BIOENG-320
Synthetic Biology

Lecture 1 Introduction
February 17, 2025

Patrick Barth
EPFL

Lecture 1 plan

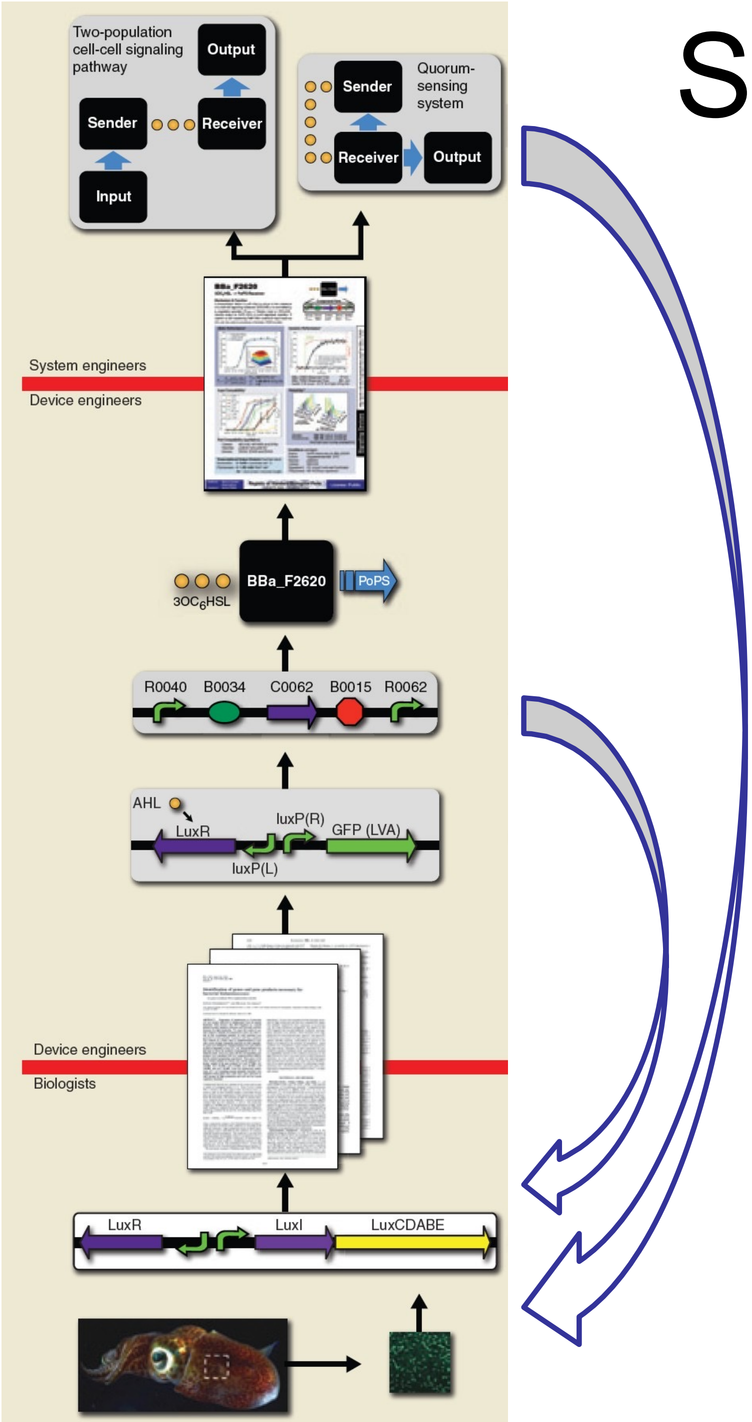
1. What is synthetic biology; why do we study it? Etc..

2. Class logic; lecture topics; schedule and logistics

What is synthetic biology?

- An *emerging* engineering discipline that seeks to make implementation of new biological function vastly more efficient, reliable, transparent and safe.

- A field dedicated to biologically engineered solutions to world problems in health, energy, environment, and security.



Synthetic biology vs. “normal” biology

Biologists want to understand how biological systems work.

Synthetic biologists want to use that understanding to build new biological systems:
Feynman’s quote: “What I cannot create, I do not understand.”

Both fields rely on the same technologies and methods.

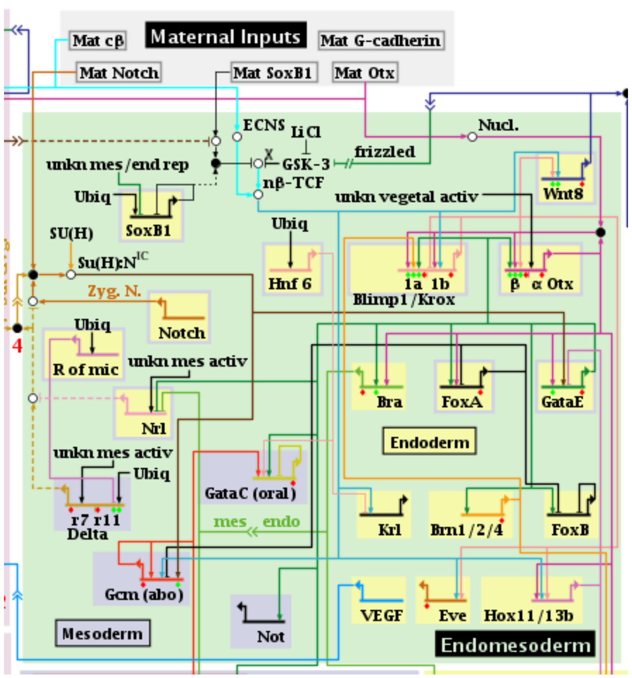
Source: Canton, Labno and Endy, Nat Biotech, 2008.

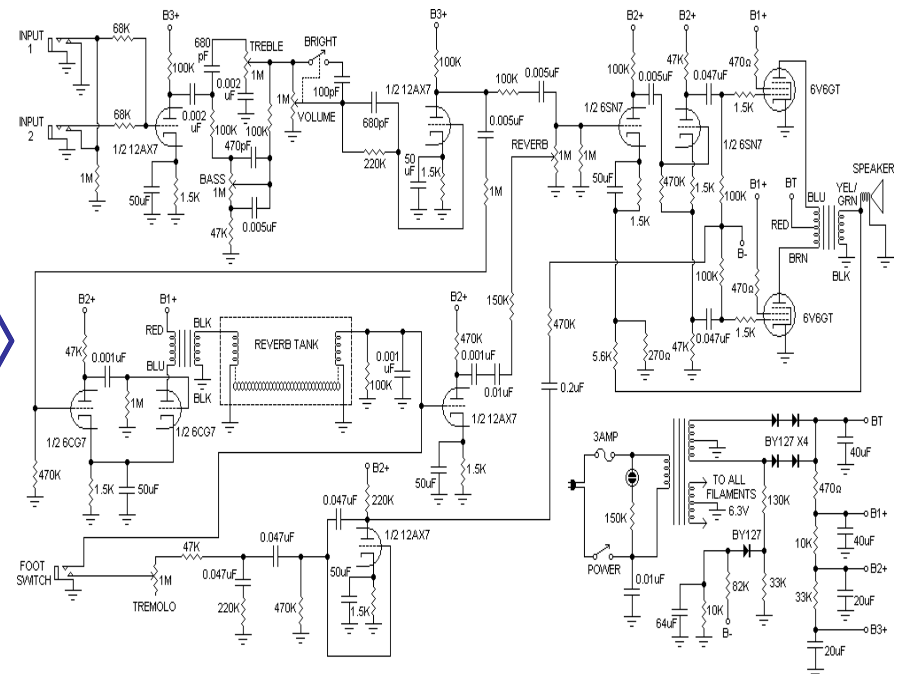
The goal of synthetic biology

Turn biology into an engineering discipline:

- Predict the behavior and robustly assemble complex biological systems from well defined and characterized parts

Endomesoderm Specification to 30 Hours

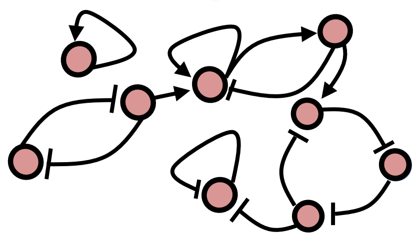


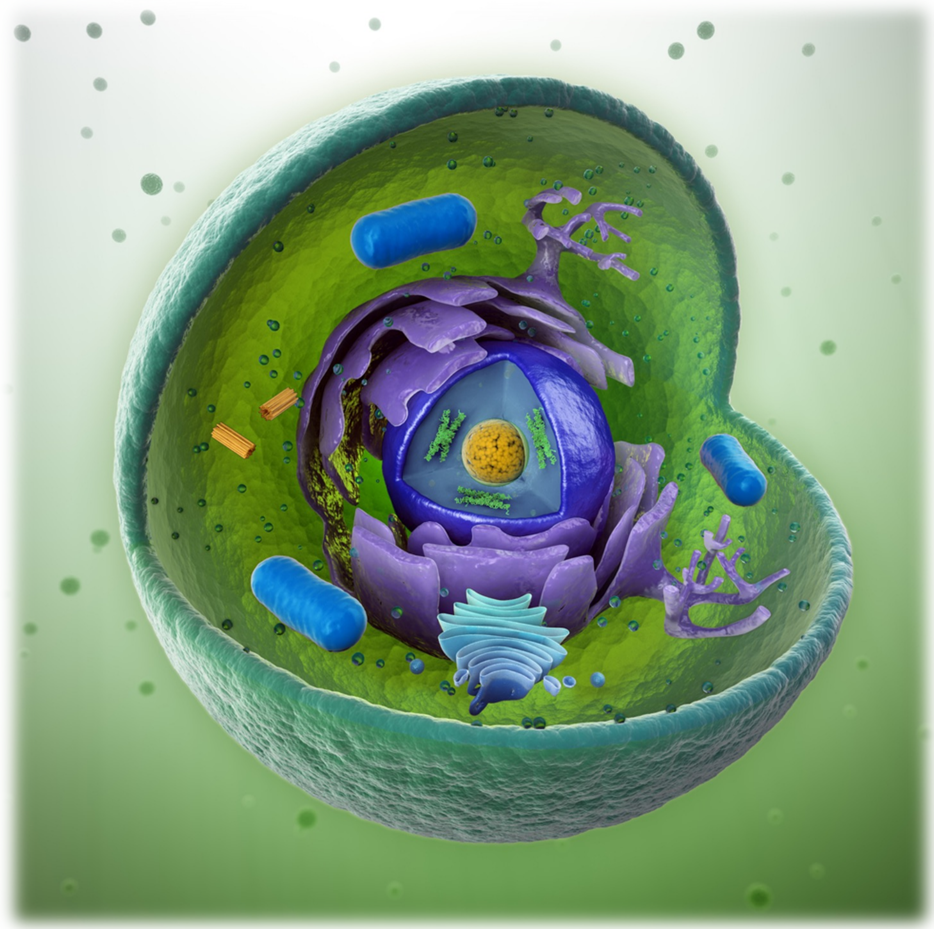


Synthetic cell biology: programming cells

```
module mux(output out1,  input in1, in2, in3);
always@(in1,in2,in3)
    begin
      case({in1,in2,in3})
        3'b000: {out1} = 1'b0;
        3'b001: {out1} = 1'b1;
        3'b010: {out1} = 1'b0;
        3'b011: {out1} = 1'b1;
        3'b100: {out1} = 1'b0;
        3'b101: {out1} = 1'b0;
        3'b110: {out1} = 1'b1;
        3'b111: {out1} = 1'b1;
      endcase
    end
endmodule
```

