Biomeng 261 Lecture 09 2017

- Gene expression & Regulation
  - Modelling via 'reaction' systems

Key Idea(s)

Today
- We can use the same basic 'reaction modelling' language to think about/analyse genetic expression & regulation processes
- genes 'switch' between various states dep. on TFs
  - use fractions/probabs. instead of conc.

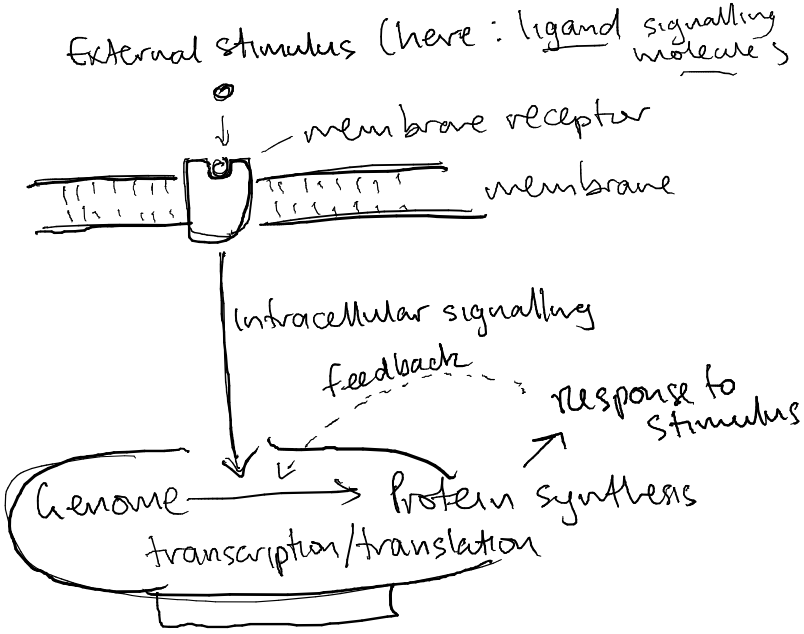
Next lectures
- However, we will also encounter issues with scaling up to large systems
  - need other, simpler approaches too (trade-offs).

Cellular Systems Biology (Recall)

- Key Pieces
  - Signal Transduction
  - Metabolism
  - gene expression } 'information'

today (regulation of)

Recall Signal Transduction picture



Now we look at the genetic processes & their regulation

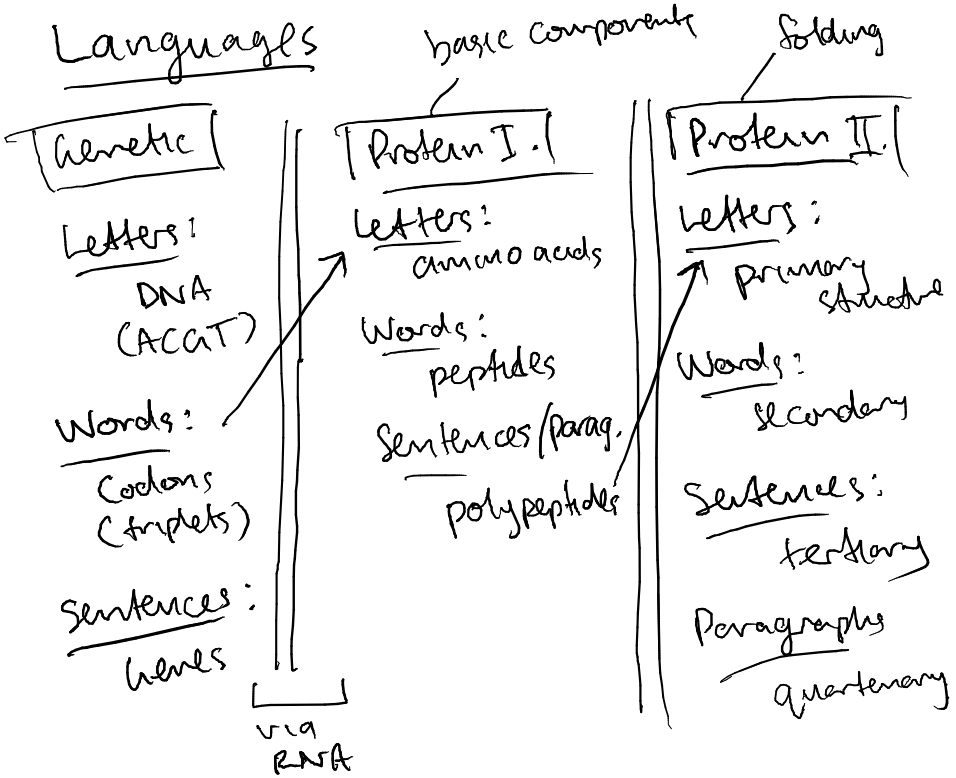
Genes & all that...

