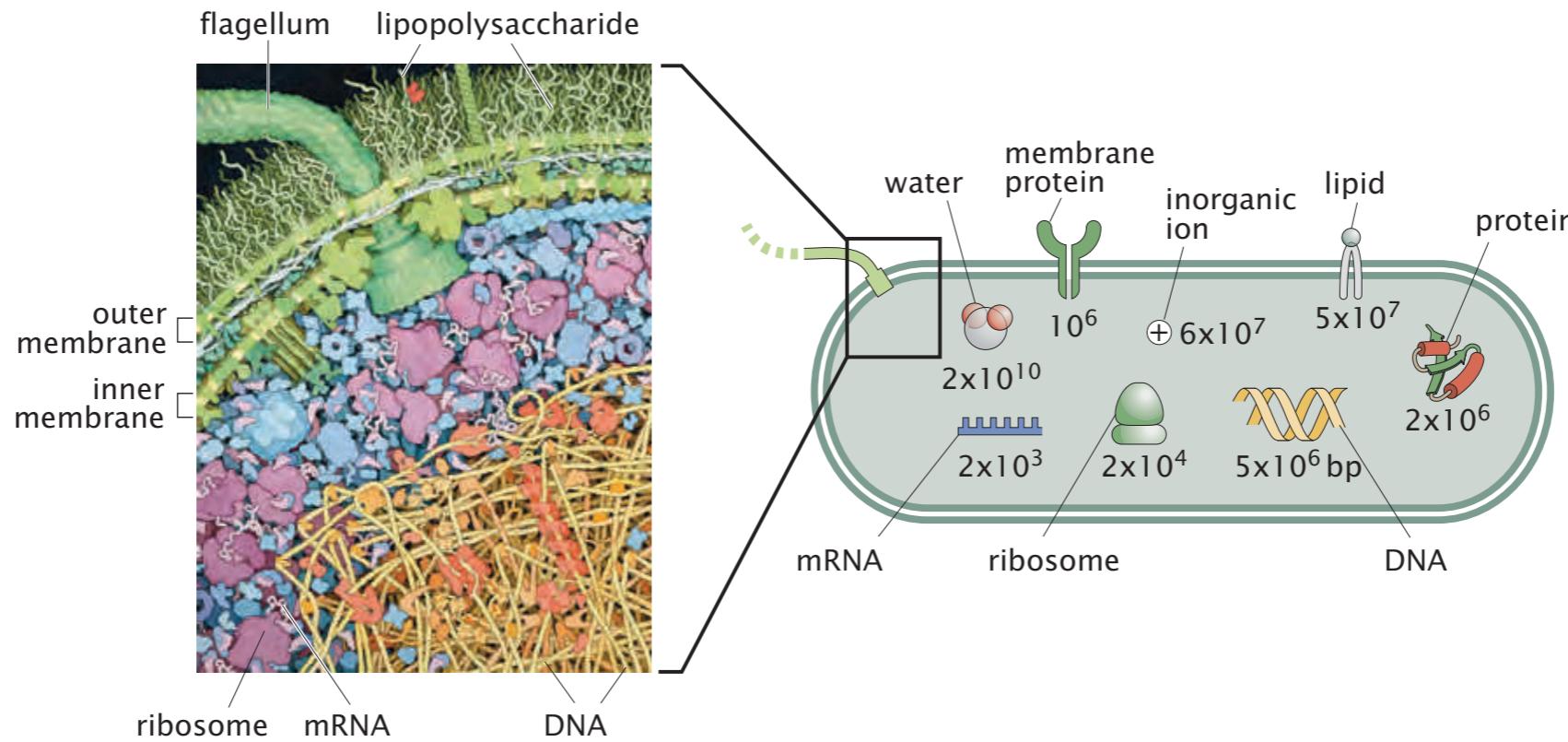


Today's class:

Rate equations and biological dynamics

*Majority of this lecture follows the chapter 15 from the book
‘Physical Biology of the Cell’ by Philips, Kondev, Theriot and Garcia , 2nd Ed*

