Linking Network Function and Topology

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Physics versus Biology

Physical laws
• Causality (Initial conditions + equations => future)
• Symmetry and simplicity
• Universal and time-invariant

Biological world
• Function centric (“purpose”)
• History dependent, detailed, and “complex”
• Evolving

Structure or form

Physical interactions

Evolutionary forces
Network function and form (topology)

For a given function, are there preferred network topologies?
Boundary formation of segmentation

Function: maintain a sharp boundary

What kinds of networks can perform this function?
Why did nature pick this network?
How would you design it?

Need at least two components
Enumeration of all 2-node networks

4x2 = 8 edges
3 possibilities per edge
3^8 = 6561 networks
An example

\[ \frac{dA}{dt} = \frac{1}{\tau_A} \left( \frac{k_1^n}{B^n + k_1^n} - A \right) \]

\[ \frac{dB}{dt} = \frac{1}{\tau_B} \left( \frac{k_2^n}{A^n + k_2^n} - \frac{A_{out}^n}{A_{out}^n + k_3^n} - B \right) \]

Functional parameters

Q=fraction of functional parameter space
Distribution of Q values

What are these 45 networks?
Four core topologies

Topological features:
- Positive loop on E
- Positive loop on W
- Mutual intercellular activation of E and W
- Mutual repression if extracellular loop
Coarse-graining the biological network
Biochemical adaptation

E coli chemotaxis

Olfactory sensing

A common feature in sensory and other pathways
Function

Signal

Output

Circuit topology ?

Design principles ?
Function and network space

### Function

- **Input**: \( I_1 \)
- **Output**: \( O_1 \)
- **Output**: \( O_2 \)
- **Output peak**: \( O_{\text{peak}} \)
- **Sensitivity**: \( \left| \frac{(O_{\text{peak}} - O_1)/O_1}{(I_2 - I_1)/I_1} \right| \)
- **Precision**: \( \left| \frac{(O_2 - O_1)/O_1}{(I_2 - I_1)/I_1} \right|^{-1} \)

### Network Topology

16038 networks

Examples
Topology-function mapping

$$\frac{dA}{dt} = k_{iA} I \frac{(1 - A)}{(1 - A) + K_{iA}} - k'_{BA} B \frac{A}{A + K'_{BA}}$$

$$\frac{dB}{dt} = k_{AB} A \frac{(1 - B)}{(1 - B) + K_{AB}} - k'_{F0B} F_0 \frac{B}{B + K'_{F0B}}$$

$$\frac{dC}{dt} = k_{AC} A \frac{(1 - C)}{(1 - C) + K_{AC}} - k'_{F0C} F_0 \frac{C}{C + K'_{F0C}}$$

Parameter sampling (10,000 sets)

$log k^*$: 0.1–10

$log k^*$: 0.001–100

$k_{cut}$: 0.1–10

$K_m$: 0.001–100
Core adaptive topology
--Negative feedback loop with a buffer
Core adaptive topology
--Incoherent feed-forward loop with a proportioner node
In NFBLB node B is an Integrator

\[
\frac{dA}{dt} = Ik_{IA} \frac{(1 - A)}{(1 - A) + K_{IA}} - F_{0}k'_{F_{0A}} \frac{A}{A + K'_{F_{0A}}}
\]

\[
\frac{dB}{dt} = E_{0}k'_{E_{0B}} \frac{(1 - B)}{(1 - B) + K'_{E_{0B}}} - Ck'_{CB} \frac{B}{B + K'_{CB}}
\]

\[
\frac{dC}{dt} = Bk'_{BC} \frac{(1 - C)}{C + C'_{AC}} - Ak'_{AC} \frac{C}{C + K'_{AC}}
\]

Consider the buffer node B

If \((1 - B) >> K'_{E_{0B}}\) and \(B >> K'_{CB}\)

\[
\frac{dB}{dt} = E_{0}k'_{E_{0B}} - Ck'_{CB}
\]

\[
C^* = E_{0}k'_{E_{0B}} / k'_{CB}
\]

--Independent of Input

\[
\frac{dB}{dt} = k'_{CB} (C^* - C),
\]

\[
B = B^* (I_0) - k'_{CB} \int_0^t (C - C^*) dt.
\]
In IFFLP node B is a proportioner

\[
\frac{dA}{dt} = I_k_{IA} \frac{(1 - A)}{(1 - A) + K_{IA}} - F_0 k'_{F_0A} \frac{A}{A + K'_{F_0A}}
\]

\[
\frac{dB}{dt} = A k_{AB} \frac{(1 - B)}{(1 - B) + K_{AB}} - F_0 k'_{F_0B} \frac{B}{B + K'_{F_0B}}
\]

\[
\frac{dC}{dt} = A k_{AC} \frac{(1 - C)}{(1 - C) + K_{AC}} - B k'_{BC} \frac{C}{C + K'_{BC}}
\]

If \( A^* \propto B^* \), \( C^* \) would be independent of input

\[
\frac{dB}{dt} = k_{AB} A - k'_{F_0B} F_0 \frac{B}{K'_{F_0B}}
\]

\[
A^* k_{AB} = F_0 k'_{F_0B} B^*/K'_{F_0B}
\]
Probability plot for all networks

395 (out of 16038) networks each has more than 10/10000 parameter sets appear in this region.
Additional feature in adaptive networks

Topology clustering

C: \( NFBLB + \text{other motifs (166)} \)

D: \( IFFLP + \text{other motifs (229)} \)

