Big picture domains

- Bioinformatics
- Molecular biophysics and biochemistry
- Systems Biology

Bioinformatics

- Infrastructure (all of CS) for integrating multiscale modeling and data
- Diversity across scales: mechanisms, materials, assays, models, labs…
- Assessment of (predictions from) models and their analysis including interaction with experiments (e.g. structure prediction)

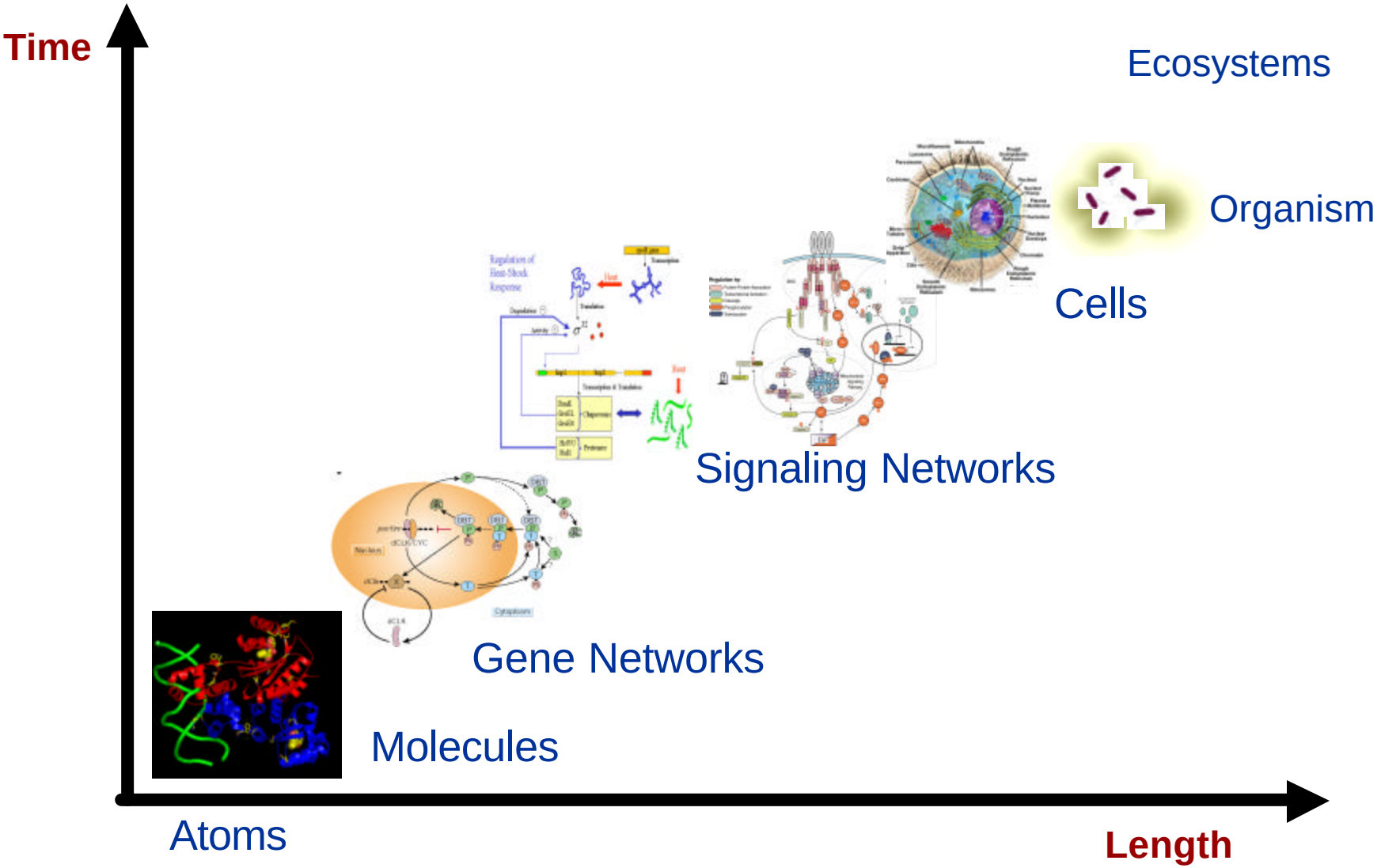
Molecular biophysics and biochemistry

- Hierarchical self-assembly of macromolecules, structures, and devices
- Dynamics of (trans)-membrane processes
- Molecular machines
- Analysis and design of energy landscapes (generalizations?)

Systems Biology

- Analysis of large scale structures/networks
- Bacterial ecosystems, biofilms, cooperative behavior
- “Horizontal within level” : heterogeneous, diverse, stiff, at every level

