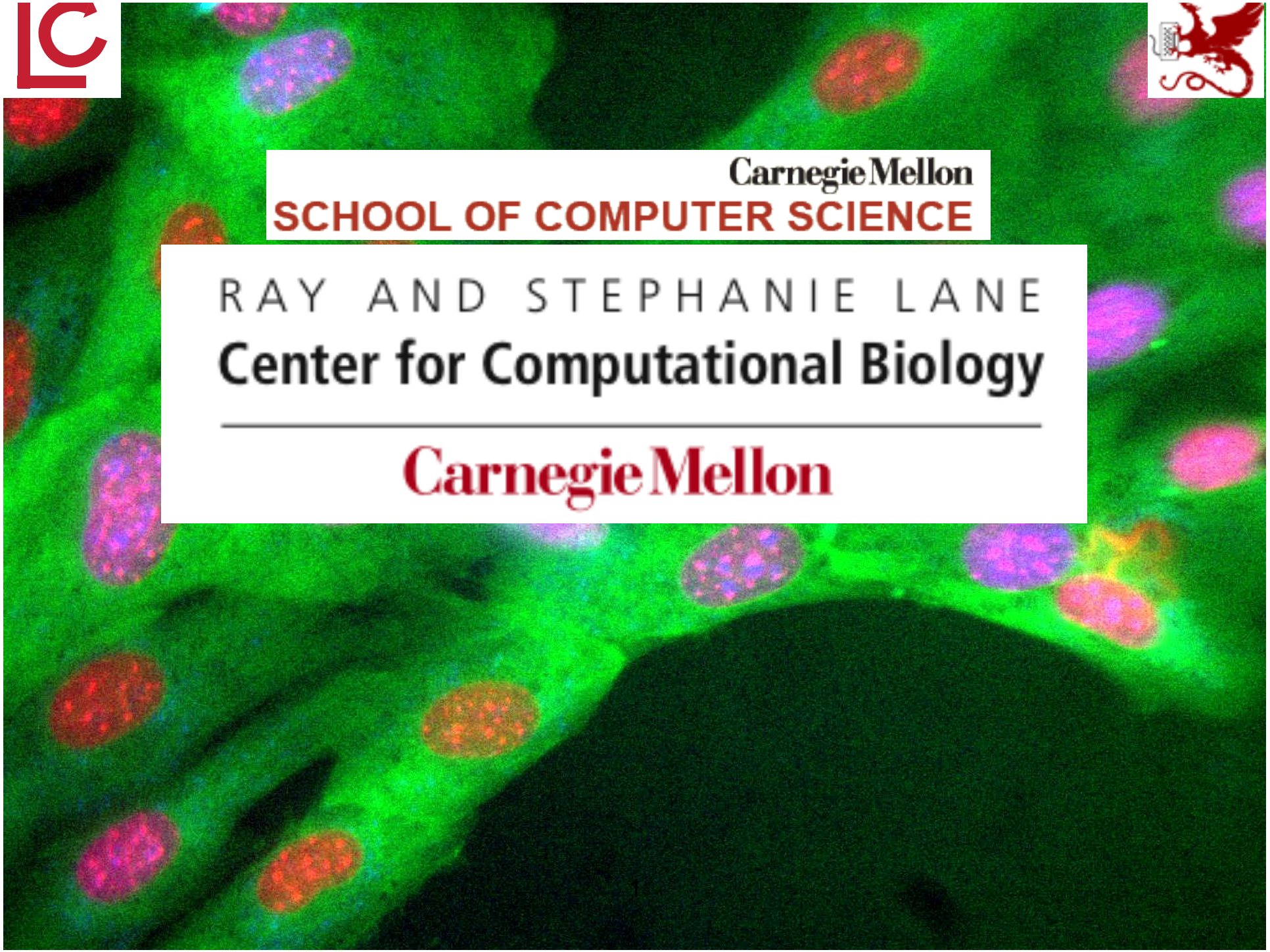

Carnegie Mellon
SCHOOL OF COMPUTER SCIENCE
RAY AND STEPHANIE LANE
Center for Computational Biology
Carnegie Mellon

What we do

- Frame biomedical problems as computational problems, especially on “omic” scale
  - What approaches ‘scale up’?
- Use and develop appropriate computational methods
- Apply to real-world problems, especially cancer

What we do

- Seek to minimize input in the form of “biological knowledge” – as much as possible tie everything to primary data
- Emphasize role for computational biology in questioning assumptions and frameworks for representation
- Seek to drive biomedical research through computation

What we don't

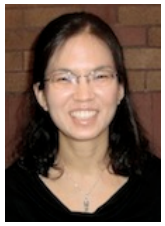
- Medical Informatics
  - Patient Records
    - Entry, Storage, Retrieval, Privacy
- Biological Computation

Faculty

- Core of Lane Center faculty with strong research programs related to computational biology
- Many affiliated faculty

Particular Research Strengths

- Interaction network inference
  - Bar-Joseph, Xing, Kim, Kingsford, Lopez, Hinman, McManus, Roeder, Schwartz, Wu
- Bioimage informatics
  - Murphy, Rohde, Kovacevic, Yang
- Multiscale modeling
  - Schwartz, Langmead, Murphy
- Active learning
  - Carbonell, Murphy, Schneider



Seyoung Kim
Assistant Professor
Lane Center for Computational Biology
Machine Learning Department
http://www.cs.cmu.edu/~sssykim

