NIST Opportunities

- Emerging from systems biology--a paradigm change in biology

- Develop technologies. For genomics, proteomics, transcriptomics, metabolomics, interactomics, pehnomics, in vivo imaging, etc.
- Data assessment and validation. For global data sets from all of the technologies mentioned above.
- Software development and integration. For the capture, storing, analysis, integration, and modeling of global data sets.

- KEY: WILL COST LOTS OF MONEY TO DO IT RIGHT. STRATEGIC PARTNERSHIPS ARE CRITICAL AS BIOLOGY MUST DRIVE EACH OF THESE OPPORTUNITIES.

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Biology will be a Dominate Science in the 21st Century

Systems approaches to biology and medicine will constitute a paradigm change in practice of biology--inflection point changing how we view and practice this science

- Change catalyzed by the complexity of biology
  - mid 1980s molecular immunology can't be done one protein and one gene at a time--systems thinking
- By genome project with parts list of all genes (and proteins)
- By new global measurement tools for DNA, RNA, proteins, interactions and biological assays--microfluidic/nanotechnology platforms
- By new computational/mathematical data mining, integration and modeling tools
- By the view biology is an informational science

What is systems biology?

Radio Waves

Sound Waves

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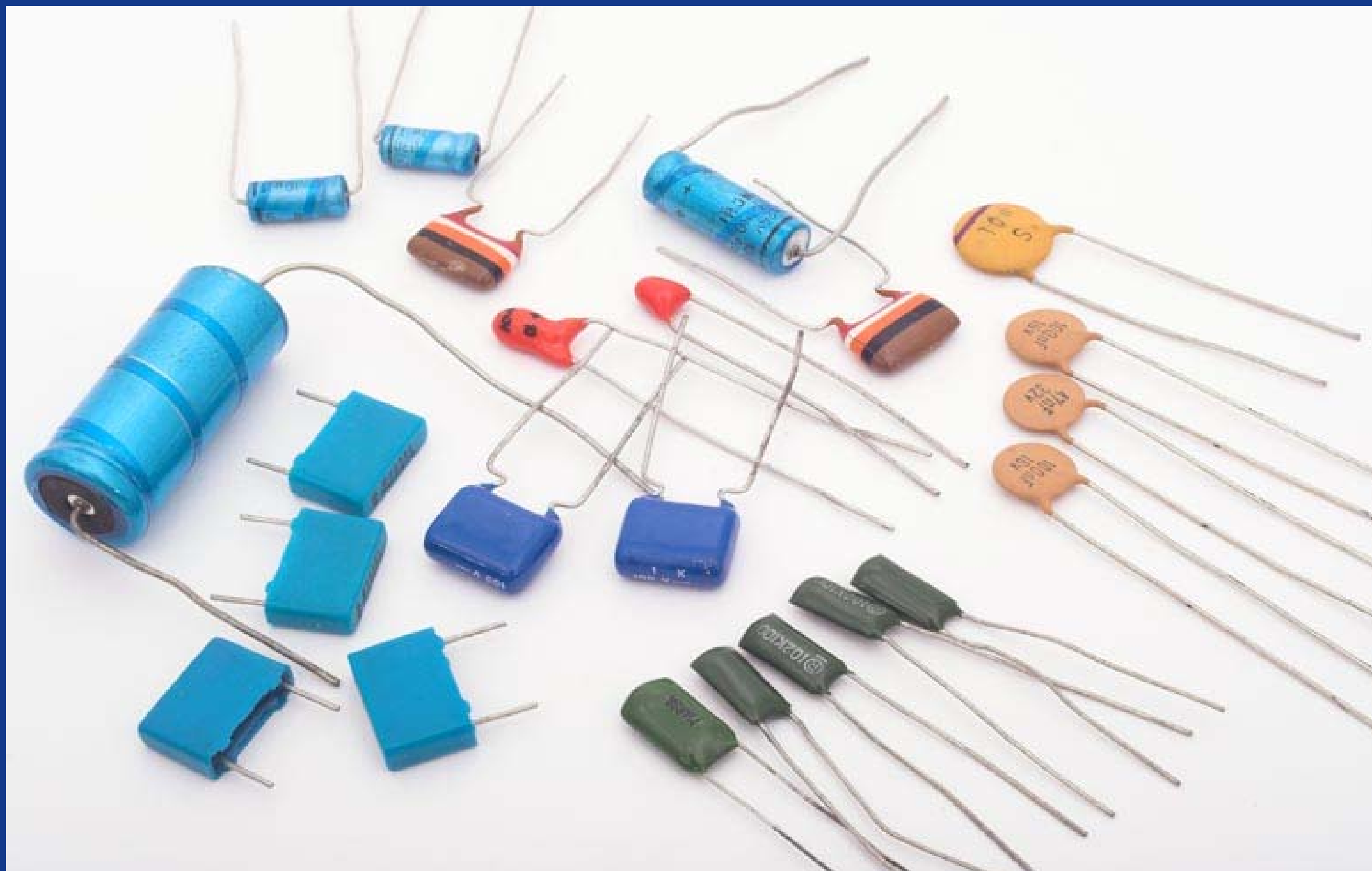

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Radio Waves

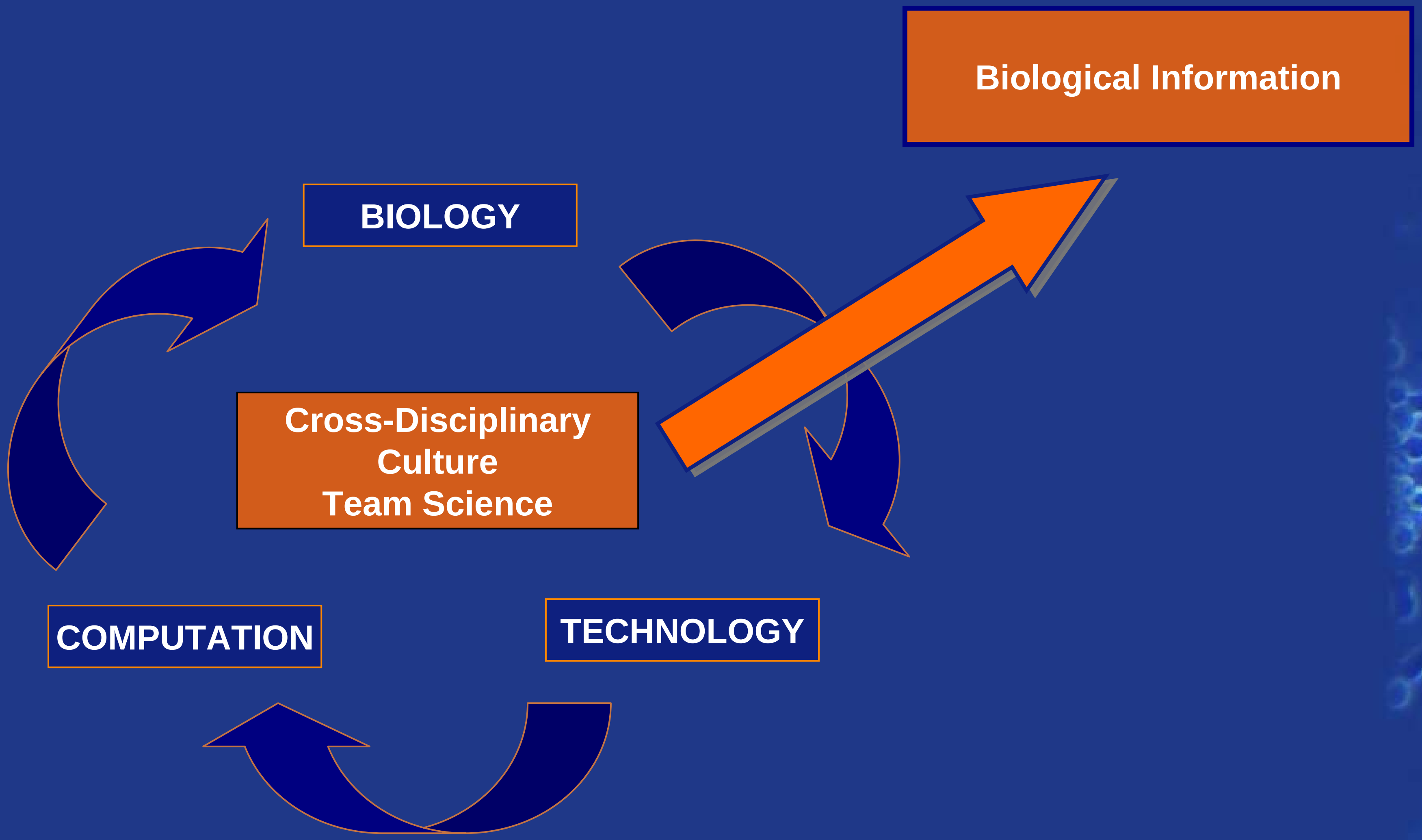
Sound Waves

Technology Has Transformed Contemporary Systems Biology

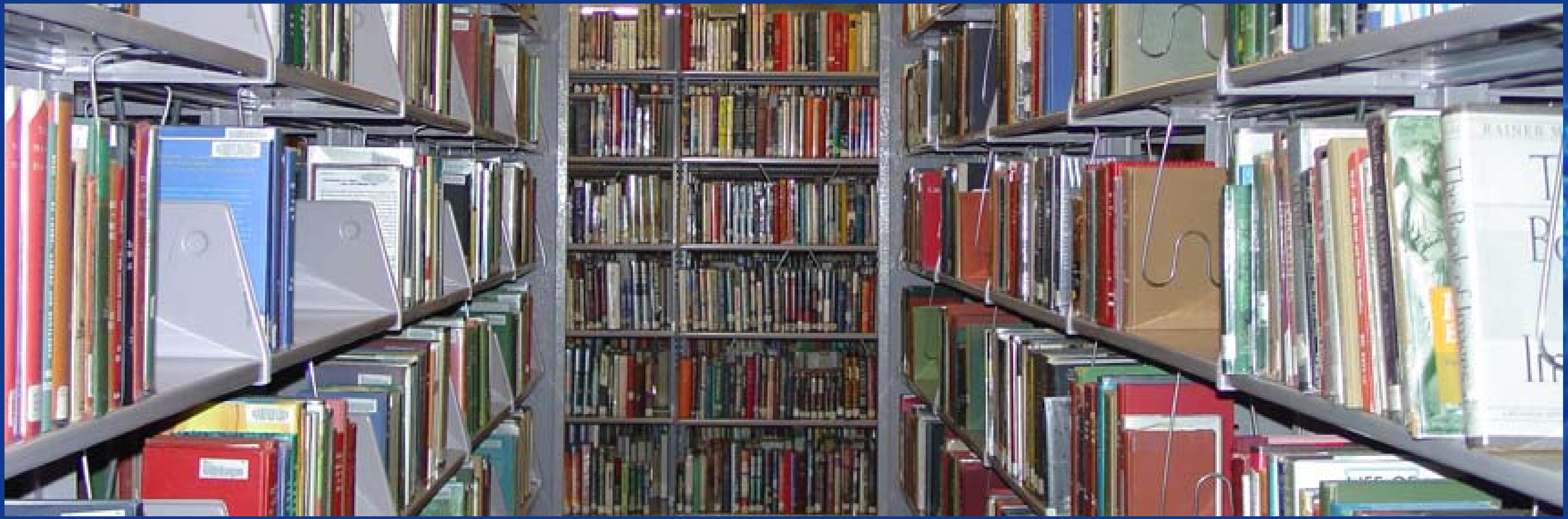
Global measurements--measure dynamic changes in all genes, mRNAs, proteins, etc, across state changes

Computational and mathematically integrate different data types--DNA, RNA, Protein, Interactions--to formulate models about systems etc.

ISB Strategy of Systems Biology



Biology is an Informational Science



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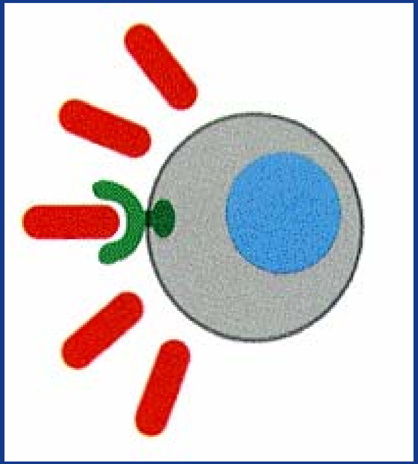
There are two types of Biological Information

- The digital information of the genome

- The environmental information that impinges upon and modifies the digital information.

