dynamic processes in cells
(a systems approach to biology)

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lecture 12
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Ca$^{2+}$ frequency decoding?

repetitive pulses in the endocrine system

hypothalamic-pituitary-gonadal (HPG) axis

decoding of GnRH pulses

LβT2 cells transfected with luciferase reporters for GnRHR and FSHβ

Implementation by “parallel cooperation”?

“parallel activation”

“cooperative gate”

100nM 5min pulse

pulses/hour
black dash-dotted = 0.125
blue dash-dotted = 0.25
pink dashed = 0.5
green dashed = 1
blue dotted = 2
red solid = 4

but how does this work at the promoter?

“In the CO-OPERATIVE GATE scenario, the transcription factors bind at independent promoter sites. After initial binding of the transcription factors to DNA the transcription factors interact to bring promoter sites in close proximity.”

oops ... but, happily, all is not lost

if both transcription factors bind to each site in a **mutually exclusive way**

and the two bindings take place **independently** of each other (no cooperativity)

that gives the partition function  

\[
(1 + [TF_1]/K_{d_{TF_1}} + [TF_2]/K_{d_{TF_2}})^2
\]

**transcriptional synergy** gives the numerator term  

\[
[TF_1][TF_2]/(K_{d_{TF_1}}K_{d_{TF_2}})
\]
oscillations - Ca^{2+} is the tip of a large iceberg!

Dynamics of the p53-Mdm2 feedback loop in individual cells

Galit Lahav^1, Nitzan Rosenfeld^1, Alex Sigal^1, Naama Geva-Zatorsky^1, Arnold J Levine^2, Michael B Elowitz^3 & Uri Alon^4

Nat Genet 36:147-50 2004

Oscillations in NF-κB Signaling Control the Dynamics of Gene Expression


Science 306:74-8 2004

Frequency-modulated nuclear localization bursts coordinate gene regulation

Long Cai^1, Chiraj K. Dalal^1 & Michael B. Elowitz^1

Nature 455:485-90 2008

oscillations - the tip of the iceberg

TNF-induced gene expression oscillates in time
Li Sun, Guozhe Yang, Mone Zaidi, Jameel Iqbal *

reviews:
**T cell signalling**

Adaptive immunity through T and B cells emerged in the vertebrate lineage.

Major histocompatibility complex (MHC) class I and II ("identity molecule")

“myeloid” = from the bone marrow
“lymphoid” = from the lymphatic system

blood work, again

platelet
red blood cell
basophil
eosinophil
mast cell
granulocytes
monocytes
B-cell
T-cell
red blood cell
T cell
platelet
two classes of T cells and MHCs

CD8+, MHC class I

CD4+, MHC class II

positive/negative T cell selection in the thymus

- Single positive CD4+ / CD8-
- Double positive CD4+ / CD8+ with working TCR
- Double negative CD4- / CD8- proliferation
- Negative/negative T cell selection in the thymus
- Self-reactive T cells eliminated
immunoglobulin superfamily - MHC and TCR

somatic recombination

TCR - MHC interaction

Hennecke, Wiley, “T cell receptor-MHC interactions up close”, Cell **104**:1-4 2001

TCR signalosome - recruited tyrosine phosphorylation

TCR complex

Love, Hayes, Cold Spring Harb Perspect Biol 2:a002485 2010

\[ \text{YxxI/Lxx(6-8)xxyYxxI/L} \]

Immune receptor Tyrosine-based Activation Motif

\[ \text{ITAM = } \]

Phospho-Tyr

Transmembrane helix
initiates multiple downstream signalling pathways.
experimental system

leukemia (RBL-5) cell line mutagenised to be deficient in antigen and MHC processing, which loads exogenously-provided peptides onto empty MHCs on the membrane *

isolated from TCR transgenic mice which are compromised for normal TCR production but can be encouraged to positively select for a particular MHC/peptide combination, in this case aa 257-264 of ovalbumin **

SIINFEKL


immunological discrimination

specificity

speed

sensitivity

Evidence that a Single Peptide–MHC Complex on a Target Cell Can Elicit a Cytolytic T Cell Response

Immunity 4:565-71 1996

digital activation of Erk

specificity from kinetic proofreading

irreversibility from phosphorylation

irreversible reactions imply that there is energy dissipation so that this system cannot reach thermodynamic equilibrium

the steady state can be calculated using the Matrix-Tree theorem

\[ \rho_i = \sum_{T \in \Theta_i(G)} \left( \prod_{j \not\rightarrow k \in T} \alpha \right) \]

but, in this case, it is better to think about it first

McKeithan, “Kinetic proofreading in T-cell receptor signal transduction”, PNAS 92:5042-6 1995h
avoiding spanning trees

\[ \frac{d}{dt} [C_i] = k_p [C_{i-1}] - (k_p + k_{-1}) [C_i] \]
\[ [C_N] = \left( \frac{k_p}{k_{-1}} \right) [C_{N-1}] \]

\[ \alpha = \frac{k_p}{k_{-1} + k_p} \]
\[ \frac{k_p}{k_{-1}} = \frac{\alpha}{1 - \alpha} \]

\[ [C_i] = \alpha^i [C_0] \]
\[ [C_N] = \alpha^{N-1} \frac{k_p}{k_{-1}} \]

\[ C_{total} = [C_0] \left( \alpha^{N-1} \frac{k_p}{k_{-1}} + \sum_{i=0}^{N-1} \alpha^i \right) = [C_0] \left( 1 + \frac{k_p}{k_{-1}} \right) \]

proportion of active TCR-pMHC complexes

\[ \frac{[C_N]}{C_{total}} = \alpha^N \]

specificity from small differences in \( \alpha \)
sensitivity and speed from interlinked feedbacks

early **negative** feedback through Shp-1 phosphatase

delayed, amplified **positive** feedback through the MAP kinase cascade

very detailed model

main TCR network, one of 10 modules described in JDesigner(*), with the resulting ODEs simulated in Matlab

quantitative immunology - a long history

“Niels Jerne is the leading theoretician in immunology during the last 30 years. In three main theories he has elucidated central issues concerning specificity, development and regulation of the immune system in a comprehensive and convincing way.”

1984 Nobel Prize press release

Jerne, “Towards a network theory of the immune system”, Annales Immunology 125C:373-89 1974

The Art of the Probable: System Control in the Adaptive Immune System

Ronald N. Germain

Science 293:240-5 2001

Pairing computation with experimentation: a powerful coupling for understanding T cell signalling

taking stock

systems biology - the paradox of dead molecules and living organisms

integration means crossing boundaries
  theory vs experiment  development vs population genetics

the evolution of complexity reveals the complexity of evolution - weak linkage

<table>
<thead>
<tr>
<th>Does evolutionary theory need a rethink?</th>
<th>POINT</th>
<th>COUNTERPOINT</th>
<th>Nature 514:161-4 2014</th>
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</thead>
<tbody>
<tr>
<td>Yes, urgently</td>
<td></td>
<td>No, all is well</td>
<td></td>
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time-scale separation can get around the complexity - linear framework

dynamical systems and landscapes - a metaphor for cellular behaviour
  monostability, bistability, excitability, oscillation

interlinked feedbacks orchestrate homeostasis and information processing
the end of the road

please remember to fill out the course evaluations or come by and tell me in person what you thought about the course – your comments are always welcome

ENJOY THE REST OF THE COURSE!