Proceedings of the All-hands Meeting for the NSF EPSCoR Research Infrastructure Improvement (RII)

Friday, May 30, 2008

NSF EPSCoR Research Infrastructure Improvement (RII) Award: Cyberinfrastructure and Science Drivers

Final Agenda – All Hands Meeting

Friday, May 30, 2008

Thomas Jefferson Room, 1-136A
Claiborne Building
1201 N. Third Street, Baton Rouge

9:00 – 9:20 a.m.	Welcome and Introductions (Khonsari)	*Page 4*
9:20 – 9:40 a.m.	Program Evaluation (Ramsey)	*Page 11*

Science Driver (SD) Presentations

9:40 – 10:10 a.m. — Small Molecule/Geno Sensors (Soper/Murphy) — *Page 25*

1) Overview of project
2) Experiments (large and small-scale)
3) Other Components
4) Links to WP - combined with collaborators from CyberTools.
5) Outreach

10:10 – 10:40 a.m. — Immuno Sensors — *Page 65*

1) Brief Overview of the original project and any changes in scope so far (Diane Blake\Ricardo Cortez)
2) Experimental Aspects (Diane Blake)
3) Computational Aspects: MD (Hank Ashbaugh+graduate student)
4) Computational Aspects: CFD (Don Gaver + graduate students)
5) Microfabrication Aspects (Mark DeCoster)
6) Outreach (Ricardo Cortez)

10:40 – 11:00 a.m. — Break/Networking

11:00 – 11:20 a.m. — Biotransport Computation (Acharya) — *Page 104*

1) Overview of project
2) Computation
3) Links to WP4
4) Outreach

11:20 – 11:40 a.m. — Biomedical Imaging/Data Mining/Data Fusion (Iyengar) — *Page 119*

1) Overview of project
2) Computation
3) Links to WP3
4) Outreach

11:40 a.m. – 12:00 p.m. — Environmental transport (Allen) — *Page 195*

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12:00 – 1:00 p.m.	Networking Lunch	

Cybertools WorkPackage (WP) Presentations

1:00 – 1:15 p.m.	WP4: Application (Jha/Acharya/Moldovan)	*Page 205*
1:15 – 1:30 p.m.	WP1: Data, Scheduling (Dua/Kosar)	*Page 218*
1:30 – 1:45 p.m.	WP2: Information (Allen)	*Page 231*
1:45 – 2:00 p.m.	WP3: Visualization (Cruz-Neira/Ullmer/Iyengar)	
2:00 – 3:00 p.m.	Breakout Sessions: WP-SD Interactions	*Page 247*
3:00 – 3:20 p.m.	Reports back from Breakout Sessions	
3:20 – 3:30 p.m.	Break/Networking	
3:30 – 4:00 p.m.	Graduate Student Presentations (One minute, One slide)	*Page 250*
4:00 – 4:30 p.m.	Outreach Activities	
4:30 – 5:00 p.m.	Wrap-Up/Action Items (Seidel, Gaver, Cortez, Murphy, Allen, Iyengar, Acharya)	

Louisiana EPSCoR RII

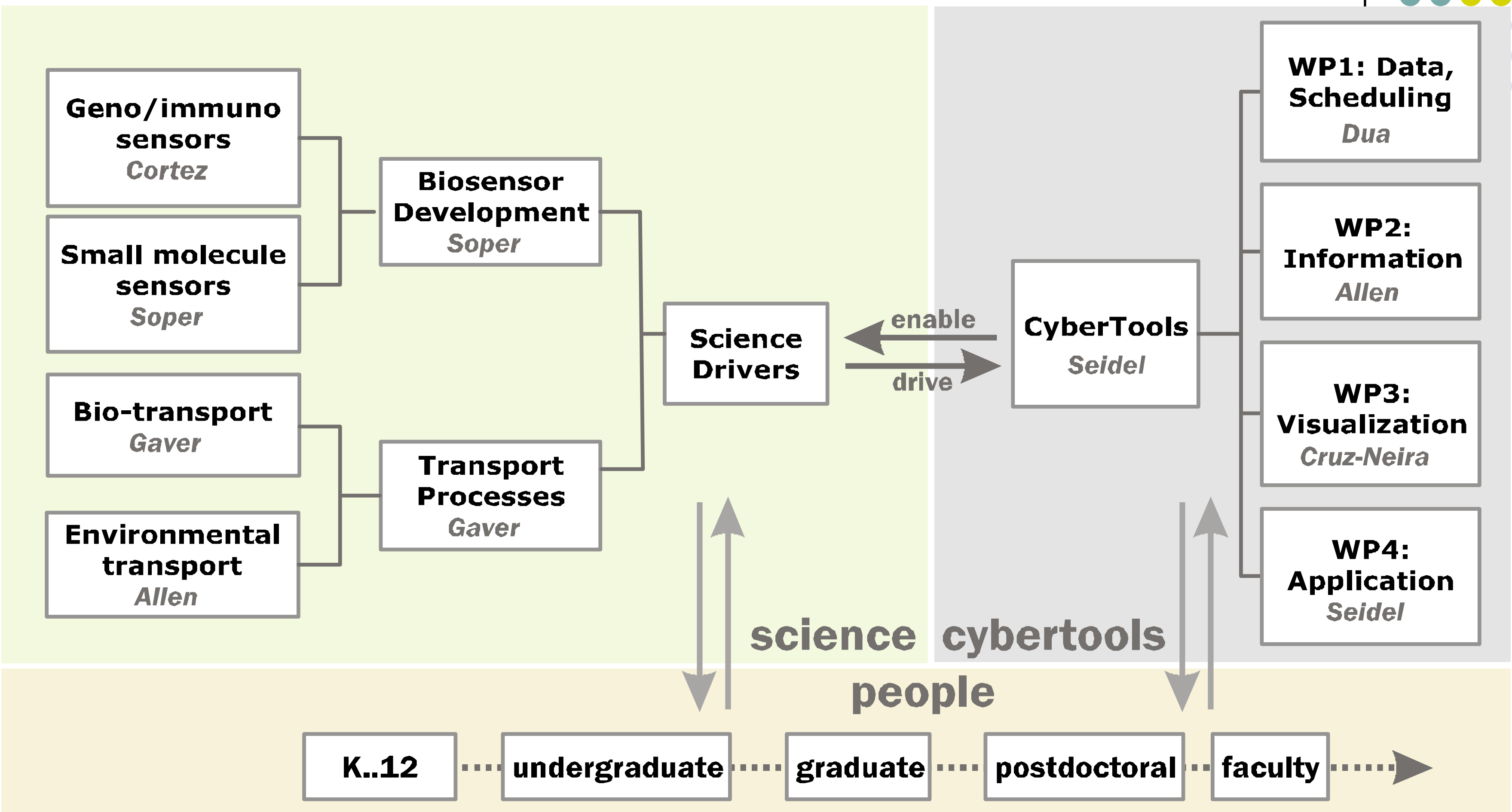
All Hands Meeting

May 30, 2008

Important Events

Cooperative Agreement Obligations:

- External Review Board Visit / Statewide Conference (tentatively August 6-7, 2008)
  - Poster Competition
- NSF Site Review / Reverse Site Visit
- Annual Report
  - Due to the Board of Regents July 15, 2008
- Evaluation and Assessment
- Graduate Student/Research Fellows Symposium (June or July)



Geno/immuno sensors
Cortez
Small molecule sensors
Soper
Bio-transport
Gaver
Environmental transport
Allen
Biosensor Development
Soper
Transport Processes
Gaver
Science Drivers
enable
drive
CyberTools
Seidel
WP1: Data, Scheduling
Dua
WP2: Information
Allen
WP3: Visualization
Cruz-Neira
WP4: Application
Seidel
science
cybertools
people
K..12
undergraduate
graduate
postdoctoral
faculty

Importance of Collaboration

- Collaboration between WPs and Science Drivers

- IOCOM System
  - Consoles
  - Desktop licenses, cameras, microphones,etc.

AGENDA

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Evaluation of Louisiana EPSCoR RII

Linda L. Ramsey
Louisiana Tech University
May 30, 2008

External Review Board

- Reviews overall program
- Evaluates research progress and significance
- Produces twice yearly reports

Evaluation Team

- External Evaluator
  - Mary Jo McGee-Brown, Qualitative Research and Evaluation for Action, Inc.
- Internal Evaluator
  - Linda L. Ramsey, Louisiana Tech University

Evaluation Team Focus

- Education (IHE) Activities
  - Interdisciplinary
- Outreach Activities (K-12, community)
- Collaboration
  - Interdisciplinary
  - Inter-institutional

Evaluation Team Focus

- Efforts to increase participation of underserved minorities at all levels of program
  - Research
  - E&O

Evaluation Team Tasks

- Produce a yearly report to NSF
  - on all Education and Outreach Activities
  - on level and types of collaborations

- Provide formative data to EPSCoR RII PI, SEC, and ERB
  - On all Education and Outreach Activities
  - On level and types of collaborations

What are we looking for:

- Is the E&O activity effective at reaching program goals?
- What implementation strategies made it effective?
- For ineffective E&O activities, what blocked them from being effective?

What are we looking for (cont):

- Descriptions of interdisciplinary and cross-institutional collaborations among research scientists, post docs, graduate students, and undergraduate students.
- Why the collaborations were successful?
- What factors blocked success of ineffective collaborations?

How will data be collected?

- Primary data collection method
  – Surveys
- Secondary data collection method
  – Informal and formal interviews, observations from program meetings, and review of program documents

Survey for Research Scientists

- Questions, comments, concerns?

Survey for Post Docs/Grad Students

- Distributed to Team Leaders
- E-mailed to Post Docs/Grad Students
- Reminder e-mails sent
- 10 of 36 have responded
  - 28% response rate
- NSF expects 85-90% data collection response rate

- What are YOUR suggestions to ensure a 100% response rate for essential evaluation surveys?

- Education Activities
  - Interdisciplinary mentoring
  - interdisciplinary course development
  - undergraduate research experiences
  - senior design projects
  - interdisciplinary seminar series for post docs
  - workshop for integrating computational methods across the curriculum

- Outreach Activities
  - EPSCoR newsletters
  - Legislative Day
  - Super Science Saturday
  - Week-long summer science camp
  - LIGO Partnership
    - An Advanced Science Portal

Science Driver 1

Genosensor

Small Molecule Sensor

Michael Murphy
Center for Bio-Modular Multi-Scale Systems (CBM2)

All Hands Meeting: 30 May 2008

Modular Systems Team

- Faculty
  - J. Göttert
  - R.L. McCarley
  - D. Moldovan
  - D.E. Nikitopoulos
  - S. Park
  - S.A. Soper
- Postdocs
  - J. Chen
  - M. Hashimoto
  - M. Hupert
  - X. Liu
  - D.S.-W. Park
  - M. Witek
- Staff
  - J. Guy
  - P. Datta
- Grad Students
  - A. Adams
  - D.O. Barrett
  - Y. Bejat
  - P.C. Chen
  - J. Choi
  - N. Elmadjoub
  - E. Evans
  - J. Feng
  - N. Kim
  - B. Laveau
  - T.Y. Lee
  - A. Maha
  - M.W. Mitchell
  - J.T. Ok
  - V. Palaparti
  - T. Park
  - C. Ramet
  - A. Roychowdry
  - Z. Song
  - B.H. You
  - K. Zanca

Outline

- Objectives
- Rationale for a Modular Approach
- Genosensor Developments
- Small Molecule Sensor Developments
- Technology Transfer
- E&O Activities
- Conclusions

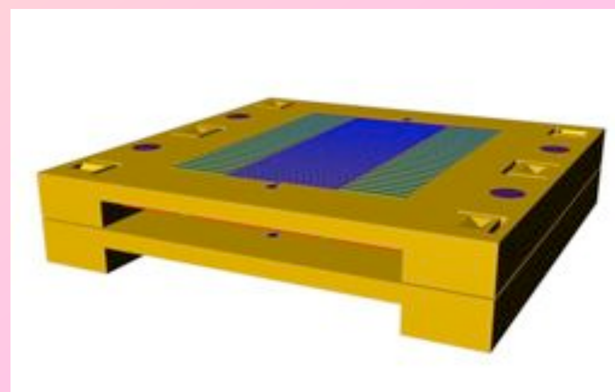
Objectives

- **Genosensor**
  - Modular system for DNA typing using *Alu* repeats
  - Three functional modules:
    - Sample preparation (cell capture, cell lysis, purification)
    - PCR
    - Detection (Gel electrophoresis, microarray)
- **Small Molecule Sensor**
  - High throughput modular system
  - Three functional modules:
    - Sample preparation (cell capture, cell lysis)
    - Solid phase reactors
    - Single molecule detection (optical, electronic)

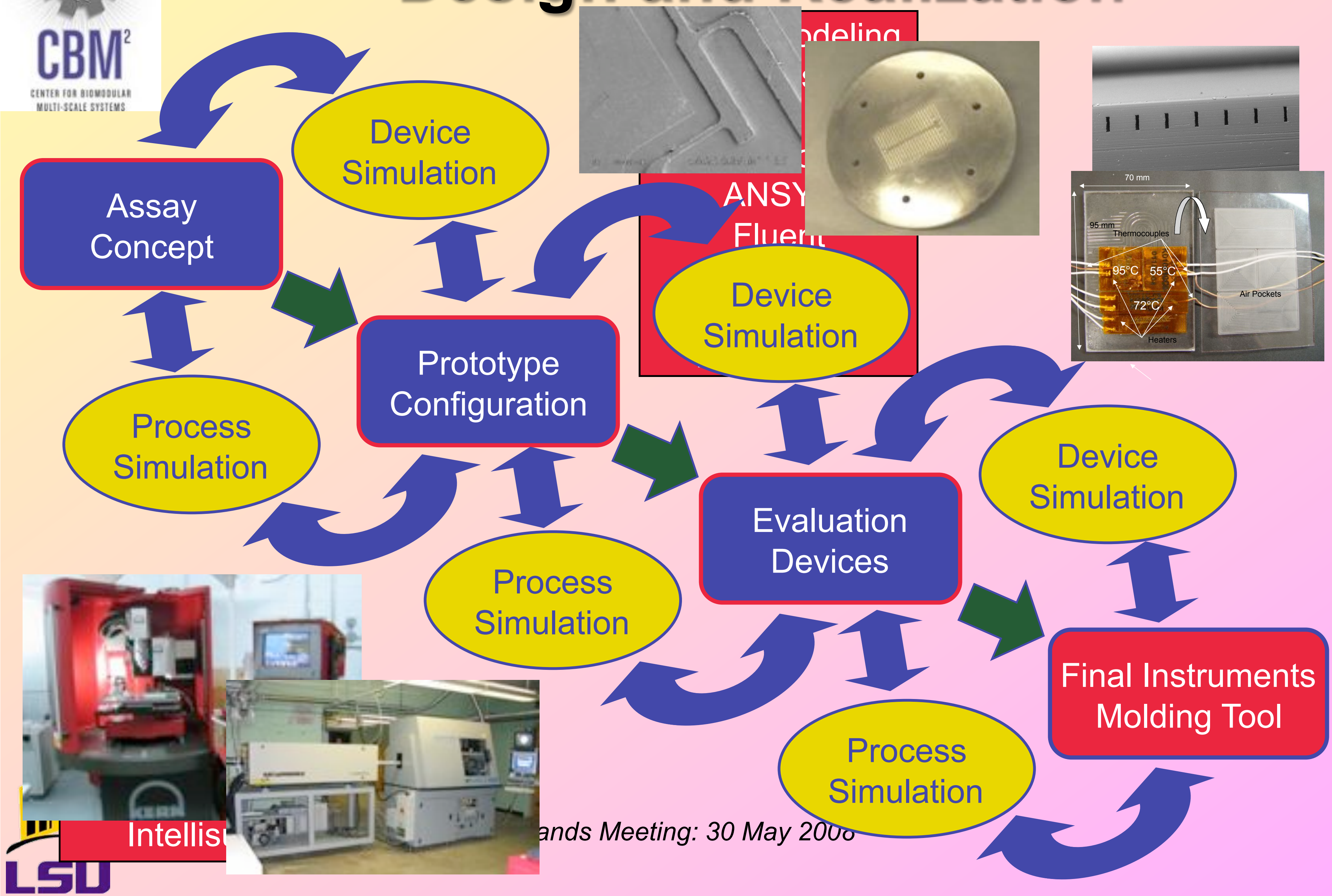
Modular Approach

- **Build more complex systems**
  - 'Stack' modules to form a more capable instruments
  - Design task specific instruments => LEGO™ for biologists and chemists
  - Scalable => single use and high throughput formats use similar technology

- **Process complexity for individual modules the same**
  - Processes/materials can be optimized at each level
  - Molding can reduce the cost of modules/components



Design and Realization

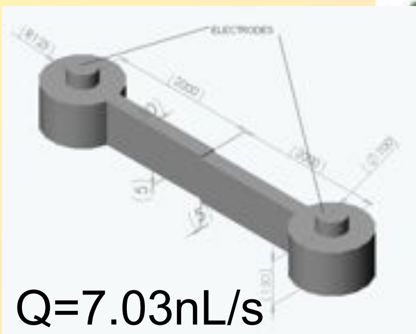


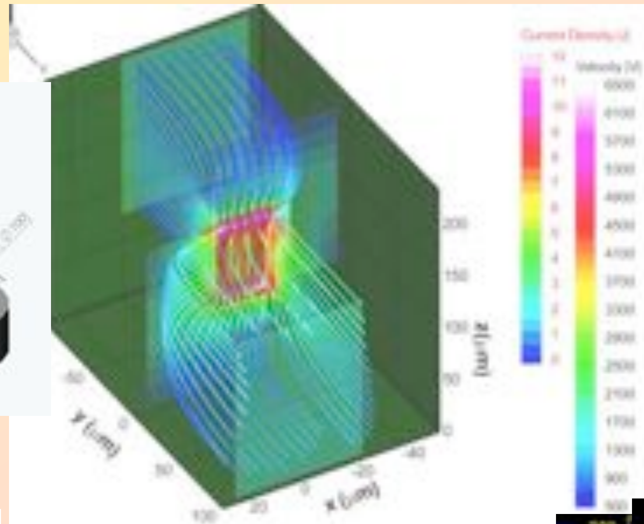
Genosensor Requirements

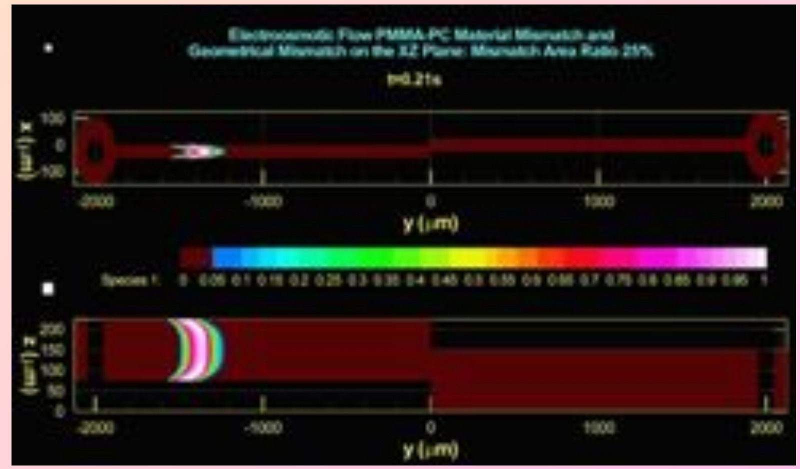
- Functional
  - Assembly technology
  - Thermal isolation
  - Improved actuation for thermal cycling/mixing
  - Improved molding
- Computational
  - Thermofluid simulation of device function
  - Simulation of flow across interconnects
  - Monte Carlo modeling of assembly variation
  - Thermofluid simulation of molding processes

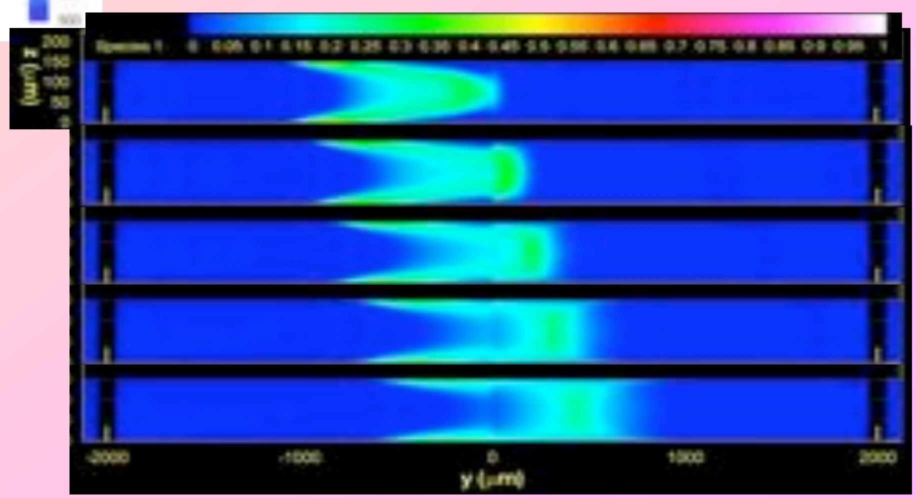
Fluidic Interconnects

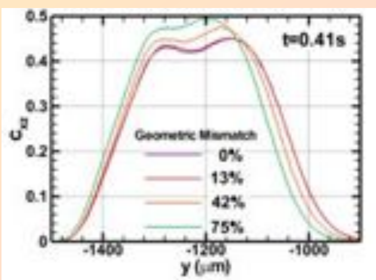
Effect of material and geometric mismatch on sample plug disruption in Electroosmotic Flow



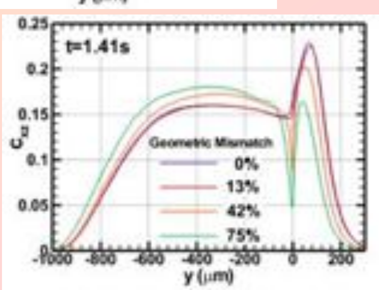


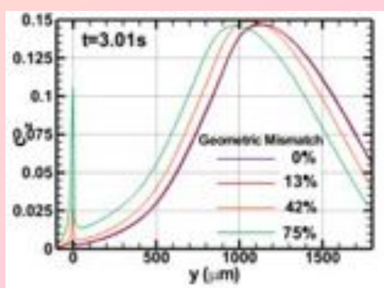






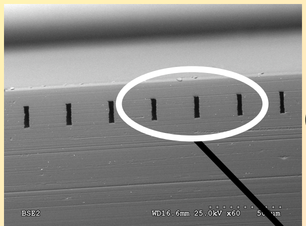
No effect for 13% geometrical mismatch





Plug re-concentration after PMMA-PC material mismatch

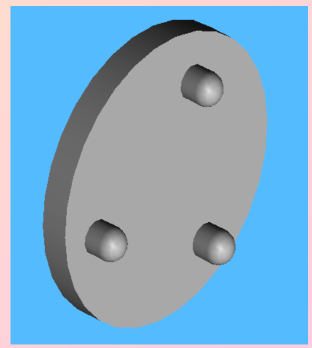
Assembly Technology

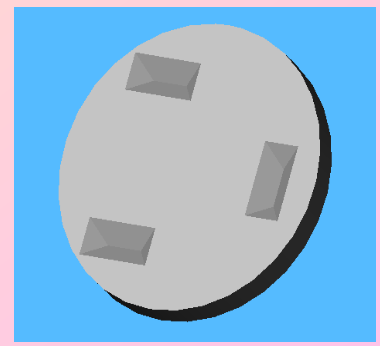


Channels thermally bonded at 155 ^{o}C, 150 psi: 50 μm wide 150 μm deep

- **Inter-Modular Assembly**
  - **Three aspects:**
    - Alignment
    - Sealing
    - Bonding
  - **Do not want to depend on having 'planar' mating surfaces**
  - **Contact between two planar mating surfaces driven by:**
    - Flatness
    - Perpendicularity of features
    - Surface roughness
  - **Control mating using dedicated alignment structures**

- **Intra-Modular Assembly**
  - **Dominated by surface contacts**
    - Fluid sealing
    - Thermal conduction
  - **Thermal fusion bonding**



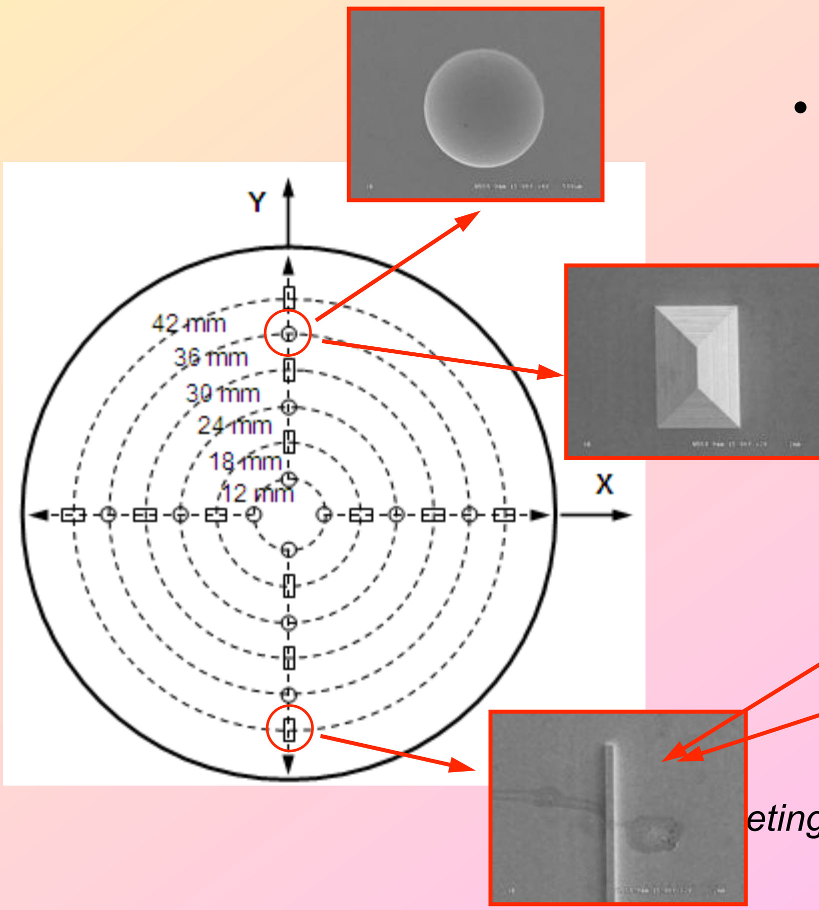


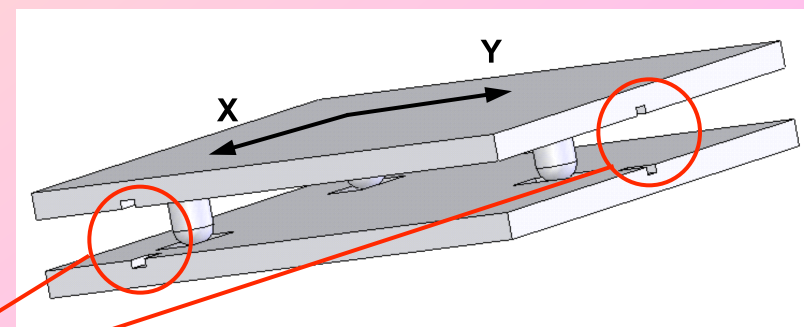
- **Alignment determined by kinematic constraints**
  - Assess with extended screw theory (Ball, 1900; Adams and Whitney, 1999)
- **Prefer passive alignment for inexpensive, reliable assembly of modules**
  - Slocum, et al., (2001) demonstrated sub-μm alignment of Si wafers using passive alignment structures

Test Structures

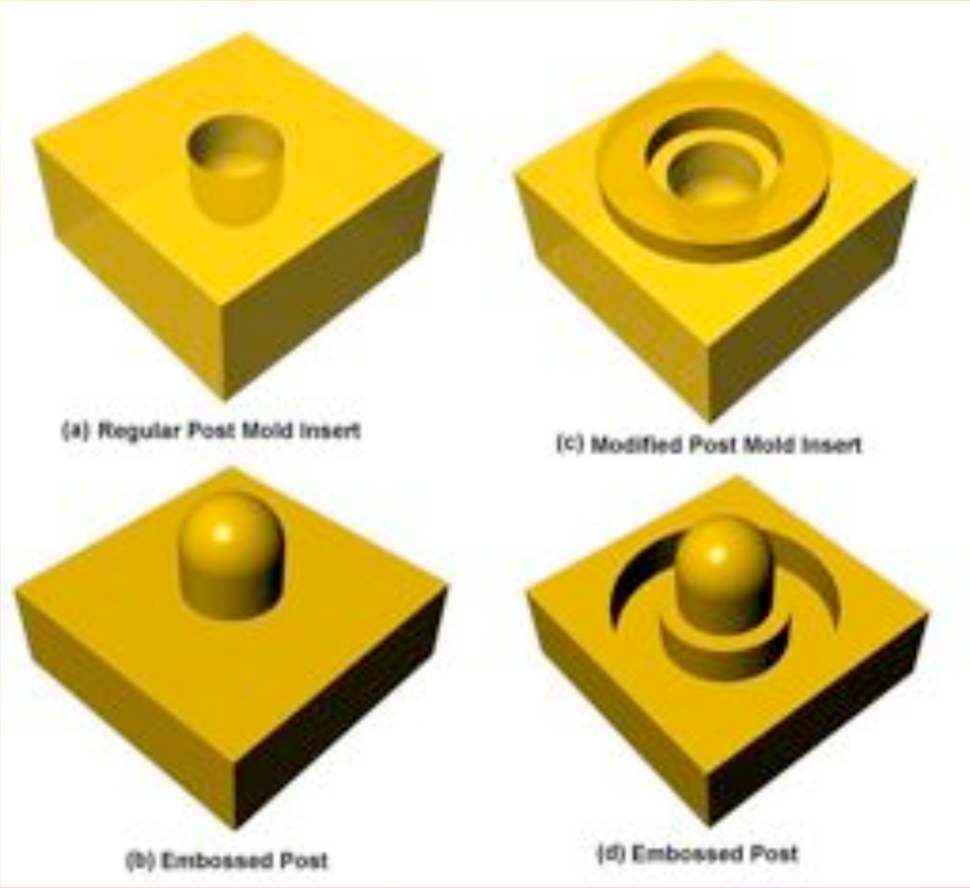
V-grooves	Depth (d)	1000 µm
	Angle	45 °
Spherical Posts	Height (h)	800 µm
	Radius (r)	500 µm

- **Two brass mold inserts micro-milled for the fabrication of test alignment structures**
- **Each insert contains**
  - V-grooves
  - Hemispherical-tipped posts
  - Alignment marks
- **Structures at different distances from the insert center**

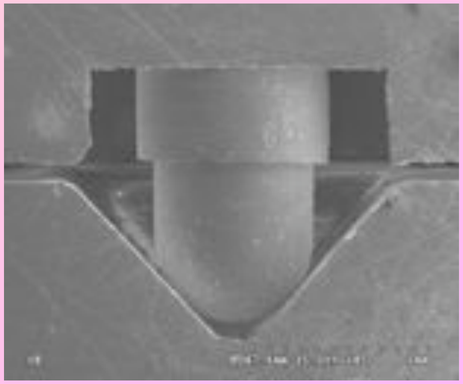




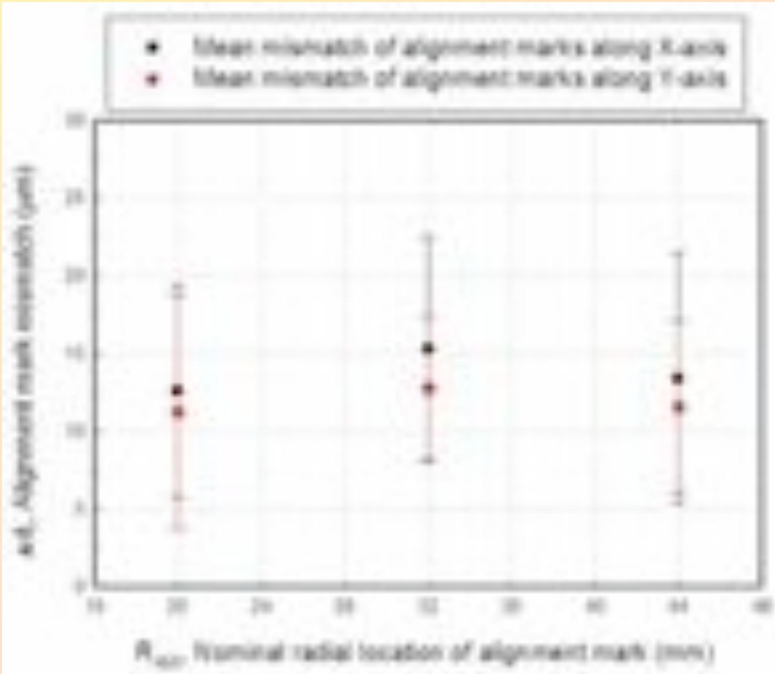
Modified Alignment Structures



- **Inconsistent alignment structure heights produced by hot embossing with original design**
- **Hypothesized that mold filling was the problem with the hemisphere-tipped posts**
- **Modified post structures to enable better filling during embossing**

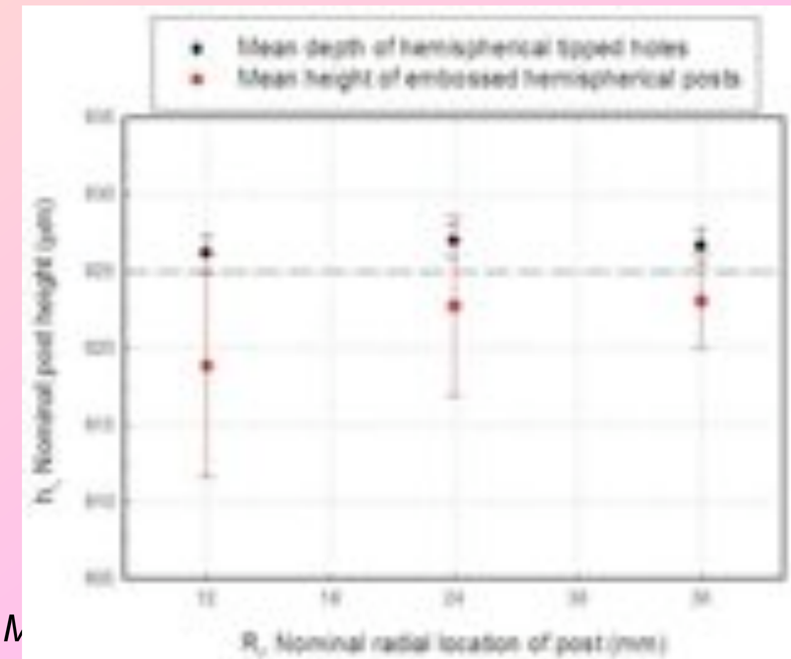


Hot Embossed Alignment

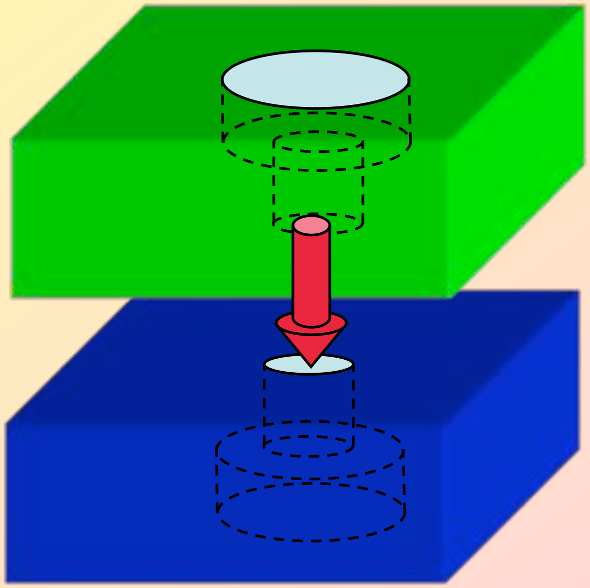


- Mean lateral offset in X- and Y-axes 10-15 μms (25 μms ~ 0.001 in)
- Not location dependent

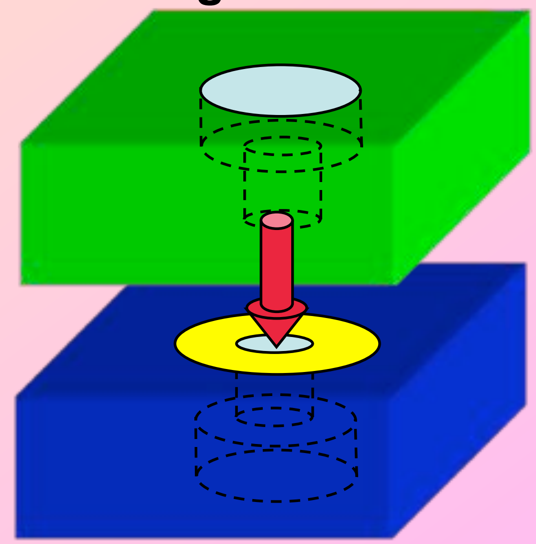
- Nominal post height 925 μms
- Mean hot embossed post height 922 ± 2 μms
- Standard deviation < 6 μms
- Not location dependent



Sealing



- Need low dead volume, no leak transfer of fluid between modules
- Seal accounts for/permits looser manufacturing tolerances



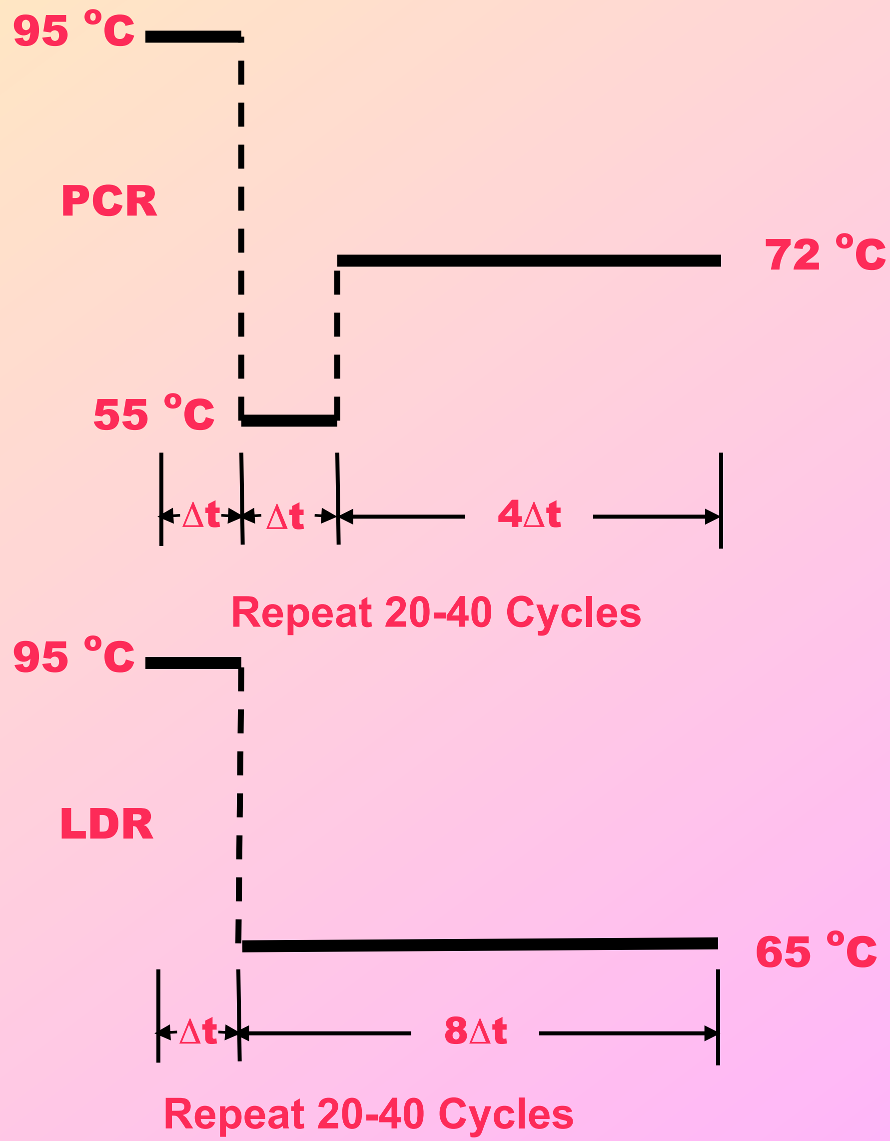
Seal Options

1. **Gasket (PDMS)**
   - Added parts
   - Adds compliance
2. **Capillaries**
   - Added parts
   - Sealing
   - Over-constraint
3. **Super/Ultra Hydrophobic Seal**

- **Modify surfaces around fluid ports**
- **Capillary forces exceed the driving force (i.e. pressure) => No leaks**
  - Gaps ~10 microns acceptable

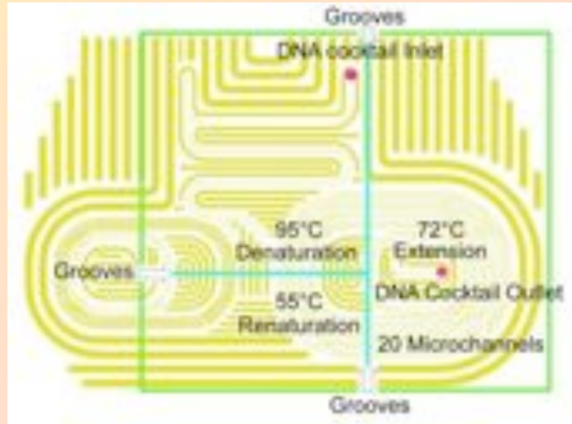
Thermal Reactions

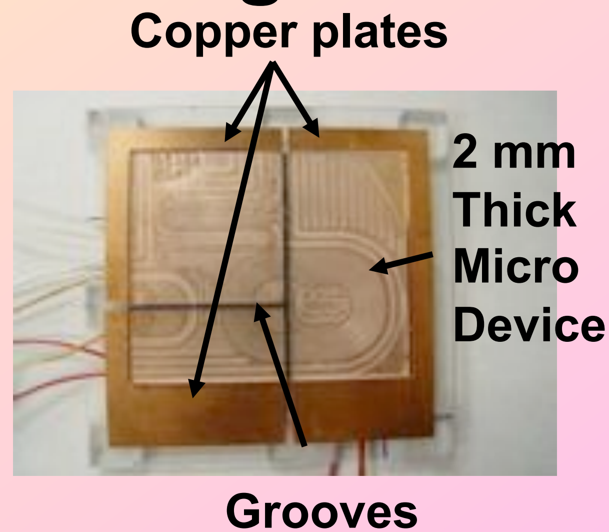
- **Thermal reactions play a key role in many assays**
- **Polymerase chain reaction (PCR) for amplification**
  - Discovered by Mullis
  - Nominal three temperature step cycle: 95 ^{o}C (denaturation), 55 ^{o}C (renaturation), and 72 ^{o}C (extension)
  - First two reactions essentially instantaneous (Wittwer, et al., 1990)
- **Ligase detection reaction (LDR) for mutation detection**
- **Two primary classes of microfabricated thermal reactors**
  - Micro-chamber (Wilding, et al., 1994; Woolley, et al., 1996)
  - Continuous flow (CFPCR) (Kopp, et al., 1998)



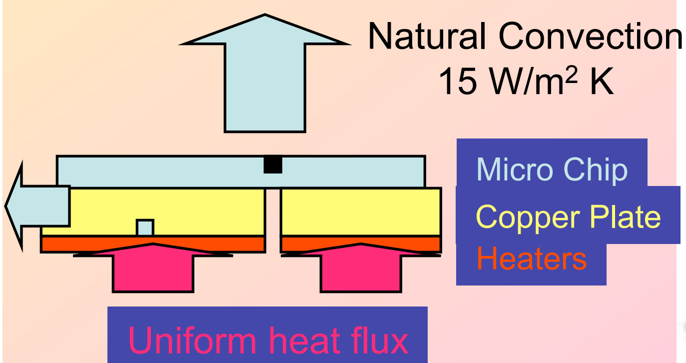
Prior Work on Thermal Management

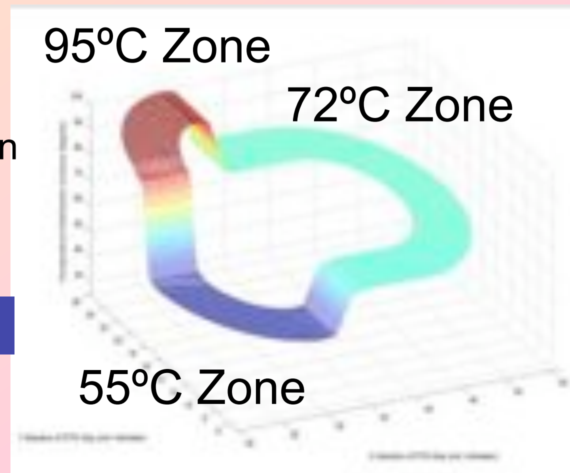
- Decrease thermal conduction (backside grooves)
- Decrease thermal capacitance (reduce substrate thickness)
- Make input constant T (copper block heaters)
- FE simulations (ANSYS, Houston, PA)
- IR thermography with ThermaCAM SC3000, FLIR Systems, MA

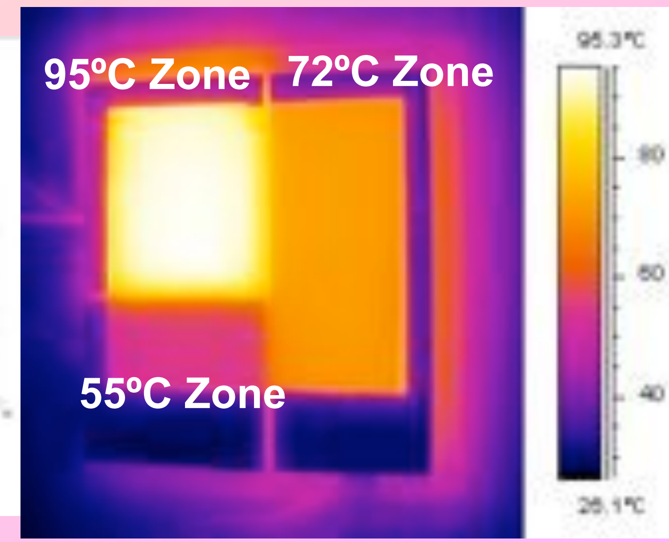




Simulation Boundary Conditions



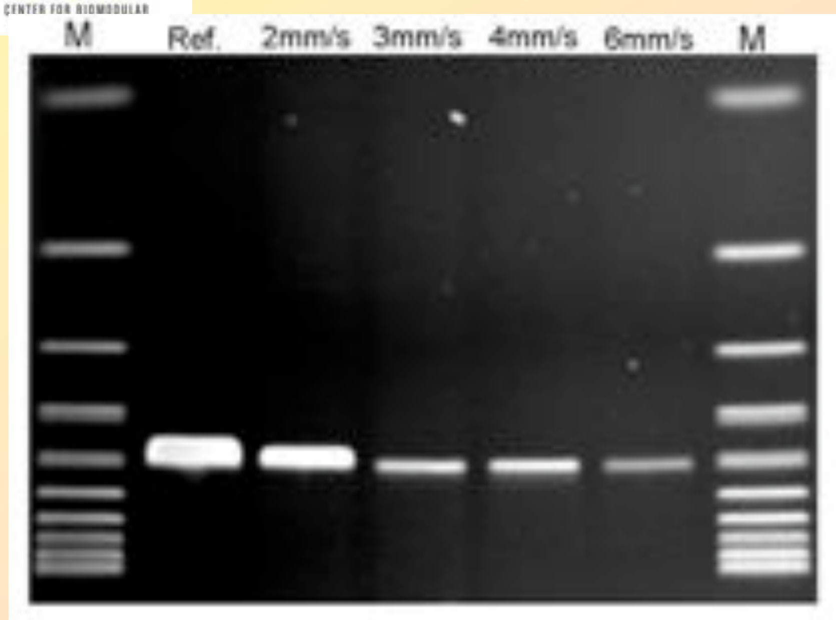


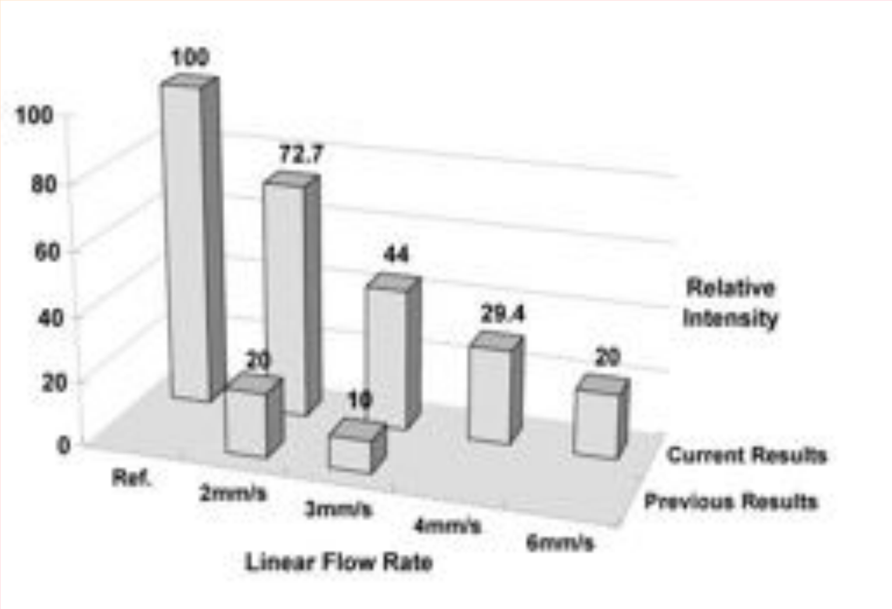


Estimated average cooling rate: 13.3 ºC/mm from 95ºC to 55 ºC

Average cooling rate: 4.1 ºC/mm from 95ºC to 55 ºC

Effect on Amplification



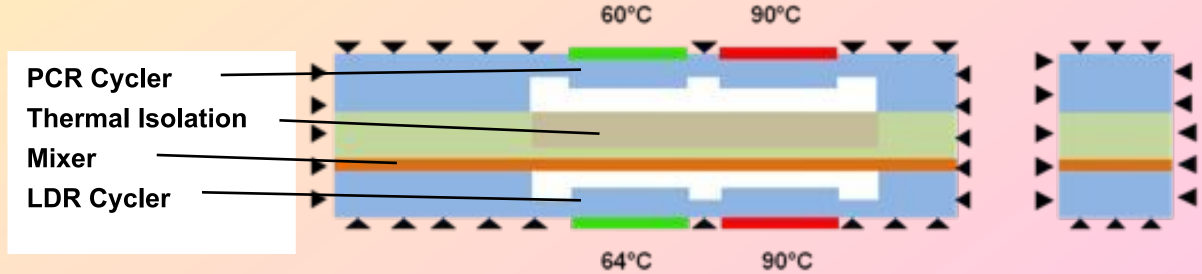


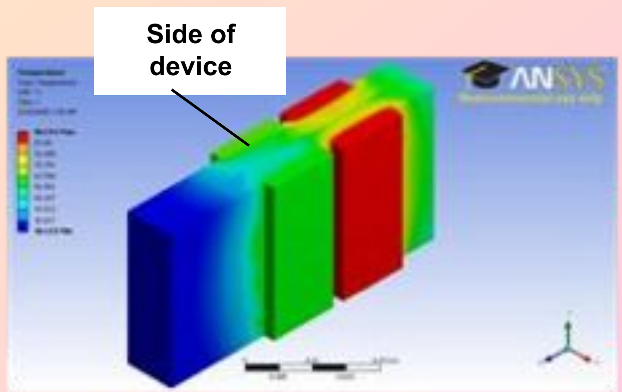
- **Same PCR cocktail as in previous experiments with 500 bp DNAs**
- **Yields as a percentage of the block thermal cycler output (90 min) were:**
  - 2 mm/s (38.7 s/cycle) => 73%
  - 3 mm/s (25.9 s/cycle) => 44%
  - 6 mm/s (12.9 s/cycle) => 20%

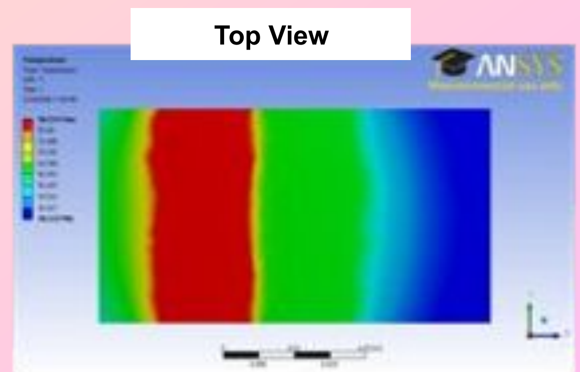
- **Improvement over Hashimoto (2004)**
  - **363% (2 mm/s)**
  - **440% (3 mm/s)**
- **At 3 mm/s, 8.6 min/20 cycles**
- **Output comparable to benchtop system in 20% of the time**
- **Chen (2008)**

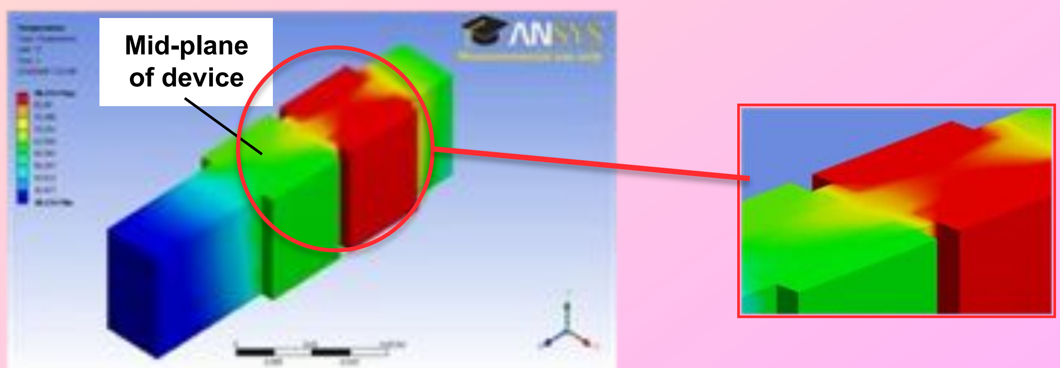
Vertical Heat Transfer in Stack

- **Heat transfer**
  - Vertical through stack
  - Limits on lateral dimensions
- **Vertical heat transfer testbed**
  - PCR + Insulator + Mixer + LDR stack
  - FE simulation (ANSYS v10.0, Houston, PA)





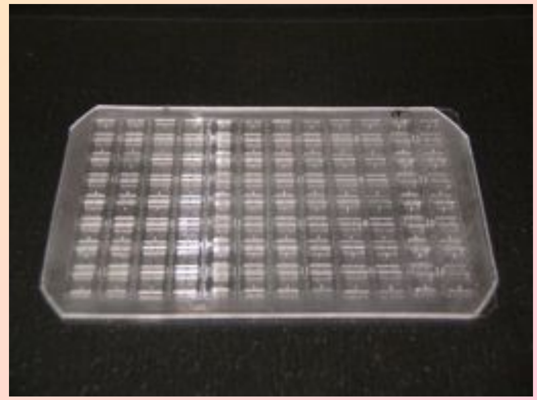


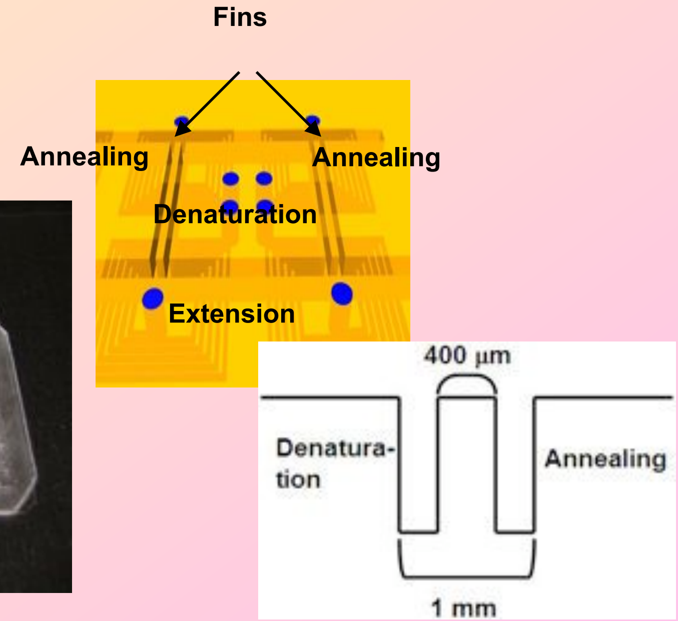


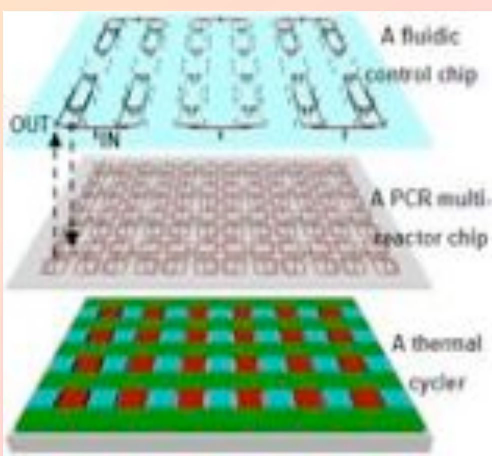
All Hands Meeting: 30 May 2008

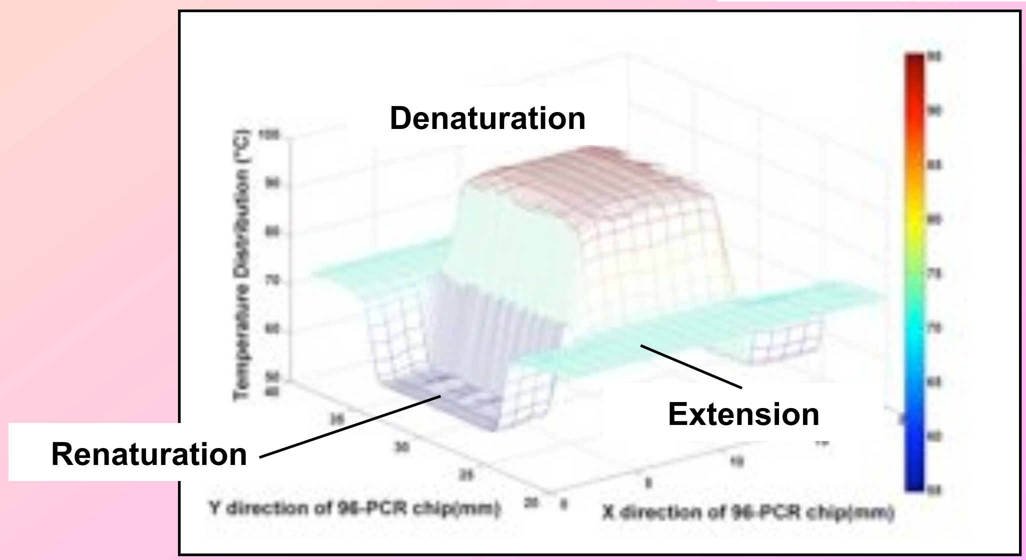
Lateral Heat Transfer Testbed

- **Lateral heat transfer testbed**
  - Multi-well PCR
  - 96 well locations
  - 125 mm x 88 mm total area
  - 8 mm x 8 mm for each location
  - FE simulation (ANSYS v10.0, Houston, PA)
  - Fins required in grooves tp increase lateral thermal resistance









Electrophoretron

Analytical Solution

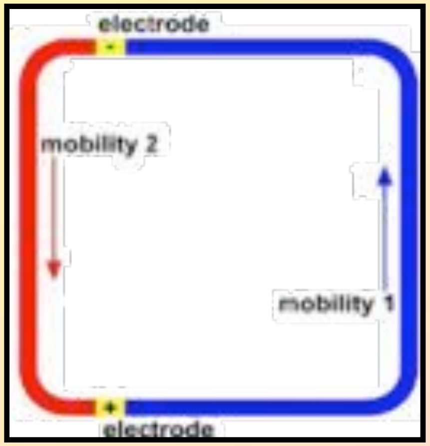


Fig 1: Schematic of the electrophoretron

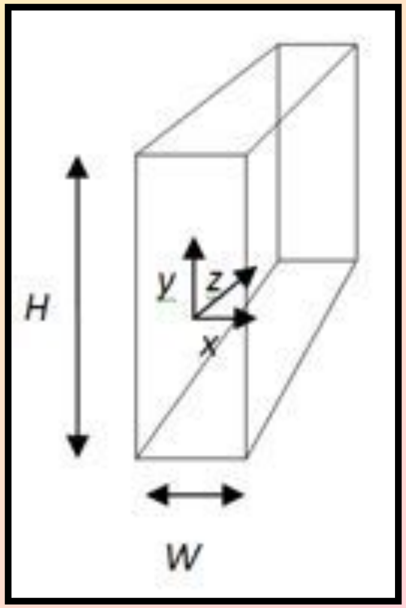


Fig 2: Coordinates and notations

- Poisson Boltzmann[1]

$$\nabla^2\Psi = k^2\Psi$$

- Navier Stokes[1]

$$\overrightarrow{\mathrm{F_e}} + \mu\nabla^2\vec{v} - \overrightarrow{\nabla p} = 0$$

- Mass conservation[2]

$$Q_1(W_1, H_1) = -Q_2(W_2, H_2)$$

$$w_i(x,y) = \frac{\Delta\varphi}{L_i}\left(\mu_{ef,i} - \frac{\pi^2}{4}F_i(x,y)\,\frac{\frac{\mu_{eo1}H_1W_1}{L_1} + \frac{\mu_{eo2}H_2W_2}{L_2}}{\frac{H_1W_1}{L_1}g_1 + \frac{H_2W_2}{L_2}g_2}\right)$$