Multi-Scale Approaches to Modeling and Analysis



Multi-Scale Approaches to Modeling and Analysis

Time & Space

Collapse to Single Axis

Data Sources for Multi-Scale Modeling

Time & Space

Organism

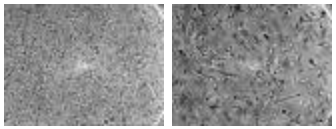
Cells

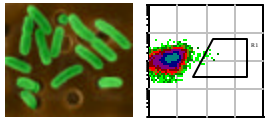
Signaling Networks

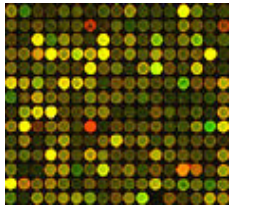
Gene Networks

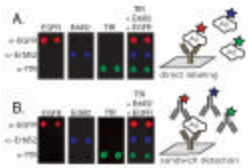
Molecules

Atoms









lux Signaling

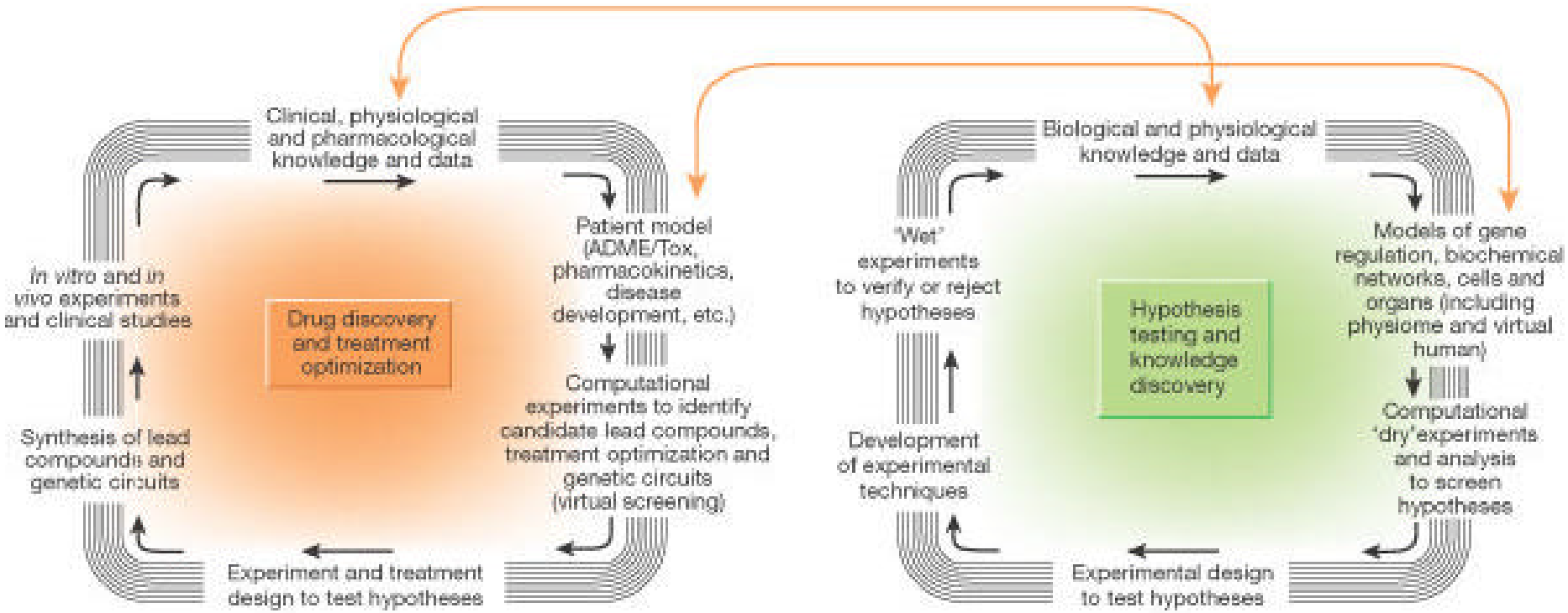
Flow Cytometry

Bacterial Display for Rapid Peptide Ligand Isolation

Localization Assay (ChIP)