IC Talk: 10:25 am
Thurs, September 4

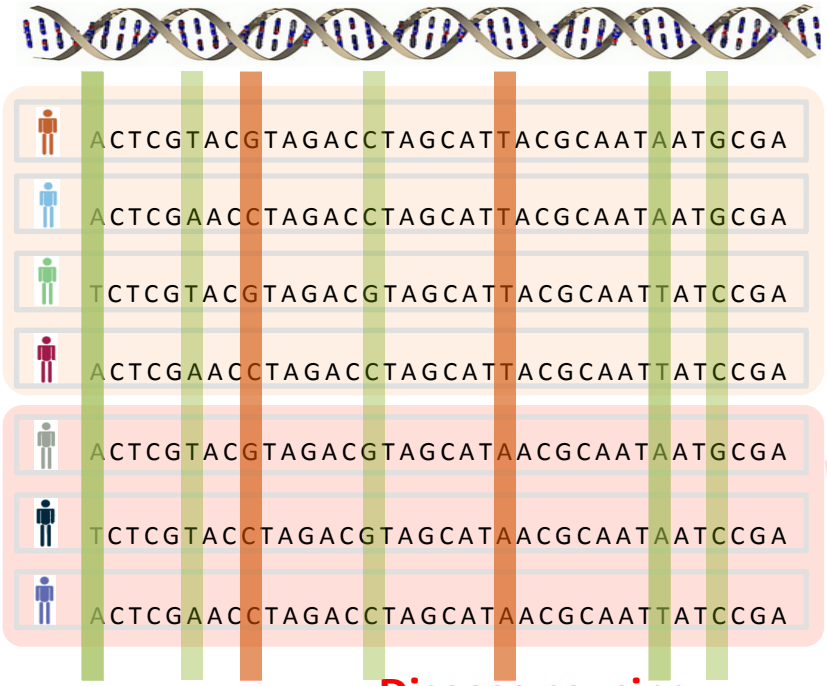
Computational Genomics

- Understanding the genetic basis of common diseases (diabetes, asthma, etc.)
- Gene network learning, evolutionary modeling
- Long-term goal: **personalized medicine**

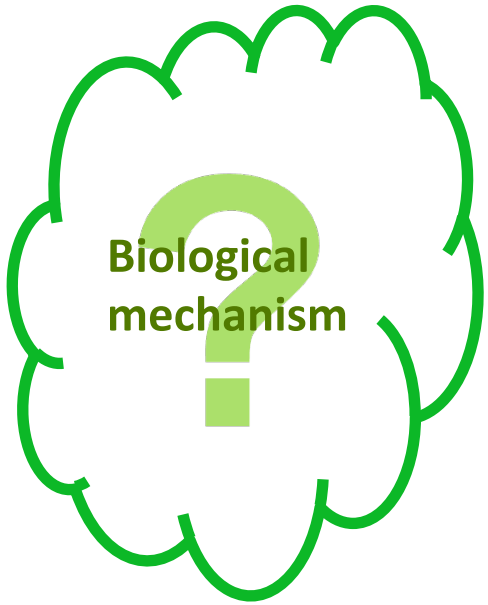
+

Machine Learning

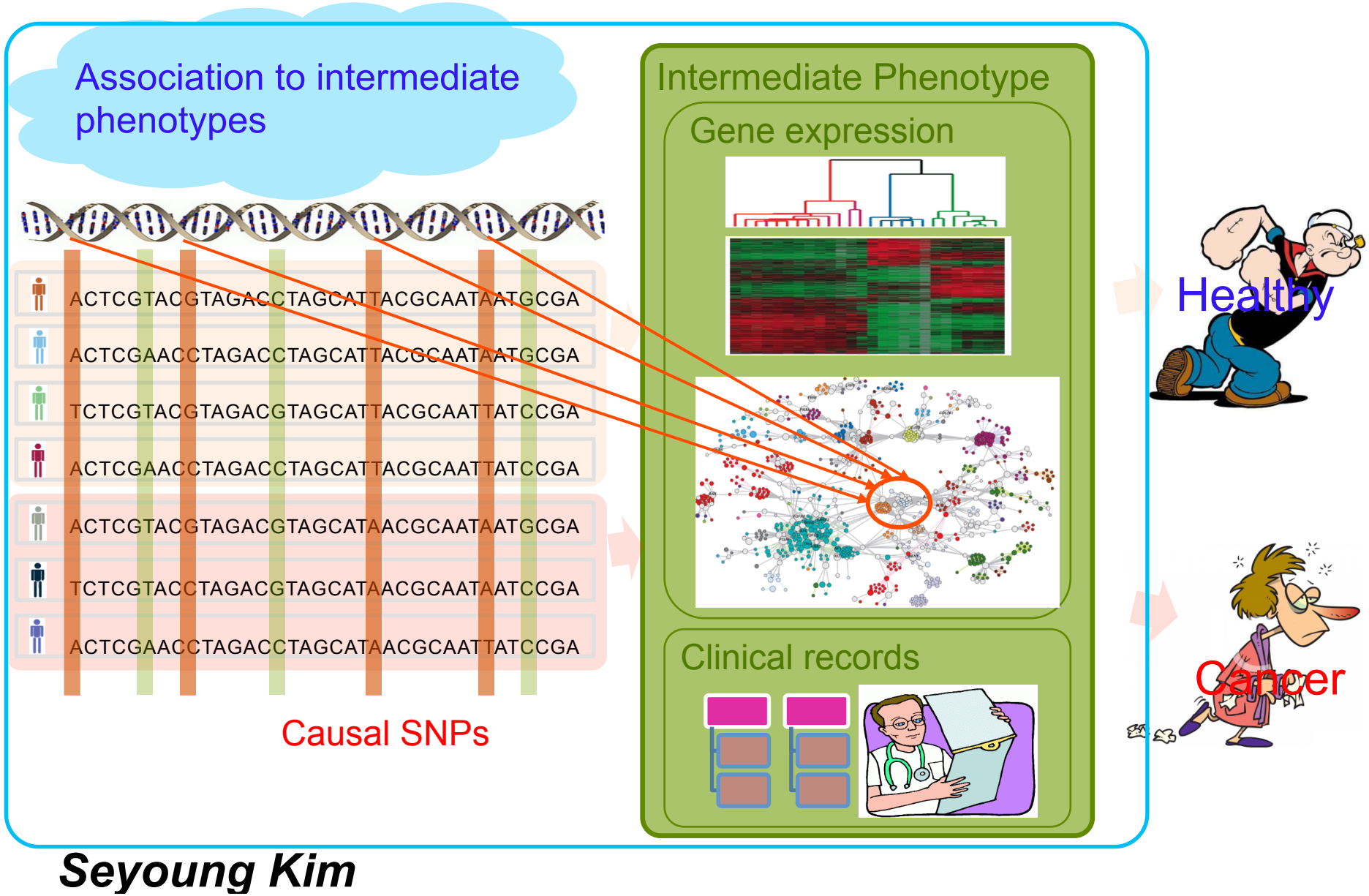
- Learning in high-dimensional space
- Probabilistic graphical models
- Feature selection, structured sparsity
- Fast optimization methods



