Research Interests

The 21st century is witnessing unprecedented advances in the understanding of biological systems at multiple levels, which range from sequencing of genomes to genome-wide profiling of gene expression, delineation of protein interaction networks and signaling networks, and detailed genetic and biochemical characterization of individual pathways and cellular components. This progress is providing the infrastructure for integrated understanding of cellular functions, which may unveil strategies to manipulate biological systems for applications in engineering and medicine. I have been addressing this challenge through two complementary approaches. My doctoral research with Prof John Yin at the University of Wisconsin focused on the application of mathematical modeling to study the dynamic behaviors of several biological systems at the cellular and genetic level. For my post-doctoral research with Prof. Frances Arnold at the California Institute of Technology, I have been designing and building *de novo* genetic circuits using well-characterized cellular components to explore biological "design principles".

In the future, I will extend from my past work and pursue a multi-disciplinary research program at the interface of engineering and biology. Specifically, I will build *de novo* gene circuits in *E. coli* to study design strategies of biological systems, by elucidating mechanisms of noise (stochastic fluctuations in gene expression levels) propagation in a gene network, by exploring strategies to effectively regulate noise, and by programming elementary developmental processes, such as cell differentiation and pattern formation. This work will serve several purposes. First, it will provide insights into how biological systems achieve reliable function despite internal and external perturbations. Second, it will generate well-defined model systems to address fundamental questions in developmental biology, ecology, and evolution. Third, it will produce well-characterized and portable genetic modules with potential applications in metabolic engineering, bio-computing, gene therapy, biopharmaceutical manufacturing, and development of novel biosensors. Complementing with the experimental work, I will develop mathematical models for well-characterized biological systems and for the *de novo* circuits that I plan to build. The computational work has primarily two roles. On the one hand, modeling of natural systems will provide insights into how these systems function and evolve, and reveal new strategies for re-engineering these networks to achieve desired functions and for constructing *de novo* gene circuits. On the other, modeling will facilitate my experimental work by testing and comparing different circuit designs, by suggesting appropriate genetic components, and guiding the fine-tuning of circuit function.

Research experience

Programming population dynamics by cell-to-cell communication

During my post-doctoral research, I am taking a combined approach of mathematical modeling and experimentation to construct gene circuits in *E. coli* with novel properties. Unlike other gene circuits built so far (3, 4, 7, 13), which have focused on behaviors of individual cells, my circuits couple intracellular gene expression with survival of the entire population. In particular, I program population dynamics by regulating expression of killer proteins using genetic modules from quorum sensing. Quorum sensing is a mechanism by which many bacteria synthesize, sense, and respond to small signaling molecules to achieve

cell-to-cell communication (12, 23) (also see proposed research). Coupled by signaling molecules, cells carrying these circuits will behave in a coordinated manner within a population. Thus the circuits are likely to resist noise (stochastic fluctuations) in gene expression and to achieve robust performance.

As a prototype example, I have designed, mathematically modeled, and experimentally constructed and characterized a population control circuit. Built upon a negative feedback loop, this circuit leads to regulated population density that resembles but differs from stationary phase bacterial growth (42) (also see Figure 1). Experimental measurement of the circuit function agrees well with modeling results. Successful construction of this circuit demonstrates the feasibility of constructing reliable self-regulatory circuits at the population level. It also lays down the conceptual foundation to program interactions among different cell populations — essentially creating "synthetic ecosystems" from well-characterized genetic modules. For example, by drawing inspiration from ecology, I have designed and analyzed by modeling a predator-prey system using quorum sensing modules to regulate death and survival of two interacting *E. coli* populations. With appropriate, biologically feasible kinetic parameters, this circuit generates stable oscillations in both population densities and gene expression levels (41). In addition to demonstrating the ability to program complex population behaviors, such synthetic ecosystems may serve as well-defined model systems to explore questions in ecology, evolution and engineering.