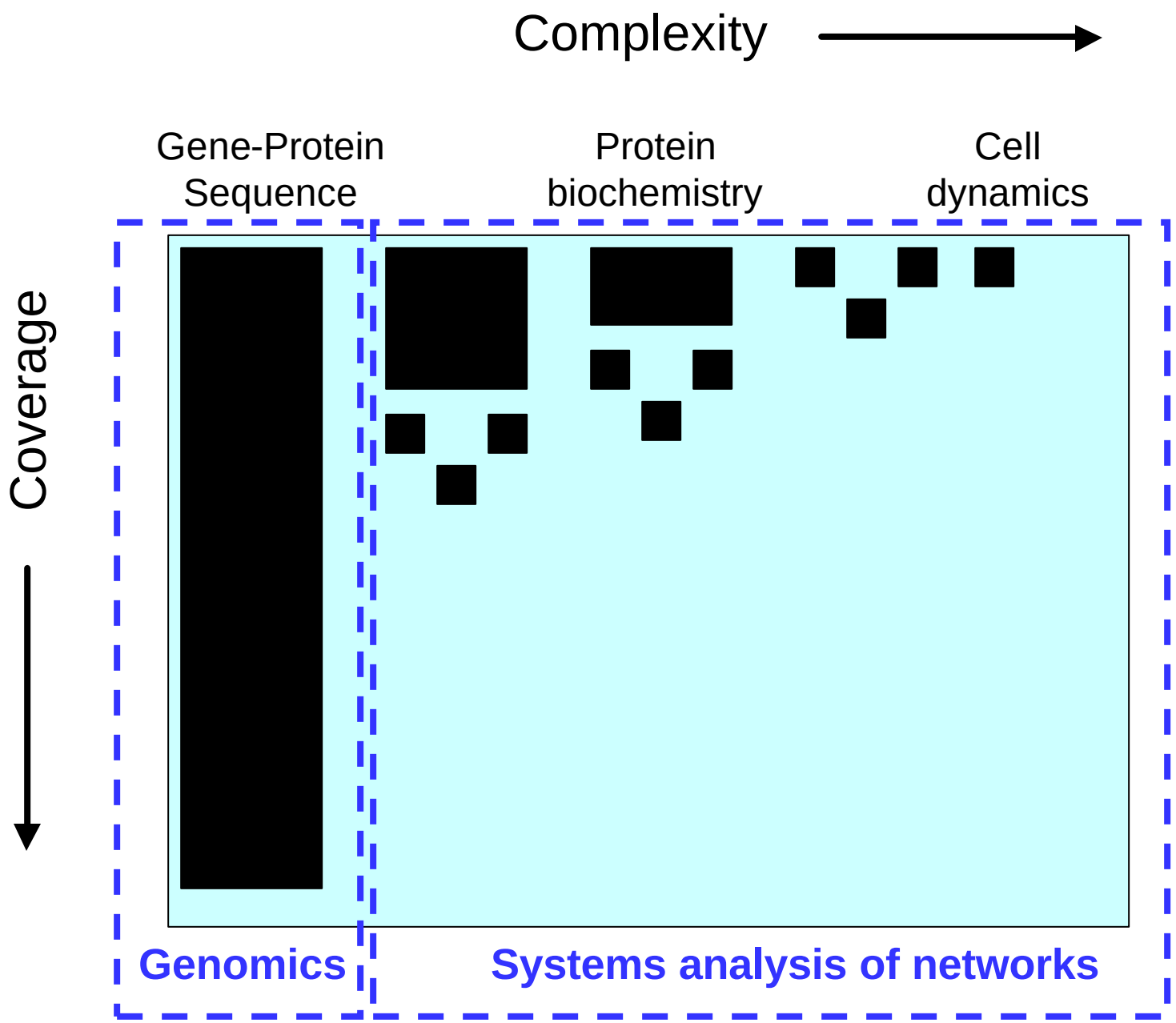
Gene Expression MicroArrays

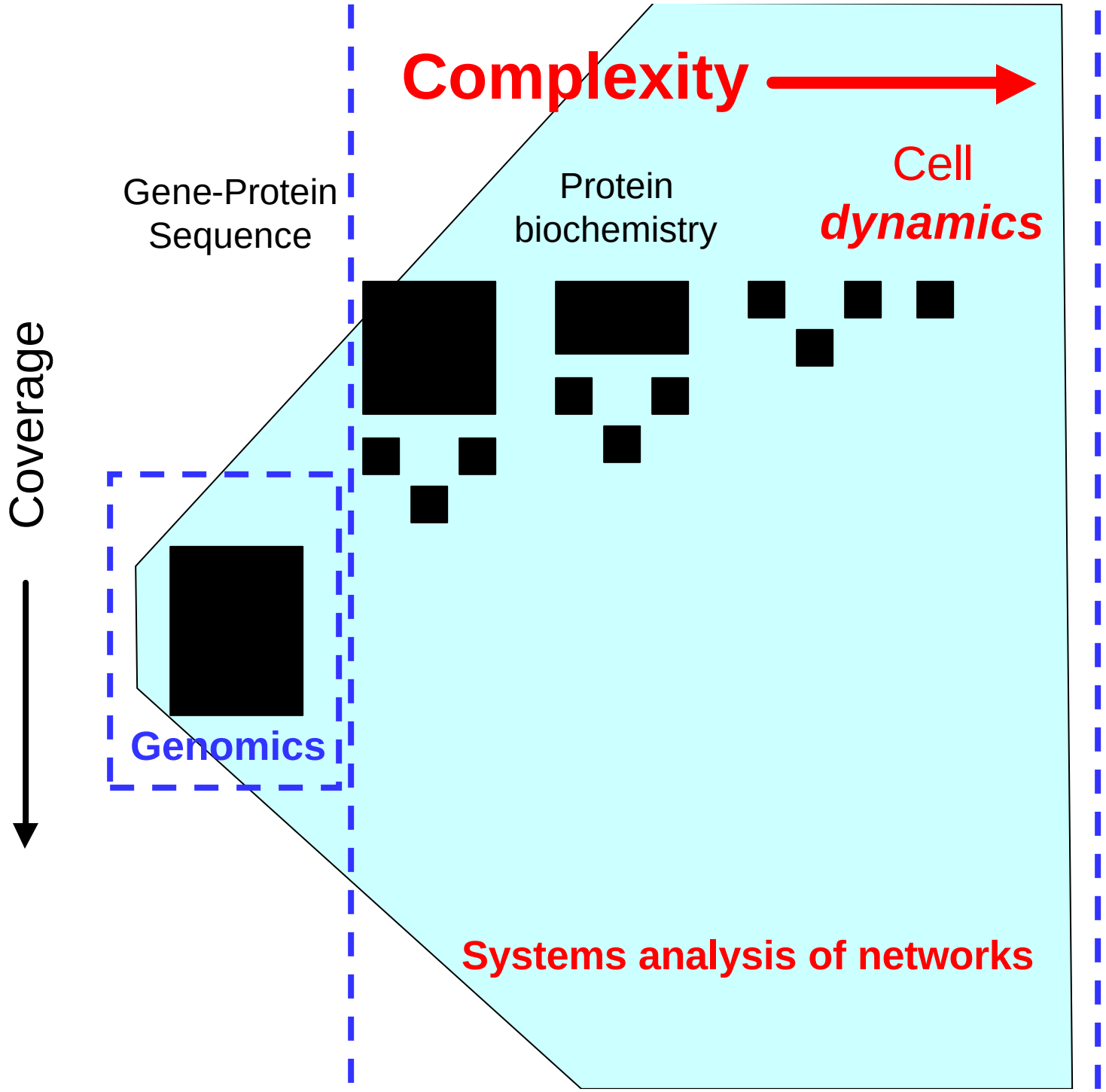
Protein MicroArrays



The iteration between experiment, modeling, and systems analysis

Kitano, Nature, 2002


Complexity
Gene-Protein Sequence
Protein biochemistry
Cell dynamics
Coverage
Genomics
Systems analysis of networks


