CPS Frontier - Collaborative Research: bioCPS for Engineering Living Cells

Calin Belta[1] (Lead PI), Doug Densmore[1] (Co-PI), Vijay Kumar[2] (PI), Ron Weiss[3] (PI),
Demarcus Briers[1], Sambeeta Das[2], Nicholas DeLateur[3], Elizabeth Hunter[2], Rachael Ivison[1], Curtis Madsen[1],
Edward Steager[2], Brian Teague[3], Prashant Vaidyanathan[1], Cristian-Ioan Vasile[3], Junmin Wang[1]
[1]Boston University, [2]University of Pennsylvania, [3]Massachusetts Institute of Technology

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 six 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 models are characterized using the same formal language, and **design space exploration** is performed to identify the design that behaves as close to the user-defined behavior as possible. The selected design's behavior is then verified using a **multicellular simulation**. If the design is validated, then **modular DNA construction** techniques are used to synthesize the genetic circuit. 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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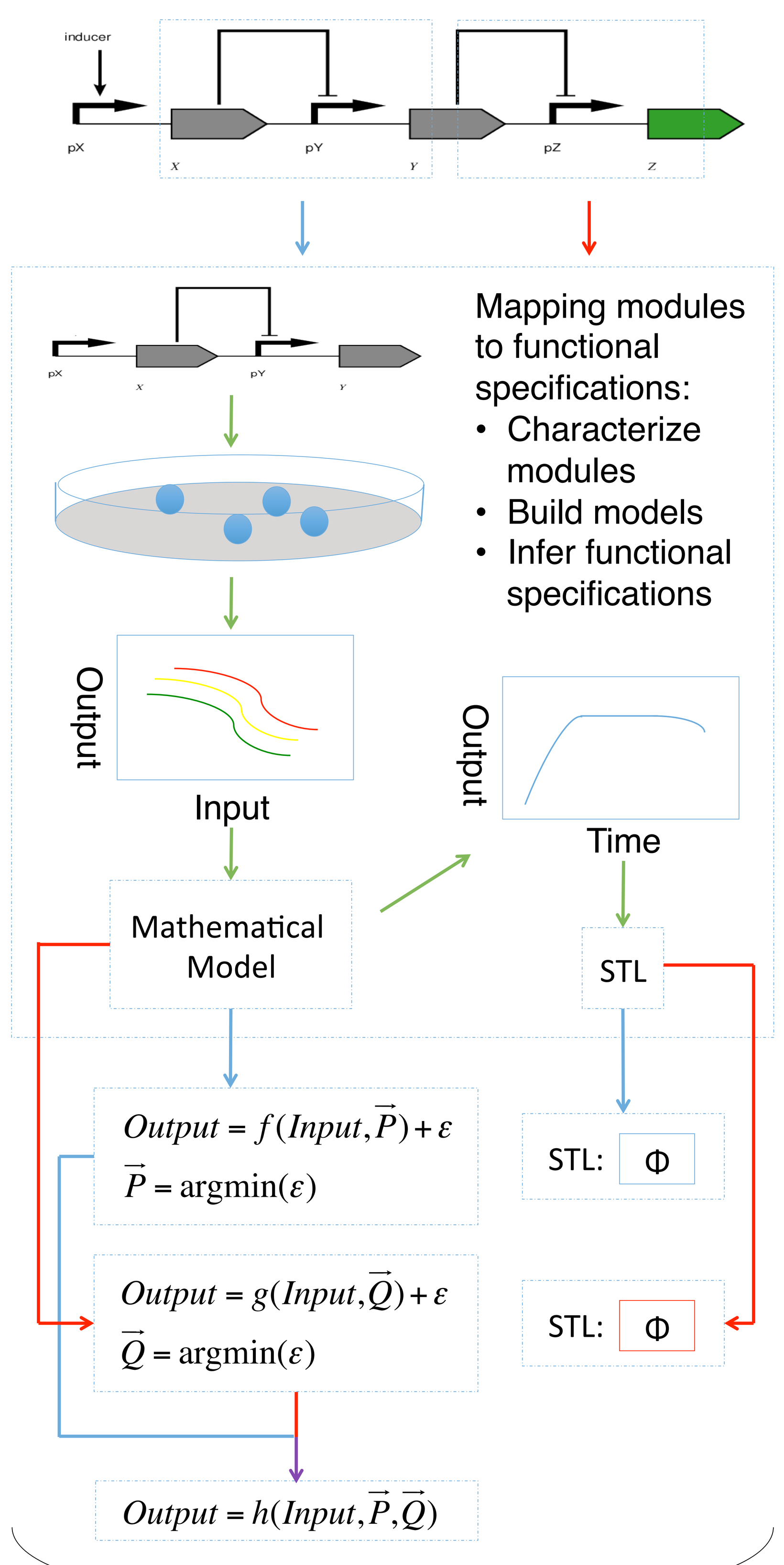
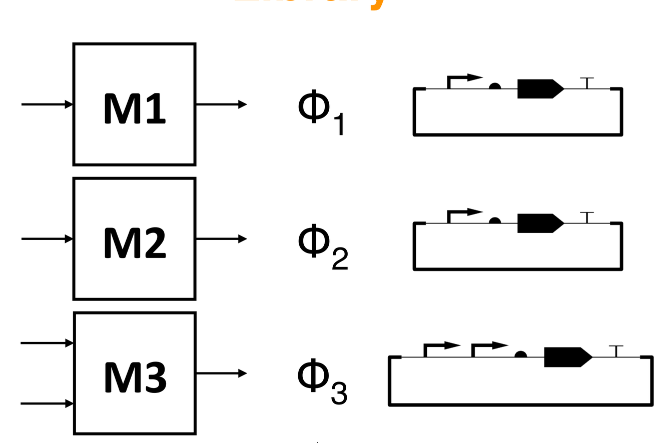
Workflow