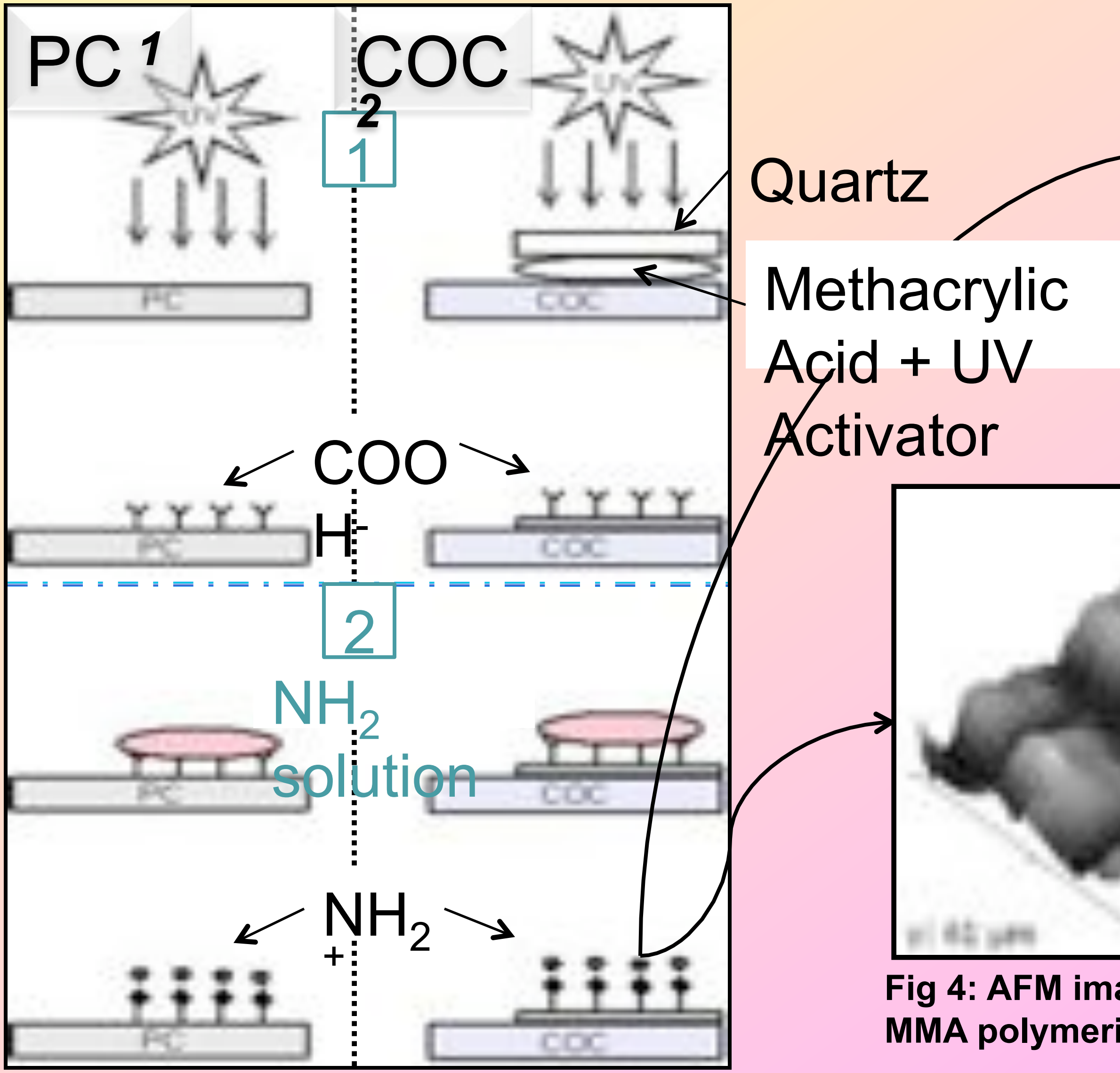
Velocity of the DNA in channel i (=1,2)

[1]*Li (2004), Electrokinetics in Microfluidics, Elsevelier*
[2]*Elmajdoub, LSU thesis (2006)*

Electrophoretron

Reversing the EOF

[1] *Elmajdoub, LSU thesis (2006)*
[2] *Pu et al.,Langmuir,23, 1577-1583 (2007)*



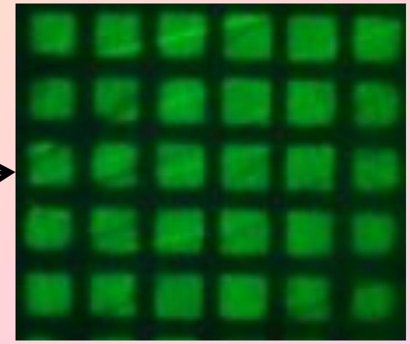


Fig 3: Fluorescence characterization of carboxylic sites on COC

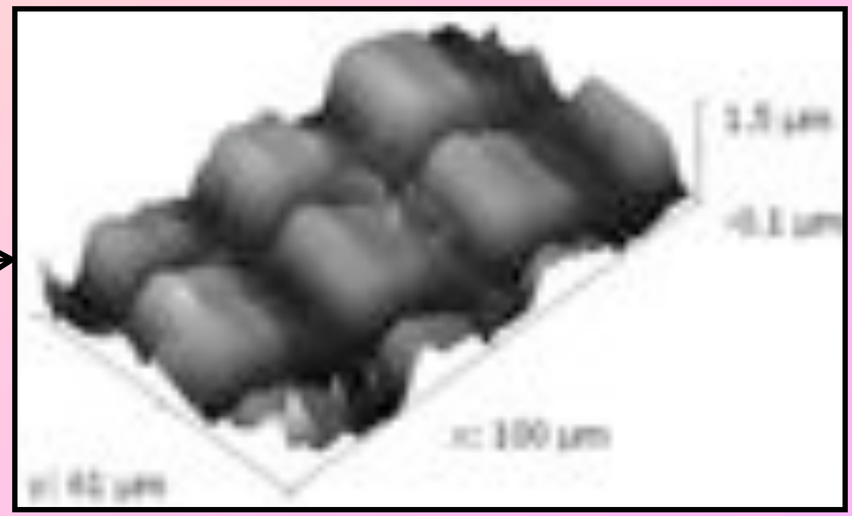


Fig 4: AFM image (AC Mode) of the thickness of MMA polymerized on COC

Injection Molding

Equipment

- Battenfeld all-electric injection molding machine
- Two Multiple Unit Dies (MUDs)
  - 1” diameter disks
  - 3”x3” inserts
- Large area MUD to accept LAMIs being fabricated (BoR ENH)

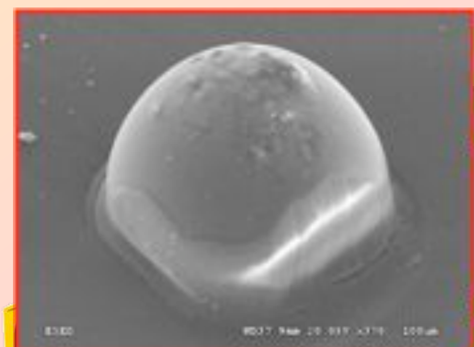
Simulation Tools

- Licenses for Moldflow and DEFORM
- Demolding analysis with ANSYS

Experiments

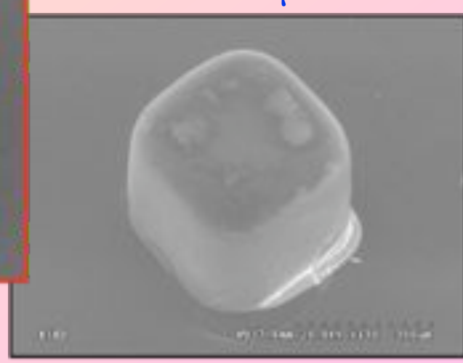
- Molding experiments to establish molding parameters
- Simulation/experiments to assess tolerance allocation
- Materials include PMMA, PC, COC

Mold T 25 °C

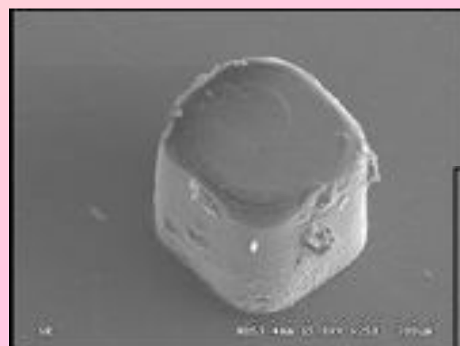


200 μm

400 μm

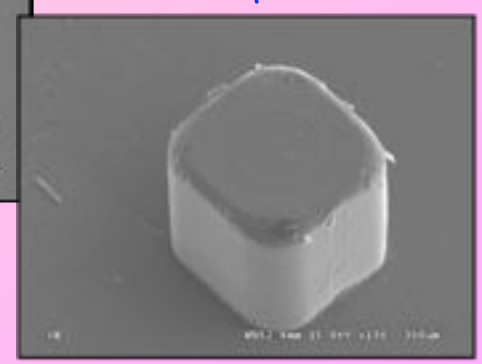


Mold T: 150 °C



200 μm

400 μm

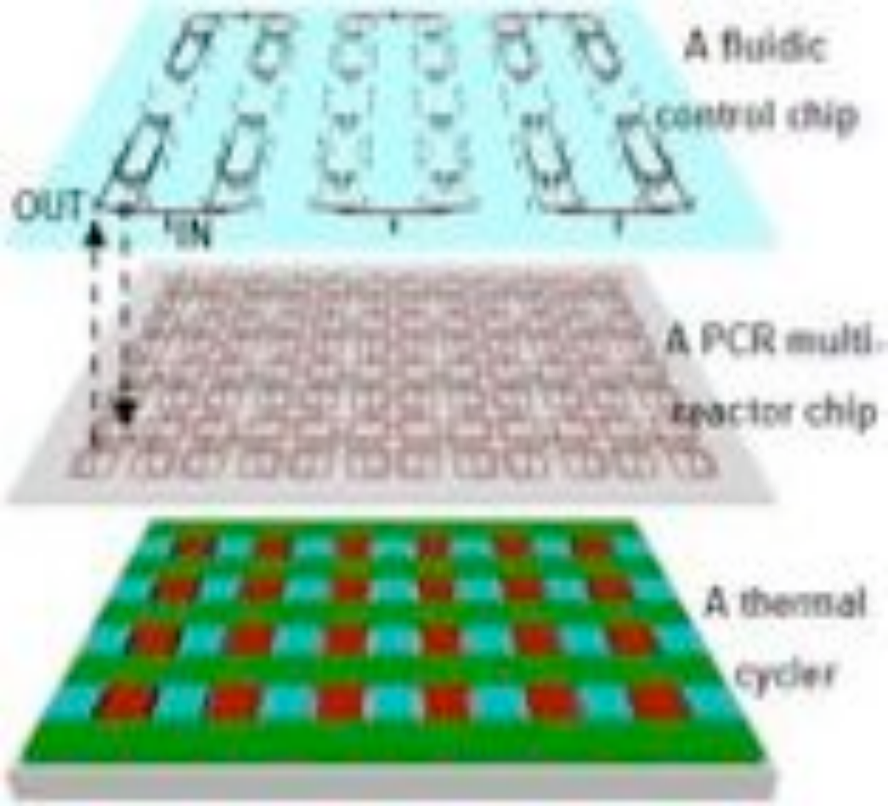


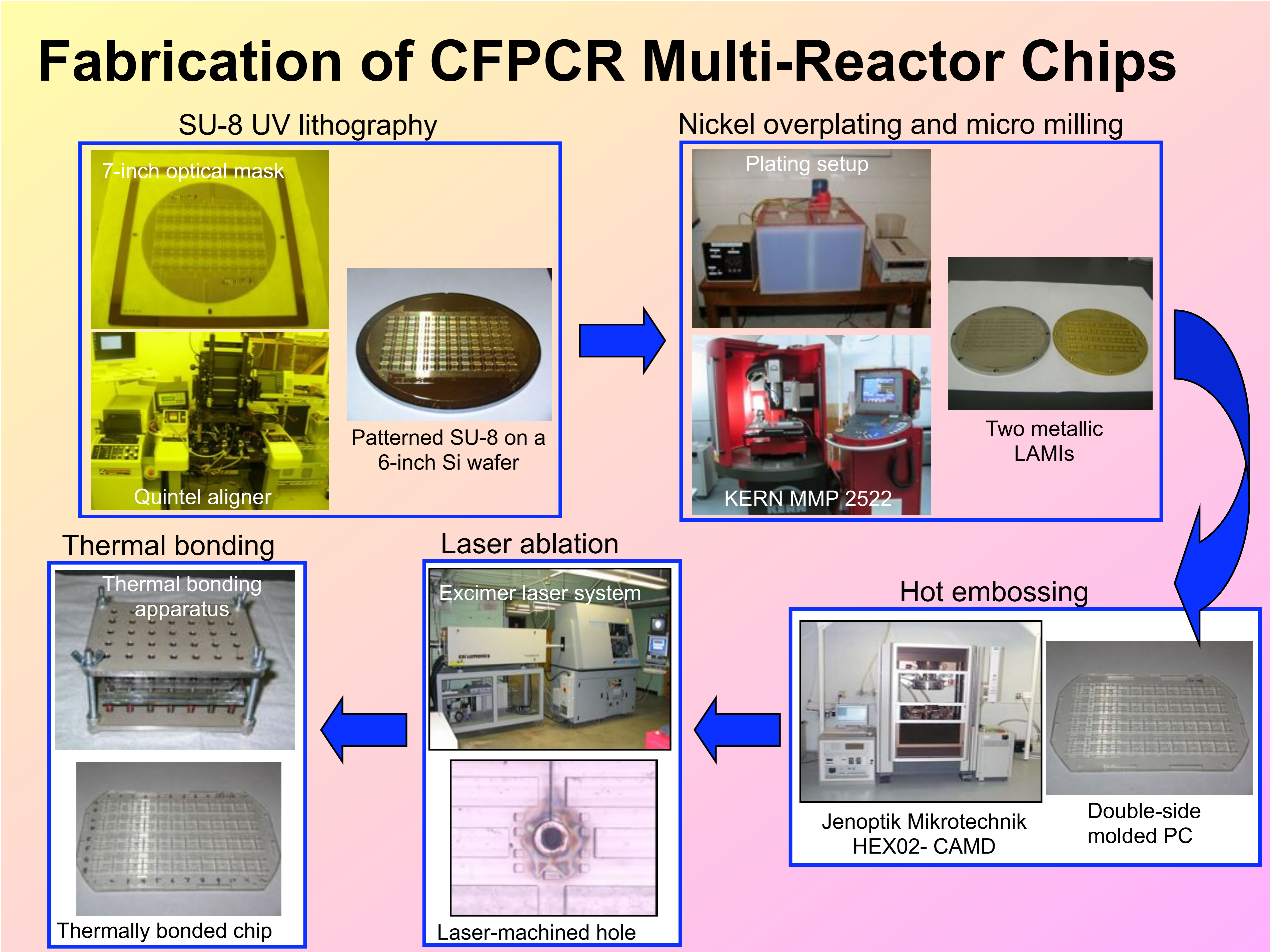
Small Molecule Sensor Requirements

- **Functional**
  - **Large area fabrication and assembly technology**
  - **Improved capture elements (SPRI)**
  - **Single molecule detection**
  - **Improved molding**
- **Computational**
  - **Thermofluid simulation of device function**
    - **Molecular dynamics (MD)/Hybrid models of molecular flow**
  - **Simulation of flow across interconnects**
  - **Monte Carlo modeling of assembly variation**
  - **Thermofluid simulation of molding processes**

Large Area Fabrication Testbed

- **High throughput (HT) = Multi-well (MW)**
- **Standard formats and layouts for micro -titer plates**
  - Widely accepted
  - Compatible with robotic processing equipment
- **Prior work on HT nucleic acid purification**
  - Solid phase reverse immobilization (SPRI)
  - Arrays of micro-posts at each well location
  - Fluid distribution network
  - Park, et al. (2008), Witek, et al. (2008)
- **Realization of a HT titer plate-based PCR multi-reactor platform**
  - Key components
    - PCR multi-reactor chip with 96 identical spiral CFPCR devices
    - Thermal actuation and control unit
    - Fluidic control unit
  - Stacking of layers with passive alignment structures

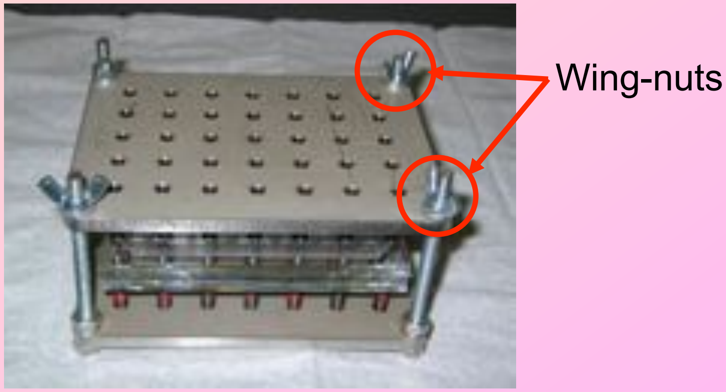



Fabrication of CFPCR Multi-Reactor Chips
SU-8 UV lithography
7-inch optical mask
Quintel aligner
Patterned SU-8 on a 6-inch Si wafer
Nickel overplating and micro milling
Plating setup
KERN MMP 2522
Two metallic LAMIs
Hot embossing
Jenoptik Mikrotechnik HEX02- CAMD
Double-side molded PC
Laser ablation
Excimer laser system
Laser-machined hole
Thermal bonding
Thermal bonding apparatus
Thermally bonded chip

Thermal Fusion Bonding Apparatus

- Design of a custom-designed thermal fusion bonding (TFB) apparatus
  - Two stainless plates with evenly spaced spring plungers (4 lbs-force each)
  - Wing-nuts used to compress the spring plungers and apply a specific, uniform load on the plastic chips
  - A calibration curve for bonding pressure generated using a load cell by measuring the compressed displacement of plungers as a function of the applied load

Custom-designed thermal fusion bonding apparatus before assembly



Custom-designed thermal fusion bonding apparatus after assembly

Methodology

High-Throughput Purification of Nucleic Acids: gDNA and mRNA

Crude Sample

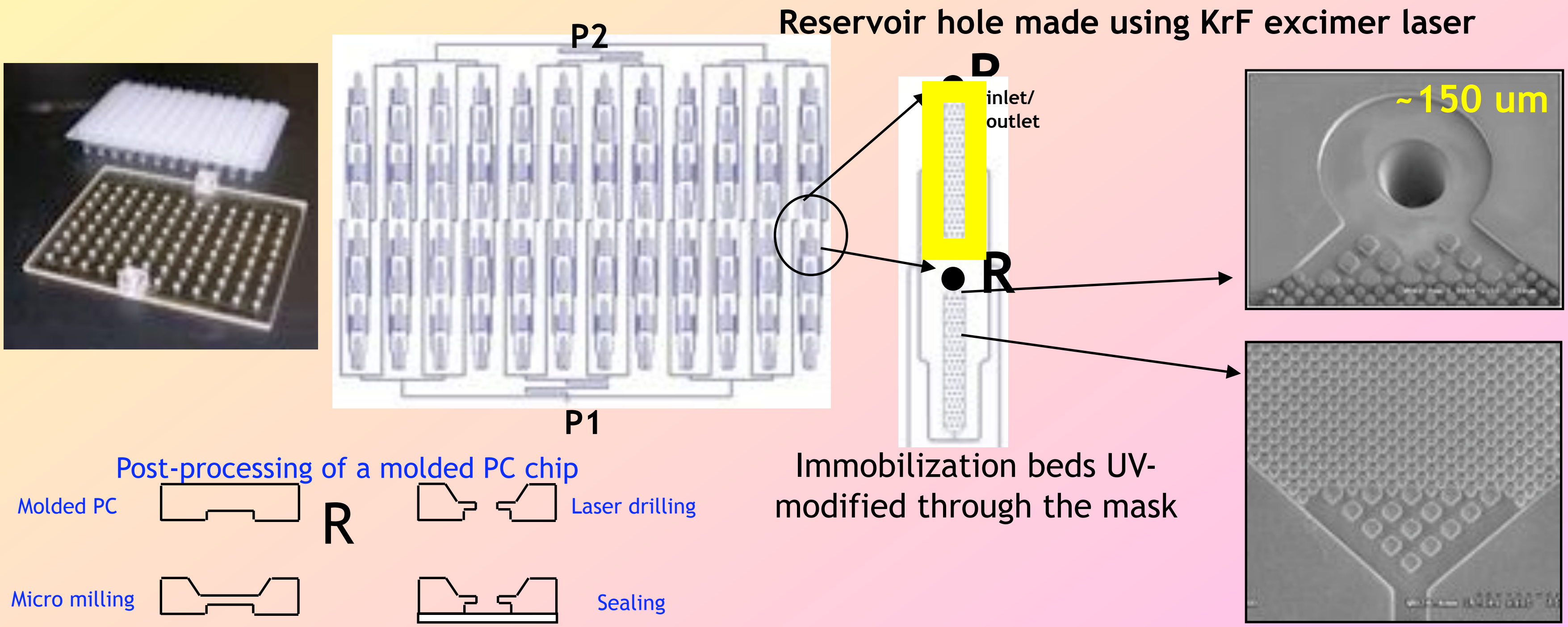
Purified DNA or RNA sample

DNA/RNA Quantitation

DNA: PCR

RNA: RT-PCR

High-Throughput 96-well Format SPRI

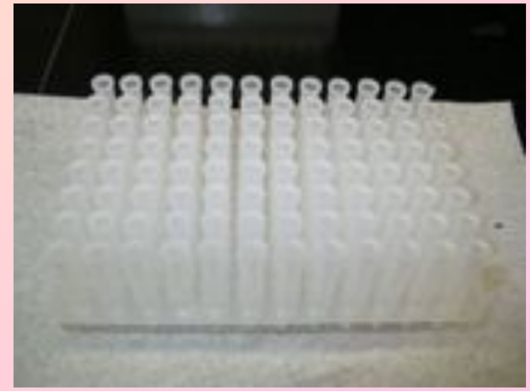


- Standard 96-well titer plate format: 12 x 8 wells, 9 mm spacing
- Simultaneous addressing of all DNA capture beds by two control ports (fluidic (P1) and vacuum (P2))
- High-surface area DNA capture beds: d=20 μm; spacing 20 μm; depth 50 μm; 3800 posts
- Each well (7 x 1 mm) has a surface area of 28.4 mm^2 , volume = 277 nL, SA/V = 103 mm^{-1}

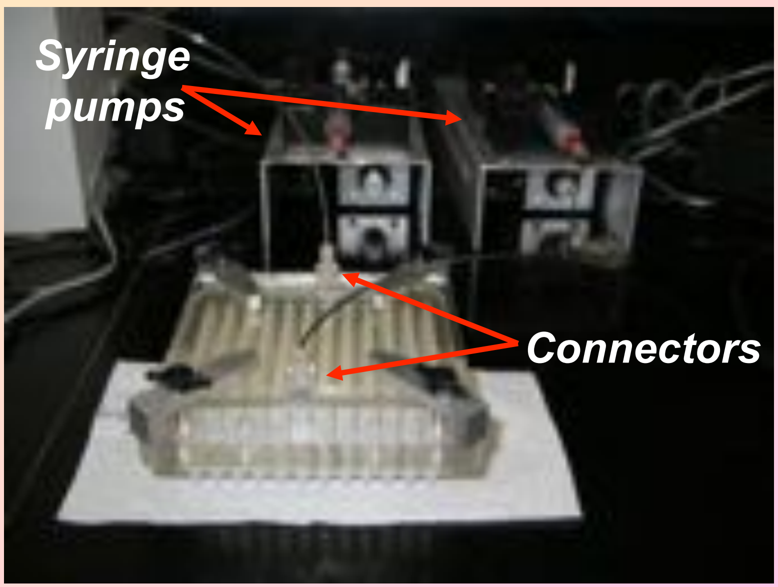
96-Well SPRI Performance

- PMMA jig made with capillaries and PDMS gaskets
- DI water dispensed at 2 mL/min and collected from each well into microfuge tubes
- About 70% of wells showed good fluidic performance
- Misalignment issues at some wells

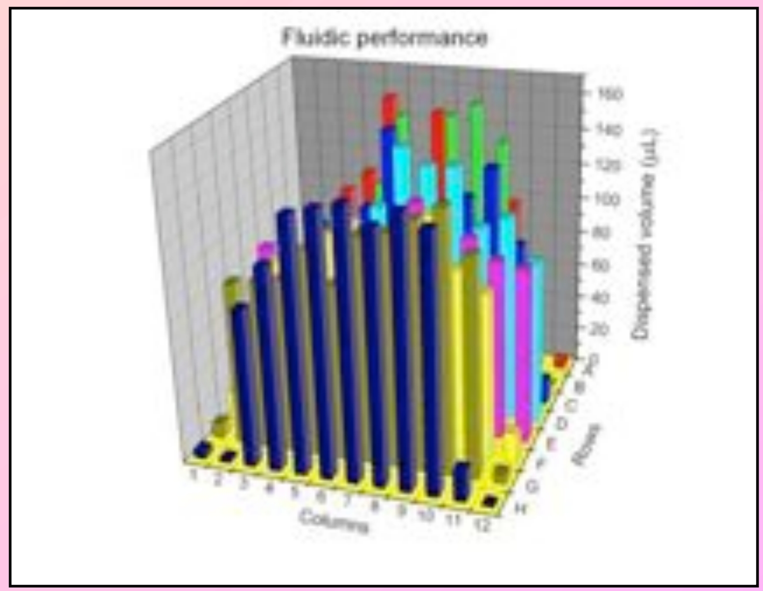
PMMA jig



Microfuge tubes

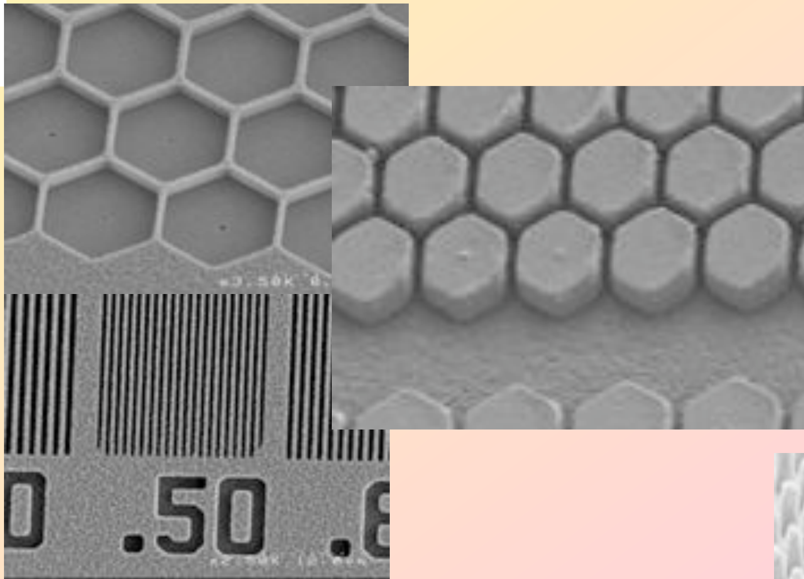


Experimental setup

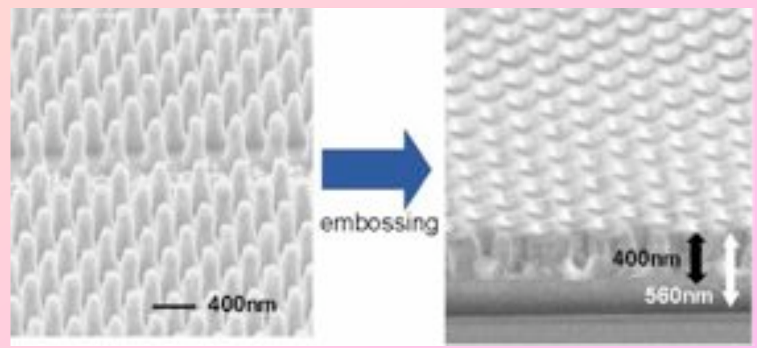


Fluidic performance results

Nanomolding/Nanoimprinting



Work by Göttert group at CAMD (Datta, et al., 2003)
- e-beam written mask from FzK
- Patterns to 0.5 micrometer
- Imprinted on Jenoptik HEX02 at CAMD

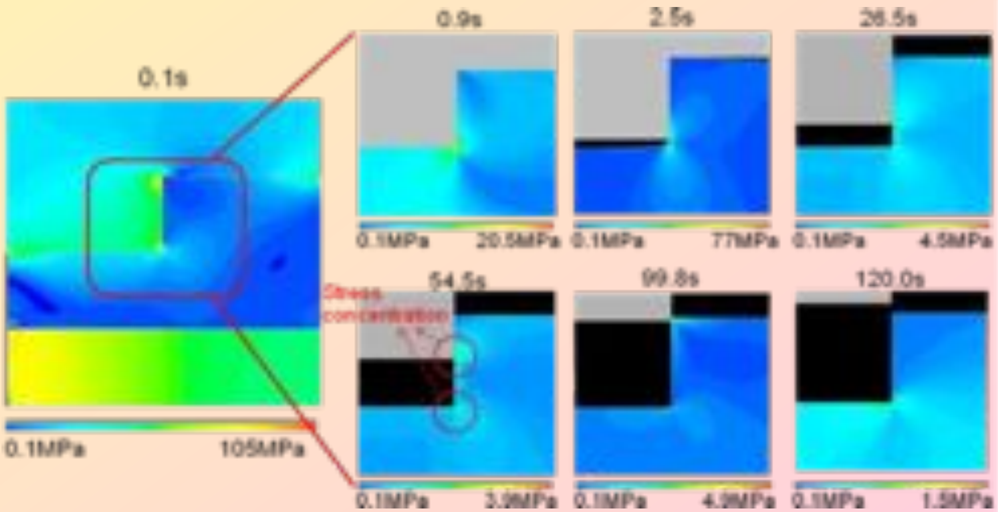


Work by Park and Schift at PSI
- e-beam written masks
- CVD anti-adhesive coatings
- Custom imprinting machine
- Injection molded polymer stamps
- Example 200 nm DIA, 400 nm tall posts in Si embossed in PMMA

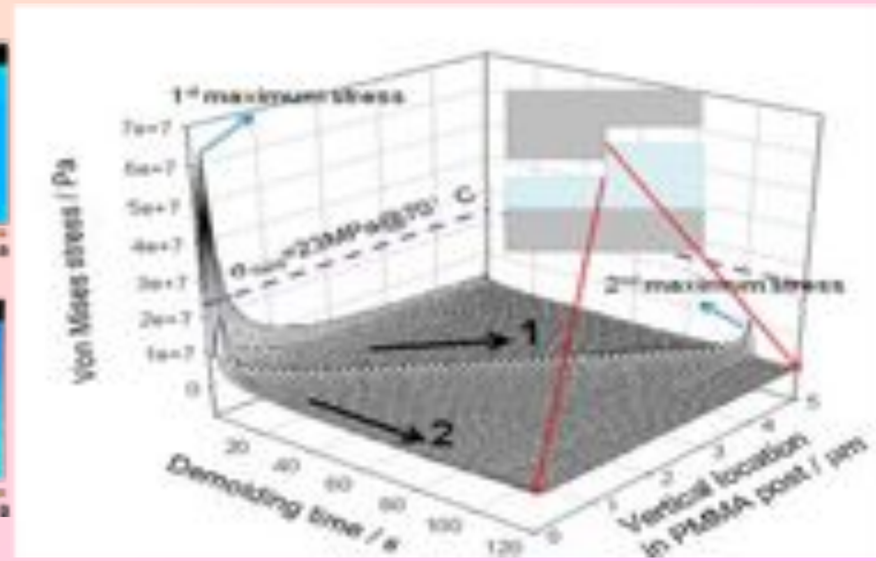
Progress:
- Park joined LSU faculty in January 2005
- CVD coating system assembled
- Obducat nanoimprinting machine installed
- Stamp fabrication at Georgia Tech (NNIN)
- Plan to measure demolding forces; MTS in

FEM Simulation of Demolding

Stress distribution vs. $t_{demolding}$



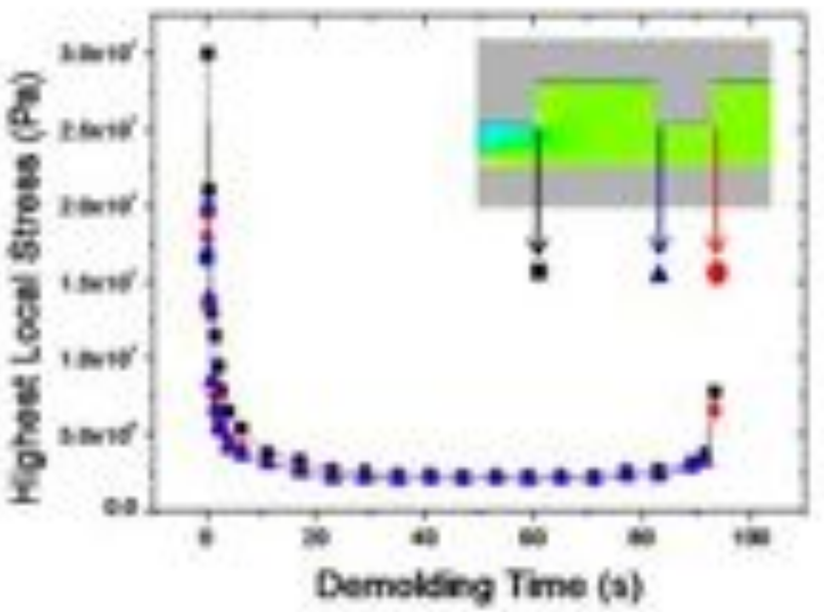
Stress vs. $t_{demolding}$
along vertical wall interface



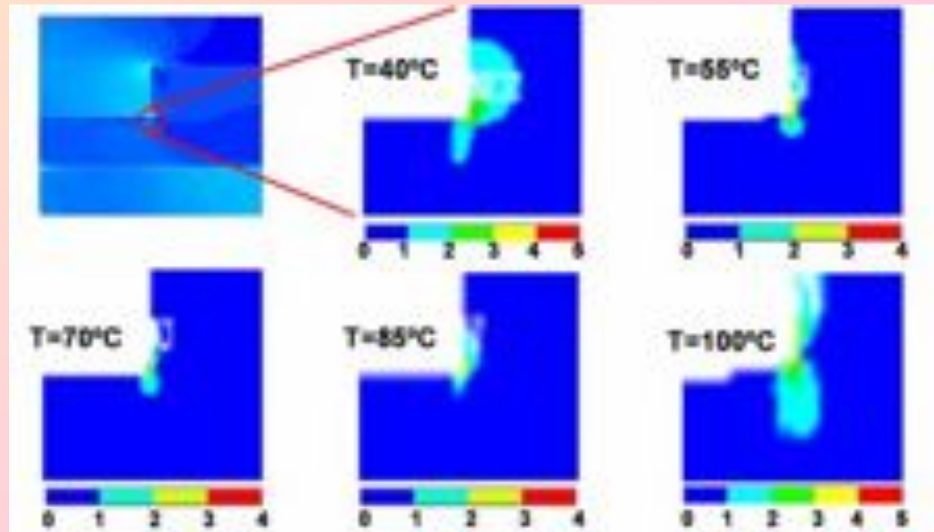
- Local stress is concentrated at two different locations: the corner region of PMMA and the contact point region with moving stamp edge.
- Local stress shows two maxima: first at the beginning and second immediately before the end → indicates when demolding failure occurs

Parametric Study on Demolding

Demolding for multiple structures



Optimization of demolding T

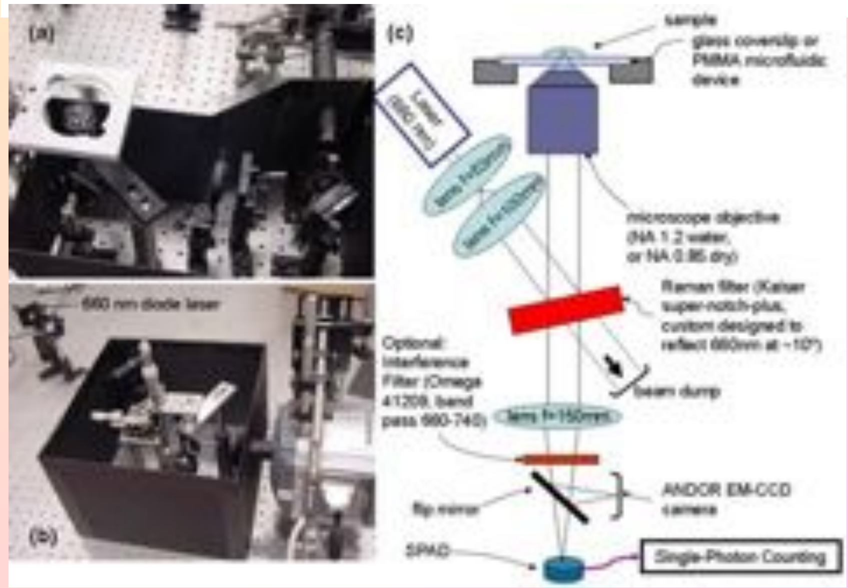


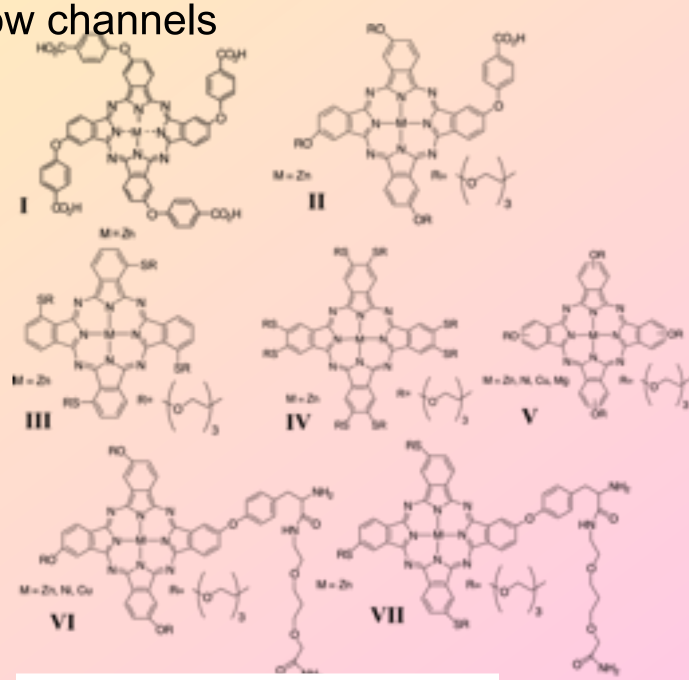
- **Higher stress at outermost structure. → An auxiliary outer structure could protect the inner structures**
- **Highest stress at different demolding T was normalized by σ_Y. → The smallest area of resist deformation was shown at 70°C.**

Optical Single Molecule Detection

- Phthalocyanines can form near-IR emitting fluorophores
- Suitable for reporter molecules for FRET detection of DNA molecules
- Will use for L1-EN detection
- Demonstrated detection of DNA in flow channels

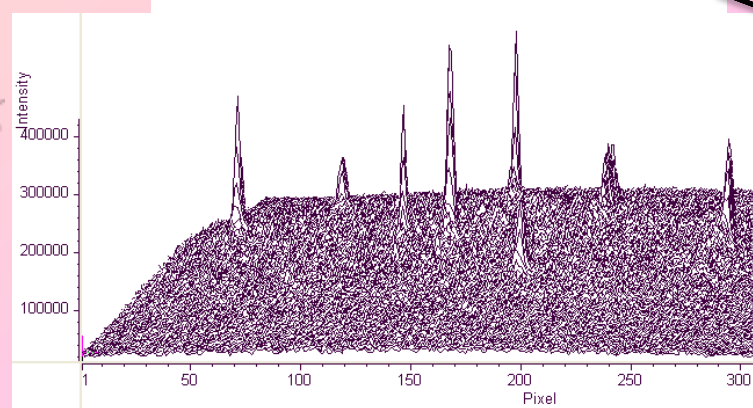
Experimental setup for testing Pc dye detection





Phthalocyanine (Pc) dyes

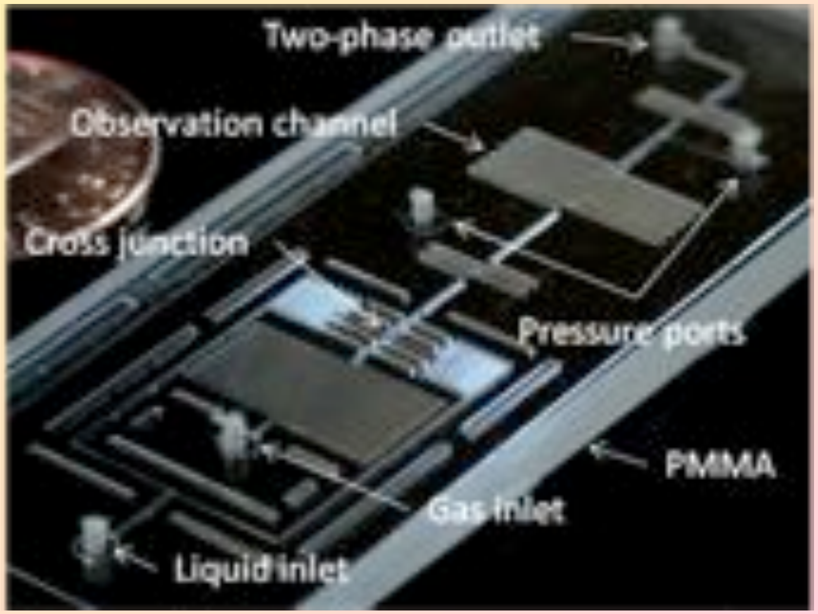
DNA molecules in flow channels



Intensity of emission from channels

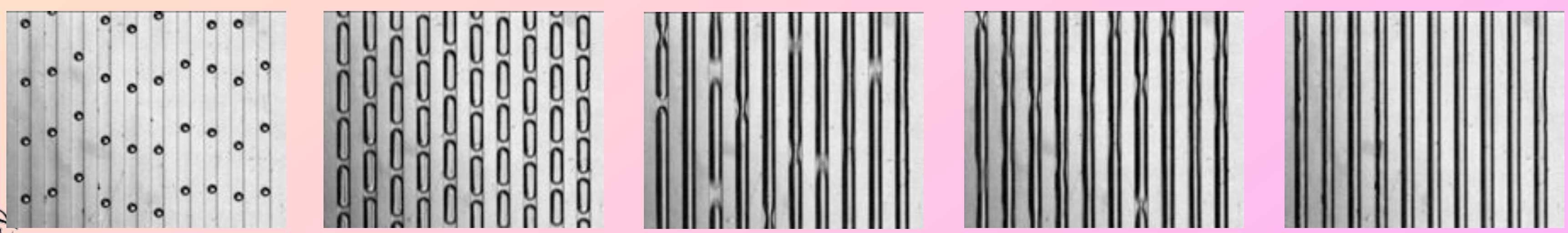
All Hands Meeting: 30 May 2008

Gas-Liquid Experiments



$$\beta = \frac{Q_L}{Q_L + Q_G}$$

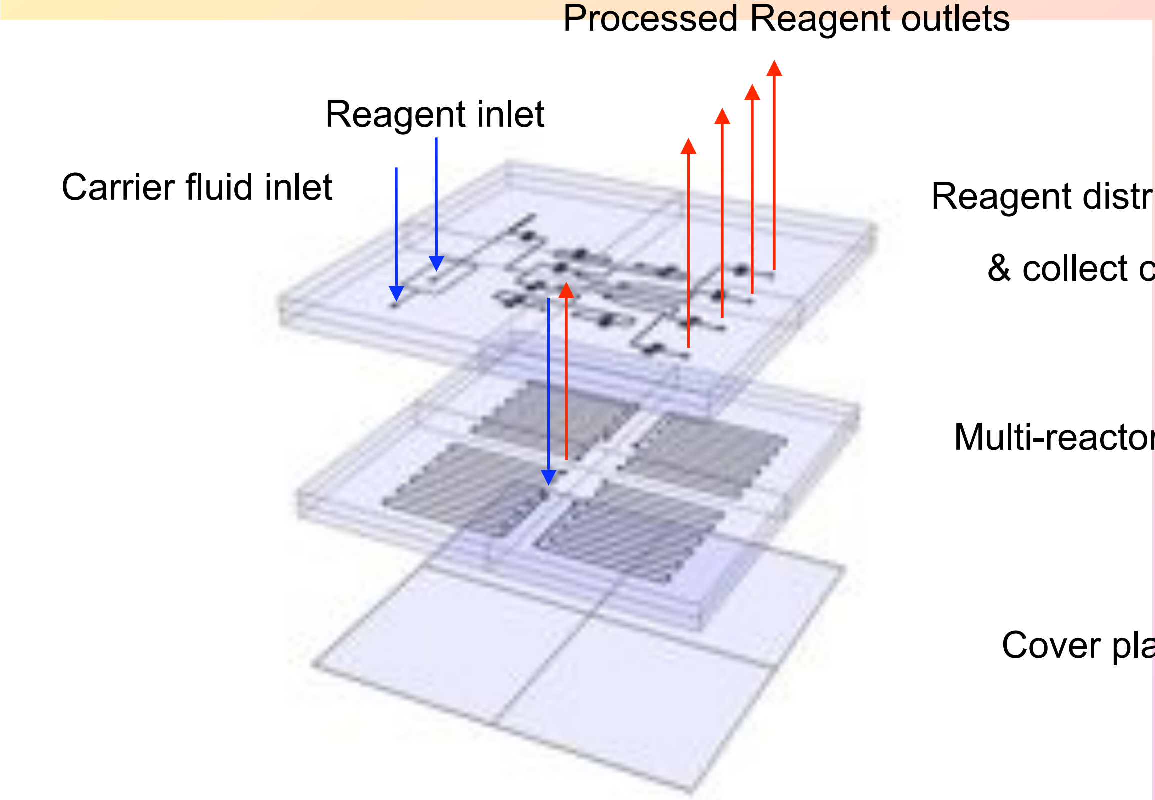
Where β *= homogenous liquid fraction*
Q_L *= gas volumetric flow rate*
Q_G *= liquid volumetric flow rate*

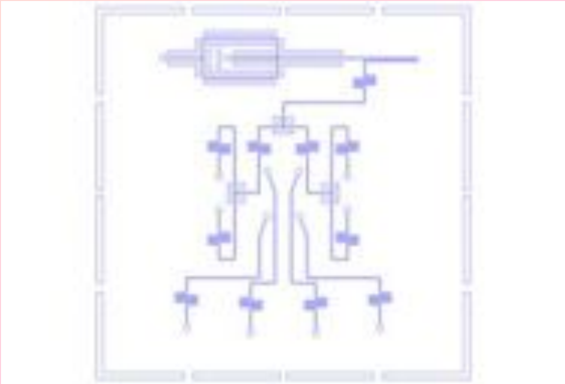


Capillary bubbly $\beta = 0.9$ | Plug $\beta = 0.2$ | Plug-annular $\beta = 0.06$ | Annular $\beta = 0.018$ | Dry $\beta = 0.002$

Liquid-Liquid Flow

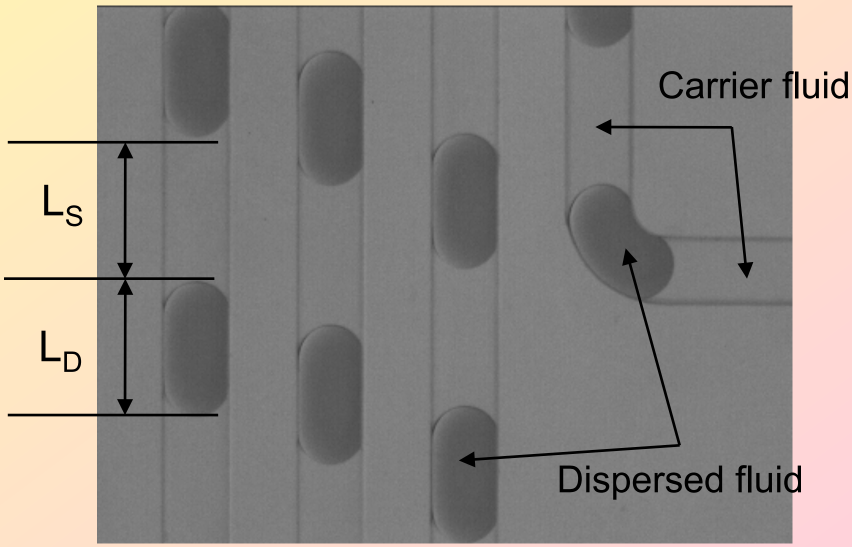
- **Design for liquid-liquid immiscible flow**

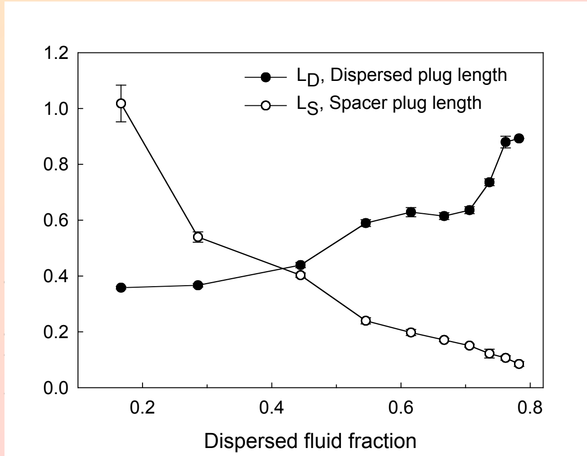


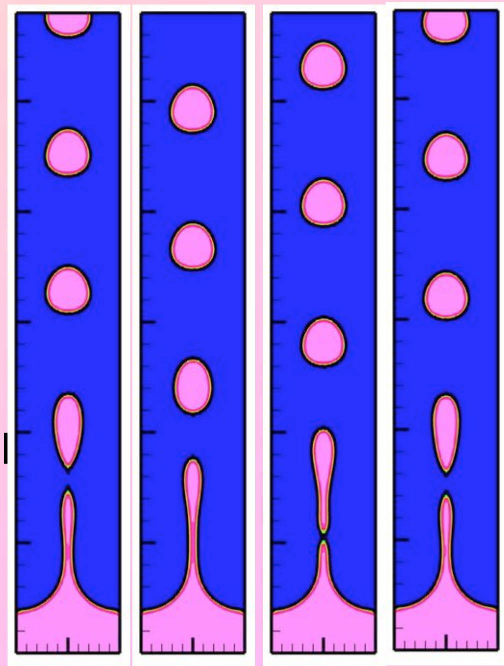


Liquid-Liquid Experiments

Dispersed and carrier fluids

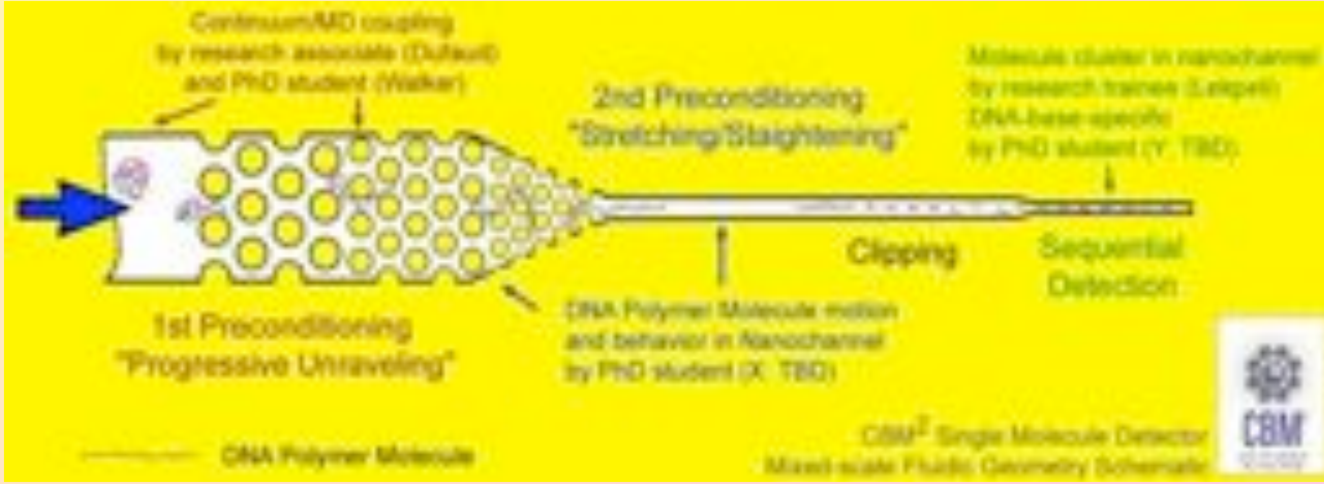




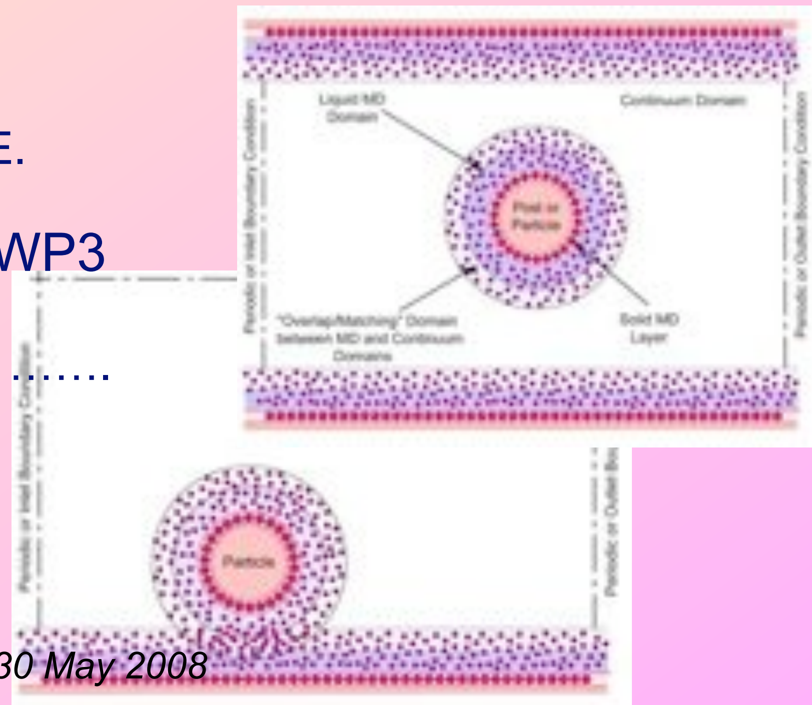


Carrier fluid – FC 3283 + 10 % v/v PFO (Perfluorooctanol)
Dispersed fluid – DI water + 1% v/v food dye

Hybrid MD/Continuum



- LSU Investigators
  - Applications
    - M. C. Murphy ● S. A. Soper ● D. E. Nikitopoulos
  - Development/Simulations – WP4/WP3
    - D. Moldovan ● D. E. Nikitopoulos
    - M. Tyagi ● S. Jha ● B. Aksoylu ● …….
- External Collaborators
    - D. T.-Dervout (UCBL-1, France)
    - D. Eyheramendy (ECM, France)



State of Affairs

- Basic MD code
  - Developed
  - Parallelized in one dimension
  - Tested on simple 2D flows
    - Couette
    - Poiseulle
  - Modification of MD code to accommodate more diverse BC and parallelization in two dimensions (in progress)
  - Documentation of the code for delivery to WP4 (in progress)
- Continuum 3D N-S Parallel Code (Velocity/Vorticity Formulation)
  - Developed (international collaboration)
  - Tested on 3D driven cavity test problem - Re[0.1,5000] (in progress)
  - Documentation of the code for delivery to WP4 (in progress)
- Continuum-MD Coupling
  - In progress
  - Will work with WP4 to develop tools to
    - Build a Modular Continuum-MD Parallel Simulation Environment under CACTUS

Technology Transfer

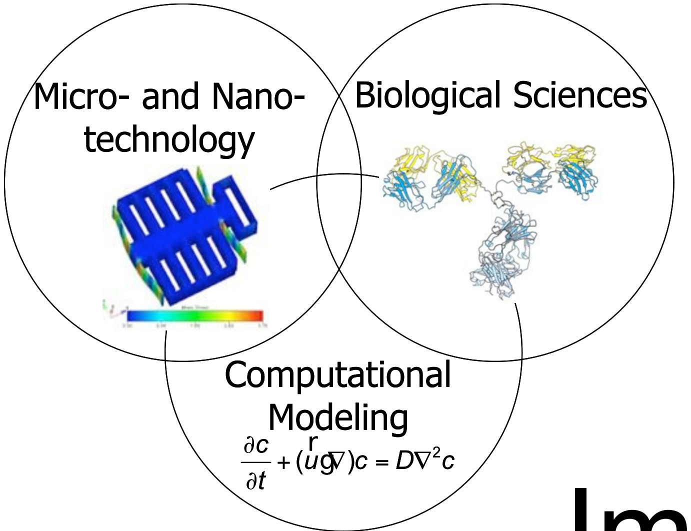
- **Intellectual Property**
  - 3 Patents Pending, 1 Provisional Patent
  - Numerous patent disclosures
  - Some inquiries from established companies
- **Start-up**
  - Biofluidica Microtechnologies, LLC
    - CEO, Dr. Yohannes Desta
  - Located at LBTC
  - Currently in private placement
  - Working with faculty on SBIR/STTR proposals for technology development

Education and Outreach

- **Graduate student and post-doc training**
  - Ongoing monthly seminar/workshop series
  - Organized by Dr. M. Witek
- **Science and Engineering Research Day**
  - July 31st (Thursday)
  - Poster session in morning
  - Two panels in afternoon
    - Computational capabilities
    - Biology needs
  - Grant writing workshop
- **Outreach Activities**
  - Continuing interaction with Girl Scouts (S. Dann)

Conclusions

- **Genosensor**
  - Functional => Progress all critical areas
  - Computational
    - Simulations of device function and interconnects with commercial packages => Limited in Scale
    - Monte Carlo modeling of assembly variation
    - Thermofluid simulation of molding processes => Commercial packages not adequate at small scales
- **Small Molecule Sensor**
  - Functional => Progress in all areas
  - Computational
    - Thermofluid simulation of device function
      - Molecular dynamics (MD)/Hybrid models of molecular flow
    - Simulation of flow across interconnects
    - Monte Carlo modeling of assembly variation
    - Thermofluid simulation of molding processes

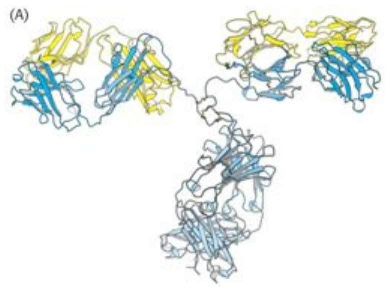


Immunosensors

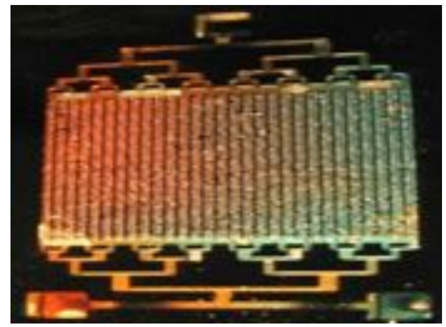
Ricardo Cortez, Diane Blake, Hank Ashbaugh, Thomas Bishop, Donald Gaver and students, and Mark DeCoster

Antibody-based Biosensor

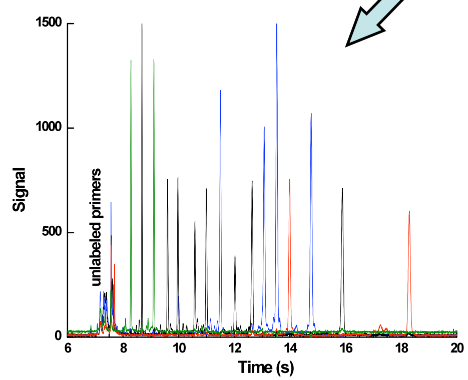
The system will be composed of microfluidic and immunosensing elements (antibodies) targeted for the analysis of biological or chemical agents. **Components**: microfluidic elements for sample pre-processing, nanoporous membranes for target pre-selection and carbon printed electrodes for electrical readout.



Biochemistry



Fluid flow / reactions in micromixer



Signal

Antibody-based Biosensor

Tulane	LaTech IfM	Xavier	UNO
Jerina Pillert Kate Hamlington Amit Jain Mehnaaz Ali Hank Ashbaugh Tom Bishop Diane Blake Ricardo Cortez Lisa Fauci Don Gaver	Senaka Kanakamedala Jie Liu Mangilal Agarwal Mark DeCoster Ji Fang Yuri Lvov	Robert Blake	Steven Rick

Experiments: characterization of antibodies, determination of assay parameters, preparation and reactivation of Apo-glucose oxidase, synthesis.

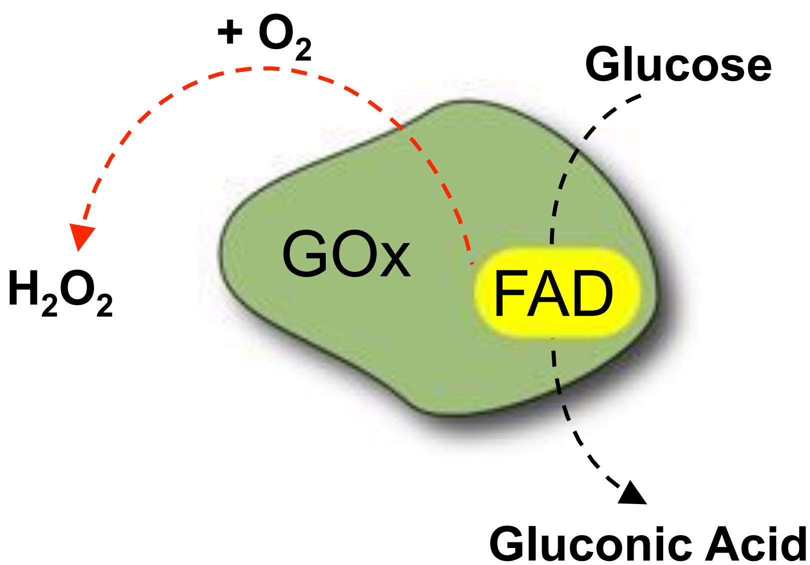
MD Simulations: antigens binding to antibody, energy minimization, loop structures, sequence alignment.

CFD Simulations: flows in microchannels, complex geometry, property optimization, reaction-diffusion-transport of concentrations, parallelization.

Manufacturing: microsensor layer fabrication, micromixer fabrication and evaluation, nanoporous membrane.