Complexity
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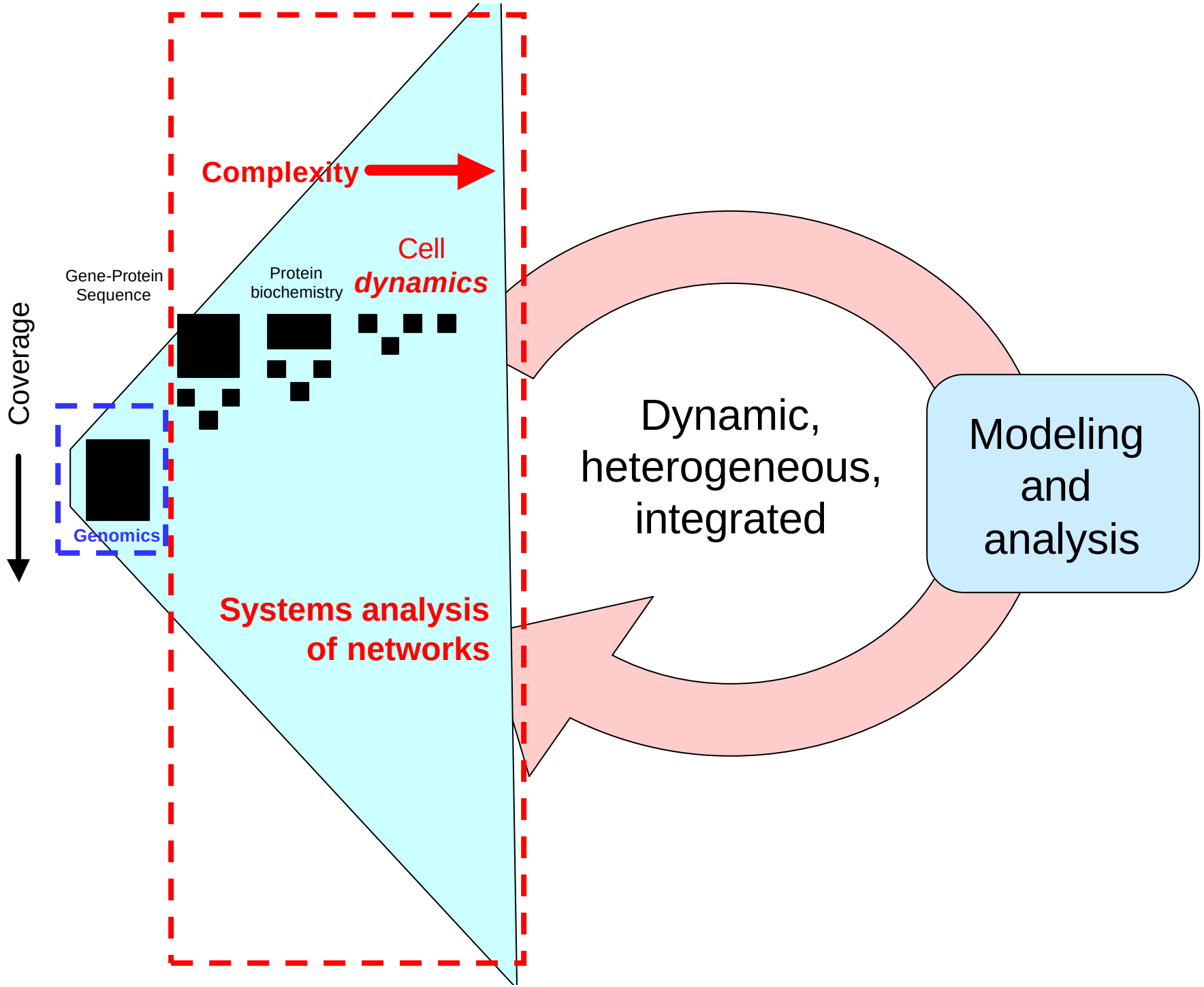
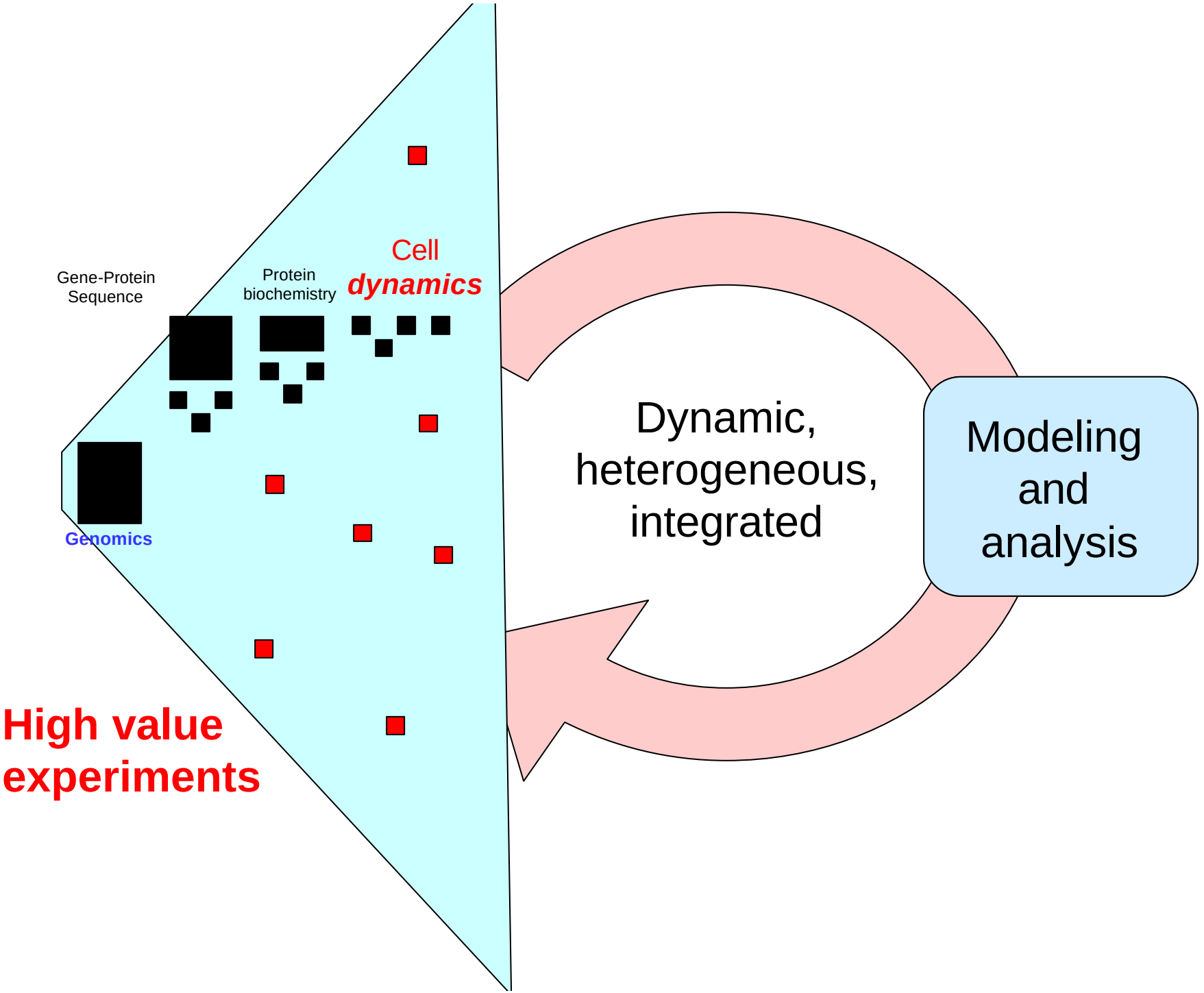

Complexity
Cell
dynamics
Gene-Protein
Sequence
Protein
biochemistry
Coverage
Genomics
Systems analysis
of networks
Dynamic,
heterogeneous,
integrated
Modeling
and
analysis


