NSF Perspectives on Research Opportunities and Progress Towards Building a Synthetic Cell

NSF Nanoscale Science and Engineering Grantees Conference
December 6, 2018
Theresa Good, Deputy Division Director
Molecular and Cellular Biosciences
National Science Foundation

Synthetic Biology

The ability to predict the behavior and design complex biological systems,

Biological systems *(i.e., cells)* rely on exquisitely complex, high fidelity, self-replicating, adaptive, and responsive machines that utilize a wide range of starting materials, and that are refined via evolution.

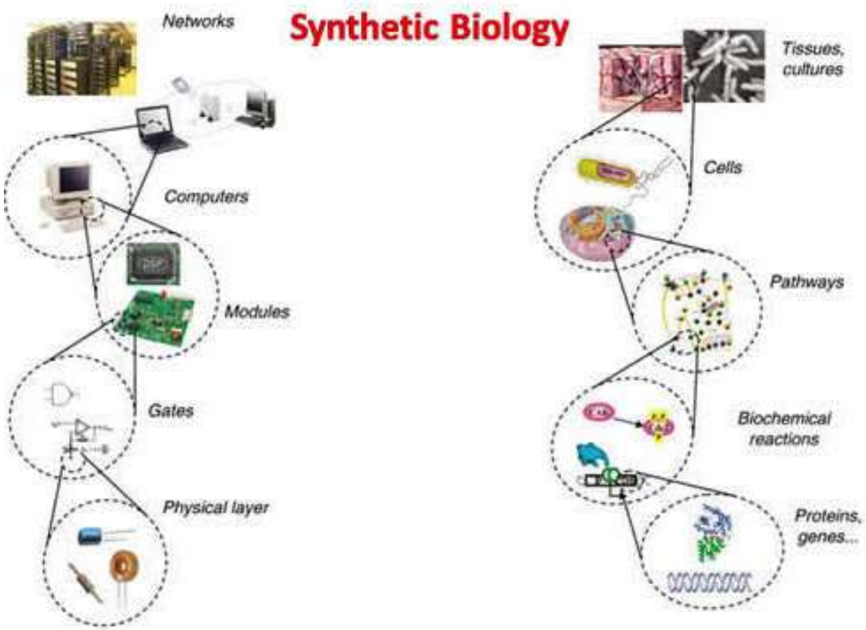
The challenge is to harness the intrinsic capabilities of biological systems:

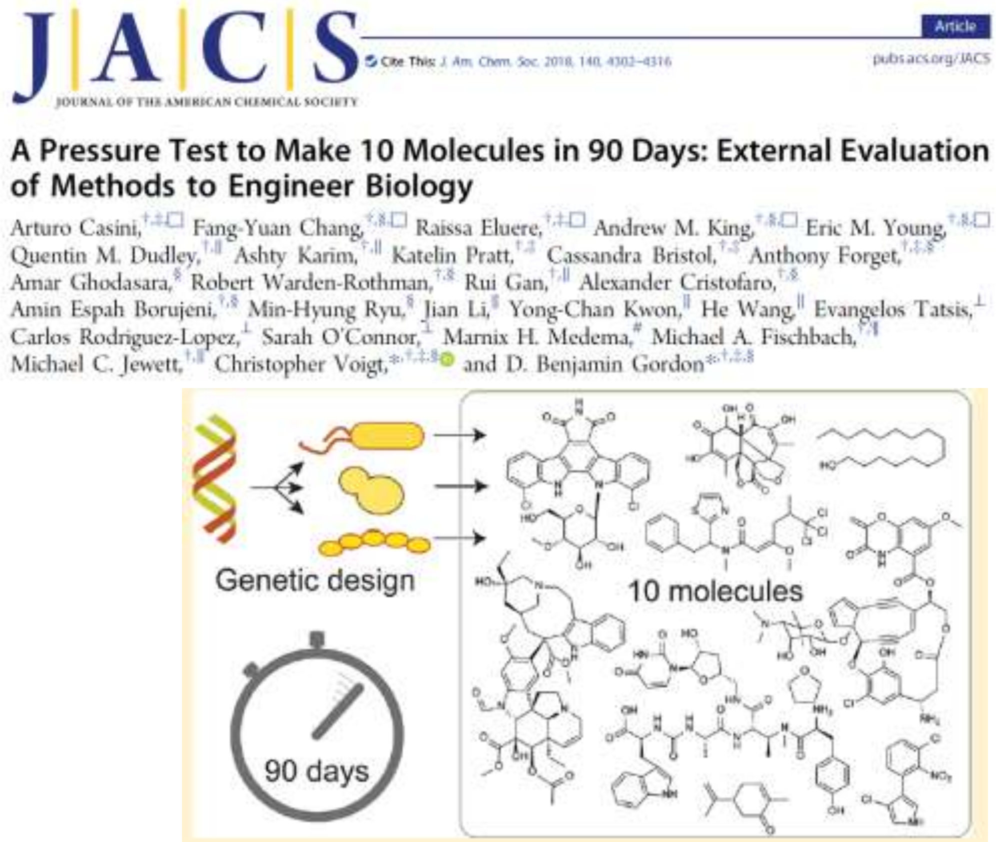
to build life like systems to explore the mechanisms that govern biology
to manufacture products that are of benefit to mankind
to cure human disease
to develop computing/ information storage devices
to use them as active materials that sense and respond to their environment

Why is building a synthetic cell a grand challenge for NSF:

- Common research challenges aimed at understanding the physical, chemical and biological principles that govern life (and building life like systems) will advance biology, engineering and related fields
- Catalyze the development of tools, techniques and methodologies for assembly, design and prediction of nanoscale molecular machines and cellular components
- Opportunities for formal and informal science education (think iGEM)
- Need to consider responsible research innovation (ELSI)

Synthetic Biology has come a long way




JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
Cite This: J. Am. Chem. Soc. 2018, 140, 4302−4316
pubs.acs.org/JACS

A Pressure Test to Make 10 Molecules in 90 Days: External Evaluation of Methods to Engineer Biology

Arturo Casini, Fang-Yuan Chang, Raissa Eluere, Andrew M. King, Eric M. Young, Quentin M. Dudley, Ashty Karim, Katelin Pratt, Cassandra Bristol, Anthony Forget, Amar Ghodasara, Robert Warden-Rothman, Rui Gan, Alexander Cristofaro, Amin Espah Borujeni, Min-Hyung Ryu, Jian Li, Yong-Chan Kwon, He Wang, Evangelos Tatsis, Carlos Rodriguez-Lopez, Sarah O'Connor, Marnix H. Medema, Michael A. Fischbach, Michael C. Jewett, Christopher Voigt, and D. Benjamin Gordon