The immunosensor will use GOx mediated glucose oxidation for signal transduction

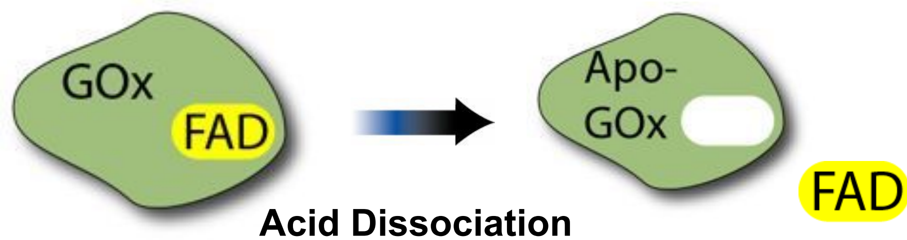
Glucose Oxidation



Glucose oxidase *requires the cofactor* ***FAD*** *for the catalysis of* ***glucose*** *to* ***gluconic acid****. This process involves the initial reduction of FAD to $FADH_2$ and consequent oxidation by molecular O_2* ***generating H_2O_2***

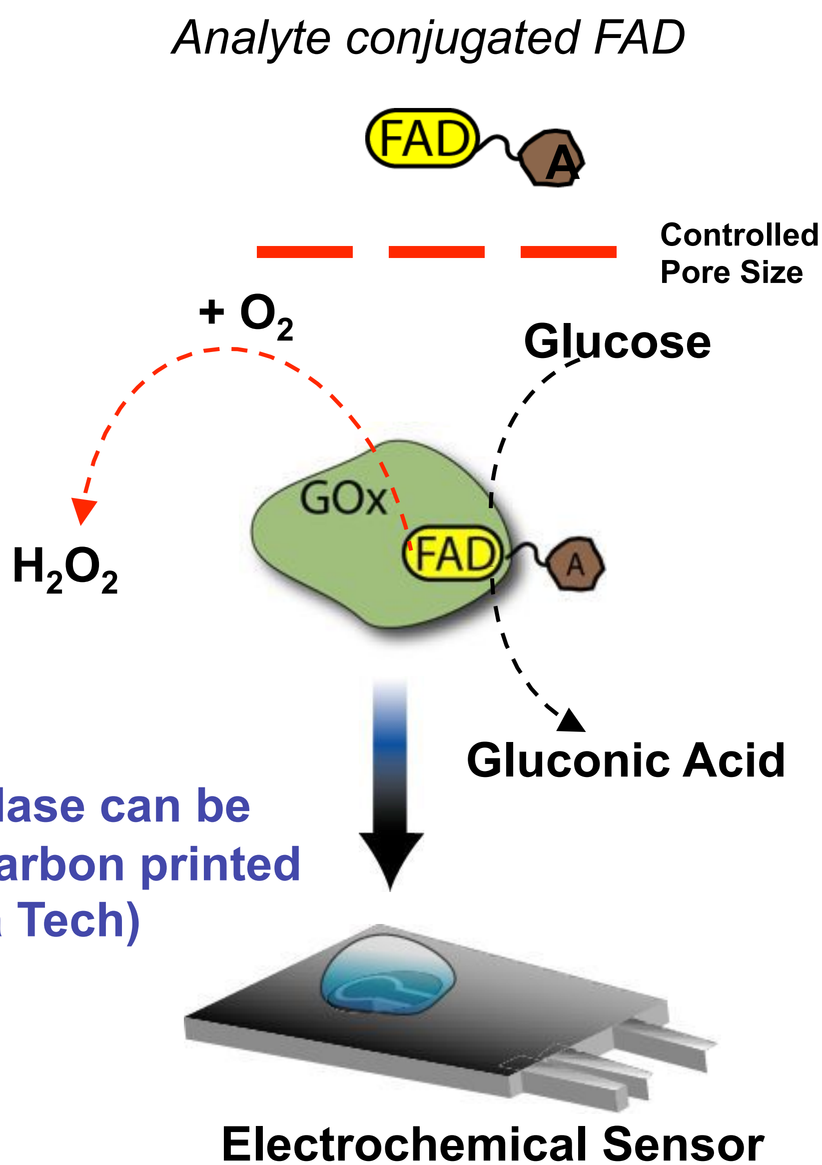
E-Chem Sensor

Enzyme activity *can be* ***modulated*** *by* ***the removal*** *and* ***introduction*** *of the cofactor* ***FAD****. The* ***cofactor*** *can be efficiently* ***dissociated*** *under acidic conditions to yield* ***apo glucose oxidase.***



Thus the cofactor FAD can be conjugated to an analyte and utilized to modulate enzyme activity.

General Strategy for E-chem Immunoassay



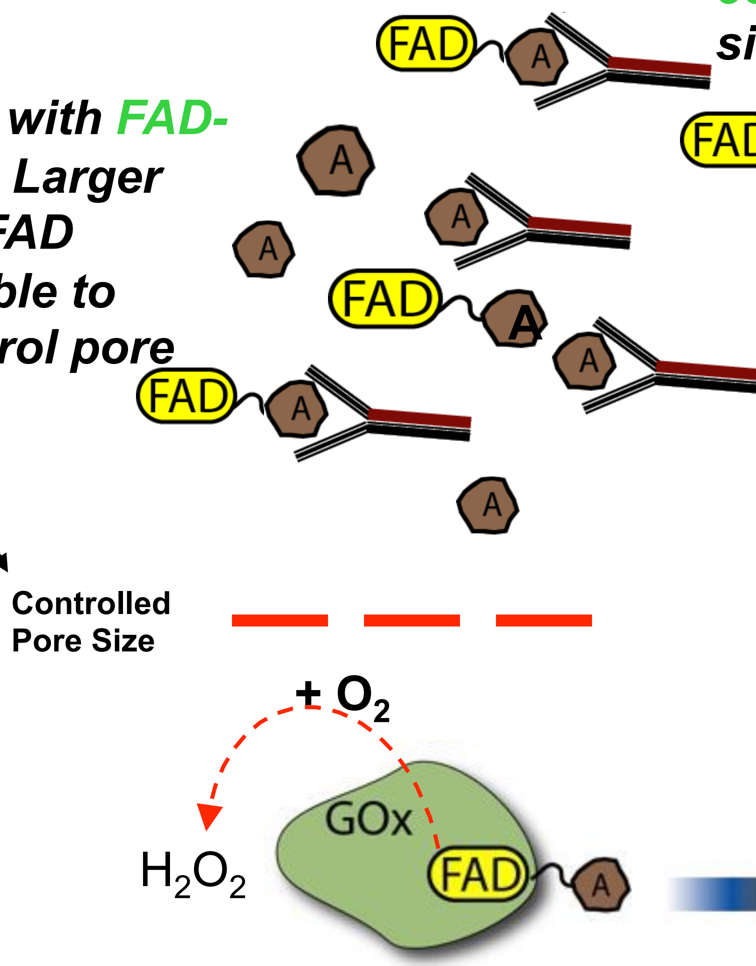
FAD-analyte mediated reactivation of the Apo-GOx in the presence of glucose.

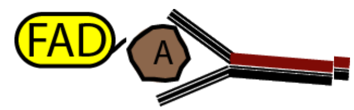
Apo-Glucose oxidase can be coated onto the carbon printed electrode (IFM, La Tech)

E-Chemical Immunoassay

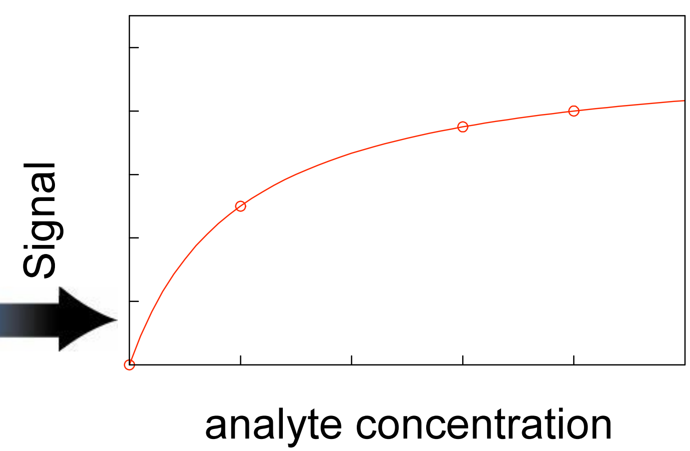
Addition of analyte from serum or environmental sample competes with the FAD-analyte conjugate for antibody binding sites…

Antibody is mixed with FAD-analyte conjugate. Larger antibody-analyte-FAD conjugate is not able to penetrate the control pore size layer.

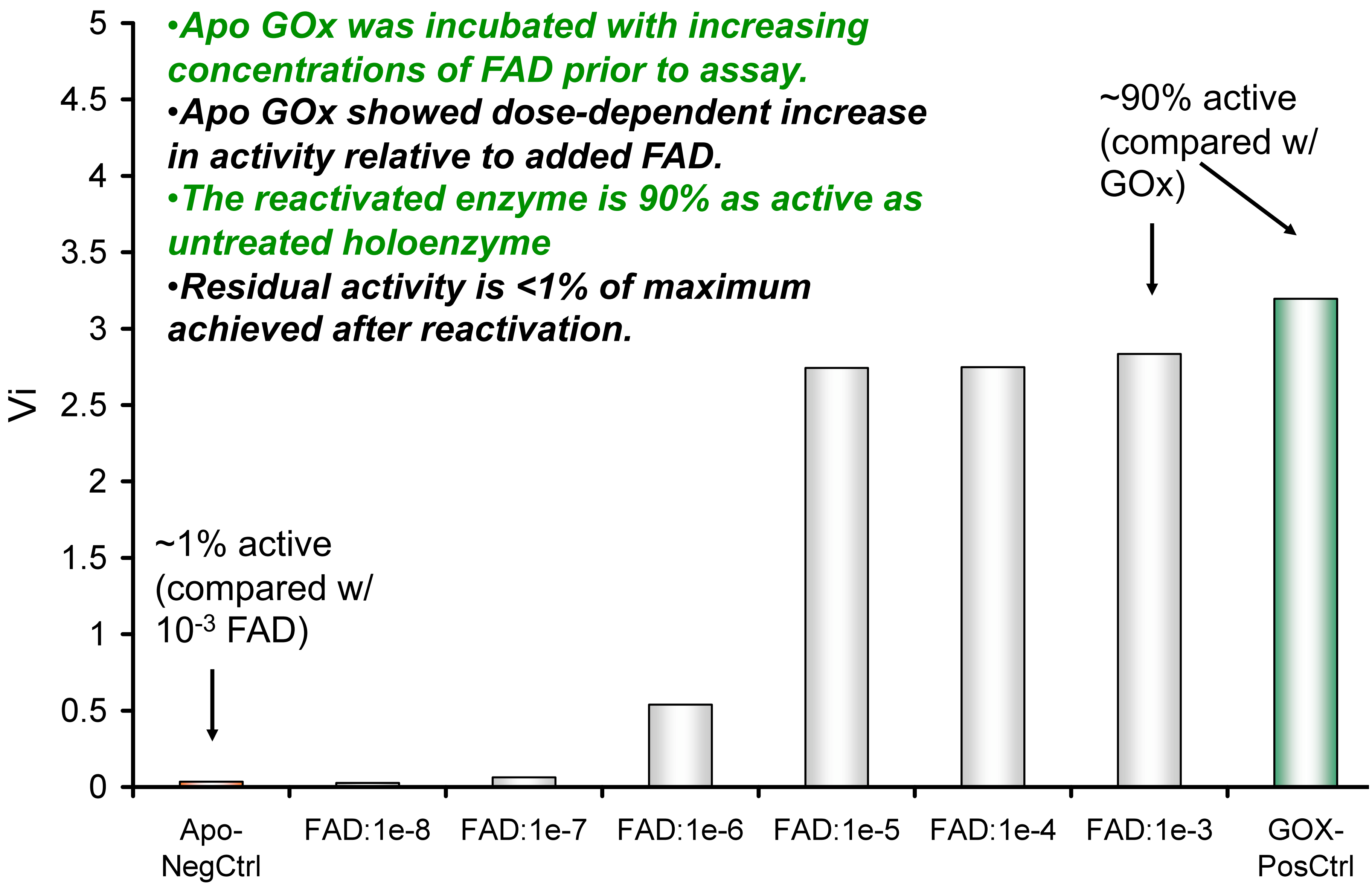




…and thus releases the conjugate. This FAD conjugate is small enough to enter pore and activate the enzyme

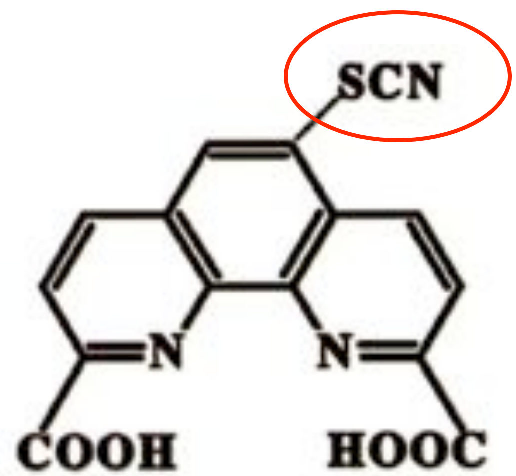


Reactivation of Apo-GOx

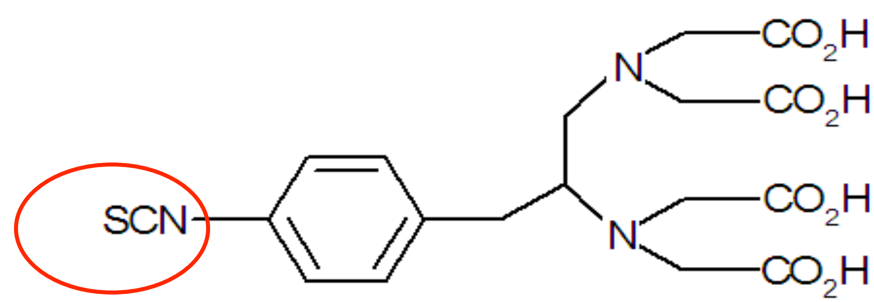


Antibody – Analyte Selection

Clone Number	Ligand	K_d (M)	Availability
4-4-20	Fluorescein	1.5×10^{-9}	Invitrogen
M49209	Fluorescein	3.6×10^{-9}	Fitzgerald International
12F6	2,9-dicarboxyl-1,10 phenanthroline (DCP)	7.5×10^{-7}	Blake et al., (2004) *Bioconj. Chem.* **15**:1125.
12F6	UO_2^{2+}-DCP	9.1×10^{-10}	Ibid
4B33	EDTA	1.3×10^{-8}	Blake lab
4B33	Cu^{2+}-EDTA	2.2×10^{-9}	Blake lab

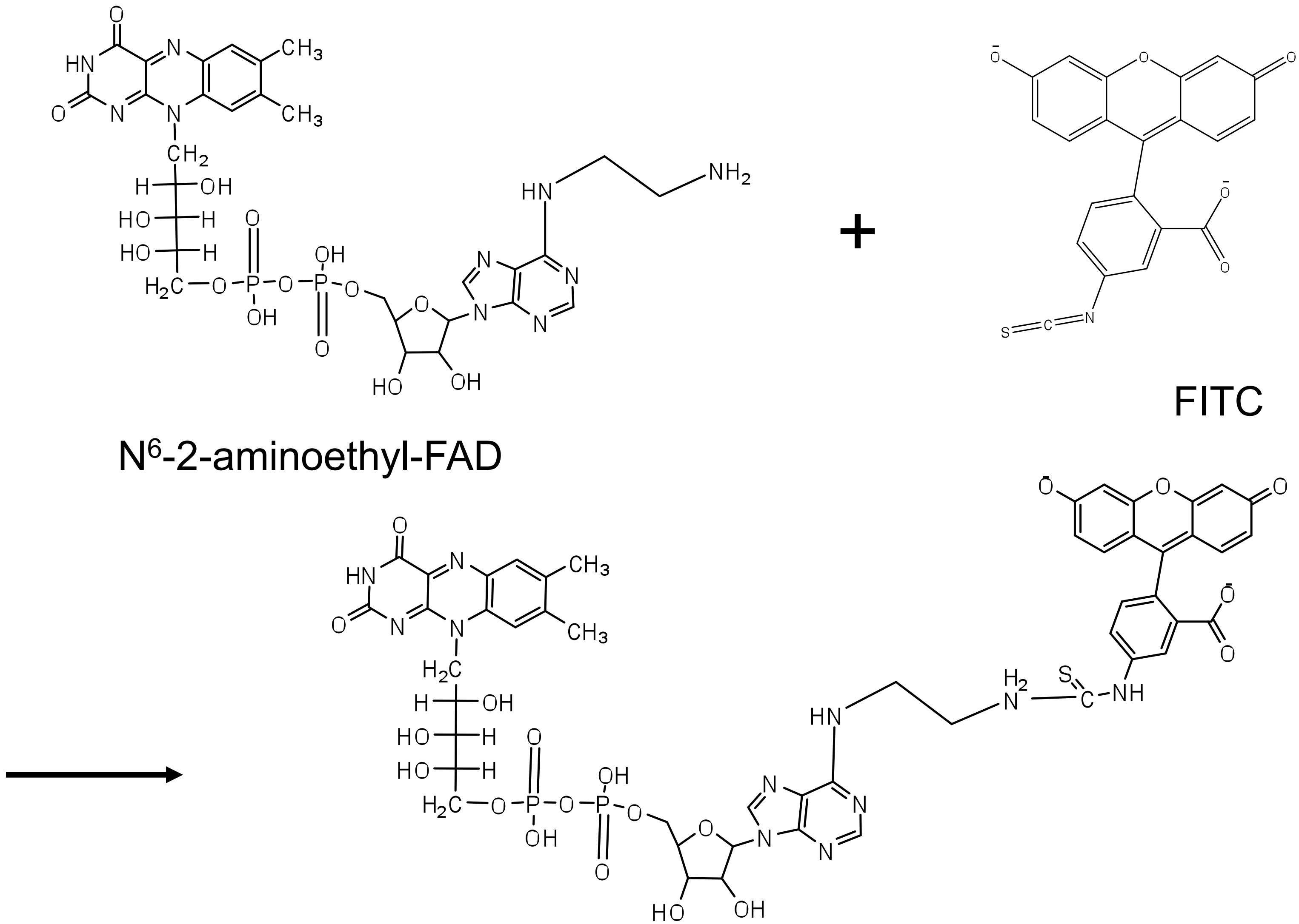


DCP



EDTA

Synthesis of FAD Conjugate



N^6-2-aminoethyl-FAD

FITC

FAD-FITC conjugate

Summary

Selection and Characterization of Antibodies

- *Commercial and in-house antibodies have been characterized*

Assays for Glucose Oxidase have been validated

- *Established linearity of initial rate versus enzyme concentration*
- *Determined inhibition of metal chelators on substrate concentration*

Apo-Glucose Oxidase has been prepared

- *Change in UV-VIS Spectra >300nm confirmed removal of FAD*
- *Purification have been optimized to yield high quantity with low residual signal; storage conditions have been developed*
- *Apo GOx has been transferred to LATech for sensor fabrication*

FAD mediated Reactivation of Apo-Glucose Oxidase

- *Reactivation of Apo GOx is dependent on FAD concentration*
- *Re-validating initial rates with the reactivated enzyme*
- *Confirming enzyme activity in the presence of selected metal chelators*

Synthesis of primary amine terminated FAD

- *Efficient synthesis of N^6-2-aminoethyl FAD*
- *Analysis and purification of the resulting FAD-FITC conjugate*
- *Reactivation of the apo enzyme with the FAD-FITC conjugate*

Immunosensors: Interdisciplinary Training

PI's: Ashbaugh, Bishop, Rick

Experimental Rotation in Blake Lab

- Ashbaugh graduate student (Jain) spent one and half weeks in Blake lab learning experimental protocols for antibody sensing.

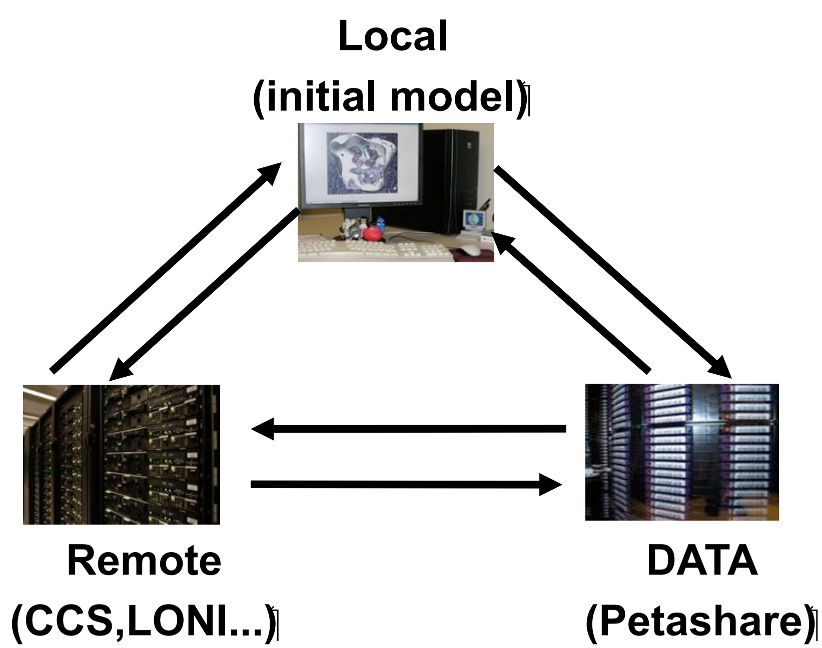
- Titer experiments performed to measure concentrations of antibody 5B2, Pb^{2+}-DTPA-benzyl-BSA conjugate, metal chelator (DTPA), and Pb^{2+}-DTPA.

- Enzyme-Linked ImmunoSorbant Assay (ELISA) used for titer of monoclonal antibody 5B2 and Pb^{2+} conjugate. Competitive inhibition ELISA used to infer the ability of DTPA and Pb^{2+} to bind to 5B2.

Simulation Protocol

1) Sequence alignment: BLAST
2) Atomic Model: MODELLER
3) REMD: AMBER, NAMD ,REDS
4) Analysis: mmtsb, ptraj,VMD, ...

Hardware Issues/Decisions:



Biosensors: Computational Aspects MD

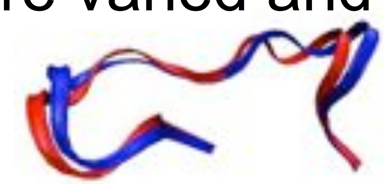
Simulations of 5B2 loop region (Test Cases)

- Binding of antigens to antibody occurs in loop domain. Aim to identify using simulations side chains in loop region that contribute to binding specificity to guide antibody engineering.

- In vacuo energy minimizations of 5B2 LC and HC loops confirm previous identification of metal binding residue Lys^{58}.

- Replica Exchange Molecular Dynamic performed of 5B2 in vacuo and implicit solvent to generate families of loop structures for minimization to determine robustness of predictions and identify spatial and dynamic correlations between key binding residues

- Initial findings: HC3 loop has more varied and flexible structure than the other five antibody loops



LC1

HC3

Biosensors: Computational Aspects MD

Simulations of 5B2 loop region (continued II)

- Replica Exchange (REMD):
  replica: several simultaneous simulations
  2 levels of parallelization
  exchange: simulations swap information

Simulation Characteristics

Loops

~1000 atoms => 2CPUS/sim
10ns run time => Gb's data;
Full REMD in 24hrs 64CPUS

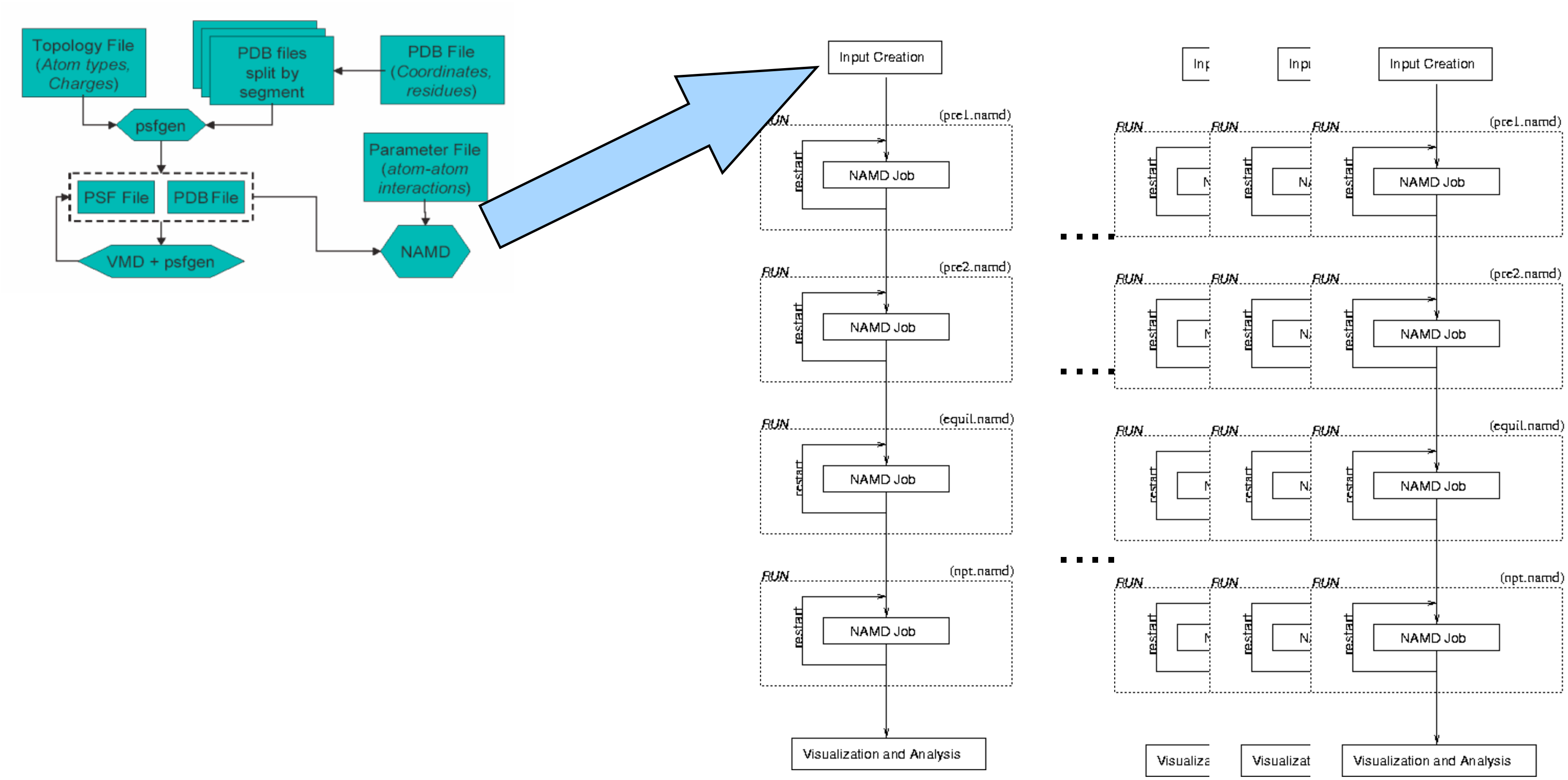
Full System

~10,000atoms => 4CPUS/sim
10ns run time => 10-100Gb data;
Full REMD in 2wks 64CPUS

Biosensors: MD Fast Track Study

A high throughput simulation workflow

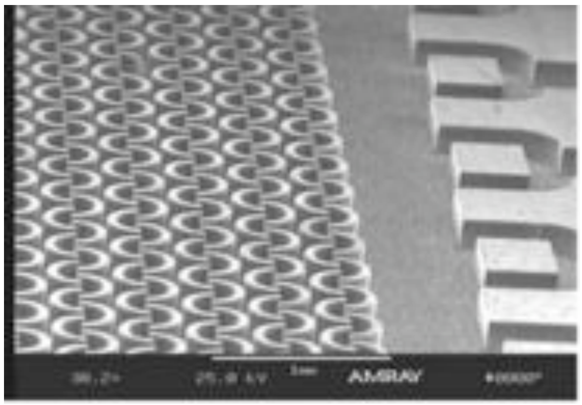
- Bishop (CCS @ TU)
- Emir Embahsi & Tevik Kosar (CCT @ LSU)



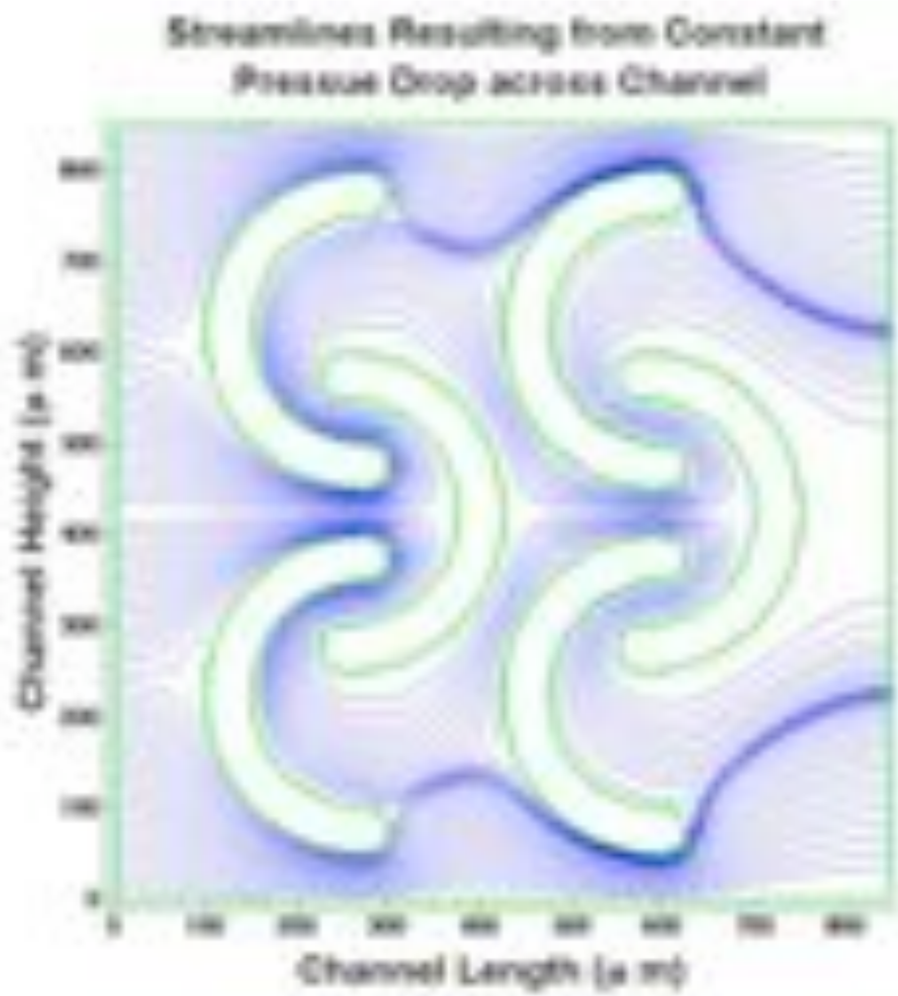
Theoretical and Computational Biophysics Group at UIUC

Flow around Ω-obstructions

Omega channels developed by IfM



- Quantify mixing characteristics in omega channels
- Optimize mixing through geometrical modifications
- Flow field modeled by Stokes & continuity equations
- Boundary Element Method used to determine velocities and surface stresses



Boundary Integral Equations

- Fluid flow is governed by Stokes & continuity equations:

$$\nabla \cdot \mathbf{u} = 0$$

$$\nabla P = \mu \nabla^2 \mathbf{u}$$

where P, μ, & **u** are pressure, viscosity, & velocity.

- The velocity, **u**, and stress, $\boldsymbol{\tau}$, on the boundaries of the domain satisfy

$$C_{ki} u_i(\mathbf{x}) + \int_S T_{ik}(\mathbf{x},\mathbf{y}) u_i(\mathbf{y}) dS(\mathbf{y}) = \int_S U_{ik}(\mathbf{x},\mathbf{y}) \boldsymbol{\tau}_i(\mathbf{y}) dS(\mathbf{y})$$

where U_{ik} and T_{ik} are the Green's functions:

$$U_{ik} = -\frac{1}{4\pi}\left(\delta_{ik} \log|\mathbf{x}-\mathbf{y}| - \frac{(x_i - y_i)(x_k - y_k)}{|\mathbf{x}-\mathbf{y}|^2}\right)$$

$$T_{ik} = -\frac{1}{\pi}\frac{(x_i - y_i)(x_j - y_j)(x_k - y_k) n_j(\mathbf{y})}{|\mathbf{x}-\mathbf{y}|^4}$$

Boundary Element Method

- Along each element **u** and **τ** are approximated as quadratic polynomials. At each node point, **u** and **τ** satisfy

$$C_{ki}u_i(\mathbf{x}) + \sum_{m=1}^{N}\int_{S_m} T_{ik}(\mathbf{x},\mathbf{y})u_i(\mathbf{y})dS_m = \sum_{m=1}^{N}\int_{S_m} U_{ik}(\mathbf{x},\mathbf{y})\boldsymbol{\tau}_i(\mathbf{y})dS_m$$

- The integrals are evaluated using Gaussian quadrature rules. The integral equation can be written as a linear system:

$$\boxed{H\mathbf{u} = G\tau}$$

- Optimization of simulation is being developed in conjunction with WP4 and will create a general purpose *CyberTool*.

Microsensor Mixing

- Analyte-FAD conjugate and analyte from serum compete to bind with antibody
- Binding and release occur spontaneously as analytes and antibody are transported by fluid motion
- A variety of flow fields will be simulated to identify flow chamber geometries and flow rates that optimize the binding and release of antibody/conjugate

Transport Equations

Each analyte/antibody satisfy a reaction-diffusion equation:

$$\frac{\partial C_i}{\partial t} + \nabla \cdot (\mathbf{u} C_i) = D_i \nabla^2 C_i + R_i$$

$\mathbf{u}$ – fluid velocity

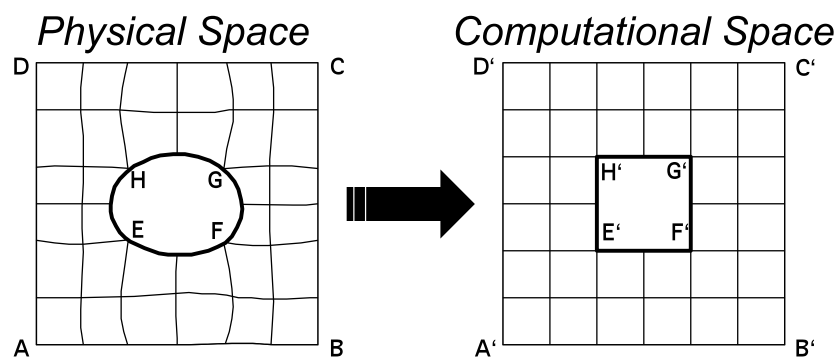
C_i – concentration of each species

D_i – diffusion coefficient

$R_i(C)$ – reaction term

Methodology:

•Transform equations into a boundary-fitted coordinate system



•Use the Finite Volume Method to solve for *concentration*

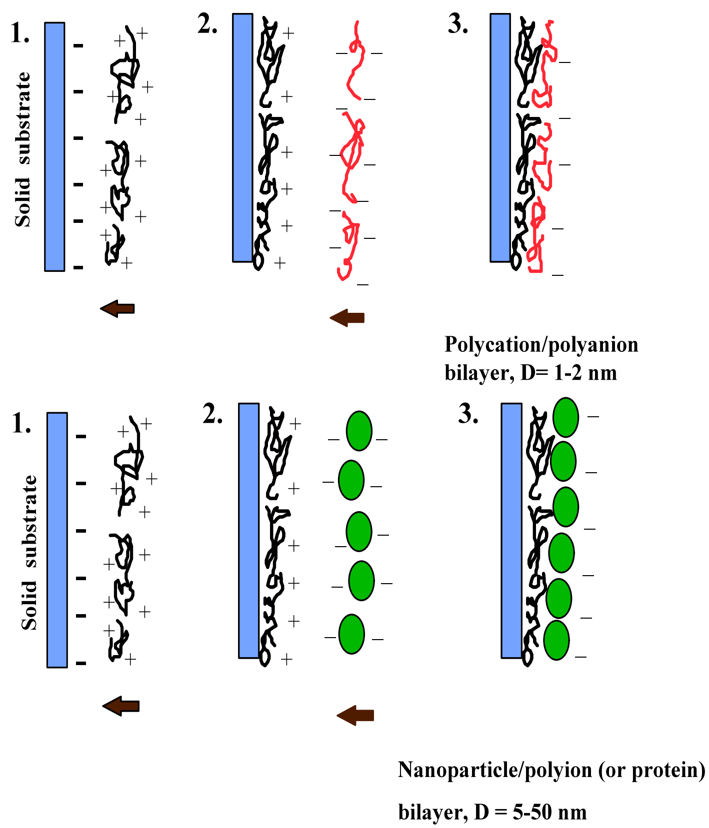
•Note: velocity field obtained from BEM code

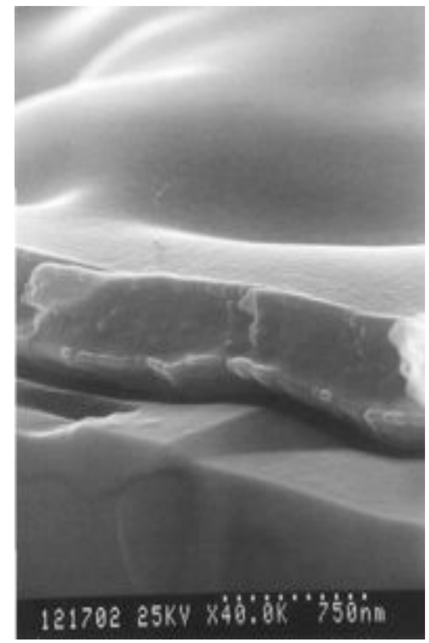
Links to Cybertools: WP4

- Current Work: parallelization of Stokes flow problem (Mayank Tyagi, Shantenu Jha, Sanjay Kodiyalam)
  - *OpenMP*

- Future Work: parallelization of source code including transport

Layer-by-Layer Nanoporous Membrane





Scheme of the layer-by-layer nanoassembly by alternate adsorption of polycations and polyanions or nanoparticles

SEM cross-section images of (glucose oxidase/PAH)$_{22}$ multilayer on quartz (left), and (40 nm silica/PAH)$_6$ film on silver electrode (right).

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Silicon wafer with oxide layer

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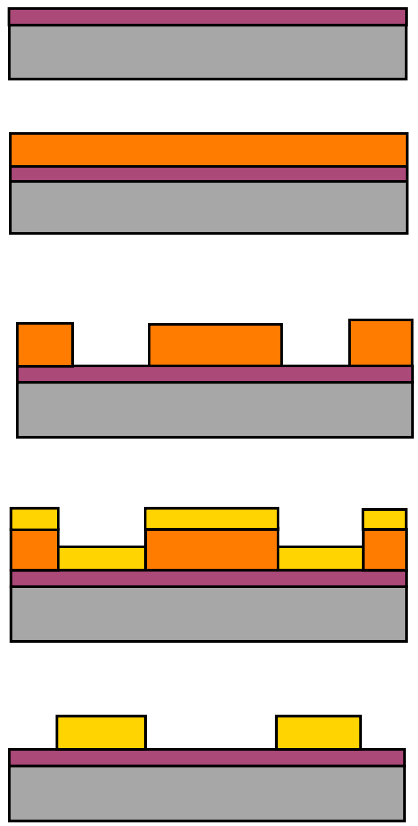
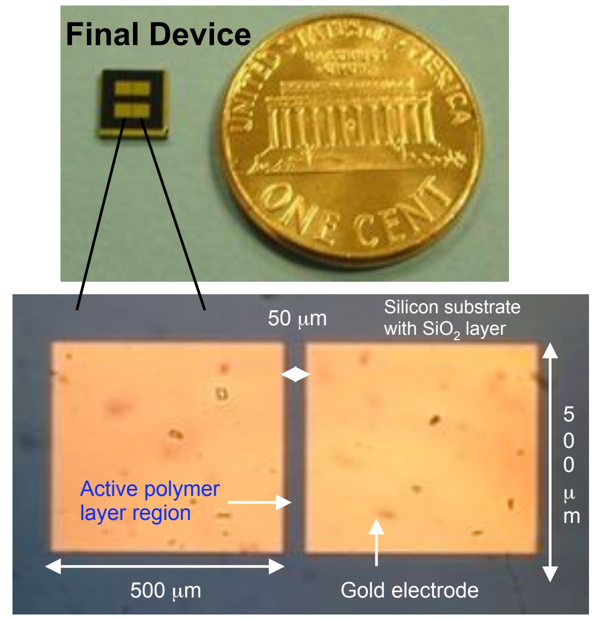
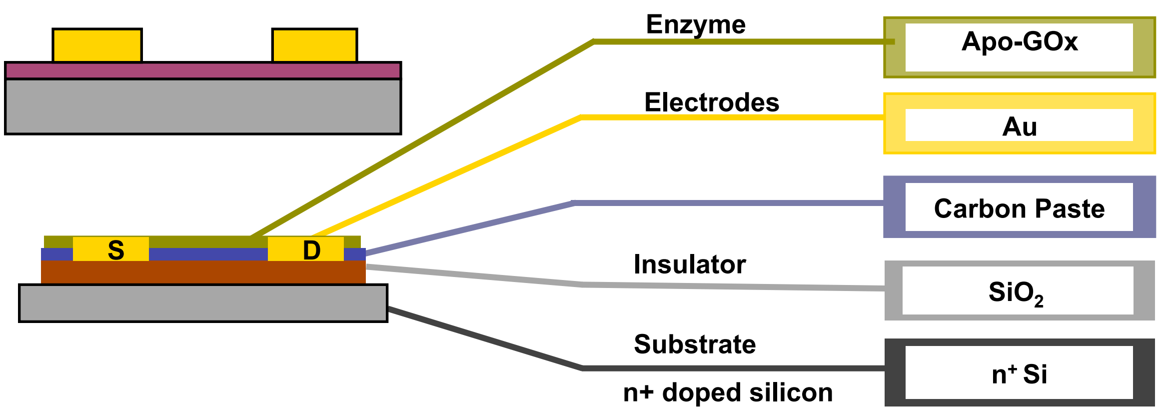
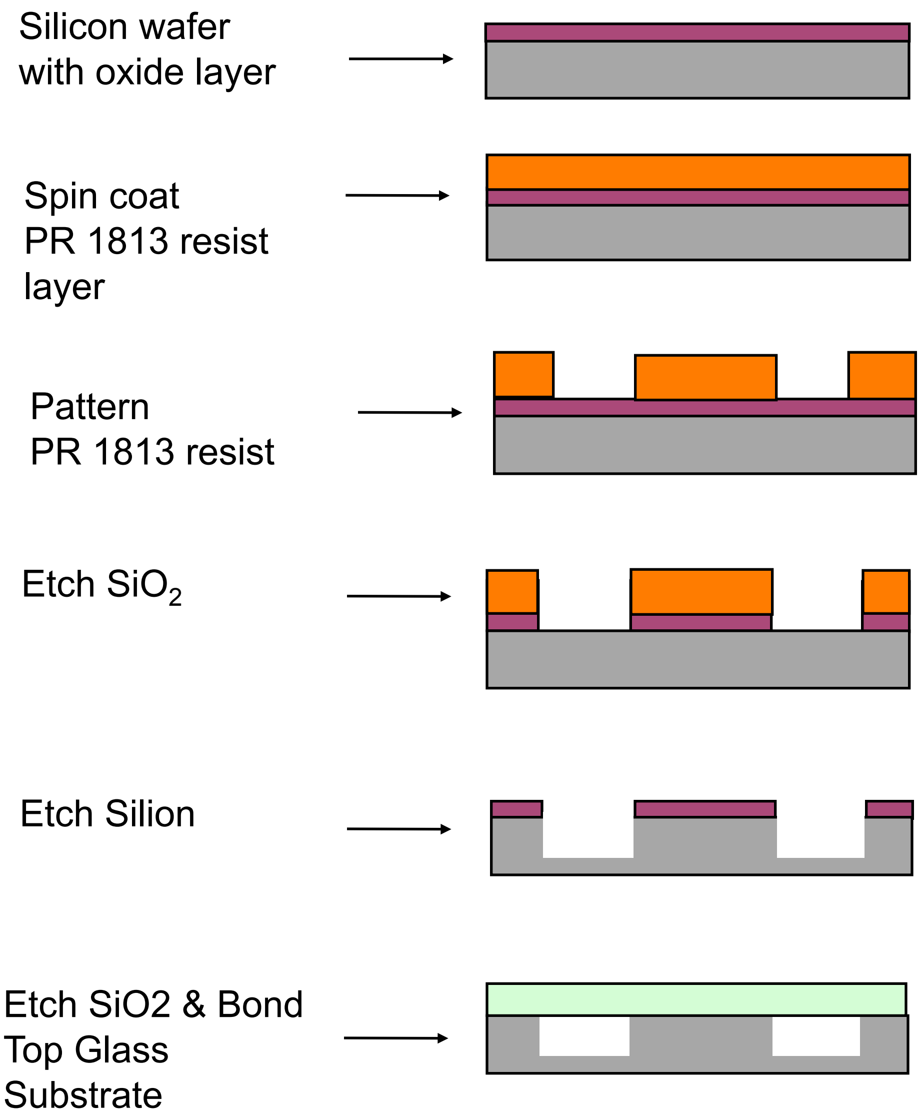


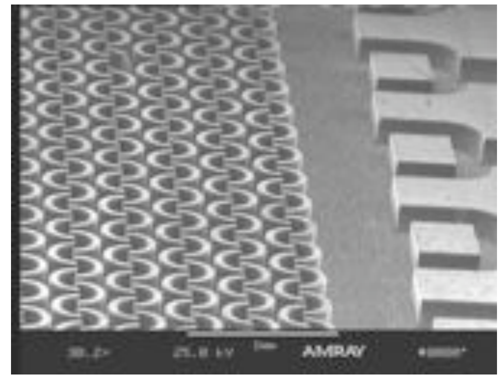


Final Device



Micromixer Fabrication





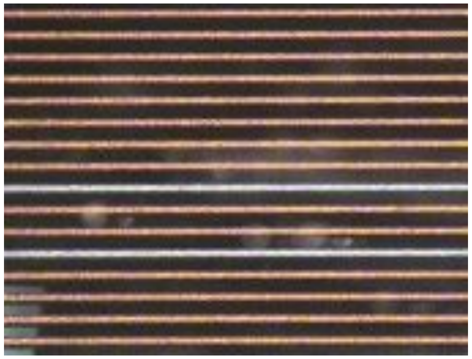
SEM → Omega Channel Micromixer

Fabrication
- Lithography
- ICP
- Bonding

Challenges
- Connectors

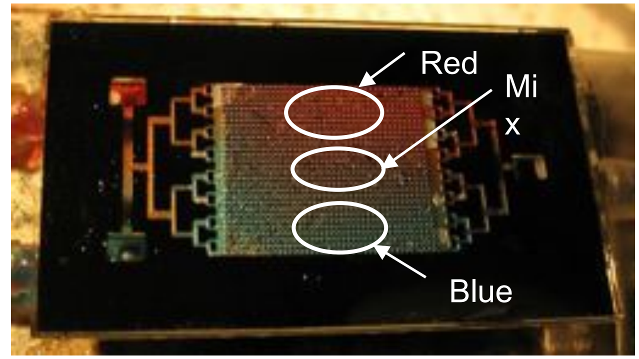
Modifications
- New set of connectors from Upchurch Scientific are being tested and evaluated

Micromixer Evaluation



Straight Channel

Omega Channel



Micromixer

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Modifications
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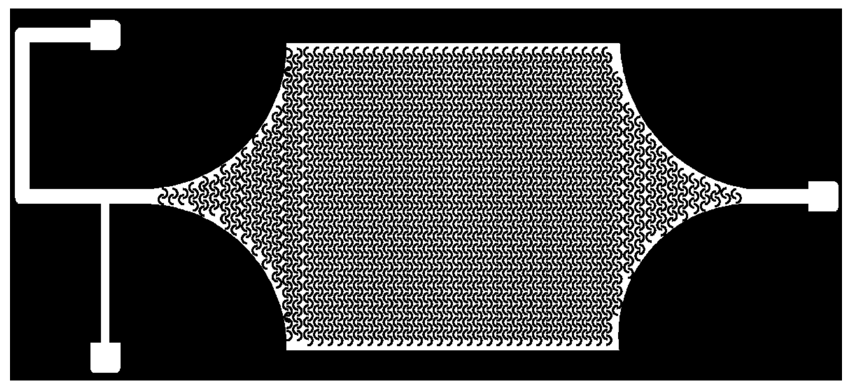
Quantification
- Image sensing software



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  - Evaluating PEDOT and carbon nanotube based microsensor for reproducibility
  - Selectivity
  - Life Time
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  - Currently testing florescence dots and dyes for evaluating micromixers.
  - Currently evaluating microscale sensor system based on carbon nanotubes
- Carbon-based Electrodes
  - Under testing and fabrication
- Microscale sensor
  - Under testing and fabrication

Education: Year 1

Deverables in K-12 & Undergraduate training:

- **High School Apprenticeships:**
  LaTech → Science project on glucose sensor
  Tulane HSC → Preparation of apo glucose oxidase

- **Design academic year projects on topics of the grant:**
  We are in the initiation phase and will begin implementing it in 2008-09. There will be a meeting before the fall semester to discuss possible projects, venues for students to carry them out, supervisors, etc.

- **Create summer research opportunities targeting primarily minorities:**
  A 5-week program at Tulane in summer 2008 has been planned for 6-8 students. Dates: June 16 – July 18. Applicants include Tulane, Dillard, Xavier, and Grambling students.

Education: Year 1

Deliverables in Graduate training:

- **Summer Internships or extended visits to other institutions:**

This includes sending Tulane students to IfM or CCT for extended visits. It also includes sending students to other institutions for the summer.

Emir Bahsi → LSU Graduate Student to Tulane University (May 2008)
Jerina Pillert & Kate Hamlington → Visit LSU CCT & IfM (July 2008)
Senaka Kanakamedala → IfM to Tulane (August 2008)

- **Multi-institutional dissertation committees:**

Cortez is on Hamlington's committee (Gaver, BME, Tulane)
Bishop is on Henry's committee (D. Blake, Biochem, Tulane)
DeCoster is on Kanakamedala's committee (Lvov, Chem, LaTech)

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Education: Year 1

Deliverables in Postdoctoral training:

- **Cross Institutional mentoring and training:**

Mehnaaz Ali (Tulane), Mangilal Agarwal (LaTech IfM), Yuen Yick Kwan from Purdue will join Tulane in August 2008

Mehnaaz Ali: A Biochemistry postdoc visited IfM to learn about the facility and microfabrication techniques.

Mangilal Agarwal: An Electrical Engineering postdoc visited Tulane to learn about biochemistry and molecular biology.

:

Outreach: Year 1

•**Publications:** Including joint authorship across institutions and participants, general audience articles

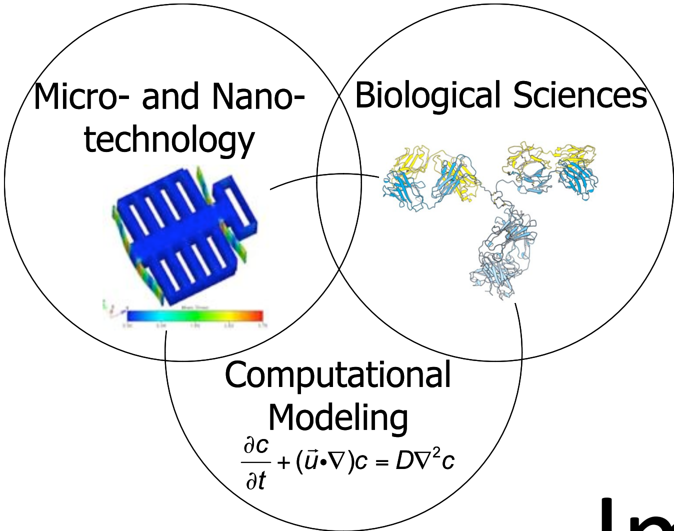
We expect this to begin after year 1.

•**Scientific and nonscientific conference presentations:**

- •BMES Talk (Oct 2008) – Gaver or Hamlington
- •ACS (August 2008) – D. Blake
- •ACS (August 2008) - Agarwal

•**Research modules:**

Not sure how Tulane participates. Perhaps a graduate student working with WP groups can contribute.



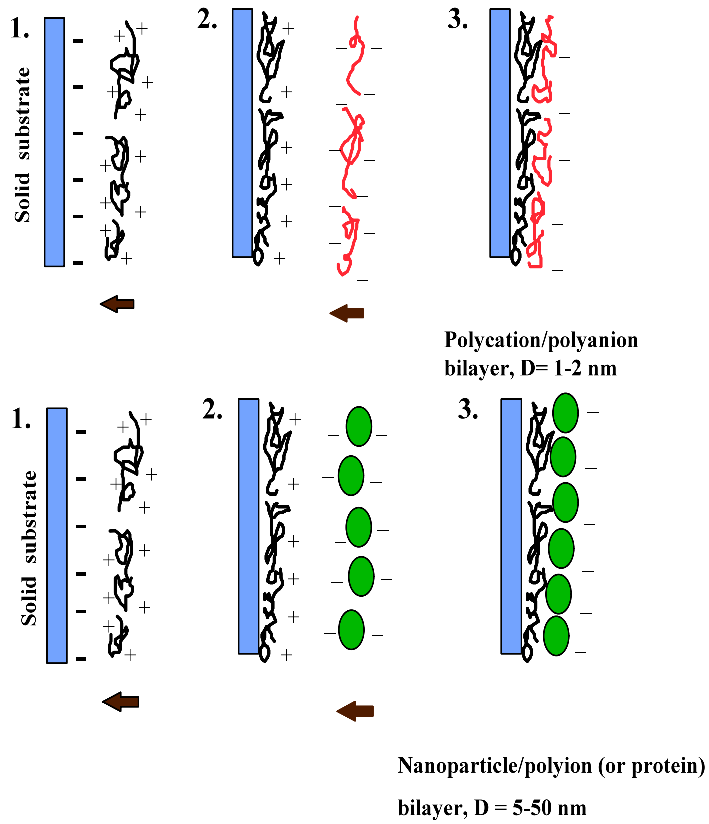
Immunosensors

Ricardo Cortez, Diane Blake, Hank Ashbaugh, Thomas Bishop, Donald Gaver and students, and Mark DeCoster

--Presentation by--
Mark DeCoster
Associate Professor
Biomedical Engineering and Institute for Micromanufacturing
Louisiana Tech University

30 May 2008
Baton Rouge, Louisiana

Layer-by-Layer Nanoporous Membrane



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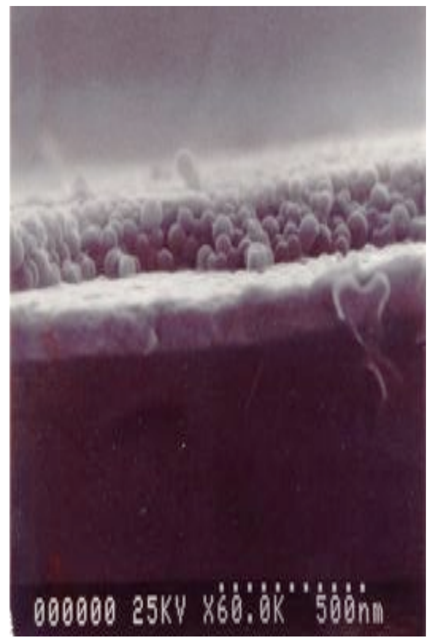

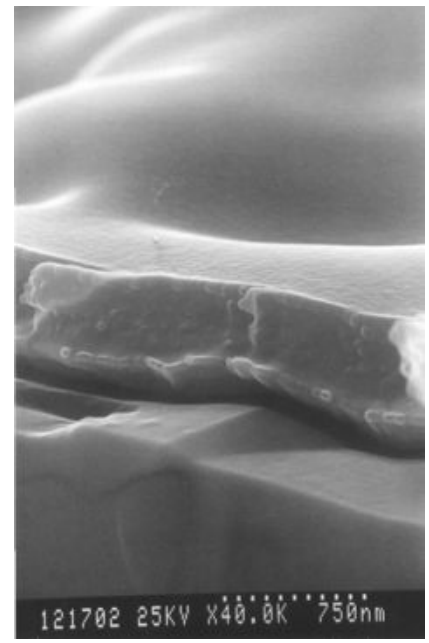

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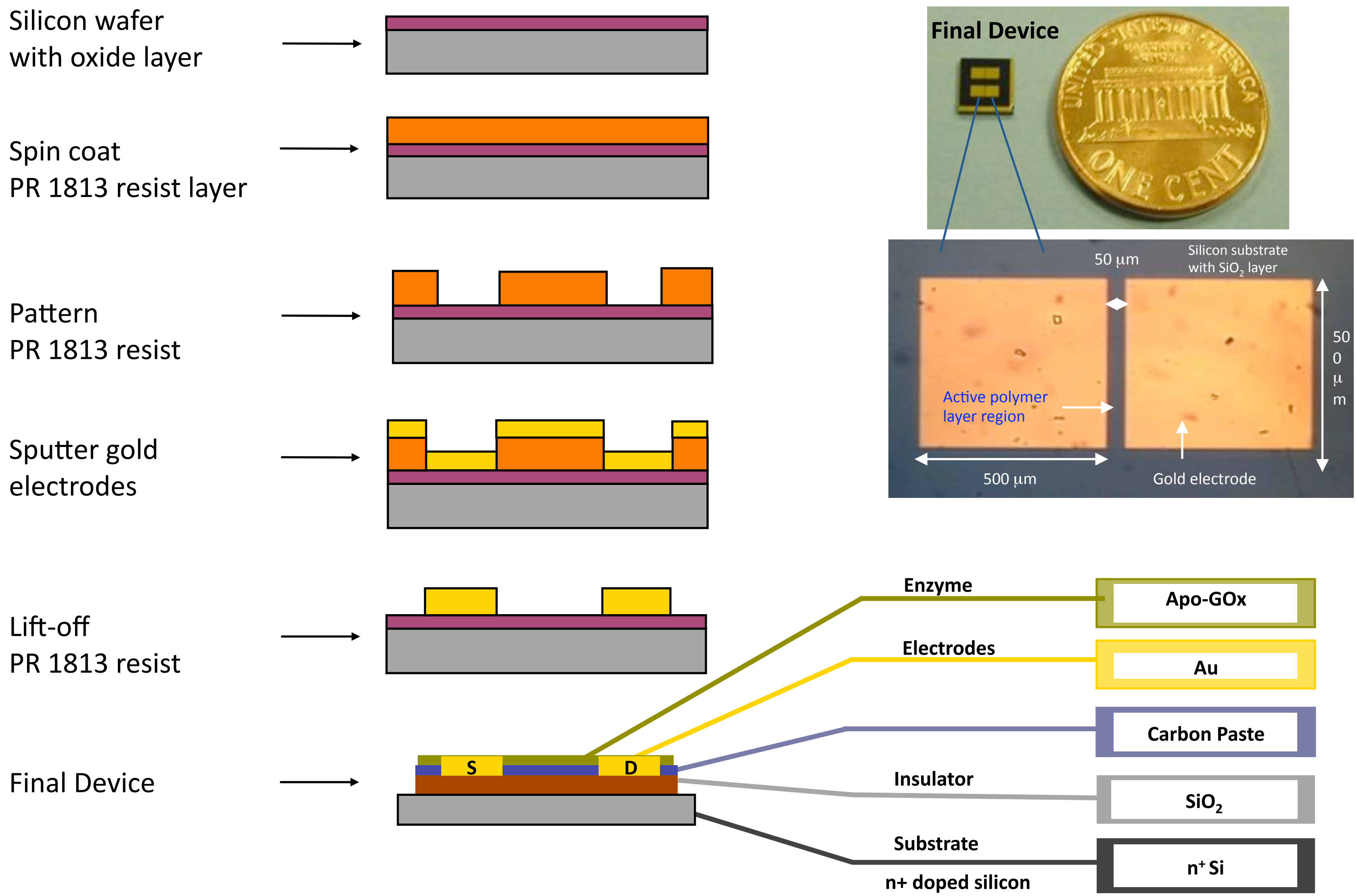


Micromixer Fabrication

Silicon wafer
with oxide layer

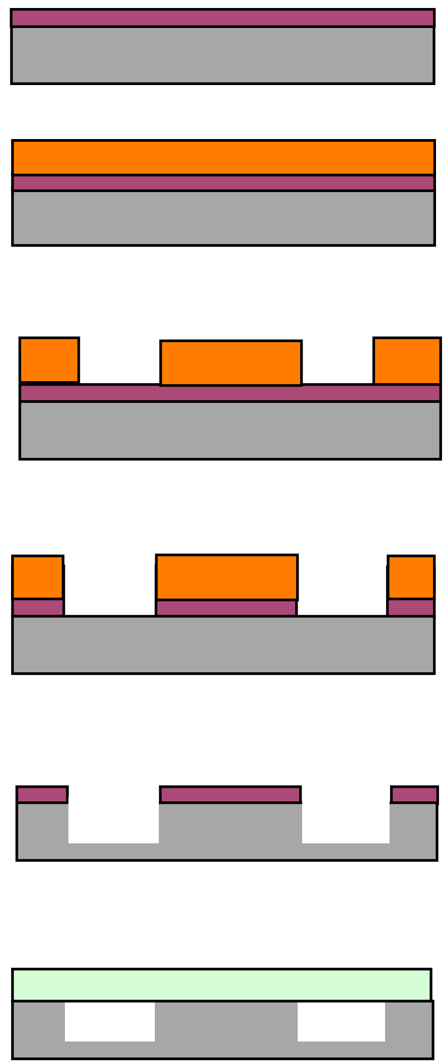
Spin coat
PR 1813 resist layer

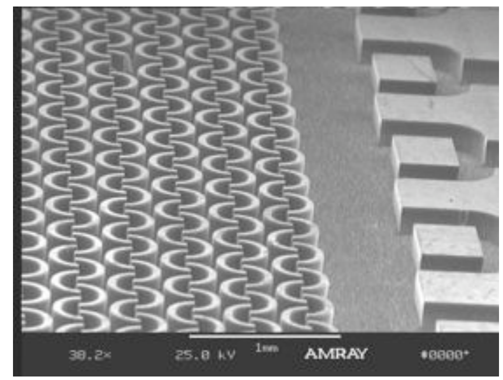
Pattern
PR 1813 resist

Etch SiO_2

Etch Silion

Etch SiO2 & Bond
Top Glass Substrate





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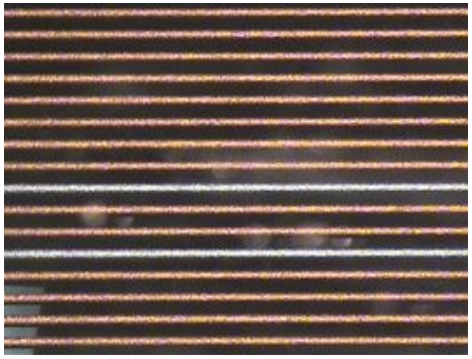

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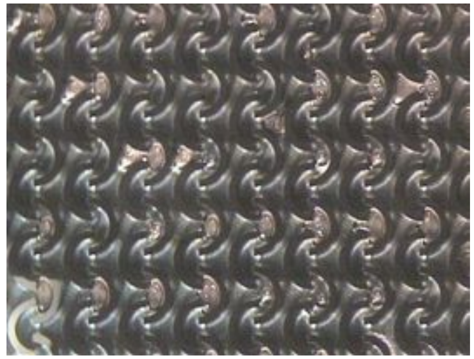

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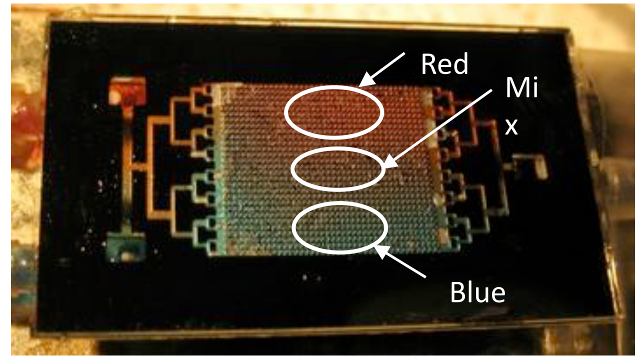

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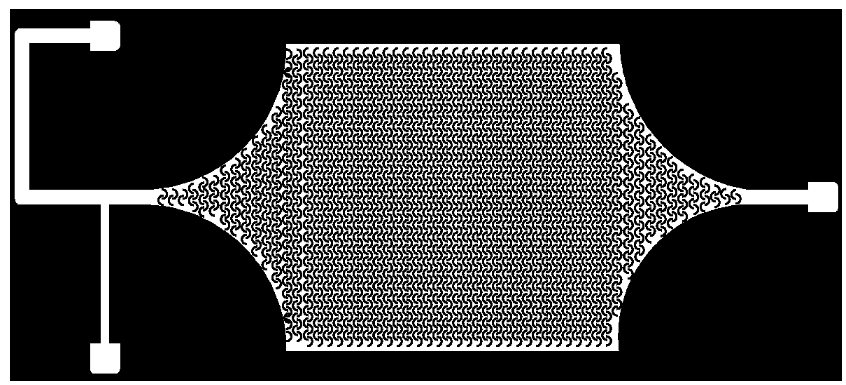