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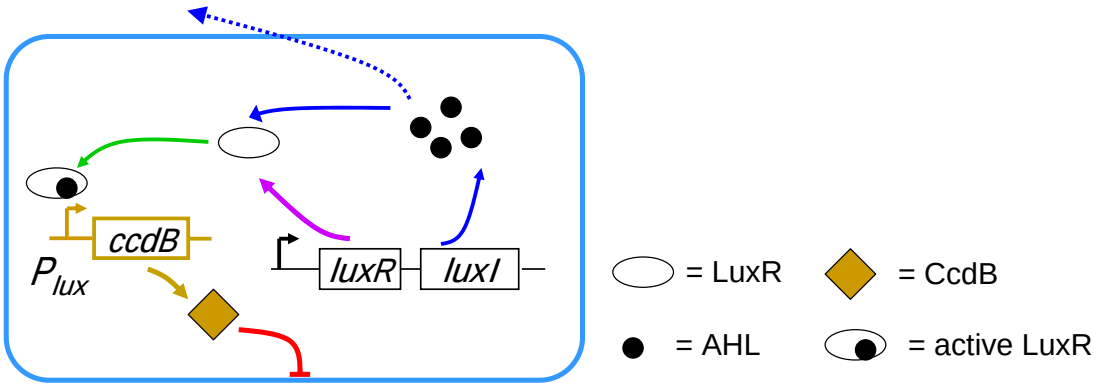

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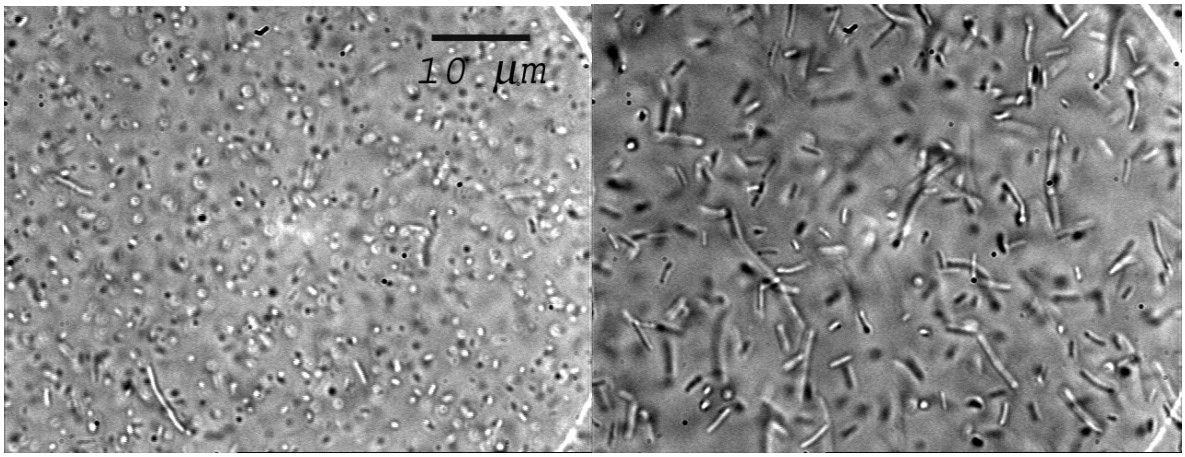

Figure 1. A population control circuit programs cell survival and death by broadcasting and sensing the current

population density. (A) Schematic diagram of the circuit. Once turned on, every cell constitutively produces LuxI, which synthesizes acyl-homoserine lactone (AHL), a small molecule that can freely diffuse into the environment. At sufficiently high cell density, intracellular AHL will accumulate to a concentration high enough to activate a transcription regulator LuxR, which in turn turns on a killer gene (ccdB), effecting a negative feedback on population growth. (B) Micrographs of cells with a population control circuit OFF (left panel) or ON (right panel). The cell density of the regulated population is noticeably lower than that of the unregulated population; many cells showed elongated phenotype due to the action of the killer protein (CcdB).

Simulating phage T7 growth

My Ph.D. thesis research focused on the simulation of the intracellular growth of bacteriophage T7, a lytic virus that infects the bacterium *E. coli*. Thanks to a rich knowledge base accumulated during the last four decades, phage T7 serves as an excellent genomic model system for exploring many fundamental and applied biological questions. The Yin group previously developed a genetically-structured simulation (9) to account for the major steps of T7 intracellular growth. I improved the simulation by recasting it in an object-oriented framework, which can be easily generalized to model other biological systems (10, 44, 48). I further extended it by incorporating a simple model to account for the host physiology, and by implementing a more mechanistic description of several steps of T7 infection. These extensions led to overall better agreement with the experiments in predicting T7 intracellular growth, and better computational performance (44, 49).

