Understanding the Rules of Life: Predicting Phenotype

Phenotype = the set of observable characteristics of an individual resulting from the interaction of its genotype with the environment.

Directorate for Mathematical & Physical Sciences
Advisory Committee Meeting
August 15, 2018

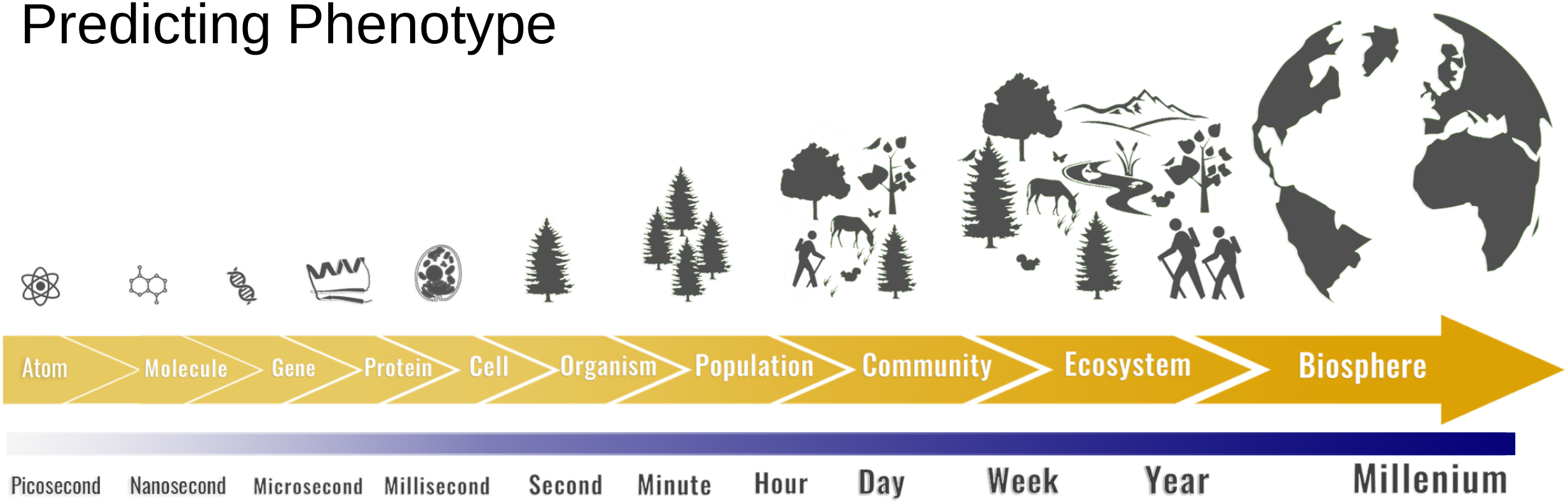
Catalina Achim (MPS)
Denise Caldwell (MPS)
Theresa Good (BIO)
Deborah Olster (SBE)

Understanding the Rules of Life: Predicting Phenotype

MPS has a long history of collaboration with BIO and support of research aligned with Rules of Life

- Funding programs in PHY, CHEM, DMS and DMR that support research at the interface with Biological Sciences
- BioMAPS and the collaboration and cofunding that led to its development
- Joint support of Physics Frontiers Centers, NSF-Simons Math-BIO Centers
- Interagency activities in synthetic biology, nanoscience, bioinspired design