input	low	high
1.aTc	0.07	15.7
2.IPTG	0.09	10.1
3.Ara	0.01	7.7

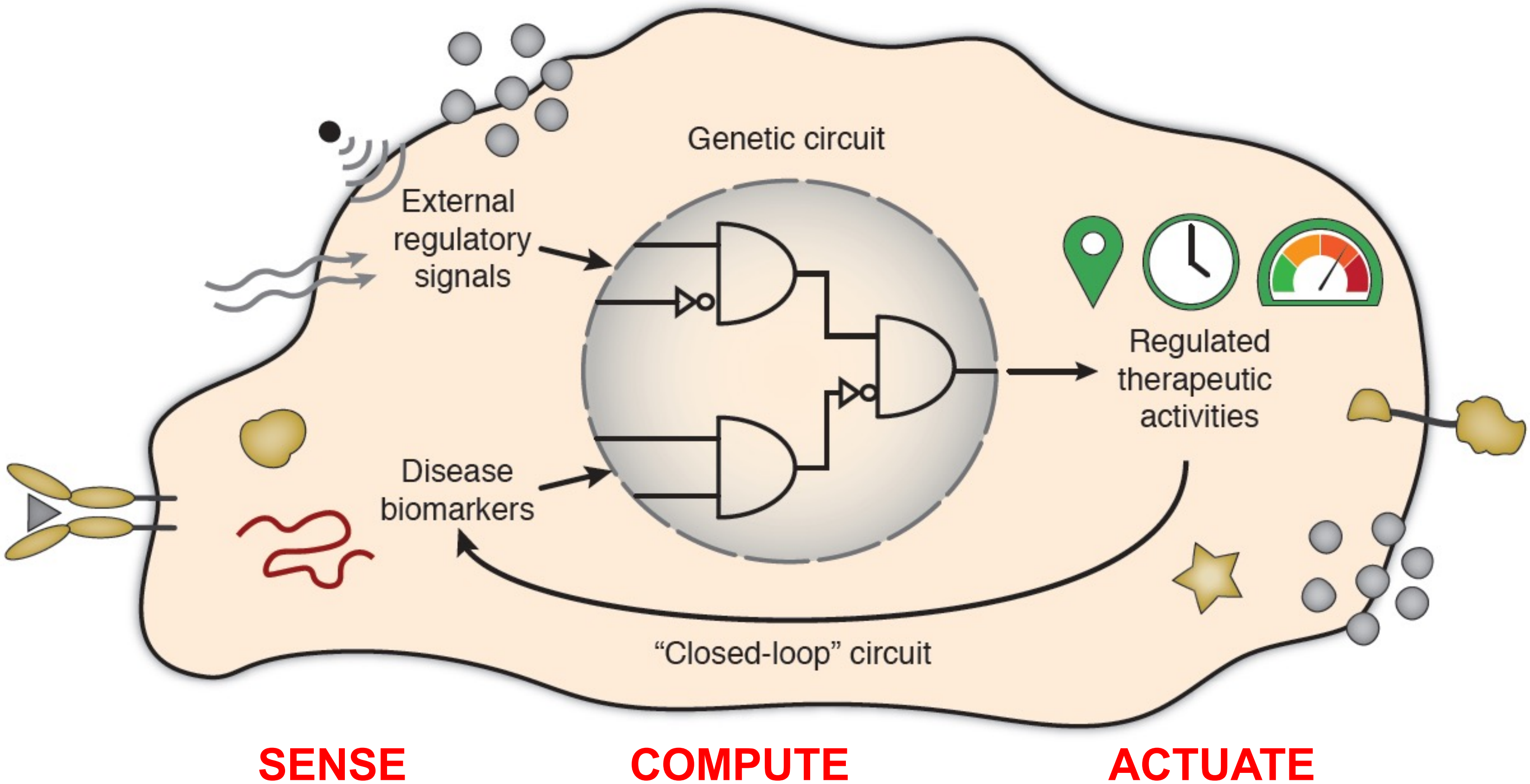




Develop an engineering discipline for programming cells reliably, efficiently, …

http://www.medicalsciencenavigator.com/?attachment_id=522

Designer bio-computing systems in cells



Sensors:
- proteins
- miRNA
- mRNA
- metabolites

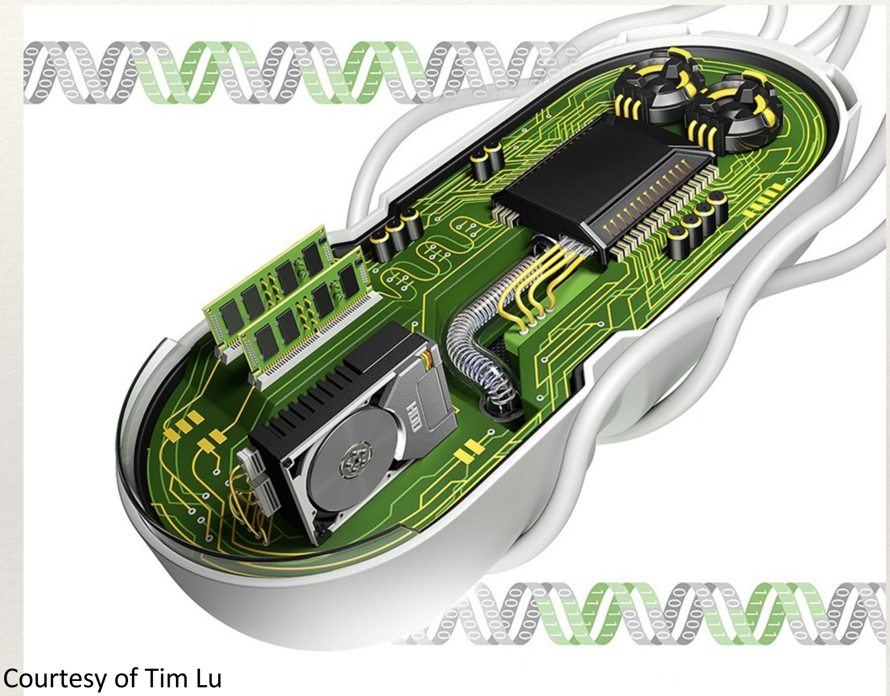
Regulation:
- transcriptional
- translational
- protein-protein

Actuators:
- cell fate
- cell death
- enzymes
- antigens, …

Different perspectives of a cell

Inspired by Michael Elowitz

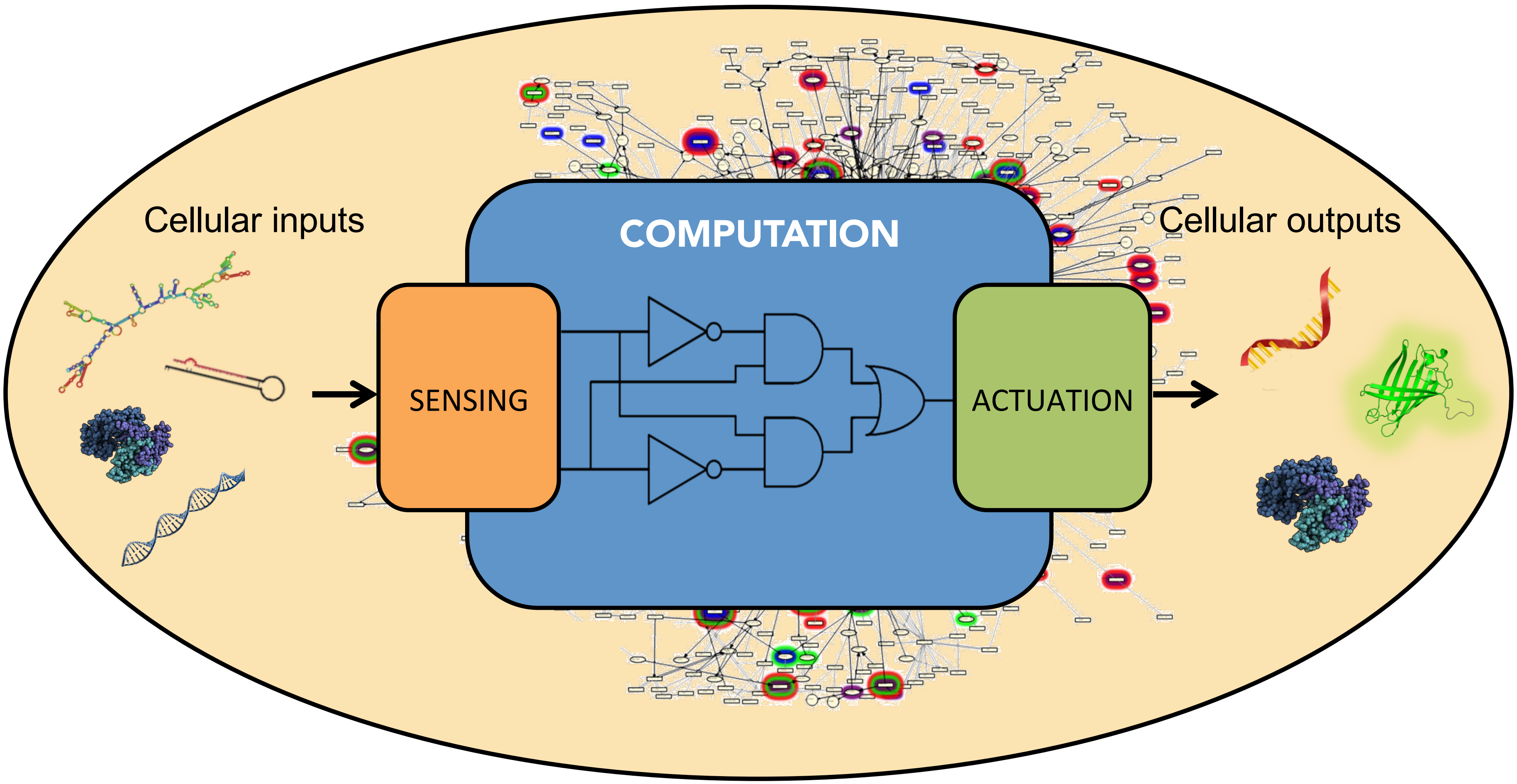
?



Courtesy of Tim Lu

Given the complexity of the cellular environment, ~~how~~ can we achieve robust engineering of cells?