By using the T7 simulation, I explored two fundamental questions about T7: its design principles as a complex system and effects of environment on its growth. While these studies concentrated on T7, I believe that they can provide insight into general principles of molecular biology. I investigated how physiology of the *E. coli* host would affect T7 growth. The predicted dependence of T7 growth on *E. coli* growth rate agreed very well with the experimental data (44). This study may lead to a better understanding of the phage growth at sub-optimal conditions, such as those that exist in nature (19) and assist our evaluation of phage therapy strategies against antibiotic-resistant bacteria (5). It also highlighted the importance of environment for viral development. In collaboration with Dr. Drew Endy (MIT) and Prof. Ian Molineux (University of Texas-Austin), I used the simulation to predict the growth of T7 mutants with reordered genetic elements in their genomes in order to better understand fundamentally how genome rearrangements may affect virus growth. The simulation results qualitatively agreed with the experimental data (10, 49). Furthermore, I recently found that the growth environment might play a key role in the design of phage T7: its genomic structure and parameters seemed to have evolved to be nearly optimal for an environment with limited resources (47).

I also used the T7 simulation as a digital organism to explore questions that have broader implications. Thanks to the ease of using the simulation to create thousands of T7 mutants and to efficiently evaluate their fitness, I was able to systematically characterize the genetic interactions among deleterious mutations (46). Such genetic interactions play a major role in a variety of fundamental biological phenomena, such as the evolution of recombination, the dynamics of fitness landscapes, and the buffering of genetic variations, but their experimental characterization has been hindered by the difficulty in generating and quantifying a large number of mutants. Along another line of research, I developed an algorithm for inferring gene functions, and validated it by using the time-series data of mRNAs and proteins generated from the T7 simulation (48). Such algorithms are potentially useful for interpreting the large volume of data generated from high-throughput technologies such as DNA micro-arrays and protein 2D gel electrophoresis.

Besides the intracellular aspects of T7 growth, I studied the replication and spread of this virus at the population level – in a growing plaque –using a reaction-diffusion model (45). Such a study is important because the expansion of a viral plaque can serve as a probe of cellular activities (20) and can sustain a potentially broader distribution of mutants than well-mixed virus cultures (38, 39).

Developing *Dynetica* – a simulator of dynamic networks

Mathematical modeling and simulation may deepen our understanding of complex systems by testing the validity and consistency of experimental data and mechanisms, by generating experimentally testable hypotheses, and by providing new insight into the behaviors of these systems. However, the application of this integrated approach in biology has been hindered by the lack of software tools to build and analyze models, particularly for researchers unfamiliar with programming and numerical methods. To meet this need, I have developed *Dynetica* –a simulator of *dy*namic *net*works that exist in a wide range of time-scales and length-scales, including chemical and biochemical reaction networks, metabolic pathways, signaling pathways, genetic networks, and ecosystems (43).

Dynetica provides an integrated environment to model dynamic networks that can be formulated into a chemical reaction network. A distinguishing feature of *Dynetica* is that it facilitates easy construction and visualization of models for genetic networks. In addition, *Dynetica* provides users the flexibility of performing time-course simulations using deterministic or stochastic algorithms. Further, *Dynetica* presents a friendly graphic interface for the user to interactively create and modify a model, to conduct simulations and to monitor the simulation progress. Finally, since it is written in Java, *Dynetica* is platform-independent, thus allowing models to be run on most modern computers and easily shared among researchers. In all, by hiding the details of numerical algorithms and offering a powerful interface for model construction and visualization, *Dynetica* allows the user to focus on the model itself and its practical relevance rather than the technical aspects of computer simulation.

Future plans

It is well appreciated that intracellular gene expression is “noisy”; that is, in each cell, levels of gene expression are subject to significant stochastic fluctuations due to small numbers of interacting molecules (8, 25, 28). Yet Nature is amazingly successful in assembling noisy, imperfect components into robust biological systems that can accurately carry out their functions. The central goal of my future research is to better understand *how* Nature achieves this task, and to apply this understanding to build robust gene circuits with novel applications. Using simple yet non-trivial gene circuits, I will address fundamental questions such as: how does cellular noise propagate in a gene network? How are characteristics of cellular noise affected by various kinds of feedback regulation, and by cell-to-cell communication? At the next level, I would like to construct more sophisticated circuits to explore questions in cell differentiation and developmental pattern formation. Essentially, I will be using *E. coli* as a simulation platform to gain insights into biological system design and control. I envision that my research will produce well-defined cellular components and genetic modules that have potential applications in biotechnology and medicine.