CCAGAAAGGC	CGAGGCTCTG	CAGCGGGAGG
GCAGGGCACA	GGGACAGCCC	CCCTCCACAG
CCAGGAGGTT	GCTTCTTCCA	GGAGGCTTTT
GCTCCCAGCT	GCTGTGAGTG	CTGCACATTC
CACTTCTGGT	GCCCACTGTG	GCCACAGCAA
GCCTCCTGGG	GAGCTGCTGA	CCCTAGGCAG
CACCCCAGTG	TTTGCCAGTG	TTTGCCCGTG
TTTGCTCGCC	AGTGTTCGCC	ACTTGTCCCT
GAAGTTGCAG	GTCCCTCCAG	GACAGTTGGC



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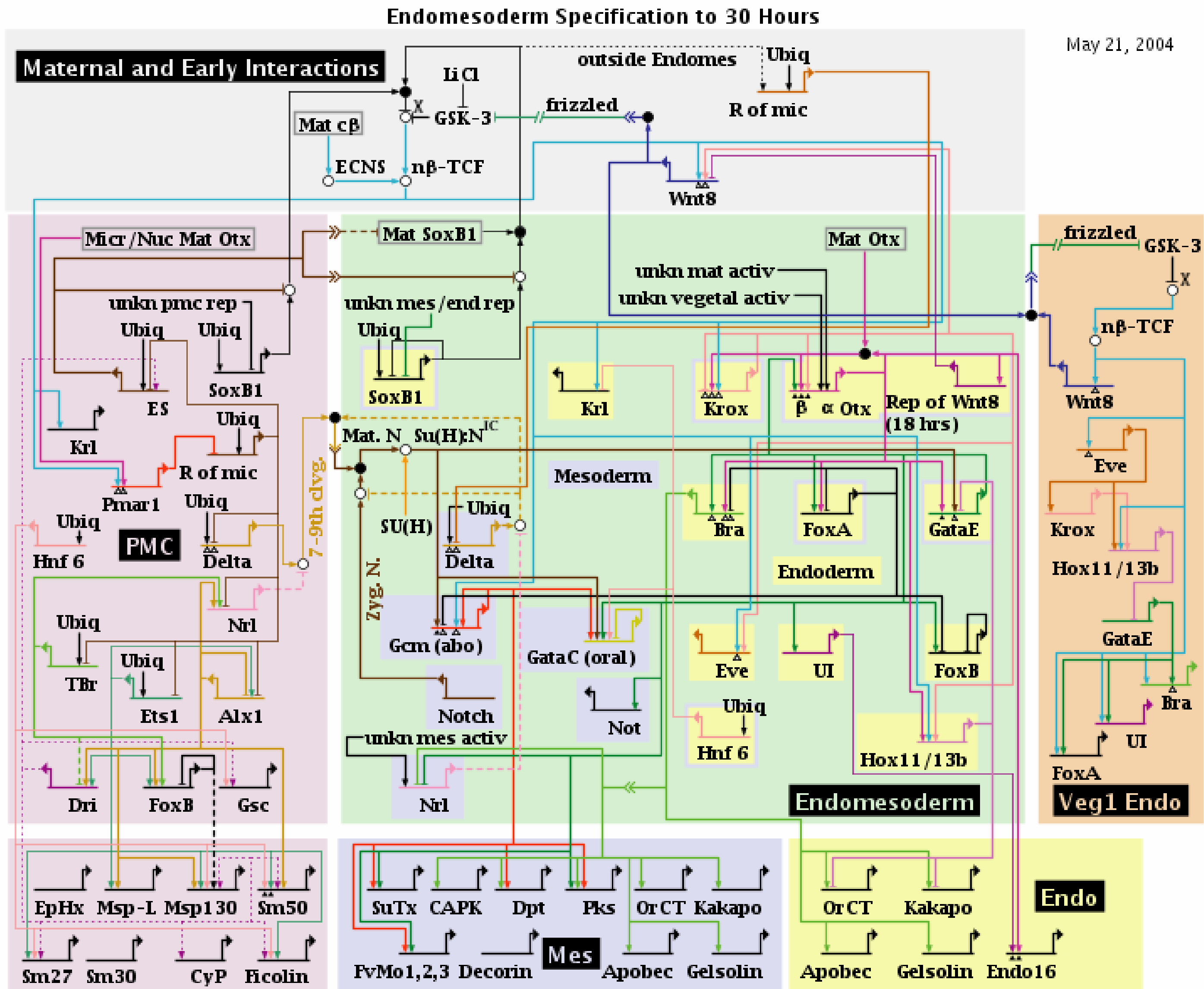
Most Sophisticated Integrated Biological Network Defined to Date



Levels of Biological Information Necessary for Systems Biology

DNA

mRNA

Protein

Protein interactions and biomodules

Protein and gene networks

Cells

Organs

Individuals

Populations

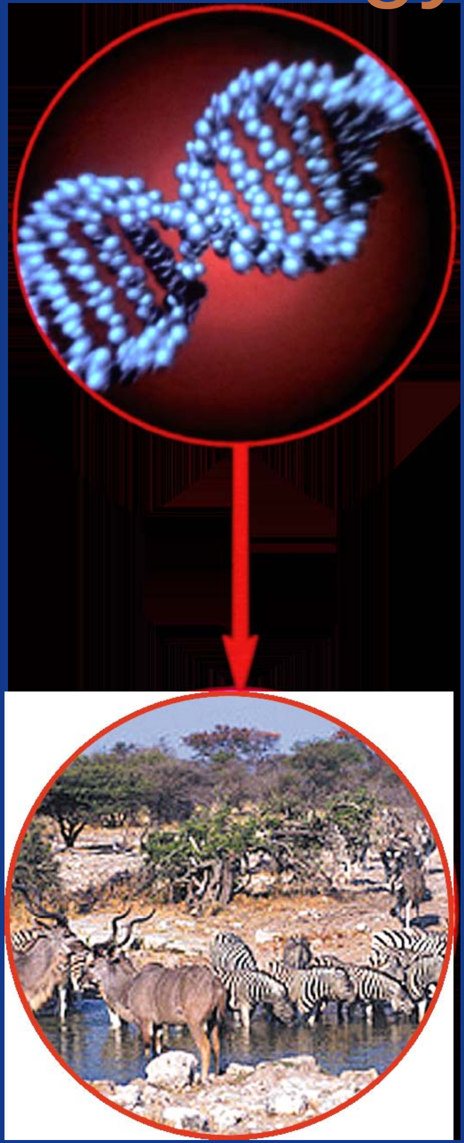
Ecologies

Top Down and Bottom Up

Level of System Analysis

Connect to Digital Core

Integration of Different Levels



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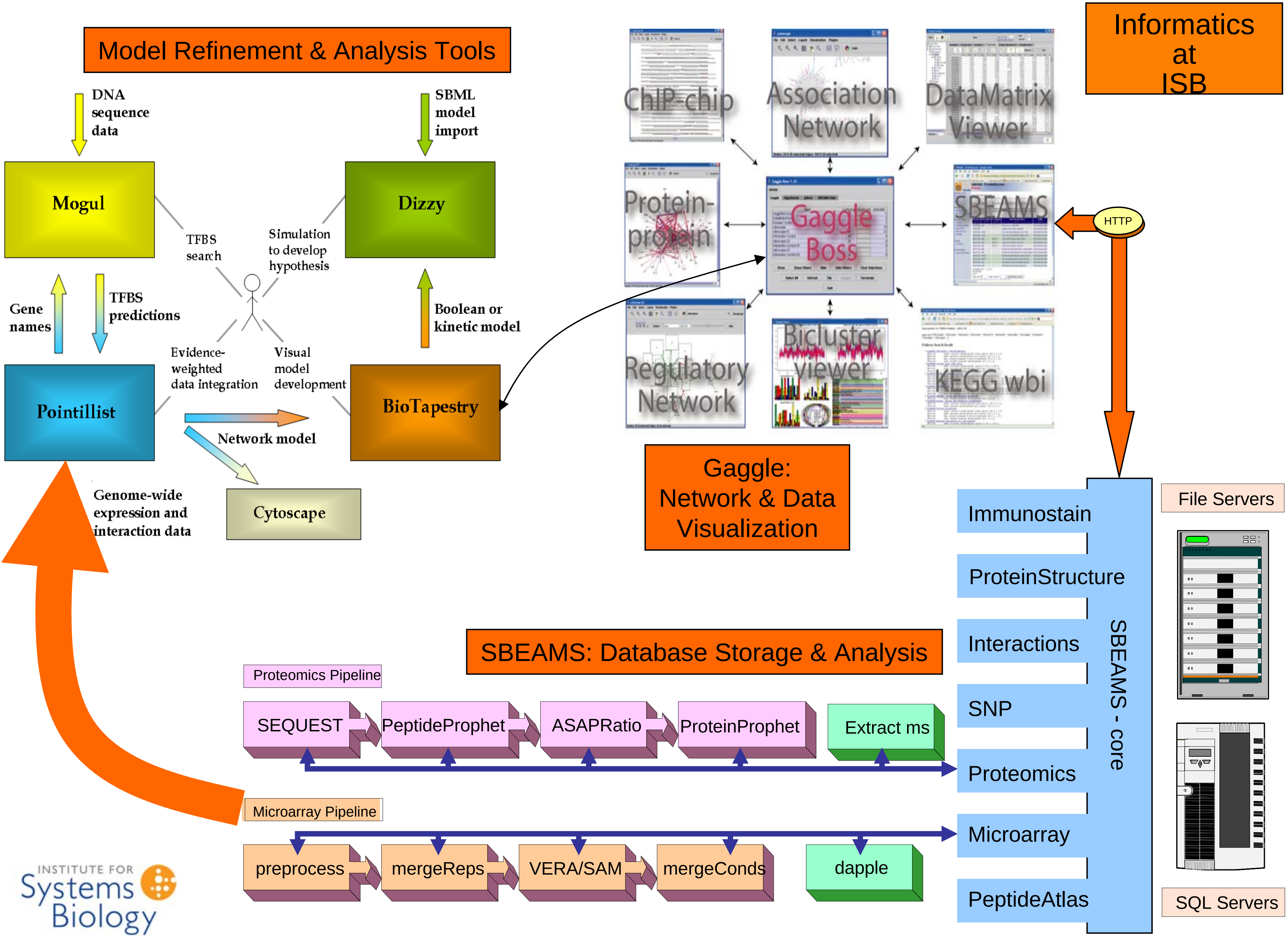

Model Refinement & Analysis Tools
DNA sequence data
SBML model import
Mogul
Dizzy
TFBS search
Simulation to develop hypothesis
Gene names
TFBS predictions
Boolean or kinetic model
Evidence-weighted data integration
Visual model development
Pointillist
BioTapestry
Network model
Genome-wide expression and interaction data
Cytoscape
ChIP-chip
Association Network
DataMatrix Viewer
Informatics at ISB
Protein-protein
Gaggle Boss
SBEAMS
HTTP
Regulatory Network
Bicluster viewer
KEGG wbi
Gaggle: Network & Data Visualization
Immunostain
File Servers
ProteinStructure
Interactions
SNP
Proteomics
Microarray
PeptideAtlas
SBEAMS - core
SQL Servers
SBEAMS: Database Storage & Analysis
Proteomics Pipeline
SEQUEST
PeptideProphet
ASAPRatio
ProteinProphet
Extract ms
Microarray Pipeline
preprocess
mergeReps
VERA/SAM
mergeConds
dapple
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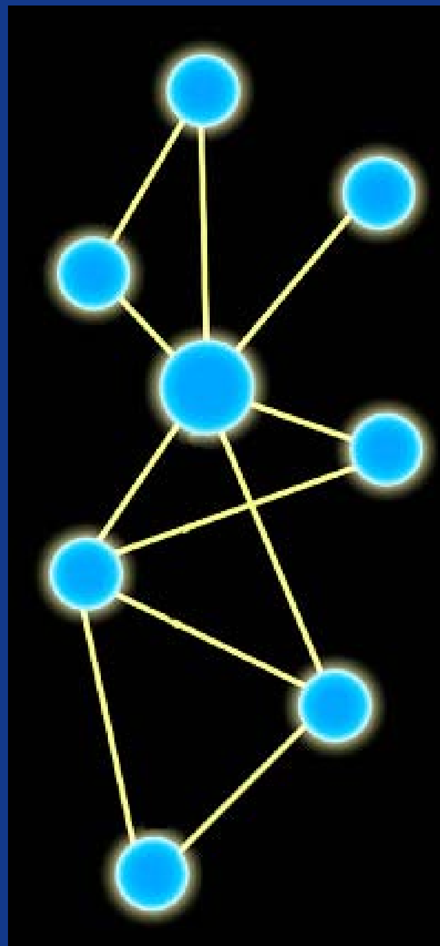
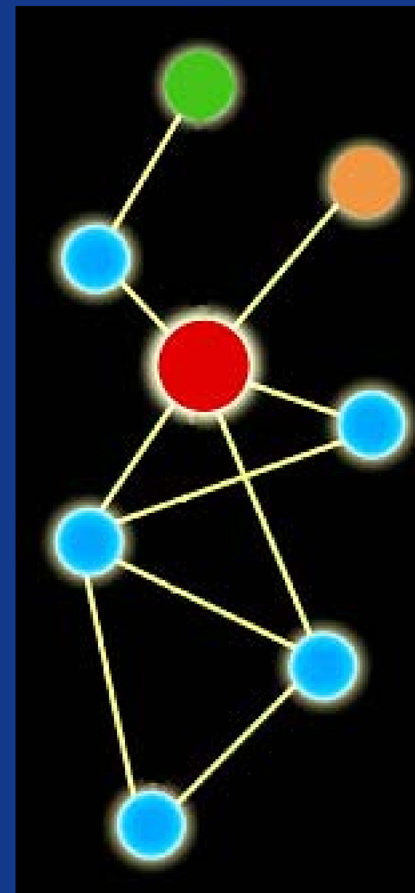
What is systems medicine?

