WORKSHOP AGENDA

Workshop on Computational Modeling and Simulation of Biological Systems
DARPA – DSO/MTO
November 18, 1999

Welcome and Introduction
Defense Advanced Research Projects Agency/Defense Sciences Office/Microsystems Technology Office, **Alan Rudolph/Anantha Krishnan**

E-CELL: Integrative Simulation of Cellular Processes
Keio University, **Masaru Tomita**

The Construction of Genomically Defined Metabolic Genotypes, and the Assessment of Their Capabilities
University of California, San Diego, **Bernard Palsson**

Localization and Population Biology
Harvard University, **David Nelson**

Some Practical Experiences with Simulation in Microfluidic System
Stanford University, **Greg Kovacs**

Scaling and Simulation Approaches to Microchemical Systems
Massachusetts Institute of Technology, **Klavs Jensen**

Tools and Methods for the Design of Complex Bioanalytical Systems
Microcosm Technologies, **John West**

Multi-Disciplinary Computational Modeling Techniques for Bio-Microfluidic Device Design
CFD Research Corporation, **Vinod Makhijani**

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Receptor Mediated Regulation of Cell Behavior—A Highly Interactive Control System
Massachusetts Institute of Technology, **Linda Griffith**

Modeling the CANARY Sensor
Massachusetts Institute of Technology, Lincoln Laboratory, **Ann Rundell**

Design Strategies for Field Deployment Trials of Bees as Active and Passive Detectors of Harmful Agents
University of Montana-Missoula, **Colin Henderson**

Data-mining at the Cellular and Molecular Level for Toxin Detection and Characterization
Carnegie Mellon University, **Andrew Moore**

Presentations of Break-out Sessions:
Red Team
Blue Team
Yellow Team

Welcome and Introduction
DARPA/DSO/MTO

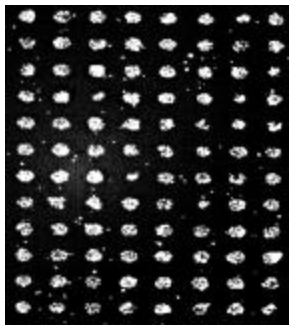
Alan Rudolph

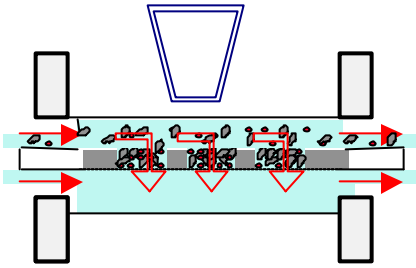
Computational Modeling and Simulation in Biological Systems

- **For living systems we should correlate process and relationships considering:**
  - **genetic blueprint**
  - **chemical interactions (VDW, ionic and hydrogen bonds)**
  - **mechanical forces (stress/strain)**
  - **environmental dynamics (aero, hydro)**
  - **sensory inputs, processing methods, and behavioral dynamics**
  - **consider scale - from macromolecular assemblies to organisms**

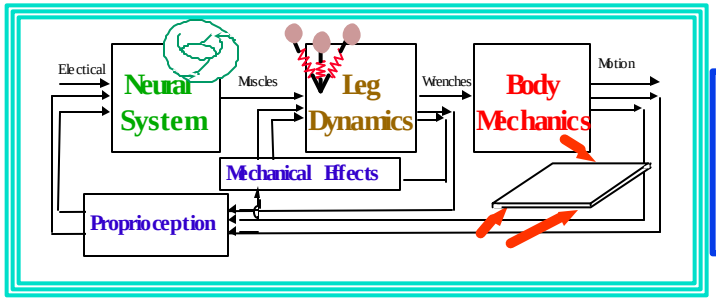
Current Computational Problems

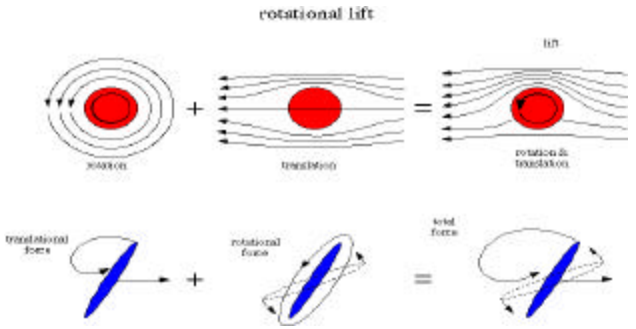
- **Optimal use or study of cells or tissues as components of working devices or materials (TBB)**
  - sensors
  - computational devices
  - actuation materials





- **Single/Group organism fitness (CBBS)**
  - control of locomotion
  - pattern or target recognition
    - » autonomous systems, robotics
  - swarm, group dynamics

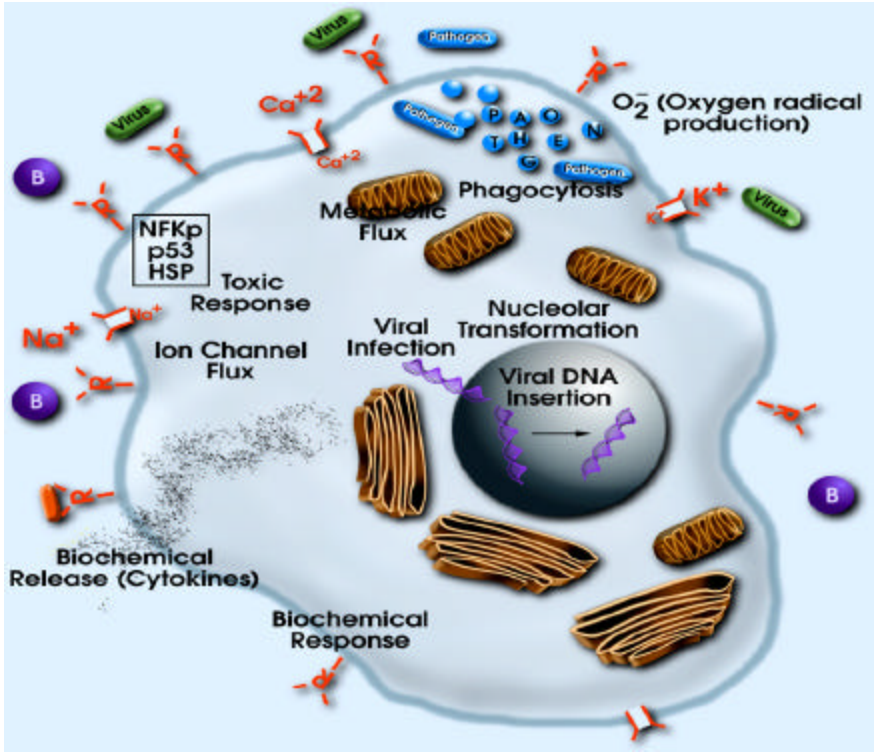




Cells As Systems

- **Cell is unit machine in biology responsible for systems level processing**
  - communicative
  - regenerative and progenic
  - self-powering/mobile

- **Cells respond to environment in specific, reproducible and redundant ways**
  - oxygen/nitrogen radicals
  - biochemical markers - cytokines/growth factors
  - morphological/structural
  - genetic



- **Cells as detector components To identify of threat**
  - processing will result in identification
  - amplification of response

How does cell information relate to tissue, organism response

- pathogenesis
- human health risk

Systems Complexity at the Organismal Scale

- **Fitness based**
  - optimize genetic passage, forage, reproduce, avoid predation
- **Force dynamics of locomotion**
  - legged, winged coordination and control
- **Neuronal processing of motor and sensory systems**
  - olfaction, vision, acoustic

Workshop
on

Computational Modeling and Simulation of Biological Systems

Organized by DARPA
DSO/MTO

November 18, 1999
Alexandria, VA

INTRODUCTION

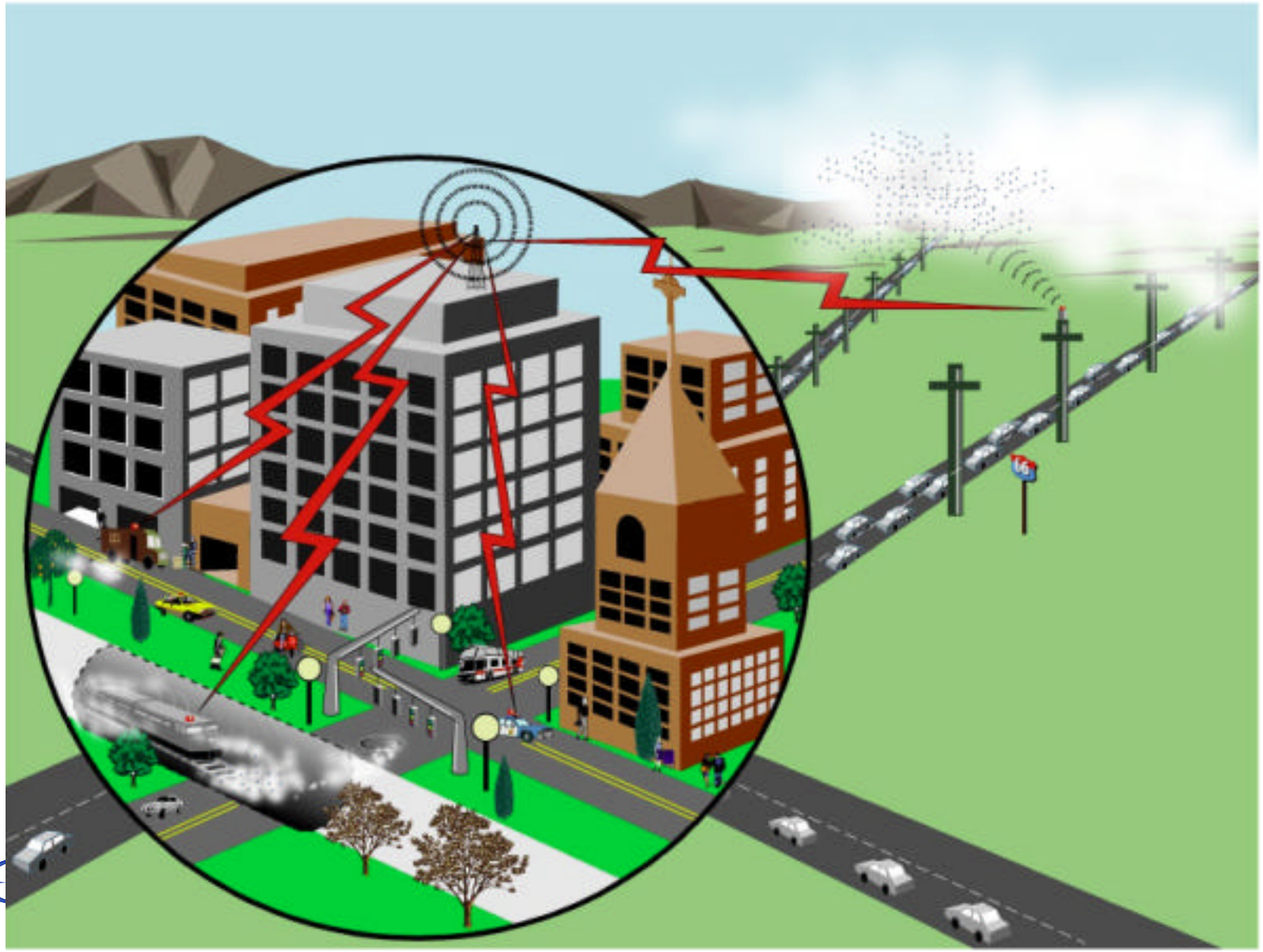
- Initially intended to facilitate collaboration between two DARPA programs
- Was expanded later to include a larger audience because of synergy with DARPA's 'Biofutures' goals and objectives
- Goal is to bring together biologists, engineers, computer scientists, mathematicians, …, to explore and discover new science/technology at the intersection of biology, systems engineering and information technology
- Long-term focus on technologies with highest relevance to National Defense and DoD needs !

DARPA Goals and Objectives

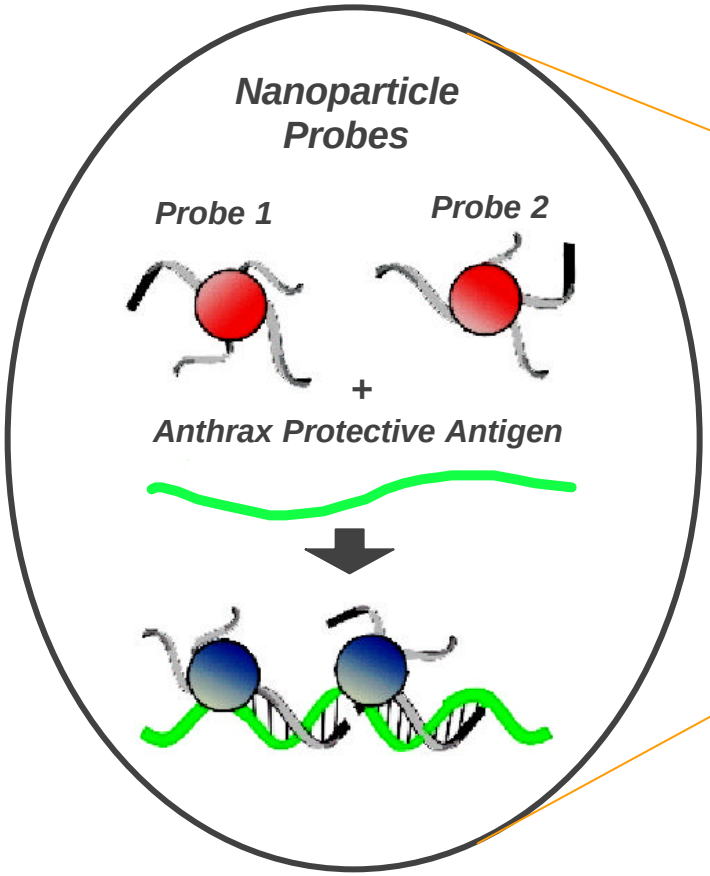
➤ SENSING AND DETECTION OF CHEMICAL & BIOLOGICAL WARFARE AGENTS

- ✦ Mimicking behavior of biological systems for military and civilian use (e.g., electronic dog's nose)
- ✦ Spin-offs in bio-medical industry for diagnostics & analysis devices, implantable sensing and drug delivery devices, etc.
- ✦ Scientific advances at the intersection of biology with traditional DoD technology, e.g., bio-materials ; bio-electronics/circuits ; self-assembled molecular structures ; nano-biotechnology ; .....

Deployment of Bio-Chem Sensors



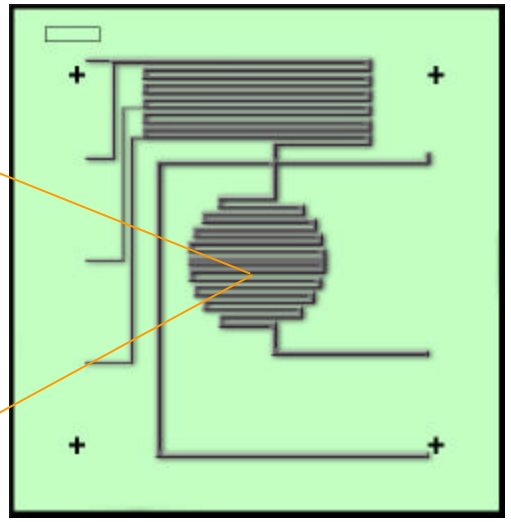
Bio-Molecular Sensor Systems



Bio-Molecular Transport and Chemistry

Interfacing with Electronics, Mechanics, Optics, ...

Bio-Chip



Molecular Recognition

Electrical Signal

Optical Signal

Mechanical Signal

Desired Sensor Attributes

- Sensitivity with small sample sizes
- Specificity in detection, i.e., no false positives
- Detection in minimum time
- Highly integrated, small size, reconfigurable
- Able to handle exposure to the environment for an extended period (Continuous sampling and processing)

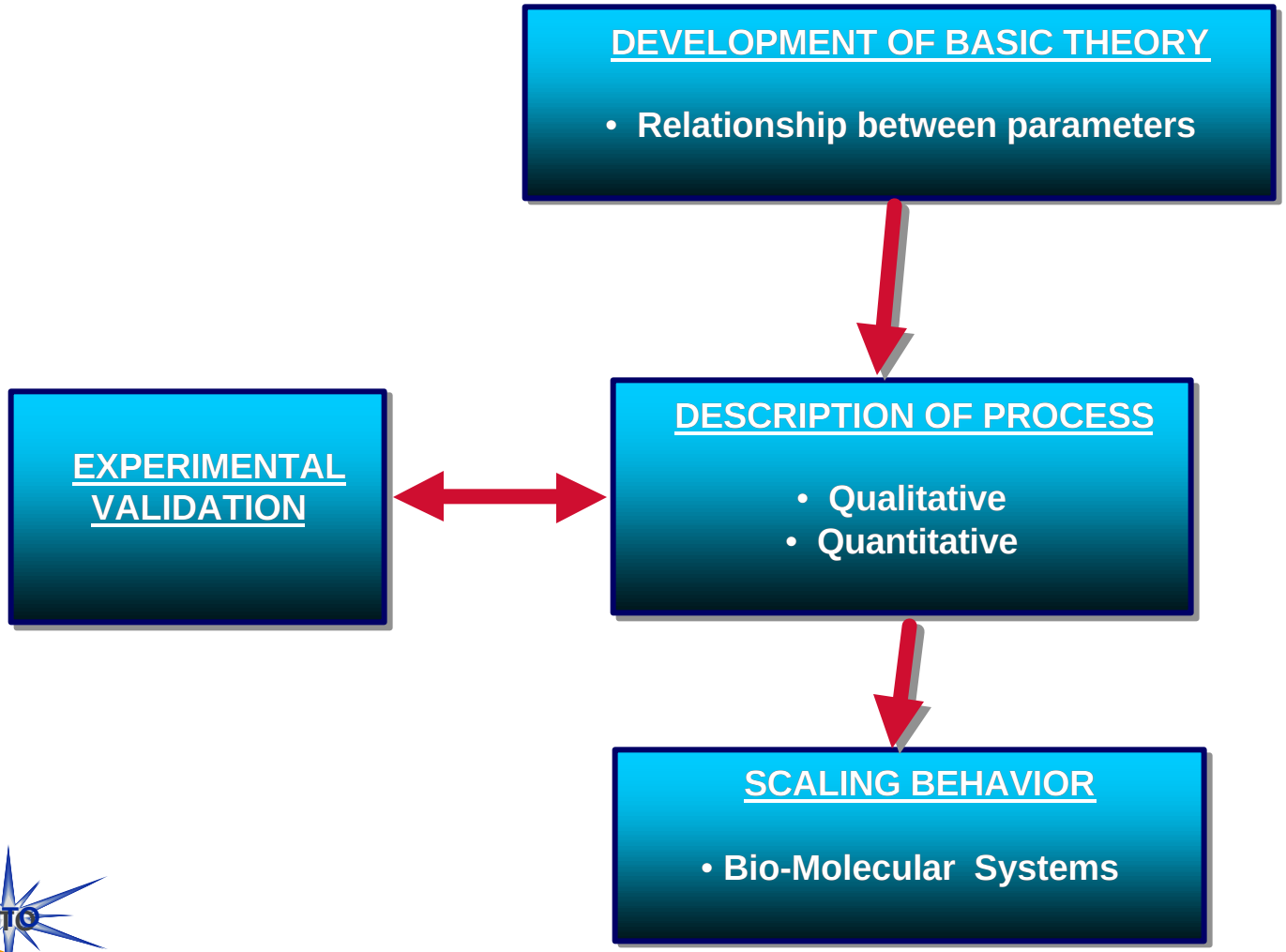
Reliable, robust, quick and portable INTEGRATED ANALYSIS SYSTEM !!

Bio-Molecular Systems Challenges

- Limited property/chemistry information on molecular recognition (enzyme-substrate, antigen-antibody, receptor-ligand, cell-cell, …)
- Lack of understanding of scaling behavior
- Lack of understanding of multi-disciplinary interaction - **Mixed Technology Integration**

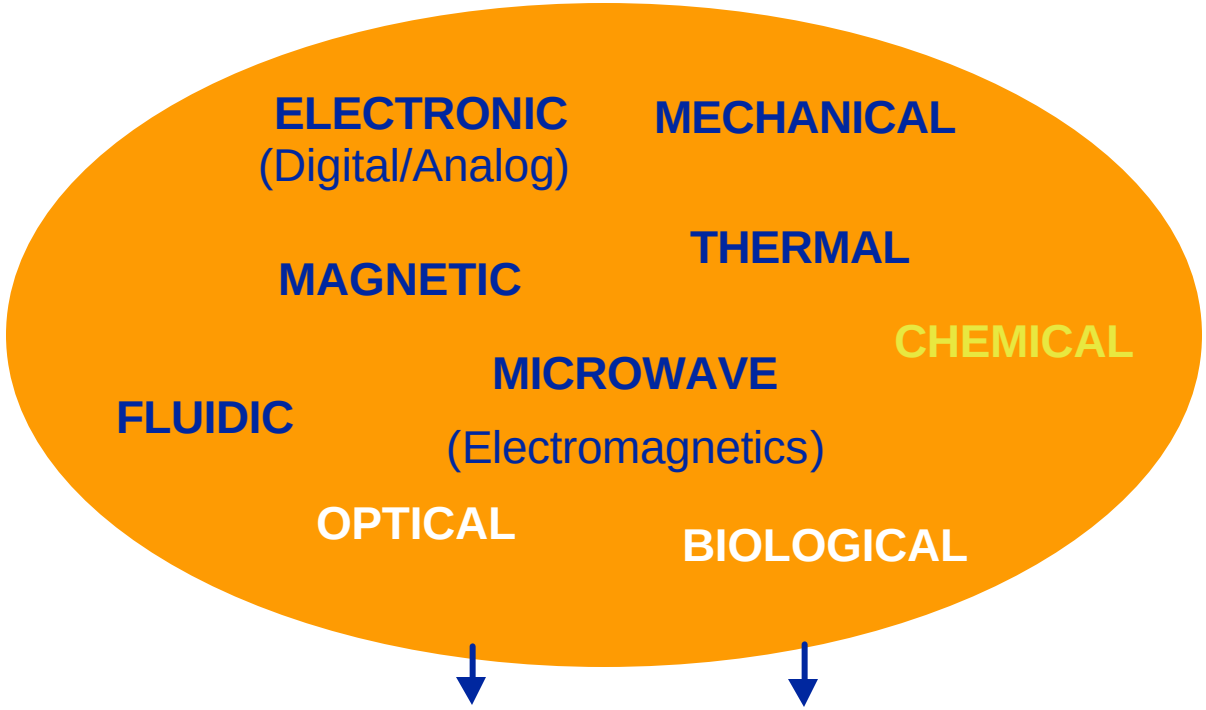
- **Modeling tools are necessary to understand complex interactions in biological systems**
- **Modeling of multi-scale, multi-disciplinary interactions will enable exploration of novel concepts and the design of integrated bio-molecular systems (bio-chips)**

Modeling and Simulation



Integrated Bio-Molecular Systems

- System technology is much more complex due to interaction of mixed technologies - electronics, mechanics, optics, fluidics, chemistry, biology, …
- Computational modeling and simulation essential for development of **Integrated System** technology !



Breakout Sessions

- Three groups of about 20 people each
- Session Leaders :

    1. Greg Kovacs, Stanford University
    2. Linda Griffith, MIT
    3. Bob Eisenberg, Rush Medical Cntr

- Session format is highly flexible ; a set of questions are provided to get the discussion going
- Session leaders will compile the comments/ views of each group and present these to the audience

Closing Comments

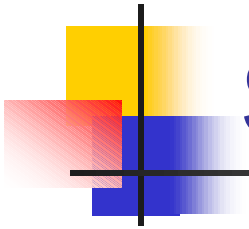
- Continue thinking about the issues that we discussed today
- Feel free to send us your ideas
- Please bring up other relevant issues that did not get discussed today ; could be topics for future workshops !
- All speakers - please submit electronic copies of your presentations to Rhonda Warner (rwarner@sysplan.com)
- Thanks for coming. Have a safe trip back !

The E-Cell Project Towards Reconstruction of the Cell

Masaru Tomita

Laboratory for Bioinformatics

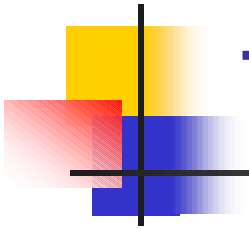
Keio University



Self-introduction-- Masaru Tomita

- Born in Tokyo
- Ph.D in Comp. Sci. from CMU (85)
- Nickname – “Tommy”
- Also Ph.D in Mol. Biol. from Keio
- Professor and Director,

  Lab. Bioinformatics, Keio University



The Cell

- A large collection of chemical reactions
- Each reaction is rather simple
- Overall behavior is quite complex

Example Rules (1)
Enzymatic Reaction

6-Phosphofructokinase ("EC2.7.1.11")

D-Fructose 6-phosphate ("C00085")

D-Fructose 1,6-bisphosphate ("C00354")

ATP ("C00002")

ADP ("C00008")

H+ ("C00080")

"C00085" + "C00002" → "C00354" + "C00008" + "C00080"

["EC2.7.1.11"]

Example Rules (2)
Complex Formation

GTP ("C00044")

elongation factor Tu ("Gxtleftu")

complex ("GXtleftu+GTP")

"Gxtleftu" + "C00044" ⟷ "Gxtleftu+GTP"

[none]

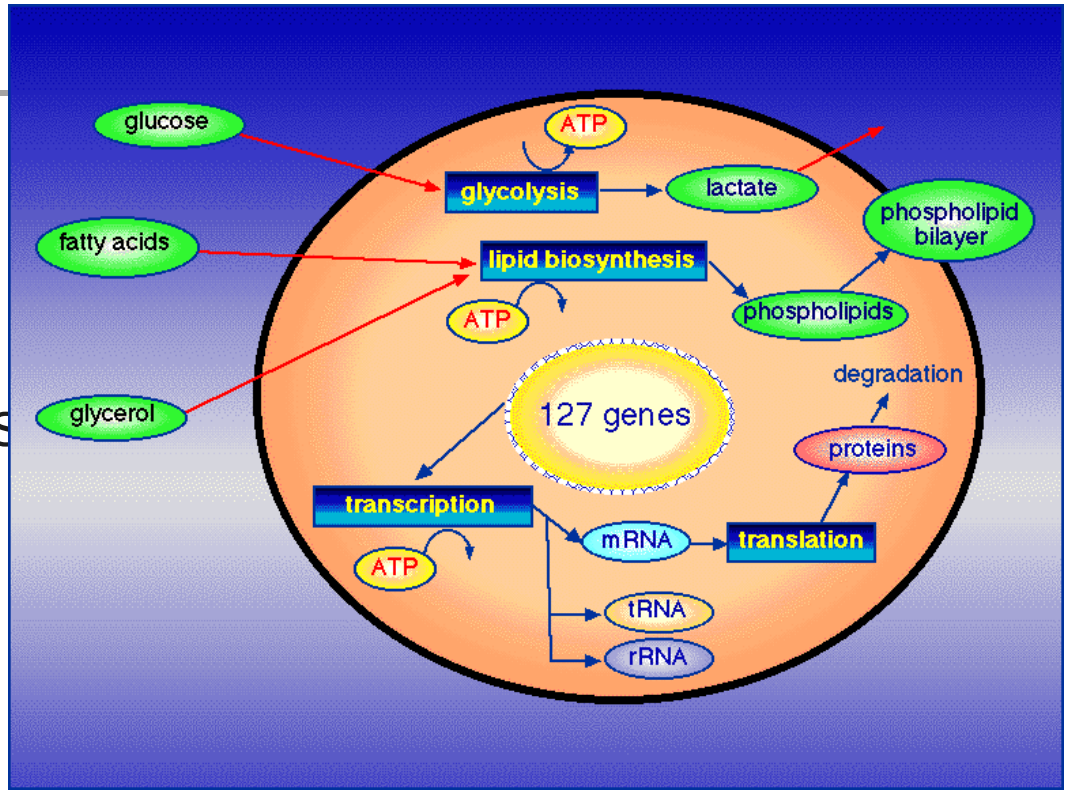
Example Rules (3)
Transportation

```
                                glycerol    ("C00116")
glycerol-uptake passive transporter("Egu001")

"ENVIRONMENT:C00116" → "CYTOPLASM:C00116"
                       ["Egu001"]
```

Construction of “Virtual Cell”

- It has:
  - **127** genes
  - **4268** molecular species
  - **495** reactions
- It performes:
  - glycolysis
  - lipid synthesis
  - transcription, translation and degradation

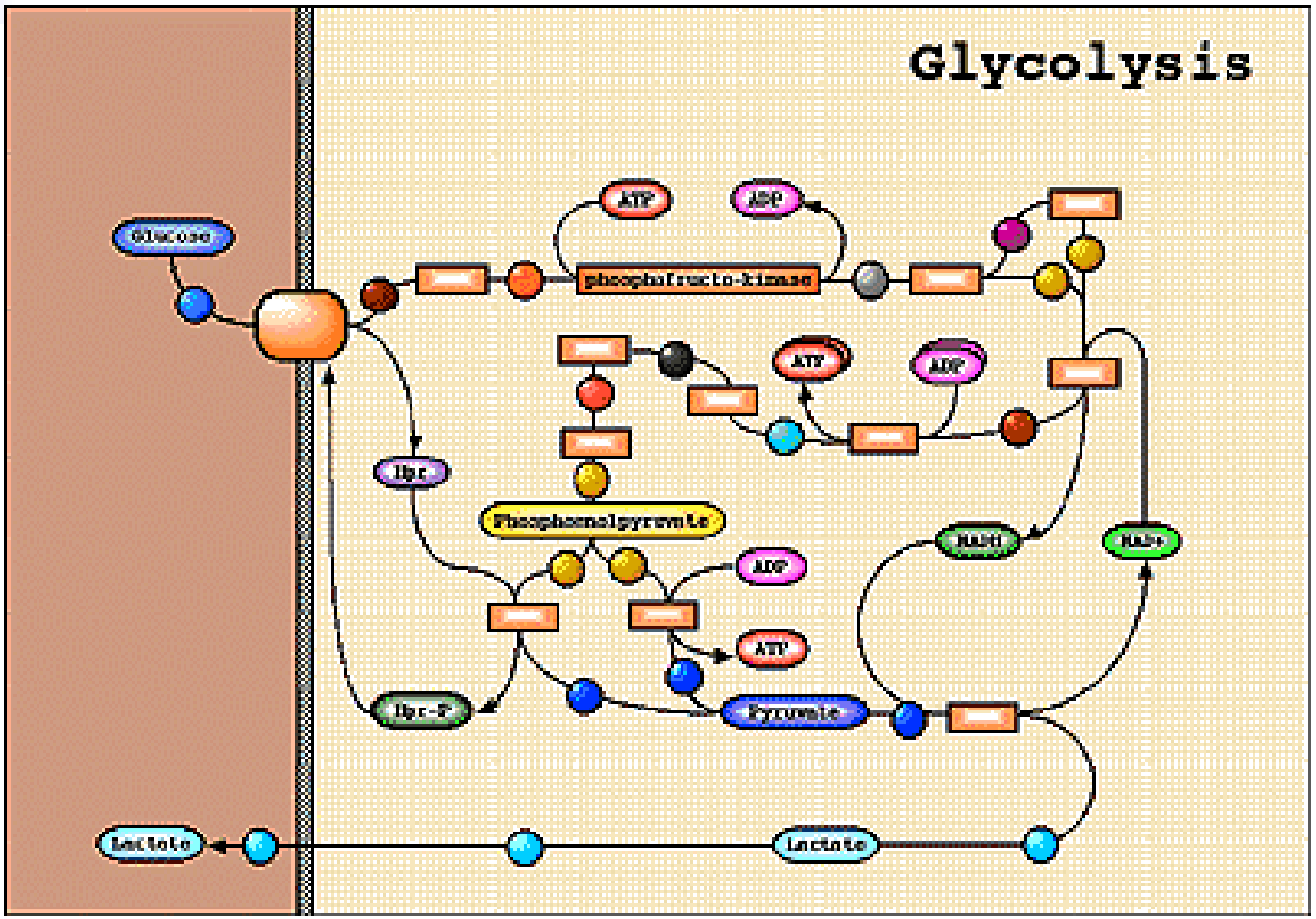


Genome of *M.genitalium*

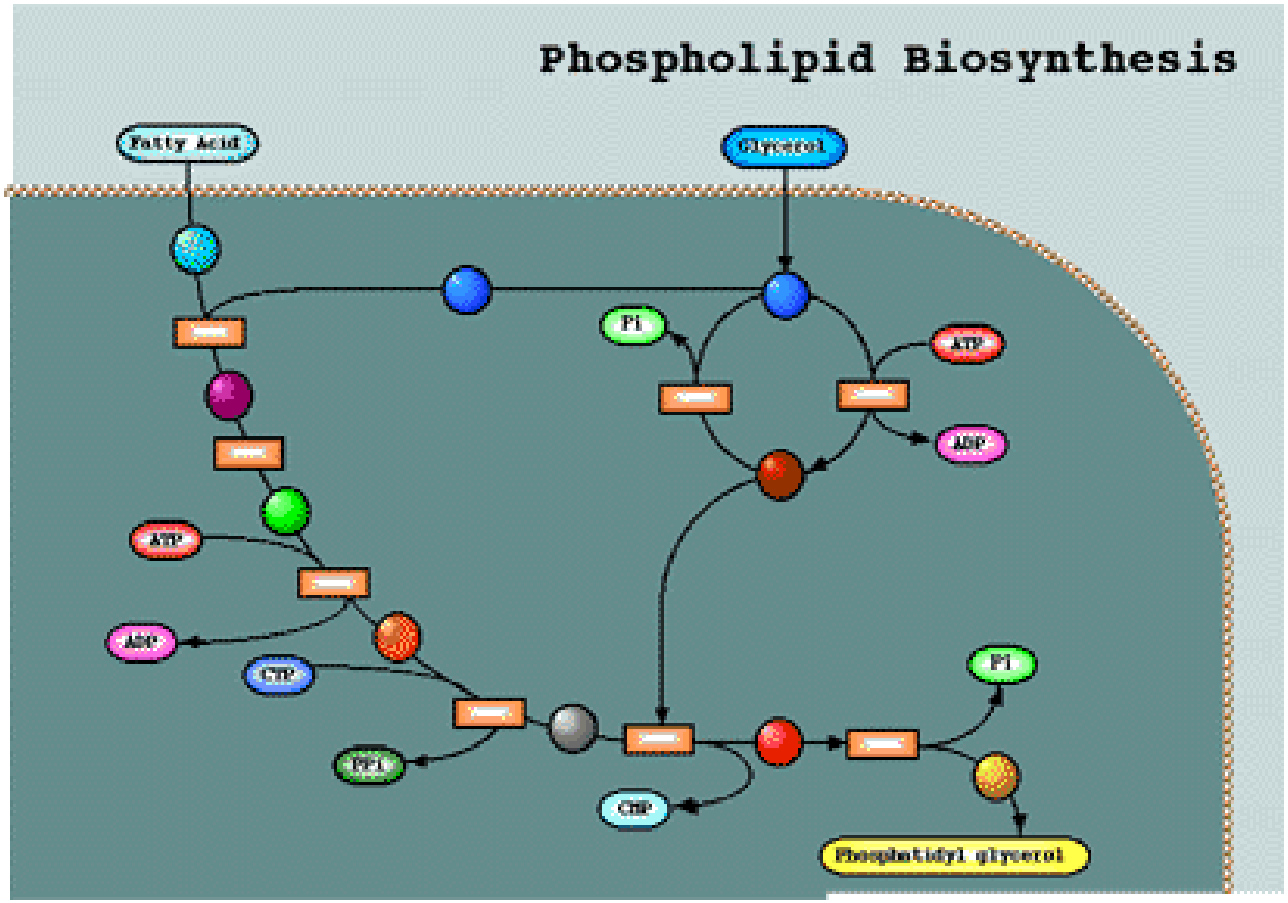
The 127 Genes

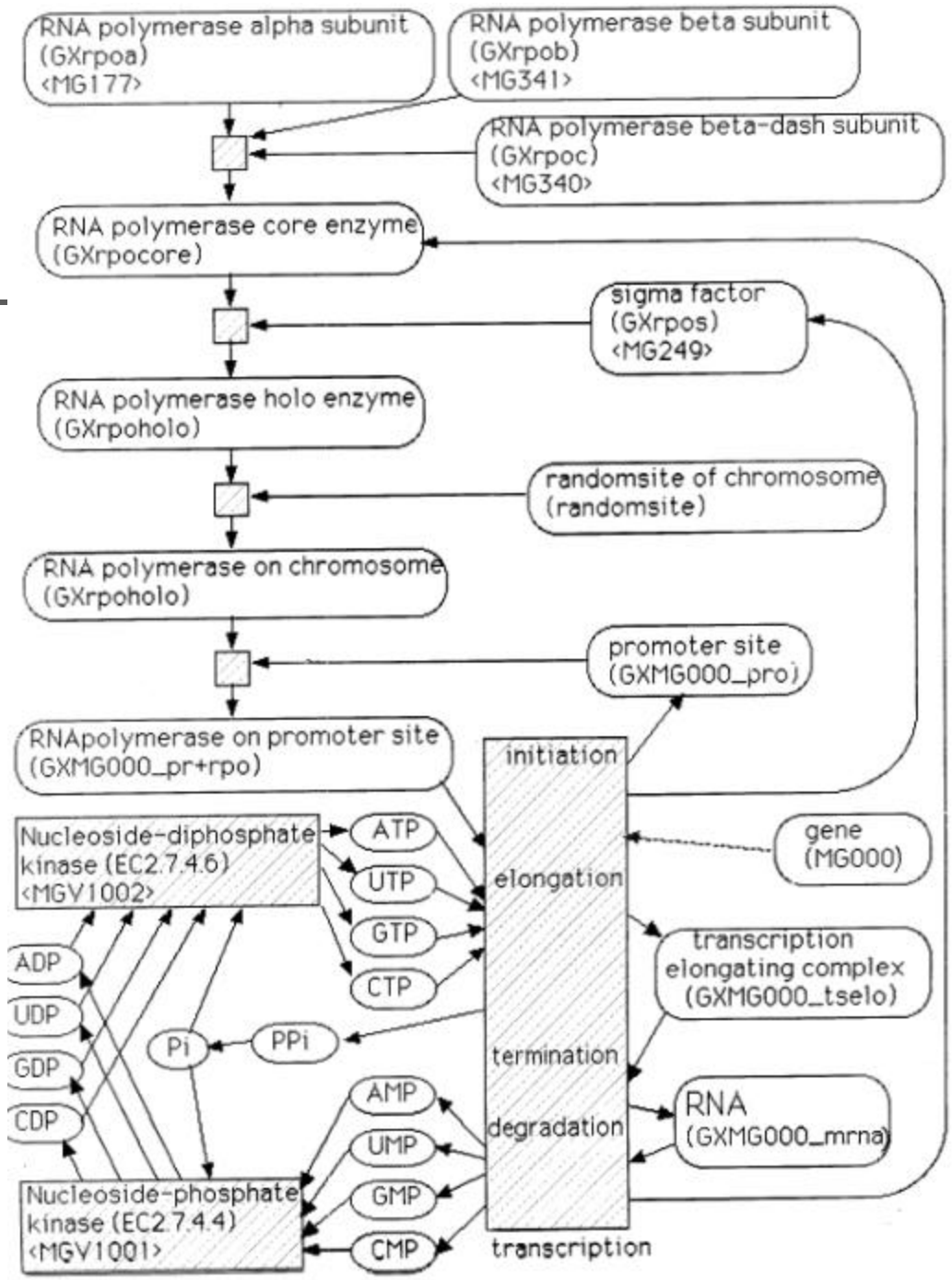
Gene type	M.gen	Other	Total
Glycolysis	9	0	9
Lactate fermentation	1	0	1
Phospholipid biosynthesis	4	4	8
Phosphotransferase system	2	0	2
Glycerol uptake	1	0	1
RNA polymerase	6	2	8
Amino acid metabolism	2	0	2
Ribosomal L subunit	30	0	30
Ribosomal S subunit	19	0	19
rRNA	2	0	2
tRNA	20	0	20
tRNA ligase	19	1	20
Initiation factor	4	0	4
Elongation factor	1	0	1
Protein coding genes	98	7	105
RNA coding genes	22	0	22
Total	120	7	127

Glycolysis Pathway



Phospholipid Biosynthesis




RNA polymerase alpha subunit
(GXrpoa)
<MG177>
RNA polymerase beta subunit
(GXrpob)
<MG341>
RNA polymerase beta-dash subunit
(GXrpoc)
<MG340>
RNA polymerase core enzyme
(GXrpocore)
sigma factor
(GXrpos)
<MG249>
RNA polymerase holo enzyme
(GXrpoholo)
randomsite of chromosome
(randomsite)
RNA polymerase on chromosome
(GXrpoholo)
promoter site
(GXMG000_pro)
RNApolymerase on promoter site
(GXMG000_pr+rpo)
initiation
elongation
termination
degradation
transcription
gene
(MG000)
transcription
elongating complex
(GXMG000_tselo)
RNA
(GXMG000_mrna)
Nucleoside-diphosphate
kinase (EC2.7.4.6)
<MGV1002>
ATP
UTP
GTP
CTP
ADP
UDP
GDP
CDP
Pi
PPi
AMP
UMP
GMP
CMP
Nucleoside-phosphate
kinase (EC2.7.4.4)
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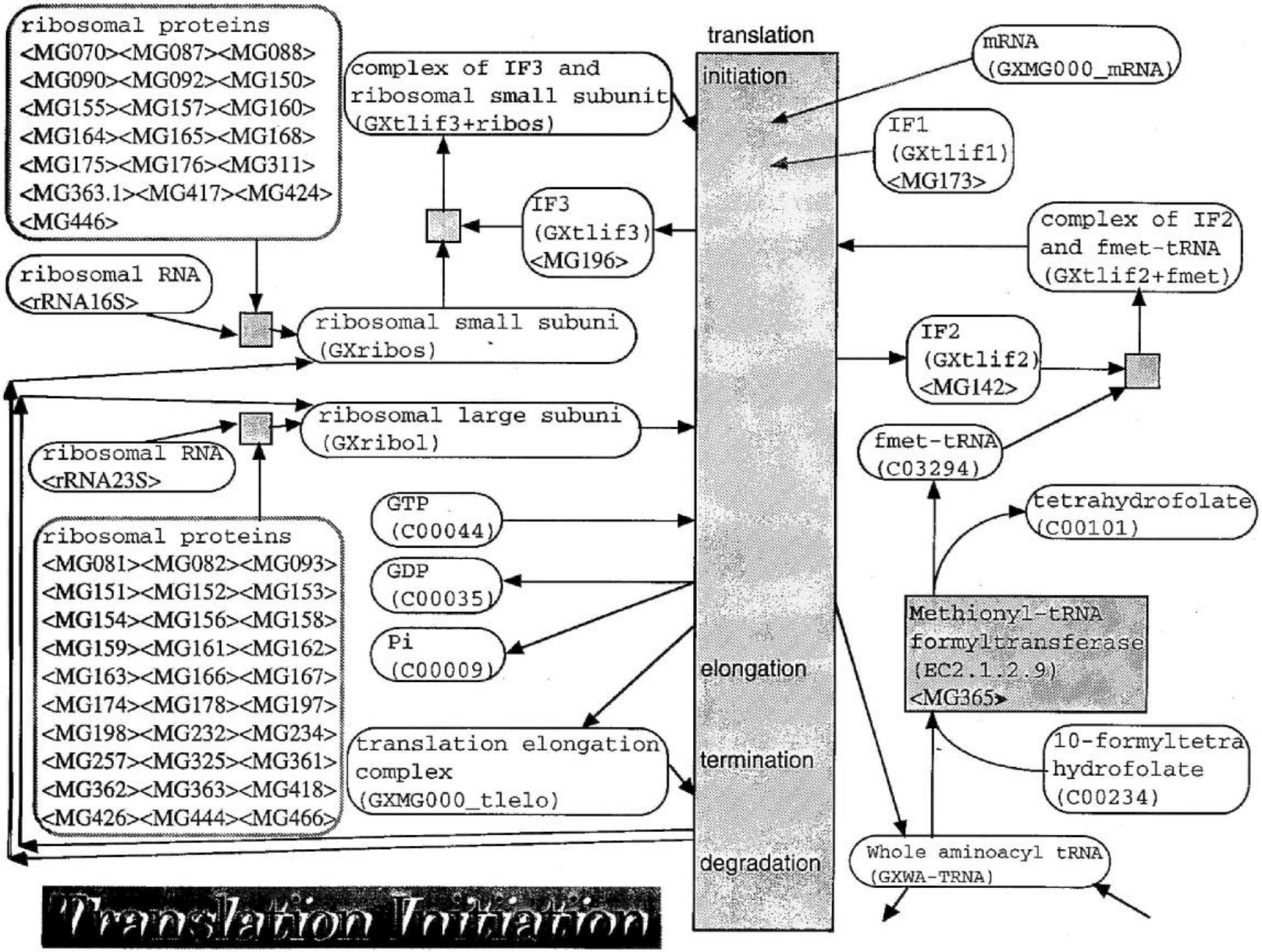
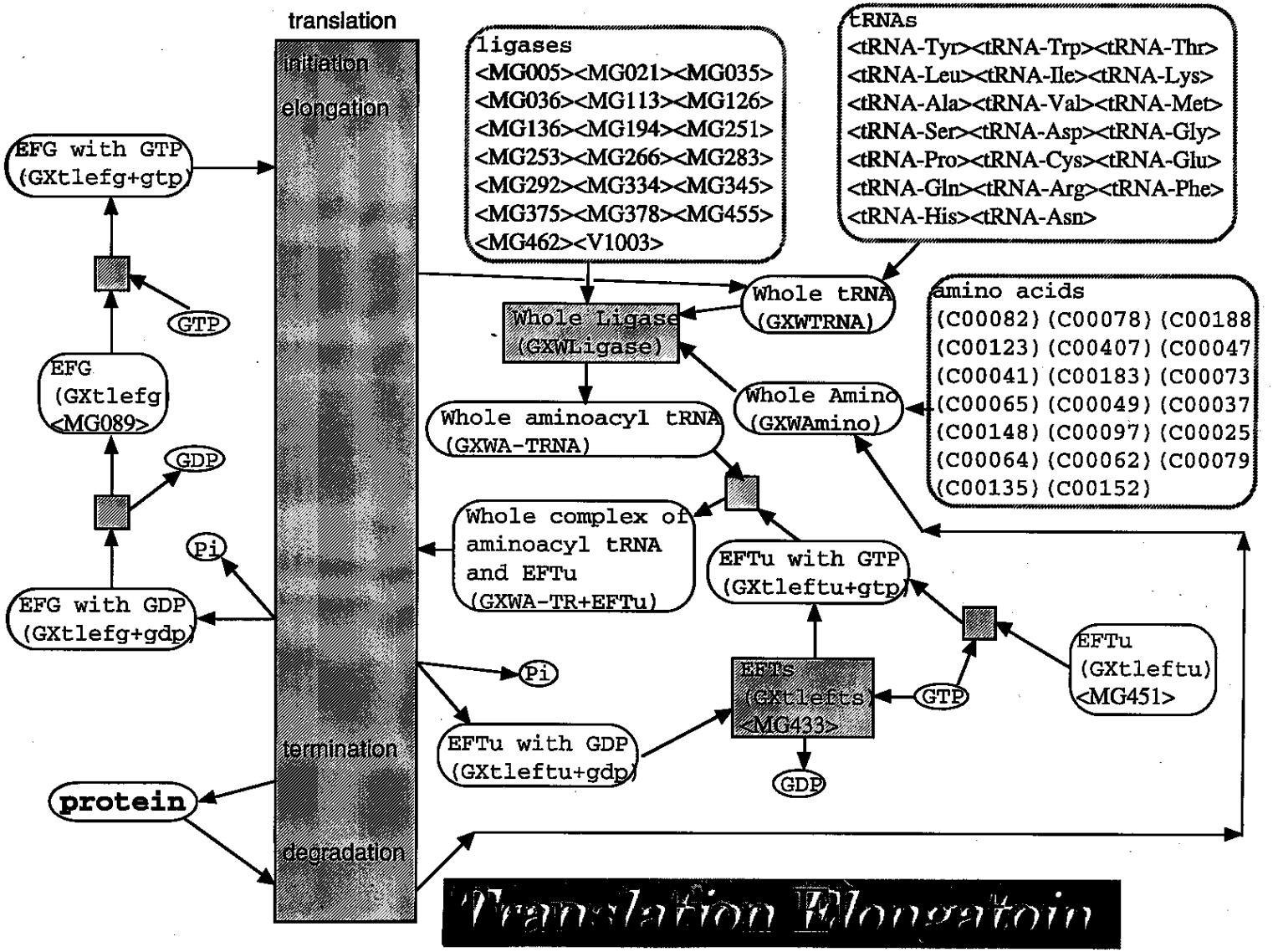
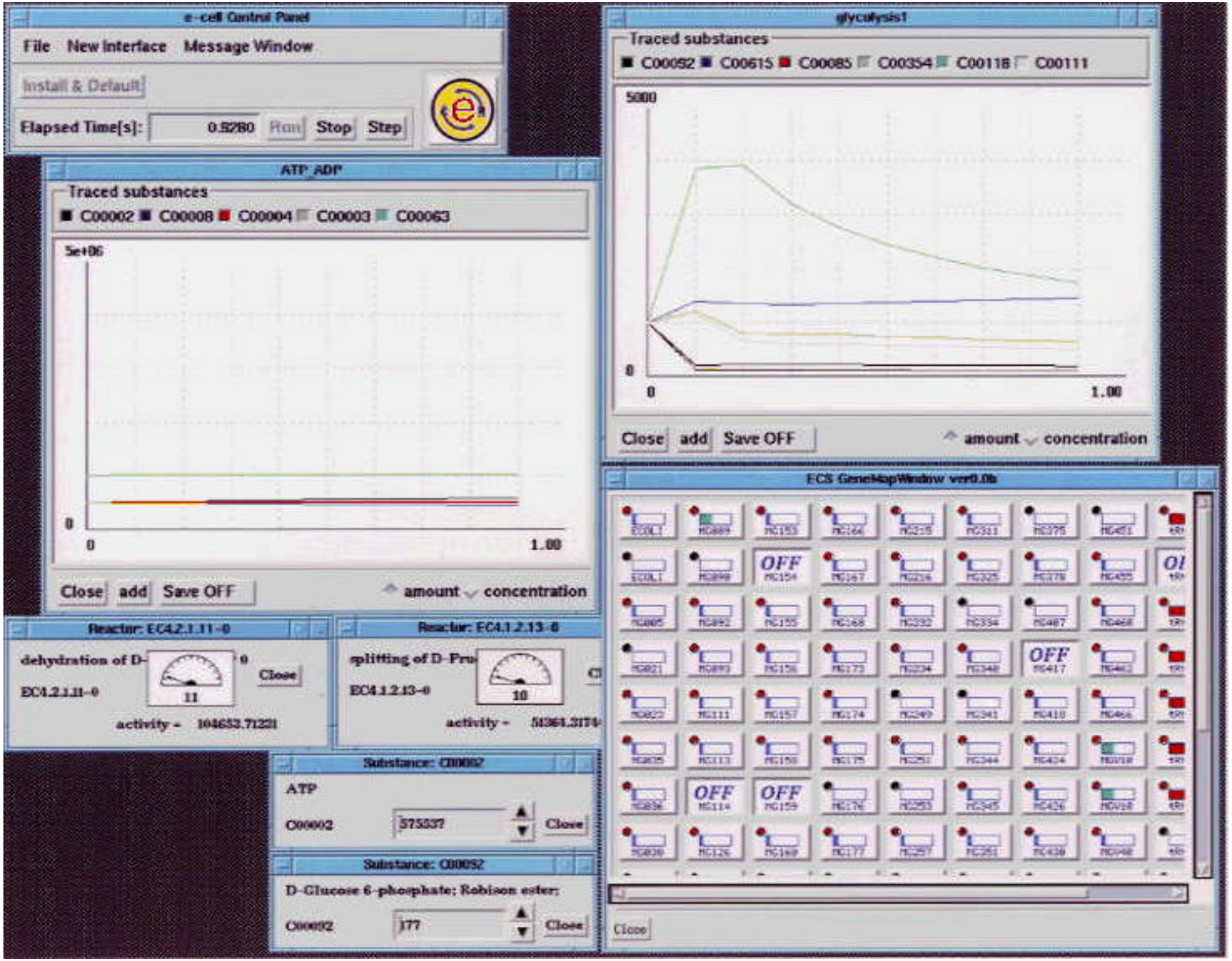
Translation Initiation

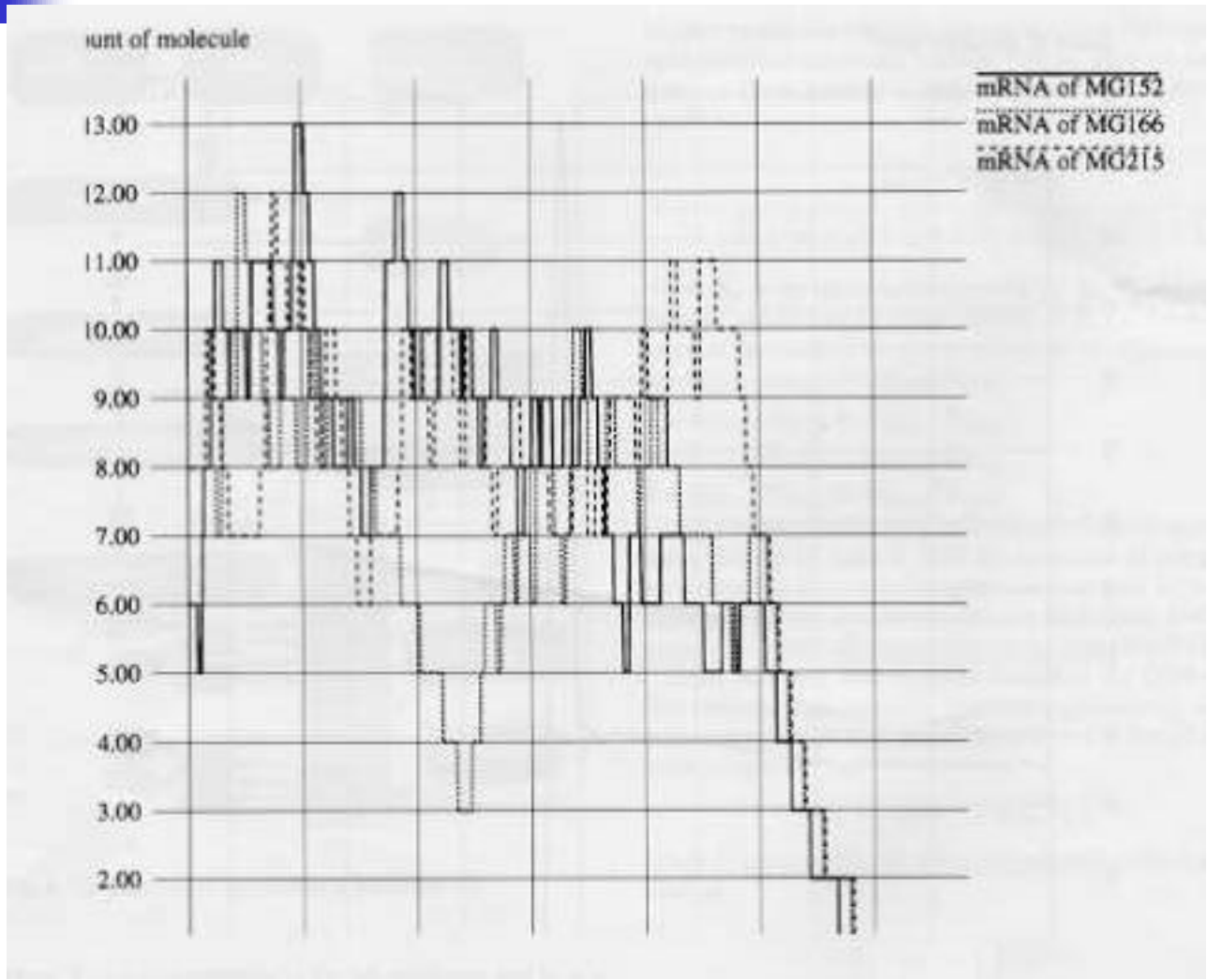


Translation Elongation




e-cell Control Panel
File New Interface Message Window
Install & Default
Elapsed Time[s]: 0.5280 Run Stop Step
ATP ADP
Traced substances
C00002 C00008 C00004 C00003 C00063
5e+06
0
0 1.00
Close add Save OFF
amount concentration
glycolysis1
Traced substances
C00092 C00615 C00085 C00354 C00118 C00111
5000
0
0 1.00
Close add Save OFF
amount concentration
Reactor: EC4.2.1.11-0
dehydration of D-
EC4.2.1.11-0
11
activity = 104653.71221
Reactor: EC4.1.2.13-0
splitting of D-Fru
EC4.1.2.13-0
10
activity = 51361.3174
Substance: C00002
ATP
C00002
575537
Close
Substance: C00092
D-Glucose 6-phosphate; Robison ester;
C00092
177
Close
ECS GeneMapWindow ver0.0b
OFF
Close

Cell Death


unt of molecule
13.00
12.00
11.00
10.00
9.00
8.00
7.00
6.00
5.00
4.00
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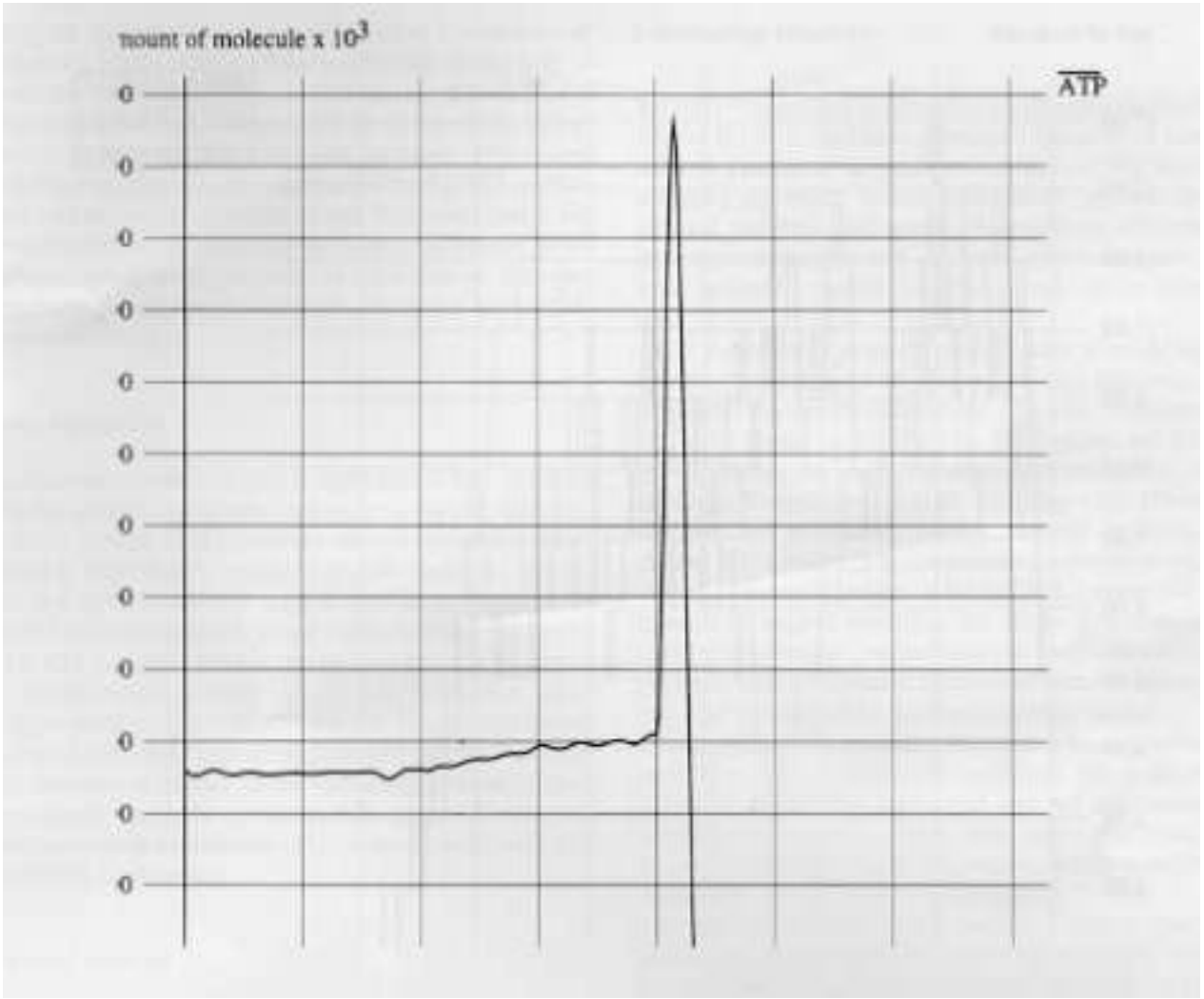
2.00
mRNA of MG152
mRNA of MG166
mRNA of MG215

ATP in Starving



Science 284.Apr 2 1999

COMPLEX SYSTEMS
NEWS

Exploring the Systems of Life

No longer content to inventory cells' molecular parts, biologists are teaming up with physicists and engineers to study how these parts work together

A rule of thumb among drugmakers is that the more tightly a compound binds to its molecular target, the more potent it will be. But not always, it turns out. Take cytokines, natural protein messengers that bind to receptors on cells and cause them to proliferate during wound healing or an immune response. A cytokine molecule follows a complex life history before and after it binds to its receptor. It shuttles in and out of cells, risking destruction by proteases, and eventually finds its way into a recycling bin once its work is done. These steps interact, adding to the complexity. When proteases destroy a cytokine molecule, for example, they can also wipe out its receptor, in a feedback that further reduces the compound's effectiveness.

By modeling these and other interactions on a computer, Douglas Lauffenburger and his colleagues at the Massachusetts Institute of Technology have found that in many cases the best way for genetic engineers to boost the potency of a cytokine drug is not by remodeling it to bind more tightly to its receptor but by altering other steps in the chain. Tweaking the structure to help it avoid destruction within the cell, for example, increases its chances of being recycled. "You would think that the stronger the binding, the more potent it would be," says Lauffenburger. "But that's often not the case."

> **"The convergence of chemistry, physics, biology, and engineering is upon us."**
>
> —Lucy Shapiro

As he and his colleagues have realized, understanding how parts of a biological system—genes or molecules—interact is just as important as understanding the parts themselves. It's a realization that's beginning to spread. Leading research universities around the United States have begun shelling out tens of millions of dollars to set up new interdisciplinary institutes and departments that will bring together specialists from physics, chemistry, engineering, computer science, mathematics, and biology to document how all the different cellular players work together in complex tasks such as determining when a cell divides and how gene expression is regulated. Says Lucy Shapiro, a developmental biologist at Stanford University: "The convergence of chemistry, physics, biology, and engineering is upon us."

The new centers will take a variety of approaches to exploring the complex systems of life. A proposed center at Stanford, for example, is likely to focus on biophysics, while one at Princeton will lean toward probing networks of genes and proteins. Drug companies, too, such as the Palo Alto, California–based start-up Entelos, are turning to computers in the hope that "in silico" biology will lead to improved therapeutics. All these efforts are a response to the growing sense that gene sequencing and other techniques will soon have isolated all the cell's individual parts and spelled out their isolated functions. Now, it's time to move beyond reductionism.

"We have generated an enormous mass of information on the molecular events that occur in cells," says Marvin Cassman, director of the National Institute of General Medical Sciences (NIGMS) in Bethesda, Maryland. "Now we need to know how all these things are integrated." John Doyle, an electrical engineer at the California Institute of Technology in Pasadena who is turning his attention toward biology, puts it this way: "Biology has spent decades trying to be like physics," trying to understand complicated systems by understanding each part at its most basic level. "Now they're interested in putting it all back together."

Doing so, says Shapiro, will take "physicists, engineers, and biologists at lab benches next to one another working on the same problem." Foremost among these problems, say Shapiro and others, will be understanding the complex chemical networks that govern cell functioning. Genome analysis, for example, has already isolated hundreds of genes that code for transcription factors, proteins that help regulate the expression of other genes. "The expression of individual genes is not being regulated by one, two, or five proteins but by dozens," says Shirley Tilghman, a molecular biologist at Princeton University. Some regulate specific genes; others work more broadly. Some sit on DNA all the time, while others

Building Working Cells 'in Silico'

Cells provide living proof of that old saw about the whole being greater than the sum of its parts. "Even if you construct a complete list of all the processes known to occur within a cell, that won't tell you how it works," says Masaru Tomita, a professor of bioinformatics at Keio University in Fujisawa, near Tokyo. But Tomita, who is a computer scientist as well as a biologist, has a scheme for exploring the effects that only emerge when those many processes interact: a simulation program that can reproduce, in simplified form, a cell's biochemical symphony.