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Science Driver: Bio-Transport Computations

Computing of Transport Processes in Biological Systems

Acharya[1,2] (Lead), Moldovan[1], Devireddy[1], Nikitopoulos[1], Gilmanov[1,2]

Louisiana State University

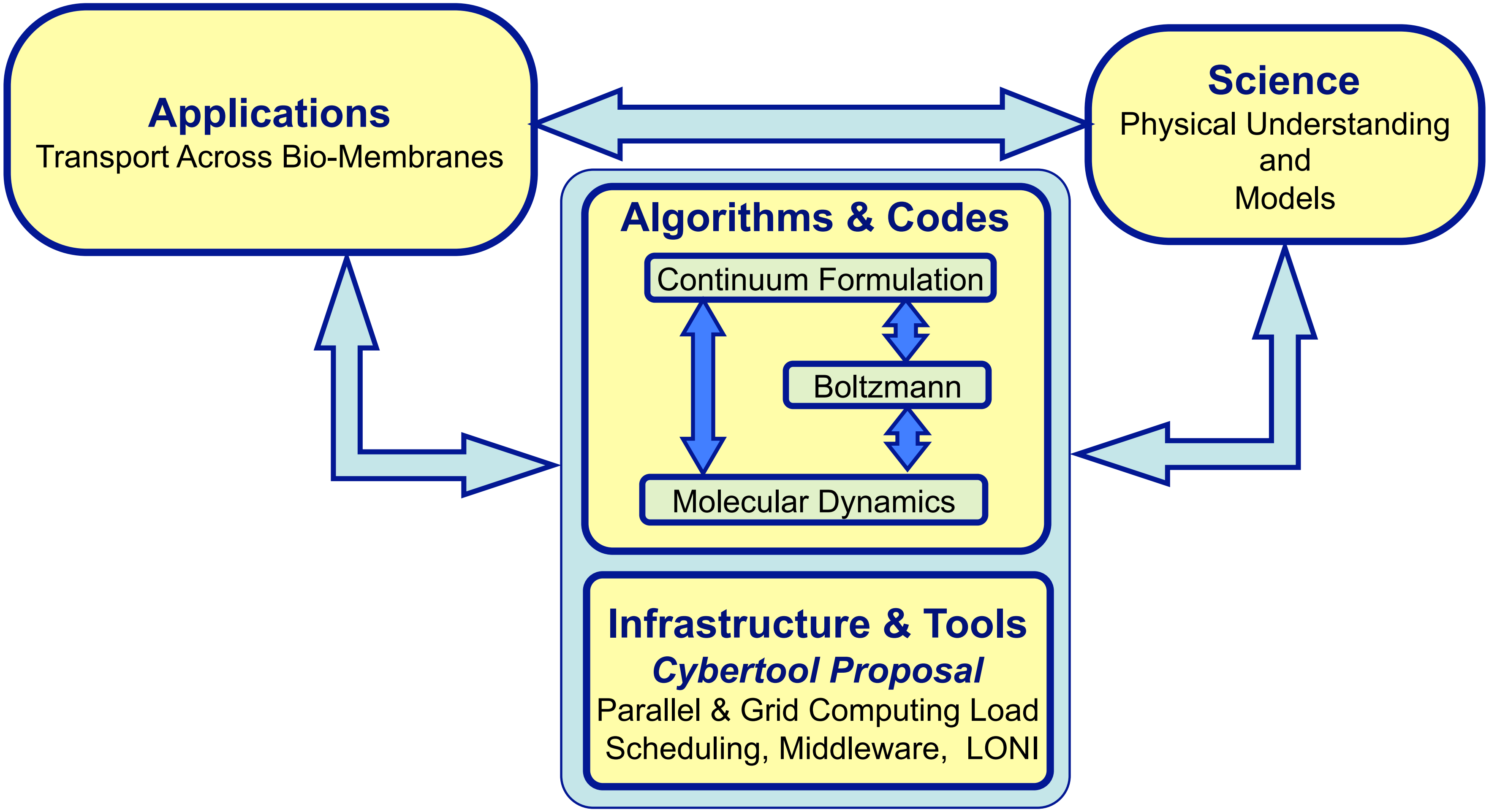
[1]Mechanical Engineering Department

[2]Center for Computation and Technology

Graduate Students: Alapati, Kalghatgi, Gilmanov

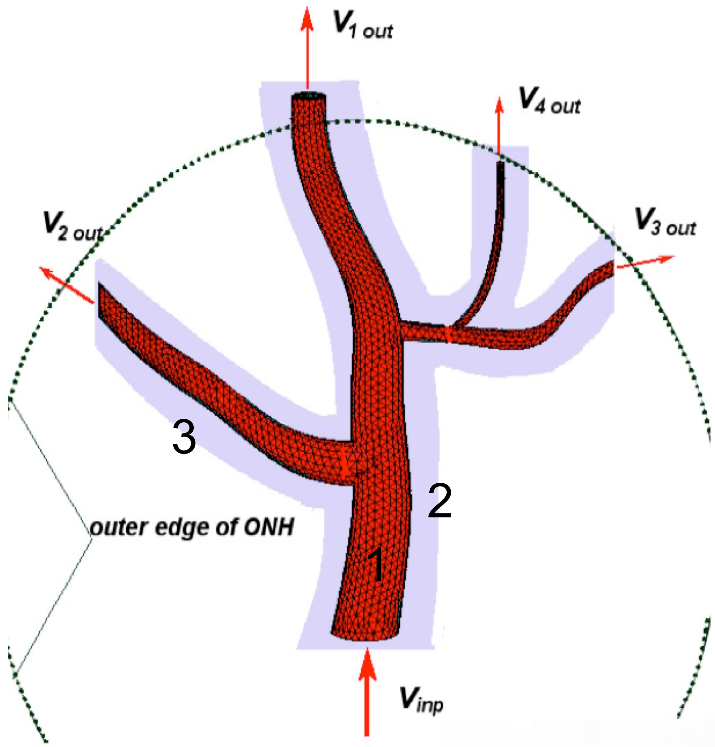
Support from the NSF EPSCoR Program & the LA-BOR Is gratefully acknowledged

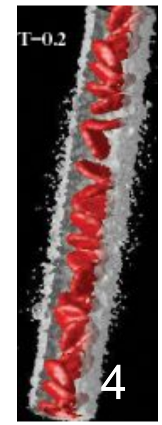
Building Blocks

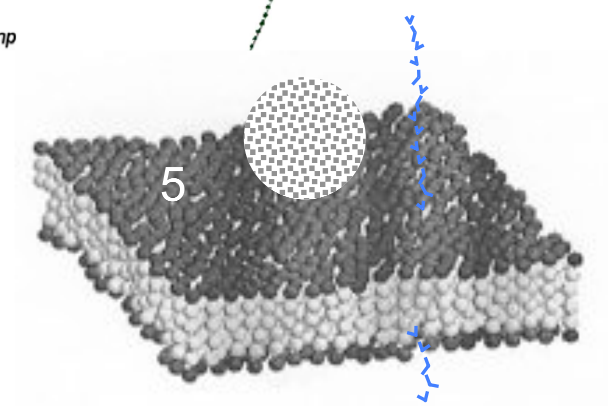


The Science Driver: Oxygen Transport in Biological Systems

- Prediction and understanding of oxygen transport in biological systems
  1. Continuum flow in larger vessels-Navier Stokes
  2. Porous media transport across vessel walls & tissues-Brinkmann
  3. Structural deformation of vessels/tissues-
  4. Particle flow in capillaries-Lattice-Boltzmann
  5. Atomistic transport across cellular interfaces-Molecular Dynamics





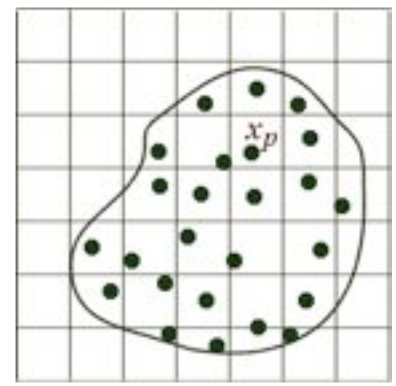


Tasks

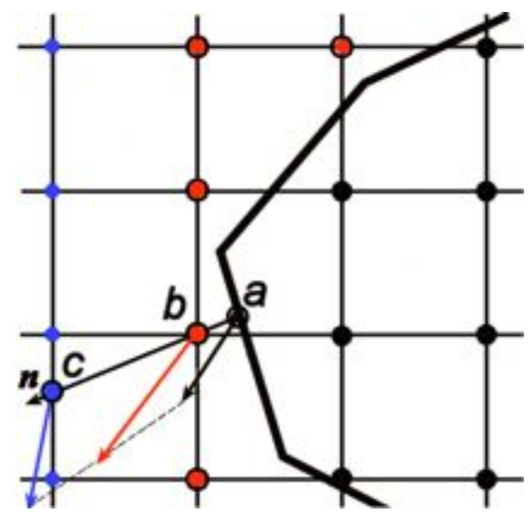
- Development of computationally efficient numerical methods or algorithms needed for biological transport calculations
- Contributing to improved science-understanding of oxygen flow/transport physics under elevated pressures
- Contributing to improved science-understanding of small molecule flow/transport physics under asymmetric concentrations and applied stresses
- Contributing to improved computational infrastructure-collaborating with the cybertools group responsible for developing the CFD toolkit

Computational Method Developments

- Continuum flow and transport calculations
  - Multiblock structured grid with continuous grid lines across block interfaces
  - Fractional step algorithm with staggered grid locations for the velocity (stored at cell faces)
  - Pressure-poisson equation for pressure
  - Consistent second order differencing for diffusion and pressure terms and upwind biased differencing for the convective terms
  - Explicit and implicit second order temporal differencing
  - Flow-structure interaction
    - Particle-based meshless calculations for structural deformations (called material point method-MPM)
  - Immersed Boundary Methodology (IBM) for resolving boundary conditions along moving interfacial surfaces

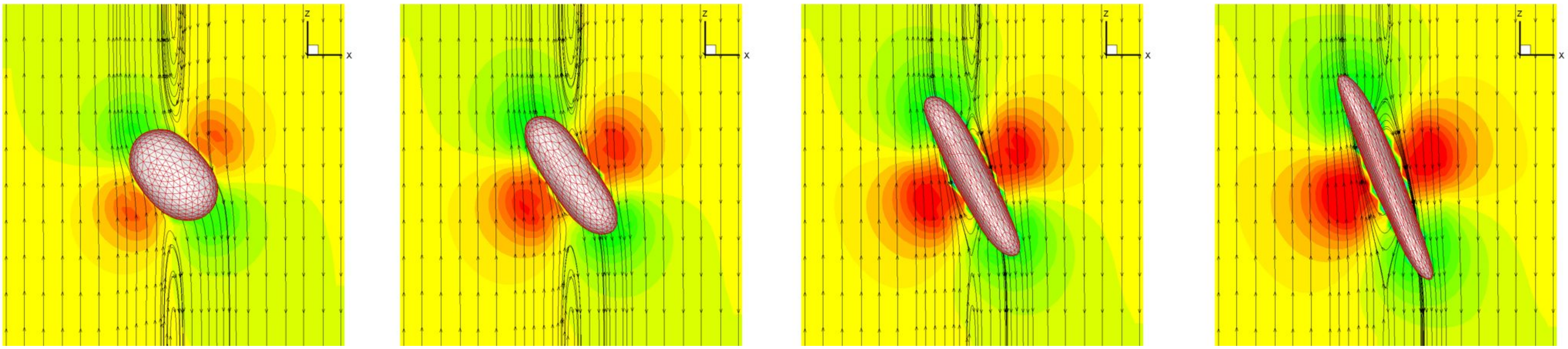


Background grid for solution of momentum equations



Ongoing Continuum Simulations: Flow-Structure Interactions

- Material-Point Method (MPM) for structural deformations
  - Arbitrary distribution of points on the solid body/surface
  - Material points are solved (deformation & stress) on a background grid that is independent from the fluid grid
  - Flow-structure coupling through boundary/interface conditions
  - Flow around deforming surface handled through IBM



Science Driver-WP4 Integration

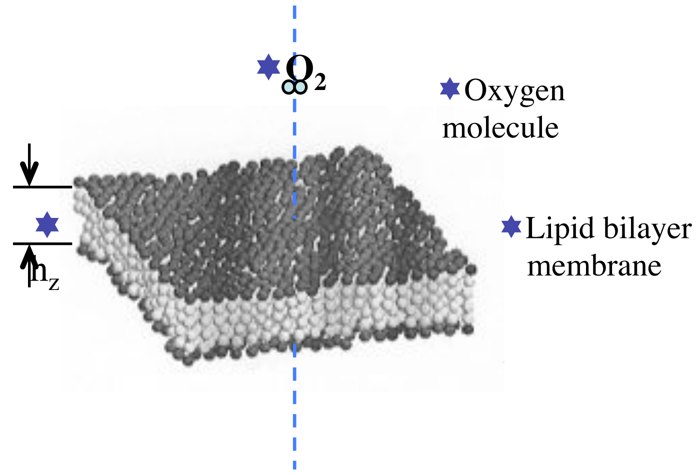
- Collaborating with the WP4 group for the development of a CFD Toolkit;
- Finite volume, multi block;
- Data array structure consistent with current structure in Cactus;
- Multi-block grid from commercial grid generators;
- Baseline code developed for laminar flow; several benchmarks being run to provide WP4 input-output files for Toolkit verification and validation;
- Long term plans are to transition to the Toolkit for the biosystems transport simulation;

- Implemented suggestions for improved performance of parallel code—seen improvements
- Discussions ongoing with Viz groups to get better access to better visualization codes (WP3)
- Discussions ongoing on use of a Lattice Boltzmann code for particle simulations
- Discussions ongoing on most effective ways of doing CFD-MD coupling

Hierarchical Continuum-MD Coupling

- Diffusion rate and permeability coefficients across vessel walls and tissues for different conditions are generally not known reliably (difficulty in in situ measurements)

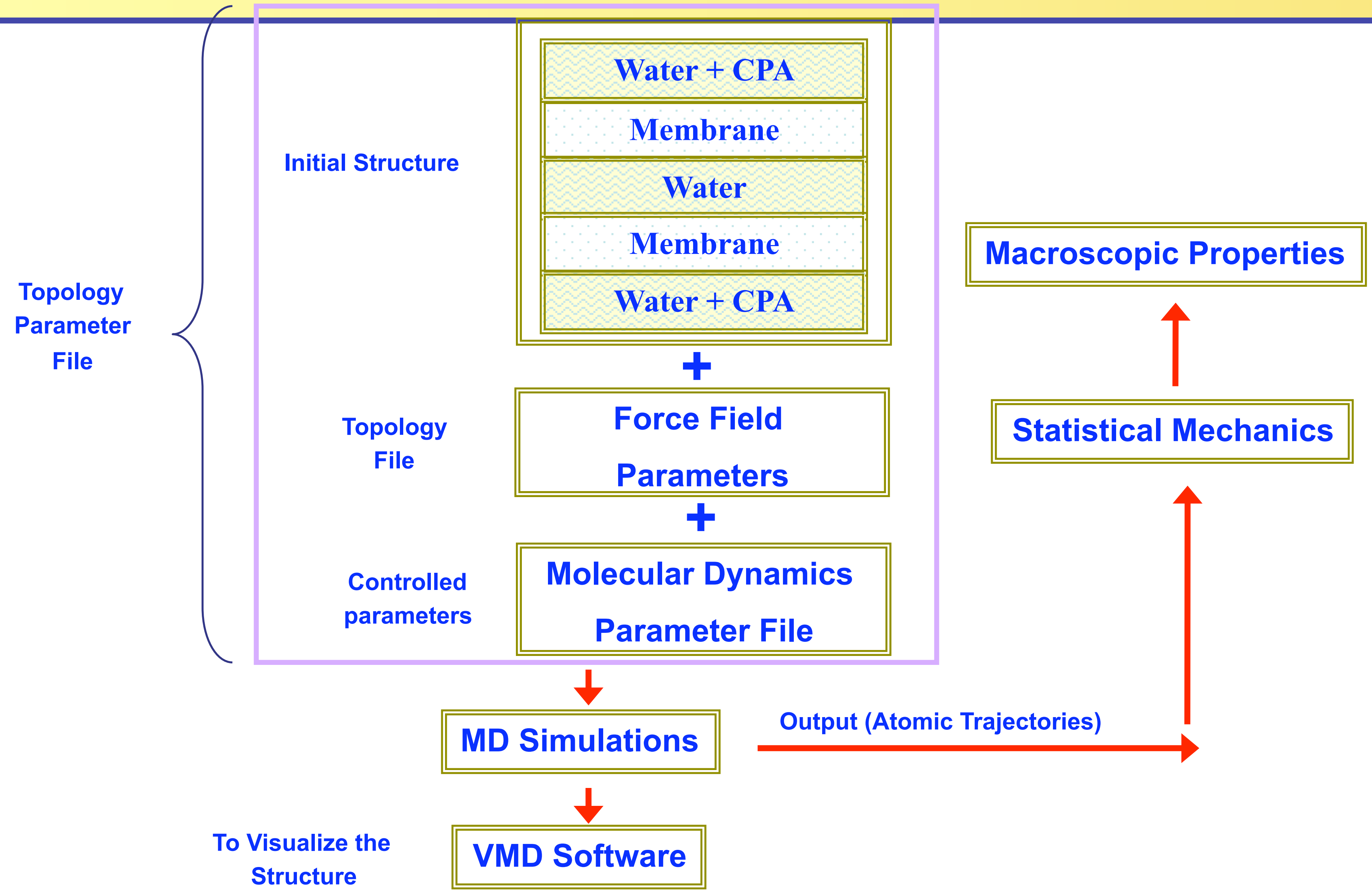
- Specifically designed MD simulations under different conditions can provide:
  - atomistic insight and molecular mechanism underlying the transport of O_2 across a lipid bilayer membrane in order to determine which details are important for the permeation process.
  - Derive the oxygen diffusivities, D_{O2}, inside the inhomogeneous region of a lipid bilayer.
  - Derive permeation rates, P_{O2}, indirectly via computation of the free energy and diffusion rate profiles of a O_2 molecule across the lipid bilayer.



$$P = \frac{1}{\int_{z_1}^{z_2} \frac{\exp(\Delta G(z)/RT)}{D(z)}\,dz}$$

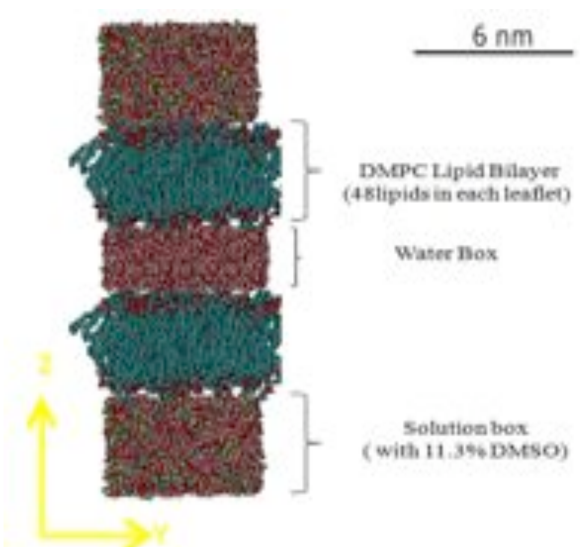
$$D = \frac{1}{3}\int_0^{\infty} \langle v(0)\cdot v(t)\rangle dt$$

MD Simulation Using “GROMACS”

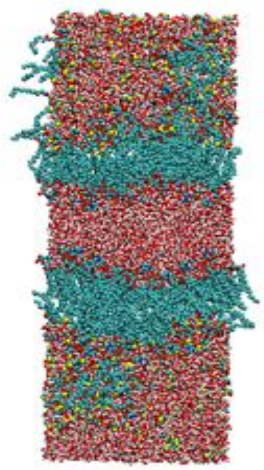


Structural changes in Lipid Bilayers

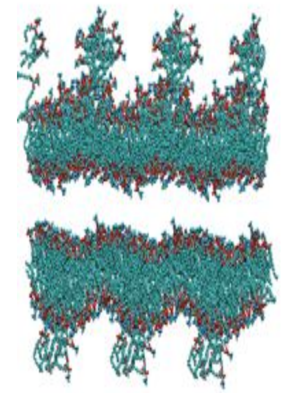
Initial system



✶(a) Whole system

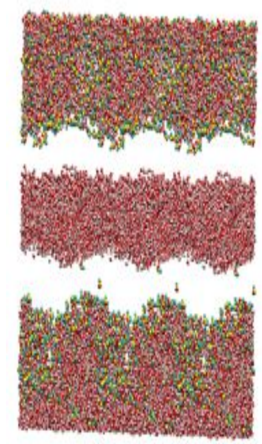


✶(b) Lipids only



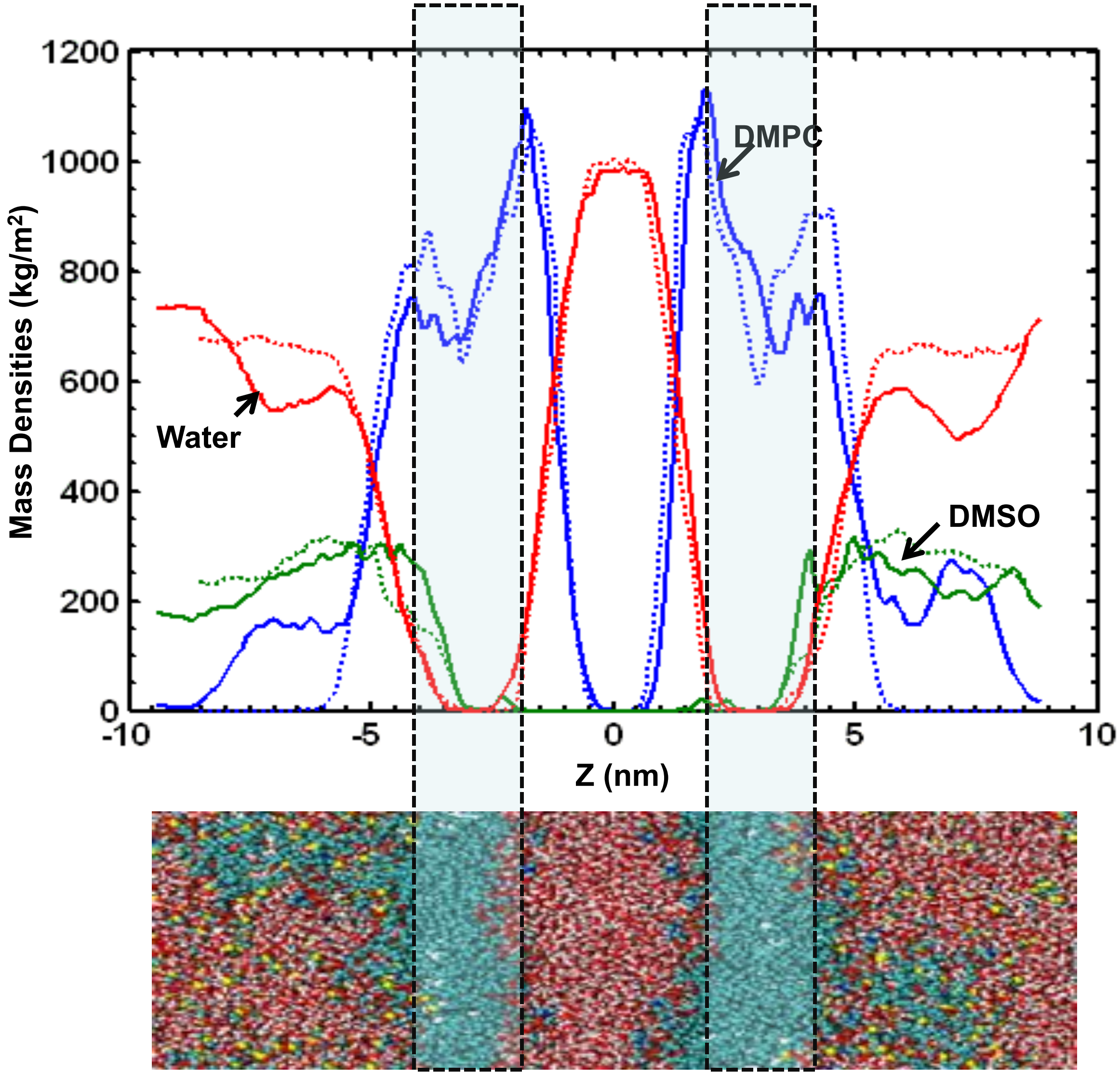
✶t=50ns

✶(c) Solution only



- No penetration of water molecules
- Data analyzed for mass density profiles, radial distribution functions, tail order parameters, and water orientation profile

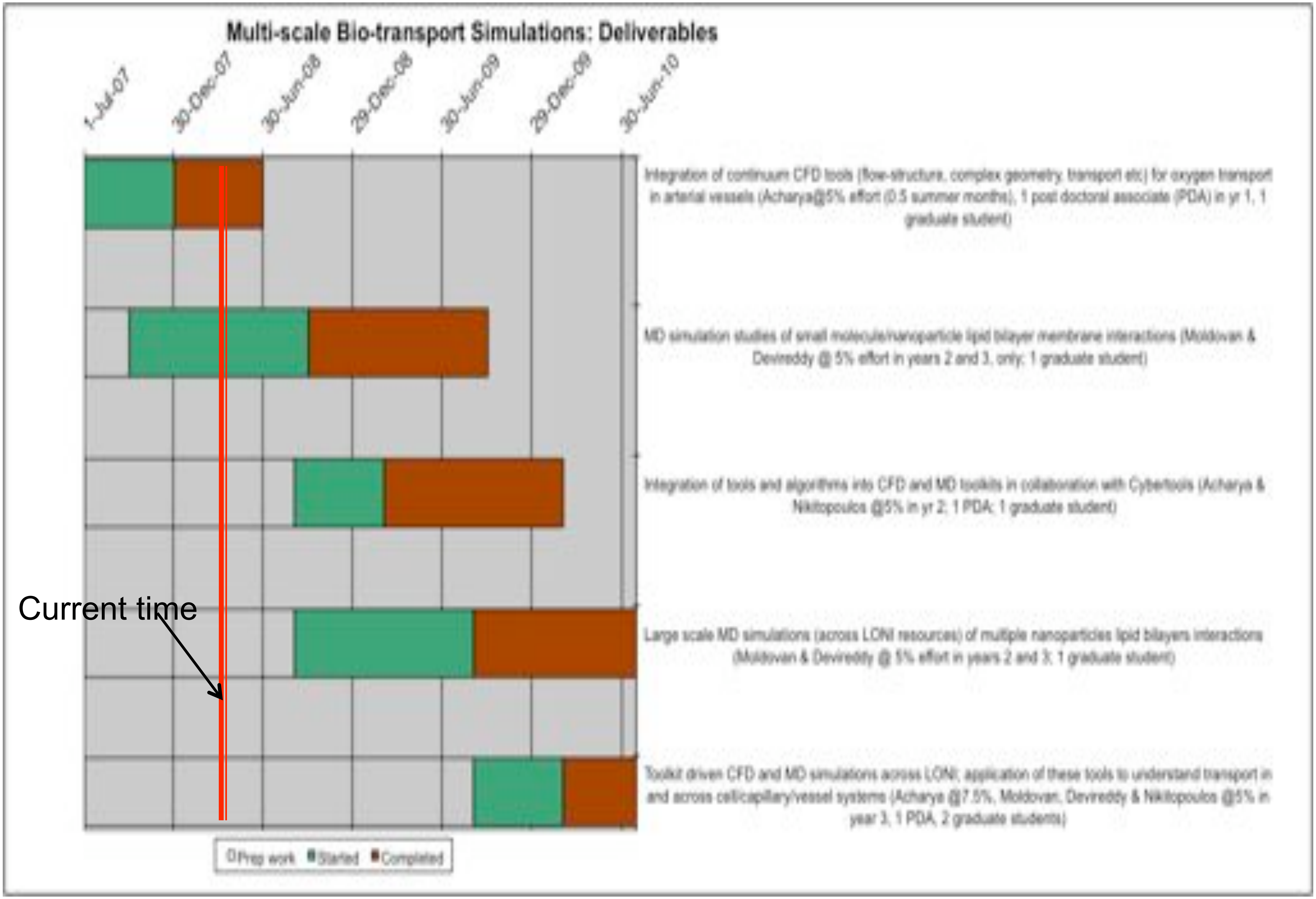
Mass density profiles of : DMPC, DMSO, and water



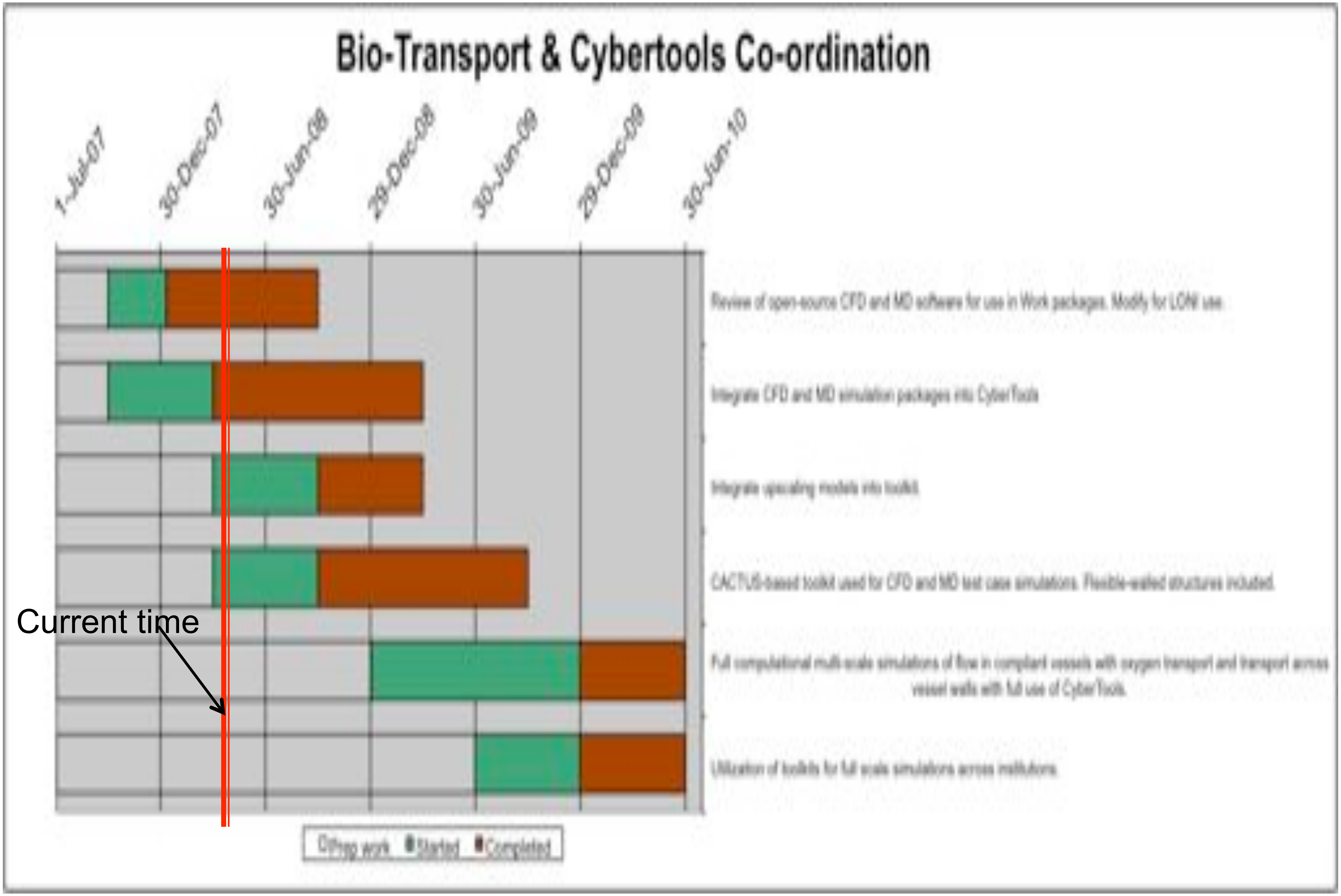
10ns profiles: dotted line ,50ns profiles: solid line

Progress to Date

- CFD
  - ✓Improvements to the IBM (pressure interpolation)
  - ✓Working on the MPM for greater robustness (implicit, parallel)
  - ✓Simulation of transport in flexible tubes
- MD
  - ✓ Simulation of small molecules across lipid bi-layers
- Collaboration with WP4
  - ✓ Regular meetings with the WP4 team
  - ✓Development of a simplified CFD code with data array structure consistent with Cactus for implementation as part of the CFD Toolkit
- CFD-MD Coupling
  - ✓Discussion on coupling strategy and approaches



Multi-scale Bio-transport Simulations: Deliverables
1-Jul-07
30-Dec-07
30-Jun-08
29-Dec-08
30-Jun-09
29-Dec-09
30-Jun-10
Integration of continuum CFD tools (flow-structure, complex geometry, transport etc) for oxygen transport in arterial vessels (Acharya@5% effort (0.5 summer months), 1 post doctoral associate (PDA) in yr 1, 1 graduate student)
MD simulation studies of small molecule/nanoparticle lipid bilayer membrane interactions (Moldovan & Devireddy @ 5% effort in years 2 and 3, only; 1 graduate student)
Integration of tools and algorithms into CFD and MD toolkits in collaboration with Cybertools (Acharya & Nikitopoulos @5% in yr 2; 1 PDA; 1 graduate student)
Large scale MD simulations (across LONI resources) of multiple nanoparticles lipid bilayers interactions (Moldovan & Devireddy @ 5% effort in years 2 and 3; 1 graduate student)
Toolkit driven CFD and MD simulations across LONI; application of these tools to understand transport in and across cell/capillary/vessel systems (Acharya @7.5%, Moldovan, Devireddy & Nikitopoulos @5% in year 3, 1 PDA, 2 graduate students)
Current time
Prep work
Started
Completed



Bio-Transport & Cybertools Co-ordination
1-Jul-07
30-Dec-07
30-Jun-08
29-Dec-08
30-Jun-09
29-Dec-09
30-Jun-10
Review of open-source CFD and MD software for use in Work packages. Modify for LONI use.
Integrate CFD and MD simulation packages into CyberTools
Integrate upscaling models into toolkit.
CACTUS-based toolkit used for CFD and MD test case simulations. Flexible-walled structures included.
Full computational multi-scale simulations of flow in compliant vessels with oxygen transport and transport across vessel walls with full use of CyberTools.
Utilization of toolkits for full scale simulations across institutions.
Current time
Prep work
Started
Completed

Concluding Remarks

- Development of improved CFD methodologies for biological systems (complex geometries, moving boundaries, multi-scale phenomena)

- Utilization of CFD and MD methodologies for improved understanding of transport processes in biological systems

- Supporting the development of Toolkit infrastructure for open source, scalable code for community usage

- CFD-MD integration for resolving/integrating atomistic effects

- Future interactions will also include the visualization groups and the portals group

BIOMEDICAL IMAGING, DATA MINING, AND DATA FUSION

Faculty: Dr. S. Sitharama Iyengar (LSU)
Dr. Nathan E. Brener (LSU)
Dr. Bijaya B. Karki (LSU)
Dr. Hilary Thompson (LSUHSC)

Project Coordinator: Dr. Dimple Juneja

Graduate Students: Dr. Hua Cao (PhD May 2008)
Rathika Natarajan (MS August 2008)
Asim Shrestha (PhD student)
Jagadish Kumar (MS student)
Gaurav Khanduja (PhD student)
Dipesh Bhattarai (PhD student)

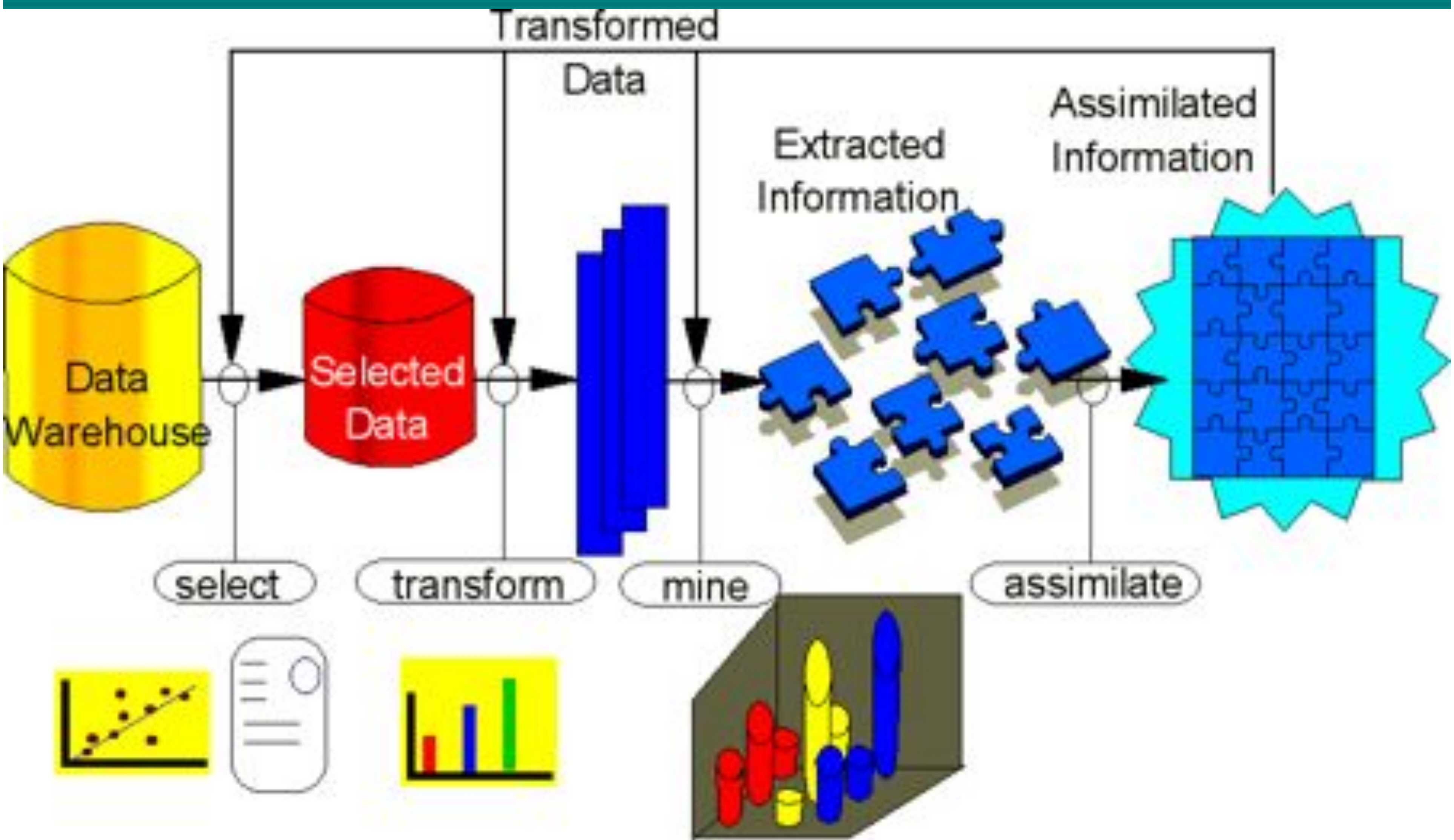
Collaborators: LSU Health Sciences Center (LSUHSC)
LATech
Air Force Institute of Technology
Indian Institute of Science

This project is funded in part by NSF/EPSCoR RII

Outline of Presentation

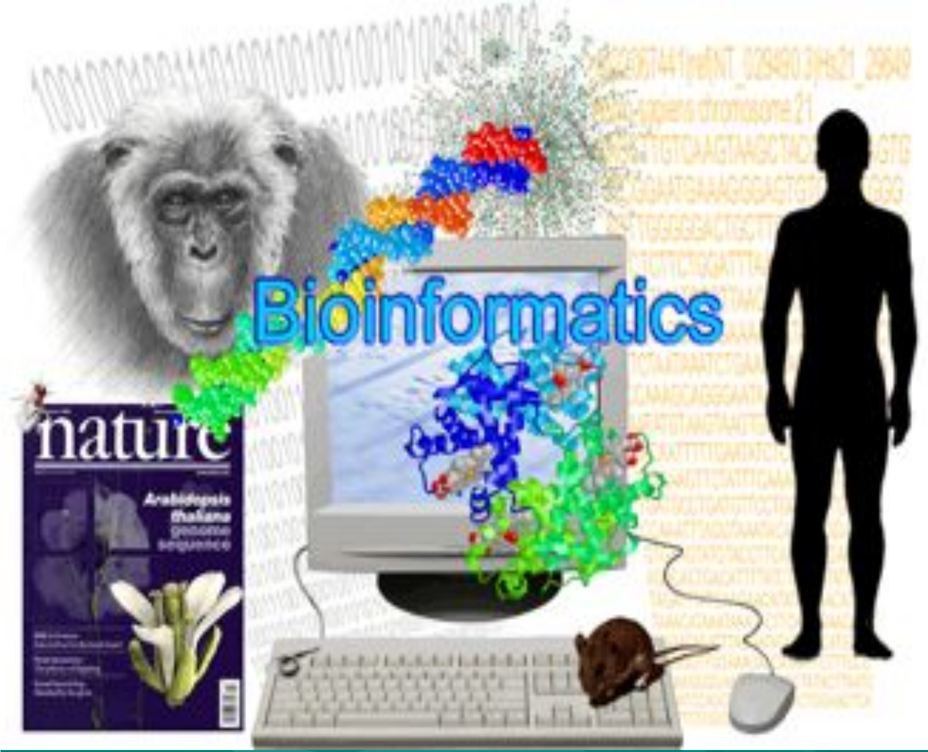
- Data Mining
  - Overview
  - Science Drivers
  - Computation
- Data Fusion
  - Overview
  - Science Drivers
  - Biomedical Images
  - Computation
- Links to WP1, WP3
  - Implementation on LONI
- Education and Outreach

DATA MINING



"Knowledge discovery in science"

DATA MINING APPLICATIONS



Protein Folding Analysis In Bioinformatics

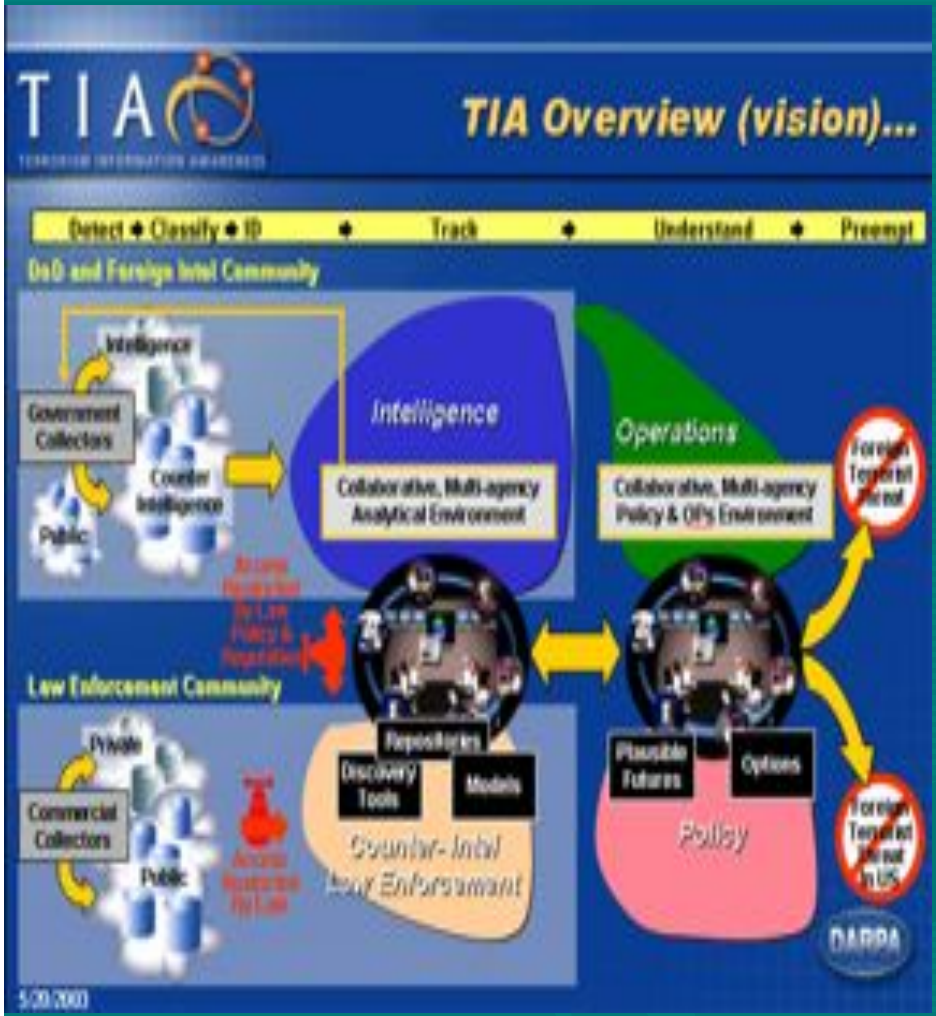
Computer-Assisted Passenger Prescreening System

DATA MINING APPLICATIONS

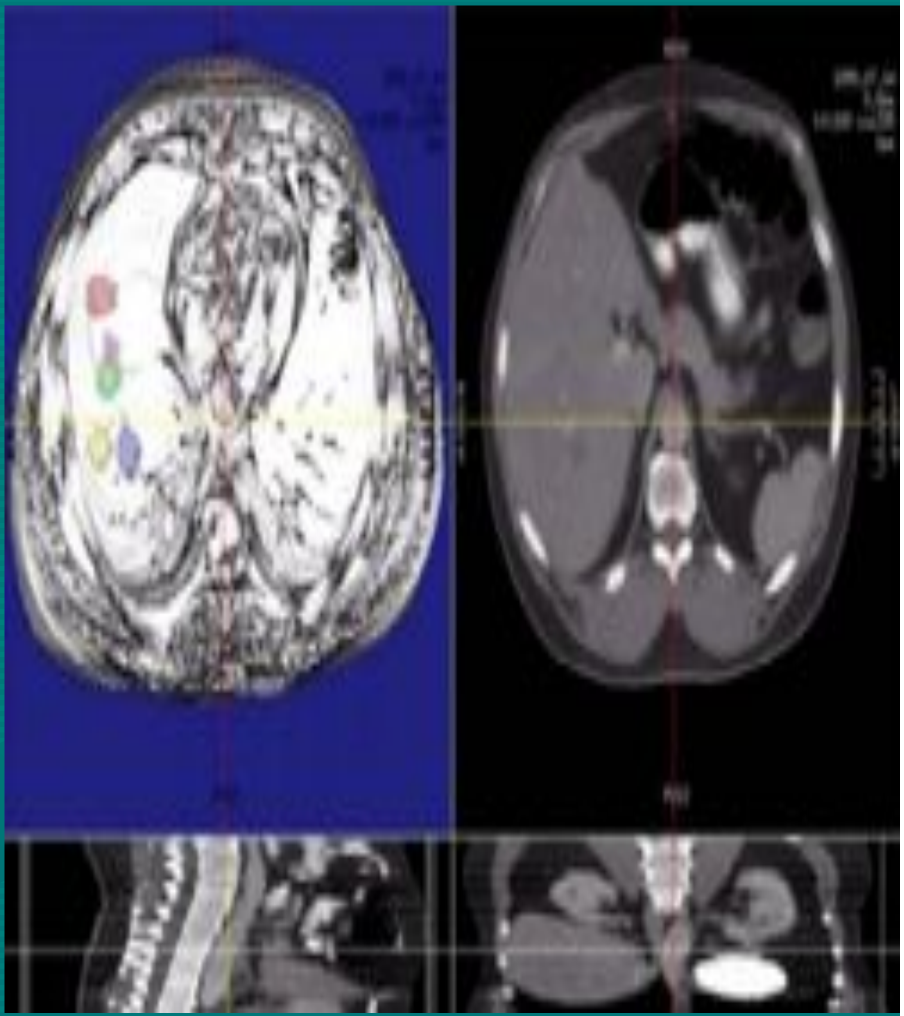
Banking, Insurance, Retailing

Classification Of Astronomical Objects

DATA MINING APPLICATIONS



Terrorism Information Awareness

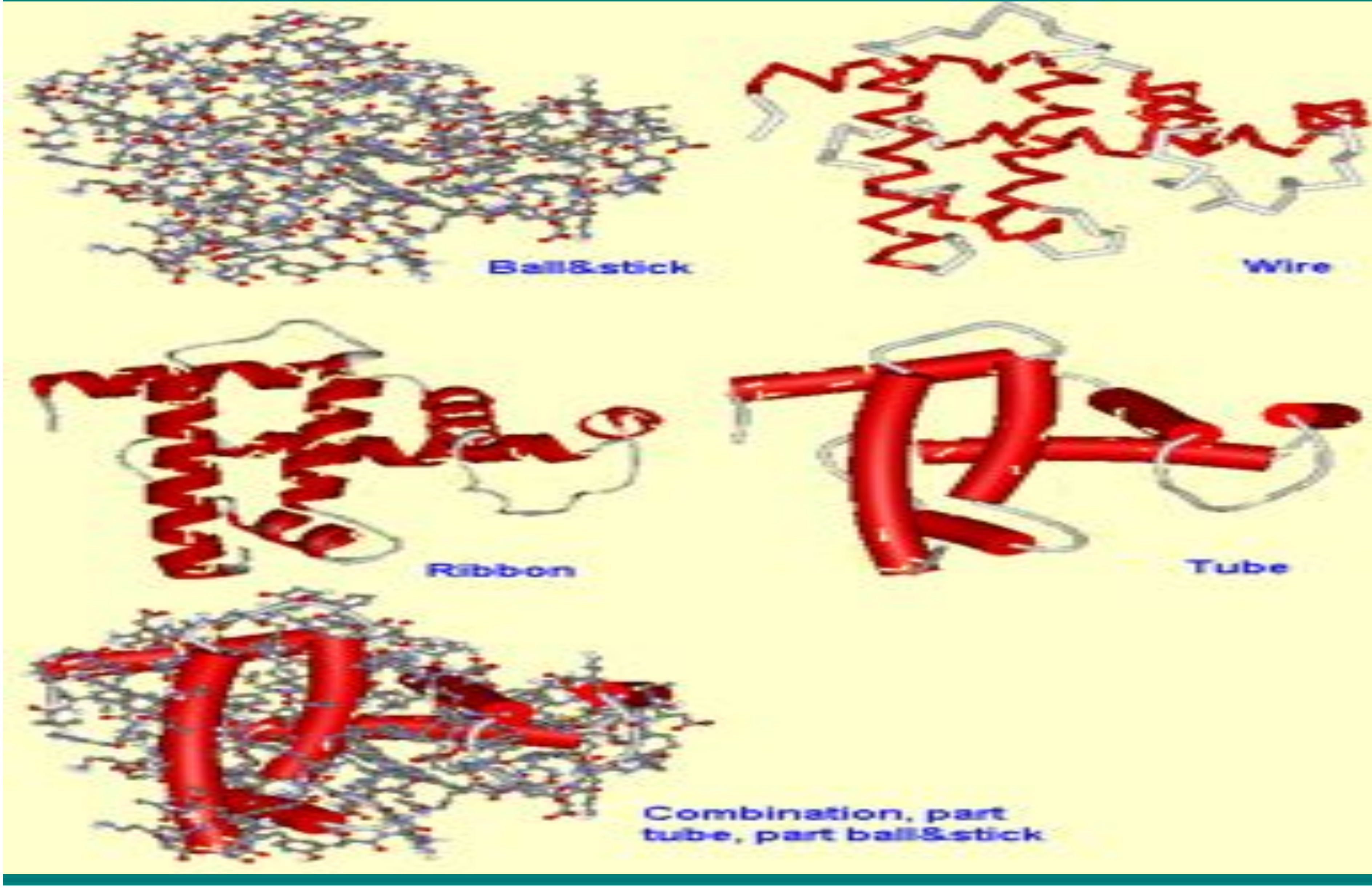


Medical Decision Support

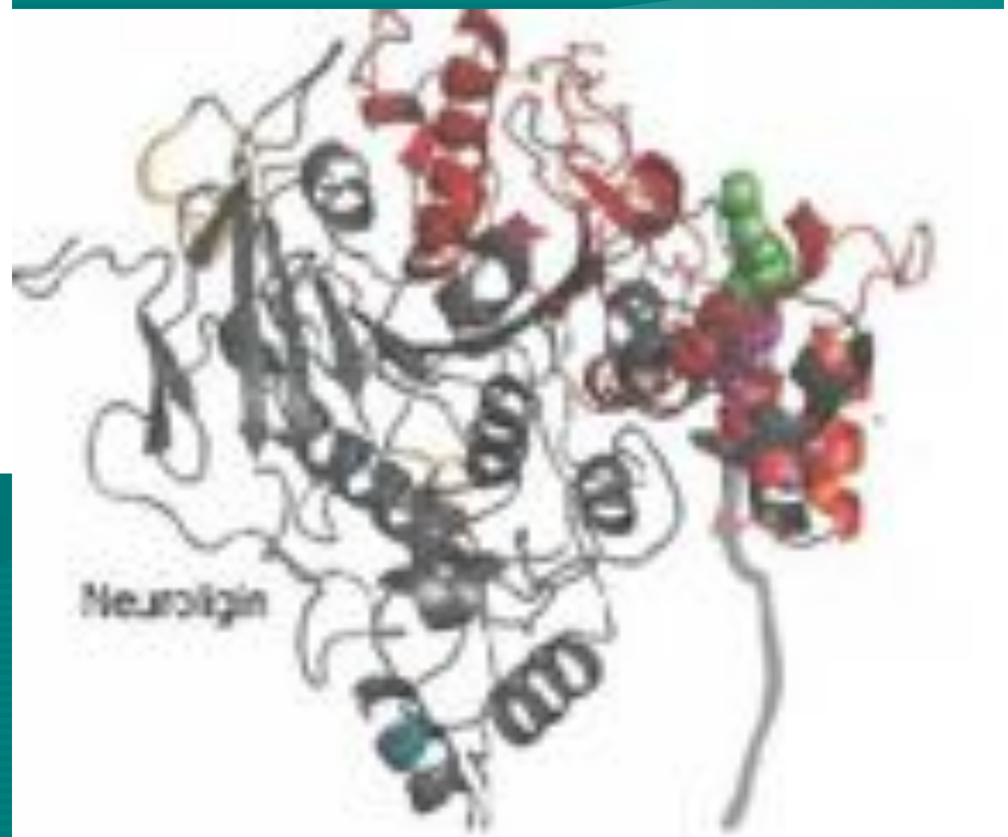
Science Drivers for Data Mining

- Small Molecule/Geno Sensors (Soper, Murphy)
- Immuno Sensors (Cortez, Gaver, Blake)
- Biotransport Computation (Acharya)
- Biomedical Images (Thompson)
- Bioinformatics
- Protein Structure and Properties

TYPES OF PROTEINS



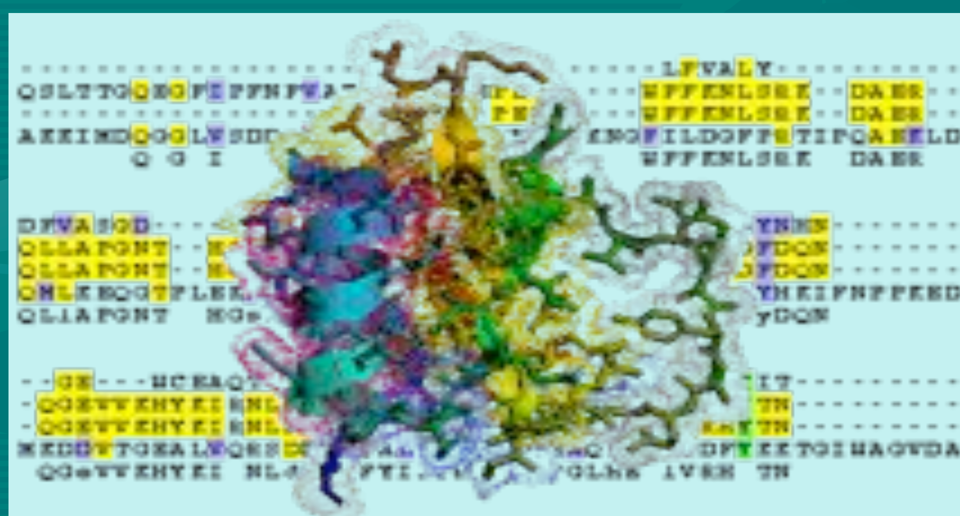
EXAMPLES OF PROTEINS



THE INFORMATION DELUGE

New protein sequence information is being produced at staggering rates.

- **The major protein databases contain over 650,000,000 protein sequences.**
- **Finding conformances in these sequences is a current problem of interest.**



A Robust Data Mining Algorithm for Clustering of Similar Protein Folding Units

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Department of Computer Science,
Louisiana State University
Baton Rouge, LA

(in collaboration with researchers at IISC Bangalore and CESAR Laboratory, ORNL)

New Data Mining Algorithm

- The properties of a protein depend on its sequence of amino acids and its 3D structure which consists of multiple folds of the peptide chain.
- If some of the properties depend primarily on the folding structure, then proteins with certain folding units may exhibit properties specific to those units.
- In that case, a classification of proteins based on folding units would facilitate the selection of proteins with certain desired properties.

New Data Mining Algorithm

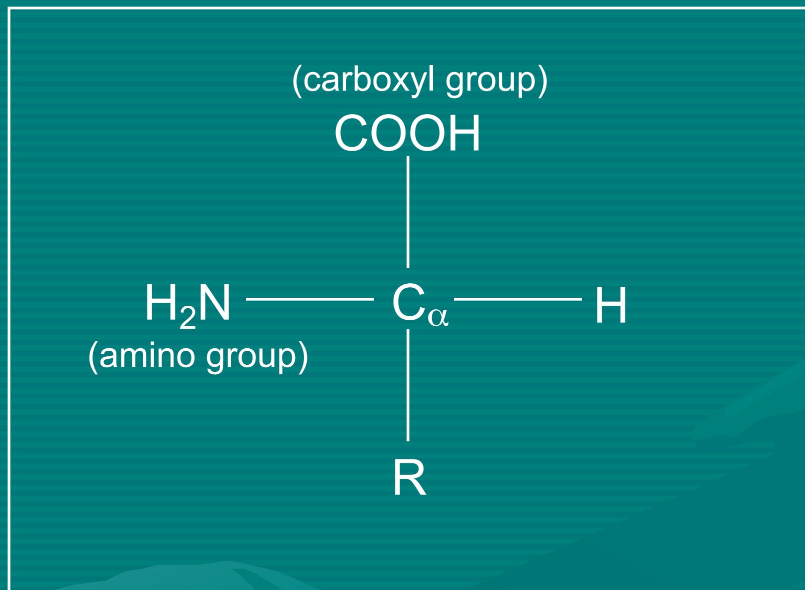
- With this in mind, we propose an efficient clustering algorithm to classify proteins according to common folding units. Our algorithm has the following steps:
  - Represent the protein structure as a series of conformational angles
  - Partition the proteins into fragments (folding units) of a specified size
  - Cluster the fragments into groups

New Data Mining Algorithm

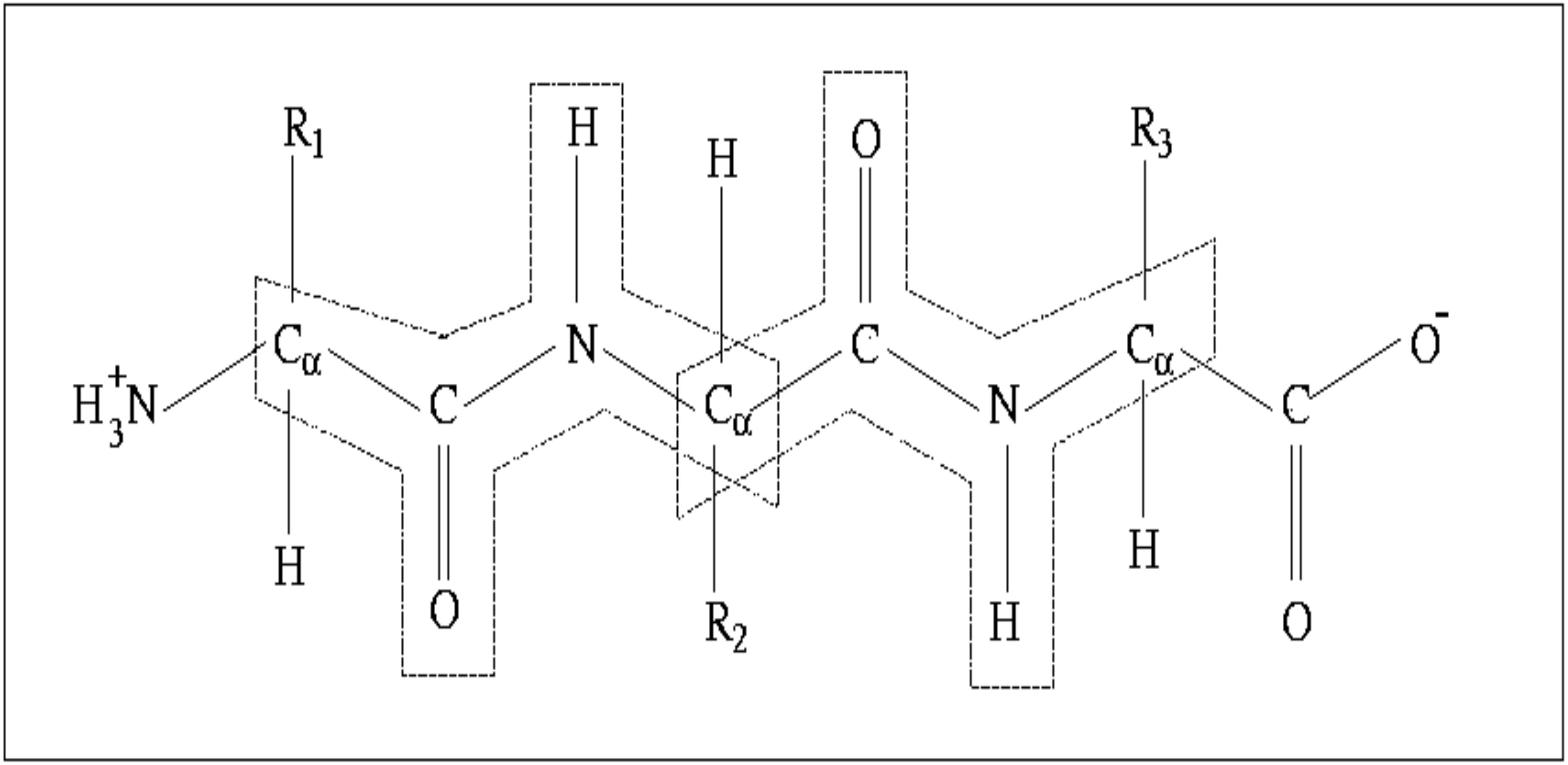
- The use of overlapped substrings makes our unique clustering technique not susceptible to noise and outliers.
- Preliminary implementation of this algorithm indicates that it has the capability to discover secondary structural elements (folding units) in proteins and can be generalized to large protein data banks.