Gene-Protein
Sequence
Protein
biochemistry
Cell
dynamics
Genomics
Dynamic,
heterogeneous,
integrated
Modeling
and
analysis
High value
experiments

Characterization Tools for Multi-Scale Modeling

Time & Space

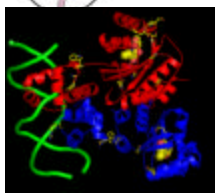
Ecosystems

Organism

Cells

Signaling Networks

Gene Networks



Molecules

Atoms

light microscopy

deconvolution

MRI, PET

electron microscopy

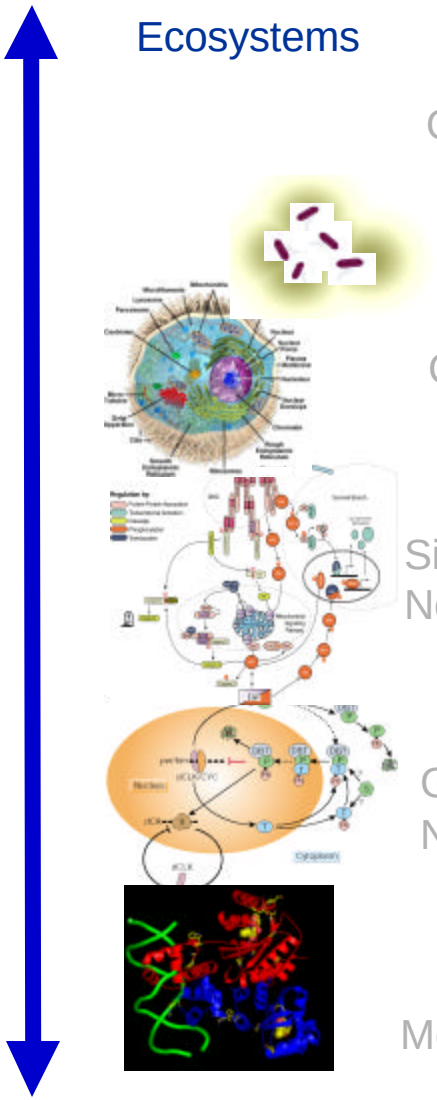
cryo

NMR, X-rays

AFM

Tools for Multi-Scale Modeling

Time & Space



Ecosystems

Organism

Cells

Signaling Networks

Gene Networks

Molecules

Atoms

Model Reduction

Bayesian Methods

Stochastic Simulation (Gillespie)

Field Theoretic Methods

Atomistic Simulation

SBML Toolkit

Multi-Scale Challenges

Time & Space

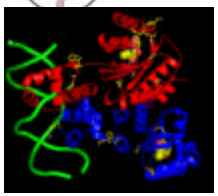
"Vertical:" connect different scales

Organism

Cells

Signaling Networks

Gene Networks



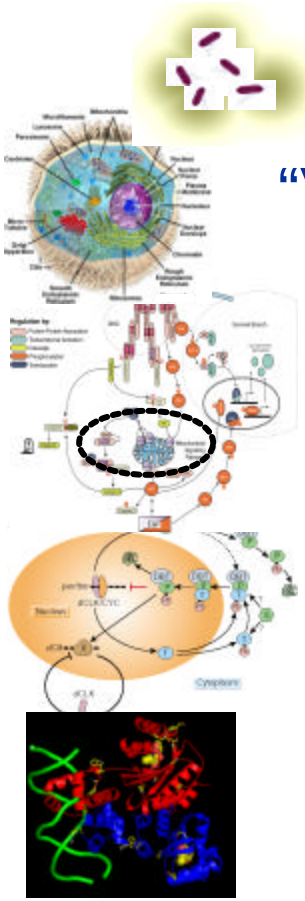
Molecules

Atoms

"Horizontal:"
each level is vast, complex network of dynamically interacting heterogeneous components