His group's E-CELL simulation software will go on the Web for public "beta" testing this June (www.e-cell.org). Other computer models of the cell are being developed, but they often try to reproduce individual cellular processes in detail. E-CELL, in contrast, is designed to paint a broad-brush picture of the cell as a whole. Such efforts "are a next logical step" now that genome sequencing is giving biologists the complete parts lists for living things, says Peter D. Karp, a bioinformaticist at Pangea Systems, a bioinformatics software company in Menlo Park, California.

E-CELL is actually a model-building kit: a set of software tools that allows a user to specify a cell's genes, proteins, and other molecules, describe their individual interactions, and then compute how they work together as a system. It should ultimately allow investigators to conduct experiments "in silico," offering a cheap, fast way to screen drug candidates, study the effects of mutations or toxins, or simply probe the networks that govern cell behavior.

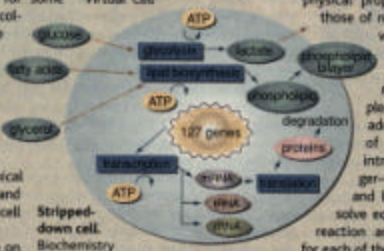
Written to run under the UNIX or Linux operating systems, the software relies on the user to input a cell's molecules, their locations and estimated concentrations within the cell, and the reaction rules that govern them. E-CELL then computes how the abundance of each substance at a particular location changes at each time increment. With a single mouse click, the user can knock out particular genes or groups of related genes, expose the cell to a foreign substance or deprive it of a nutrient, and then run the simulation again. Graphical interfaces allow the user to monitor the cell's changing chemistry.

Tomita's group has used early versions of E-CELL to construct a hypothetical cell with 127 genes, which they figured was a minimal set for a self-sustaining cell in their system. Most of the genes were based on those of *Mycoplasma genitalium*, a microbe that has the smallest known gene set of any self-replicating organism. But the genes for some vital cellular processes still have not been identified in the mycoplasma, so the group added genes from other organisms. The virtual cell "lives," maintaining a simple, stable metabolism: It takes up glucose from the virtual culture medium, generates the enzymes and proteins to sustain internal cell processes, and exports the waste product lactate.

This bare-bones cell has already delivered one surprise. As expected, starving it of glucose causes a drop in levels of adenosine triphosphate (ATP), a key compound that provides the energy for many intracellular processes. But unexpectedly, before ATP levels drop they briefly rise. The reason, Tomita suspects, is that the early part of the ATP-producing pathway itself consumes ATP. Cutting the supply of glucose shuts down the early stages of the pathway, stopping ATP consumption there even while ATP continues to be produced from intermediary metabolites further down the pathway. Tomita thinks the effect may eventually be confirmed in living cells.

More surprises could be forthcoming when E-CELL is eventually put to work simulating whole cells of real organisms. Tomita admits that because building models with E-CELL depends on understanding the functions of large numbers of genes, the software is not likely to prove really useful for molecular biologists for some time. But he and his colleagues designed the program so that it should easily scale up to simulating the thousands of genes in a real cell. "Tomita and his group have done a fantastic job of engineering a 'graphical cockpit' for initializing and monitoring a whole-cell simulation," says Karp.

For greater realism on a smaller scale, users can turn to a different model-building kit: the Virtual Cell developed by physiologist Leslie Loew and computer scientist James Schaff of the University of Connecticut Health Center in Farmington. Rather than downloading software to run on their own computer, Virtual Cell users will simply run their simulation on Loew's host computer via the Internet. More important, rather than simulating an entire cell at once, as a biochemical system, Virtual Cell



Stripped-down cell. Biochemistry simulated by E-CELL software.

will eventually enable cell biologists to study how a cell's shape, volume, and other physical features affect individual biochemical processes.

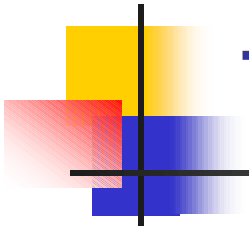
Loew's team builds its Virtual Cell models using precise measurements of how molecules diffuse and react within living cells, which they make by labeling key molecules and observing them with a video microscope. The result is a computerized cell with physical properties resembling those of real cells—a framework in which users can unleash specific biochemical reactions. For example, a researcher can add a certain amount of calcium—a key intracellular messenger—and then sit back and let the Virtual Cell solve equations describing reaction and diffusion rates for each of the molecular participants affected by calcium. Then the program generates a movie of the process. "The simulations are comfortable for the biologists to use because they are based on real image data," Loew explains.

In the case of calcium, the simulation not only looked much like the calcium waves measured in actual cells—indicating that the simulation was realistic—but it also predicted the dynamics of an intermediary molecule called IP3, which cannot be monitored inside the cell itself. (Demonstrations of Virtual Cell can be accessed at www.nrcam.uchc.edu)

"These two approaches can complement each other very well," Tomita says. And both are attracting growing interest from other biologists. Tomita says that when he first starting describing his plans for E-CELL, "I was dismissed as a naïve computer scientist." Now he gets e-mail requests for information on his simulation software nearly every day. Loew, too, has found that "interest has begun to mushroom." He adds, "[Cell biologists] are getting to the point that they are realizing that without computers we are never going to be able to organize all this information."

—DENNIS NORMILE

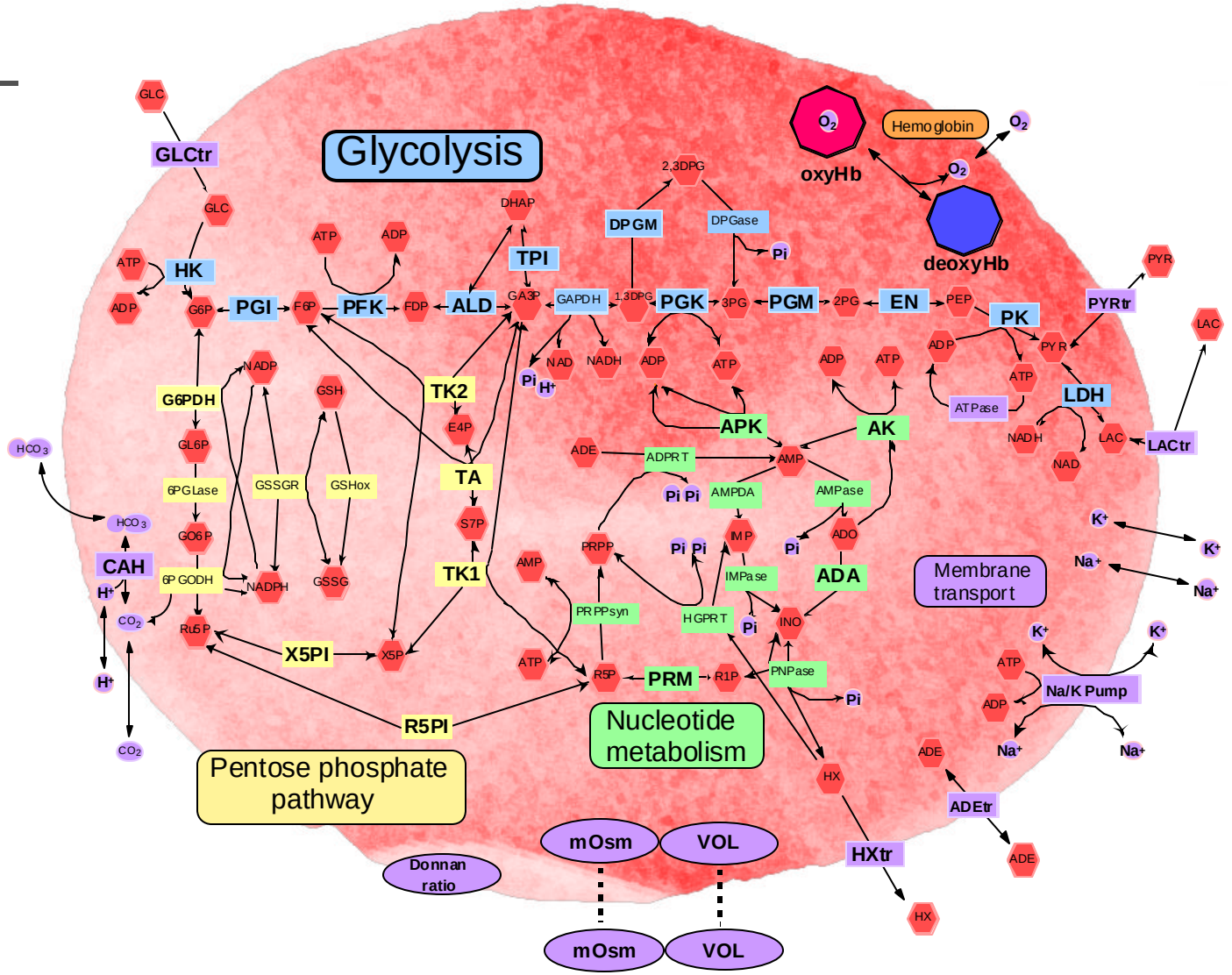
With reporting by Elizabeth Pennisi.



The E-Cell Project

- System.group
  - E-Cell software development (.)
  - Mathematical analysis (3)
- Modeling.group
  - Human erythrocyte (6)
  - Mitochondria (2)
  - *E.coli* chemotaxis (2)
  - Gene expression/replication system (6)

The Erythrocyte Model



Enzymes and Reactions of Human Erythrocyte (Basic model)

Enzyme or Reaction	ID	Group	Reactor	Reaction mechanism
Glutathione turnover	GSHox	PPP	GSHoxReactor	Mass action
Glutathione reductase (NADPH)	GSSGR	PPP	GSSGRReactor	Ordered Bi Ter mechanism
Glucose 6-phosphate dehydrogenase	G6PDH	PPP	G6PDHReactor	Ordered Bi Bi mechanism
6-Phosphogluconolactonase	6PGLase	PPP	MichaelisUniUniReactor	Michaelis Menten mechanism
6-Phosphogluconate dehydrogenase	6PGLDH	PPP	GL6PDHReactor	Ordered Bi Ter mechanism
Ribose 5-phosphate isomerase	R5PI	PPP	UniUniReactor	Uni Uni mechanism
Xylulose 5-phosphate isomerase	X5PI	PPP	UniUniReactor	Uni Uni mechanism
Transketolase I	TK1	PPP	PingPongBiBiReactor	Ping-Pong Bi Bi mechanism
Transketolase II	TK2	PPP	PingPongBiBiReactor	Ping-Pong Bi Bi mechanism
Transaldolase	TA	PPP	PingPongBiBiReactor	Ping-Pong Bi Bi mechanism
Hexokinase	HK	Glycolysis	HKReactor	
Phosphoglucoisomerase	PGI	Glycolysis	UniUniReactor	Uni Uni mechanism
Phosphofructokinase	PFK	Glycolysis	PFKReactor	
Aldolase	ALD	Glycolysis	OrderedUniBiReactor	Ordered Uni Bi mechanism
Triose phosphate isomerase	TPI	Glycolysis	UniUniReactor	Uni Uni mechanism
Glyceraldehyde phosphate dehydrogenase	GAPDH	Glycolysis	RapidEquilibriumReactor	Mass action
Phosphoglycerate kinase	PGK	Glycolysis	RapidEquilibriumReactor	Mass action
Diphosphoglycerate mutase	DPGM	Glycolysis	DPGMReactor	Michaelis Menten mechanism
Diphosphoglycerate phosphatase	DPGase	Glycolysis	MichaelisUniUniReactor	Michaelis Menten mechanism
Phosphoglyceromutase	PGM	Glycolysis	RapidEquilibriumReactor	Mass action
Enolase	EN	Glycolysis	RapidEquilibriumReactor	Mass action
Pyruvate kinase	PK	Glycolysis	PKReactor	
Pyruvate transport process	PYRtr	Transport	RapidEquilibriumReactor	Mass action
Lactate dehydrogenase	LDH	Glycolysis	RapidEquilibriumReactor	Mass action
Lactate transport process	LACtr	Transport	RapidEquilibriumReactor	Mass action
Leak of Potassium	K_Leak	Transport	LeakageReactor	
Leak of Sodium	Na_Leak	Transport	LeakageReactor	
Sodium/potassium pump	Pump	Transport	PumpReactor	
AMP phosphohydrolase	AMPase	NM	MassActionReactor	Mass action
Adenosine deaminase	ADA	NM	MichaelisUniUniReactor	Michaelis Menten mechanism
Adenosine kinase	AK	NM	MichaelisBiBiReactor	Michaelis Menten mechanism
Adenylate kinase	APK	NM	RapidEquilibriumReactor	Mass action
Adenosine triphosphate phosphohydrolase	ATPase	NM	MassActionReactor	Mass action
Adenosine monophosphate deaminase	AMPDA	NM	MichaelisUniUniReactor	Michaelis Menten mechanism
Inosine monophosphatase	IMPase	NM	MassActionReactor	Michaelis Menten mechanism
Purine nucleotide phosphorylase	PNPase	NM	RapidEquilibriumReactor	Mass action
Phosphoribosyl pyrophosphate synthetase	PRPPsyn	NM	PRPPReactor	
Adenine phosphoribosyl transferase	ADPRT	NM	MichaelisBiBiReactor	Michaelis Menten mechanism
Hypoxanthine-guanine phosphoryl transferase	HGPRT	NM	MichaelisBiBiReactor	Michaelis Menten mechanism
Hypoxanthine transport process	HXtr	NM	HXTRReactor	
Magnesium complexation of ATP	MgATP_maker		ComplexReactor	Mass action
Magnesium complexation of AMP	MgAMP_maker		ComplexReactor	Mass action
Magnesium complexation of ADP	MgADP_maker		ComplexReactor	Mass action
Magnesium complexation of 2,3DPG	MgDPG_maker		ComplexReactor	Mass action

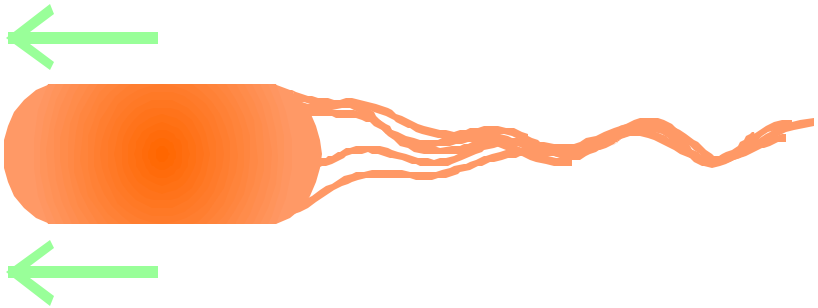
Metabolic intermediates of human erythrocyte: Steady-state concentration (Basic model)

Metabolic intermediate	ID	Predicted	Initial	Predicted/Initial	Observed
1,3-Diphosphogrycerate	13DPG	1.83E-04	4.00E-04	4.58E-01	4.00E-04
2-Phosphogrycerate	2PG	4.16E-03	1.40E-02	2.97E-01	1.40E-02 • } 5.00E-03
3-Phosphogrycerate	3PG	4.62E-02	4.50E-02	1.03E+00	4.50E-02
Adenosine	ADO	8.93E-06	1.20E-03	7.44E-03	1.20E-03 • } 3.00E-04
Dihydroxy acetone phosphate	DHAP	1.35E-01	1.40E-01	9.62E-01	1.40E-01 • } 8.00E-02
Erythrose 4-phosphate	E4P	1.17E+00	4.70E-04	2.48E+03	-
Fructose 6-phosphate	F6P	6.39E-02	1.60E-02	3.99E+00	1.60E-02 • } 3.00E-03
Fructose 1,6-diphosphate	FDP	1.14E-02	7.60E-03	1.50E+00	7.60E-03 • } 4.00E-03
Glucose 6-phosphate	G6P	1.96E-01	3.80E-02	5.16E+00	3.80E-02 • } 1.20E-02
Glyceraldehyde 3-phosphate	GA3P	6.24E-03	6.70E-03	9.32E-01	6.70E-03 • } 1.00E-03
Gluconolactone 6-phosphate	GL6P	7.62E-06	1.17E-05	6.51E-01	-
Gluconate 6-phosohate	GO6P	2.72E+00	1.86E-01	1.46E+01	-
Glutathione	GSH	3.21E+00	3.21E+00	1.00E+00	3.21E+00 • } 1.50E+00
Glutathione	GSSG	1.03E-04	1.06E-04	9.74E-01	-
Hypoxanthine	HXi	9.32E-06	2.00E-03	4.66E-03	2.00E-03
Inosine monophosphate	IMP	5.03E-03	1.00E-02	5.03E-01	1.00E-02
Inosine	INO	3.32E-08	1.00E-03	3.32E-05	1.00E-03
Potassium	Ki	1.26E+02	1.35E+02	9.36E-01	1.35E+02 • } 1.00E+01
Lactate	LACi	1.20E+00	1.10E+00	1.09E+00	1.10E+00 • } 5.00E-01
Nicotinamide adenine dinucleotide	NAD	8.87E-02	6.20E-02	1.43E+00	-
Nicotinamide adenine dinucleotide	NADH	3.13E-04	2.70E-02	1.16E-02	-
Nicotinamide adenine phosphate	NADP	8.06E-05	9.60E-05	8.39E-01	-
Nicotinamide adenine phosphate	NADPH	6.58E-02	6.58E-02	1.00E+00	6.58E-02
Sodium	Nai	2.27E+01	1.00E+01	2.27E+00	1.00E+01 • } 6.00E+00
Phosphoenolpyruvate	PEP	1.89E-02	1.70E-02	1.11E+00	1.70E-02 • } 2.00E-03
5-Phosphoribosyl 1-phosphate	PRPP	6.91E-05	5.00E-03	1.38E-02	5.00E-03 • } 1.00E-03
Pyruvate	PYRi	6.00E-02	7.70E-02	7.79E-01	7.70E-02 • } 5.00E-02
Inorganic phosphate	Pi	1.30E-01	1.00E+00	1.30E-01	1.00E+00
Ribose 1-phosphate	R1P	2.12E-05	6.00E-02	3.53E-04	6.00E-02
Ribose 5-phosphate	R5P	2.81E-04	3.30E-02	8.52E-03	-
Ribulose 5-phosphate	RU5P	1.48E-04	1.29E-02	1.15E-02	-
Sedoheptulose 7-phosphate	S7P	7.49E-02	2.30E-01	3.26E-01	-
Xylulose 5-phosphate	X5P	4.30E-04	3.90E-02	1.10E-02	-
2,3-Diphosphogrycerate	2,3-DPG	4.21E+00	4.50E+00	9.36E-01	4.50E+00 • } 5.00E-01
Adenosine diphosphate	ADP	2.20E-01	2.70E-01	8.16E-01	2.70E-01 • } 1.20E-01
Adenosine monophosphate	AMP	2.42E-02	8.00E-02	3.02E-01	8.00E-02 • } 9.00E-03
Adenosine triphosphate	ATP	1.57E+00	1.54E+00	1.02E+00	1.54E-00 • } 2.50E-01

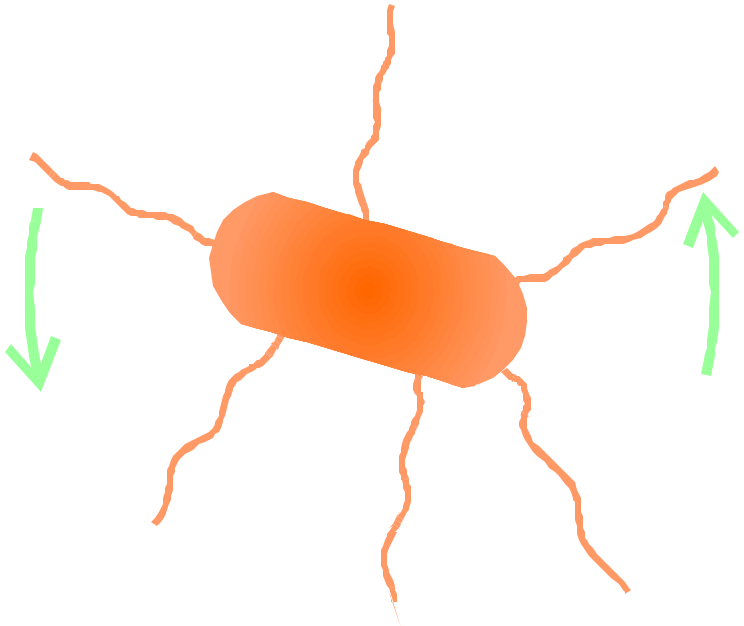
Hereditary Anemia

- Enzyme deficiency in erythrocyte
  - Hexokinase
  - G6PDH
  - Phosphofructokinase
  - Pyruvate kinase
  - Etc.
- Kinetic parameters of these defective enzymes are available
- .Pathological analyses

Chemotaxis: Swimming Behaviour of *E coli*

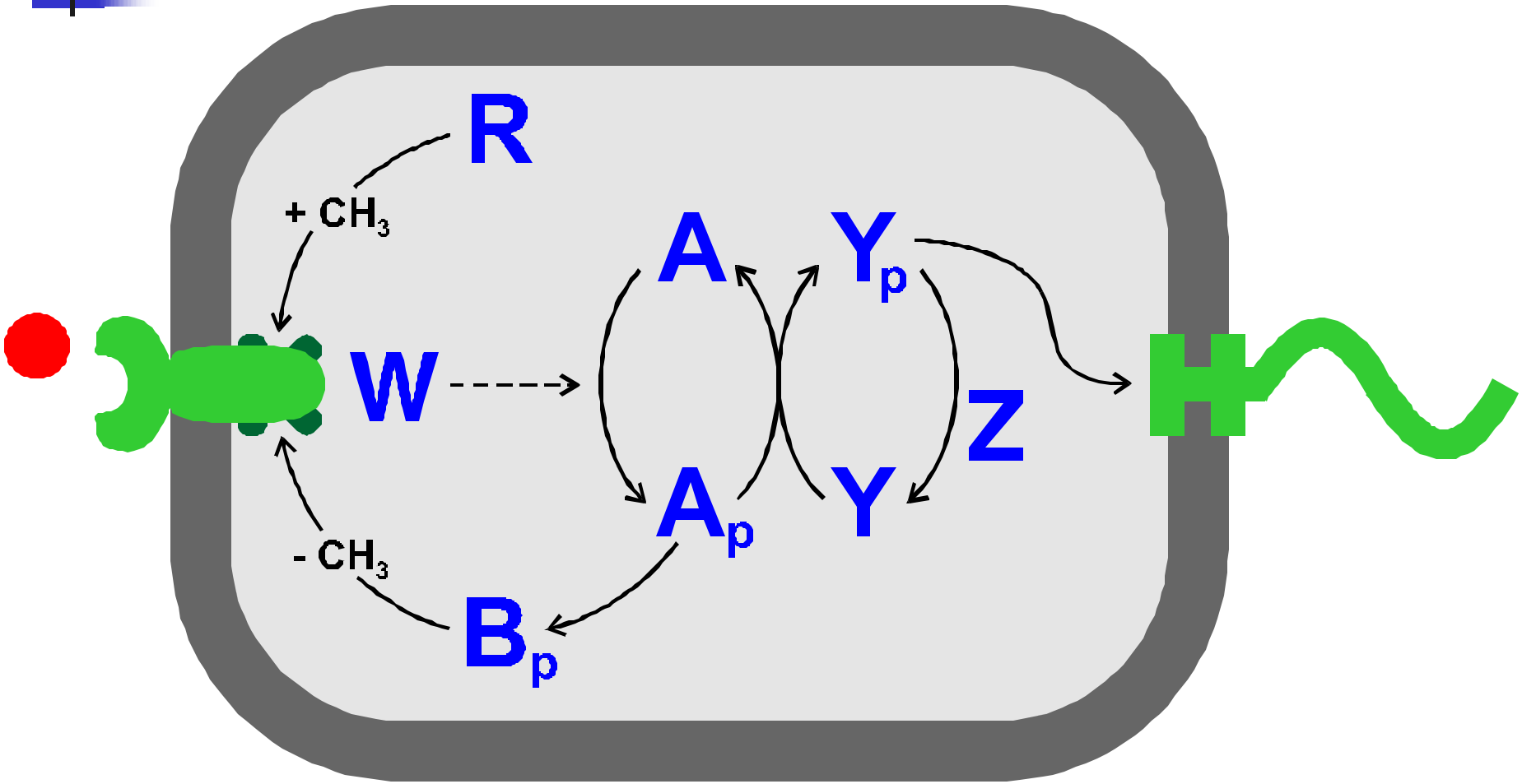


Anti-clockwise flagella rotation

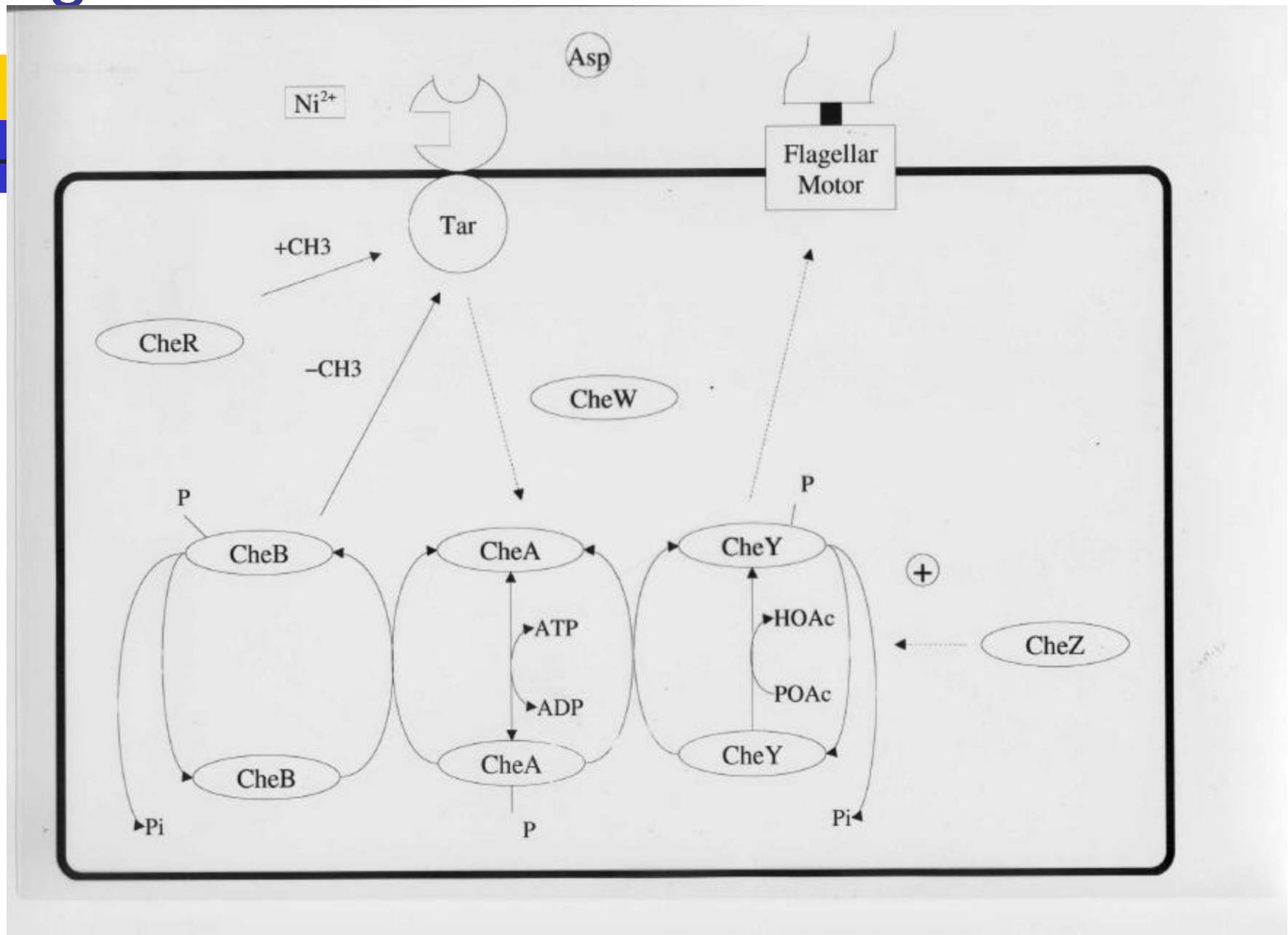


Clockwise flagella rotation

“Sense” and “Memorize” attractant concentration



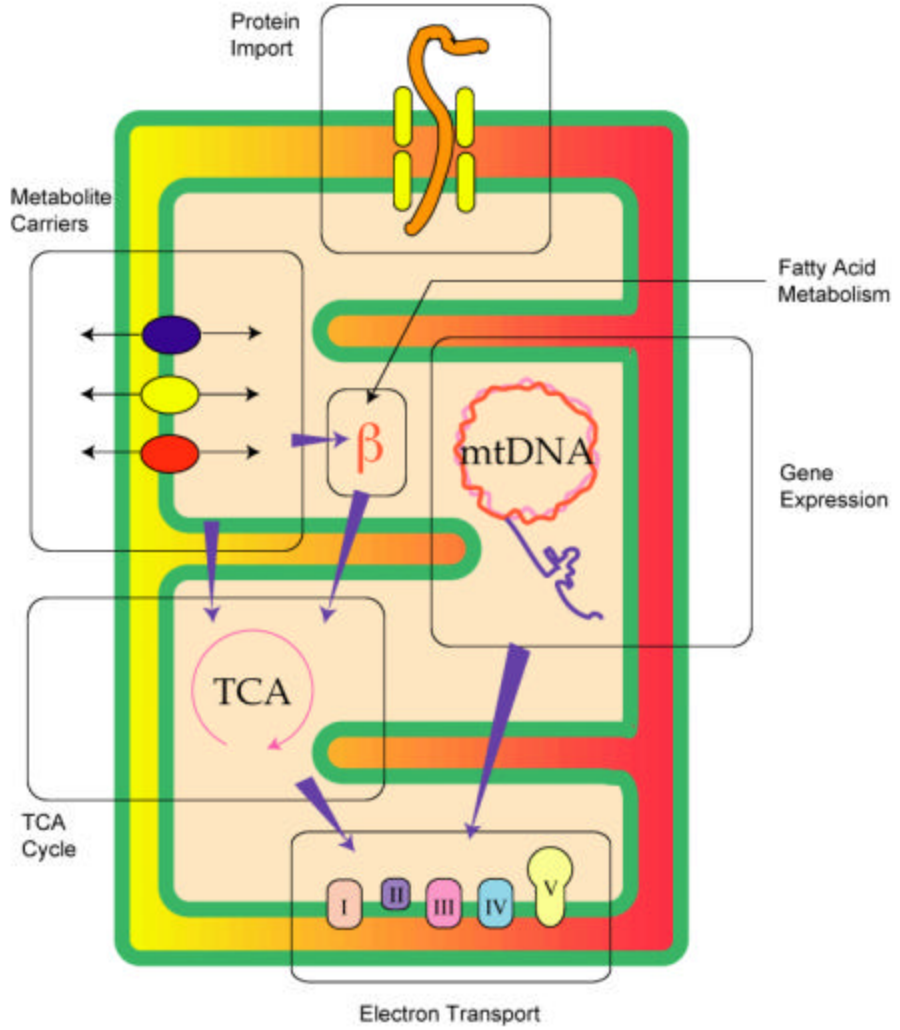
Signal Transduction for Chemotaxis

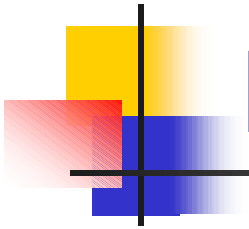


Modeling Mitochondria

- Gene expression system
- Protein transport
- **Metabolite Carriers**
- **TCA Cycle**
- **Electron Transport**
- Fatty Acid Metabolism

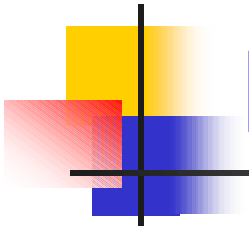
- 37 genes
- 30 enzymatic reactions





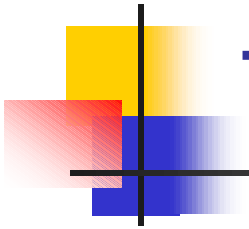
Kinetics – bad news is…

- Not enough quantitative data
  - Kinetic parameters
  - Steady state concentration
  - Flux rates etc.



Kinetics – good news is…

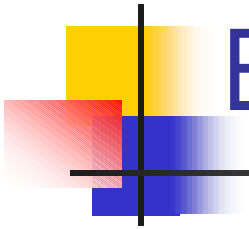
- Changing kinetic parameters does not often affect qualitative behavior (Barkai and Leibler 1996)
- Precise values not necessary for most parameters
- E-Cell may tell what parameters are crucial/sensitive



Towards modeling real cells

- Genome / proteome / metabolome analyses
- Systematic analyses of quantitative data
- Software engineering

- International consortium
- Standardize knowledge representation



E-Cell Software Release

- The E-Cell software has been made available for the public (beta version)
- Available from
  - **http://www.e-cell.org/**
  - User's manual in English and Japanese
- **Windows version in 2000**

Localization And Population Biology

David Nelson
(nelson@cmt.harvard.edu)

❄ Population biology in an inhomogeneous environment with convection. Steady States and "Fisher Waves"

❄ Non-Hermitian growth operators as a description of convecting bacteria in random media

❄ Complex eigenvalue spectra ➜ localized AND extended states in one and two dimensions

❄ Chaotic eigenvalue spectra for delocalized states in d = 2 ⟷ Burgers' equation with noise

Collaborators: **Nadav Sherb (Jerusalem)**
Karin Dahmen (Illinois)
Yural Oreg (Harvard)

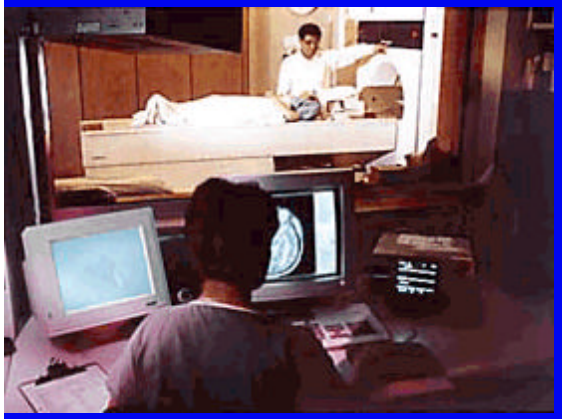
No presentation available

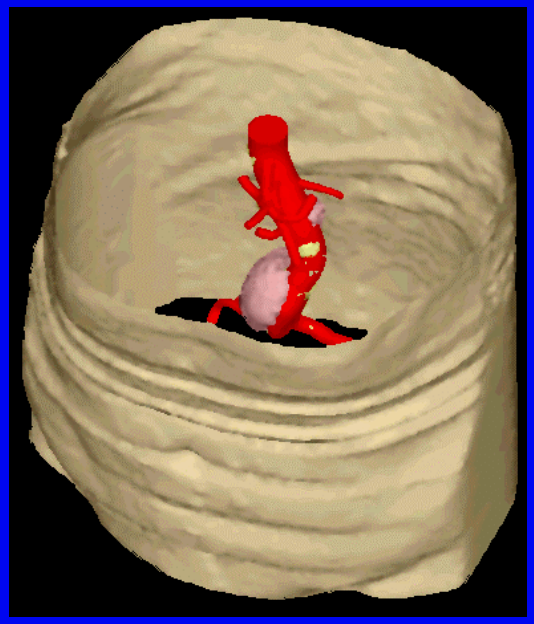
Some Practical Experiences with Simulation in Microfluidic Systems

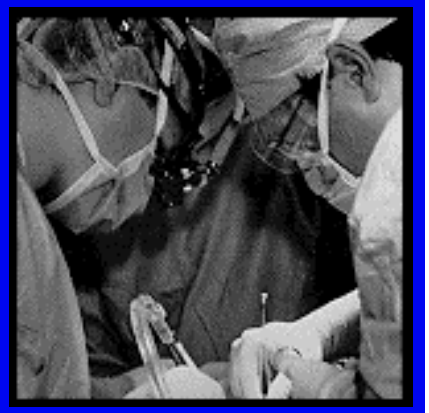
DARPA Workshop
Nov. 18, 1999, Arlington, VA

Gregory T. A. Kovacs, M.D., Ph.D.
Stanford University Department of Electrical Engineering
kovacs@cis.stanford.edu

BIOFLUIDICS AND VASCULAR DEVICES



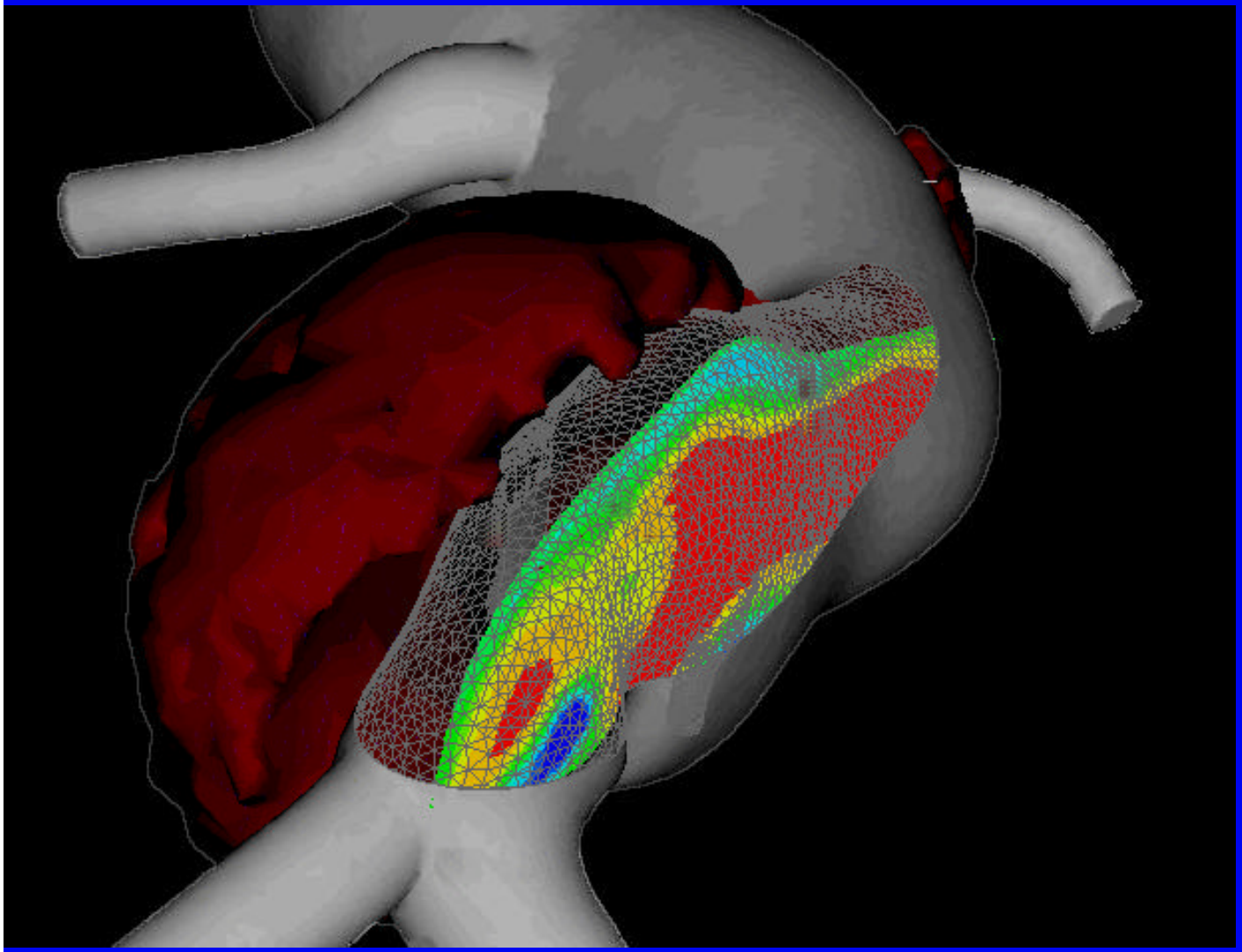




Patient-specific models constructed from diagnostic imaging data.

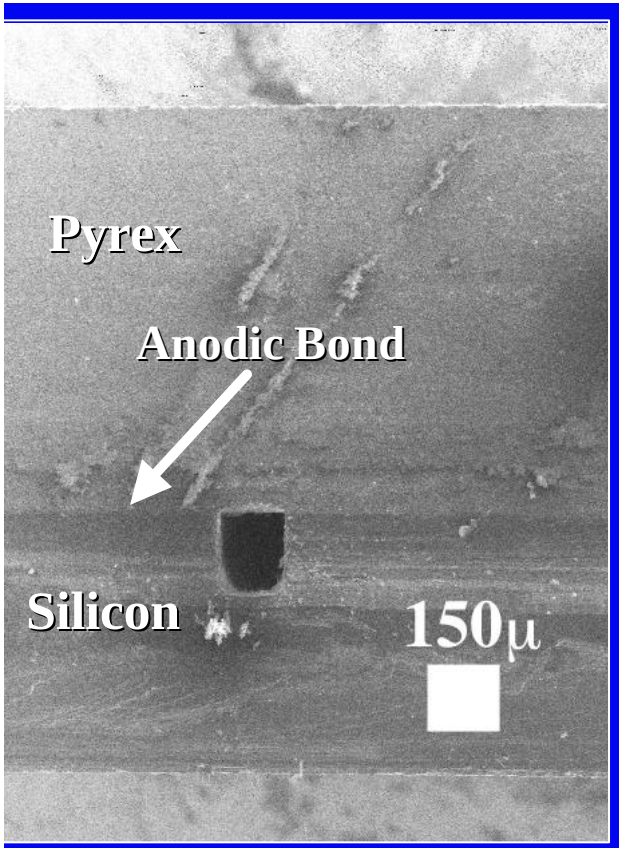
Computer simulations of blood flow to evaluate alternate treatments.

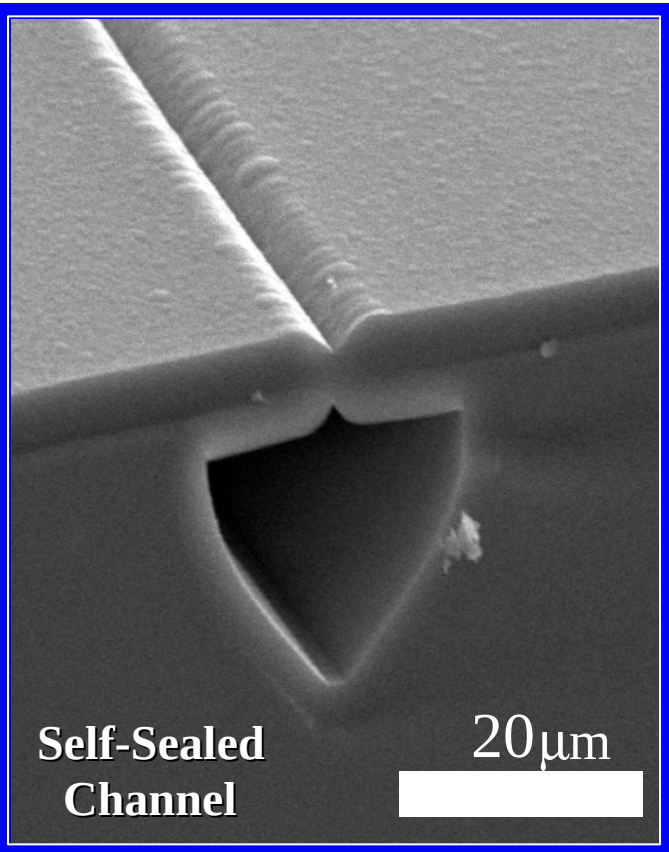
Courtesy Prof. Charles Taylor

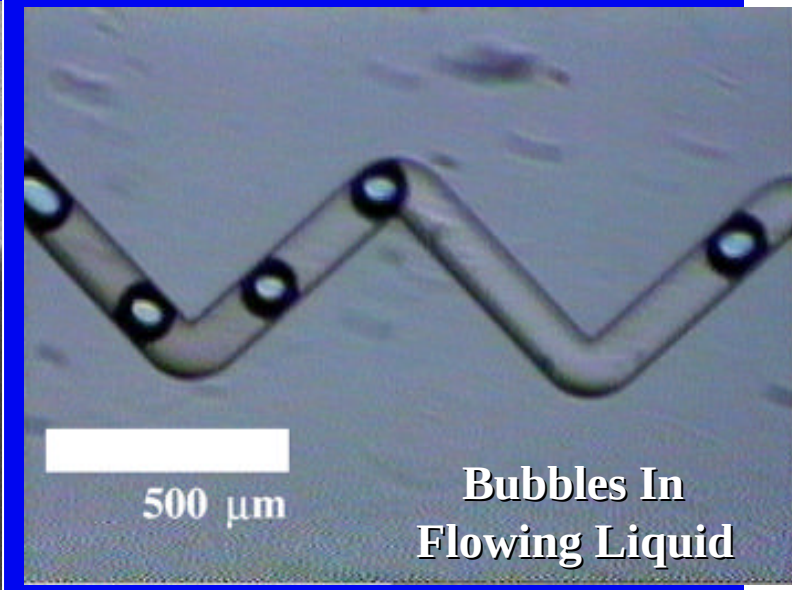


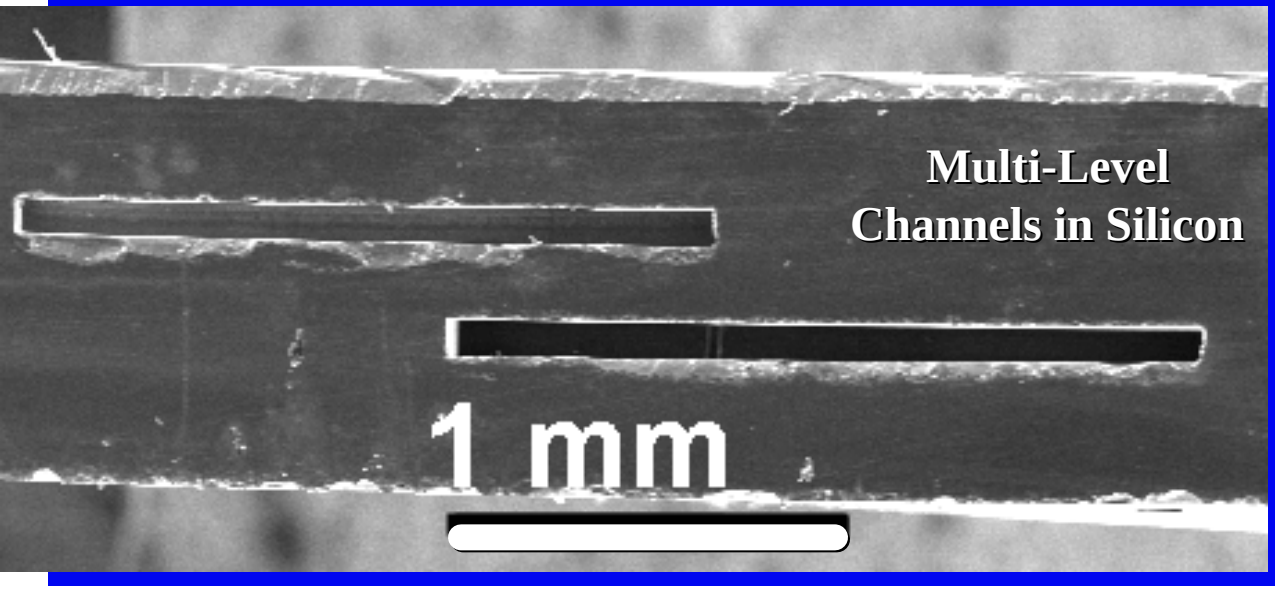
Courtesy Prof. Charles Taylor

G. Kovacs, Stanford Universit









EXAMPLE MICROFLUIDIC CHANNEL STRUCTURES

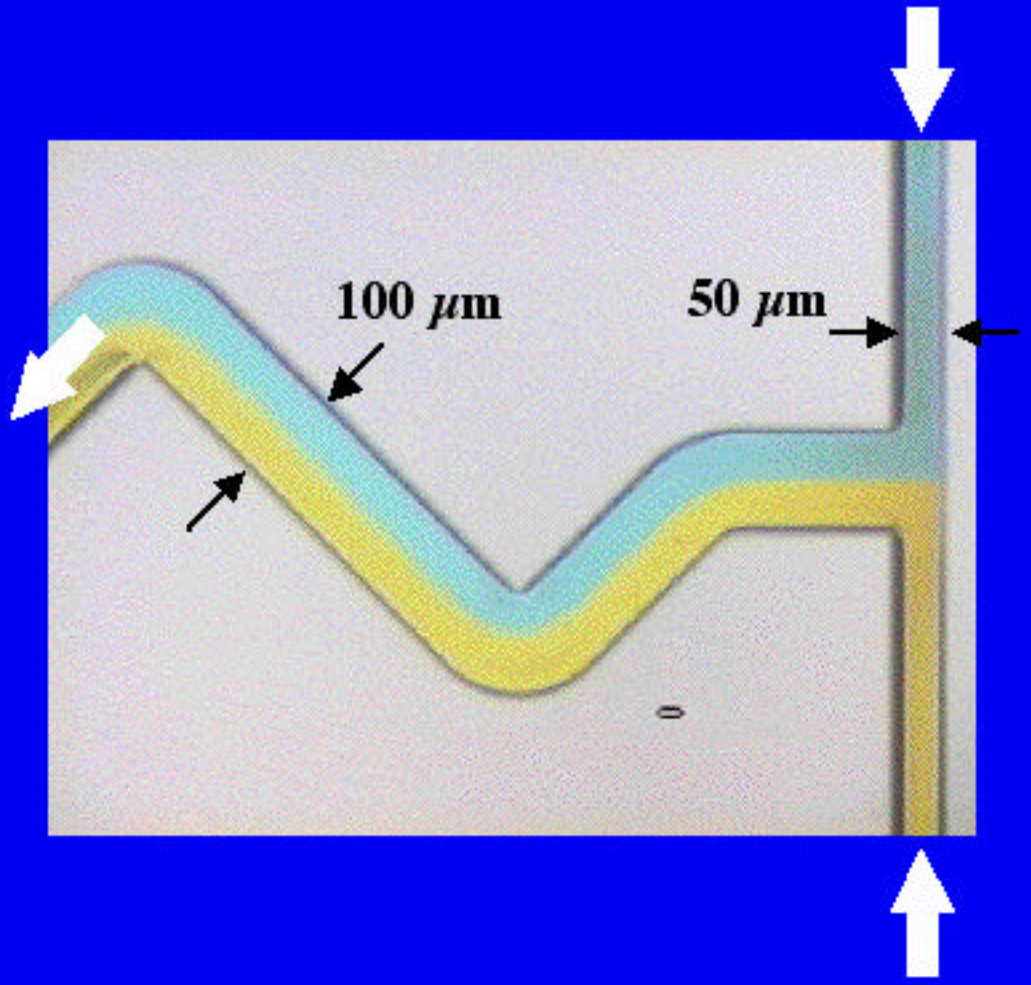
G. Kovacs, Stanford Universit

FLOWS AT LOW REYNOLDS NUMBER

Q = 10 µl/min

v = 67 mm/s

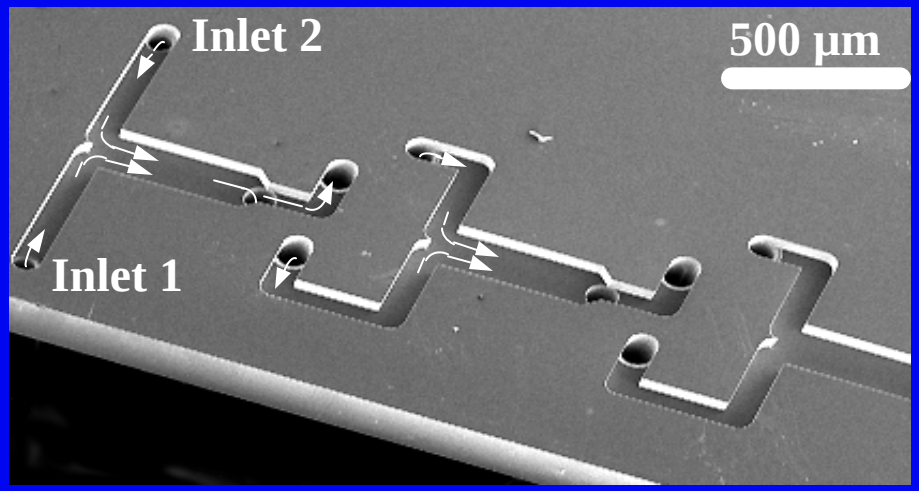
R_e = 4.4



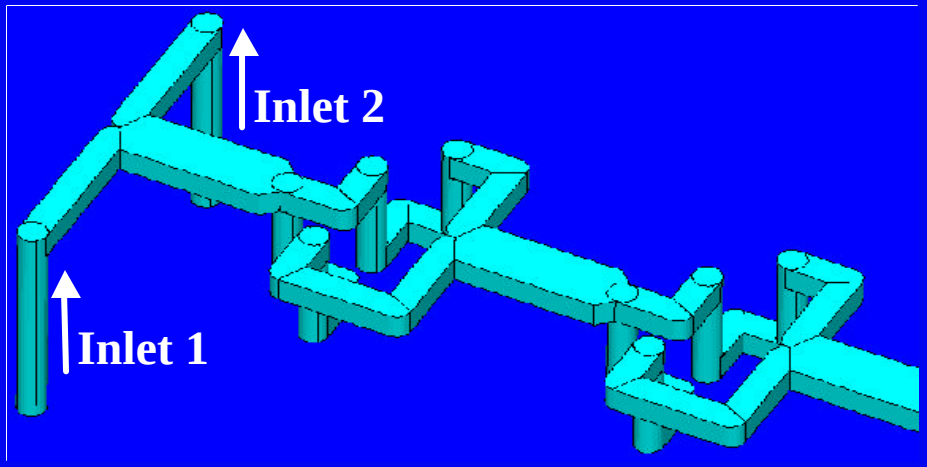
Two parallel streams of dyed water showing mixing by diffusion only.

Laminating Mixer: Structure

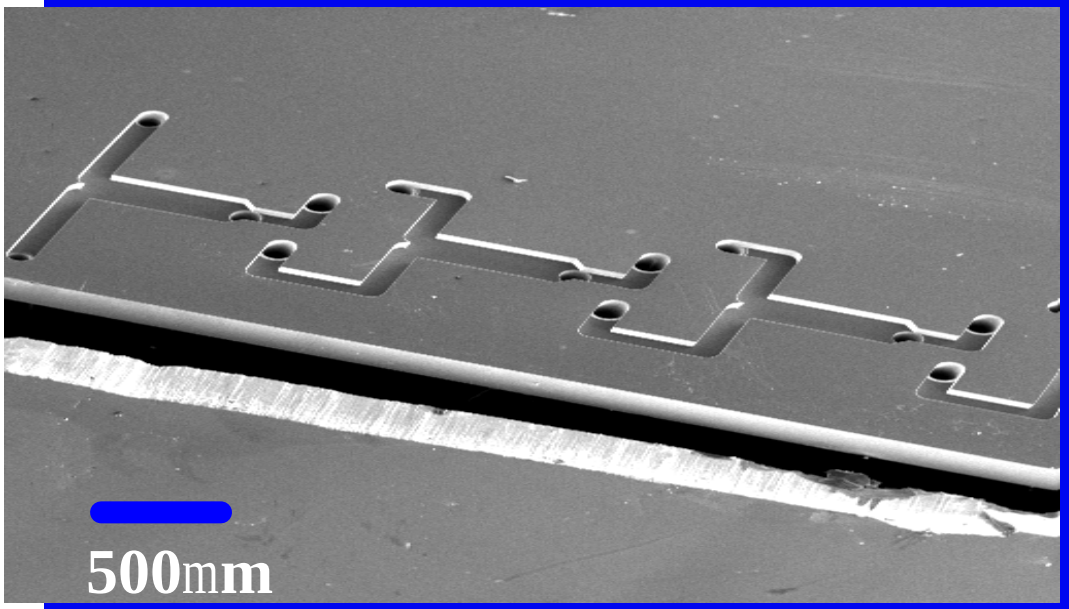
- **SEM Photograph:**



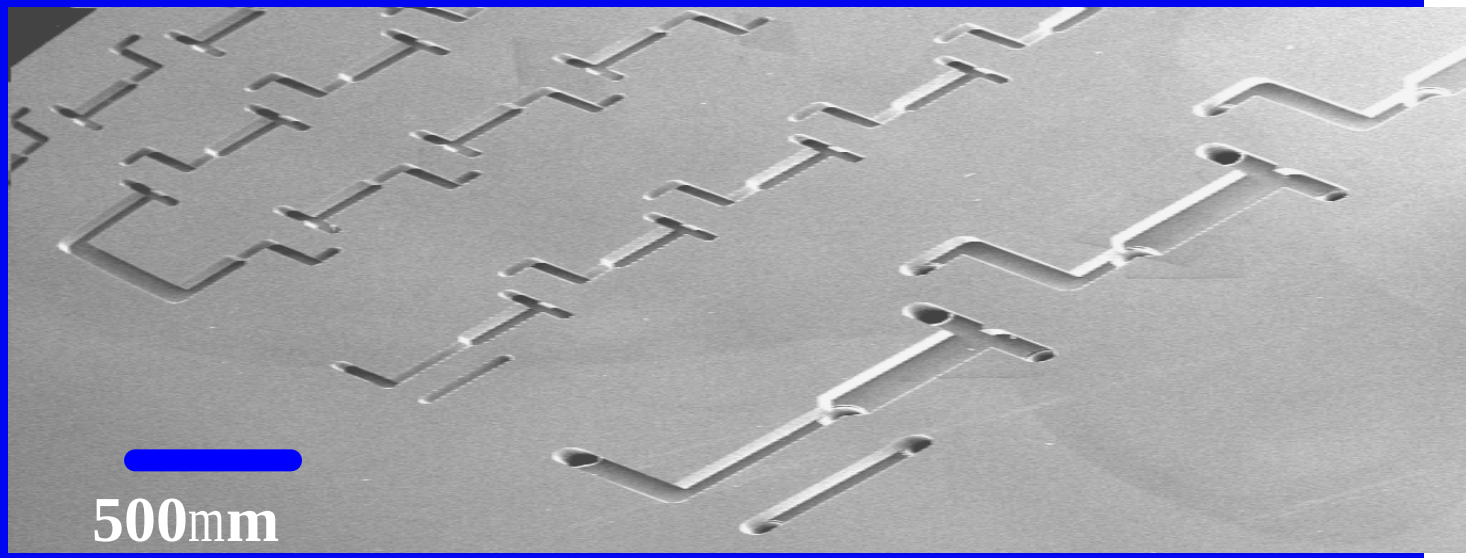
- **Illustration of Multi-Levels:**



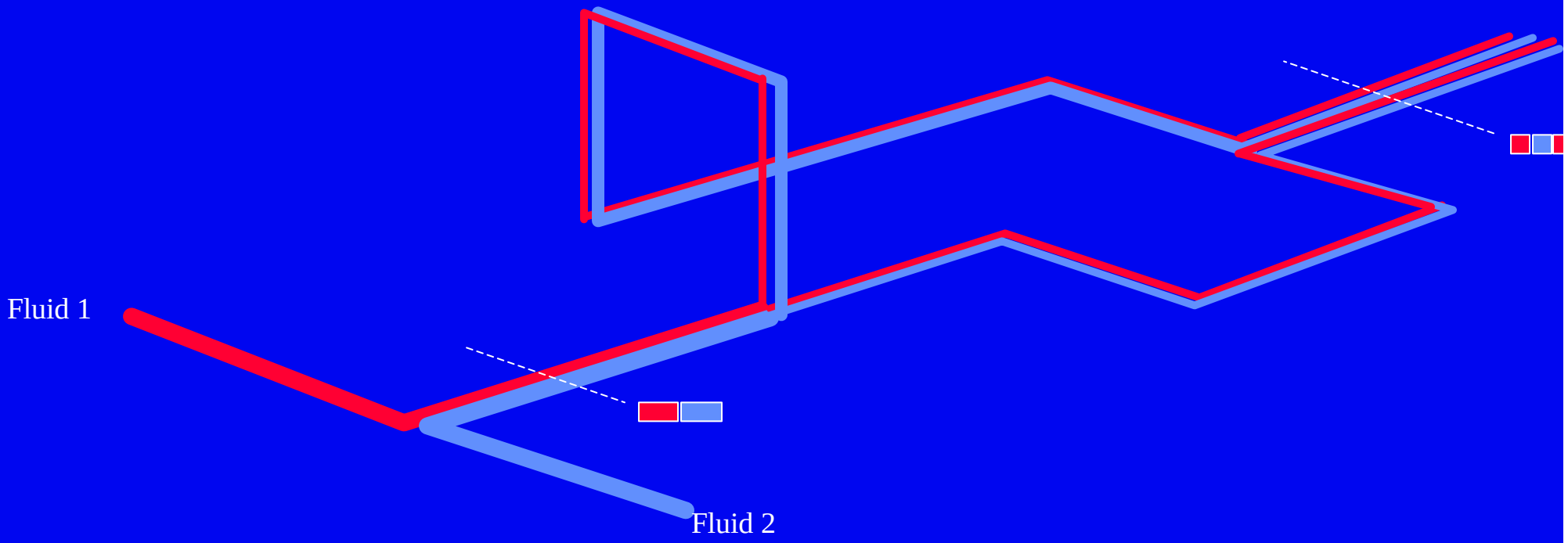
Laminating Mixer: Fabrication



SEMs of top level of channels and vias of a multilevel mixing structure.



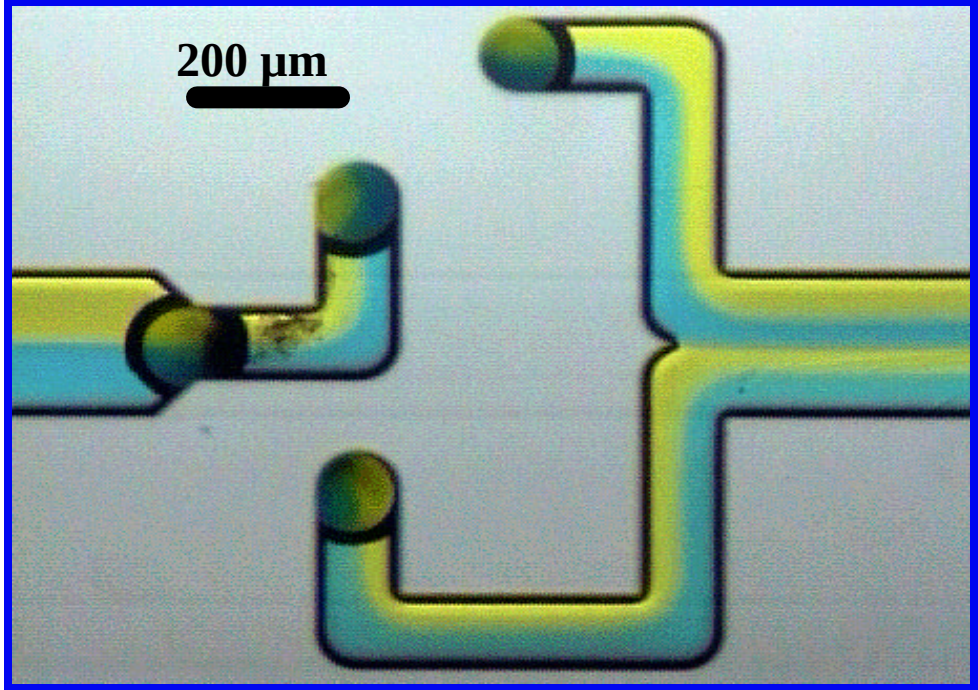
Laminating Mixer: Illustration



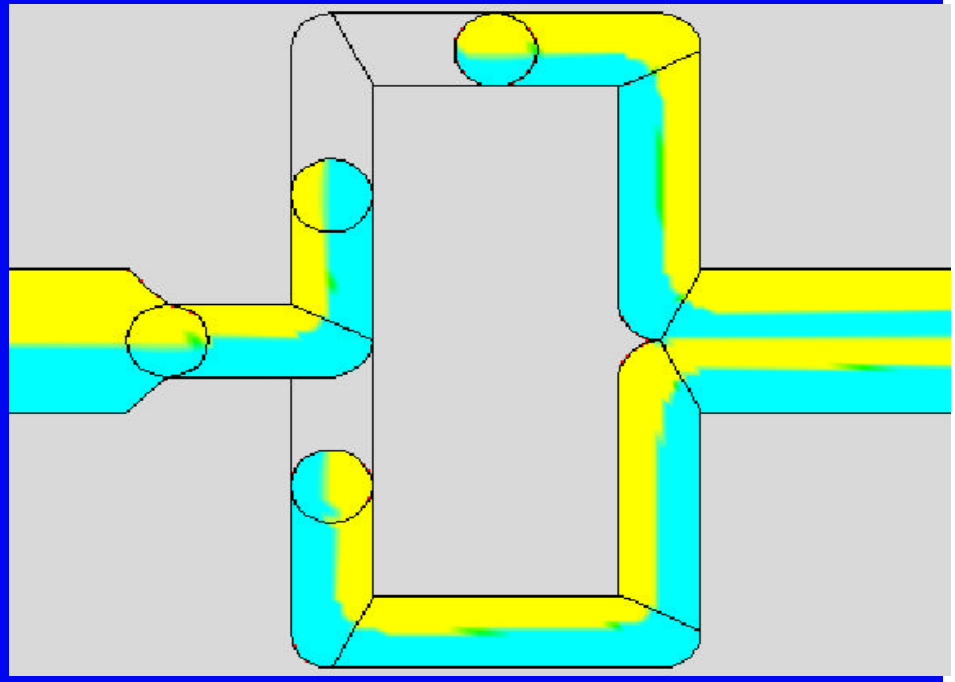
The laminar flows are separated and rejoined after a cross-over is performed using the second level of channels. Only one stage is shown here.