Disease Arises from Disease Perturbed Networks



Non-Diseased



Diseased

dynamics of pathophysiology

diagnosis

therapy

prevention

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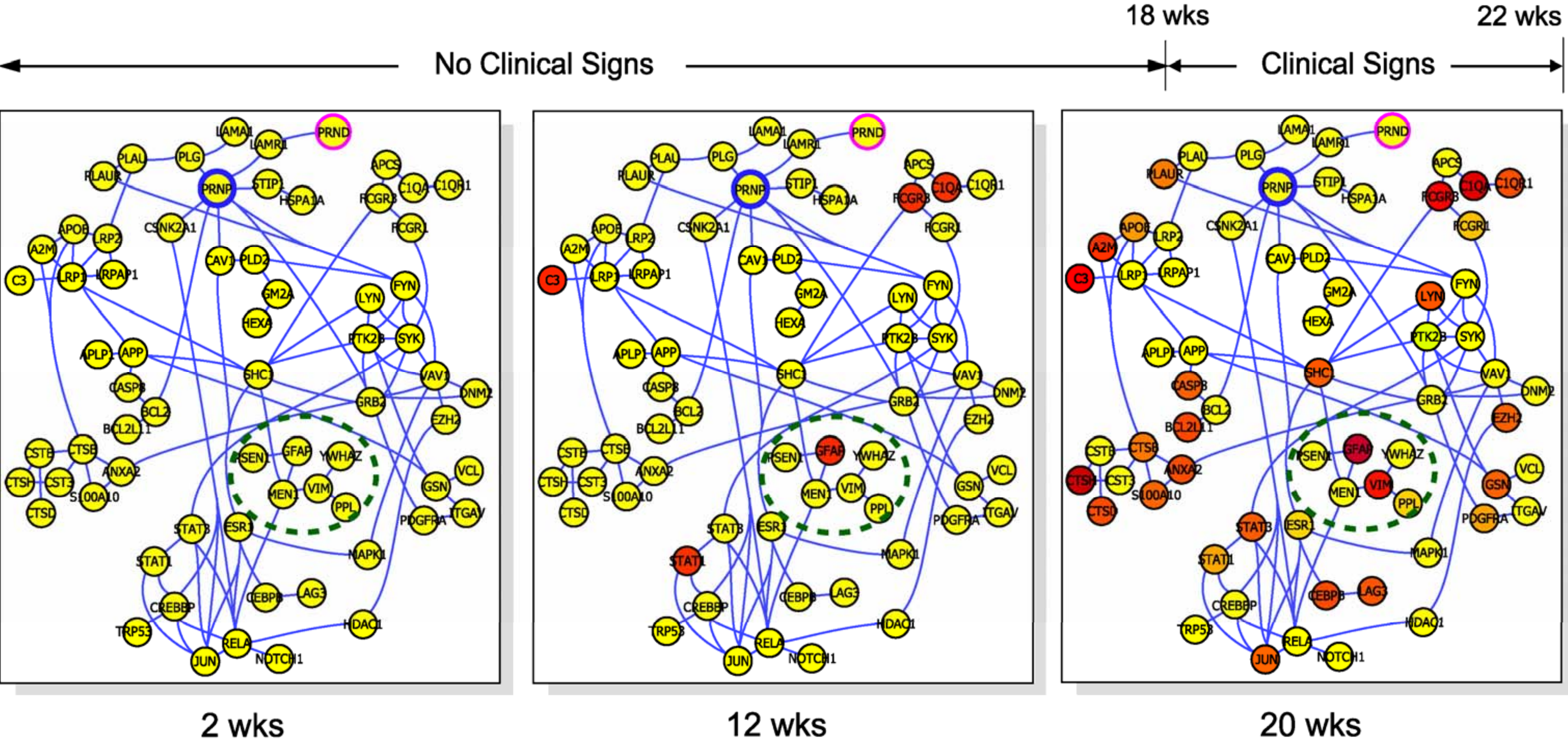
Dynamics of a Prion Perturbed Network



Towards Predictive Medicine

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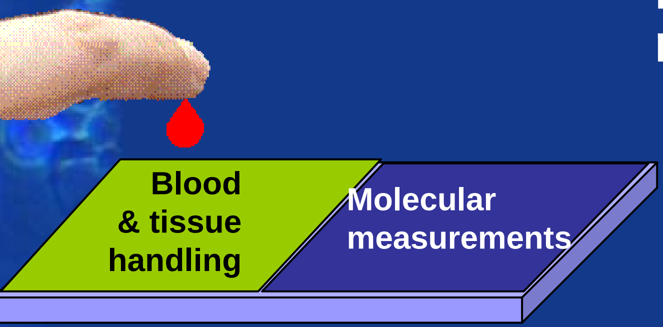
Organ-Specific Blood Proteins Will Make the Blood a Window into Health and Disease

- Perhaps 50 major organs or cell types--each secreting protein blood molecular fingerprint.
- The levels of each protein in a particular blood fingerprint will report the status of that organ. Probably need 10-50 organ-specific proteins per organ.
- Need to quantify 500-2500 blood proteins from a droplet of blood.
- Key point: changes in the levels of organ-specific markers will assess all diseases or environmental challenges for a particular organ

In vitro diagnostics

Quantitate 1000-2000 organ-specific proteins to:

identify disease;
stratify disease;
progression of disease;
response of disease to therapy etc.



Fundamental Materials/Chemical Issues

- Scalable & Simple Detection Technologies
- Multiple Functions Integrated onto Microfluidics Chips
- Protein Capture Agents
- Manufacturability

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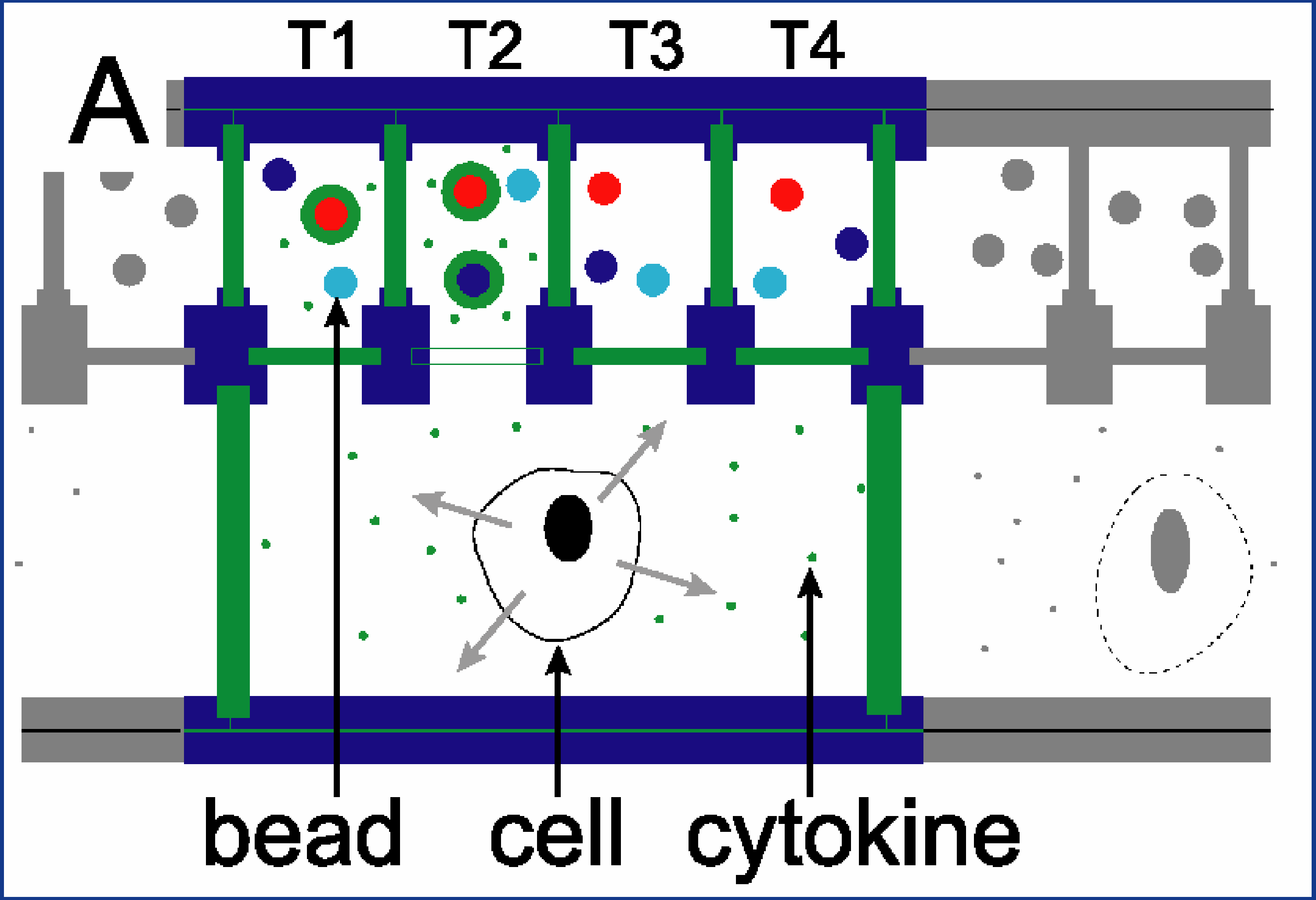
Multiplexed ELISA for secreted proteins



Sensitivity for detection of proteins secreted from cells
-how much TNFα from a single macrophage?

10^6 cells/ml (in a plate experiment): → ~1 ng/ml TNFα

→ 10^{-6} ng/cell (10^{-15} g/cell)

Mass of TNFα is 58 kDa: 9.6 x 10^{-11} ng/molecule

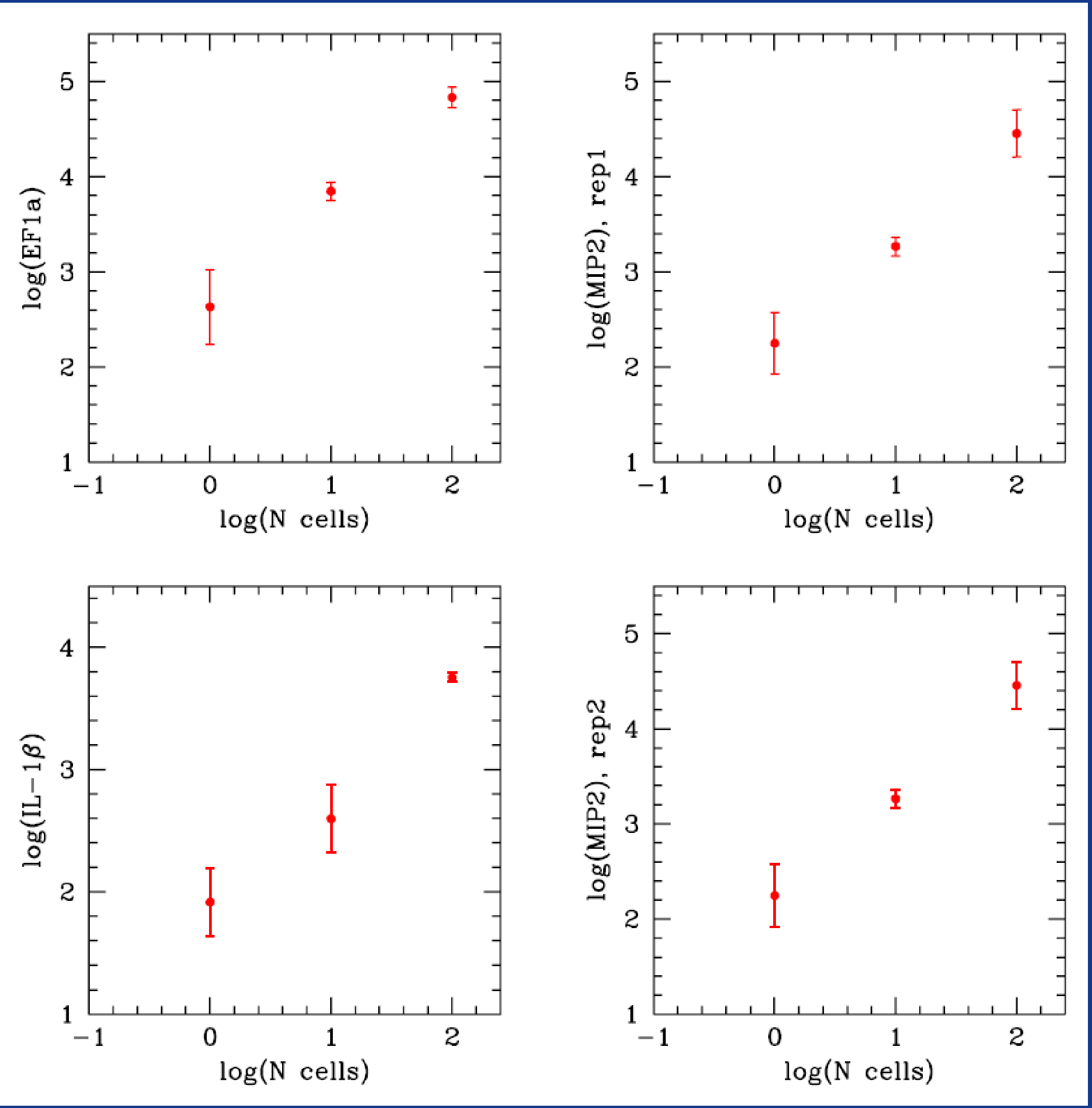
→ 10^4 molecules/cell

<u>Our sensitivity:</u> TNFα or MIP2.
50-100pg/ml in 1nl
Amount: 100pg*10^{-6}ml
→ 10^{-16} g (~femtograms)