Understanding the Rules of Life: Predicting Phenotype

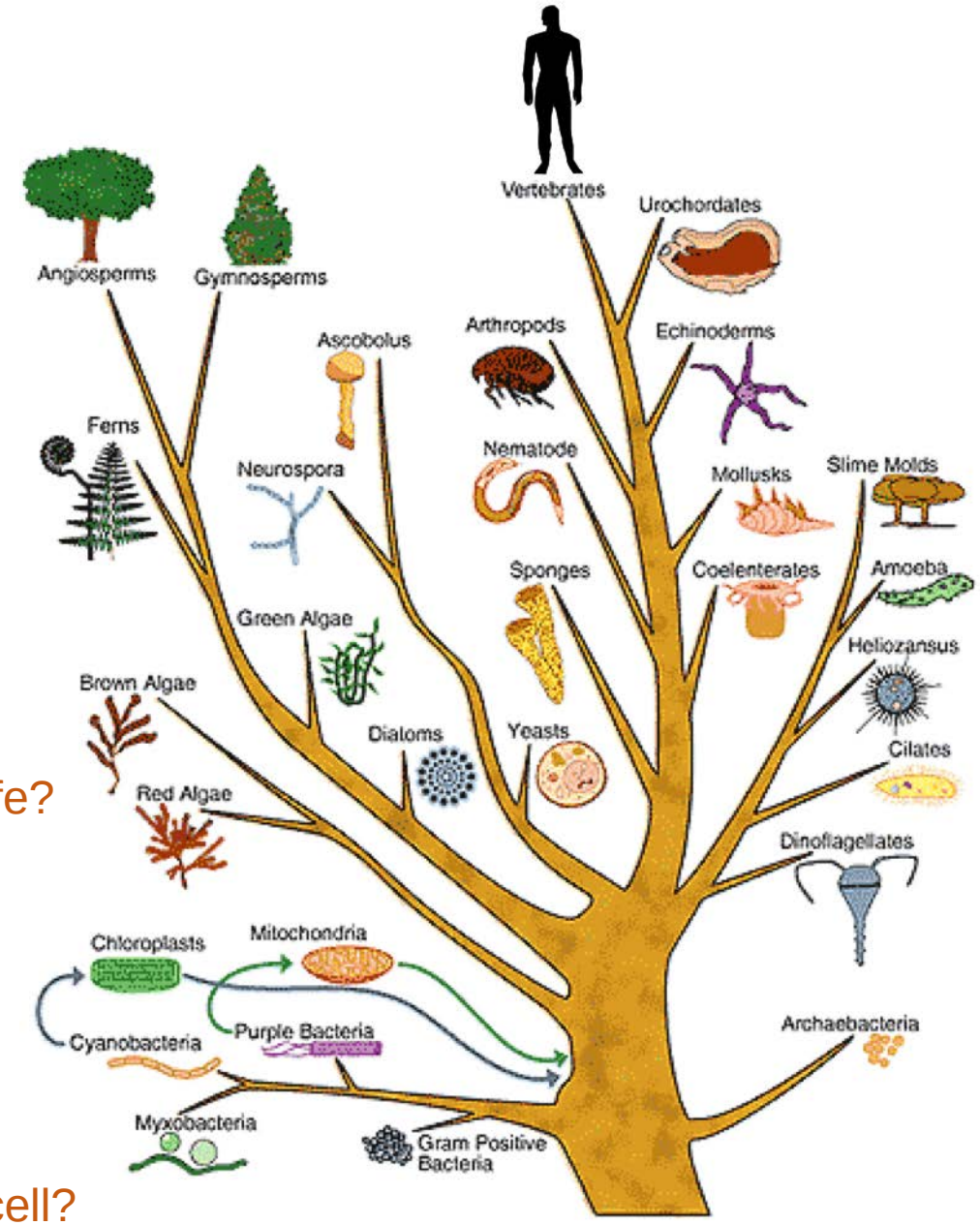


- Address diversity of solutions biological systems use to support life processes
- Convergent approach focused on theory
- Rules at all scales: Minimal, Interaction, Complexity
- Training and infrastructure to ensure capacity

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?



