Statistical Physics View

* Potential and equilibrium

$\nu_1 X_1 + \dots \rightleftharpoons \dots \nu_m X_m$

ν: stoichiometric coefficients

chemical potential $\mu_\alpha = -T \left.\frac{dS}{dN}\right|_{E, N_\beta} = k_B T \ln c/c_0 + \mu^\circ(\epsilon, T)$

"availability" — concentration — internal energy

$\Delta G_r \equiv -\nu_1 \mu_1 - \dots + \dots + \nu_m \mu_m$ "chemical force"

$-\Delta G_r$ free energy change for a forward step

$\Delta G_r < 0 \Rightarrow$ forward reaction

$\Delta G_r > 0 \Rightarrow$ backward

$\Delta G_r = 0 \Rightarrow$ equilibrium

ΔG_r° standard free energy change

~~depends on m~~

$\Delta G_r^\circ \equiv -\nu_1 \mu_1^\circ - \dots + \dots + \nu_m \mu_m^\circ$

$\Delta G_r = 0$ equilibrium

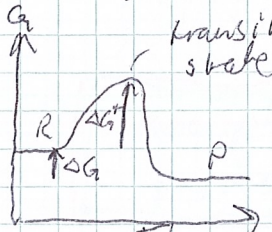
$$\frac{X_{k+1}^{\nu_{k+1}} \cdots X_m^{\nu_m}}{X_1^{\nu_1} \cdots X_k^{\nu_k}} = K_{eq} = e^{-\Delta G_r^\circ / k_B T}$$

ΔG_r° μ° look tables

* Reaction rates

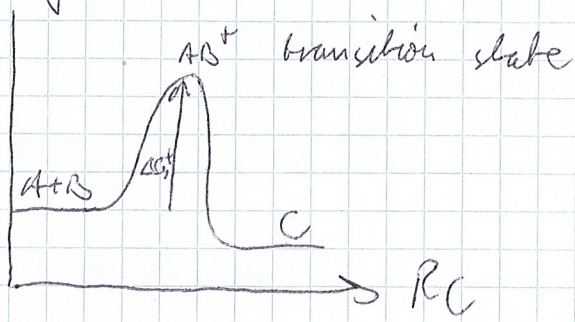
+ Reaction coordinate

- Chemical reactions reflect random walks in a free energy landscape of molecular configurations
- reaction coordinate ≡ valley in energy landscape
- Transition state: highest point along RC



* Transition state theory

$A + B \rightarrow C$



$A + B \rightleftarrows AB^{\ddagger} \rightarrow C$

(equilibrium)

$$K_{eq}^{\ddagger} = \frac{c_{AB^{\ddagger}}}{c_A \cdot c_B}$$

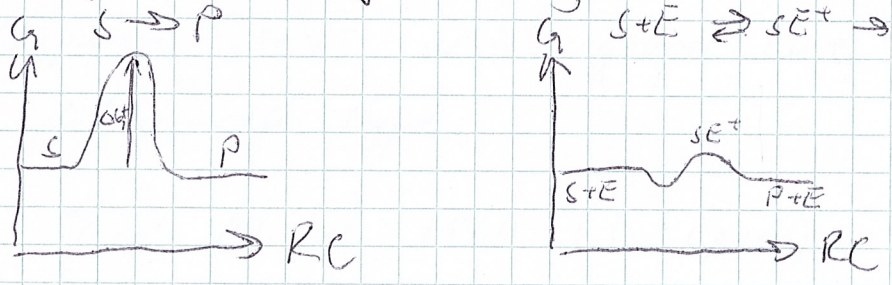
rate $v \propto c_{AB^{\ddagger}} = K_{eq}^{\ddagger} c_A c_B$

$$k_{obs} = \frac{k_B T}{h} K_{eq}^{\ddagger} = \frac{k_B T}{h} e^{-\Delta G^{\ddagger}/k_B T}$$

Eyring equation

Enzymes

Enzymes act by lowering the activation barrier

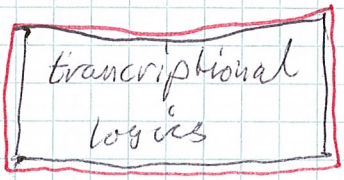


Transcription (Shea-Ackers, 1985)

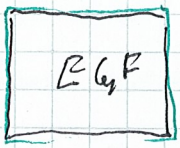
$$P = \frac{Z_{active}}{Z_{active} + Z_{inactive}} = \frac{Z_{active}}{Z}$$ — "partition function"

ex. 2 TF I, J

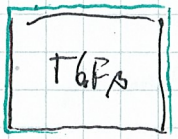
$$Z = \sum_{i,j=0,1} [I]^i [J]^j e^{-\Delta G_{ij}/RT}$$



