Systembiologi ~~Dynamics~~ II

TEK292
(2008) (2013)

"Test" mass action
$\emptyset \rightleftarrows X$
$A + A \rightleftarrows C$

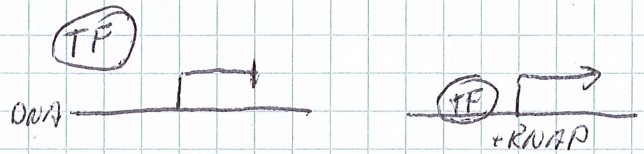
Gene regulation

* Central dogma of molecular biology

  DNA → RNA → Protein

  Replication Transcription Translation

* Regulation
  - Proteins (transcription factors) regulate transcription



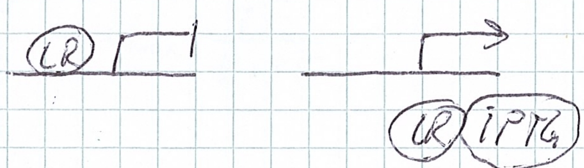
TF → P activates

TF ⊣ P inactivates

  - RNA regulates RNA (siRNA, miRNA)
  - Other ways...

The "expression state" which genes are active can define cell type.

(ex) Jacob Monod 1961 (lac operon)



lac operon	Sea Urchin	Boolean plant flower

(ex) Boolean lac-operon

LR ↘ lac$_p$
IPTG ↗

LR	IPTG	Lac Operon
0	0	1
0	1	1
1	0	0
1	1	1

Michaelis - Menten

$$TF + DNA \underset{k_2}{\overset{k_1}{\rightleftharpoons}} TD \qquad DNA + TD = 1$$

Equilibrium : $TD = \frac{k_1}{k_2} TF \cdot DNA = \frac{k_1}{k_2} TF (1 - TD)$

$$TD \left(1 + \frac{k_1}{k_2} TF\right) = \frac{k_1}{k_2} TF$$

$$\boxed{TD = \frac{TF}{K + TF}} \qquad K = \frac{k_2}{k_1}$$

Relative amount in bound state $\frac{TD}{TD + DNA}$.
Fraction of time TF bound

Also:

$$\boxed{DNA = 1 - TD = \frac{K}{K + TF}}$$

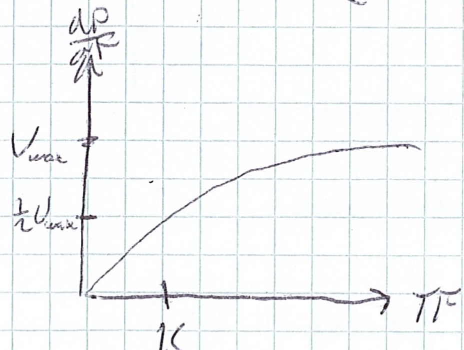
Fraction of time with unbound DNA.

Transcription

- TF activator

$TD \xrightarrow{V_{max}} P$ $\qquad V_{max}$ transcription rate at bound state (TD)

$$\frac{dP}{dt} = V_{max} \frac{TF}{K + TF}$$



Compare enzyme kinetics

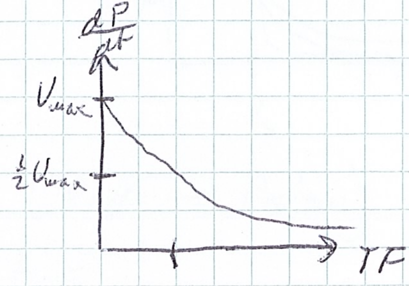
TF ⟺ substrate
DNA ⟺ enzyme
P ⟺ product

Difference? $\qquad$ TD or TF + DNA alter transcription

- TF repressor

$$DNA \xrightarrow{V_{max}} P$$ transcription at unbound state (DNA)

$$\frac{dP}{dt} = V_{max} \frac{K}{K + TF}$$



Also combination possible, e.g. leakage

* Slow "response" for Michaelis Menten
  Rate changes slowly when alternating TF concentrations

  e.g. "off" $0.1\ V_{max} = \frac{V\ TF}{K + TF}$ $TF \sim \frac{K}{9}$

  "on" $0.9\ V_{max} = \frac{V\ TF}{K + TF}$ $TF \sim 9K$

  81 - fold change needed to switch between on/off state

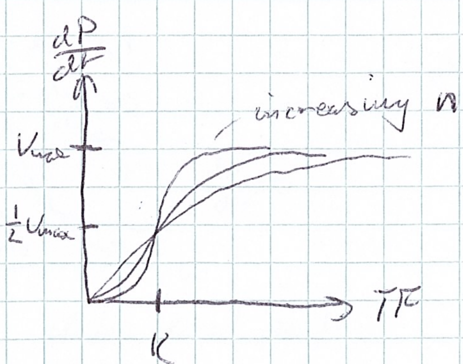
* Hill equation
  Common "development" of M-M formalism