Biodesign within the context of a cell



Bioengineering: a rapidly evolving field

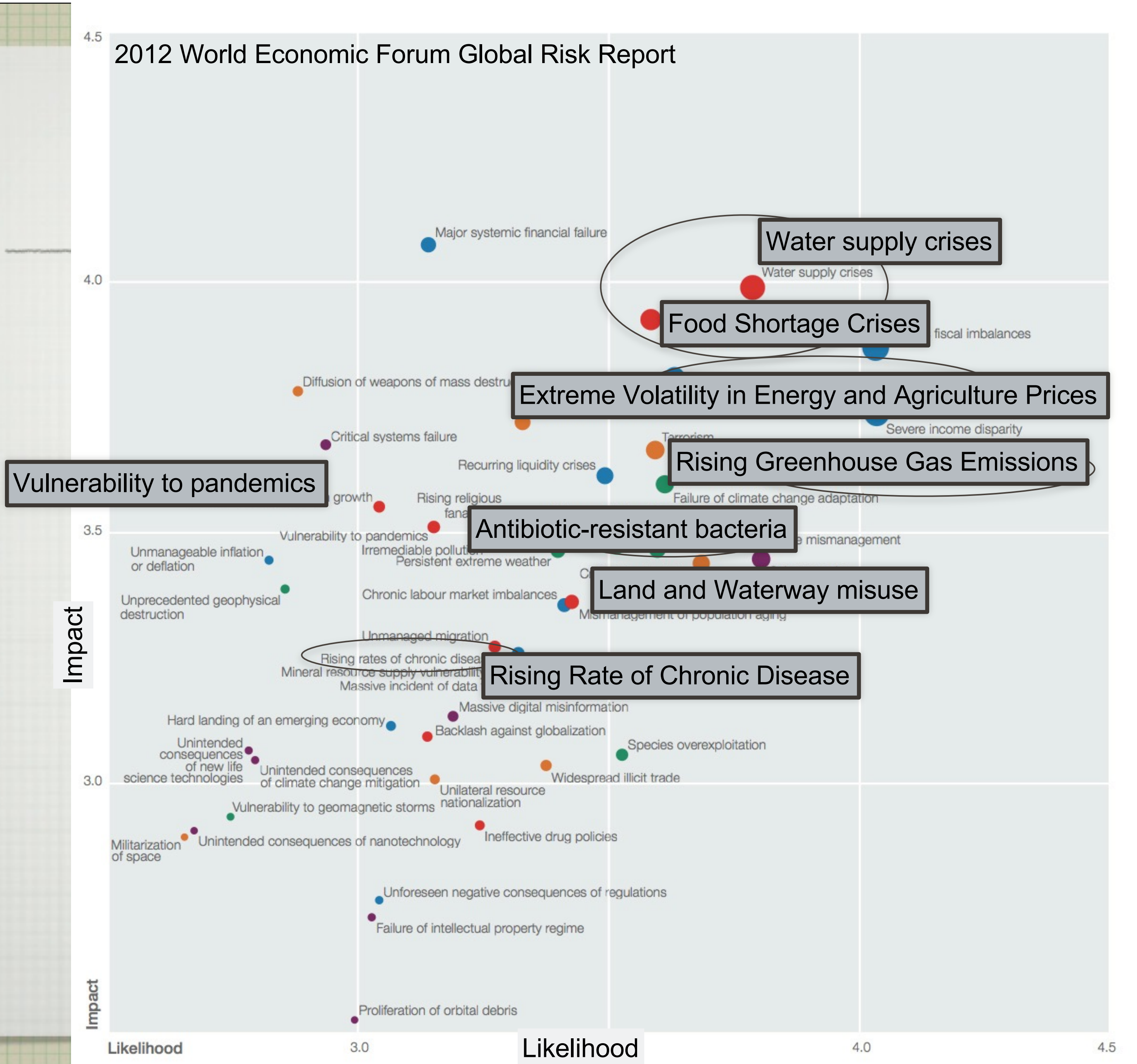
So far: manipulation/reprogramming of native systems; custom built parts for specific applications; low transferability

Future: a real engineering discipline implementing new biological functions predictably, efficiently, reliably, and safely

The promise of synthetic biology

Tapping the power of biology for:

- Biotechnology:
  - Bio-fuels: break down of raw material and synthesis of fuels
  - Synthesis of: biologicals, fine chemicals, industrial chemicals, polymers
- Environment:
  - Monitoring of environmental contaminants
  - Control of environmental parameters
  - Green energy
- Human Health:
  - Diagnostics
  - Therapeutics
- Basic Science:
  - Novel methods for manipulating biological systems
  - Generation of protocells and minimal cells


2012 World Economic Forum Global Risk Report
Water supply crises
Food Shortage Crises
Extreme Volatility in Energy and Agriculture Prices
Rising Greenhouse Gas Emissions
Vulnerability to pandemics
Antibiotic-resistant bacteria
Land and Waterway misuse
Rising Rate of Chronic Disease
Major systemic financial failure
Diffusion of weapons of mass destru
Critical systems failure
Recurring liquidity crises
Severe income disparity
fiscal imbalances
Failure of climate change adaptation
Rising religious
Vulnerability to pandemics
Irremediable pollution
Persistent extreme weather
Unmanageable inflation or deflation
Unprecedented geophysical destruction
Chronic labour market imbalances
Mismanagement of population aging
Unmanaged migration
Rising rates of chronic disea
Mineral resource supply vulnerability
Massive incident of data
Massive digital misinformation
Hard landing of an emerging economy
Backlash against globalization
Species overexploitation
Unintended consequences of new life science technologies
Unintended consequences of climate change mitigation
Widespread illicit trade
Unilateral resource nationalization
Vulnerability to geomagnetic storms
Ineffective drug policies
Militarization of space
Unintended consequences of nanotechnology
Unforeseen negative consequences of regulations
Failure of intellectual property regime
Proliferation of orbital debris
Impact
Likelihood
4.5
4.0
3.5
3.0
3.0
4.0
4.5

Biology Solutions for Big Problems

Water supply crises

Land and Waterway misuse

Rising Greenhouse Gas Emissions

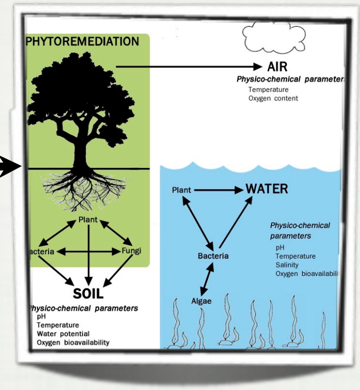
Extreme Volatility in Energy and Agriculture Prices

Food Shortage Crises

Antibiotic-resistant bacteria

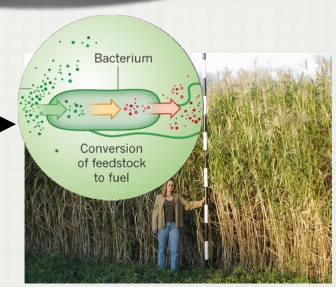
Rising Rate of Chronic Disease

Vulnerability to pandemics

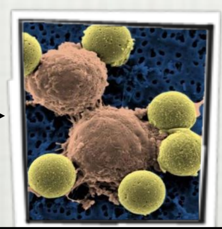


Natural, stimulated and engineered plants and microbes

clean soil, water and air

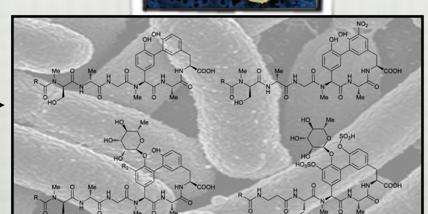


Microbes and plants optimized for renewable food and chemical production



New engineered T-cell therapies for cancer

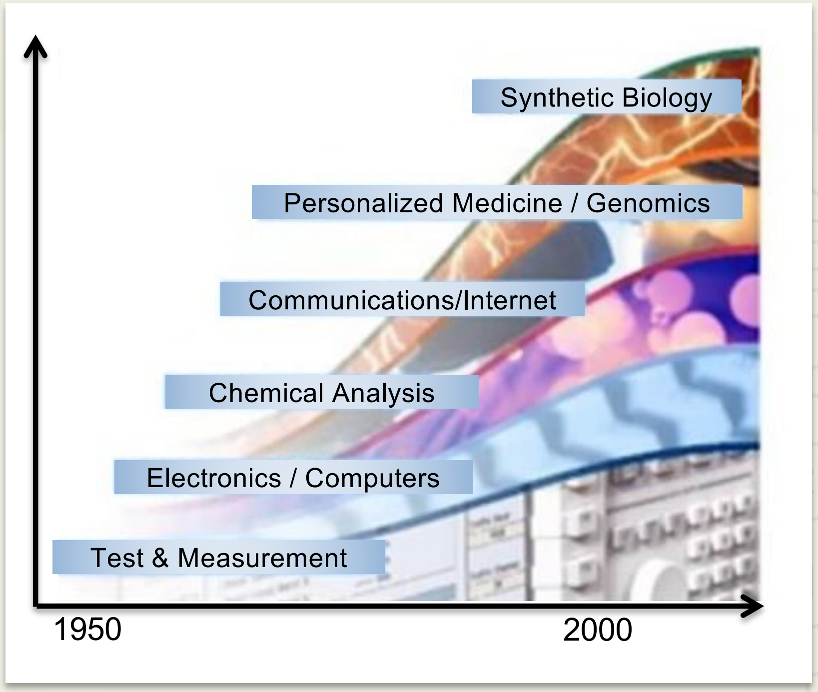
Microbial “gut” communities for treating Crohn’s disease



Cellular production of new antibiotics and on-demand synthesis of new viral vaccines. Synbio therapies.