~~Large networks~~
"Stora" modeller



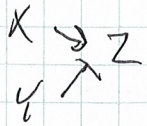
$\frac{d\,R_{ef}}{dt}$



$\frac{d\,Swadl}{dt}$

Multipla transkriptions faktorer

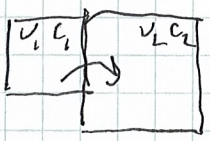
Aktivator - Repressor



Transport

- elevation linear reaktioner
- rumslig fallover spelar roll

(ex)



Antalet molekyler som kommer i 1
= ——— " ——— kommer in i 2

$$V_1 \frac{dC_1}{dt} = -V_2 \frac{dC_2}{dt}$$

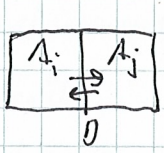
Diffusion

Passiv transport som drivs av koncentrationsskillnader

$$\frac{dc}{dt} = D \frac{\partial^2 c}{\partial x^2} \qquad j = -D \frac{\partial c}{\partial x}$$

flöde per area enhet

(ex) Diskreta celler (transport över membran)



$$\frac{dA_i}{dt} = -D A_i + D A_j$$

Vanlig ?

(ex) Många grannar

$$\frac{dC_i}{dt} = D \sum_{j}^{\text{Grannar}} (C_j - C_i)$$

Parameter uppskattningar

- Modellens beteende beror på parametervärden
- Hitta rätt parametervärden (alternativt undersöka parameterrymden) utgör ofta en stor del i ett systembiologiprojekt

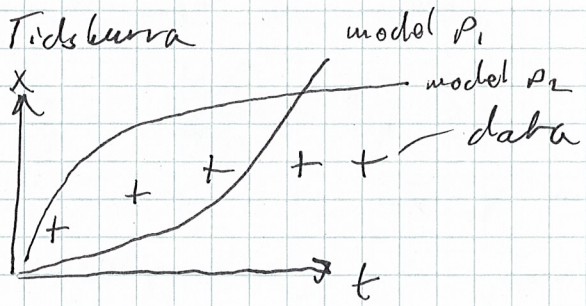
* Experimentella mätningar

Optimalt, men oftast svårt att göra direkt i organismen

* Reverse engineering

- Hitta parametervärden genom att optimera modellens beteende mot experimentell data
- Datan beror indirekt på parametervärdena

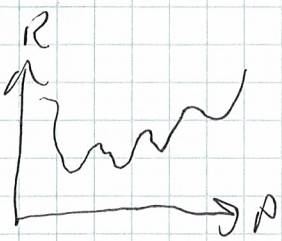
(ex)



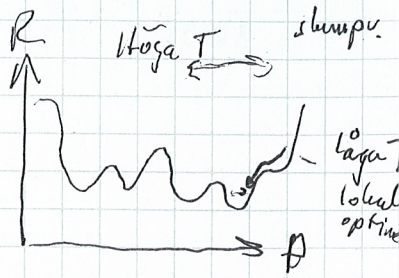
Mean squared error $$R(\bar{p}) = \frac{1}{NM} \sum_{t}^{N} \sum_{i}^{M} \left(x_i^{model}(t, \bar{p}) - x_i^{exp}(t) \right)^2$$

Optimering

- Hitta globalt minimum till $R(\bar{p})$
- Svårt, många dimensioner (parametrar)
- Tidskrävande



(+ Lokal optimering
- Gå neråt i R givet lokalt landskap
- Hamnar i närmsta lokala minimum
- Omstarter kan förbättra)



+ Simulerad kylning
  - lokala parameter steg
  - acceptera steg med sannolikhet

$$P = \begin{cases} e^{-\Delta R/T} & \Delta R > 0 \\ 1 & \Delta R < 0 \end{cases} \qquad \Delta R = R_{new} - R_{old}$$

Start
sänk T långsamt
- Höga T ⇒ bästa stegen accepteras
- Låga T ⇒ nästan bara förbättringar accepteras
- Hittar globalt minimum om T sänks tillräckligt långsamt

+ Andra metoder, t ex genetiska algoritmer

Modellanalys

* Robusthet

Kvantitativt mått på modellens känslighet för parameterändringar

$$S_p = \frac{dC/C}{dp/p} = \frac{dC}{dp}\frac{p}{C}$$

Relativ ändring i C när p ändras

C ~ modellegenskap, t ex jämviktskoncentration, amplitud, ...

* Störningar
  - Kan avslöja nya egenskaper hos systemet
  - Skall förutsägas av modellen

(ex)

	lokal	global
genetisk	mutanter siRNA	blockera transkription
omgivning	lokal appliering av molekyler	temperatur chock ta bort "lösa"

TGrFp projekt?