New Data Mining Algorithm

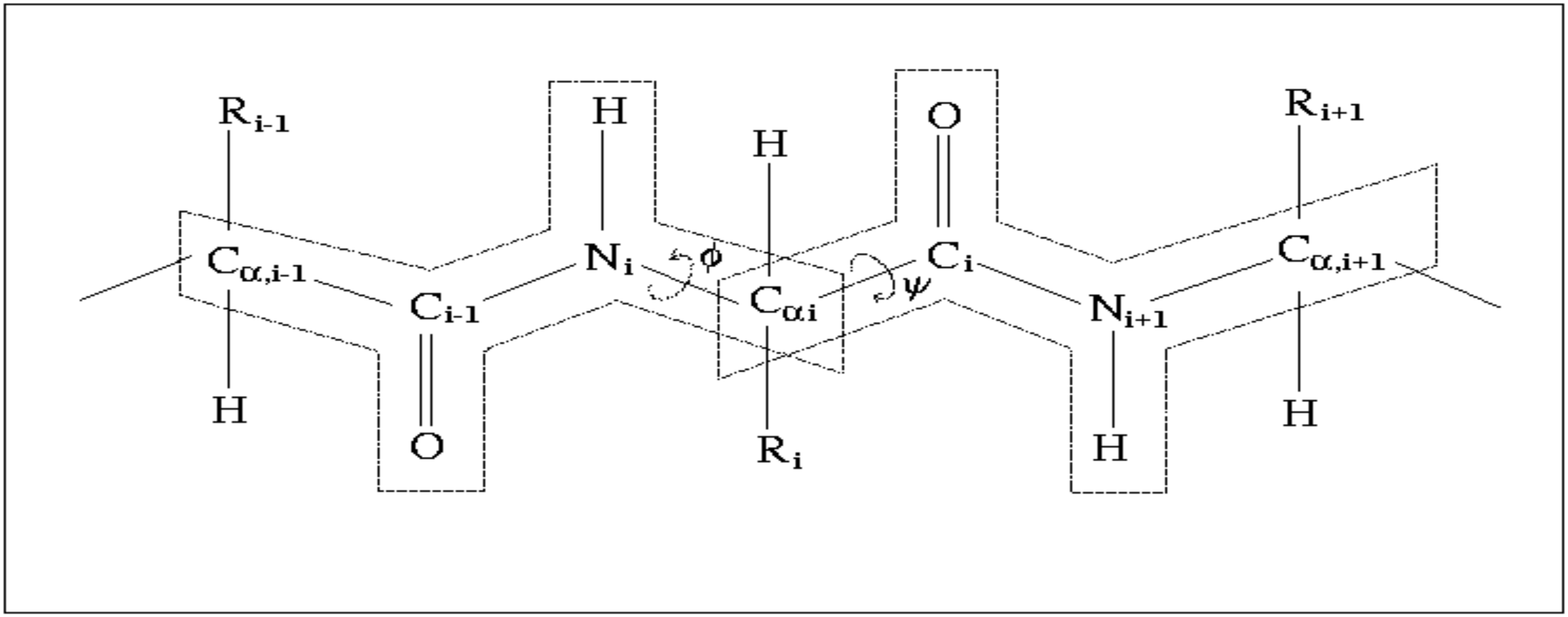
- The algorithm is applied to a set of 20 randomly selected proteins from the Protein Data Bank and a set of 12 non-homologous α/β protein structures from the PDBSELECT.



The basic structure of an amino acid



A polypeptide chain made of three amino acids. The atoms within each dotted polygon are coplanar and rigidly bonded.



The use of the two conformational angles ϕ and ψ instead of atomic coordinates reduces the number of parameters and thereby enables the algorithm to be applied to a larger set of proteins.

DATA STRUCTURE REPRESENTATION SCHEME

- The Protein Data Bank (PDB) and PDBSELECT are archives of experimentally determined structures of proteins.
- The archives contain the coordinates of each atom in the proteins.
- The atomic coordinates of the backbone atoms are extracted and are used to compute the conformational angle pairs.

GROUPING ALGORITHM

- **For each protein to be included, we compute the following series of conformational angles:**

$$\{ (\phi,\psi)_1 \ (\phi,\psi)_2 \ (\phi,\psi)_3 \ (\phi,\psi)_4 \ (\phi,\psi)_5 \ \ldots \ (\phi,\psi)_{n-2} \}$$

where n is the number of amino acids used to obtain the fragments and the range of the conformational angles is –180º to 180º .

GROUPING ALGORITHM - Continued

- **The peptide chain is then decomposed into a series of overlapping fragments of length 8:**

Fragment 1: [$(\phi,\psi)_1$ $(\phi,\psi)_2$ $(\phi,\psi)_3$ $(\phi,\psi)_4$ $(\phi,\psi)_5$ $(\phi,\psi)_6$ $(\phi,\psi)_7$ $(\phi,\psi)_8$]

Fragment 2: [$(\phi,\psi)_2$ $(\phi,\psi)_3$ $(\phi,\psi)_4$ $(\phi,\psi)_5$ $(\phi,\psi)_6$ $(\phi,\psi)_7$ $(\phi,\psi)_8$ $(\phi,\psi)_9$]

Fragment 3: [$(\phi,\psi)_3$ $(\phi,\psi)_4$ $(\phi,\psi)_5$ $(\phi,\psi)_6$ $(\phi,\psi)_7$ $(\phi,\psi)_8$ $(\phi,\psi)_9$ $(\phi,\psi)_{10}$]

GROUPING ALGORITHM - Continued

- **We define the distance between two points A_i and A_j, DIST(A_i , A_j) , as**

$$DIST(A_i , A_j) = \left((\phi_{i1}-\phi_{j1})^2 + (\psi_{i1}-\psi_{j1})^2 + (\phi_{i2}-\phi_{j2})^2 + (\psi_{i2}-\psi_{j2})^2 + \ldots + (\phi_{i8}-\phi_{j8})^2 + (\psi_{i8}-\psi_{j8})^2 \right)^{1/2}$$

where

$$A_i = [(\phi_{i1}, \psi_{i1}) , (\phi_{i2}, \psi_{i2}) , \ldots (\phi_{i8}, \psi_{i8})]$$

$$A_j = [(\phi_{j1}, \psi_{j1}) , (\phi_{j2}, \psi_{j2}) , \ldots (\phi_{j8}, \psi_{j8})]$$

- **For every (ψ - ψ), if |ψ - ψ|>180, then**

GROUPING ALGORITHM - Continued

- **Let j be the index that labels the groups. We define the center of group j , C_j , as**

$$C_j = [(\phi_{j1}, \psi_{j1}), (\phi_{j2}, \psi_{j2}), \ldots (\phi_{j8}, \psi_{j8})]$$

where

$$\phi_{jm} = \Sigma\phi_{im} / N_j$$

$$\psi_{jm} = \Sigma\psi_{im} / N_j$$

$$(i = 1, 2, .. N_j ; m = 1, 2, \ldots 8),$$

N_j is the number of points in the group, and the sum is over i. Such groups are regarded as folding units in our current work.

GROUPING ALGORITHM - Continued

ALGORITHM

- **Input: A set of points in 16-dimensional space and a distance measure R.**

- **Output: A set of groups into which the points have been divided, where every point in a group is within the distance R of the group center.**

Begin:

I. Start a stack with all of the points in it.

GROUPING ALGORITHM - Continued

II. Do an operation "pop up" of a point A_1 , create group 1, with center C_1 equal to A_1, set N_1 to 1.

III. While (stack is not empty)

{

a. Do an operation "pop up" of a point A_p .

b. Compute the distances between A_p and each existing group center C_j (suppose we have k groups now, then $1<=j<=k$).

GROUPING ALGORITHM - Continued

c. Suppose when $j=j_{min}$, the distance is a minimum.

If DIST(C_{jmin}, A_p) > R Then

Create a new group k+1, with center C_{k+1} equal to A_p, set N_{k+1} to 1.

Else

1. Insert A_p into group j_{min}, add 1 to N_{jmin} .

2. Compute the new center C'_{jmin} of group j_{min} .

GROUPING ALGORITHM - Continued

3. For $i=1, 2, \ldots N_{jmin}$

{

i. Re-compute the distance $DIST(A_{jmin,i}, C'_{jmin})$ between the point $A_{jmin,i}$ in group j_{min} and the new group center C'_{jmin}.

ii. If $DIST(A_{jmin,i}, C'_{jmin}) > R$, push $A_{jmin,i}$ into the stack, subtract 1 from N_{jmin}, go to step 2.

}

}

GROUPING ALGORITHM - Continued

IV. a. For each group, re-calculate the distances between the contained

points and all of the group centers.

b. If there is any point that has a shorter distance with another group center than with its own group center, move it to the other group where the distance is shorter.

c. If there are no such points, go to END

GROUPING ALGORITHM - Continued

V. a. Re-compute all the group centers.

b. If any point is no longer within distance R of the center of its group, push it into the stack.

c. If there are points in the stack, go back to step III.

d. If there are no points in the stack, go back to step IV.

END

Table 1: A short list of proteins that were randomly selected

PDB Entry	Name of the Protein	Amino Acids Selected	Points Derived
1ash	HEMOGLOBIN (DOMAIN ONE)	1 – 146	137
1bsr	RIBONUCLEASE(BOVINE, SEMINAL) (CHAIN A)	1 – 124	115
1cca	CYTOCHROME C PEROXIDASE	4 – 294	282
1cew	CYSTATIN	9- 116	99
1clm	CALMODULIN (PARAMECIUM TETRAURELIA)	4 – 147	135
1crn	CRAMBIN	1 – 46	37

Table 1: A short list of proteins that were randomly selected - Continued

1ctt	CYTIDINE DEAMINASE	4 – 294	282
1erb	RETINOL BINDING PROTEIN COMPLEX WITH N-ETHYL RETINAMIDE 2	2 – 174	164
1fut	RIBONUCLEASE F1	1 – 107	98
1hng	CD2 (RAT) (CHAIN B)	2 –176	166
1hoe	ALPHA-*AMYLASE INHIBITOR HOE-467*A	1- 74	65
1lbu	HYDROLASE METALLO (ZN) DD-PEPTIDASE	1 – 213	204
1mka	BETA-HYDROXYDECANOYL THIOL ESTER DEHYDRASE (CHAIN A)	1- 171	162

Table 1: A short list of proteins that were randomly selected - Continued

1mng	MANGANESE SUPEROXIDE DISMUTASE (CHAIN A)	1 – 203	194
1pkp	RIBOSOMAL PROTEIN S5	4 – 148	136
1udi	URACIL-DNA GLYCOSYLASE	18 – 244	218
1utg	UTEROGLOBIN(OXIDIZED)	1 – 70	61
1yal	CARICA PAPAYA CHYMOPAPAIN	1 – 218	209
2vab	MHC CLASS I H-2KB HEAVY CHAIN	1 – 274	265
5pti	TRYPSIN INHIBITOR	1 – 58	49

Table 2: The top 5 groups detected by our grouping algorithm

Group Name	A	B	C	D	E
ϕ_1	-67.8	-118.0	-105.2	-81.8	-80.7
ψ_1	-39.1	139.9	127.0	132.4	-36.7
ϕ_2	-67.0	-117.6	-120.8	-64.6	-107.8
ψ_2	-37.3	139.6	141.4	48.4	106.2
ϕ_3	-67.2	-120.3	-119.2	-63.2	-106.6
ψ_3	-38.6	140.4	126.9	-29.4	130.9

Table 2: The top 5 groups detected by our grouping algorithm - Continued

ϕ_4	-67.3	-118.3	-120.8	-72.1	-114.4
ψ_4	-38.1	139.2	138.6	-35.5	130.7
ϕ_5	-68.1	-113.8	-115.5	-71.7	-102.6
ψ_5	-36.6	137.6	143.2	-34.6	119.9
ϕ_6	-65.8	-111.5	-113.8	-66.7	-105.7
ψ_6	-36.1	134.9	132.3	-32.5	121.1
ϕ_7	-68.1	-113.7	-85.4	-69.5	-104.5
ψ_7	-35.2	128.4	132.0	-32,4	112.3
ϕ_8	-70.8	-112.4	-15.5	-72.9	-105.5
ψ_8	-31.6	141.0	-29.6	-30.5	127.1

Table 2: The top 5 groups detected by our grouping algorithm - Continued

Points in the Group	202	109	42	40	38
The Nearest Points	1mka 81-90	1cew 92-101	1hng 75-84	1udi 133-142	1mka 121-130
Sources of Points	1ash: 1 1bsr: 11 1cew: 15 1mka: 16 1mng: 60 1udi: 43 2vab: 56	1bsr: 16 1cew: 13 1hng: 27 1mka: 11 1mng: 1 1udi: 2 2vab: 39	1bsr: 2 1cew: 2 1hng: 11 1mka: 7 1mng: 3 1udi: 3 2vab: 14	1bsr: 6 1cca: 1 1cew: 3 1mka: 4 1mng: 9 1udi: 13 2vab: 4	1bsr: 8 1cew: 4 1hng: 7 1mka: 5 1udi: 5 2vab: 9

FOLDING UNITS PRODUCED BY THE GROUPING ALGORITHM

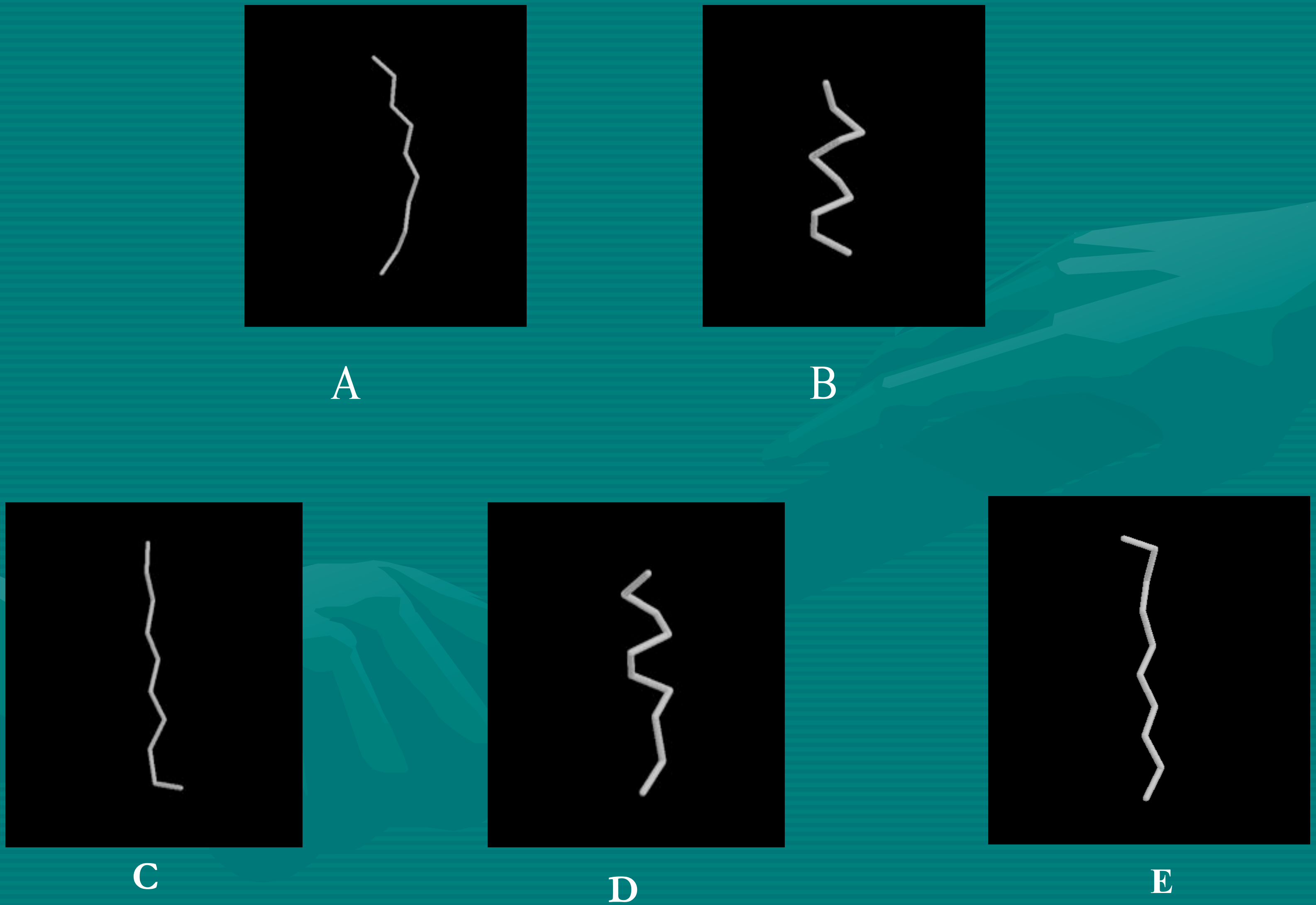


Table 3. A List Of Non-homologous α/β Proteins

PDB code	Name of the protein	# fragments
1byi_	Dethiobiotin Synthase	208
1g66A	Acetyl xylan esterase II	191
1ga6A	Serine-carboxyl proteinase	353
1gci_	Subtilisin	205
1i1wA	Endo-1, 4-beta-xylanase	286
1ixh_	Phosphate binding protein	305
1muwA	Xylose isomerase	370
1mxtA	Cholesterol oxidase	482
1n55A	Triosephosphate isomerase	233
1o7jA	L-asparaginase	309
1ug6A	Beta-glycosidase	410
7a3hA	Endoglucanase	284

Table 4: The Group Centers Of The Top 5 Groups

Group Name	A	B	C	D	E
ϕ_1	-62.7	-66.2	-61.2	-61.8	-74.7
ψ_1	-41.5	-40.7	-41.7	-41.7	136.6
ϕ_2	-63.2	-63.0	-63.1	-64.2	-64.1
ψ_2	-42.3	-42.1	-41.1	-42.9	-33.7
ϕ_3	-62.8	-63.3	-63.9	-61.9	-63.3
ψ_3	-42.9	-41.2	-42.7	-43.9	-37.7

Table 4: The Group Centers Of The Top 5 Groups - Continued

ϕ_4	-62.7	-63.5	-62.2	-64.1	-69.8
ψ_4	-42.8	-43.2	-43.1	-40.2	-35.9
ϕ_5	-62.7	-62.8	-64.0	-67.2	-61.8
ψ_5	-42.7	-42.4	-40.9	-28.4	-44.3
ϕ_6	-62.9	-63.9	-66.7	-91.6	-61.5
ψ_6	-42.8	-39.0	-28.8	-0.1	-41.5
ϕ_7	-62.6	-69.4	-90.3	79.8	-64.3
ψ_7	-42.7	-28.9	-0.9	19.3	-42.1
ϕ_8	-63.3	-94.4	78.1	-84.7	-65.8
ψ_8	-40.8	-6.52	20.3	139.2	-40.5

Table 4: The Group Centers Of The Top 5 Groups - Continued

Fragments in the Group	443	87	52	39	38
The Nearest Fragment	1n55A 110 – 117	7a3hA 85 – 92	1ug6A 63 – 70	1o7jA 264 – 271	1i1wA 244 – 251
Description of the fragments	An α - helix [α_8]	An α - helix with type I β turn at the C terminal [α_7-βI]	An α - helix with type I β turn at the C terminal followed by an α_L residue [α_6-βI-α_L]	[α_5-βI-α_L-β]	[β-α_7]

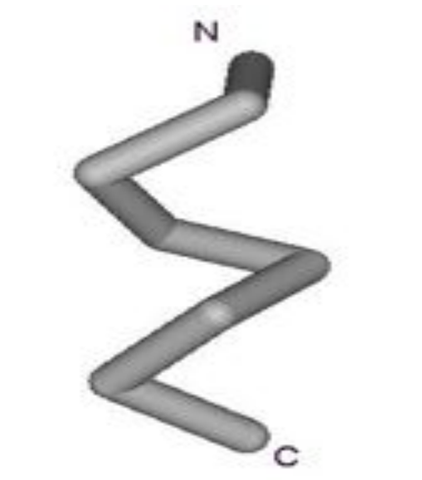
βI – refers to type I β turn

Table 5: The First 10 Ranked Clusters Identified With The Fragment Length (FL) Varying From 6 To 9

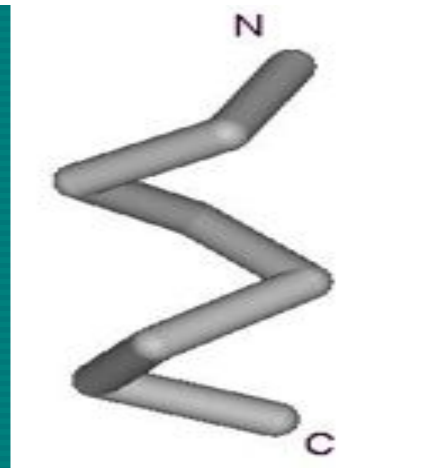
Cluster Number	FL 9	FL 8	FL 7	FL 6
1	α_9 (367)	α_8 (443)	α_7 (522)	α_6 (626)
2	$\alpha_{8\gamma}$ (81)	$\alpha_{7\gamma}$ (87)	$\alpha_{6\gamma}$ (97)	$\alpha_{5\gamma}$ (107)
3	$\alpha_{7\gamma}\ \alpha_L$ (45)	$\alpha_{6\gamma}\ \alpha_L$ (52)	$\alpha_{5\gamma}\ \alpha_L$ (55)	$\beta\ \alpha_5$ (59)
4	$\alpha_{6\gamma}\ \alpha_{L\beta}$ (39)	$\alpha_{5\gamma}\ \alpha_{L\beta}$ (39)	$\beta\ \alpha_6$ (53)	$\alpha_{4\gamma}\ \alpha_L$ (55)

Table 5: The First 10 Ranked Clusters Identified With The Fragment Length (FL) Varying From 6 To 9 - Continued

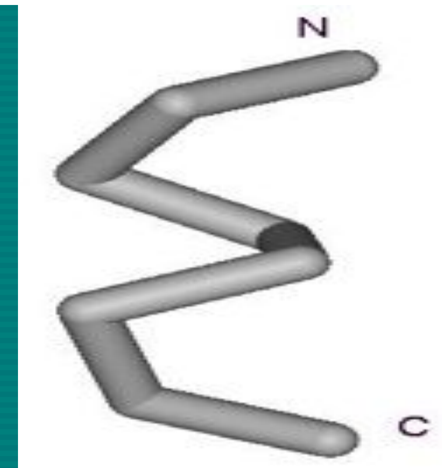
5	$\beta\ \alpha_8$ (35)	$\beta\ \alpha_7$ (38)	$\alpha_{4\gamma}\ \alpha_{L\beta}$ (39)	β_6 (50)
6	$\alpha_{7\gamma}\ \beta$ (32)	$\alpha_{6\gamma}\ \beta$ (33)	$\beta_{6\alpha}$ (32)	β_6 (41)
7	$\beta_{2\alpha7}$ (30)	$\alpha_{5\gamma}\ \beta\ \gamma$ (26)	$\alpha_{5\gamma}\ \beta$ (30)	$\alpha_{3\gamma}\ \alpha_{L\beta}$ (39)
8	$\alpha_{5\gamma}\ \alpha_{L\beta2}$ (26)	$\beta_{2\alpha6}$ (26)	$\alpha_{4\gamma}\ \beta\ \gamma$ (29)	$\alpha_{4\gamma}\ \beta$ (39)
9	$\alpha_{5\gamma}\ \alpha_3$ (25)	$\alpha_{4\gamma}\ \alpha_3$ (26)	$\beta_{2\alpha5}$ (28)	$\alpha\ \gamma\ \alpha_{L\beta3}$ (34)
10	$\alpha_{2\gamma}\ \alpha_6$ (24)	$\alpha_{2\gamma}\ \alpha_5$ (25)	$\alpha\ \gamma\ \alpha\ \beta_4$ (28)	$\beta_{2\alpha4}$ (33)



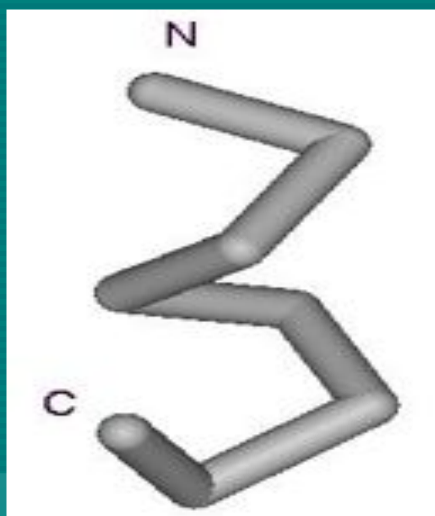
A



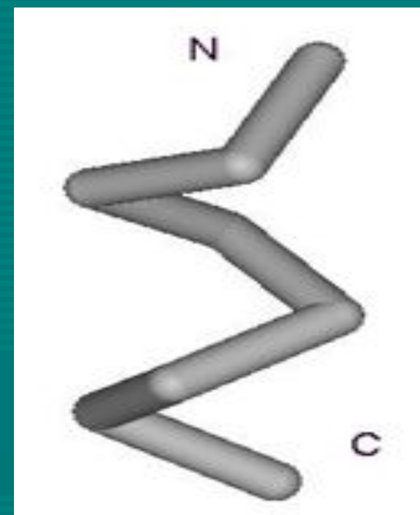
B



C



D



E

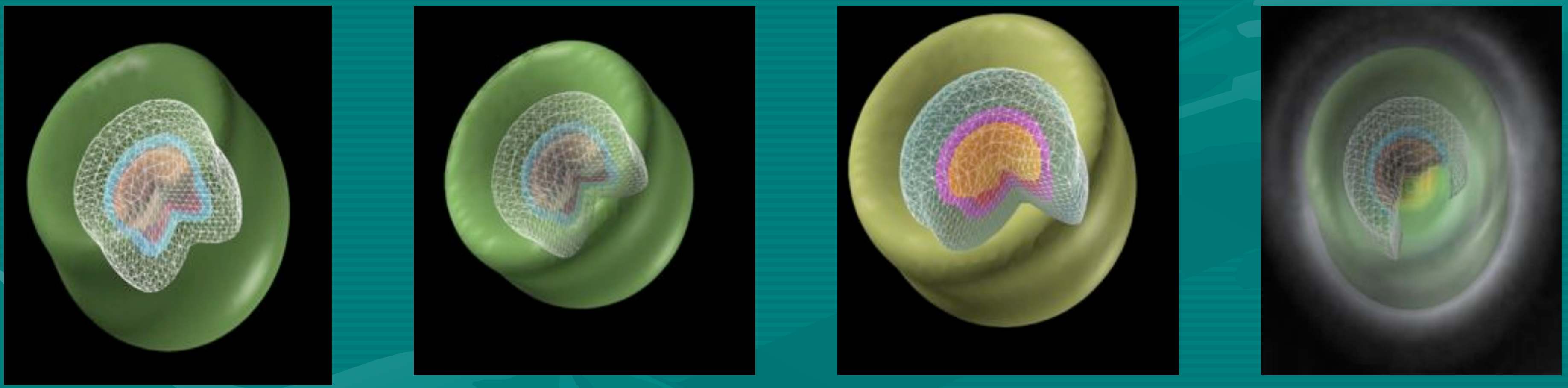
C_α traces of nearest fragments for the first five clusters listed in Table 4. The amino and carboxyl terminal ends of the fragments are denoted as N and C.

CONCLUSIONS & FUTURE WORK

- This paper describes a unique clustering algorithm that can be used to classify proteins according to similar folding units.
- This classification has the potential to facilitate the selection of proteins with specific desired properties.
- The preliminary implementation of the algorithm indicates that it has the capability to discover secondary structural elements (folding units) in proteins and can be generalized to large protein data banks.

DATA FUSION APPLICATIONS

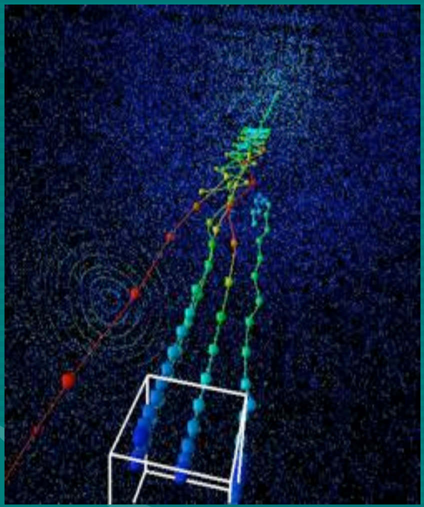
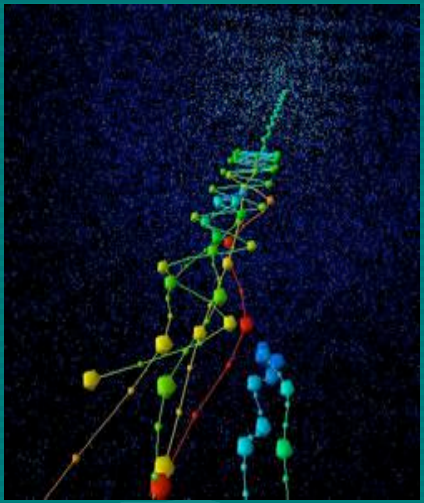
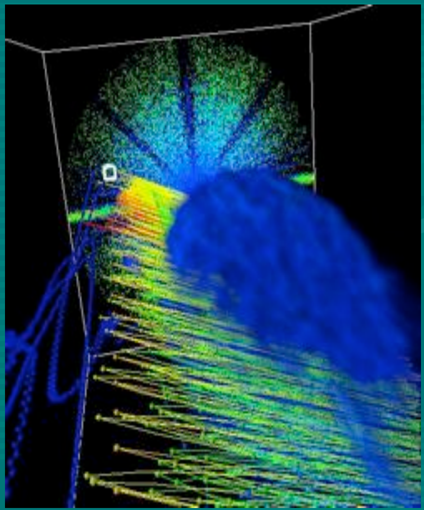
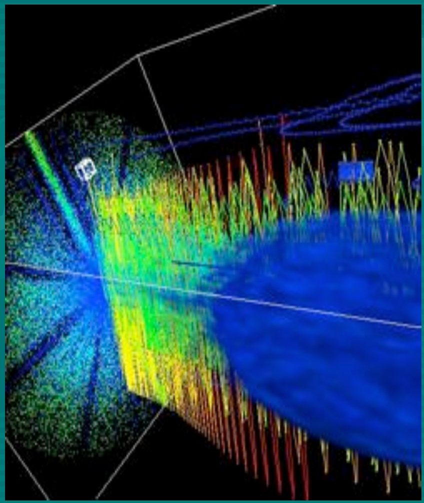
Computational Astrophysics



Fused Images of a Supernova

DATA FUSION APPLICATIONS

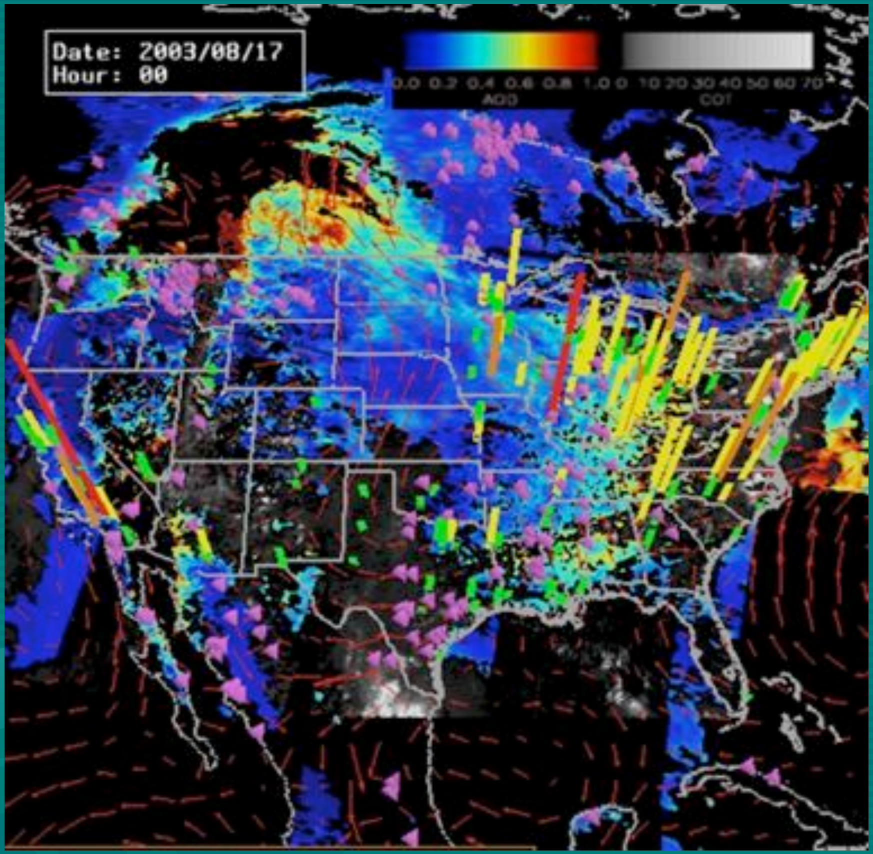
Analysis of Sub Atomic Particle Movement

Fused Images help in showing the trajectories and velocities of subatomic particles

DATA FUSION APPLICATIONS

Hurricane Tracking

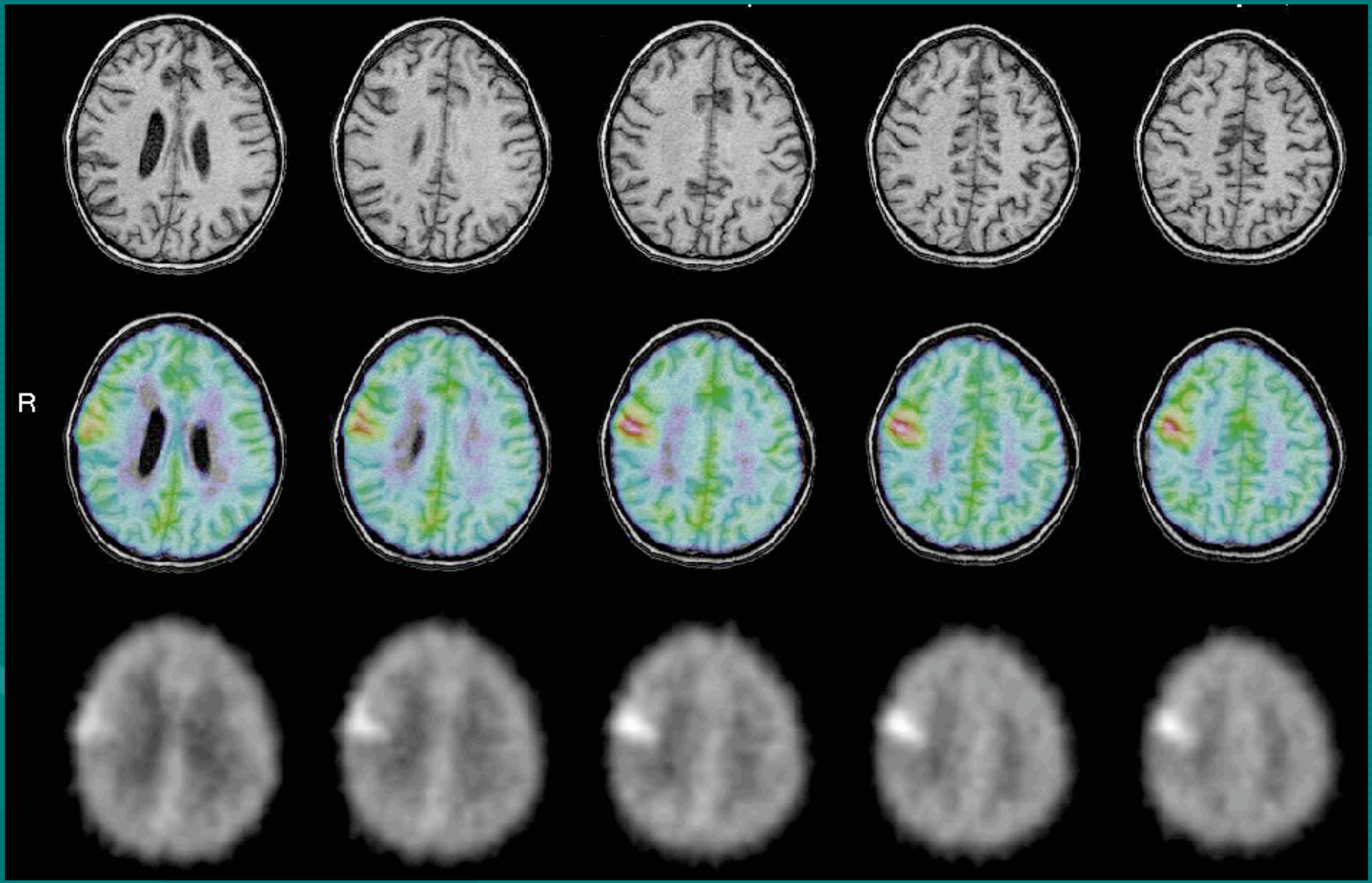


Fused images help to track the movements of hurricanes

Science Drivers for Data Fusion

- Small Molecule/Geno Sensors (Soper, Murphy)
- Immuno Sensors (Cortez, Gaver, Blake)
- Biotransport Computation (Acharya)
- Environmental Transport (Allen)
- Biomedical Images (Thompson)
- Medical Diagnosis and Decision Making
- Opthalmology

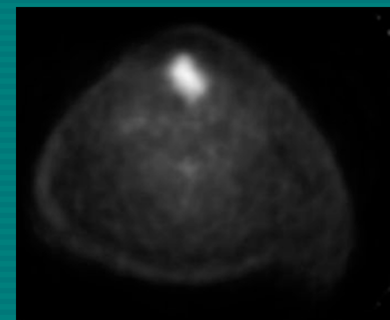
Fusion of Biomedical Images



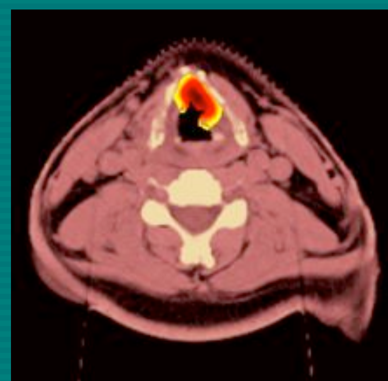
Fusion of MRI and PET images of human brain

Fusion of Biomedical Images

CT image



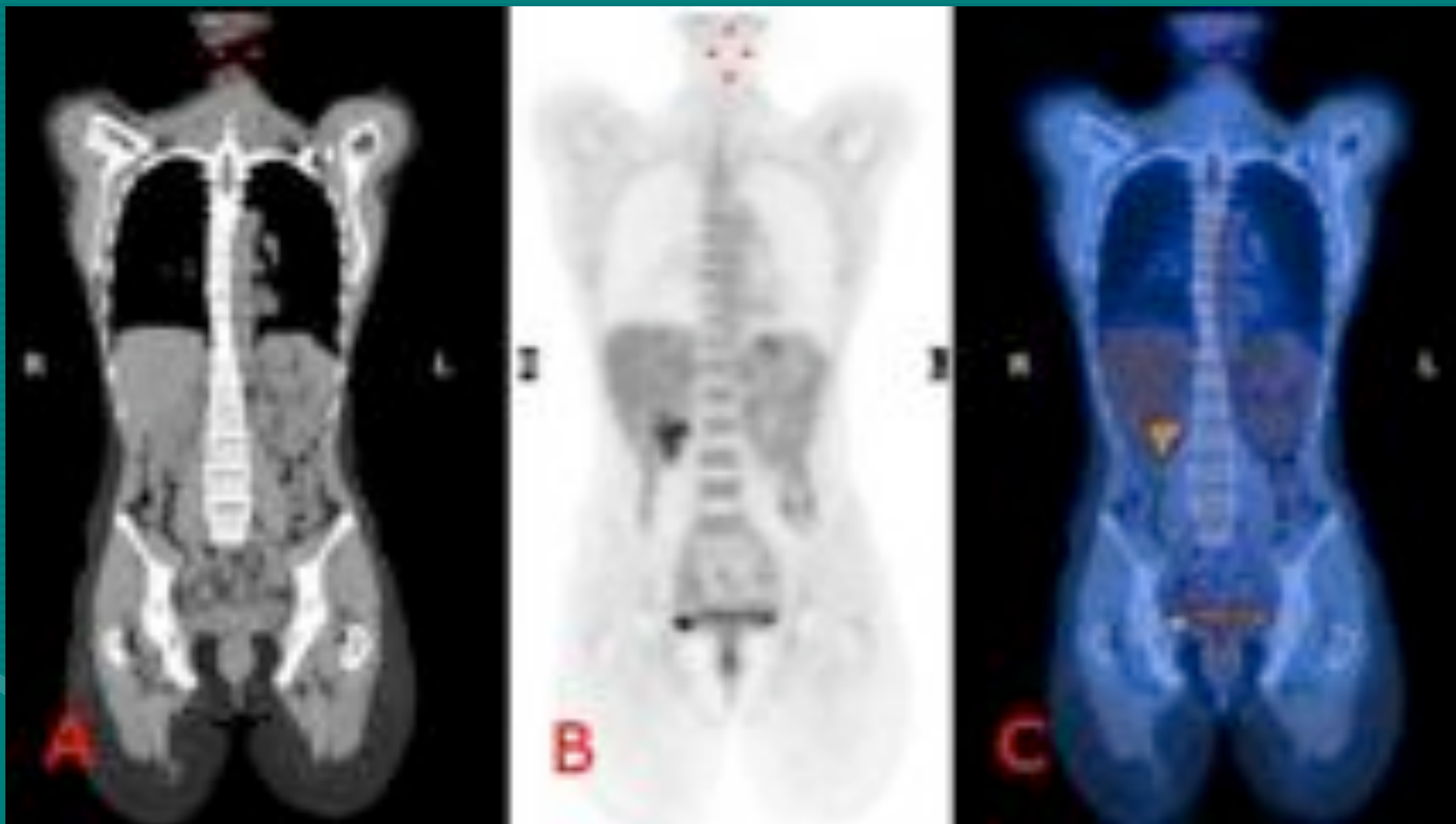
PET image



Composite CT/PET image

The CT image exhibits clear anatomical features while the PET image reveals the cancerous region. The composite image contains both the anatomical and cancer details to assist clinical diagnosis and treatment.

Fusion of Biomedical Images



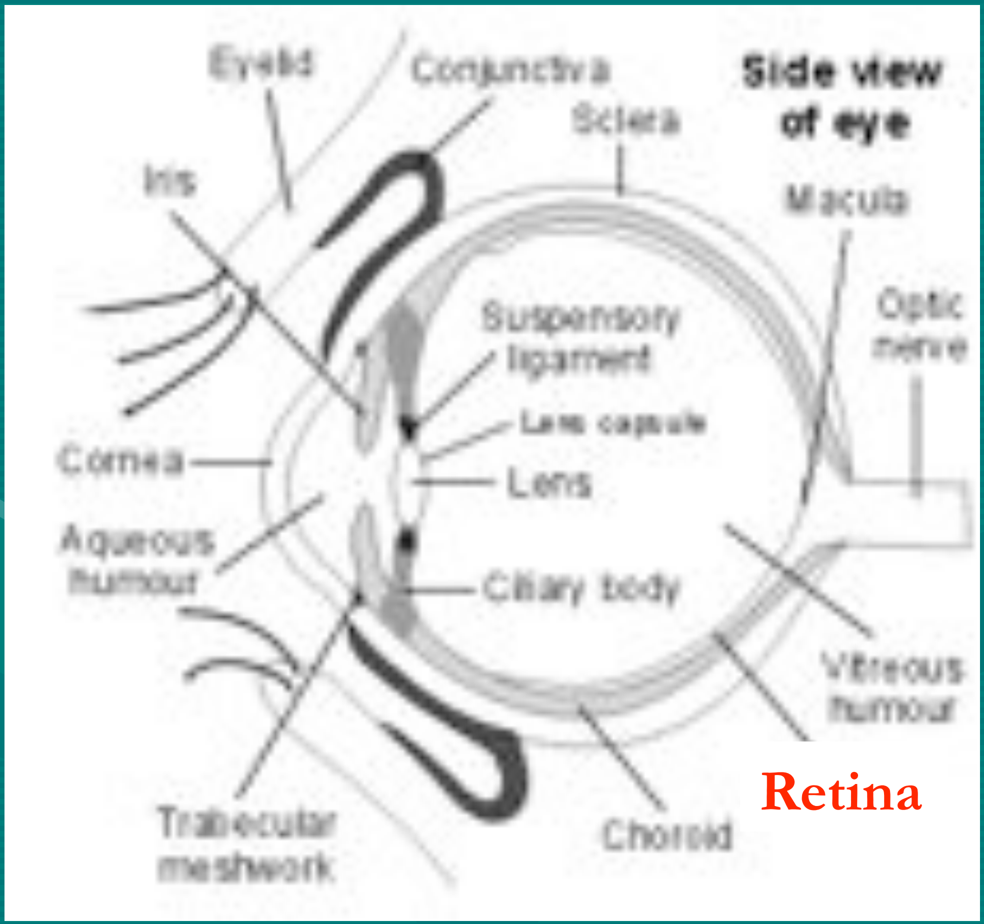
CT image

PET image

Fused CT and PET image

Introduction

- Retina



- The retina is a nerve layer that senses the light passing through the lens, sends it to the optic nerve, and then onto the brain.

- There are many blood vessels next to the retina, which take oxygen and nutrients to the cells of the retina.

Introduction (Cont.)

- Experimental Materials and Subjects

Modality 1 – Fundus color image

Modality 2 -IVFA grayscale image

Introduction (Cont.)

- The subjects of the retinal images were Cynomolgus monkeys of 4 to 4.5 years of age and 2.5 to 3 kg body weight with normal eyes.

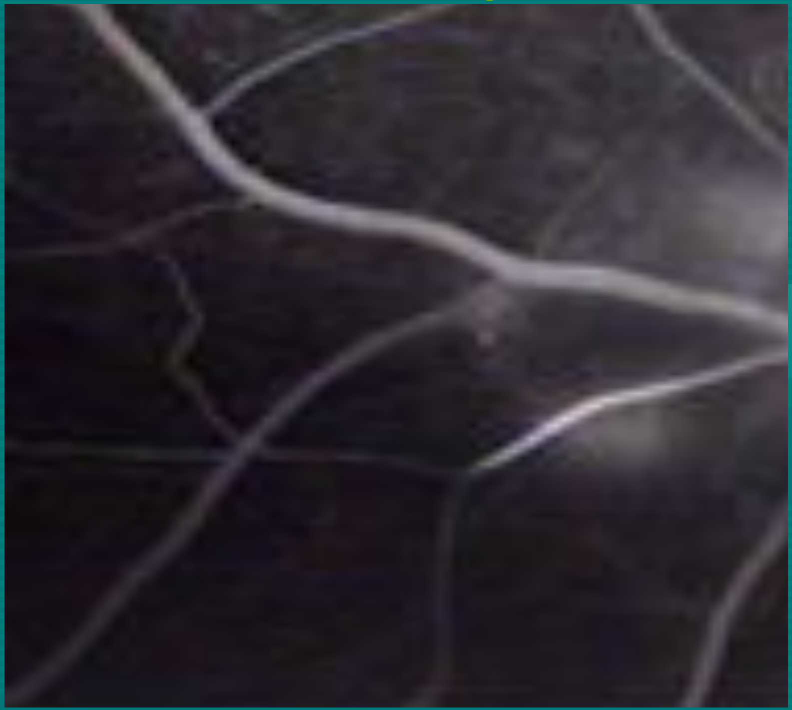
- The use of animals was approved by LSU Health Sciences Center Institutional Animal Care and Use Committee.

Retina Pathology Images

Fundus Image

The spots indicate ruptured blood vessels. Red spots are new blood, yellow spots are old blood

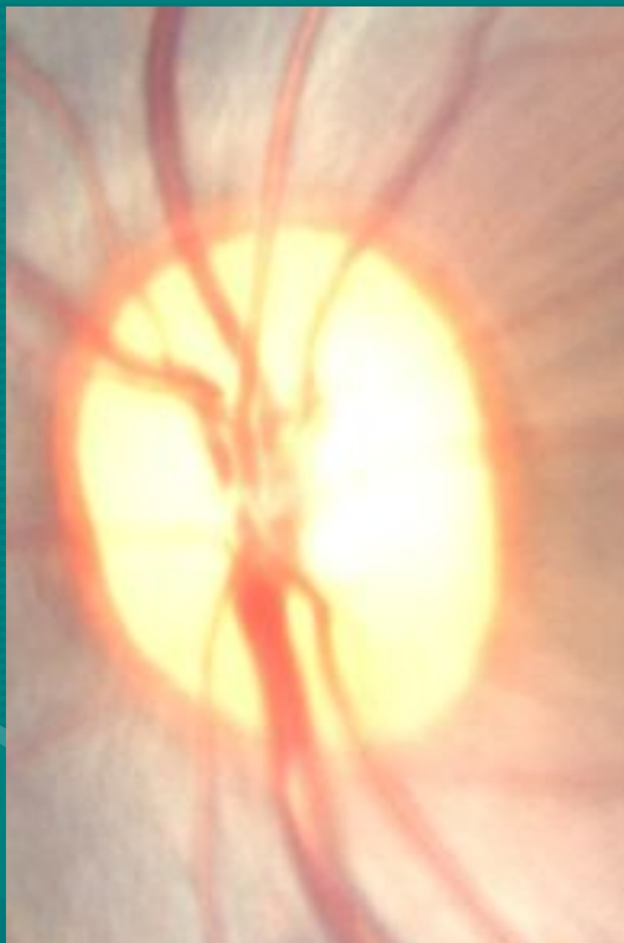
IVFA Image



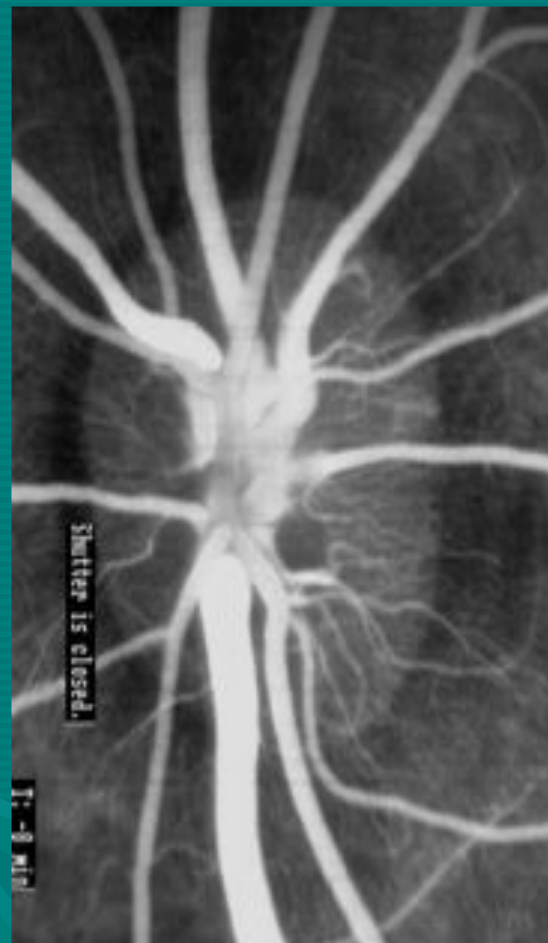
The bright areas indicate ruptured or blocked blood vessels

The ophthalmologist cannot tell where the Fundus pathologies and IVFA pathologies are located with respect to each other because they are on different images.

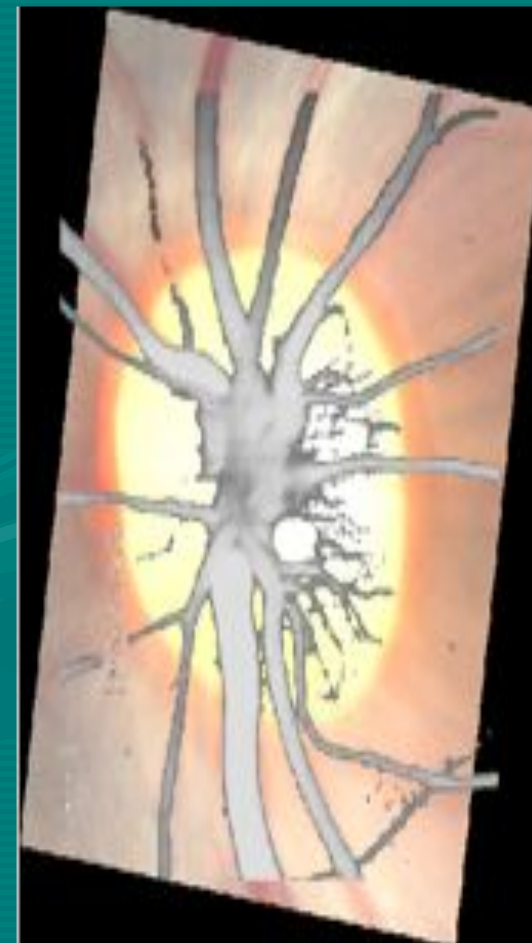
Fusion of Retinal Images



A



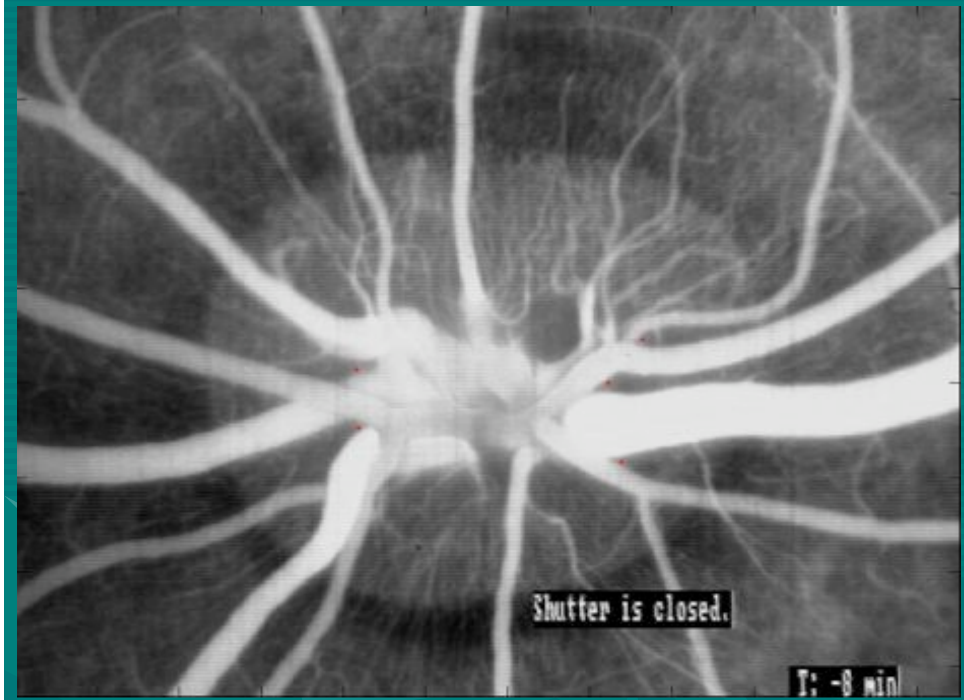
B



C

A and B are a Fundus and IVFA image, respectively, and C is the composite (fused) image of A and B.

Control Point Detection

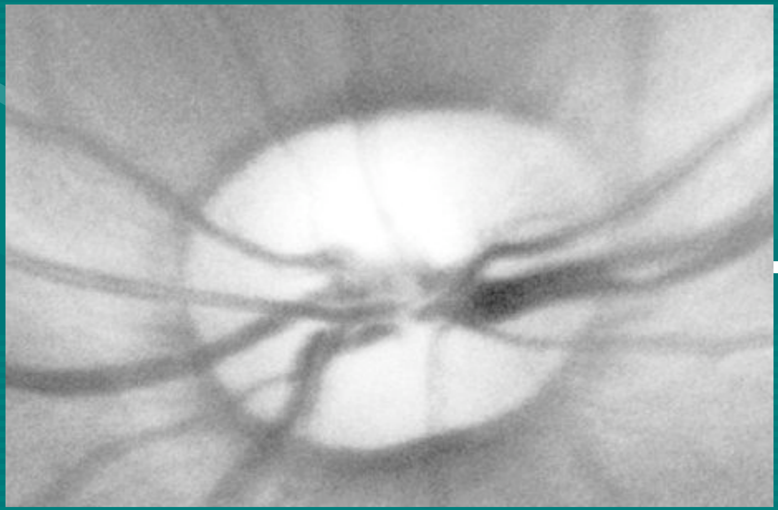


IVFA Grayscale Image

BW Image

Control Point Detection (Cont.)

Fundus Color Image

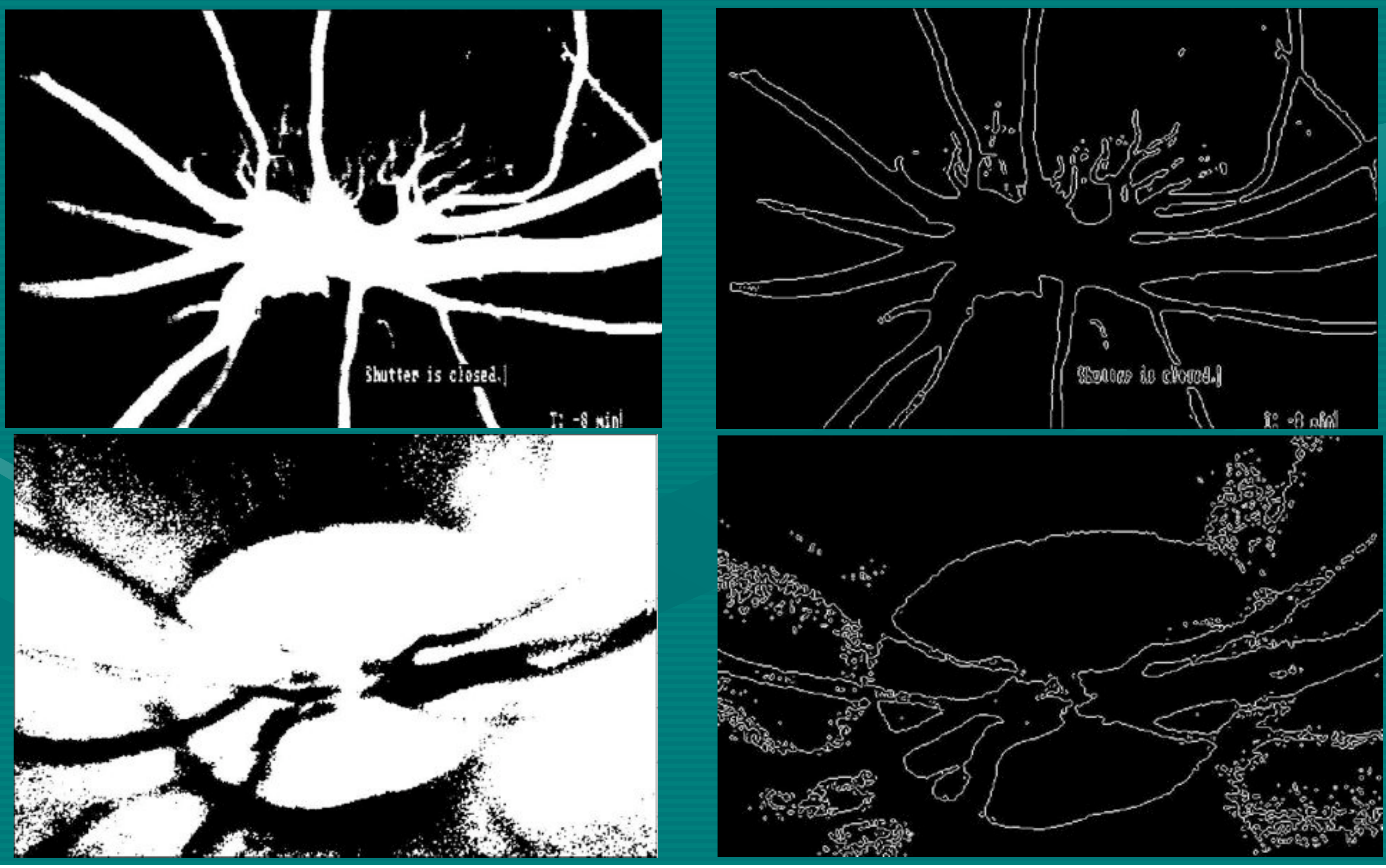


Grayscale Image

BW image

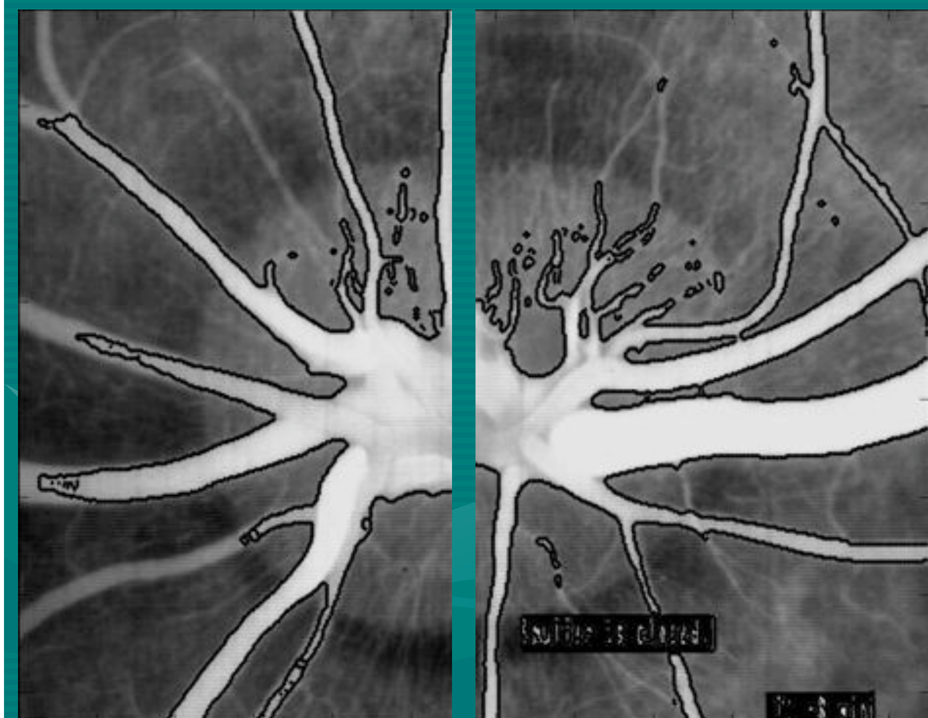
Control Point Detection (Cont.)