  - Activation

  $$\frac{dP}{dt} = V_{max} \frac{TF^n}{K^n + TF^n}$$

  K ~ Hill constant

  n ~ Hill coefficient



(ex) Two transcription factors bind

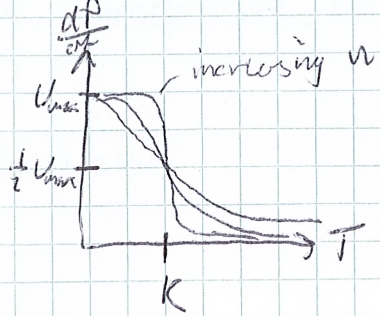
$$T + T + D \underset{k_2}{\overset{k_1}{\rightleftharpoons}} TD$$

equilibrium $TD = K' T^2 D = K' T^2 (1 - TD)$

$$\boxed{TD = \frac{T^2}{K^2 + T^2}}$$

- Hill repression

$$\frac{dP}{dt} = V_{max} \frac{K^n}{K^n + T^n}$$



* What about translation (RNA → Protein)

Transcription rate limiting.

Translation typically:

(i) left out i.e $\frac{dP}{dt} = \frac{VT}{K+T}$ (P – protein)

(ii) modelled simplistic $\frac{dP}{dt} = kR$ (R – RNA)

(ex) Bistable switch (computer exercise)

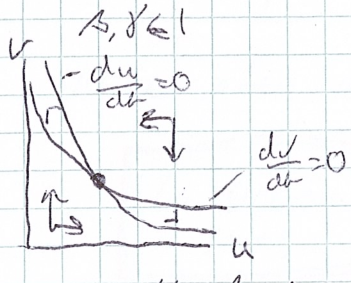
u ⇄ v

$$\frac{du}{dt} = \frac{\alpha_1}{1+v^\beta} - u$$

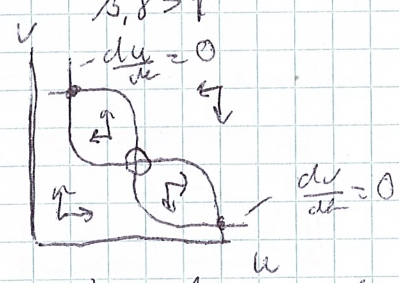
$$\frac{dv}{dt} = \frac{\alpha_2}{1+u^\gamma} - v$$

$$\frac{du}{dt} = 0 \Rightarrow u = \frac{\alpha_1}{1+v^\beta}$$

$$\frac{dv}{dt} = 0 \Rightarrow v = \frac{\alpha_2}{1+u^\gamma}$$



One stable fixed point

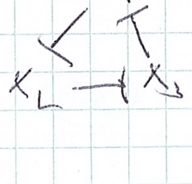


Bistable switch

Three fixed points, two stable

[Bistable switch]

(ex) Repressilator (Computer exercise)



$$\frac{dm_2}{dt} = \alpha_0 + \frac{\alpha}{1+p_1^n} - m_2$$

$$\frac{dp_2}{dt} = \beta m_2 - \beta p_2$$

[repressilator slide]

- oscillations possible

* Combining input from several transcription factors

(ex) activator and repressor

X → Z

Y ⊣ Z

$$P_{X,\,bound} = \frac{X}{K_1 + X} = \frac{X/K_1}{1 + X/K_1}$$

$$P_{Y,\,unbound} = \frac{K_2}{K_2 + Y} = \frac{1}{1 + Y/K_2}$$

Assume independent:

$$P_{X\ bound\ AND\ Y\ unbound} = P_{X\ bound} \cdot P_{Y\ unbound} =$$

$$= \frac{X/K_1}{1 + X/K_1 + Y/K_2 + X \cdot Y/K_1 \cdot K_2}$$

$$\frac{dZ}{dt} = V_{max} \cdot P_{X\,\&\,Y\,ub}$$

[activator repressor]

(ex) lac Operon

Transcription if not only LR present

$$\dot{P}_{transcription} = \frac{V_{max}\left(1 + k_1 I + k_3 I \cdot LR\right)}{1 + k_1 I + k_2 R + k_3 I \cdot LR}$$

Note also different rates possible.

[lac Operon MM] [lac Operon experimental] [slides on cooperativity]

* Modelling of large networks

(ex) $Raf + Ras\,GTP \underset{k_{-28}}{\overset{k_{28}}{\rightleftharpoons}} Raf\,Ras\,GTP$

$$Raf^{*}\,P1 \xrightarrow{k_{43}} Raf + P1$$

$$\frac{dRaf}{dt} = ?$$

[EGF network]

(ex)

(1) (2) $\frac{dSmad1}{dt} = ?$

[TGFβ network]