In all cells, the 'info' required for regulating cell function is stored or coded in its

— genome —

└ all genetic material
eg DNA, RNA etc

Languages



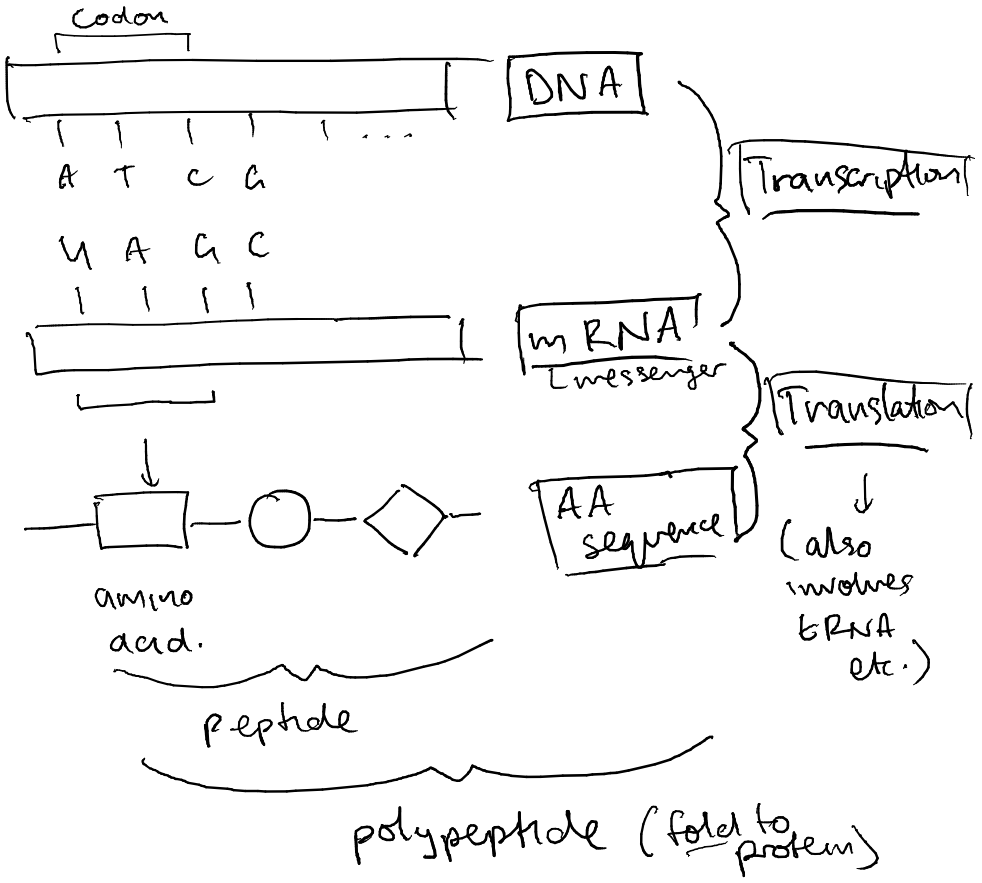
Gene expression

DNA → Protein/Polypeptide

?

