SimBios: NIH Center for Biomedical Computation

Physics-based Simulation of Biological Structures

Dr. Alain Laederach

Dr. Jonathan Dugan

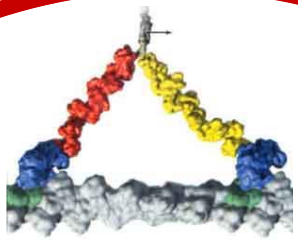
Dr. Jung-Chi Liao

Dr. Paul Mitiguy

What is Simbios?

Physics-based Simulation of Biological Structures

Aerospace

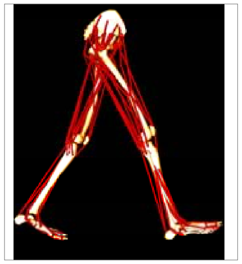


Myosin Dynamics

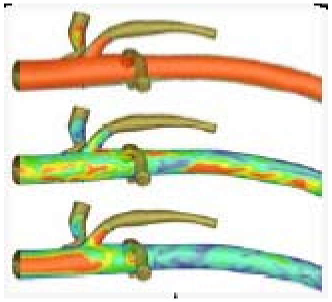
Planes, Trains, & Automobiles

RNA Folding

F=ma



Neuromuscular Biomechanics



Cardiovascular Dynamics

Agriculture & Construction

Machines & Manufacturing

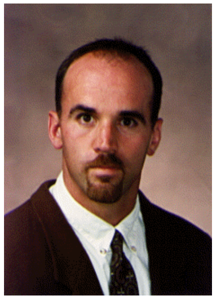
Who is Simbios?

- Visionaries

- Leaders

Russ Altman: Principal Investigator
Professor of Genetics, Bioengineering,
Medicine & Computer Science

Scott Delp: Principal Investigator
Chair: Department of Bioengineering,
Mechanical Engineering, Orthopaedic Surgery



Charles Taylor: Cardiovascular Dynamics
Mechanics & Computation, Bioengineering,
Surgery, Pediatrics, Radiology

…

- Staff (medical, computer, physics, …)

Jeanette Schmidt: Executive Director
Mathematics, Computer Science,
Biological Algorithms, Bioinformatics,
Genomics

Christopher Bruns: Computational Biology,
Biochemisty, Molecular Biology,
Computer Science

Michael Sherman: Chief Architect,
Molecular Dynamics, Computer Science,
Biosimulation, Multibody Mechanics

Bill Katz: Senior Scientist, M.D. Ph.D.
Computer-aided Treatment Planning,
Medical Imaging Analysis, Science Writer

…

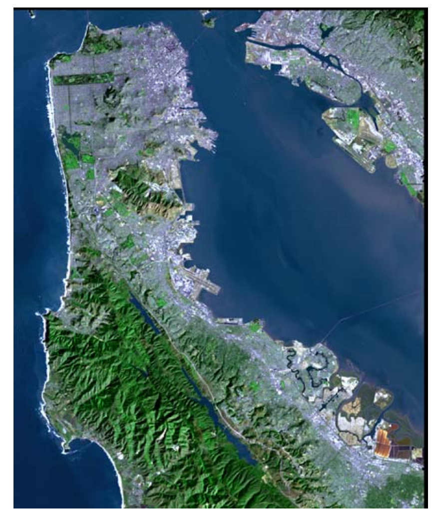
Where is Simbios?

Medical Research
Stanford Hospital
Packard Hospital

Engineering
Physics & Chemistry
Computer Science

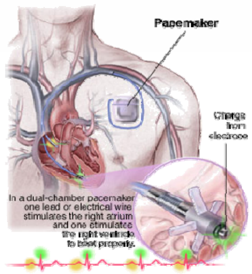
Stanford University

Clark Center

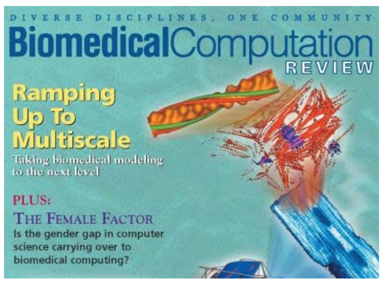


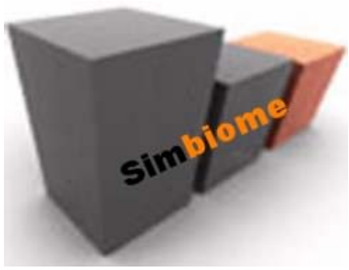
Silicon Valley

Simbios Overview



- **Scientific Applications & Collaboration**
- **SimTK Simulation Toolkit**
- **Biosimulation Superforge: simtk.org**
- **Dissemination & Training**

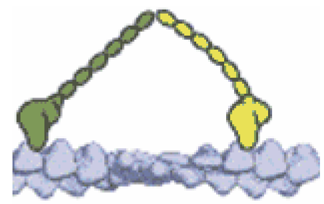




Scientific Applications

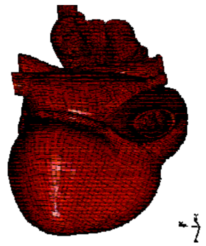
- **RNA Folding**
  (PI: Dan Herschlag   Presenter: Alain Laederach)

- **Myosin Dynamics**
  (PI: James Spudich   Presenter: Jung-Chi Liao)



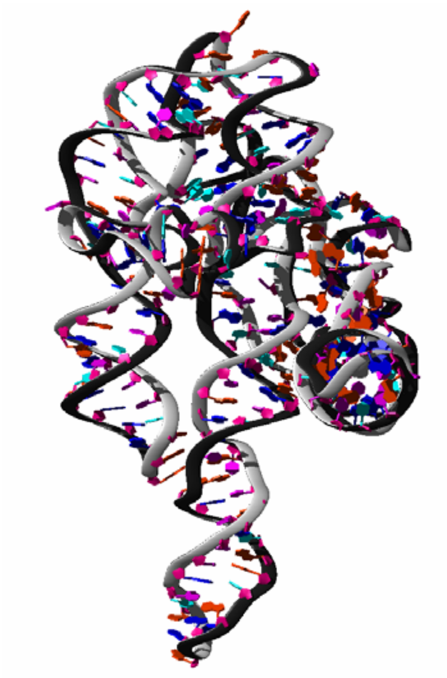
- **Neuromuscular Biomechanics**
  (PI: Scott Delp   Presenter: Paul Mitiguy)

- **Cardiovascular Dynamics**
  (PI: Charles Taylor   Presenter: Paul Mitiguy)

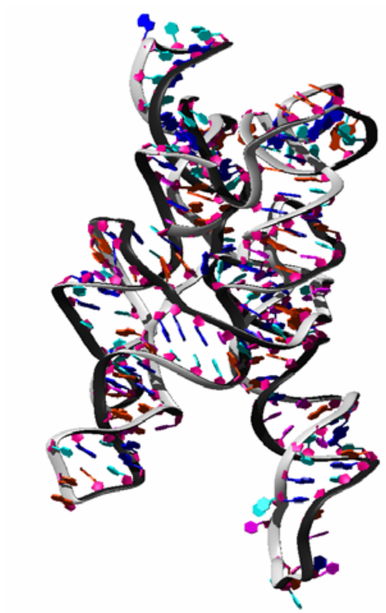


RNA Folding: Objectives

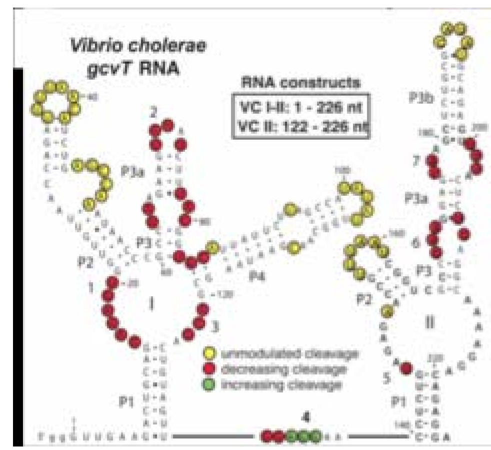
Understand structure & function of RNA



Tetrahymena group I ribozyme, Golden et al. 2004, *Science* 282, 1998



Azoarcus group I ribozyme, Adams et al. 2004, *Nature* 430, 2004



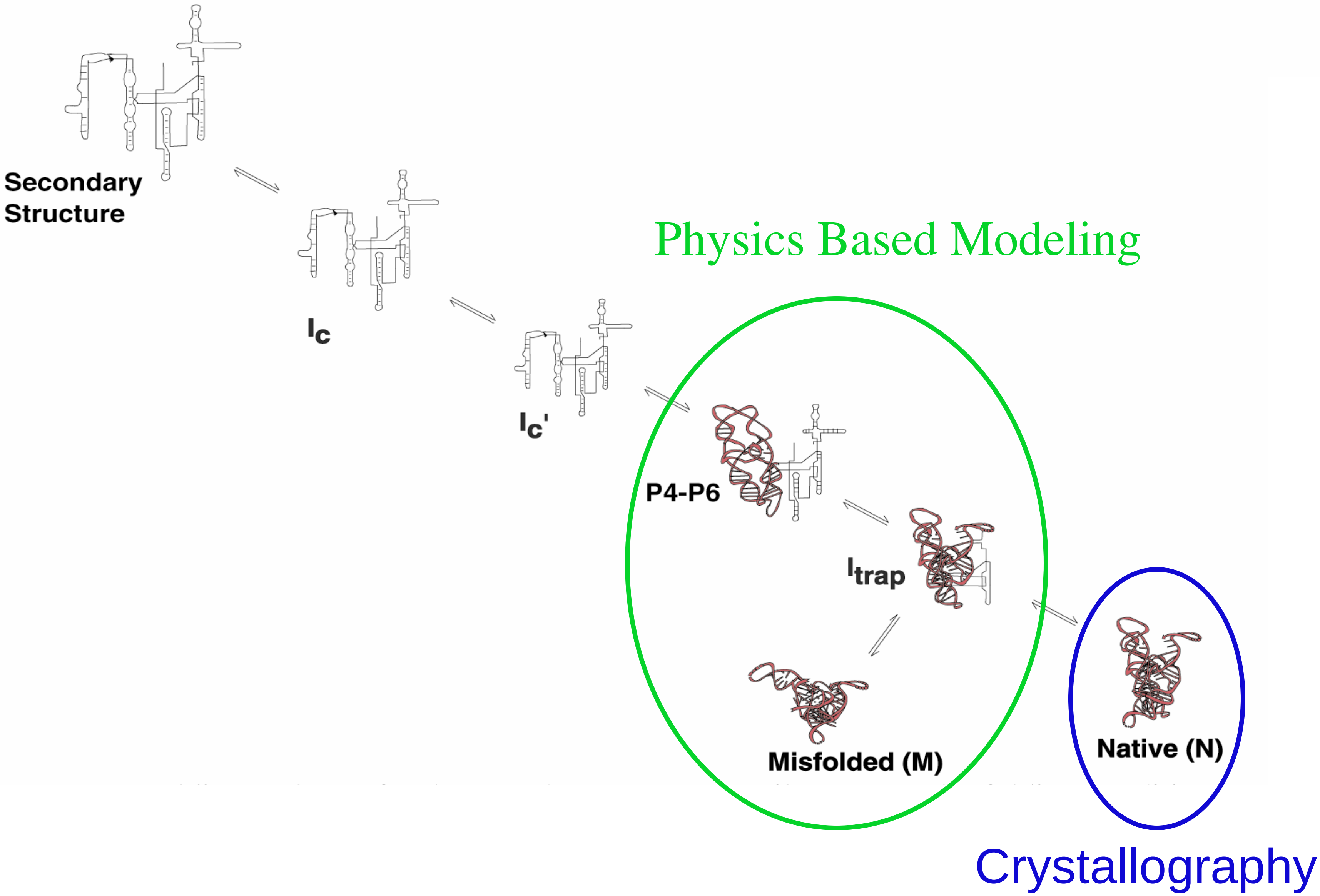
A Glycine-Dependent Riboswitch That Uses Cooperative Binding to Control Gene Expression

Maumita Mandal,[1] Mark Lee,[2] Jeffrey E. Barrick,[2] Zasha Weinberg,[3] Gail Mitchell Emilsson,[1] Walter L. Ruzzo,[3,4] Ronald R. Breaker[1*]