Cells are chemical factories



When we took a molecular census of an E-coli cell we ignored time completely

In fact, everything inside the cell is in a constant state of material flux

Homeostasis is essentially a **steady-state**

Living things adapt by altering the inner-workings of the factory

Gene expression changes during the cell cycle

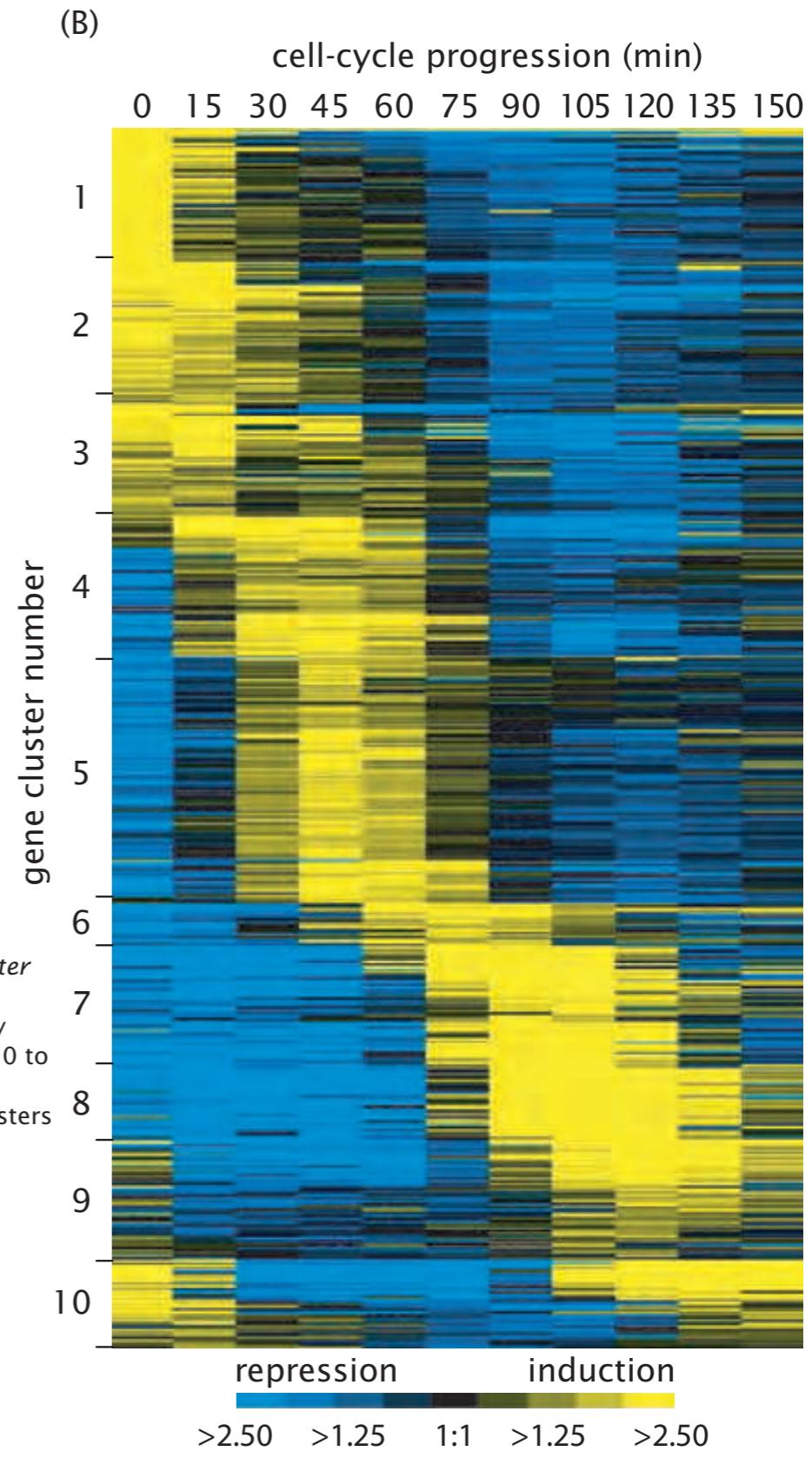
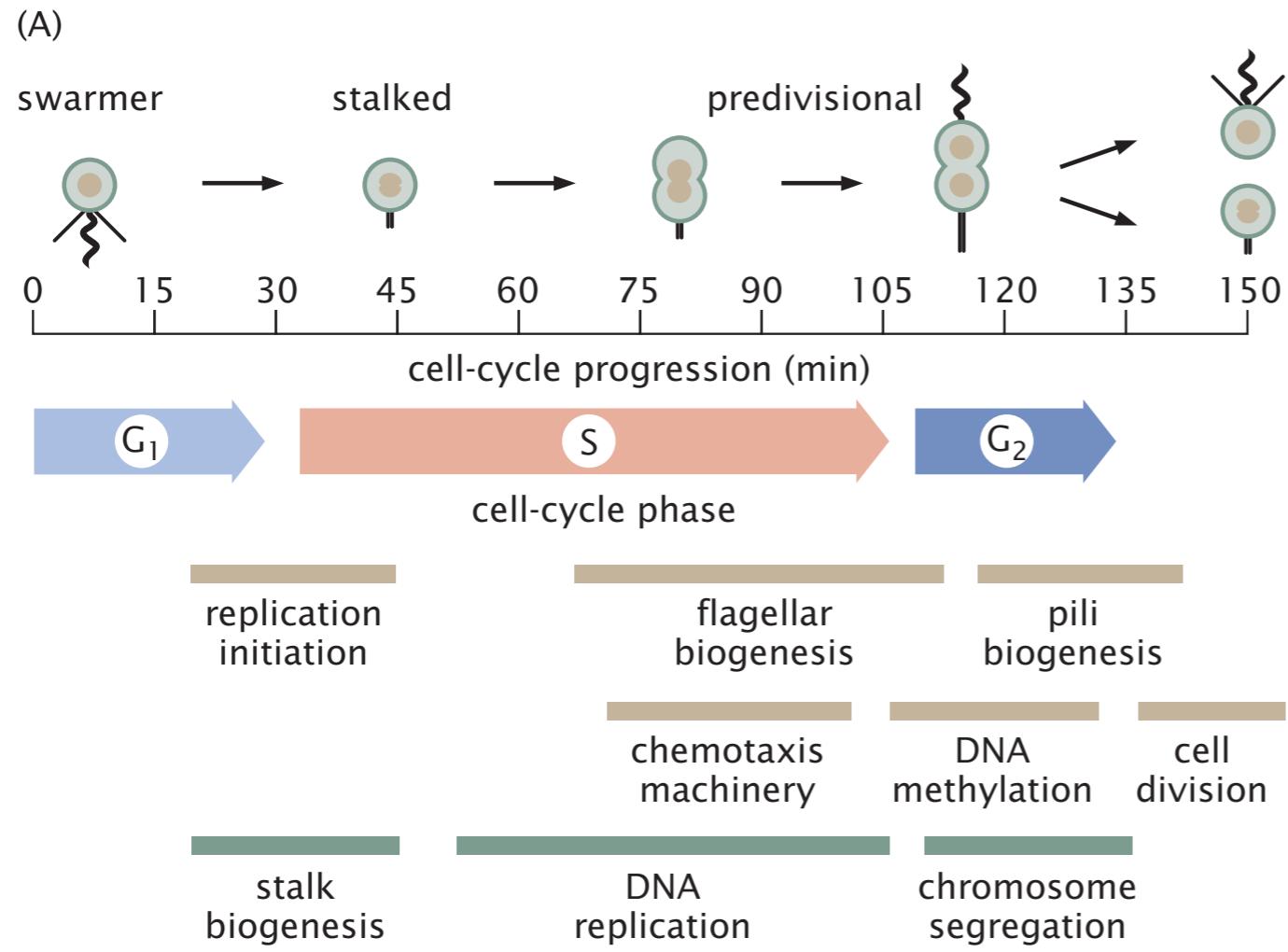


