CYBERNETICS JOINS SYNTHETIC BIOLOGY

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Abstract: *Synthetic biology is a new discipline focused on understanding what system principles are implemented inside cells and how they can be used to build new living organisms with novel functions. The department of cybernetics at the University of West Bohemia is currently developing a synthetic biology laboratory that will integrate traditional engineering tools into cellular experiments. The laboratory is to be integrated with new and existing courses as well university wide research.*

Keywords: *synthetic biology, laboratory design*

WHY THIS IS THE RIGHT TIME

Synthetic biology is a new discipline focused on understanding what system principles are implemented inside cells and how they can be used to build new living organisms with novel functions. The emergence of this discipline is a consequence of several breakthroughs in biology beginning with the discovery of the DNA double helix. These breakthroughs have resulted in a vast array of tools that are used today for gathering a wide variety of reliable data (intracellular molecular concentrations, genome sequences, binding affinities, etc.) and for reliably synthesizing many biomolecules (short DNA sequences can be ordered online and arrive in days).

The relevance of cybernetics to this discipline is clear. Many of the same system and control principles developed over the past 100 years for electrical and mechanical systems indeed govern intra and inter cellular behaviors. Here are some examples: complex feedback networks regulate enzyme production in response to changes in nutrient availability, genes preform nested Boolean computations when toggling between dormant and growing expression profiles, highly optimized decisions are made when selecting which nutrients to import in order to maximize ATP production, redundant genes and parallel pathways are used for robustness to gene damage and nutrient shortage. Indeed, many researchers in synthetic biology come from a technical, rather than a biological, background.

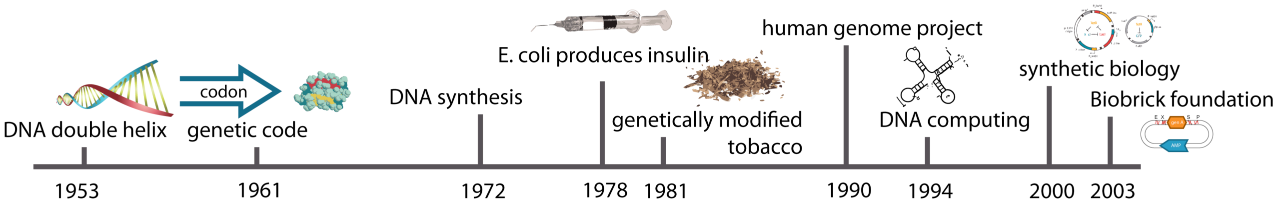

Fig. 1: timeline of the post DNA biological breakthroughs leading to the recent emergence of synthetic biology.

Of course, the idea of synthesizing new living organisms is nothing new. Once the genetic code was mapped, biologists immediately began to cut and paste genetic instructions into living organisms to create bacteria that produce insulin, plants that resist infection, and animals with traits required for specific clinical studies. What separates synthetic biology from genetic engineering is the goal of developing scalable principles applicable to designing new complex functions. It is believed that systems and engineering training and intuition are necessary to lead the research in the appropriate direction [1,2] that in many ways contrasts biological philosophy [3]. The success of this approach is evidenced by the effort of the Biobrick foundation (www.biobricks.org), which has focused on developing a catalog of easy to use biological parts instead of pure science.

THE SYNTHETIC BIOLOGY TOOLKIT

For an engineering technology to spread from select specialists to general craftsmen, it must be built on a set of basic building blocks with easy composition protocols. Automobile engines, electrical circuits, computers, and information technology all underwent this transformation before becoming garage technologies. A strong effort is currently underway to transform biology in the same way [4]. Leading this effort is the Biobrick Foundation (Cambridge, USA), which has defined a DNA template, similar to the Lego snap and fit, that enables easy composition of DNA parts called plasmids. The so called Biobrick parts, function like higher level programming rules that researchers with non-traditional backgrounds in electrical engineering or cybernetics can reason about and use to build new functions inside living organisms. The number of parts maintained by the Biobrick foundation is currently in the thousands and grows every year. The parts have been used by researches to build signaling pathways, intercellular communication mechanisms, Boolean gates, binary switches, oscillators, and organized metabolic pathways.

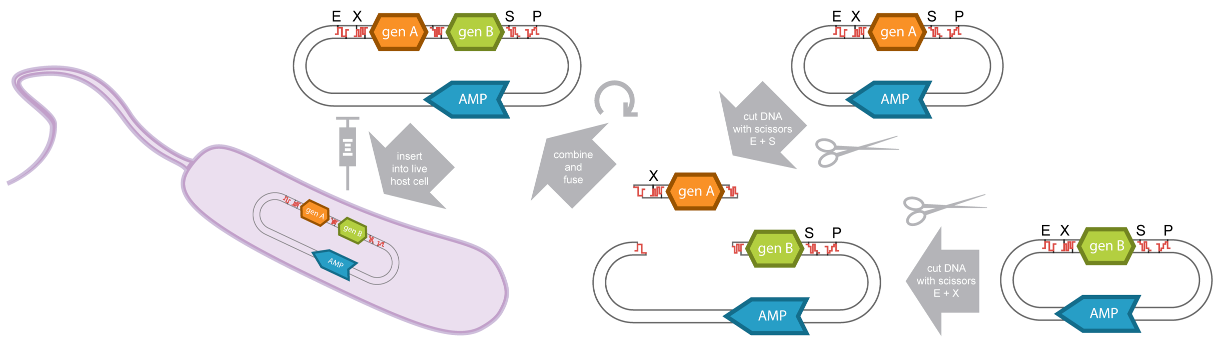

Fig. 2: The Biobrick parts and composition protocol.