Science, Vol 306, Issue 5694, 275-279 , 8 October 2004

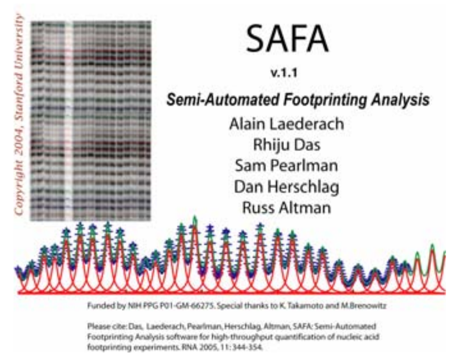
About 2% of genes in *Bacillus subtilis* are regulated by riboswitches

RNA Folding: Objectives

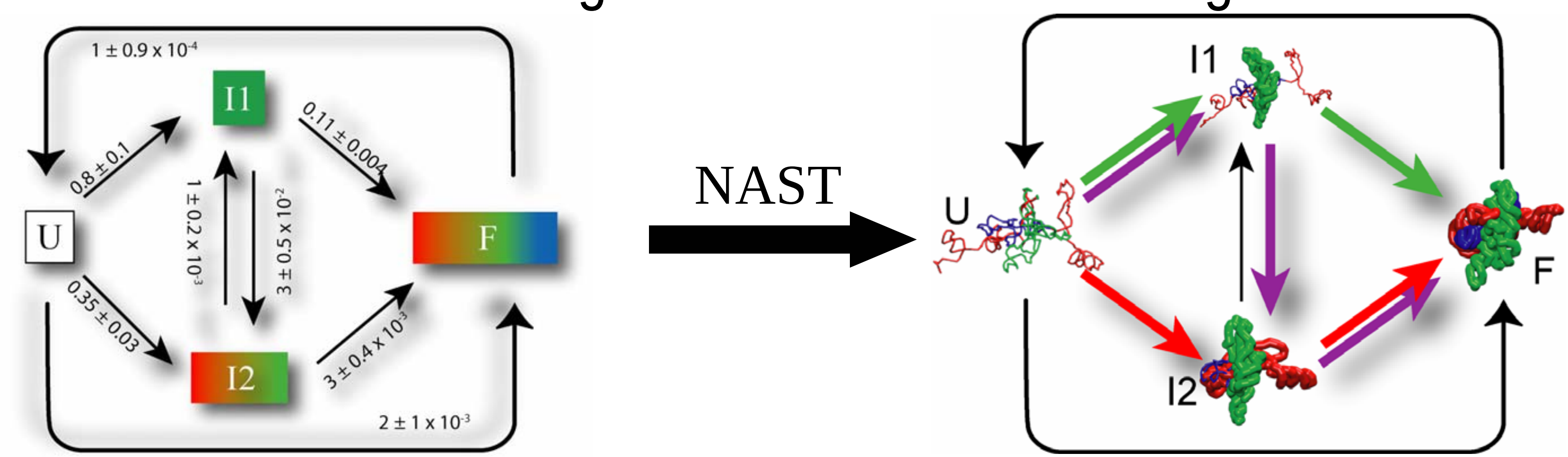


RNA Folding: Successes

- SAFA
  - Quantitative Footprinting Gel Analysis
  - Over 300 registered users

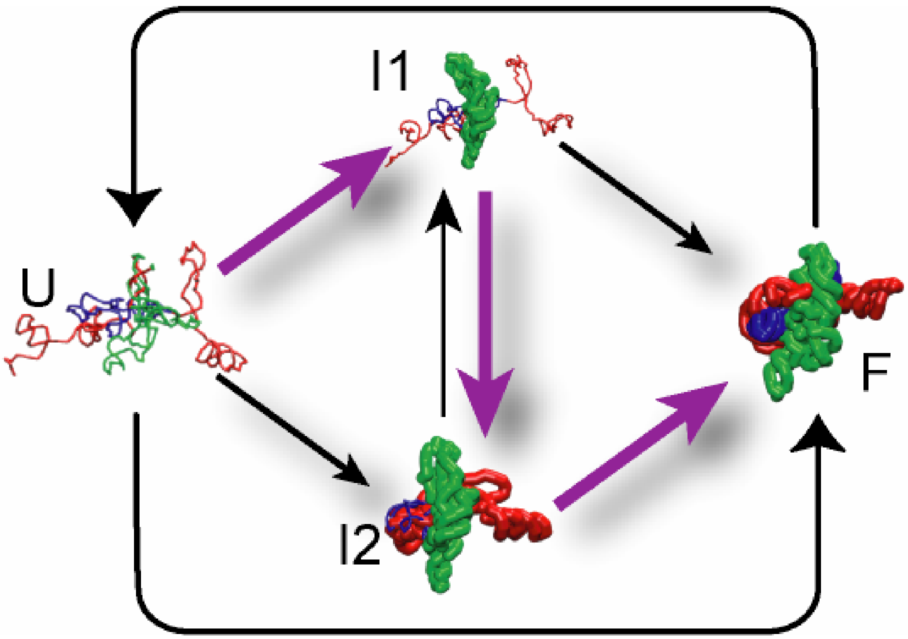


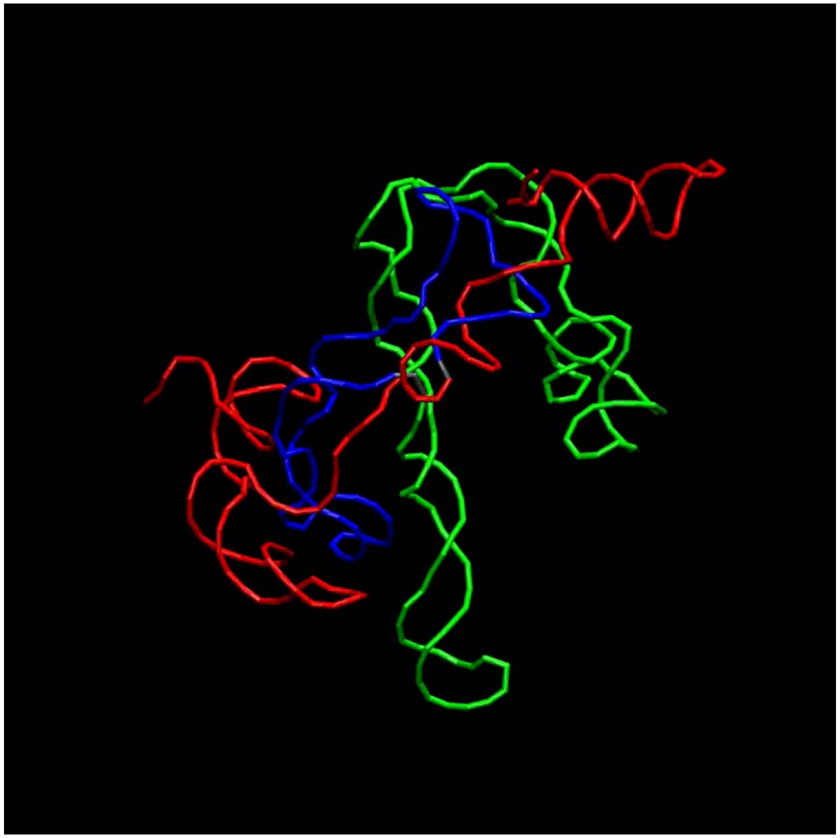
- KinFold
  - Kinetic Modeling Software for RNA Folding



RNA Folding: Successes

- NAST
  - Nucleic Acid Simulation Tool





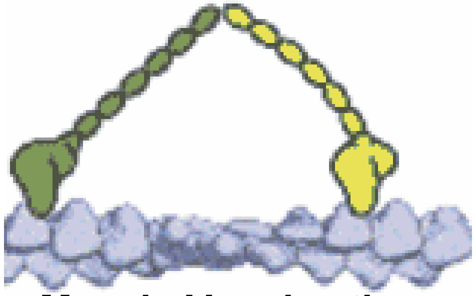
RNA Folding: Challenges

- Forward Prediction of RNA Folding Pathways
- Integration of experimental conditions
- Folding Pathway Alignments
- Co-Transcriptional Folding

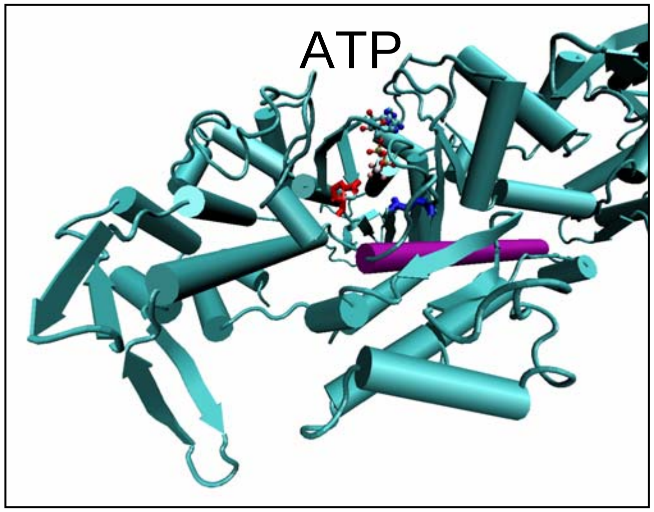
Myosin Dynamics: Objectives

Model the fundamental source of motive force in living systems

- Myosin: a model system in molecular scale to study mechanical effects on enzyme functions
- Simulate the dynamics to complement experiments in spatial/temporal resolutions
- Develop computational methods to understand structure-function relationship
- Understand how mechanics regulates chemistry
- Understand how energy transmits within the enzyme

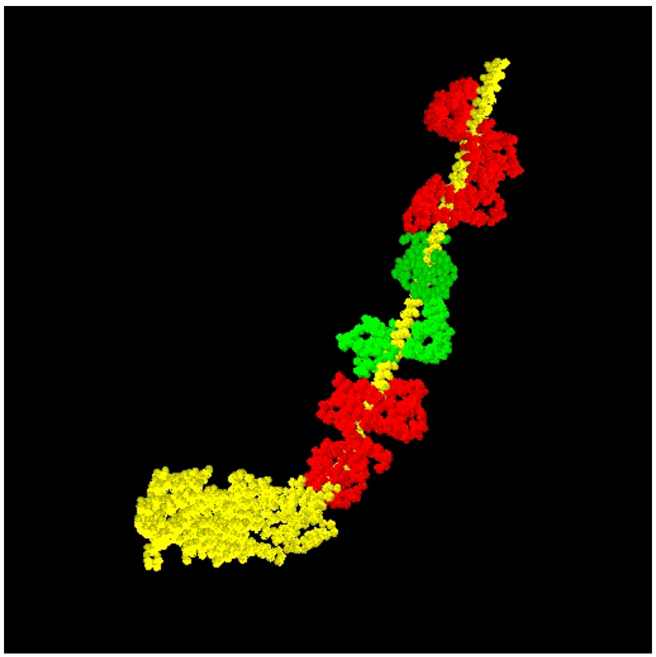


Myosin V and actin

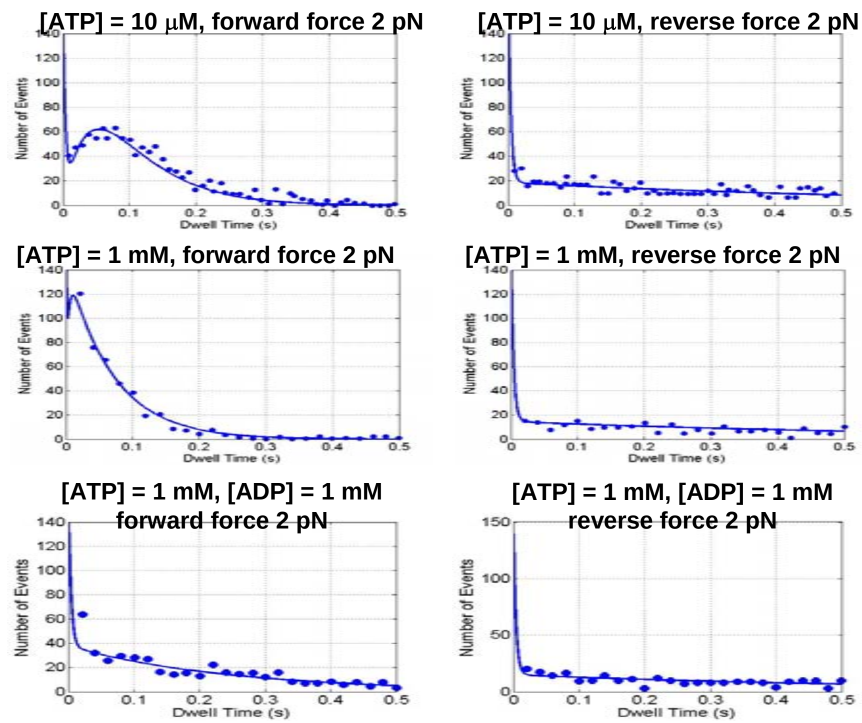


Myosin Dynamics: Successes

- Normal mode analysis to study the neck rigidity
- Identify the power stroke step by fitting dwell-time distributions