Complementing with the experiment, I will analyze the dynamic behaviors of the *de*

novo circuits and experimentally well-characterized quorum sensing systems by mathematical modeling. On the one hand, the modeling work will facilitate the experimental work by guiding the experimental design, and by revealing "design principles" employed in natural systems. On the other, by focusing on well-characterized systems and emphasizing a strong tie between computation and experimentation, I plan to systematically examine the advantages and limitations of various modeling approaches.

Specifically, my future work will focus on several interconnected projects, which involve application of both experimental and computational techniques.

I. Characterizing noise propagation in gene networks

To understand how to regulate noise in a biological system, it is crucial to first understand the nature of noise and how cellular noise propagates in a genetic network. Recent experimental work has provided insights into the origin and nature of noise in gene expression (8, 25). However, characteristics of noise propagation have yet to be investigated despite their importance for designing reliable gene circuits or re-engineering existing systems. For example, a gene circuit may become non-functional simply because noise in gene expression is amplified from one stage of the network to the next, making the final circuit output completely unpredictable. Yet in other cases (e.g. cell differentiation), noise amplification may be exploited to generate phenotypic diversity (28).

For my future research, I would like to explore how noise propagates in a gene network, such as a cascaded gene expression pathway shown in Figure 2. In this simple transcriptional activation pathway, A, B, and C are transcription regulatory genes. The protein product of gene A activates expression of gene B by binding to its promoter, whose protein product subsequently activates expression of C. Expression of these genes will be monitored by measuring levels of different fluorescent proteins co-expressed with them using a flow cytometer or a fluorescent microscope. The noise in the expression of each gene can be approximately characterized as the distribution of the corresponding protein level in individual cells across the population.

A basic question I would like to ask is how do the expression patterns of A, B, and C differ? Moreover, does noise in gene expression amplify as we move downstream of the cascade? How does the expression noise depend on various parameters underlying the function of this network, such as promoter strengths, ribosome binding site strengths, and protein stability? If there is feedback control (for example, suppose protein product of B inhibits expression of A, or there is self-regulation at each stage of the cascade), how will it affect noise characteristics at different stages? Answers to these questions will lay down the empirical foundation for designing robust gene circuits.

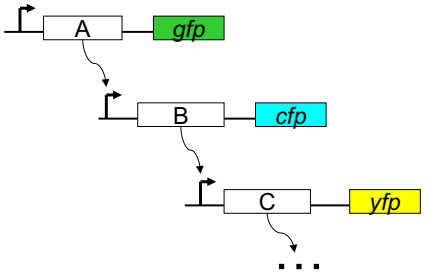

Figure 2. Measuring expression noise at different stages of a simple genetic pathway. In this pathway, constitutively expressed A activates expression of B, which activates that of C. Expression level of each gene is to be monitored by measuring fluorescent proteins (*gfp*, *cfp*, and *yfp* represent genes for green, cyan, and yellow fluorescent proteins) co-expressed with A, B, or C.

II. Regulating cellular noise by cell-cell communication

To achieve reliable function using components that are noisy and inaccurate at the single cell level, biological systems must effectively regulate the function of these components. Decades of work in developmental biology has revealed very sophisticated regulatory networks that dictate the precise programming of development processes (for example, see (6). It has been long recognized that feedback control is one of the key mechanisms for gene regulation. Extensive studies, mostly theoretical ones, have explored the potential regulation properties and biological implications of various feedback control schemes, in terms of their kinetic features and ability to resist parametric perturbations (29-33). In engineering, feedback control has been elegantly exploited to enhance metabolite production rates while reducing the negative impact by metabolic imbalance (11). Using a synthetic gene circuit, a recent study demonstrates that negative feedback can reduce noise in gene expression (4).

In addition to feedback control, cell-to-cell communication (as in bacterial quorum sensing systems) may also be important for noise regulation. Theoretical work has suggested that synchronization by cell-to-cell communication is crucial for the proper function of many rhythmic processes in physiology, despite intrinsic or extrinsic perturbations (16). My post-doctoral research indicates that cell-to-cell communication can indeed serve as an internal synchronization factor and facilitates robust circuit performance. However, the potential role of cell-to-cell communication for regulating intracellular noise has been under-appreciated to date, and has yet to be studied in depth. In my future research, I will address this challenge using well-characterized quorum sensing modules. One approach, for example, is to directly compare expression patterns of a reporter gene, such as *gfp*, regulated by a quorum sensing module and that regulated by a non-quorum sensing transcription activator (Figure 3). Comparison of expression patterns of *gfp* from these two systems, measured at the single cell level, using a flow cytometer or a fluorescent microscope, will offer insights into the timing and strength of expression from a quorum sensing module and its effectiveness in reducing noise. These constructs can be further augmented with feedback control to investigate noise regulation with more sophisticated strategies.