Laminating Mixer: Operation

Experiment:



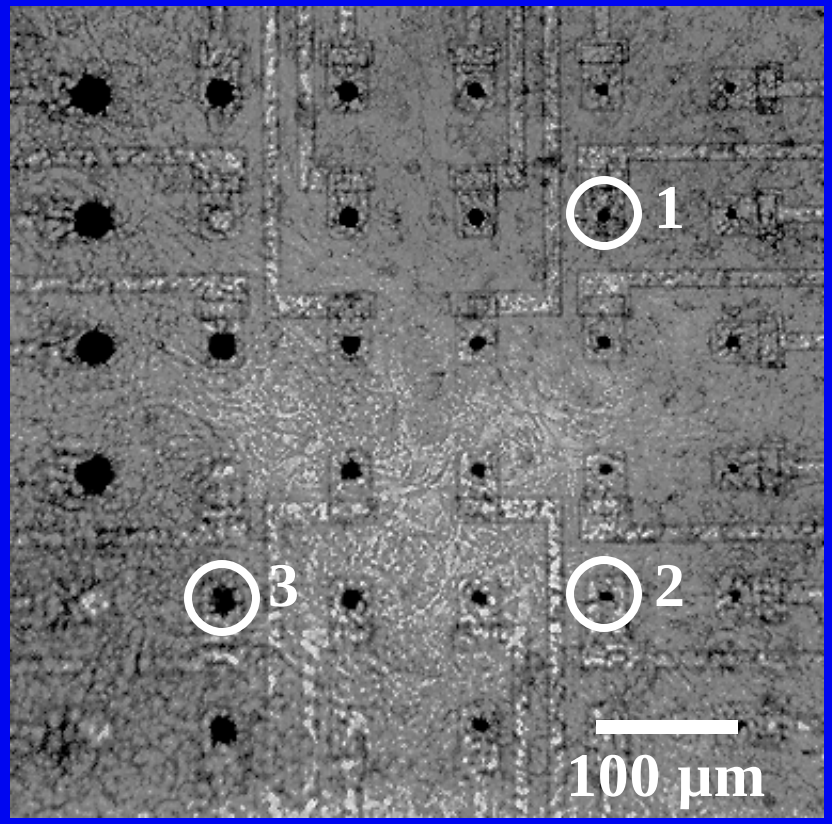
Simulation:

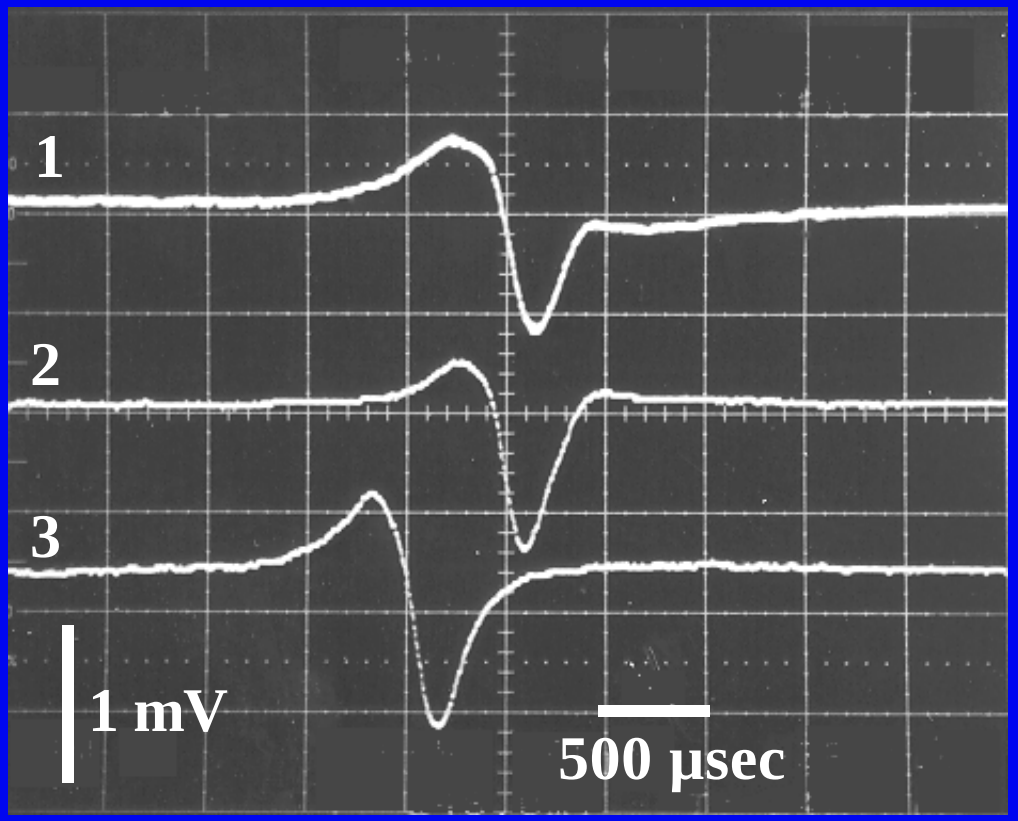


Modeling Requirements for a Portable Cell-Based Biosensor

- **Cell-based biosensors use living cells as the front-end of their transduction pathways.**
- **The cells must be maintained within a regulated environment that provides for their physiological requirements.**
- **Modeling aids in the design for at least two environmental requirements:**
  - **Thermal regulation (37 °C for mammalian cells) in flowing liquid**
  - **Gas exchange (Supply of O_2 and removal of CO_2) in static liquid**

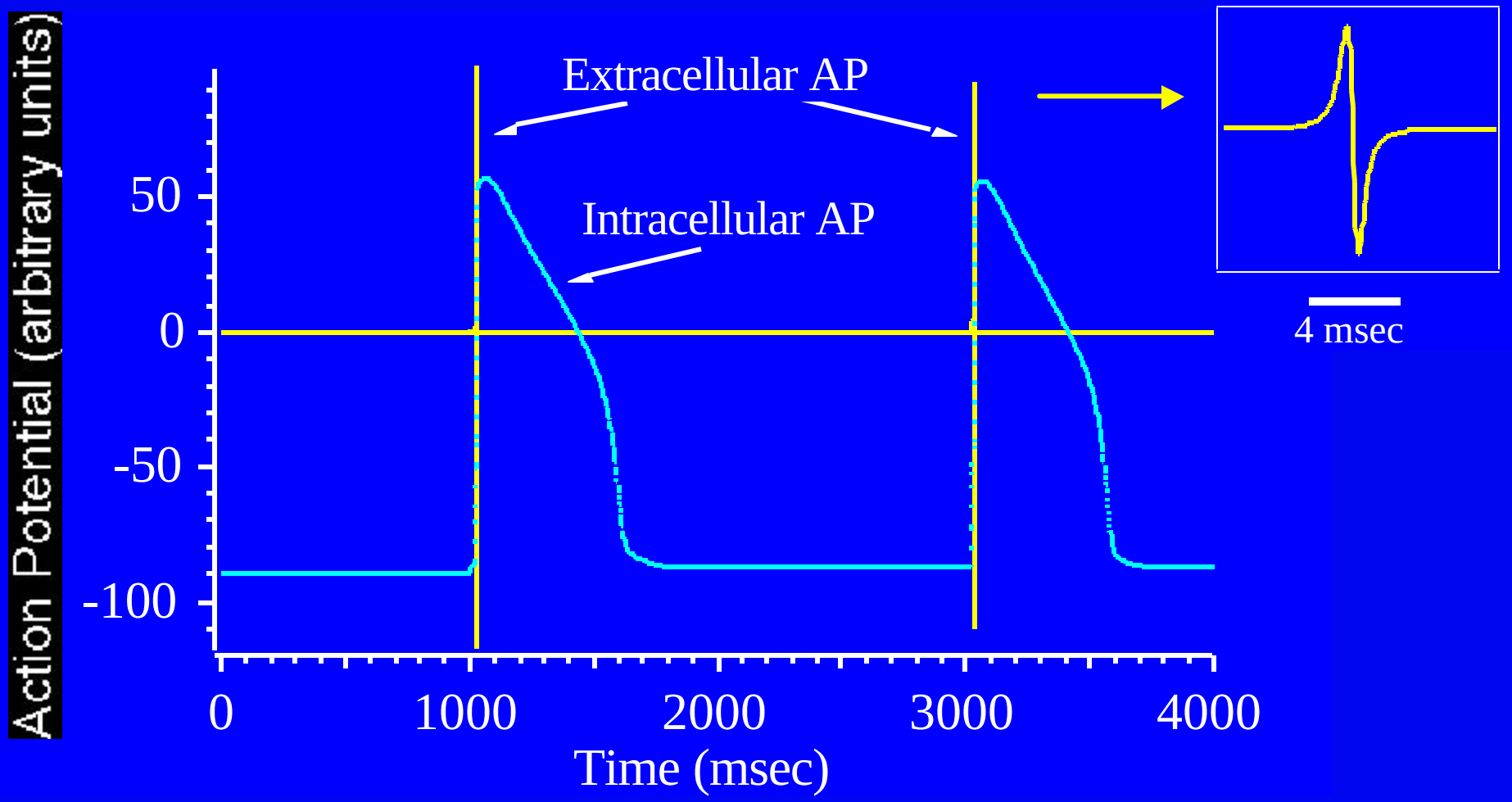
Chick Myocardial Cell AP Recordings



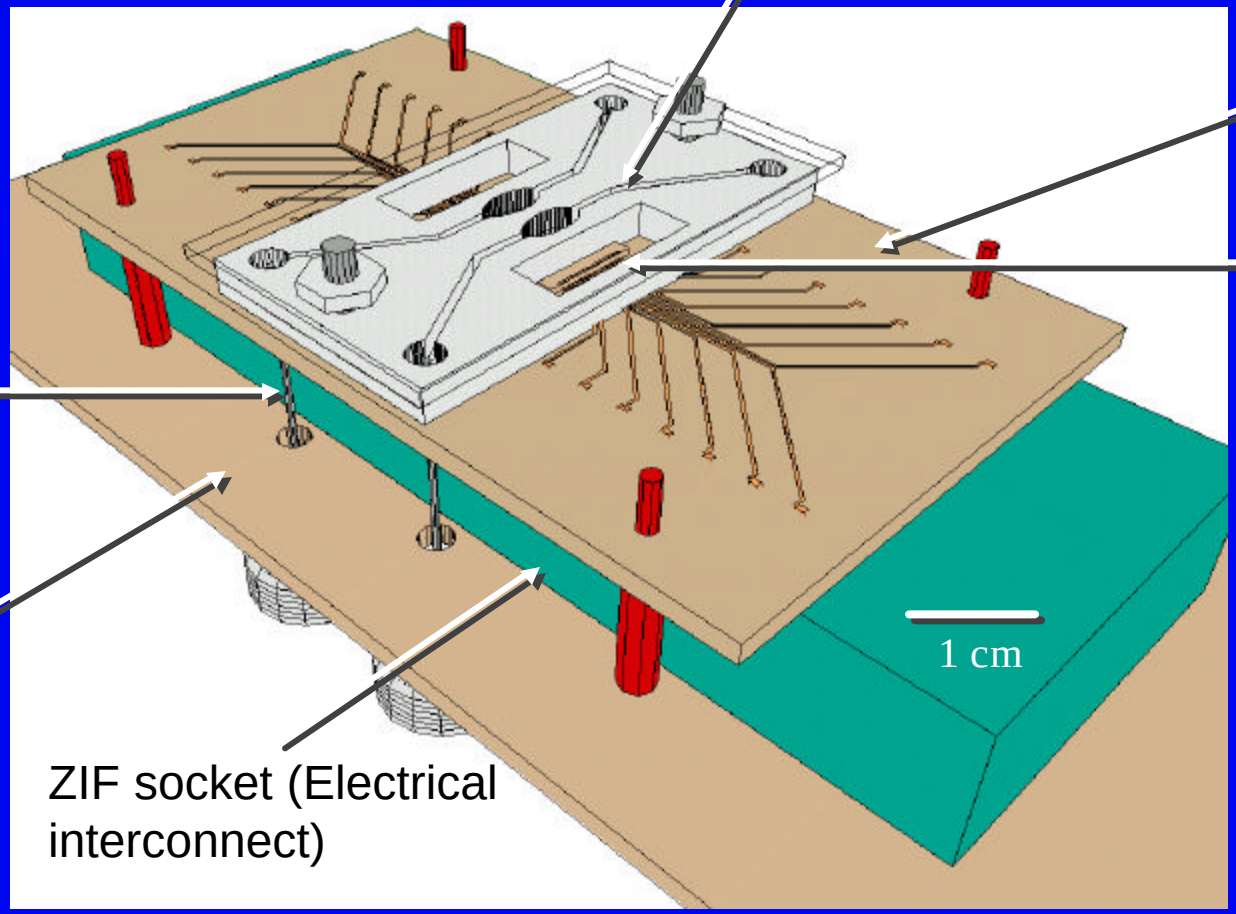


G. Kovacs, Stanford Universit

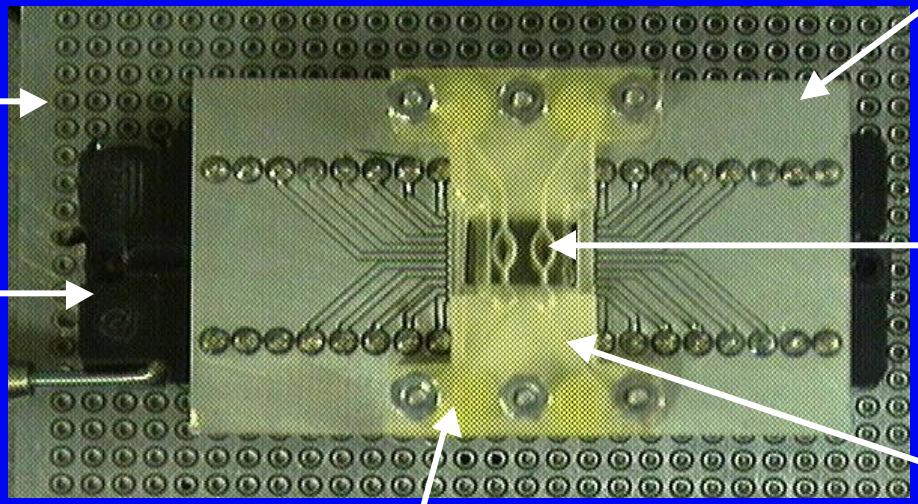
Simulated Cardiac Action Potential



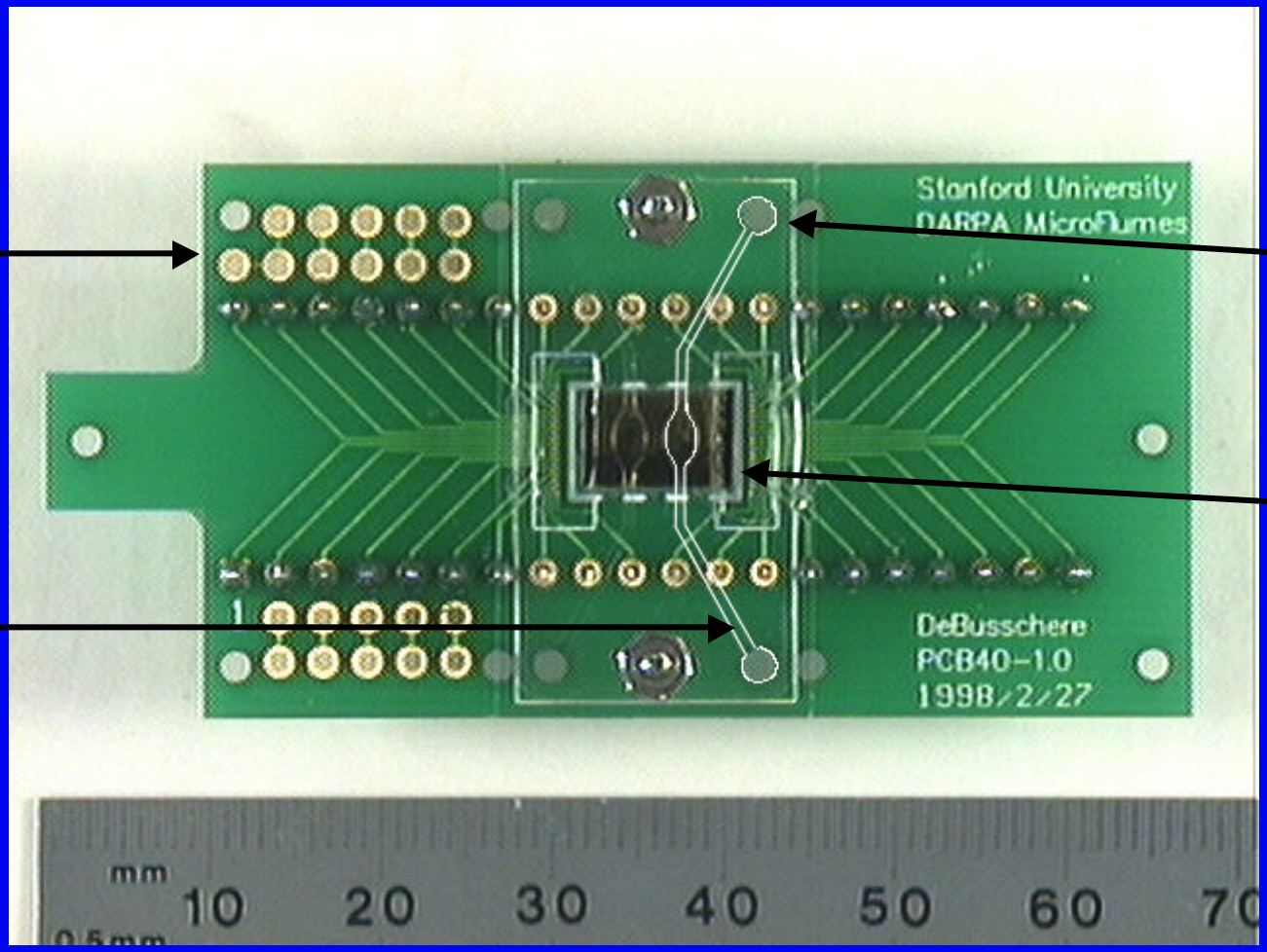
Cell Cartridge CAD Design



Hybrid Biosensor Stereo Lithography (SLA) Prototype



ntegrated Cell Cartridge for Hand-Held Biosenso



Cartridge PC Board

Septa (Fluidic Interconnect)

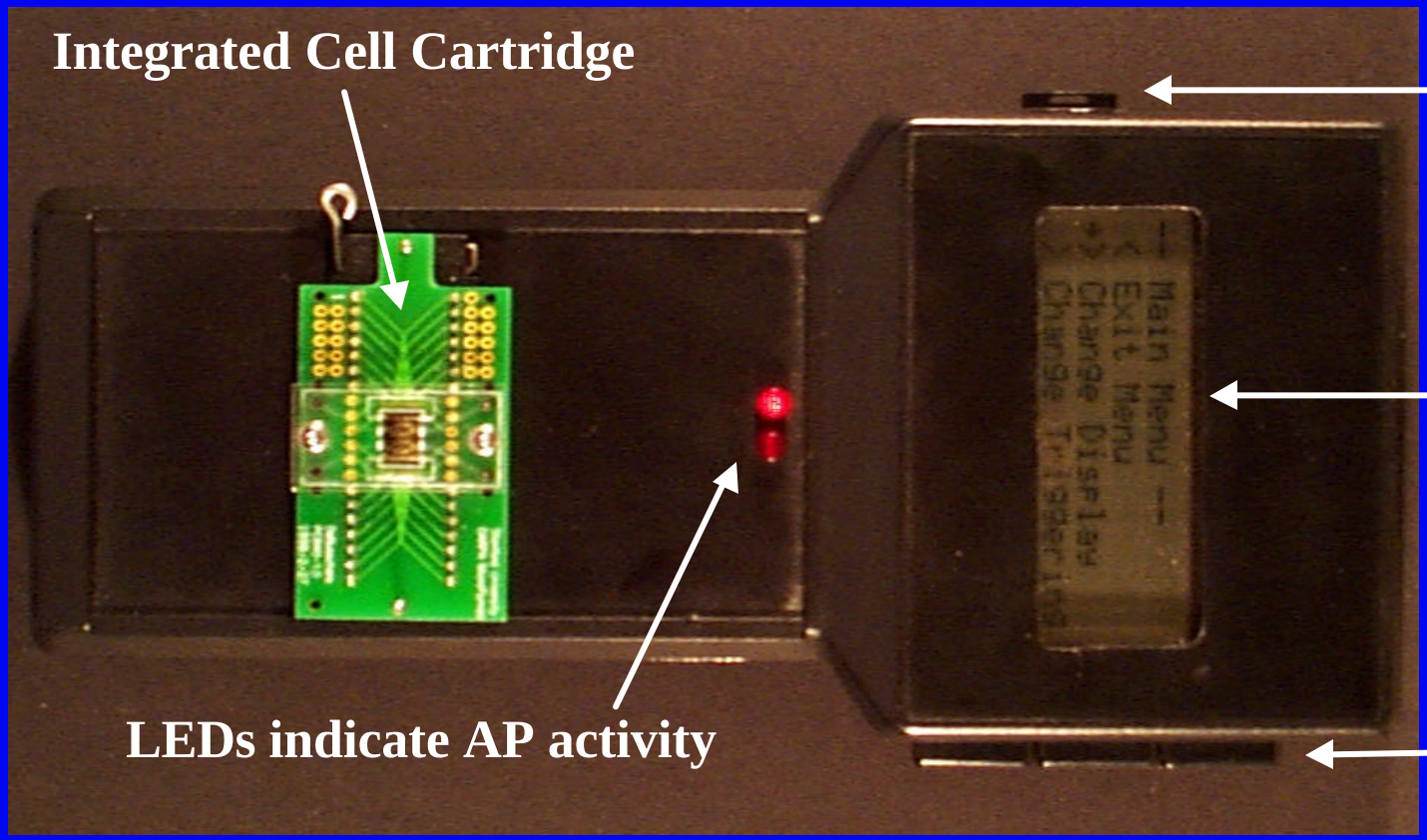
Silicon Die & Chambers

Highlighted Fluidics Channel

Design: D. DeBusschere, Stanford University

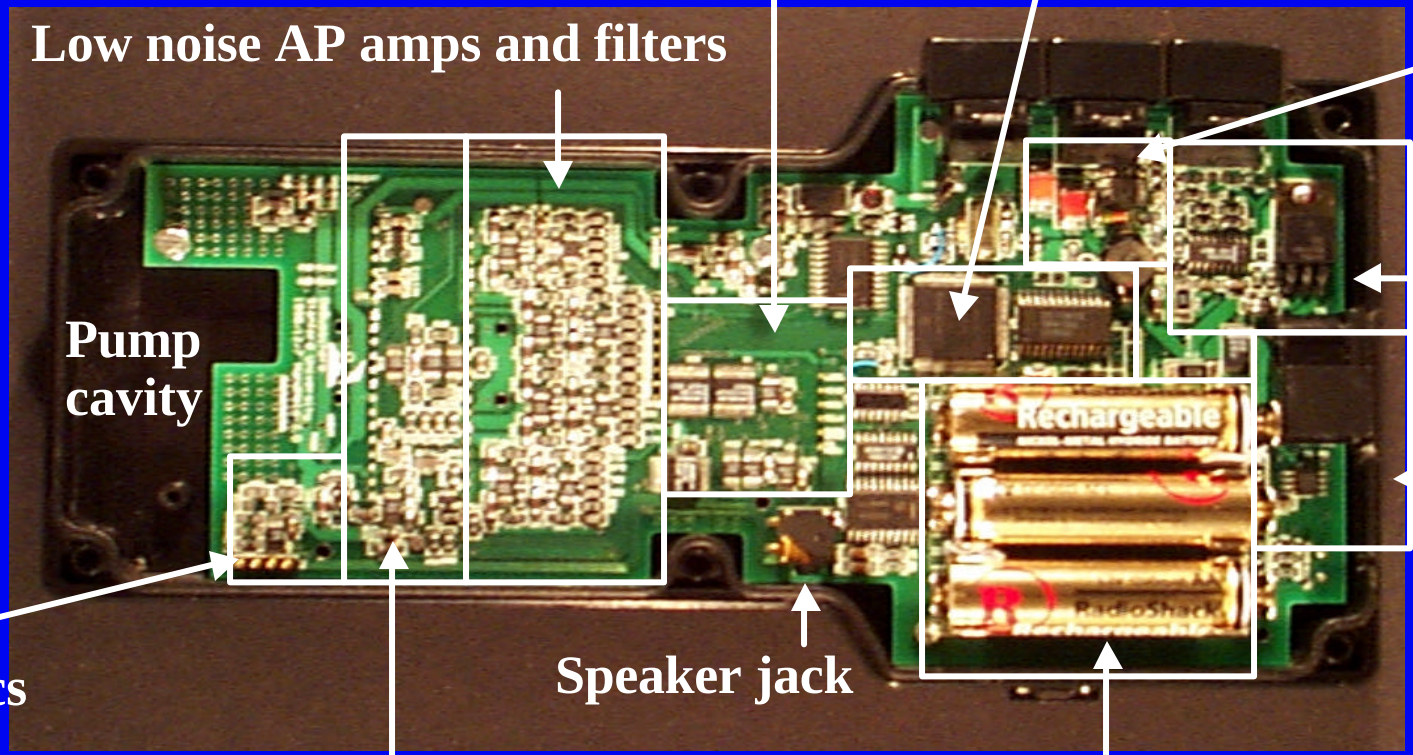
G. Kovacs, Stanford Universit

Prototype Hand-Held Biosensor



Design: D. DeBusschere, Stanford University

“Guts” of the Biosensor



Mixed signal (Stimulation DAC, ADCs, etc.)

Microcontroller & SRAM

Low noise AP amps and filters

DC-DC converter

Battery charger

Pump cavity

Serial uplink allows monitoring and analysis by host PC

Pump control electronics

Speaker jack

pH & Temp amps

Rechargeable batteries

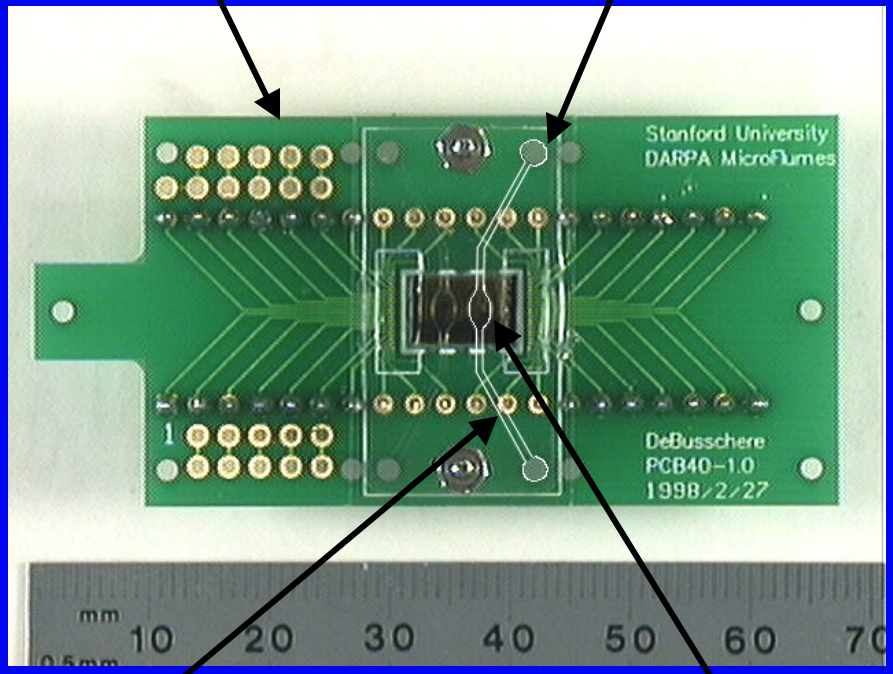
Design: D. DeBusschere, Stanford University

G. Kovacs, Stanford Universit

Thermal Modeling of Cartridge

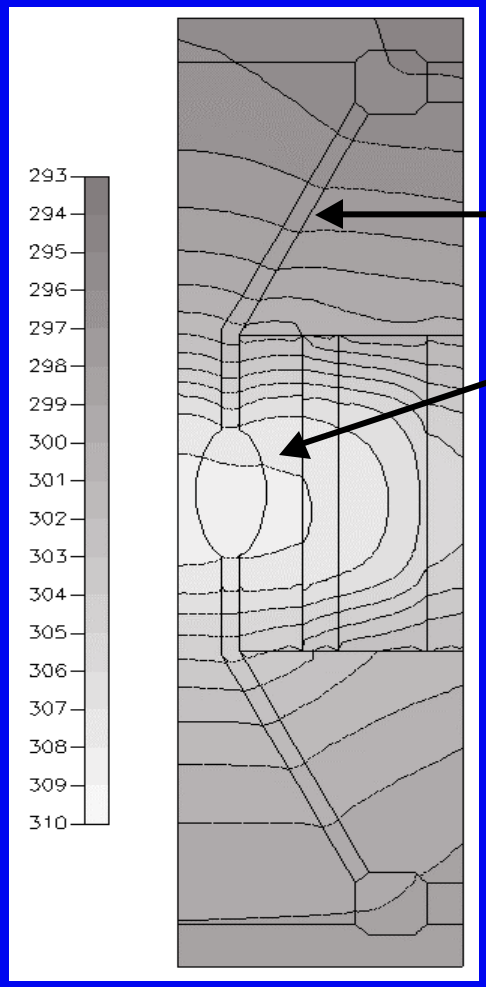
Cartridge PC board

Septum (fluidic Interconnect)



Highlighted fluidics channel

Silicon die & chambers

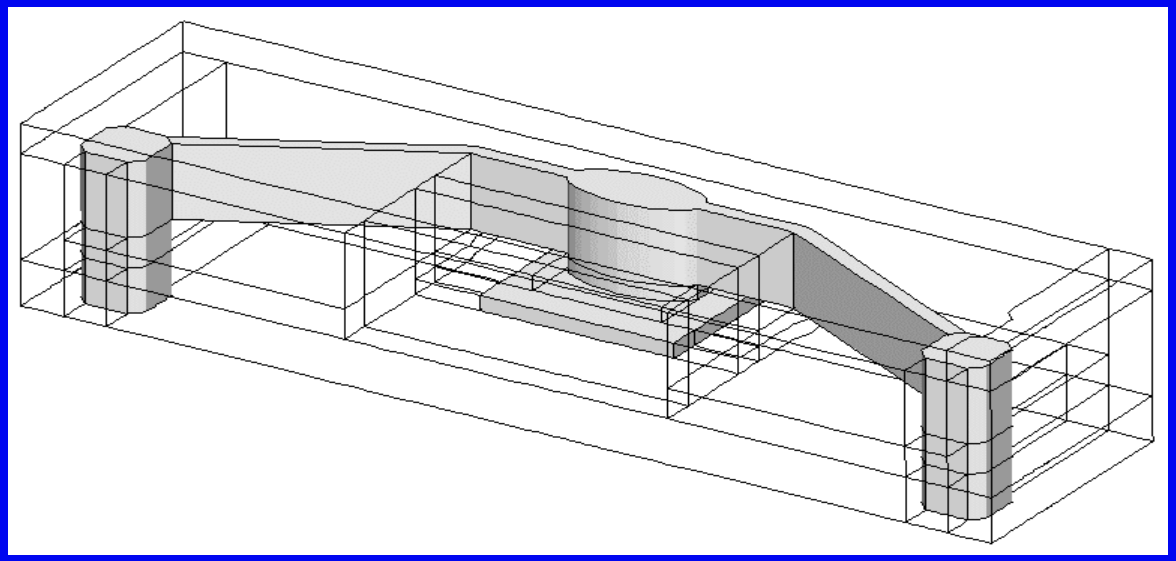


Fluidics Channel

Silicon Die & Chamber

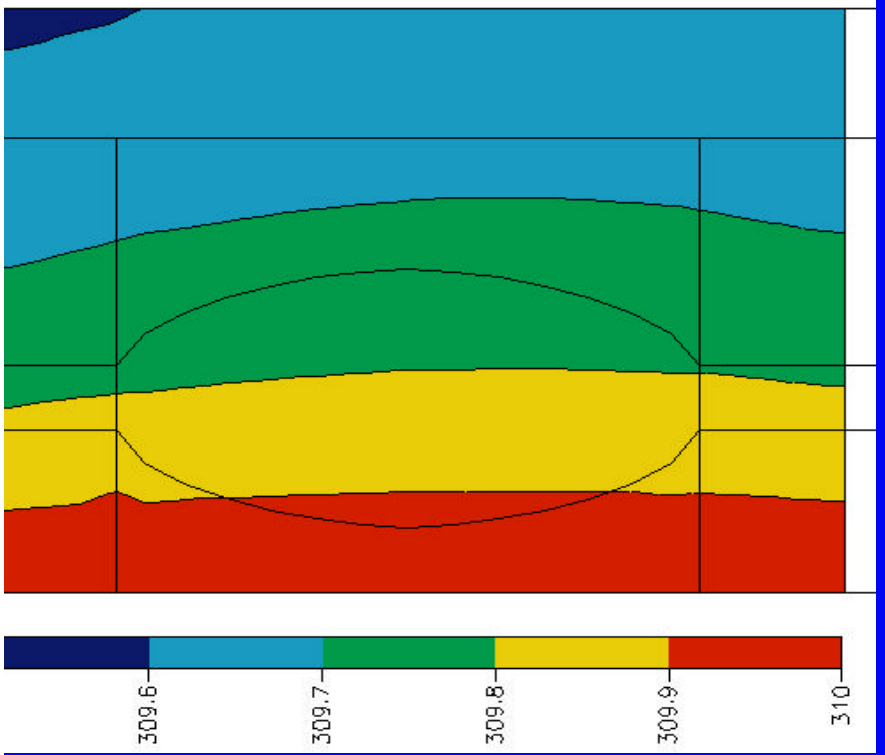
Predicted Regulation at Cells Better Than 0.1 °C at 10 mL/min flowrate.

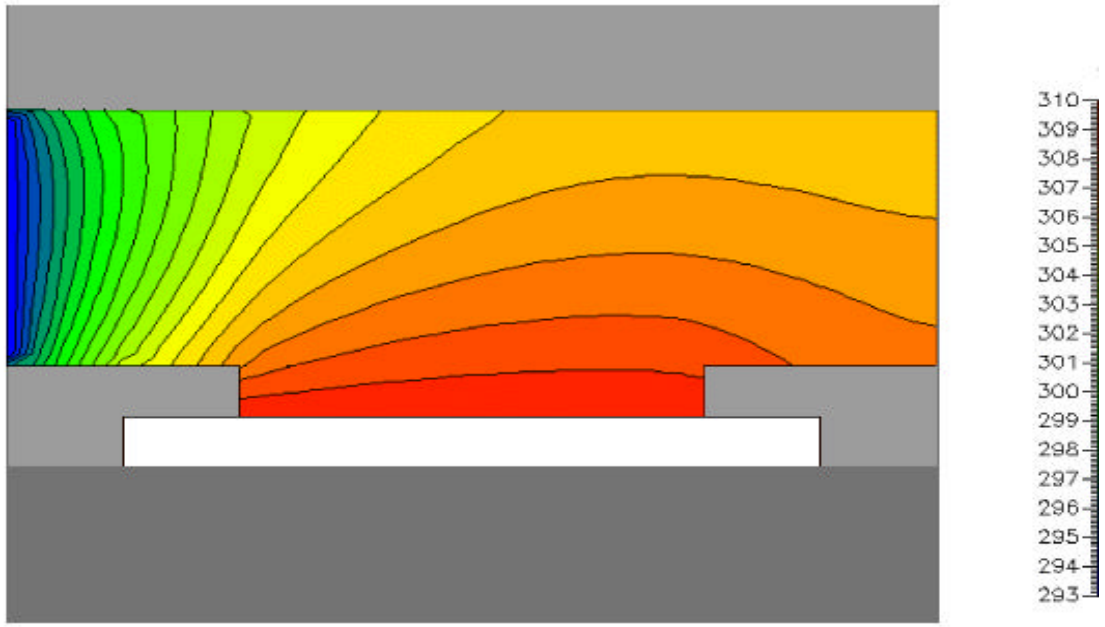
Model/Mesh



- Half-symmetrical model used for thermal and gas diffusion simulations
- The fluid channels and silicon die have been filled in with gray.

Additional Thermal Flow Analyses

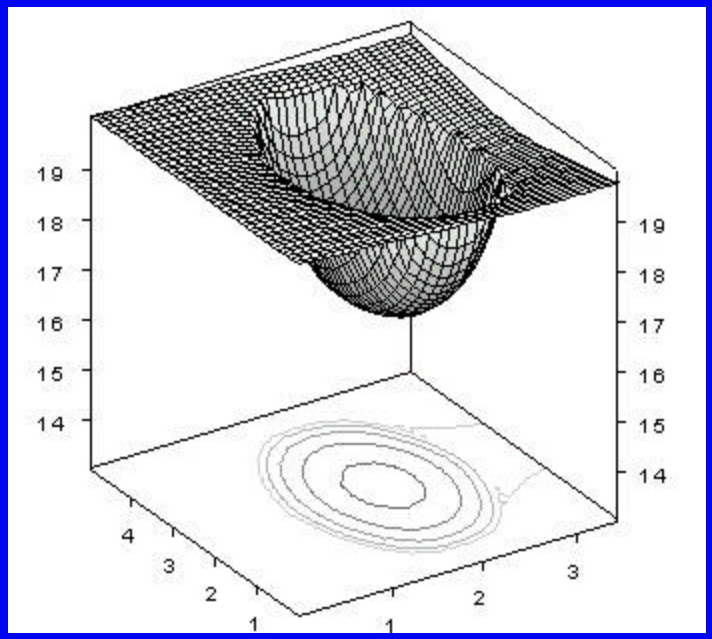




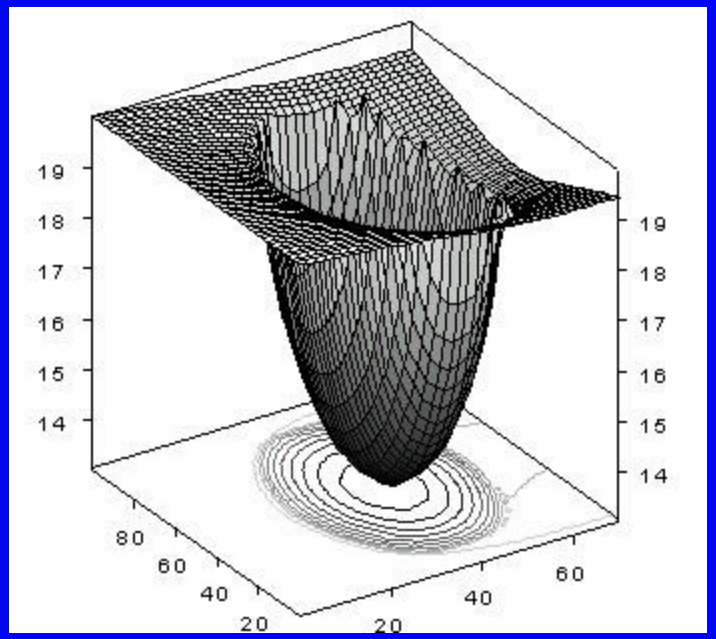
- **All thermal plots assume a 10 uL/min flow rate.**

Modeling of Oxygen Diffusion

kPa O_2



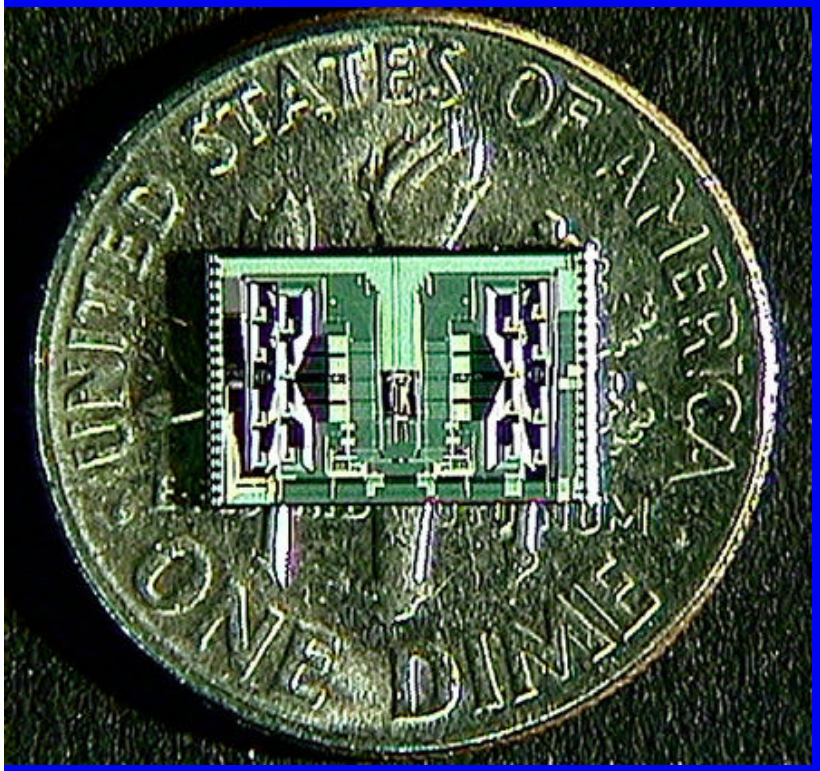
20 x10^{-18} mol/(cell•sec)

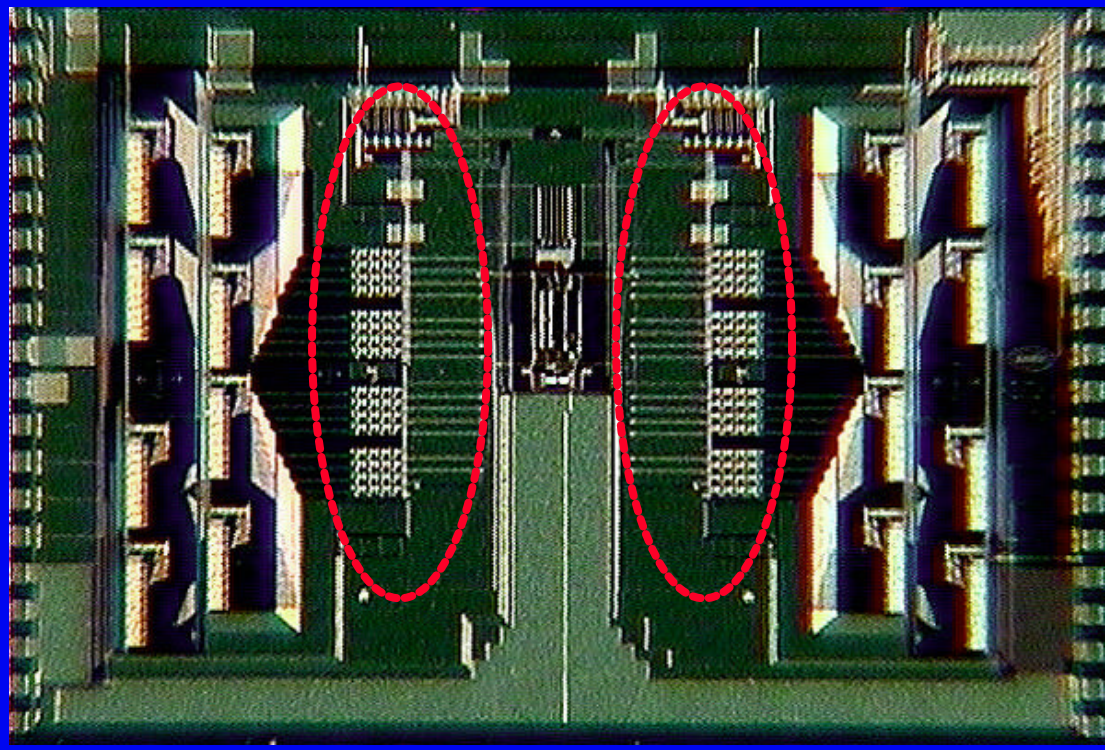


40 x10^{-18} mol/(cell•sec)

- **Computer simulation of oxygen diffusion through gas-permeable chamber walls and the culture media to the cells.**
- **The simulations indicate that the design will be able to provide sufficient oxygen to meet metabolic requirements.**

CMOS Interface Chip





Harder Things to Model

- **Mass transport with and without chemical interactions:**
  - **Adsorption/absorption**
  - **Specific binding**
  - **Contact angle effects**
- **Surface morphology effects.**
- **Bubbles and particles (and cells).**
- **Menisci.**
- **Multi-fluid systems (hydrocarbon/water, air/water, etc.).**
- **Ultrasonic energy effects.**
- **High-fidelity action potential generation/control.**

Conclusions

- **Modeling tools have been extremely valuable in developing several microfluidic devices.**
- **No integrated tool set yet exists, and we use a patchwork of different software to meet our needs.**
- **Many important areas in microfluidics are not yet addressed by modeling tools (bubbles, cells, surfaces, chemistry, multiple fluids).**
- **Continued improvement in modeling for microfluidics will enable next-generation devices and make the design process much more efficient.**
- **To be useful, simulation tools must give correct answers on a much shorter timeframe than building and testing physical devices.**

THANKS TO OUR SPONSORS!

- **Defense Advanced Research Projects Agency.**
- **National Science Foundation.**
- **Office of Naval Research.**
- **Corporate members of the Center for Integrated Systems.**
- **General Motors, Inc.**
- **Analog Devices, Inc.**
- **Medtronic, Inc.**
- **William Hewlett and the late David Packard.**
- **The family of the late Robert Noyce.**

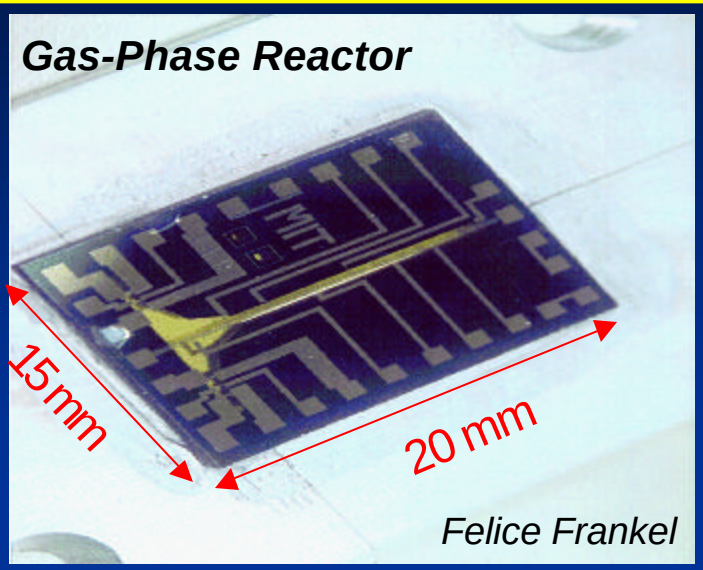
Scaling and Simulation Approaches for Microchemical Systems

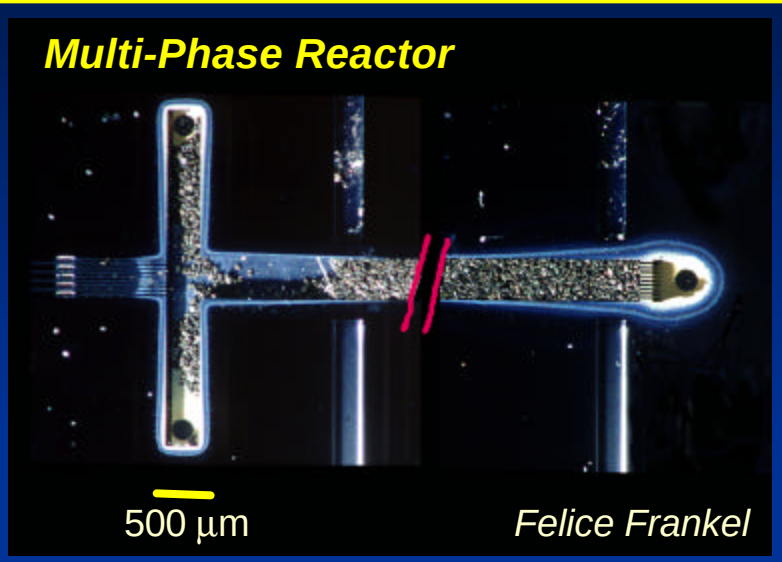
Klavs F. Jensen

Departments of Chemical Engineering and Materials Science & Engineering
Massachusetts Institute of Technology, Cambridge, MA 02139, USA

(617) 253-4589 (voice) (617) 258-8824
kfjensen@mit.edu

MicroChemical Systems - Motivation

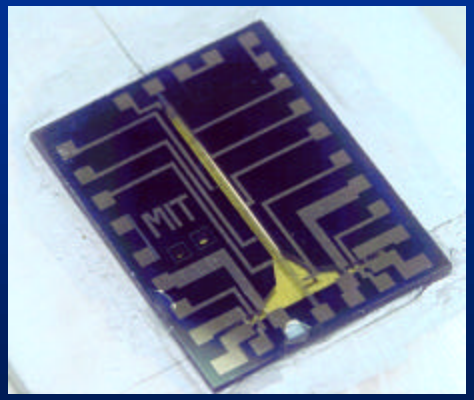


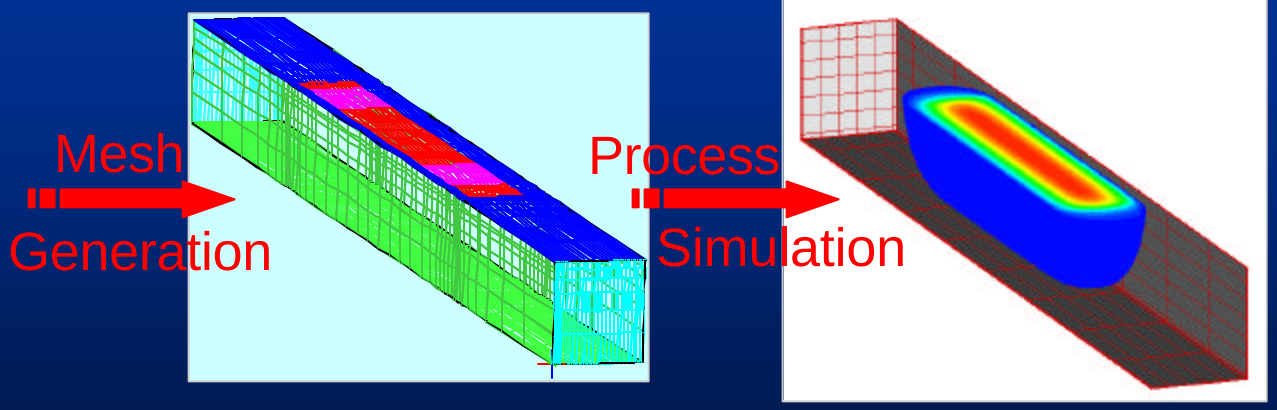


- Advantages:
  - Integration of chemical transformations with sensors and actuators
  - Portable, flexible, and smart devices
  - Packaged system for distributed - on demand - on time - manufacturing
  - Fast scale-up to production by replication
  - Safety - less inventory - safe handling of reactive, hazardous chemistry
  - Performance - access to extreme operating conditions
  - New methods for high throughput reaction/catalyst screening

Simulation of Microchemical Systems

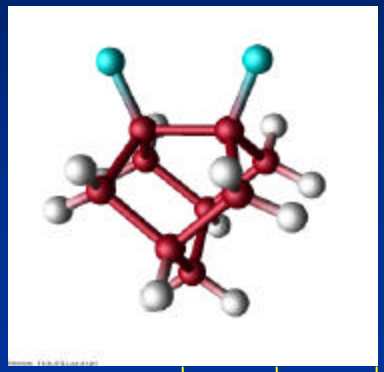
- **Approach**
  - **CAD based finite element mesh generation with materials characteristics and boundary condition definition**
  - **Coupled fluid flow, heat and mass transfer, with chemical kinetics**
- **Design of new microchemical systems**
  - **Iterative redesign process is *time consuming and expensive***
- **Integration and scale-up of microchemical systems**
  - **Optimization and simplified models for control systems**



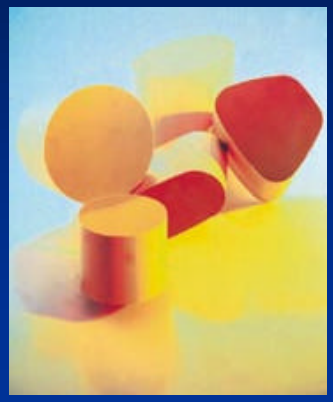


Chemical Processes Involve Multiple Scales

Molecular chemistry



Catalyst Particle



Chemical Reactor

1 nm **1 ㎜** **1 mm** **1 m**

Quantum Chemistry Molecular Dynamics

Monte Carlo - Continuum Equations

Macroscopic Continuum Equations - Finite Element/Finite Difference methods

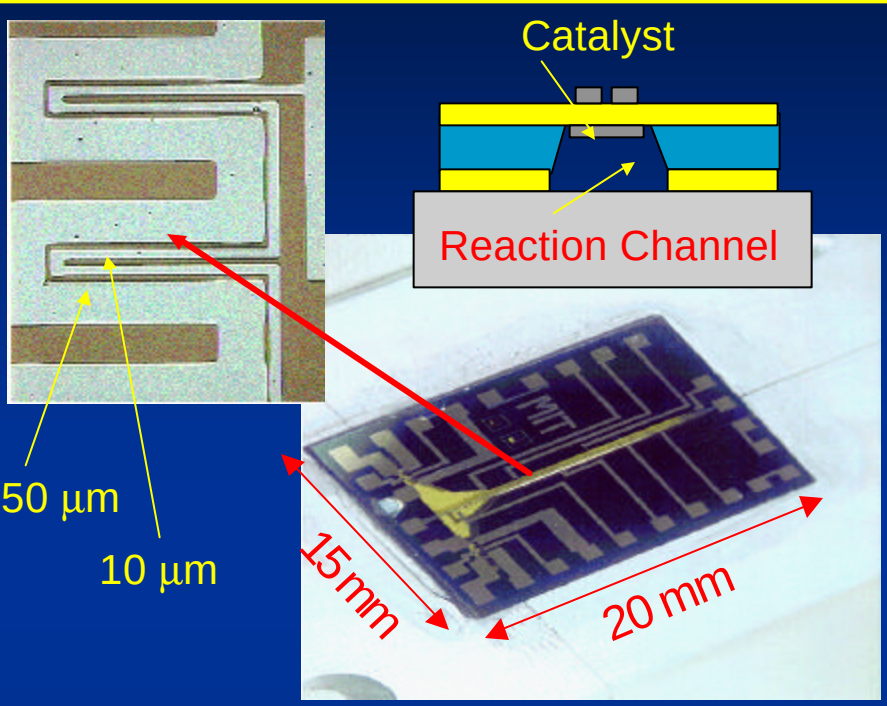
Molecular data individual transitions

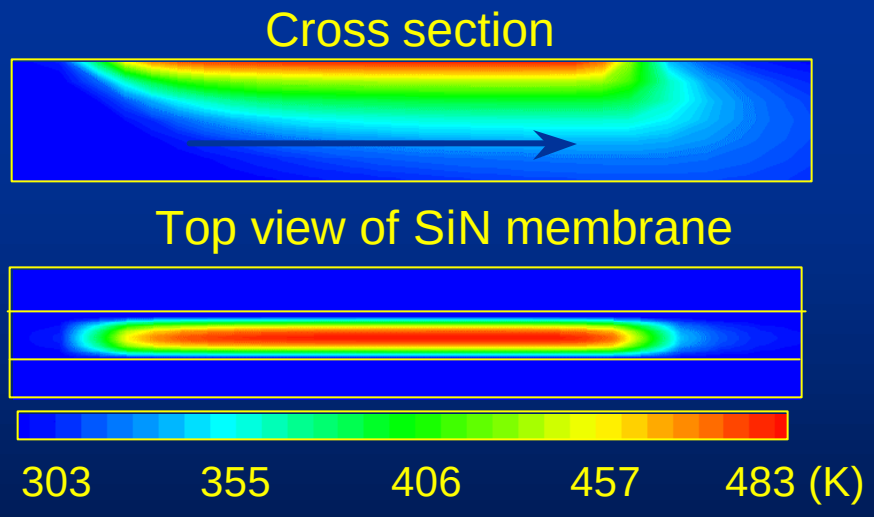
Average rates and fluxes

Kinetic rate expressions, boundary conditions

Membrane Based Gas Phase Microreactor

- **Integrated heater and sensors**
- **Catalyst placed on under side of membrane**
- **Reaction energy localized to membrane**
- **Reactions:**
  - **Partial oxidation, pyrolysis, and hydrogenation**



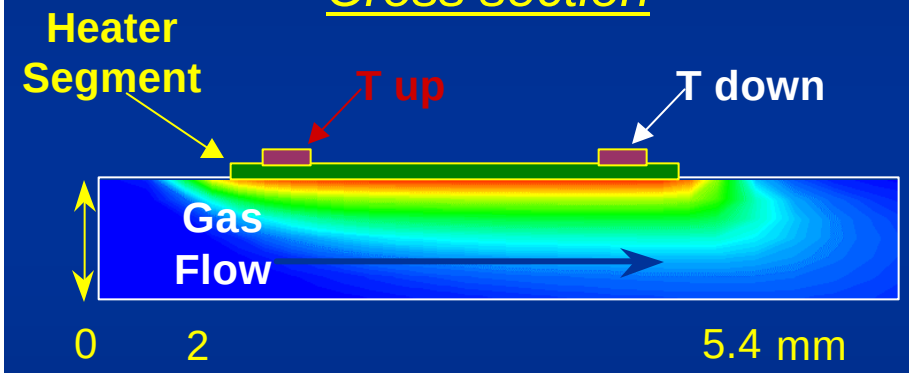


- **Issues:**
  - **Catalyst deposition**
  - **Control**
  - **Heat dissipation for highly exothermic reactions**
  - **Robustness**

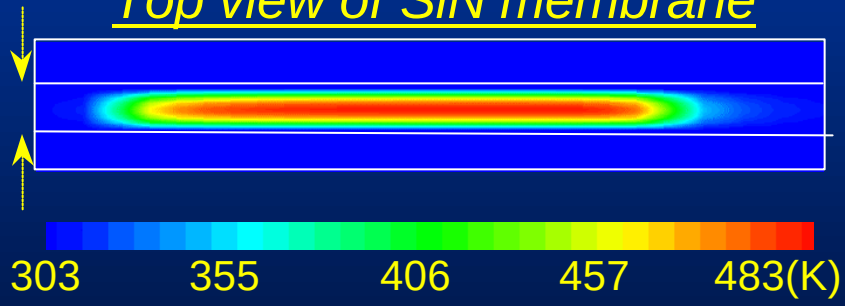
Thermal Modeling

- Prediction of Temperature vs. Power curves
- Membrane design (with Abacus)

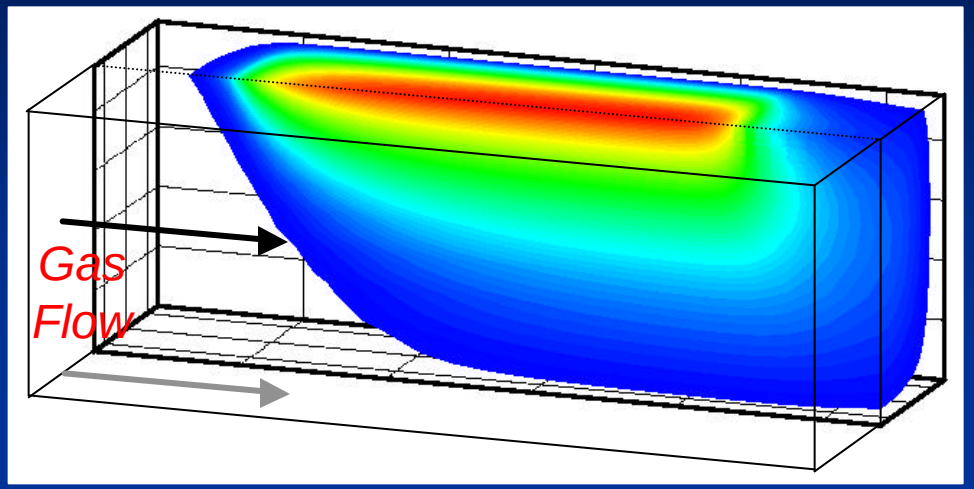
Cross section

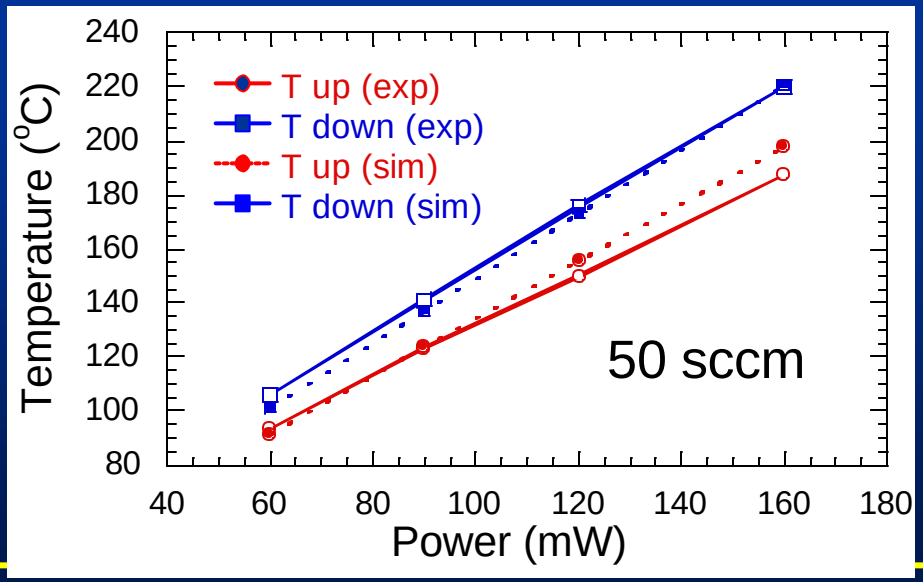


Top view of SiN membrane



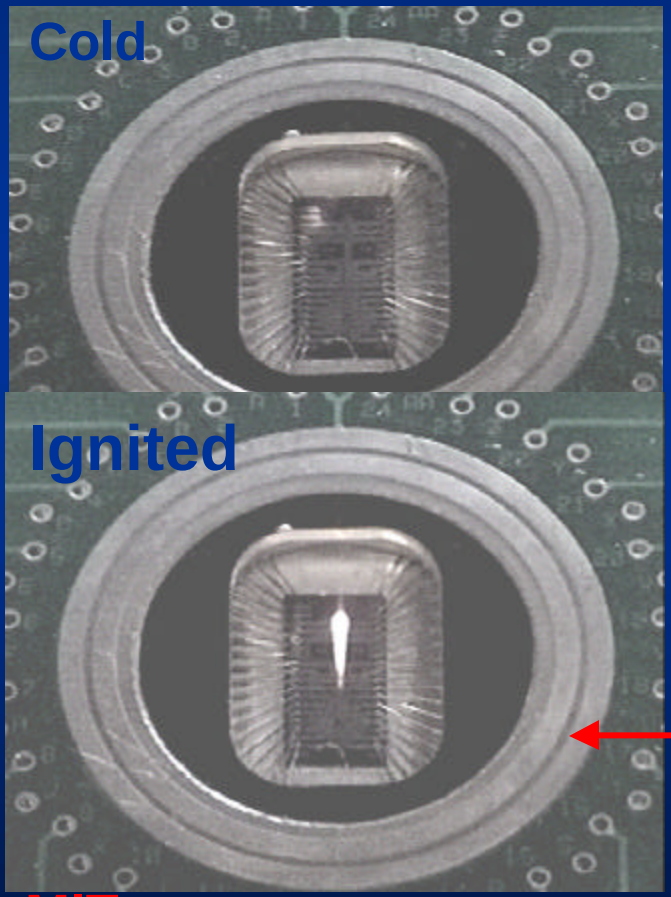
Computational Domain

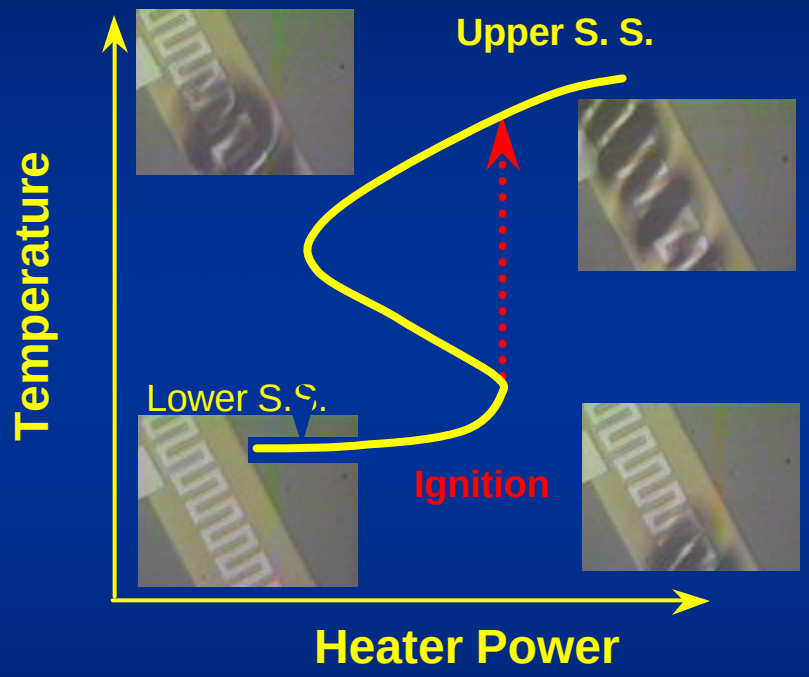




Ignition/extinction Behavior

- Highly exothermic, fast reactions with potential for thermal runaway. Used to produce important chemical intermediates, conversion and selectivity are critical issues