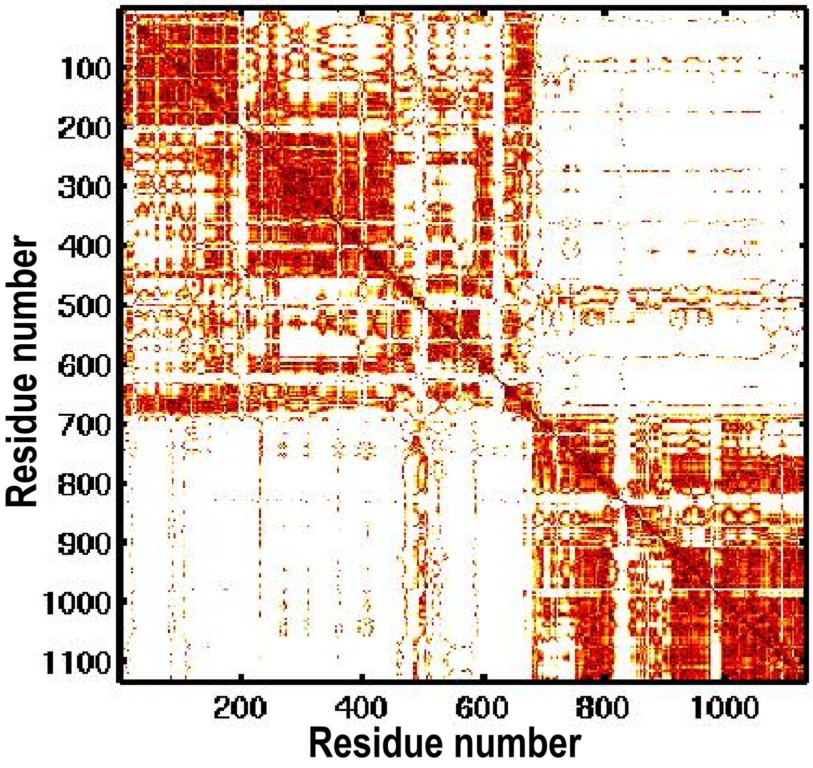
Motion of the lowest frequency mode



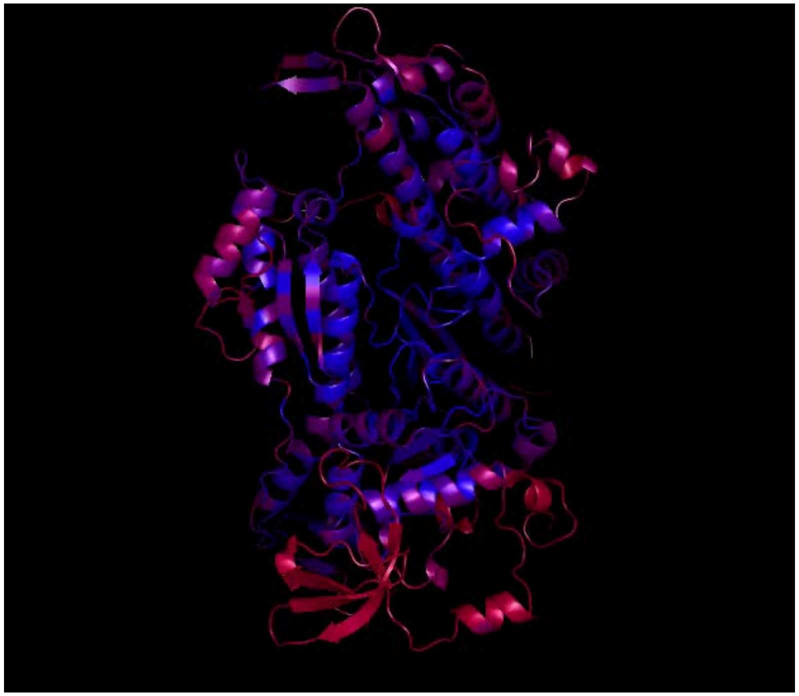
Petrone P & Pande VS *Biophys J* 90:1583 (2006)

Myosin Dynamics: Successes

- Distance difference maps reveal rigid sections



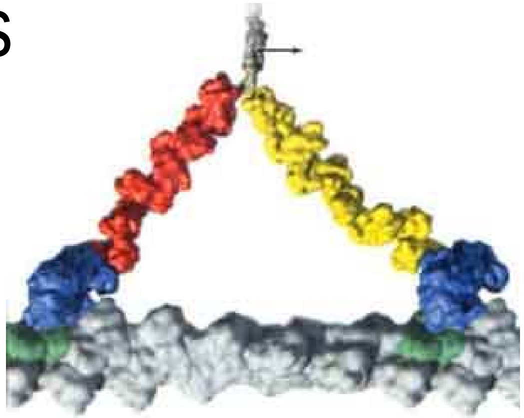
- Energy transmission path
  - Blue: most conserved
  - Magenta: least conserved



Conservation scores

Myosin Dynamics: Challenges

- Develop coarse-grained models of myosin that are consistent with observed large-scale movements
- Determine the force transmission among the catalytic site, the lever arm and the actin binding site
- Develop a physics-based model to explain how the mechanical force affects kinetic rates



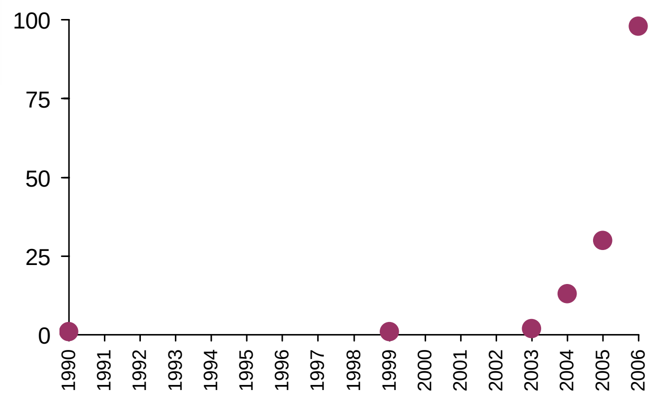
Neuromuscular Biomechanics: Objectives

Improve treatment of movement disorders

- **Understand how neuromuscular impairments effect motion**
- **Provide a scientific basis for treatment**
  - **Botox injections**
  - **Tendon transfers**
  - **Physical therapy**
- **Application to cerebral palsy, stroke, spinal cord injury, birth defects, …**

Connecticut Children's Medical Center
Stiff-knee Gait from Cerebral Palsy

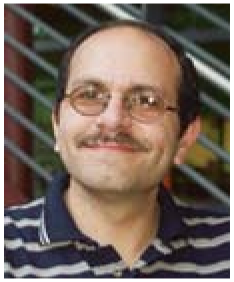
Neuromuscular Biomechanics: Successes



Number of 3D muscle-actuated gait simulations

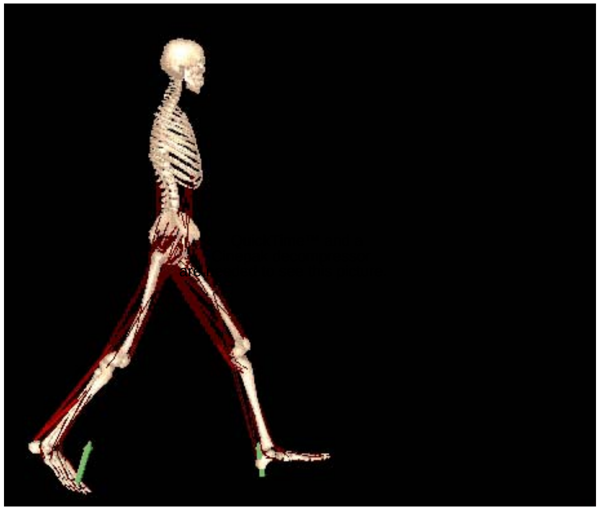
Dr. Clay Anderson

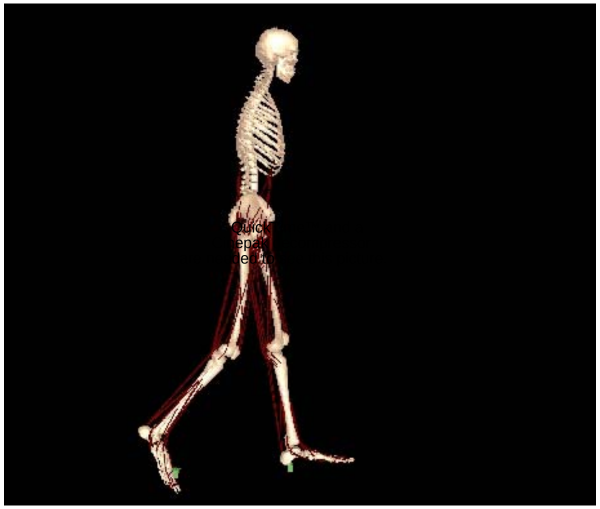
Dr. Allison Arnold



Dr. Ayman Habib

1000x faster algorithms (from weeks to minutes)
Hundreds of subject-specific motion simulations