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

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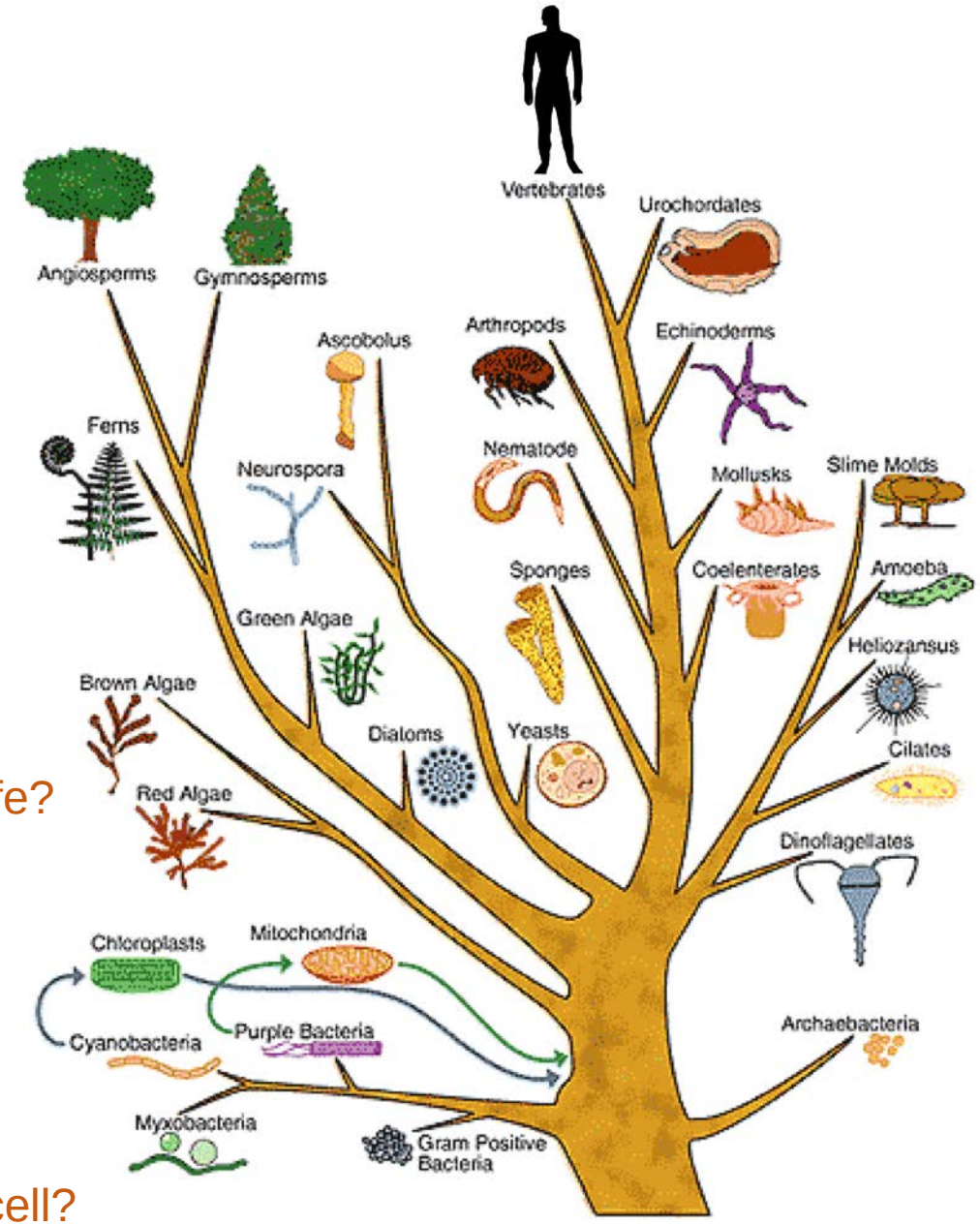

What mechanisms of signaling are used between cells and between organisms, and how do they change as a function of time and length scales and in different environments?

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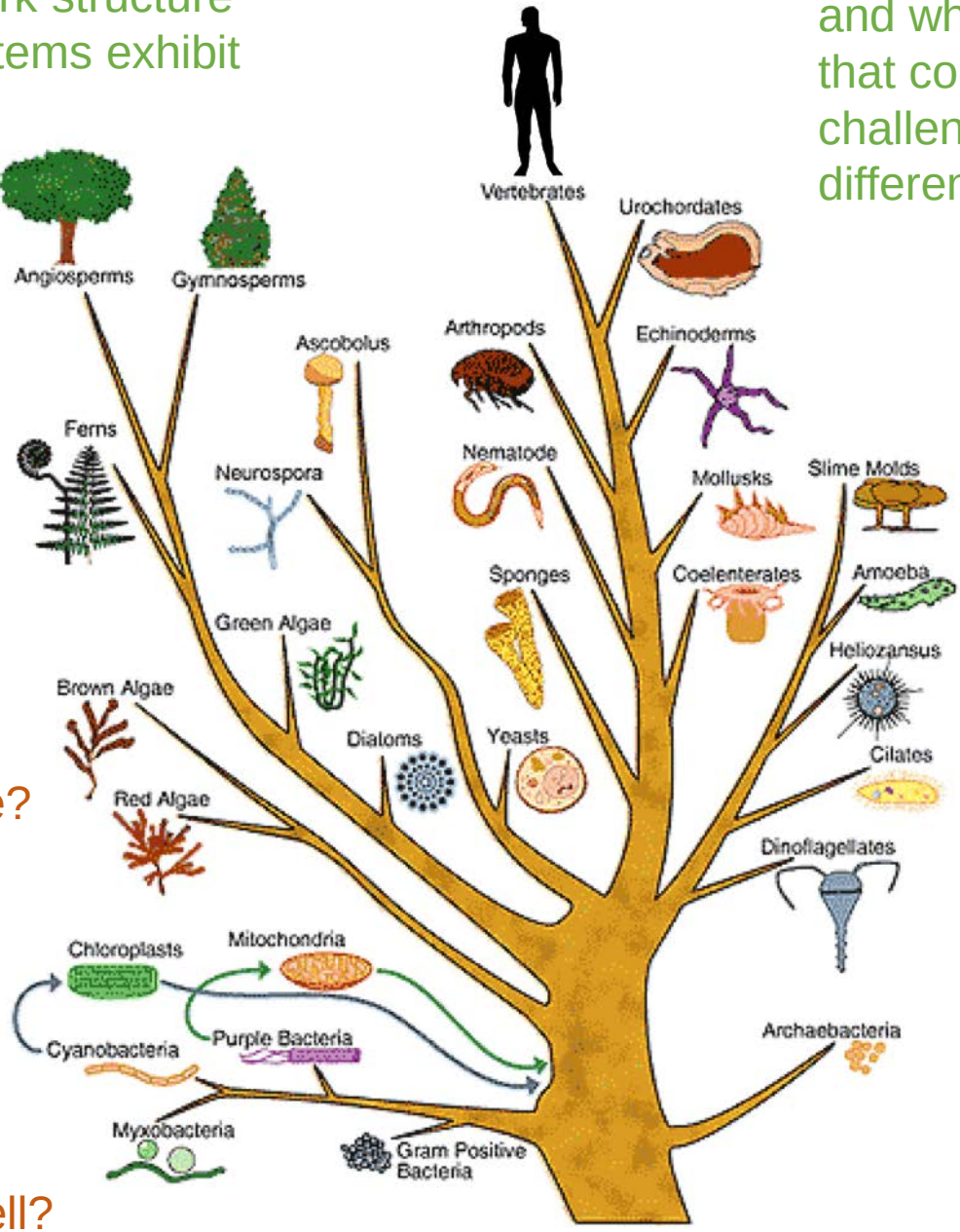
What regulatory network structure ensures that living systems exhibit robustness to noise?