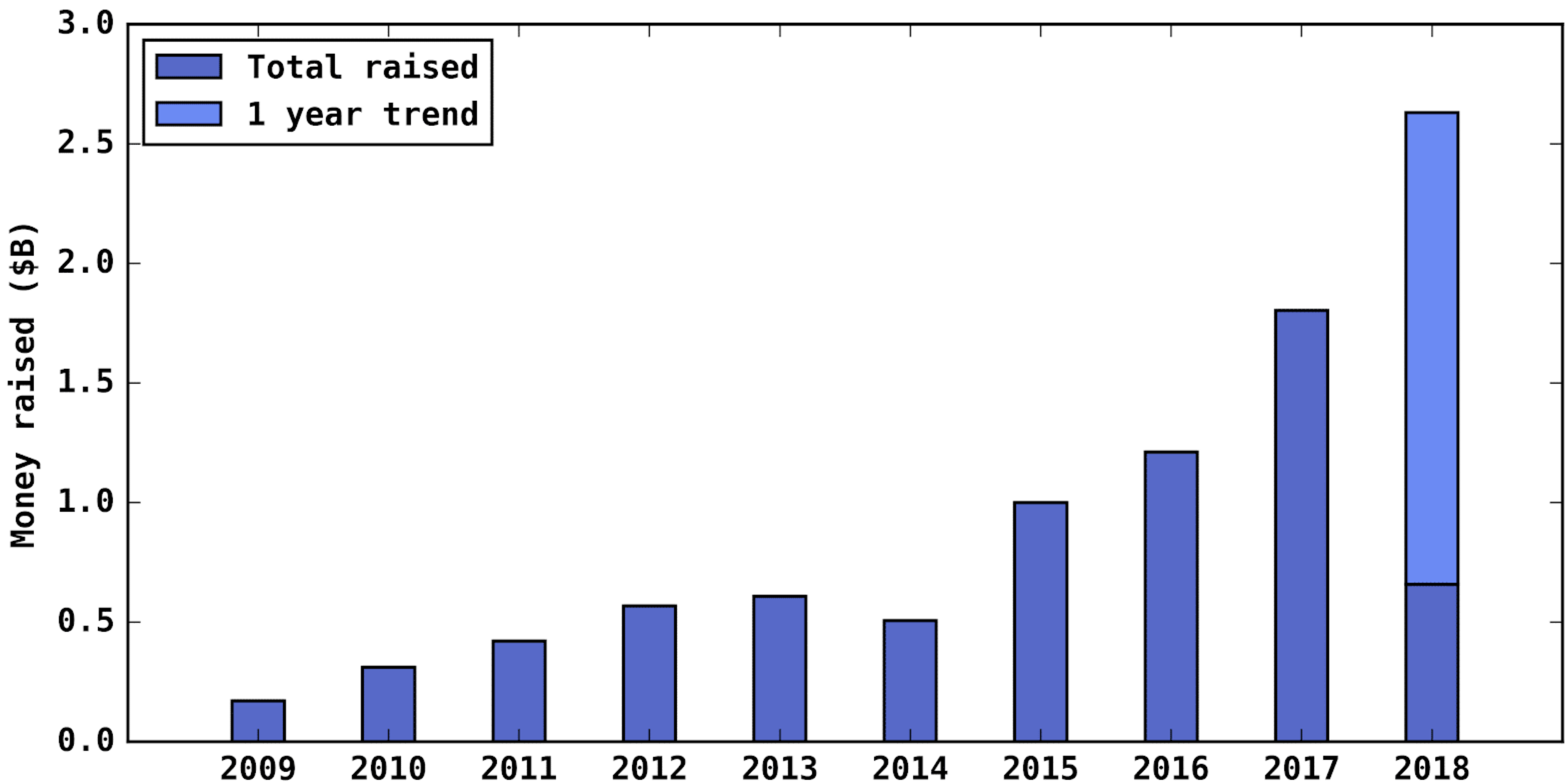
Global Challenges Demand Biomanufacturing

The Age of Biology is Here…
Full Mainstream Adoption and Impact May Take Decades



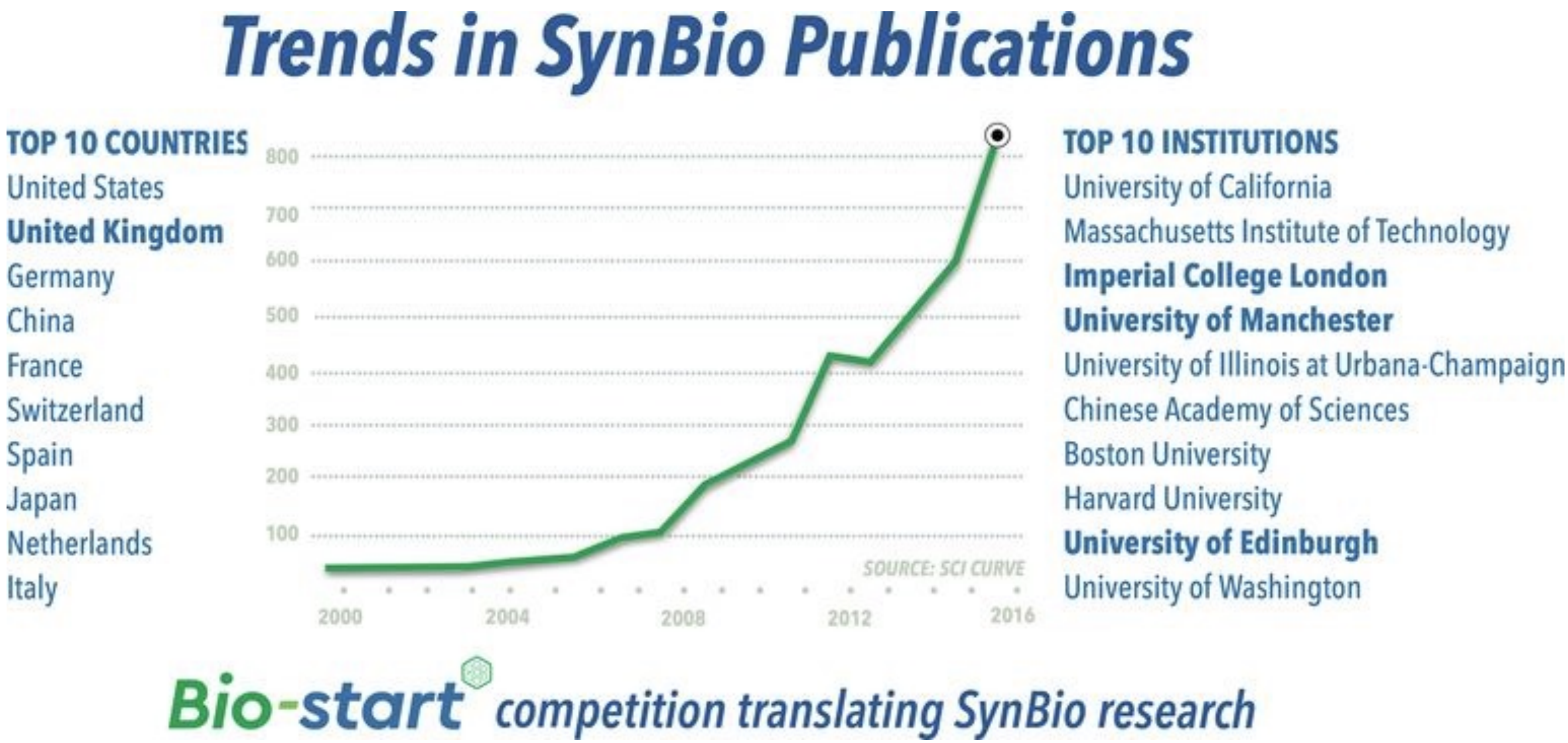
Darlene Solomon, Industrial Views on Synthetic Biology

Recent growth in synbio investments



http://synbiobeta.com/

Growth in synbio publications



http://www.synbicite.com/news-events/synbicite-blog/synthetic-biology-publications-top-ten/

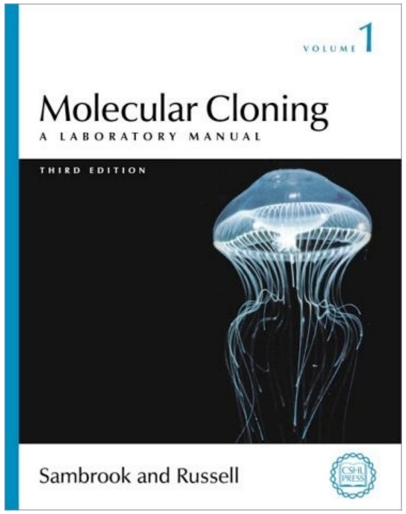
Why now?

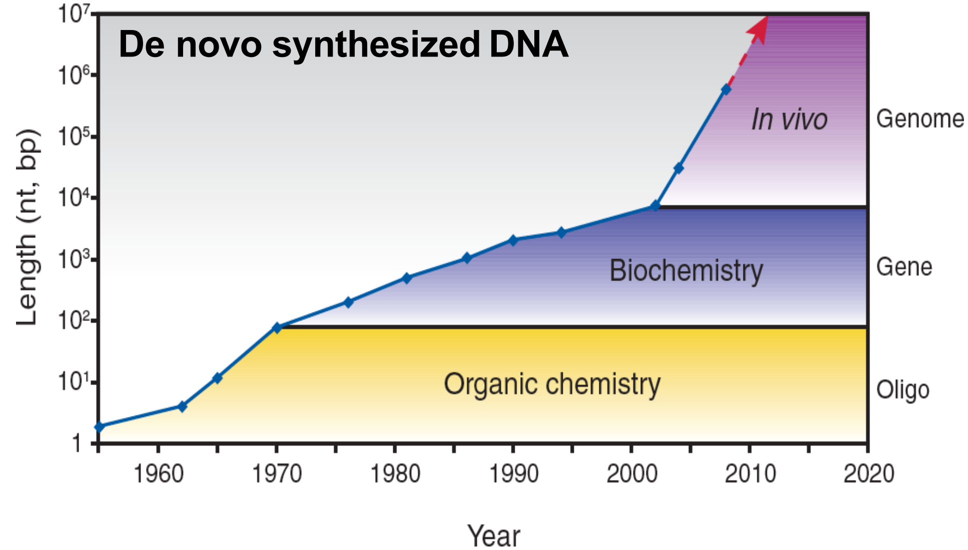
Synthetic biology is a “young” discipline; the first two synthetic networks were created in 2000.

Why has it gained so much momentum recently?