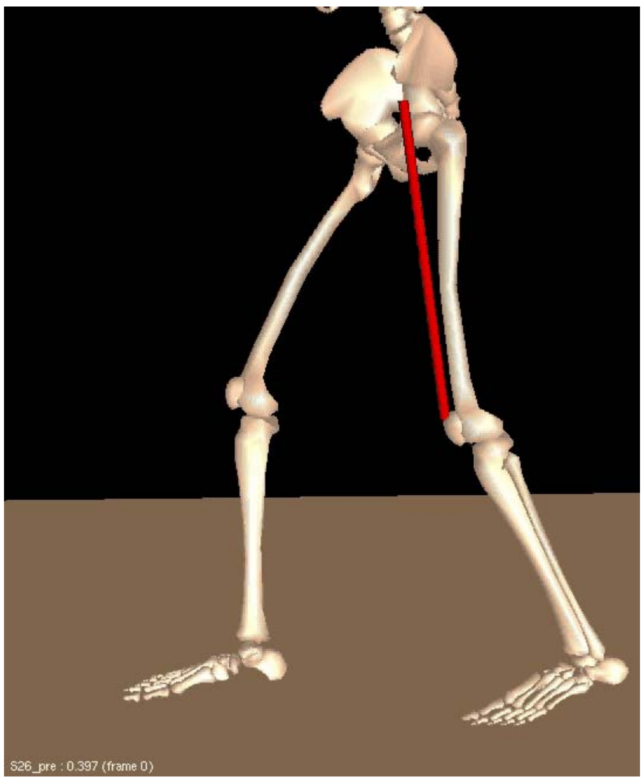




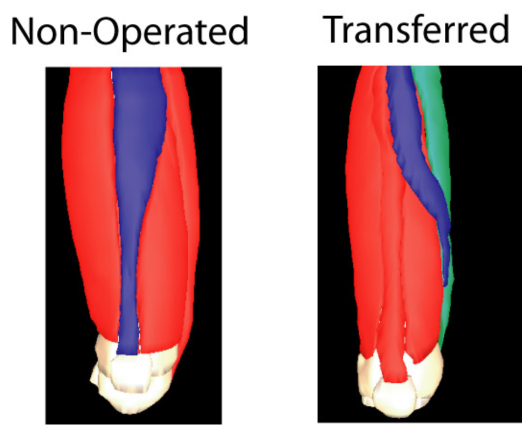
Neuromuscular Biomechanics: Successes

Simulation of tendon transfers

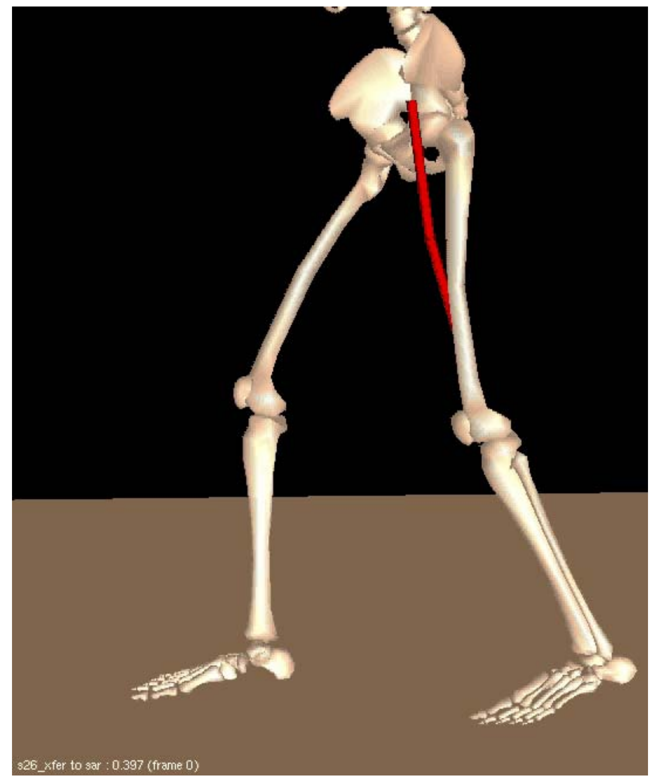
Simulation of botox injection



Pre-tendon transfer



Rectus-femoris tendon transfer



Post-tendon transfer

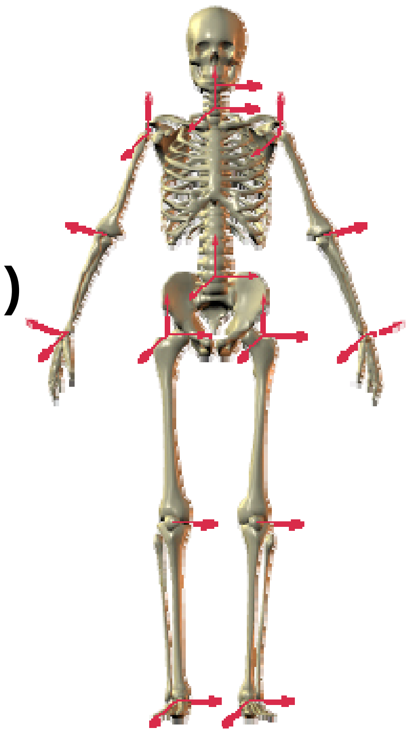
Neuromuscular Biomechanics: Challenges

•**Improved control algorithms for more accurately handling contact**

•**Integration of motion capture data with modeling, optimization, simulation, control, and analysis.**

•**Validation of subject-specific models**

•**Modeling muscle pathology (spasticity, contracture, …)**



Cardiovascular Dynamics: Objectives

Impact surgical, pharmacological, and catheter treatment of cardiovascular disease.
Cardiovascular disease: Number one killer in the U.S. of both men and women.

- **Construct a virtual aorta (image, create, and validate)**
- **Model blood flow and vessel wall deformation in normal subjects and patients with congenital and acquired diseases**

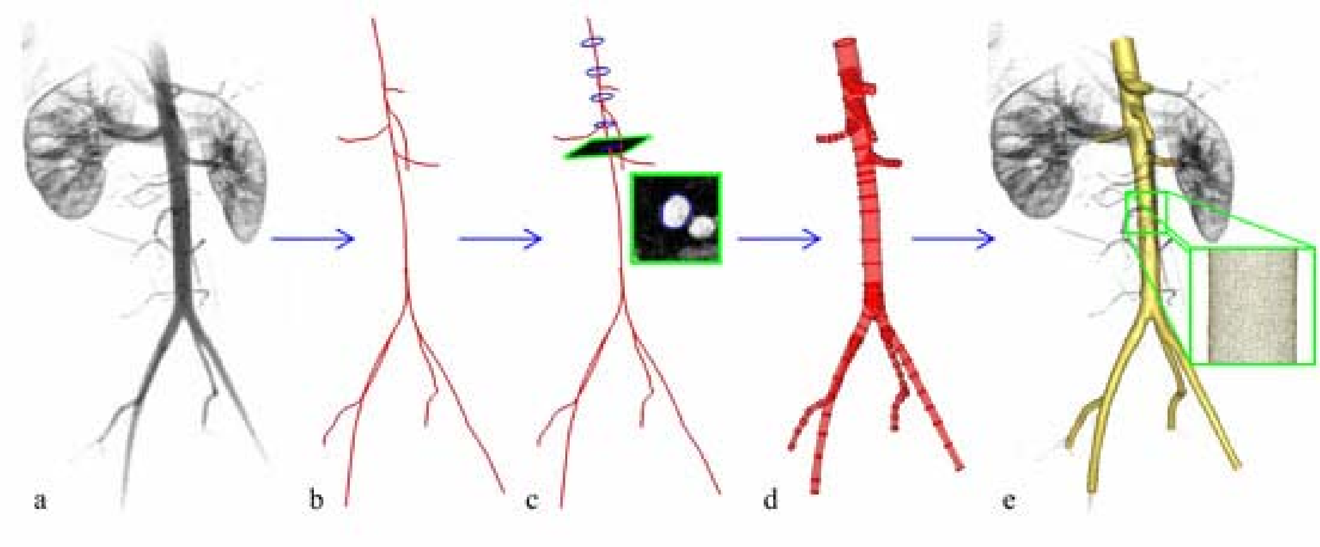
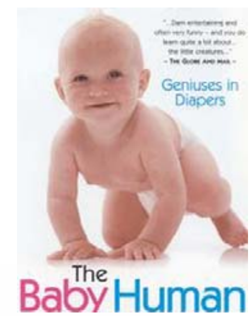
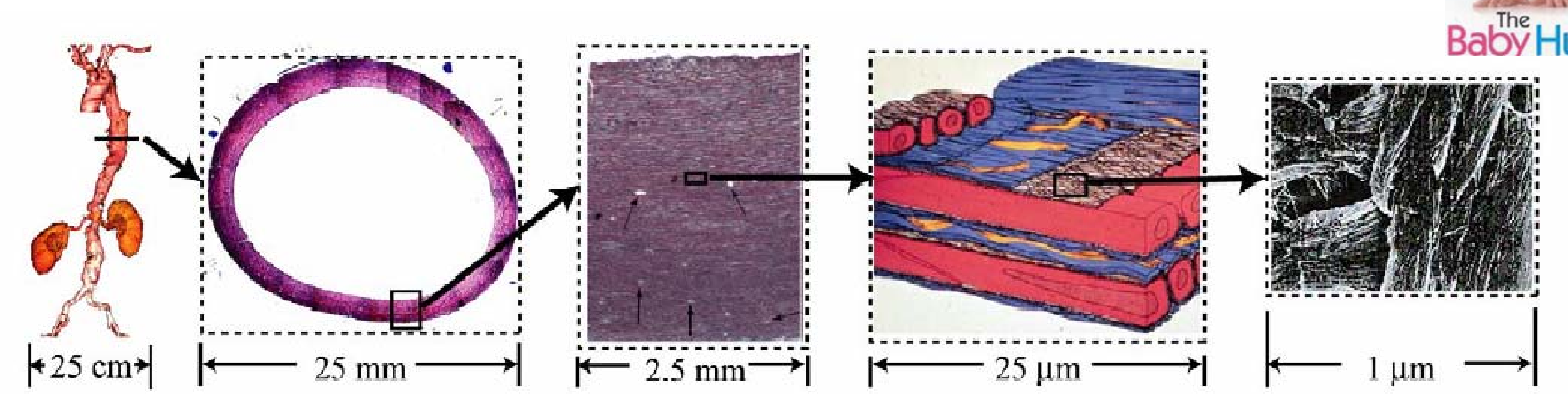


Image the aorta → **Convert the image to an Finite Element Mesh** → **Determine deformation & blood flow**

Cardiovascular Dynamics: Objectives



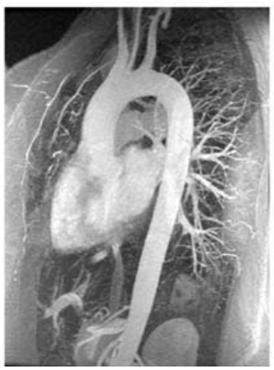
- Create a 3D model of the medial lamellar unit (MLU), the building block of large blood vessels in all mammals
- Validate and improve the model using new imaging techniques
- Scale the microstructural model to find macroscale properties

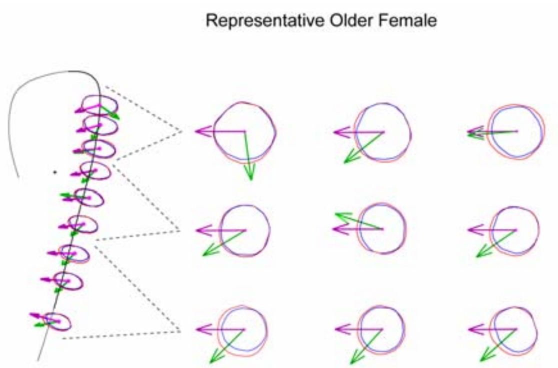


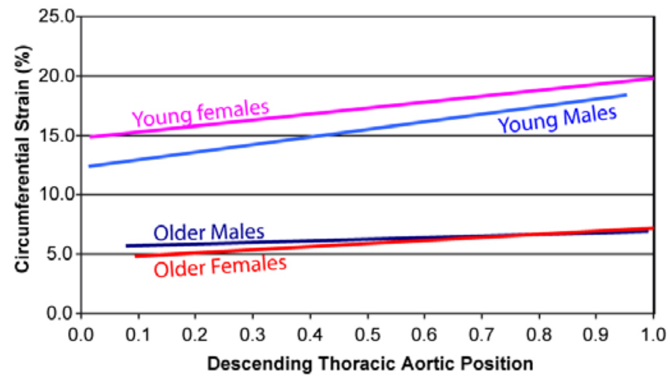
Aorta & lungs **Diameter of aorta** **Aorta Thickness** **Length of MLU Thickness ≈12 µm** **Collagen Fibers**

Cardiovascular Dynamics: Successes

Quantified wall motion of human thoracic aorta in young and older normal subjects using 4D MRI methods.







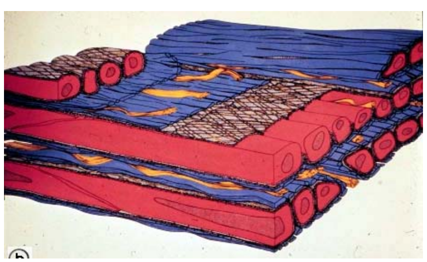
Green: **Primary direction of aorta wall motion**
Magenta: **Orients aorta cross-section**

Young: More elastin
Older: Less elastin, more collagen fibers (%)

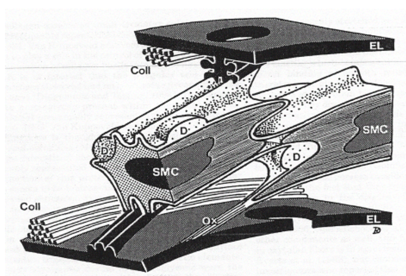
Cardiovascular Dynamics: Successes

Obtained and currently segmenting 3D nanostructural data of aorta MLU via SBFSEM (serial block face scanning electron microscopy).

Previous models of MLU



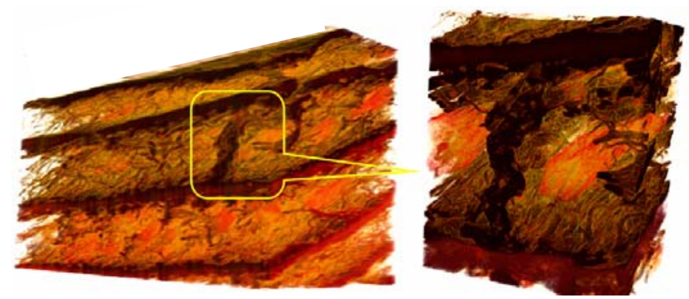
Clark & Glagov, 1985



Dingemans, 2000

Blue – Elastin ½-life of 45-90 days
Red – Collagen fiber ½-life of 70 years

New 3D data from SBFSEM (30nm resolution)

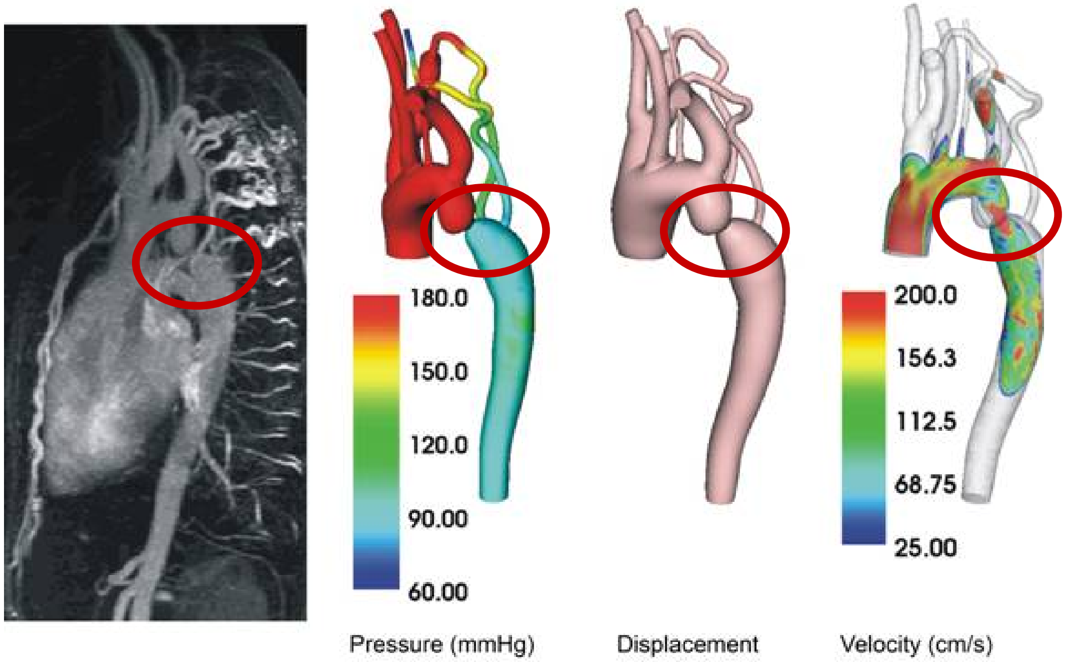


Brown – Elastin lamellae and interlamellar fibers
Orange – Nucleus of smooth muscle cell

Cardiovascular Dynamics: Successes

Progress in modeling aortic blood flow and vessel wall motion in children with aortic coarctation and adults with abdominal aortic aneurysms.