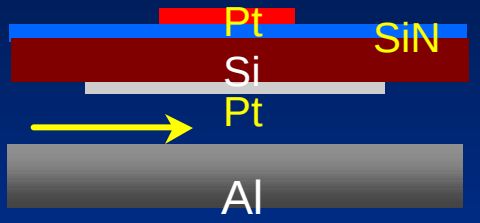


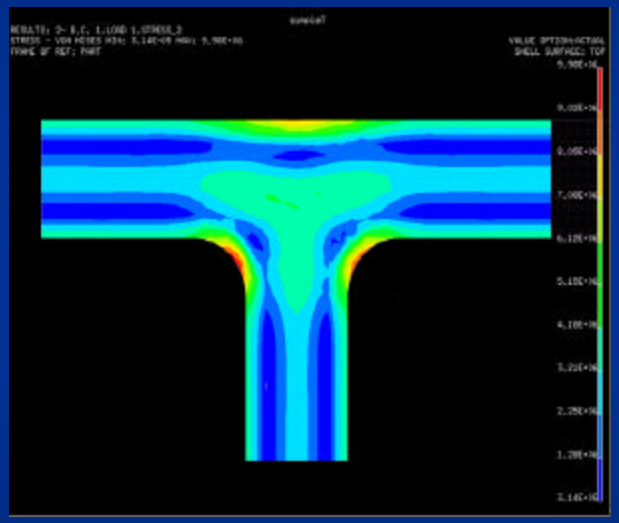
Butane dehydrogenation

- **Autothermal reactor operation.**
- **Operating temperatures 800-950 °C.**

Use of Simulations for New Reactor Designs

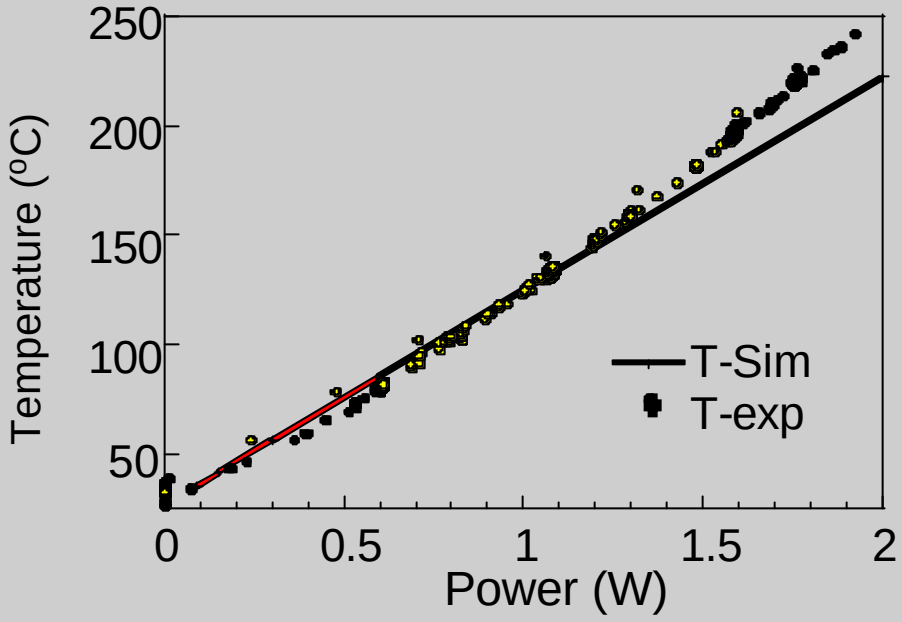
- **Goals:**
  - **Increase heat transfer from reaction zone to quench ignition/extinction behavior**
  - **Increase robustness of membrane**





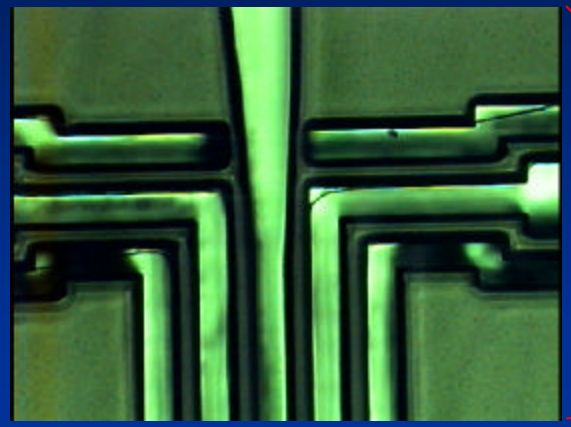
- **Membrane construction**
- **Membrane geometry**

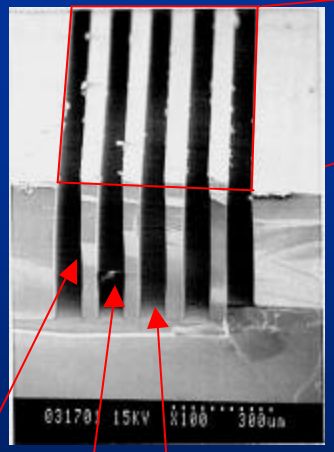
Use simulations to evaluate new membrane materials/thickness before making device

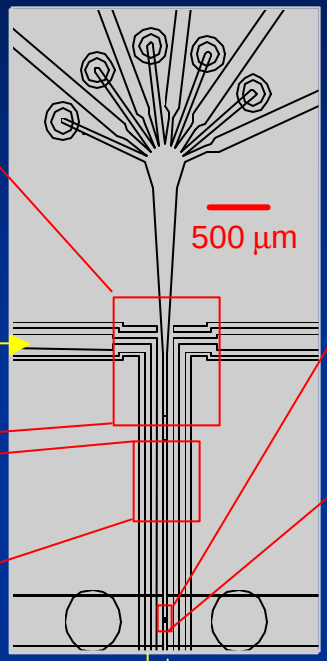


Microreactor for Liquid Phase Chemistry
Integrated Heat Exchangers and Temperature Sensors

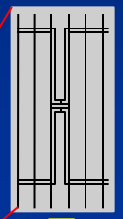
Heat Exchanger



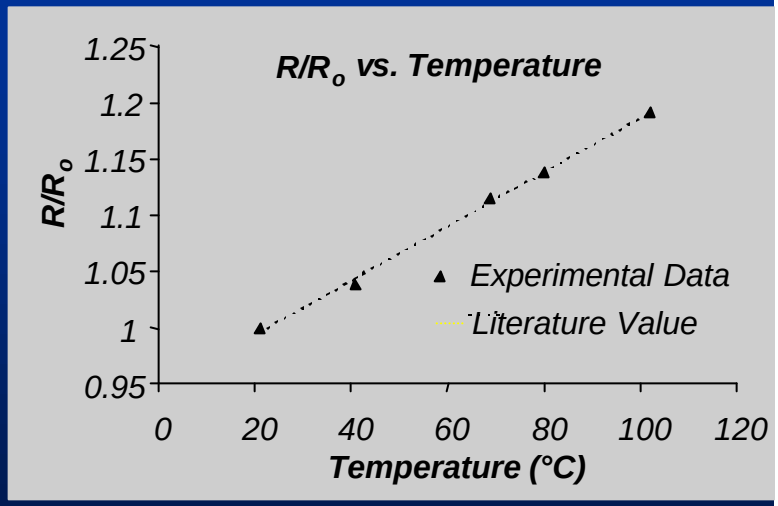




Thin-Film Temperature Sensor

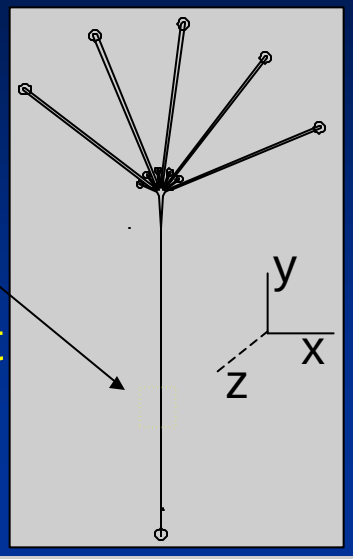


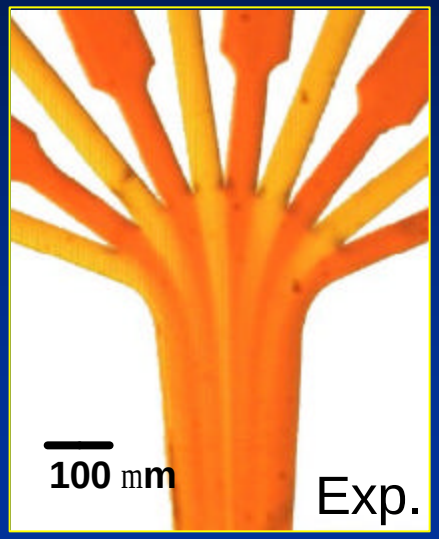
U = 1500 W/m^2°C

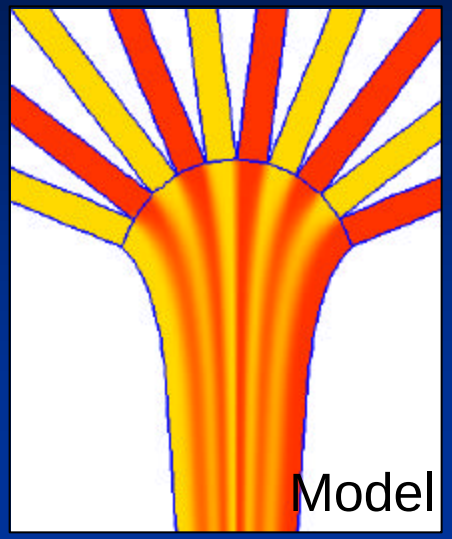


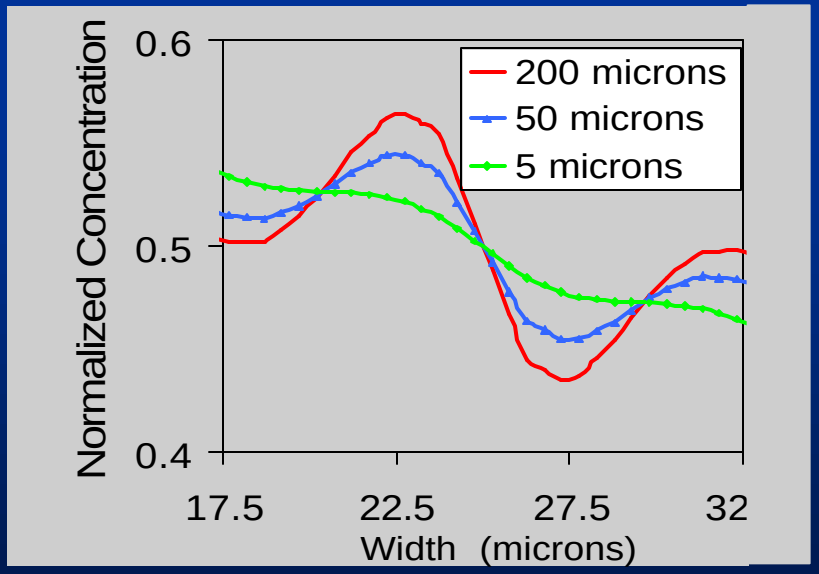
MIT

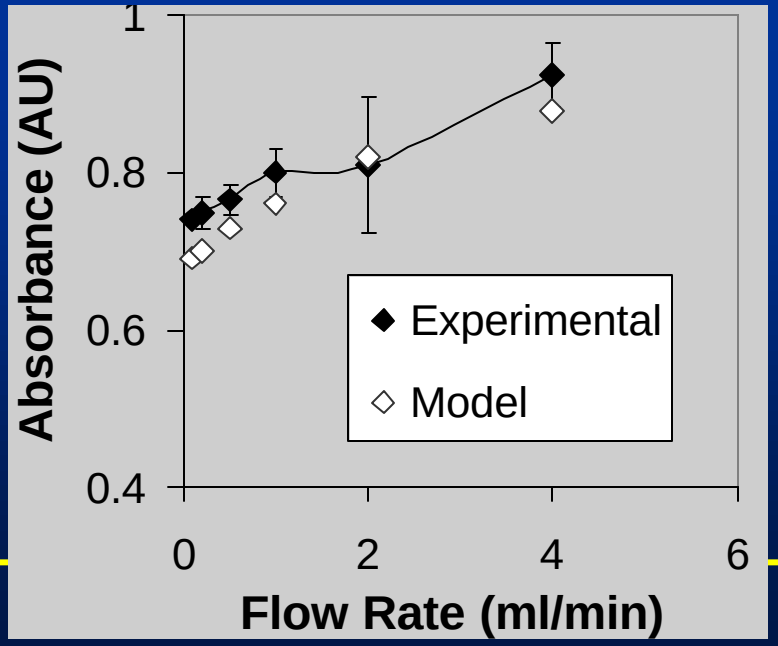
Simulation of Mixing Data: Acid-Base Reaction



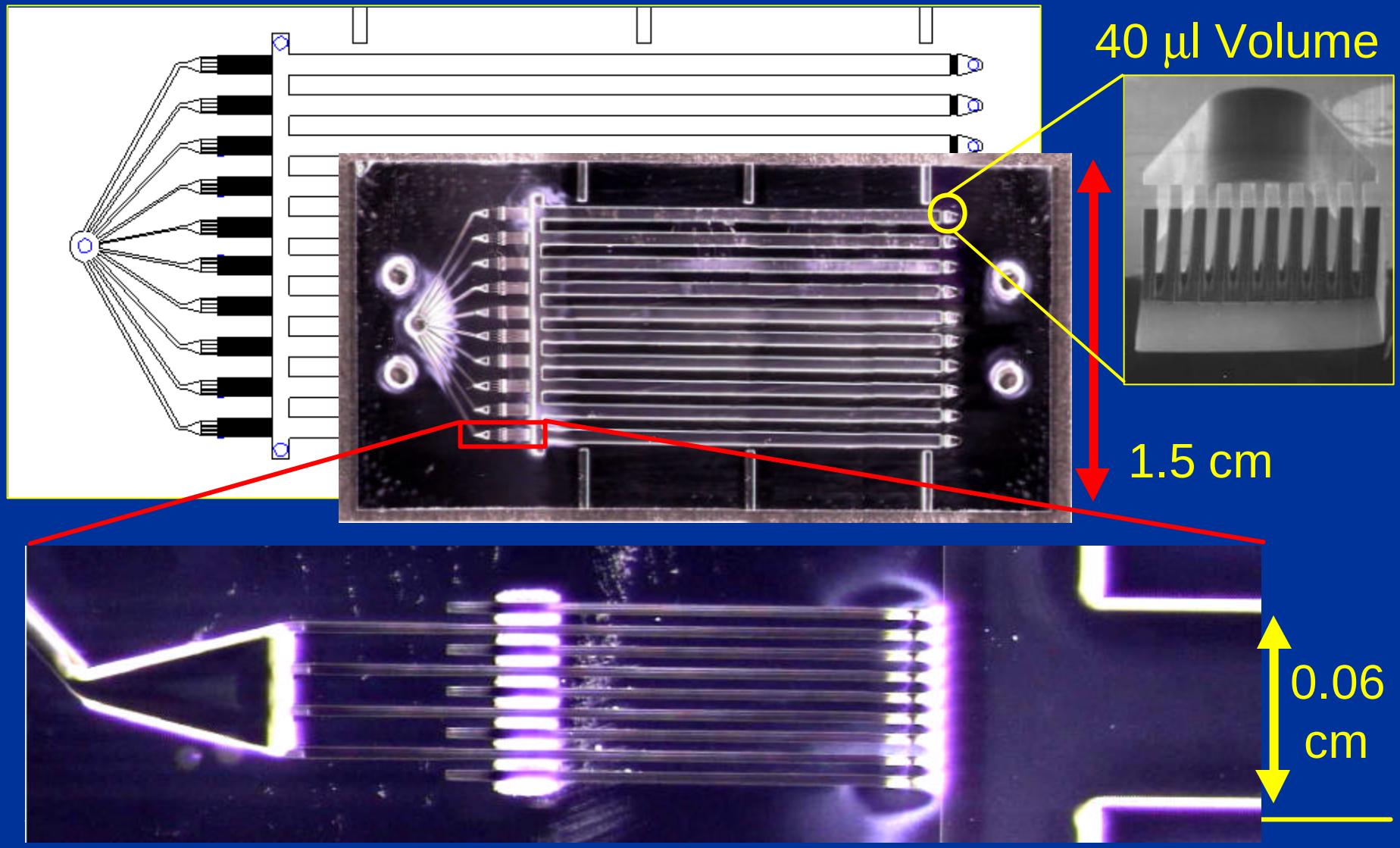




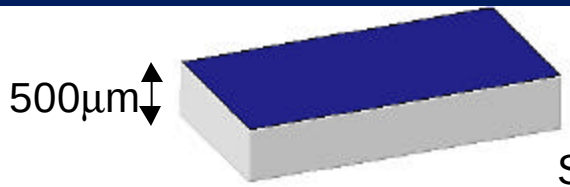




Multi-Channel Packed-Bed Reactor



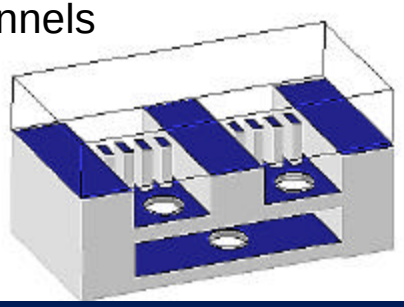
Fabrication Process



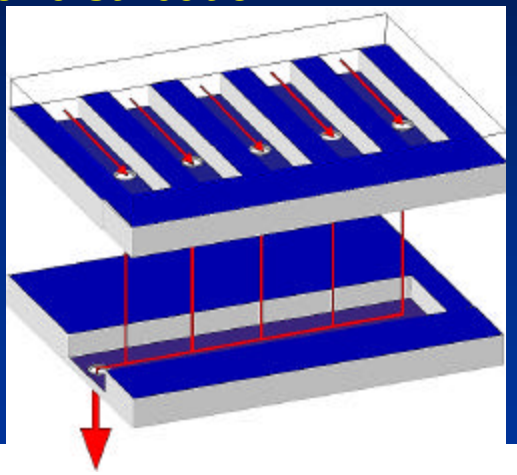
Silicon

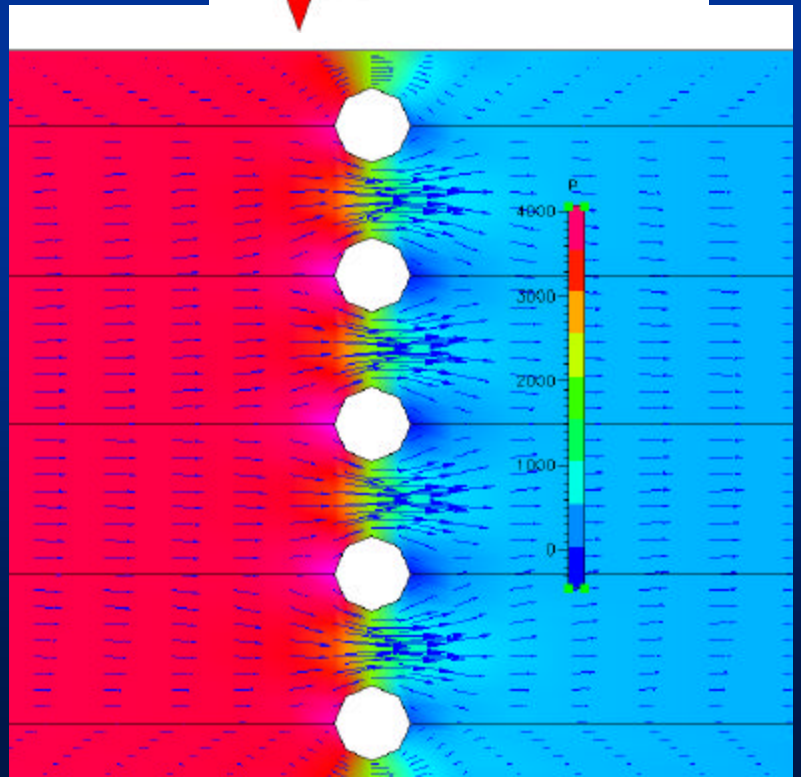
Pattern and deep reactive ion etch top-side to form channels; etch back-side to form access ports

Fusion bond two layers of silicon; Anodic bond Pyrex wafer to cap top channels



Channel array for distribution and collection

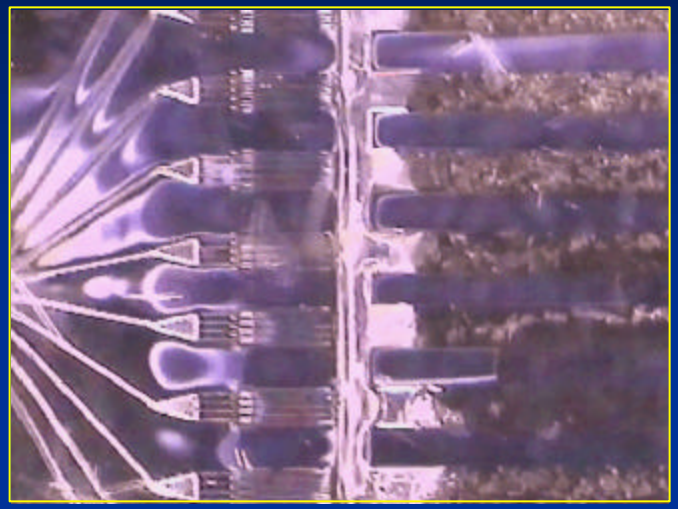


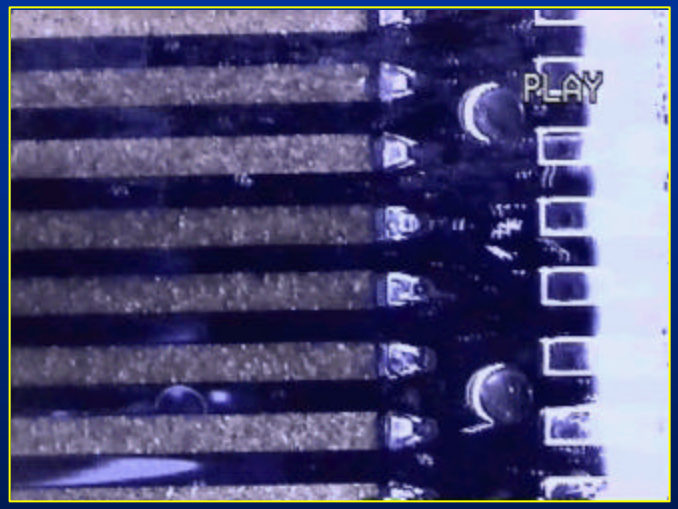


Simulation provides insight into fluid distribution and pressure drops

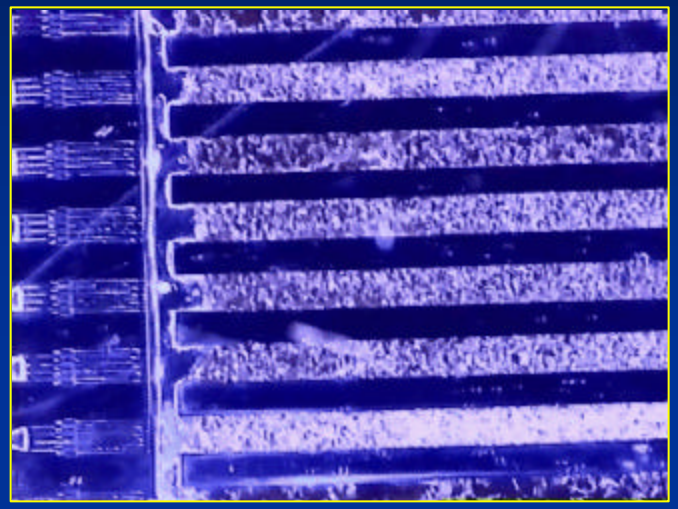
Distribution of Fluids to the Catalyst

Poor distribution and channeling





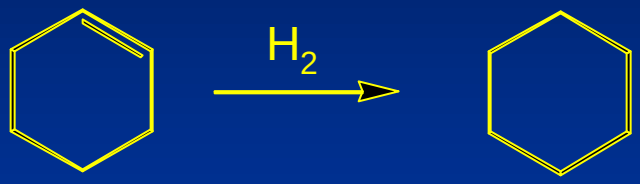
Even distribution



- **Detailed structure of multiphase flows can generally not be predicted with standard CFD tools**

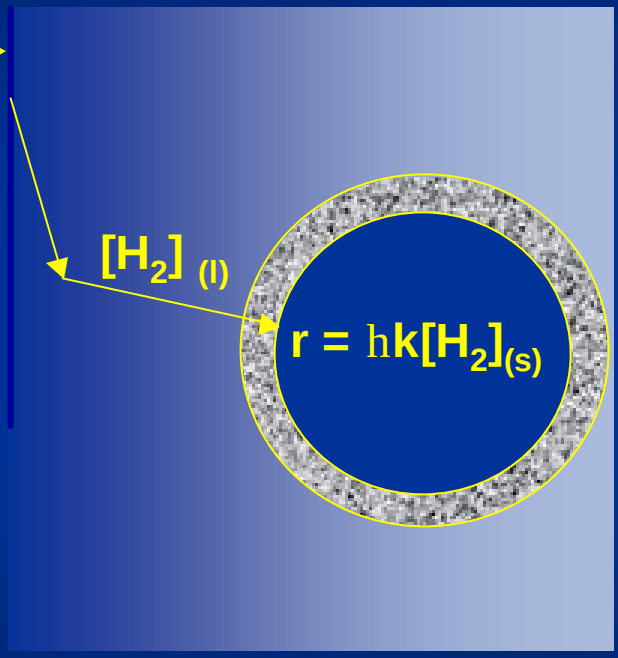
Model Reaction and Mass Transfer

Example: Cyclohexene hydrogenation



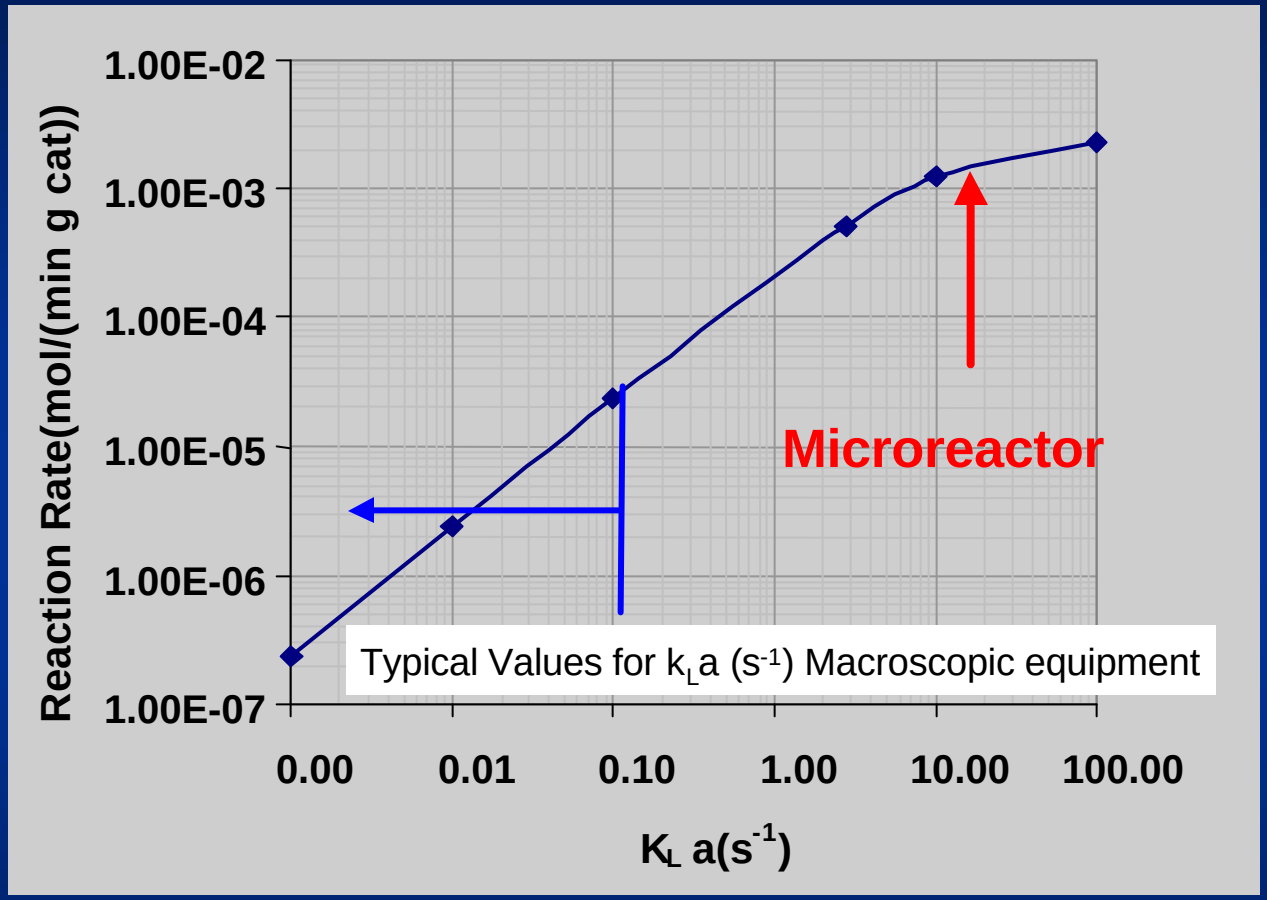
$$\text{Rate} = \frac{[H_2]_{(i)}}{\frac{1}{k_l a_i} + \frac{1}{k_s a_s} + \frac{1}{?k}}$$

gas-liquid liquid-solid intra particle



Strategy : Average over length scale - starting with smallest dimension
Equate fluxes across boundaries

Multiphase Microreactor Mass Transfer Characteristics

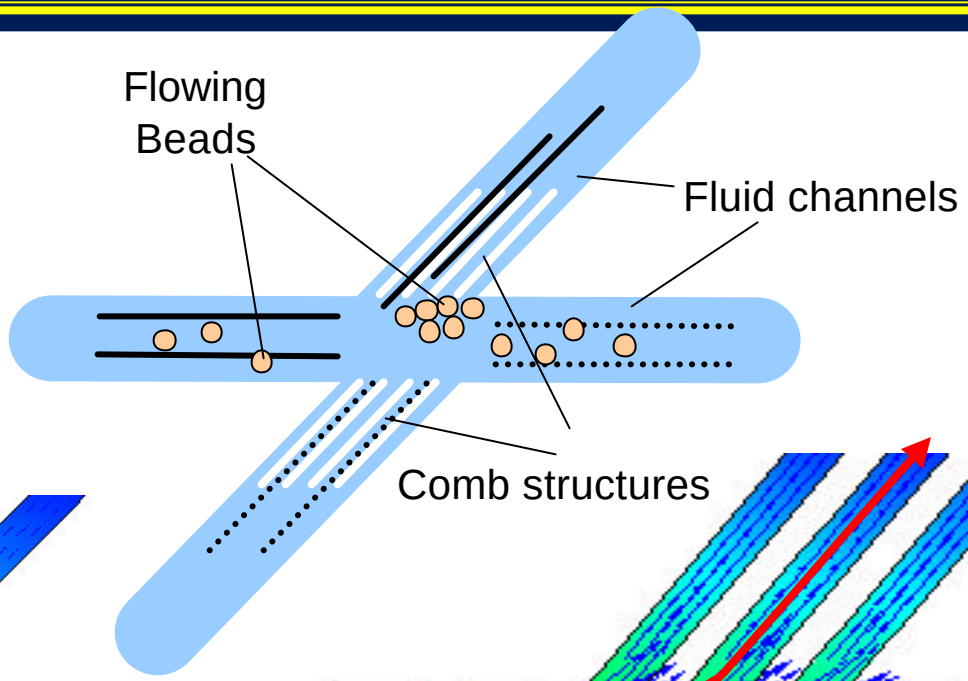


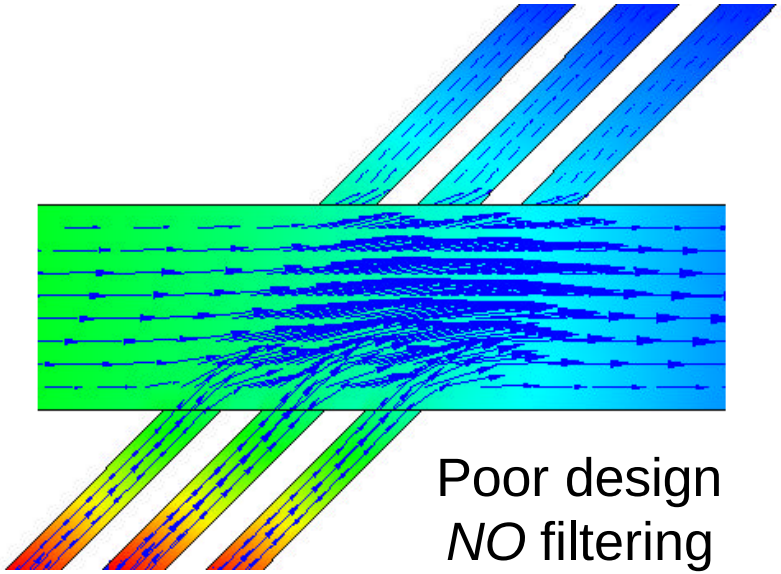
- **100 fold improved mass transfer in microfabricated device**

Using CFD to Design A Filter

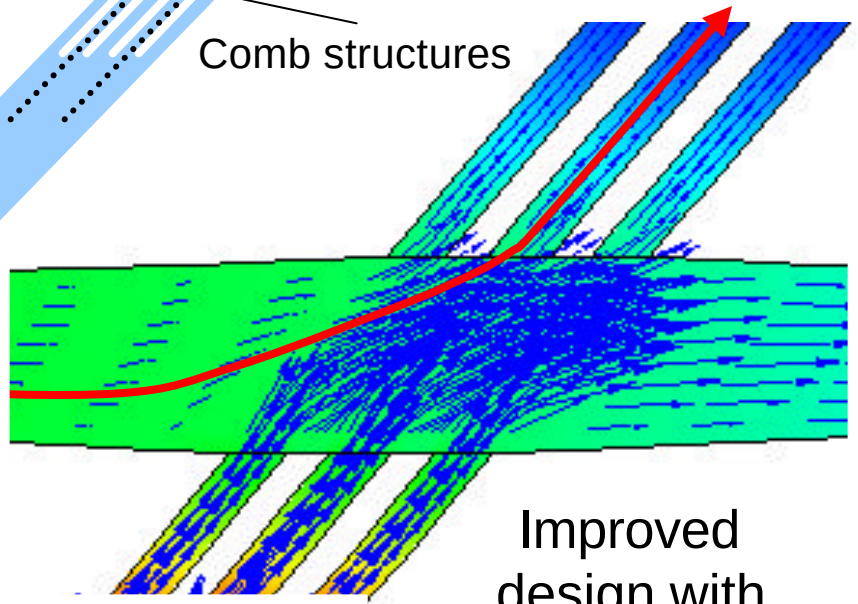
- Transport simulations help guide the design of microfluidic components

  - a microfilter for separation of beads from a process stream



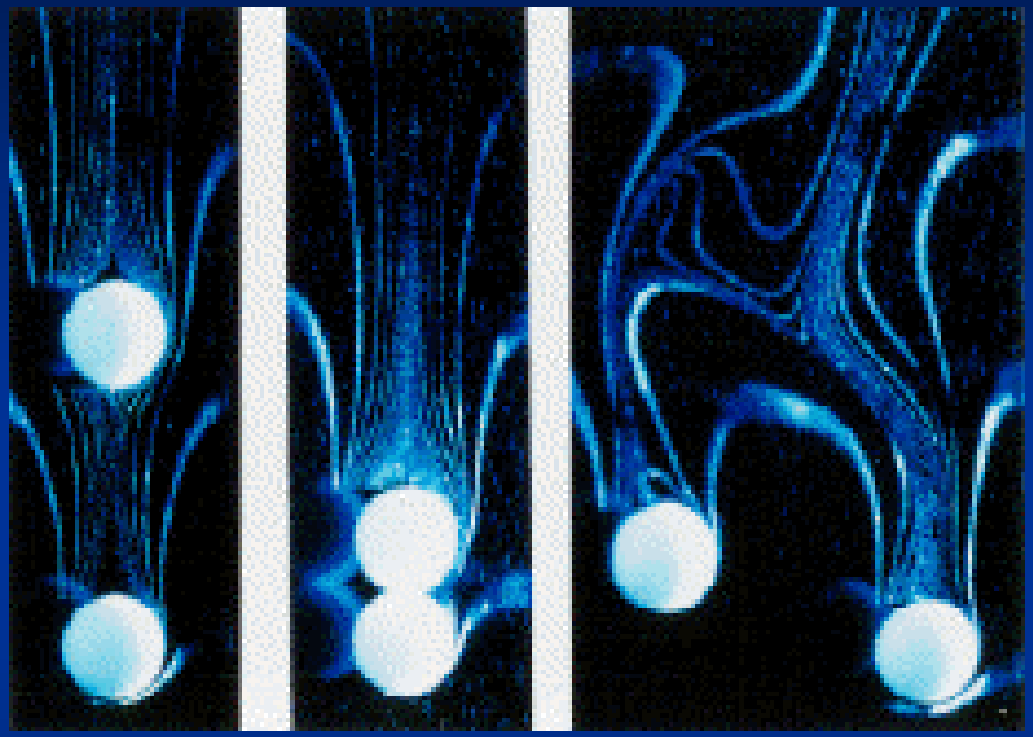


Poor design
NO filtering
only mixing



Improved
design with
particle filtering

Particle Laden Flows



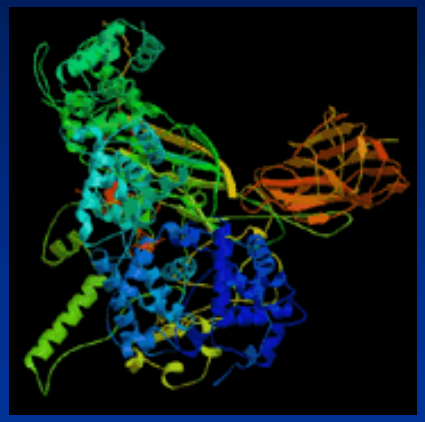
Particles drafting, kissing and tumbling in Newtonian liquid

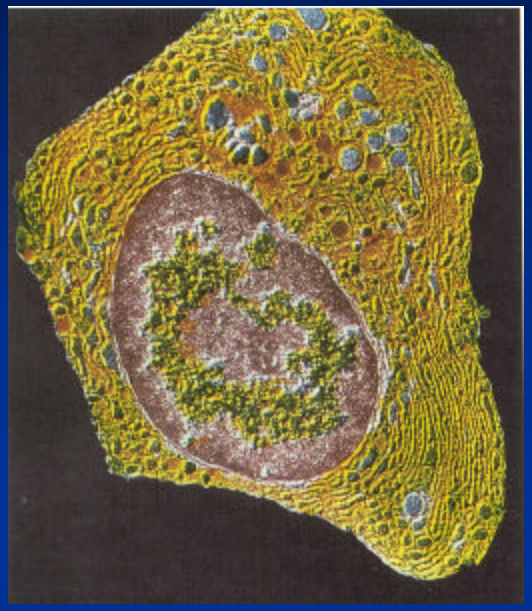
- **Particles draft, kiss, and chain in non-Newtonian fluids**
- ***Daniel D. Joseph**** **University of Minnesota**

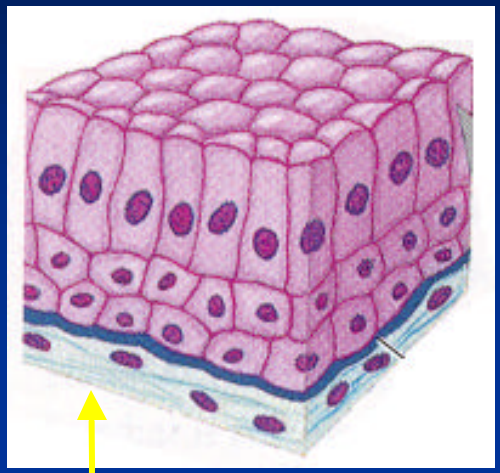
- **Simulations of particle (virus, cells, dirt…) laden flows require state-of-the-art computational approaches**

*www.aem.umn.edu/Solid-Liquid_Flows/

Simulation of Bio-MicroFluidic Devices Involves Multiple Scales







- **Multiscale modeling - "quantum-to-process" - is beginning to be realized for metal deposition in semiconductor manufacturing, simple gas-solid catalytic systems, but the problems are far more complex for biological systems**

Bio-MicroFluidic Device

Summary - Needs

- **Homogeneous flows in microfluidic systems can be simulated, but problems exist with:**
  - **multiphase systems, concentrated particle laden flows, free surface/surface tension flows, and surface chemistry**
- **Extension to bio-microfluidic systems will require:**
  - **Strategies for handling multiscale biological simulations**
  - **Methods for "lumping" fundamental biomolecular chemistry chemistry into kinetic rate expressions and boundary conditions suitable for transport simulations**
  - **Fundamental understanding of intra and extra cellular signaling, transport, reaction pathways, as well as interactions with other surfaces**
- **Microfluidic systems could be useful in developing systems for making experimental measurements of reaction and interaction parameters needed for design of systems**

Acknowledgements

- **Supported by:**
  - **DARPA MicroFluidics Program (Dr. Abe Lee)**

- **Coworkers**
  - **Martin A. Schmidt**
    - **Professor Electrical Engineering and Computer Science - Director of the Microsystems Technology Laboratory**
  - **Sameer Ajemera, Aleks Franz , Samara L. Firebaugh, Tamara Floyd, Rebecca Jackman, Matthew Losey, David Quiram**

Tools and Methods for the Design of Complex Bioanalytical Systems

John West

Microcosm Technologies

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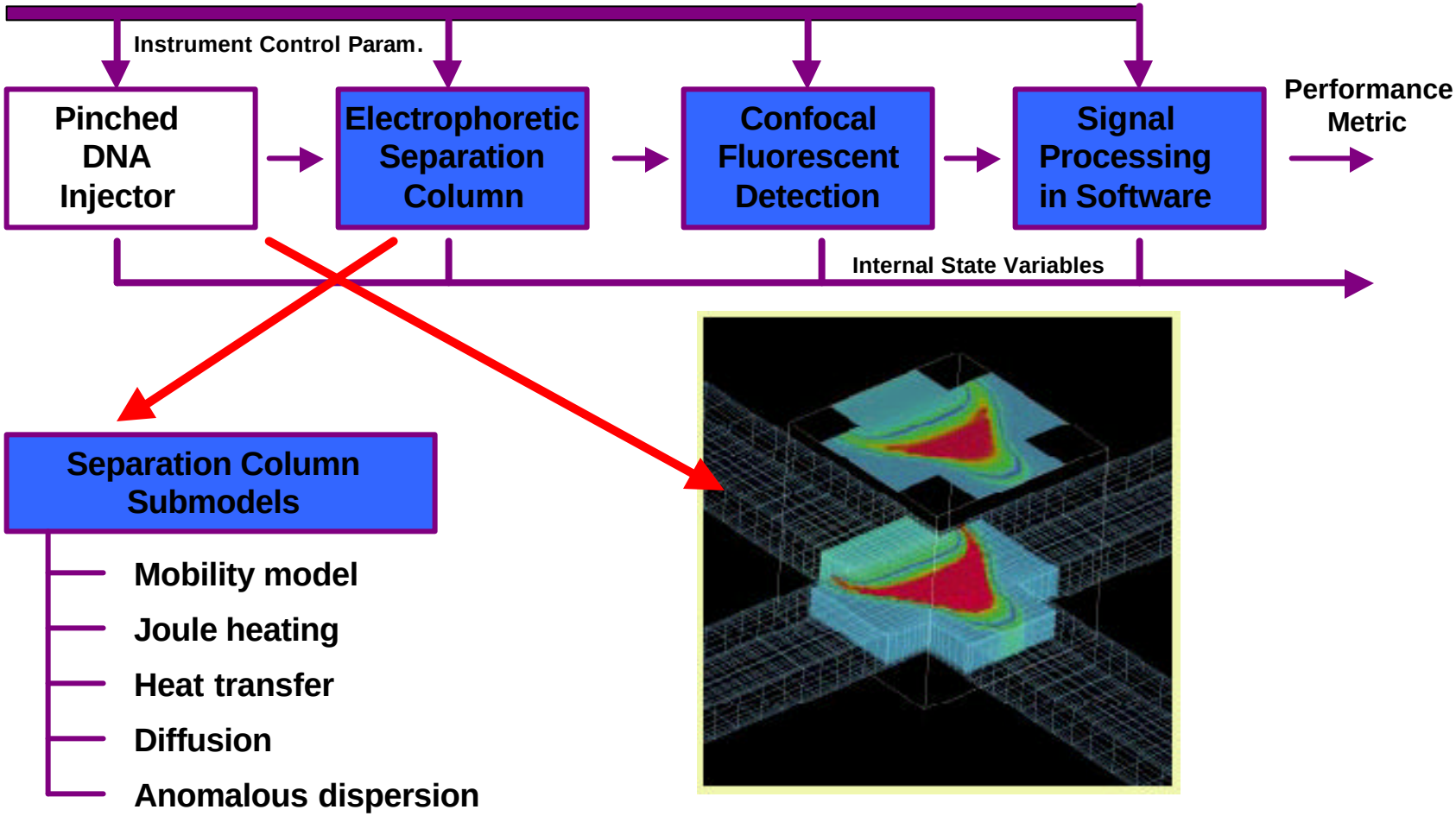
CAD for Biochemical Microfluidics

Example system model : Microfabricated SNP-Scoring DNA Sequence Reader



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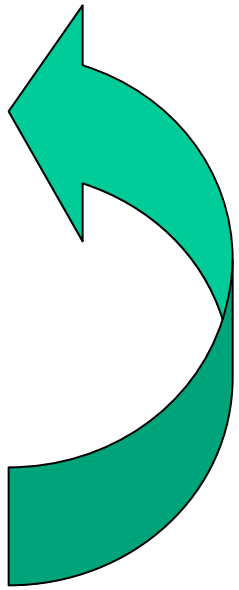
Microcosm provides practical coupling between system and component level modeling

System level model
Based on coupled non-linear multiphysics differential equations



Automatic extraction of reduced-order model from FEM with non-linearities and coupling.

Component level model
Based on finite element analysis (or related techniques)

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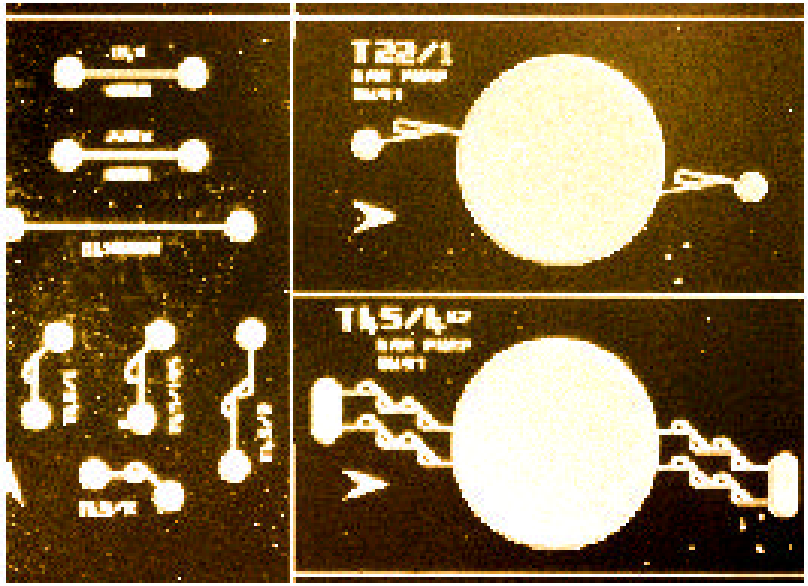
Example: System and component modeling

Silicon micro-pump with no-moving-parts valves

- University of Washington design
- Silicon micromachined diaphragm pump, piezoelectrically driven
- No-moving-parts design supports transport of particles, cells
- Valves - asymmetrical flow resistors (with diodicity)



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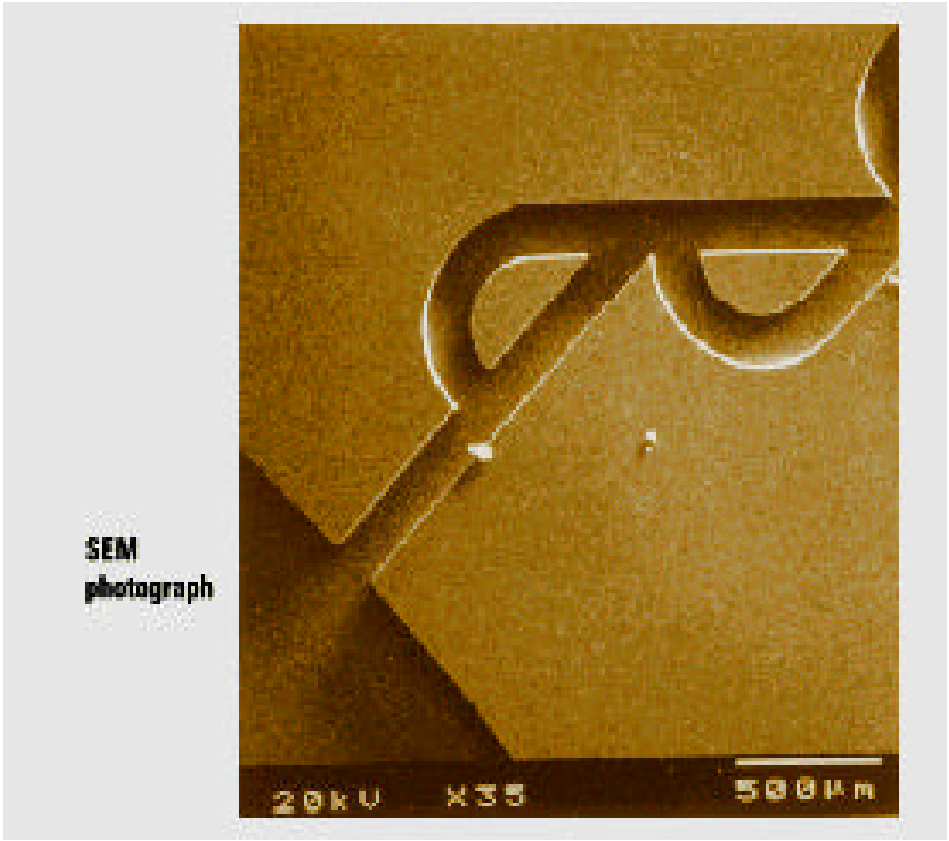
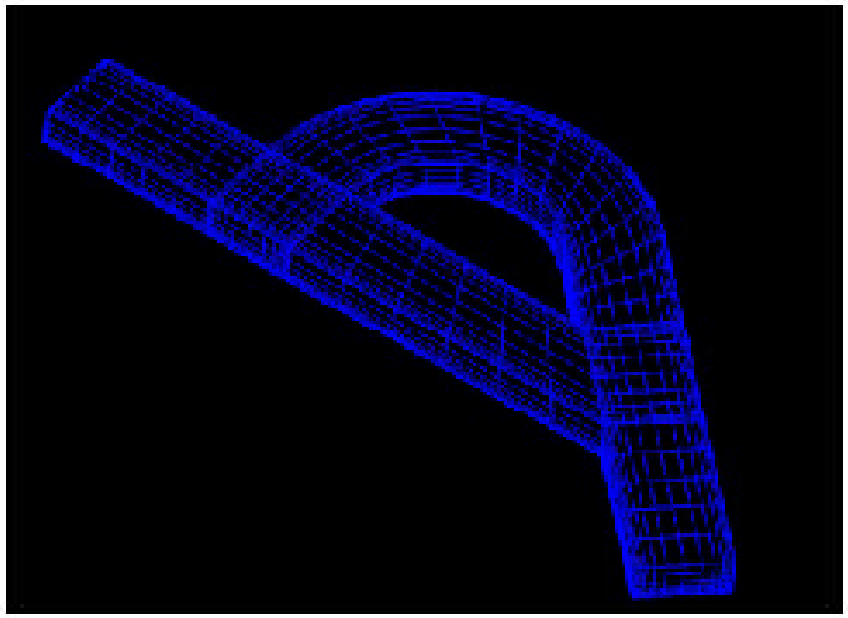
System modeling example continued: No-moving-parts valve and corresponding meshed solid model





Meshed solid model

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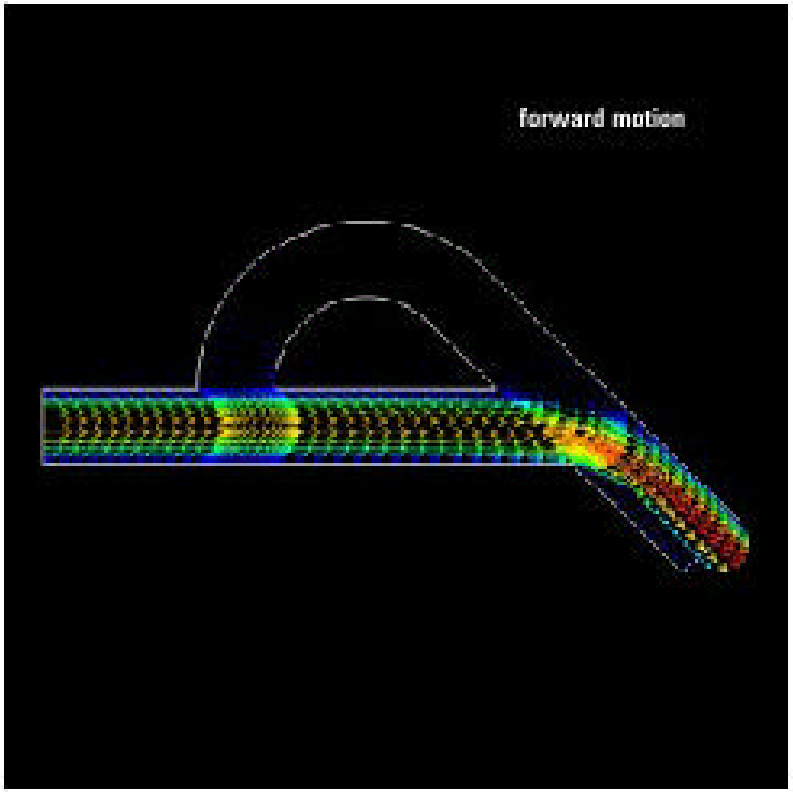
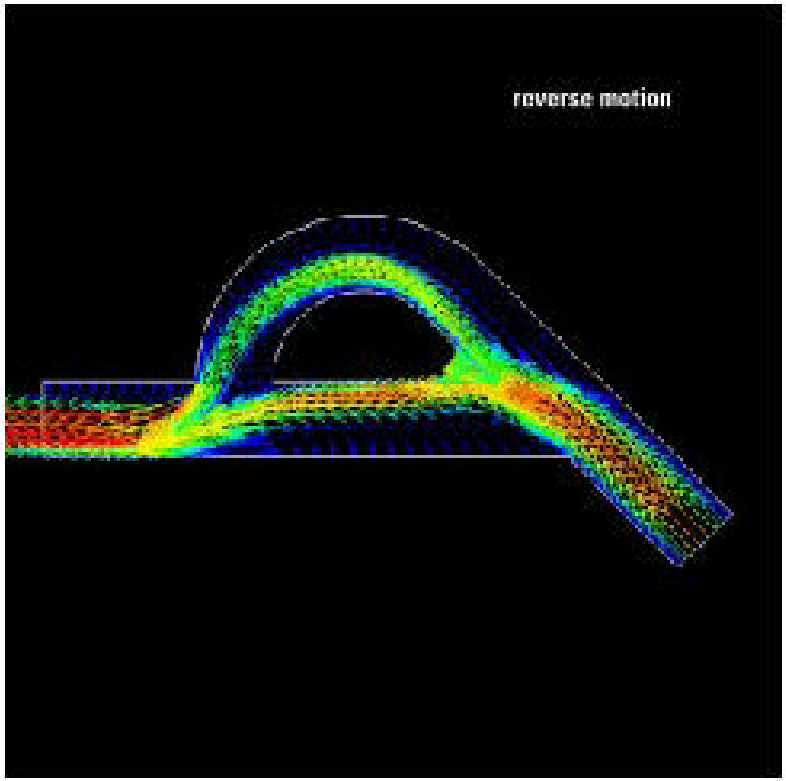
System modeling example, continued

Simulation shows asymmetrical pressure-driven flow





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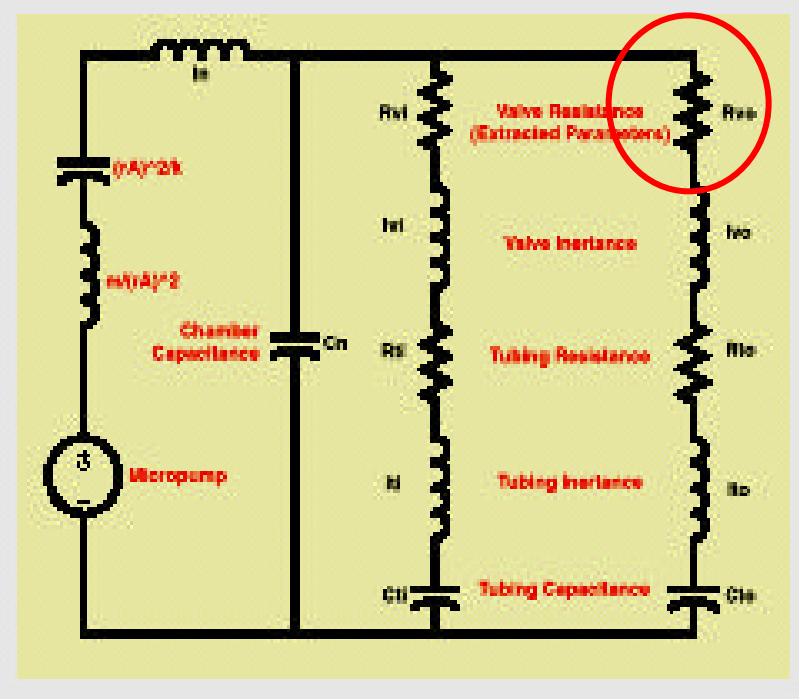
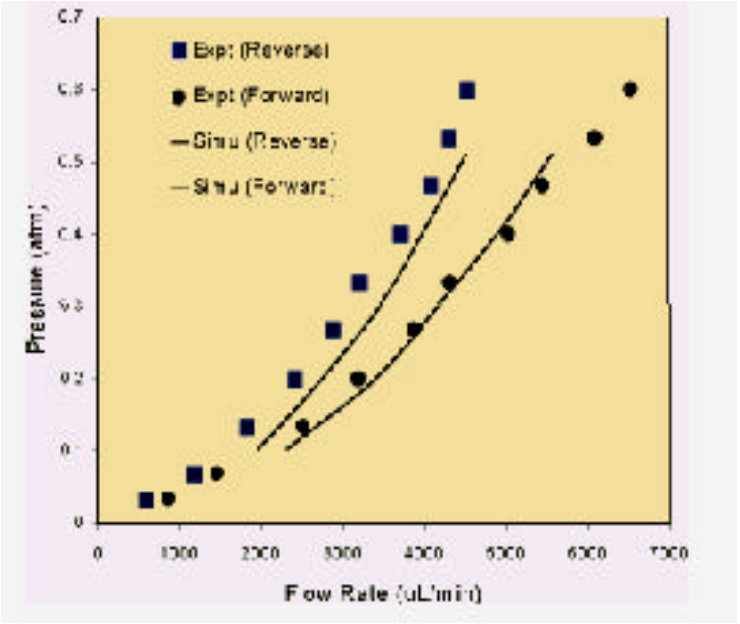
System modeling example, continued

Pump system model : Contains reduced-order-model of component (valve) extracted from FEM

Captures diodicity, non-linearity & full 3D geometry





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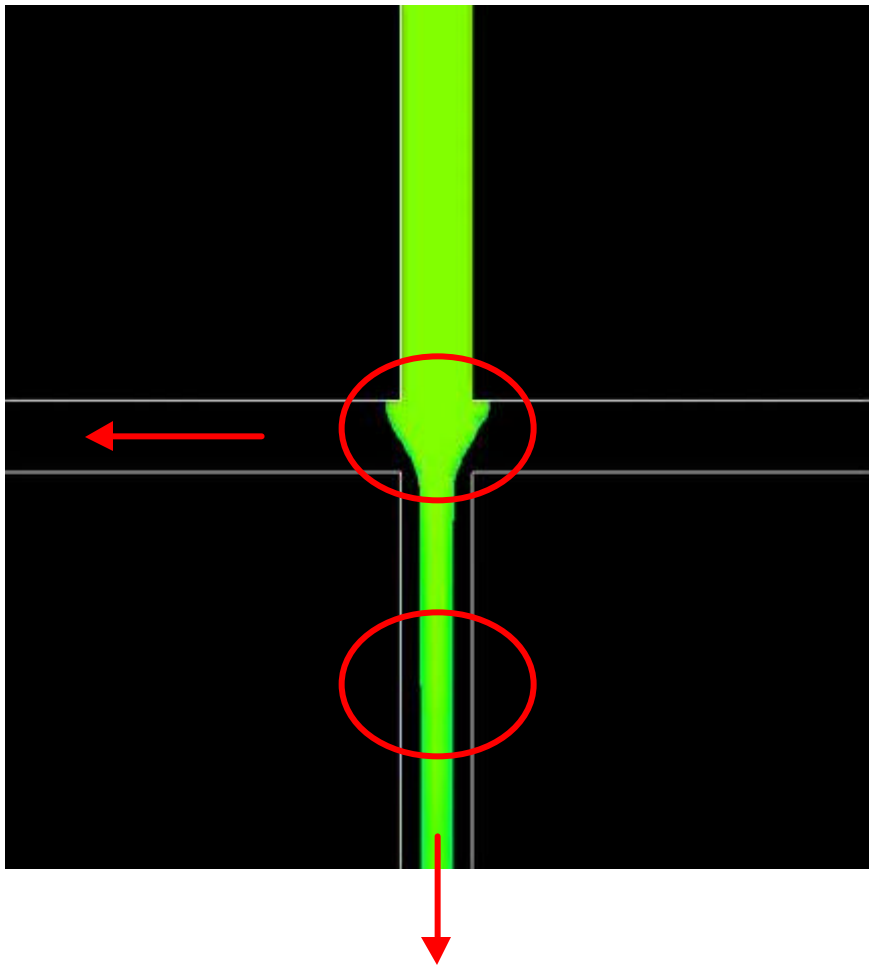
Application Example: Pinched injection in an electrophoretic capillary column



This is what one normally injects - a wide trapezoid...