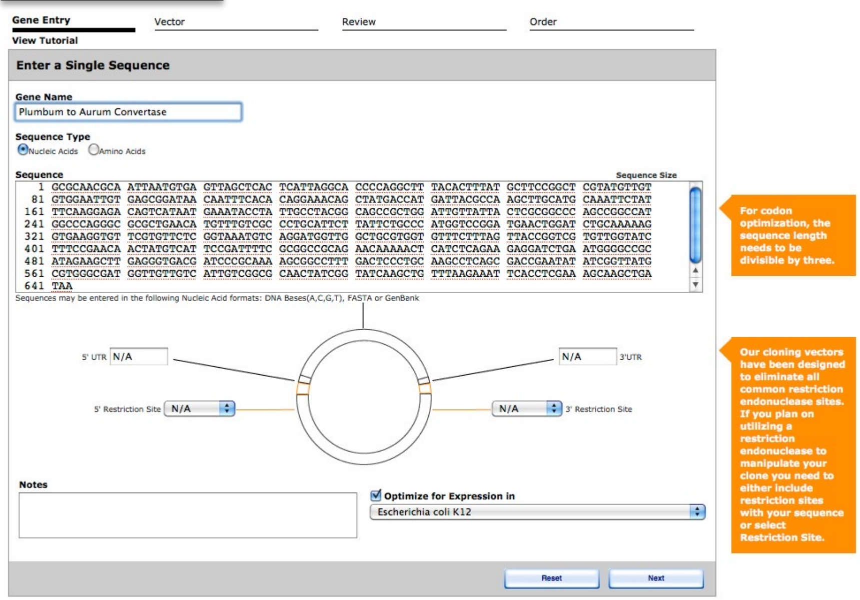
DNA Synthesis and Sequencing

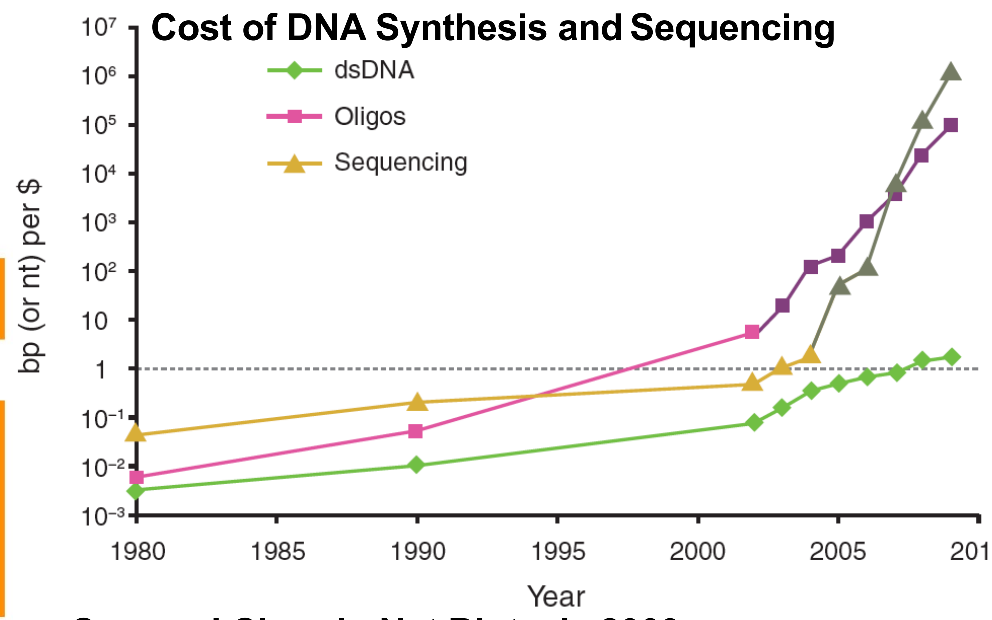
Now





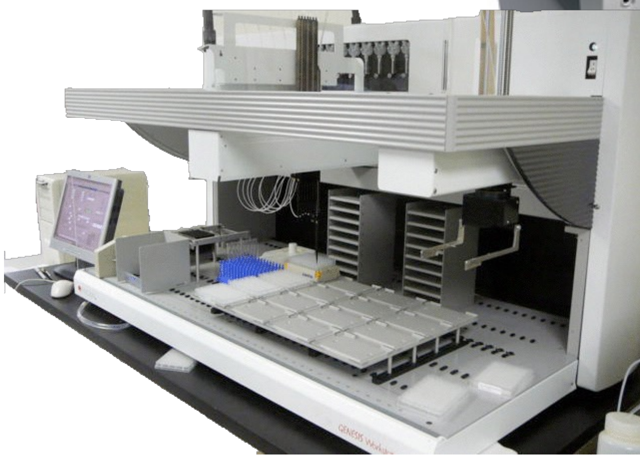
Future

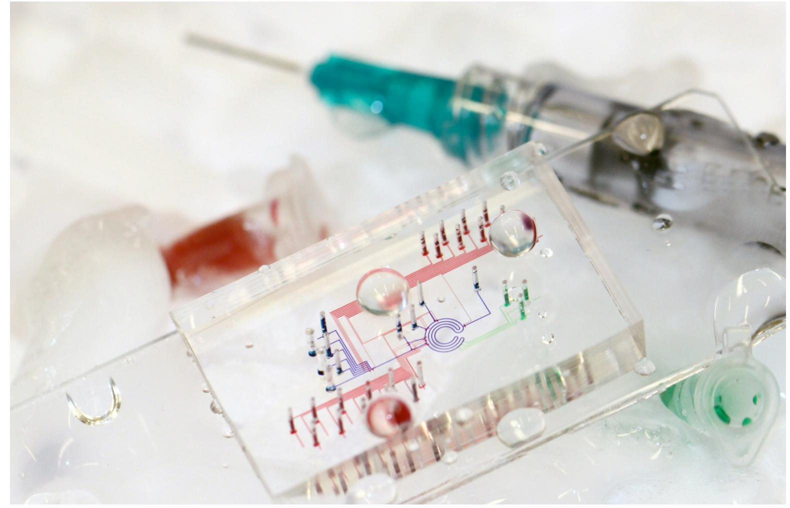




Carr and Church, Nat Biotech, 2009.

Automation and Miniaturization





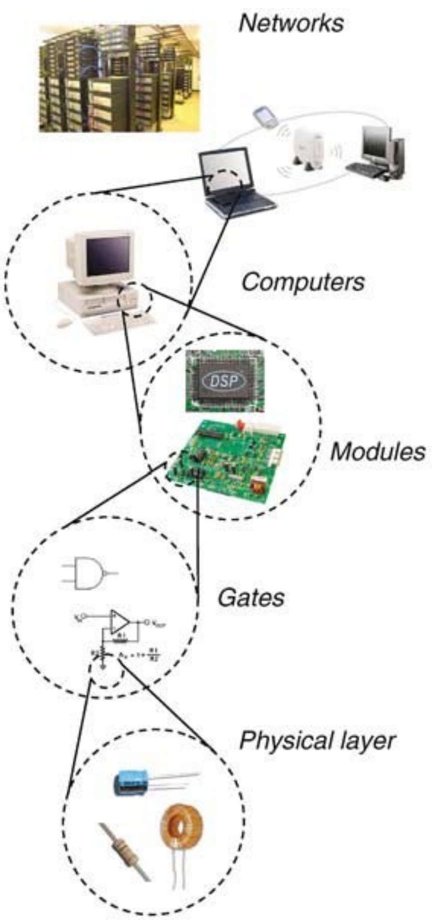
Hundreds to thousands of device variants can be generated and routinely screened:

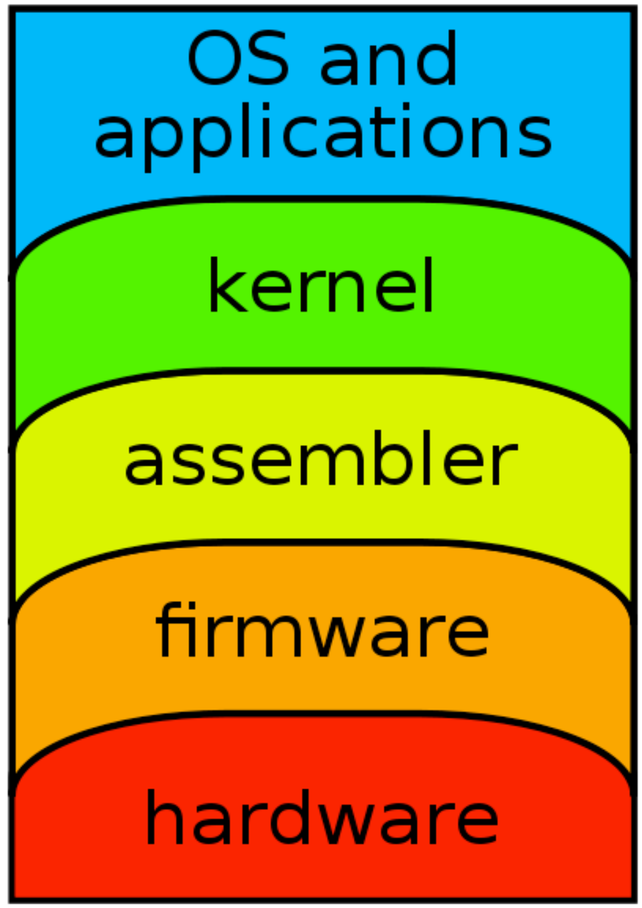
- FACS and microplate readers
- Liquid handling robots

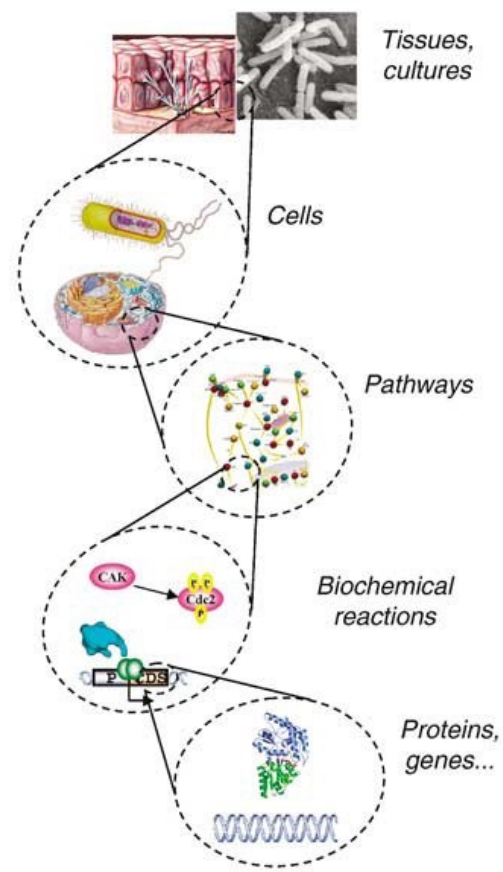
Miniaturization also increases throughput and enables new measurements/methods:

- Molecular interactions
- Cell based assays
- …

Hierarchy and Abstraction

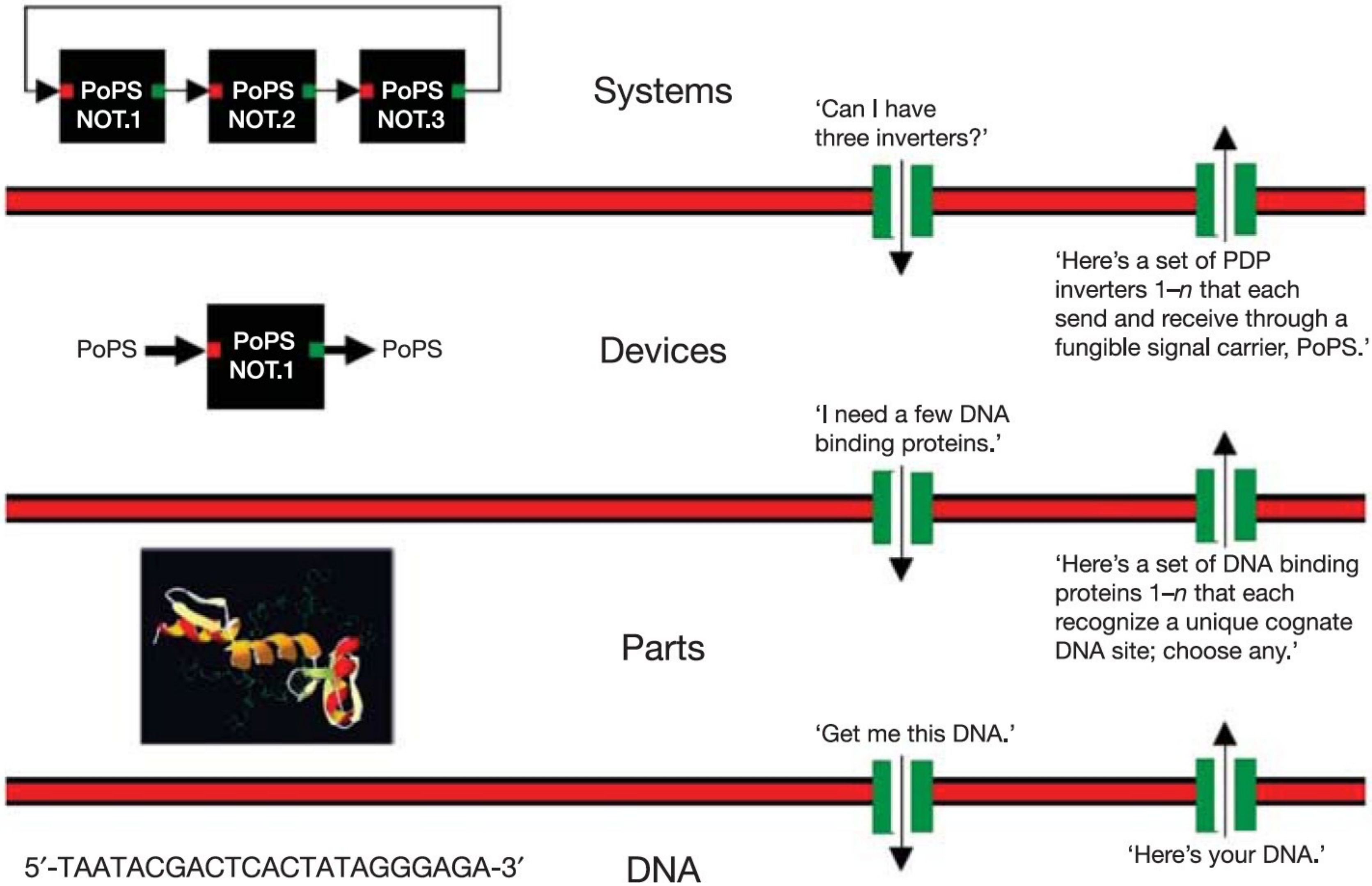






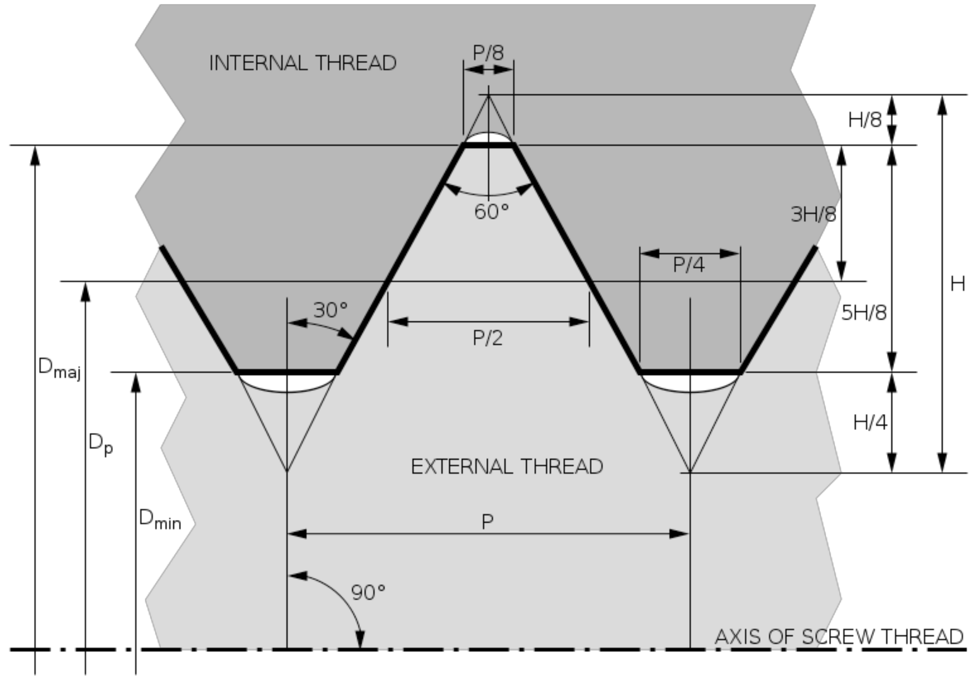
Sources: Andrianantoandro et al., Mol Sys Bio, 2006 and Wikipedia

Hierarchy and Abstraction



Source: Endy, Nature, 2005.

Standardization



Standardization **enables progress** by creating compatibility and eliminating the need to constantly re-invent.

Facilitates sharing of information, methods and materials (open-source…).

Sources: www.ideaphotos.com and Wikipedia

Standardization

Source: Wikipedia

What to standardize in synthetic biology?

Methods and Parts

We need several robust methodologies for part synthesis and integration. (in the future this will become less important, as complete custom parts and devices will be commercially available)

Characterization

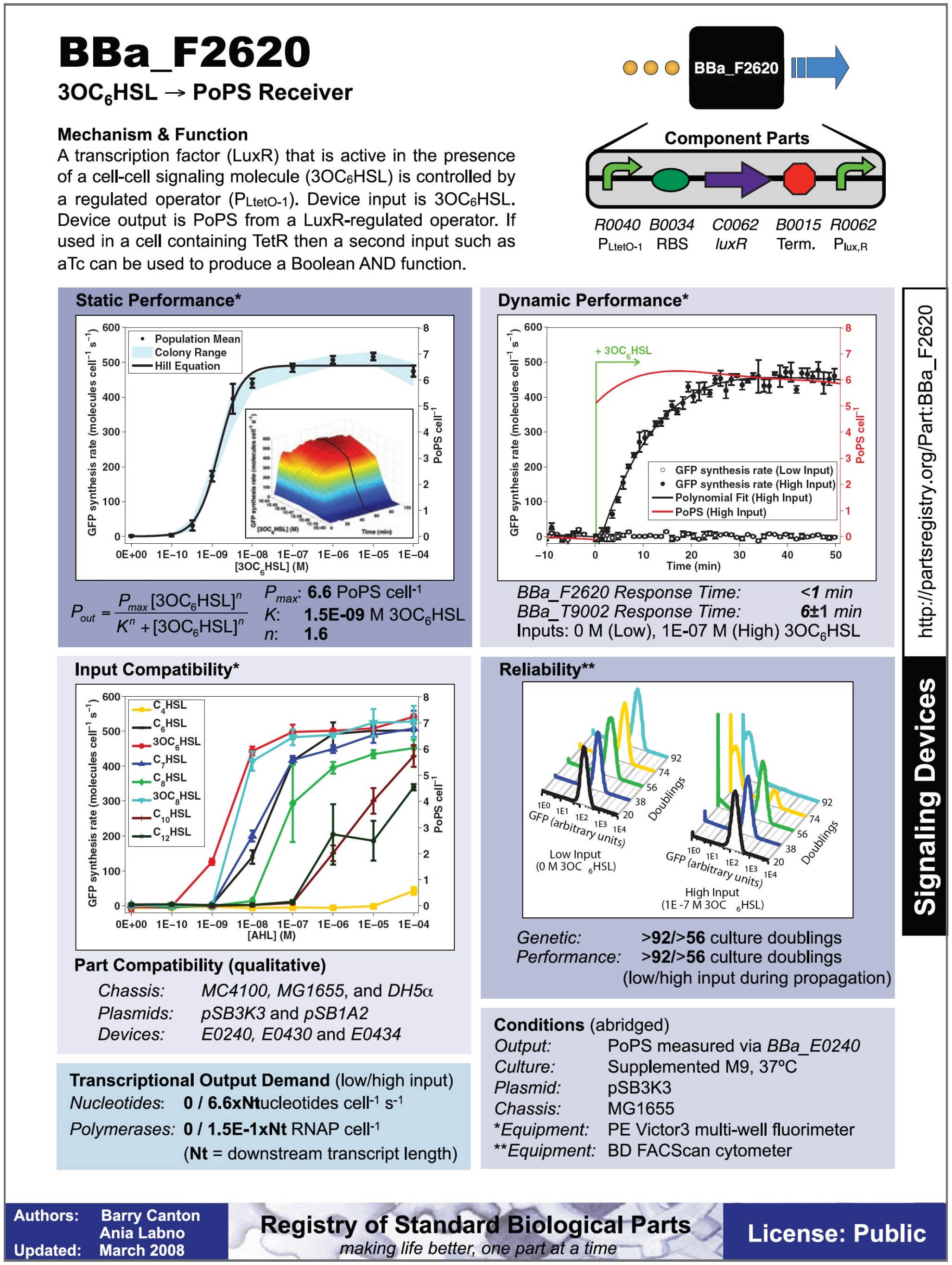
We need to determine standards for characterizing the functionality of individual parts and devices. This information must be precise and consistent. One compounding factor is that biological systems are not isolated!

Host cells / genetic backgrounds

Several standard host cells should be used for implementing genetic circuits to guarantee consistency and functionality of parts and devices.

Nomenclature

A standard nomenclature is necessary throughout synthetic biology.



Datasheet

Endy and coworker proposed a datasheet containing the major characteristics of a device.

We will need multiple datasheets for various parts and devices, depending on their functionality / characteristics.

Huge experimental space if parts and devices are dependent. Where do we expect this dependence to be minimal? Breakpoints?!

Source: Canton, Labno and Endy, Nat Biotech, 2008.

Logic

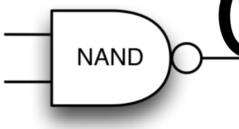
- Many biological networks can be described using logic elements

- **NAND** and **NOR** gates are the foundation of logic: all other logic functions can be generated using only **NAND** or **NOR** gates

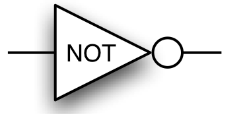
INPUT	A	0	0	1	1	Meaning
	B	0	1	0	1	
OUTPUT	FALSE	0	0	0	0	Whatever *A* and *B*, the output is false. Contradiction.
	A AND B	0	0	0	1	Output is true if and only if (iff) both *A* and *B* are true.
	A $\not\rightarrow$ B	0	0	1	0	*A* doesn't imply *B*. True iff *A* but not *B*.
	A	0	0	1	1	True whenever *A* is true.
	A $\not\leftarrow$ B	0	1	0	0	*A* is not implied by *B*. True iff not *A* but *B*.
	B	0	1	0	1	True whenever *B* is true.
	A XOR B	0	1	1	0	True iff *A* is not equal to *B*.
	A OR B	0	1	1	1	True iff *A* is true, or *B* is true, or both.
	A NOR B	1	0	0	0	True iff neither *A* nor *B*.
	A XNOR B	1	0	0	1	True iff *A* is equal to *B*.
	NOT B	1	0	1	0	True iff *B* is false.
	A $\leftarrow$ B	1	0	1	1	*A* is implied by *B*. False if not *A* but *B*, otherwise true.
	NOT A	1	1	0	0	True iff *A* is false.
	A $\rightarrow$ B	1	1	0	1	*A* implies *B*. False if *A* but not *B*, otherwise true.
	A NAND B	1	1	1	0	*A* and *B* are not both true.
	TRUE	1	1	1	1	Whatever *A* and *B*, the output is true. Tautology.