Adrian Ozinsky

Institute for Systems Biology

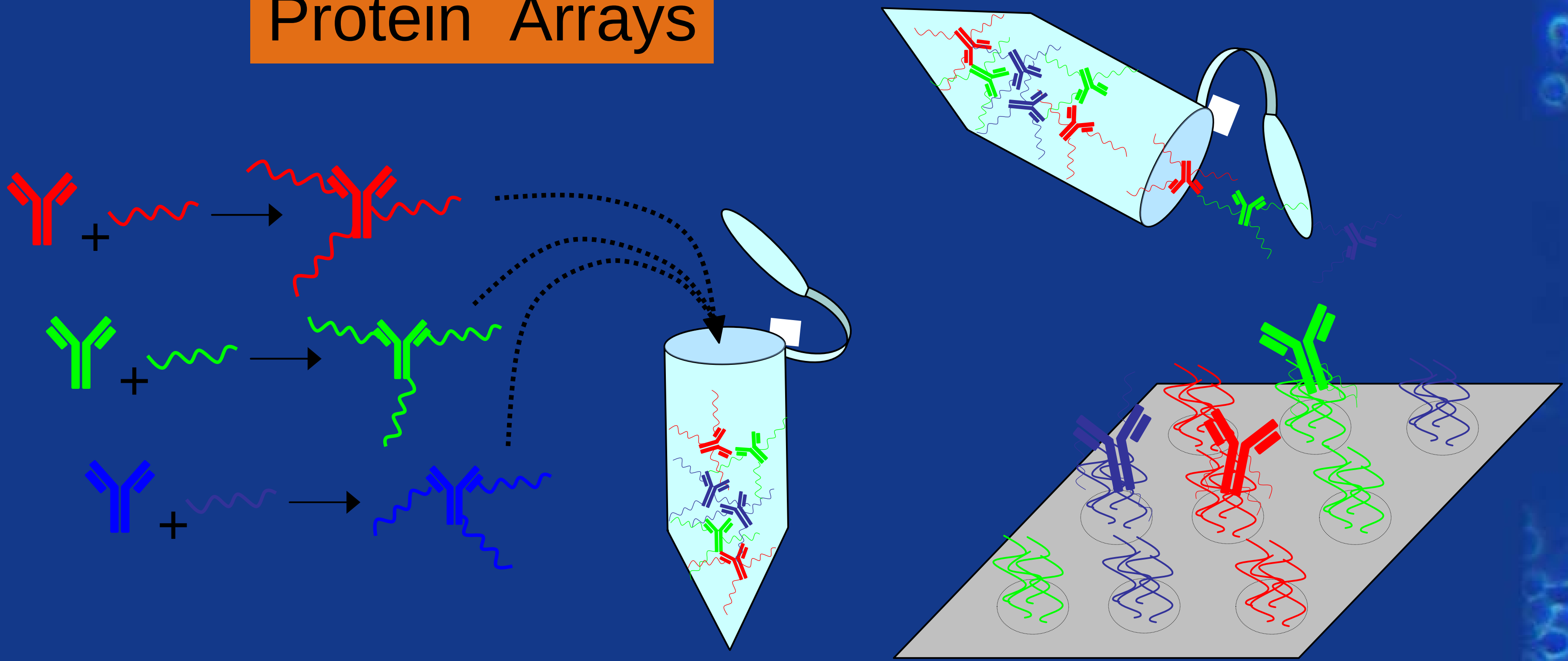
Sensitivity for single cell mRNA measurements.



RAW 264.7 cells stimulated for 2 hours with 30 ng/ml LPS

1, 10, 100 cells sorted per well

Protein Arrays



DNA-Encoded Antibody Library scheme.

Ryan Bailey and Jim Heath

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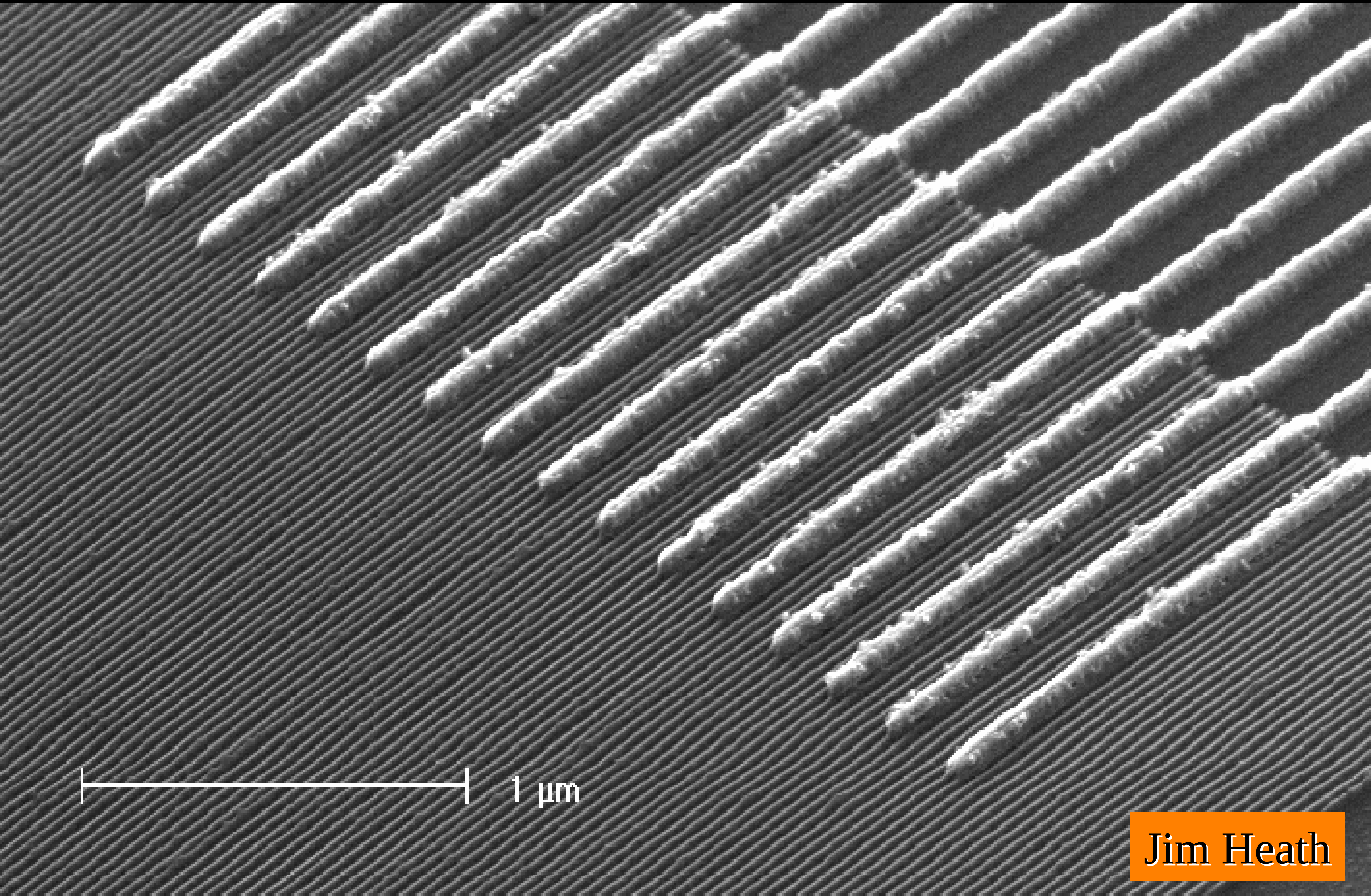
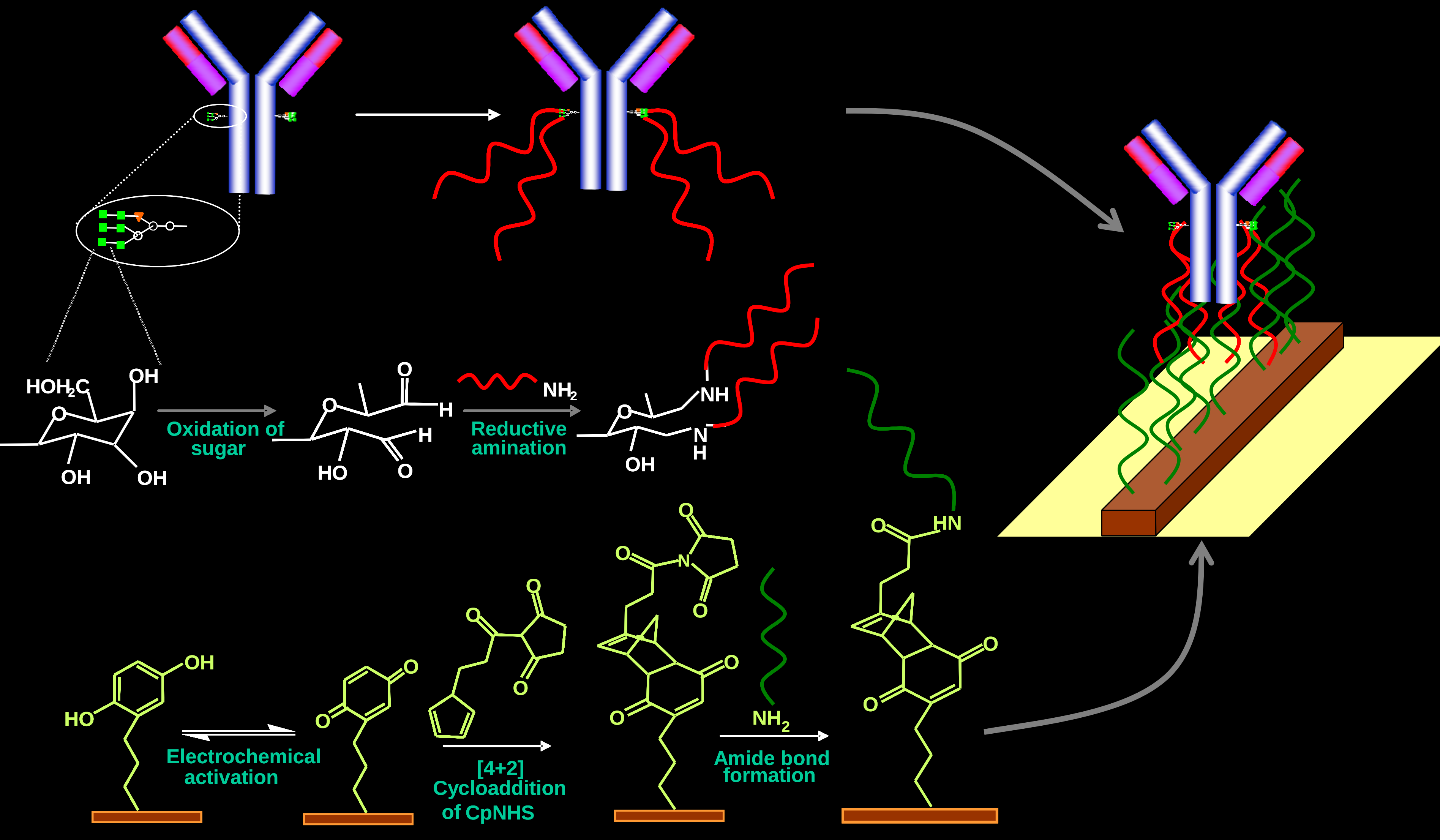
This Entire Circuit is Much Smaller than a Single Cell:

Systems Biology at the Single Cell Level: ~1000 measurements



Capture agent chemistry, as applied to nanotechnology, is a challenge

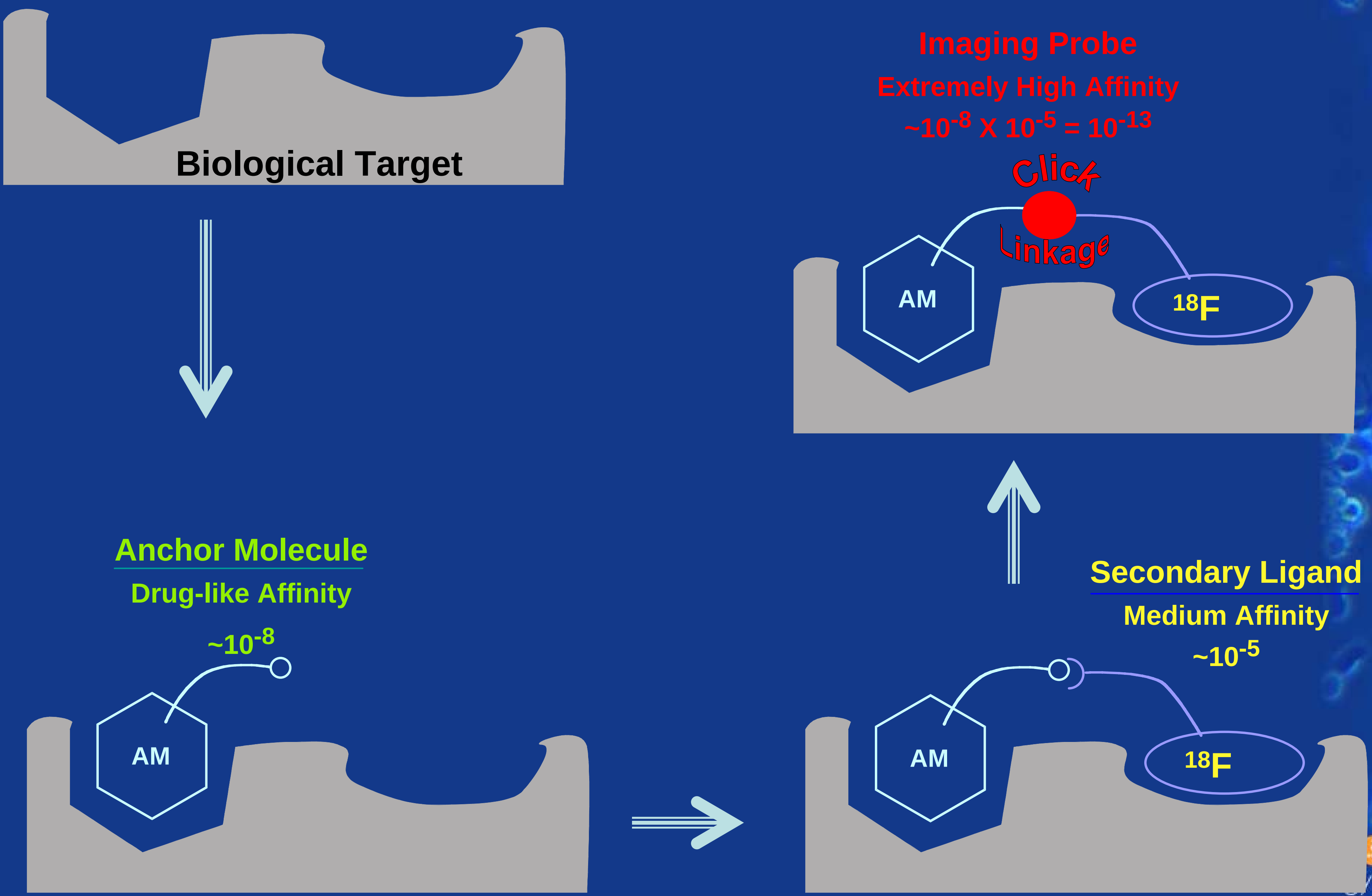


R. Bailey, et al., Heath group (2005)

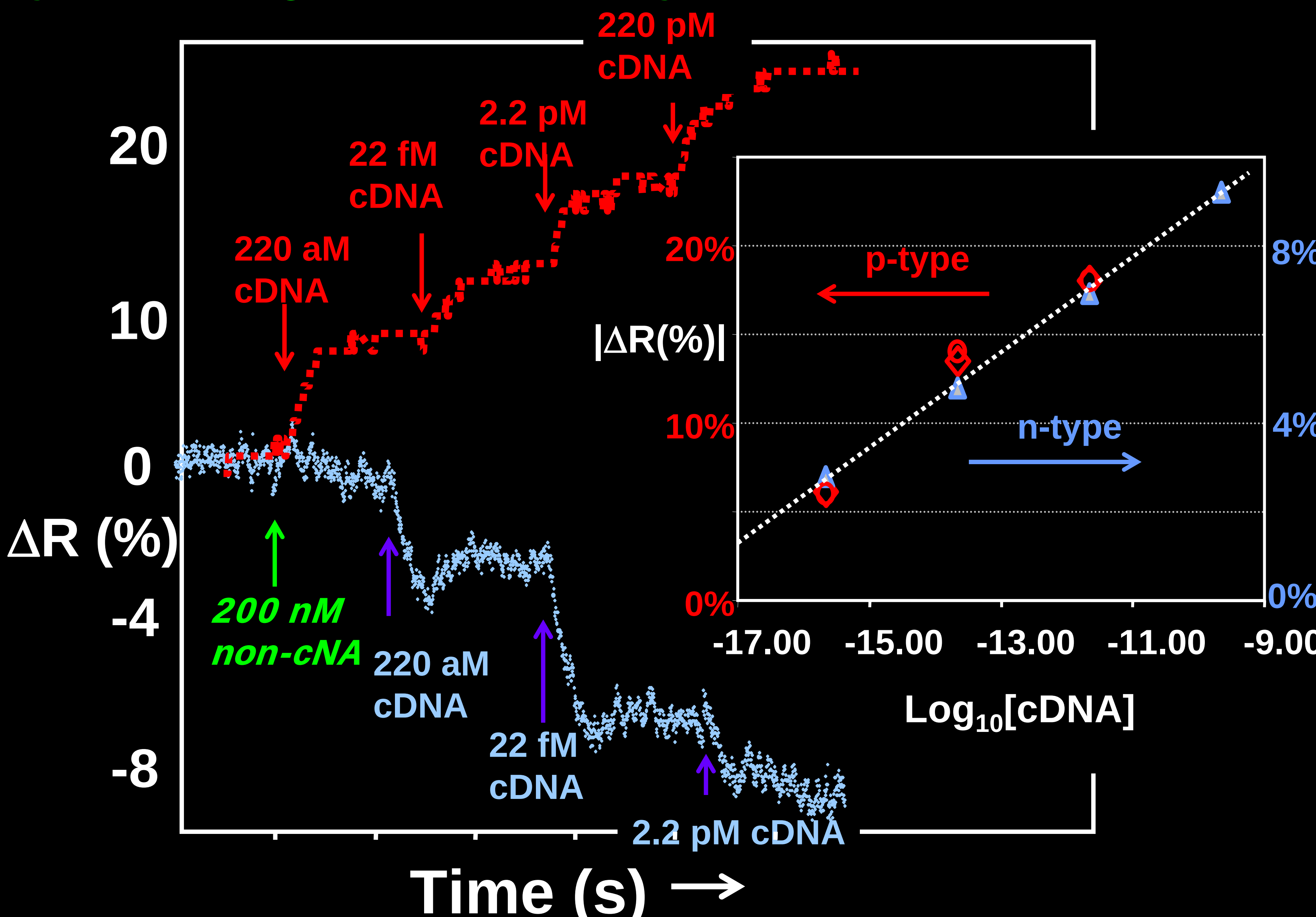
New Technologies for Protein Capture Agents

in situ click chemistry (developed by Sharpless & Kolb)

Hartmuth Kolb



Real Time Nanowire Sensing in 0.14M electrolyte (PBS); dynamic range=10^6; sensitivity to ~40 attoM



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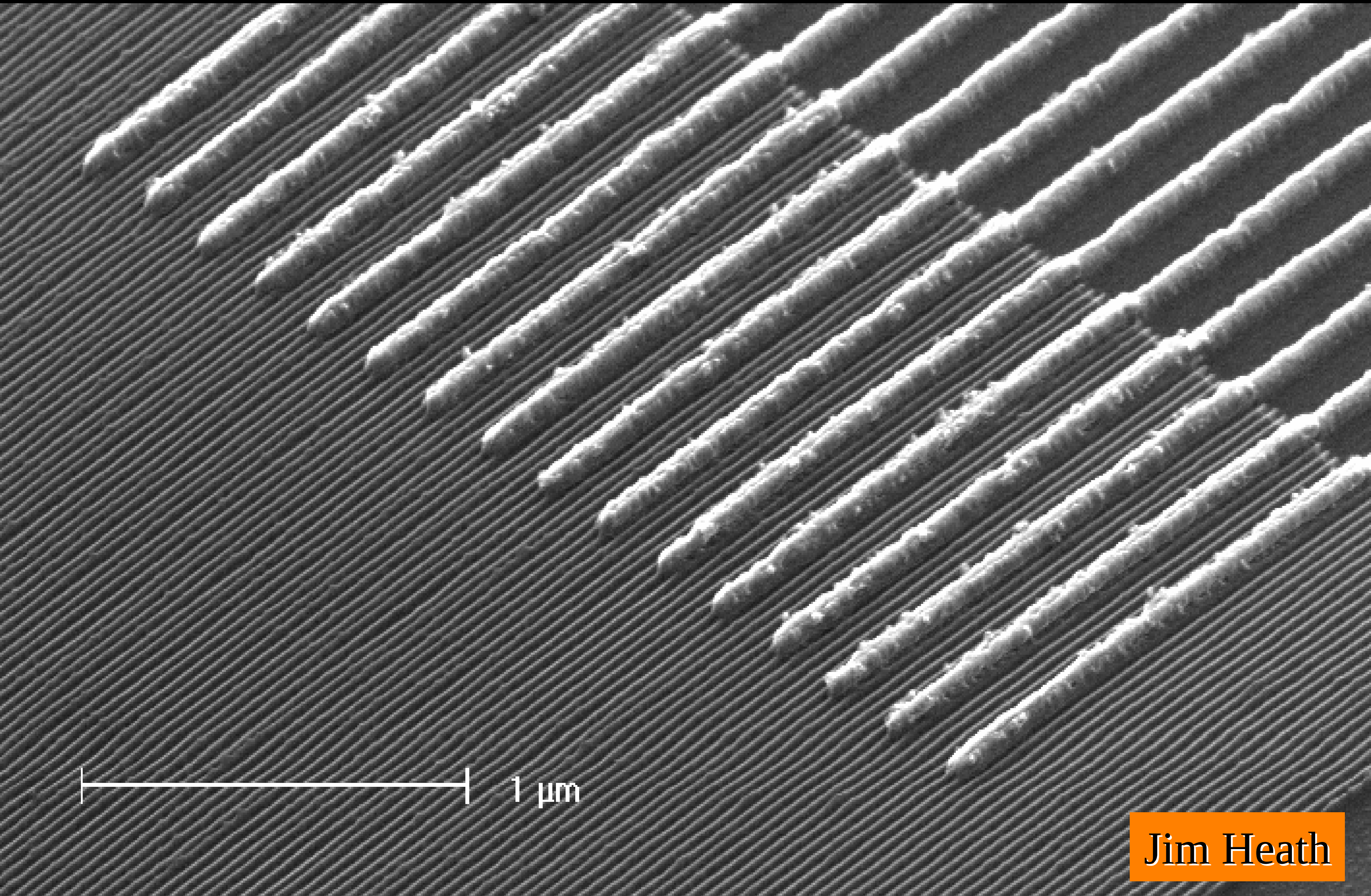
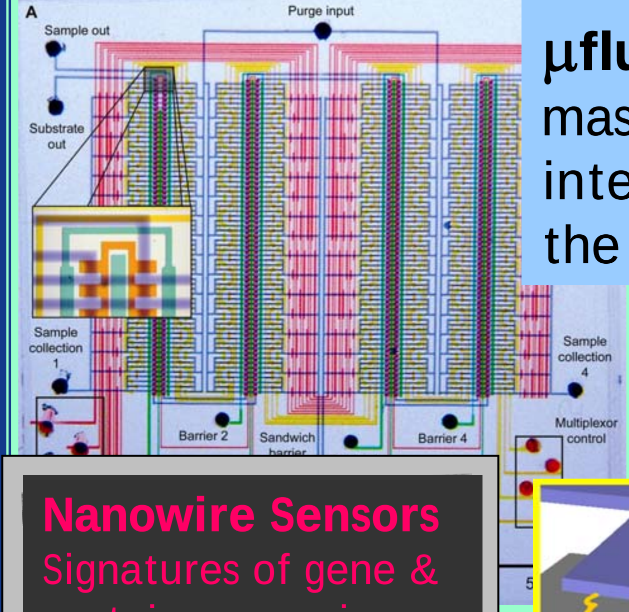
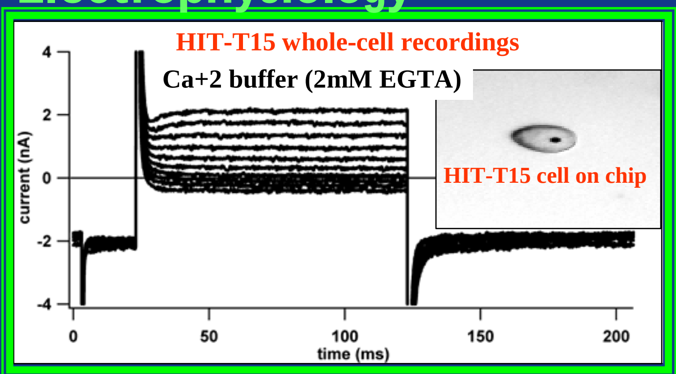