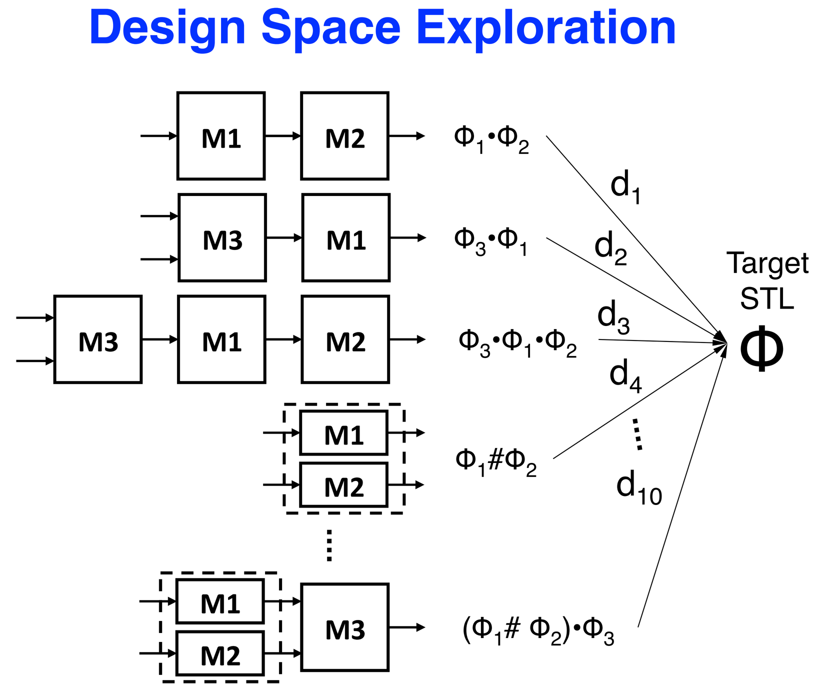
Modeling



Library



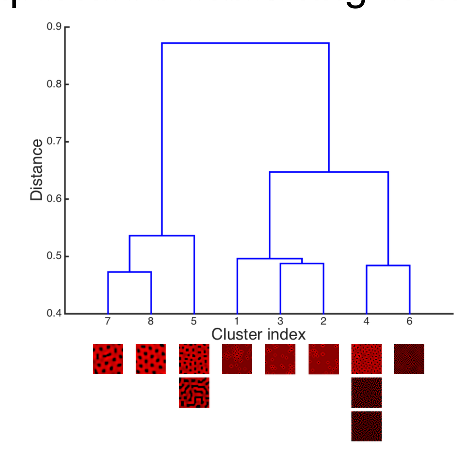
Design Space Exploration



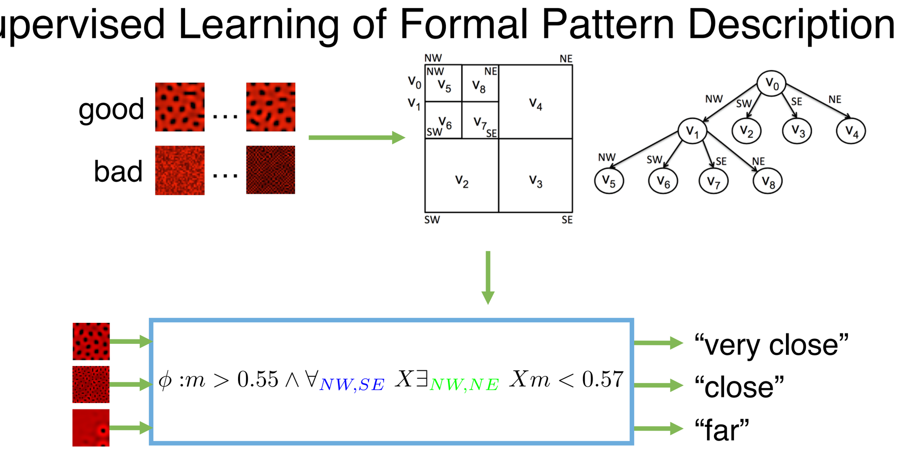
$min(d_1, d_2, d_3, d_4, d_5, d_6, d_7, d_8, d_9, d_{10}) = d_{10}$