Child with Aortic Coarctation

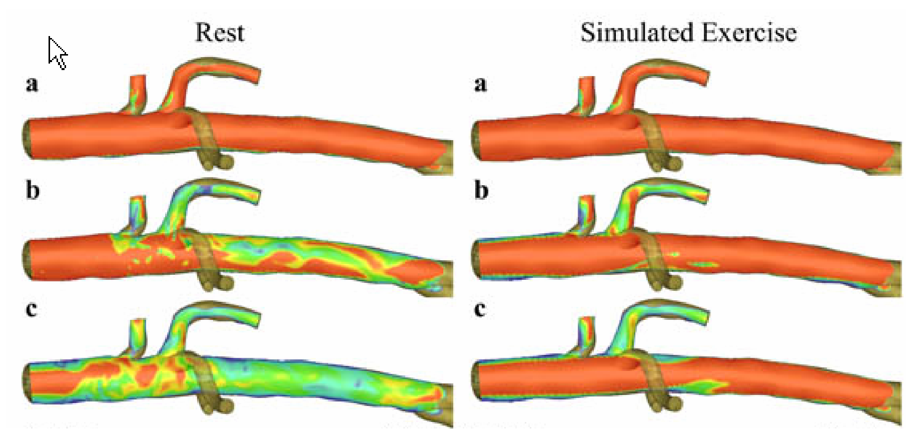


To simulate 10 heart-beats (10-human seconds) it takes 64-256 parallel processors one week.
It requires a 5 million element FEA mesh. It requires a nonlinear FEA solver and fluid/structure interaction.

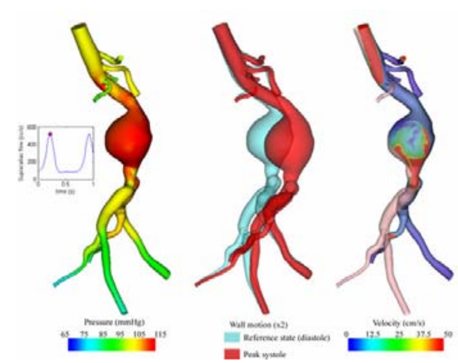
Cardiovascular Dynamics: Challenges

- Automated techniques for creating
  - Time-varying image-based models from 4D MRI data
  - Microstructural computational models from 3D microscopy data
- Nonlinear homogenization techniques to infer macroscale tissue properties from microscale data
- Incorporation of external tissue support in coupled blood flow – vessel deformation simulations

Dr. Christopher Zarins
Chief Vascular Surgeon



Aortic Blood Flow & Stress



Abdominal Aortic Aneurysm

Software Challenges

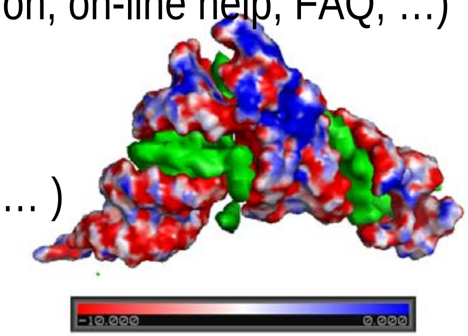
- **Integration of complex software modules**
  (Modeling, imaging, mathematics, dynamics, controls, visualization, data reduction, …)

- **Fast & Efficient**
  (Processor, parallelization, memory, numerical accuracy & stability, time-scales, …)

- **Maintainable**
  (Licensing, multi-platform, quality assurance, documentation, training, bug-tracking, reusable, …)

- **Accessible for beginning-users**
  (Easy-to-use interface, installation, examples, training, documentation, on-line help, FAQ, …)

- **Extensible for expert-users**
  (Connections to MATLAB, CAE tools, scripting & automation tools, …)



Collaboration

Related efforts with Complementary Missions

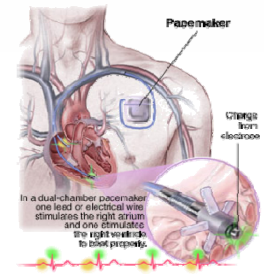
- Independently-funded investigators in simulation
- Established physical simulation tools
- Physiome projects
- Other NCBCs
- P41 Centers (NCRR)
- NSF Multi-scale modeling initiative
- Efforts at DOE & DARPA in simulation

Collaboration

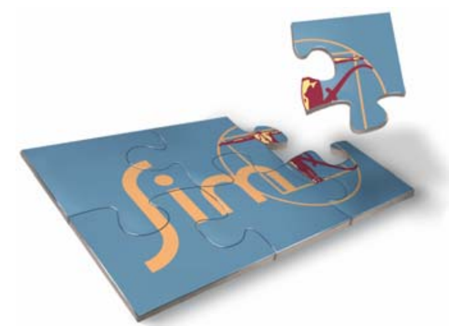
Typical features in NIH Collaborating R01/R21 programs

- Extend existing Simbios DBPs with additional expertise & software development goals
- Introduce new potential DBPs to Simbios
- Use Simbios software tools for new applications
- Use Simbios infrastructure for software & model dissemination/development