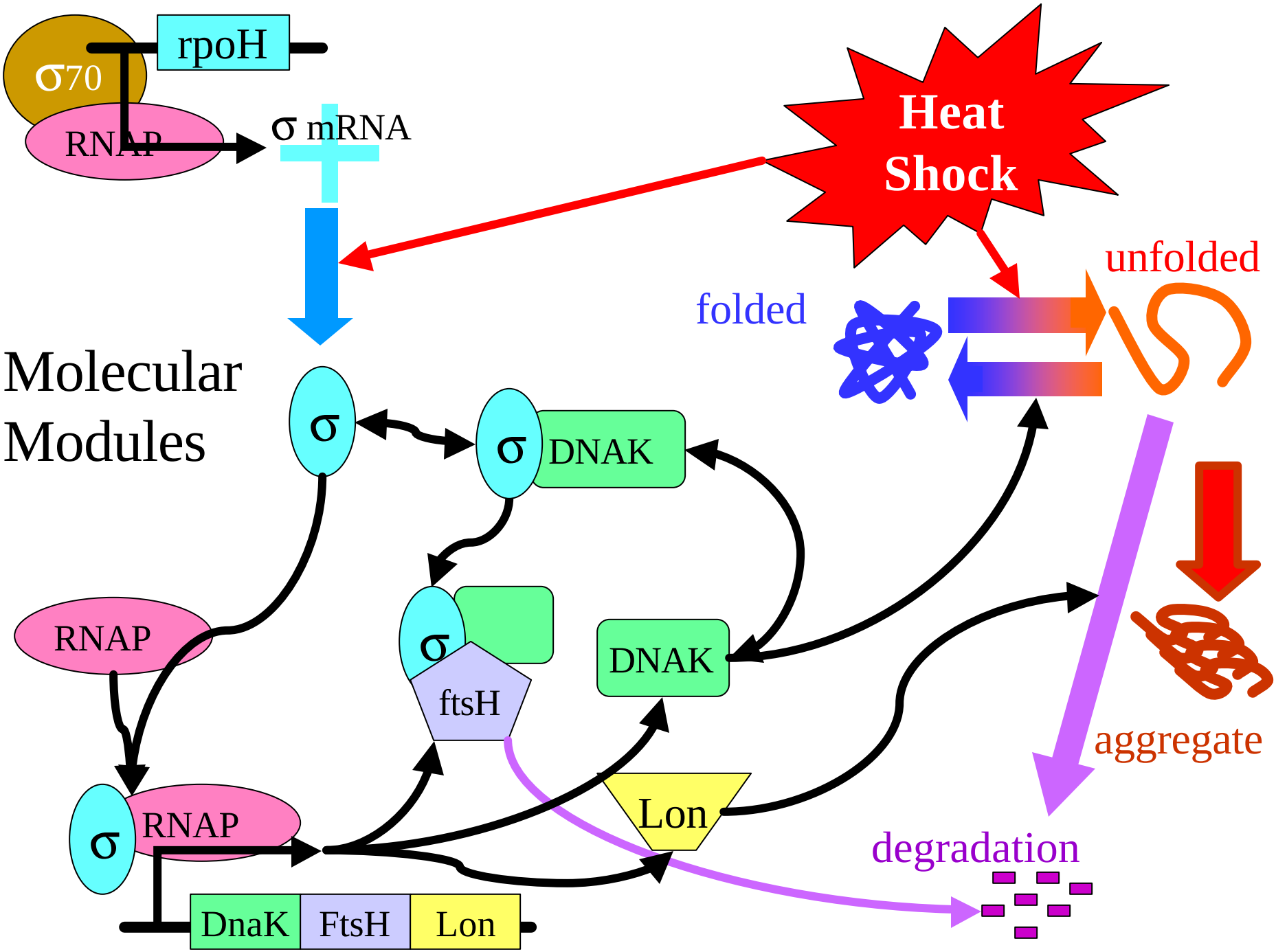
Time & Space

Network issues are intertwined

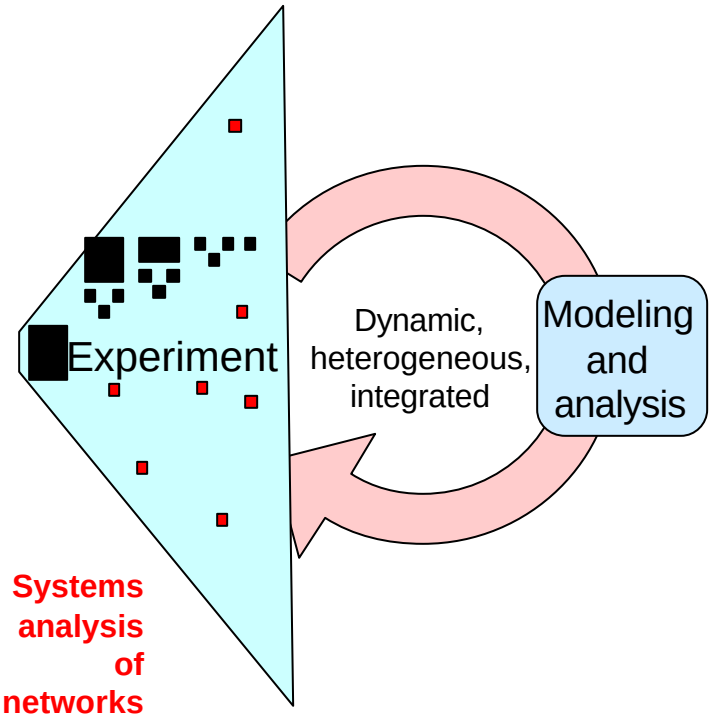


“Vertical”

“Horizontal”

