Nov 8: **Eric Deeds**, University of California at Los Angeles
"The evolution of cellular individuality"

Nov 15: **Daniel Merkle**, University of Southern Denmark
"Graph rewriting and chemistry"

Nov 22: **Jean Krivine**, Paris Diderot
"From molecules to systems: the problem of knowledge representation in molecular biology"

Nov 29: **Eric Smith**, Earth Life Sciences Institute, Tokyo
"Easy and Hard in the Origin of Life"

Dec 6: **Massimiliano Esposito**, University of Luxembourg
"Thermodynamics of Open Chemical Reaction Networks: Theory and Applications"

Dec 13: **Yarden Katz**, Harvard Medical School
"Cells as cognitive creatures"

Jan 17: **Aleksandra Walczak**, ENS Paris
"Prediction in immune repertoires"

Jan 24: **Tommy Kirchhausen**, Harvard Medical School
"Imaging sub-cellular dynamics from molecules to multicellular organisms"
1. The Topology of the Possible
(La représentation de l’information biologique)

2. Propagation of Genetic, Phenotypic, and Molecular information
(Limites de la transmission de l’information biologique)
Mutation and (Simple) Darwinian Selection

\[ I_i \quad Q_{ii} f_i \quad I_i + I_i \]

\[ Q_{ji} f_i \quad I_i + I_j \quad j \neq i \]

\[ \dot{x}_i = \sum_{j=1}^{n} Q_{ij} f_j x_j - f(t) x_i \]

with \[ f(t) = \sum_{j=1}^{n} f_j x_j \]

\[ \dot{x}_i = \left( Q_{ii} f_i - f(t) \right) x_i + \sum_{j \neq i}^{n} Q_{ij} f_j x_j \]
**Error Thresholds**

**Genotypic Error Threshold**

\[ p_c = 1 - \sigma_m^{-\frac{1}{l}} \approx \frac{\ln \sigma_m}{l} \]

**Phenotypic Error Threshold**

\[ p_c = 1 - \left( \frac{1 - \lambda_m \sigma_m}{(1 - \lambda_m) \sigma_m} \right)^{1/l} \]
Putting it All Together

folding

“representation” of phenotype by an equivalence class

GUUGAGGUAGGCACUCGCCGCUGACUACCUA.....CCUAGGCAAUUUGCGGCCUCUGAGCGGG

amplification

selection

error threshold(s)

\[ Q_{mm} f_m < \frac{f_m(t)}{f(t)} \]

\[ (1 - p)^t \]

\[ + \sum_{j \neq i}^n Q_{ij} f_j x_j \]
2. (part 2)
The Propagation of Genetic, Phenotypic, and Molecular information
**Basics**

**Reaction Velocity (flux)**

\[ T + E \xrightarrow[k_+]{k_-} ET \]

**Equilibrium**

\[ v_+ = v_- \]

\[ v_+ = k_+ [E][T] \]

\[ v_- = k_- [ET] \]

**Equilibrium Constant**

\[ \frac{k_+}{k_-} = \frac{[ET]_eq}{[E]_eq[T]_eq} = \exp \left( -\frac{\Delta G^\Theta}{RT} \right) \]

**Connects energetics with kinetics**

**Kinetic Equilibrium**

\[ \Delta G = 0 \]
\[ k_+ = \omega \exp\left(-\Delta G^*/RT\right) = \omega' \]

\[ k_- = \omega \exp\left(-\Delta G^*/RT\right) \exp(\Delta G^\ominus /RT) = \omega' \exp(\Delta G^\ominus /RT) \]
Kinetic Proofreading Problem

**assume**

discriminating factor

at steady-state

error rate

\[ a \equiv k_+ [F] = k_+ [T] \]

\[ b = \exp \left( - (\Delta G_F^\Theta - \Delta G_T^\Theta) \right) \leq \exp \left( - \Delta G_{FT}^\Theta \right) \]

\[ [ET] = \frac{a[E]}{a'b + v} \quad \text{and} \quad [EW] = \frac{a[E]}{a' + v} \]

\[ \eta = \frac{v[EW]}{v[ET]} = \frac{[EW]}{[ET]} = \frac{a'b + v}{a' + v} \]
Kinetic Proofreading Scheme

\[ \eta = \frac{[EF^*]}{[ET^*]} = \frac{b(a'b + q)(a'c + (a + c)q)}{(a' + q)(a'bc + (a + c)q)} \]

drawing after Jeremy Owen
Proofreading Schemes

Energetic discrimination

- Short time: wrong, right
- Long time: wrong, right

Kinetic discrimination

- Short time: wrong, right
- Long time: wrong, right

3. Modeling cellular information processing
Signaling: A Circulatory System of Information

Tasks:
cell fate, division, repair, cell death, motility, morphology, ...