BW Image | **Canny Edges**

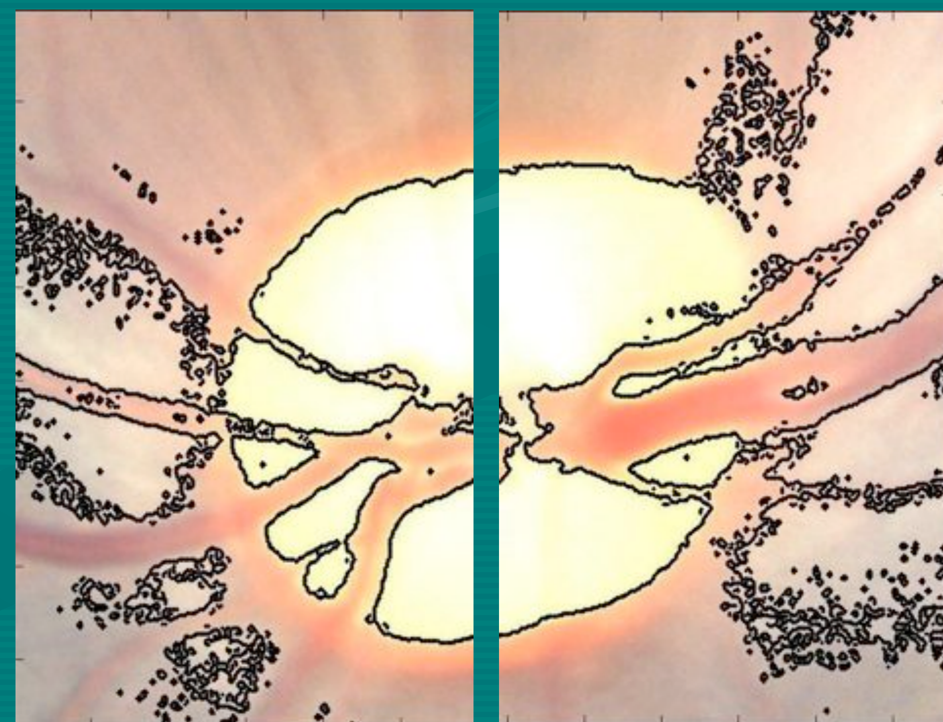


Adaptive Exploratory Algorithm

Reference Image

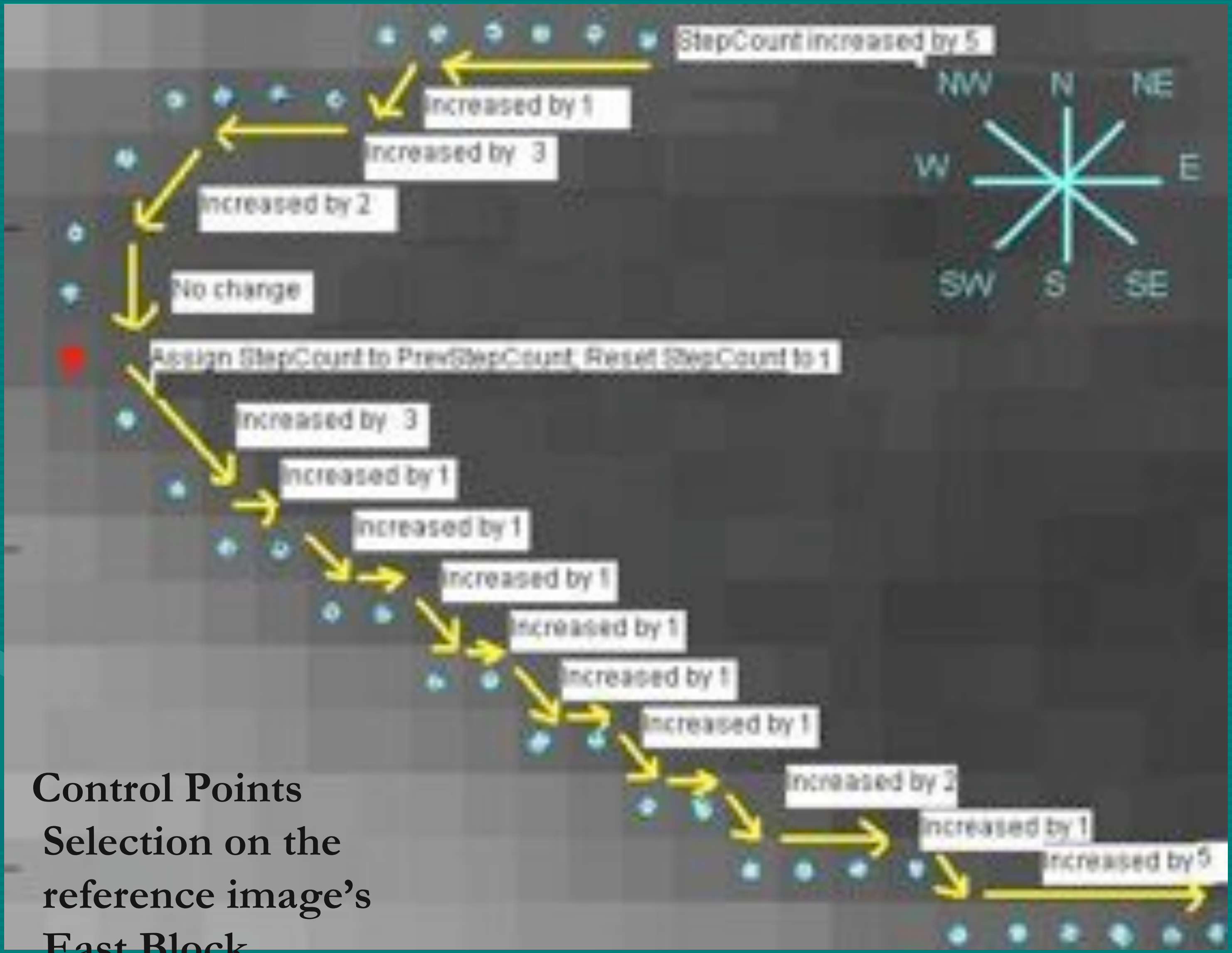


Input Image



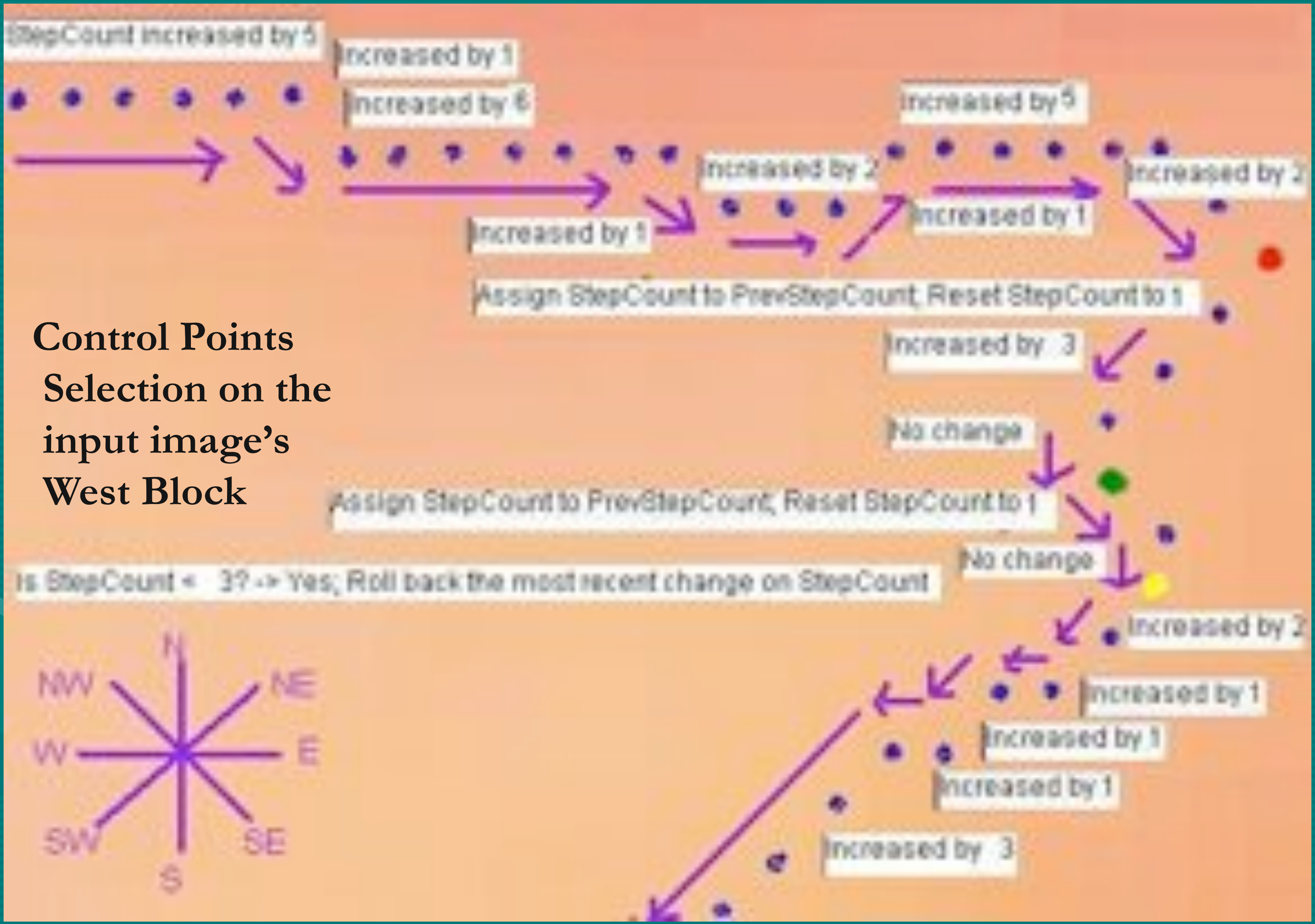
West Block East Block West Block East Block

Adaptive Exploratory Algorithm



Control Points Selection on the reference image's East Block

Adaptive Exploratory Algorithm

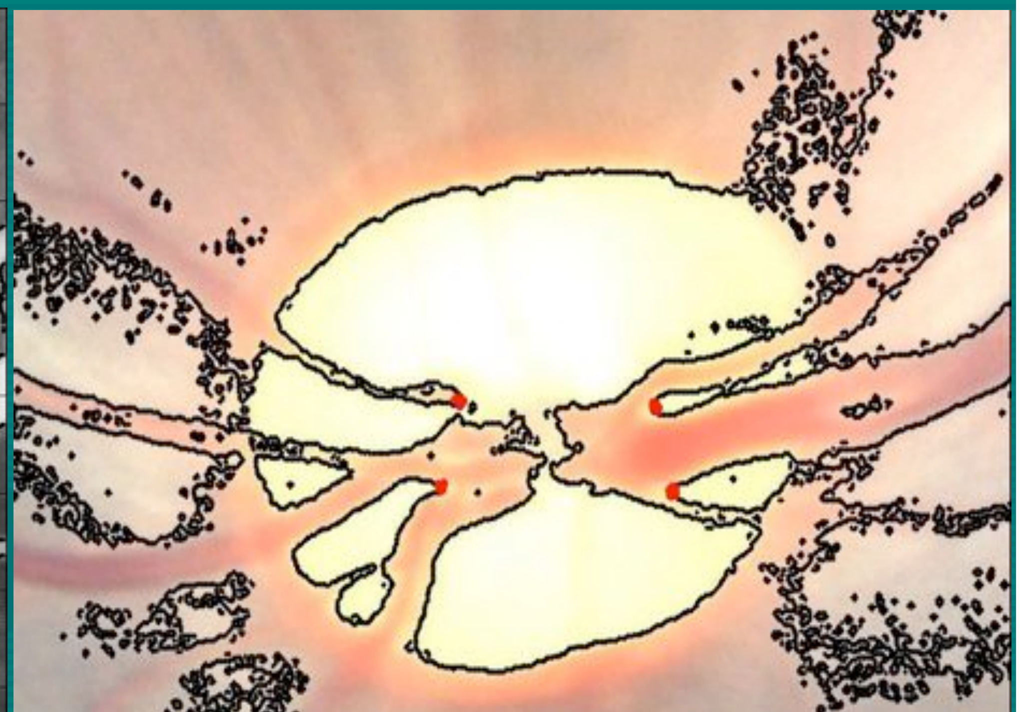


Control Points Selection on the input image's West Block

Control Points Selected by Adaptive Exploratory Algorithm

Control Points

5 control pointes selected



4 control points selected

Control Point Matching Algorithm

- The image registration model requires three pairs of corresponding control points.

- Suppose image I1 has n control points, and image I2 has m control points, and m < n, then m will be the number of control point groups. One pair of control points will be selected from each group.

- For each group, we calculate the distance |d| between the control point from I2 and all of the control points in I1 using $\sqrt{(x_1 - x_2)^2 + (y_1 - y_2)^2}$ The pair with minimum |d| is chosen as the control point pair for that group.

Control Point Matching Algorithm

- After a control point pair is selected from each group, the three pairs with the smallest distance |d| are chosen as the three pairs for the image registration model.
- Shape Similarity Criteria: The assumption to use distance as the measurement of the control point pair is that no huge rotation, shearing or translation occurs between the two images, thus, the same features on each image are close to each other.

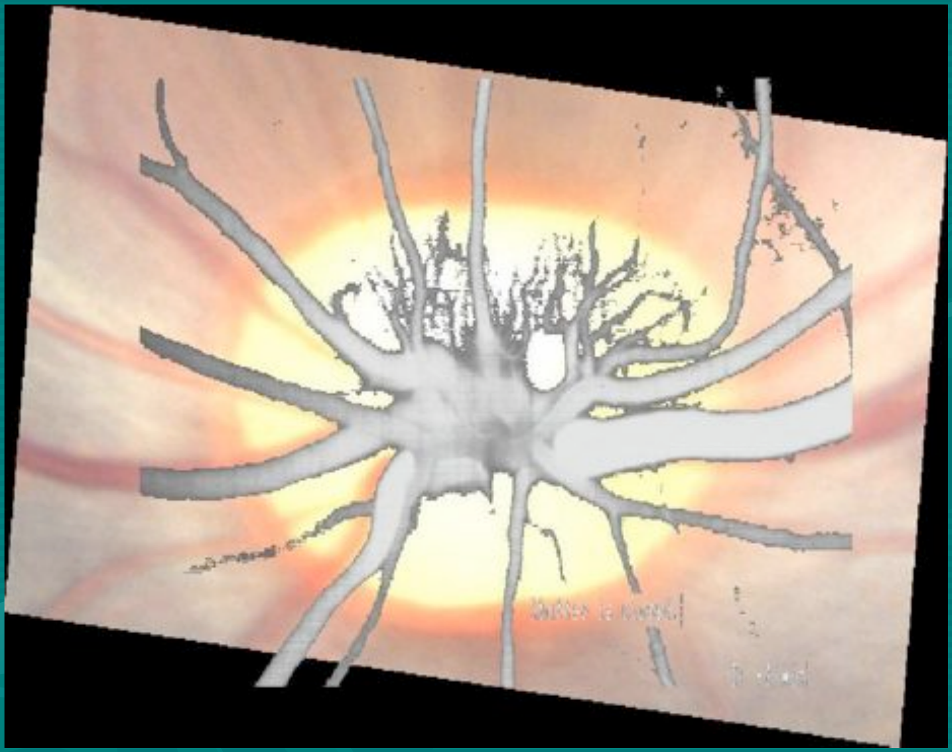
Image Registration Parameters

- **Computation of Parameters**

Once the coordinates of three pairs of control points are obtained, one can solve the following matrix equation to get the image registration parameters $\{a_1, a_2, a_3, a_4, b_1, b_2\}$.

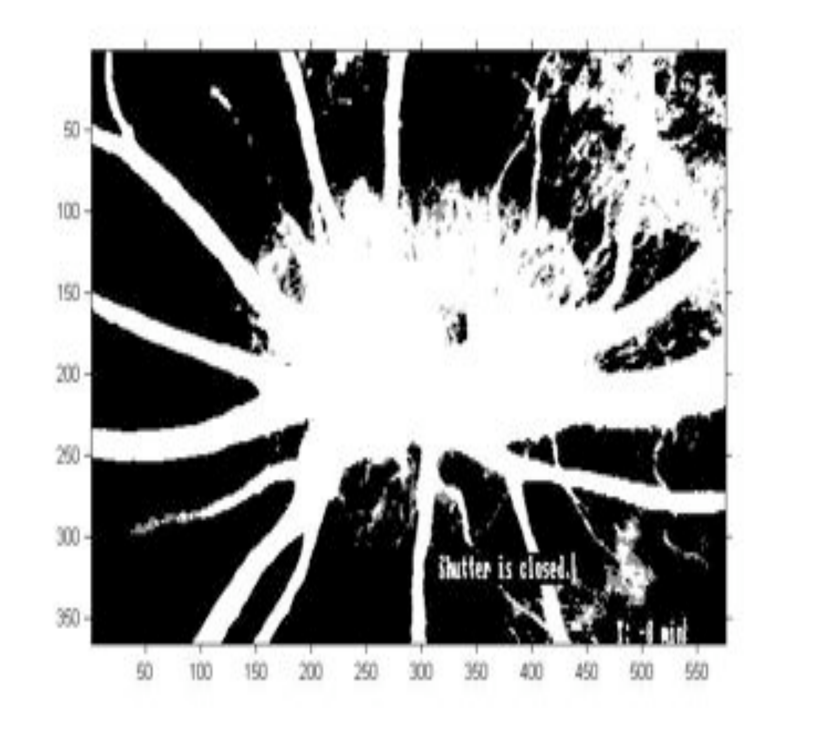
$$\begin{bmatrix} u_1 \\ v_1 \\ u_2 \\ v_2 \\ u_3 \\ v_3 \end{bmatrix} = \begin{bmatrix} x_1 & y_1 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & x_1 & y_1 & 1 \\ x_2 & y_2 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & x_2 & y_2 & 1 \\ x_3 & y_3 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & x_3 & y_3 & 1 \end{bmatrix} \begin{bmatrix} a_1 \\ a_2 \\ b_1 \\ a_3 \\ a_4 \\ b_2 \end{bmatrix}$$

Initial Image Registration

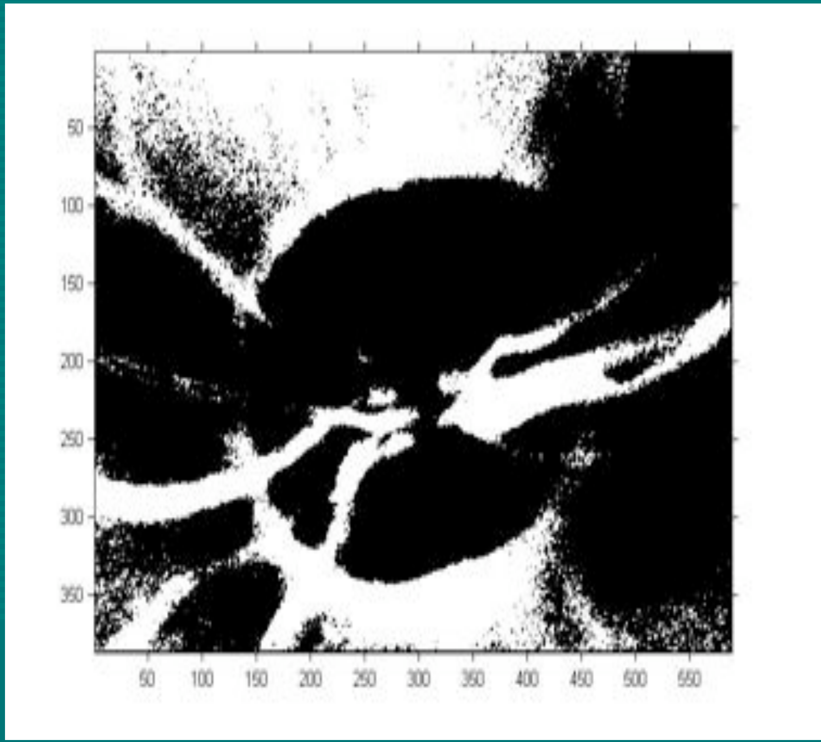


Fused image from initial control points selection

Mutual Pixel Count Algorithm



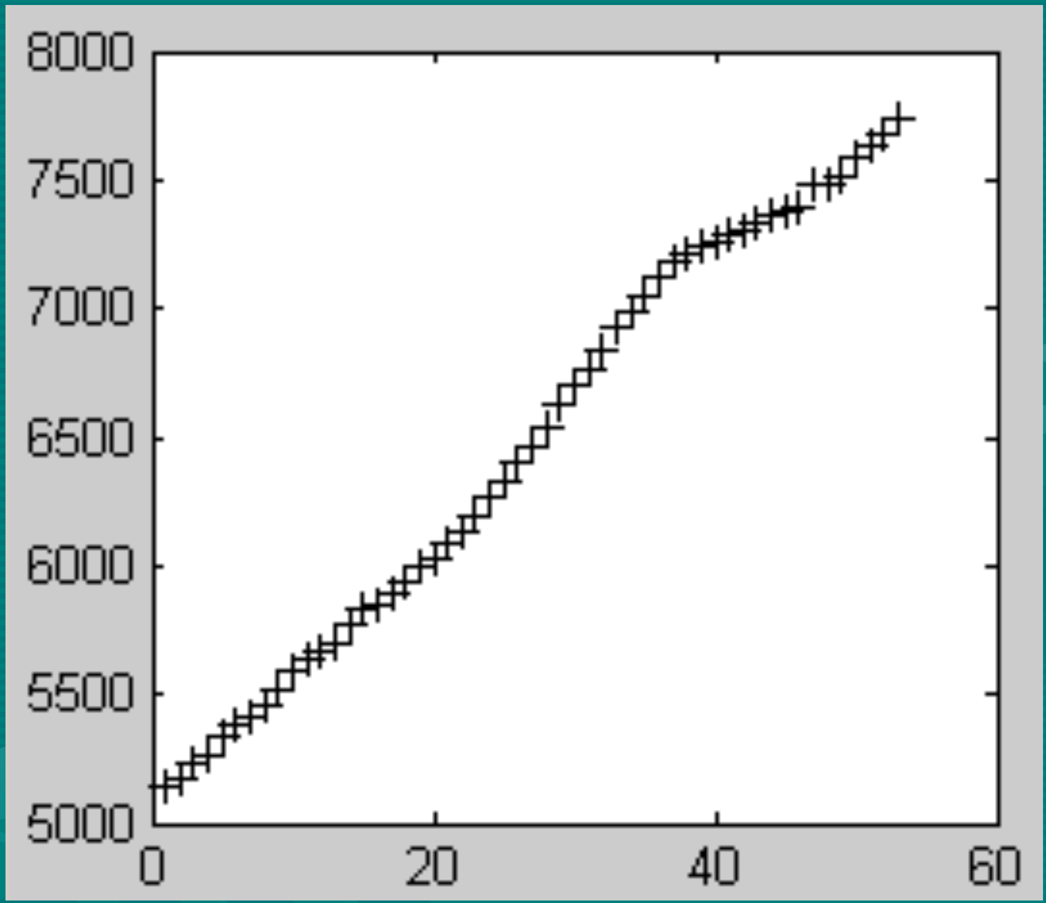
BW image of the IVFA grayscale image



BW image of the Fundus color image

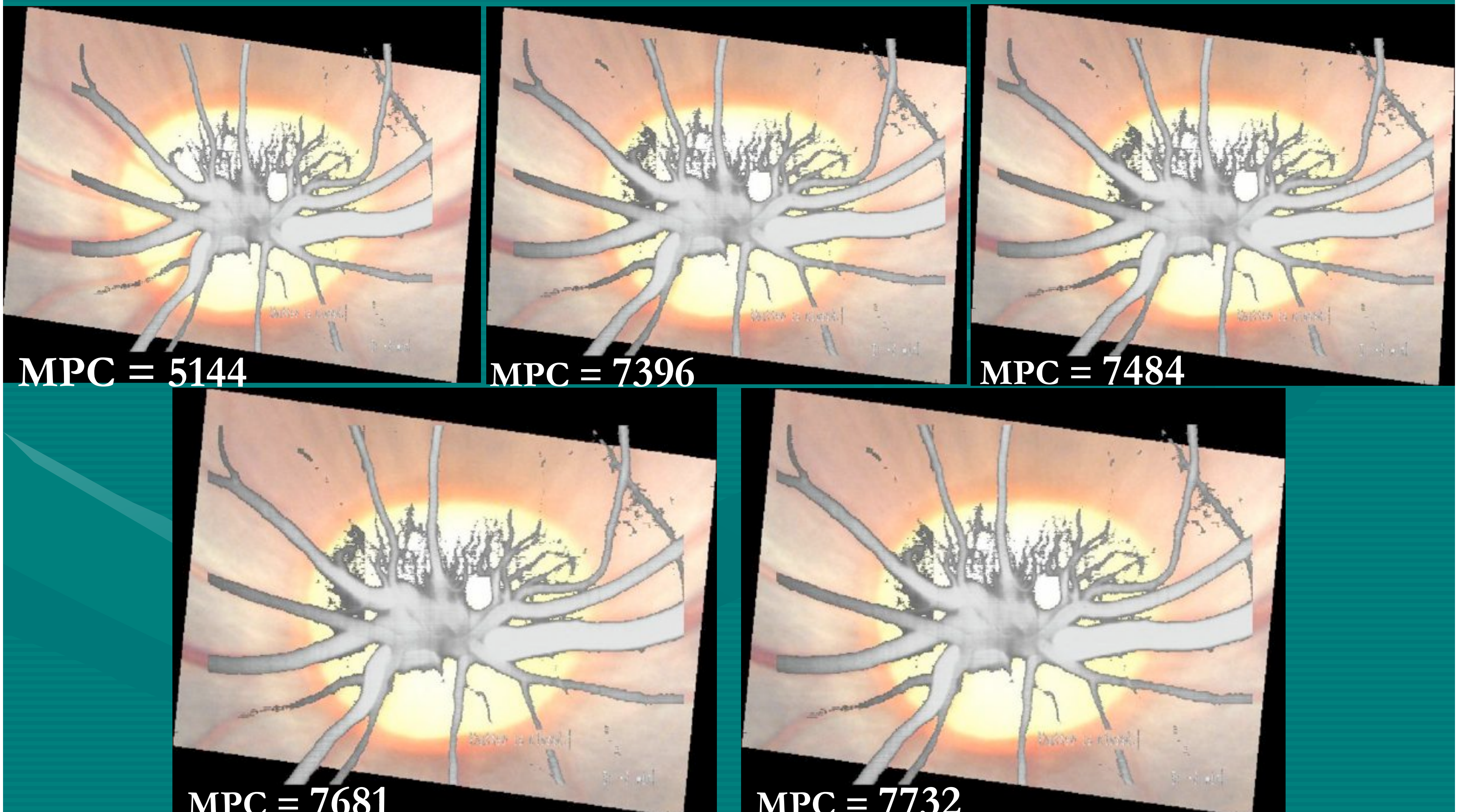
The calculation of the Mutual Pixel Count for these images is done iteratively to get the best fused image

Mutual Pixel Count Algorithm

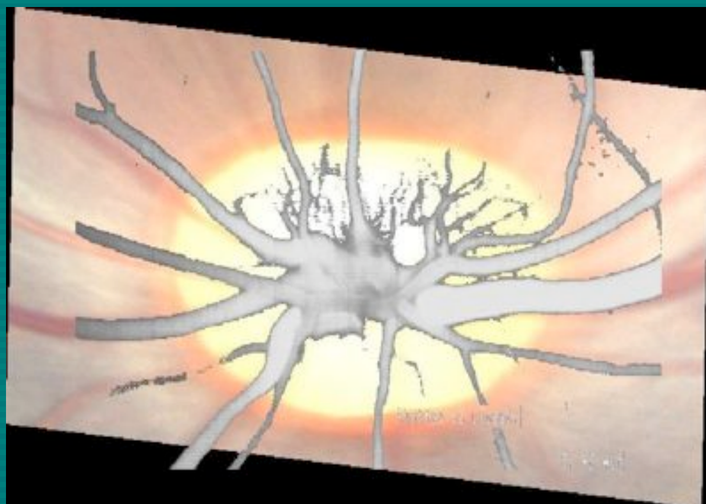


The Mutual Pixel Count (MPC) increases during the iterations

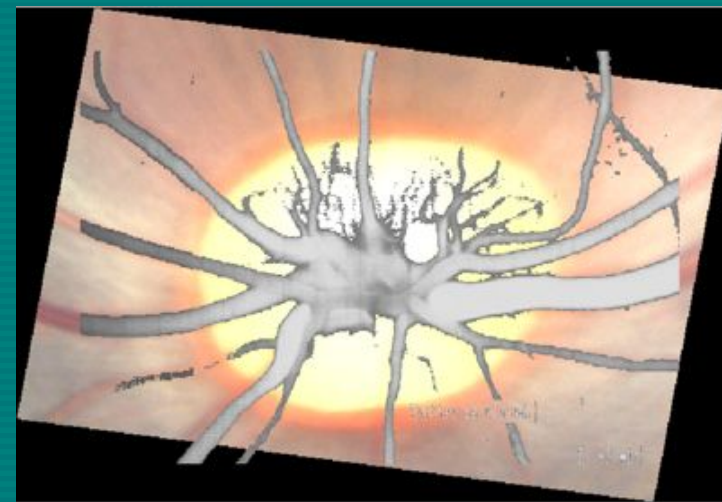
Mutual Pixel Count Algorithm



Comparative Analysis



Initial fused image by manual registration
(human interactive time is 2 minutes)



Fused image after manual adjustment
(human interactive time is 30 minutes)

Fused image by our automatic scheme (running time of 13 seconds)

Conclusion and Future Research Direction

- Fusing biomedical images is a challenging problem
  - Many different types of images
  - Non-uniform intensities of the involved images
- The proposed method is a promising step towards useful clinical tools for diagnosis of retinal disease
- The future plan is to extend the proposed method from monkey to human retinal images

Links to Work Packages

- Cybertools for Data Mining (WP1)
- Cybertools for Data Fusion/Visualization (WP3)

Implementation on LONI

- LONI Portal
- Queen Bee
- TeraGrid
- PetaShare

Education and Outreach

- Undergraduate Student Training
  - Academic year projects
  - Summer research programs
- Graduate Student Training
  - MS, PhD projects
  - Multi-institutional thesis/dissertation committees
  - Summer internships
- Outreach
  - Provide research results to scientific communities and public audiences
  - Make cybertools available to the scientific community

Publications

1. K. Manikandan, Debnath Pal, S. Ramakumar, Nathan E. Brener, S. Sitharama Iyengar and Guna Seetharaman, "Functionally Important Segments in Proteins Dissected Using Gene Ontology and Geometric Clustering of Peptide Fragments", Genome Biology, Vol. 9, Issue 3, article R52 (2008).

2. H. Cao, N. Brener, H. Thompson, S.S. Iyengar and Z. Ye, "A Novel Automated Retinal Image Fusion Using Adaptive Exploratory Algorithm and Mutual Pixel Count Maximization", IEEE 40th Southeastern Symposium on System Theory, New Orleans, LA, March 16-18, 2008, p. 122.

3. H. Cao, N. Brener, H. Thompson, S.S. Iyengar and Z. Ye, "Automated Registration and Fusion of the Multi-Modality Retinal Images", IEEE 40th Southeastern Symposium on System Theory, New Orleans, LA, March 16-18, 2008, p. 371.

4. Hua Cao, Nathan Brener, Hilary Thompson, S.S. Iyengar and Zhengmao Ye, "Automated Control Point Detection, Registration, and Fusion at Fuzzy Retinal Vasculature Images", 17th IEEE International Conference on Fuzzy Systems (IEEE-FUZZ 2008), Hong Kong, China, June 1-6, 2008 (to appear).

Questions or comments?

Science Drivers Environmental Transport

Gabrielle Allen (LSU), Ram Iyengar/Nat Brener (LSU)

SCOOP, UCOMS, COMI, CERA, …

Motivation

- "… ability to couple models, invoke dynamic algorithms, locate appropriate data and computational resources, and create necessary workflows on demand"
- "… influence and adopt CyberTools, improve storm surge forecasting, and its broader impact on event-driven computing scenarios''

Objectives:

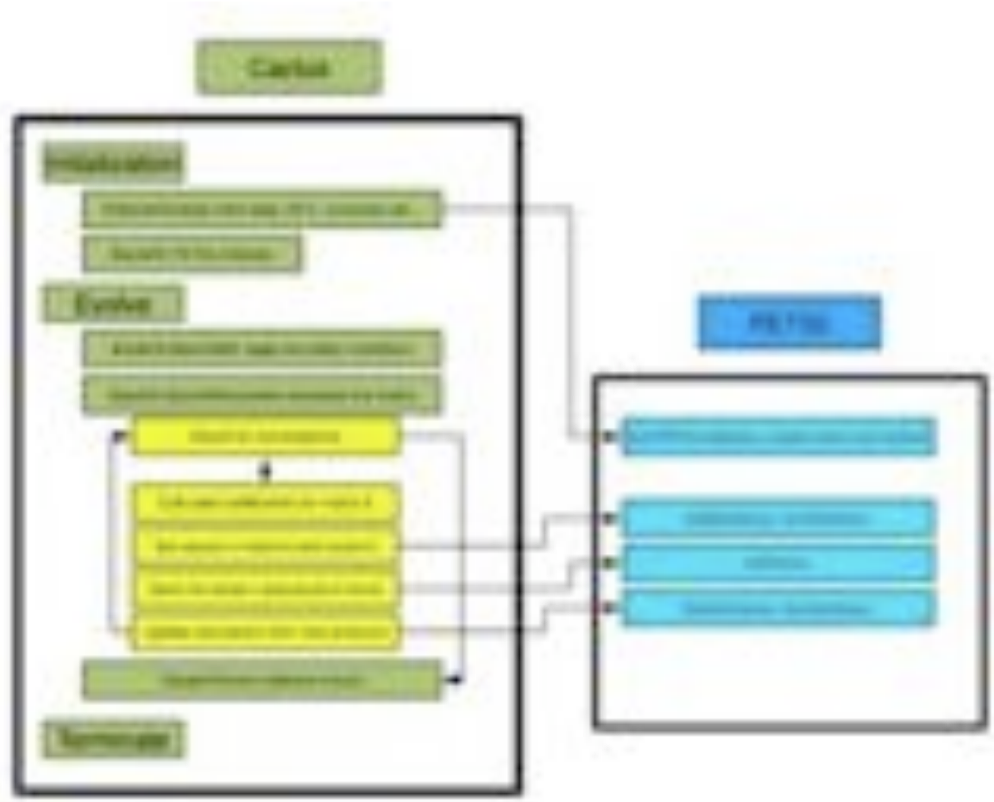
1. DDDAS Support (on-demand algorithms and infrastructure)
2. Decision Support Algorithms

People

- Gabrielle Allen, Nat Brener, Tevfik Kosar
- Students: Jiang Lei (Fall08), Jagadish Kumar
- Associated
  - SCOOP Team (particularly Archit) *On-demand*
  - UCOMS Team (particularly Dr Chris White, Dr Mayank Tyagi) *Ensembles, MultiPhase Flow in Porous Media*
  - COMI Team (Dr Jim Chen, Dr Mayank Tyagi, …) *Shallow Water Equations*
  - CERA Team (Dr Robert Twilley, Carola Kaiser, …) *Hurricane Predictions for State*
  - Undergraduates: Alex Clary (ECE), Alex Nagelberg (CS), John Lewis (CS), Razvan Carbunescu (CS), Elena Caraba (Math)

Multiphase Flow in Porous Media

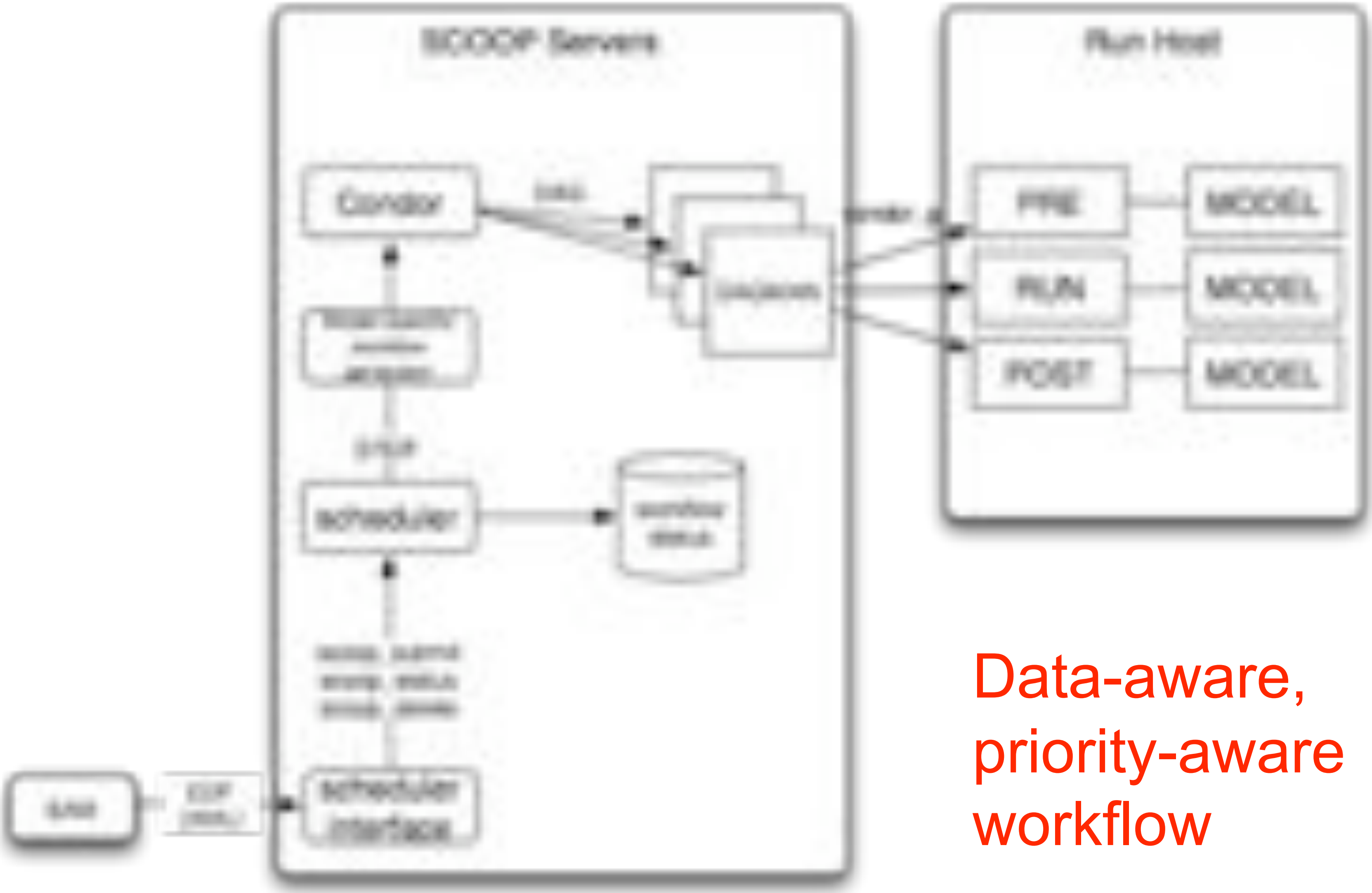
- DOE UCOMS Project
- Developing Black Oil toolkit ir Cactus Framework
  - Black oil: three phases (oleic, aqueous, vapor), three components (oil, water, gas). Water & gas are immiscible. Gas soluble in oil but not in water. Fluids in thermodynamical equilibrium.
  - Solver: IMPES (Implicit pressure, explicit saturation). PETSc used for pressure equation.
  - Aim: highly parallel, high throughput, access to Cactus and CyberTools tools.
  - 3D cartesian, structured grid, cell-centered



Shallow Water Equations

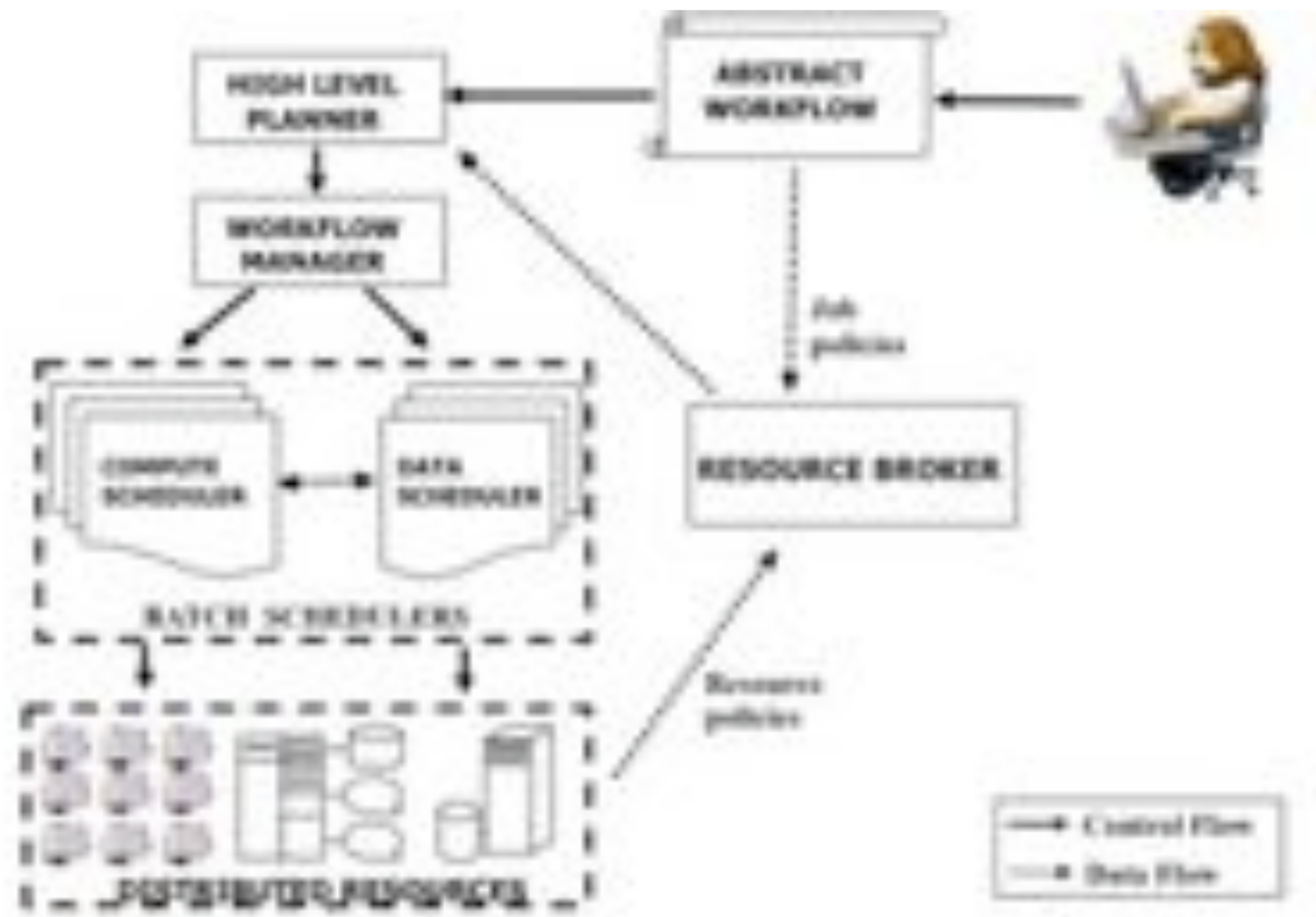
- COMI Project: Boussinesq equations, incorporating new science terms for shallow water flow in muddy waters
- Track 1: Importing FUNWAVE model into Cactus
  - Uses existing tools/components
  - 2D (depth averaged), structured cartesian grid, finite difference, explicit. Want to get parallelization, I/O, AMR, access to CyberTools.
- Track 2: New code
  - 2D (depth averaged), spectral-element methods on unstructured grids, will use DG (hp-adaptivity)
  - Driving Cactus UG development (end of summer)

SCOOP Workflow

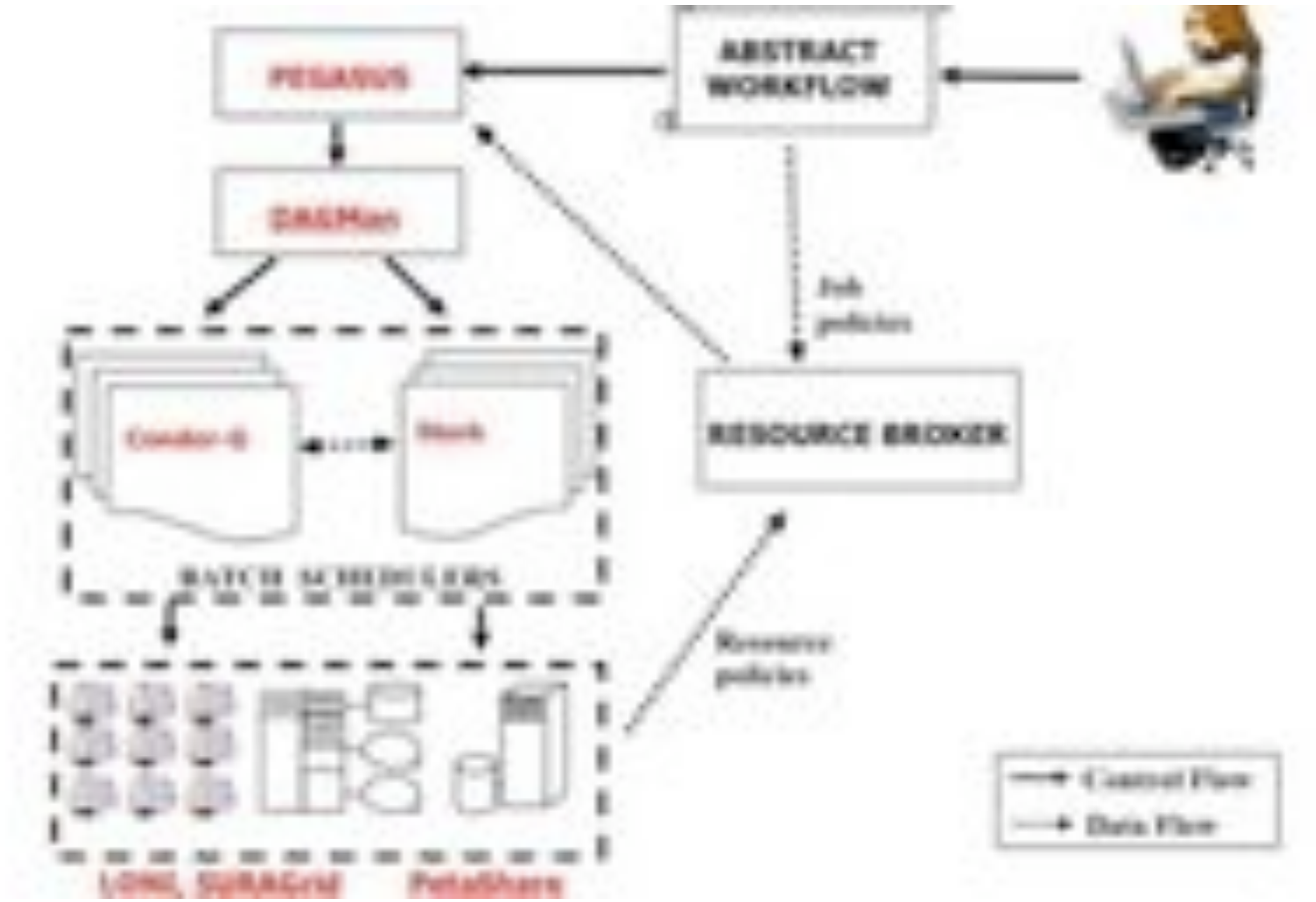


Data-aware,
priority-aware
workflow

UCOMS Workflow



UCOMS Workflow



On-Demand and DDDAS

- Scheduling algorithms for urgent/priority computing (Archit, Jiang)
- Algorithms for ensemble modeling (Jagadish)
- Verification/assimilation with live sensor data
- Use of e.g. SPRUCE Urgent Computing Tokens, HARC (Swathi/WP1)
- Integrating COMI and CERA models into SCOOP cyberinfrastructure.

Connection to WPs

- WP1: SCOOP, UCOMS workflows (Globus, Condor, Spruce, PetaShare, …, HARC)
- WP2: Leveraging work in existing portals for SCOOP, UCOMS
- WP3: Providing data for viz. Undergrad students working with WP3 (Jinghua Ge). Geospatial data (e.g. Google Map, MapServer integration), terrain rendering.
- WP4: Providing unstructured mesh, AMR, spectral element. Existing components feeding into Application Manager design. Cactus-SAGA interface.
- Other science drivers: Mayank is main interface

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Cybertools WP4: Status and Plans

S Jha, M Tyagi

WP4: The Vision

- Capture and analyze the application characteristics and requirements of the science drivers
- Facilitate the use of computational infrastructrure, including but not limited to LONI, for advancing science
  - In the short-term (6-12 months): help deploy applications and the design of tools to facilitate utilisation of infrastructure
  - In the longer-term (1-3 years): design of application managers and toolkits – that abstract the common requirements and usage modes of applications
- Work not only with Science Drivers to provide direct support, but also interface with other Cybertool WPs

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WP4: Personnel

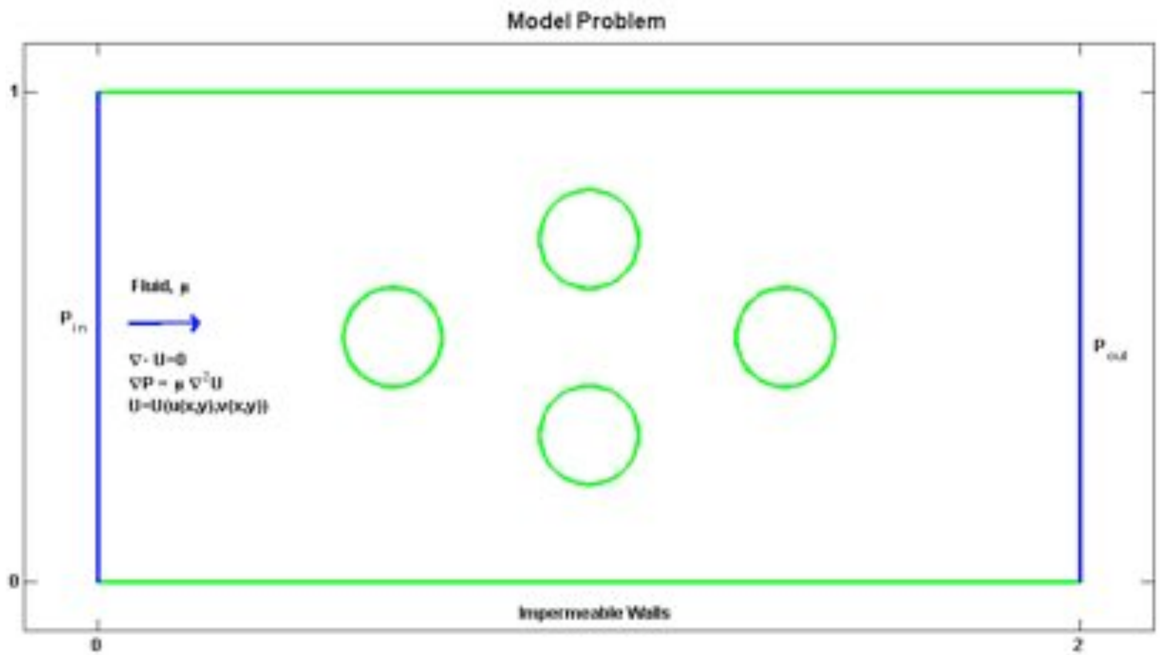
- Science Drivers:
  - Steve Soper, Dimitris
  - Sumanta Acharya
  - Don Gaver, Jerrina Pillert, Dave Halperin
  - Tom Bishop
  - Gab Allen, Erik Schnetter
- HPC/LONI/CyD:
  - Honggao Liu (LONI)
  - Dan Katz and Tae-Woo Lee (CyD)
  - Joohyun Kim, Hartmut Kaiser (Software Architect)
- To come on board
  - Joao Abecasis (SAGA GA), 1 Cactus-SAG GA (TBD)
  - 2 post-docs (positions open, TBD)

WP4: Connection to SD (1)

Simulate Microfluidic Mixing Chamber

- Microfluidic Mixing Chamber:
  - Characterize the **flow field** with internal objects
  - Track antibody concentration by solving **transport** (reaction-convection-diffusion) equations
  - Modify geometries to **optimize mixing**
- Current WP4 efforts involve assisting with the parallelization (Tyagi)
- Near term goal: Use this as the model problem for the BEM component of the CFD toolkit

WP4: Connection to SD (2)
Model Microchannel Problem



- 2D channel with internal cylindrical obstacles
- Constant pressure drop across the channel
- Flow field described by Stokes & continuity equations
- Boundary Element Method (BEM) used to determine velocities and surfaces stress

WP4: Connection to SD2 Hybrid MD/Continuum

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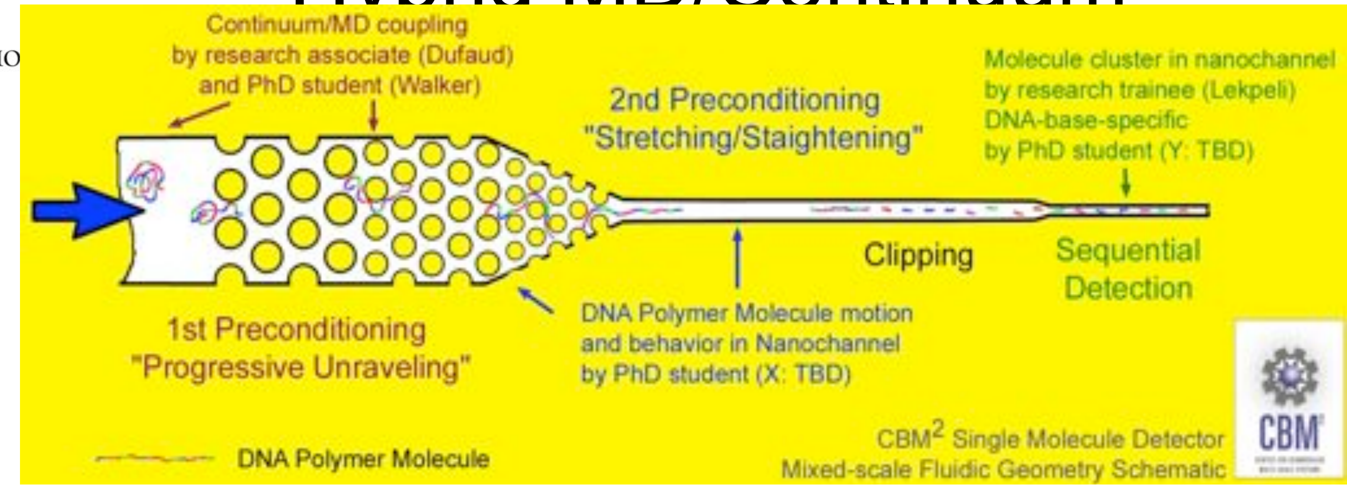
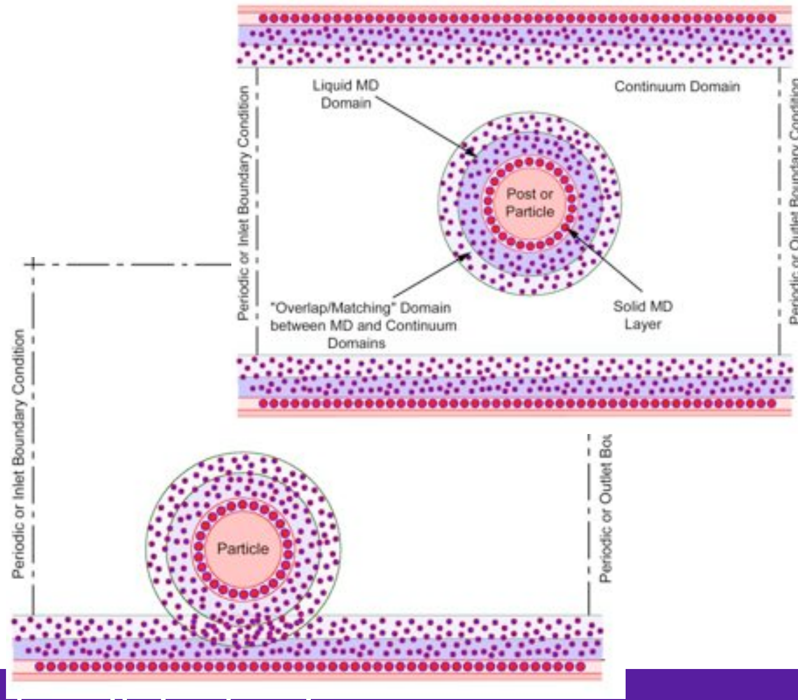


- CFD Aspects (Details in the following slide)
- MD aspects (Recap: The process by which one generates the atomic trajectories of a system of N particles by direct numerical integration of Newton's equations of motion with appropriate specification of an interatomic potential and suitable initial boundary conditions)
- Coupling issues (Discussions and planning stage)



WP4: Connection to SD2

General Solution Methods (CFD)

- Solution Schemes (2nd order in time and space)
  - Velocity:
    - Spatial Discretization (2nd order central differences)
    - Use of MultiGrid method to solve resulting linear system
    - Use of Domain Decomposition (DD) to better balance multi-grid operational and communications loads
    - Use dual Schur complement DD method
      - Obtain solution on sub-domain interfaces by solving Schur complement systems
      - Find Lagrange multipliers to satisfy solution continuity on interfaces
      - Solve Schur complement and Lagrange multiplier linear systems using Conjugate Gradient Method
      - Obtain solution inside the sub-domains by directly solving the local problem in each sub-domain
    - Conjugate Gradient Method: Solve linear system iteratively by minimizing the quadratic functional of the residual in Krylov subspace for each iteration
- Parallelization in two dimensions using MPI

Indicates an "existing" or "easy to modify" type capability

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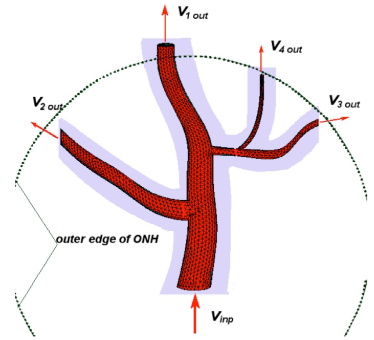
WP4: Connection to SD3
Biotransport Computation



- Main driver for “multi-block and finite volume method”
- Mesh generation is handled by commercial packages.