Needs:
- transcription & translation } from one language to another. } uses RNA

Transcription & Translation



Simplistic overall balance eqn's.

Process

transcription translation

DNA → mRNA → Protein

'R' 'P'

(Amounts/Conc.)

$$\frac{dR}{dt} = J_{transcription} - J_{R\,degradation}$$

(goal.)

$$\frac{dP}{dt} = J_{translation} - J_{P\,degradation}$$

→ Note: mRNA is 'created' but is then translated, not used up directly!
→ degrades instead

Notation

we'll often use v instead of J here

ie $\frac{dR}{dt} = v_{transcription} - v_{R\,deg.}$ — etc —

Main focus: transcription & its regulation.

Goal

→ 'constitutive' equation for overall transcription rate.

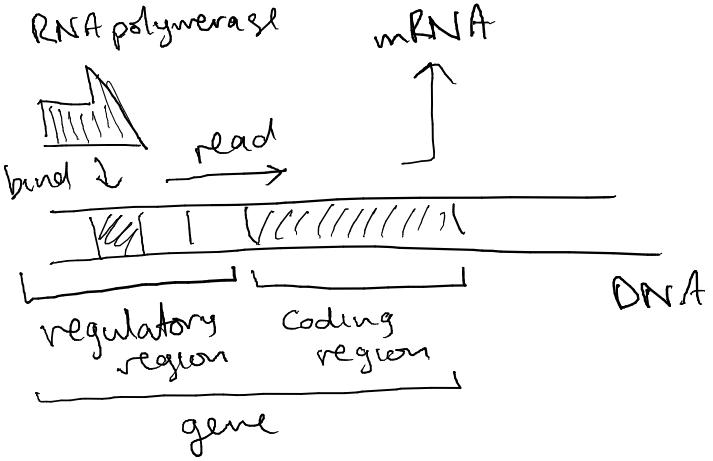
↳ will derive from 'underlying' model of gene states

What do we need to include?

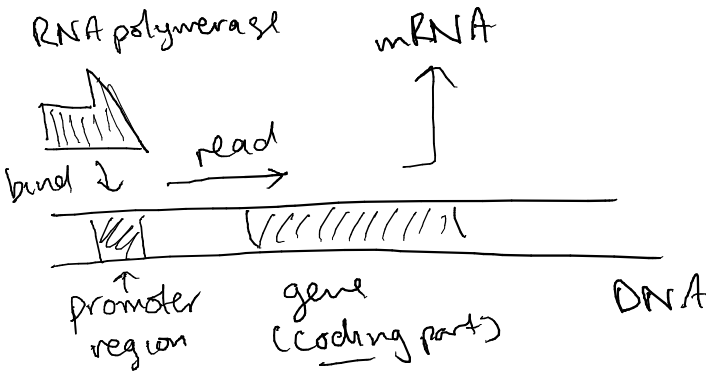
- Simple models
  - prokaryotic } easier
  - eukaryotic } same ideas just more complicated

(see slides / biol. textbooks)

Transcription: view of underlying process

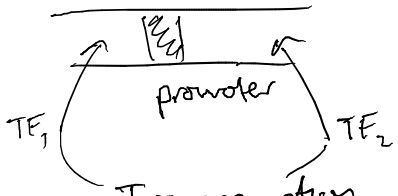


Transcription: simple model I. Underlying process.



Extra complexity: regulation!
Within regulatory region

(eukaryotes: many TFs involved)



Transcription factor binding regions

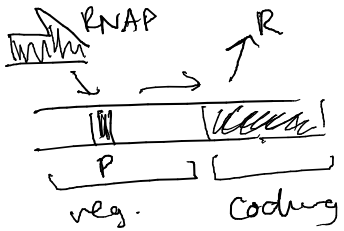
'regulate'

⇒ affect RNAP binding/transcription

Regulation types:
- Activator: enable/help binding of RNAP
- Repressor: block/decrease binding

Autoregulation: gene codes for own activators & repressors → +ve autoreg, -ve autoreg.