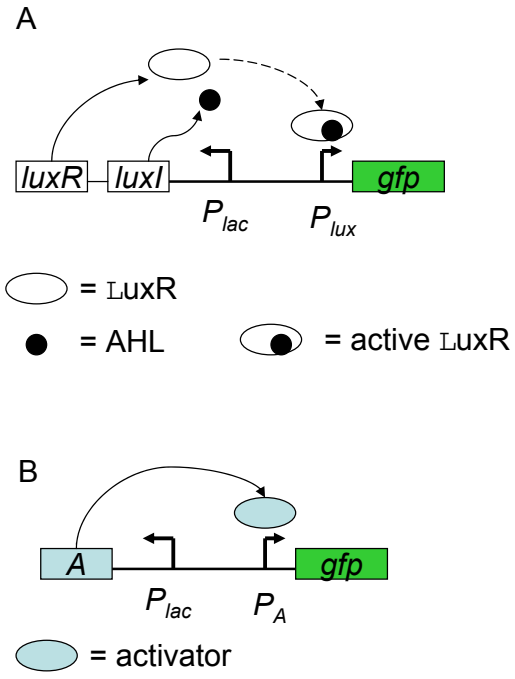

Figure 3. Testing the role of noise regulation by cell-to-cell communication. In (A), GFP expression is to be activated by the *luxI/luxR* quorum sensing system. The transcriptional activator LuxR is activated by a small chemical (AHL, or acyl-homoserine lactone) that is produced from LuxI, and accumulates only when population density is high enough due to its free diffusion across cell membrane. In other words, GFP expression is regulated by population growth, and will only occur when the population density is high enough. In (B), GFP expression will be turned on by an activator that does not require a small molecule to activate.

III. Programming differentiation and pattern formation in *E. coli*

A fundamental question in developmental biology is how the genetic information encoded in a fertilized egg programs the complex processes that eventually lead to the formation of an adult body. I plan to address this question by taking a bottom-up approach, complementary to the top-down approach traditionally taken for the study of developmental processes. In particular, I will investigate design principles of developmental circuitry by building gene circuits to mimic two elementary developmental processes – differentiation and pattern formation. I will seek answers to two basic questions: what is the minimal mechanism that can realize such developmental processes? What additional elements or regulatory structures are needed to achieve robust behaviors? I believe lessons learned by constructing and testing such simple yet non-trivial systems can provide insights into how real developmental processes work. From an engineering perspective, this research will reveal strategies to program populations of cells for robust and reliable behaviors, and enable the development of novel biosensors.

To program differentiation, I will use genetic elements from quorum sensing to implement a "toggle-switch" that responds to changes in the population density (Figure 3). The output of the circuit can be monitored by using fluorescent proteins as the reporter. Past work has shown that circuits with this logic can demonstrate bi-stable behavior with appropriate parameters, with each cell "locked-up" in primarily producing one of the repressors (and, consequently, one of the fluorescent proteins). It will be interesting to explore how the function of the circuit is similar to or different from the toggle switch acting in a single cell. And how does quorum sensing affect performance of the circuit in terms of robustness? If the circuit indeed demonstrates bi-stable function, it may result in three possible outcomes: it may randomly turn some cells green yet others red; it may also predominately turn the population into only one of two colors. It will be intriguing to explore how the circuit outcome will depend on changes in circuit parameters. In the long term, I plan to couple these circuits to survival or death of subpopulations. This will provide an synthesized model systems to study programmed cell death, an important component of eukaryotic developmental processes (22).