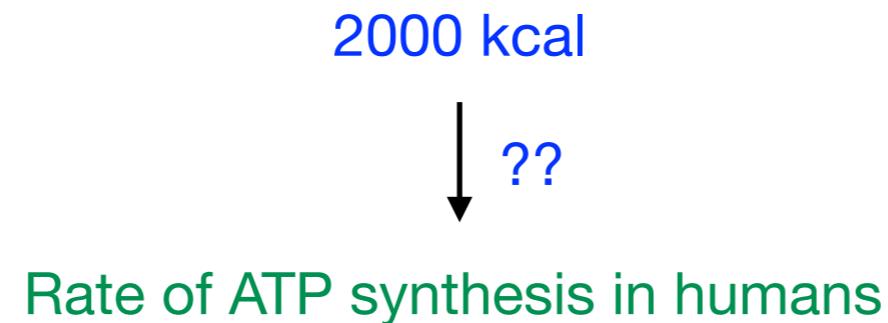
Figure 3.23: Gene expression during the cell cycle for *Caulobacter crescentus*. (A) The 150 minute cell cycle of *Caulobacter* is shown, highlighting some of the key morphological and metabolic events that take place during cell division. (B) The microarray data show how different batteries of related genes are expressed in a precise order. The genes are organized by time of peak expression. Each row corresponds to the time history of expression for a given gene, with time running from 0 to 150 minutes from left to right. For each gene, yellow indicates the time with the highest level of gene expression and blue indicates the time with the lowest level of gene expression. From top to bottom, the genes are organized into different clusters associated with different processes such as DNA replication and chromosome segregation. (Adapted from M. T. Laub et al., *Science* 290:2144, 2000.)

To quantify such changes we need to develop the machinery to describe chemical transformations.

We shift our focus to population scale changes of molecules (concentrations) in time

Rates of biological transformations: an everyday example

How much energy the human body consumes in a day through diet?



What do we need?

Energy liberated for ATP hydrolysis 12 kcal/mol

Also assume half of total diet is converted into ATP 1000 kcal/day

Then, total amount of ATP synthesized in a day = $1000/12 \approx 80$ mol/day

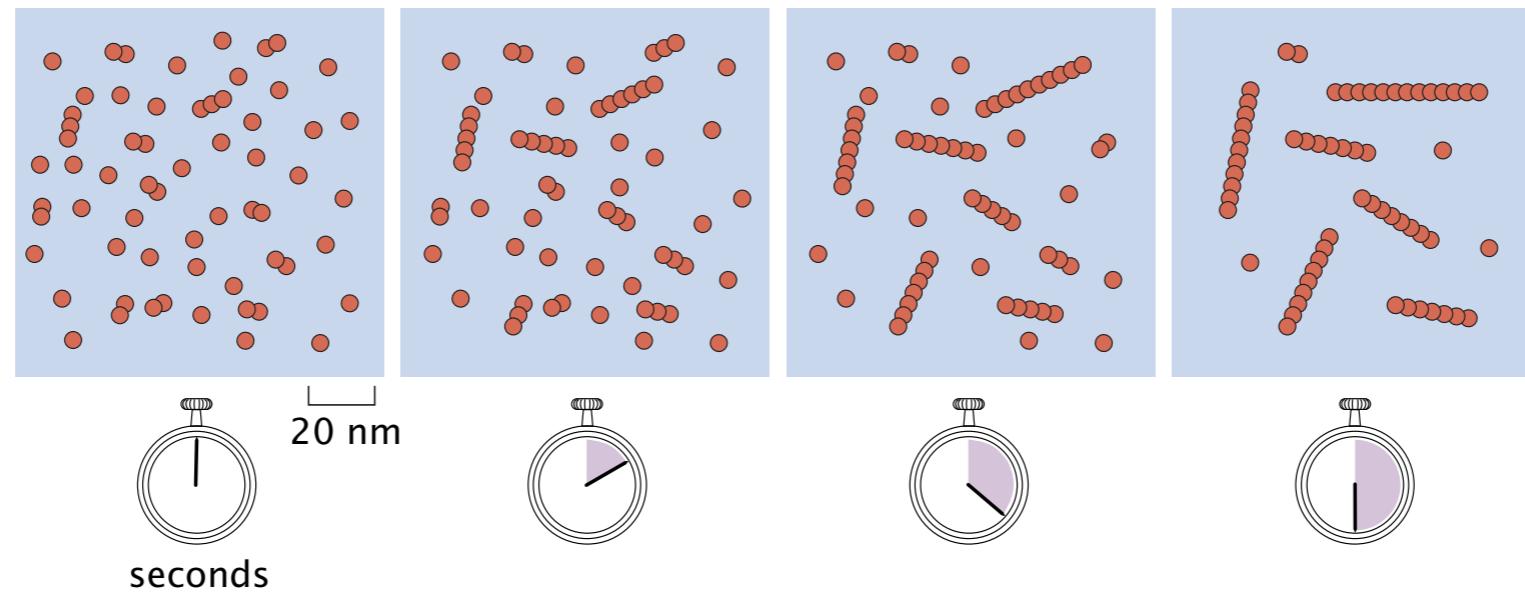
Molecular wt of ATP \approx 500 g/mol Total amount of ATP made per day \approx 40 kg

Does this mean human body has 40 kg ATP at any moment of time?