...But this is what you would like to inject - a piece of the narrow stream headed for the waste well

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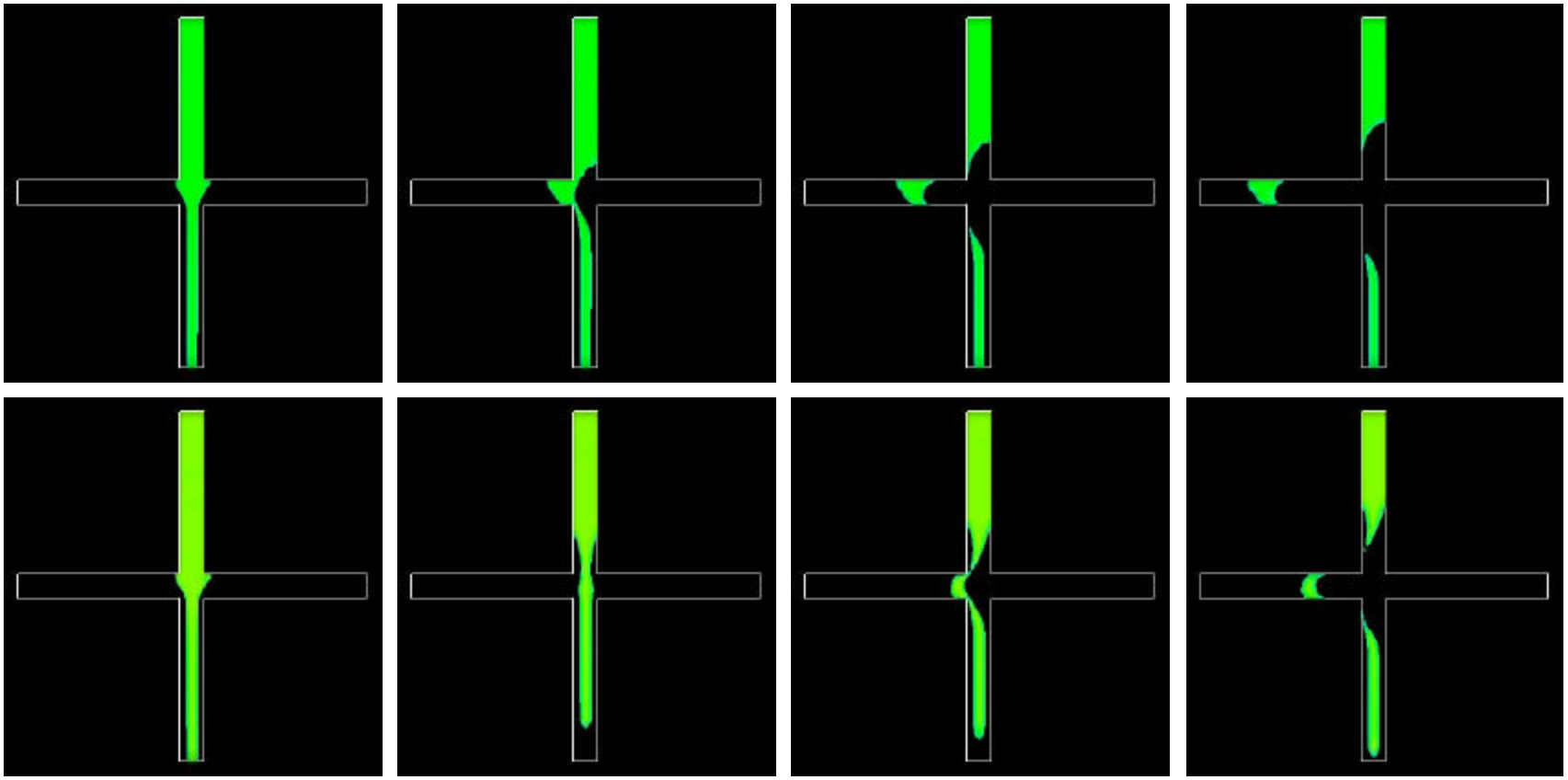
So Microcosm simulated reversal, just before injection

Top row: Normal injection

Bottom row : Reversal added before injection



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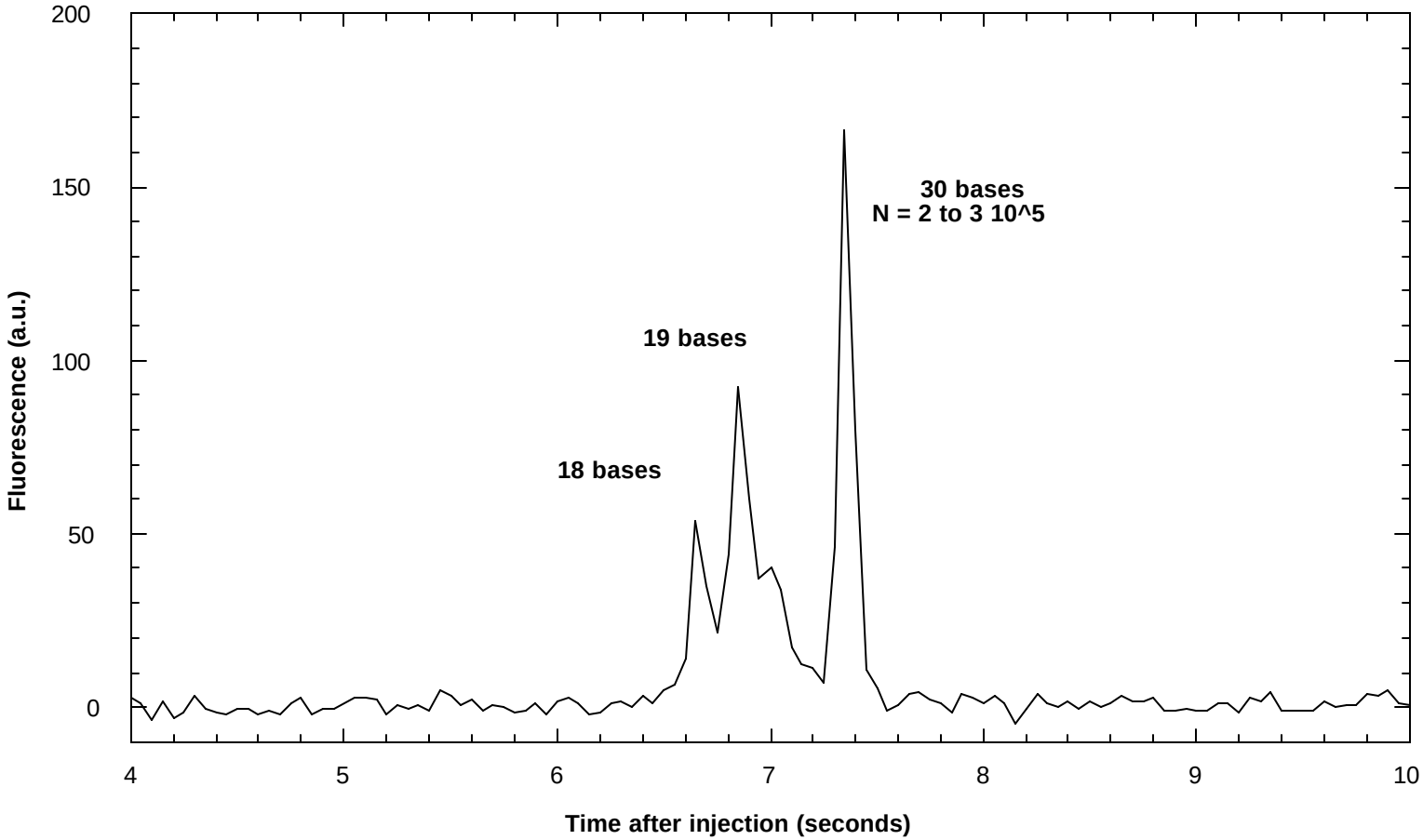
1st result : “The world’s fastest DNA separations”

(Dr. Luc Bousse, Caliper Technologies, 9/20/99 SPIE meeting, Santa Clara CA)



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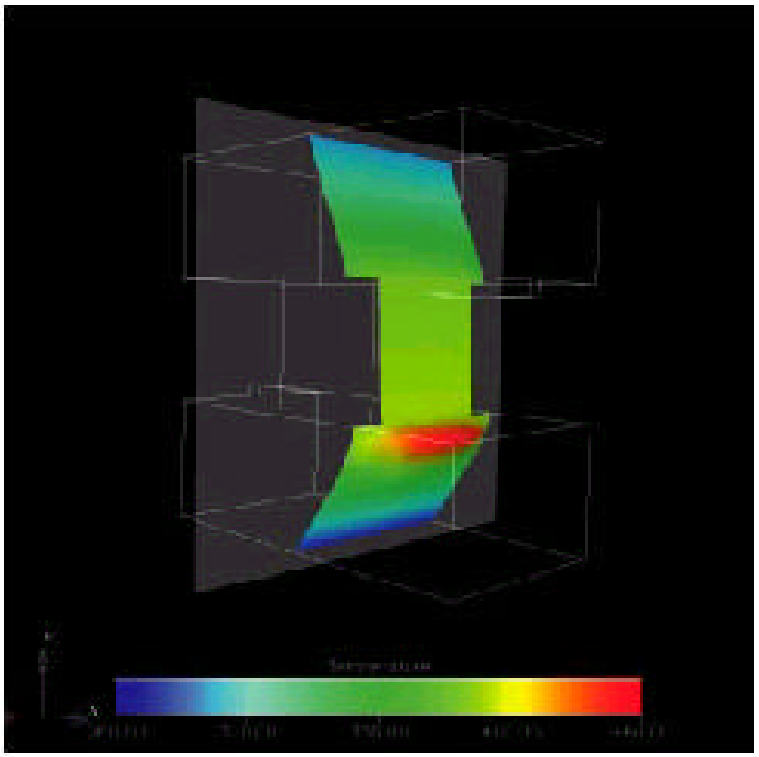
2nd possible result : Returning microfluidics to silicon ?

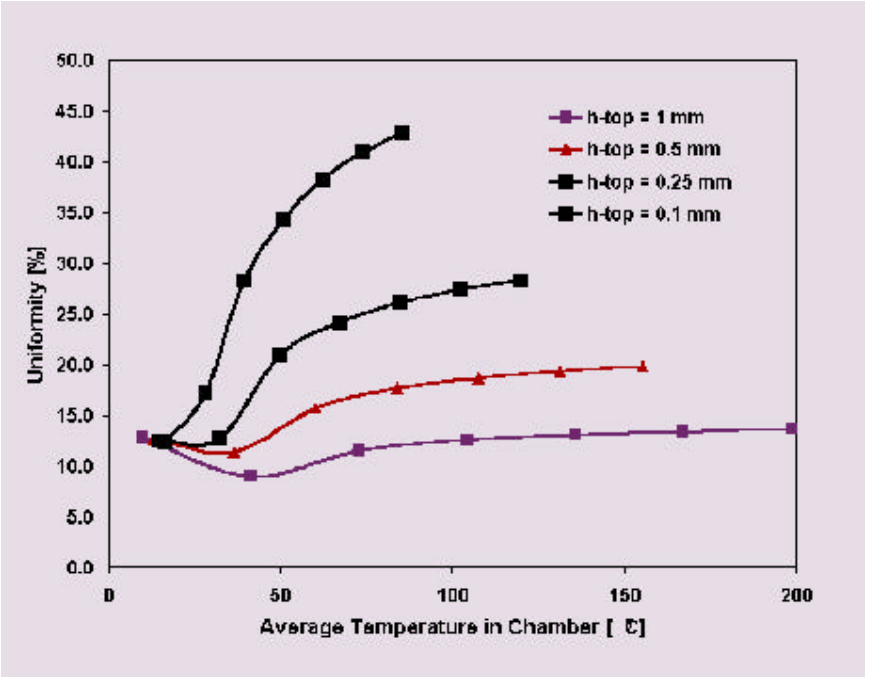
- Sharper injection allows separation in shorter channels
  - (this data is from a 5mm channel)
- Shorter channels reduce the total voltage required for separations
  - (this data was from 150 V total)
- Bringing voltages down may make electrophoretic separations possible in silicon
  - (current standard designs use over 1,000 volts, difficult in wet silicon)

Application Example:

Thermal Modeling in a Microreactor

Simulation can optimize reactor yield, purity





FlumeCAD couples fluid flow, heat transfer & chemistry

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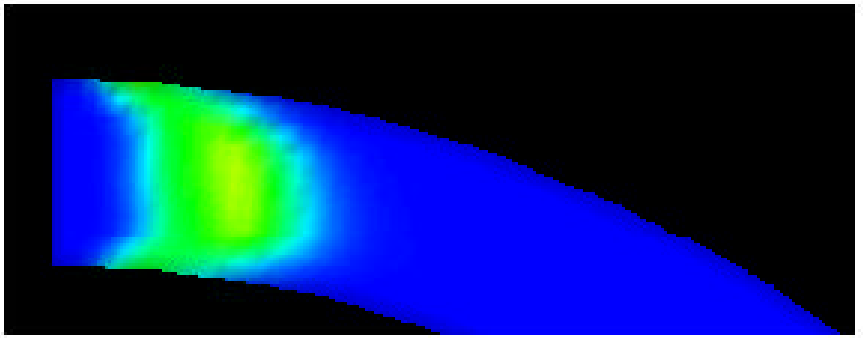
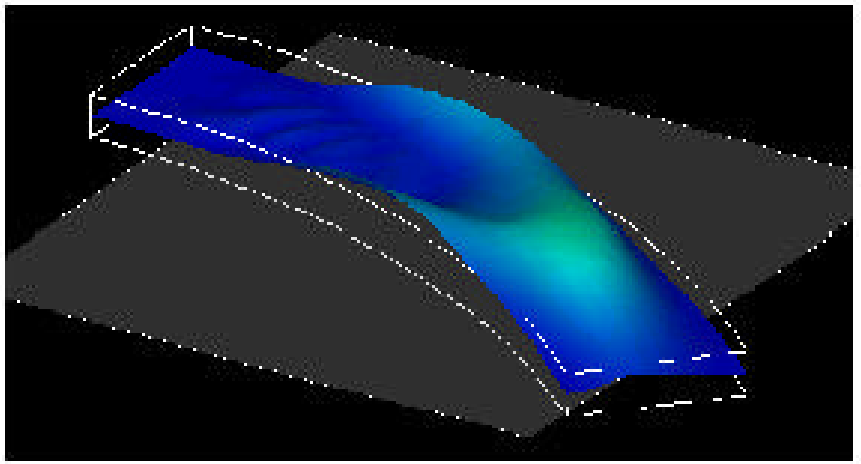
Application Example:

Analysis of Pressure Driven Flow

Comparison of Caged Fluorescence Imaging with Simulation





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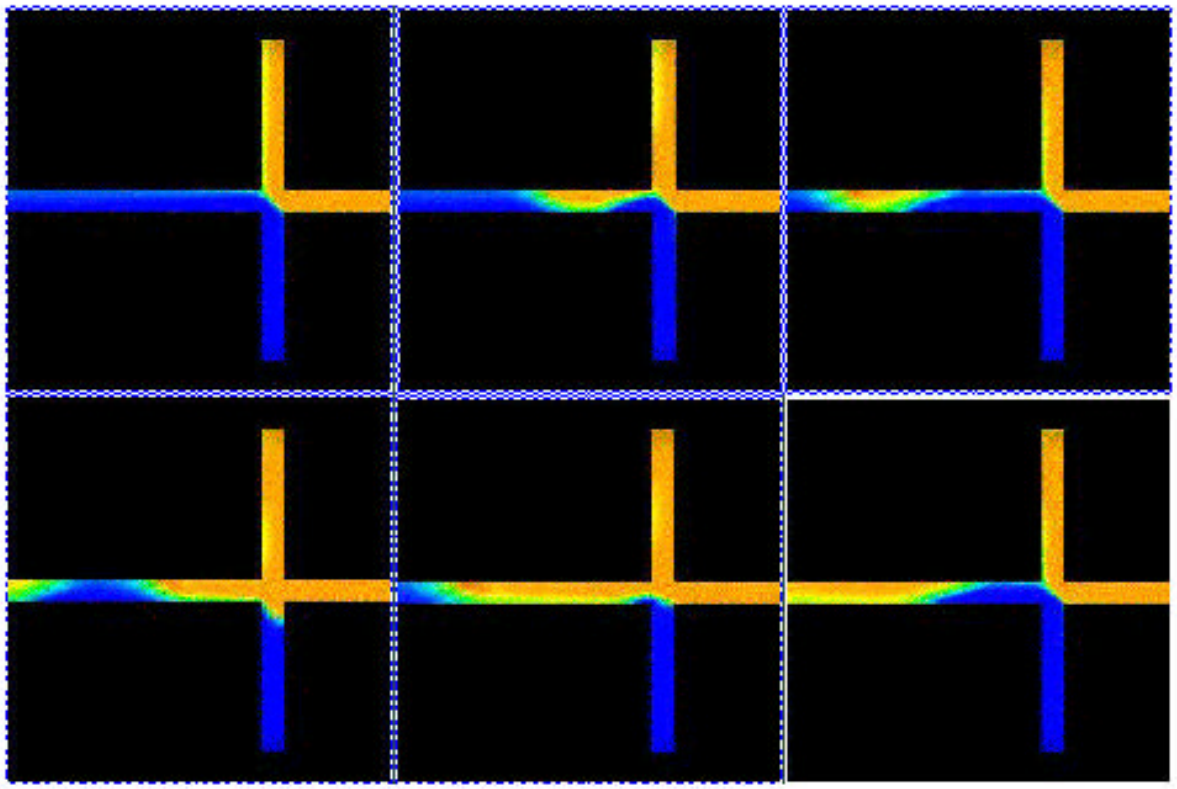
Application Example:

Electro-osmotic dispensing

Analysis can test robustness to zeta potential and geometry variations



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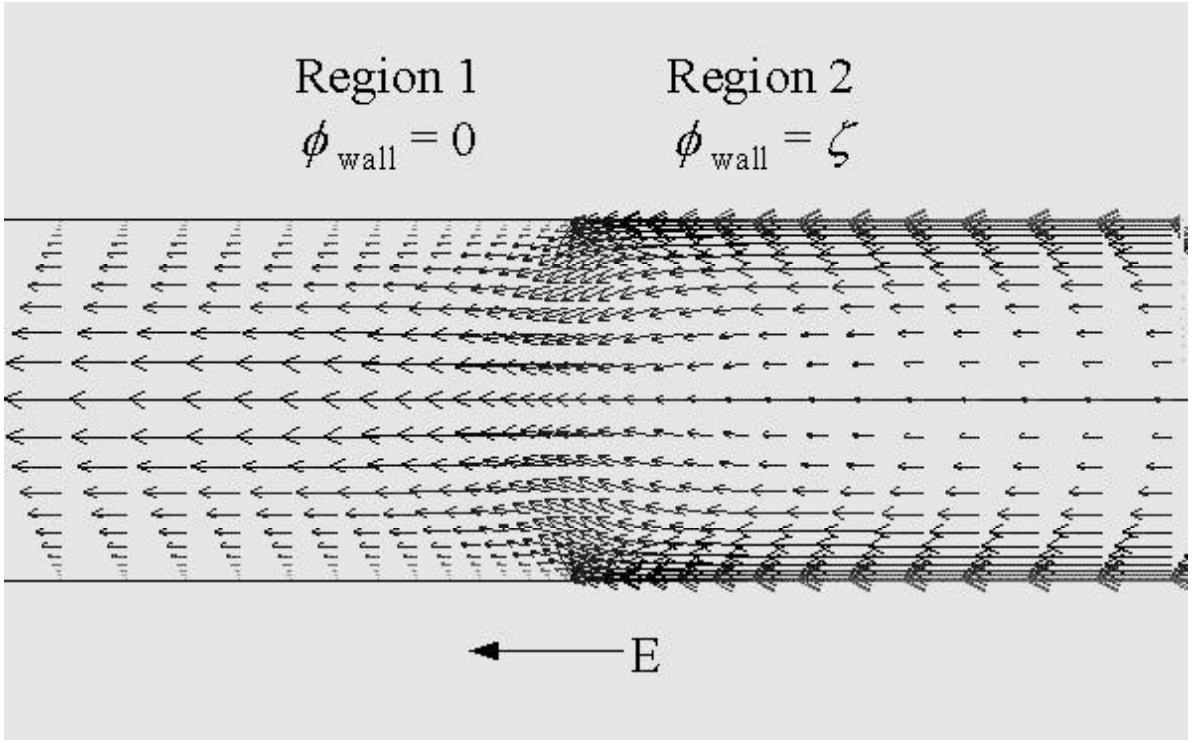
Application Example:

Manipulation of zeta potential along a capillary

Control of zeta potential is crucial to electro-osmotic designs
(and most electrophoretic ones too)



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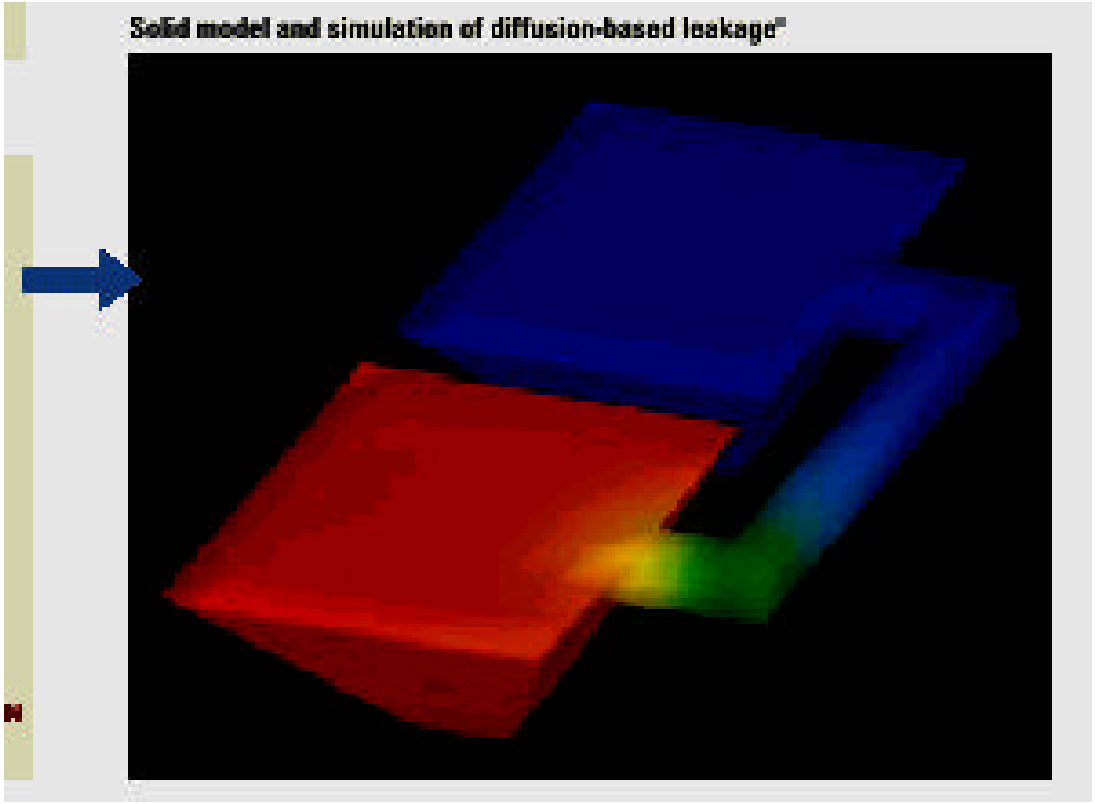
Application Example:

Diffusion in PCR on a chip

Analysis can optimize cycle times and control micro-well cross-contamination



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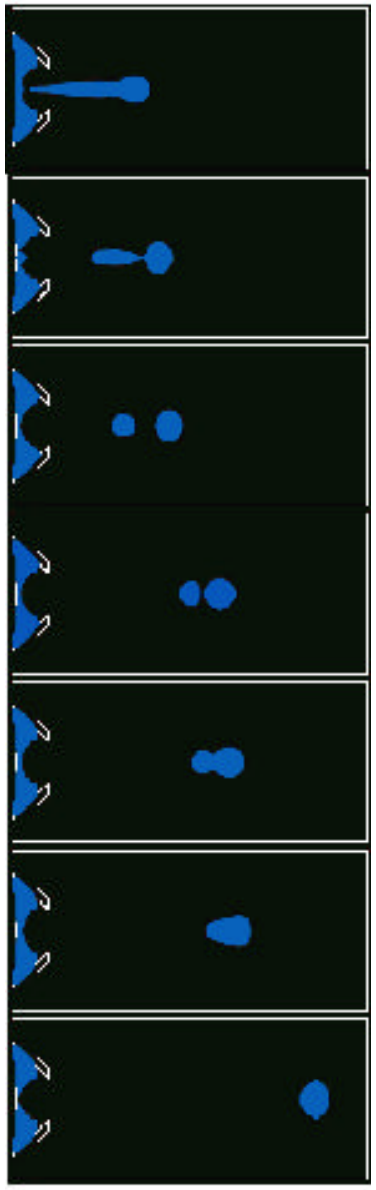
New : DropSim

Droplet formation in microfluidic systems

- Control droplet formation, generation of satelites, etc
- Volume-of-fluids solver coupled with Microcosm's:
  - Simulation management
  - System modeling
  - Visualization
- User interface optimized for droplet 2-phase flow problems
- A new module, 1st available with FlumeCAD v 4.6
- Drops can be ink, or DNA, or...



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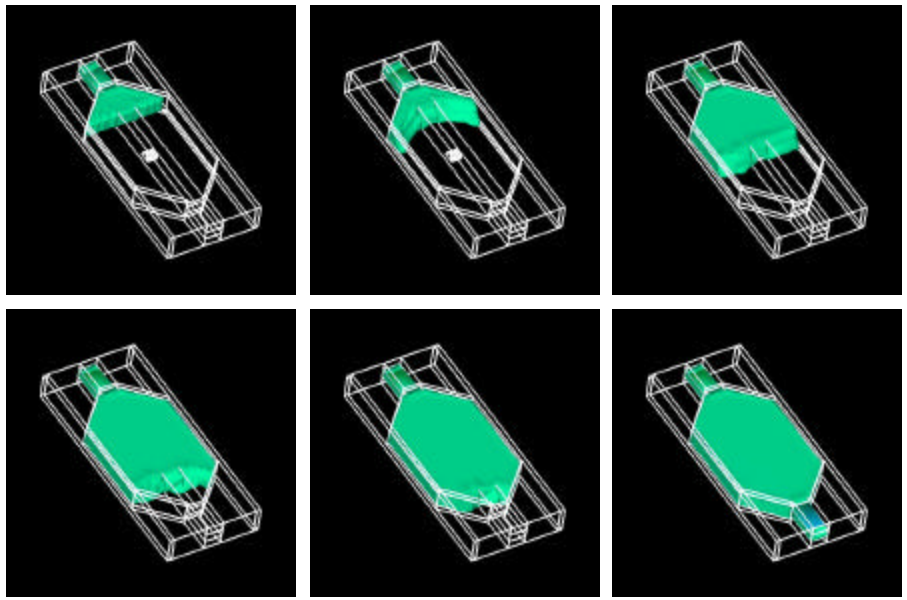
New : BubbleSim

- Optimized for bubble and filling 2-phase flow designs
- Volume-of-fluids solver coupled with Microcosm's:
  - Simulation management
  - System modeling
  - Visualization
- A new module, 1st available with FlumeCAD v 4.6



Chamber filling example

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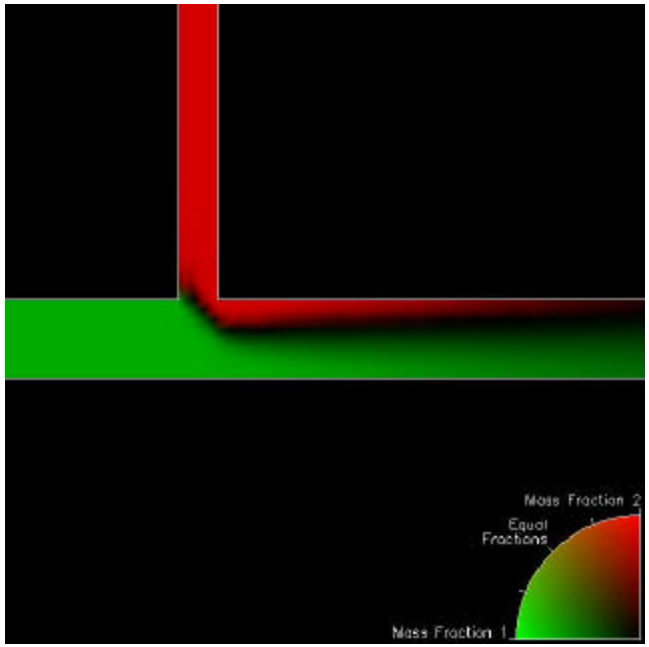
New : ReactSim

- Chemical reactions:
  - in the volume of the fluid
  - on surfaces
- Fully coupled to thermal and electrokinetic models
- Example applications:
  - Mobility-shift assays
  - Microfluidic sample prep
  - Hybridization-based systems
- New module, 1st available with v 4.6



Example : binding assay

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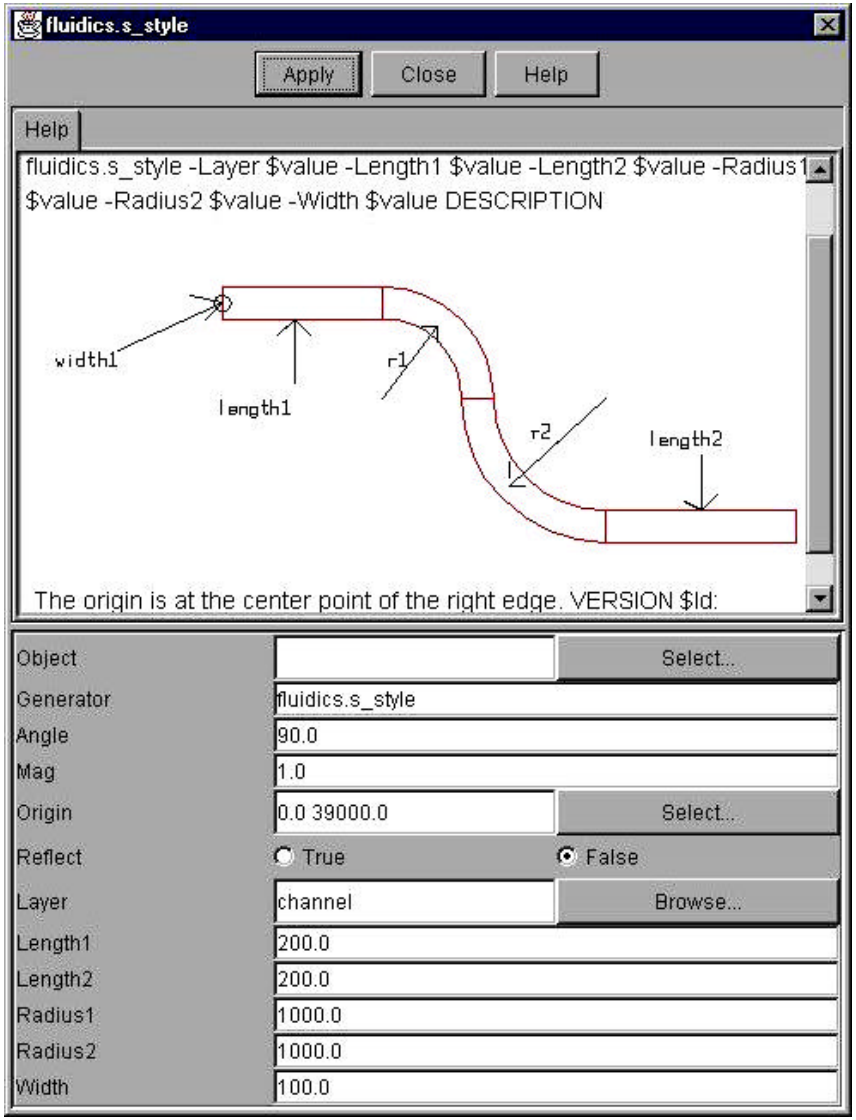
New : Catapult

A microfluidics-specific layout editor, new in V 4.6



Fluidic element generators move creation/editing to the level of parameterized structures - Standard and user-created

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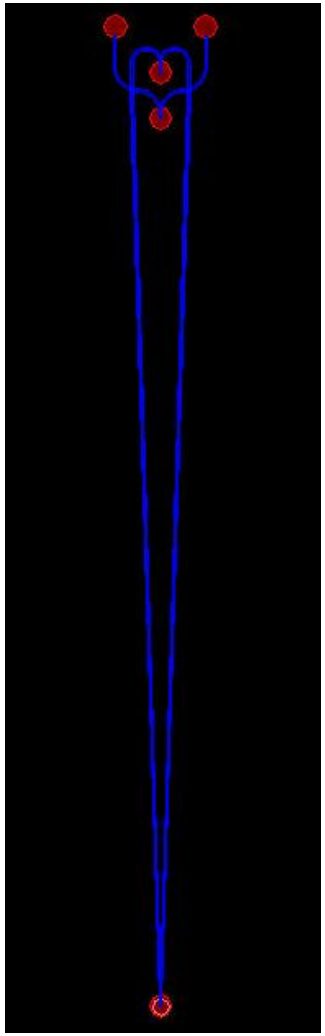
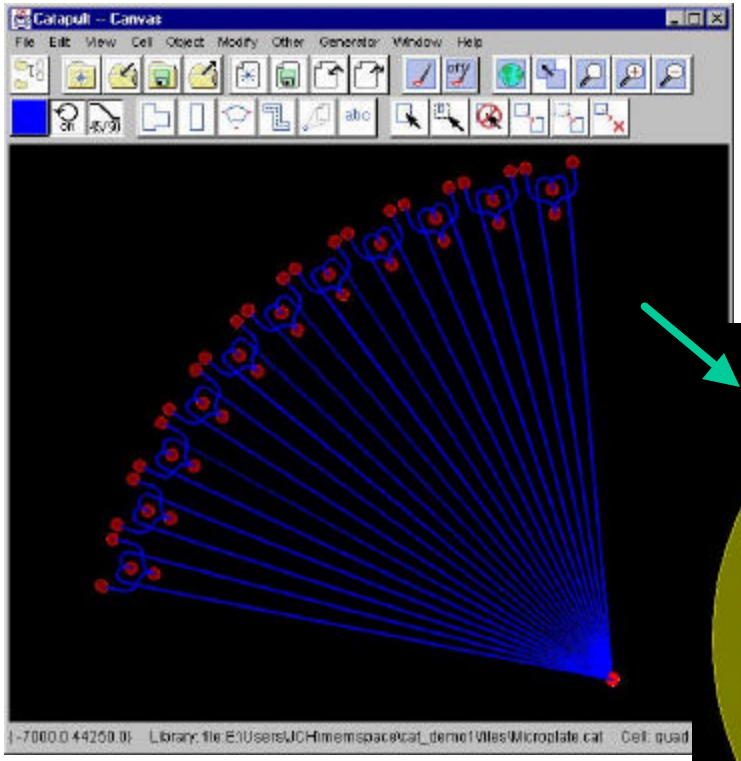
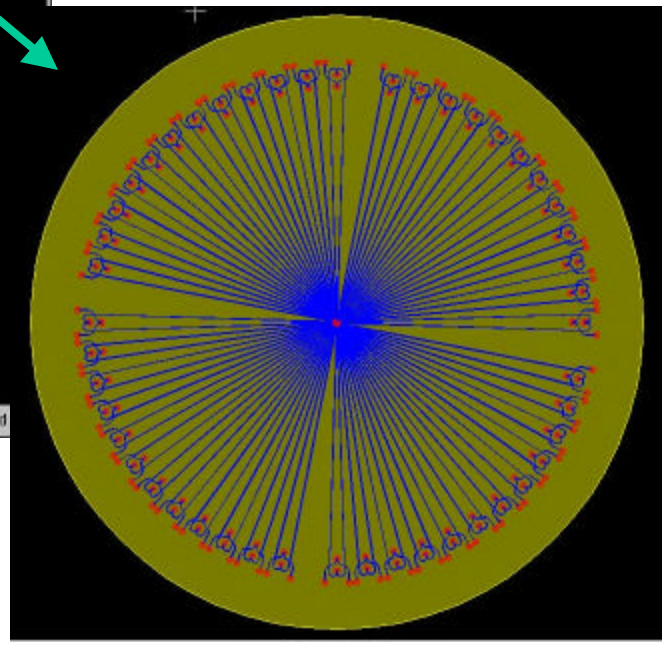
New : Catapult

Example of hierarchical design with object generators







Parallel DNA sequencer design published by Prof. Mathies, UC Berkeley

Editing a channel width in an object used to create one channel (left) will affect all 96 in the mask(right).

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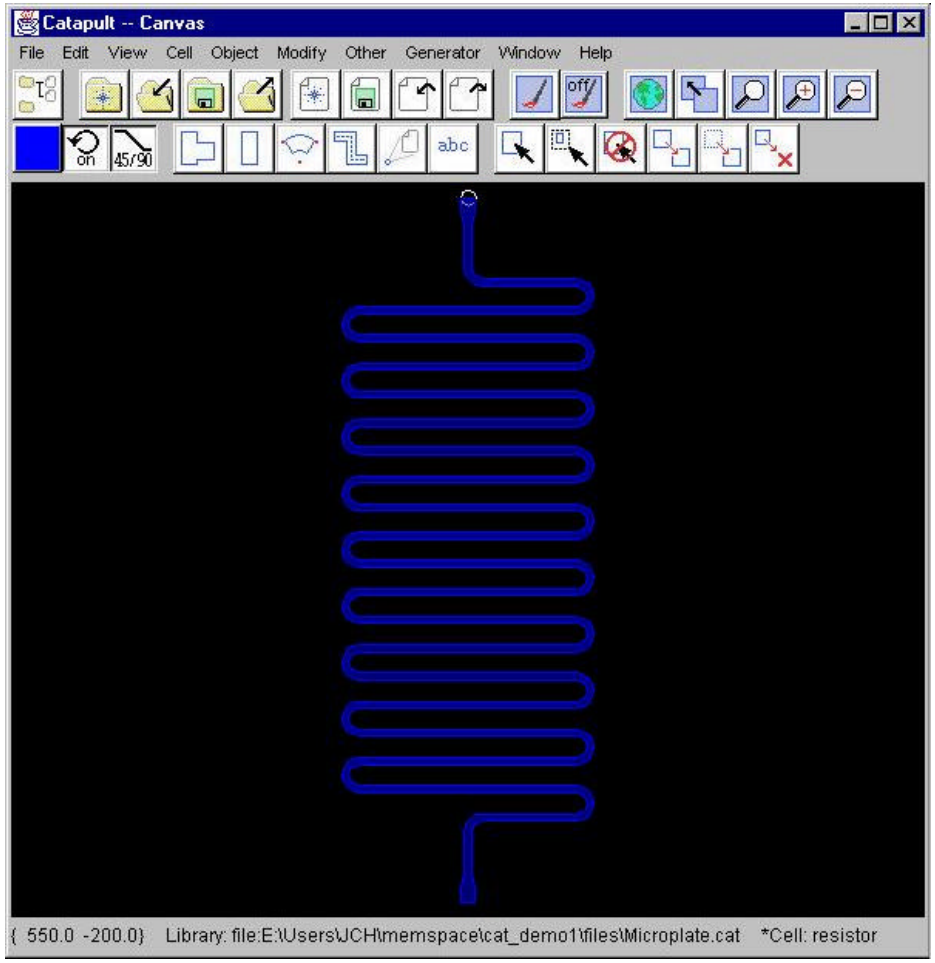
New : Catapult

Example : Complex fluidic structures generated from parametric descriptions



Change channel width and it redraws automatically...

Change # meanders and it redraws, keeping the distance between inlet and outlet constant, so the meander stays connected to the rest of the fluidic circuit, automatically.

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Detection is a Problem in Microfluidics...

- Fluorescence has become the standard for detection in biochemical instrumentation due to a combination of sensitivity and selectivity
- But the optical systems used for fluorescence detection are typically macroscopic...
- New optical technologies enable micro-optical readouts:
  - GaN diode lasers emit down to 400 nm
  - Optical MEMS support optical system miniaturization
  - Sandia has already published an integrated system
    - SPIE. Santa Clara. Sept. '99

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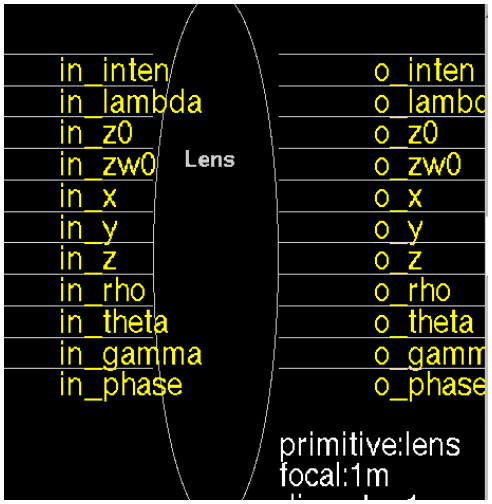
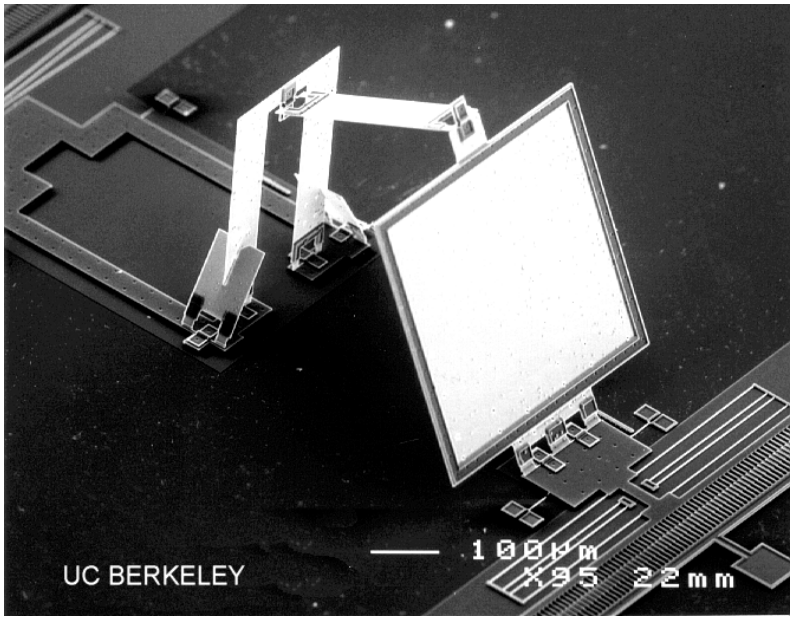
Optical MEMS at Microcosm (coming…)

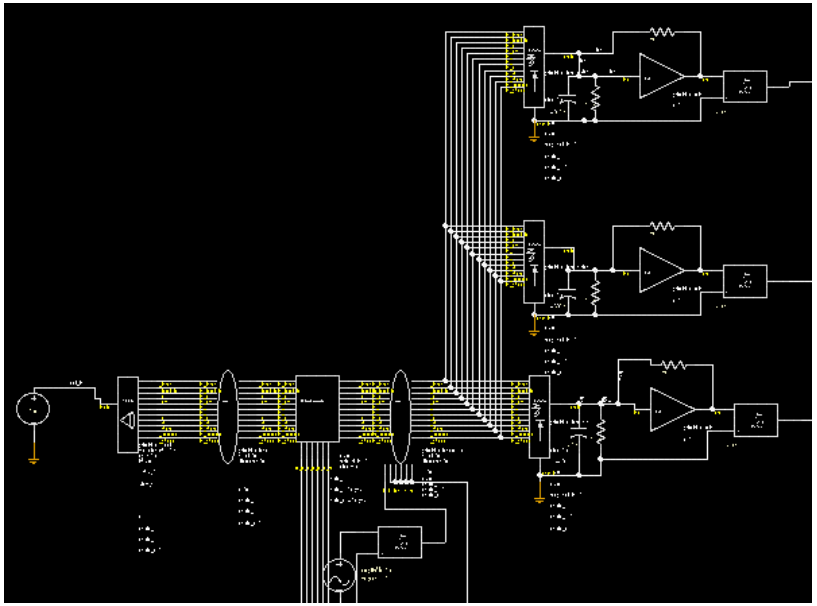
Microcosm is a microsystems company, not just a fluidics company



Optical system modeling



BSAC Mirror and comb drive actuator



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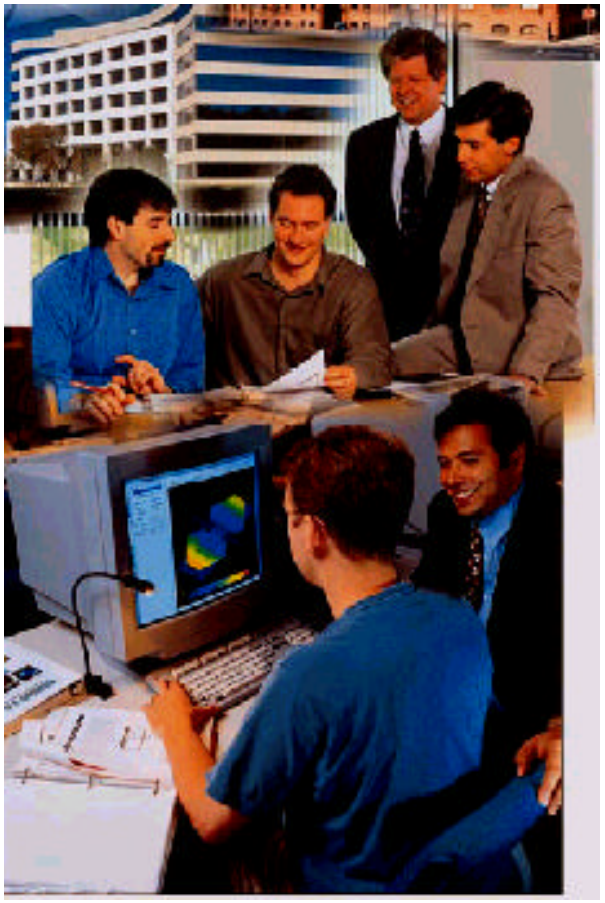
Design & modeling on a contract basis

Capture the value of our tools and expertise without building in-house fixed costs



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Microcosm Technologies, Inc

CAD for Microfluidic Instruments

- Focus on Mol. Biology applications
  - e.g. molecular transport, not just CFD
- Whole instrument modeling
  - made practical by extraction of reduced order models from FEM
- Optical MEMS integration
- Services: design, analysis, fabrication...

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Questions ?

- Contact info:
  - John West
  - Microcosm Technologies
  - johnwest@memcad.com
  - Web sites :
    - www.flumecad.com (Microfluidics)
    - www.memcad.com (MEMS)

MICROCOSM TECHNOLOGIES
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CFD Research Corporation

215 Wynn Dr. , Huntsville, AL 35805 TEL: (256) 726-4800 FAX: (256) 726-4806

MULTI-DISCIPLINARY COMPUTATIONAL MODELING TECHNIQUES FOR BIO-MICROFLUIDIC DEVICE DESIGN

By

Vinod B. Makhijani and Andrzej Przekwas
CFD Research Corporation

Presented at

Workshop on
Computational Modeling and Simulation of Biological Systems

DARPA - DSO/MTO
November 18, 1999

INTRODUCTION

Discuss and Demonstrate Several Applications of Advanced Multi-Disciplinary Computational Code, CFD-ACE+MEMS for Design and Analysis of Microfluidic Biodiagnostic Devices

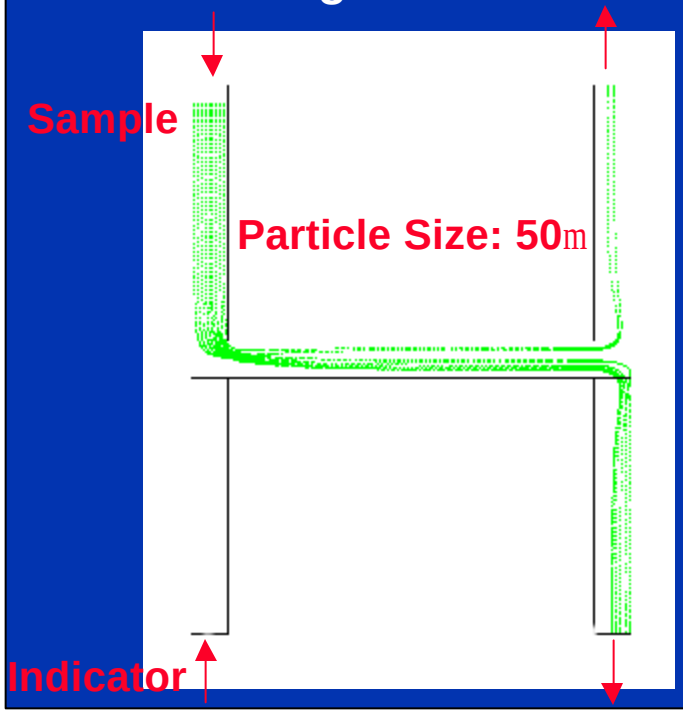
Capabilities of CFD-ACE+MEMS Include:

- **Flow, Thermal and Mass Transport Analyses;**
- **Biochemical Reaction Kinetics (Bulk Flow/Surface Reactions);**
- **Mixing and Multi-Phase Calculations;**
- **Electrokinetics, Electrostatics and Electromagnetics;**
- **Structural Dynamics;**
- **Virtual Controls;**
- **Reduced Models for System-Level Simulation;**
- **Interface to MCAD, ECAD**

PARTICLE/CELL SEPARATION

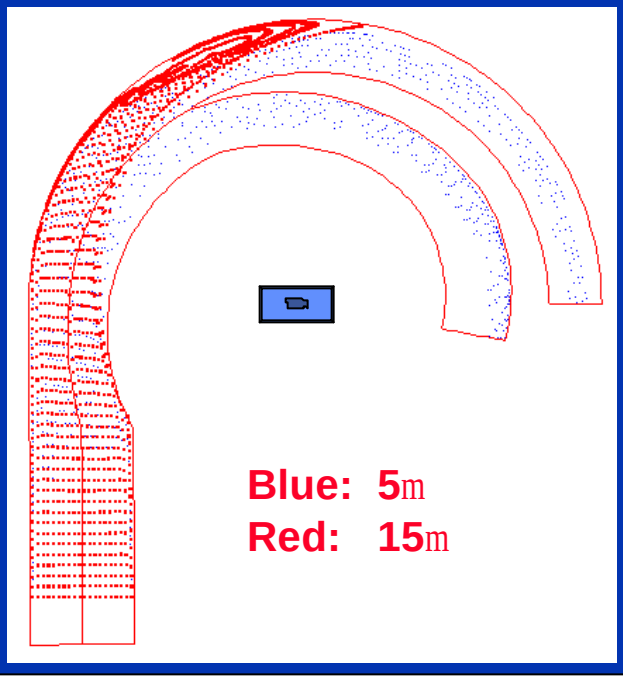
H-Filter
(University of Washington)

- Separation of Particles or Cells in Biological Fluids
- Separation Based on Diffusivity or Centrifugal Force



Aerosol Separator
(Mesoscale Systems Tech.)

- Separation of Pathogens in Air
- Analyzed Performance at Different Flow Rates

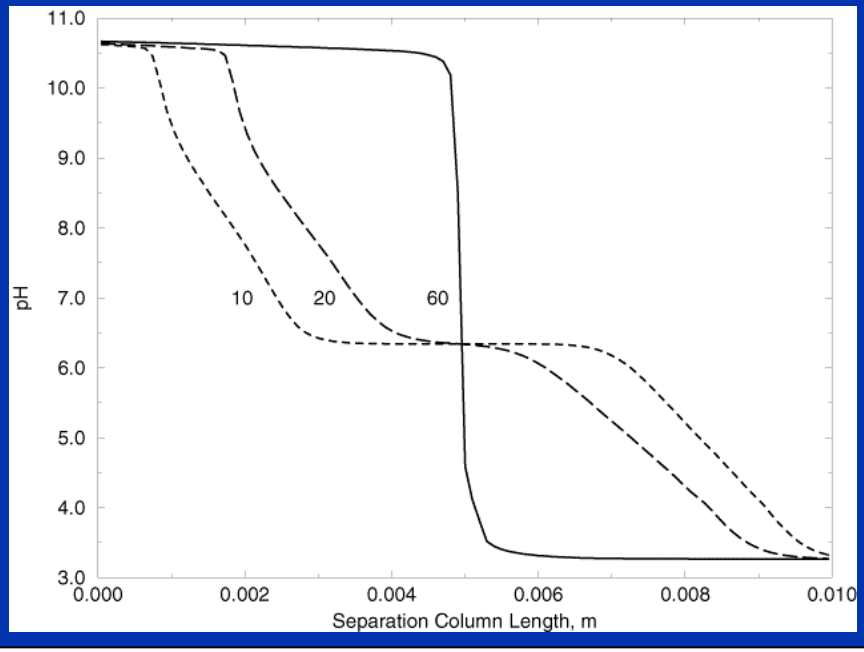


ELECTROPHORESIS MODELING

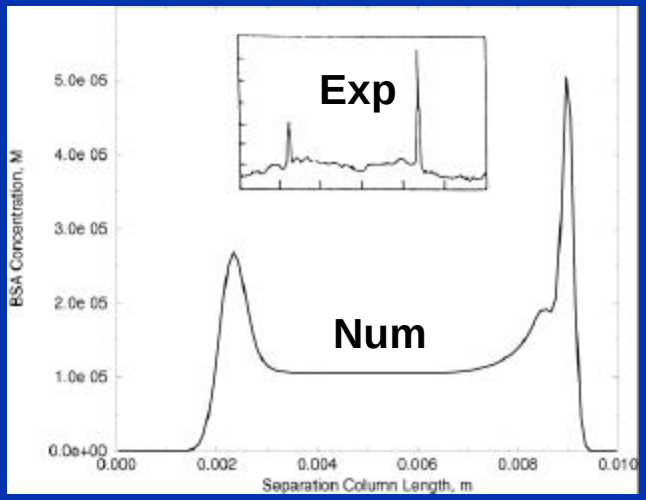
Iso-Electric Focussing

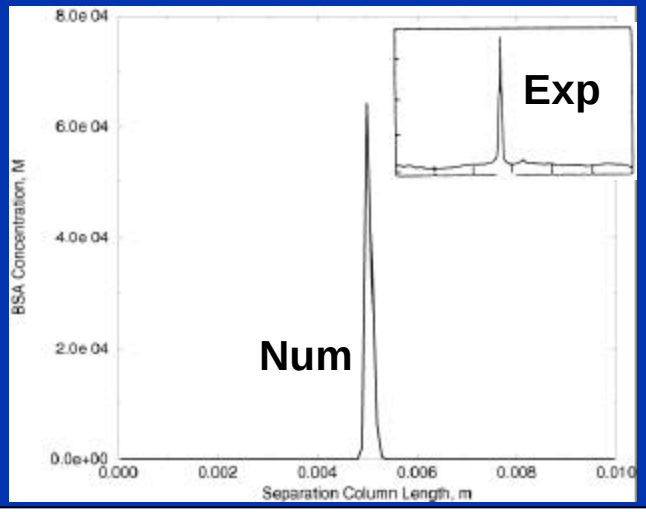
- **Separation of BSA Protein (0.68 mg/mL)**
- **Buffer: Arginine and Glutamic Acid (15mM each)**
- **Current Density: 5 A/m^2**
- **pH Gradient Setup by Buffer**

pH Distribution at Different Times

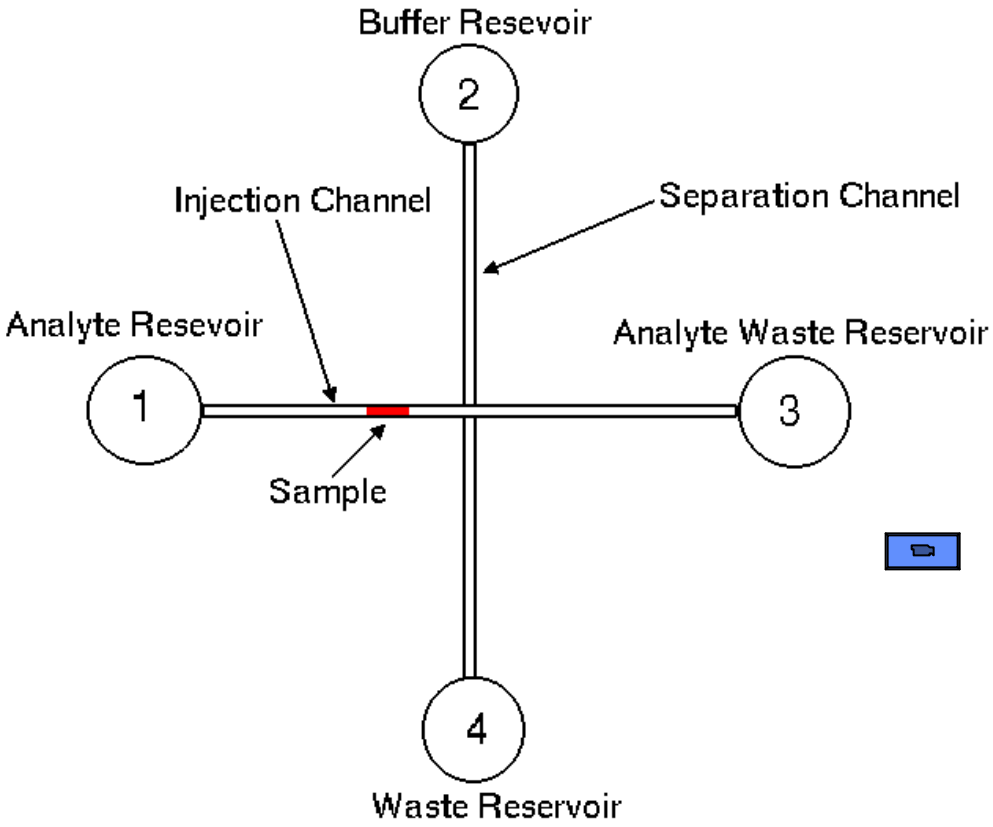


BSA Concentration Distribution

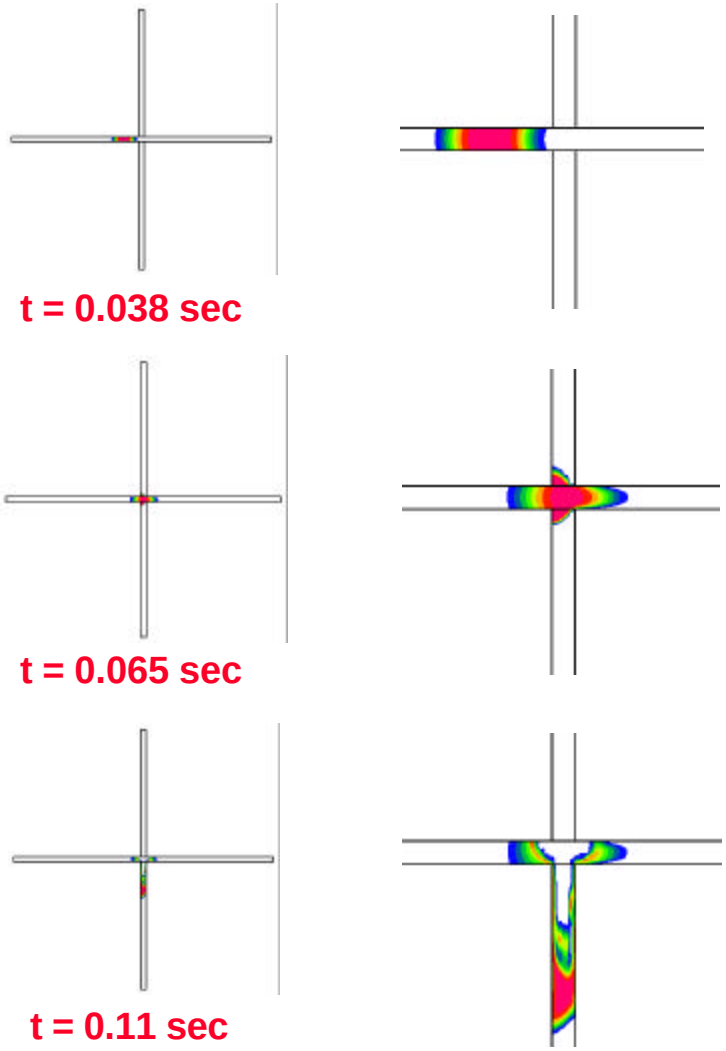




ELECTROKINETIC SWITCHING



- **Voltage Switching Between Injection and Separation**
- **Sample Plug Shape Controlled by Voltage in Separation Channel**

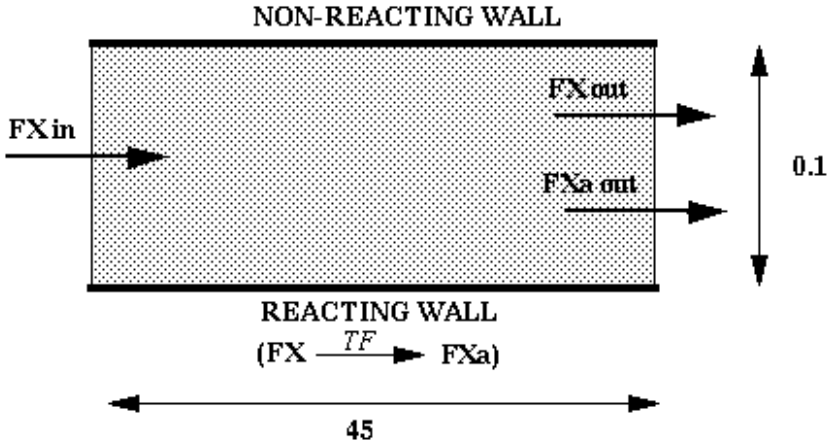


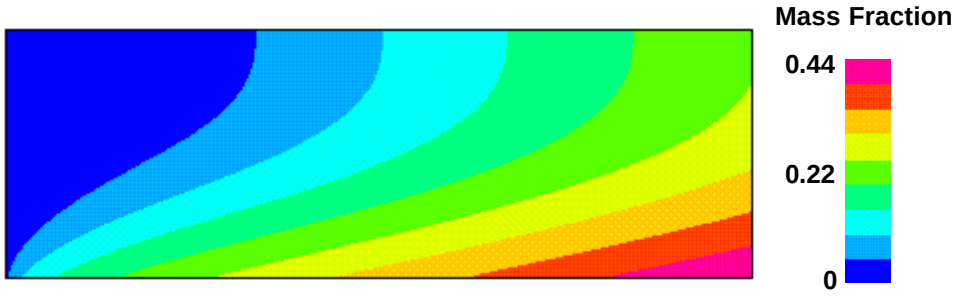
Sample Mass Fraction Distributions at Different Times

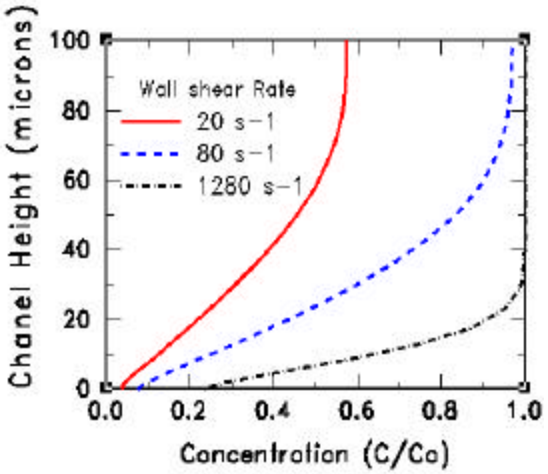
BIOCHEMICAL KINETICS MODELING

Enzyme-Catalyzed Surface Reactions

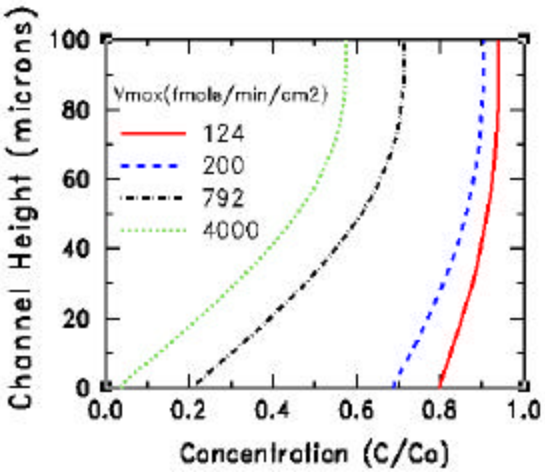
Conversion of Factor X (FX) to Factor Xa (FXa) by Tissue Factor - Factor VII (TF: FVIIa) Catalytic Complex on Layer of Cultured Vascular Smooth Muscle Cells in a Microflow Chamber (Reaction Based on Michaelis-Menten Kinetics)