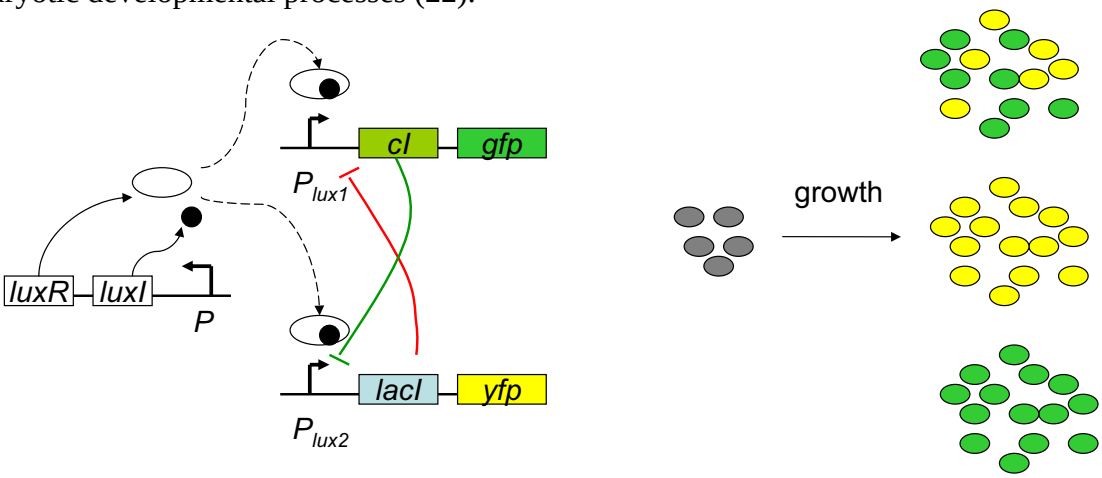

Figure 4. A population-level "toggle switch" that can realize differentiation of *E. coli* cells into subpopulations. In this circuit, *luxR* and *luxI* genes will be placed under the control of a constitutive promoter. Two repressor genes (*cI* and *lacI*) are placed under modified *lux* promoters incorporating the binding sites for these repressors, so that expression of *cI* protein will turn off expression of *lacI*, and vice versa. The output of the circuit is

production of fluorescent proteins reporting the state of each cell. This circuit shares the basic logic of the toggle switch designed by Garner et. al, but it will act at the population level, in response to population density changes. The panel on the right shows three possible outcome of the circuit as a population grows.

To program pattern formation, I will draw inspiration from the large body of theoretical research pioneered by Alan Turing, who 50 years ago proposed an elegant reaction-diffusion model to explain pattern formation during development (37) (Figure 5A). The Turing model involves the interactions between two substances, an activator (A) and an inhibitor (I). The activator activates its own synthesis and that of the inhibitor, whereas the inhibitor inhibits production of both. If the inhibitor diffuses faster than the activator, stable waves of activator concentrations will be generated, resulting in periodic spatial patterns. Since its appearance, the Turing model, as well as its many variants, has been used to simulate patterning of slime molds, spatial distribution of ant colonies, the polar organization of the limb, and pigment patterns of mammals, fish, and snails.

While past work has focused on explaining patterns existing in Nature or generating interesting patterns in the computer, I believe it is equally intriguing and important to explore whether such pattern formation can indeed be realized from scratch in the lab, by implementing *de novo* gene circuits. For example, the basic logic of the Turing model can be realized using a gene circuit shown in Figure 5B. In this circuit, the quorum sensing signal serves as the diffusive inhibitor, whereas a transcription activator (A) serves as the activator. The system output can be monitored using a reporter gene, such as *gfp*. Because the quorum sensing signal has greater diffusivity than proteins, the condition for generating stable patterns is satisfied. According to predictions from the Turing model (if it is correct), this system should be able to generate spatial patterns in terms of GFP levels with appropriate kinetic parameters. I will use this system to address several questions: Can spatial patterns indeed emerge from a homogeneous initial state? If so, are these patterns stable? How do they depend on various kinetic parameters characterizing individual components? In addition to addressing questions in developmental biology, I envision that this system will also serve as a well-defined experimental system to explore broader questions in self-organization and complexity, and novel modes of computation technologies.