Disease causing genetic variations



Genetic Basis of Complex Diseases



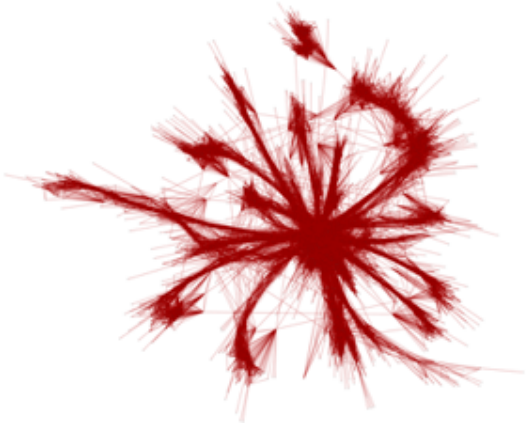
Seyoung Kim

Carl Kingsford

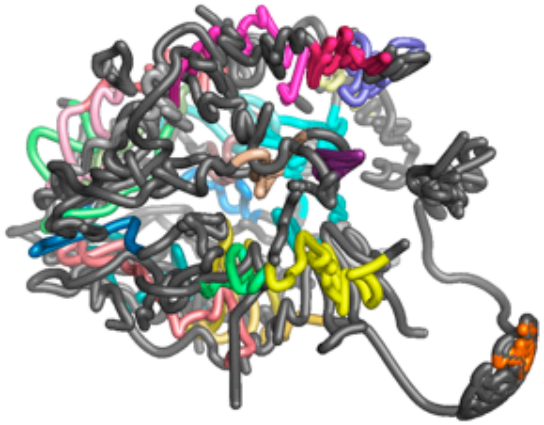
Relating Genome 3D Structure to Its Function

The eukaryotic genomes are huge collections of molecules packed into a small space.

"3C" experiments produce a graph where nodes are genome locations and edges give weights related to the # of times the locations were spatially close.



Experimental "3C" graph



Yeast Genome Structure
Duan et al., 2010

Q: Can we model the spatial structure from pairwise proximities measured from a population of cells?

e.g. Duggal et al., WABI 2013, and Duggal et al., *Alg. Mol. Biol.* 2012

Q: Can we develop efficient statistical tests to determine if a set of genomic positions are significantly close or not?

e.g. Wang et al., BCB 2013

Carl Kingsford

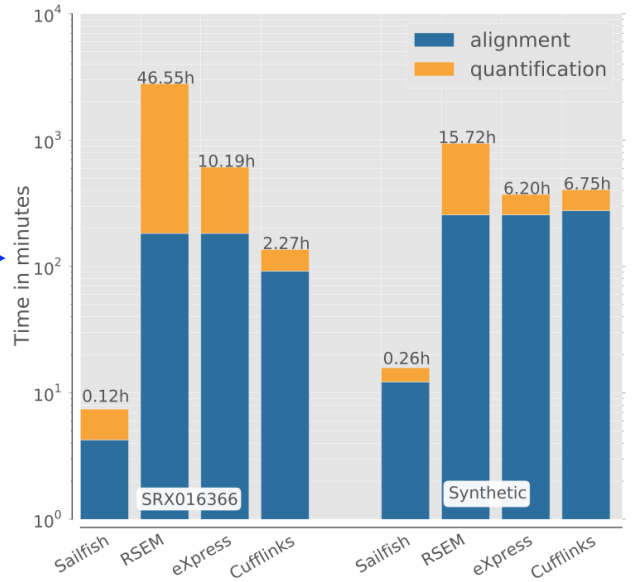
Fast Genomic Sequence Analysis

Huge amount of genomic sequence data available now (a single public database has > 1,587 **terra**bases of sequence)

Our tool, called Sailfish, can estimate gene expression from next-generation sequencing data 20 – 70 times faster than existing algorithms.

Patro et al., arXiv:1308.3700

Speed will be crucial for personal genomics.



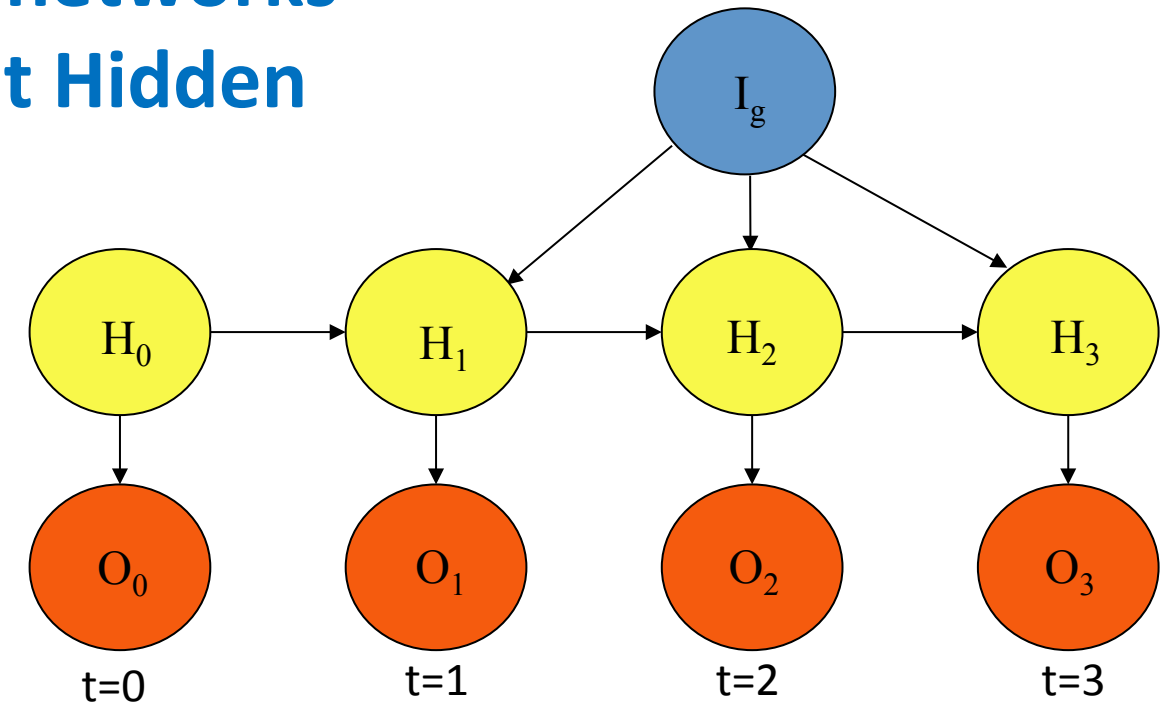
Q: How do you efficiently *search* for complex structures (e.g. spliced sequences, patterns of TF binding sites) when traditional sequence alignment is too slow?