Overview 'reaction'



1. $P + RNAP \longrightarrow P:RNAP$

promoter, RNA polymerase

&

2. $P:RNAP \longrightarrow P + RNAP + R$

↑ mRNA

Note: as if R 'created out of nothing'

→ created from other chem. species in cell

→ depends on level of modelling!

→ we will consider various 'gene states'

Gene regulatory states

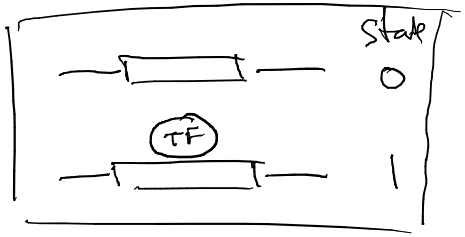
→ In general there may be various transcription factors bound to the regulatory region of a gene

→ we model the gene as being in various 'regulatory states' & switching bet. them

→ each state has a different contrib. to overall transcription flux

State-P.I.

Example:



$$TF + G \underset{k_-}{\overset{k_+}{\rightleftharpoons}} TF:G$$

transcription factor — gene state 0 — gene state 1

States: various representations I.

1. $TF + G \underset{k_-}{\overset{k_+}{\rightleftharpoons}} TF:G$

↓

2. $TF + G_0 \underset{k_-}{\overset{k_+}{\rightleftharpoons}} G_1$ } States G_0, G_1

↓ (using) combine

$$J_+ = k_+[TF][G_0]$$

$$J_- = k_-[G_1]$$

3. ⇒ $G_0 \underset{k_-}{\overset{k_+[TF]}{\rightleftharpoons}} G_1$ } Note! combine [TF] into rate param.

⇒ switching states $G_0 \rightleftarrows G_1$

Concentrations? →

States: Fractional/Occupancy Probabilities

- Rather than concentrations we will work in terms of the fractional/occupancy probabilities of each state of a given gene.

  (then average over many cases to get overall flux.)

- Again, each state will then have a different transcription rate

Underlying gene state fractions ⇒ $x_0 \underset{k_-}{\overset{k_+[TF]}{\rightleftharpoons}} x_1$ (gene is switching states)

where $x_0 + x_1 = 1$ (all state probabilities/fractions)

(Basically: divide everything by $c_0 + c_1 + \ldots = \text{const.}$)

Interpretation: x_0 = probability of gene being in state 0

etc ⇒ will then 'average' over.

... More state representations ...

Finally... instead of just

$$x_0 \underset{k_-}{\overset{k_+[TF]}{\rightleftharpoons}} x_1$$

we will also picture this as:

$$x_0 \underset{K_D}{\overset{[TF]}{\rightleftharpoons}} x_1$$

(divide rates by k_+)

where $K_D = \frac{k_-}{k_+}$ = (equil.) dissociation constant

Note:

⇒ same relative rates

(we will only consider equilibrium, so units issue not important!)

only relative rates matter here

States & transcription rates

- gene can be in multiple states
- rapidly switch between
  - ↳ will assume quasi-equil.
  - ↳ gives equilibrium occupancy probabilities
- add up contributions of each state to v

Combining Contributions to overall flux:

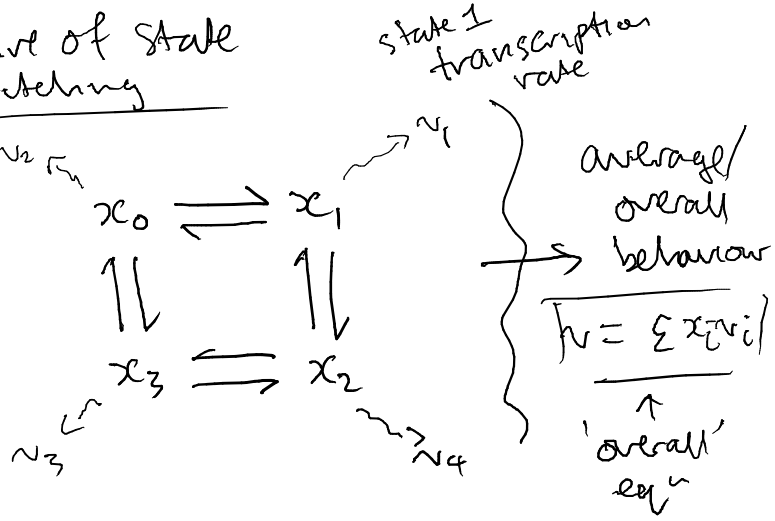
overall constit. eqn.