Networks with NFBLB

Networks with NFBLB + NFBL

Networks with NFBLB + NFBL + self loop on B

Networks with IFFLP + NFBL

Positive regulations

Negative regulations

No regulation
Linear analysis

Adaptation precision: steady state property

\[
\begin{align*}
\frac{dA}{dt} &= f_A(A, B, C, I) = 0 \\
\frac{dB}{dt} &= f_B(A, B, C) = 0 \\
\frac{dC}{dt} &= f_C(A, B, C) = 0
\end{align*}
\]

\[
\begin{bmatrix}
\Delta A^* \\
\Delta B^* \\
\Delta C^*
\end{bmatrix} = -
\begin{bmatrix}
\frac{\partial f_A}{\partial A} & \frac{\partial f_A}{\partial B} & \frac{\partial f_A}{\partial C} \\
\frac{\partial f_B}{\partial A} & \frac{\partial f_B}{\partial B} & \frac{\partial f_B}{\partial C} \\
\frac{\partial f_C}{\partial A} & \frac{\partial f_C}{\partial B} & \frac{\partial f_C}{\partial C}
\end{bmatrix}^{-1}
\begin{bmatrix}
\frac{\partial f_A}{\partial I} \\
0 \\
0
\end{bmatrix} \Delta I
\]

\[
\Delta C^* = \Delta I \frac{\partial f_A}{\partial I} \begin{bmatrix} N \end{bmatrix}
\]

\[
N =
\begin{bmatrix}
\frac{\partial f_B}{\partial A} & \frac{\partial f_B}{\partial B} \\
\frac{\partial f_C}{\partial A} & \frac{\partial f_C}{\partial B}
\end{bmatrix}
\]
Error = \frac{1}{\text{Precision}} = \frac{\Delta C^*/C^*}{\Delta I/I} = \frac{I}{C^*} \frac{\partial f_A}{\partial I} \frac{|N|}{|J|} = 0

Error = 0 requires |N| = 0 AND |J| \neq 0

Correspondence between matrix terms and regulations

|J| = \begin{vmatrix}
\frac{\partial f_A}{\partial A} & \frac{\partial f_A}{\partial B} & \frac{\partial f_A}{\partial C} \\
\frac{\partial f_B}{\partial A} & \frac{\partial f_B}{\partial B} & \frac{\partial f_B}{\partial C} \\
\frac{\partial f_C}{\partial A} & \frac{\partial f_C}{\partial B} & \frac{\partial f_C}{\partial C}
\end{vmatrix}

|N| = \begin{vmatrix}
\frac{\partial f_B}{\partial A} & \frac{\partial f_B}{\partial B} \\
\frac{\partial f_C}{\partial A} & \frac{\partial f_C}{\partial B}
\end{vmatrix} - \begin{vmatrix}
\frac{\partial f_B}{\partial A} & \frac{\partial f_C}{\partial A} \\
\frac{\partial f_B}{\partial B} & \frac{\partial f_C}{\partial B}
\end{vmatrix}
An arrow diagram with labeled nodes and arrows. The text includes mathematical expressions and conditions. The main equation is:

\[ |N| = \frac{\partial f_B}{\partial A} \frac{\partial f_A}{\partial B} - \frac{\partial f_B}{\partial B} \frac{\partial f_A}{\partial A} = 0 \]

\[ \text{or} \]

\[ \frac{\partial f_c}{\partial A} \neq 0 \Rightarrow \frac{\partial f_B}{\partial B} = 0 \rightarrow f_B = g(A, C) \text{ or } f_B = B \cdot g(A, C) \]

The diagram also includes a class label:

**NFBLB class**

The determinant of the Jacobian matrix is given by:

\[ |J| = \begin{vmatrix} \frac{\partial f_A}{\partial A} & \frac{\partial f_A}{\partial B} & \frac{\partial f_A}{\partial C} \\ \frac{\partial f_B}{\partial A} & 0 & \frac{\partial f_B}{\partial C} \\ \frac{\partial f_C}{\partial A} & \frac{\partial f_C}{\partial B} & \frac{\partial f_C}{\partial C} \end{vmatrix} \]

\[ |J| < 0 \]

B is a buffer node.

At least one negative feedback loop.
Incoherent feedforward

Robustly achieving $|N|=0$

$f_B = \alpha A + g(C)B$

B is a proportioner node

IFFLP class

Incoherent feedforward
Design table of adaptation circuits

Combinations that improve the performance (Examples)

**NFBLB**
- Minimal network
  - $Q=5$ ($C^* = \text{const}$)
- One additional self-loop on B
  - $Q=5$ ($C^* = \text{const}$)
- One additional NFBL
  - $Q=27$ ($C^* = \text{const}$)
- One additional NFBL
  - $Q=49$ ($C^* = \text{const}$)

**IFFLP**
- Minimal network
  - $Q=8$ ($A^* = \text{const}$)
- One additional NFBL
  - $Q=8$ ($\alpha A^* + \gamma C^* = 0$)
- One additional NFBL
  - $Q=16$ ($B^* = \text{const} \cdot A^* / C^*$)
- Two additional NFBL
  - $Q=72$ ($B^* = \text{const} \cdot A^* / C^*$)
  - $Q=133$ ($B^* = \text{const} \cdot A^* / C^*$)

Robustness ($Q$) of adaptation networks

Parameter ranges for $K_m$
- Unconstrained
- Linear
- Saturated

See supplement for a comprehensive list.
Adaptation circuit of E coli
Summary

• Robust functionality constrains the choices of circuit topology

• Evolution may repeatedly converge on these solutions

  -- Francois & Siggia, 2008

• Design principles to understand complex biological systems

• Guide to synthesize artificial biological circuits

• How far can we go???
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Postdoc position available!