Step 1: Each Biobrick part contains a gene that the cell expresses to make proteins. To place the genes on a single DNA plasmid, the parts are cleaved with specific enzymes. The choice of enzymes decides the order in which the genes appear on the new part.	Step 2: The enzymes leave the cleaved DNA with uneven ends. Some enzymes are complementary and leave ends that stick together. To combine the original parts, simply mix parts with complementary ends together in solution.	Step 3: The new Biobrick part contains a genetic network that codes a set of instructions for the cell. The instructions are uploaded to the cell by electrically or thermally shocking the cell increasing its membrane porosity to absorb the exogenous DNA.

In addition to Biobrick parts, the community has identified a set of well-established tools from molecular biology that are sufficient for synthesis and analysis. Well documented and easy to operate tools are favored over expensive sophisticated tools that take years to learn. There are also examples of experimental innovations by researchers with technical backgrounds that are motivated by dynamical systems theory, e.g., sinusoidal pressure changes in yeast in order to measure the frequency response and estimate the transfer function model.

Table 1: Standard set of experimental tools.

Equipment type	**Uses**
Microscope	Cell visualization and single cell lineage measurements. Quantitative measurements of intracellular substrate concentrations are obtained by combining microscopy with fluorescence tagging.
Fluorometer	Population fluorescence assays. Long-term studies are possible with integrated temperature regulators, shakers, and continuous nutrient supply.
Spectrophotometer	Characterization of cell density to study cell growth. Verification of DNA concentration and purity in solution before sequencing or using the DNA in cell transfection.
Thermocycler	Versatile DNA amplification tool useful in genotyping, RNA measurements, mutagenesis.
Electroporator	Cell transfection by a high voltage electric shock.
Electrophoresis	DNA filtering for isolation of DNA fragments and characterization of fragment lengths.
Other general tools required for solvent separation, organism storage and growth, and sterilization: centrifuge, incubator, autoclave, refrigerator, freezer, deep freezer, UV germicidal lamp.	

THE CELL CYBERNETICS LAB AT UWB

The department of cybernetics at the University of West Bohemia has currently developed a synthetic biology laboratory to integrate traditional engineering tools with Biobrick technology. The lab is headed by M.Sc. Daniel Georgiev, Ph.D., who joined the department last fall as a visiting scholar from the University of Washington, Seattle. Dr. Georgiev studied synthetic biology as a postdoctoral scholar. Like many researchers in this area, however, his background is technical. He received his Ph.D. in systems and control from the University of Michigan, Ann Arbor.

Other groups with more traditional cybernetic expertise are also involved: the robotics and control group of Prof. Ing. Miloš Schlegel, CSc., is interested in experiment automation and micromanipulation, the image-processing group of Ing. Miloš Železný, Ph.D., is interested in automating data analysis, specifically cell tracking and characterization in time-lapse image sequences, the biocybernetics group of Ing. Lucie Houdova is expected to implement their statistical experimental analysis and design tools. Outside of the department, collaborations with the faculty of electrical engineering and the faculty health studies are planned.

The lab is also integrated into a new course titled Introduction to Cellular System Modeling, taught by Dr. Georgiev. The course will introduce third year students to fundamental biological principles and modeling tools. In addition, the course will culminate with semester projects that students will be able to test in the Cell Cybernetics Lab. This course is modeled after a similar course taught at the University of Washington where at the end of the semester students build cells with oscillatory circuits or genetic switches. Select students will also be invited to compete in the international genetically engineered machine competition (iGEM) where they will work in a team to develop a new Biobrick function.

In the longer term, the lab's research objective is to increase speed, reliability, and feasibility of current experimental methods by incorporating the biological system into the design process. The experimental tools and methodologies developed will straddle both sides of the border that separates biology and engineering. The expected research outputs are technical tools with compatible genetic kits that automate handling, regulate experimental conditions, or manipulate the physical system in a way that is compatible with the biological design.

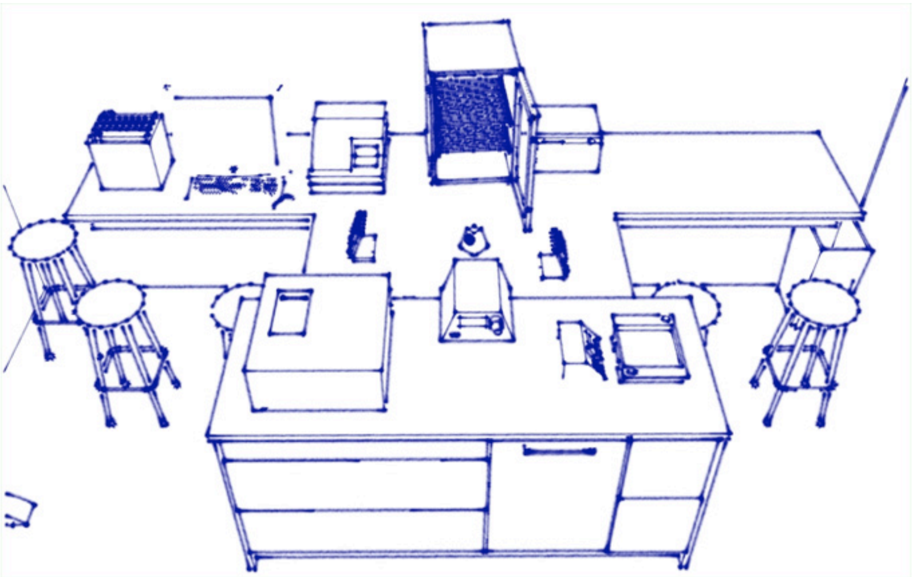

Fig. 3: The cell cybernetics lab construction plan.

FOR ANYONE INTERESTED

Research at the cell cybernetics lab will begin this September. For more information see ccy.zcu.cz or stop by for a visit.

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