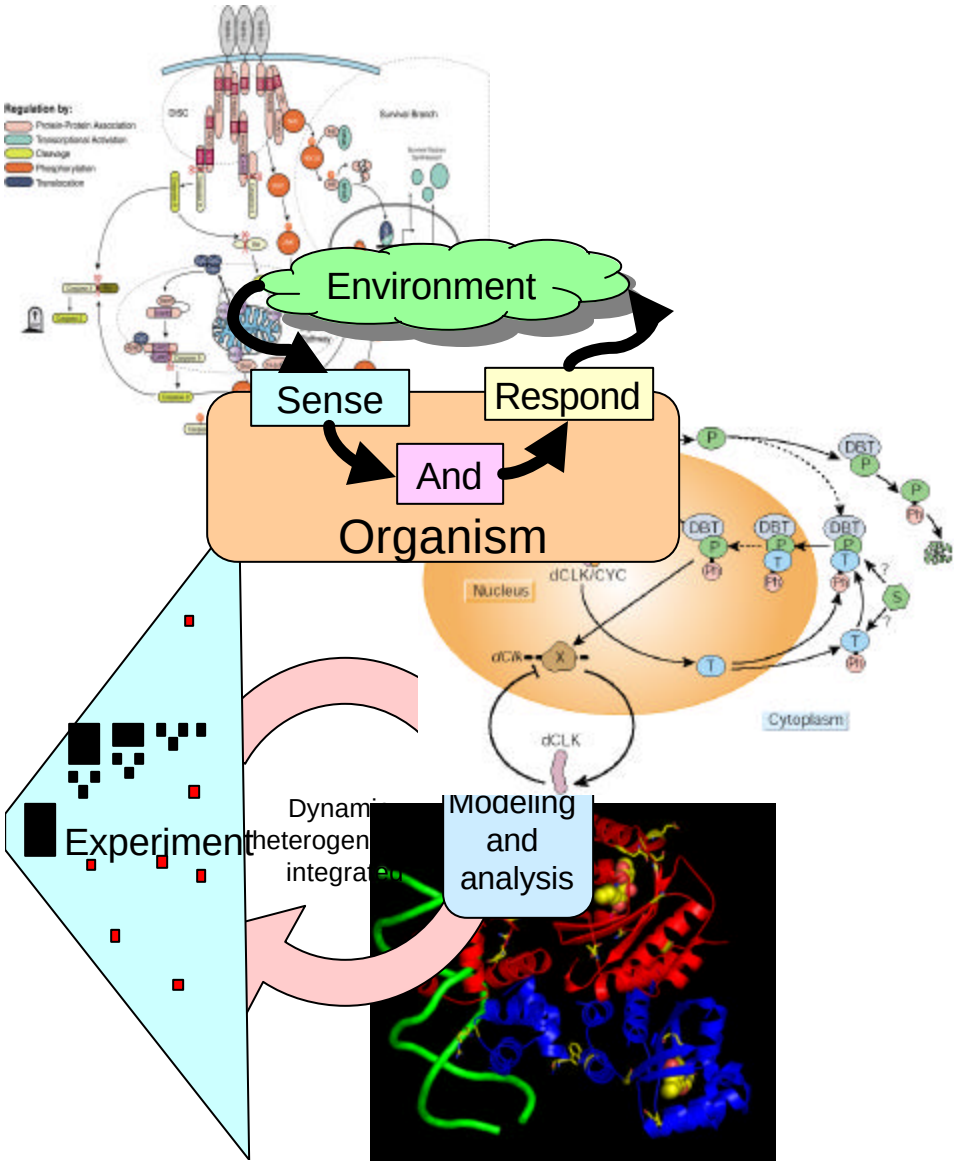

σ70
rpoH
RNAP
σ mRNA
Heat
Shock
unfolded
folded
Molecular
Modules
σ
σ
DNAK
RNAP
σ
ftsH
DNAK
aggregate
σ
RNAP
Lon
degradation
DnaK
FtsH
Lon

Key Theory Challenges and Breakthroughs

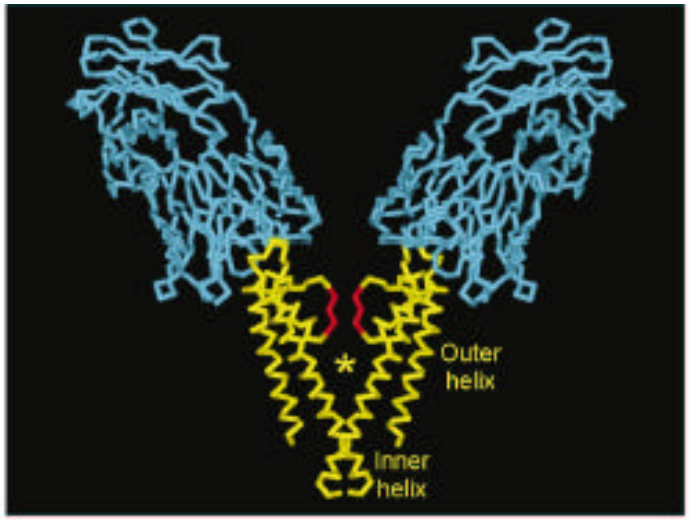


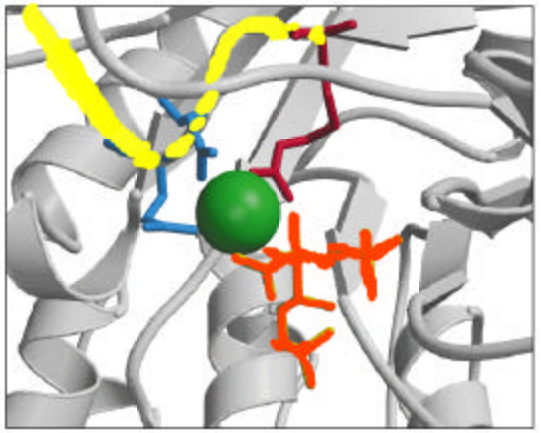
- Simulation alone is inadequate.
- Many biologically relevant questions require exponentially large number of simulations to resolve (NP-hard).
- For example, proving that a model structure cannot explain a data set, no matter what parameters are chosen.
- Systematic (polynomial time) nested relaxations (guaranteed to converge) for robustness analysis (necessity of lyapunov-like methods) for complex networks.
- Extends to creating barrier functions that can invalidate sets of models with respect to data.
- Builds on operator theory, real algebraic geometry, control, dynamical systems, computational complexity, numerical analysis.
- See poster for details and relevance to biological networks.

