Finding Algorithms in Biological Networks

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Cells Compute

- No survival without computation!
  - Finding food
  - Avoiding predators
- How do they compute?
  - *Clearly* doing “information processing”
  - But can we actually catch nature running an (optimal) *algorithm*?

A Consensus Algorithm

- Population Protocols
  - Finite-state identity-free agents (molecules) interact in randomly chosen pairs
  - Each interaction (collision) can result in state changes
  - Complete connectivity, no centralized control (well-mixed solution)

- A Population Consensus Problem
  - Find which state $x$ or $y$ is in majority in the population
  - By converting the whole population to $x$ or $y$

- Approximate Majority (AM) Algorithm
  - Uses a third “undecided” state $b$
  - Disagreements cause agents to become undecided
  - Undecided agents believe any non-undecided agent

- With high probability, for $n$ agents
  - The total number of interactions is $O(n \log n) \Rightarrow$ fast (optimal)
  - Correct outcome if the initial disparity is $\omega(\sqrt{n} \log n) \Rightarrow$ robust
  - In parallel time, converges in $O(\log n)$

Worst-case scenario, starting with $x=y$, $b=0$:

\[
x + y \rightarrow y + b \\
y + x \rightarrow x + b \\
b + x \rightarrow x + x \\
b + y \rightarrow y + y
\]
A Plain Biological Implementation

Approximate Majority (AM)

Epigenetic Switch

Figure 1. Basic Ingredients of the Model

Theory

Theoretical Analysis of Epigenetic Cell Memory by Nucleosome Modification

Dana Angluin, James Aspnes, David Eisenstat
A Simple Population Protocol for Fast Robust Approximate Majority

2007

2007
Obfuscated Implementations?

- Mutual Inhibition & Self Activation
- Mutual Inhibition & Mutual Anti-activation
- Switching
- Better Switching

Cell cycle transitions
Polarity establishment
Gene networks
Construction of a genetic toggle switch in Escherichia coli

Septation Initiation

SIN inhibiting Byr4, absence of SIN activating Byr4

The G2/M cell cycle switch

Phosphorylation network dynamics in the control of cell cycle transitions

The “new” cell cycle switch

Universal control mechanism regulating exit of M phase
Influence Networks

Inhibition vs Activation

Usually modeled by sigmoid (e.g., Hill or Reinitz) functions

We model them by 4 mass action reactions over 3 species $x_0$, $x_1$, $x_2$

They actually implement a Hill function of coefficient 2:

$$r_{21} = 0.1$$

$$r_{10} = 10.0$$

$$r_{01} = 0.1$$

$$r_{12} = 10.0$$

Approximate Majority

Reaction Network

Influence Network
Network Emulation: MI emulates AM

• For *any* rates and initial conditions of AM, we can find *some* rates and initial conditions of MI such that the (6) trajectories of MI retrace those (3) of AM:

  \[ z = x \]
  \[ y = x \]
  \[ y_0 = x_0 \]

• How do we find these matching parameters? By a network morphism!
Emulation is a Network Morphism

A mapping of species and reactions

Homomorphic mapping

Initial conditions:
\[ z_0 = y_2 (= x_0) \]
\[ z_1 = y_1 (= x_1) \]
\[ z_2 = y_0 (= x_2) \]

Less trivial than you might think:
It need not preserve the out-degree of a node!
Approximate Majority Emulation Zoo

(→ homomorphism and stoichiomorphism (transitive))
Approximate Majority Emulation Zoo

- Homomorphism and stoichiometry (transitive)
Emulation Theorem

**Theorem:** If \( m \in (S, R) \rightarrow (\hat{S}, \hat{R}) \) is a CRN reactant morphism and stoichiomorphism then it is a CRN emulation.

reactant morphism \[ m^T_s \cdot \rho = \hat{\rho} \cdot m^T_r \]

stoichiomorphism \[ \varphi \cdot m_r = m_s \cdot \hat{\varphi} \]

emulation \[ \forall \hat{\nu}. \ F(\hat{\nu} \cdot m_s) = \hat{F}(\hat{\nu}) \cdot m_s \]

Thus, for *any initial conditions* of \((\hat{S}, \hat{R})\) we can initialize \((S, R)\) to match its trajectories. And also (another theorem), for *any rates* of \((\hat{S}, \hat{R})\) we can choose rates of \((S, R)\) that lead to emulation.

\( F \) is the differential system of \((S, R)\), given by the law of mass action, \( \hat{\nu} \) is a state of \((\hat{S}, \hat{R})\), \( \varphi \) is the stoichiometric matrix and \( \rho \) is the related reactant matrix. \( m_s \) and \( m_r \) are the characteristic 0-1 matrices of the morphism maps \( m_s \) (on species) and \( m_r \) (on reactions). Homomorphism implies reactant morphism.
$\mathcal{m} \in \text{MI} \rightarrow \text{AM}$ is an emulation:
it maps $z \rightarrow x$ and $\sim w \rightarrow x$

We can replace AM with MI in a context. The mapping $\mathcal{m}$ tells us how to wire MI to obtain an overall emulation:

Each influence crossing the dashed lines into $x$ is replaced by a similar influence into both $z$ and $\sim w$. The latter is the same as an opposite influence into $w$ (shown).

Each influence crossing the dashed lines out of $x$ is replaced by a similar influence from the same side of either $z$ or $\sim w$. The latter is the same as a similar influence from the opposite side of $w$ (shown), and the same as an opposite influence from the same side of $w$. 
Nature likes a good algorithm

The cell cycle switch can exactly emulate Approximate Majority