Effect of Wall Shear Rate



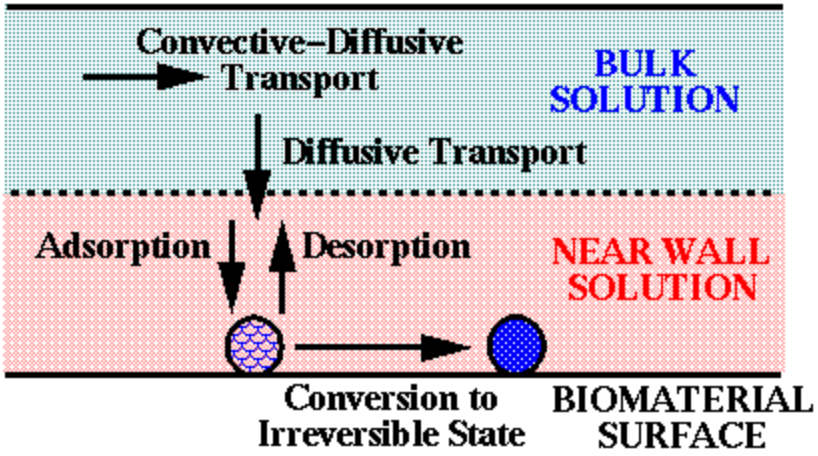
Effect of Reaction Rate

Vmax (fmole/min/cm^2)	Wall Shear Rate (s^{-1})	Numerical Flux (fmole/min/cm^2) CFD-ACE+MEMS	Experimental Mean Flux (fmole/min/cm^2)
792	1280	532.5	593±32
200	80	138.9	138±33
124	20	85.5	95±20

Model Validation

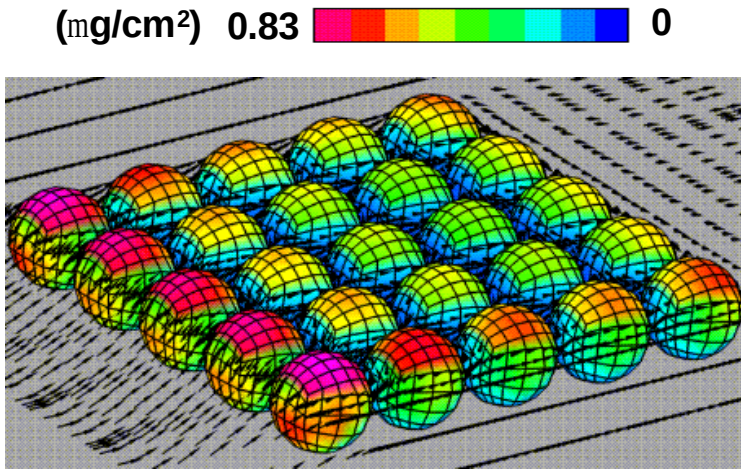
BIOCHEMICAL KINETICS MODELING

Competitive Multi-Protein Binding Kinetics

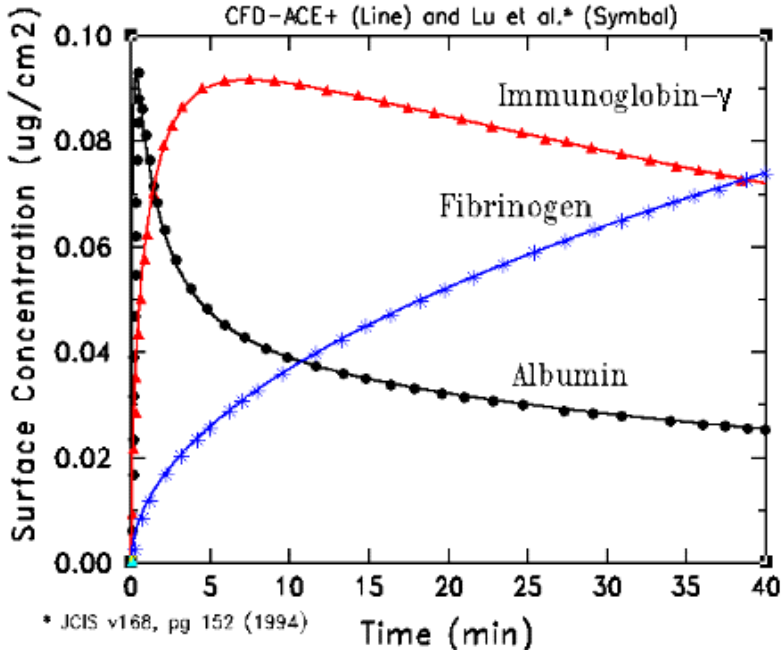


Schematic of Processes

- Convective-Diffusive Multi-Species Transport
- Competitive Adsorption Kinetics (2nd Order)
- Desorption Kinetics (1st Order)
- Conversion from Reversible to Irreversible State
- Validation: Reversible Surface Adsorption w/o Convection for a Dilute Plasma Solution with 3 Proteins in 1- D Domain



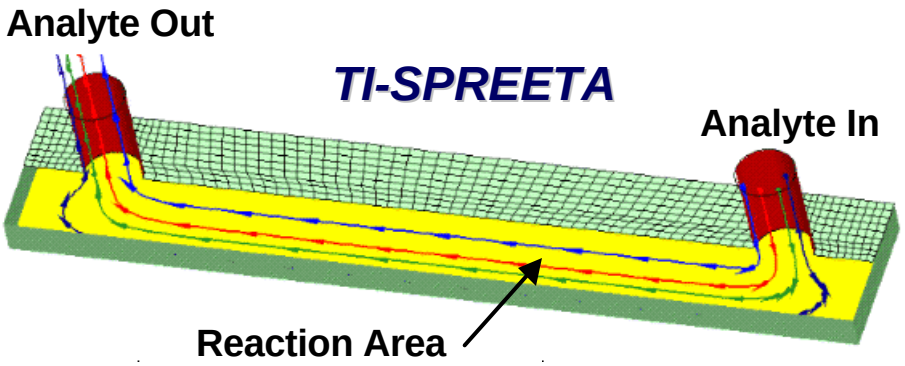
Albumin Deposition on Microbead Array



Model Validation

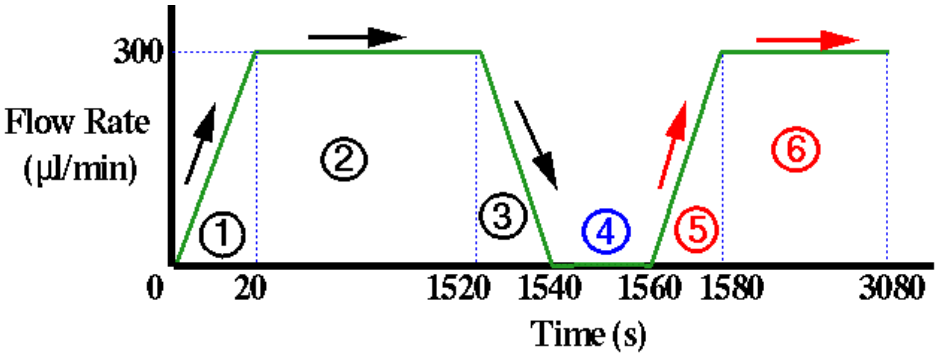
DIRECT BINDING ASSAY

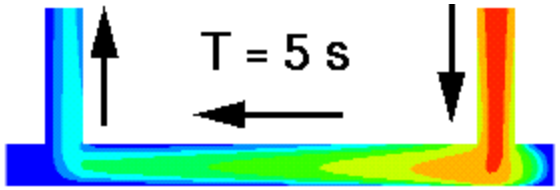
Antibody-Antigen Binding Kinetics in an Optical Biosensor System



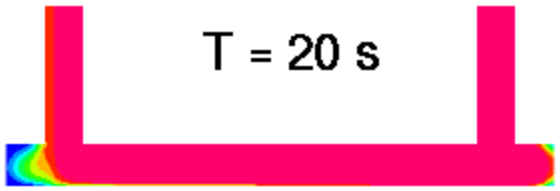
STAGE 1 – Turn on analyte flow (20 s)
STAGE 2 – Constant analyte flow (25 min)
STAGE 3 – Turn off analyte flow (20 s)
STAGE 4 – Disconnect analyte supply and connect buffer supply (20 s)
STAGE 5 – Turn on buffer flow (20 s)
STAGE 6 – Constant buffer flow (25 min)

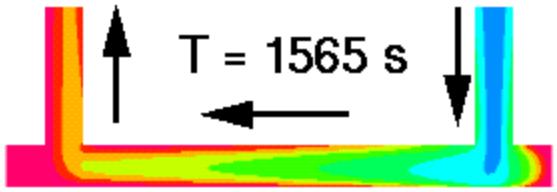
Flow Traces in the Biosensor Flow Cell

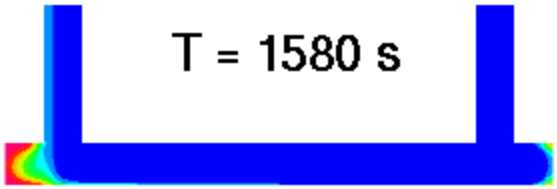




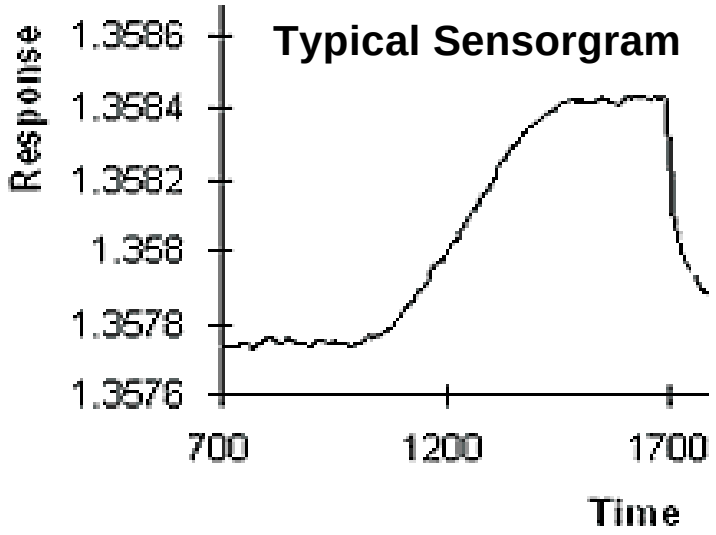
Non-dim. Analyte Conc. 1 0

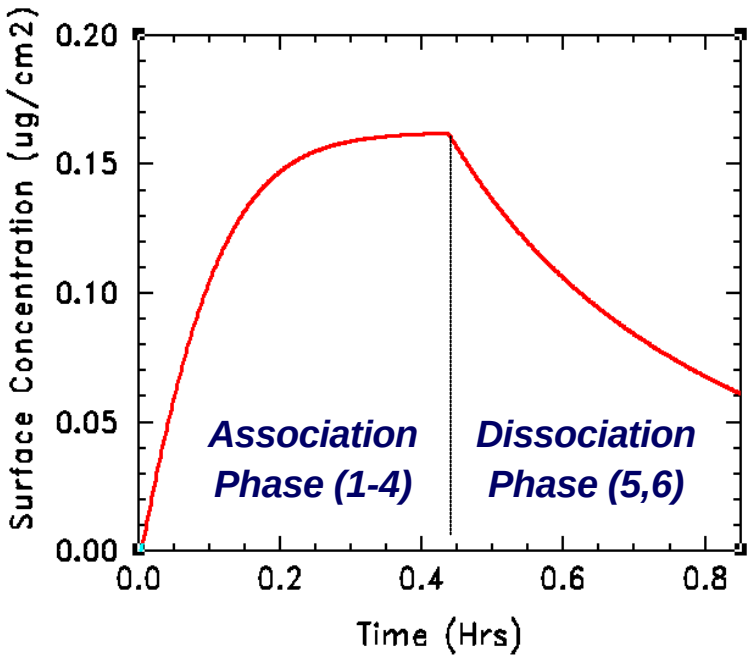




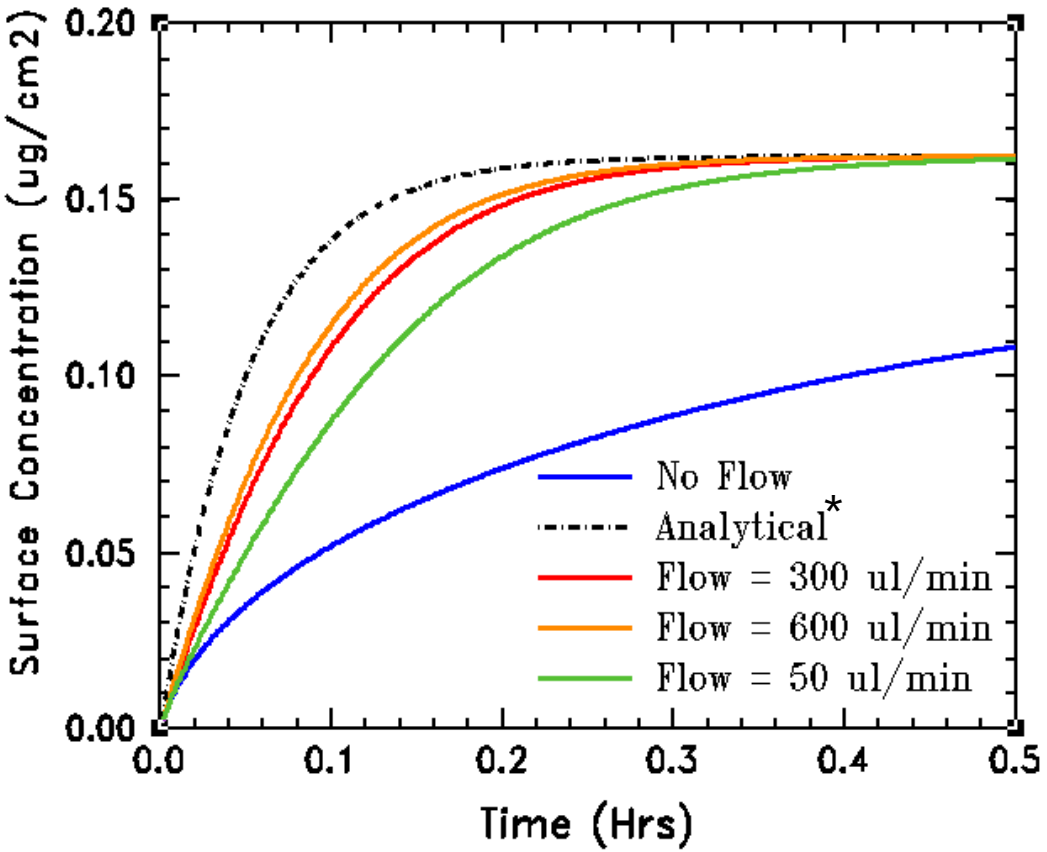


DIRECT BINDING ASSAY (Contd.)





Baseline Case (300 ml/min)

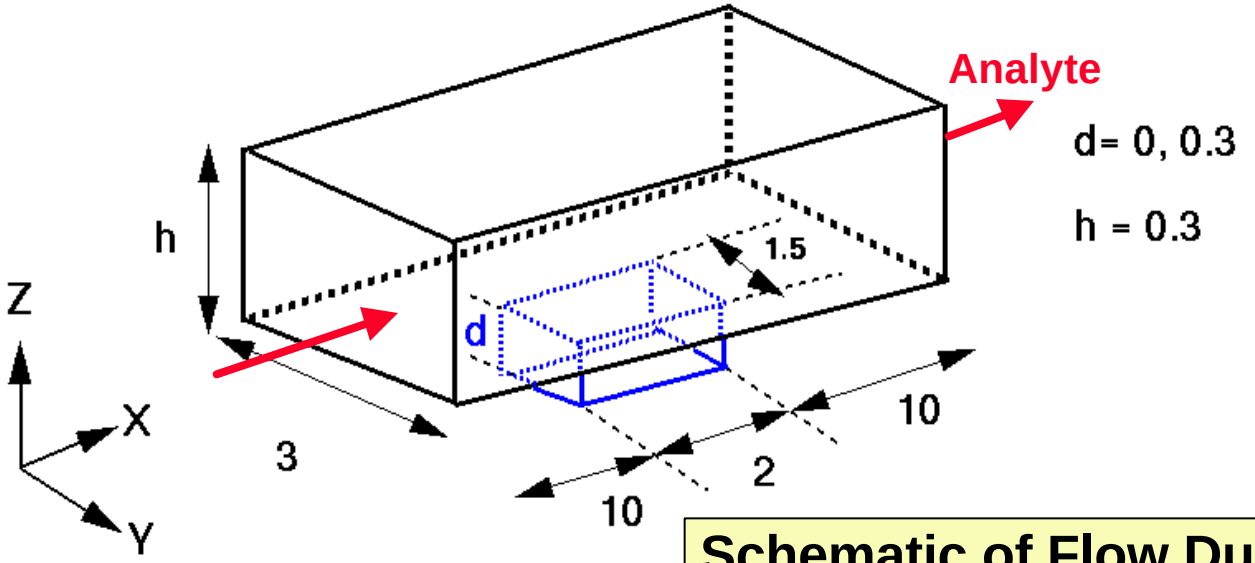


Effect of Analyte Flow Rate on Surface Binding Kinetics

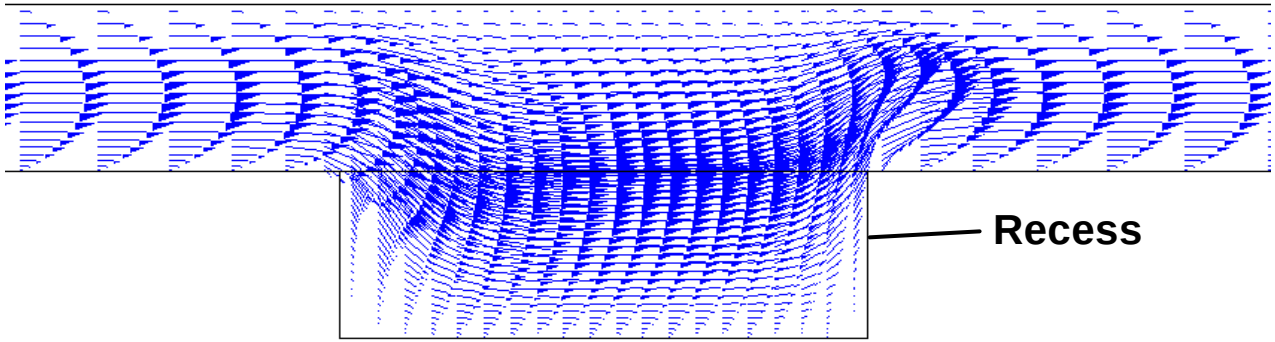
(Based upon Rapid-Mixing Assumption)*

APPLICATION (CANARY Biosensor System)

Objective: Investigate Effect of Sample Flow Rate and Flow Duct Geometry on Surface Binding in the Biosensor



Schematic of Flow Duct

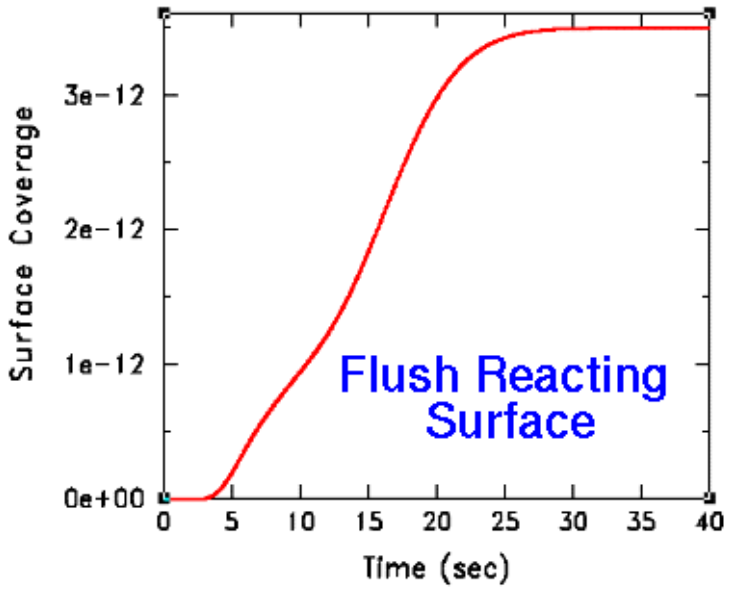


Flow Velocity Vectors in Transverse Cross-Sectional Plane

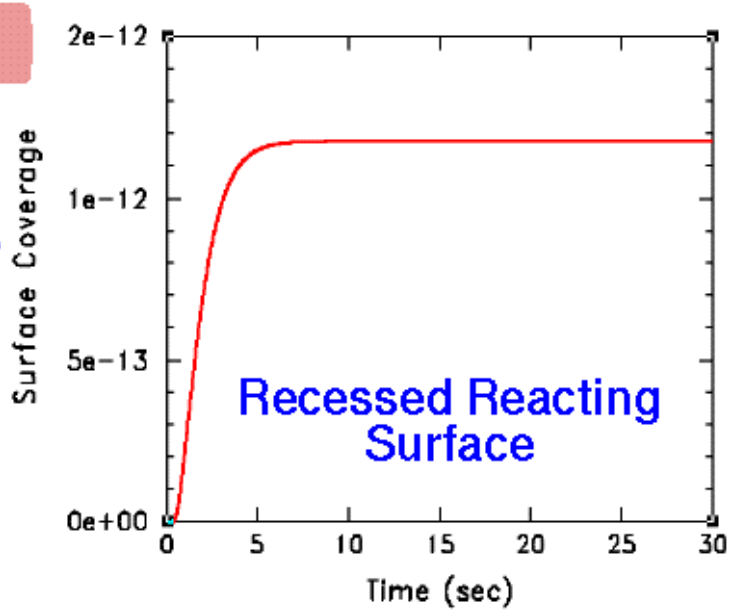
- Antigen Molecules Bind to 2-D B-Cell Patch Along Flush/ Recessed Surface
- Direct Binding Assay Model Used in Study
- Sample Flow Rates Evaluated: 5, 50 µl/s
- Fluid Shear Stress Levels Along Binding Site Within Acceptable Range

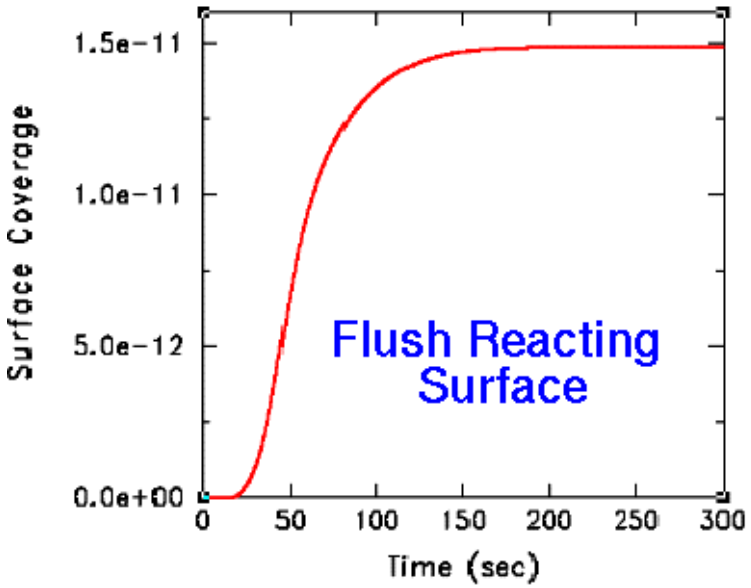
APPLICATION: CANARY Biosensor (Contd)

RESULTS

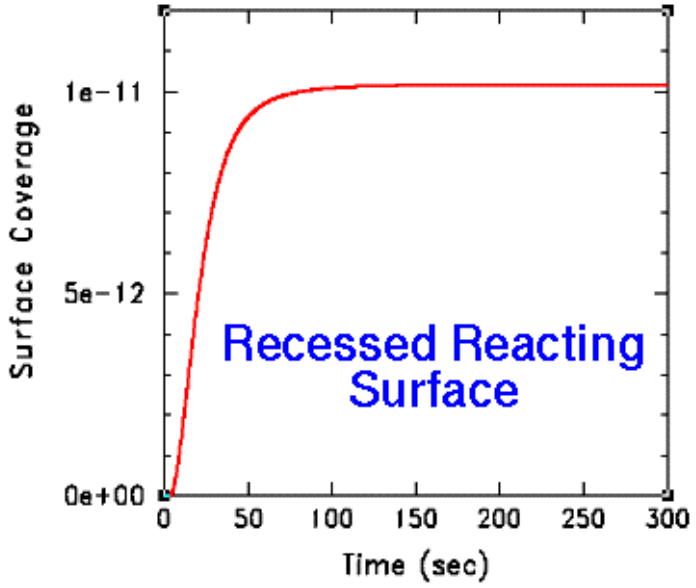


10 μL Sample Injected at Flow Rate = 50 μL/s

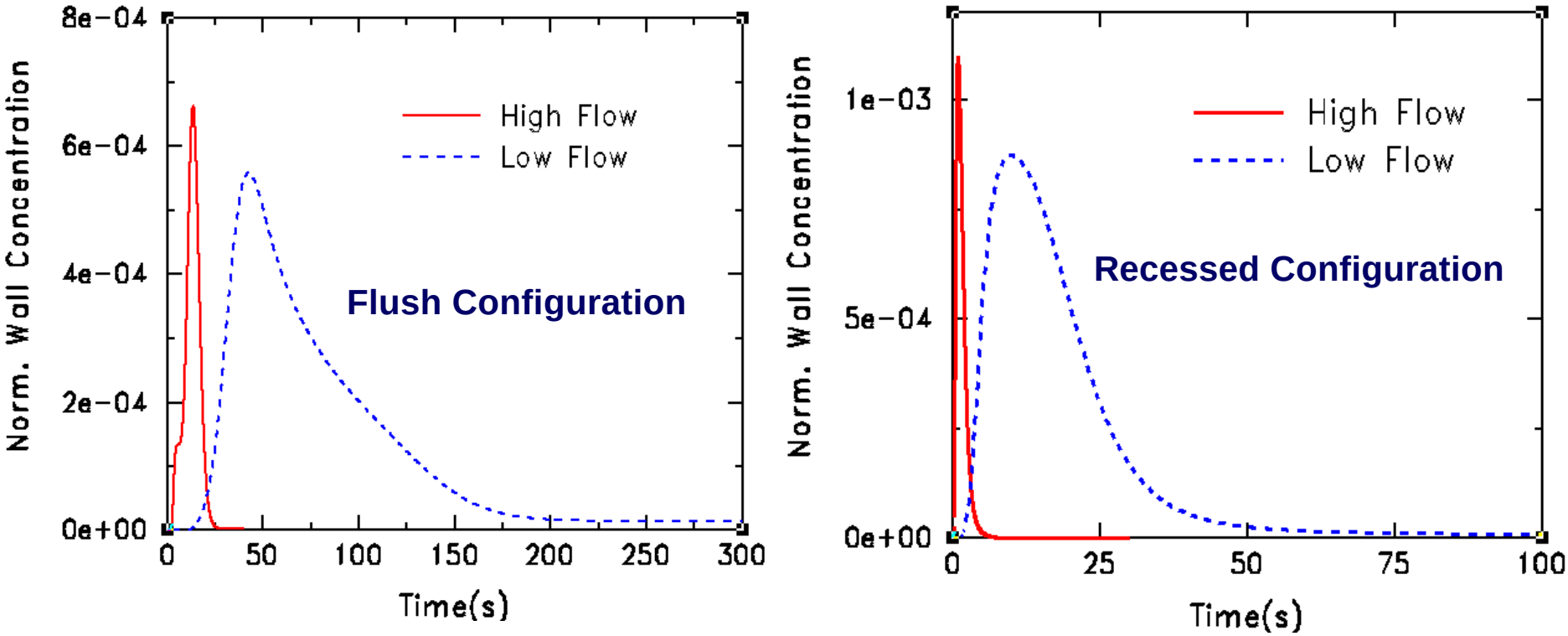




10 μL Sample Injected at Flow Rate = 5 μL/s



APPLICATION: CANARY Biosensor (Contd)

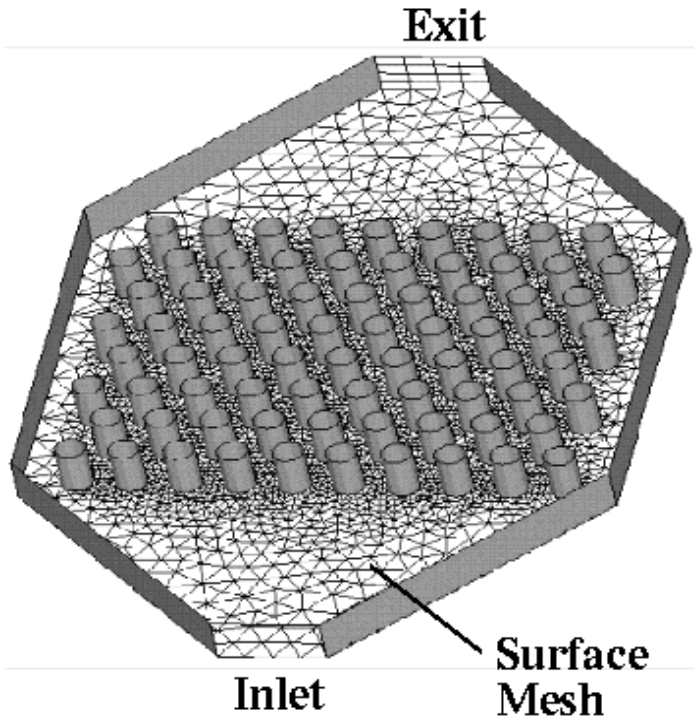


Transient Variation in Near Wall Analyte Concentration

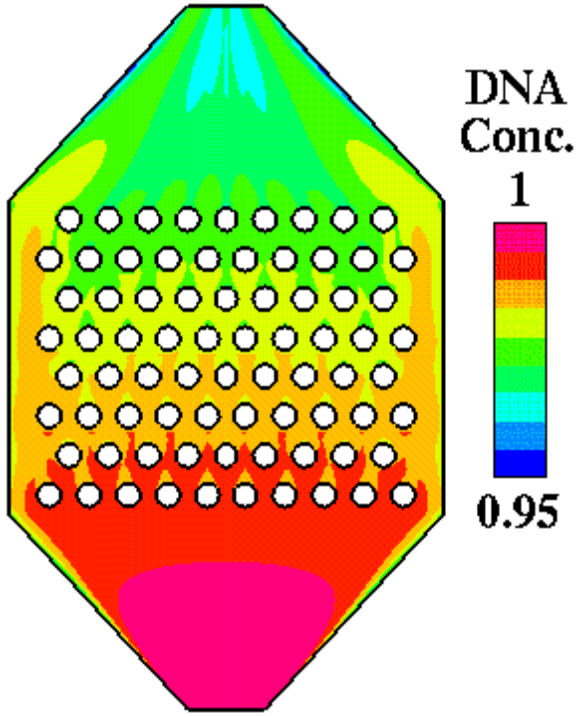
- Geometry of Flow Cell and B-Cell Patch as well as Sample Flow Rates Can be Optimized Using Current Model to Improve Biosensor Performance (Rapid Detection with Improved Sensitivity)

DNA FILTRATION CHIP

- Simulation of Convective–Diffusive Transport + Surface Binding Kinetics of DNA in Extraction Chamber (Model Based on Cepheid Bio–chip)
- Binding Reaction Modeled as First–Order Reaction
- Binding Rate Constant Determined through Comparison with Cepheid's Experimental Data (Christel et al., 1998)

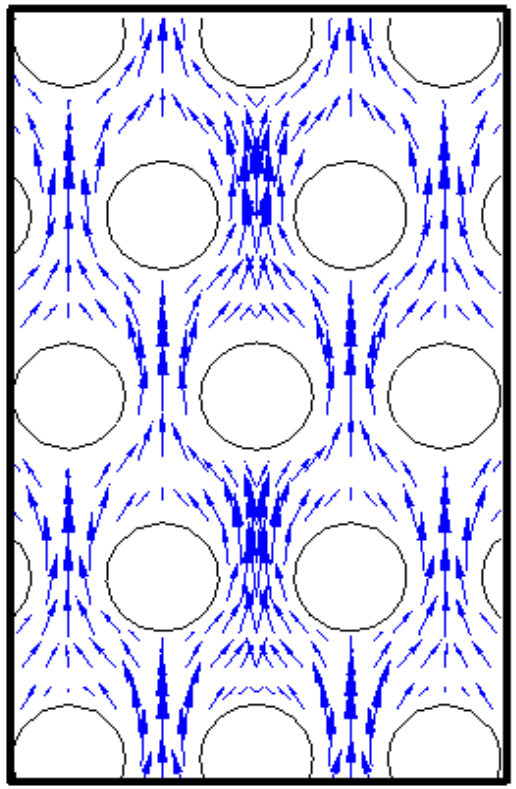


Geometric Model of DNA Extraction Chip



Capture Efficiency = 1.25%

DNA Capture



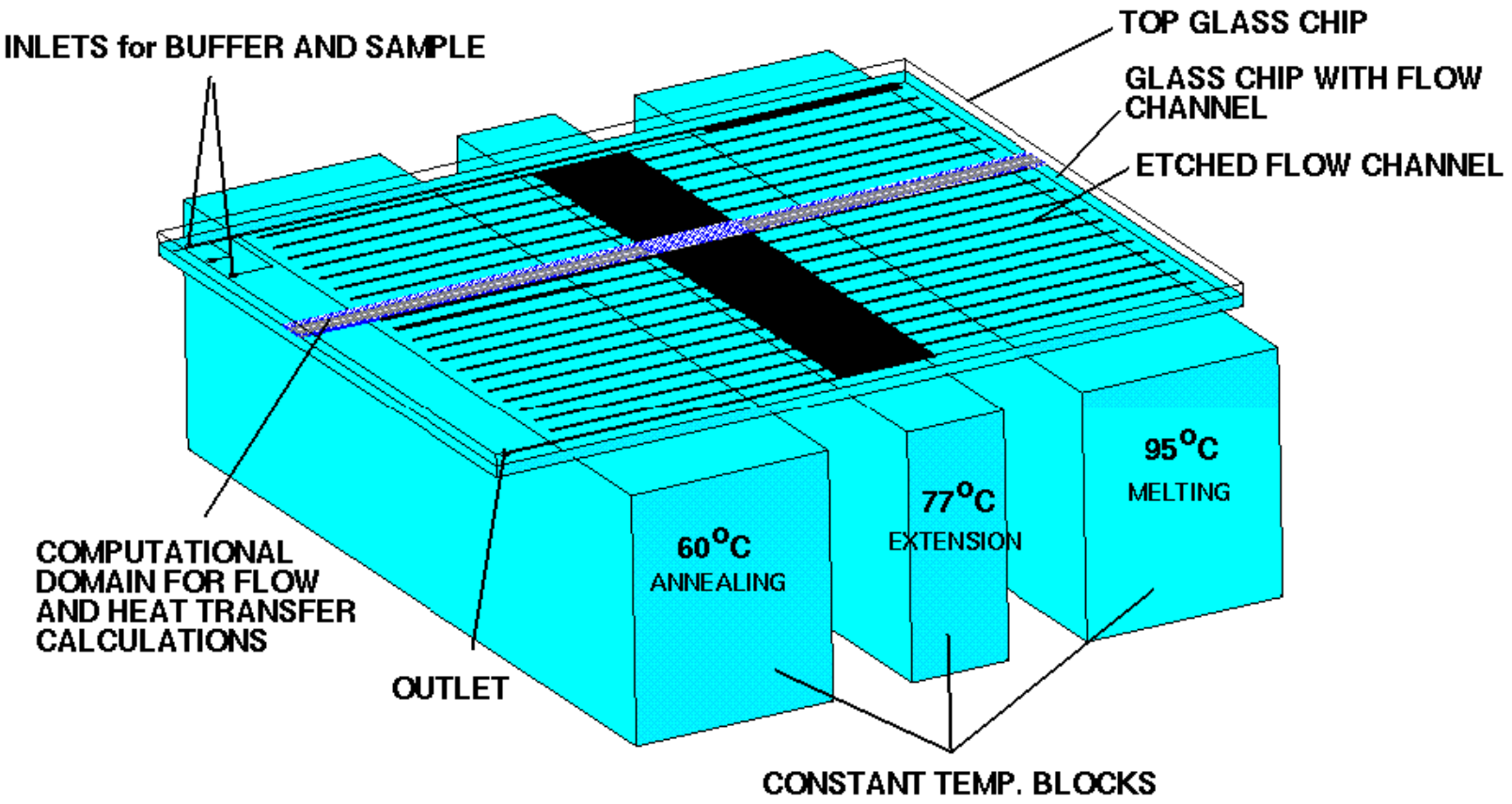
Velocity Vectors Around Pillars

CONTINUOUS FLOW PCR REACTOR

CFDRC

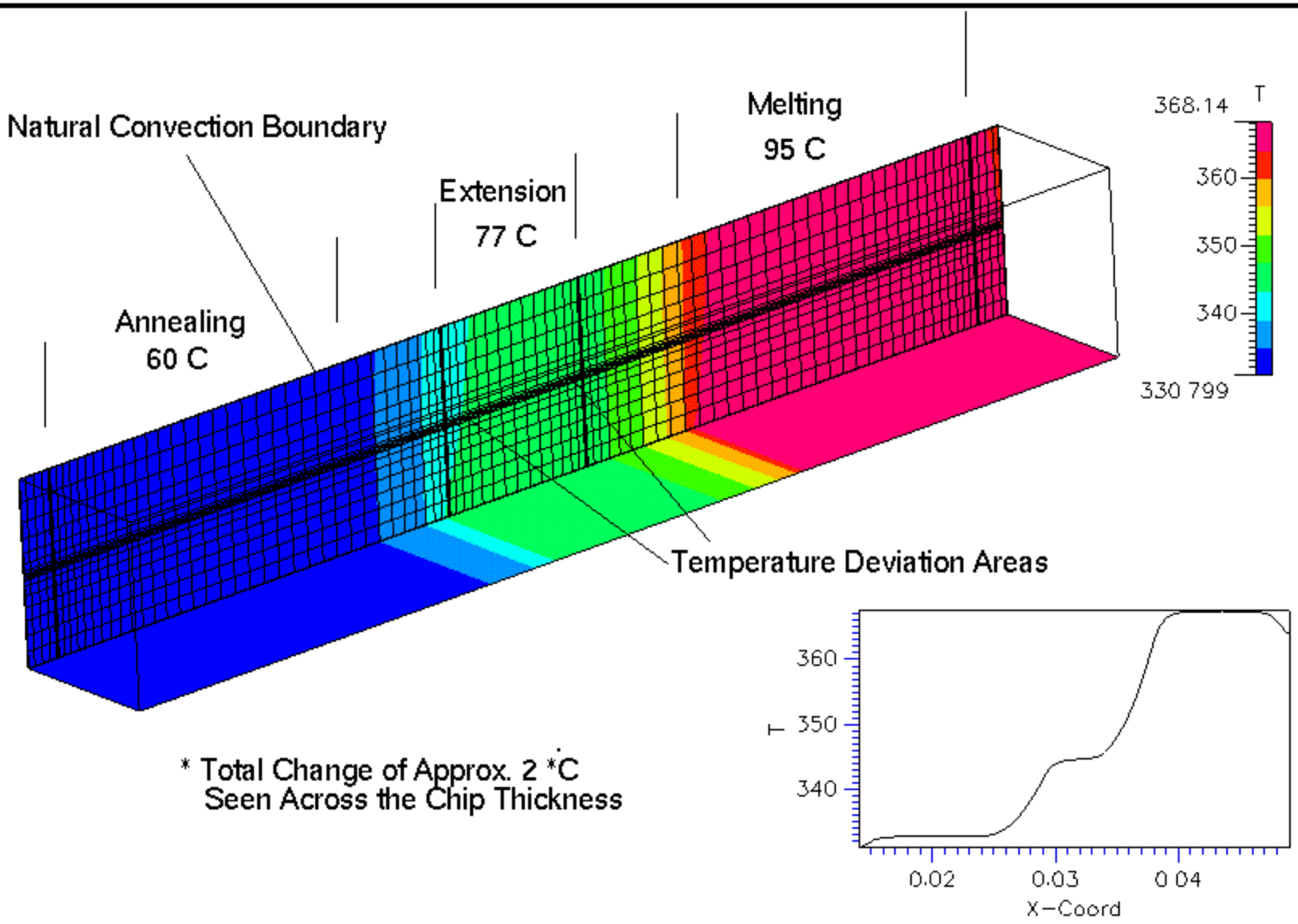
Design by Kopp et.al. (Science, 1998)

Single Loop Selected for High-Fidelity Simulations



Temperature Field in a Single Flow Loop

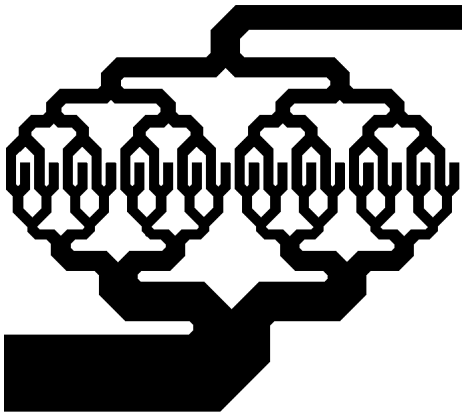
CFDRC



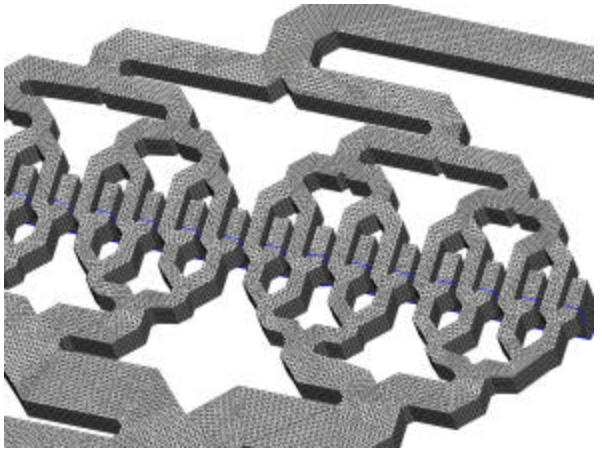
* Total Change of Approx. 2 *C
Seen Across the Chip Thickness

LAYOUT-SOLIDS-MESH-SIMULATION

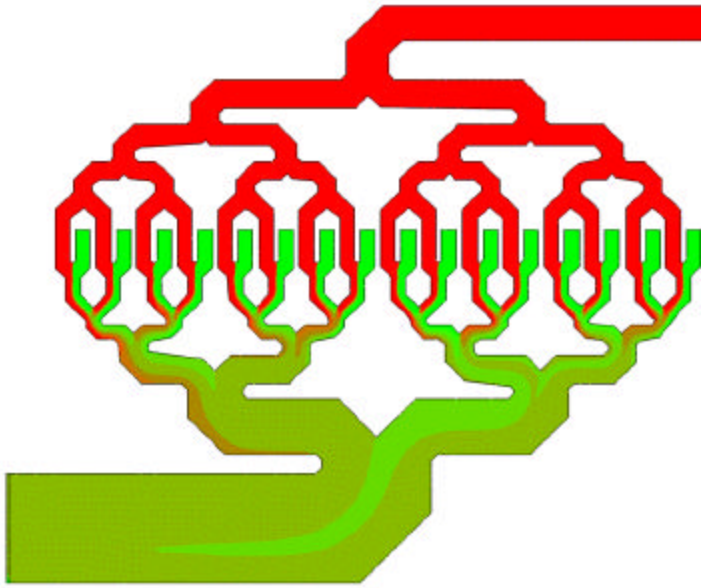
Mixing in a Static Micromixer



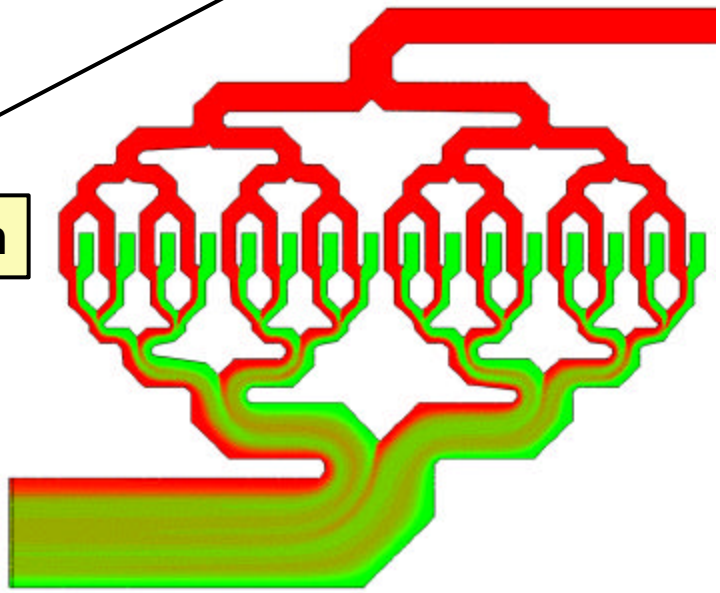
CFD-MicroMESH



Layout → Solid → Mesh → Simulation



First-Order Upwind Scheme

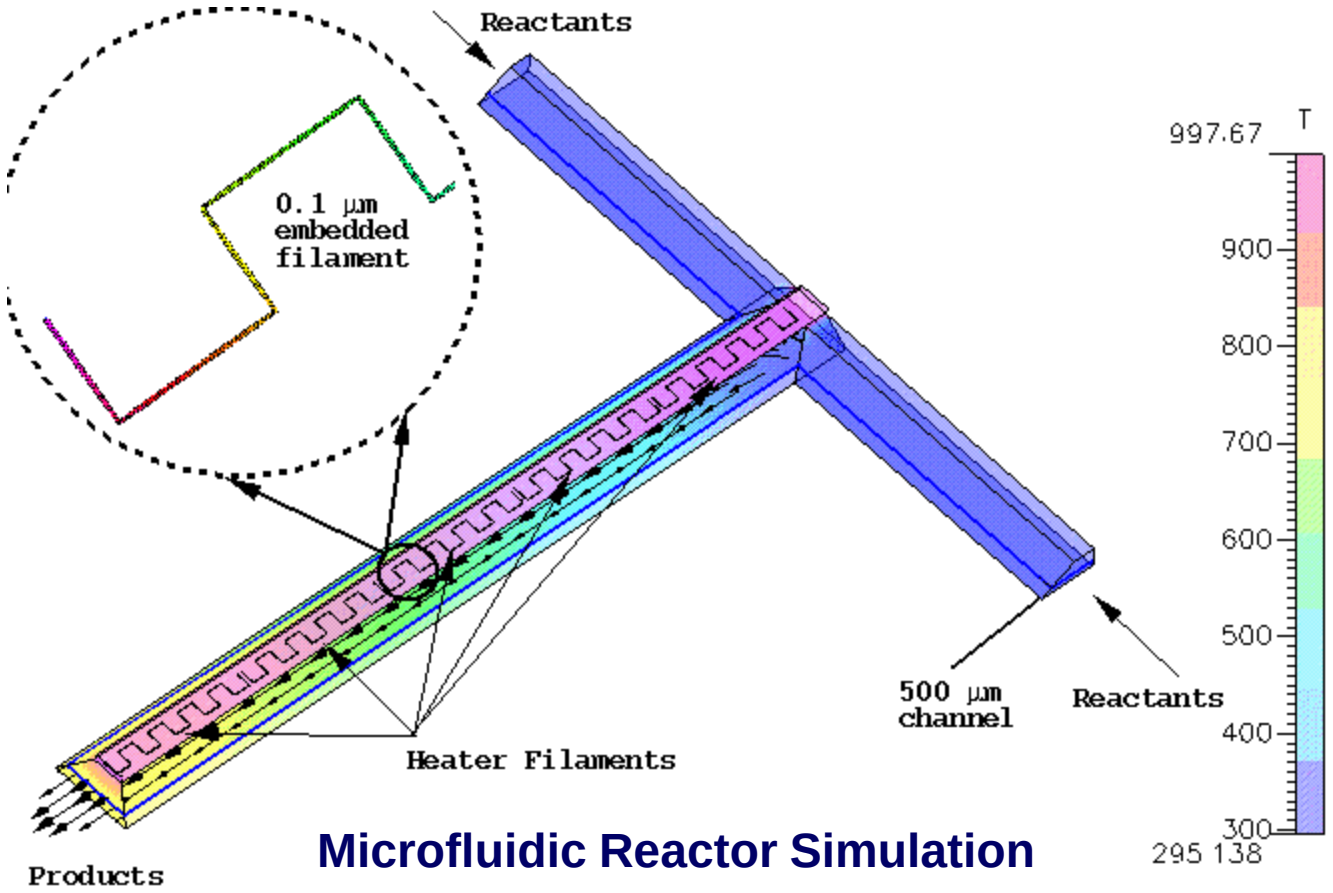


Higher-Order TVD Scheme

MIXED-DIMENSIONALITY CAPABILITY

Filament Capability

- **Filament : Thread or Thin, Flexible Thread-like Object**
- **Purpose: Embedded Additional Domains to Existing Base Grid**
- **Usage: Ideal for Shapes with Multiple Length Scales (Very Small+ Very Large)**
- **Gridding: Independent of Base Domain for Multiple, Arbitrary Shape Filaments**
- **Solution: Full Coupling Between Base Domain and Filament Physics**



Microfluidic Reactor Simulation

ON-GOING/FUTURE DEVELOPMENTS

SIMULATION OF DNA AMPLIFICATION

- Fundamental Modeling of PCR has not been Explored Yet
- Application of ACE+ Multistep Chemical Kinetics Capability for PCR Simulation

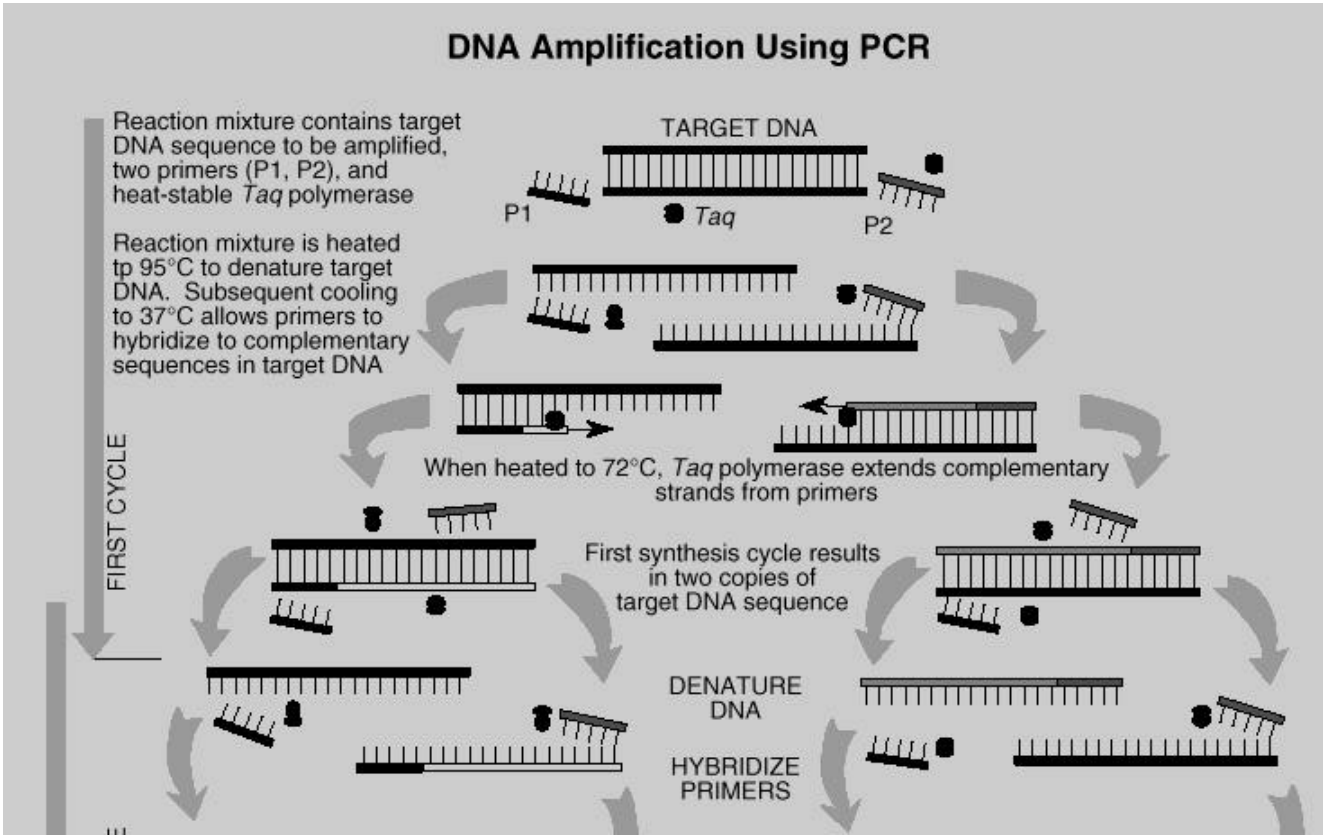
$$s_1 s_2 \underset{\leftrightarrow}{\overset{k_D^+, k_D^-}{}} s_1 + s_2$$

$$s_1 + p_2 \underset{\leftrightarrow}{\overset{k_A^+, k_A^-}{}} s_1 p_2$$

$$p_1 + s_2 \underset{\leftrightarrow}{\overset{k_A^+, k_A^-}{}} p_1 s_2$$

$$s_1 p_2 \xrightarrow{k_E} s_1 s_2$$

$$p_1 s_2 \xrightarrow{k_E} s_1 s_2$$

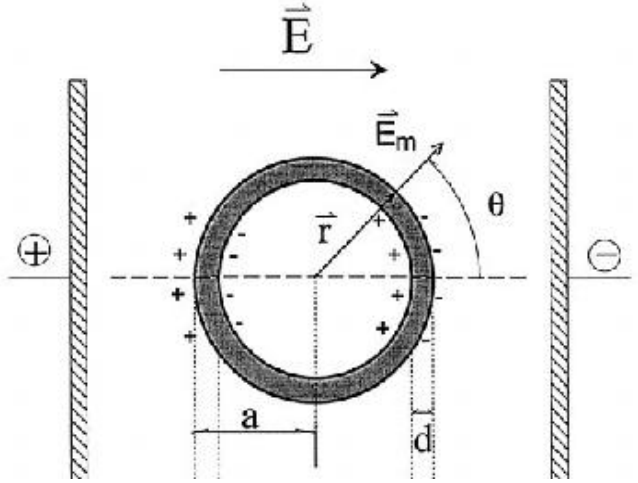


$$\frac{d[s_1]}{dt} = k_D^+ [s_1 s_2] + k_A^- [s_1 p_2] - k_D^- [s_1][s_2] - k_A^+ [s_1]$$

ON-GOING/FUTURE DEVELOPMENTS

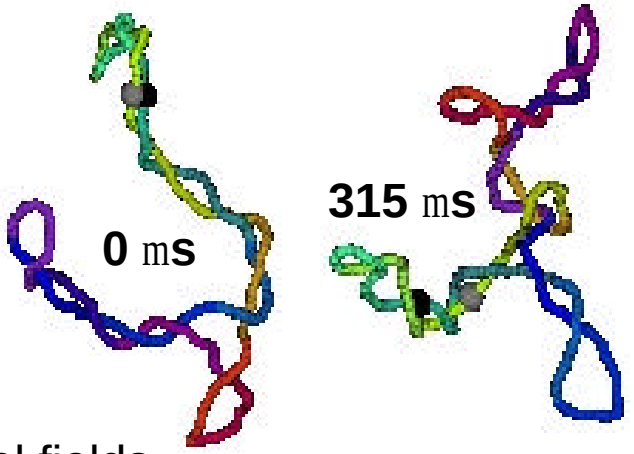
Modeling Cell Electroporation

- Cell membrane electroporation (CME) opens up lipid-protein membanes.
- Can be controlled by E-pulses
- Can be used to extract intacellular components, implant foreign genes, deliver drugs, in-vivo PCR?
- Computational modeling of CME to optimize cell lysis region in bio-chip



DNA Transport and Behavior in External Fields

- Transport and behavor of DNA in external fields: shear, temp., concentrations, electrostatic, electromagnetic,...
- DNA electroelastodynamics (EED) simulated at various levels: Atomistic, Molecular, Brown. Dyn., Bead-Worm, FEM,...
- Investigating application of ACE+ Filament Module for coupling DNA EED and DNA transport in external fields.



CONCLUSION

Multi-Disciplinary Computational Modeling Techniques Can Be Effectively Applied for the Design and Analysis of Microfluidic Biodiagnostic Devices and Biochemical Assays

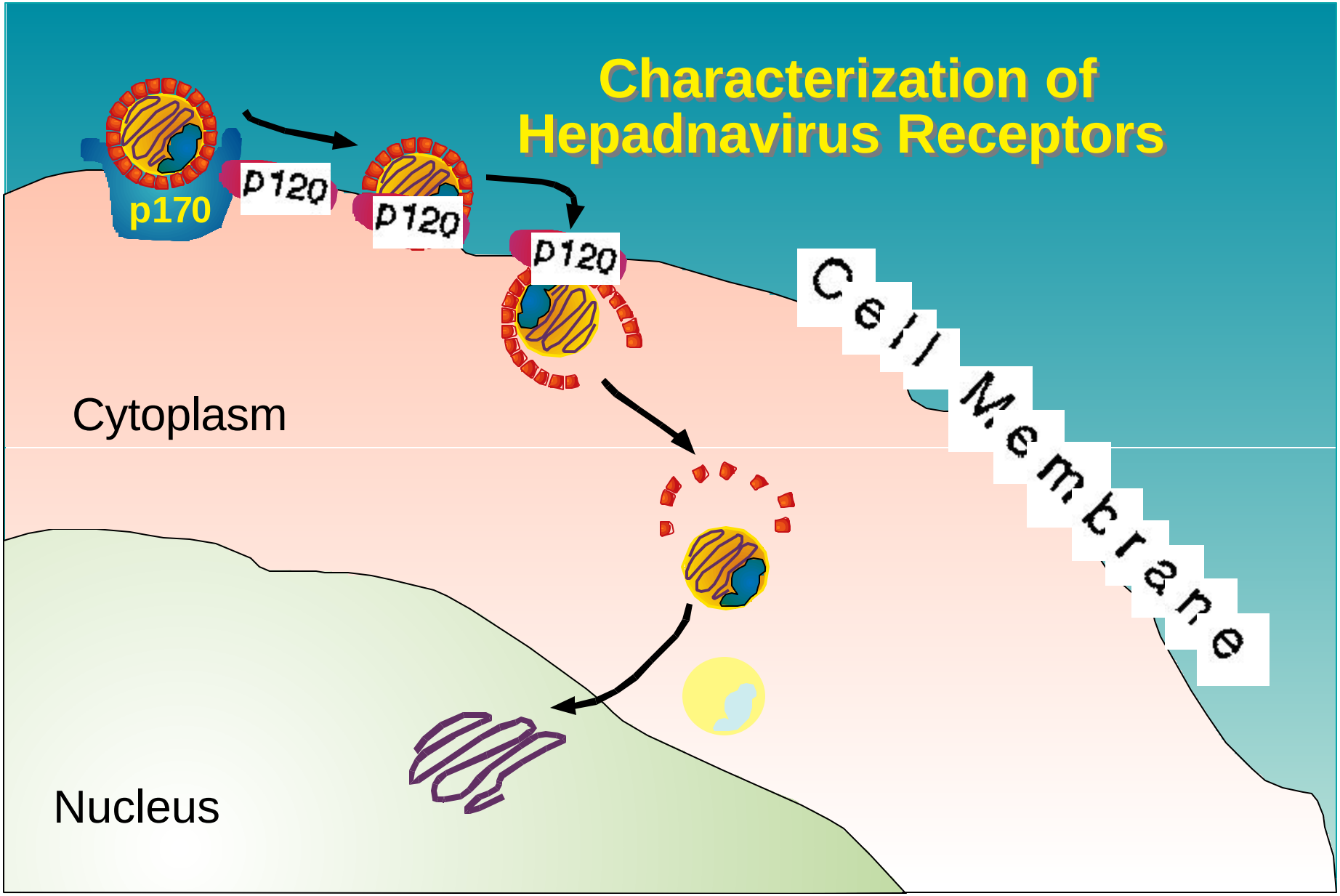
Acknowledgements

Funding for this work was obtained through grants from the DARPA/MTO Composite CAD Program and from the NIST ATP Program

Receptor Mediated Regulation of Cell Behavior
A Highly Interactive Control System

Massachusetts Institute Of Technology

Linda Griffith

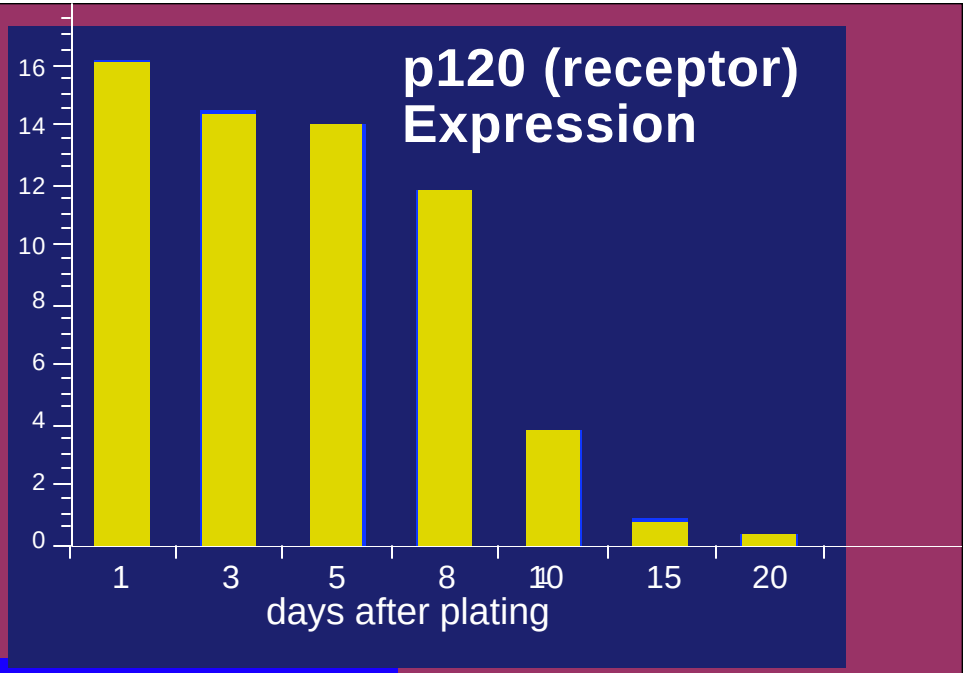

Characterization of
Hepadnavirus Receptors
p170
p120
p120
p120
Cell Membrane
Cytoplasm
Nucleus

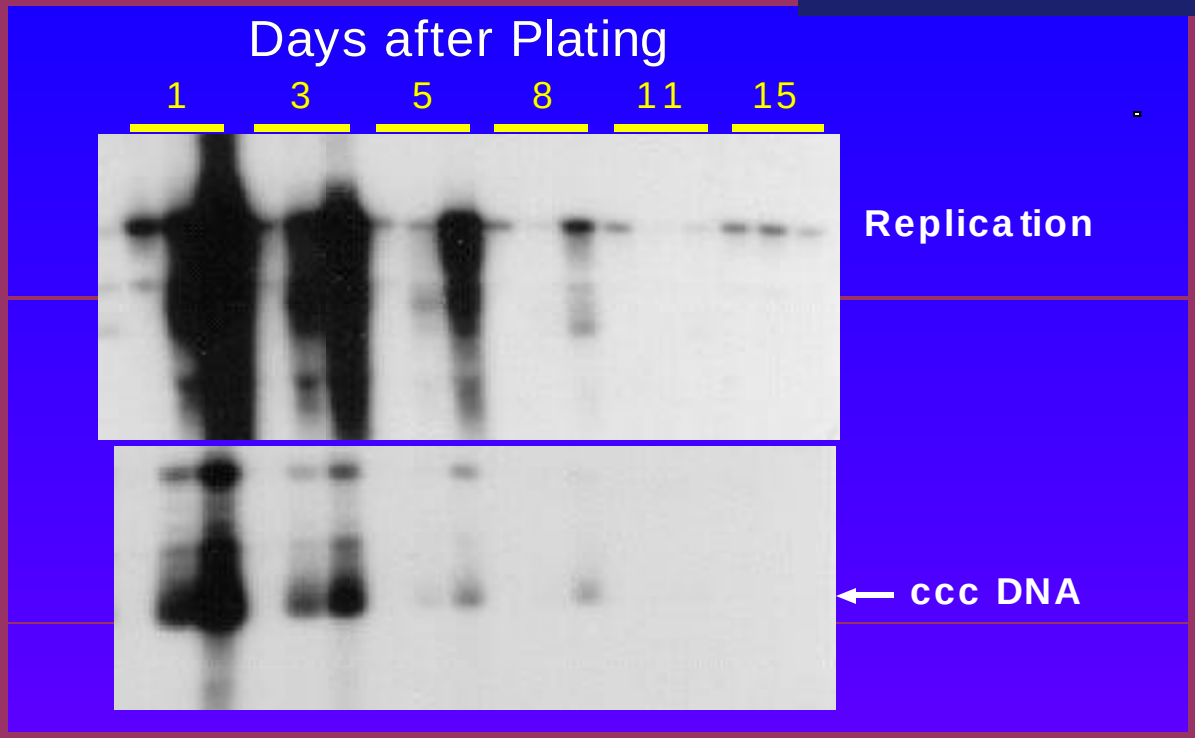
Viral Entry into Cells (cccDNA)

& Viral Replication

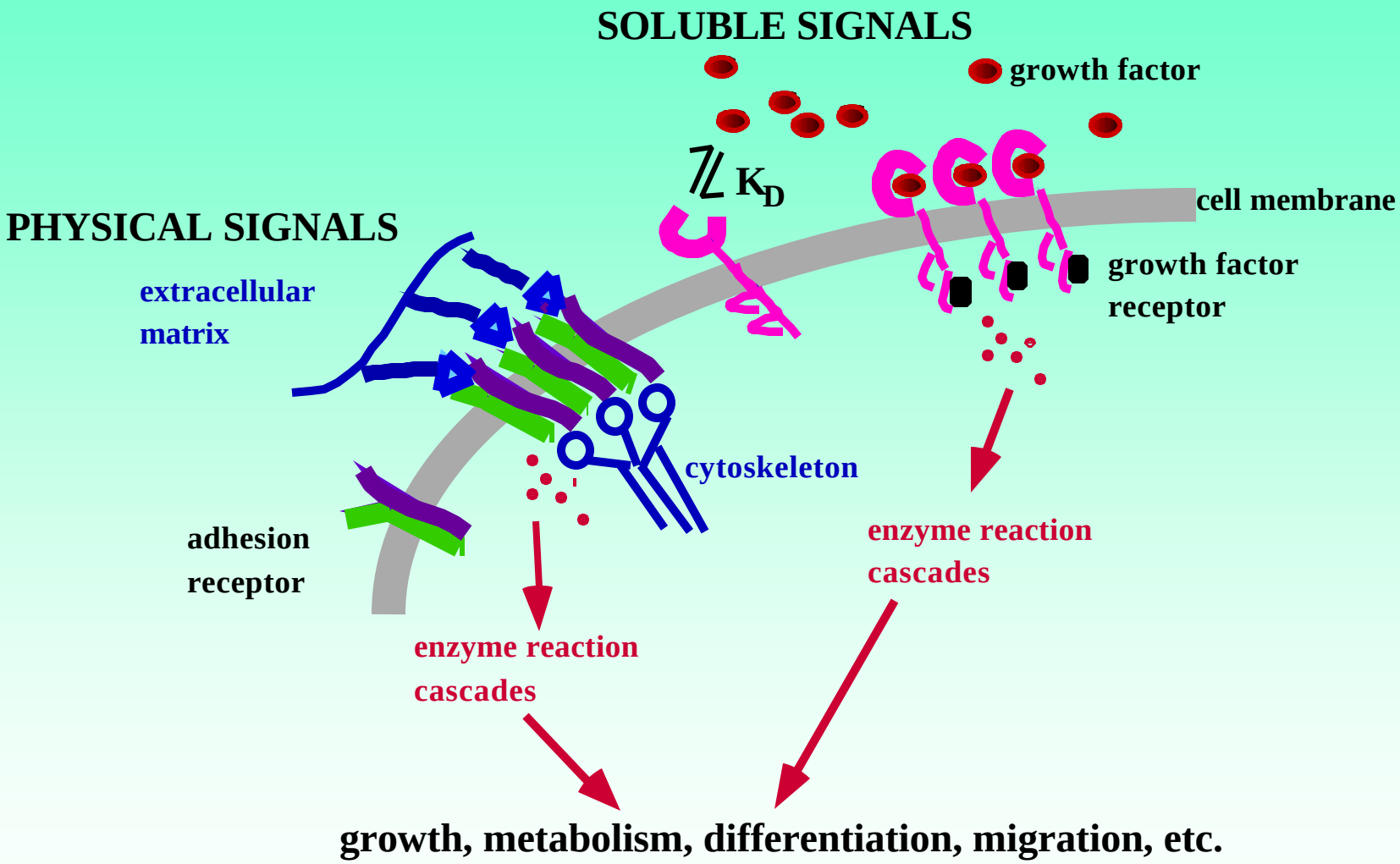
Decline Concordantly with

Loss of Receptor Expression





Receptors -- Cellular "Thermostats"



100-1000 different types per cell!