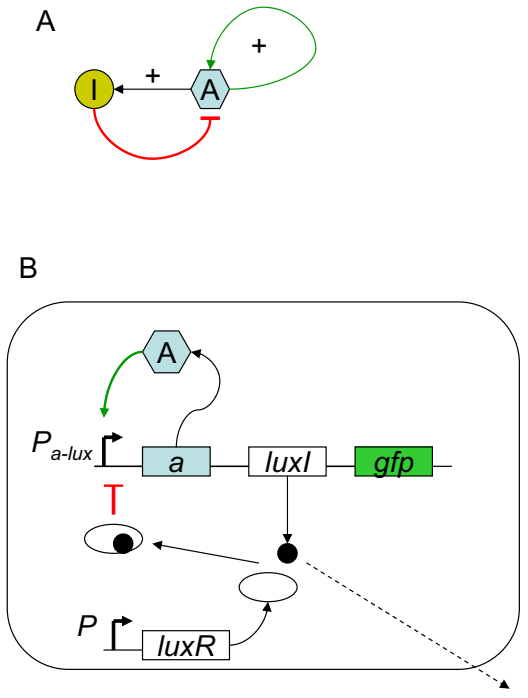

Figure 5. Programming pattern formation in *E. coli*. (A) The basic logic of the Turing model. The activator (A) activates its own synthesis and that of its inhibitor (I). If I diffuses faster than A, this system can generate stable spatial patterns in terms concentrations of these substances. (B) A genetic circuit that can realize the Turing model. A is a transcription activator that promotes its own expression and that of *luxI* via an engineered promoter ($P_{a\text{-}lux}$), which can be activated by A but inhibited by active LuxR. The signaling molecule (AHL) synthesized by LuxI protein can activate LuxR, which is constitutively expressed from promoter P. The active LuxR will in turn inhibit synthesis of both A and LuxI by binding to the promoter $P_{a\text{-}lux}$, effecting negative regulation shown in (A). Note that AHL serves as the diffusive inhibitor I shown in (A). Symbols are as in Figure 3 unless otherwise noted.

Successful construction of these circuits requires the use of appropriate genetic elements. For example, it has been shown that for a toggle switch to work, the genetic elements must satisfy certain constraints (13). To this end, mathematical modeling will be useful for determining the constraints for selecting genetic elements. However, the design goal of a circuit may sometimes pose constraints that existing components do not satisfy. In this case, I plan to fine-tune the kinetic parameters of individual components by directed evolution, a well-established technology for optimizing protein functions *in vitro* and *in vivo* (1, 2). Recent work has demonstrated the use of directed evolution to optimize a genetic inverter (40). I anticipate that a similar strategy of mutagenesis and screening may facilitate tuning of kinetic parameters to achieve desired behaviors and allow me to explore circuit function in different regions of the parameter space.

IV. Modeling synthetic and natural biological systems

1. *Modeling as a design tool*

Mathematical modeling will play a critical role in my future research. I will use modeling as a design tool for the *de novo* gene circuits proposed above. Modeling will serve to test and refine circuit design, to guide choice of cellular components and fine-tuning of circuit performance. Comparison of experimental results against modeling results will not only improve the understanding of how a circuit functions, but it may also improve estimation of parameters characterizing individual components. In some cases, I plan to model these gene circuits using both deterministic models based on ordinary differential equations (ODEs) and stochastic models that explicitly account for effects of small numbers of interacting molecules. This strategy will be particularly useful for projects studying mechanisms of noise propagation and regulation.

2. *Computational biology of quorum sensing (QS)*

I also plan to develop models for well-characterized bacterial quorum sensing (QS) systems. Study of quorum sensing has over the last couple of decades been established as an exciting new subdiscipline of microbiology. In addition to the LuxI/LuxR system from bacterium *V. fischeri*, more than two dozen other QS systems (all analogous to the LuxI/LuxR system) have been characterized in detail by biochemical, biophysical, and genetic approaches (23). Despite differences in their "implementation", these systems share a common basic logic: Individual bacterial cells synthesize a small molecule – a small chemical for gram-negative bacteria or a small peptide for gram-positive bacteria, which accumulates as the population density increases. When the concentration of the small molecule reaches a threshold, it will activate a transcription activator that will turn on expression of target genes responsible for diverse physiological functions, such as bioluminescence, production of antibiotics, biofilm development, and pathogenicity.

I will initially focus on a multilayered hierarchical QS system from bacterium *Pseudomonas aeruginosa*. *P. aeruginosa* is a gram-negative pathogenic bacterium that can infect a broad range of hosts, such as mammals (including human beings), insects, and plants (36). It has been found that two cascading QS systems, the LasI/LasR and RhlI/RhlR systems, play a key role in regulating expression of virulence genes. Because of its broad clinical implications, *P. aeruginosa* has been actively studied in recent years, and its genome has been sequenced (35). I anticipate that computational analysis of the two QS systems will lead to better understanding of their function and reveal novel targets for drug development.

