Computational Modeling of Gene Networks

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Introduction

- Gene expression regulation can be modeled as a network
- Connectivity and kinetics matter
- Artificial gene networks can perform a number of desired functions
  - Oscillator
  - Toggle switch
  - Logic Gates
- Due to time and expense of in vivo experiments, computational modeling a valuable tool

In vivo Synthesis of a NAND gate


Modeling Stochastic Systems

- Biological level: deterministic kinetics break down at low concentrations
- More accurate: stochastic kinetics
  - Based on the probability a reaction occurring or not
- Stochastic model reduces to deterministic solutions at thermodynamic limit
- Unless system is very simple, probability function cannot be solved analytically
- Gillespie algorithm provides solutions to stochastic systems
  - Yields exact solutions, but slow and computationally costly
  - Use Hybrid algorithms
    - Combines both stochastic and deterministic methods, choosing the appropriate method based on the system’s current conditions

Model Assumptions

- Cell is a homogenous, well-stirred medium
- Simulations were run over 100,000s
- Cell volume: $1 \times 10^{-15}$L, division every 30+ min
- Per cell: 270 RNA polymerases, 900 ribosomes
- 1 promoter, 1 operator per gene
- All other species set initially to zero
- Excess inducers, when added
- Kinetic constants estimated from literature

Results

- GFP Expression - no induction - averaged over 100 trials
- GFP Expression - IPTG only - averaged over 100 trials
- GFP Expression - with aTc only - averaged over 100 trials
- GFP Expression - both IPTG and aTc - averaged over 100 trials

Conclusions

- A few differences in relative intensities
- Possible explanations
  - Stochastic nature of simulations, need more trials
  - In vivo vs. isolated system
  - Kinetic constants
    - Current model: symmetric, order-of-magnitude estimates
    - Overall, results consistent with in vivo genetic network logic circuit
    - Motivates need to continue studying gene networks
  - Other topologies
  - Other operons

References