Learning Patterns

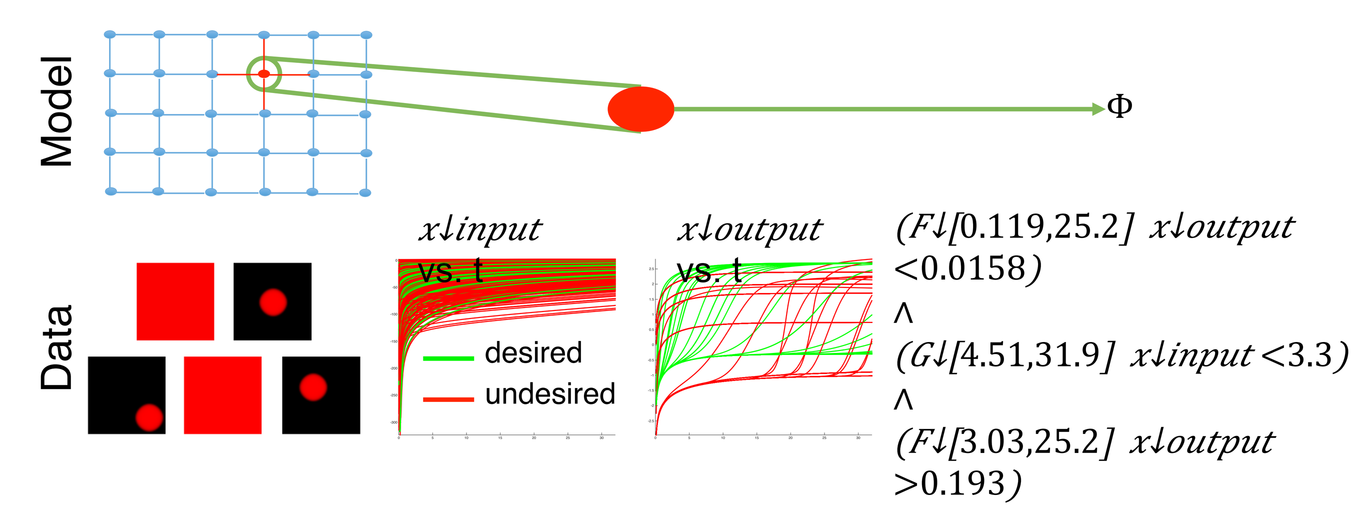
Unsupervised Clustering of Images



Supervised Learning of Formal Pattern Description



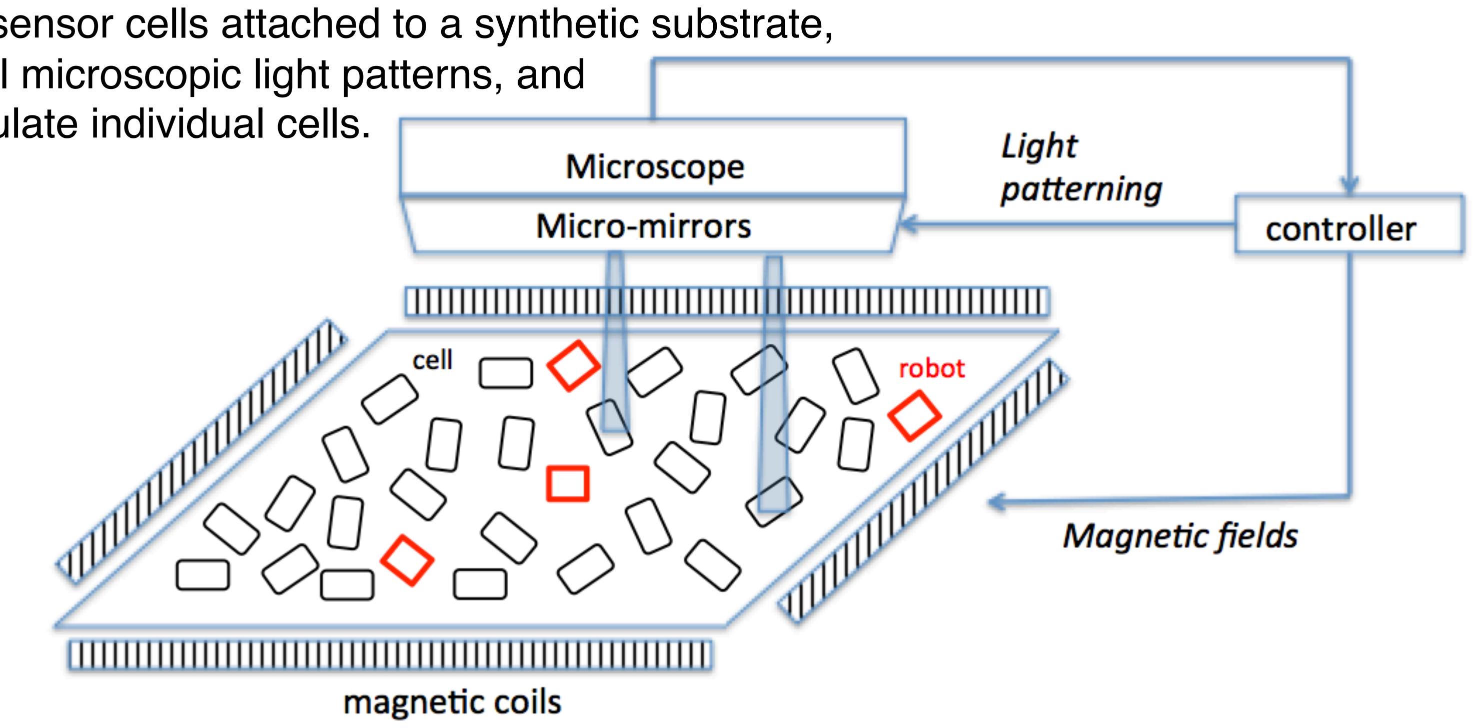
Learning Local Behavior Specifications

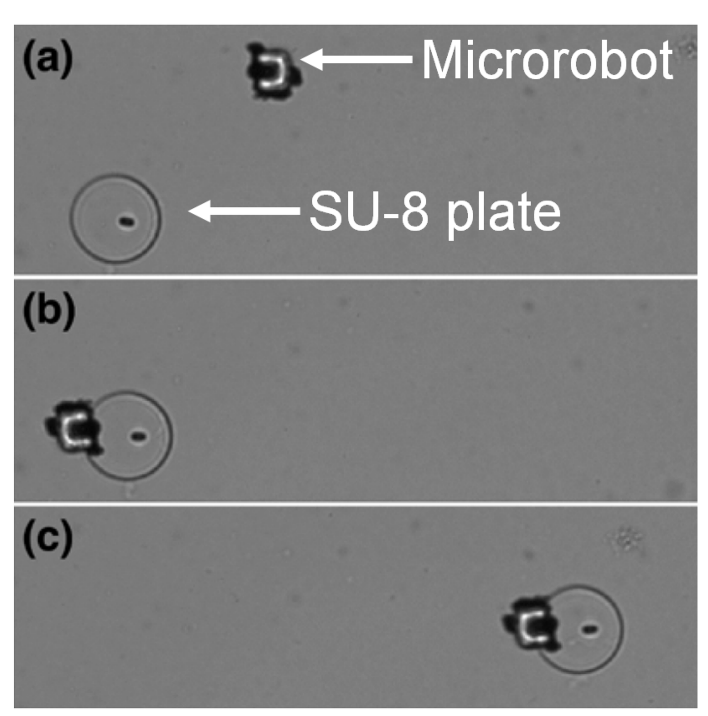