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



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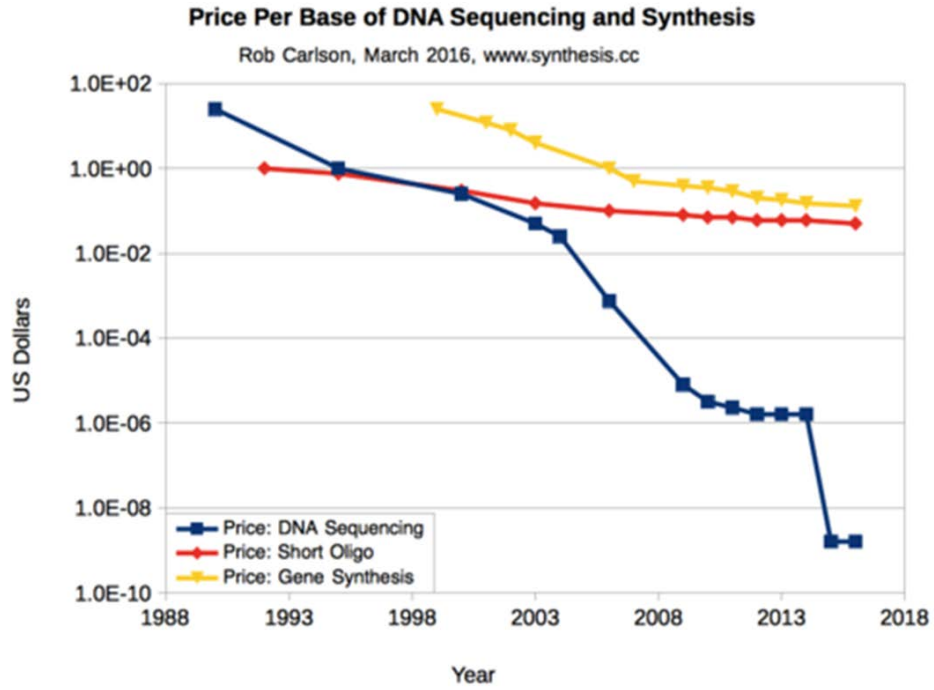
Why Invest in Understanding the Rules of Life Now?