The Nanolab

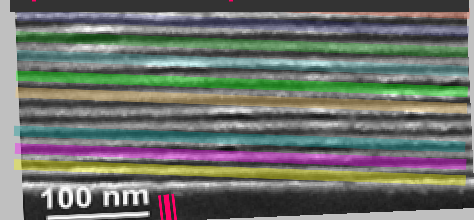


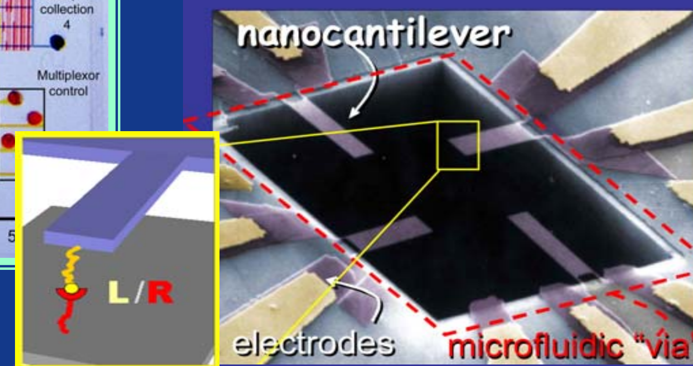
µfluidics-
massively parallel fluidic interconnects to integrate the nanosensor arrays

Electrophysiology



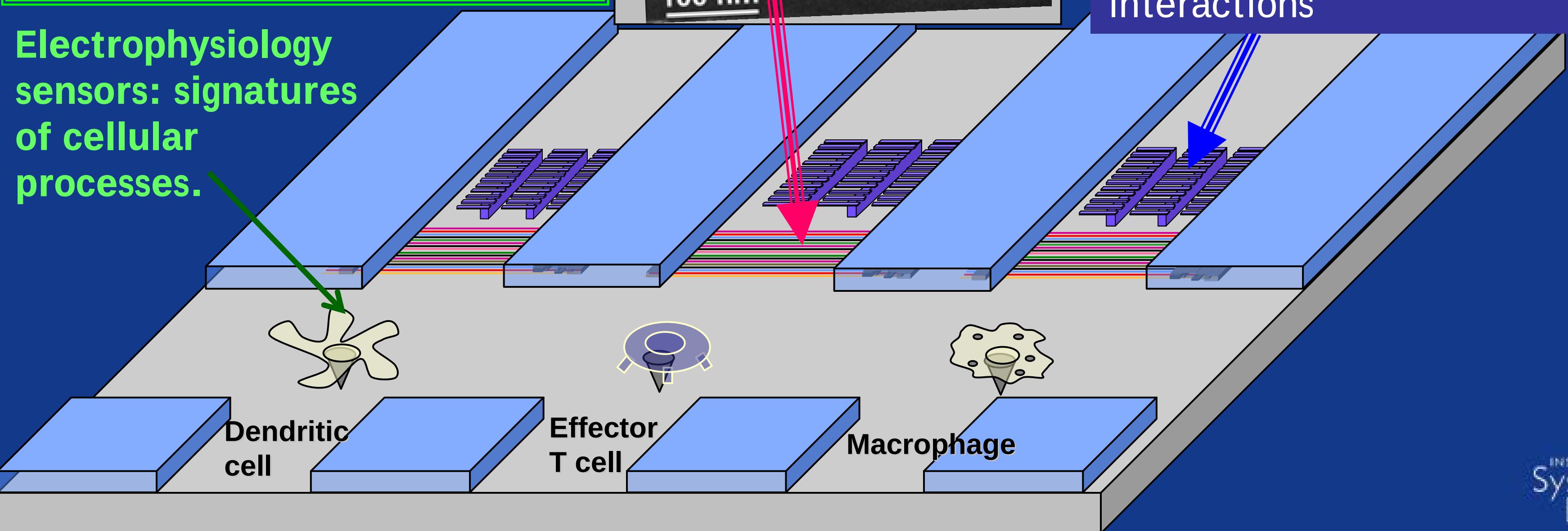
Nanowire Sensors
Signatures of gene & protein expression





Nanomechanical Sensors
Protein-protein & Protein-DNA interactions

Electrophysiology sensors: signatures of cellular processes.



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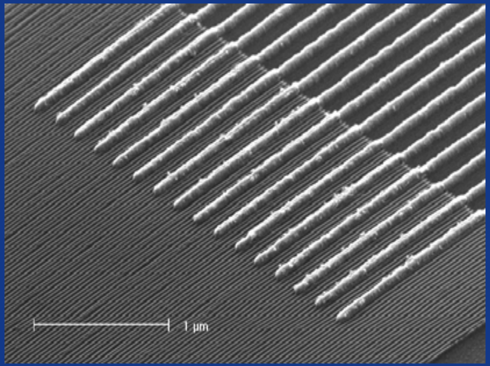
A Nano-Device to Sequence Single DNA Molecules

- Sequence one billion DNA molecules simultaneously for 100 base pairs
- Uses:
  - Sequencing of individual human genomes rapidly and inexpensively--eventually from single cells
  - Sequencing the complete transcriptomes of organs or cell types and eventually individual cells
  - Analyzing other dynamic genomic information on a global basis--gain/loss variants, epigentic changes, transcriptomes, SNPs, etc.

Predictive, Preventive, Personalized and Participatory Medicine

- Driven by systems approaches to disease and new measurement technologies (nanotechnology) P4 will emerge over the next 10-20 years



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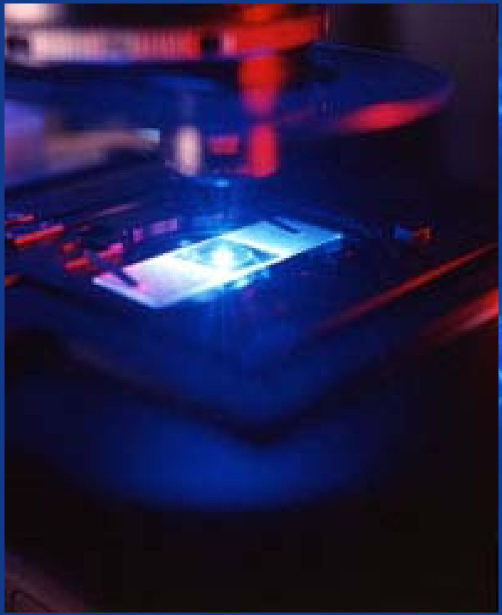
Predictive, Preventive, Personalized and Participatory Medicine (P4)

- Predictive:
  - Probabilistic health history--DNA sequence
  - Biannual multi-parameter blood protein measurements
  - In vivo diagnostic measurements to stage and localize disease



How can billions of measurement on each patient be reduced to coherent hypotheses about the health and disease of each patient?

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Blood Is a Window into Health and Disease

- Read the organ-specific secreted molecular fingerprints
  - Correlation with cellular state change
  - Decipher underlying network changes

- The blood fingerprints will permit:
  - Early diagnosis
  - Disease stratification
  - Follow disease progression
  - Follow response to therapy
  - Early detection of adverse drug reactions
  - Stratify patients with regard to drug responsiveness
  - Aid in titrating drug doses
  - Monitor drug side reactions
  - Environmental toxins
  - Development
  - Aging
  - Environmental exposures

Predictive, Preventive, Personalized and Participatory Medicine (P4)

- Predictive:
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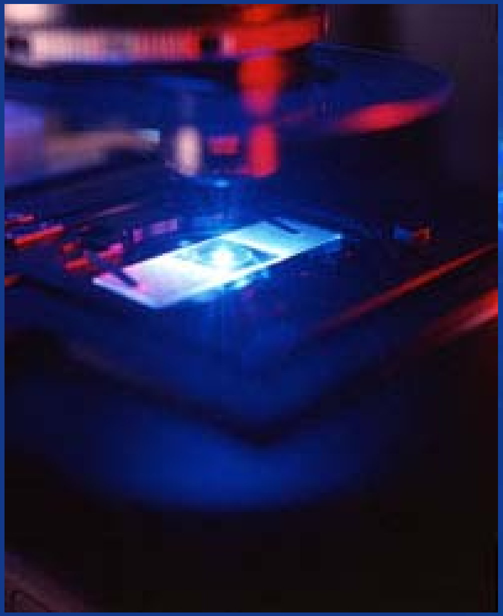
  - Biannual multi-parameter blood protein measurements
  - In vivo diagnostic measurements to stage and localize disease
- Preventive:
  - Design of therapeutic and preventive drugs via systems approaches



Drugs to cure (reengineer disease-perturbed networks) and to prevent (networks from becoming disease-perturbed).