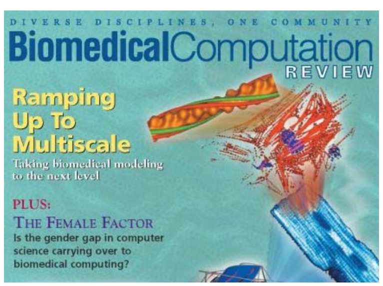
Simbios Overview

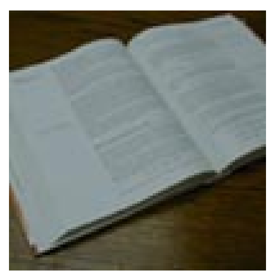


- **Scientific Applications & Collaboration**
- **SimTK Simulation Toolkit**

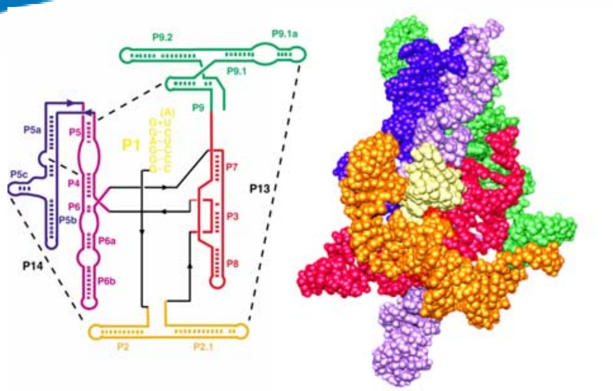


- **Biosimulation Superforge: simtk.org**
- **Dissemination & Training**

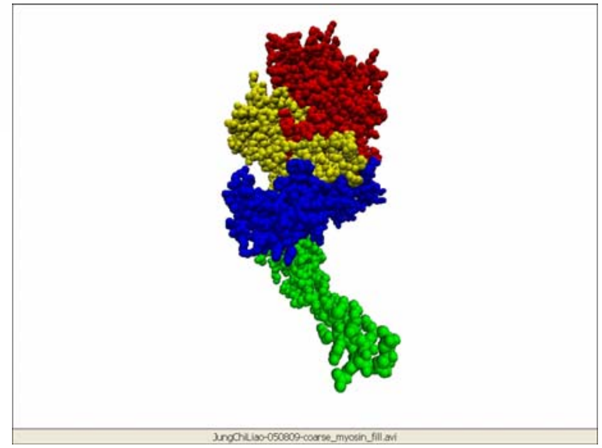




SimTK: Simulation Toolkit

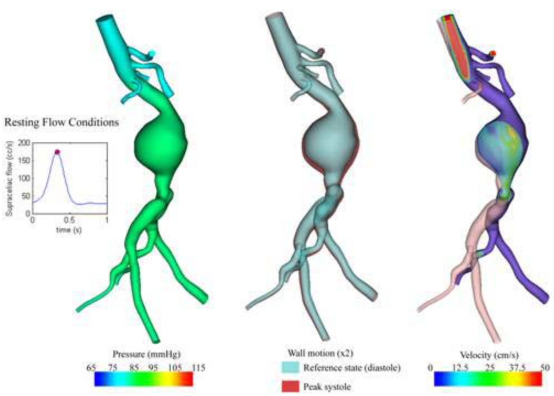


RNA Folding

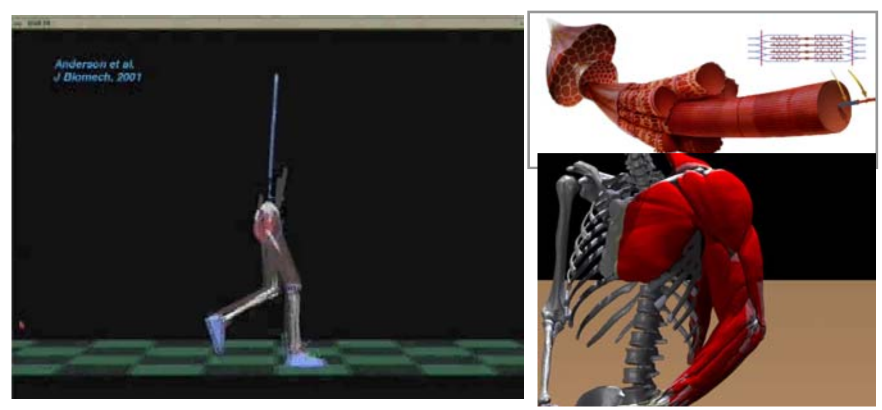


Myosin Dynamics

$$\mathbf{F} = m\,\mathbf{a}$$



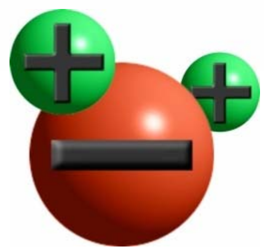
Cardiovascular Dynamics



Neuromuscular Biomechanics

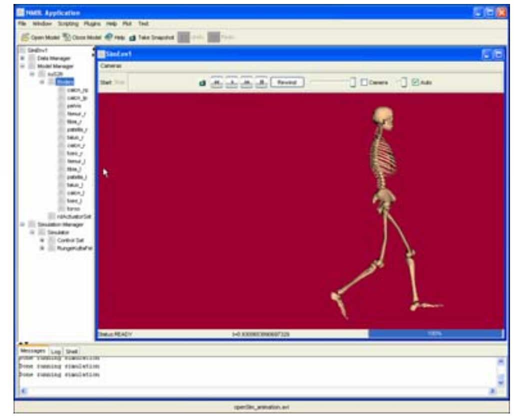
SimTK: Simulation Toolkit

- **Applications**



ISIM

TorRNAdo



OpenSim

- **Libraries & Algorithms**

Simbody

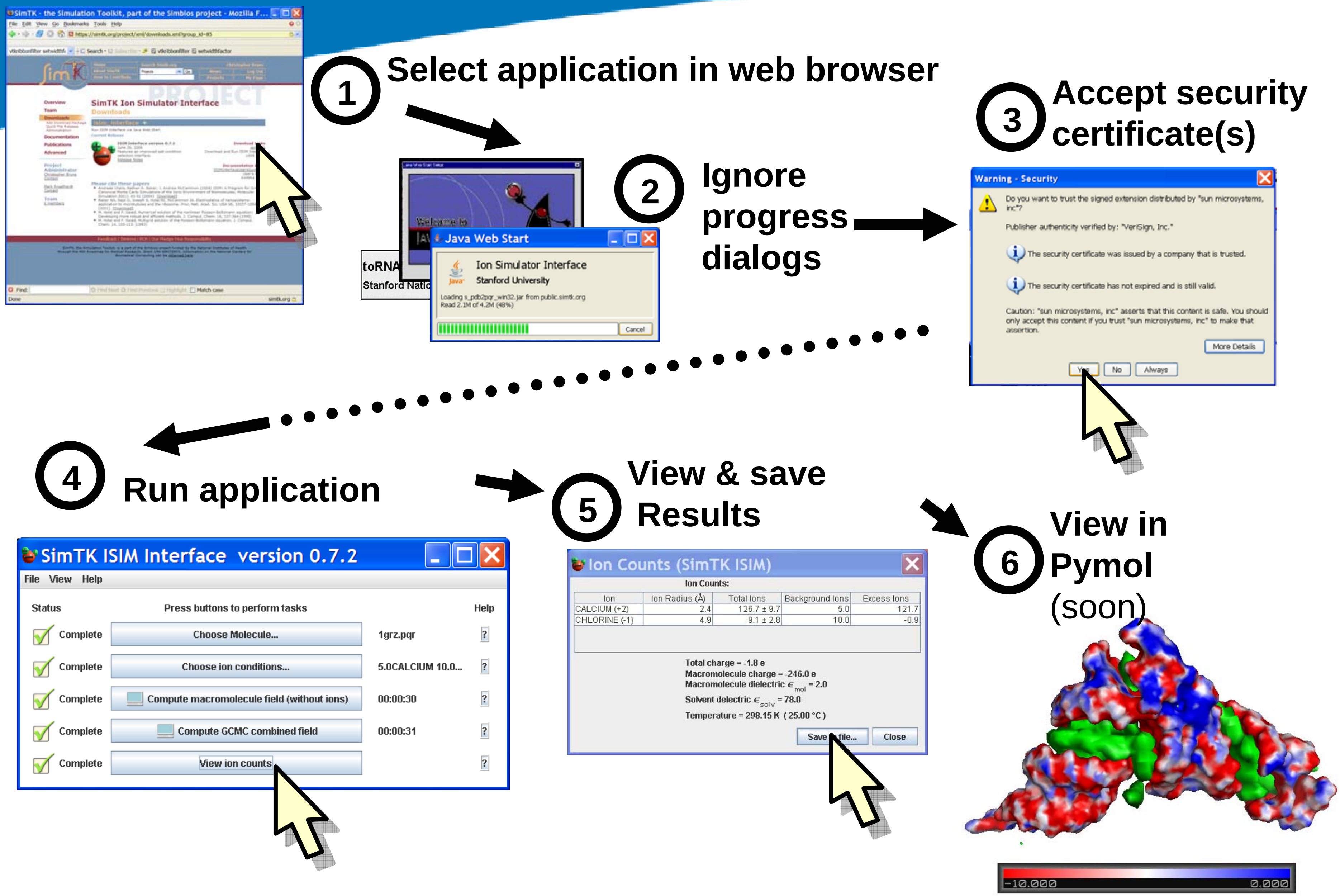
SimTK LAPACK

SimTK CVODE

SimTK Optimize

- **Models and Resources**

Running SimTK ISIM Interface



SimTK Simulation Toolkit: Core

Applications

GUI Tools | Documentation Tools | Installation

Modeling

Linear Algebra

Multi Body Dynamics
Simbody
PRrobot
•

Integrator
ODE
DAE

Contact
Rigid
Penalty
•

Optimize
Sim Anneal
Genetic
SQ Prog

Control
PD

PDEs
Solids
Fluids

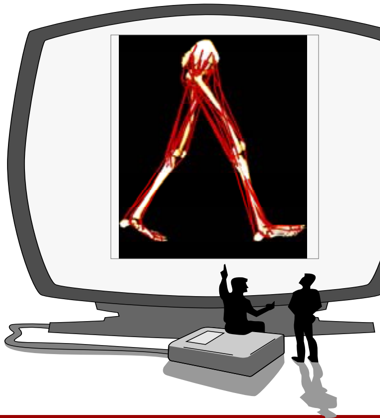
Meshing

Monte Carlo

Force Fields

SimTK Simulation Toolkit: Core

Applications



Gait Simulation

GUI Tools | Documentation Tools | Installation

Modeling

Linear Algebra

Multi Body Dynamics
- Simbody
- PRrobot
- •

Integrator
- ODE
- DAE

Contact
- Rigid
- Penalty
- •

Optimize
- Sim Anneal
- Genetic
- SQ Prog

Control
- PD

SimTK Simulation Toolkit: Core

Applications

Neuromuscular dynamics

GUI Tools | Documentation Tools | Installation

Modeling

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- Simbody
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- •

Integrator
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- Sim Anneal
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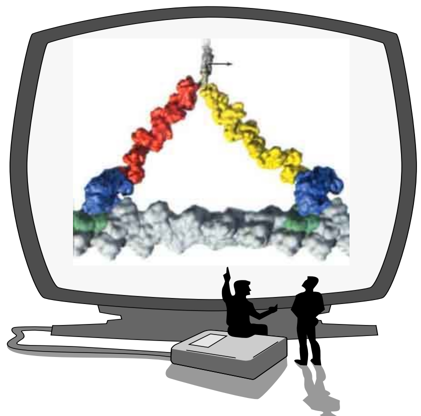
- SQ Prog

PDEs
- Solids

Meshing

SimTK Simulation Toolkit: Core

Applications



Myosin Dynamics

GUI Tools | Documentation Tools | Installation

Modeling

Linear Algebra

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PRrobot
•

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Penalty
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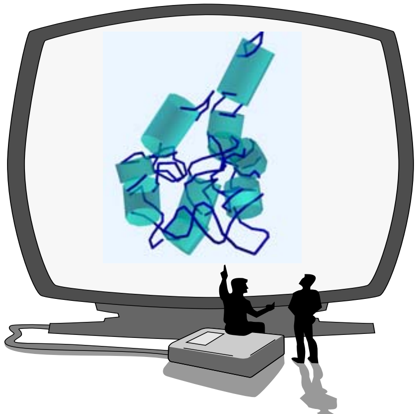
SimTK Simulation Toolkit: Core

Applications



RNA Folding

GUI Tools | Documentation Tools | Installation

Modeling

Linear Algebra

Multi Body Dynamics
Simbody
PRrobot
•

Integrator
ODE
DAE

Contact
Rigid
Penalty
•

Optimize
Sim Anneal
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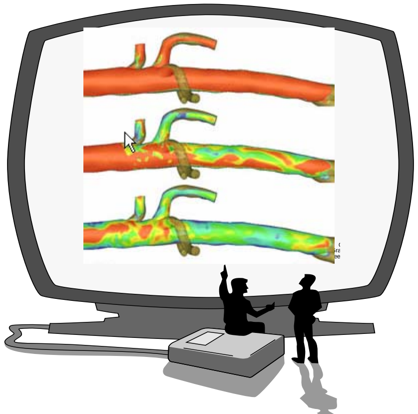
Force Fields