CELL SIGNALING TECHNOLOGY
www.cellsignal.com
Signaling: A Circulatory System of Information

not a physical network, but a network of possibility

molecular species

18 868 902 333 942 991 917 533 566 435 344 349

degradation

recycling

endocytosis

small GTPase

MAPK cascade

transcription

Ca signaling

cell cycle
Start with simplicity...
\[ B + A \xrightarrow{k_1 \quad k_{-1}} BA \]

\[
\frac{k_1}{k_{-1}} = K = \frac{[BA]}{[B][A]}
\]

\[
B_t = [B] + [BA]
\]

\[
\frac{[BA]}{B_t} = \frac{[A]}{[A] + K_d}
\]

\[
K_d = K^{-1}
\]
$B + A \xrightleftharpoons[k_1]{k_{-1}} BA$

collapse all binding curves into one by using the dimensionless variable

$$\frac{[BA]}{B_t} = \frac{[A]}{[A] + K_d}$$

$$\frac{[BA]}{B_t} = \frac{\alpha}{\alpha + 1}$$
\[ B + A \xrightleftharpoons[k_{-1}\ k_1]{k_d} BA \]

\[ \frac{[BA]}{B_t} = \frac{\alpha}{\alpha + 1} \]

\[ a_t = \frac{A_t}{K_d} \]

\[ b_t = \frac{B_t}{K_d} \]

red: equilibrium solution in terms of free \( A \)
blue: equilibrium solution in terms of known parameters

\[ \frac{[BA]}{B_t} = \frac{2a_t}{1 + a_t + b_t + \sqrt{(1 - a_t + b_t)^2 + 4a_t}} \]
Binding Equilibria As “Prefixes”

\[ B + A \xrightarrow{k_1} BA \xrightarrow{k_2} B + P \]

\[
\frac{v}{v_{\text{max}}} = \frac{\alpha}{\alpha + 1}
\]

\[
v \div \frac{dP}{dt} = k_2[BA] = k_2B_t \frac{\alpha}{\alpha + 1}
\]

when \( A_t \gg B_t \)

with \( \alpha = \frac{[A]}{K_m} \)

range of “zero order kinetics”

range of “intermediary order kinetics”

range of “first order kinetics” (linear regime)

\( k_1, k_{-1} \gg k_2 \) quasi-equilibrium of ES

\( A_t \gg B_t \) quasi-steady state of ES

\( A_t \gg K_m \) enzyme is saturated

\[
[A] = K_m = \frac{k_{-1} + k_2}{k_1}
\]
Binding Equilibria As "Prefixes"

\[ B + A \xrightleftharpoons[k_1]{k_{-1}} BA \xrightarrow{k_2} B + P \]

\[ A_t \gg B_t \quad \checkmark \]

\[ A_t \nless B_t \]
a scaffold protein with $n$ binding partners
$2^n (+1)$ molecular species

$n2^{n-1}$ reactions
Lost In (Combinatorial) Space

$n$ binding sites (disordered)

\[ \frac{[BA_n]}{B_t} = \left( \frac{\alpha}{\alpha + 1} \right)^n \]

\[
\left( \frac{\alpha}{\alpha + 1} \right)^n = \frac{1}{(1 + \frac{1}{\alpha})^n} \to 0
\]

for any finite $\alpha \geq 0$ as $n \to \infty$
\[ \binom{n}{j}/2^n \]

\[ \frac{[BA_n]}{B_t} = \left( \frac{\alpha}{\alpha + 1} \right)^n \]
Sequential Binding
Sequential Binding & All-Or-None

**Sequential Binding**

\[
\frac{[BA_n]}{B_t} = \frac{\alpha^n (1 - \alpha)}{1 - \alpha^{n+1}}
\]

**All-Or-None Cooperativity (Hill)**

\[
\frac{[BA_n]}{B_t} = \frac{\alpha^n}{1 + \alpha^n}
\]

\[\frac{\alpha^n (1 - \alpha)}{1 - \alpha^{n+1}} \xrightarrow{n \to \infty} \begin{cases} 0 & \text{for } \alpha \leq 1, \\ (\alpha - 1)/\alpha & \text{for } \alpha > 1 \end{cases}\]

\[\frac{\alpha^n}{1 + \alpha^n} \xrightarrow{n \to \infty} \begin{cases} 0 & \text{for } \alpha < 1, \\ 1 & \text{for } \alpha > 1 \end{cases}\]

A threshold for large \( n \)

A step-function for large \( n \)
**Binding Logic**

\[ v = k_2 B_t \left( \frac{\alpha}{1 + \alpha} \right)^2 \]

or

\[ v = k_2 B_t \frac{\alpha}{1 + \alpha} \frac{\gamma}{1 + \gamma} \]

or

\[ v = k_2 C_t \frac{\alpha \beta}{1 + \beta + \alpha \beta} \]

sequential: first BC, then ABC

\[ v = k_2 C_t \frac{\alpha \beta}{1 + \alpha \beta} \]

(this is non-competitive inhibition)
Increase total B. What happens?