The basic utility of my models is to explain experimental observations and to predict system behaviors under different conditions. By employing well-established computational techniques, such as parametric sensitivity analysis and bifurcation analysis, I will examine how quantitative and qualitative behaviors of these systems depend on kinetic parameters that characterize individual components and reactions. Modeling results may suggest new experiments for further elucidation of these QS systems. Moreover, they will highlight components key to the proper function of these systems. These components may represent potential drug targets in the case of *Pseudomonas aeruginosa.*

At the next level, I will employ modeling to investigate the biological significance of cell-to-cell communication for regulating cellular behaviors. In particular, I will analyze to what extent cell-to-cell communication may play a role in regulating cellular noise originating from individual cells. To address this question, I will take a multi-scale approach that will account for population-level behavior as well as the stochastic dynamics of intracellular gene expression. I anticipate using two methods to account for intracellular noise. Remaining in an ODE framework, the first entails adding a random term to every differential equation in the model to introduce random noise. This approach provides a straightforward means to assess how system dynamics may be altered by intrinsic and extrinsic noise (18, 28). Alternatively, I will use the Gillespie algorithm (14) to characterize random fluctuations due to small numbers of interacting molecules. Following a Monte Carlo procedure, the Gillespie algorithm predicts the time evolution of the system by determining when and in what order the next reaction is going to occur. This algorithm has a rigorous theoretical foundation, and is shown to give *exact* solution for a network of elementary reactions occurring in a well-stirred environment (14, 15). This project will complement with the work proposed in Project II and provide a theoretic foundation for designing robust circuits based on cell-to-cell communication.

A longer-term goal of my modeling research is to identify and characterize cellular modules or regulatory motifs embedded in quorum systems. Many researchers have argued that biological systems consist of many conserved functional modules or motifs (17, 27), such as the lysis-lysogeny switch of bacteriophage λ (26) and various bacterial operons (21). Much progress has been made recently to identify cellular modules based on the topology of biochemical networks (24, 34). My focus will be on the functional properties of these modules. QS systems are advantageous for such work because all those characterized to date show clear modularity in terms of their genetic network structure. Specifically, I will extend from the model of the LasI/LasR-RhlI/RhlR system and develop models for other QS systems. Comparative studies on the structures and dynamics of these systems may then reveal key regulatory modules that are conserved. I envision that elucidation of cellular modules in QS systems may provide insights into the regulation by and evolution of cell-to-cell communication, and suggest novel strategies for constructing useful *de novo* gene circuits.

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Teaching Interests

A primary function of a university is to provide its students with the best education that it can offer, and I look forward to participating in this education process. Because of my training and research experience in Chemical Engineering, Molecular Biology, Computational Biology, and software development, I will enjoy teaching many undergraduate and graduate courses offered by the Biocomplexity program. These courses will include Chemical Reaction Kinetics, Thermodynamics, Transport phenomena, Mathematical Biology, Computational Biology, Numerical/Computational Methods, and Computer Modeling of Biological Systems. I am particularly interested in developing and teaching a course to cover topics in engineering design or modification of biological systems guided by mathematical modeling and computer simulation. Aimed towards senior undergraduate students and graduate students, this course will review the application of engineering principles in kinetics, thermodynamics, and transport phenomena to better understanding of natural biological systems or designing novel systems using cellular components.

I served as a teaching assistant for two undergraduate courses (*Biochemical Engineering* and *Thermodynamics of Mixtures*) at the University of Wisconsin-Madison. My responsibilities involved leading discussion sessions, answering questions, preparing homework or exam questions and solutions, and grading. I completely dedicated myself to these tasks and made sure that my students received the best education I could offer. Also, I used TA evaluations to get feedback from students and advisors, and improved my teaching skills based on the feedback. Because of my services, I was nominated by the students, along with five other TAs, as one of the best TAs in the Chemical Engineering department in the fall semester of year 2000.

At the California Institute of Technology, I had the opportunity to give two lectures (*Noise in Biological Systems* and *Synthetic Ecosystems*) for a graduate course, *Introduction to the Design of Biological Molecules and Systems*. The first lecture dealt with implications of stochastic processes in biology, and strategies to characterize them computationally and experimentally. The second surveyed computational and experimental techniques for the design and construction of *de novo* gene circuits to program population dynamics in bacteria. In preparing these lectures and the homework sets, I tried to convey the relevant concepts and techniques by illustrating their applications with specific examples from the literature or my own work. Both the lectures and the homework sets were well-received by the students.

In addition to classroom teaching, I had extensive supervising experience in the past three years. During my doctoral research, I mentored three undergraduate students. As a post-doctoral researcher, I have advised the research of two undergraduate students and two graduated students, including the thesis work of one of the undergraduates. I worked closely with these students by guiding them to incrementally solve problems, and sharing with them my knowledge and experience in doing research. In the meantime, I have learned how to divide a research project into relatively independent sub-projects that are challenging, yet small enough for each student to complete in a reasonable time frame.