Cell Migration Speed:

Effects of Adhesion Molecule (Peptide) "X"

Lab A: cells move fast on "X"

Lab B: cells move slowly on "X"

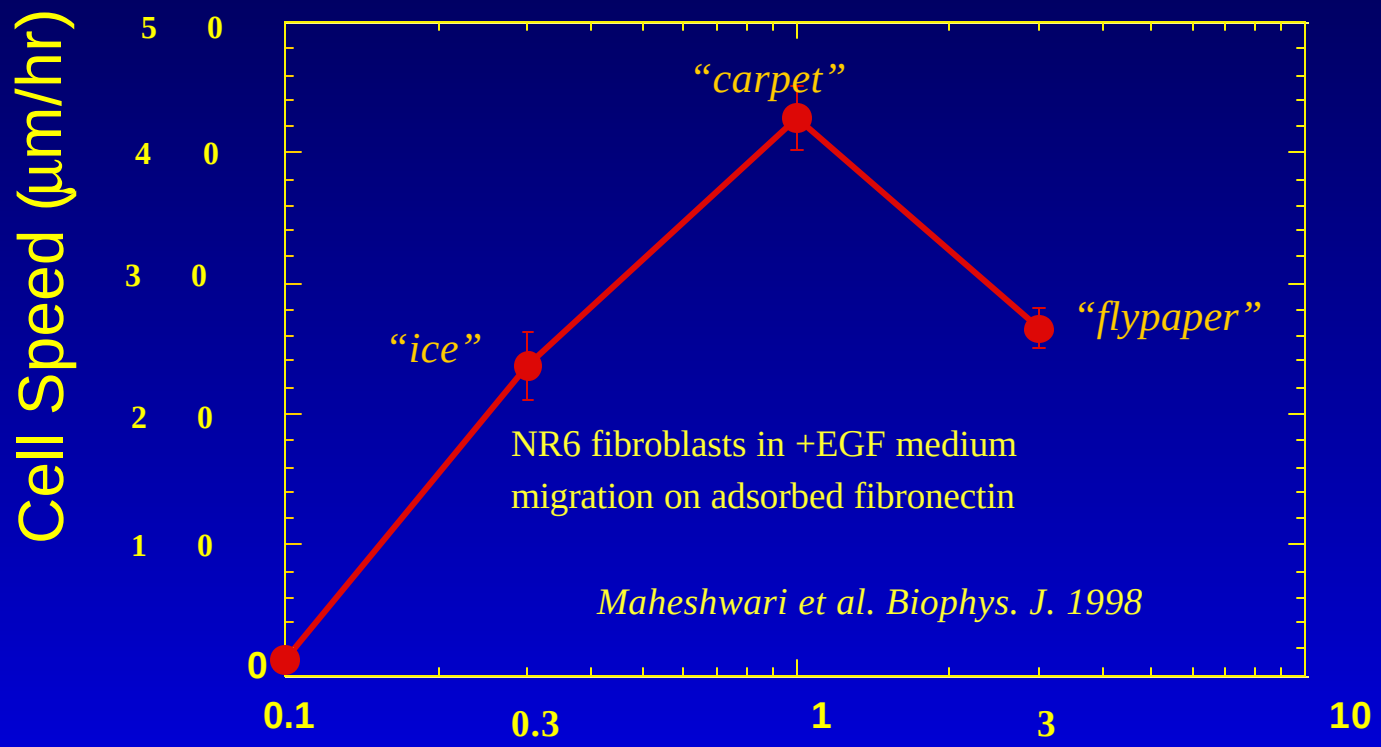
???

Student "GM" DATA

DATE	Cell Speed (micron/hour)
7/15/97	22 ± 3
8/12/97	41 ± 3
9/30/97	25 ± 2

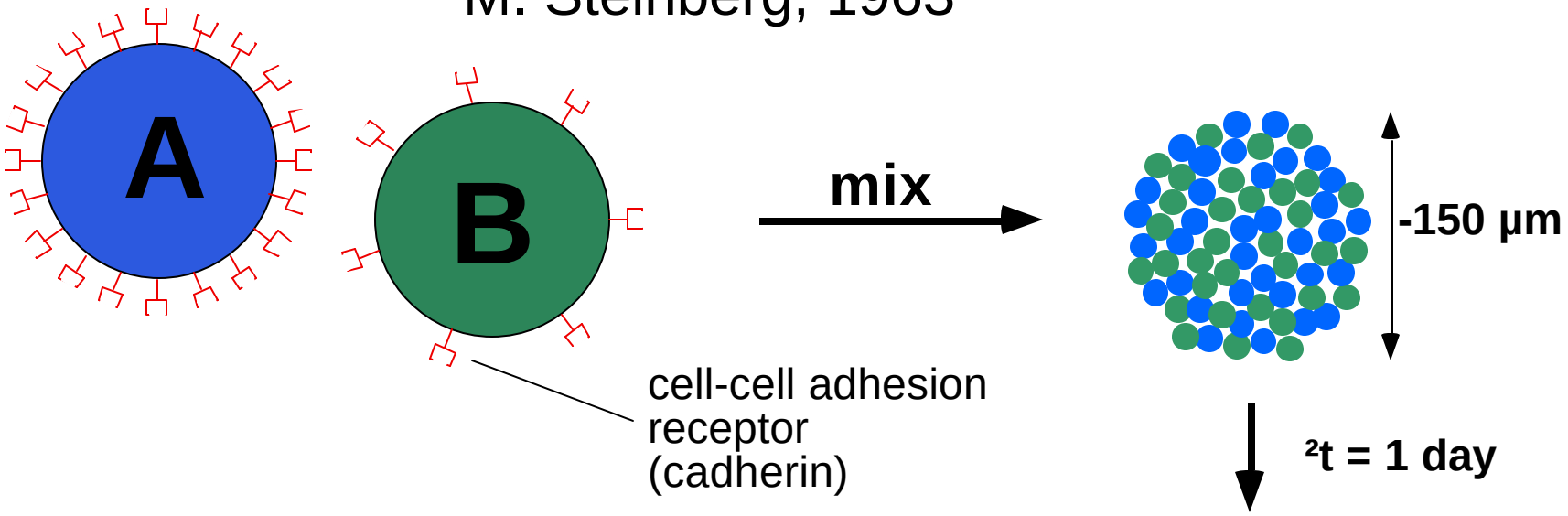
Should "GM" be fired?!

"GM" Data in Context



Adhesion-Based Cell Sorting
(cellular "self-assembly")

M. Steinberg, 1963



relative strengths of adhesion

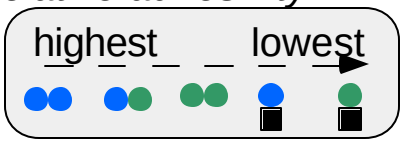
Cell Sorting on Surfaces

Adhesive Interactions

- cell type A - cell type A
- cell type B - cell type B
- cell type A - cell type B
- cell type A - surface
- cell type B - surface

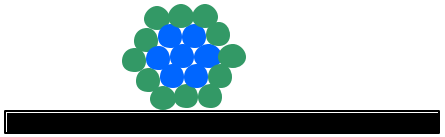
Cell-Cell Forces > Cell-Surface Forces

relative adhesivity



¾

predicted outcome



Cell-Surface Forces > Cell-Cell Forces

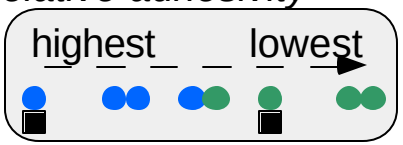
relative adhesivity

¾

predicted outcome

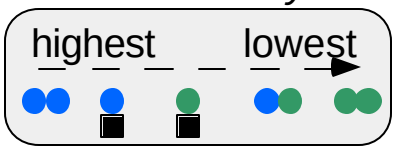
Intermediate (examples)

relative adhesivity

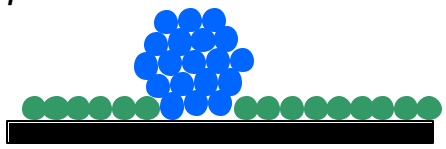


predicted outcome

relative adhesivity

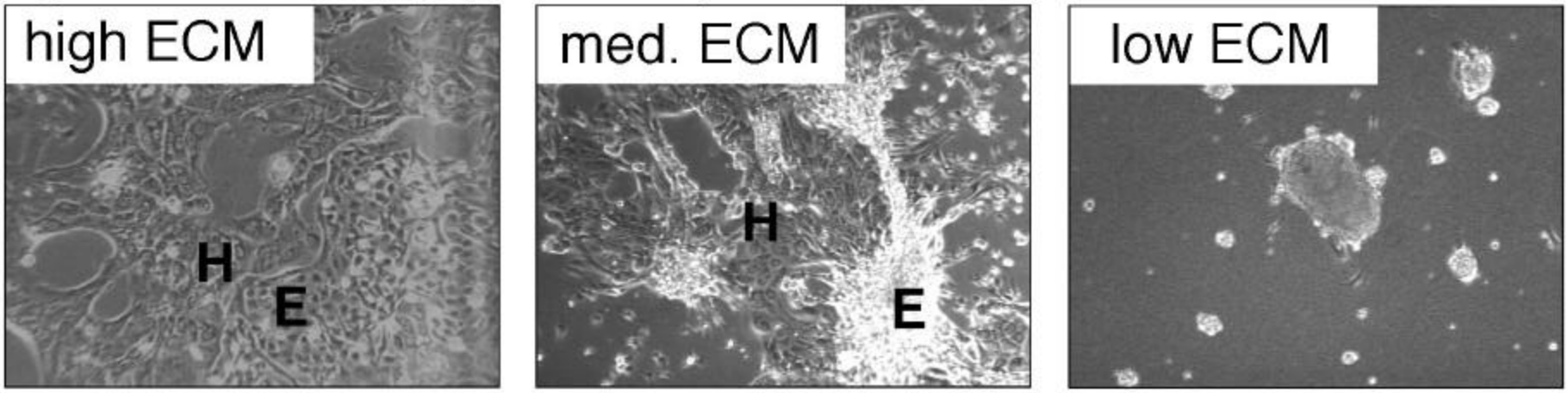


predicted outcome

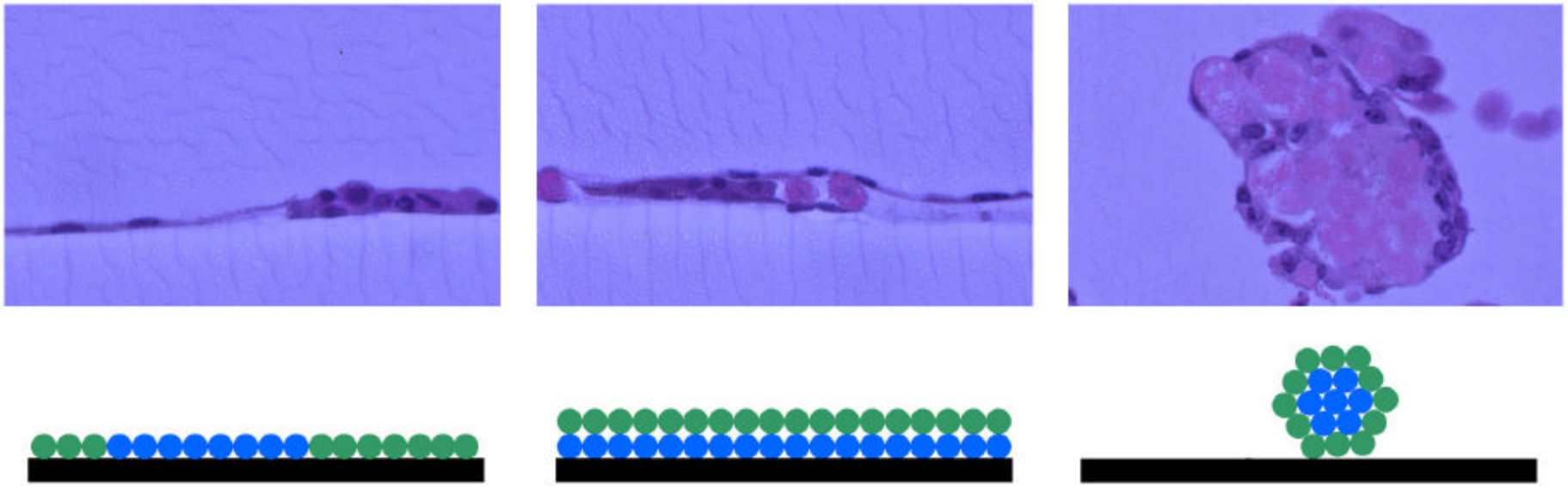


Hepatocyte/Endothelial Cell Sorting

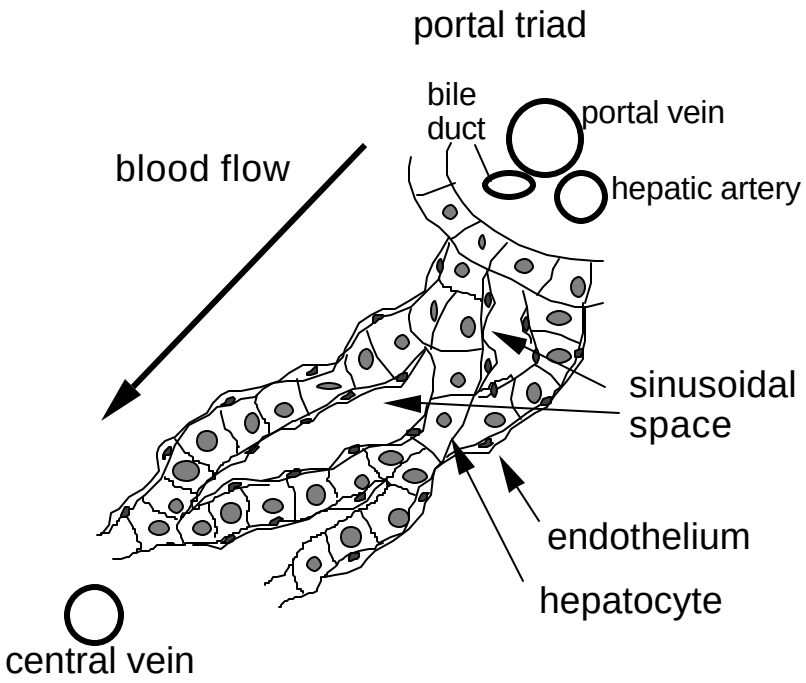
light microscopy (top view)



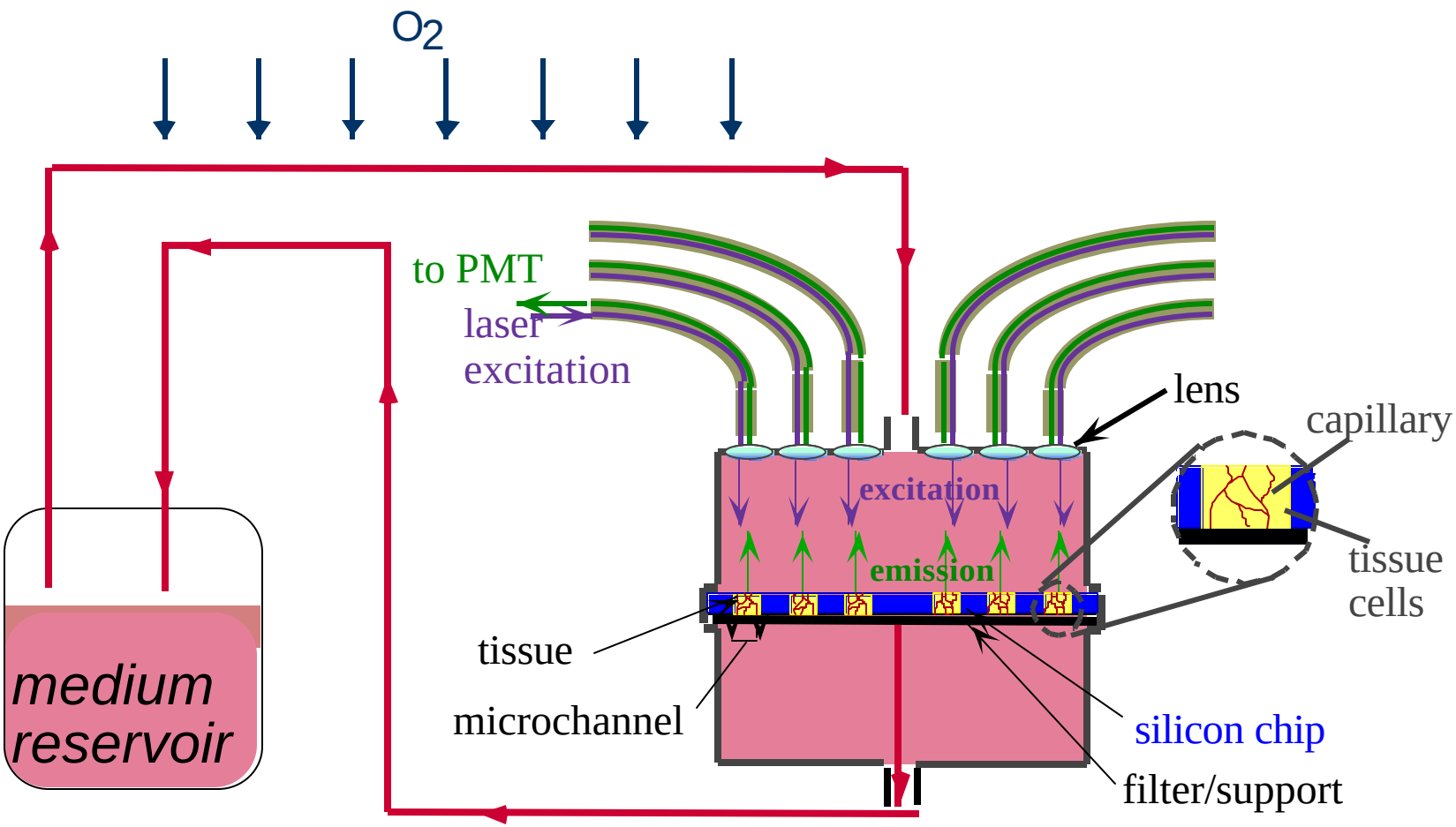
histology (vertical cut; hematoxylin & eosin stain)



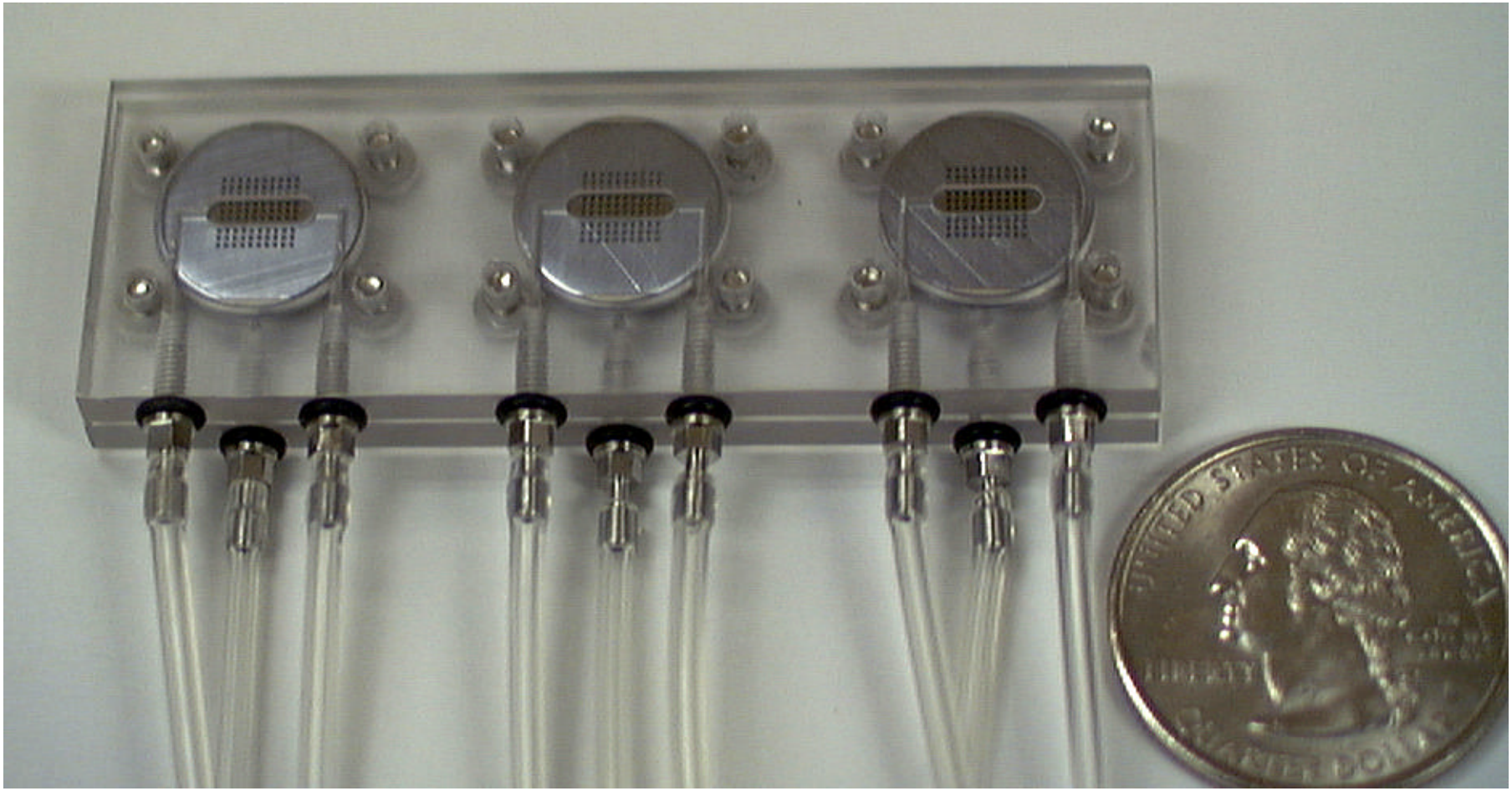
Basic Structural Unit (Capillary Bed) of Liver



Vascularized Tissue Sensor System Components



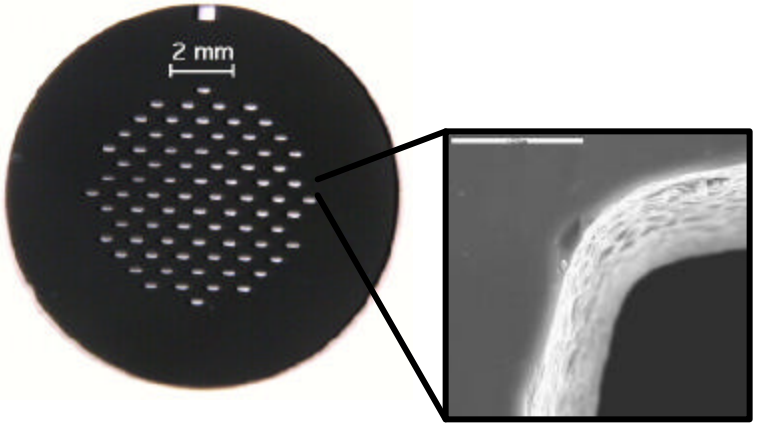
Polycarbonate Bioreactor Array



Microfabricated structures for tissue engineering

griffith, powers, et al. '9

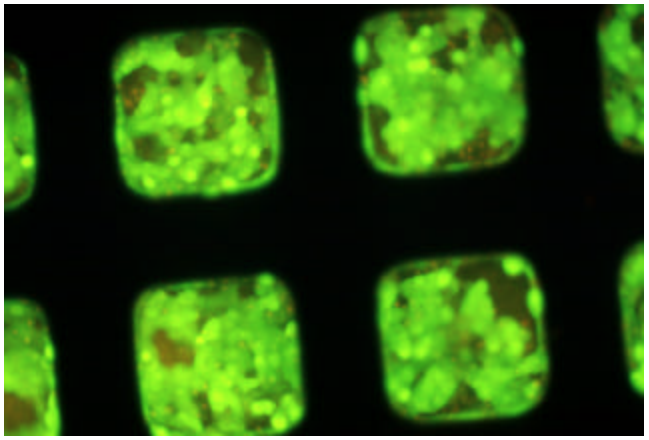
liver



DRIE silicon scaffolds, 250 micron deep channels

liver cells

perfusion bioreactor



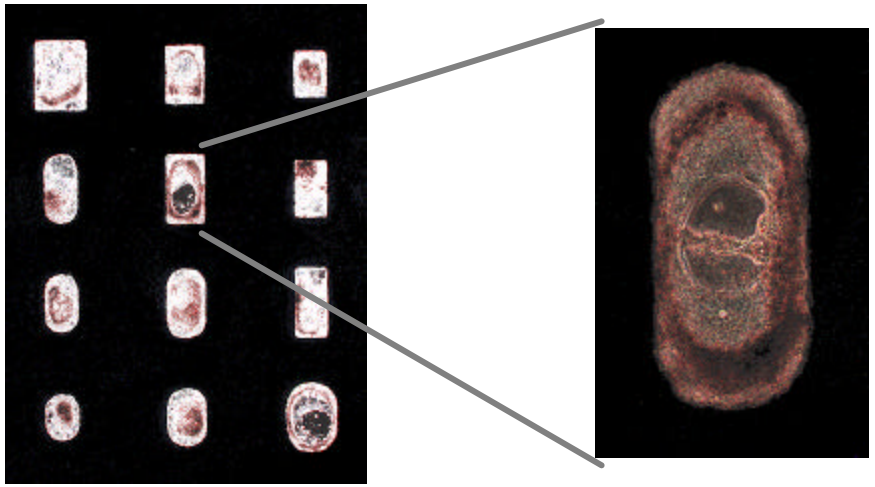
Calcein AM/ethidium homodimer stain; 0.2 mm x 0.2 mm channels

mouse ES cells

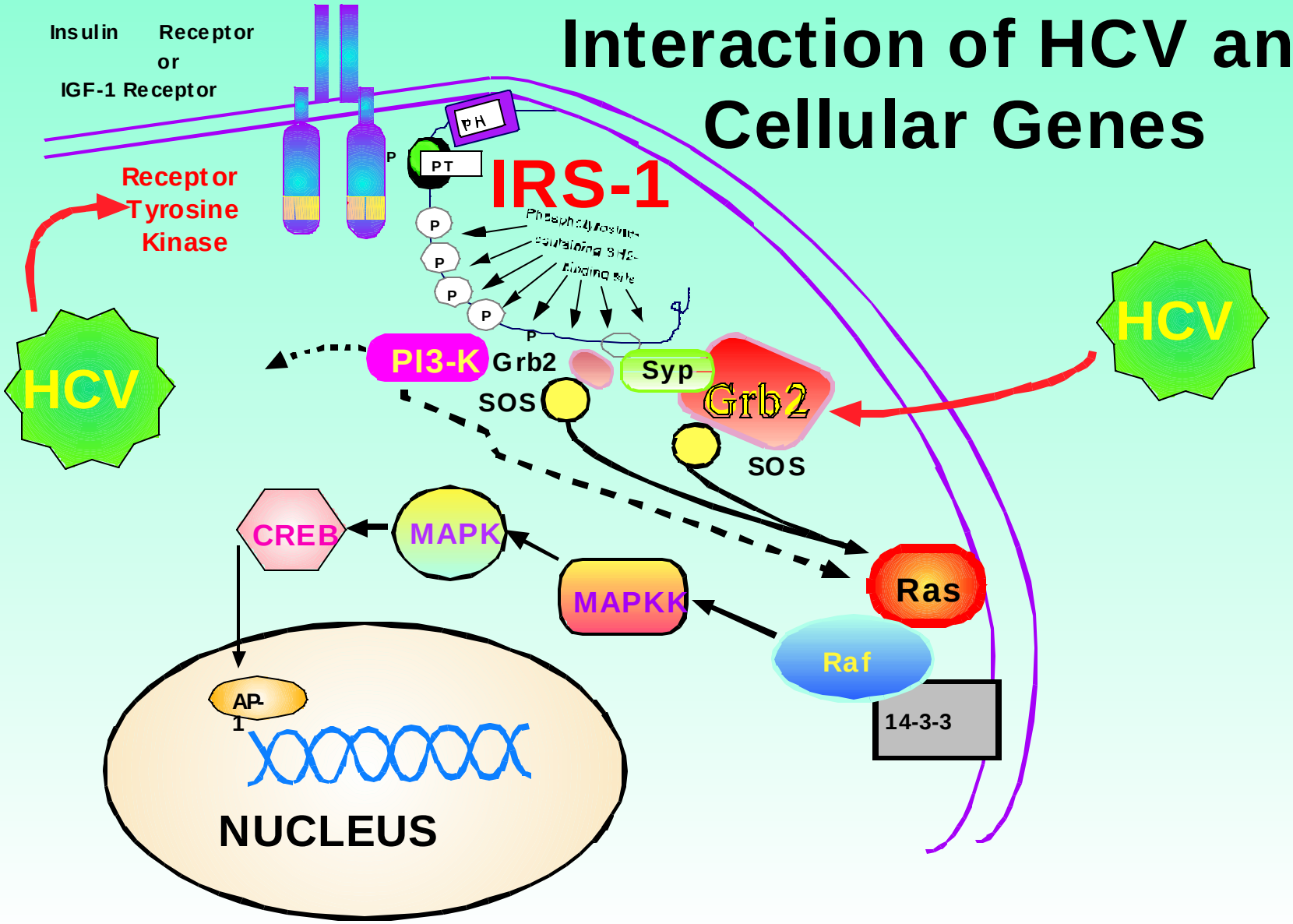
Non-classical embryoid body formation in DRIE silicon scaffolds.

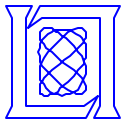
Optimal channel size > 600 μm.

Static culture.



Interaction of HCV and Cellular Genes





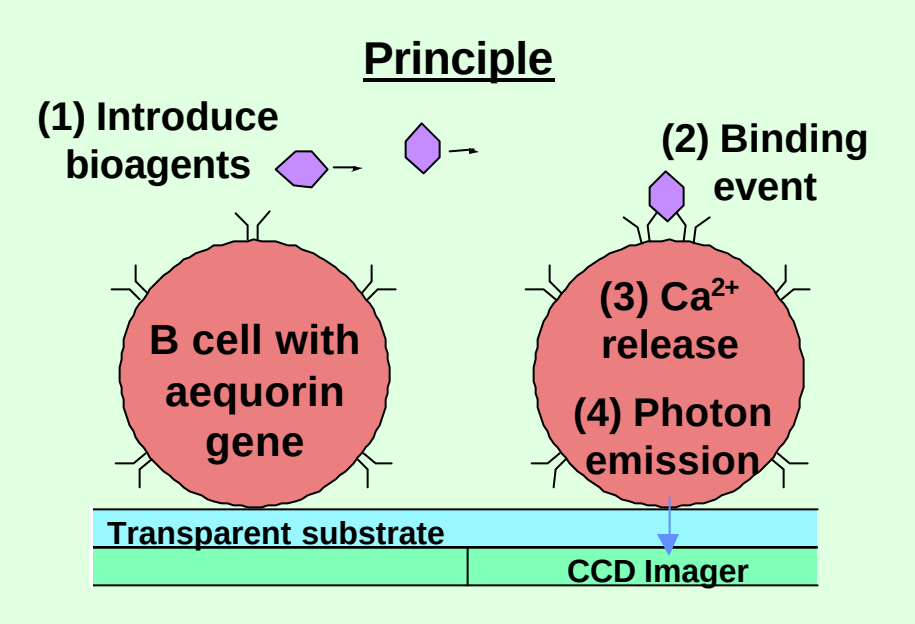
Modeling the CANARY Sensor

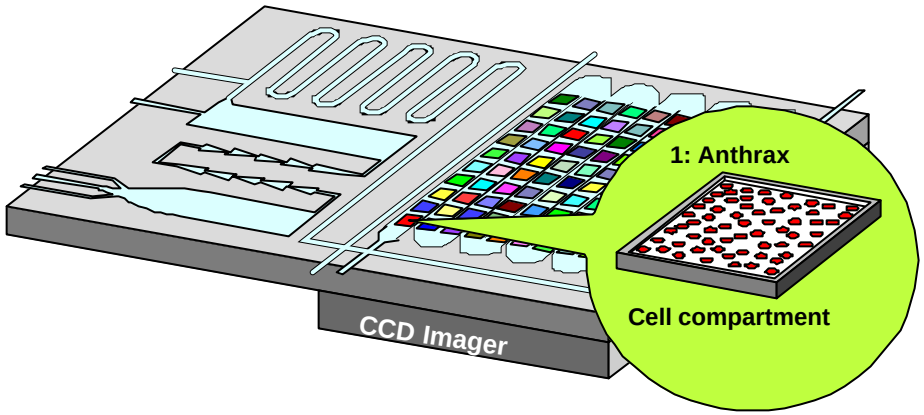
Computational Modeling and Simulation of Biological Systems

Ann Rundell
MIT Lincoln Laboratory
11/18/99

Funded by DARPA , TBB program
Initiated March 1, 1999

Description of the CANARY Sensor





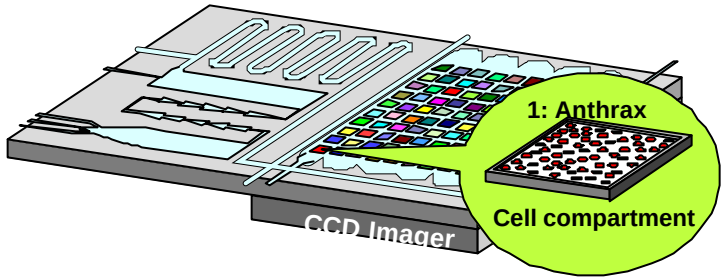
- Rapid ID of bio-agent near single particle level
- Identifies biological agent by exploiting the specificity & signal amplification of B cells
  - Cells have been transfected with an aequorin gene to make them emit photons when activated by the appropriate antigen

Objectives of Modeling the CANARY Sensor

- **Assist sensor design**
  - **Model modules**
    - **agent delivery**
    - **sensing mechanism**
    - **detection system**
    - **signal processing**
  - **Explore various module configurations**
  - **Evaluate trade-offs for components**
  - **Design system to optimize sensor/system performance**

- **Predict system performance**

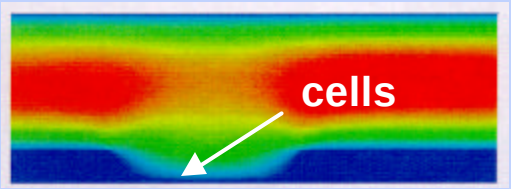
Computational Approach



Binding State Data

Transport of Antigen to Cells

Microfluidic CFD*

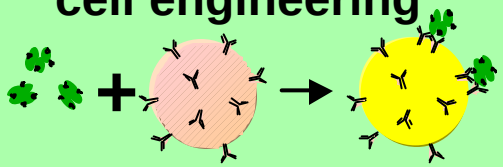


- Improve antigen presentation to B-cells
- Understand design tradeoffs

Photon Emission of Cell Response to Antigen

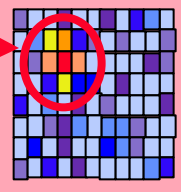
1) Empirical
2) Phenomenological

- Understand relationship of signal transduction pathway elements
- Anticipate results of cell engineering



Photon Detection

- Compare various strategies for photon detection
  - Intensifier & CCD, PD, or APD
- Develop algorithm to detect antigen stimulated photon generation



* in collaboration with CFDRC

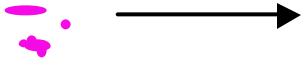
Factors Contributing to Sensor Performance

Modeling Tasks	Transport of Antigen to Cells*	Cell Response	Photon Detection	Data
Performance Measures				
Sensitivity	likelihood of encounter	dosage	noise & resolution	
Response Time	time to encounter	cell response time	processing time	
False Alarms	shear stress	affinity,valency dosage, resting emission	noise & resolution	
Storage and operating lifetimes		coelenterazine consumption		
Design Optimization				
Design of fluid flow	mechanical configurations			
Cellular engineering vs. imaging system design		receptor density, affinity, Ca^{2+}storage, Aequorin	noise & resolution, intensifier, (CCD,PD,APD)	
Algorithm development		cell emission (stimulated, resting)	noise & resolution	

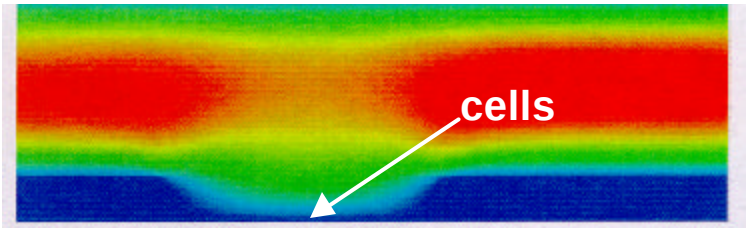
* in collaboration with CFDRC

Transport of Antigen to Cells

Antigen Particles



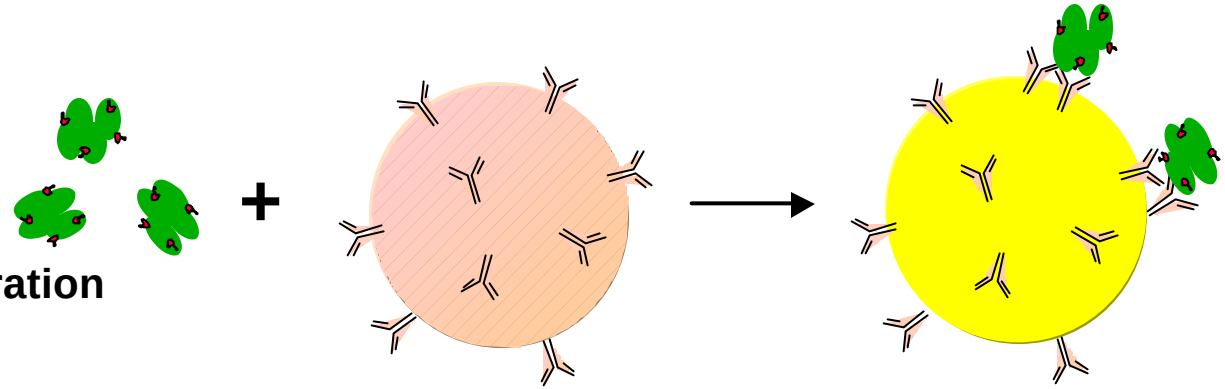
Velocity Profile Across Well Configuration



- Transport dynamics dependent upon physical properties of antigen
  - buoyancy
  - mass
  - geometrical shape (sphere, rod, asymmetric, etc.)
  - surface roughness
- Diffusion describes transport of ligand molecules, very small antigens << 1㎛ diameter
- Suspect that active transport (fluid flow lines) important for large buoyant particles
- Modeling in collaboration with CFDRC

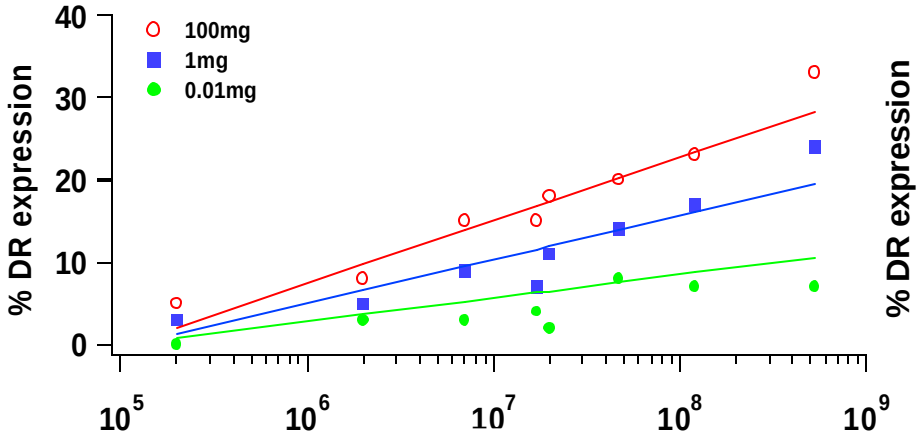
Development of Empirical Model

Antigen
- valence
- affinity
- concentration

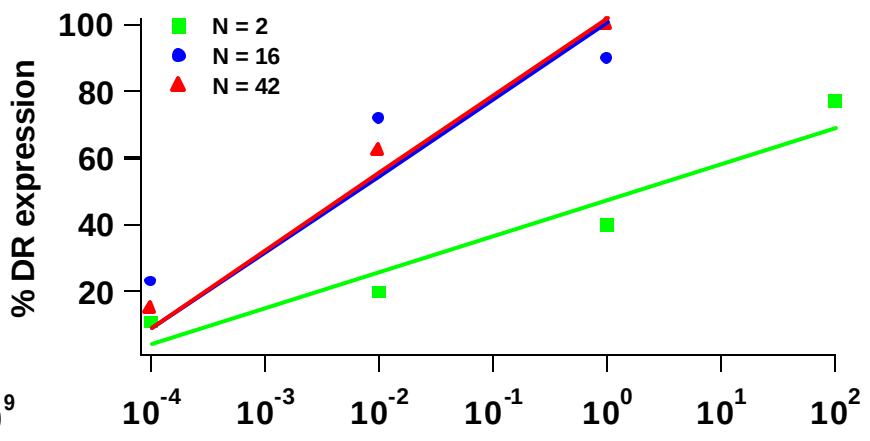


Cell stimulation = k* f_b(valency)* f_k(affinity)*f_r(concentration)

Valency (N)



Affinity (M^{-1})

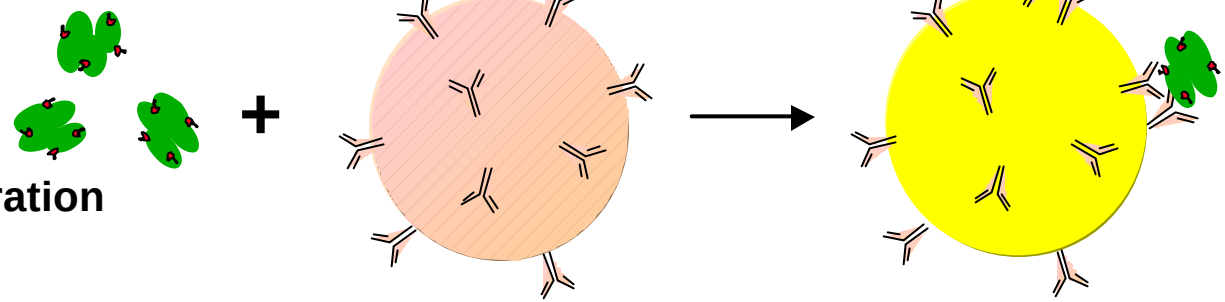


Concentration (mg/ml)

[1]Mongini, et al. "Membrane IgM-mediated Signaling…"*Journal of Immunology,* 1992

[2]Mongini et al. "Affinity Requirements…" *Journal of Immunology,* 1991

Development of Phenomenological Model



Binding of surface receptors → **Production of IP_3** → **Calcium dynamics** → **Photon generation**

Perelson & Sulzer*, Wofsy & Goldstein, Paek & Schramm, DeLisi

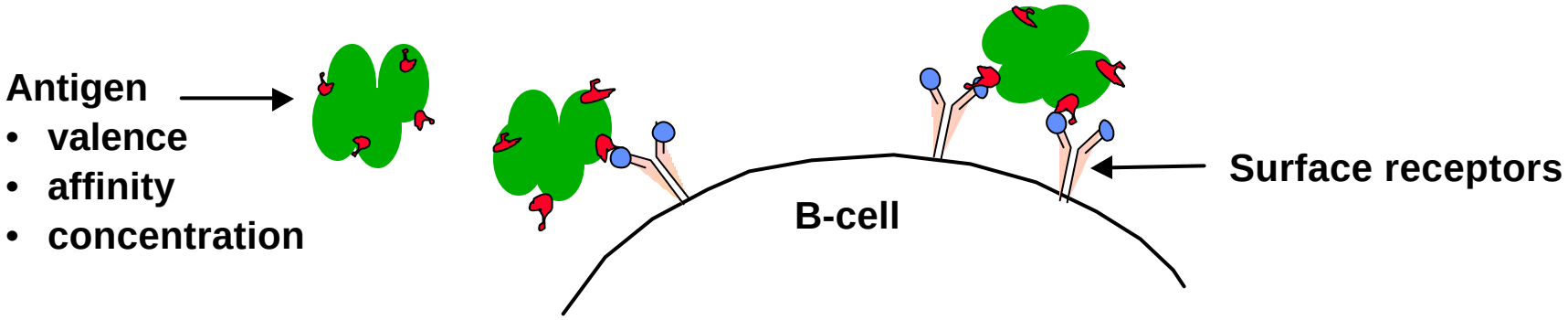
Similar mechanism by Lauffenburger and Linderman

Keizer & Smith*, Othmer-Tang

Shimomura, Button & Brownstein Allens, Blinks, & Prendergast*

* Models incorporated into CANARY phenomenological model

Modeling the Binding of Antigen to the Cell Surface Receptors



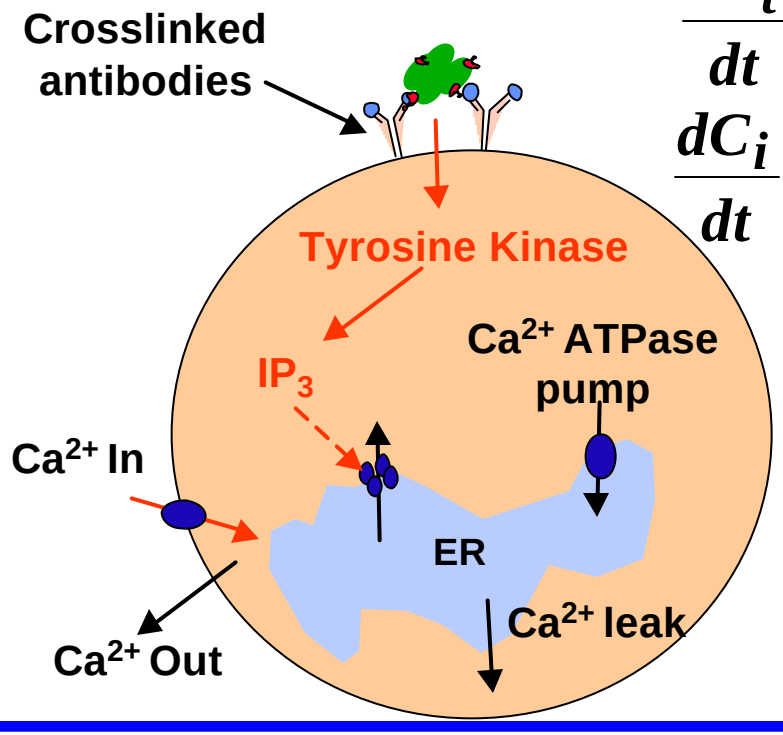
$$\frac{d}{dt}\left[\text{Ag–R}\right] = \boxed{\text{Binding of free antigen with free receptor}} - \boxed{\text{Dissociation of complex}} - \boxed{\text{Crosslinking of complex with free receptor}} + \boxed{\text{Dissociation of crosslinked complex}}$$

eg. $$\frac{dx_1}{dt} = Nk_1A_gR_f - k_{-1}x_1 - (N-1)k_2x_1R_f + 2k_{-2}x_2$$

- Model based upon recent work by Sulzer and Perelson, 1996
  - Sequential binding events
  - Homogeneous distribution of antigen and receptors in cell volume

Antigen Encounter and Subsequent Increase in Intracellular Ca^{2+}

- Structure of Ca^{2+} model by Smith, Lee, Oliver, and Keizer, 1996
- ✓ **Model** extracellular Ca^{2+} influx reflecting physiology: increased rate with emptying of internal Ca^{2+} stores
- **Model** IP_3 as a function of crosslinked antibodies

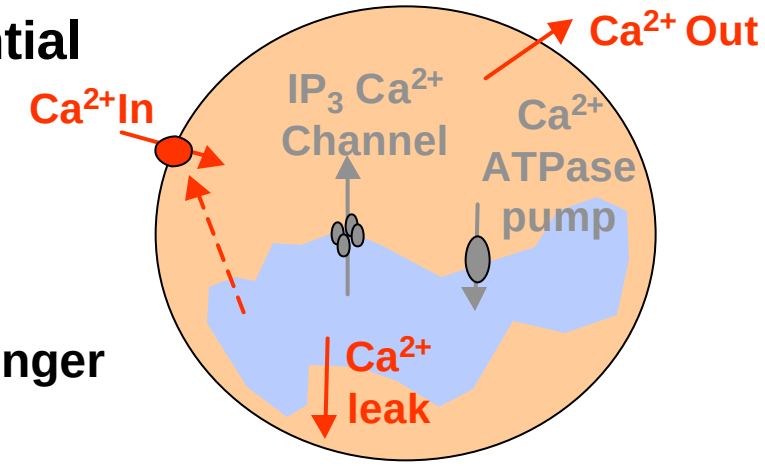


$$\frac{dC_t}{dt} = b_i\left(J_{in} - J_{out}\right)$$

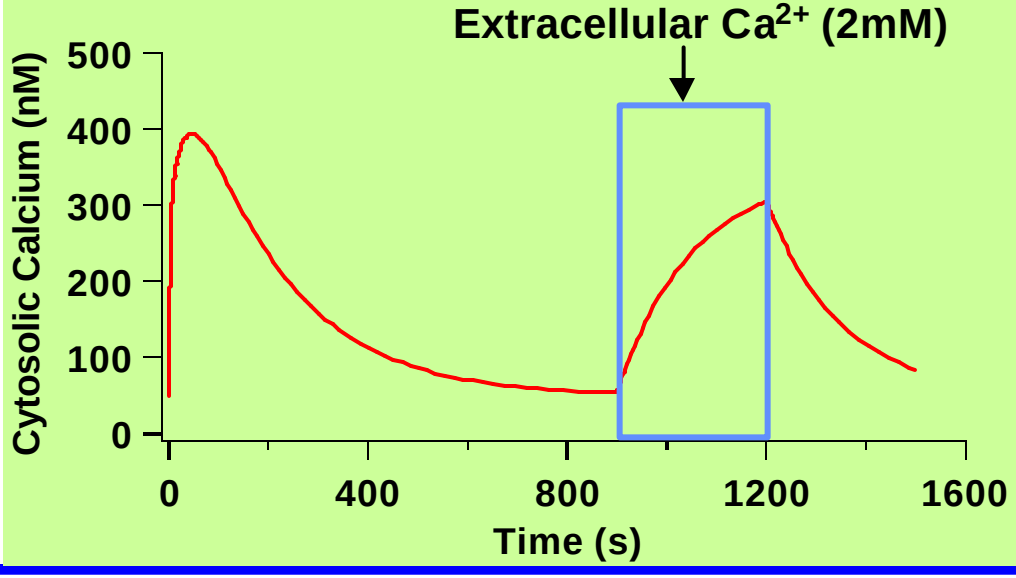
$$\frac{dC_i}{dt} = b_i\left(J_{ip3} + J_{leak} - J_{pump} + J_{in} - J_{out}\right)$$

Modeling Extracellular Ca^{2+} Influx

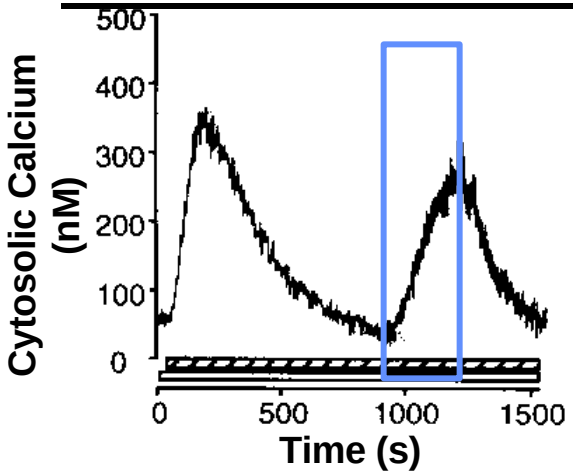
- Previously modeled as an exponential increase
- Model assuming
  - Activated by the depletion of the internal Ca^{2+} stores
  - J_{in} is regulated by a soluble messenger



Simulation Results



Hashimoto[1] Thapsigargin Results with DT40 B-cells



[1]Hashimoto et al. "Inhibitory Modulation of B Cell …", *J of Biol Chem*, pp 11203-11208, 1999.