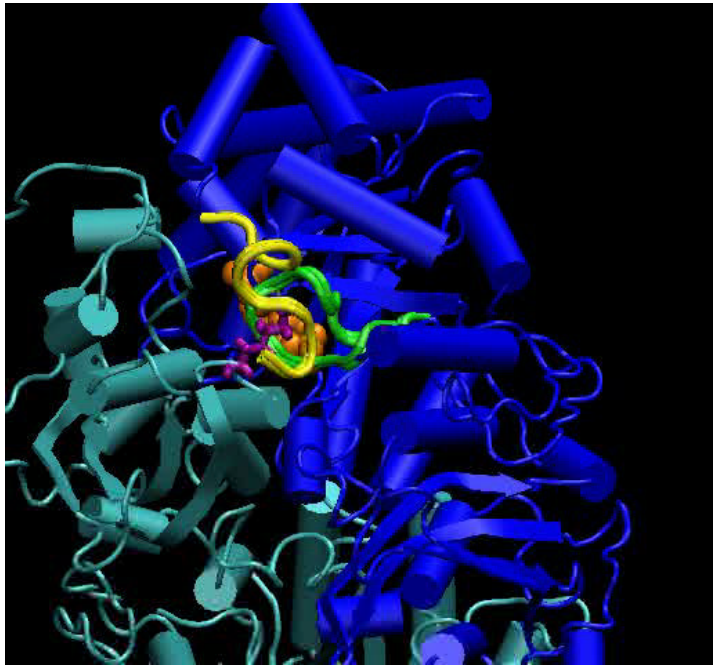
Multidisciplinary Challenges

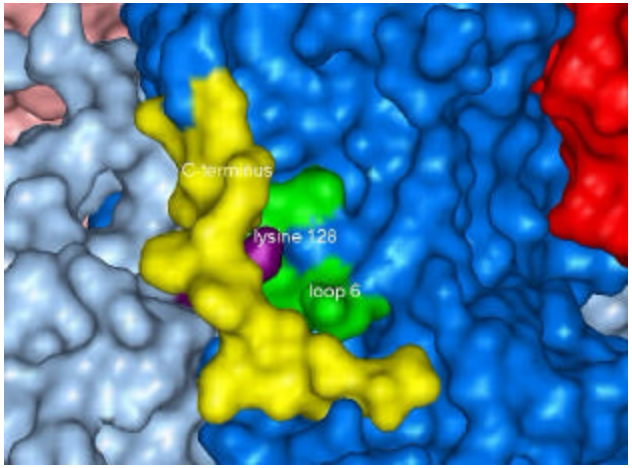


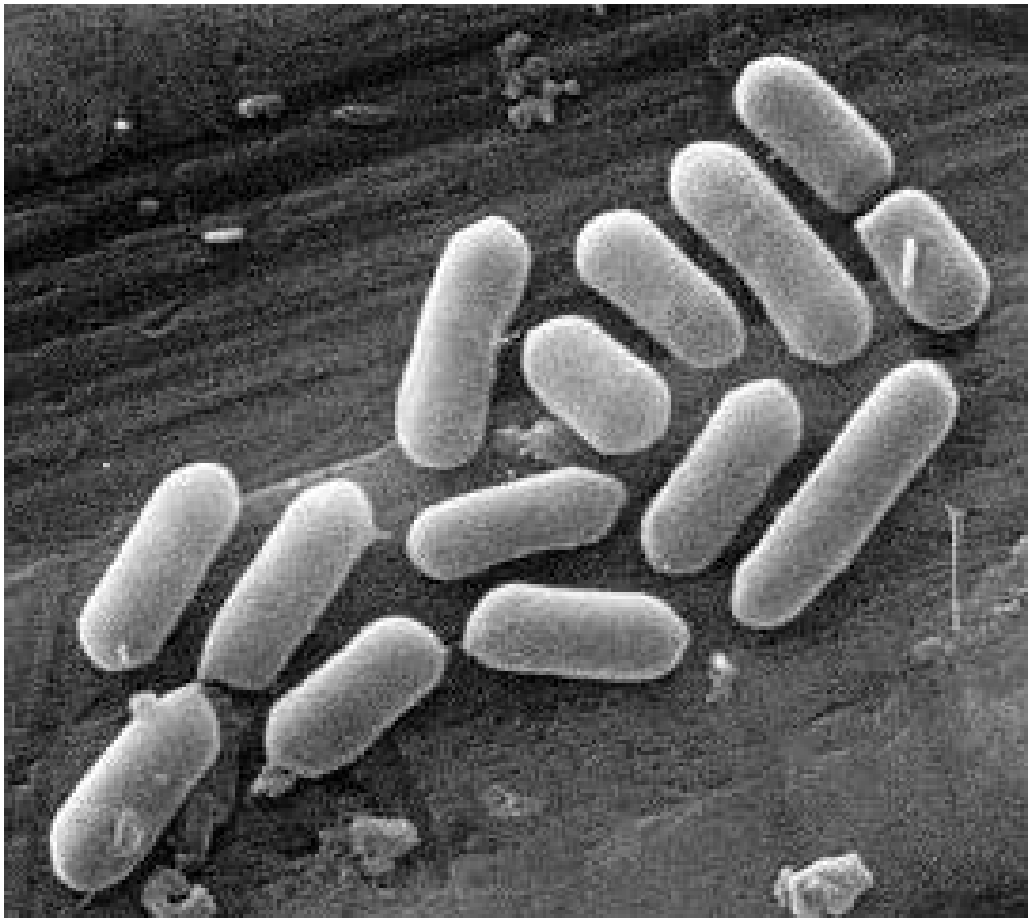
- Organisms exhibit sophisticated behavior
- Integrating sensing, decision, and response into networks
- Which are built directly at the molecular level
- To understand the resulting complex heterogeneous multiscale networks we need equally integrated, flexible teams of domain experts
- Who build on existing domain strengths but create fluid and dynamic interactions to address problem-driven challenges

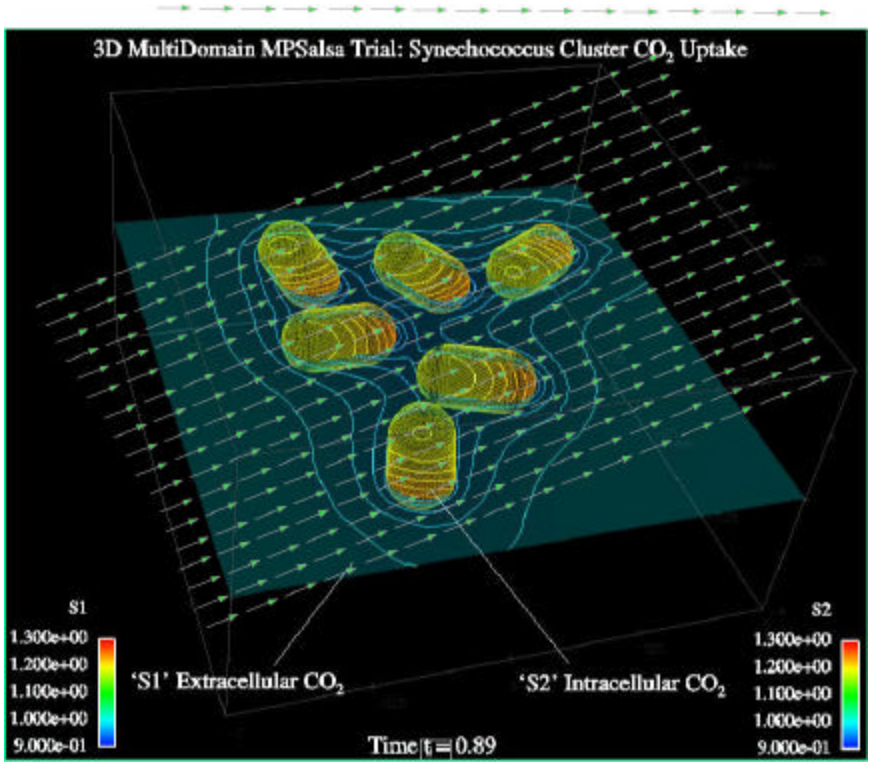

Outer
helix
Inner
helix






C-terminus
lysine 128
loop 6




3D MultiDomain MPSalsa Trial: Synechococcus Cluster CO_2 Uptake
S1
1.300e+00
1.200e+00
1.100e+00
1.000e+00
9.000e-01
'S1' Extracellular CO_2
'S2' Intracellular CO_2
S2
1.300e+00
1.200e+00
1.100e+00
1.000e+00
9.000e-01
Time|t=0.89