http://www.neuroproductions.be/logic-lab

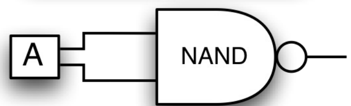
Compound Logic Gates

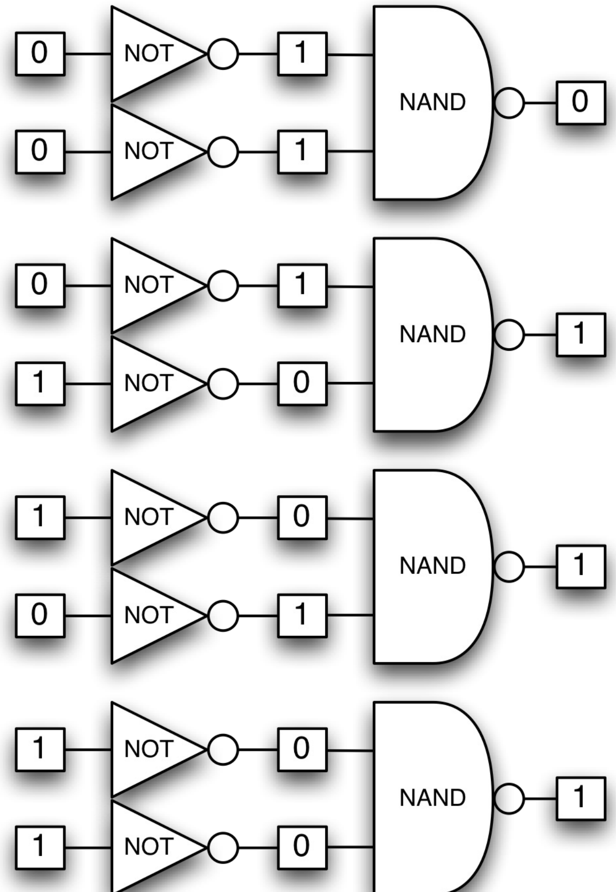


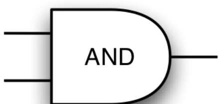
Input A	Input B	Output
0	0	1
0	1	1
1	0	1
1	1	0



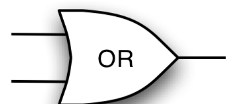
Input A	Output
0	1
1	0



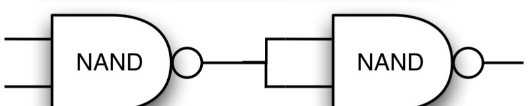


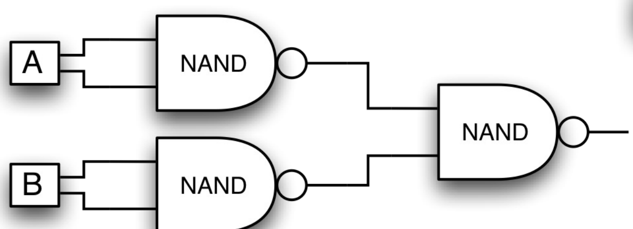


Input A	Input B	Output
0	0	0
0	1	0
1	0	0
1	1	1



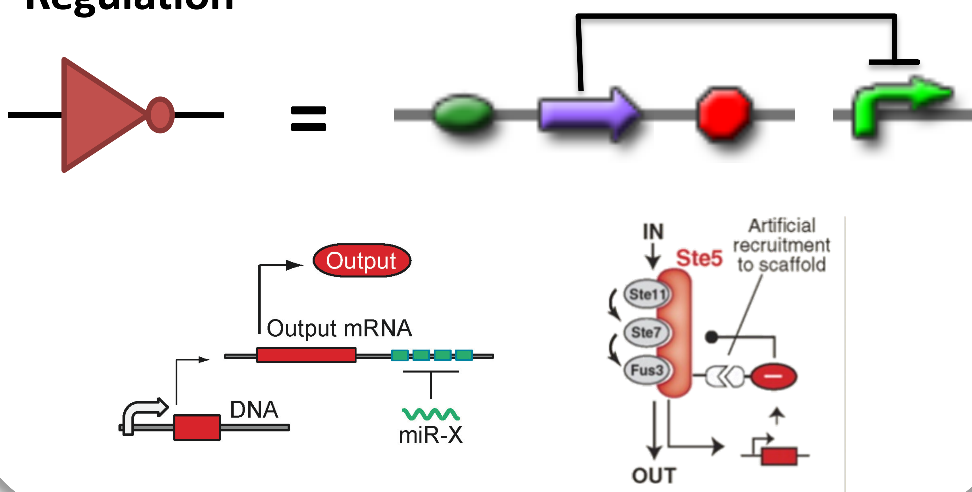
Input A	Input B	Output
0	0	0
0	1	1
1	0	1
1	1	1



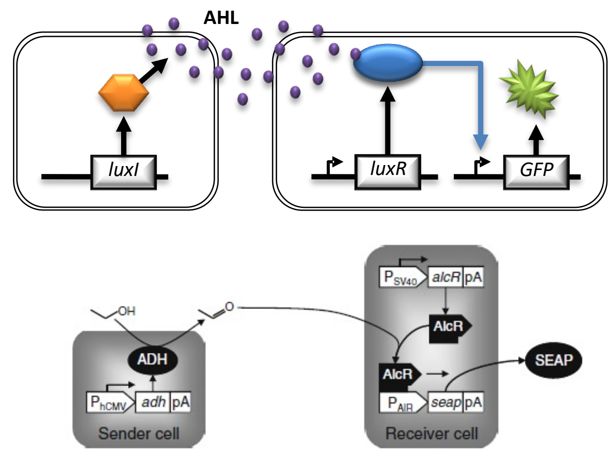


Library of parts and devices (partial list)

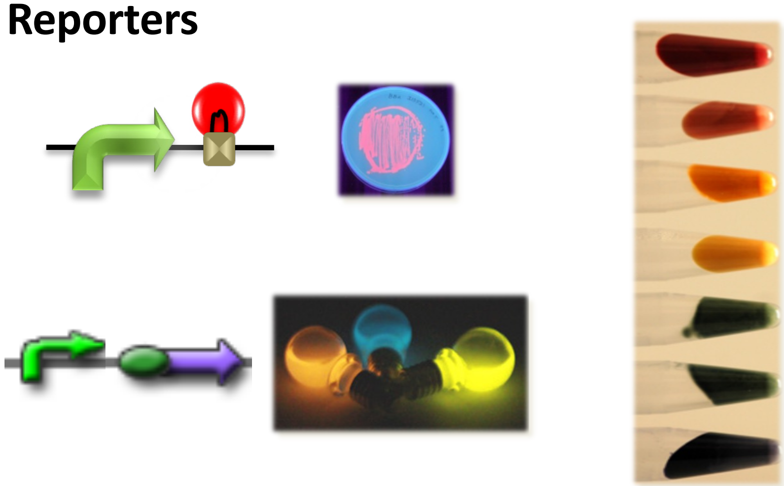
Regulation



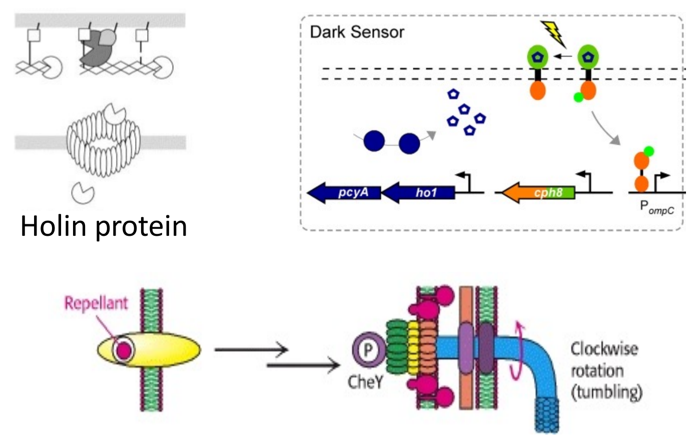
Cell-cell communication



Reporters



Interface with cell & environment



Decoupling and Orthogonal Systems

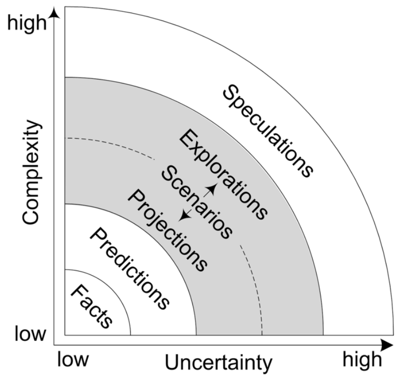
One problem with engineered biological systems is that they are biological systems!

The engineered system can't be isolated from the native system (cell). Therefore it is bound, often in unpredictable ways, to interact with the environment. Compounding this problem is the fact that biological systems are constantly changing…

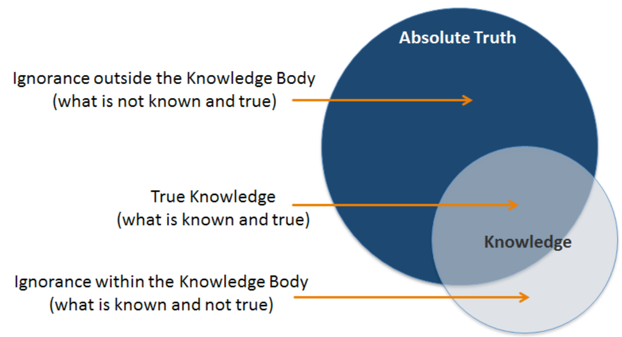
What to do about that?

- One could engineer orthogonal systems, which limit the interaction with the native system. This is difficult though and can only get you so far (how orthogonal can you really be?)
- One could do without the native system (cells)
- One could build protocells/minimal cells

What is different in biology?



Uncertainty



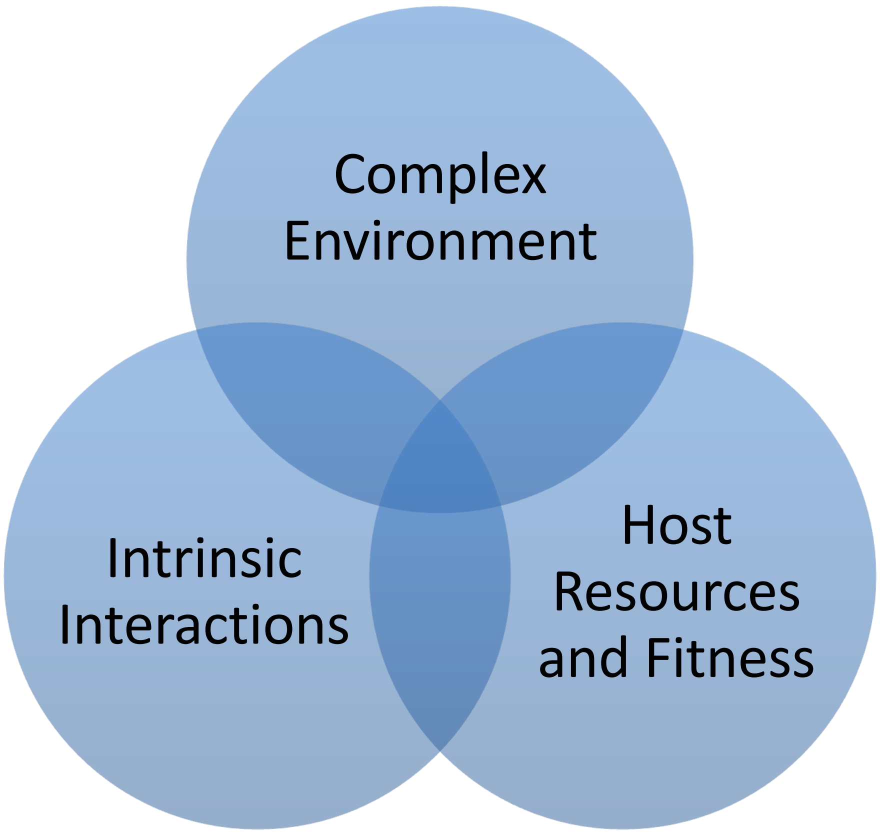
Ignorance

Growth and Mutation

<u>Challenges in engineering biological systems:</u>

- Rules of composition
- Noise
- Cellular context
- Environmental conditions
- Persistence
- Genetic mutations
- Crosstalk
- Cell death
- Incomplete models

Making life difficult (to engineer)



Key questions and thoughts

- What types of parts might be useful for engineering biological circuits?
- What sort of complicated functions inherent to the cell would we need to control?
- What might go wrong if we don't control these inherent functions?
- Bottom-up assembly vs. top-down design ? *(Pros and cons for each…)*
- Biomimetism versus artificial life?