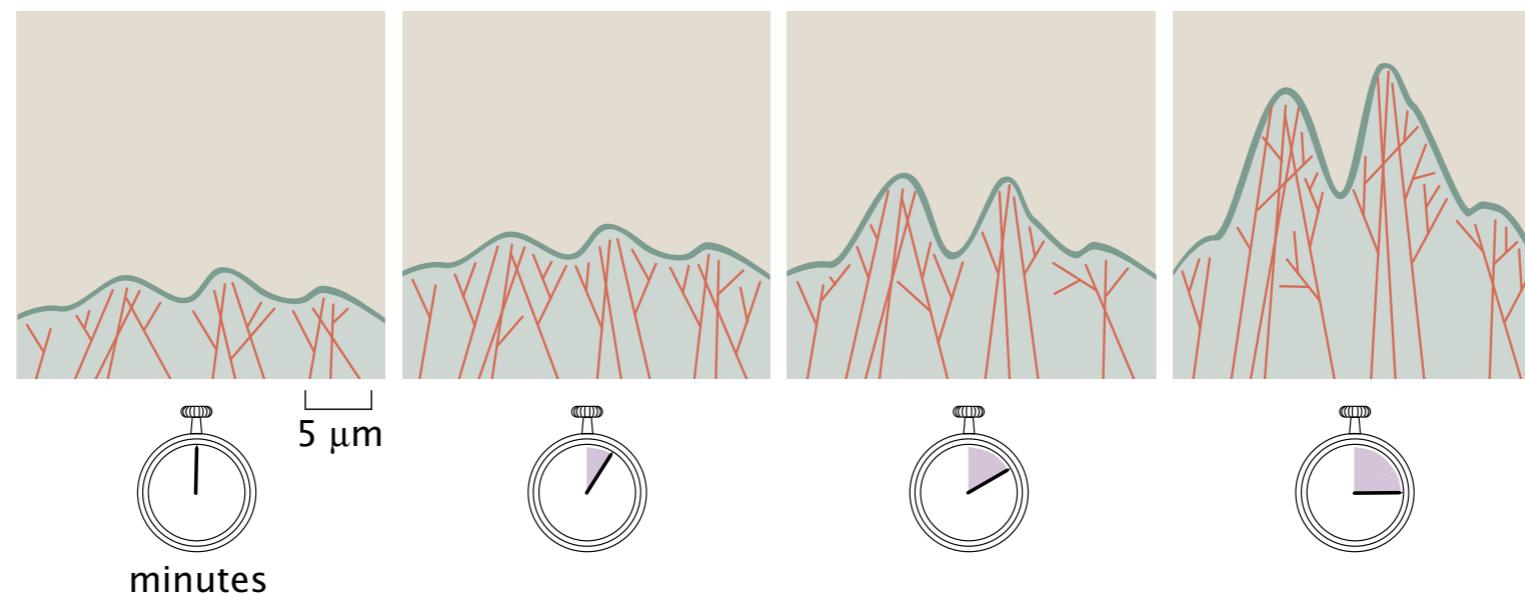
Obviously not! This is the total turnover per day.

