

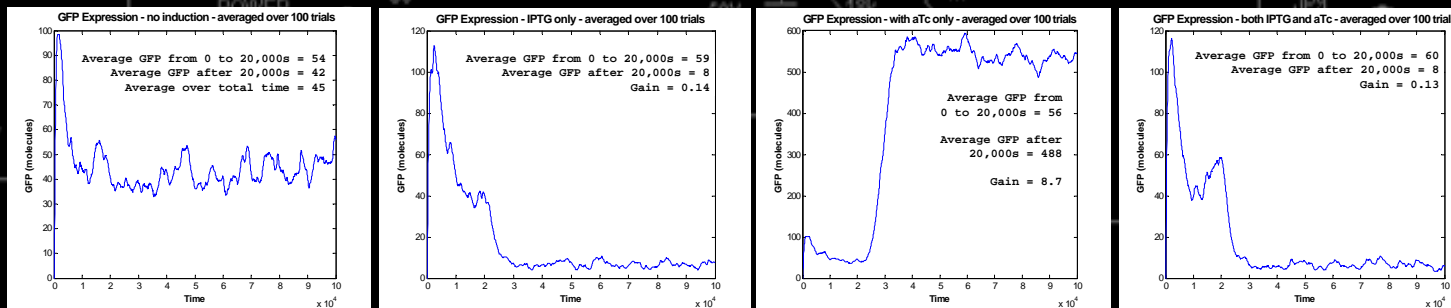
Computational Modeling of Gene Networks

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Introduction

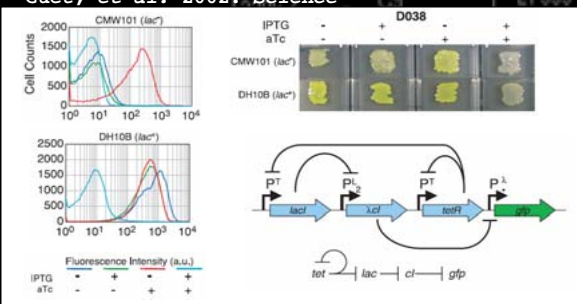
- Gene expression regulation can be modeled as a network
- Connectivity and kinetics matter
- Artificial gene networks can perform a number of desired functions
 - Oscillator
 - Toggle switch
 - Logic Gates
- Due to time and expense of *in vivo* experiments, computational modeling a valuable tool

Results



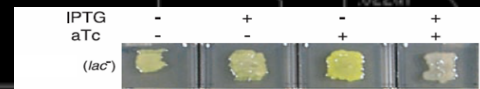
In vivo Synthesis of a NAND gate

Guet, et al. 2002, Science



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



Guet's results

IPTG	-	+	-	+
aTc	-	-	+	+
Relative intensity	50	10	600	10

Our results

- What is the relationship between network topology and displayed phenotypes?
- Can behavior of a genetic logic circuit be predicted?

Our project

- Computationally model a gene network that displays logic-gate-like behavior



- Are results consistent with experiment?
- What happens if we alter our model?

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 ± 4 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

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
 - Optimization of networks

References

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