Continuum flow and transport calculations

- Multiblock structured grid with continuous grid lines across block interfaces
- Fractional step algorithm with staggered grid locations for the velocity (stored at cell faces)
- Pressure-poisson equation for pressure
- Consistent second order differencing for diffusion and pressure terms and upwind biased differencing for the convective terms
- Explicit and implicit second order temporal differencing
- Flow-Structure interaction
- Particle-based meshless calculations for structural deformations (called material point method-MPM)
- Immersed Boundary Methodology (IBM) for resolving boundary conditions along moving interfacial surfaces

Non-continuum Effects

- Atomistic (Molecular-Dynamics) simulations of particle/molecule transport across cellular interfaces
- Upscaling or coarse-graining calculations for averaged property information needed for continuum calculations

A Model Problem (SD2 and SD3)
Driven-Cavity Flow

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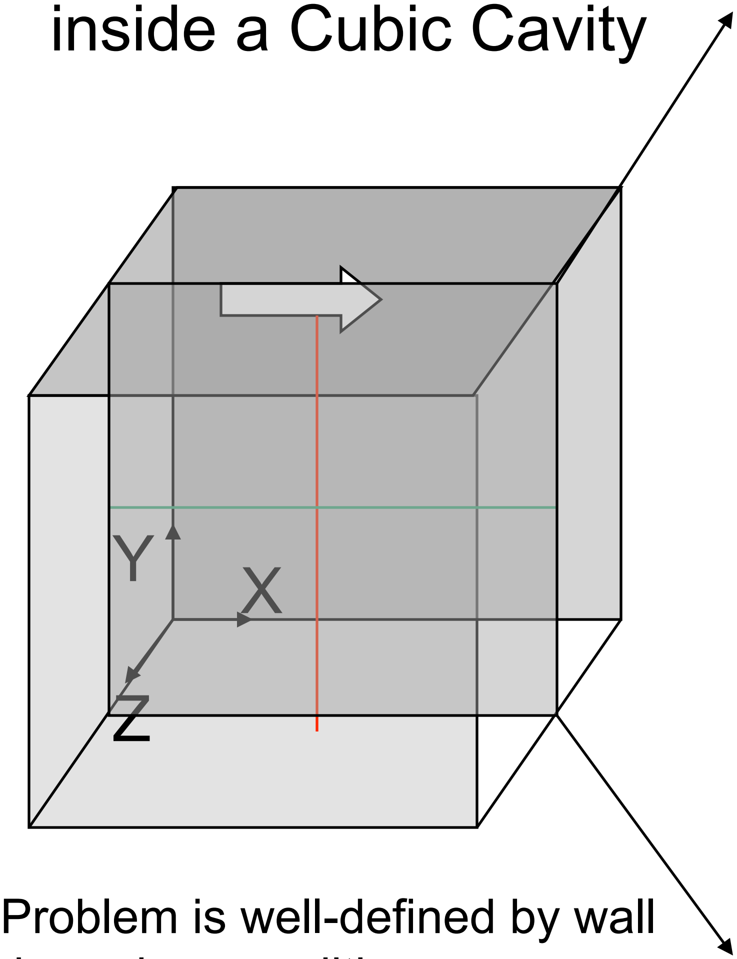
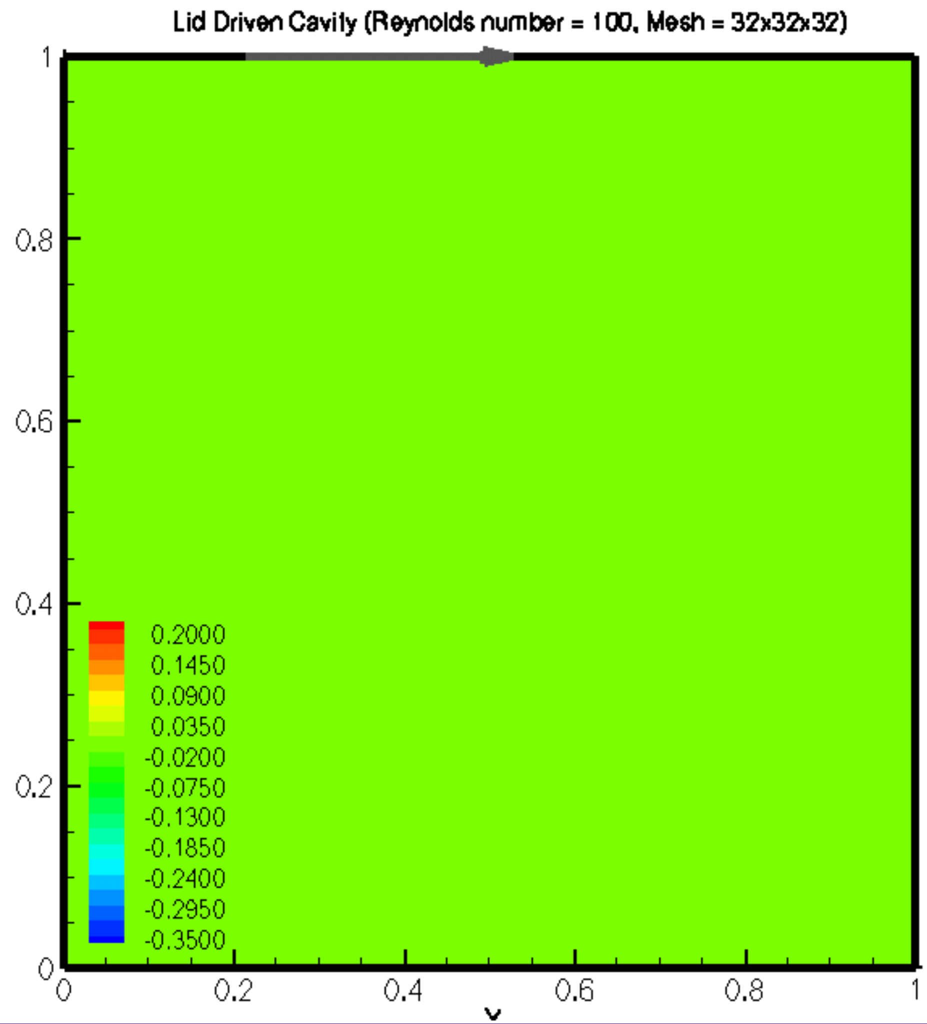
Moving Lid Drives the Flow inside a Cubic Cavity





Problem is well-defined by wall boundary conditions

WP4: Connection to SD4 Environmental transport

- Main driver for “unstructured mesh and numerics” support for the cactus toolkit.
- Leverages significant development from the COMI project into the cybertools project.
- Development of spectral element library interface along with unstructured mesh support will enable h-p refinement capabilities for coastal applications.
- SCOOP (On-demand)
- CERA
- UCOMS

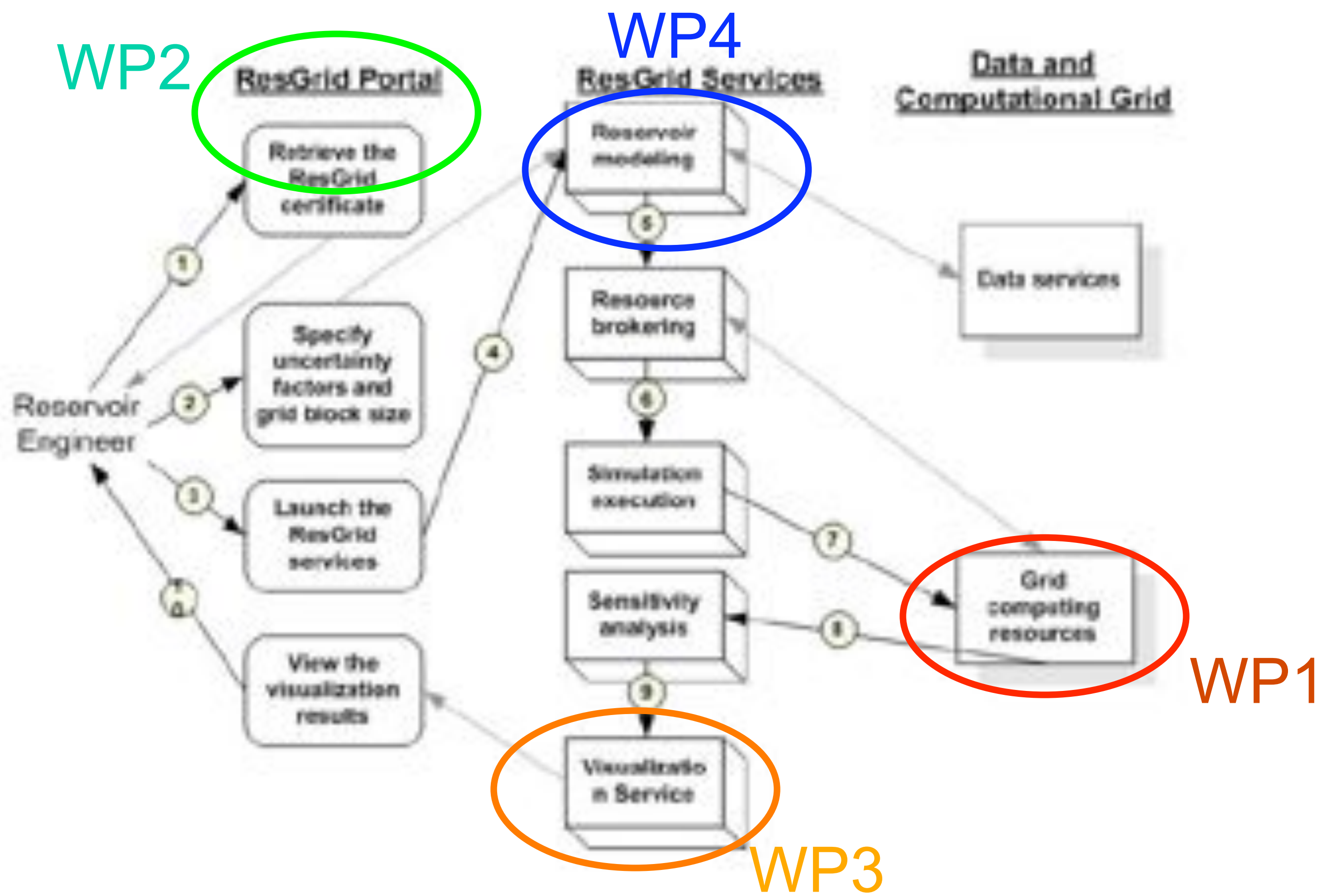
Connection to other WP

- WP1 (Scheduling and Data Services):
  - Working with WP1 team to define infrastructure and deployment requirements (eg Globus, SAGA etc.)
  - Facilitating high-throughput MD and other simulations with data-intensive, complex data-management needs (Bishop, Tulane)
- WP2 (Info Services and Portals):
  - Application Manager(s) developed using SAGA etc., will integrate with portal and gateway development
- WP3 (Visualization Services):
  - Still exploring, but SAGA will provide "application level" interface to Visit, Wish etc.,
    - e.g., Merzky presented first draft of message API

Leveraging other funded projects

- NSF-SDCI (ALPACA: Application level performance, correctness & accuracy assessment PI: Schnetter, co-PI: Allen, Tyagi) Eclipse PTP and parallel debugging integration with Cactus framework.
- NSF (XiRel: AMR and scaling to large number of processors for astrophysical flow codes PI: Allen, co-PI: Schnetter)
- DOE (UCOMS: Ensemble simulations, workflows, data management, integrations of sensor data (experimental) with the computations using Cactus-BlackOil, PI: White, co-PI: Allen, Kosar, Tyagi)
- ….More

Example: ResGrid UCOMS (SD4: Environmental Transport)



Work Package - I
Scheduling and Data Services

Tevfik Kosar, Sumeet Dua et al

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The Team

- Senior Personnel: Allen, Brenner, Katz, Kosar (LSU), Dua, Box (Tech)

- WP-1 Funded Personnel:

  Postdoc-1 (Kosar/Allen) : Krzysztof Rzadca
  Postdoc-2 (Dua) : TBD
  Grad-1 (Katz) : Promita (50%), Swathi(50%)
  Grad-2 (Box) : Thanadech
  Grad-3 (Iyengar) : Jagadish (50%), Rathika (50%)

- WP-1 Supporting Personnel:

  LONI: Prats, Honggao
  CCT: Archit (HARC), Shantenu(Task farming), Andrei (Data/Viz)
  Other: Vinay, Ibrahim, Jack, Ismail, Emir, Mehmet, Esma, Sirish

WP1 in a Nutshell

- Motivation: Enable domain scientists to focus on their primary research problem, assured that the underlying infrastructure will manage the low-level cpu scheduling and data handling issues.
- Use Case: A domain scientist should be able do:
  - Submit a simulation with a single click
    - Which may run on hundreds of processors across the state & access distributed data
  - Get informed when results are ready
- All low level details should be transparent to the domain scientist

Low Level Issues

- Select suitable resources
  - Arch, SW, availability
- Interact with different schedulers
  - PBS, LoadLeveler, Condor
- Advance reservations & preemptions
- Co-allocation of multiple resources
  - CPU, network, storage
- Access data at remote/multiple sites
- Recovering from failures
- Efficient & easy extraction of useful data

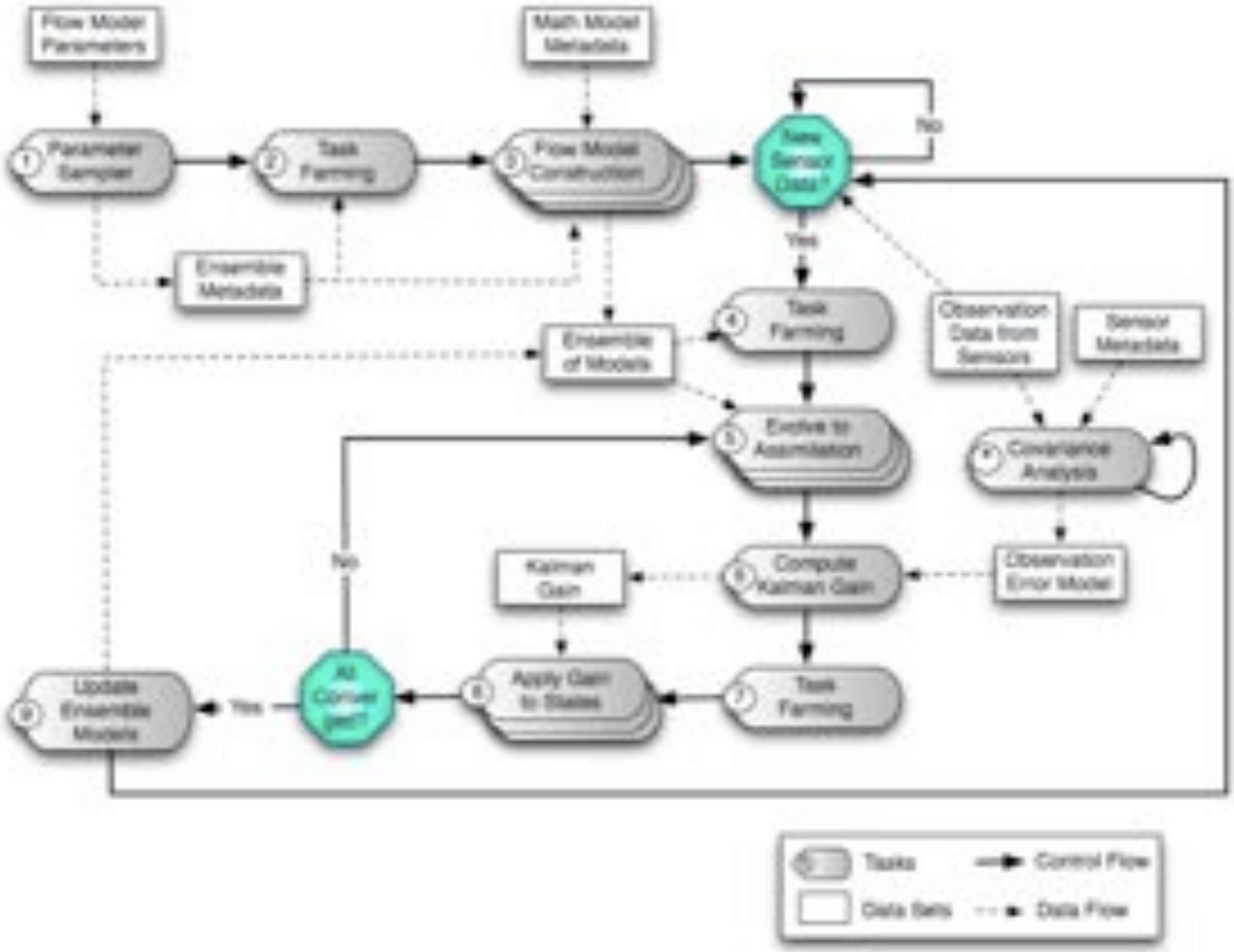
WP1 Deliverables

- Infrastructure Deployment
  - file systems, grid SW, extended SW services
- Data Archival & Retrieval Services
  - distributed storage, data scheduling
- Scheduling Services
  - workflows, co-scheduling, task farming
- High Availability
  - uninterrupted (24/7) HW & SW services
- Metadata Extraction & Indexing
  - data mining, information retrieval

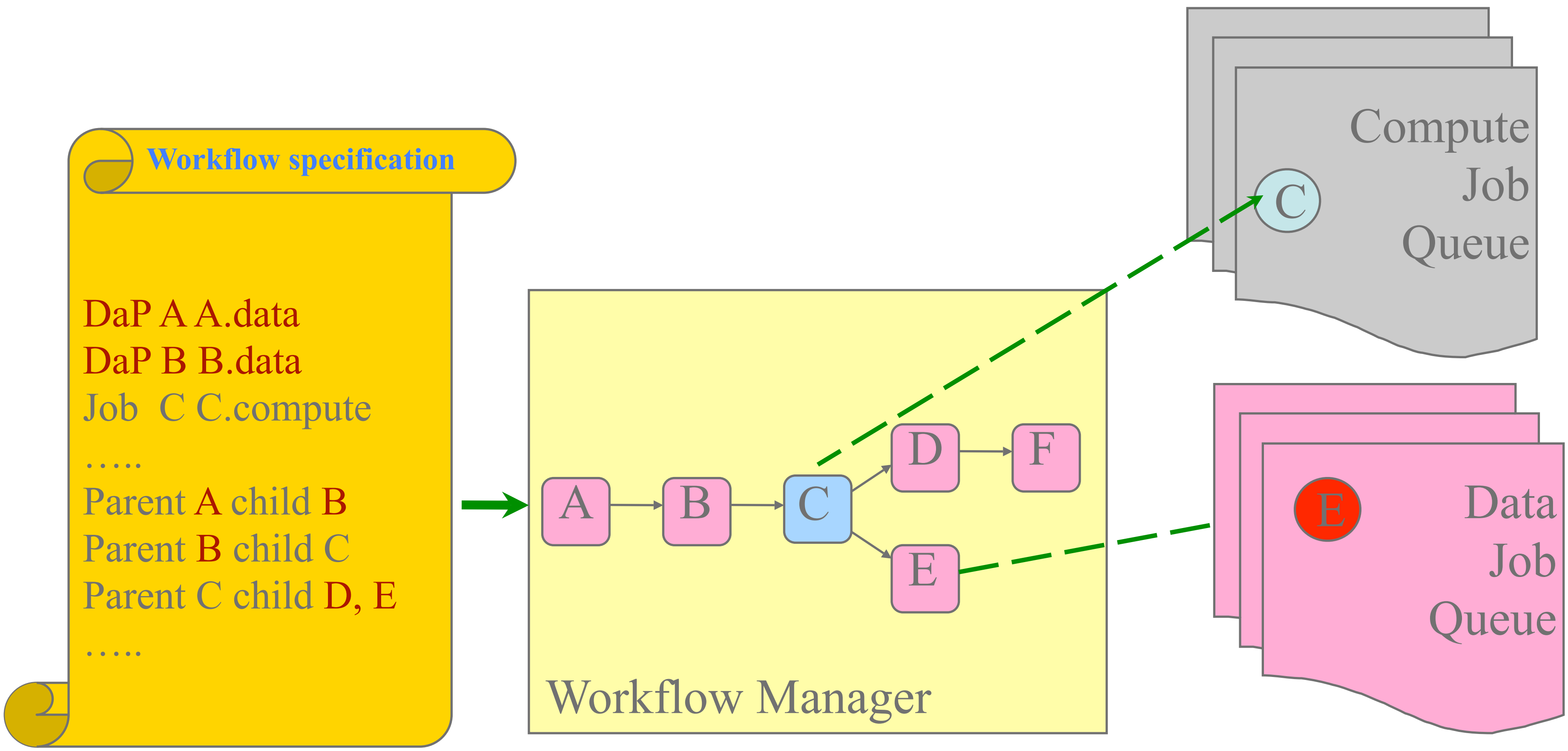
WP1 - SD Connections

- Biomolecular Dynamics - Bishop (workflow and data)
- Biomedical Imaging - Thompson (data mining)
- Coastal Modeling - SCOOP (workflow, data, scheduling)
- Reservoir Modeling - UCoMS (workflow, data, task farming)
- Numerical Relativity - Schnetter (data)
- X-Ray Tomography - Butler (data)
- Coastal Imagery - Earth Scan Lab (data)
- High Energy Physics - Greenwood (data)
- Scientific Visualization - Benger (data)
- ... more

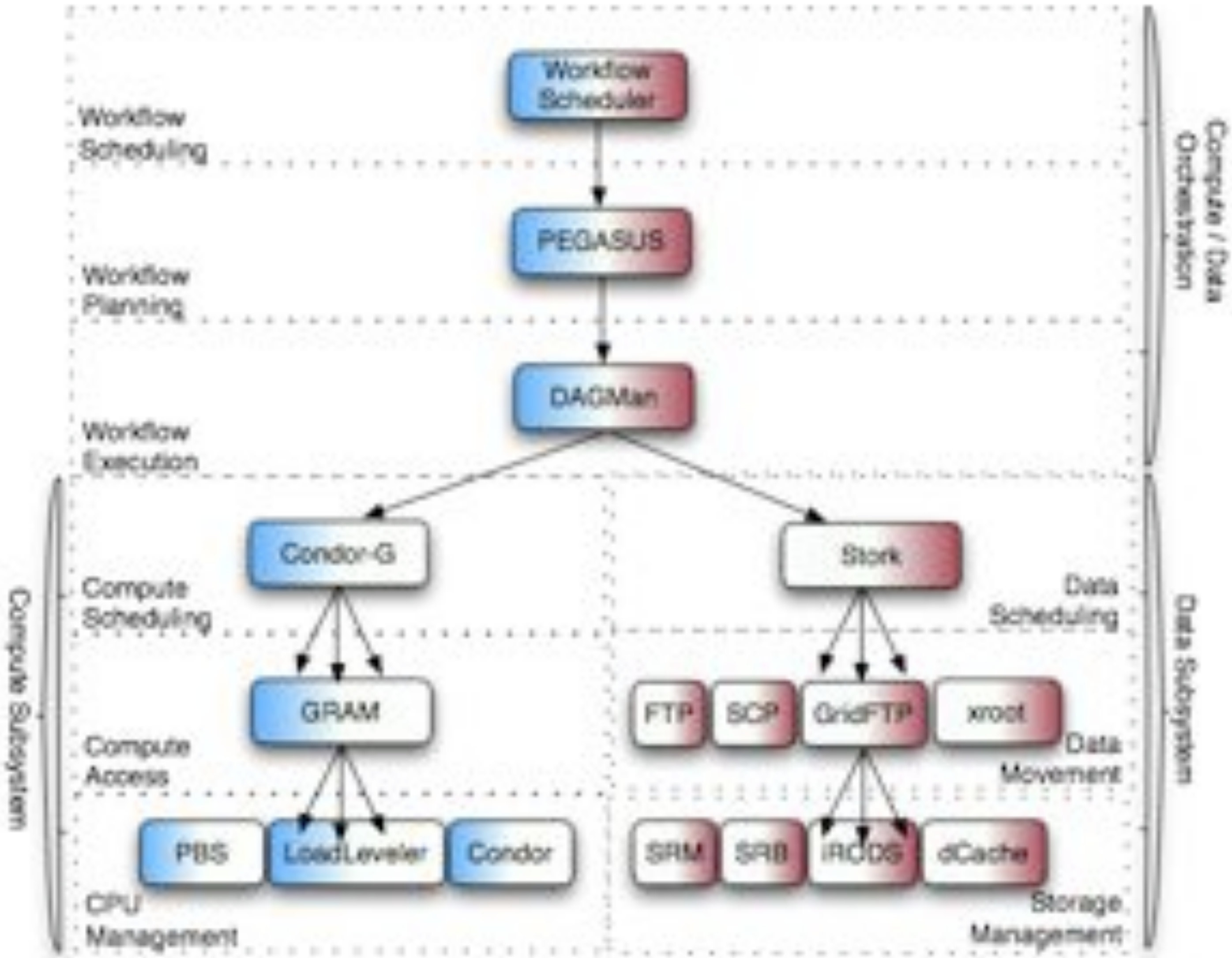
UCoMS Workflow



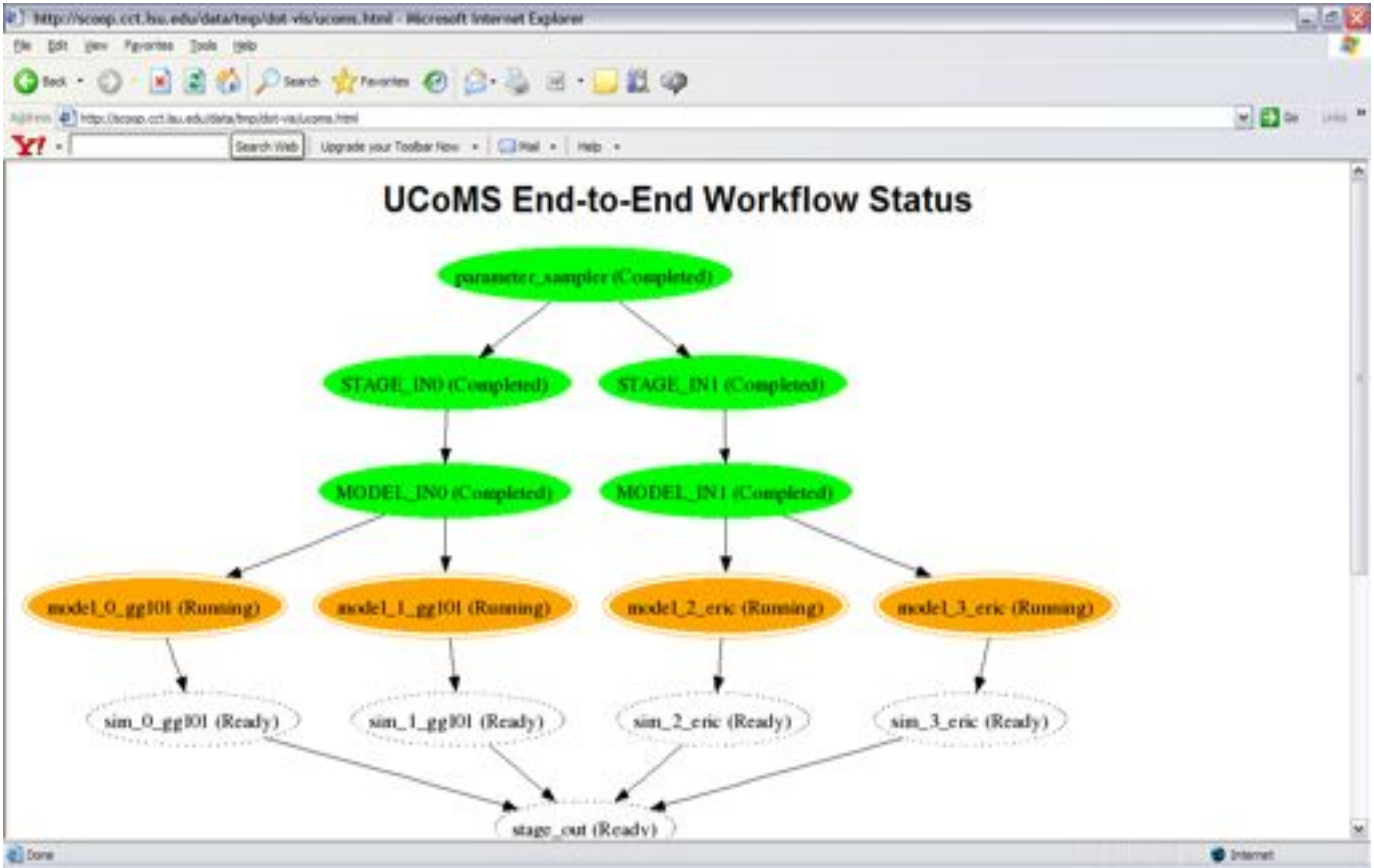
Workflow Execution



The Big Picture



Monitoring Workflows via Web



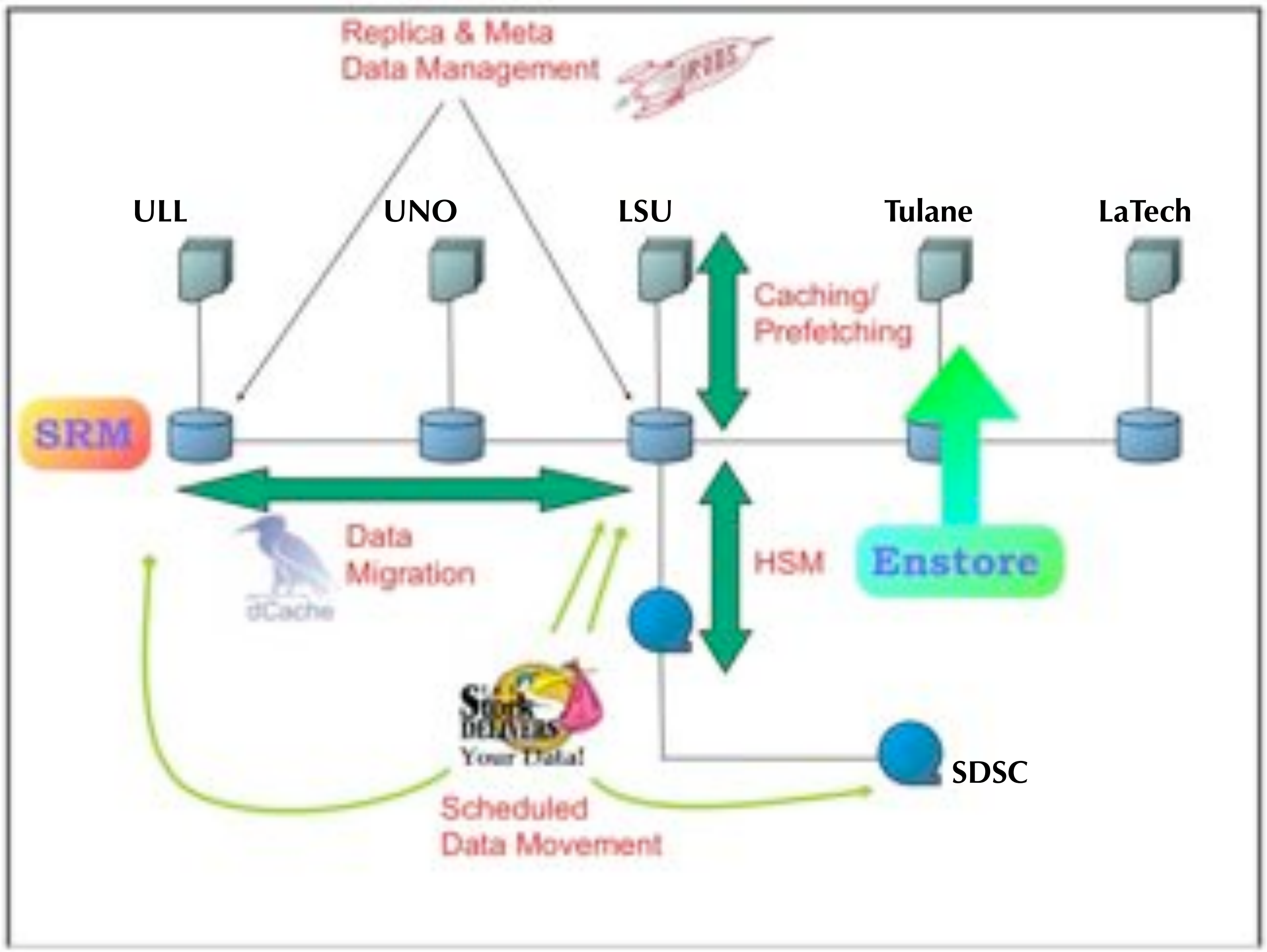
petafs

User-level Virtual File System
- NO need to change OS/kernel
- NO need to change code
- NO relinking
- NO recompiling

petashell

POSIX Shell Interface
- All of the above
- Without privileged access

PetaShare Core



Web interface:

PetaSearch

petashell

- a POSIX compatible shell interface to PetaShare

```
$ petashell

psh% cp /tmp/foo.txt /petashare/tulane/tmp/foo.txt
psh% vi /petashare/tulane/tmp/foo.txt
psh% cp /tmp/foo2.dat /petashare/anysite/tmp/foo2.dat

psh% genome_analysis genome_data -->
psh% genome_analysis /petashare/uno/genome_data

psh% exit
$
```

Accepting Allocation Proposals

1) Title of the Project:
2) Short Description of the Project (Approximately 250 words):
3) Project Web Page (if any):
4) Project PI and Affiliation:
5) Other Senior Personnel:
6) If none of the project participants are associated with PetaShare, please specify a PetaShare contact person:
7) Amount of Storage Allocation Asked:
   - In Short Term (first 6 months):
   - In Long Term (after 6 months):
8) Preferred Storage Site(s):
   - [ ] LSU (available)
   - [ ] UNO (available)
   - [ ] ULL (soon)
   - [ ]Tulane (soon)
   - [ ] LSUHSC (soon)
   - [ ] LaTech (after May)
   - [ ] Other ___________
9) Check if your application includes any of the following:
   - [ ] MPI jobs
   - [ ] Batch jobs
   - [ ] Real-time Visualization
   - [ ] Data Streaming
10) Please specify from which platforms you will be accessing this storage:
   - [ ] Linux
   - [ ] AIX
   - [ ] Windows
   - [ ] Other ___________

http://www.petashare.org

Send an email to: kosar@cct.lsu.edu

Workpackage 2
Information Services & Portals

Gabrielle Allen (LSU), Sumeet Dua (LATECH)
Kate Stamou (LSU), Prathyusha Akunuri (LONI)

Motivation

"…simplified interfaces that enable non-expert users to interface to resources and services, collect information, monitor and steer jobs, and support collaborations …"

Objectives:

1. Information Services (MonaLisa, GPIR, NWS)
2. Portals (LONI, Application, Services)

The Team

- Gabrielle Allen (LSU), Sumeet Dua (LATECH)
- Staff: Prathyusha Akunuri (LONI) + ….
- Students: Kate Stamou
- Undergrads: Mohammed Diabi, Colby Jordan, Edwin Lee
- TBA: Students from science drivers, Postdoc at LATECH (Info services)

Collaborations

Internal:

- SAGA group: APIs for application information, NWS
- SCOOP/SURAGrid: GPIR, application information service
- XiRel: Application description
- Cactus group: Existing portlets, service for application announcing
- CyD: Development of information database for LONI users/ applications (PURR)
- LONI: Development of LONI portal

External:

- PSNC, Poland: GridSphere and Vine Toolkit development (Colby Jordan will intern at PSNC in summer)
- AEI, Germany: D-Grid Application Information Services and Portlets
- Cardiff, UK

LONI Portal

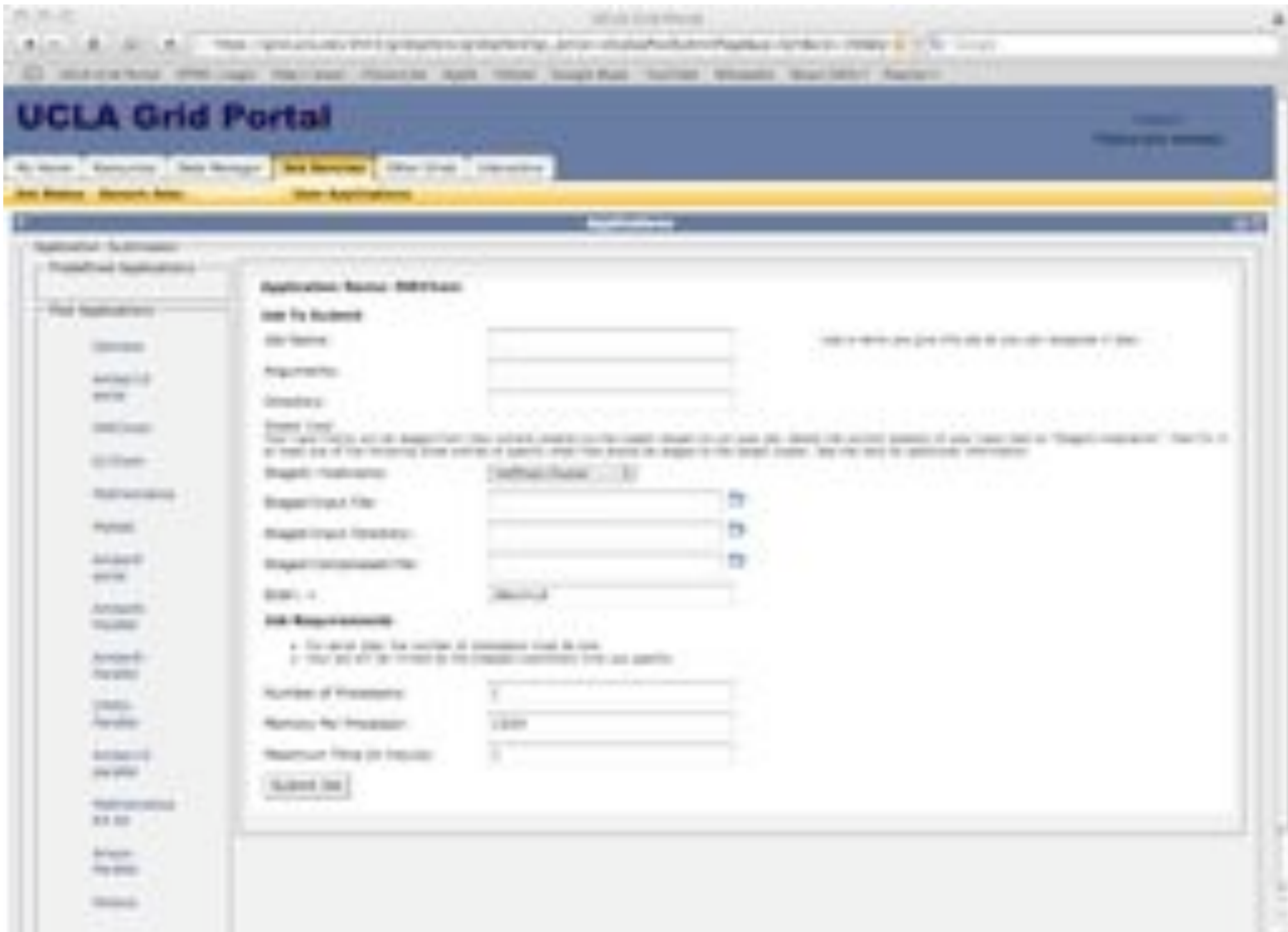
- Production Portal (LONI)
- Test Portal (LONI)
- Development Portal (CCT)
  - New server

Machine Monitoring

Co-Scheduling (HARC)

WP1: HARC Project

Generic Application Portals

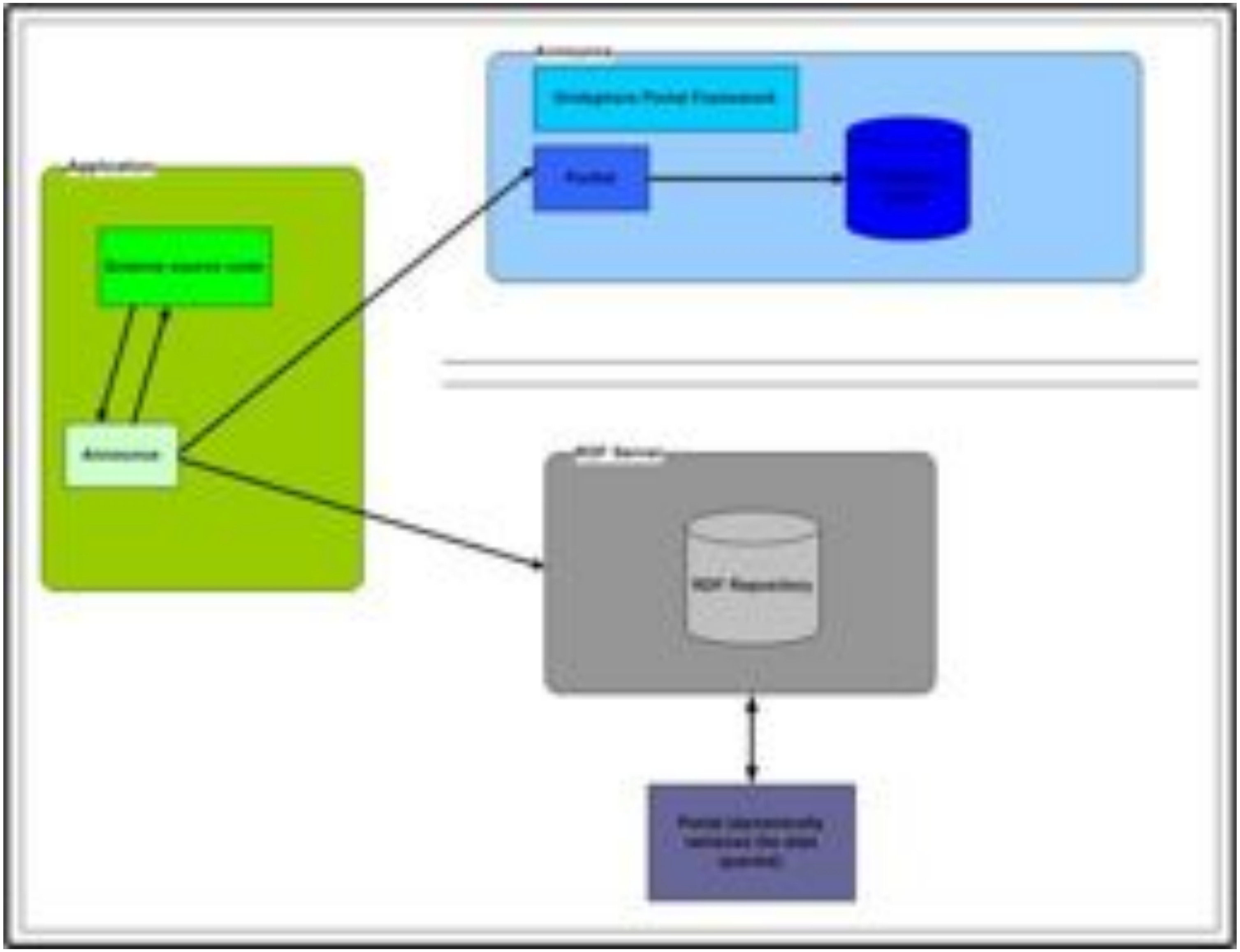


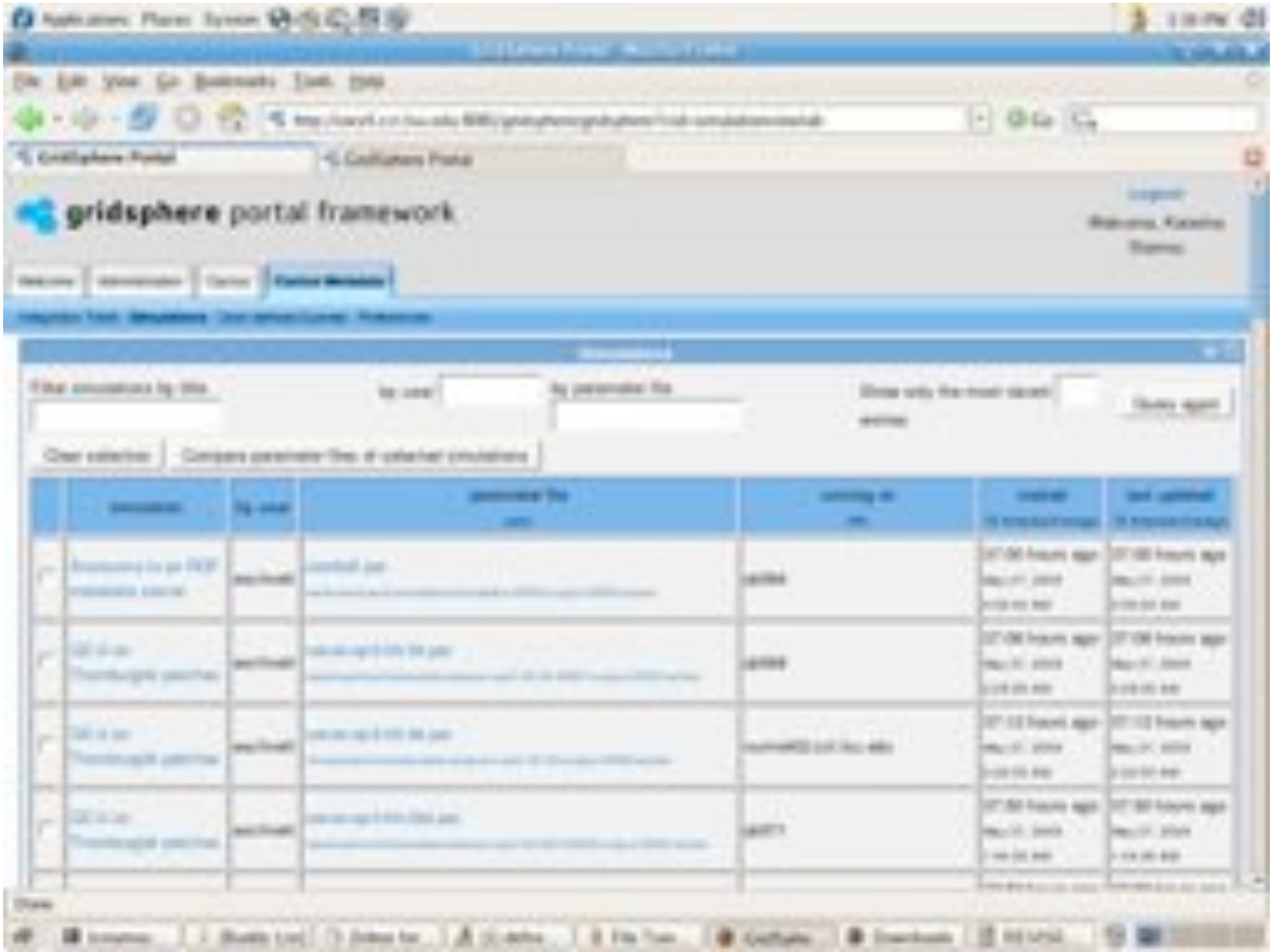
Machine Monitoring

http://fortytwo.cct.lsu.edu/teragrid/teragrid.html

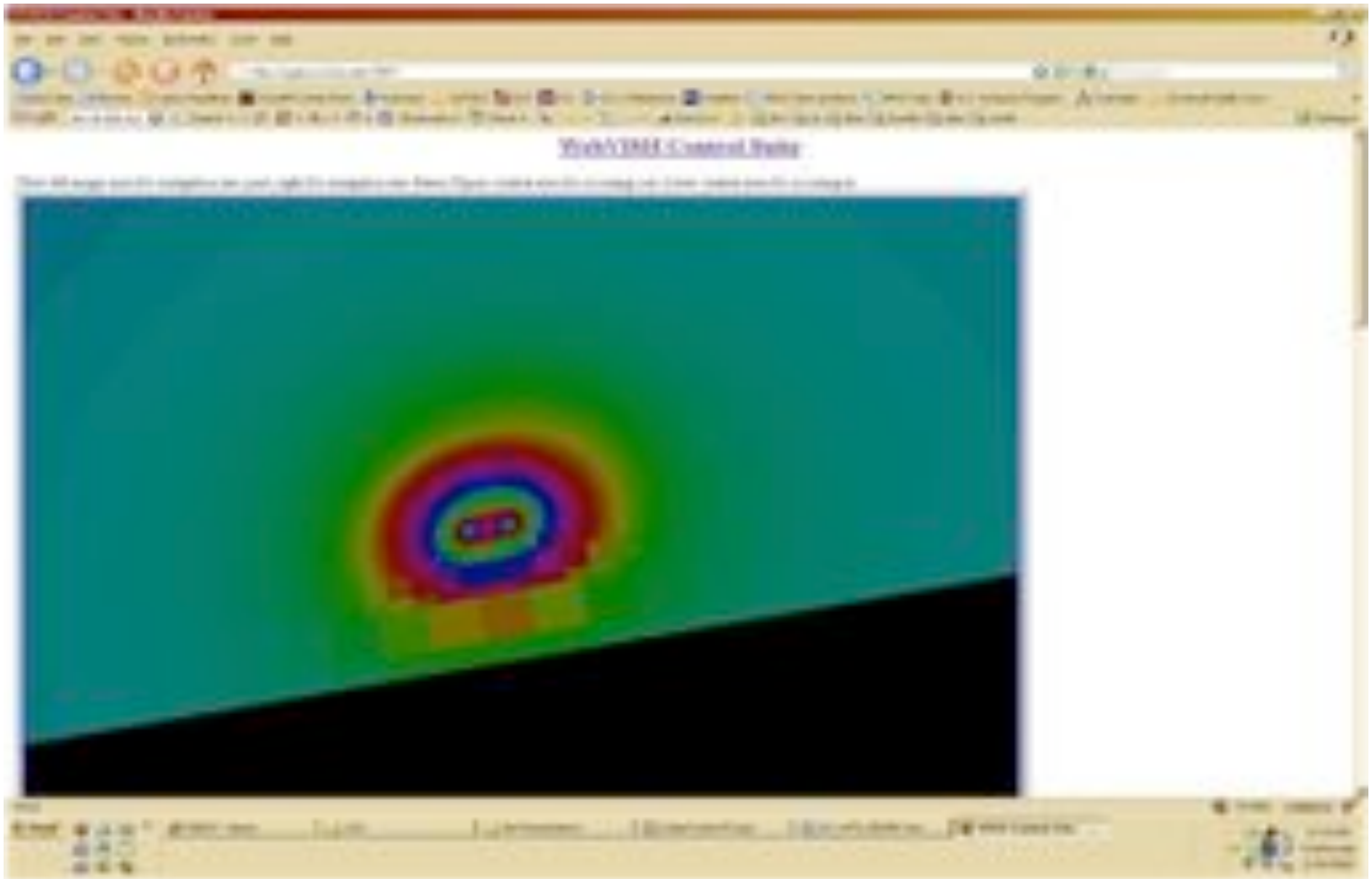
SAGA Group (WP4)

Application Announcing




gridsphere portal framework

Visualization



Demo: http://cygnus.cct.lsu.edu:7007/

WP3: Vish Framework

Connections to WPs

- WP1: Student project over summer to develop portal to monitor grid services. Want to have LONI interfaces for all services.
- WP3: Student project over summer between portals and tangibles. Vish web interface.
- WP4: So far mainly through existing portal efforts in SCOOP/UCOMS/NumRel. Application monitoring project will use SAGA. Initial discussions about Application Managers
- Science Drivers:
  - Time to start talking with these (Prathyusha)

Outreach

- Two undergrads with summer project to develop K-12 Black Hole Portal
  - Simple, explanative interface to run parallel black hole simulations on LONI machines
  - Connect to VISH visualization
  - Provide gravitational waveforms and show how these related to LIGO detection data.
- One undergrad with summer project to develop grid service status portlet
  - Integrate into Second Life Virtual World

What We Need

- Scientists:
  - What web/portal interfaces are people already using/ developing
  - Who has ideas of what interfaces they would like to have?
  - WP3 Meetings Monday 1pm.
- Need end-to-end science driver scenarios now to drive information services
  - What is the important information?
  - How to access it?
  - Interfacing with other efforts: PetaShare, PURR, Cactus Announce

Kate’s Demo & Questions

Breakout Sessions: WP-SD Interactions

- What is your expectation of how the interaction between the WPs and Science Drivers <u>will change your research horizons</u> over the next two years?
- How could we increase utilization of the WPs by the Science Drivers?

Success is at the "interface"

Breakout Sessions: WP-SD Interactions

- WP-SD deliverables: Refine WP-SD goals and deliverables
- Problems: Define Challenges you are facing and develop solutions to, or strategies to solve, problems
- Demos: Status of demonstration of tools/ model problems developed by each WP/SD ?
  - *Must be ready by the end of the summer when we have the all-state and NSF review meetings.*

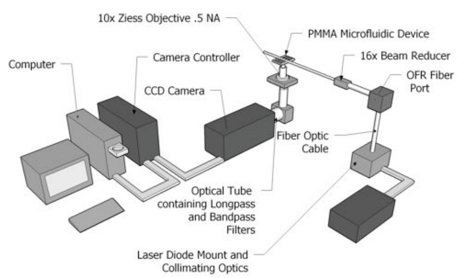
Action items

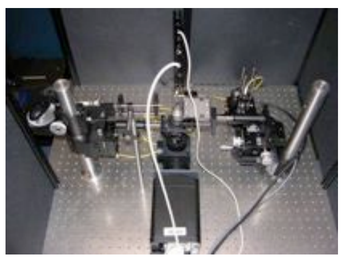
- Designate a team of SD and WP graduate students/Research fellows to coordinate a workshop in late June and July
- Develop joint posters

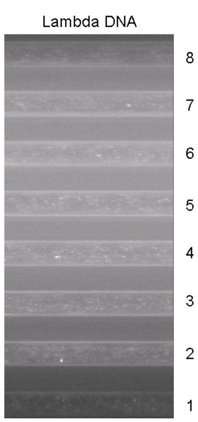
Single-Molecule Sensor Platforms

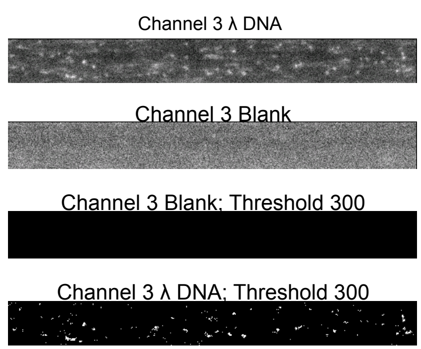
Jason M. Emory, Louisiana State University Department of Chemistry and
Center for BioModular Multi-Scale Systems (CBMM) PI: Steven A. Soper

- High Throughput Screening (HTS)
  - Point Mutations associated with Colorectal Cancer on *K-ras* gene
    - Diagnostic/prognostic value only when screening all 19 *K-ras* mutations
  - Multi-channel detection using CCD for a spatial multiplex

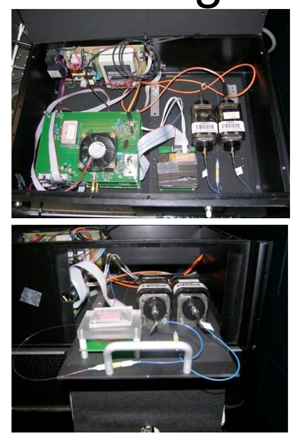


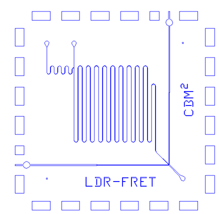


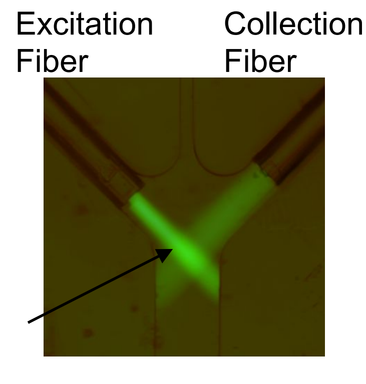




- Compact, Field-Deployable Single-Molecule Detection (SMD) for Pathogenic Bacteria







- Conclusions
  - HTS showed 276 molecules s^{-1} per channel or 2208 molecules s^{-1} for eight channels
  - Compact, field-deployable SMD removed bulky optics by integrating optical waveguide fibers
    - Eliminates the need for technical skilled operator

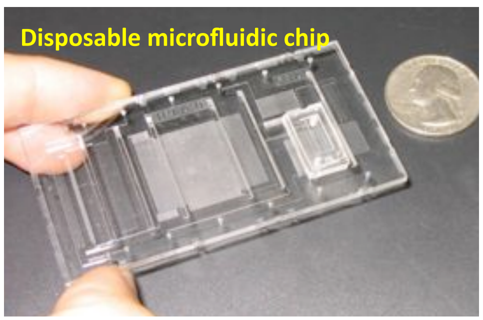
Universal and Field-Deployable Genosensor Platform

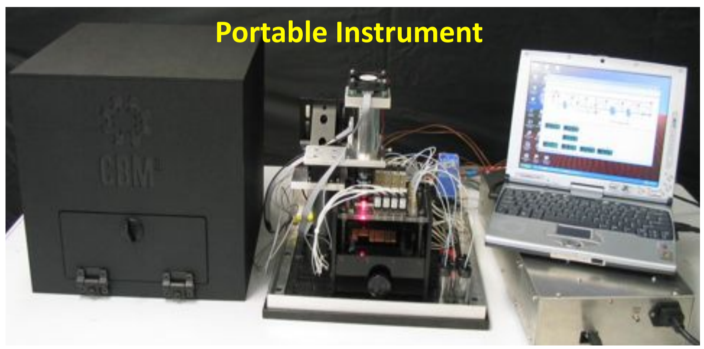
Mateusz L. Hupert, Steven A. Soper, Michael C. Murphy, and Jost Goettert Research Groups,
LSU Department of Chemistry, Department of Mechanical Engineering, Center for Advanced Microstructures and Devices (CAMD), and Center for BioModular Multi-Scale Systems (CBMM)

<u>Goal:</u> Develop a portable microfluidic-enabled system for *in vitro* molecular diagnostics for point-of-use applications (medical diagnostics, forensics, pathogen detection)

Load sample and reagents → **Load chip into instrument** → **Press "RUN"** → **Read Results**

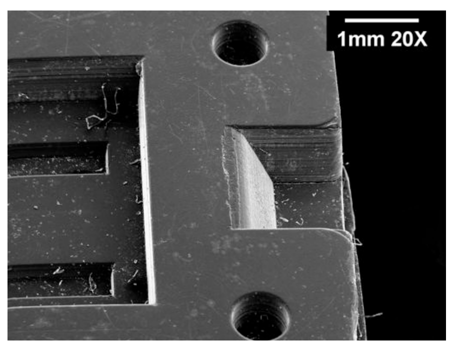
LIPLA System: Cell **L**ysis, DNA **I**mmobilization, **P**CR, **L**DR, and Micro-**A**rray Detection

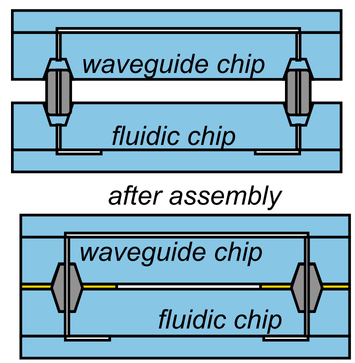


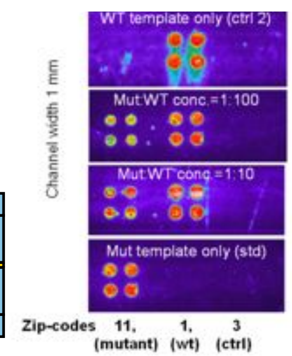


- **Fully integrated with sample-in-answer-out capabilities**
- **Low-cost, disposable polymer microfluidic chips**
- **Minimal user intervention**
- **Reconfigurable – performs different molecular assays**

- molding of multidimensional structures,
- integration and assembly of microfluidic modules,
- sample and reagents flow in microchannels, mixing,
- integration of biochemical assays
- thermal management



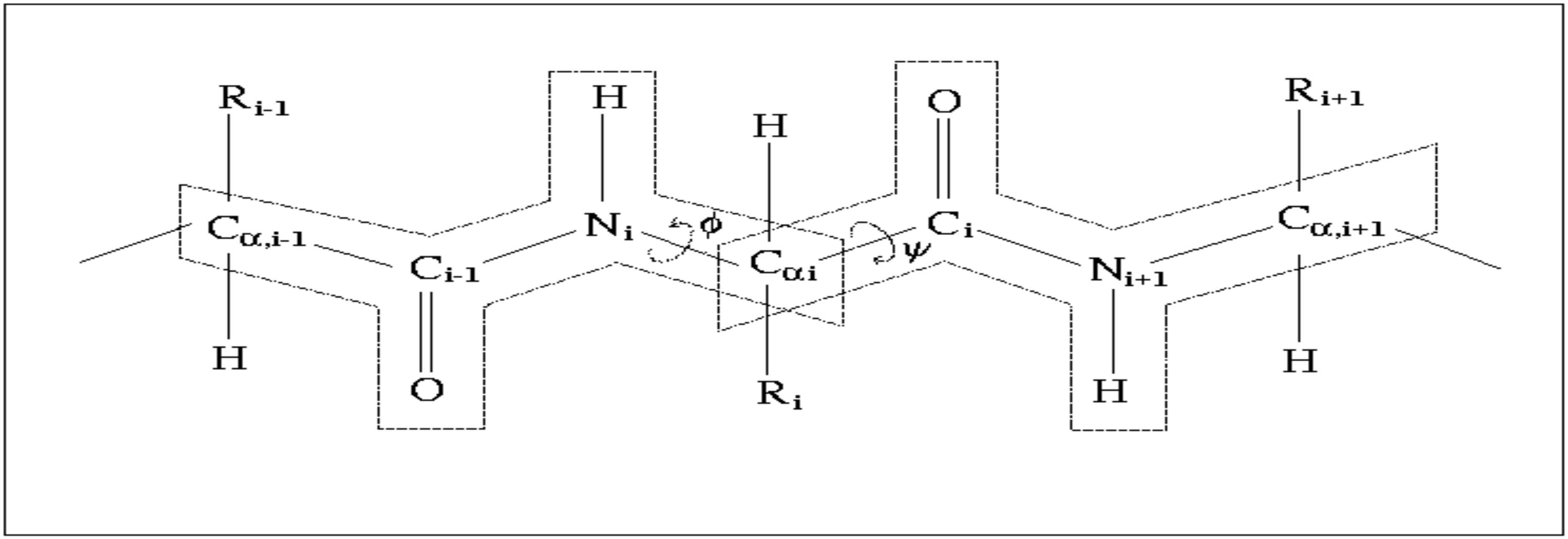


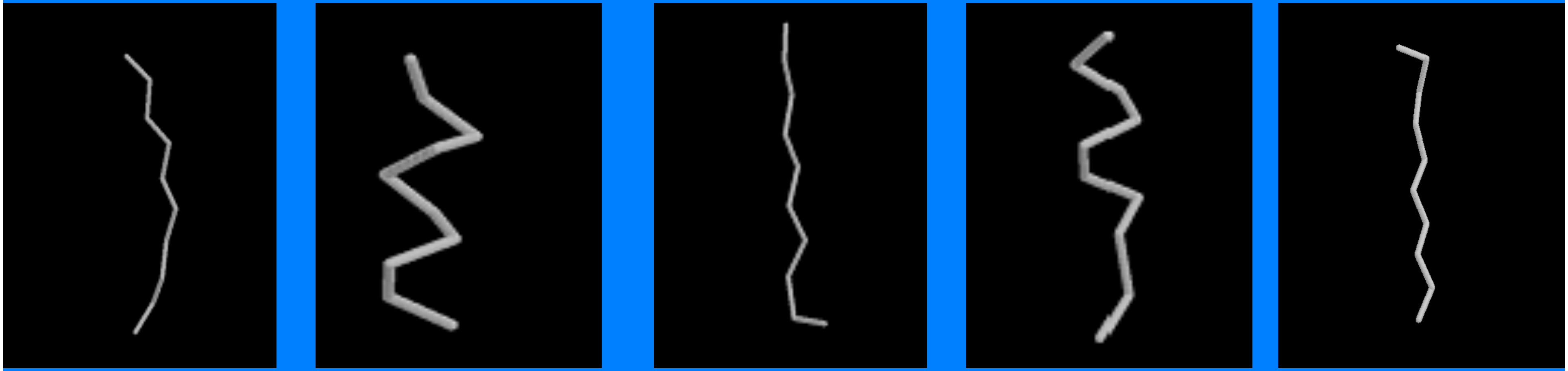


Funding: NSF-EPSCoR, Louisiana BoR

A Robust Data Mining Algorithm For Clustering Of Similar Protein Folding Units

Z. Li, N.E. Brener, S.S. Iyengar, D. Juneja, G. Seetharaman, S. Dua





A B C D

E FOLDING UNITS PRODUCED BY THE DATA MINING ALGORITHM

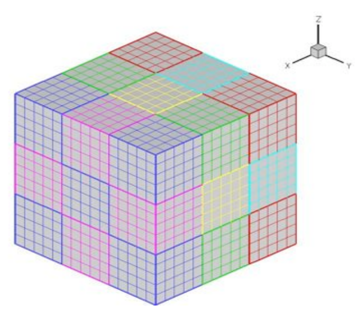
N-S Solver on Structured Multi-Block(MB) grid for Incompressible Laminar Flow for CFD Toolkit

Bio-Transport Science Driver: P. Kalghatgi (Ph. D Stu.), S. Acharya (Prof-Mech. Engng)
WP4 Collaborator- Prof. S. Jha and Prof. M. Tyagi

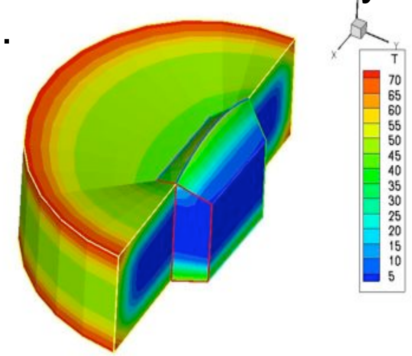
Routines to be ported as CFD Thorns in Cactus.

ReadCgns.c
Alloc_Memory.c
Connect.c
Geom.c
Metric.c
Init.c
Diffusion_flux.c
Convection_Flux.c
Fractional_Step.c
PressurePoission.c

- CGNS Interface, Imports MB Grids & BC's from commercial grid generator in 'xxxx.cgns' format.
- Staggered/Non-staggered approach of Gilmanov & Sotiropolous on MB Curvilinear Grid.
- 2nd Order Accurate FV Discretization (CD for Diffusion & QUICK for Convection, Second order time integration)
- BC's tagged to each Boundary Cell Face to support partial block connectivity in generalized manner.
- Hypre solver for efficient parallel linear solver.
- Validation problems 3D Diffusion and Lid-driven Cavity and Developing laminar flow in pipe.