Dynamics of the cytoskeleton

(A) *in vitro* polymerization



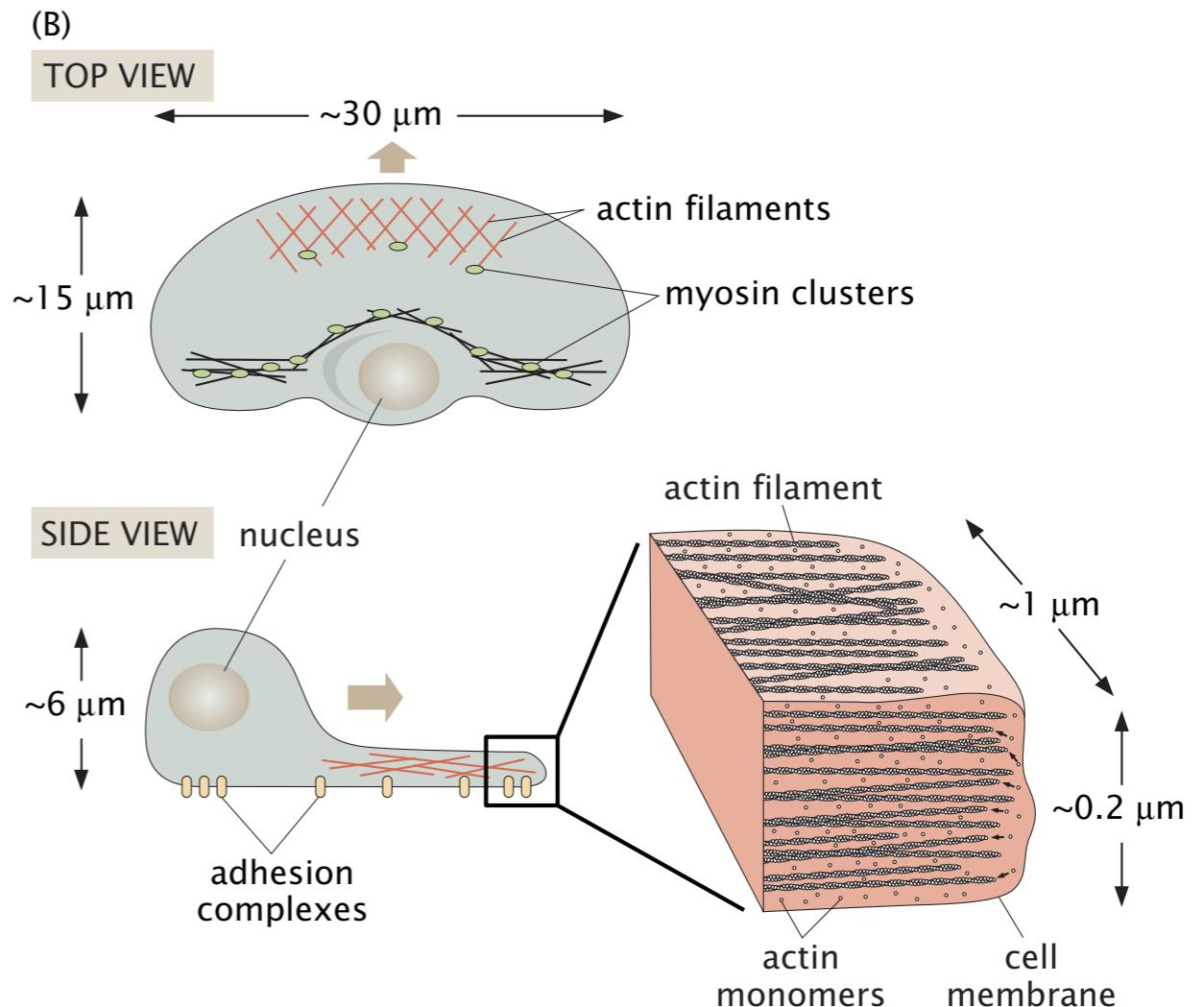
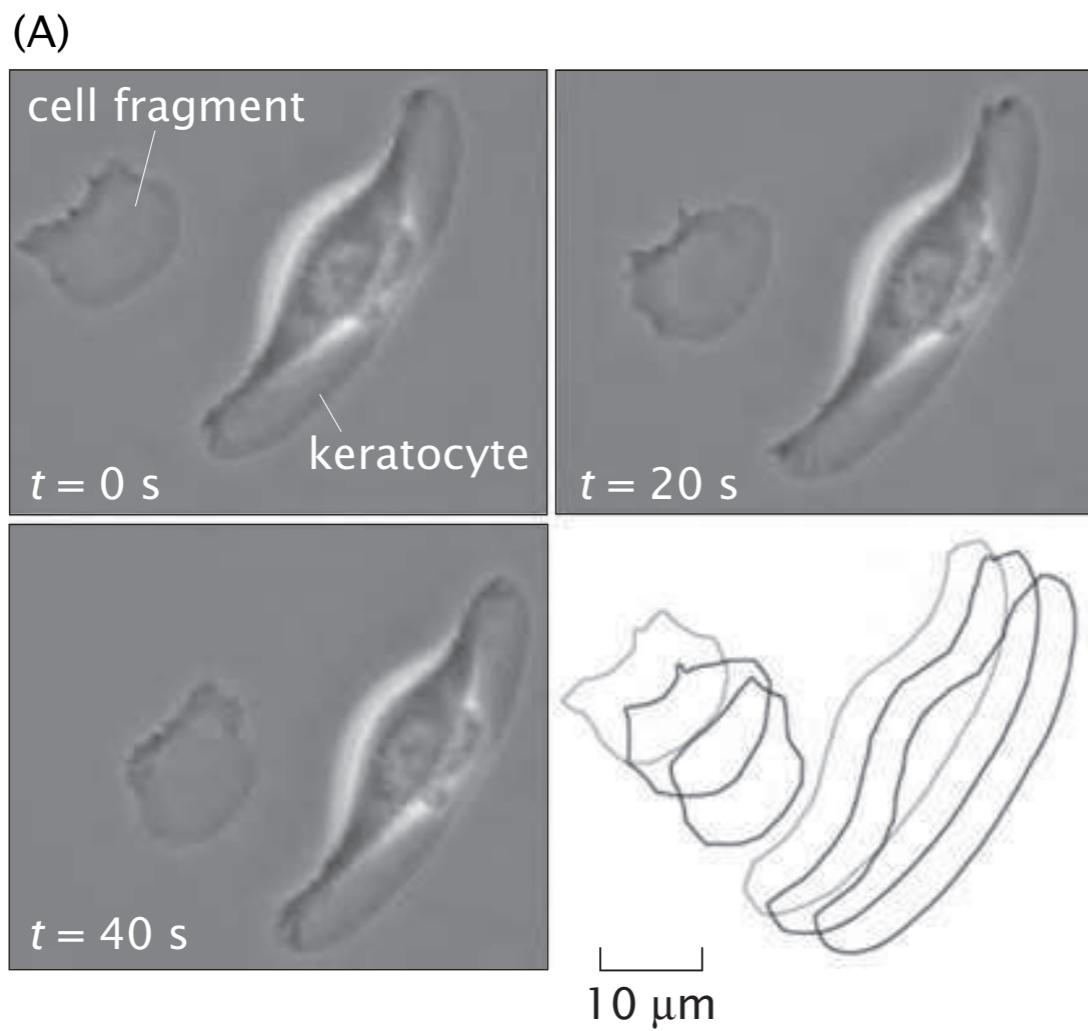
(B) *in vivo* polymerization



Points to note here

1. *In vitro*, actin polymerization can create polymers in less than a minute
2. *In vivo*, the process is more complex (monomer conc, depolymerization, ATP hydrolysis, regulatory proteins etc) and time-consuming, so happens over several minutes

Cytoskeletal dynamics and motion of cells



Can we use this to estimate the rate of actin polymerization?