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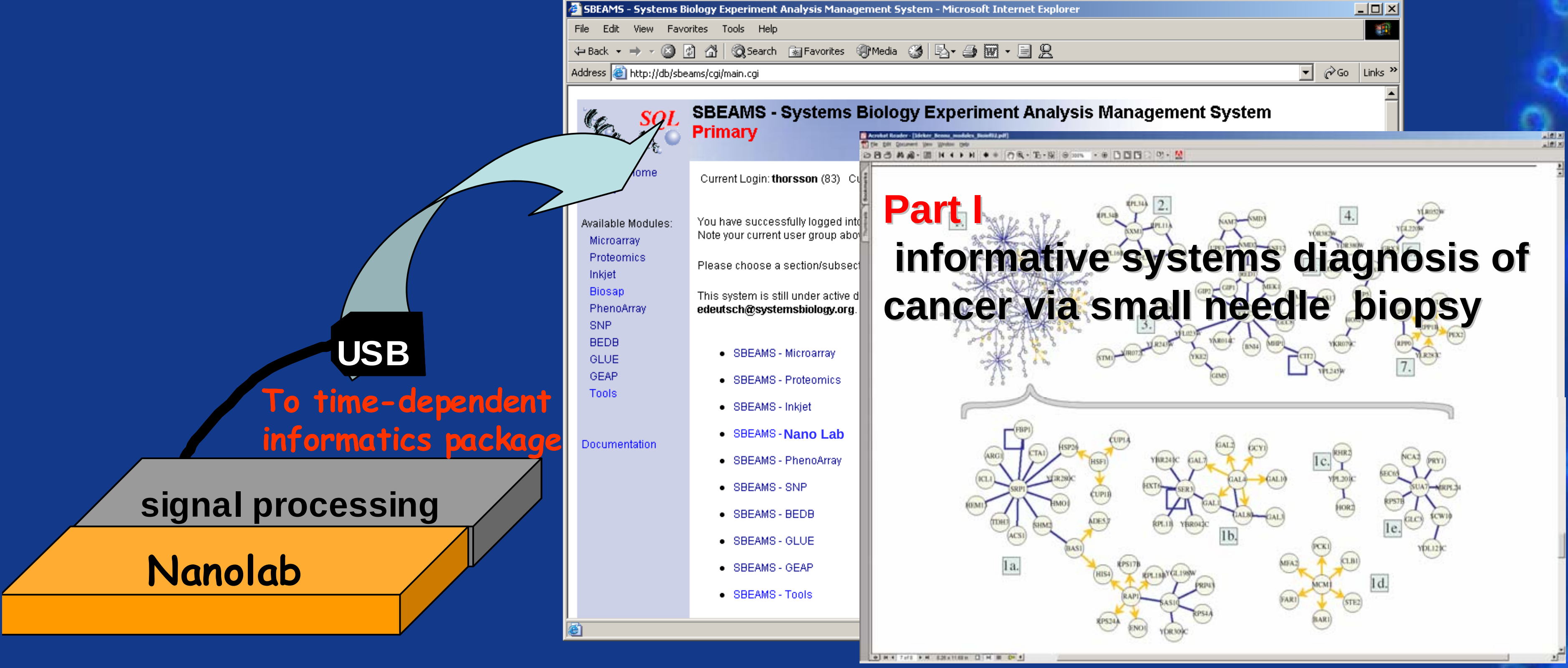
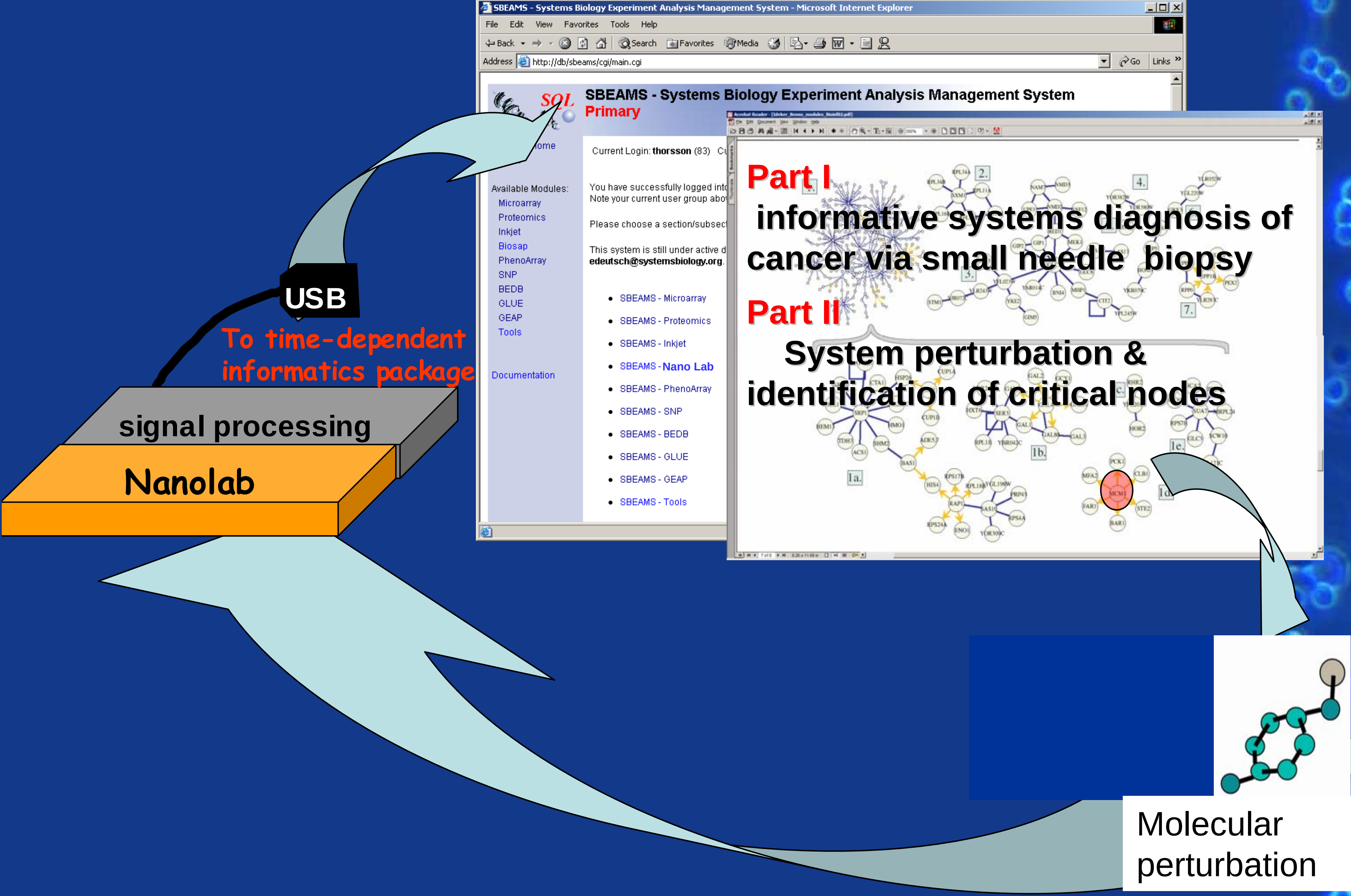


The Alliance for NanoSystems Biology


SBEAMS - Systems Biology Experiment Analysis Management System - Microsoft Internet Explorer
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Back Search Favorites Media
Address http://db/sbeams/cgi/main.cgi
Go Links
SOL
SBEAMS - Systems Biology Experiment Analysis Management System
Primary
Home
Current Login: thorsson (83)
Available Modules:
Microarray
Proteomics
Inkjet
Biosap
PhenoArray
SNP
BEDB
GLUE
GEAP
Tools
Documentation
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Note your current user group abo
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edeutsch@systemsbiology.org.
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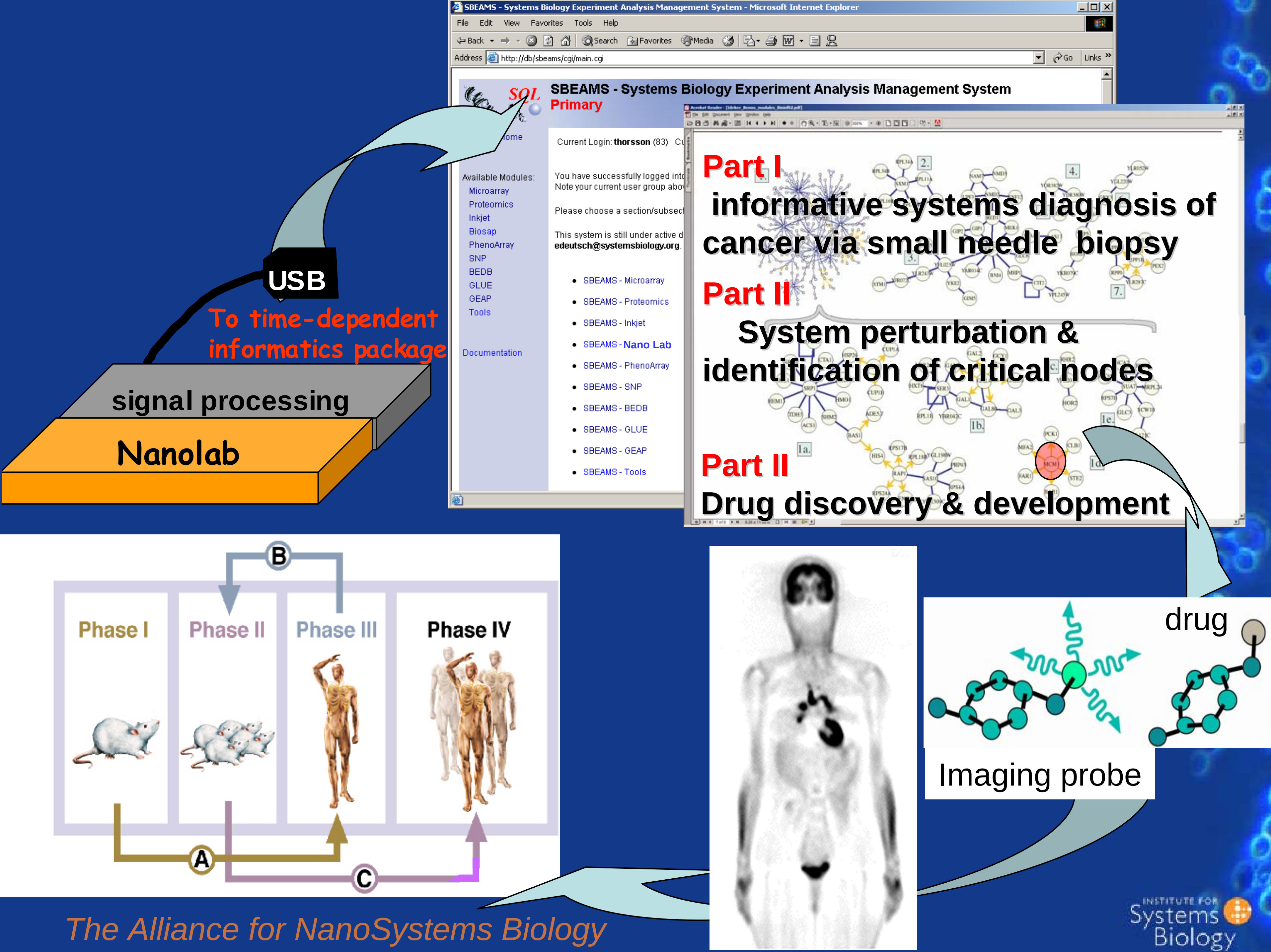
SBEAMS - Proteomics
SBEAMS - Inkjet
SBEAMS - Nano Lab
SBEAMS - PhenoArray
SBEAMS - SNP
SBEAMS - BEDB
SBEAMS - GLUE
SBEAMS - GEAP
SBEAMS - Tools
Part I
informative systems diagnosis of cancer via small needle biopsy
Part II
System perturbation & identification of critical nodes
USB
To time-dependent informatics package
signal processing
Nanolab
Molecular perturbation



USB
To time-dependent informatics package
signal processing
Nanolab
SBEAMS - Systems Biology Experiment Analysis Management System - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Address http://db/sbeams/cgi/main.cgi
SBEAMS - Systems Biology Experiment Analysis Management System
Primary
Current Login: thorsson (83)
Available Modules:
Microarray
Proteomics
Inkjet
Biosap
PhenoArray
SNP
BEDB
GLUE
GEAP
Tools
Documentation
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SBEAMS - Microarray
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SBEAMS - Inkjet
SBEAMS - Nano Lab
SBEAMS - PhenoArray
SBEAMS - SNP
SBEAMS - BEDB
SBEAMS - GLUE
SBEAMS - GEAP
SBEAMS - Tools
Part I
informative systems diagnosis of cancer via small needle biopsy
Part II
System perturbation & identification of critical nodes
Part II
Drug discovery & development
Phase I
Phase II
Phase III
Phase IV
A
B
C
drug
Imaging probe
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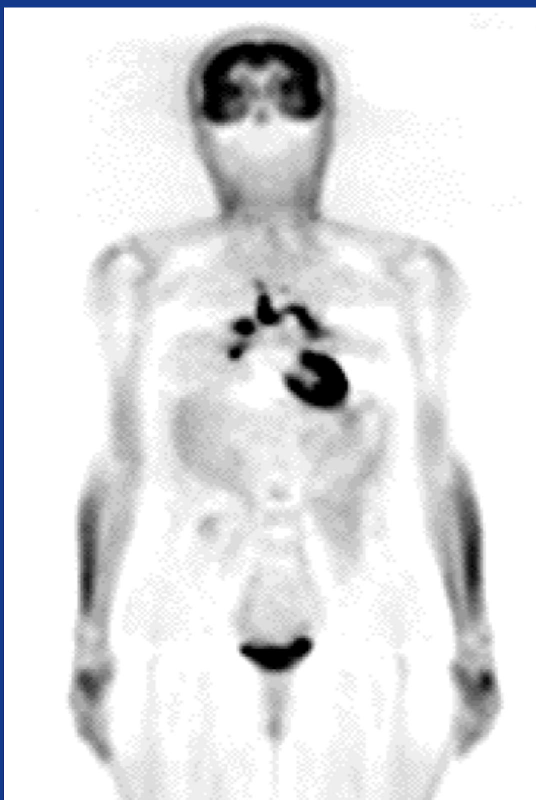
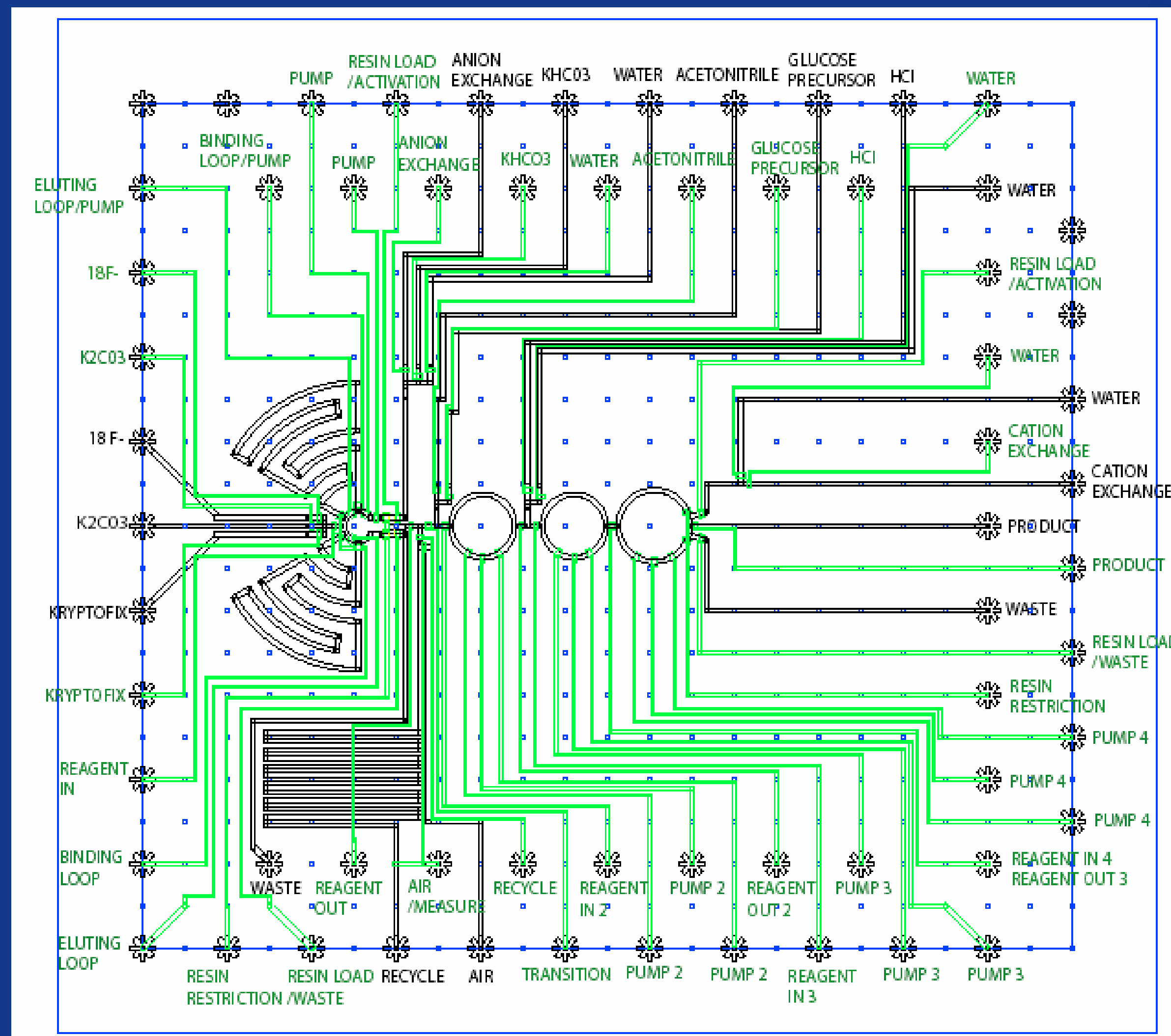
Institute for Systems Biology