MB Grid

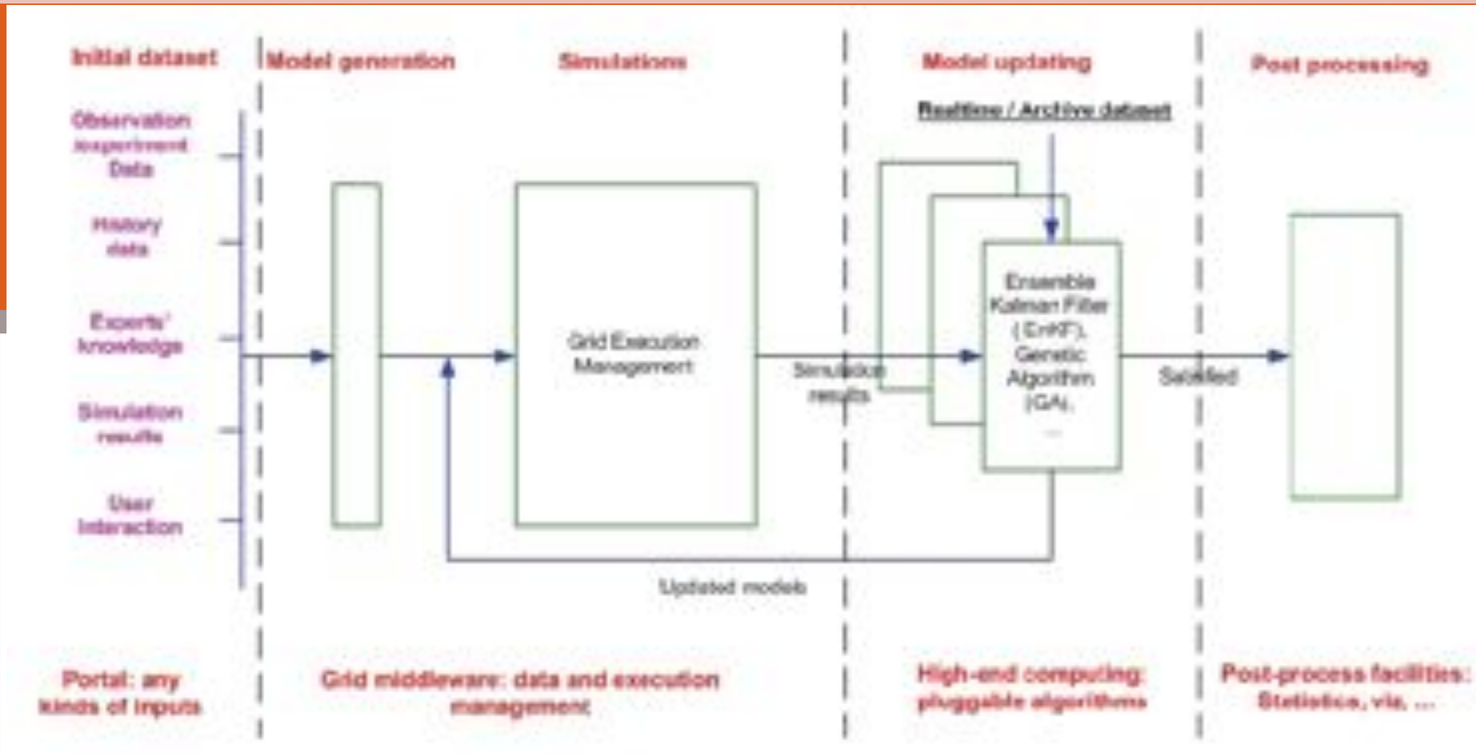


Partial 1-to-1 Connectivity

Jagadish kumar
Department of Electrical Engineering
jmohan1@lsu.edu

COASTAL MODELING

N.E.Brener, S.S. Iyengar, Gabrielle Allen, Jagadish Kumar, Zhou Lei



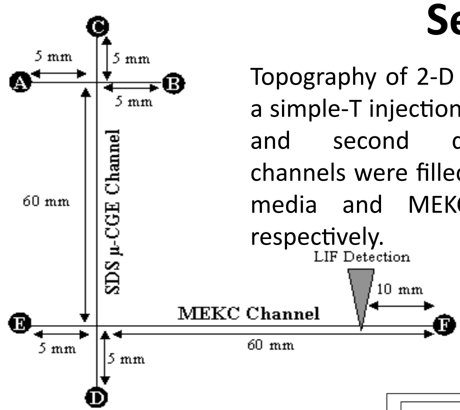
- Model explains implementation of Grid Enabled Ensemble Subsurface modeling
- We aim to adapt this reservoir modeling algorithm to apply to a coastal modeling scenario
- This scenario has challenges in scheduling algorithms, and in parallel algorithms for EnKF, GA, etc.

Marcel Ritter

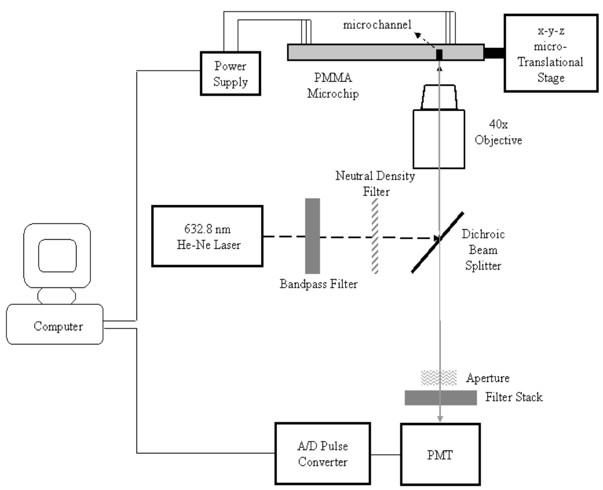
- **Visitor (student) from University of Innsbruck, Austria**
  - Group of Computer Science / Infmath (Visualization)
- **Computing Integral Lines in Large Numerical Datasets**
  - Applications:
    - Geodesics in Numerical Spacetimes (ode 2nd order)
    - Pathlines/Streamlines in Velocity Fields (ode 1st order)
  - On Demand Data Loading (e.g. NumRel ~20TB)
  - Interactive Visualization
  - Realtime rendering techniques
  - Complex Datasets: AMR, Multiblock
  - Feature Extraction: Lines, Bundles (Convergence), Surfaces
  - Tool of Cybertools of WP3

Serum Protein Separation on Microfluidic Platforms

By John K. Osiri

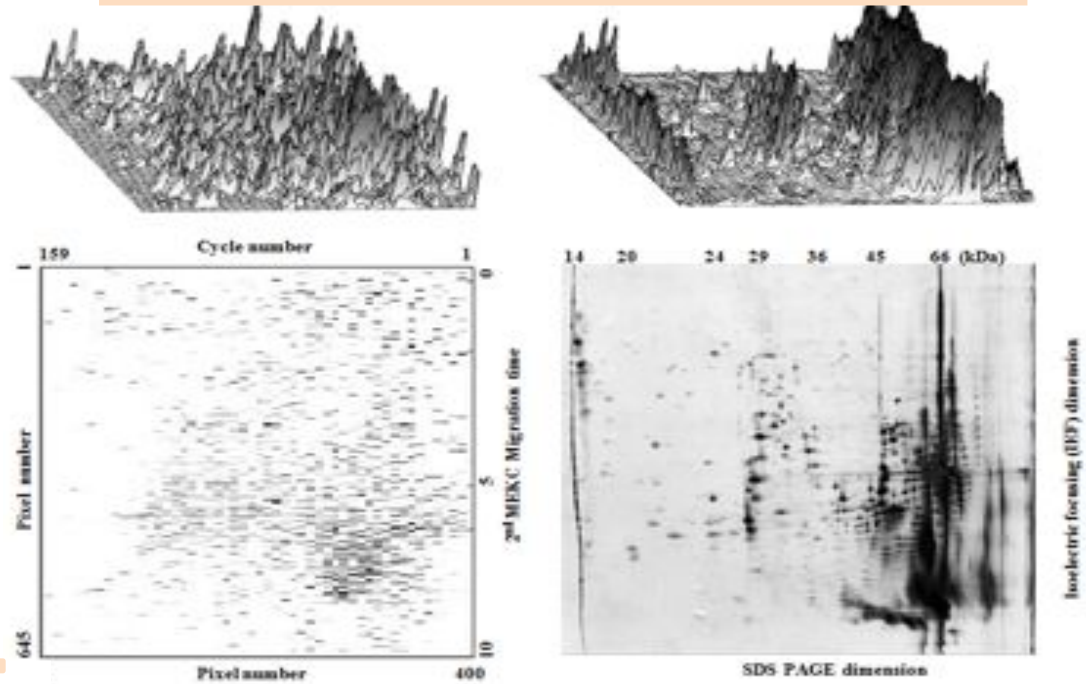


Topography of 2-D chip with a simple-T injection. The first and second dimension channels were filled with gel media and MEKC buffer, respectively.



Microchip
SDS µ-CGE × MEKC

Conventional
IEF × SDS PAGE



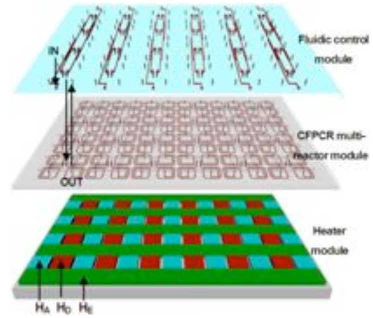
Courtesy: Amersham Pharmacia Biotech

2-D Separation Platform	Average Spot Size (pixel)	**Number of Spots**	2-D Peak Capacity	**Sample volume (uL)**	**2-D Separation Time (min)**	Potential Separation Rate (proteins/min)
SDS µ-CGE × MEKC	418	**767**	6700	**450**	**30**	223
IEF × SDS PAGE		**394**	-	**2**	**>1800**	-

Design, Fabrication, and Performance of Small Footprint Continuous Flow PCR Devices for a 96-Well CFPCR Multi-Reactor Platform

D. S. Park[1], P.-C. Chen[1], B. H. You[1], N. Kim[1], T. Park[1], T. Y. Lee[1], P. Datta[1], Y. Desta[2], S. A. Soper[1], D. E. Nikitopoulos[1], and M. C. Murphy[1]
[1]Louisiana State University, [2]BioFluidica Microtechnologies, Baton Rouge, LA

Summary – Small footprint (8x8 mm²) continuous flow (CF) PCR devices was designed, fabricated, and used to amplify DNA fragments as part of a 96-well CFPCR multi-reactor platform. A variety of spiral CFPCR devices were designed and fabricated by UV-LIGA technique for a nickel large area mold insert (LAMI), and grooves and fins by micro-milling for a brass LAMI. Double-sided micro molding in polycarbonate (PC) with two LAMIs was done using hot embossing. The molded PC chips was sealed in a custom-designed thermal fusion bonding apparatus. Small footprint, 20- and 25-turn CFPCR devices showed successful DNA amplification of 99-bp target DNA fragments from a 48k bp λ-DNA template. Development of a heater module and a fluidic control module is underway for the realization of a high throughput CFPCR multi-reactor platform.

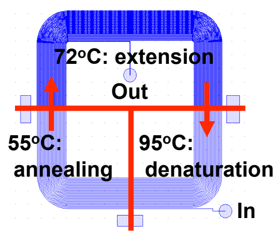


CFPCR multi-reactor platform

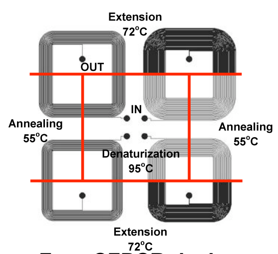
Small footprint CFPCR devices for a CFPCR multi-reactor chip module

- Design of a CFPCR multi-reactor chip
- Fabrication of CFPCR multi-reactor chips (LAMI fabrication, micro molding, sealing)
- Demonstration of DNA amplification capability

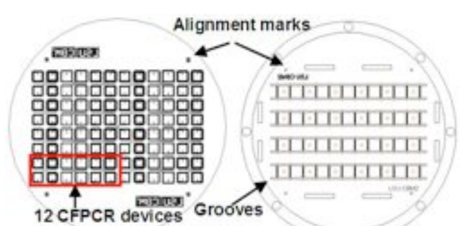
■ Design of a CFPCR Multi-Reactor Chip



Spiral CFPCR device with three temperature zones (20- and 25-turns)



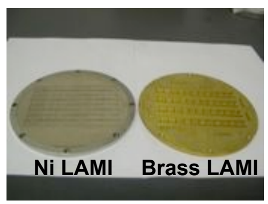
Four CFPCR devices sharing temperature zones



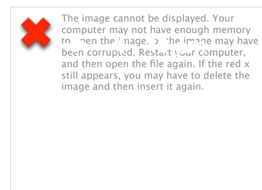
Nickel LAMI Brass LAMI

- ❑ Sharing of temperature zones applied to a group of 12 CFPCR devices and extended to all 96-well CFPCR devices in a nickel LAMI
- ❑ Grooves and fins for thermal isolation in a brass LAMI
- ❑ Alignment marks for double-sided micro molding

■ Fabrication of Metallic LAMIs

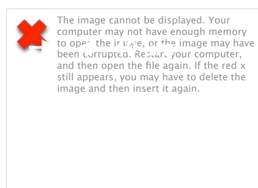


Two metallic LAMIs



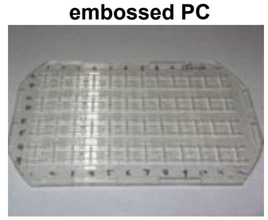
Microchannels in Ni

■ Double-Sided Micro Molding and Sealing

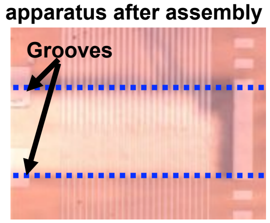


Microchannels in hot embossed PC

Thermal fusion bonding apparatus after assembly

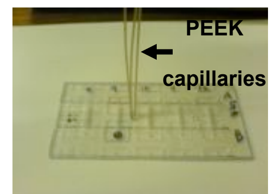


Sealed 96-well PC chip



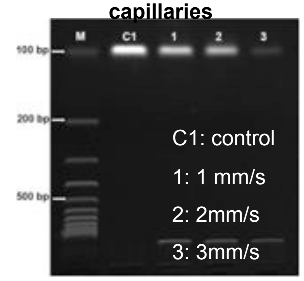
Sealed microchannels

■ DNA Amplification of 99-bp DNA Fragments

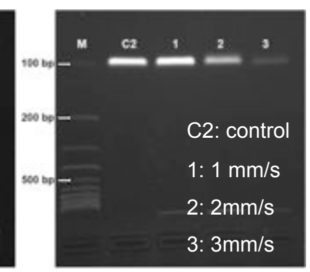


10-well CFPCR multi -reactor chip with capillaries

- ❑ 96-well CFPCR chips cut into 10- or 12-well format
- ❑ Template: 48k bp λ-DNA
- ❑ Thermal cycling with three copper plates (94°C for denat., 63°C for anneal., and 72°C for exten.)
- ❑ Different flow velocities used (1,2, and 3 mm/s)



Gel image for 20-turn CFPCR devices



Gel image for 25-turn CFPCR devices

- ❑ Reaction times as fast as 5.1 min for 20-turn CFPCR devices at 3 mm/s
- ❑ Testbed for other thermal reactors such as LDR
- ❑ Development of a heater module and a fluidic control module for complete CFPCR platform

SCOOP Multi - Model Priority Scheduling System

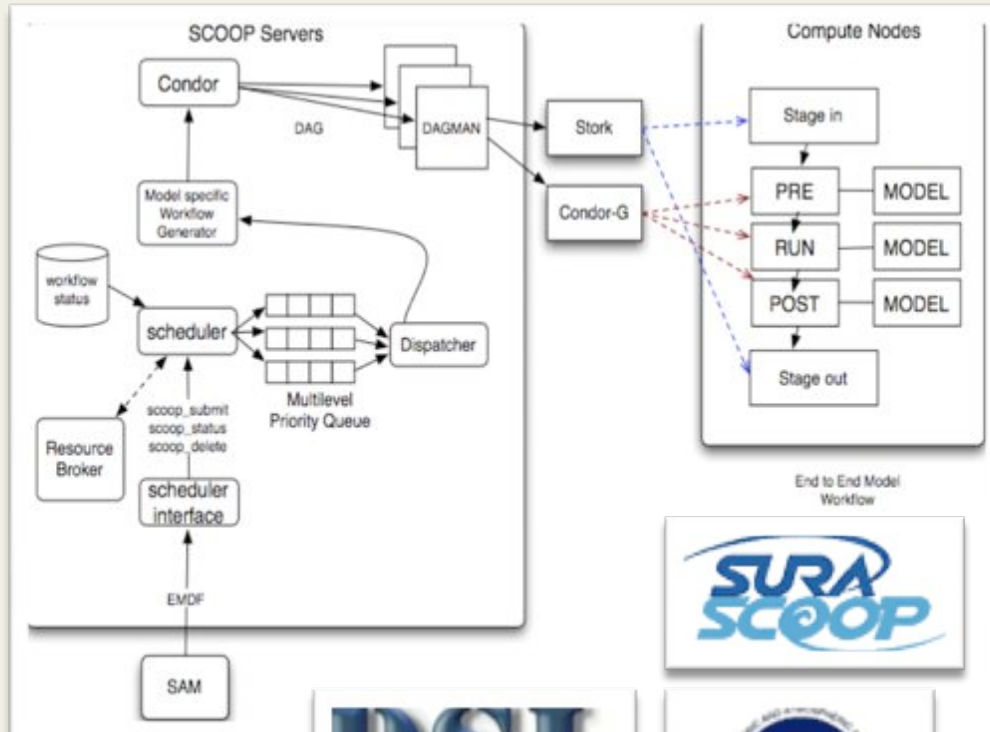
Requirements:

1. **Arbitrary** Input track arrival
2. Tracks are **of varied importance** to the domain scientists.
3. **Multiple** resources available
4. Resources providing On demand, relatively high priority & equal priority during **allocatio**n.
5. Workflow **management** system for every end to end workflow
6. **Multiple** models with similar priority requirements.

Solution:

1. Muti model priority based workflow scheduling system
2. Condor daemon, inheriting all the **reliability** features from Condor system.
3. DagMan for workflow management and monitoring.

- **Wavewatch II**I model runs are **scheduled**.
- Soon **ADCIRC** will be managed **simultaneously** along with the Wavewatch III.
- Workflows now running simultaneously at **multiple clusters**.
- **Most important workflow's results** are obtained first.
- Scheduling system **is modular** for accommodating new models.

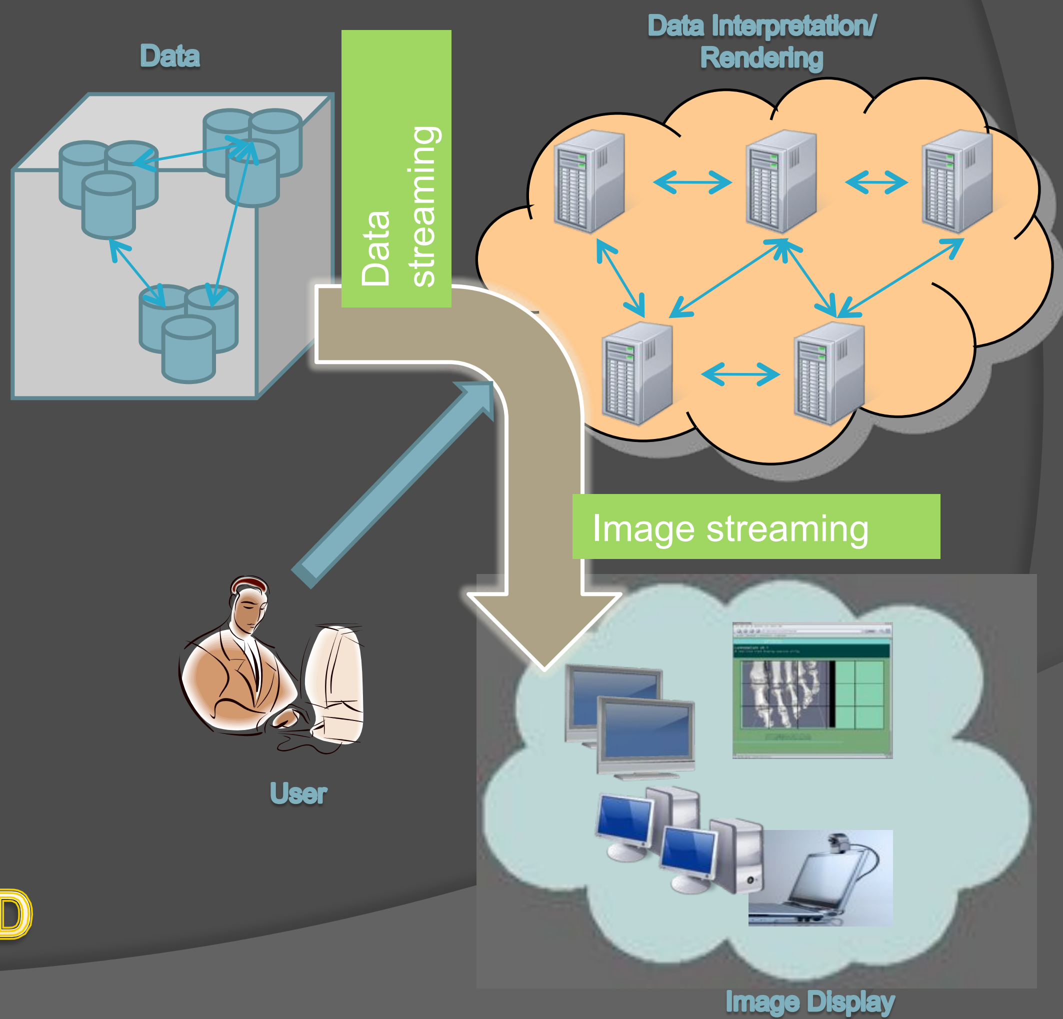


EAVIV Project – WP3

- Vinay C. Amatya, Jinhgua Ge, Andrei Hutanu, Cornelius Toole
LSU/Computer Science/CCT
email: vamatya at cct dot lsu dot edu

- Objective: Optimization of Visualization Pipeline
- Discrete View of the Visualization-pipeline:
  - Data Scheduling/Streaming
  - Rendering – Scheduling
  - Video/Image Scheduling/Streaming Optimization
- Video/Image Streaming Optimization:

  Present Choices
  - SAGE
  - ULTRAGRID



Biotransport: Effect of Small Molecules

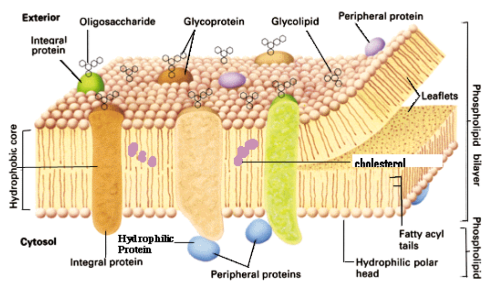
Raghava Alapati, M.S. Candidate (Mechanical Eng., LSU)

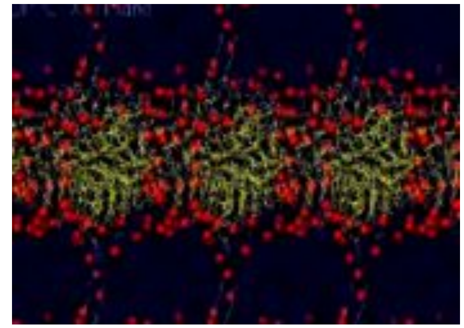
Research Advisors: Dr. Moldovan & Dr. Devireddy

Group Leaders: Dr. Acharya & Dr. Jha (WP4)

RESEARCH OBJECTIVES

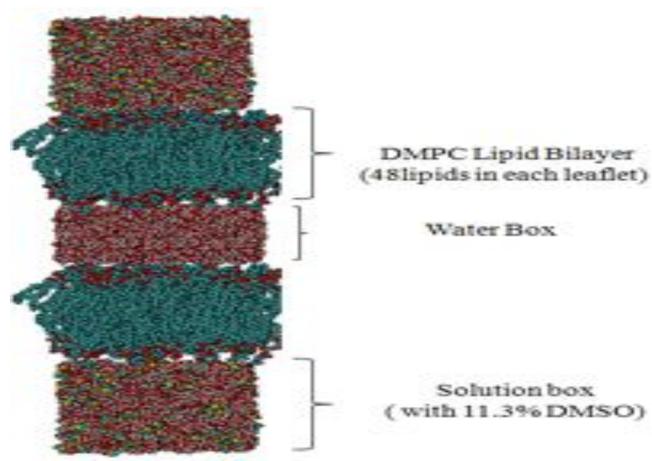
Investigate the role of small molecules on structural and permeation properties of lipid bilayers.





SIMULATION SYSTEM

- 48 lipids each in four leaflets
- Pure water & DMSO-water
- GROMACS
- LONI Environment



ACKNOWLEDGEMENTS: National Science Foundation/ EPSCoR Award No. (EPS-0701491)

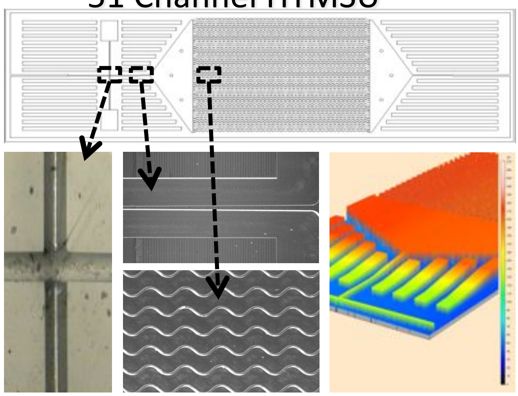
Immunosensors Enabling Early Cancer Diagnostics and Prognostics Using Microfluidic Platforms

by André A. Adams

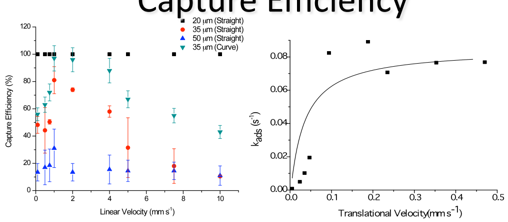
Prof. Steven A. Soper's Research Group, Louisiana State University, Department of Chemistry

Center for Biomodular Multi-Scale Systems

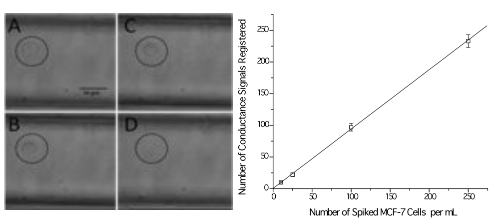
51 Channel HTMSU



Experimental and Modeled Capture Efficiency



Cell Release and Recovery Rates



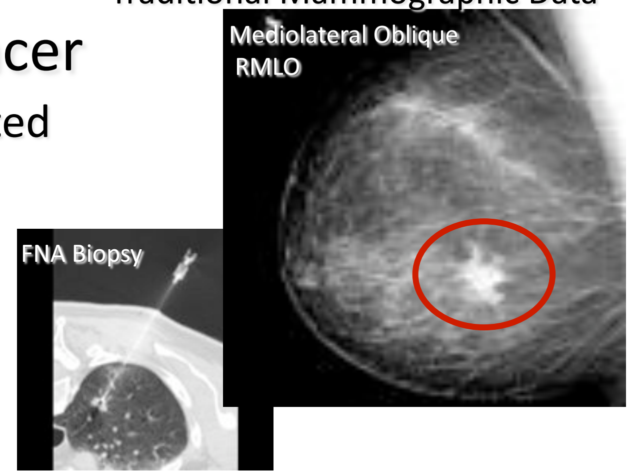
❑Model System: Breast Cancer

- ❑225,000 cases in the US detected primarily by mammography
- ❑Misses ~10% of all tumors
- ❑High rate of false positives
- ❑Typical treatment
  - Excision of suspect tissue
  - Chemotherapy/Radiation
  - Continued monitoring

❑CTC Capture System

- ❑Process 1 mL blood sample
- ❑t = ~30 min.
- ❑No need for pretreatment
- ❑Nondestructive
- ❑97% Recovery rate

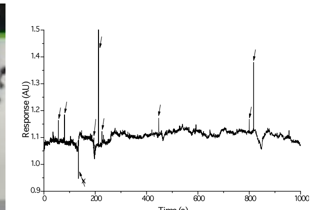
Traditional Mammographic Data



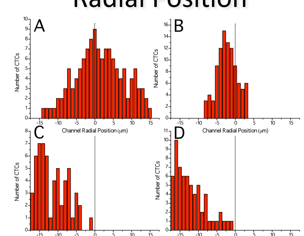
Enumerating Circulating Tumor Cells

Apparatus

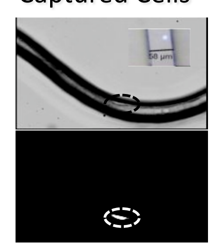
Enumeration



Radial Position



Captured Cells

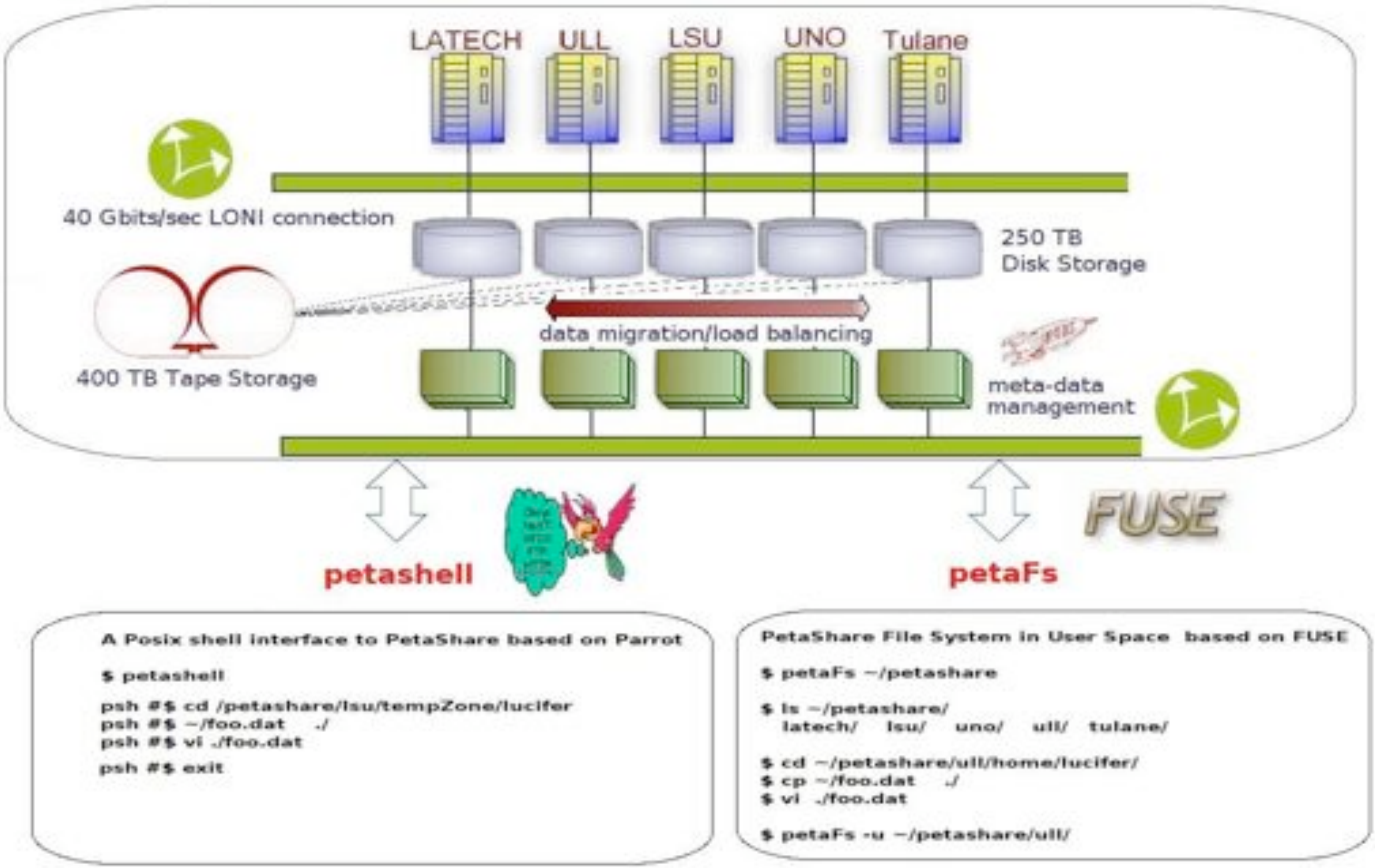


Soper, SA, Adams AA *et al.*, "Identifying Circulating Tumor Cells at Ultralow Concentrations", 2008 U.S. Patent and Trade Office, Provisional Patent Application: 61/053,727

Adams, AA *et al.*, "Highly Efficient Circulating Tumor Cell Isolation from Whole Blood and Label-free Enumeration Using Polymer-Based Microfluidics with an Integrated Conductivity Sensor", 2008, JACS.

Acknowledgements: NSF EPSCoR and Louisiana Board of Regents

PetaShare:
Enabling Data Intensive Research



DSL Distributed System Laboratory
www.dsl.csc.lsu.edu

inspired from *M. Balman, I. Suslu, T. Kosar, Distributed Data Management with PetaShare, Poster presentation at ACM SIGAPP 15th Mardi Gras Conference, Baton Rouge, Jan 2008.*

NSF EPSCoR Research Infrastructure Improvement (RII) Award: Cyberinfrastructure and Science Drivers
All Hands Meeting / May 30, 2008
Claiborne Building, at 1201 N. Third Street, Baton Rouge, LA
Presented by: *Mehmet BALMAN*

Cybertools: http://cybertools.loni.org

STORK: A Scheduler for Data Placement Activities

Data placement activities as **"first class citizens"** in the Grid just like the computational jobs. http://storkproject.org

Ex: **submit file**

```
[   dest_url = "gsiftp://eric1.loni.org/scratch/user/";
    arguments = "-p 4 –dbg -vb";
    src_url = "file:///home/user/test/";
    dap_type = "transfer";
    verify_checksum = true;
    verify_filesize = true;
    set_permission = "755" ;
    recursive_copy = true;
    network_check = true;
    checkpoint_transfer = true;
    output = "user.out";
    err = "user.err";
    log =  "userjob.log"; ]
```

Protocols:

file:/	->	local file
ftp://	->	FTP
http://	->	HTTP
gsiftp://	->	GridFTP
srb://	->	SRB (Storage Resource Broker)
irods://	->	iRODS

Extended list of features :

- Recursive directory copy
- Checksum and file size comparison
- File Permission Modification

- Support for heterogeneously
- Protocol translation using Stork memory buffer/Disk Cache
- Flexible Job Representation and Multilevel Policy Support
- Run-time adaptation
- Dynamic protocol selection, Run-time Protocol Auto-tuning
- Failure Recovery and Efficient Resource Utilization

CAPTURE OF VERY RARE CIRCULATING TUMOR CELLS FOR HUMAN BREAST CANCER DIAGNOSIS AND MONITORING

Taehyun Park[1,2], Daniel Park[2], Jason Guy[2], Proyag Datta[4], Steven A. Soper[2,3], Michael C. Murphy[1,2]
[1]Department of Mechanical Engineering, Center for Biomodular Multi-Scale Systems (CBM[2]),
[3]Department of Chemistry, Louisiana State University, [4]Center for Advanced Microstructures and Devices (CAMD),
Louisiana State University, Baton Rouge, LA 70806

MOTIVATION

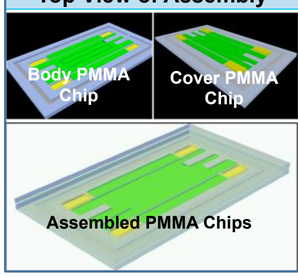
Easy, Fast, Inexpensive, and Comfortable

OBJECTIVES

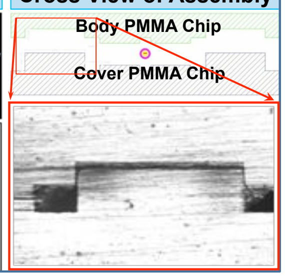
- Assembly of PMMA chips with minimum tolerance
- Preparation of a single or precise numbers of cells
- Delivery of the collected cells without any cell loss or clogging
- Capture of very rare CTCs in peripheral whole blood

ASSEMBLY AND SEALING

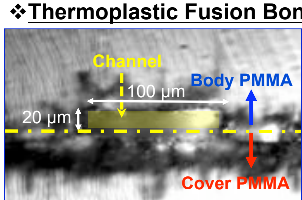
Top View of Assembly



Cross View of Assembly



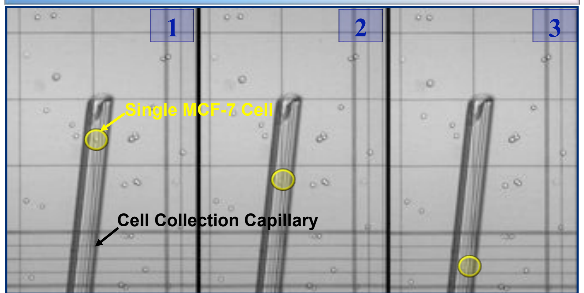
❖Thermoplastic Fusion Bonding Process.



Cross view of channel part

Material	UV modified PMMA
Temperature	101 [℃]
Pressure	10 [psi]
Time	Over 60 [min]

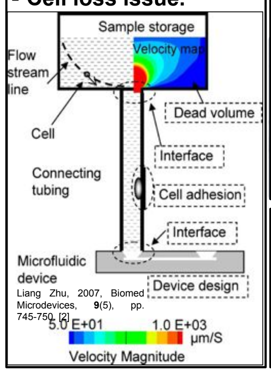
RARE CELL COLLECTION



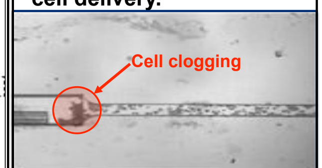
The yellow circles indicate a single target MCF-7 cell

RARE CELL DELIVERY

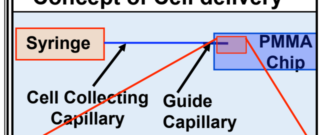
▪ Cell loss issue.

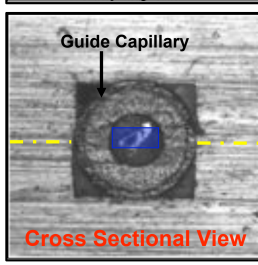


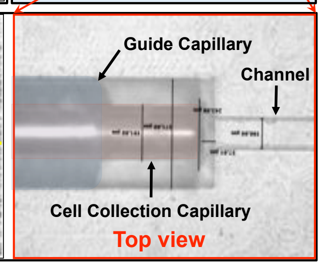
▪ Example of incorrect cell delivery.



▪ Concept of Cell delivery

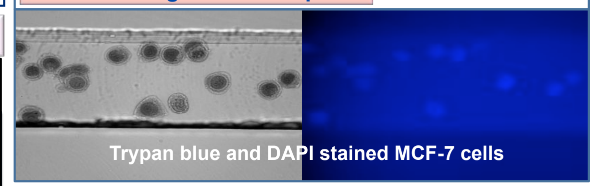




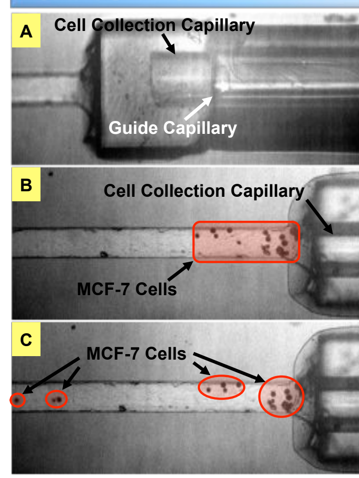


CELL CAPTURE PROCESS

- PMMA Micro Channel Chip
  - ↓ UV Exposure
- COOH-Modification of Channel
  - ↓ EDC, Ethylenediamine
- NH2-Modification of Channel
  - ↓ EDC, Anti-EpCAM
- Anti-EpCAM Functionalization
  - ↓ MCF-7 Preparation
- DAPI Staining and Cell Capture



CAPTURE OF RARE MCF-7 CELLS



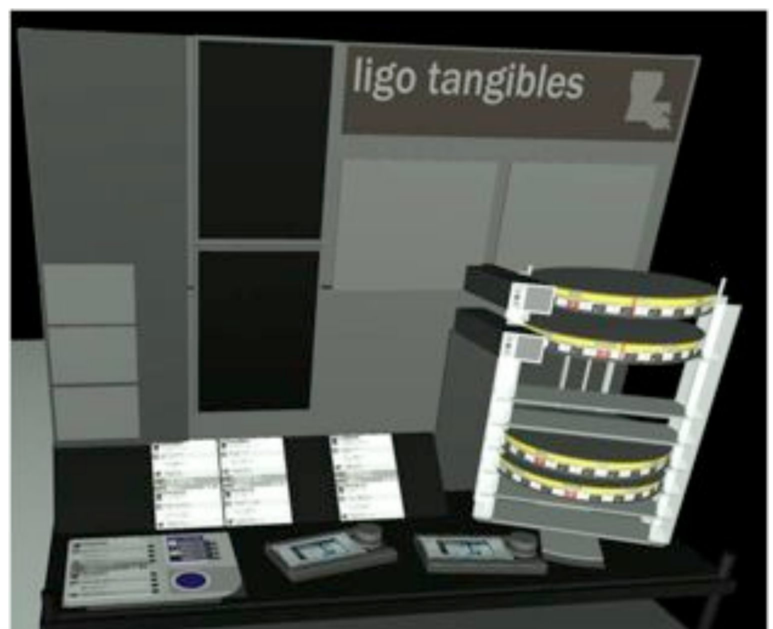
A. Cell collection capillary is inserted to deliver MCF-7 cells into the channel.

B. 14 MCF-7 cells were captured in a anti-EpCAM functionalized channel.

C. All MCF-7 cells remained after PBS rinse.

LIGO Outreach Tangibles

- Goals:
  - To develop & deploy low cost interactive exhibits at LIGO Science Education Center & middle schools through Louisiana that
    - Engage students & others in science concepts relevant to LIGO
    - Are a platform for disseminating results from LIGO scientific community
- Multidisciplinary effort involving
  - Computer scientists & engineers, scientists, graphic designers, and educators
- Grad Students
  - Cornelius Toole, Srikanth Jandhyala, Rajesh Sankaran, Santanu Majumdar, Phil Winfield
- Undergrads
  - John Douthat, Zack Dever, Ian W. Smith, Alvin Wallace



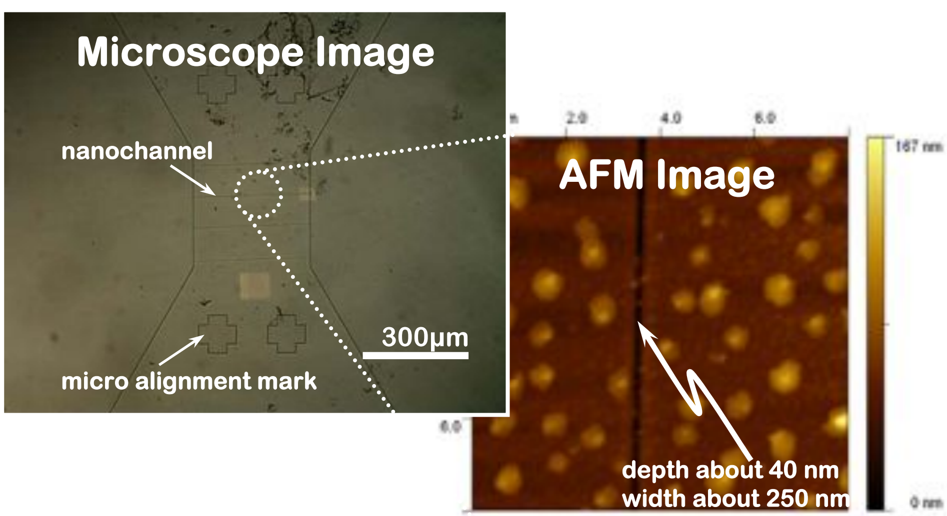
Low Cost and High Throughput Fabrication of Nanochannel and Nanopore in Analytical Devices

Junseo Choi, Sunggook Park (LSU-ME), Steven A. Soper (LSU-CH)

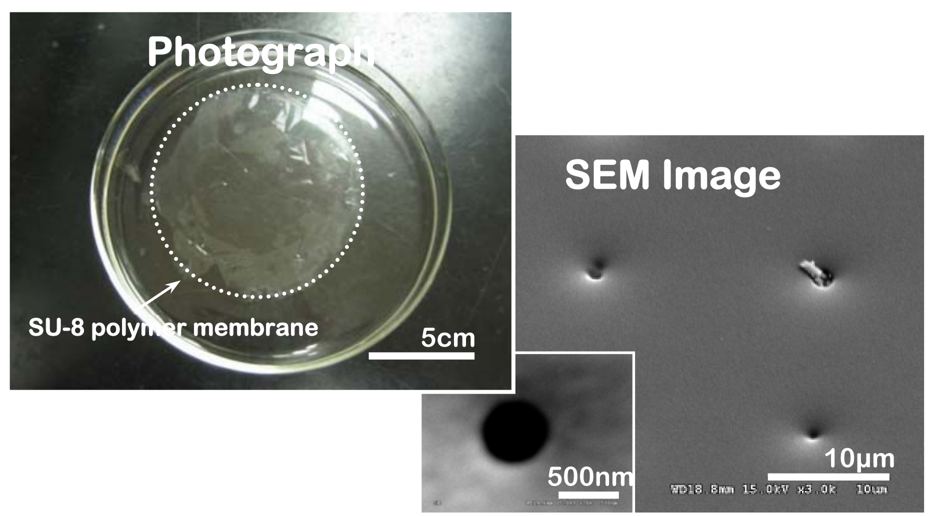
- **GOAL**: To develop fluidic devices using nanopore and nanochannel technologies that enable acquisition of chemical/biochemical information to near real time irrespective of the target to be detected.

- **APPROCH**: Low cost and all-parallel fabrication methods

Nanochannel

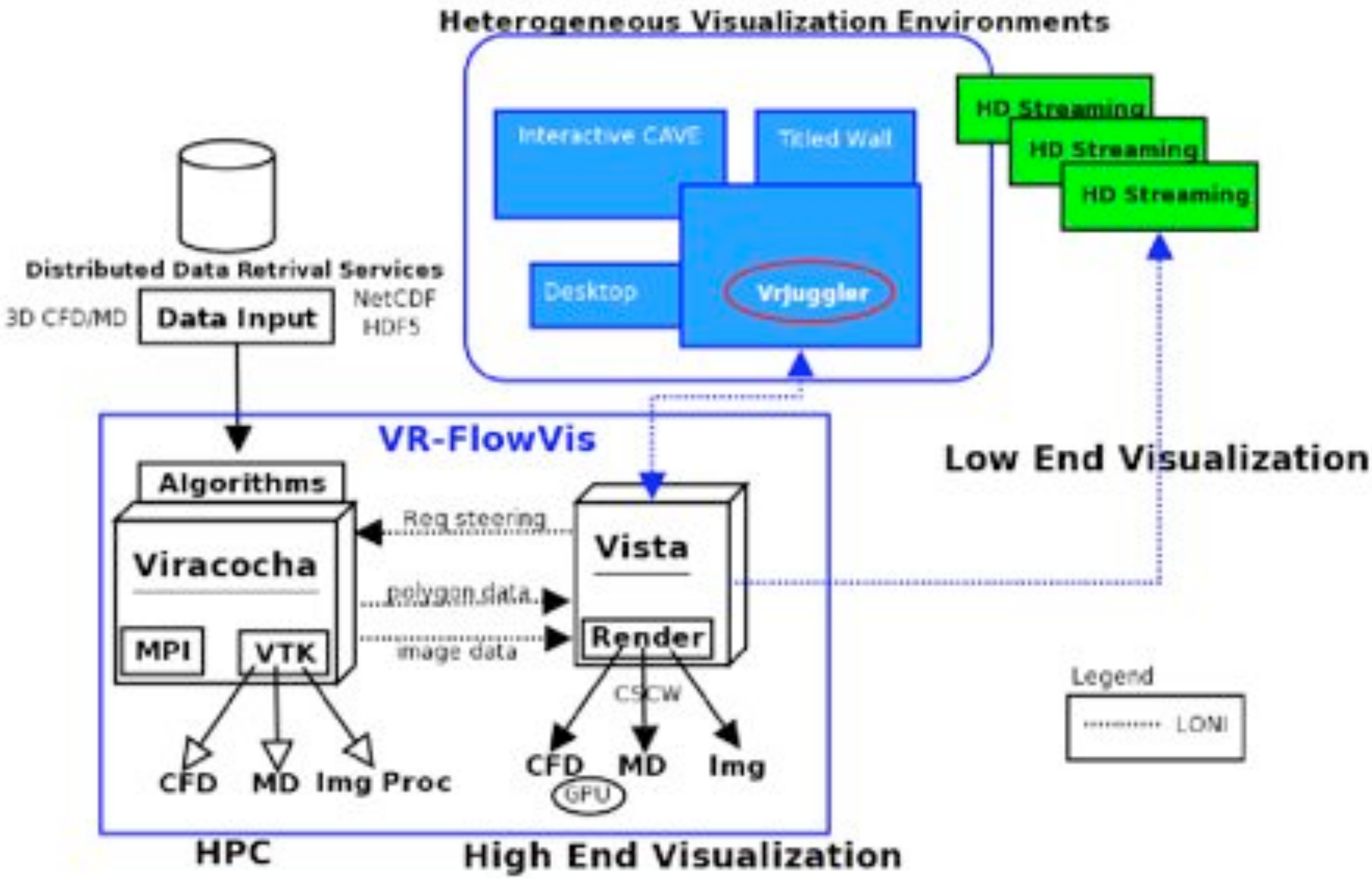


Nanopore



VRFlowVis

- Nikhil Shetty & Vignesh Nateshan



A MODULAR MICROFLUDIC APPROACH TO MUTATION DETECTION WITH POLYMER MEMS TECHNOLOGIES

Tae Yoon Lee[1,2], Kyudong Han[1,3], Dimistris E. Nikitopoulos[1,2], Steven A. Soper[1,2,4], Mark A. Batzer[1,3] and Michael C. Murphy[1,2]
[1]Center for BioModular Multi-Scale Systems, [2]Department of Mechanical Engineering, [3]Department of Biological Science,
[4]Department of Chemistry, Louisiana State University, Baton rouge, LA 70803, USA

A microfluidic modular system was designed for detecting point mutations through the PCR/LDR analysis. Each functional device was developed from the results of on- and off-chip experiments to enhance the capability of device.

MATERIALS AND METHODS

Genomic DNA & Chemical reagents →

Polymerase chain reaction (PCR)

↓ ← Exonuclease

Purification of PCR products

↓

Mixing in laminar flow

DNA Ligase with buffer → ↓ ← Short allele-specific synthetic probes

Ligase detection reaction (LDR)

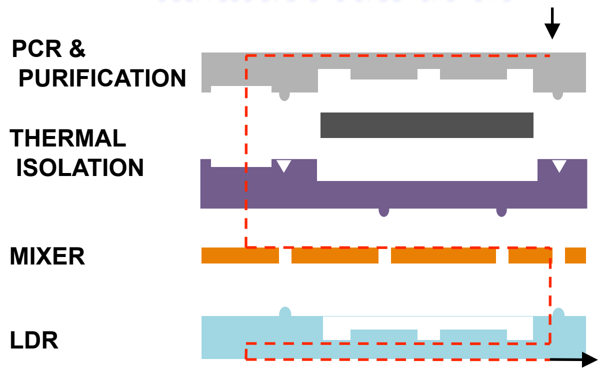
↓

Gel electrophoresis or Microarray

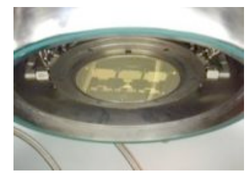
↓

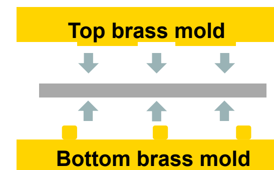
Waste

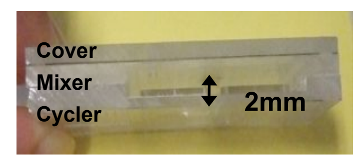
DESIGN CONCEPTS



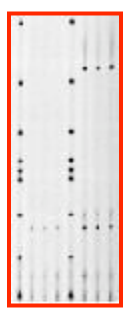
FABRICATION

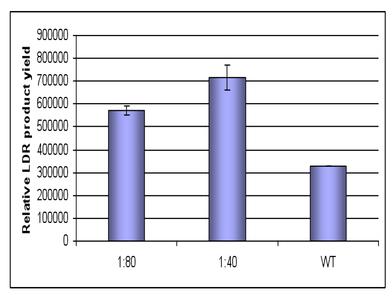


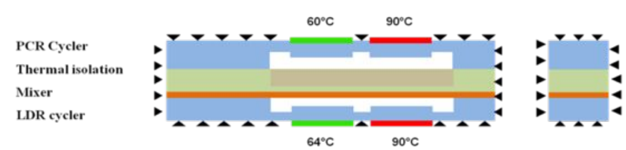


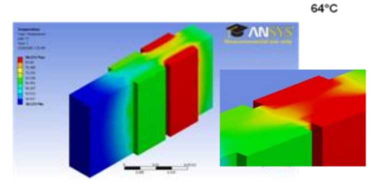


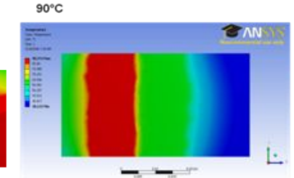
PRELIMINARY RESULTS











Genosensor Platform for Human Identification

Małgorzata A. Witek, PIs: Steven A. Soper and Mark A. Batzer Research Groups, LSU
Department of Chemistry, Department of Biological Sciences,
Center for BioModular Multi-Scale Systems (CBMM)

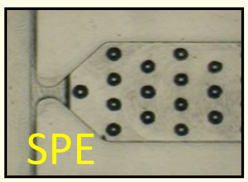
- Human Identification via ***Alu* elements fingerprinting**
- *Alu* represent the **most abundant** class of short interspersed **elements in the human genome**.
- *Alu* are **identical by descent**,

→ determination of individuals geographic origins of suspects in criminal investigations, **paternity testing**, and **gender identification.**

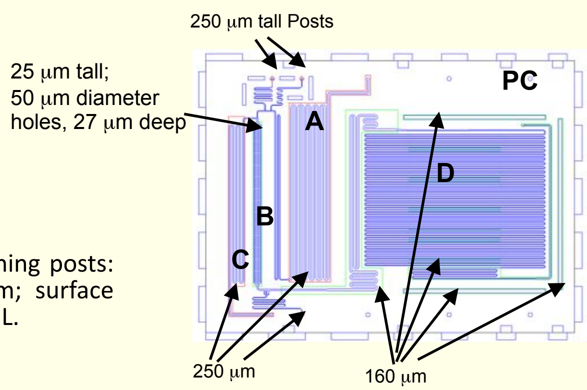
Forensic Science International 153 (2005) 117–124

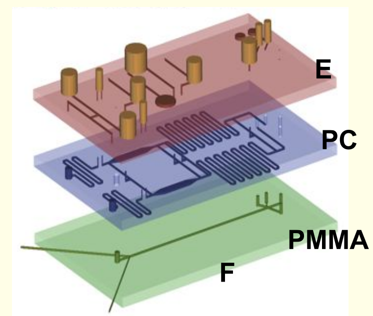
The modular integrated system : (A) cell lysis; (B) SPE of gDNA; (C) PCR buffer loading; (D) Continuous Flow Polymerase Chain Reactor (CFPCR) with dual depth channels; (E) reagent dispensing module; (F) μCE;

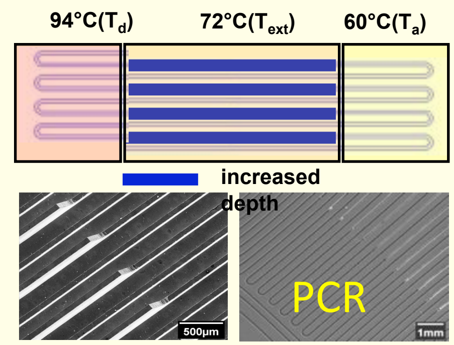
The system contains fluidic chip and the support peripherals for fluidic control and detection



Micrograph of SPE bed containing posts: d = 100 μm; spacing 200 μm; surface area = 13 mm^2, volume = 310 nL.







Dual-depth CFPCR, channel width = 80 μm, channel length =1450 mm, volume =12.7μL.

System Characteristics

1. Fully integrated
2. Low cost ($5,000)
3. Easy to use
4. High sensitivity detector
5. Flexible architecture

System modeling and simulation required for optimizing the performance of miniaturized systems: assembly, integration, geometrical architectures, and materials selection

Financial Support: NSF EPSCoR and Louisiana Board of Reagents

MAY 30th, ALL HANDS MEETING

CBM² CENTER FOR BIOMODULAR MULTI-SCALE SYSTEMS

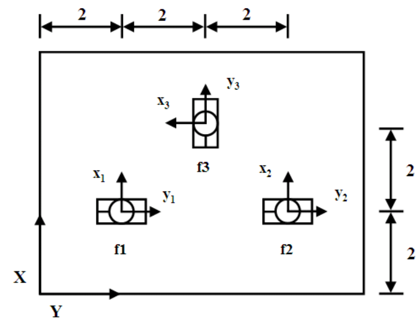
LSU

Microassembly Technology for Modular, Polymer Microfludic Devices

B. H. You, P.-C. Chen, D. S. Park, S. A. Soper, D. E. Nikitopoulos, and M. C. Murphy

[1]Louisiana State University, Baton Rouge, LA 70803, U.S.

Summary – Passive alignment structures can prevent infinitesimal motions between and minimize misalignment of modular, polymer microfluidic devices. The motion and constraint of passive alignment structures were analyzed for the design of assembly features using screw theory. A combination of three v-groove and hemisphere-tipped post joints constrained all degrees of freedom of the two mating microdevices without over-constraint. To validate the designed passive alignment scheme, hot embossing experiments were conducted using a micromilled brass mold insert, containing alignment features. Prototype alignment structures have dimensional and location variation. The alignment accuracy of the stacked polymeric plates was estimated by the mismatches between alignment marks of two plates. The mismatches ranged from 11 µm to 16 µm along the X-and Y-axes.



Exactly Constrained Assembly Without Over-constraint

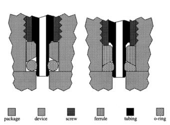
$$RT = Reciprocal\left\{\bigcup_{i=1}^{n} Reciprocal(Ti_{ref})\right\} = [\ ]$$

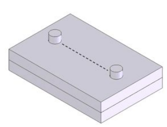
$$WR = Reciprocal\left\{\bigcup_{i=1}^{n} Reciprocal(Wi_{ref})\right\} = [\ ]$$

■ Design of Assembly Features

► Conventional assembly of microfluidic devices

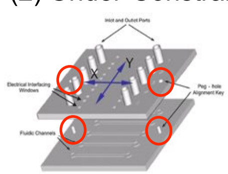
(1) Over-constrained assembly

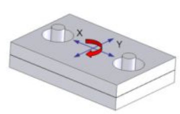




Two Pin-in-Hole Pairs ➡ Over-constraint

(2) Under-Constrained assembly

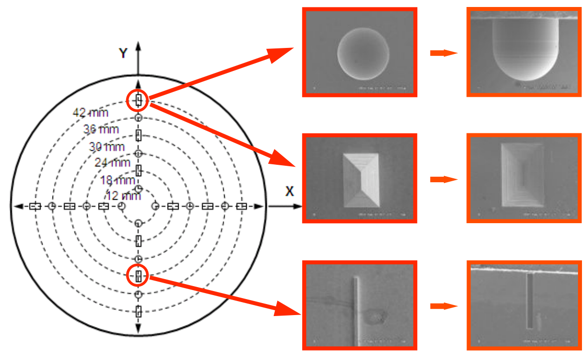




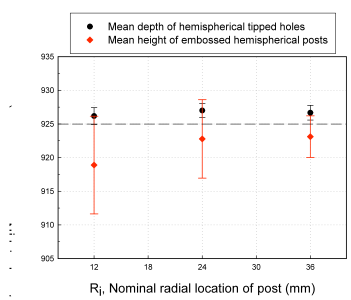
Over-sized Holes ➡ Under-constraint

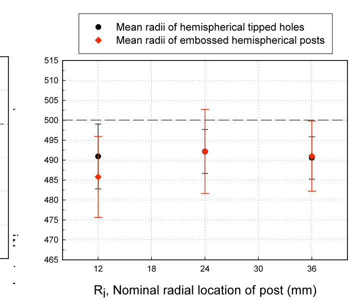
The problem with the conventional assembly of microfluidic devices to date is the design of assembly features without motion and constraint analysis. Kinematic design of the assembly features is needed to prevent under-constraint and over-constraint in assembly so that precise, inexpensive assembly, enabling reliable microfluidic interconnections, can be achieved.

■ Mold Inserts and Replication

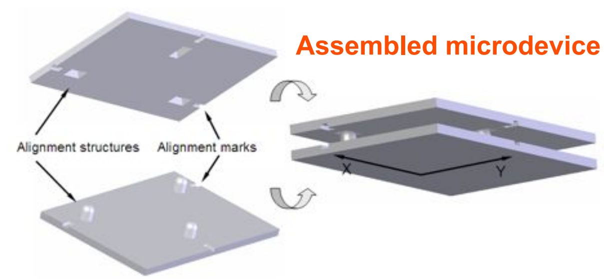


■ Dimensional Variation of Assembly Features

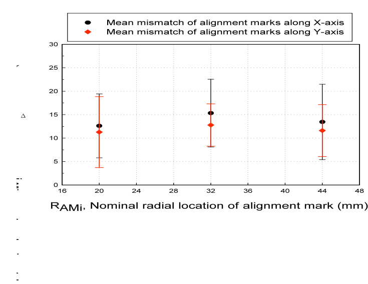




■ Assembly of Modular, Polymer Microdevices



► Mismatches of X- and Y-axes in assembly



BALANCING THE USE OF REMOTE I/O VERSUS STAGING IN DISTRIBUTED ENVIRONMENTS

Ibrahim H Suslu & Tevfik Kosar

Department of Computer Science and Center for Computation & Technology (CCT)

Louisiana State University, Baton Rouge, LA

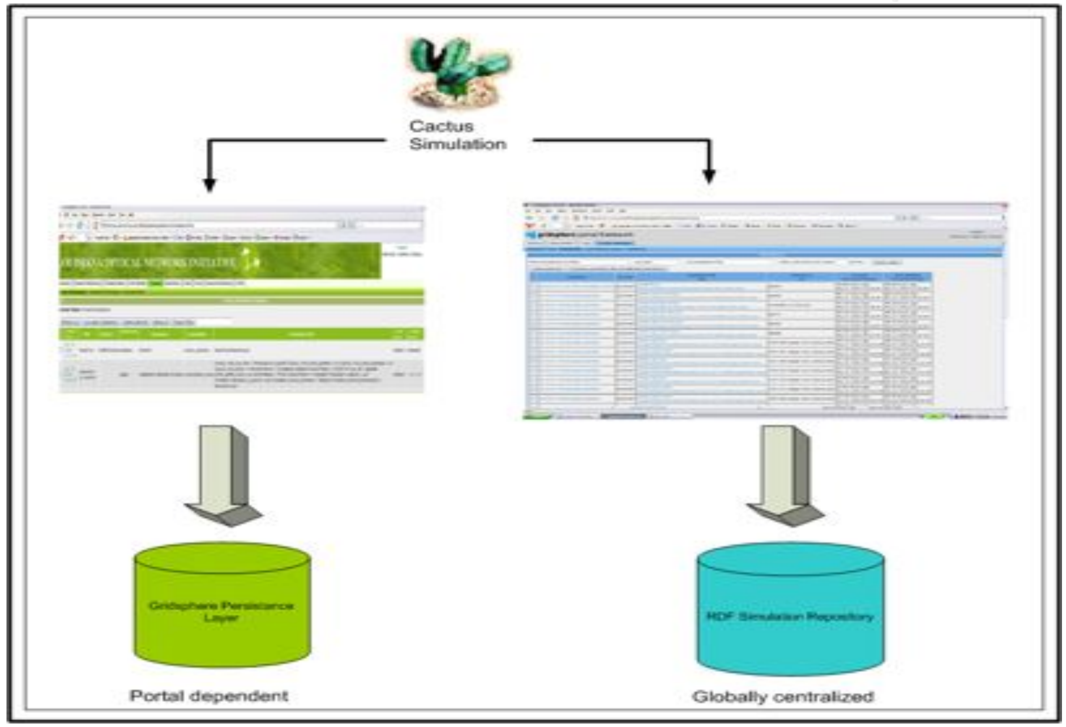
- Developing a generic model which can be applied to most data intensive distributed applications to decide the best data access model (staging or remote I/O)
- UCoMS
  - Utchem
  - Blackoil

Application Information and Portals

CENTER FOR COMPUTATION & TECHNOLOGY

We are researching mechanisms for using portals to collect and provide runtime information from simulations.

We are starting by looking at existing work in Cactus, SAGA, and the German D-Grid project.



My research interests include: distributed authorization and access control, cactus simulation-specific information services provision and portal visualization.

Katerina Stamou, kstamou@cct.lsu.edu, CCT/LSU