From analysis of the images above

Average speed of the cell $v_{cell} = 0.2 \mu\text{m/s}$

Size of an actin monomer is $l_m \approx 3 \text{ nm}$

Assuming any cell movement is linearly proportional to growth of actin filaments

$$\frac{dN_a}{dt} = \frac{v_{cell}}{l_m} = \frac{0.2}{3} \approx 70 \text{ monomers/s}$$

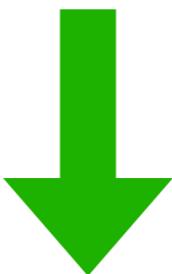
Time needed to add one monomer \approx 14 ms !

A quantitative theory of biological reaction dynamics

A quantitative toolkit to describe the rates of transformation is necessary for understanding the biological processes

A good quantitative theory must answer the following questions

- How many molecules are there?
- Where are they?
- When are they there?



The rate equation paradigm

Chemical concentrations vary in both space and time

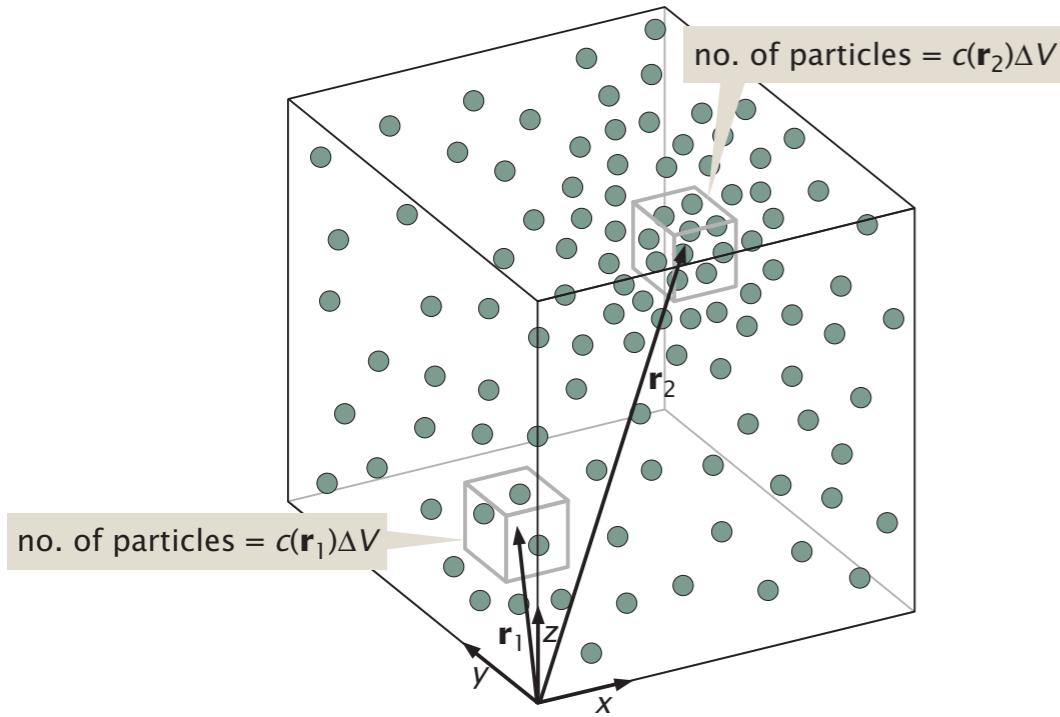


Figure 13.9: Schematic illustrating the definition of a concentration field. The system is divided up into small boxes of volume ΔV . The overall concentration field is changing sufficiently slowly that in each small box the “concentration” is constant.

$c_i(\vec{r}, t)$ = number of molecules of type i per unit volume at position \vec{r} at time t

Here concentration is a ‘field variable’ - that varies in space

This field captures the effect that chemical state of a system can develop spatial non-uniformity and time variation

Size of the small box of volume ΔV is

- much larger than the mean spacing of molecules
- much smaller than the size of the box

Two things to keep in mind before using this concept

- When molecules are localized to a certain organelle/regions of space - local concentrations are better than global concentrations
- When number of molecules is small, individual trajectories need to be examined

Rate equations describe the time evolutions of concentrations

let's consider a set of chemical reactants with concentrations $\{c_j\}$, for simplicity $c_j = c_j(t)$



$$(c_1, c_2, c_3, \dots, c_n)$$

The fundamental postulate of the rate equation paradigm is

$$\frac{dc_i}{dt} = f(\{c_j\}; \{k_i\}) \quad \text{where } f(\{c_j\}; \{k_i\}) = f(c_1, c_2, c_3, \dots, c_n; k_1, k_2, k_3, \dots, k_m)$$