Q: How can you *transmit* large collections of sequences (between collaborators, from the sequencer, to the cloud)?

Q: How can you *compress* sequence data so that you can still analyze it in its compressed form ("functional compression")?

Modeling dynamic networks with Input – Output Hidden Markov Models

Input (Static TF-gene interactions)

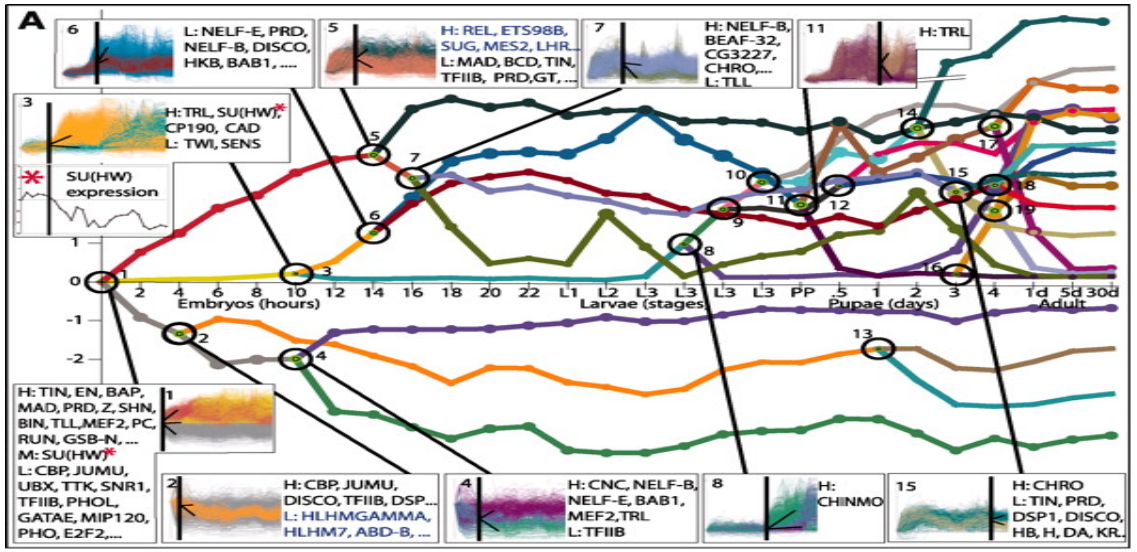


Hidden States (transitions between states form a tree structure)

Emissions (Distribution of expression values)