$$v_{transcription} = \sum_{s=0}^{m-1} x_s v_s$$

where x_s: probability of gene being in state s

v_s: transcription rate (flux) for state s.

Picture of state switching

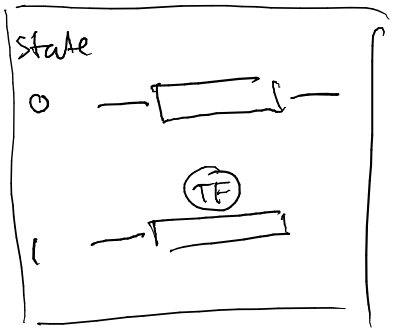


- multiple states with different occupancy probabilities x_i — we will find quasi-equil.
- each state has transcription rate v_i
- overall transcription rate $= \sum x_i v_i$ } 'average over'
  - ↑ will use quasi-equil.

[gene states : 'micro states'
overall flux : 'macro' effect]

Example: Single TF.

Two gene-state model



$$x_0 \underset{k_-}{\overset{k_+[TF]}{\rightleftharpoons}} x_1$$

$$\left(\text{or } x_0 \underset{K_d}{\overset{[TF]}{\rightleftharpoons}} x_1\right)$$

Steps

1. Assume gene-state model in equilibrium (+ total fraction = 1)
2. Find fractions $x_0, x_1, \ldots$
3. Find overall transcription $r = r_0 x_0 + r_1 x_1 + \ldots$
4. Det. r_0, r_1 etc depending on whether TF is activator / inhibitor etc →

1a) Equilibrium

$$x_0 \cdot k_+ [TF] = x_1 k_-$$

$$\Rightarrow \frac{x_1}{x_0} = \frac{k_+}{k_-}[TF] = \frac{[TF]}{K_d}.$$

1b). Total fraction = 1 (recall enzymes & E_0)

$$\Rightarrow x_0 + x_1 = 1$$

2. Two equations for x_1 & x_2

combine:

$$\Rightarrow x_0 + x_0 \frac{[TF]}{K_d} = 1$$

$$\Rightarrow \boxed{x_0 = \frac{K_d}{K_d + [TF]}}$$

& $\boxed{x_1 = \frac{[TF]}{K_d + [TF]}}$

3. $v_{transcription} = x_0 v_0 + x_1 v_1$

$$= \frac{K_d}{K_d + [TF]} \cdot v_0 + \frac{[TF]}{K_d + [TF]} \cdot v_1$$

4. Suppose TF is activator (for example)

→ increases transcription.

& suppose is required for transcription

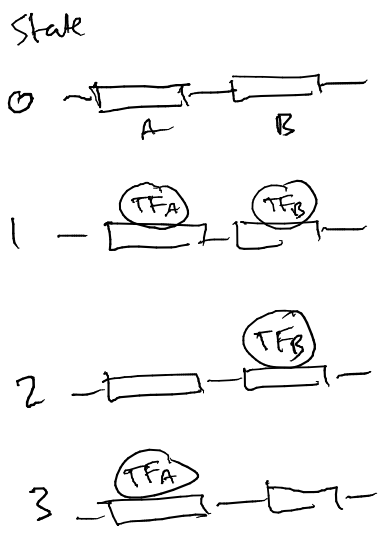
→ no transcription without.