Current Status of Modeling IP_3 Dynamics

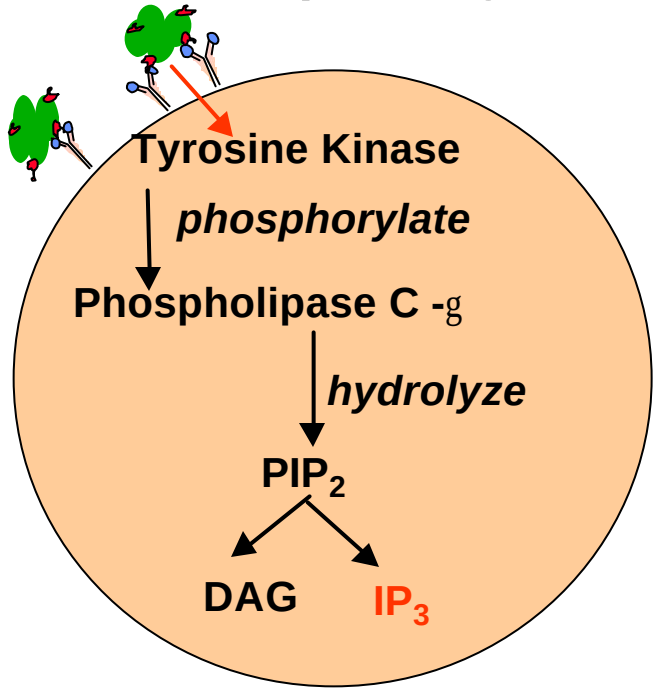
- **Recent elucidation on Tyrosine Kinase activation pathway may assist modeling IP_3 production**

Previous model by Smith et al.

$$\frac{dIP_3}{dt} = v_6(t)\frac{C_a}{C_a + k_6} - v_7 IP_3$$

Approximated by $1-e^{-at}$

Does not account for antigen binding dynamics



Activation of Tyrosine Kinase

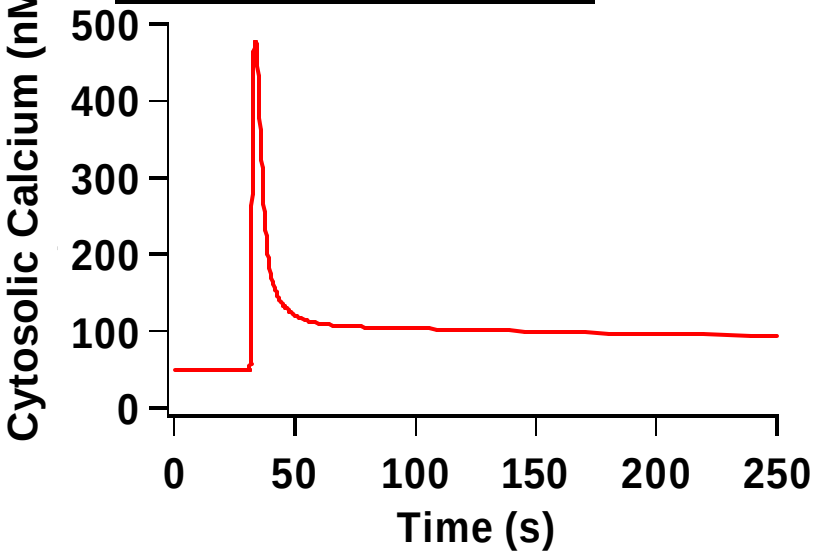
$$\frac{dTy}{dt} = \text{cross link formation} * \text{fraction of receptors bound} * \text{intrinsic affinity of bond} - \text{Half-life}$$

Production of Inositol Triphosphate

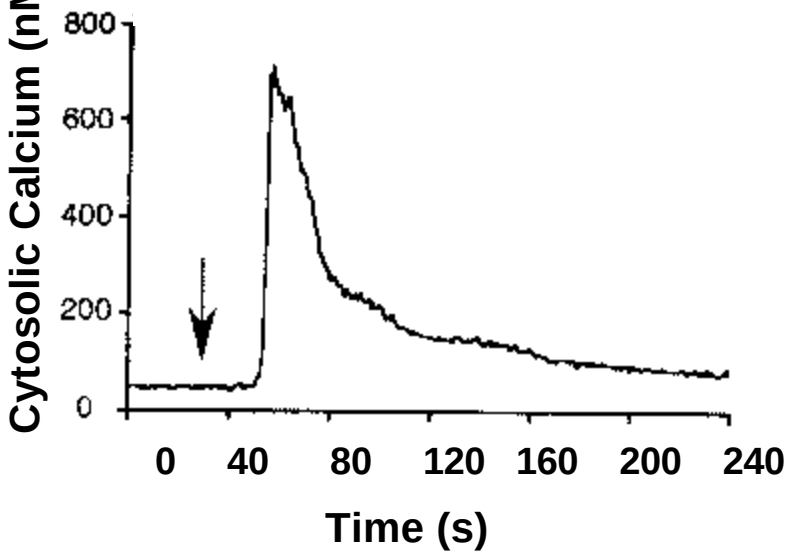
$$\frac{dIP_3}{dt} = v_6 T_y - v_7\left(IP_3 - I_{eq}\right)$$

Antigen Stimulation: Comparison of Model Simulation with Experimental Results

Simulation Results

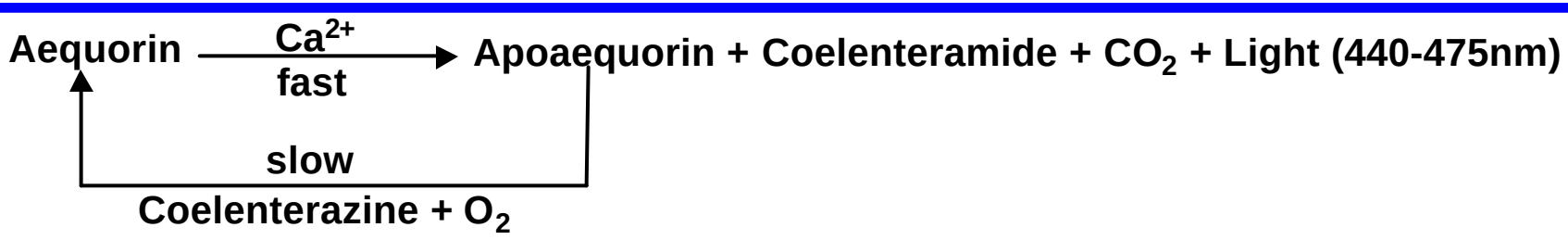


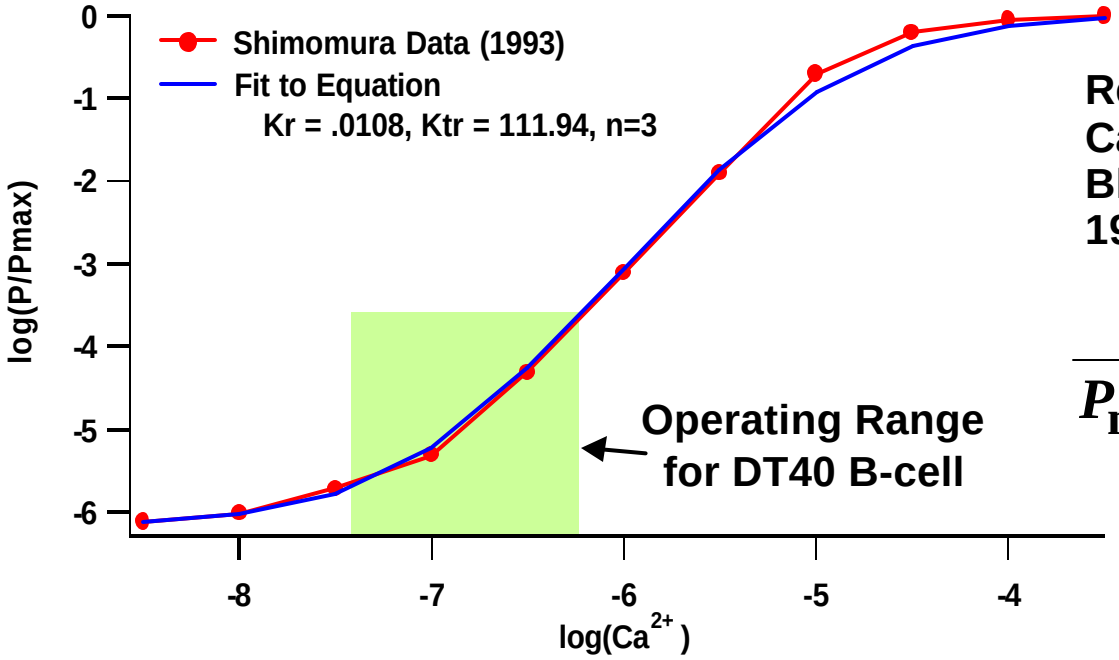
Hashimoto Experimental Results with DT40 B-cells



- **Rapid onset**
  - Experimental data includes antigen transport and diffusion dynamics
- **Narrow Ca^{2+} peak**
  - Experimental data includes diffusion of Ip_3 from production site to activation site and Ca^{2+} distribution through cytoplasm
- **Plateau of Ca^{2+} response**
  - Empirical model used for Tyrosine Kinase activation and Ip_3 production

Modeling Photon Generation

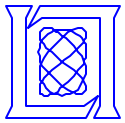




Relationship to convert Ca^{2+} to photons from Allen, Blinks and Prendergast, 1977

$$\frac{P}{P_{max}} = \left(\frac{1 + k_r C_a}{1 + k_{tr} + k_r C_a} \right)^n$$

- **Determine where CANARY B-cell range is**
- **Desirable range of B-cell calcium flux Î [50nM - 10mM]**



Reflections on the Objectives of the Modeling of Biological Systems Workshop

- **Important Biological Processes that need to be modeled**
  - Particle transport to surface
  - Cellular signal transduction mechanisms
- **Using modeling to assist the understanding of complex biological systems**
  - Identification of dominant processes
  - Provides support for hypothesis of operation
- **Modeling's ability to assist design of complex integrated bio-systems**
  - Evaluate input/output relationships of biological components
  - Evaluate tradeoffs between traditional instrumentation engineering vs. cellular or tissue engineering
  - Identify theoretical limitations of biological components
- **Roadblocks/Challenges to achieving modeling objectives in a reasonable time period**
  - Complex nature of biological processes
  - Models are not mature
  - Data to support/validate modeling effort

Design Strategies for Field Deployment Trials of Bees As Active and Passive Detectors of Harmful Agents

Presenters: Colin Henderson & Jerry Bromenshenk

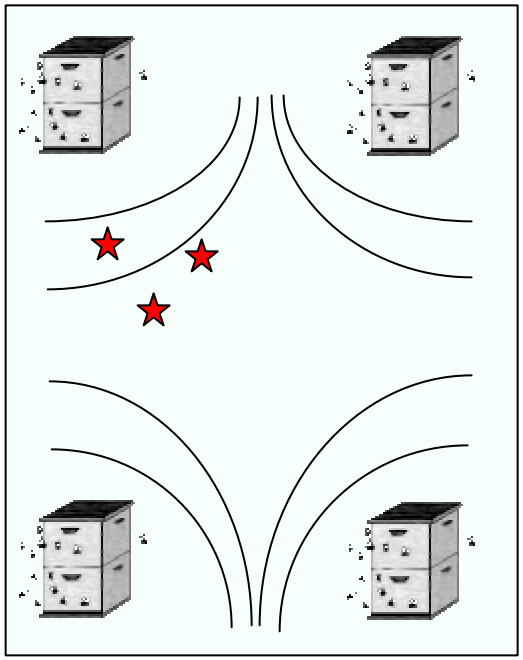
- Bee Alert! Research Team
- The University of Montana-Missoula
- US Army Center for Environmental Health Research
- Oak Ridge National Laboratories
- Sandia National Laboratories
- Pacific Northwest National Laboratories
- Ohio State University
- Monmouth Aerosol Research Laboratory

Now & Then

Sixty beekeeping in the low countries, as depicted by Pieter Brueghel (1565). Detail

Bee Real-Time Surveillance Modes:

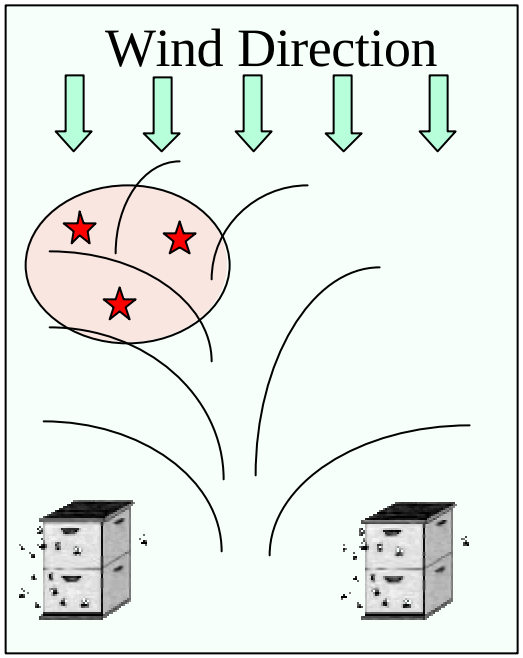
Undirected Flight
(Arrange Hives)



Bees Forage Outward From Hives

Influenced Flight

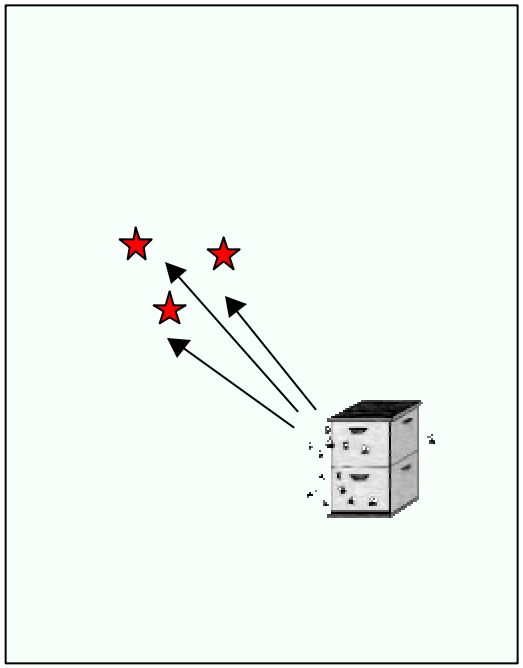
(Attract Bees)



Bees Forage Upwind toward Semiochemical Treated Area

Directed Flight

(Train Bees)



Bees Direct Search toward Target Agent Or Device

The University of Montana

Semiochemical

Agent of Harm

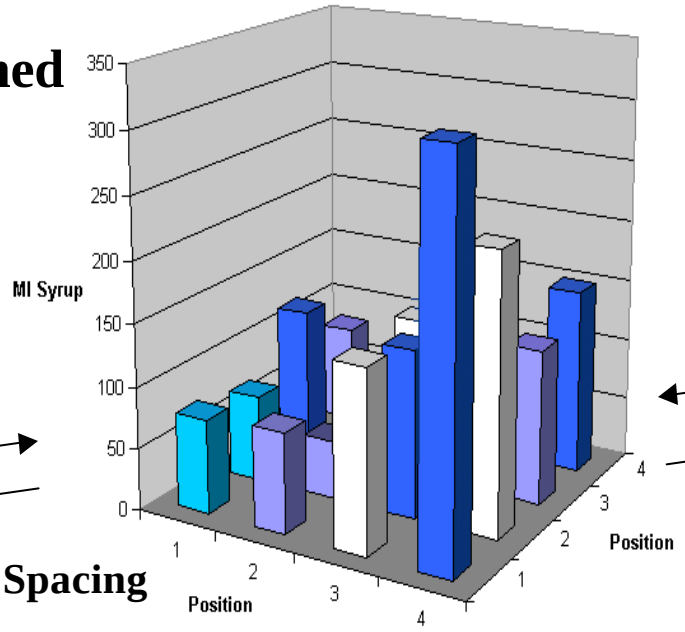
Sandia Cafeteria Trials

Wind

Cafeteria GH-4

Syrup Consumed in 2 Hrs

Bees Initially Unconditioned to Explosives



Anise Lure

Hive

75 m

75 m

1 m Grid Spacing

	1	2	3	4
1	76	81	146	319
2	69	47	135	225
3	117	78	75	125
4	80	100	103	150

DNT

TNT

RDX

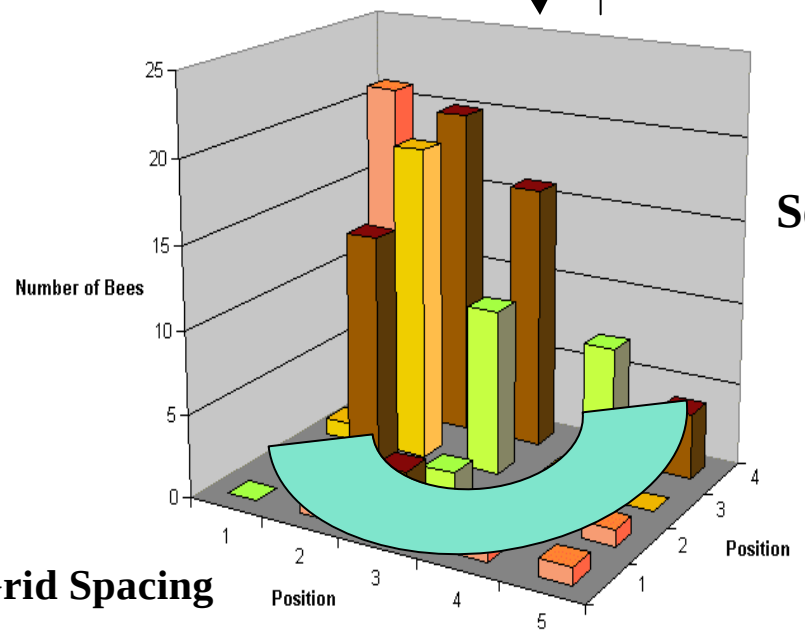
ANISE

Missoula Cafeteria Trials

Hive

75 m

Bees Conditioned to Acetophenone



Soils in Petri Dishes

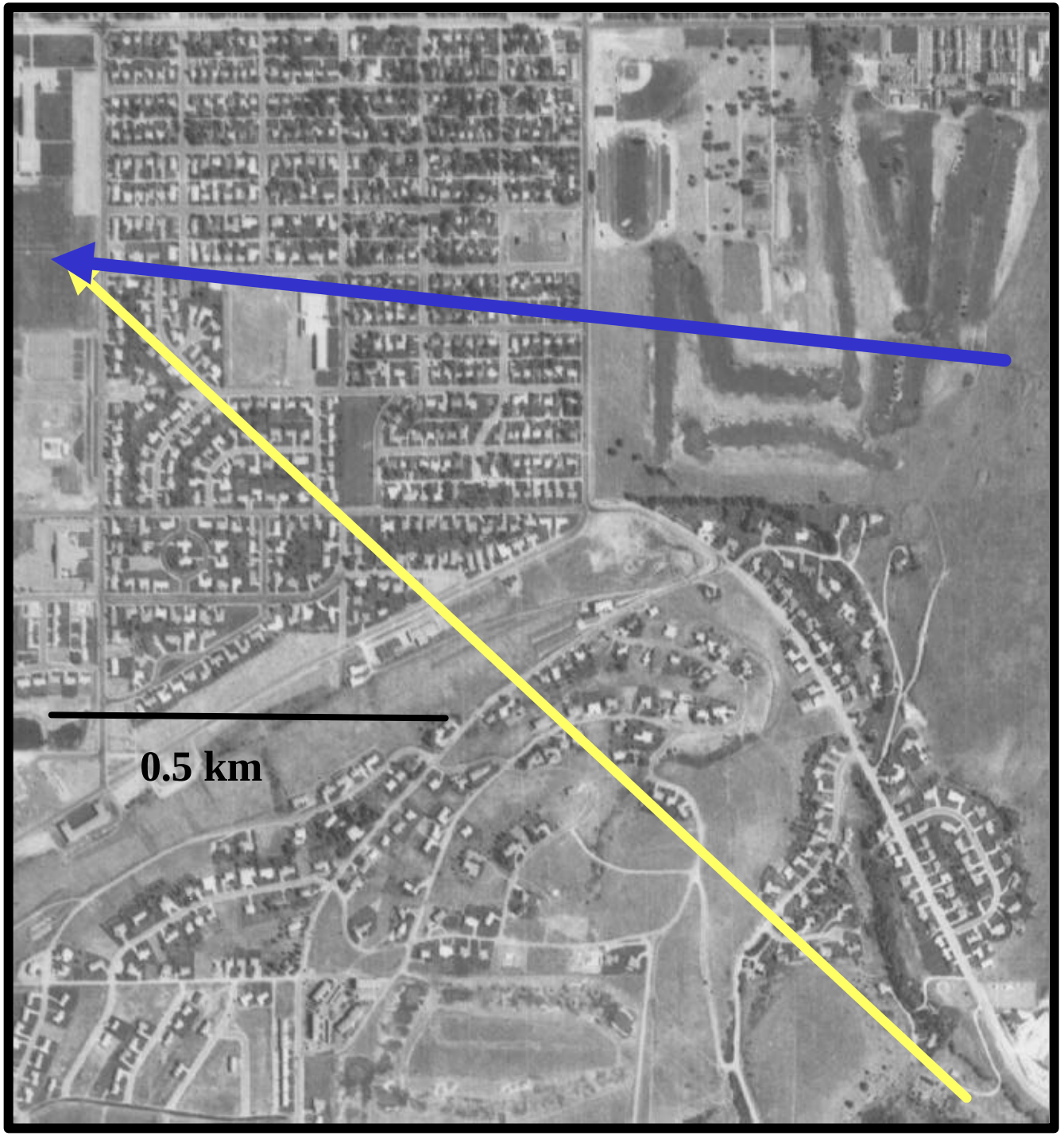
Wind

1 m Grid Spacing

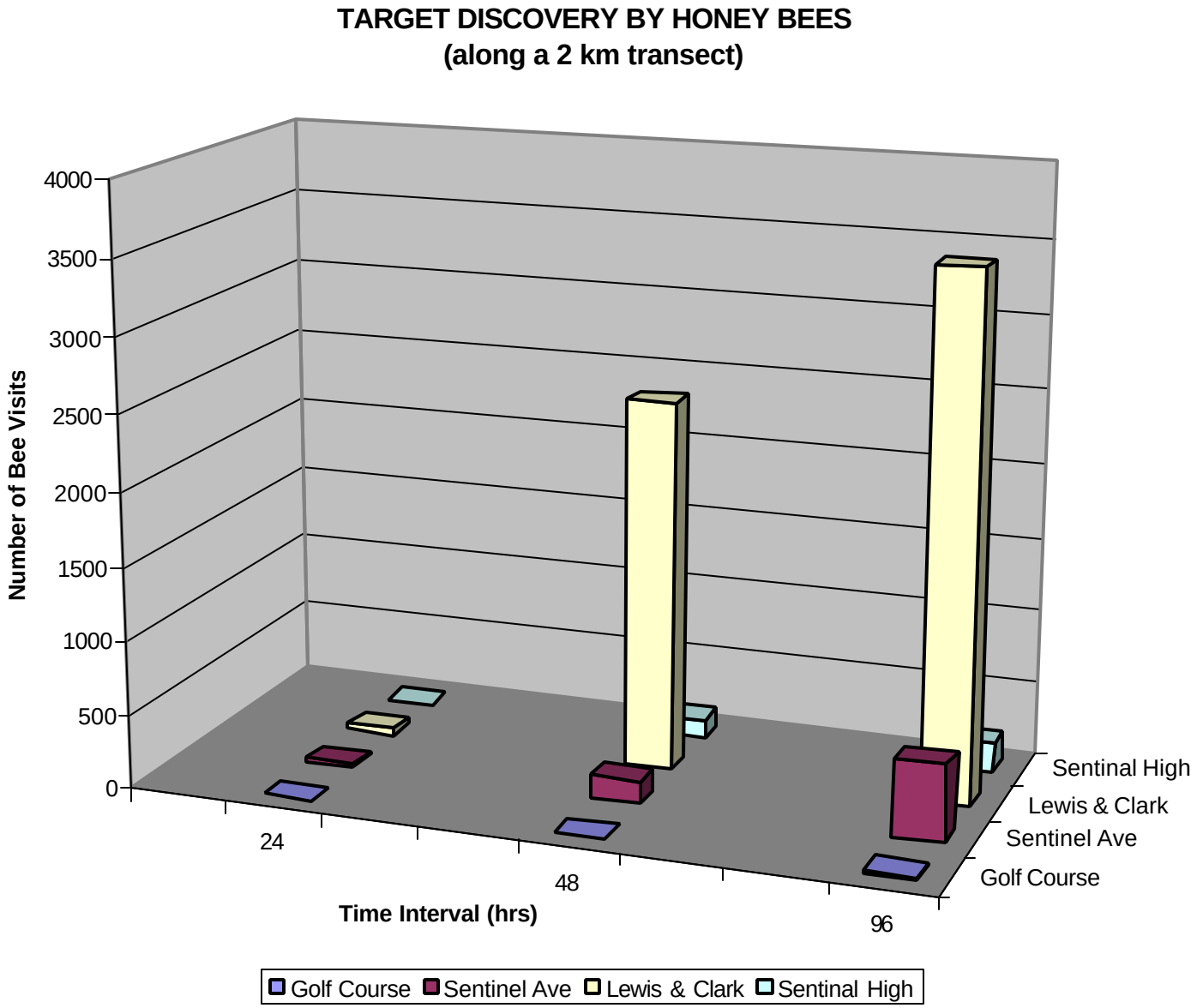
	1	2	3	4	5
1	0	1	4	1	1
2	0	15	2	0	1
3	1	19	10	1	0
4	21	20	16	7	4

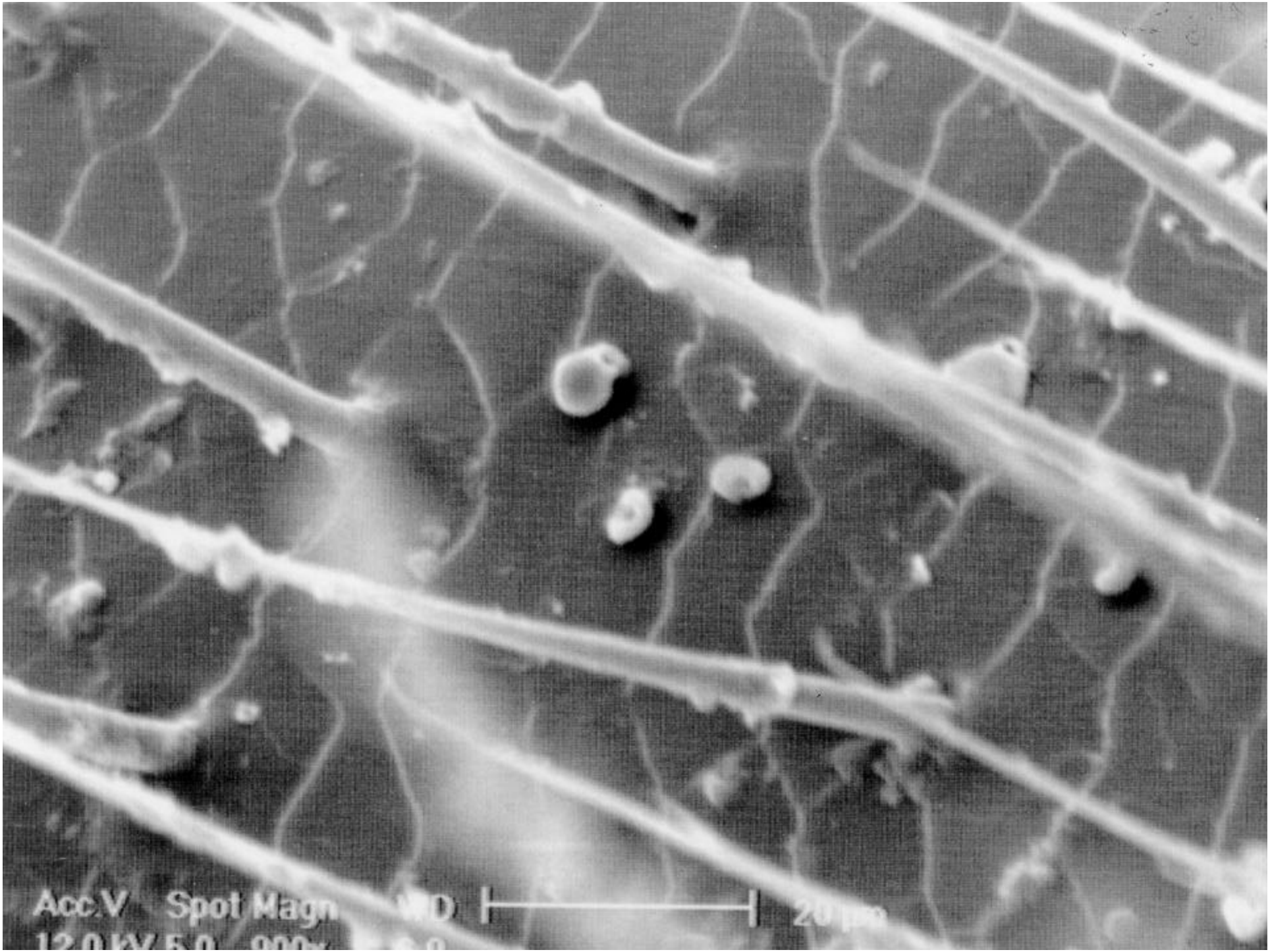
Soil +

- **NONE**
- **ETOH**
- **ACPH**
- **ETOH +ACPH**


0.5 km

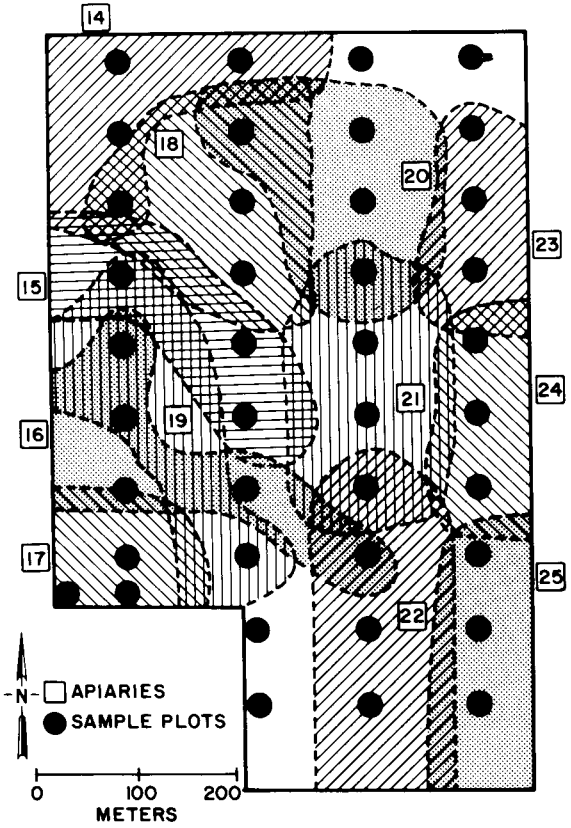
49 FLAGS, 7X7GRID,~ 6 METER SPACING BETWEEN FLAGS												
5 FLAGS, RANDOM SELECTION, MARKED WITH ANISE OIL SCENT												
		0	**0**	**0**	**0**	**0**	**0**	**0**				
		0	**0**	**0**	**0**	**0**	**0**	**0**				
		0	**0**	**0**	**0**	**0**	**26**	**1**				
	West								East			
		5	**0**	**0**	**0**	**18**	**0**	**0**				
		0	**0**	**1**	**4**	**1**	**0**	**0**				
		0	**0**	**13**	**0**	**0**	**0**	**0**				
		0	**1**	**1**	**1**	**0**	**0**	**0**				

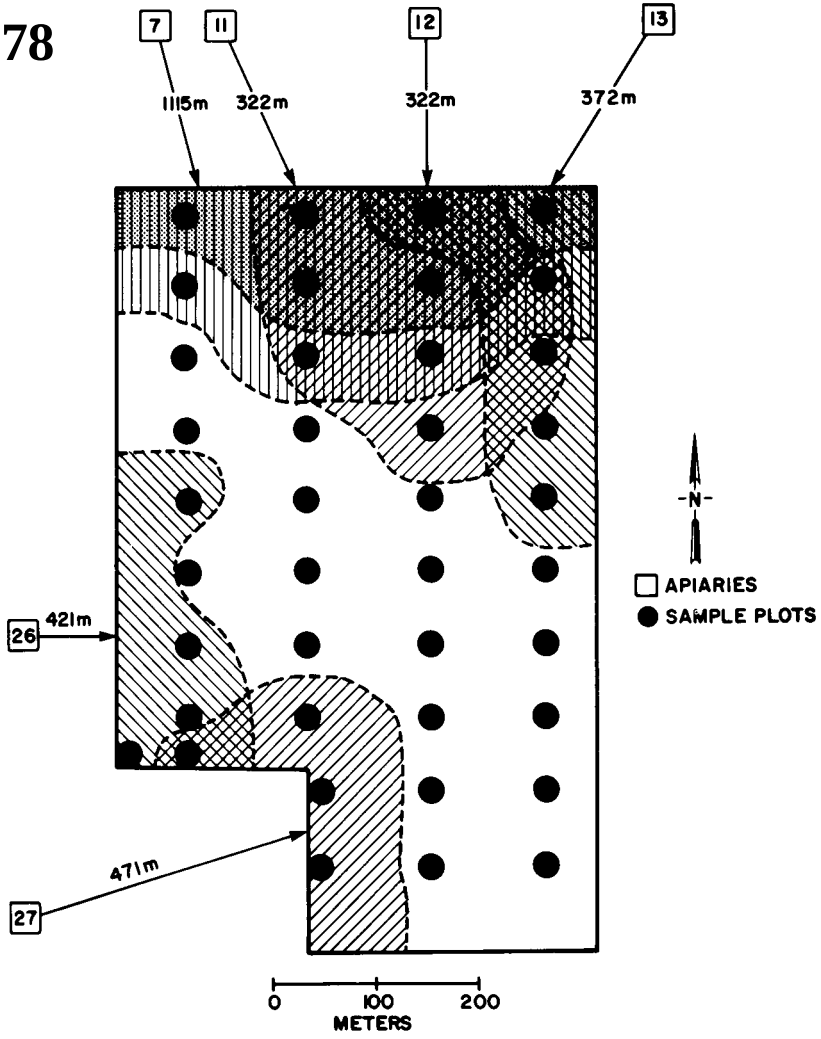

TARGET DISCOVERY BY HONEY BEES
(along a 2 km transect)
Number of Bee Visits
4000
3500
3000
2500
2000
1500
1000
500
0
24
48
96
Time Interval (hrs)
Sentinal High
Lewis & Clark
Sentinel Ave
Golf Course
Golf Course
Sentinel Ave
Lewis & Clark
Sentinal High


Acc.V Spot Magn

Bee Foraging Territories in Alfalfa

Gary *et al.*, 1978





@ 50% of Bees in Each Area Came from the Nearest Hives

Foraging Strategy of a Honey Bee Colony

Honey Bee Foraging Distances, Meters

Temperate Forests, Northeastern U.S. (Visscher and Seeley, 1982, Estimates from Recruitment Dances)

Range		Mean		Percentile			
Low	High	Mean	1 SD	50th	90th	95th	99th
50	10,100	2260	1890	1650	5000	6000	7700

95% of the Foraging Sites Covers an Area of 113 km^2

Proving Suitability for Field Deployment

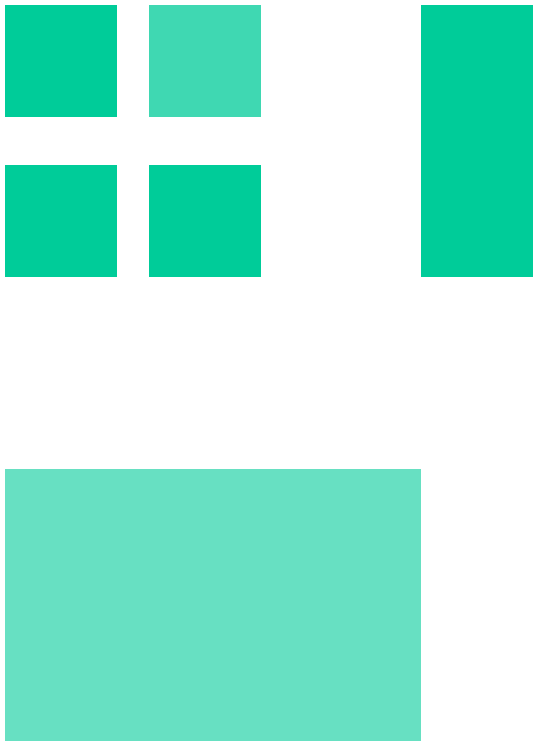
- Active Detection
  - Detection efficiency in simulated trials
    - latency
    - accuracy of detection and location
  - Detection limits
    - sensory limitations in field conditions
      - chemical
      - environmental

Proving Suitability for Field Deployment

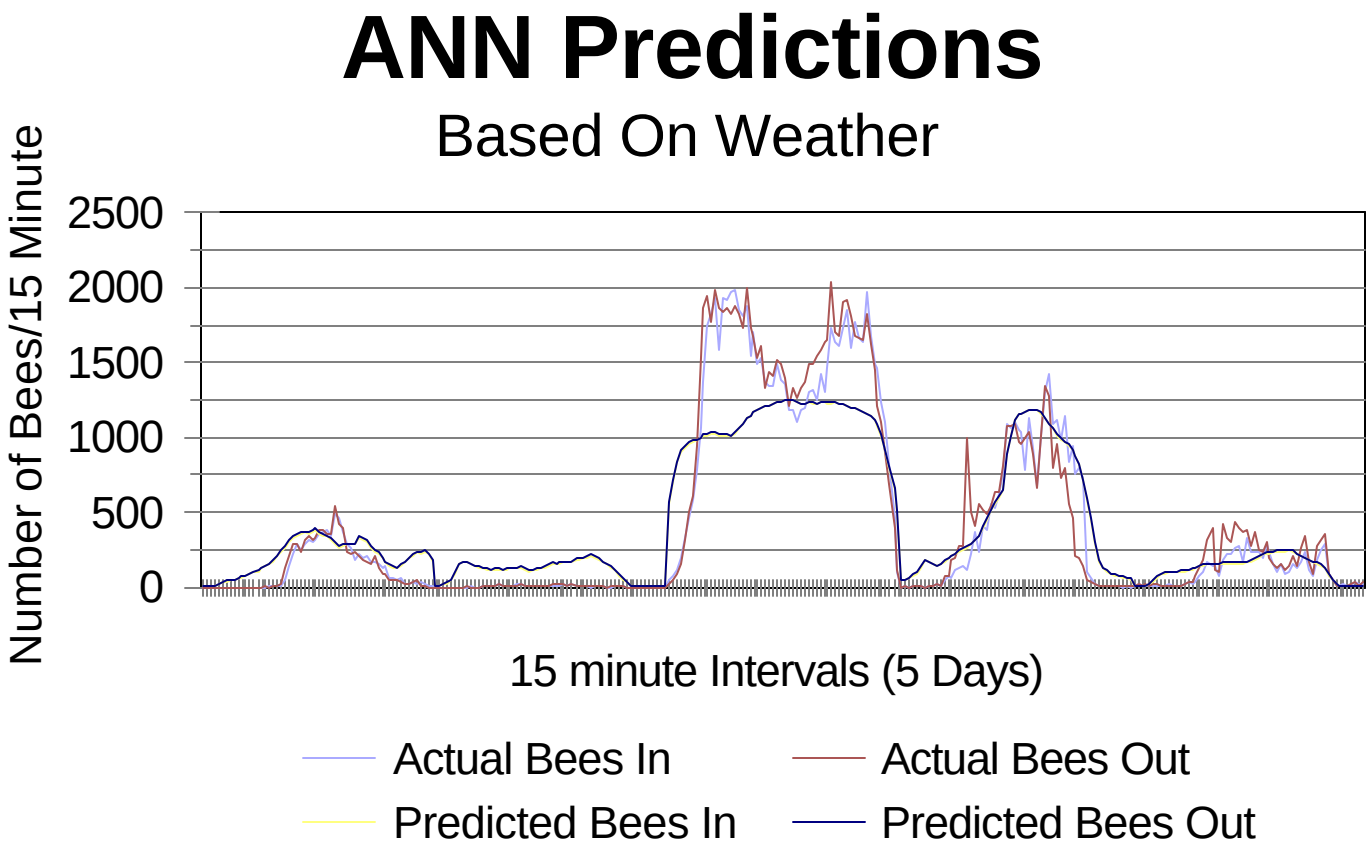
- Passive Detection
  - spatial / temporal model of bee dispersal from hive
    - naive hives
    - acclimated
  - dispersal in complex environments
    - natural environments
    - urban environments

Bee Movement In and Use of Complex Environments

- Diffusion processes?
- Instinctive biases?
- Habitat density/qualitative differences & filter effects



Artificial Neural Networks Recognize Patterns of Bee Responses (to weather, chemical exposures, etc.)



Data- and Knowledge-Mining at the Cellular and Molecular Level for Toxin Detection and Characterization

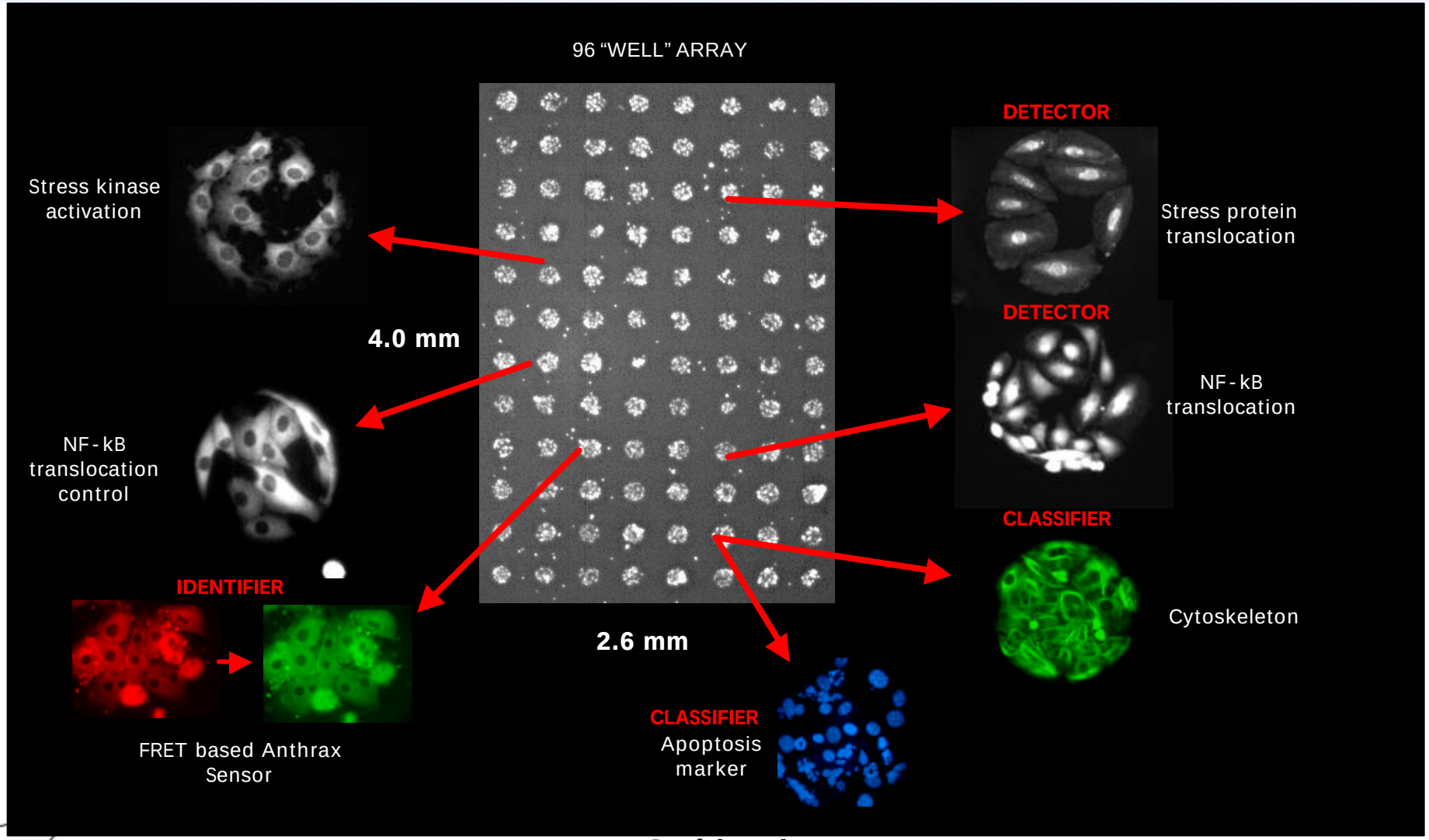
William B. Busa, Ph.D. (wbusa@cellomics.com)
Cellomics, Inc.
http://www.cellomics.com

Andrew W. Moore, **Ph.D.** (awm@cs.cmu.edu)
Carnegie Mellon University
And Schenley Park Research Inc.
http://www.cs.cmu.edu/~AUTON

CELLOMICS™

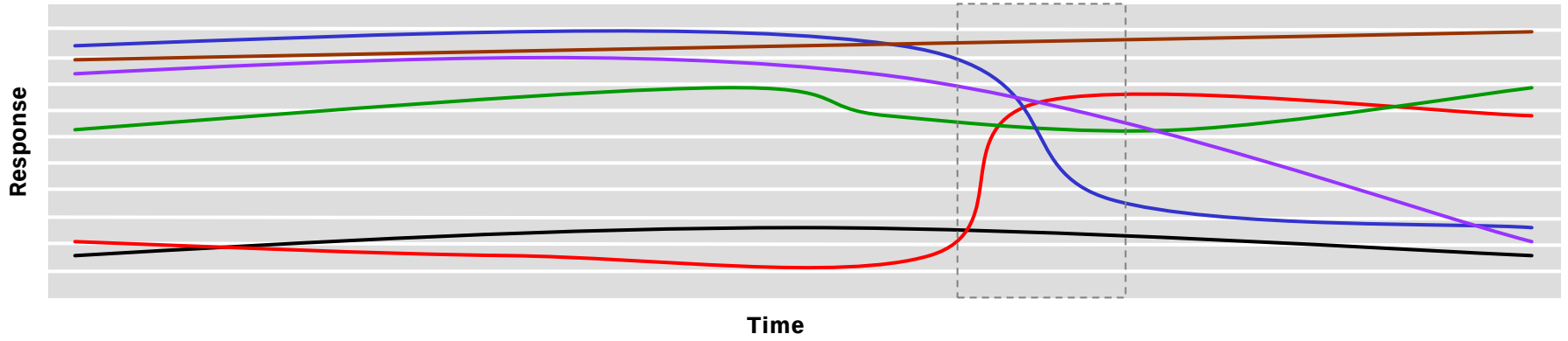
Cellomics CellChip™ + Aclara Microfluidics Permit Integrated High-Throughput/High-Content Cell-Based Analysis

96 different assays in a footprint of 0.1 cm²



CELLOMICS

Analyzing Multi-Parameter Cellular Biosensor Data In Real Time



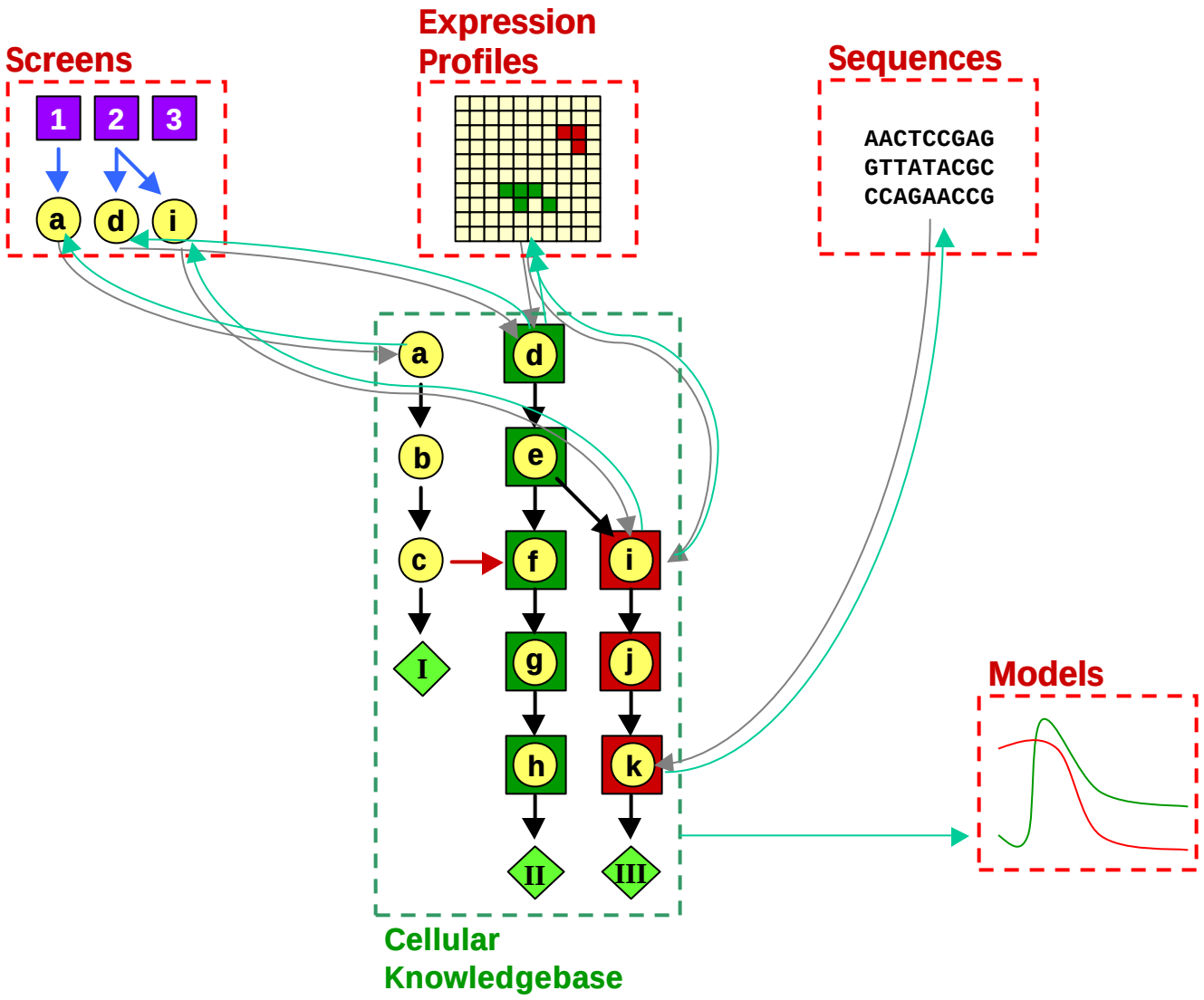
IDENTIFICATION: ANTHRAX (P = 0.99)

CLASSIFICATION: COMBUSTION PRODUCTS (P = 0.60);
ORGANOPHOSPHATES (P = 0.10);
PROTEASE INHIBITORS (P = 0.05)

DETECTION: ANOMALOUS CELL STRESS; UNKNOWN

CELLOMICS™

Linking Data to Domain Knowledge…and Vice Versa



CELLOMICS™

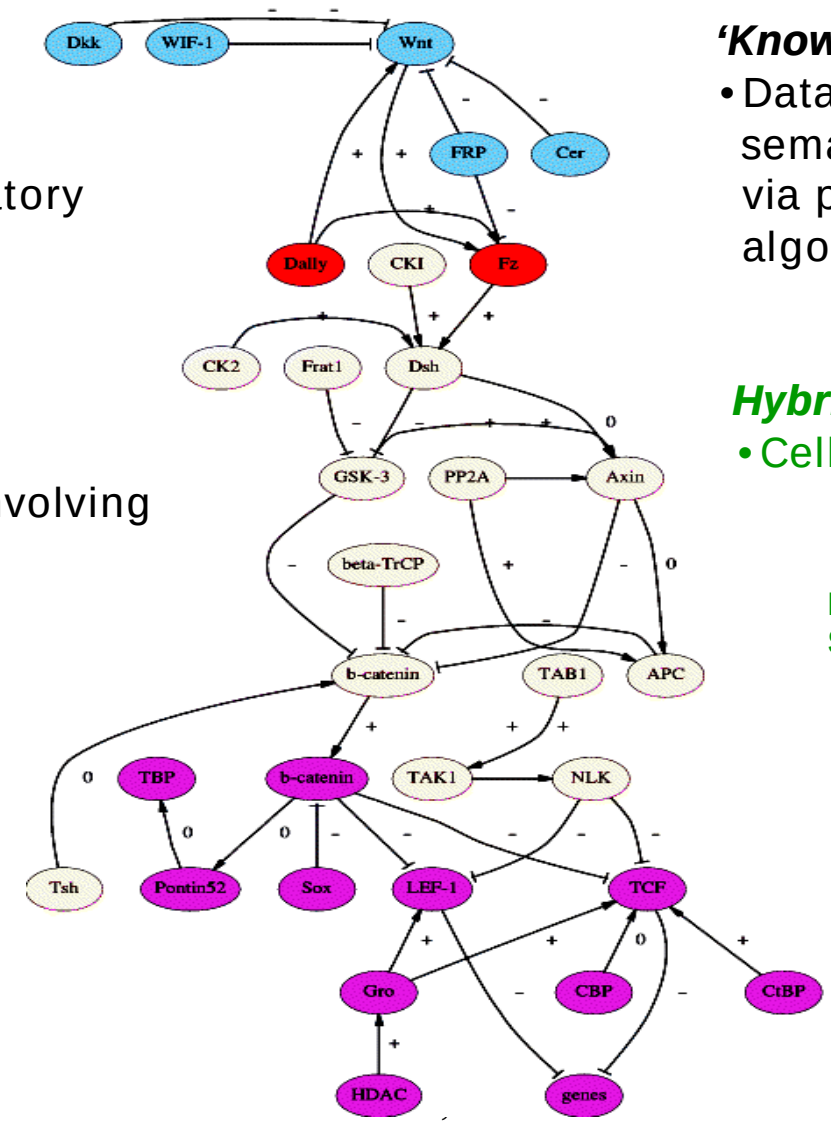
Cellular 'Wiring Diagrams' for Threat Analysis, Therapeutic Development, and Biological Modeling: Populating the Knowledgebase

Expert System:

- Recruited authorities
- 'Army of scribes'
- Community collaboratory

Computational Approaches:

- Numerous projects involving homology detection, expression profiling, etc.

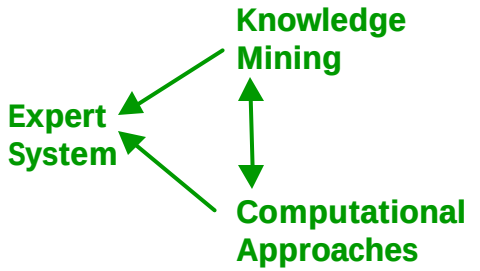


'Knowledge Mining':

- Data & text mining + semantic analysis, via public & proprietary algorithms.

Hybrid System:

- Cellomics Knowledgebase



Wnt/beta-Catenin pathway from: *Science's Signal Transduction Knowledge Environment (http://www.stke.org)*

CELLOMICS™

Computational Modeling and Simulation in Biological Systems

Review of Discussions of Group Red

Computational Modeling and Simulation in Biological Systems

What are the important biological processes to be modeled?

- Metabolic processes -- properties are knowable
- Spatial and spatial-temporal localization
- Information content of signals -- processing and analysis -- Ca^{2+}
- Virulence and infectivity
- Responses to gradients and thresholds
- Switches and decisions
- Non-linear, R-D, pattern formation, moving boundry conditions
- Integration of scales of analysis -- vertical
- Modern computations need leavening with biophysics
- Molecules through populations -- native *versus* engineered
- Cell-environment interactions
- Physiological and metabolic simulations of tissues and organs
- Approximation of *in situ* conditions -- identify critical parameters
- In vivo versus in vitro -- relevance of information
- Feedback and process control -- diagnosis program

http://www.mbl.edu/MOBS/

Modeling of Biological Systems

A Multidisciplinary Course

MOBS

MOBS Course Brief Schedule -- Spring 2000

March 25, 2000 through May 4, 2000

The MOBS Course curriculum is organized into thematic cassettes, each lasting six to ten days in length. Topics will be covered with lectures, demonstrations, hands-on laboratory work and discussions with the faculty.

Cassette 1 Introduction to Modeling, including model formulation and management, and introduction to laboratory practices.
Faculty include: Hummel, Leibholz and Silver

Cassette 2 Cell Structure and Dynamics, including assembly of the cytoskeleton, reaction/diffusion and chemical dynamics, and compartmentalized metabolic systems
Faculty include: Herzfeld, Pearson, Ponce-Dawson, Silver, and Wastney

Cassette 3 Molecular Structure and Dynamics, *including* moleuclar dynamics, electrostatics, force field development, free energy calculations and molecular simulations.
Faculty include: Eisenberg, Kollman, and Petsko

MOBS Course Home Page

Proceed to the next page

Computational Modeling and Simulation in Biological Systems

What are the immediate defense goals?

- Biodetection
- Antifouling
- Computational linguistics
- Implantable devices
- New vistas for sensors
- Virulence
- Fully sensored battlefield
- Optimization of near term biosensors
- Communicaiton and dialog with cells -- know youcellf
- Knowledge of non-biological impacters

Computational Modeling and Simulation in Biological Systems

I What computational approaches will enable which approaches?

- Multi-scale
- New statistical approaches for very large data bases
- Diagnostic mathematics
- Classical dynamics
- Continuum to discrete and averaged models
- Simplified representation of coupled motion of ions and water
- Structure of water

Computational Modeling and Simulation in Biological Systems

I What computational approaches will enable which approaches?

- Multiple scale
- Tissue and cell modeling
- New statistical methods for large data bases
- Fast algorithms for molecular dynamics
- Methods for computational electronics
- New methods

Computational Modeling and Simulation in Biological Systems

II What is the current state-of-the-art in computational modeling in the field of biology?

- **Under-supported**
- Target of active prejudice from experimentalists
- No field will benefit more from next iteration of Moore's Law

Computational Modeling and Simulation in Biological Systems

III What are the important biological processes to be modeled? … and for what purpose?

- Three categories:
- Technological -- biosensors broadly defined
- Cells as Integrated systems and decision processes
- Cells and tissues as natural nanosystems
- Cells and proteins/nuclec acids as ionic machines

- Medical/Clinical

- Scientific

Computational Modeling and Simulation in Biological Systems

IV What critical experiments/data are needed ?

- **Everything has to be coordinated with specific biological experiments**

Computational Modeling and Simulation in Biological Systems

V How can current capabilites be extended?

- Visible success
- Permanent multi-disciplinary institutions

Computational Modeling and Simulation in Biological Systems

VI How can current modeling shed light on multi-disciplinary and multi-scale biological phenomena and facilitate understanding of scaling relationships?

- No understanding without modeling
- Education of the end-users how to usefully model
- Multi-disciplinary Institutes focused on project

Computational Modeling and Simulation in Biological Systems

VII How can modeling become potential tools in the future to enable the design of integrated biosystems?

- Integration of multi-parameter
- Standard libraries of essential components
- Hierarchy of standardized scalable tools
- Open source development
- Integration of specialized tools from enterprises
- Need to learn to be predictive, not just descriptive
- Improvements in prediction, understanding, knowledge

Computational Modeling and Simulation in Biological Systems

VIII What are the roadblocks/challenges and how can we achieve the above objectives in a reasonable time period?

- **People**
- **Biologists receptive to computation and theory**
- **Empiricists sensitive to biology**
- **Nexus of Empiricists and Theorists**

Thank you

BLUE TEAM

Break Out Presentation

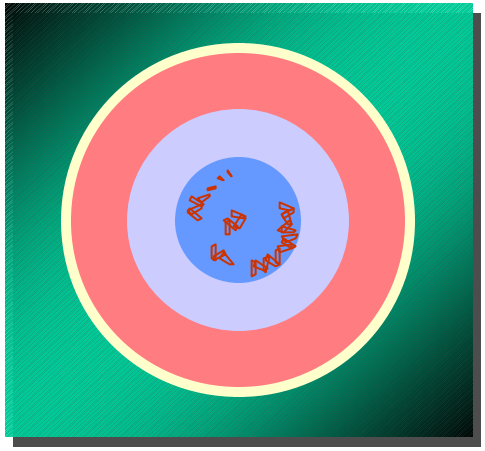
Tools

- Experimental
- Computational
  - Physico-chemical models
  - Information Systems /Data mining
- Biological Process
- Problems (perceived) of interest

1. Biological Process

- Cell Response to Stress

  [Problems: cell response to toxin, soldier response to toxin, or pathogen in field]



Hypothesis–Cell Exhibits Signature Responses to Different Kinds of Stress → Modeling Can Help Uncover

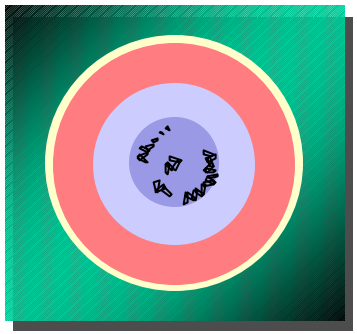
Response to Stress

Apply Stress

Basic Q ➡ **Can we distinguish Different kinds of stress?**

Anthrax
Small Pox
Nerve gas
Osmotic Shock

Process measured signals to define specific stimulus



System = Cell
Interacting Cells
Soldier

Measured Response

No Production (s-h)
Cytokine secretion
Calcium release
Change in gene expression (h-day)

Computational Tools that Exploit Empirical Data Sources

- **Combining Evidence**
  - **Computational Diagnosis**
  - **Data Mining**
  - **Probabilistic Networks**
- **Decision Theory**
  - **Attacking a Spread of Disease**
  - **Rapid Treatment Design**
- **Optimal Sensor Design via**
  - **Coding Theory**
  - **Information Theory**

Use Methods From Graphical Models

Current State

Some Subset of Known Stresses → Semi–mechanistic basis for predicting responses

Modeling

- Computational Transport Processes in ufluid systems
- Computational Tools that exploit empirical data sources
- Mechanistic Models of complex cell behaviors (Data-Limited)

Future

Future

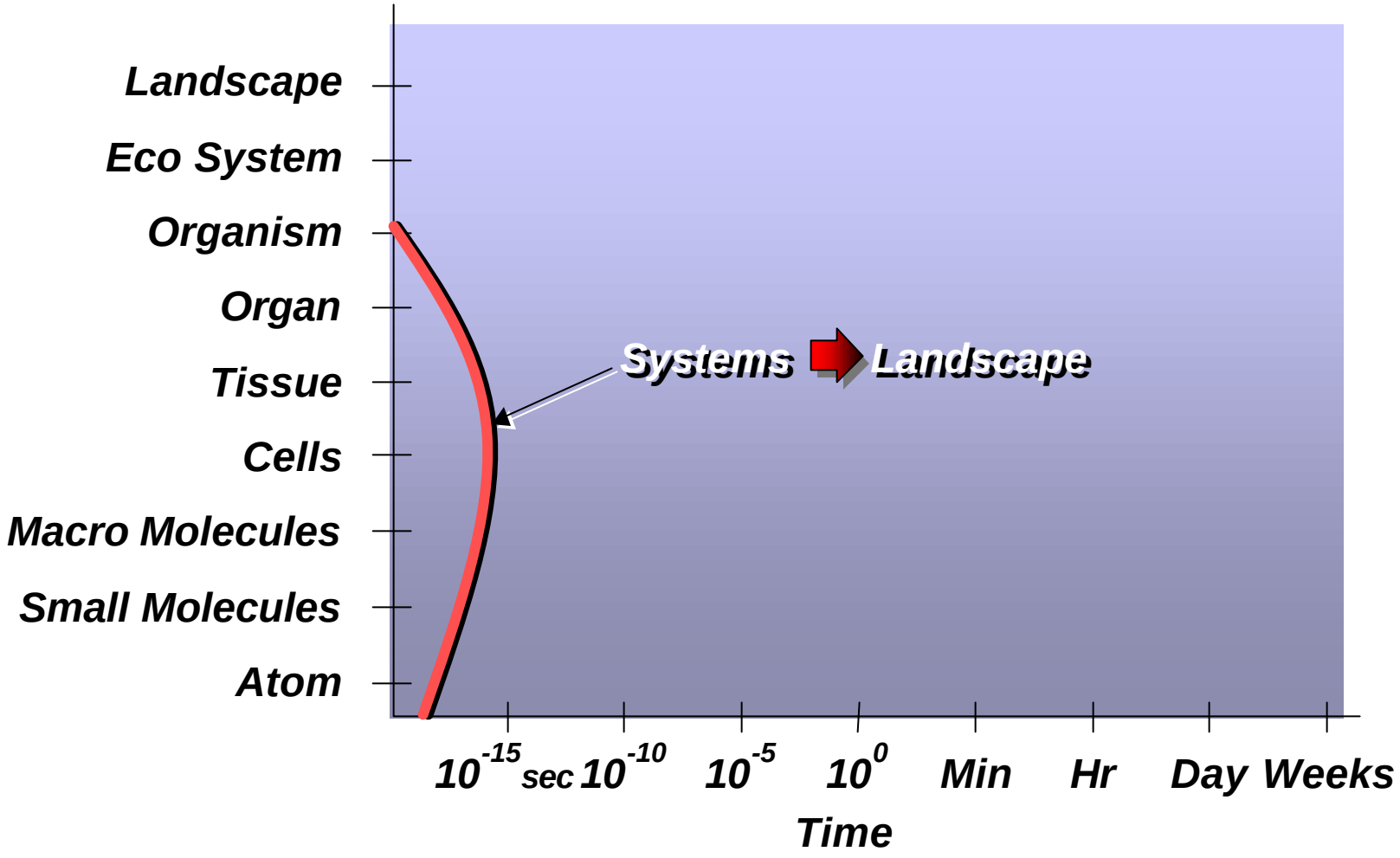
Some larger
subset of known stresses

➡ Semi mechanistic and correlative basis for predicting responses

Need

Problem Definition!

- Organize large amount of existing biological data into hierarchical structures
  - ➡ What has been measured?
  - ➡ What can be measured?
  - ➡ What new measurement methods are on horizon?
  - ➡ Efficient “packaging” of problems for improved computational models


Landscape
Eco System
Organism
Organ
Tissue
Cells
Macro Molecules
Small Molecules
Atom
Systems
Landscape
10-15 sec
10-10
10-5
100
Min
Hr
Day
Weeks
Time

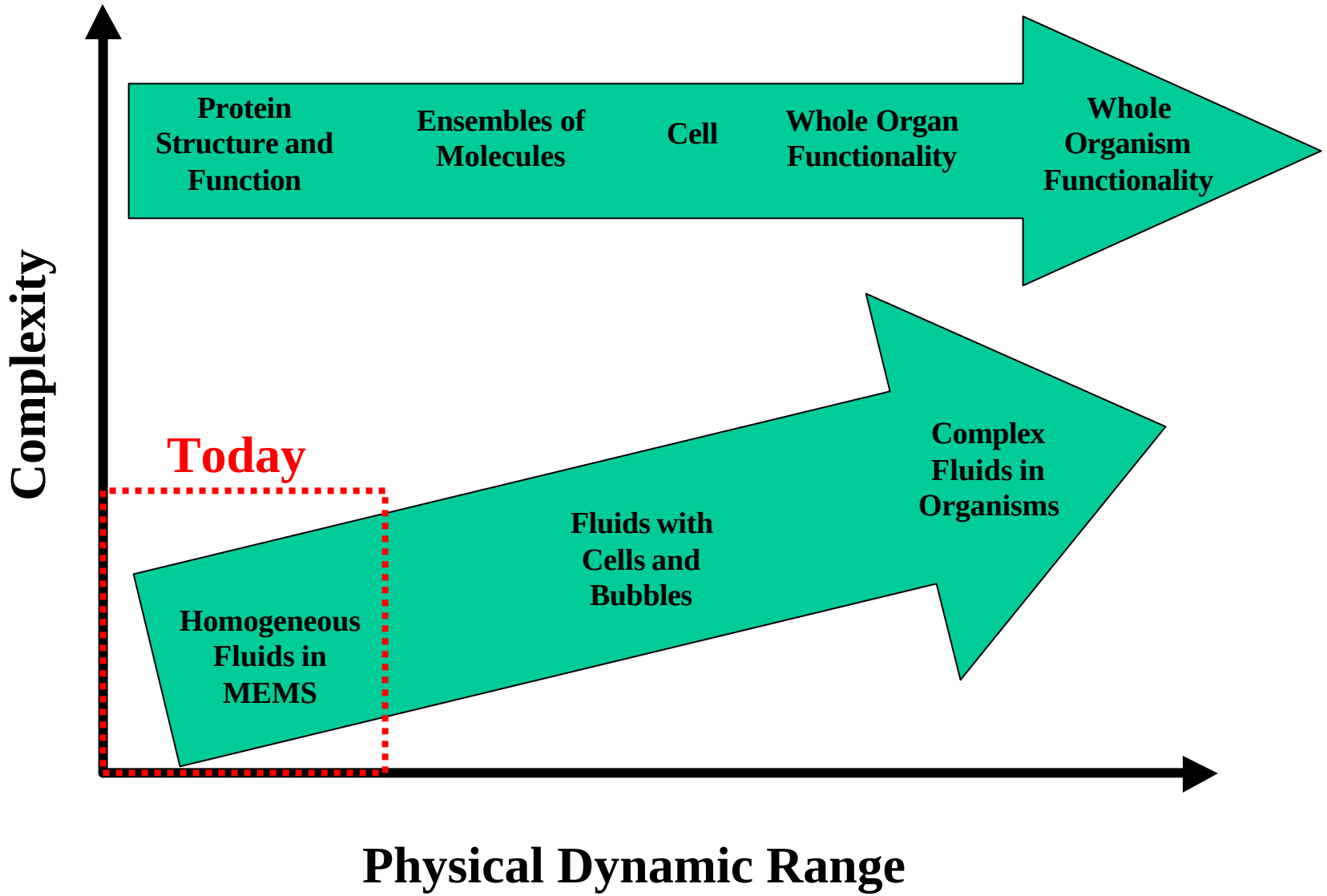
GO YELLOW TEAM!!!

Key Benefits of Modeling

- Predictive simulation for design.
- Doing things that you cannot physically do (e.g., infect humans, test nuclear weapons, etc.).
- Introduce probabilistic issues.
- Computer-driven optimization.

Physical Scales of Simulation

- Molecules/atoms (e.g., protein form/function).
- Molecular ensembles ?
- Fluids (e.g., computational fluid dynamics).
- Cells (e.g., differential equations, feedback).
- Organs ?
- Organisms (e.g., simple feedback models).
- Populations (e.g., simple ecology models).


Protein Structure and Function
Ensembles of Molecules
Cell
Whole Organ Functionality
Whole Organism Functionality
Complexity
Today
Homogeneous Fluids in MEMS
Fluids with Cells and Bubbles
Complex Fluids in Organisms
Physical Dynamic Range

Envelope of Feasible Modeling

- You can’t fully model what you do not understand.
- However, modeling with incomplete knowledge can drive experiments and lead to new knowledge.
- Should co-fund experimental work to expand the envelope of simulation possibilities and to calibrate models.

Software Embodiments

- Need standards for interoperability and user interface.
- Case-by-case codes developed by skilled researchers tend to be lost unless captured within commercial codes.
- Need “wide physical dynamic range” simulation capability.

General Points

- Need tighter coupling between user and modeler communities.
- Need to define spatial and/or numerical resolution of simulations required for specific tasks or parts of tasks.
- Need to expand simulation capabilities (bubbles, particles, menisci, inhomogeneous fluids, chemistry, dilute analytes, etc.).

High Yield Opportunities

- Interoperability.
- Focus rather than “whole waterfront” funding.
- Optimization for some defined functions.
- Using simulation to address complexity (even with closed-form equations, simulation is needed for this).