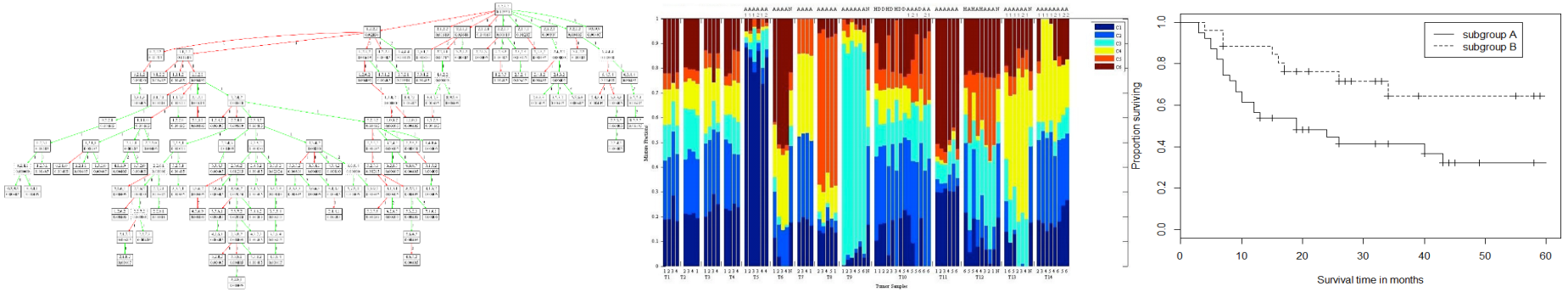
Fly development

***Science* 2010**

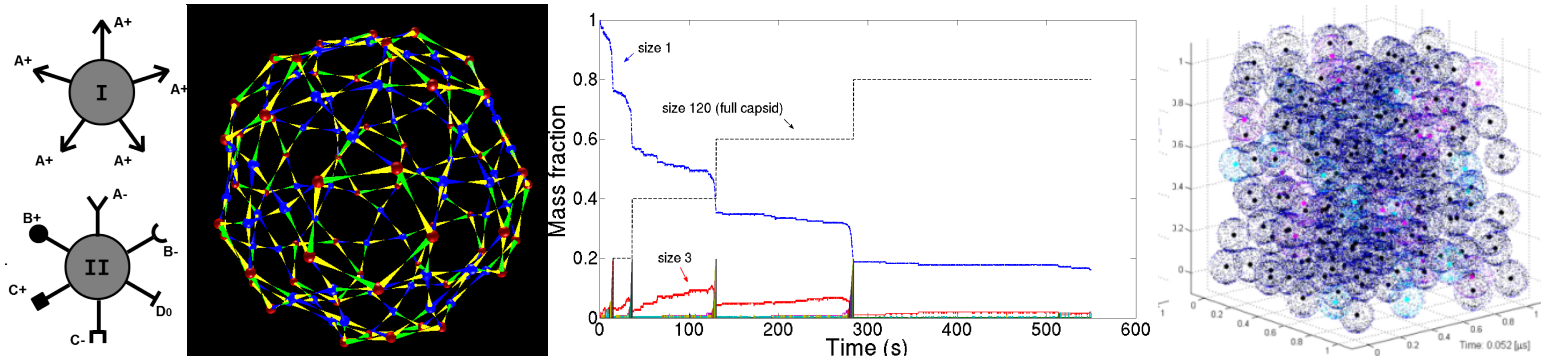


Ziv Bar-Joseph

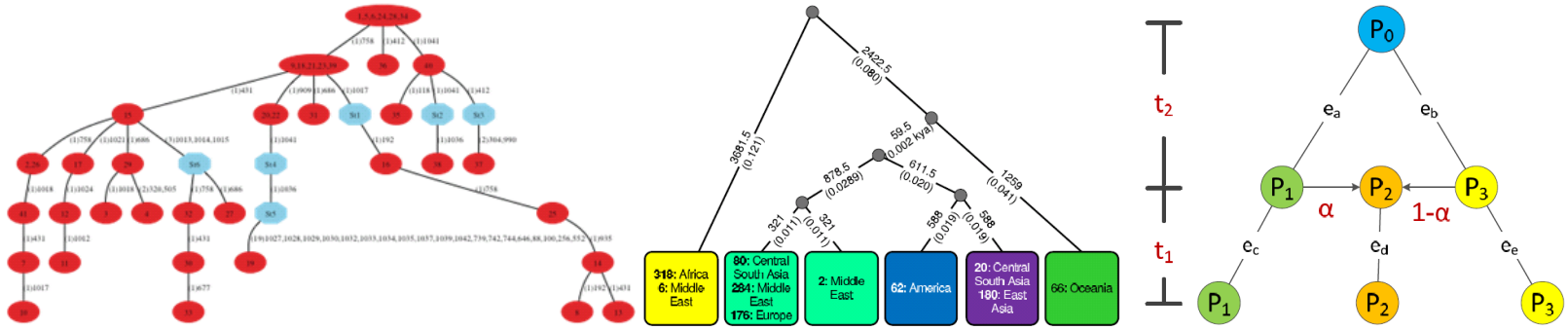
Russell Schwartz



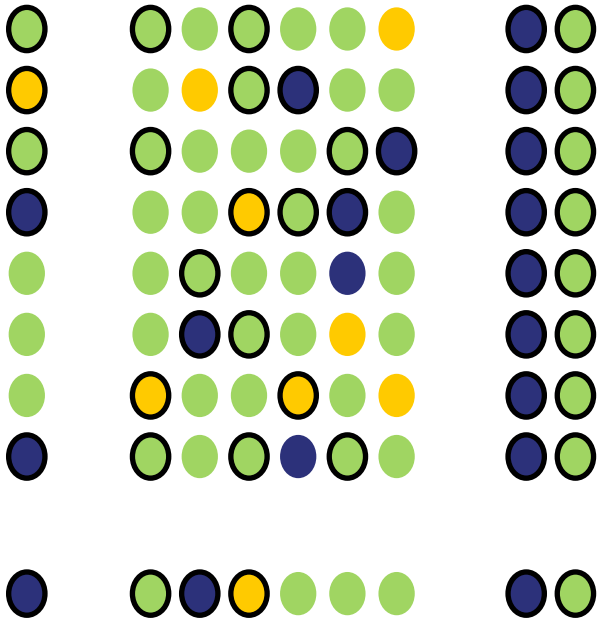
Tumor evolution and heterogeneity



Simulation and model inference for macromolecular assembly



Models and algorithms for phylogenetics and population genetics



Murphy, Schneider, Langmead

ACTIVE LEARNING FOR DRUG DISCOVERY

Assumption/Framework

- Exhaustive experimentation will permit understanding of biological systems
  - We can always do whatever experiments/ measurements needed
  - Drug development can be done by focusing initially on specific target and then checking toxicity of chosen drugs

