CPS: Frontier: Collaborative Research: bioCPS for Engineering Living Cells

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Goal and Motivation

We aim to create a next-generation biological cyber-physical system (bioCPS) in which desired global behaviors can be achieved in populations of living cells through the identification and characterization of local behaviors. The ability to synthesize systems that control biological patterning could lead to advances in manufacturing, amorphous computing, tissue engineering, and drug development. For instance, differentiation of pluripotent stem cells in tissue or organoid engineering can be mapped to a pattern formation control problem.

To achieve this goal, we equip cells with sensing, communication, and decision making capabilities using methods from synthetic biology. Additionally, micron-scale mobile robots assist in optimizing the formation of patterns by affecting communication through opto-genetic triggering of genetic circuits or by moving cells and signals.

Workflow Summary

Our workflow involves five main steps. First, experimental data is collected and fed into an analysis method that creates **mathematical models** for biological modules and their compositions. Simultaneously, a desired pattern or behavior is defined by a user and is converted into a formal specification using **machine learning** techniques. Next, the biological modules are composed using a structural specification, and **design space exploration** is performed on their associated models using **simulation** and model checking to identify the design that best realizes the user-defined behavior. The selected design's behavior is then verified using **experimental design**. Finally, **microrobotics** are utilized in the physical system to aid in communication and sensing and to provide precise top-down control of cellular patterning.

