



# Physics-based Simulation of Biological Structures

An NIH National Center for Biomedical Computing  
Supported by NIH Roadmap for Medical Research U54GM072970

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(Departments of Genetics & Bioengineering)

Scott Delp, PhD  
(Department of Bioengineering)  
Stanford University



# Outline

- Simbios Overview
- Simbios science highlights
- Community building goals for Simbios
  - SimTK
  - Biomedical Computation Review

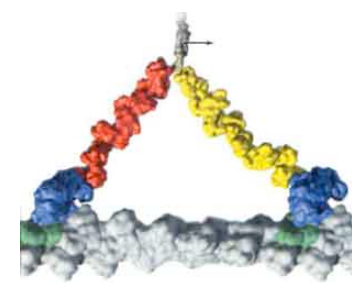
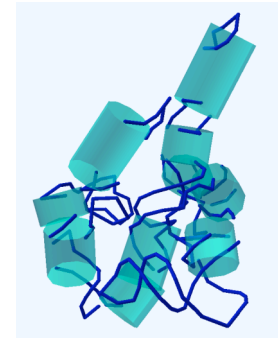
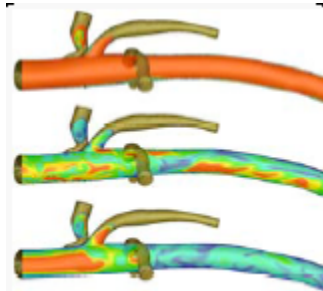
# What is Simbios?

## Physics-based Simulation of Biological Structures

- Goal: to develop and disseminate a Simulation Tool Kit (SimTK) that will:
  - stimulate groundbreaking biomedical research
  - enable development and sharing of accurate physics-based models and simulations of biological structural dynamics
- The initial driving biological projects of Simbios span a range of scales:
  - simulating RNA folding
  - myosin dynamics
  - neuromuscular dynamics
  - cardiovascular mechanics