Biological Cyber-Physical Systems

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

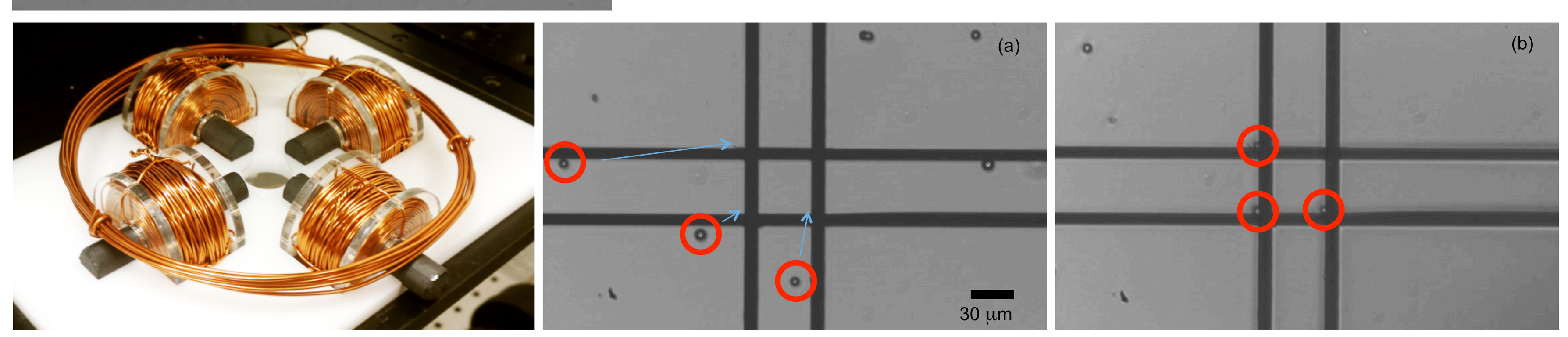
- Carry sensor cells attached to a synthetic substrate,
- Control microscopic light patterns, and
- Manipulate individual cells.