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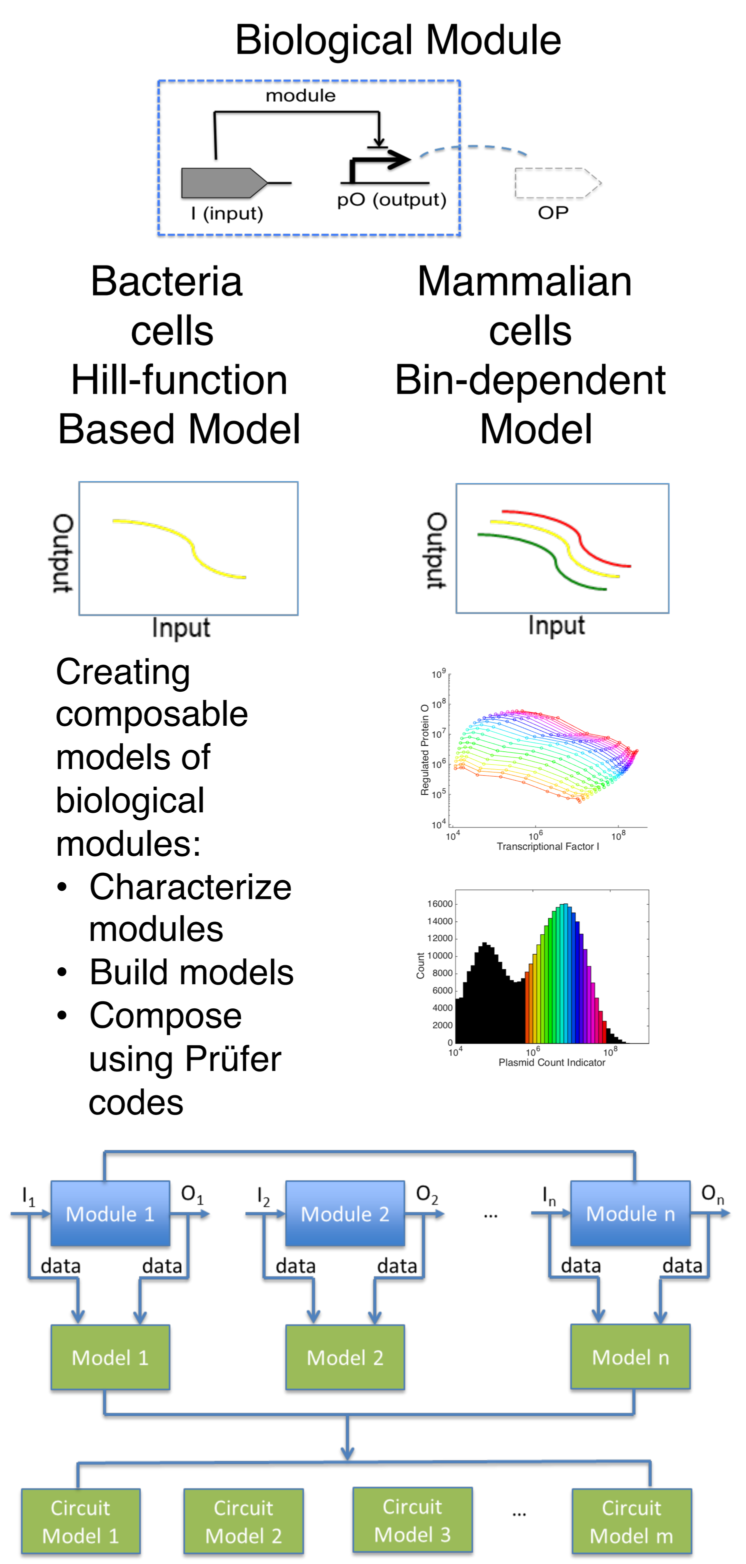
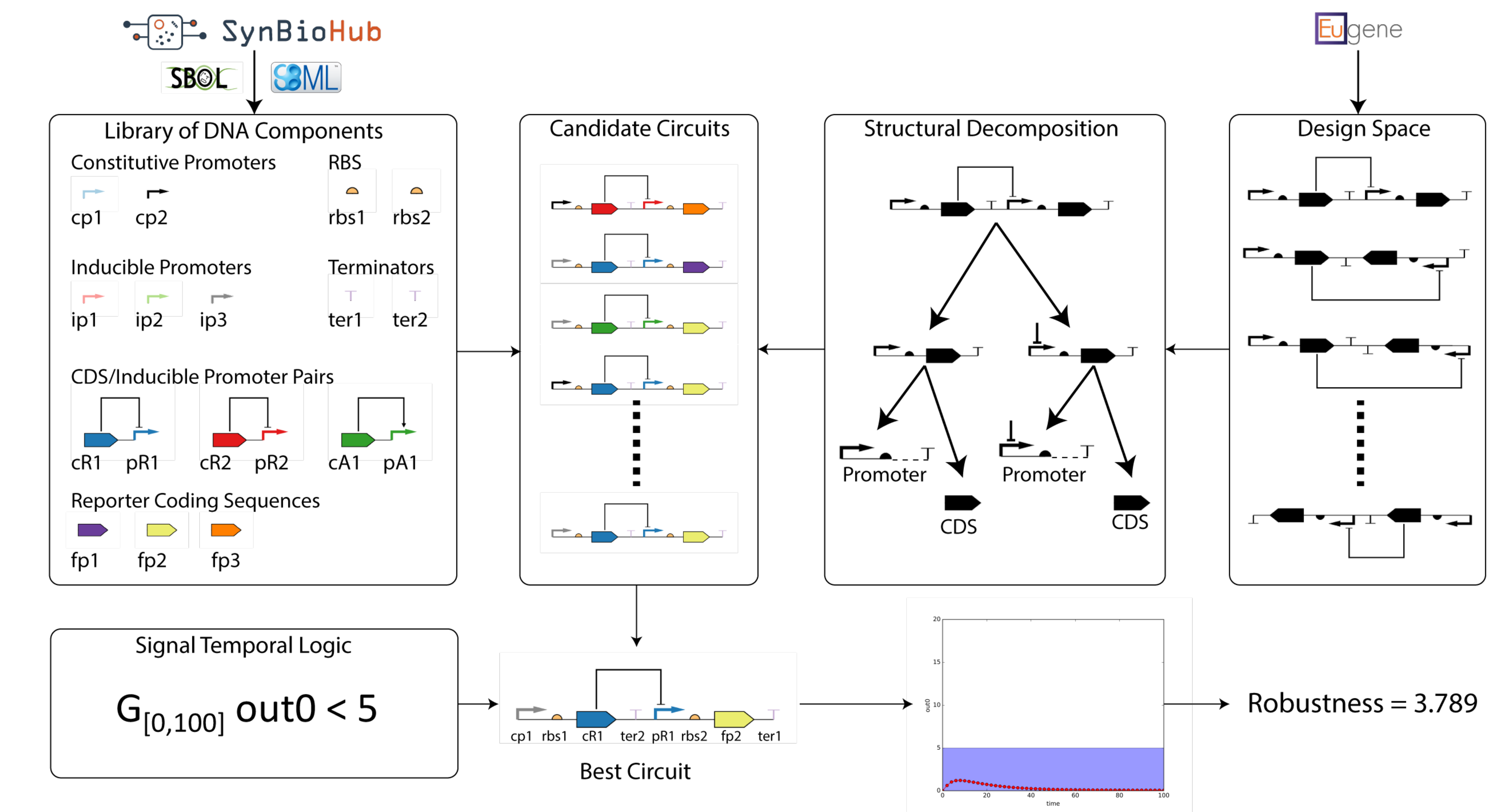
Workflow