Impact on Society: ethical issues

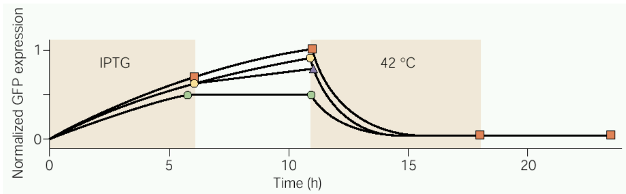
"Since synthetic biology is described as an engineering approach towards biology,
it seems convenient to use similar language to describe its inner workings.
These are terms that interdisciplinary researchers, engineers, data scientists, designers
and investors can understand. Through a technical lens, living organisms can be viewed as
controllable, modular systems that can be simply taken apart, standardised and re-assembled.
This point of view is beneficial for regarding single cells as mini drug-factories, or holy
Grails for cheap commercial production.

From manipulation to creationism
Yet, objectifying biological phenomena is a crucial conceptual step towards justifying its
exploitation. Machines and computers are designed and built by humans,
with each part made to serve a specific purpose. Machine metaphors cultivate an artificial
worldview into biological sciences, allowing researchers to break apart and assemble life
with a clear moral conscience. Many synthetic biology experiments focus on rebuilding an
organism from scratch in order to support a hypothesis of underlying its design. However,
the development of new "living machines" opens a philosophical debate about the nature
of life itself, and more importantly, whether humans can be creators of completely
new forms of life."

Dr. Joachim Boldt (research outreach)

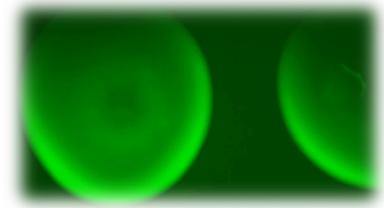
Applications: examples

Synbio: prototypes to systems to applications



Toggle switch

Oscillator



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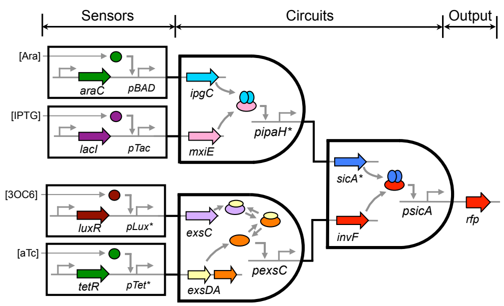
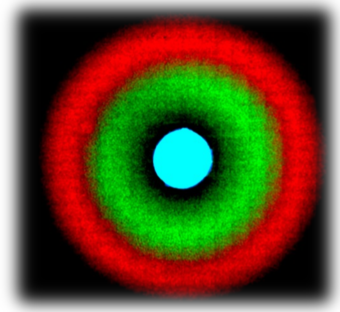
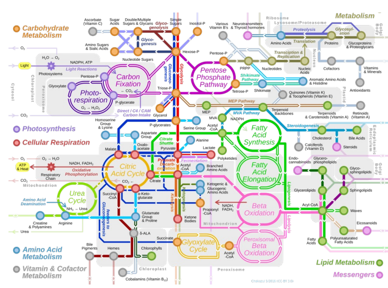


Multi-input functions

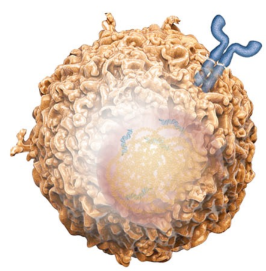
Synchronized Oscillators



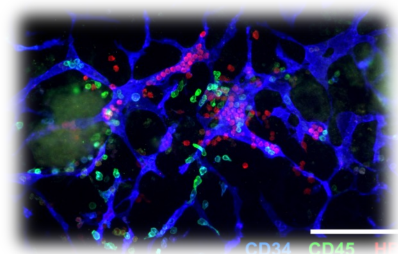
Band detect



Designer metabolic pathways in bacteria



Engineered T cells for cancer

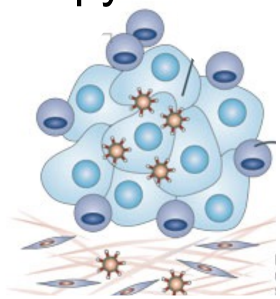


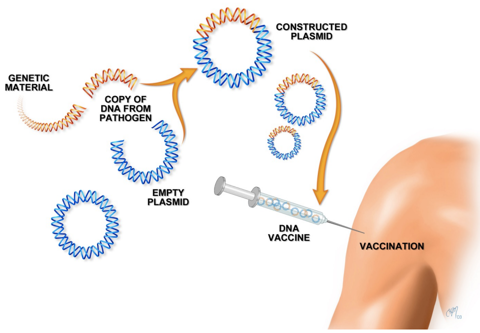
Programmable Organoids

time & scale

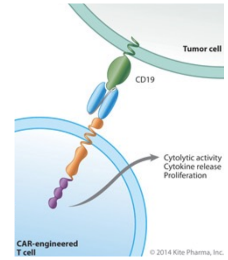
Synthetic biology health related applications

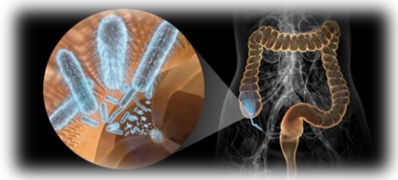
- ***In vivo* gene circuit delivery**
  - Oncolytic virus immunotherapy
  - Rare diseases
  - DNA/RNA Vaccines

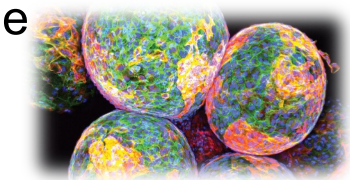




- **Cell-based therapies**
  - CAR T cells
  - Engineered tissues
  - Encapsulated beta cells
  - Engineered microbiome

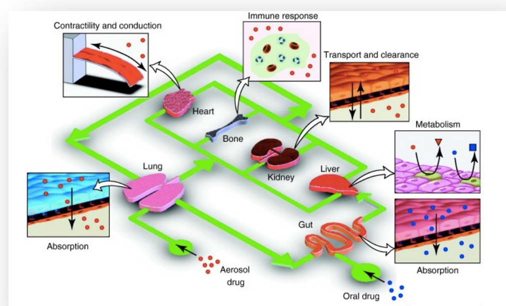




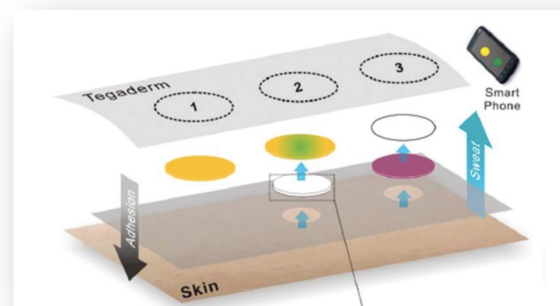


- **Biomanufacturing**

- **Drug development**



- **Diagnostics**



Lecture 1 plan

1. What is synthetic biology; why do we study it? Etc..

2. Class logic; lecture topics; schedule and logistics

Synthetic Biology: Lecture series

From molecules to circuit to cell engineering

Protein engineering (Patrick Barth)

Protein circuits (Patrick Barth)

Cell engineering (Patrick Barth)

Gene circuits (Sahand Rahi)

Scale
Complexity

Synthetic Biology: Lecture series

Lectures 2-5: **Protein engineering** (**Patrick Barth)**

1. Concepts and challenges in protein structure prediction and design

2. Design of protein fold and stability

3. Design of protein-ligand binding

4. Design of protein functions and selectivity

Synthetic Biology: Lecture series

Lecture 6-8 : **Mini protein design project**

Learn and apply state of the art AI-based approaches to tackle a molecular engineering challenge

Synthetic Biology: Lecture series

Lectures 9-11 : **Protein circuits** (**Patrick Barth)**:

Design of protein parts, interaction systems and protein-based circuits for robust cellular regulation and control

Systems biology concepts in pathways reprogramming; principles of synthetic pathways; interface with native components.

Synthetic Biology: Lecture series

Lectures 9-11 : **Cell engineering** (**Patrick Barth)**:

Towards eukaryotic cell engineering: application in synthetic cell engineering for cancer immuno therapy

Efforts and strategies toward building a synthetic cell from scratch; relationship with reductionist minimal genome approaches; applications in pathway and cell engineering.

Synthetic Biology: Lecture series

Lectures 12-13: **Gene circuit engineering** (**Sahand Rahi**):

Gene circuits in Synthetic Biology

Basic elements in the architecture of genetic circuits; Principles for the design of synthetic genetic circuits; Standardization in the components and methods in systems biology; Introduction to mathematical modeling and design.

Synthetic Biology: Lecture series

Lecture 14: **Recap and Questions/Answers session** (**Patrick Barth, EPFL)**

Synthetic Biology: Administrivia

- **Instructors**: Patrick Barth/ Sahand Rahi
- **Time:** Mon 13:00 – 15:00 (lectures) / Thu 9:00-11:00 (Exercises)
- **Moodle:** lecture slides, lecture notes, exercises
- **Location:** on campus
- **Office hours:** Barth/ Rahi/ Aye– By appt.
- **TA's:** Lorenzo Scutteri, Remo Battig, Naman Mishra, Yu Meng
- **Grading: Graded exercises during exercise sessions, Mini project & Final open-book exam** / mix of questions on concepts/knowledge covered during the lectures and questions similar to those covered during the exercise sessions

Synthetic Biology: Administrivia

Grading:

- **Graded exercises / mini project during exercise sessions: 40% of the final grade**

- **Final open-book exam:** mix of questions on concepts/knowledge covered during the lectures and questions similar to those covered during the exercise session

Preparation to final exam:

- Problem solving similar to final exam

- Mock exam