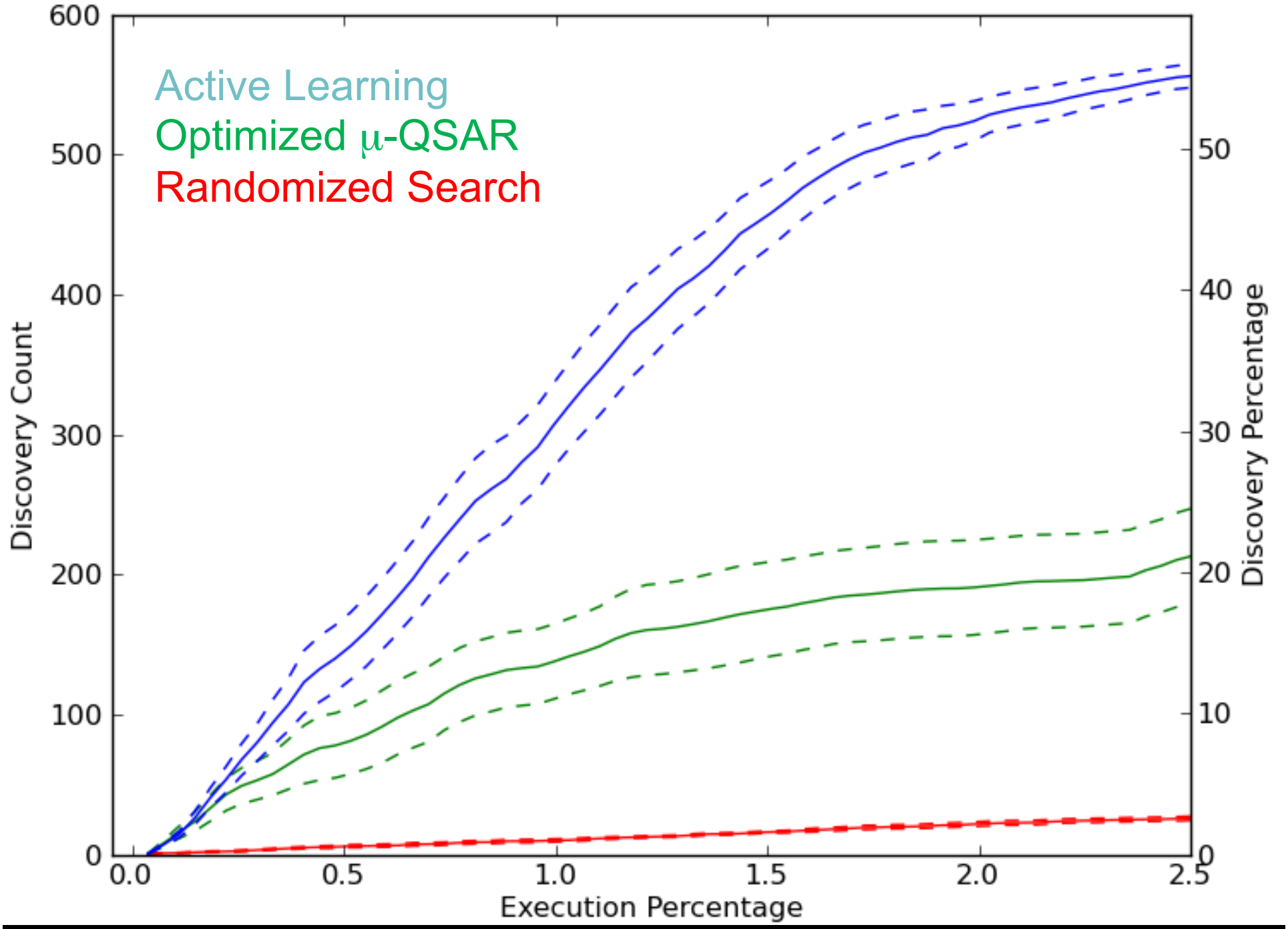
Problem

- Drugs fail late in development because of unanticipated side effects
- Only real solution is to choose drugs with desired effect on target and no undesired effect
- This requires determining the effects of millions of potential drugs on tens of thousands of potential targets

Solution

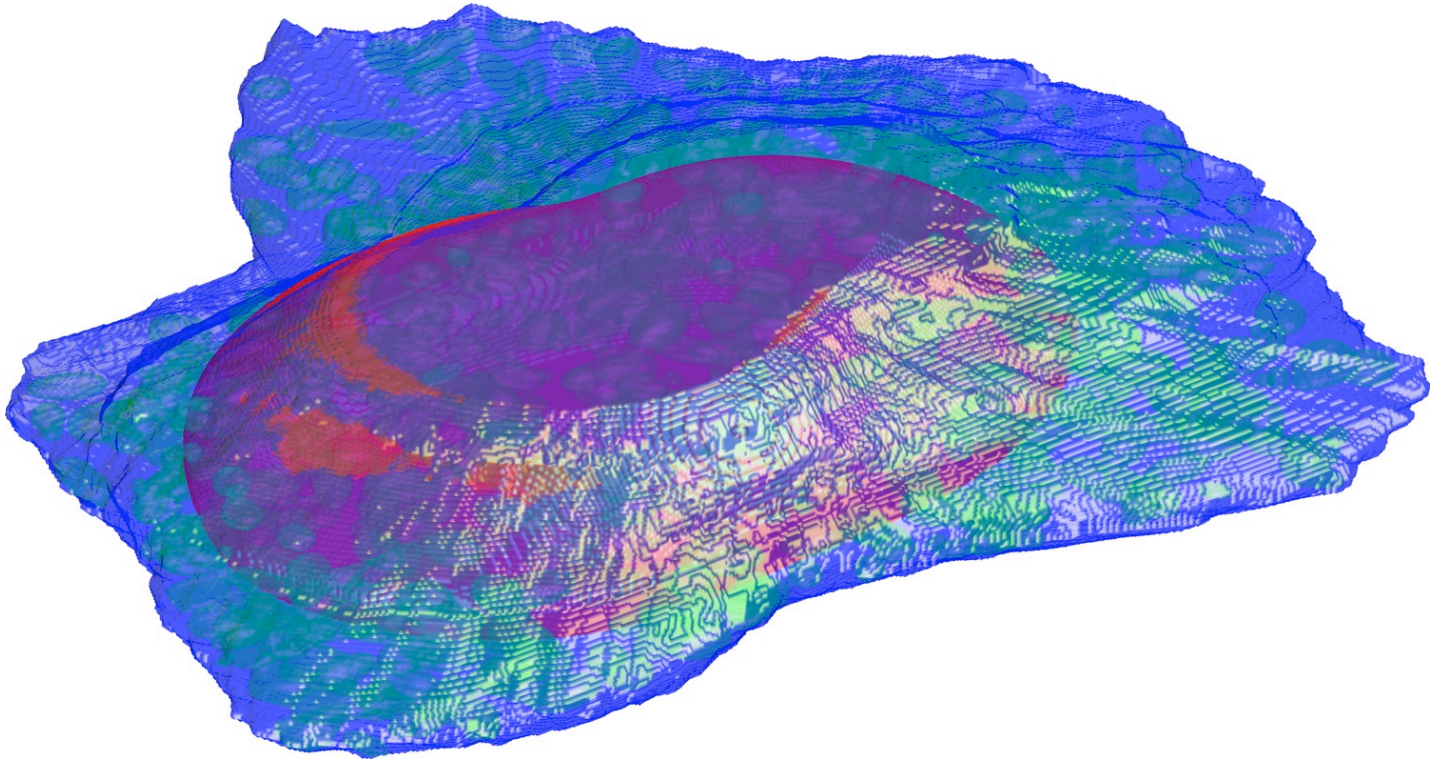
- Build model to predict full matrix from whatever data we have
- Use active learning to choose new experiments

- This and other relevant topics covered in Course 02-750 Automation of Biological Research


Active Learning
Optimized μ-QSAR
Randomized Search
Discovery Count
Discovery Percentage
Execution Percentage
0
100
200
300
400
500
600
0
10
20
30
40
50
0.0
0.5
1.0
1.5
2.0
2.5

Paradigm shift

- Exhaustive experimentation will permit understanding of biological systems
- Paradigm shift: Computer control over experiment choice – active learning
- New company, Quantitative Medicine, commercializing this technology



Murphy, Rohde

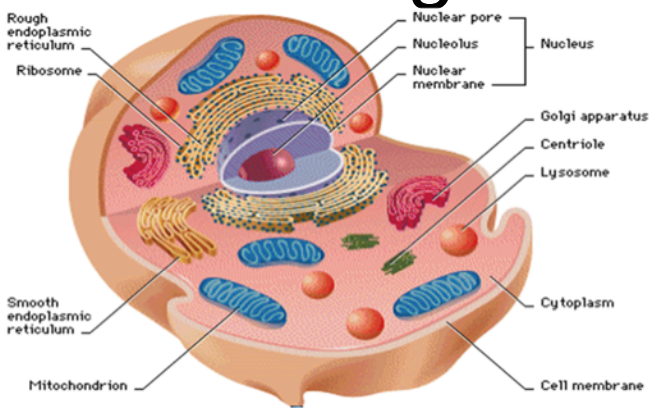
IMAGE-DERIVED GENERATIVE MODELS OF SUBCELLULAR ORGANIZATION

Assumption/Framework

- Words are a good way of representing information about the spatial organization of cells and the subcellular localization of proteins