\[
\frac{[BA_2]}{B_t} = \left(\frac{\alpha}{1 + \alpha}\right)^2
\]
\[
\frac{[BA_n]}{K_d} = b_t \left( \frac{2a_t}{1 + a_t + nb_t + \sqrt{(1 - a_t + nb_t)^2 + 4a_t}} \right)^n
\]

\[b_t = \frac{1}{2} (1 + a_t) \quad \text{(for } n = 2)\]
A Do-Undo Loop

\[ A + T^o \xrightarrow{k_{1}^A}{k_{-1}^A} AT^o \xrightarrow{k_{2}^A} A + T^* \]

\[ B + T^* \xrightarrow{k_{1}^B}{k_{-1}^B} BT^* \xrightarrow{k_{2}^B} B + T^o \]

\[ T = [T^o] + [T^*] \]

\[ \frac{dT^*}{dt} = \frac{k_{2}^A A_t (T_t - [T^*])}{K_m^A + T_t - [T^*]} - \frac{k_{2}^B B_t [T^*]}{K_m^B + [T^*]} \]
Guanine nucleotide exchange factor

GTPase-activating protein

small G proteins

heterotrimeric G proteins

(a variety of combinations from 23 $G_{\alpha}$, 6$G_{\beta}$, 12$G_{\gamma}$ subunits)
A Do-Undo Loop

\[
\frac{d[T^\bullet]}{dt} = \frac{k_2^A A_t (T - [T^\bullet])}{K_m^A + T - [T^\bullet]} - \frac{k_2^B B_t [T^\bullet]}{K_m^B + [T^\bullet]}
\]

with \( T = [T^\circ] + [T^\bullet] \)

\[
\frac{[T^\bullet]}{T} = \frac{2r}{1 + r + (K - r)t_B + \sqrt{(1 + r + (K - r)t_B)^2 - 4r(K - r)t_B}}
\]

dimensionless

with \( K = \frac{K_m^B}{K_m^A} \)

\[
t_B = \frac{T}{K_m^B}
\]

\[
r = \frac{k_2^A a_t}{k_2^B b_t} \quad a_t = \frac{A_t}{K_m^A} \quad b_t = \frac{B_t}{K_m^B}
\]
The Do-Undo Loop: An “Atom” Of Molecular Control

\[ K = \frac{K_m^B}{K_m^A} = 1 \]

steady-state solution of

\[ \frac{d[T^\bullet]}{dt} \approx k_2^A A_t - k_2^B B_t \]

(saturated regime)

\[ \log_{10} t_B \]

\[ K_m^A = K_m^B = 0.74 \, \mu M \]
sequential binding

\[
\frac{[BA_n]}{B_t} = \frac{\alpha^n(1 - \alpha)}{1 - \alpha^{n+1}}
\]

sequential phosphorylation w/ linear kinetics

\[
\frac{[T(n)]}{T} = \frac{r^n(1 - r)}{1 - r^{n+1}} \quad \text{with} \quad r = \frac{k_2^A a_t}{k_2^B b_t}
\]

The Do-Undo Loop Chain

\[
\frac{\alpha^n(1 - \alpha)}{1 - \alpha^{n+1}} \xrightarrow{n \to \infty} \begin{cases} 0 & \text{for } \alpha \leq 1, \\ (\alpha - 1)/\alpha & \text{for } \alpha > 1 \end{cases}
\]
The Do-Undo Loop Cascade

\[ r_i = \frac{k^A_i T_{i-1}}{k^B_i B_i} \quad \text{and} \quad r_i = r \quad i = 2, \ldots, n \]

\[ r_1 = \frac{k^A_i A}{k^B_i B} \quad \text{the input variable} \]

\[
\begin{array}{c|c|c}
\frac{[T^\bullet_n]}{T_n} = & r_1 & r^{n-1}(r - 1) \\
& r_1 + \frac{r - 1}{r^n - 1} & r^n - 1
\end{array}
\]
\[
\frac{T_n - T_{\bullet n}}{T_n} = \frac{r_1}{r_1 + \frac{r - 1}{r^n - 1}} \frac{r^{n-1}(r - 1)}{r^n - 1}
\]

notice the scale difference between \(n=3\) and \(n=5\)
The Do-Undo Loop Cascade With “Depth” and “Width”

parameters from Huang/Ferrell

“122” cascade
The Do-Undo Loop With Feedback: Memory

\[
\frac{d[T^\bullet]}{dt} = \frac{k_2^A A_t (T - [T^\bullet])}{K_m^A + T - [T^\bullet]} + \frac{k_2^T [T^\bullet] (T - [T^\bullet])}{K_m^T + T - [T^\bullet]} - \frac{k_2^B B_t [T^\bullet]}{K_m^B + [T^\bullet]}
\]

\[
E_a = 40
S = 200
K_m^{(a)} = 1100
K_m^{(b)} = 200
K_m^{(a)} = 11
k_2^{(a)} = 0.1
k_2^{(b)} = 10
k_2^{(s)} = 1
\]