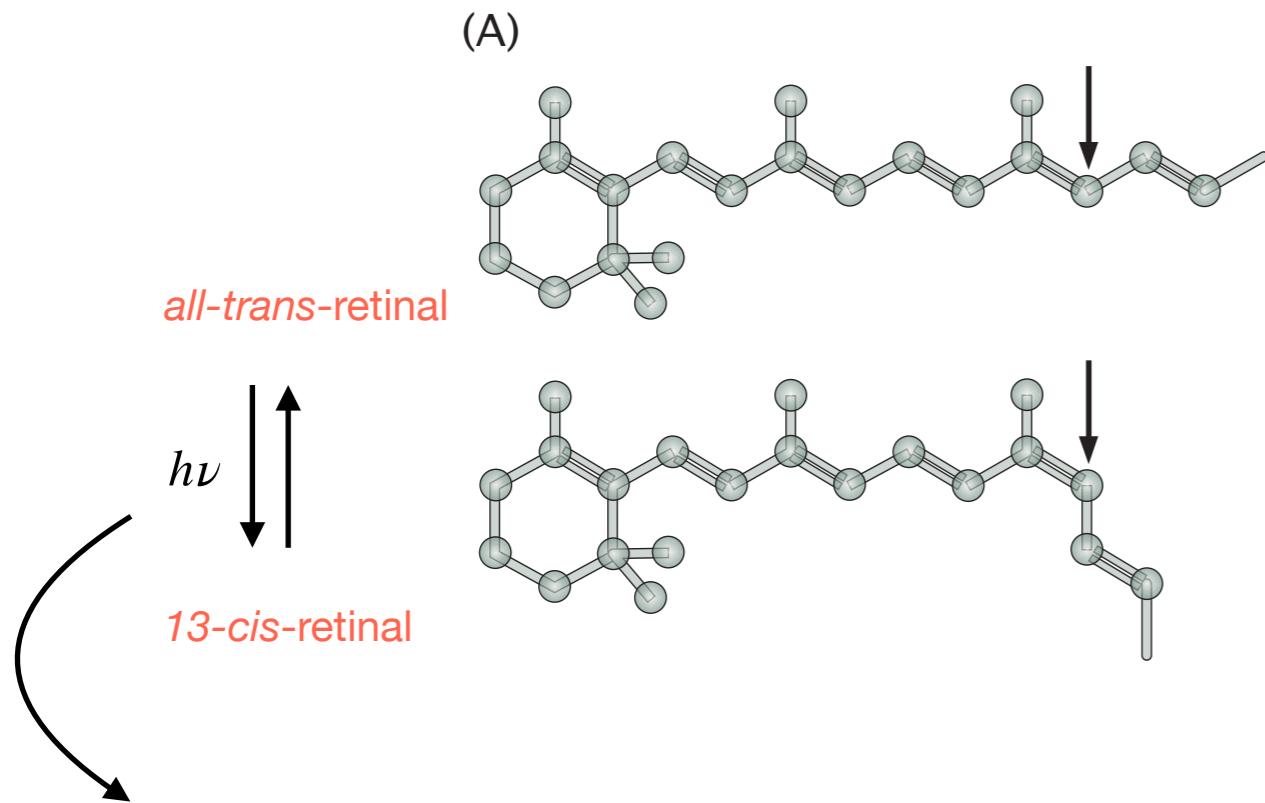


k_i are rate constants that dictate how fast reactions go

Any c_i changes in time depending on all c_j that couple to it

Next let's consider specific examples of reactions to learn about precise forms of $f(\{c_j\}; \{k_i\})$

Decay of macromolecules as an example



This isomerization reaction is utilized by the transmembrane protein 'bacteriorhodopsin' in photosynthetic archaea for transmembrane proton transport.

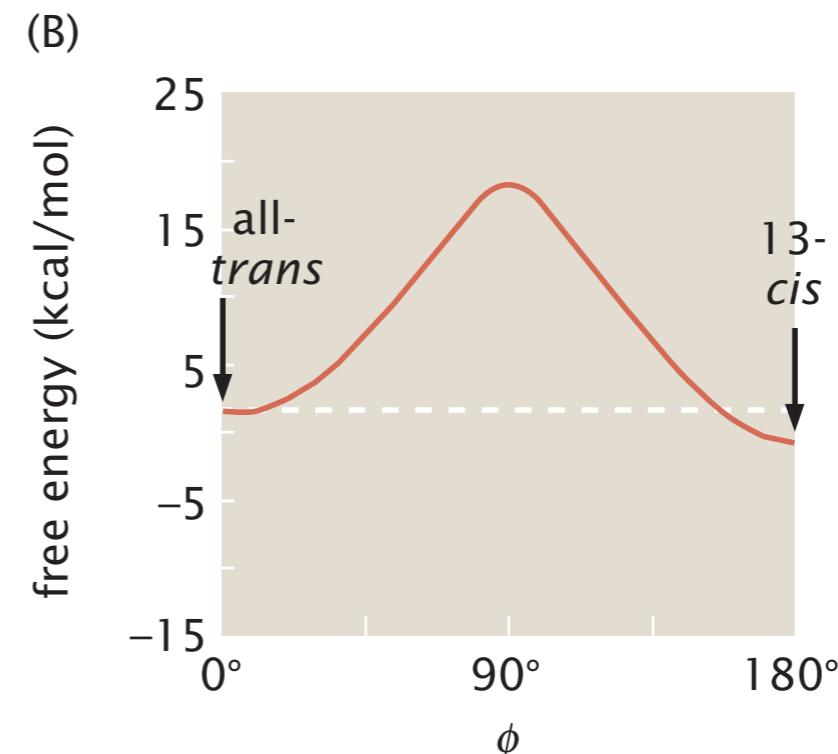
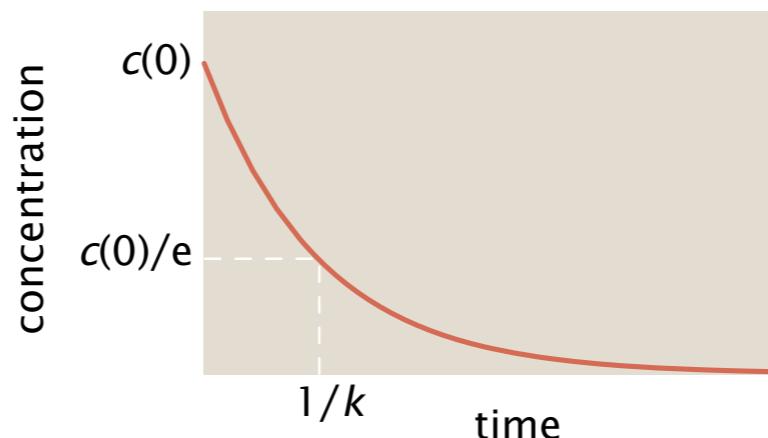
The rate equation takes the form:

$$\frac{dc(t)}{dt} = f(c; k) = -kc(t) \implies c(t) = c(0)e^{-kt}$$

k = rate of decay

Unit of k ? $1/\text{time}$

Concentration profile?



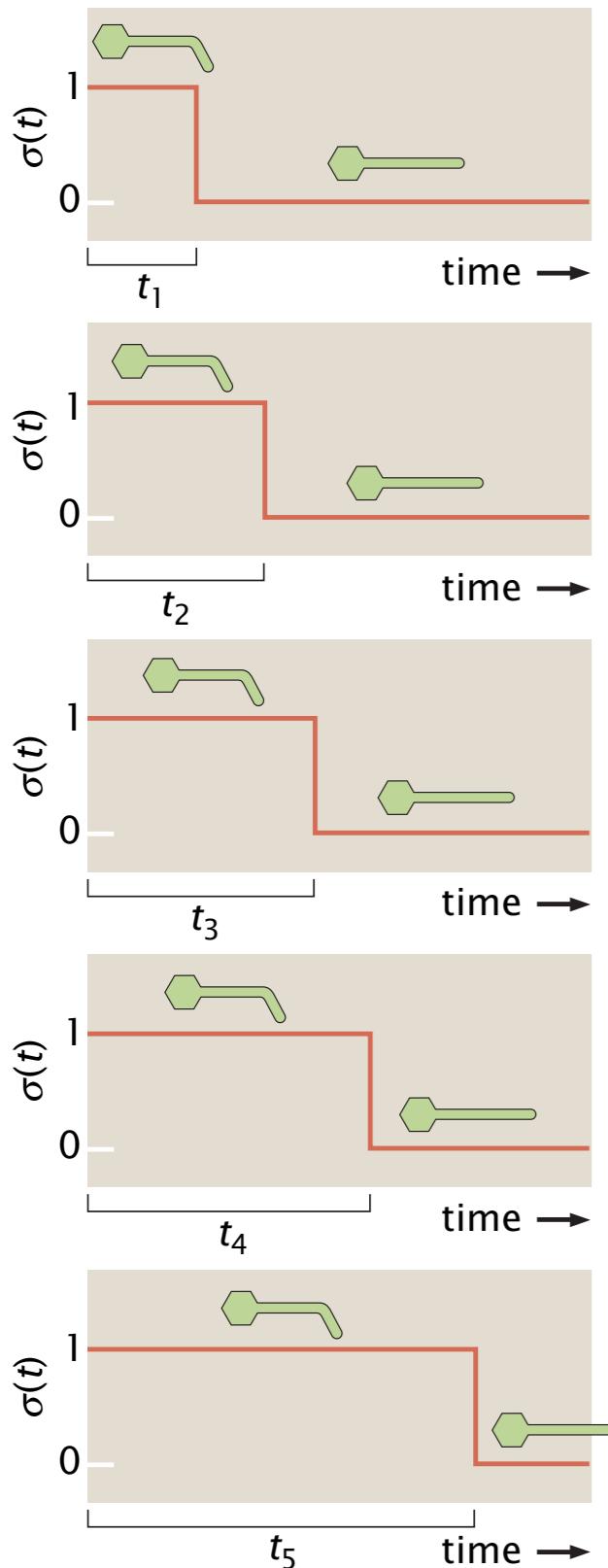
Angle of rotation around C atom at position 13

13-cis-retinal decays with time into *all-trans*-retinal following first-order kinetics

We can define a characteristic time

$$\tau = \frac{1}{k} \quad c(\tau) = \frac{c(0)}{e}$$

A single-molecule view of degradation



Microscopic trajectories of a system undergoing decay from state '1' to state '0'

$$\sigma_i(t) = \begin{cases} 1 & \text{if } t < t_i, \\ 0 & \text{otherwise} \end{cases}$$

where t_i = waiting time associated with the i -th trajectory

In this picture, rate constant k characterizes the average life-time of the macromolecules - this only works for a huge collection of molecules

Now let's analyze the trajectories

First, discretize time into steps of Δt , so any time $t = N\Delta t$

If a molecule survives till N steps and decay at the $N + 1$ -th time step, then probability of that process is

$$P(t) = \frac{(1 - k\Delta t) \times (1 - k\Delta t) \times (1 - k\Delta t) \times \dots \times (1 - k\Delta t) \times k\Delta t}{N \text{ time steps}}$$

where $k\Delta t$ = probability of decay during a given time step

$(1 - k\Delta t)$ = probability of decay not happening during a given time step

$$\text{Rewriting, } P(t) = (1 - k\Delta t)^N k\Delta t = \left(1 - \frac{kt}{N}\right)^N k\Delta t \approx ke^{-kt} \Delta t$$

Therefore, the probability of decay in time interval between t & $t + \Delta t$ is: $P(t) = \frac{1}{\tau} e^{-t/\tau} \Delta t$