# SimTK: Simulation Toolkit



**GUI Tools | Documentation Tools | Installation**

## Modeling

**Linear  
Algebra**

**Multi  
Body  
Dynamics**

Simbody  
TAO  
•

**Integrator**  
ODE  
DAE

**Optimize**  
Sim Anneal  
Genetic  
SQ Prog

**Monte  
Carlo**

**Force  
Fields**

**Control**  
PD

**Contact**  
Rigid  
Penalty  
•

**Meshing**

**PDEs**  
Solids  
Fluids







# Simulation of structural dynamics

## Linear Algebra

**GUI Tools | Documentation Tools | Installation**

### Modeling

**Linear Algebra**

**Multi Body Dynamics**

Simbody  
PRrobot

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**Meshing**

**Monte Carlo**

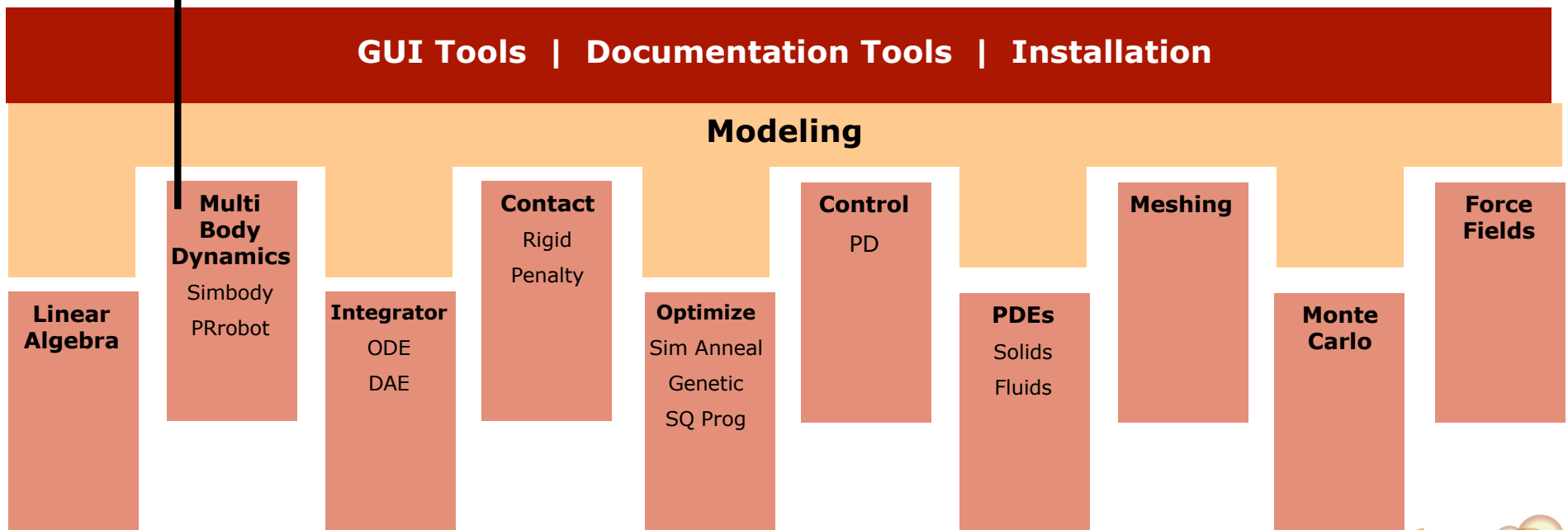
**Force Fields**





# Simulation of structural dynamics

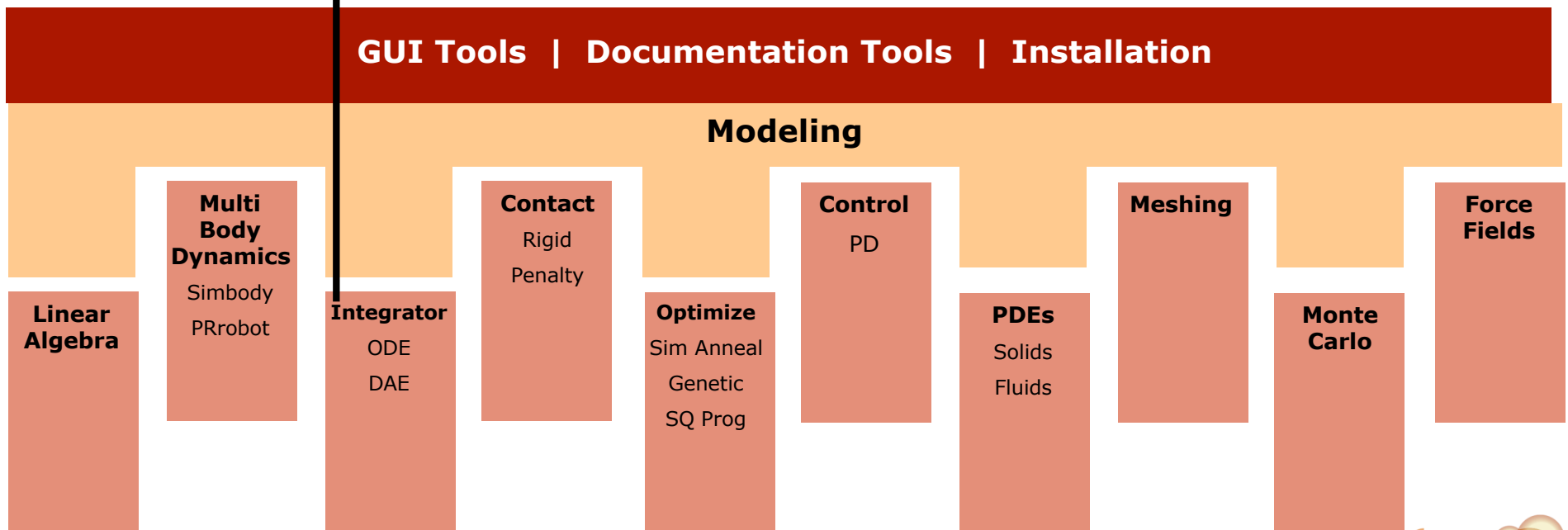