Tom Knight, Drew Endy, MIT circa 2004

2018

History of Funding in Synthetic Biology

DOE funds 4 Bioenergy Centers

UK names synthetic biology one of 8 great technologies, invests 60 M GBP

DOE Agile Biofoundry

NSF/JST Metabolomics for a low carbon society

NIST Genome in a Bottle

DARPA announces Living Foundries

NSF participates in ERASynBio

DARPA 1000 molecules $110M

SynBERC funded

Safe Genes

SD2

Advanced Plant Technologies

SBIR synbio

STTR synbio

Directed Evolution

CBiRC funded

1998 2004 2006 2007 2008 2009 2011 2012 2013 2015 2016 2017

EBRC funded

First iGEM competition

DARPA convenes first synbio meetings

Synthetic biology sandpit w/ EPSRC

Systems & Synthetic Biology NSF

NIIMBL funded

Nitrogen fixation ideas lab w/BBSRC

Metabolic Engineering

DOE funds 3 Bioenergy Centers at $25M/year ea

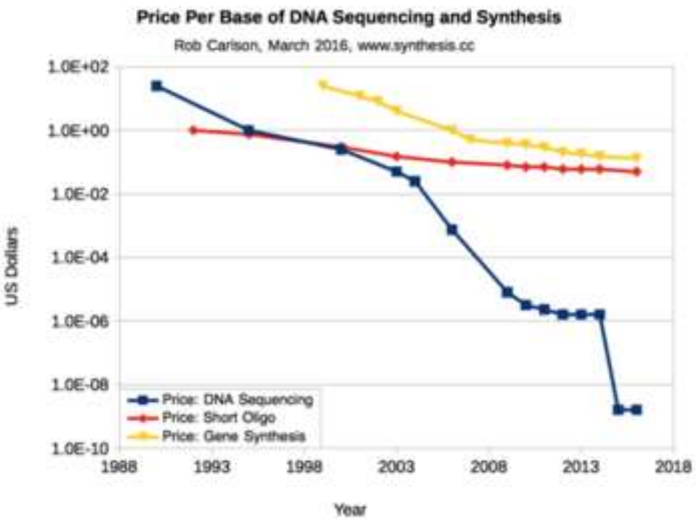
Enhancing photo-synthesis sandpit w/ BBSRC

Synthetic Biology part of NSF budget request for 1st time

Why shift focus from building synthetic gene circuits to building synthetic cells?

Research in the life sciences has fundamentally changed in the last 2 decades, **enabled by advances in other fields**.

- Advances in DNA sequencing, synthesis and assembly
- Reduced costs of DNA sequencing and assembly
- Discovery & development of CRISPR-Cas and other genome editing tools
- **Advances in microfluidics**
- **Advances in nano-fabrication**
- Advances in automation
- Advances in environmental, biological and behavioral sensor technologies
- Advances in artificial intelligence
- Advances in systems biology/ computation
- Advances in optical and imaging methods
- Advances in single molecule measurement techniques
- Advances in theory



Why Focus on Building a Synthetic Cell?

We have spent decades taking cells and organisms apart such that we can describe them at the molecular level. However, going in the other direction—from molecule to cell to organism—is the harder and more important goal of biology.

The tools of classical biology alone will not help us put those cells and organisms back together.

"Isn't it the hierarchical spatial organization that turns molecules into organisms? "

Daniel A. Fletcher, Bottom-Up Biology: Harnessing Engineering to Understand Nature. Developmental Cell - Volume 38, Issue 6, p587–589, 26 September 2016

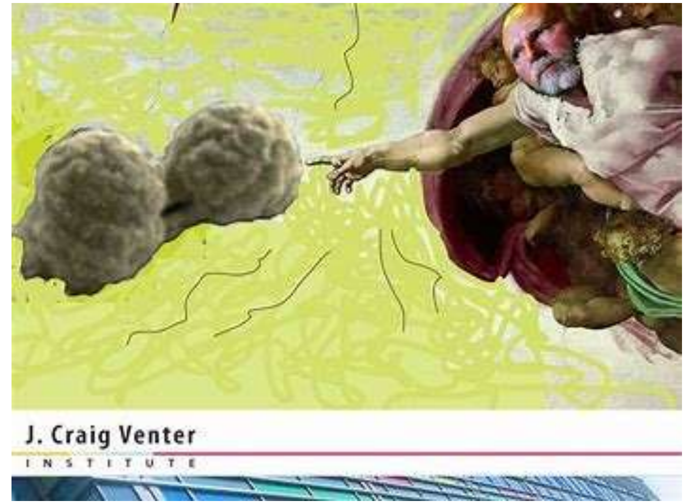
Building a Synthetic Cell has come a long way

Synthetic Red Blood Cells

Benefit or Detriment to Society?