SimTK Simulation Toolkit: Core

Applications



Cardiovascular Dynamics

GUI Tools | Documentation Tools | Installation

Modeling

Meshing

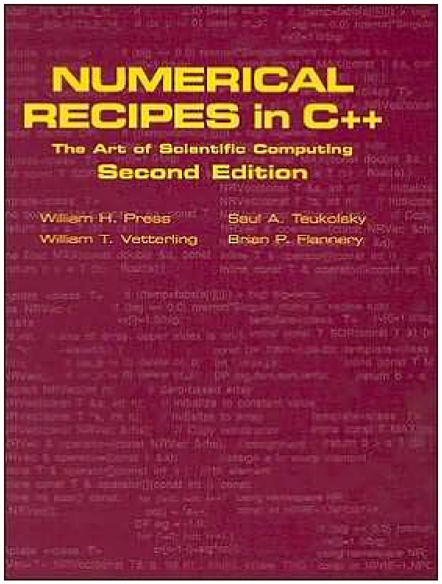
Linear Algebra

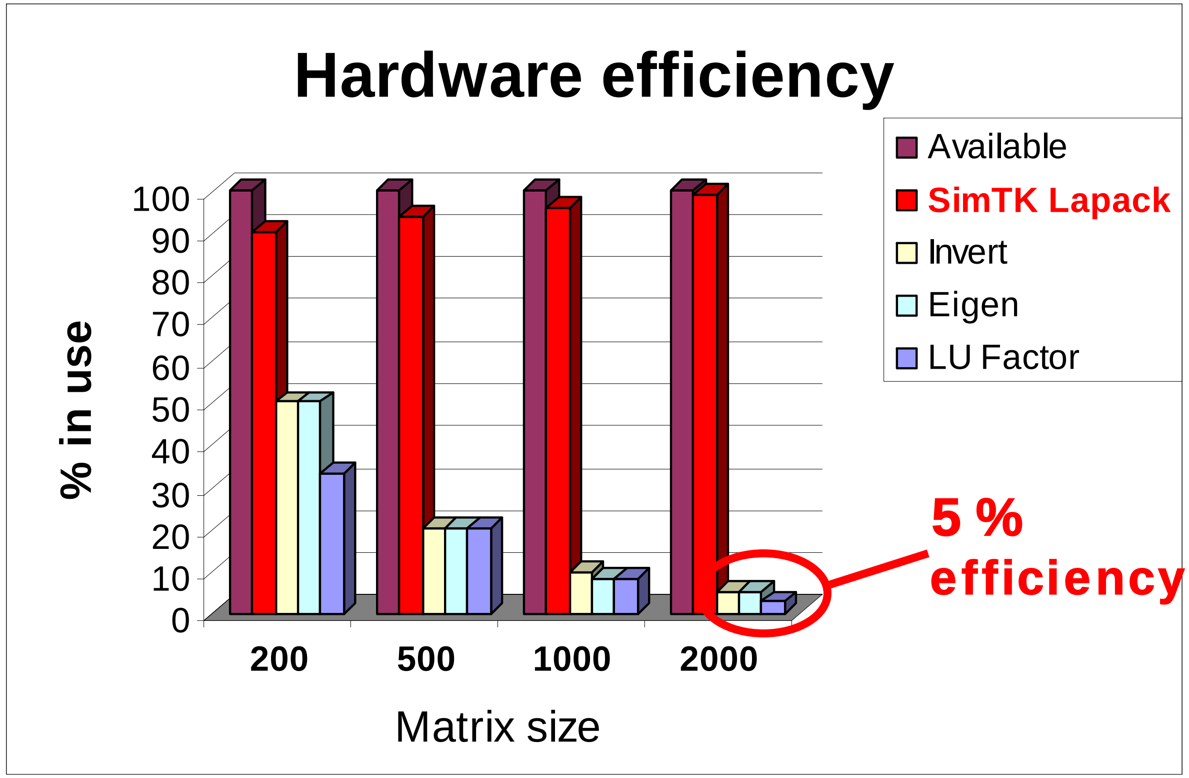
Integrator
ODE
DAE

Optimize
Sim Anneal
Genetic
SQ Prog

PDEs
Solids
Fluids

SimTK Simulation: Linear Algebra

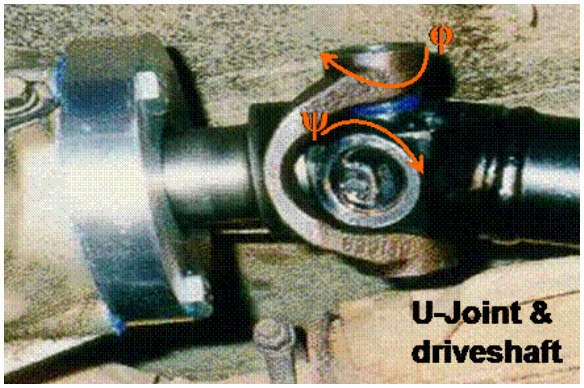


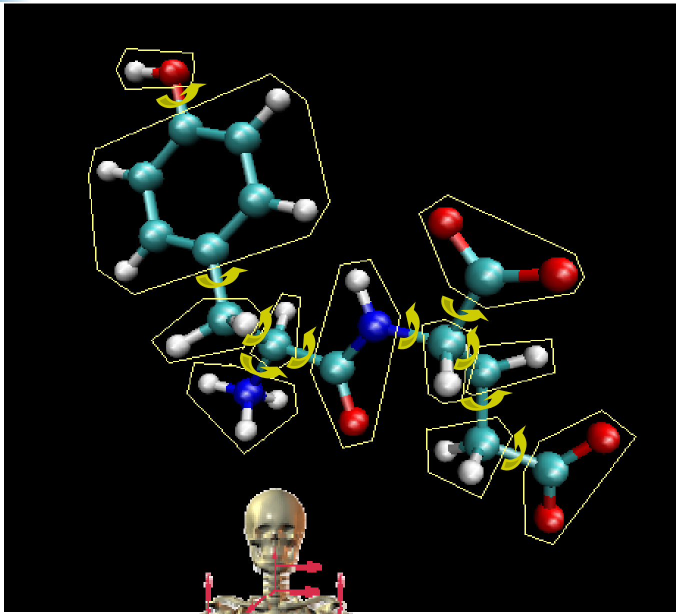


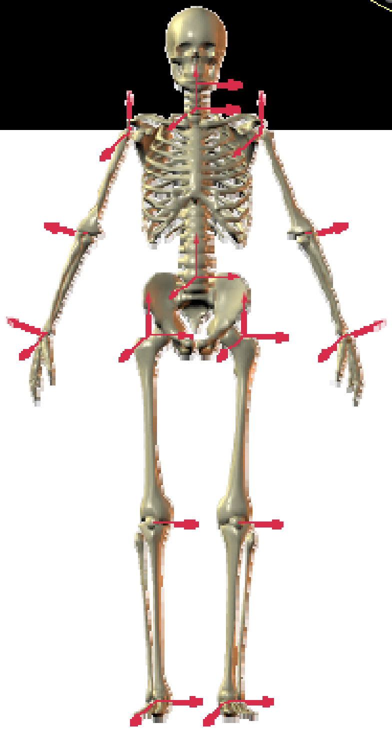
- Numerical Recipes is **20X** slower!
- 95% of hardware is wasted.
- Much worse on Macintosh
- Visit simtk.org/home/lapack

Jack Middleton

SimTK Simulation Toolkit



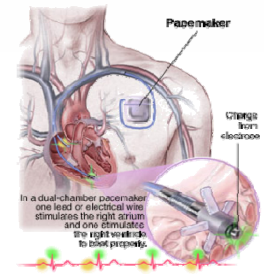




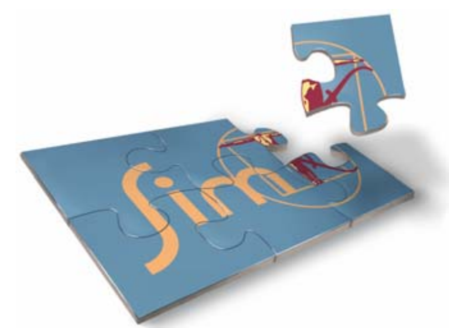
Multibody Dynamics

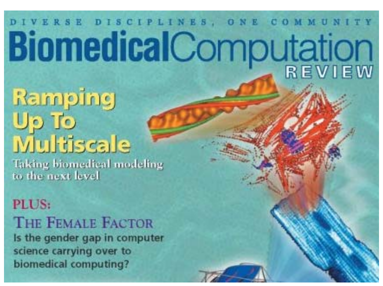
F	**Forces**
=	**Algorithms**
m	**Mass and Inertia**
a	**Motion and constraints**

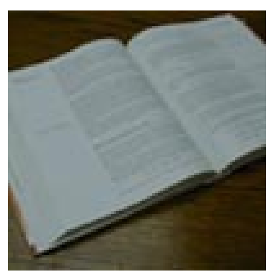
Simbios Overview



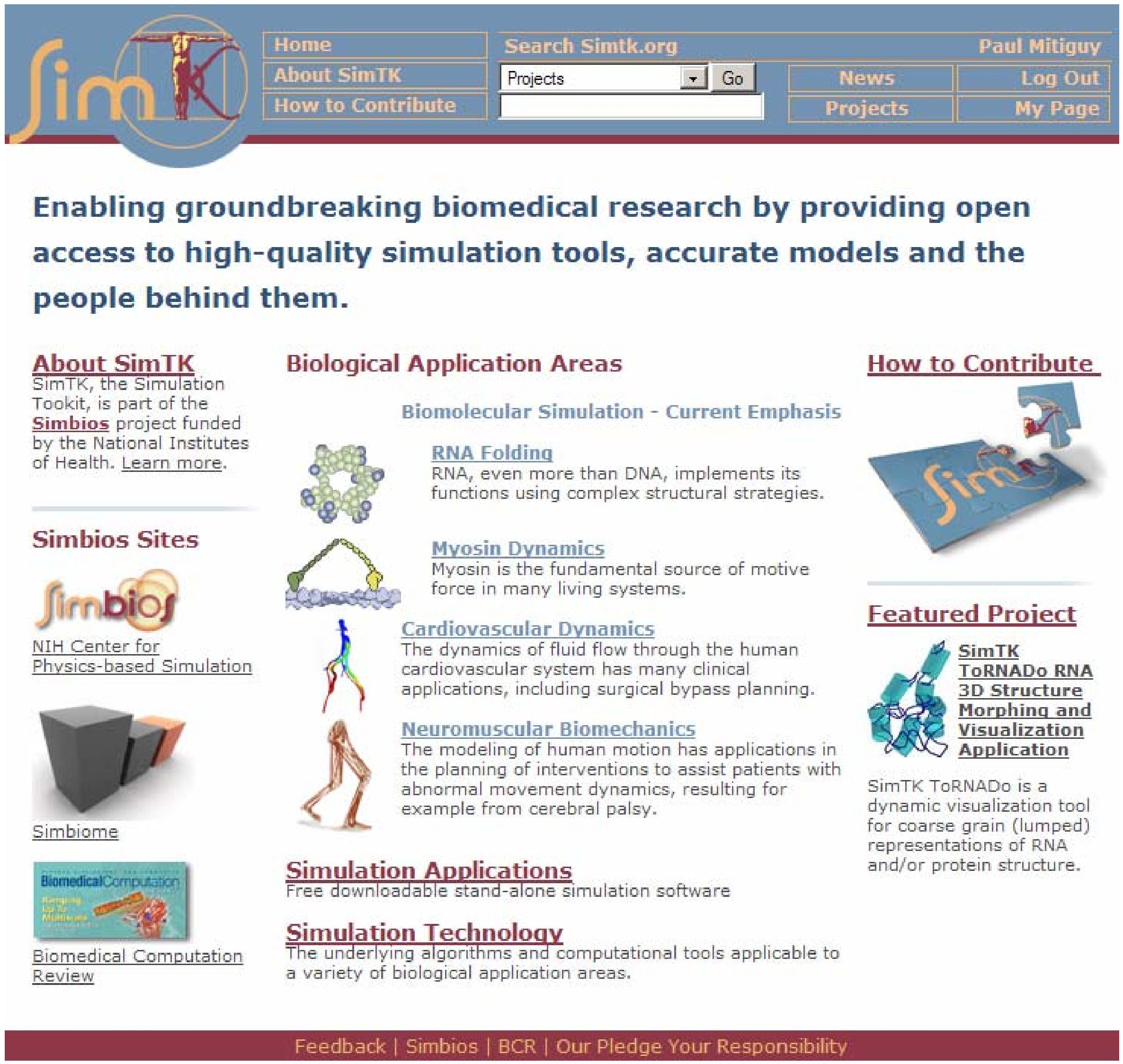
- **Scientific Applications & Collaboration**
- **SimTK Simulation Toolkit**
- **Biosimulation Superforge: simtk.org**
- **Dissemination & Training**







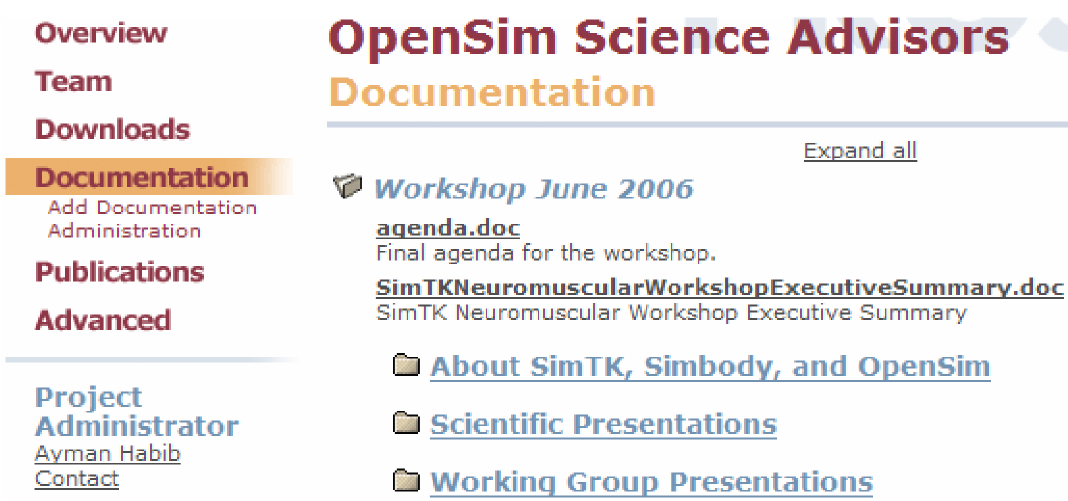
Biosimulation Superforge: simtk.org



Biosimulation Superforge: simtk.org

Collaboration in Research & Teaching

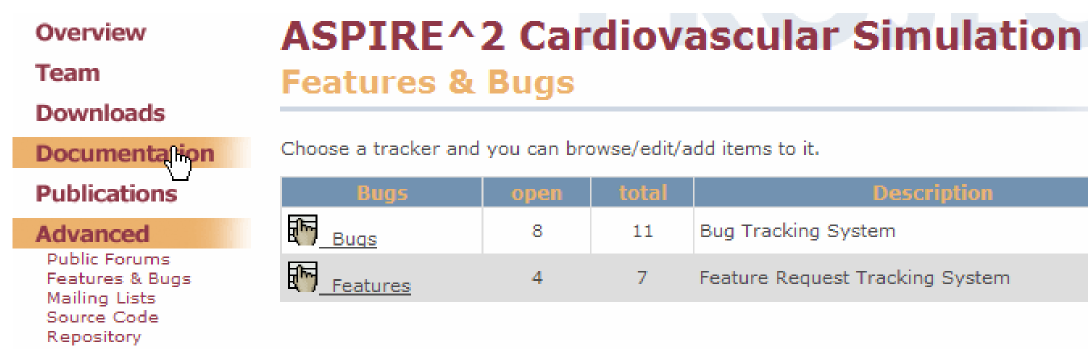
- Community: Broad impact & visibility
- Share algorithms, applications, models, & publications
- Curriculum, training material, and graphics



Biosimulation Superforge: simtk.org

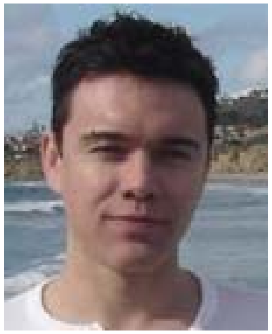
Distributed Development & Deployment

- •Secure, scalable, distributed development (you control access)
- •Software development, testing, discussion, and download
- •Mailing lists, forums, bug & feature database, news, blogs, …
- •Backups, off-site storage, …



Biosimulation Superforge: simtk.org

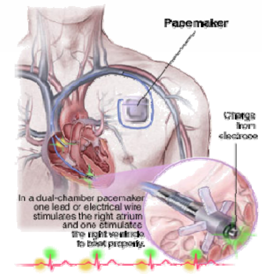
Visitors to a simtk.org project



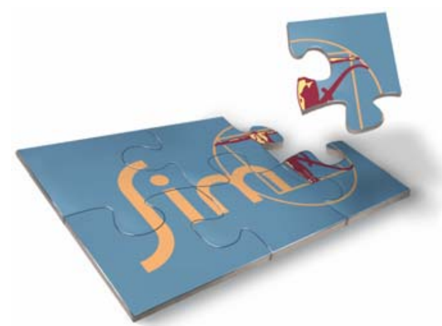
Dr. Bryan Keller

Simbios Overview

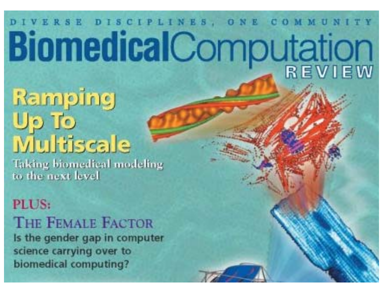
- **Scientific Applications & Collaboration**

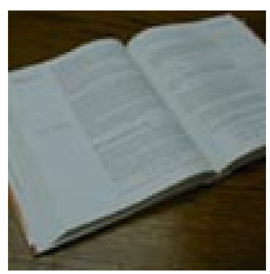


- **SimTK Simulation Toolkit**
- **Biosimulation Superforge: simtk.org**



- **Dissemination & Training**





Simulation in Science

- **It is one thing to create software**

  Interoperable, standardized, integrated, collaborative, networked, interactive, compatible, domain-relevant, coordinated, coherent, unified, collaborative

- **It is another thing to create useful software**

  Accessible & extensible (connection to high-use software)

- **It is yet another thing to create software that is used**

  Course and curriculum creation, adoption in related courses, extension to related fields, professional training, careers in biosimulation, commercialization

Simulation in Science

“But there’s a major challenge. How do we get the new computational tools and resources into the hands of researchers who will use and test them?”