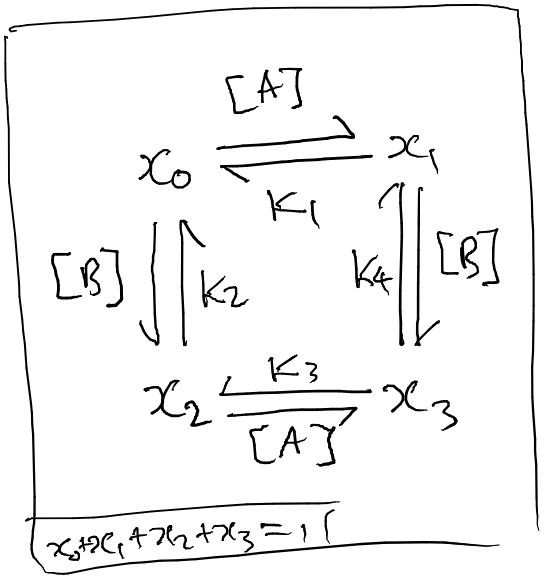
⇒ set $v_0 = 0$

$$v = \frac{[TF]}{K_d + [TF]} \cdot v_1 \quad \text{i.e.}$$

Exercise: what if TF is a repressor?

Multiple TFs: two TFs ⇒ Four gene states.





Steps: $\frac{x_1}{x_0} = \frac{[A]}{K_1}$; $\frac{x_2}{x_0} = \frac{[B]}{K_2}$

$$\frac{x_3}{x_1} = \frac{[B]}{K_4} \Rightarrow \frac{x_3}{x_0} = \frac{[B]}{K_4} \cdot \frac{[A]}{K_1}$$

Solve for x_0

$$\Rightarrow x_0 = \frac{1}{1 + \frac{[A]}{K_1} + \frac{[B]}{K_2} + \frac{[A][B]}{K_1 K_4}}$$

(then $x_1 = \cdot x_0$, $x_2 = \cdot x_0$, $x_3 = \cdot x_0$)

So

$$v_{transcription} = x_0 v_0 + x_1 v_1 + x_2 v_2 + x_3 v_3$$

$$= x_0 \left[v_0 + v_1 \frac{[A]}{K_1} + v_2 \frac{[B]}{K_2} + v_3 \frac{[A][B]}{K_1 K_4} \right]$$

where $x_0 = \dfrac{1}{1 + \frac{[A]}{K_1} + \frac{[B]}{K_2} + \frac{[A][B]}{K_1 K_4}}$

use as 'constit' eq.

Recall:

$$\frac{dR}{dt} = v_{transcription} - v_{Rdeg}$$

$$\frac{dP}{dt} = v_{translation} - v_{Pdeg}.$$

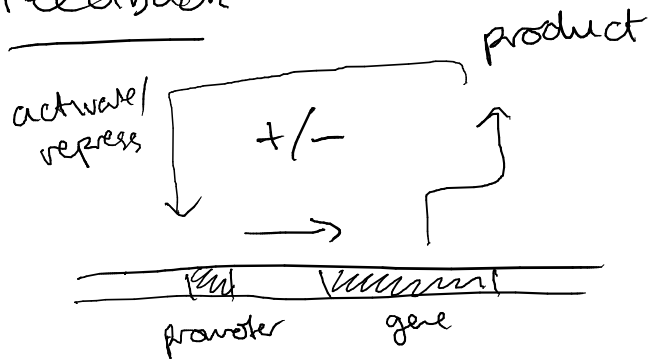
Simplistic: eg $v_{Rdeg} = k_{Rdeg} \cdot R$

actually much more complicated!

$v_{Pdeg} = k_{Pdeg} \cdot P$

$v_{translation} = k_{translation} \cdot R$

Feedback



Gene product affects own transcription

↓

autoregulation!

self

{ positive (↑ transcription)
negative (↓ transcription)

will briefly look at example next time

+

look at larger scale expression/regulation