How do we learn and represent

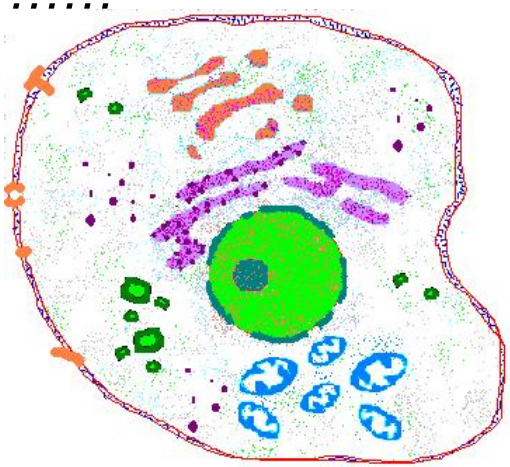
- the number, sizes, shapes, positions of subcellular structures
- the distribution of proteins across those structures
- how structures and distributions change between cell types, in presence of perturbagens, or over time?



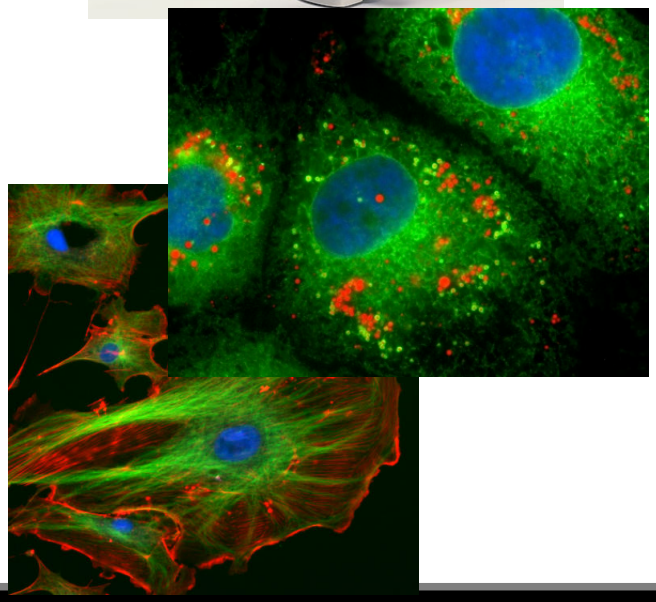
Subcellular Location Analysis

"Where" (in which type of organelle) is the protein of interest located?

Lysosome?
Mitochondria?
Golgi?
……



Fluorescence Microscopy



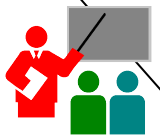
Descriptive vs. Generative Models

- If the task is to test which of two (or more) possibilities is true, can use *descriptive features*
  - Is this an apple or orange? can be answered by measuring color or texture
- But if the task is to understand as much as possible, a *generative model* is better
  - What does an apple look like? requires a generative model