Scenario

For many years, scientists have sought to design synthetic red blood cells (sRBCs) that can transport oxygen throughout the body. In 1957, Thomas Chang, then an undergraduate student at McGill University in Montreal, experimented with improvised materials in his dormitory to construct a permeable "cell" that carried hemoglobin, the iron-containing molecule in red blood cells responsible for oxygen transport in the body.



Scientists Create Synthetic Organism

By Robert lee Hotz
Updated May 21, 2010 12:01 a.m. ET

at a cost of $40M

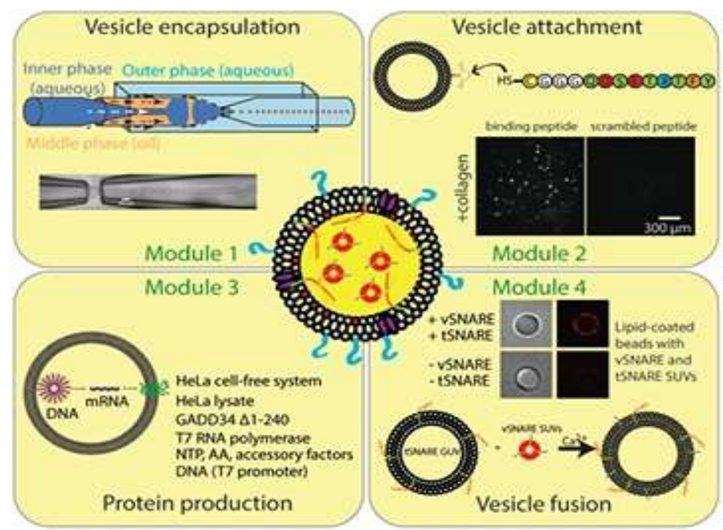
DNA cytoskeleton for stabilizing artificial cells

Chikako Kurokawa[a], Kei Fujiwara[b], Masamune Morita[c], Ibuki Kawamata[d], Yui Kawagishi[d], Atsushi Sakai[a], Yoshihiro Murayama[a], Shin-ichiro M. Nomura[d], Satoshi Murata[d], Masahiro Takinoue[c,1], and Miho Yanagisawa[a,1]

[a]Department of Applied Physics, Tokyo University of Agriculture and Technology, Tokyo 184-8588 Japan; [b]Department of Biosciences and Informatics, Keio University, Kanagawa 223-8522, Japan; [c]Department of Computer Science, Tokyo Institute of Technology, Kanagawa 226-8502, Japan; and [d]Department of Robotics, Tohoku University, Sendai 980-8579, Japan

Edited by Dan Luo, Cornell University, Ithaca, NY, and accepted by Editorial Board Member Herbert Levine May 30, 2017 (received for review February 9, 2017)

Bottom-up synthetic biology: modular design for making artificial platelets
Sagardip Majumder and Allen P Liu
2018 Phys. Biol.



Are all of the components of living systems essential in a synthetic cell?

- Compartmentalization
- Information maintenance and transmission
- Energy uptake/conversion
- Raw material uptake/conversion
- Growth and Division
- Adaptation and Response to Environment
- Homeostasis

Design and Engineering of Synthetic Cells and Cell Components (NSF DESYNC^3, 2018)

1 Conference, 12 EAGERs and 3 RAISEs funded in FY2018

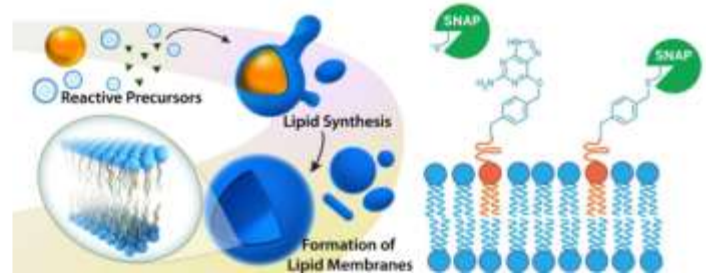
A platform for Modular Pseudo-Organelles for Compartmentalization and Control of Pseudo-Cell Processes
Engineering multi-compartmentalised synthetic minimal cells
Enzyme cascades in synthetic membraneless organelles
Membraneless organelles by design: a biomimetic approach
Synthetic Biogenesis of Eukaryotic Cells
Moving information across synthetic membranes via engineered sensors
Bottom-up Synthetic Cells Capable of Darwinism, the Archetypal Trait of Life