John Whitmarsh: Acting Director, National Institute of Health (NIH)
Biomedical Computational Review, Winter 2005/06, pg. 8.

Top Ten Challenges of the Next Decade – by Eric Joacobsson

“Promoting the Use of Computational Biology in Education“

Eric Jacobsson: Director, NIH Center for BioInformatics and Computational Biology (NIGMS).
Biomedical Computational Review Summer 2005, pg. 15.

Simulation in Science

Q: "Computational biologists often have worked in relative isolation, creating code that doesn't get used by anyone else once their doctorate or other research project has been completed. How are you motivating people to care about creating tools for other scientists to use?"

A: "That's one of our grand challenges, frankly. It's really a different mentality to put our heads together and come up with a product or tool that will be used by others."

Arthur Toga: Principal Investigator, NIH Center for Computational Biology (CCB).
Biomedical Computational Review Summer 2005, pg. 21.

Simulation in Science

Q: "What are the biggest challenges you face getting Simbios started?"

A: The biggest challenge is efficiently supporting creative researchers and translating their work to be used by hundreds of other researchers – the interface between software and research. They are two very different cultures that must be brought together to succeed.

**Russ Altman: Principal Investigator, NIH Center for Physics Based Simulation of Biological Structures (Simbios)
Biomedical Computational Review Summer 2005, pg. 21.**

Simulation in Science

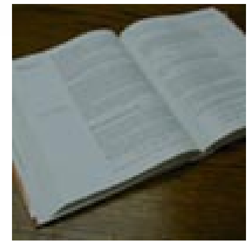
Q: "What is MAGNet's biggest challenge going forward?"

A: "Our biggest challenge is the ability to make the biomedical research community aware of the vast array of resources that we hope to create and to make these accessible to people with a strong biomedical training but relative limited computational expertise."

Andreas Califano: Principal Investigator, NIH Center for Multiscale Analysis of Genomic and Cellular Networks (MAGNet)
Biomedical Computational Review Winter 2005/06, pg. 13

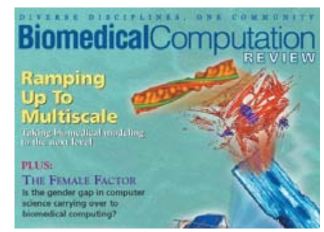
Dissemination & Training

- **User & Simbios Conferences**
  OpenSim Advisor Conference, SimMolecule Advisor Conference, Simbios Science Advisory Board, Simbios Annual Conference, BCATS



- **BioSimulation Education & Training**
  BioE215 Spring 2007 & Fall 2007, SPCD, Summer Training Workshop

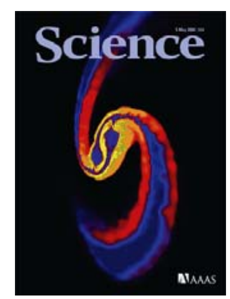
- **Scientific Conferences**
  Visit the dissemination project on www.simtk.org for a full list of conferences



- **Scientific Outreach**
  Biomedical Computation Review www.BiomedicalComputationReview.org

- **Simbiome**
  Curated BioSimulation Resource www.Simbiome.org

- **Public & Media Outreach**
  Press release, news, magazine & newspaper articles, community presentations



Metrics for Software Success

1. Number of end-users

A. End-user applications (Interaction via mouse & keyboard)
B. Libraries (Programmers who interface through API)
C. Core Source Code (Developers working on related applications)

2. Quality of Science

A. Impact on medical practitioners
B. Impact on medical research
C. Impact on BioSimulation Education (Kindergarten - PostDoc)
D. Publications in journals

Biomedical Computation Review: Quarterly

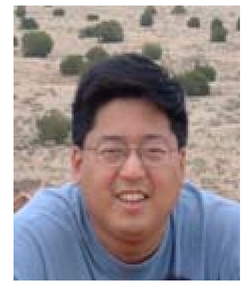
A magazine (not a journal) to foster a wide community of those interested in various aspects of biomedical computation

Who?

Editorial Advisory Board
Simbios Program & Science Officers
Professional science writers
Community contributions

What?

Editorials, Editor's picks
News Bytes, Book Reviews
Featured Lab, Under the Hood
Seeing Science



Executive Editor: David Paik

Managing Editor: Katharine Miller

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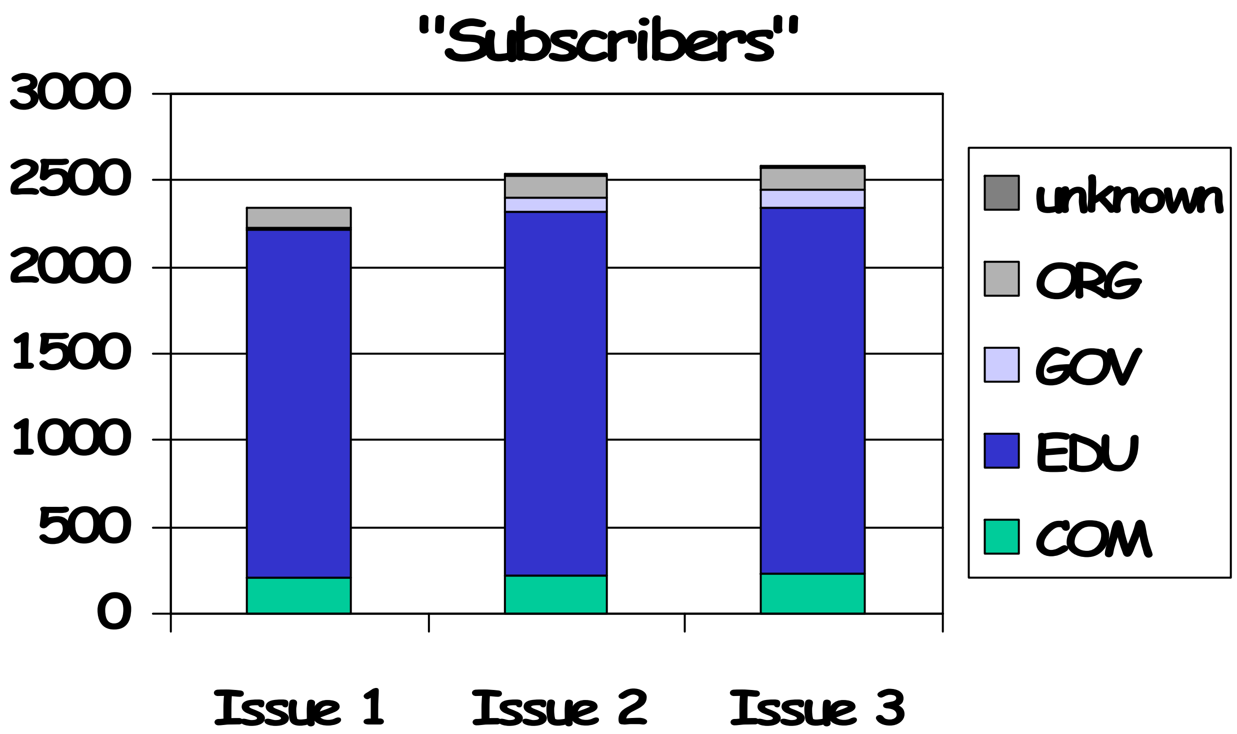
www.BiomedicalComputationReview.org

Biomedical Computation Review: Circulation

Print circulation ≈ 2500 (academic, industry, government)



Biomedical Computation Review: Visibility

100 most recent website visitors
Average: 300 distinct visitors/month

Bogota, Columbia
Tel Aviv, Israel
Assam, India
Kenya

Palestinian Territories
Iran
Brazil
Romania

Brussels
Egypt
Satellite Access

Simbiome: www.simbiome.org

- **Electronic resource inventory system**
  - **Search Online “Yellow Pages”**
    Simbiome Search Engine, Google search of Simbiome, Google WWW search
  - **Resources for physics-based simulation**
    Applications, algorithms, models, and images (open-source, academic, & commercial)
  - **Extension to NIH biomedical resources**
- **Trusted, curated content management**
  Submission, versioning, review & approval by site admin, curators and submitters, content owners
- **Open Source: Download at simtk.org**

Simbiome

Simbiome is a trusted, online electronic resource that organizes and presents **relevant resources** for physics-based simulation of biomedical structures and related entities in biology and life sciences.

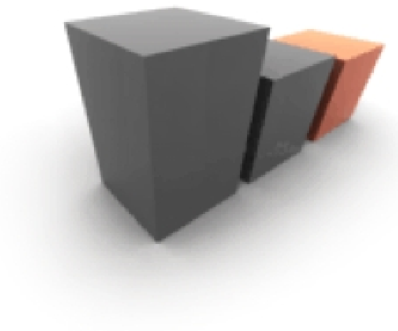
Jonathan Dugan **Logout**
My Account

Select An Area: **About** **Resources** **Organizations** **Search** **Help** **Admin** **SiteAdmin**

List all Resources

Search Simbiome: **Search** Advanced

Simbiome, the Resource Inventory for Simbios



Welcome to Simbiome!

Simbiome has recently been updated. We appreciate your feedback: please send comments to:

feedback@simbiome.org

Simbios Sites
National Center for Biomedical Computation

Simbios
NIH Center for physics-based simulation and modeling at Stanford.

SimTK
Host, manage and participate in application development for physics-based life science computation.

BioMedical Computation Review
Diverse disciplines, one community: quarterly journal covering biomedical computation news and science.

Ruby on Rails

- **Agile web development framework**
- **Free and Open Source**
- **Minimal code, easy to alter**
- **Separation of Model, View, Controller**

Amber Force Fields

Scripps Research Institute

molecular force fields for dynamics simulations

http://amber.scripps.edu/#ff

Edit This Entry

Summary Assembled by Curation Team

Database or Data Source	
Four force fields are available: a re-parameterization of an all-atom protein force field (ff03), based on quantum calculations in a continuum solvent environment; a major extension of the General Amber Force Field (gaff), that expands the range of applicable molecules, particularly for conjugated systems; a new version of the "glycam" carbohydrate force field (glycam04) developed in Rob Woods` group; and a "QM/MM" facility by which part of the system can use energies and forces derived from a semiempirical Hamiltonian such as AM1 or PM3.	
Development Stage	6 - Mature
Keywords	biomolecular simulation, molecular, force fields
Resources with Similar Function	
Related Resources	Amber - Molecular Dynamics Search Google

Last Updated on: Mon Jul 10 11:48:51 EDT 2006 Page hits 35, Clicks 5, Version 6 (6)

Suggest Update

Acknowledgements

simbios

Funding: NIH Roadmap Grant U54 GM072970

Peter Lyster (PO)

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Scott Delp

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Michael Sherman

David Paik

Clay Anderson

Ayman Habib

Jon Dugan

Blanca Pineda

Bill Katz

Jung-Chi Liao

Jack Middleton

Chris Bruns

Bryan Keller

Mary O' Connell

Alain Laederach

Mary Draney

Faculty ….

What is Simbios?

Physics-based Simulation of Biological Structures

- **Create biosimulation tools, models, & infrastructure**
- **Test with driving biological problems**
- **Deploy to biomedical researchers & students…**
- **Impact biomedical progress in:**
  - **Rehabilitative research & therapy**
  - **Surgical and drug treatments**
  - **Design of prosthesis**
  - **Understand structure and function of RNA & Myosin**