Alternative: Generative Modeling

- Human cognition

examples



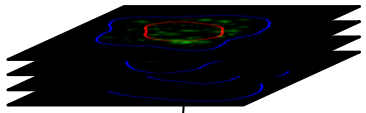
Learn

Mental model

Write

Generated examples

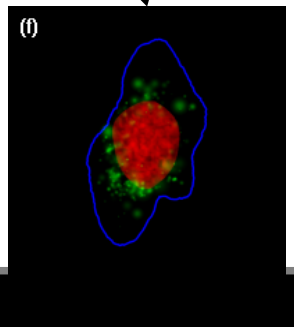
- Generative model



Training images

MODEL

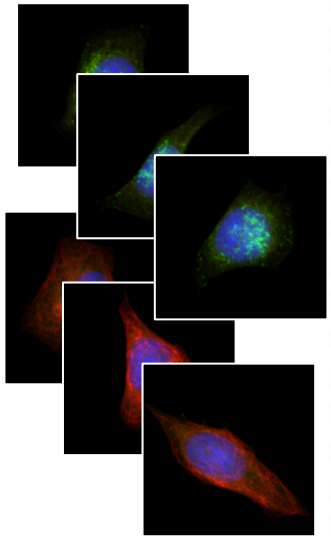
Statistical generative model



Generated image

CellOrganizer

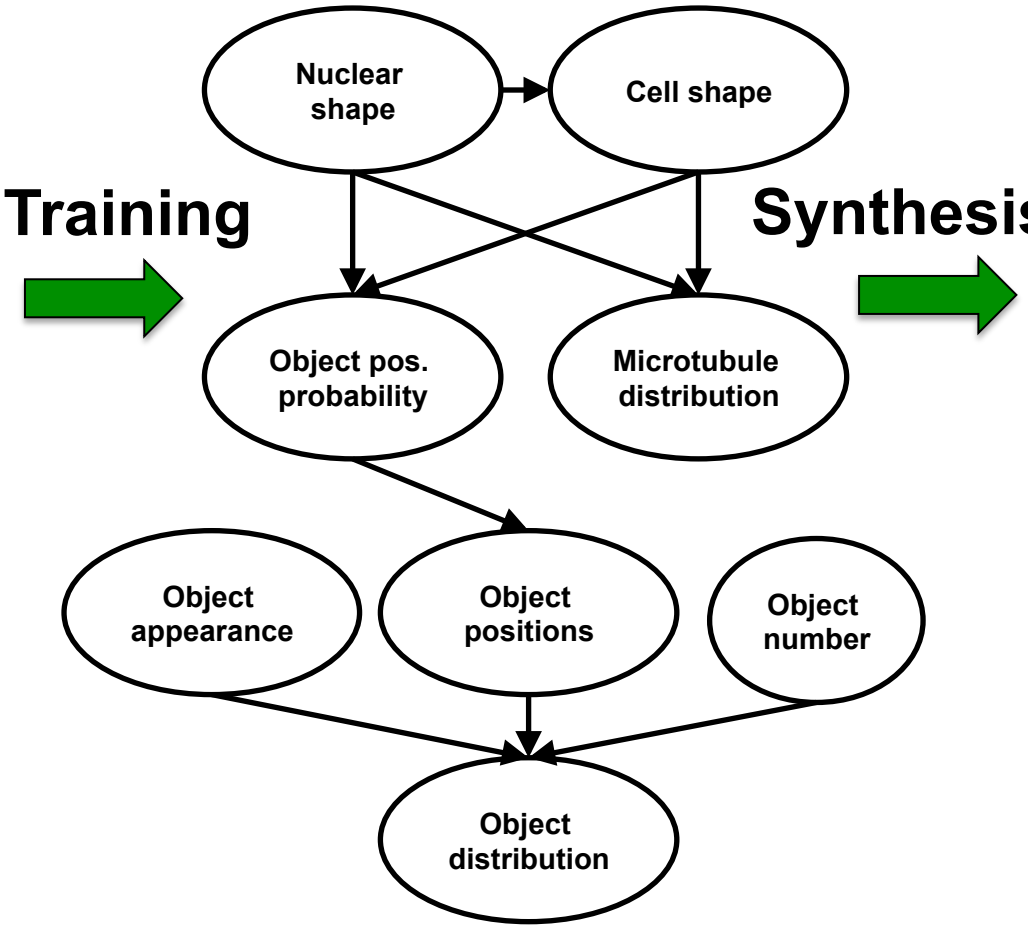
Cell Images



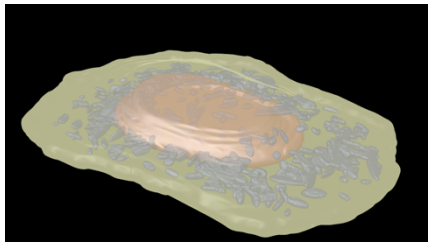
Statistical Model

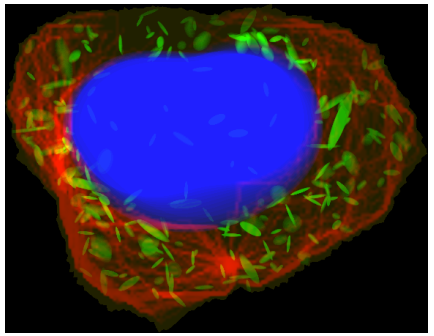
Training

Synthesis

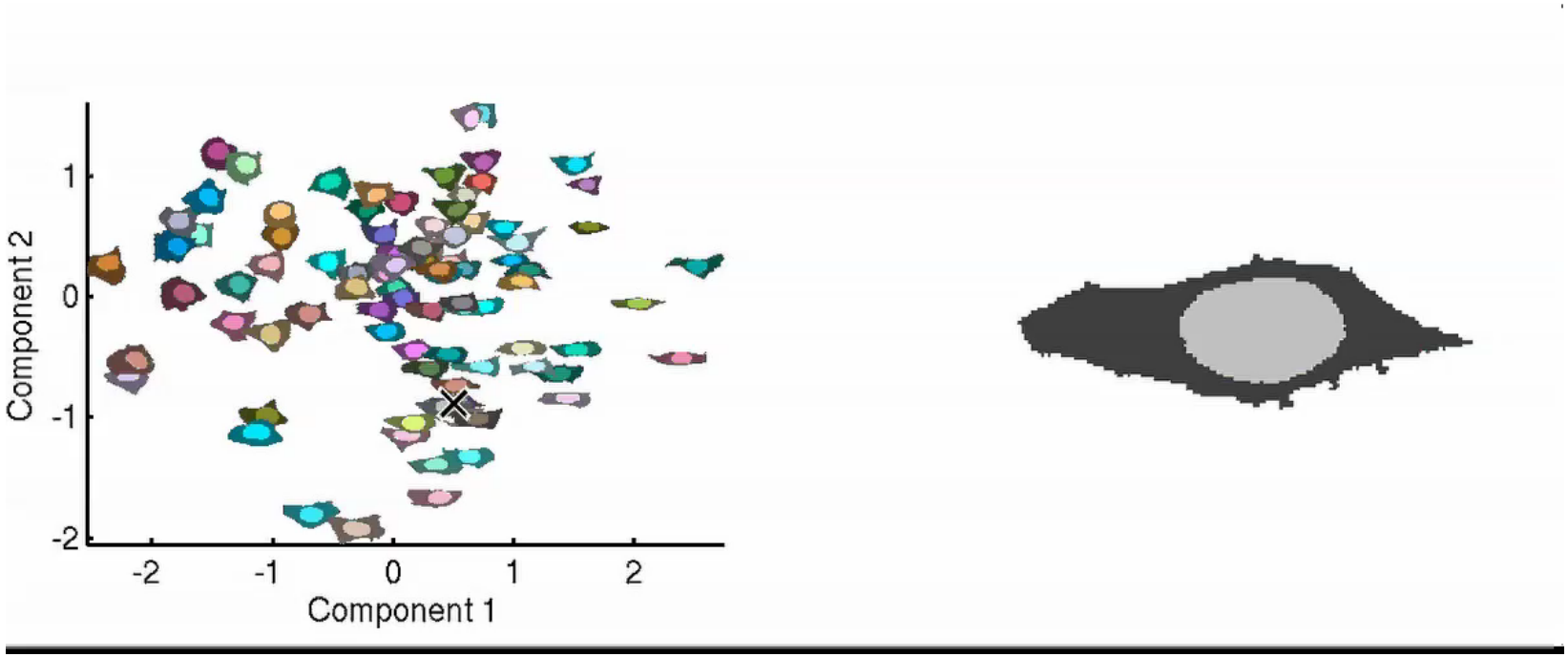


Synthetic Images





Synthetic movie of cell/nuclear shape dynamics



3D HeLa

Synthetic movie of cell and nuclear shape changes during neuronal differentiation

Big Future Issues

- Learning multiscale dynamics
- Learning deeper conditional structure (pattern causality)
  - Organelles on cell framework
  - Organelles on organelles
  - Proteins on organelles
  - Proteins on proteins
  - All of above on perturbagens

Pattern Causality

- Need variations on existing methods (such as Granger Causality, Convergent cross mapping) appropriate for images/ spatial distributions

Paradigm shift

- Words are a good way of representing information about the spatial organization of cells and the subcellular localization of proteins

- Paradigm change: Generative statistical models

Summary

- Computational biology research requires investigators with deep knowledge of biology, computer science, math, statistics to develop rigorous approaches and reformulate paradigms for biomedical research

Summary

- Opportunities for computer scientists to
  - help solve framed computational biology problems
  - help formalize solutions, e.g.
    - prove convergence
    - establish bounds