A Self-evolving independent ATP battery for Pseudocells
Mimicking Mitochondria: Developing Synthetic Pathways to Power Pseudo-Cell Functions using Diverse Fuel Resources
Using synthetic energy-harvesting materials at the cell surface to reduce low potential ferredoxins within the cytosol for metabolic applications
Programmable control of metabolism in synthetic cells using intrinsically disordered proteins

Emergent mechanics of synthetic cells
Programmable Porous Lipid Sponges as Synthetic Cell Factories
Engineering Microbial Differentiation
Membrane-based cell-free systems for scalable production of plant natural products

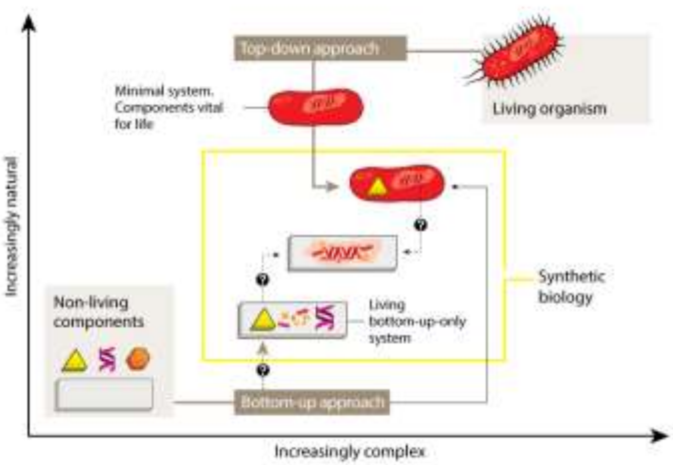
Some the current activities:

NSF STC at UCSF/UC Berkeley SFSU
Center for Cellular Construction

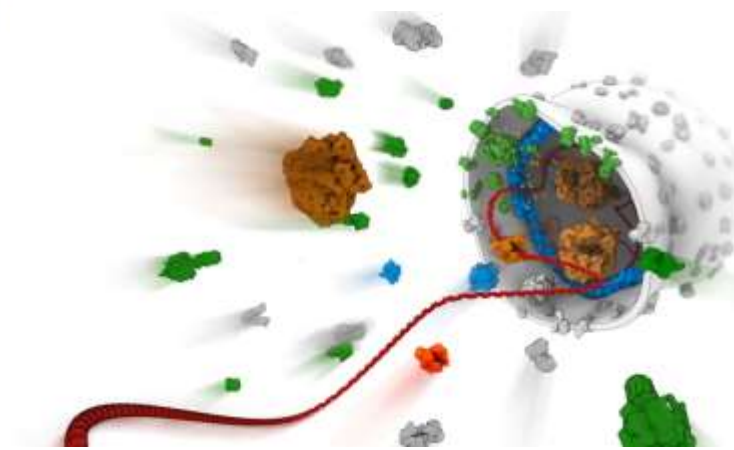


Artificial Cell MURI UCSD/ DoD

BUILD A CELL



MaxSynBIO (Germany)

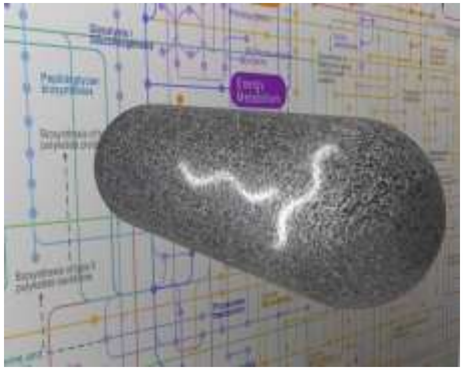


Synthetic cell FET Flagship (EU)