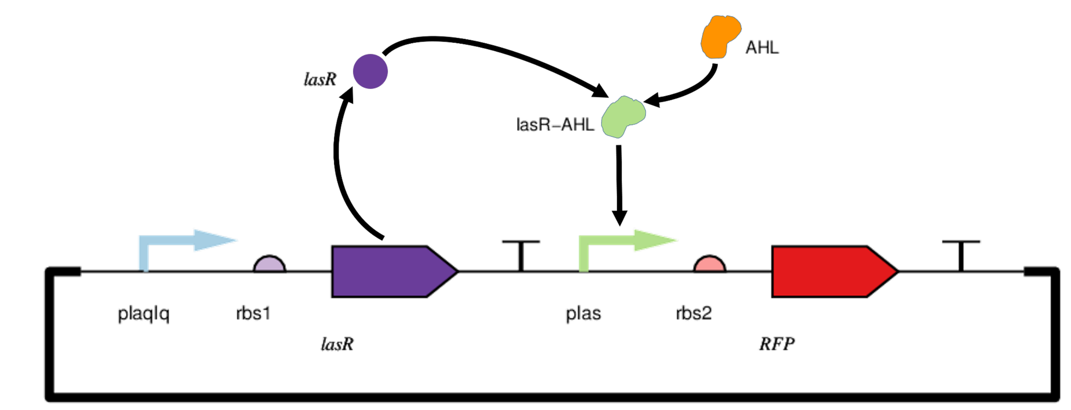
We explore microrobot-based cellular placement and actuation using magnetic manipulation (collaboration with SRI International). In this image, a magnetically controlled microrobot moves an 80 uM SU-8 plate, which is on the order of the size of a mammalian cell.

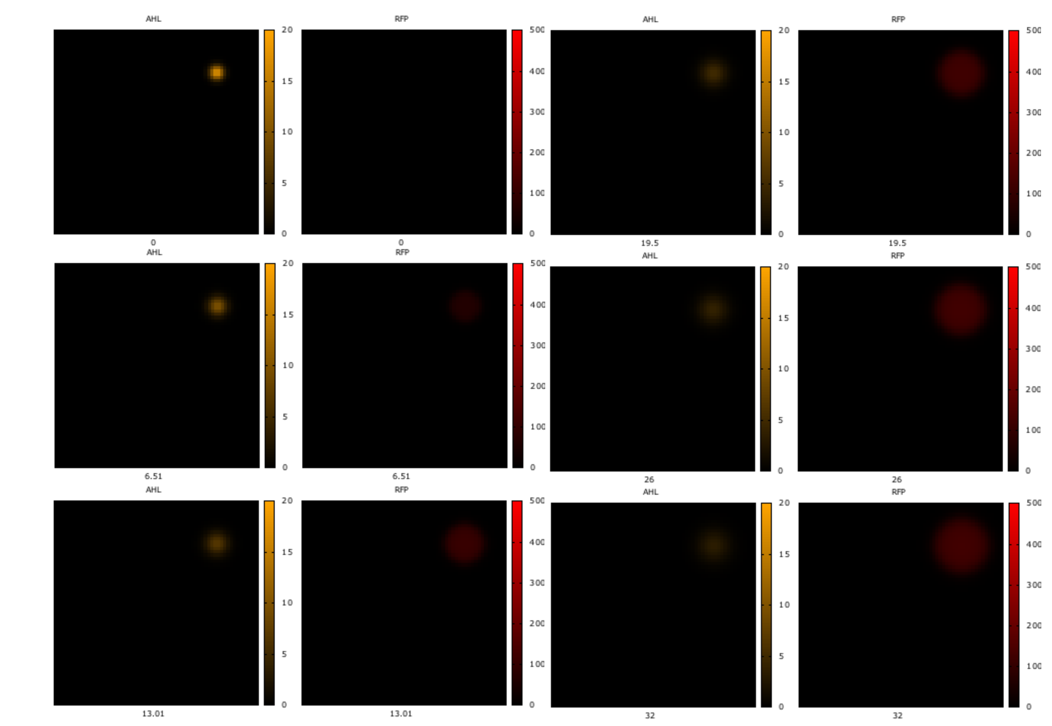
For fine-scale control, microwires are patterned in a substrate creating significant local variations in magnetic fields. By controlling the interaction of these fields, we can simultaneously and independently control several magnetic microrobots.



