Analyzing Information Exchange in Engineered Molecular Communications Between Biological Cells

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Background

Communication in Nature
- Biological cells naturally perceive, elaborate, and exchange information for adapting to specific environmental conditions, or to influence how other cells behave. [1]

Examples of Natural Prokaryotic Cell Signaling
- Formation of biofilms
- Launch of virulent attacks
- Conception of effective bioluminescence

Uses for Engineered Cell Signaling [2]
- Intelligent drug delivery
- Cancer treatment
- Bioremediation

Molecular Communication (MC)
- MC theory is a new paradigm in computer communications research, which studies information exchange at the nanoscale level. [3]
- The goal of MC research is to develop efficient methods of communication at the nanoscale level, however MC research currently lacks the tools for directing the transmission and reception of information-bearing molecules.

Synthetic Biology
- Successful experimental examples of cell-to-cell molecular communication have been demonstrated using tools from synthetic biology. [2]
- However, a clear theoretical foundation for the characterization of cell signaling systems has not yet been achieved.

Purpose

- This study uses novel abstractions from MC, tools from synthetic biology, and metrics from information theory to characterize an engineered cell signaling system in terms of communication performance and the system's dependence on design parameters.
- The communication performance of the LuxR-LuxI cell signaling system will be estimated in terms of:
  - Input upper bound
  - Output upper bound
  - Achievable information rate
- The aim of this characterization is to form the basis for information theoretic characterizations of cell signaling systems. Effective characterizations are an essential contribution to enable a forward engineering approach in cell communications.

Computational Model

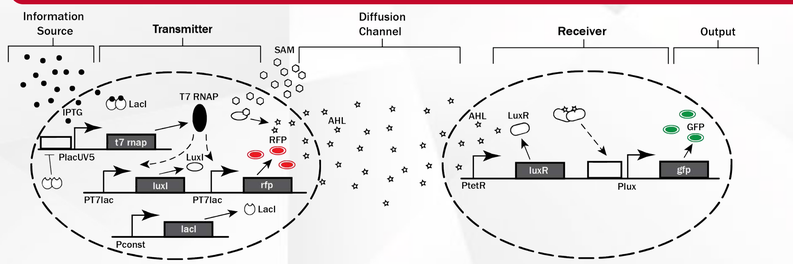

Figure 1. The LuxR-LuxI Cell-to-Cell Molecular Communication System.

Description of the LuxR-LuxI Cell Signaling System
- One of the very first engineered cell communication systems, the LuxR-LuxI quorum sensing circuit, has been adapted into a intercellular communication circuit that includes transmitter cells and receiver cells (**Figure 1**).

Transmitter
- Given a significantly high input of IPTG:
  - Repression of the T7lac promoters is inhibited by LacI-IPTG binding.
  - Both RFP and LuxI proteins are synthesized.
  - LuxI binds SAM molecules in the environment to synthesize signaling molecules (AHL).
  - AHL diffuses out of the transmitter cells and increases the concentration of AHL in the environment.

Receiver
- The luxR gene is constitutively expressed.
- AHL from the environment diffuses through the receiver cells' membrane and binds to LuxR.
- The LuxR-AHL complex dimerizes, binds to the operator region upstream of the lux promoter, and activates the expression of gfp, the receiver cell output.

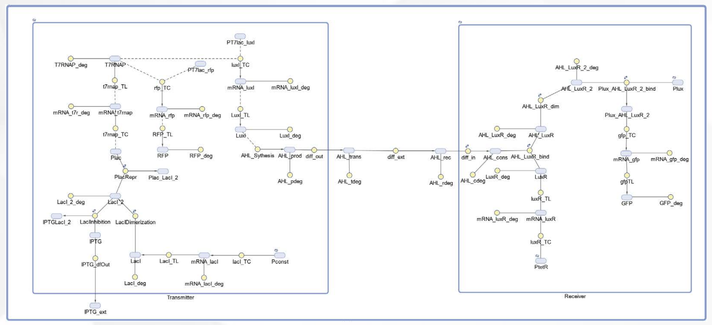

Figure 2. SimBiology Model of the LuxR-LuxI Cell Signaling Circuit

Computational Modeling
- Computational Chemical Kinetic (CCK) models were developed in SimBiology.
- Diffusion of the AHL signaling molecules out of the cell is modeled by mass action equations, while diffusion of AHL into the cells is dependent on the total cell density.

Preliminary Information Exchange Param's

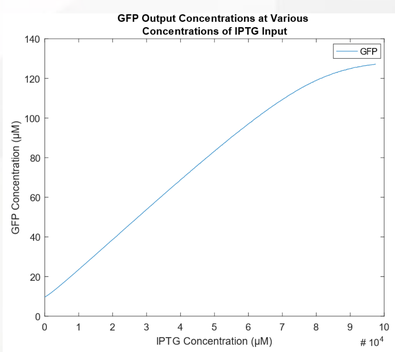

Figure 3. Receiver Cell Output (GFP) from the IPTG Input Range.

IPTG Input Range
The theoretical input range of IPTG to achieve gfp expression state change is estimated to be approximately
$0\ \mu M\ to\ 97,505\ \mu M$

GFP Output Range
The theoretical output range of gfp expression is estimated to be approximately
$9.67 \mu M\ to\ 128.40\ \mu M$

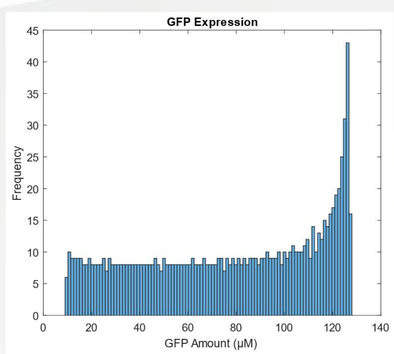

Figure 4. Frequency of GFP Expression Levels.

Conclusions

- Up until this point, reliable engineering of information exchange at the nanoscale level has been limited by the lack of methodology for characterizing cell signaling circuits in terms of communication performance and dependence on design parameters.
- This work took an interdisciplinary approach to form some of the necessary methodologies to develop an information theoretic characterization of MC systems.
- Despite biological complexity, this research suggests that a forward engineering approach to engineered MC systems is possible by using synthetic biology tools to direct the transmission and reception of information-bearing molecules.

Future Work

- Use wet-lab data to evaluate the differences between theoretical and experimental results.
- Optimize our *in silico* models based on wet-lab data.
- Analyze how noise effects the reliability of the system through stochastic simulations.
- Implement a population level model that takes into account cell growth, cell division, and diffusion based on cell density.
- Determine the entropy, mutual information, bits per symbol, and other capacity related metrics of the LuxR-LuxI cell signaling system.

Acknowledgements

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References

[1] D. L. Nelson and M. M. Cox, Lehninger Principles of Biochemistry, 4th ed. W.H. Freeman, 2005.

[2] S. Payne and L. You, "Engineered Cell-Cell Communication and Its ApplicaStions." Advances in biochemical engineering/biotechnology, 2013.

[3] I. F. Akyildiz, F. Brunetti, and C. Bl´azquez, "Nanonetworks: A new communication paradigm," Computer Networks, vol. 52, no. 12, pp. 2260–2279, 2008.

TelePathy: Telecommunication Systems Modeling and Engineering of Cell Communication Pathways (PI Dr. M. Pierobon, Co-PI Dr. N. R. Buan)
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