Synthetic Cell Ideas Lab ($10M):

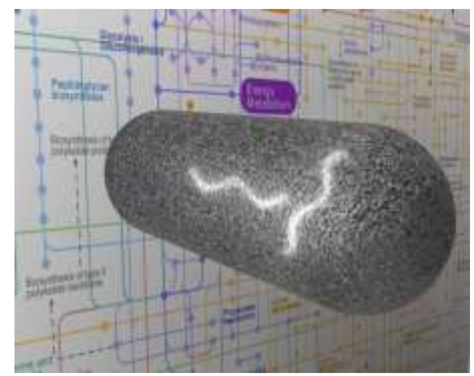
Can we design, build and control a synthetic cell? Realizing this grand challenge will enable us to uncover the **molecular and physical organization** of cells and cellular systems that enable **robust transmittal of information**, **capture and transformation of energy**, and **adaptation and regulation** of cellular systems that make life possible.

- Impacts on basic research, biomanufacturing, materials
- Opportunities for formal and informal science education
- Need to include ethics, societal impacts; mathematical, computational and engineering tools; theory from physics; deep knowledge of biology and chemistry

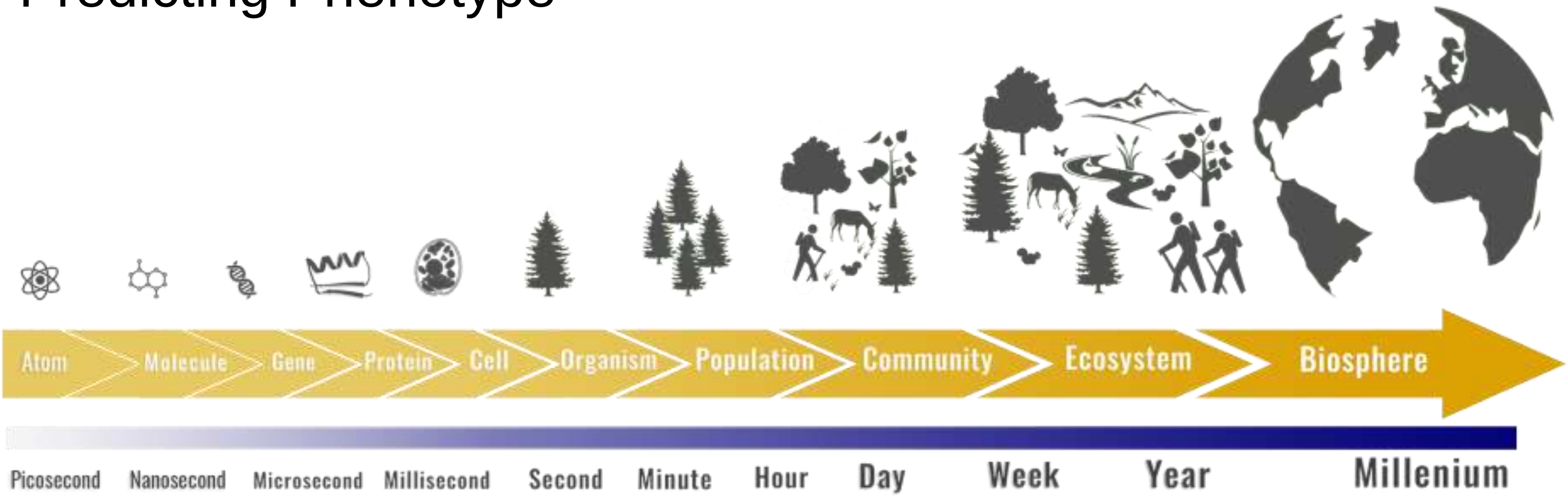


Understanding Rules of Life Solicitations: Synthetic Cell – An Ideas Lab Activity ($10M)