Multicellular Simulation

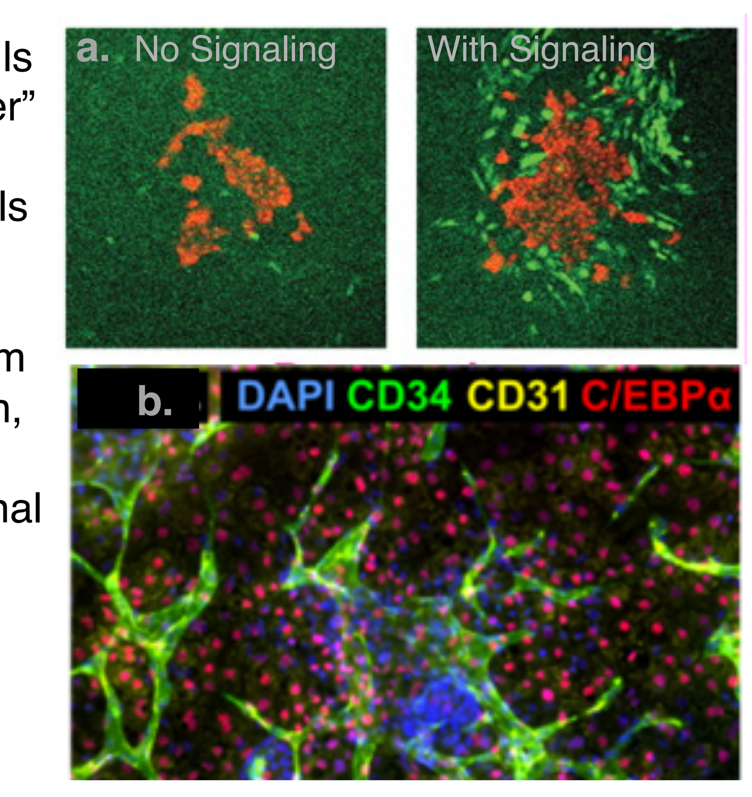
Genetic Circuit Diagram



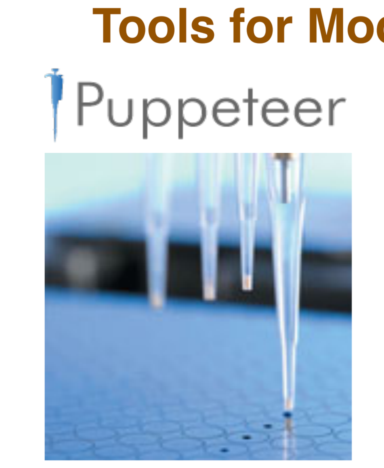


Experimental Design

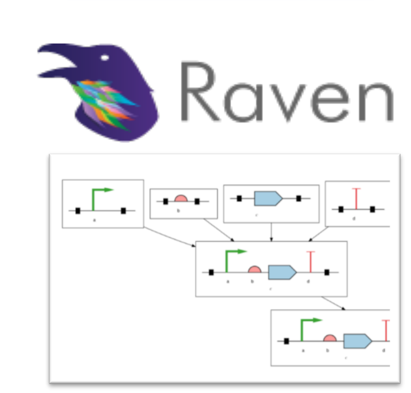
In (a), the red cells express a "sender" module, and the nearby green cells are "receivers". Genetic circuits could control stem cell differentiation, giving rise to synthetic functional tissues such as embryonic liver tissue (b).



Tools for Modular DNA Construction



Puppeteer plans the actual DNA manipulations necessary to build the synthetic genetic circuits. It can execute them automatically on a liquid handling robot.



Raven uses dynamic programming to plan the DNA assembly of synthetic genetic circuits.