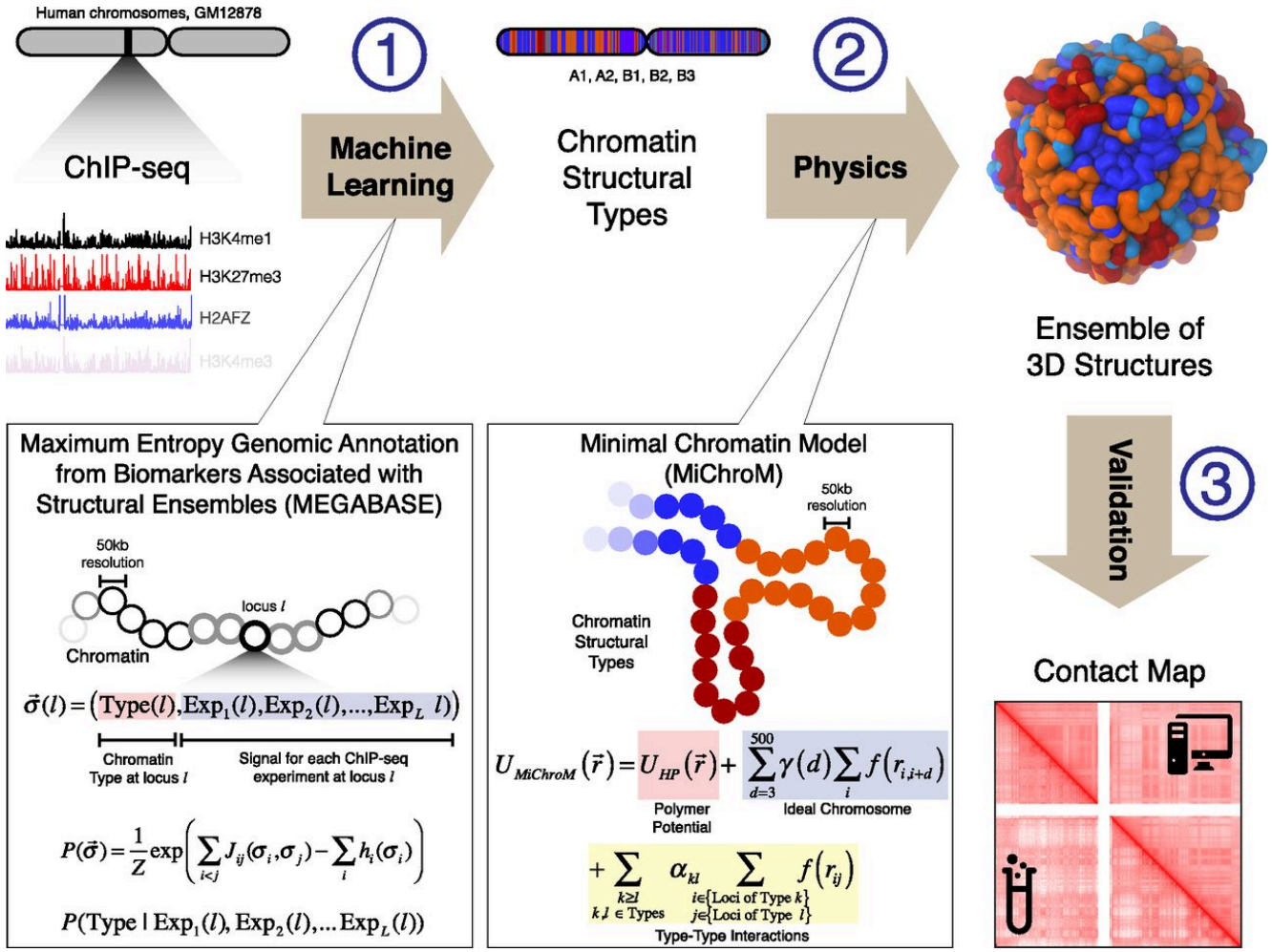
Research in the life sciences has fundamentally changed in the last 2 decades, **enabled by advances in other fields**. A convergent approach integrating many disciplines is needed to elucidate the rules of life.

- Advances in DNA sequencing, synthesis and assembly
- Reduced costs of DNA sequencing and assembly
- 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
- Discovery & development of CRISPR-Cas and other genome editing tools



Topics of Interest from Across the NSF (1)

Using fundamental theory from physics to understand and predict 3D chromatin structure, and how structure governs expression & phenotype



Michele Di Pierro et al. *PNAS* 2017;114:12126-12131

Topics of Interest from Across the NSF (2)

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

Topics of Interest from Across the NSF (3)

Using ancient DNA to gain insight into the origins of humans, the adaptation of humans to environment, patterns of human migration, and how human diversity arises from social and environmental interaction.

Understanding the Rules of Life Dear Colleague Letters

- Growing Convergent Research at NSF (2017)
  - Research Coordination Network: Cross Scale Processes Impacting Diversity
  - Research Coordination Network for Exploration of Life's Origins
- Rules of Life: Forecasting and Emergence in Living Systems (FELS, 2018)
- Signals in the Soil (SitS, 2018)
- Design and Engineering of Synthetic Cells and Cell Components (DESYNC^3, 2018)

- Solicitations (FY 2019) – stay tuned!

Outcomes for Science and Society

"More Stakeholders, Broader Opportunities, Broader Impact"