Preproposals Due: November 30, 2018
Ideas Lab held: February 25, 2019 – March 1, 2019
Full Proposals Due: May 13, 2019



Synthetic Cell is Part of the NSF Big Idea Understanding the Rules of Life: Predicting Phenotype



- Address diversity of solutions biological systems use to support life processes
- Convergent approach focused on theory
- Rules at all scales: Minimal, Interaction, Complexity
- Scale Invariant Rules
- Training and infrastructure to ensure capacity

Understanding the Rules of Life: Predicting Phenotype

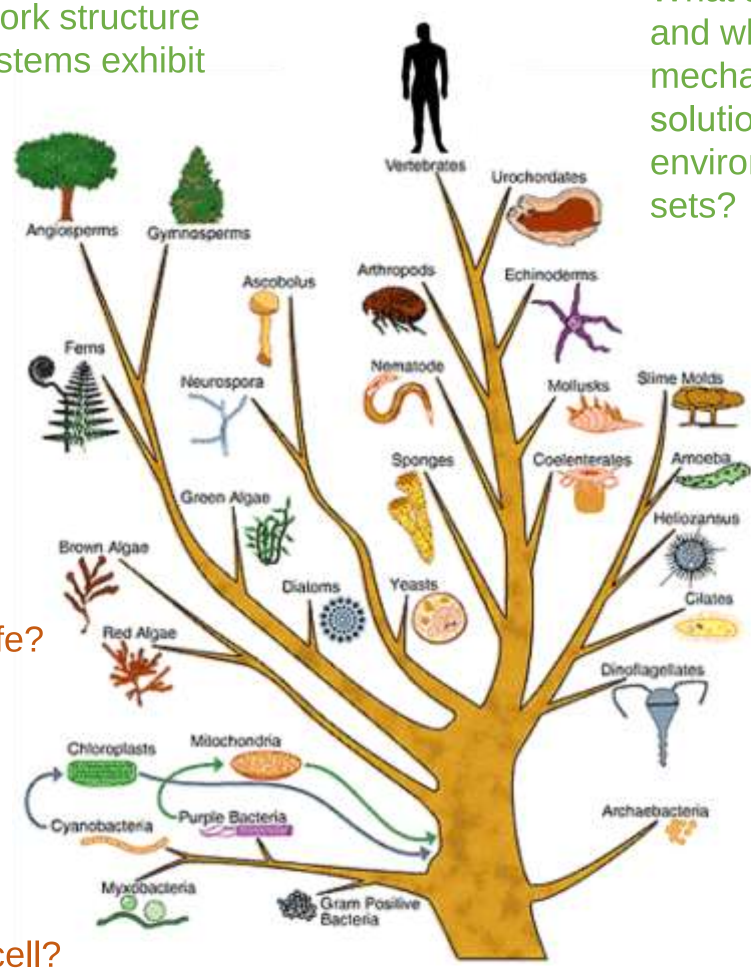
What regulatory network structure ensures that living systems exhibit robustness to noise?

What different mechanisms enable adaptation and homeostasis in different environments and at different time scales?

How do the same basic biochemical building blocks generate the vast diversity of life?

Could another set of genetic polymers be used to sustain life?

What is the minimal cell?



What are the set of constant mechanisms and what are the set of variable mechanisms that comprise the optimal solution to life’s challenges? What environments give rise to different solution sets?

What mechanisms of signaling are used between cells and between organisms, and how do they change as a function of time and length scales and in different environments?

The challenge to build a synthetic cell: “What I cannot create, I do not understand.” – Richard Feynman

Outcomes for Science and Society

"More Stakeholders, Broader Opportunities, Broader Impact"