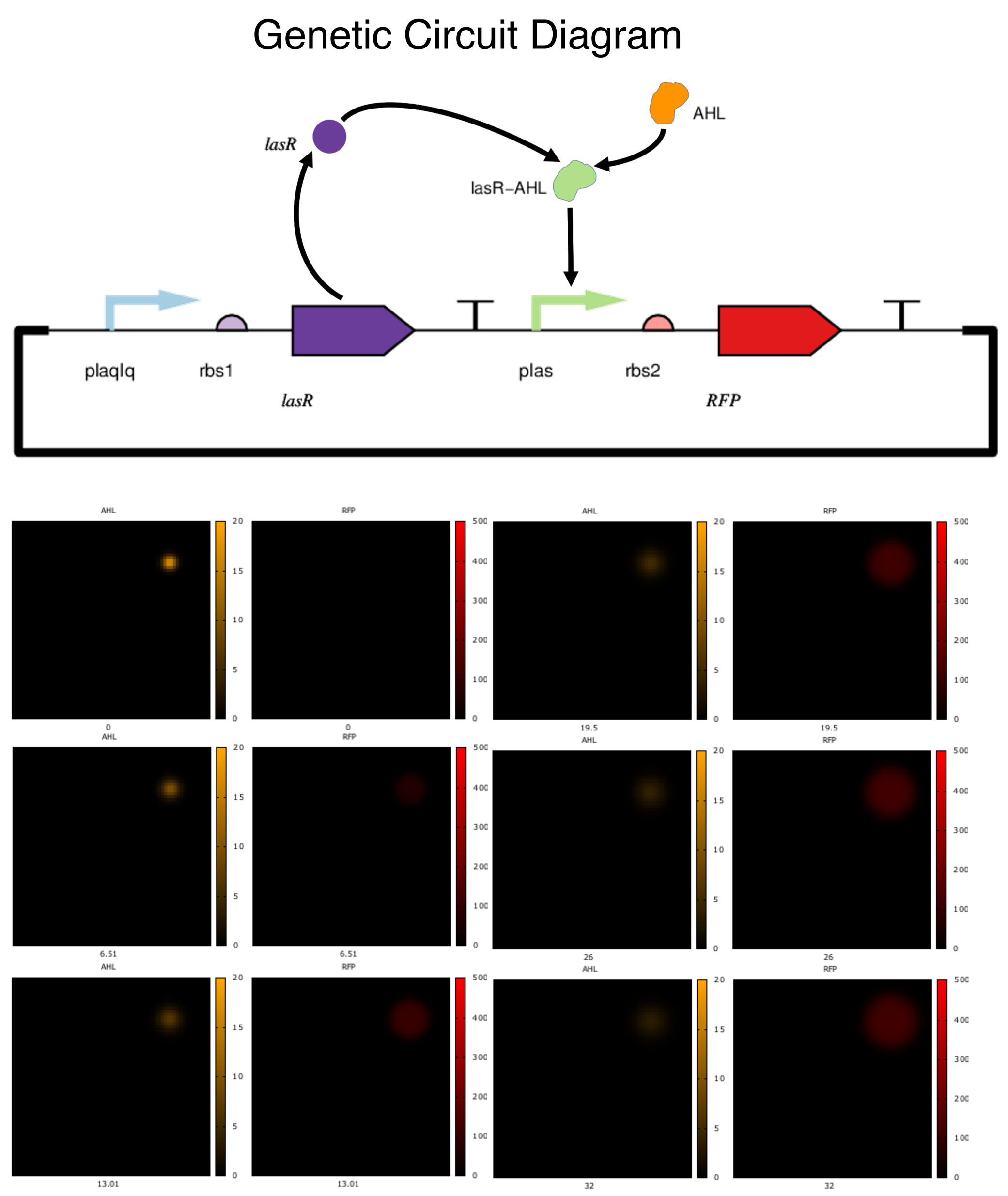
Modeling



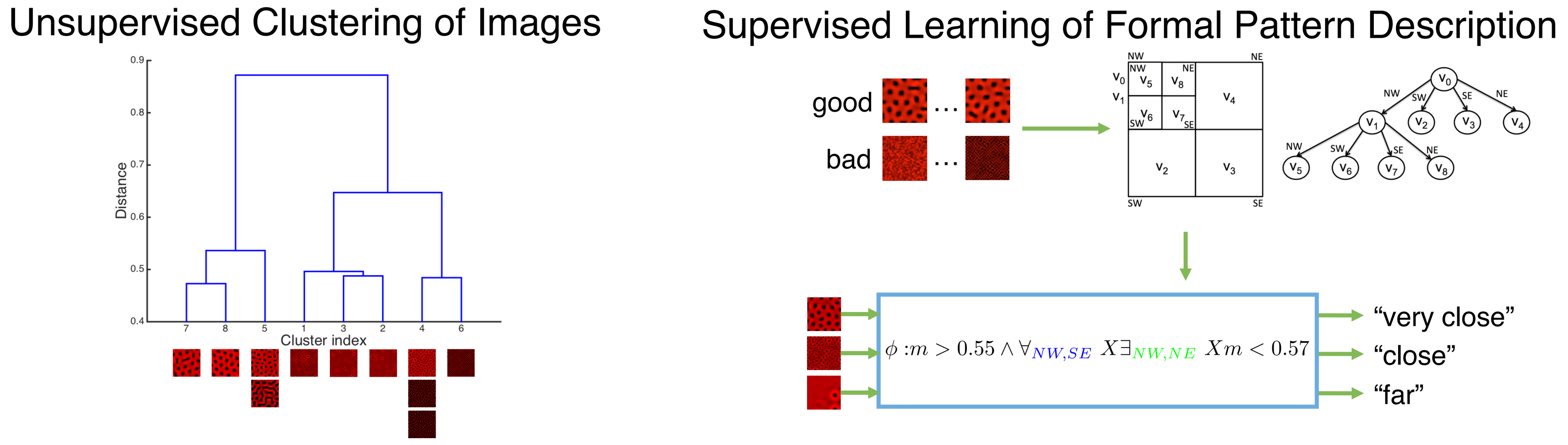
Design Space Exploration



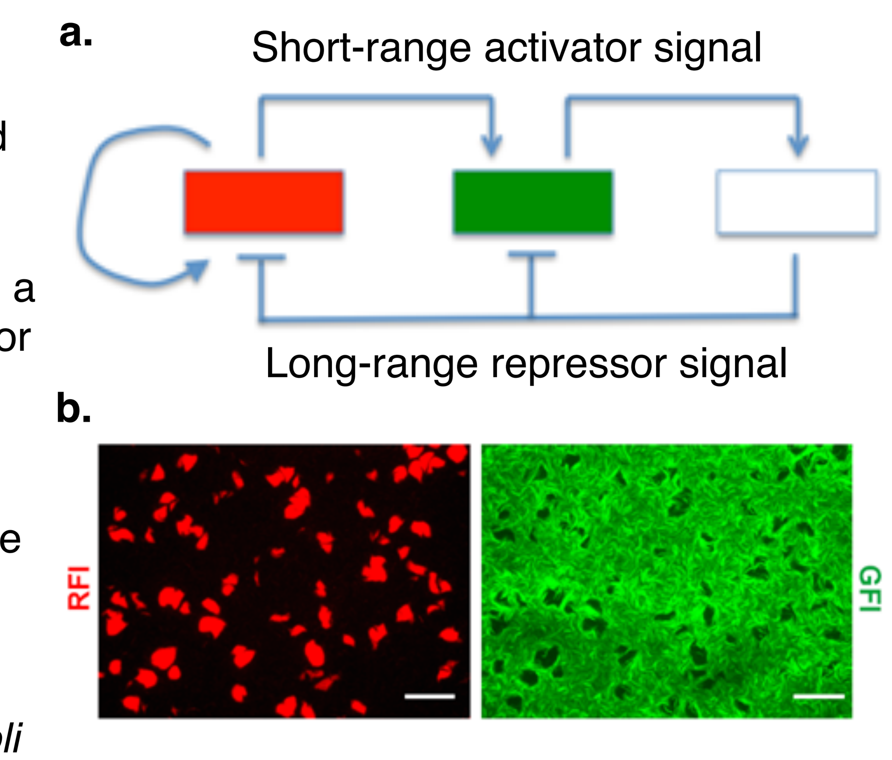
Multicellular Simulation



Learning Patterns

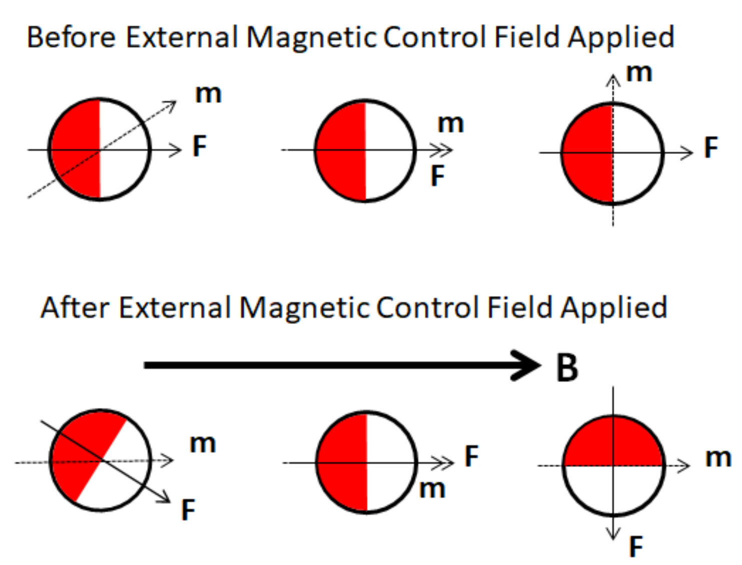


Experimental Design

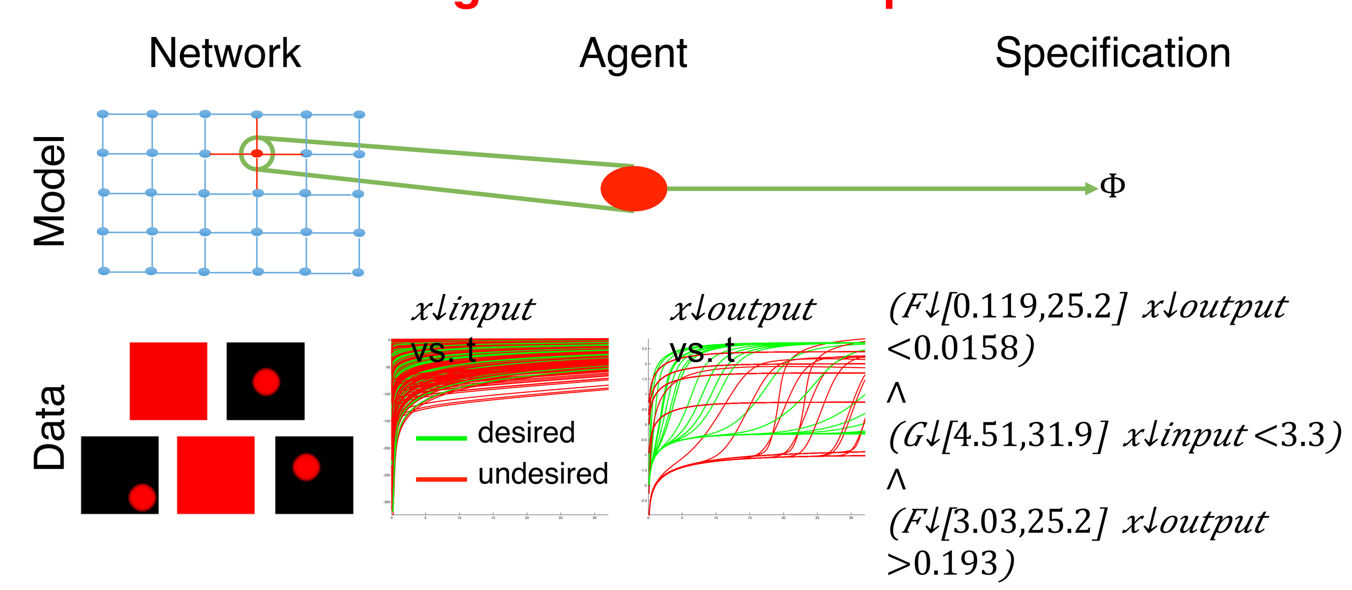


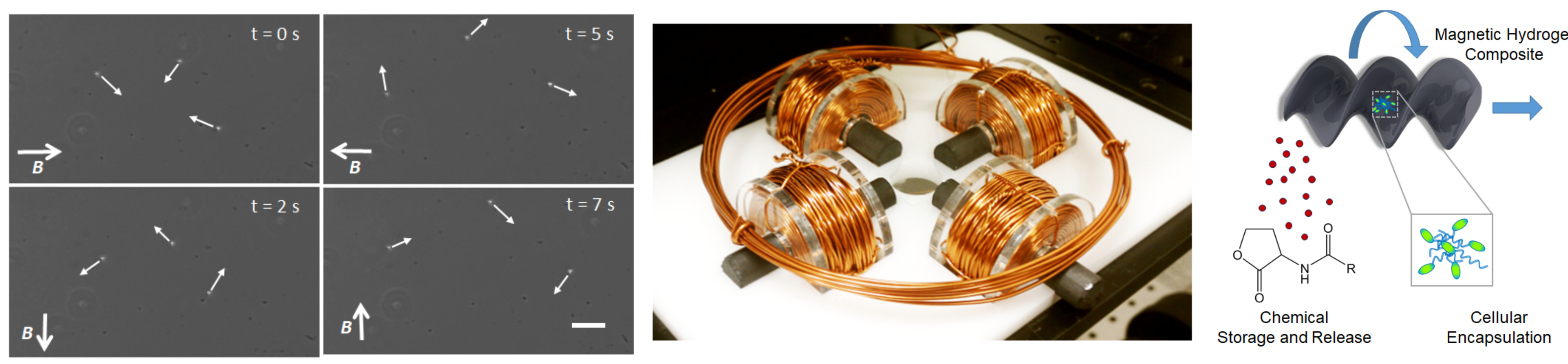
Traditional Turing reaction-diffusion patterns are formed by the combined action of a short-range activator and a long-range repressor (a). Appropriate tuning of biological and physical parameters can give rise to patterns in cell response, such as the micrographs of fluorescent *E. coli* in (b).

Microrobots



Learning Local Behavior Specifications





We explore microrobot-based cellular placement and actuation using magnetic manipulation (collaboration with SRI International). In this image, multiple microrobots are controlled in the same workplace by combining their magnetic actuation with catalytic motion. This is achieved through motion differentiation through the use of paramagnetic microrobots which assume different magnetizations in the same field. A catalytic cap helps regulate the direction of motion of the microrobot allowing for independent motion and steering control. Additionally, microrobots can be manufactured in helical structures, which are propelled via uniform rotating magnetic fields. This allows for the robot to "swim" through media spanning orders of magnitude in viscosities.

Biological Cyber-Physical Systems

Microrobots are used for communication, sensing, and control in cellular networks. They can:

- Carry sensor cells attached to a synthetic substrate,
- Control microscopic light patterns, and
- Manipulate individual cells.