The Nanolab & Molecular Imaging of Disease: *Dramatically expanding the molecular language of imaging probes*

1 cm² of plastic = 50 doses of a molecular imaging probe





Predictive, Preventive, Personalized and Participatory Medicine (P4)

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- Preventive:
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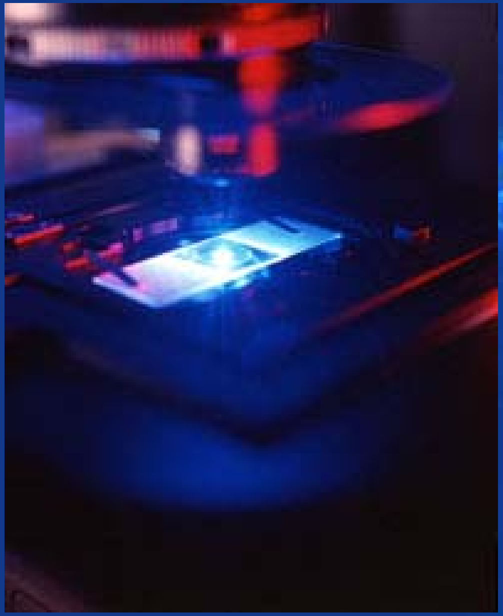
- Personalized:
  - Unique individual human genetic variation mandates individual treatment



Focus on wellness

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Predictive, Preventive, Personalized and Participatory Medicine (P4)

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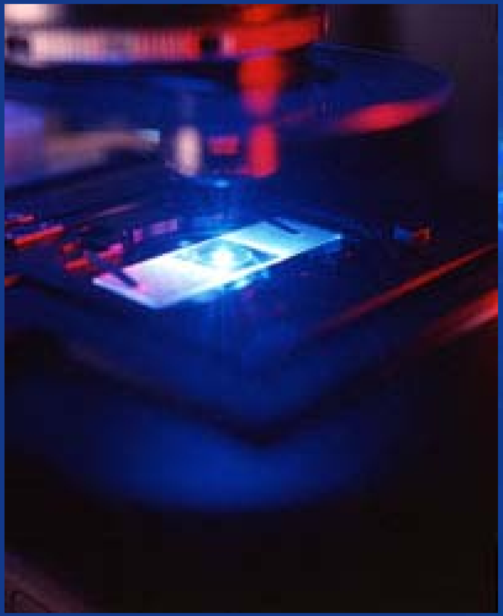
- Preventive:
  - Design of therapeutic and preventive drugs via systems approaches
- Personalized:
  - Unique individual human genetic variation mandates individual treatment
- Participatory:
  - Patient understands and participates in medical choices



Patient and physician education

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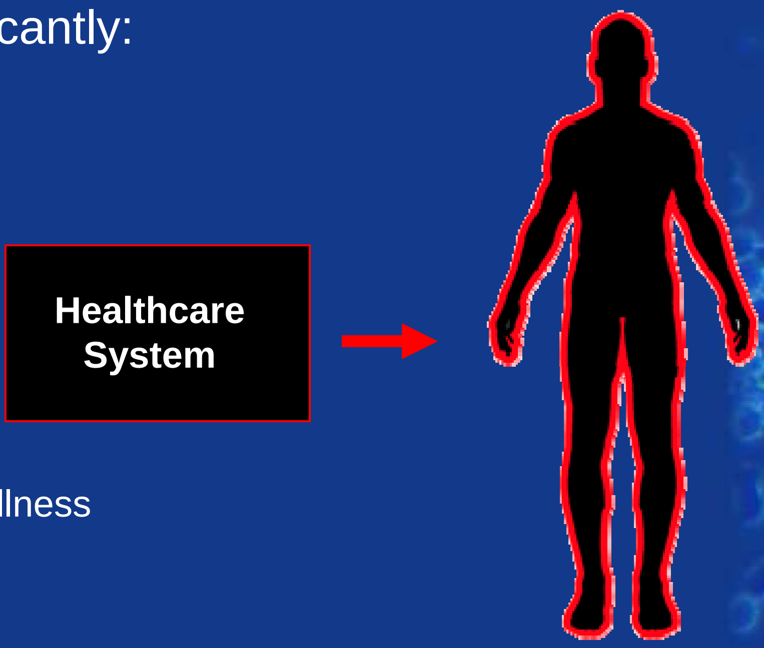
Systems Biology and P4 Medicine Will Transform the Health Care Industry

Will impact the health care system significantly:

- Pharmaceuticals
- Biotechnology
- Healthcare industry
- Health insurance
- Medicine--diagnostics, therapy, prevention, wellness
- Nutrition
- Assessments of environmental toxicities
- Academia and medical schools



New ideas need new organizational structures

Cooperation and Balance Between Big and Small Biology is Essential

Big Science--Cross Disciplinary Systems Biology

↕

Small Biology

Big problems (cross-disciplinary) in science

Examples of Big Science Problems

- P4 medicine
- IT of P4 medicine
- Bio-energy
- Aging
- Cancer
- Immunity
- Stem cells
- Bioterrorism

Require cross-disciplinary, coordinated strategic partnerships

Big Problem Approach for P4 Medicine: Integrating Medicine, Biology, Technology and Computation/Math

- Validation of the blood molecular fingerprint for each organ
- Correlate these fingerprints with health and disease states
- Develop/invent the blood measurement technologies--
  discovery (proteomics) high throughput assays (nanotechnology).
  Optimize specific capture agent discovery (antibodies, aptamers,peptides)
- *In vivo* imaging to follow disease, drug response, drug effectiveness, drug dosage determinations etc.
- Develop new mathematical methods for extracting maximum information from blood fingerprints & genomes
- Develop new computational techniques for building dynamic networks from massive amounts of integrated data
- Systems approaches in a model organism to invent new approaches to the discovery of drug targets
- Re-engineering of networks with drugs (diseased back to normal)
- Handling the enormous personalized data sets--security, mining, reporting, etc
- Education of patients (and physicians) to the realization of participatory medicine
- Establishing companies to efficiently use these technologies for human health--coordinated and efficient transfer of technology from academia to industry

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Alliance for NanoSystems Biology

CALTECH

Jim Heath	Chemistry--nanotech
Michael Roukes	Physics--nanotech
Steve Quake	Applied Physics--microfluidics

ISB

Lee Hood	Immunology, Technology, Genomics
Alan Aderem	Immunology
Adrian Ozinsky	Microfluidics, Immunology

UCLA

Mike Phelps	Medical Pharmacology--molecular imaging
Charles Sawyers	Medicine--cancer

ISB Strategic Partnerships

- Academic
- Industrial
- National Laboratories
- International

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Features of Strategic Partnerships

- Focus around big scientific problems with clear milestones--key question--what will each partner bring?
- Strategic partnerships must create and exist within cross disciplinary environments
- Select best partners in field to achieve milestones rapidly--thus shortening time table for achievement
- Chose few strategic partnerships and work hard to make effective
- New strategies for funding--as government funding generally inadequate
- Partner with academics and industry. Think about new strategies.
- International partnerships?
- Leadership!

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Why should NIST get involved with systems biology?

Systems biology will catalyze:

Health Care

Biotechnology

Agriculture

Energy

Nutrition

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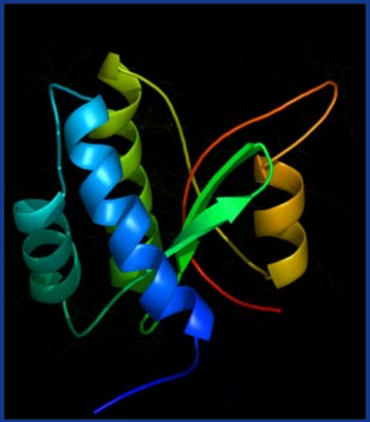
Computational / Mathematical Challenges in Systems Biology

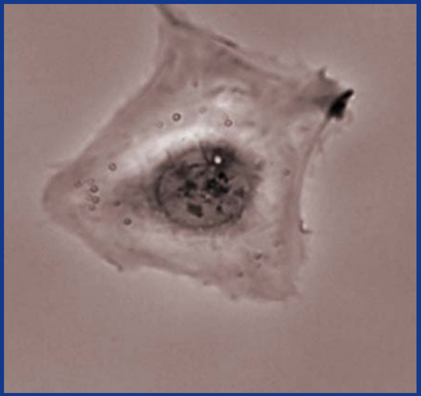
1. How to fully decipher the (digital) information content of the genome
2. How to do all-vs-all comparisons of 1000s of genomes
3. How to extract protein and gene regulatory networks from 1 & 2
4. How to integrate different multi-scale high-throughout data types dependably
5. How to visualize & explore large-scale, multi-dimensional data
6. How to convert static network maps into dynamic mathematical models
7. How to predict protein structure (3-dimensional) and function ab initio
8. How to identify signatures for cellular states (e.g. healthy vs. diseased)
9. How to build hierarchical models across multiple scales of time & space
10. How to reduce complex multi-dimensional models to underlying principles
11. Text searching to integrate data and literature
12. Security for enormous amounts of personalized human data

Digitalization of Biology and Medicine: Grand Challenge for Chemistry

- Analysis of single molecules and single cells--*in vitro* and *in vivo*
- A revolution that will transform medicine even more than digitalization transformed information technologies

Lower the cost of medicine





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NIST Opportunities

- Emerging from systems biology--a paradigm change in biology
- Develop technologies. For genomics, proteomics, transcriptomics, metabolomics, interactomics, pehnomics, in vivo imaging, etc.
- Data assessment and validation. For global data sets from all of the technologies mentioned above.
- Software development and integration. For the capture, storing, analysis, integration, and modeling of global data sets.
- KEY: WILL COST LOTS OF MONEY TO DO IT RIGHT. STRATEGIC PARTNERSHIPS ARE CRITICAL AS BIOLOGY MUST DRIVE EACH OF THESE OPPORTUNITIES.

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