## Multibody Dynamics





# Simulation of structural dynamics

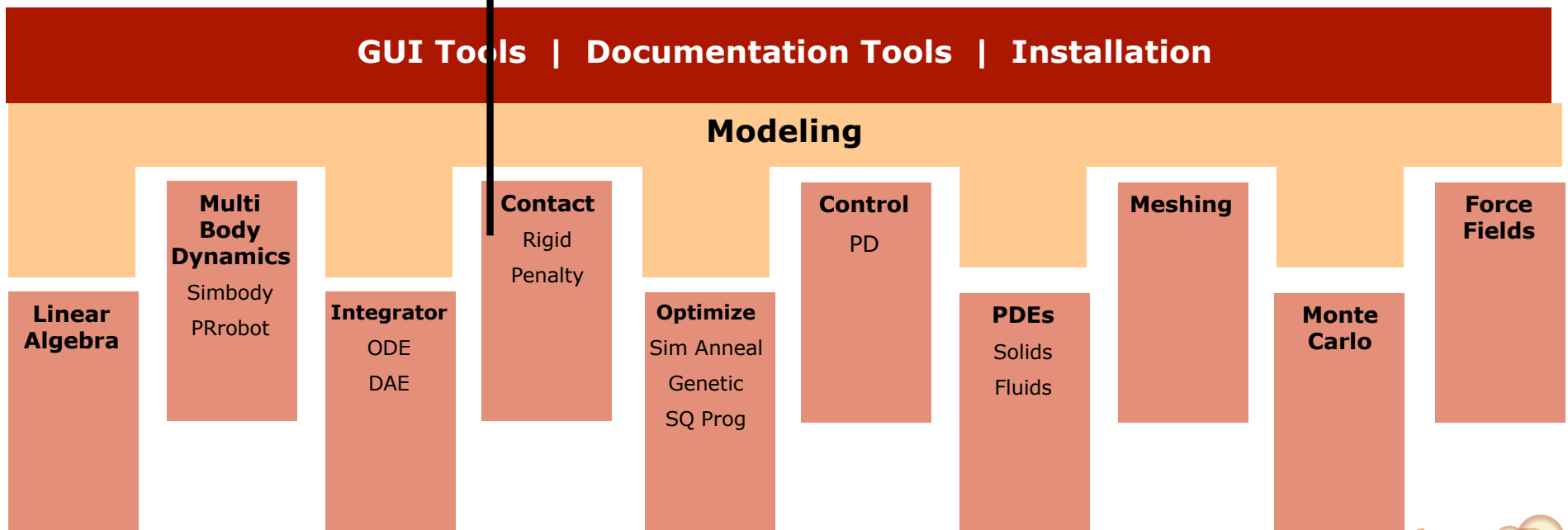
## Integrators





# Simulation of structural dynamics

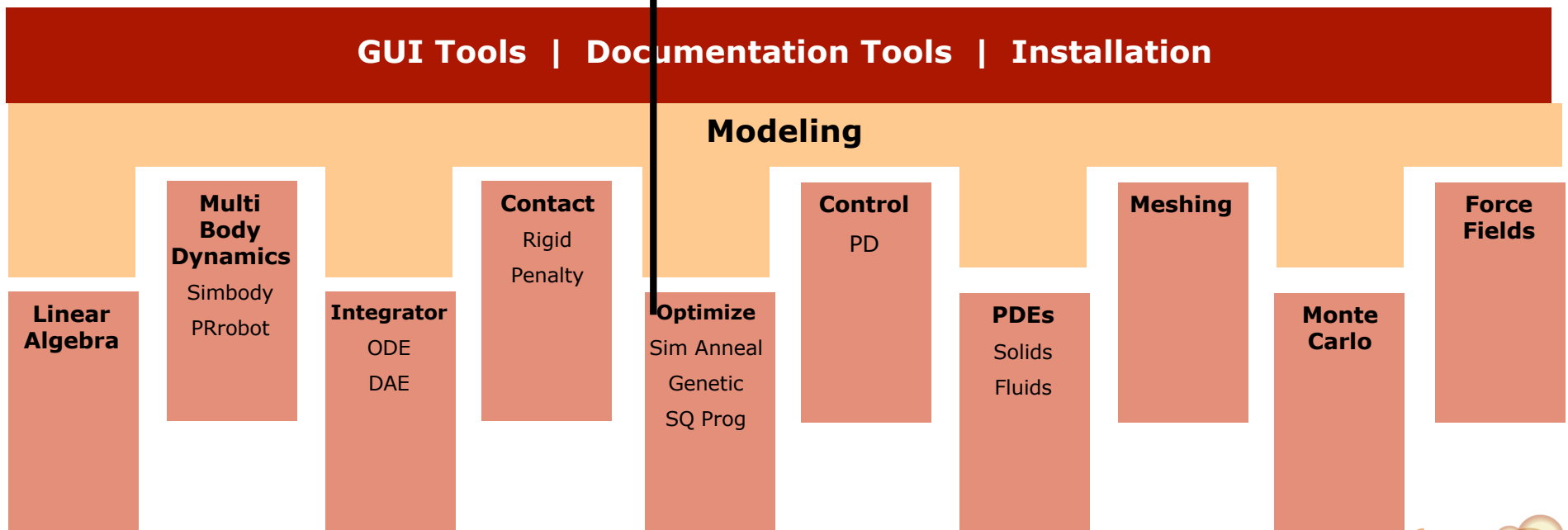
## Contact models





# Simulation of structural dynamics

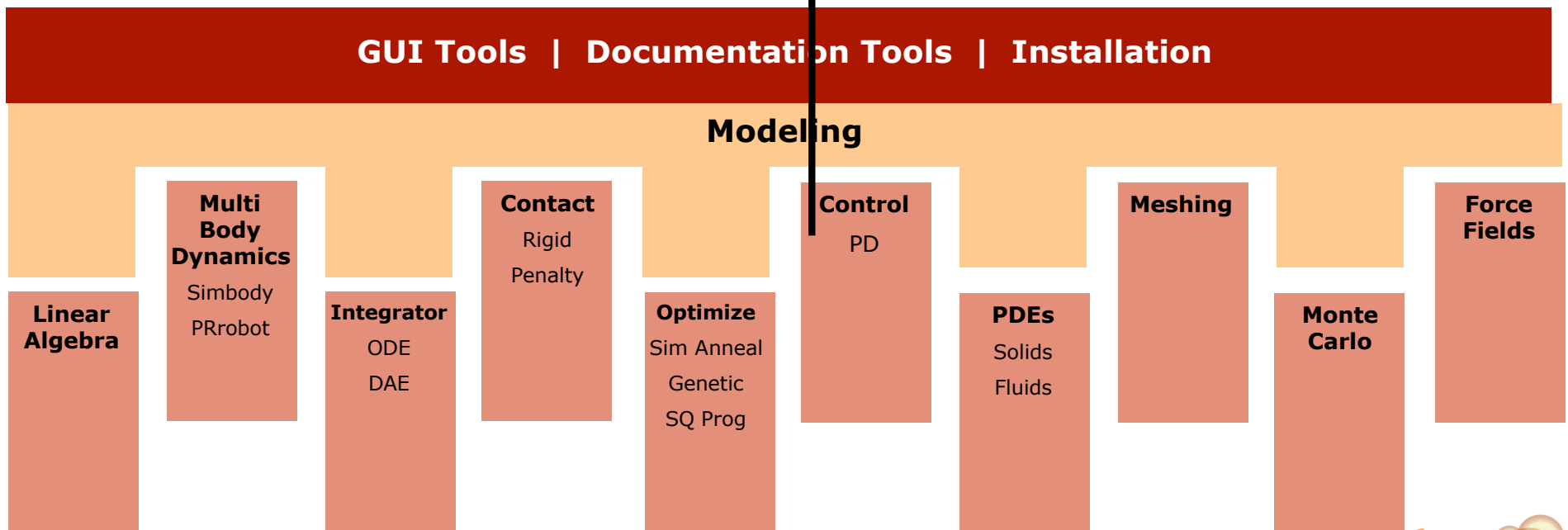
## Optimizers





# Simulation of structural dynamics

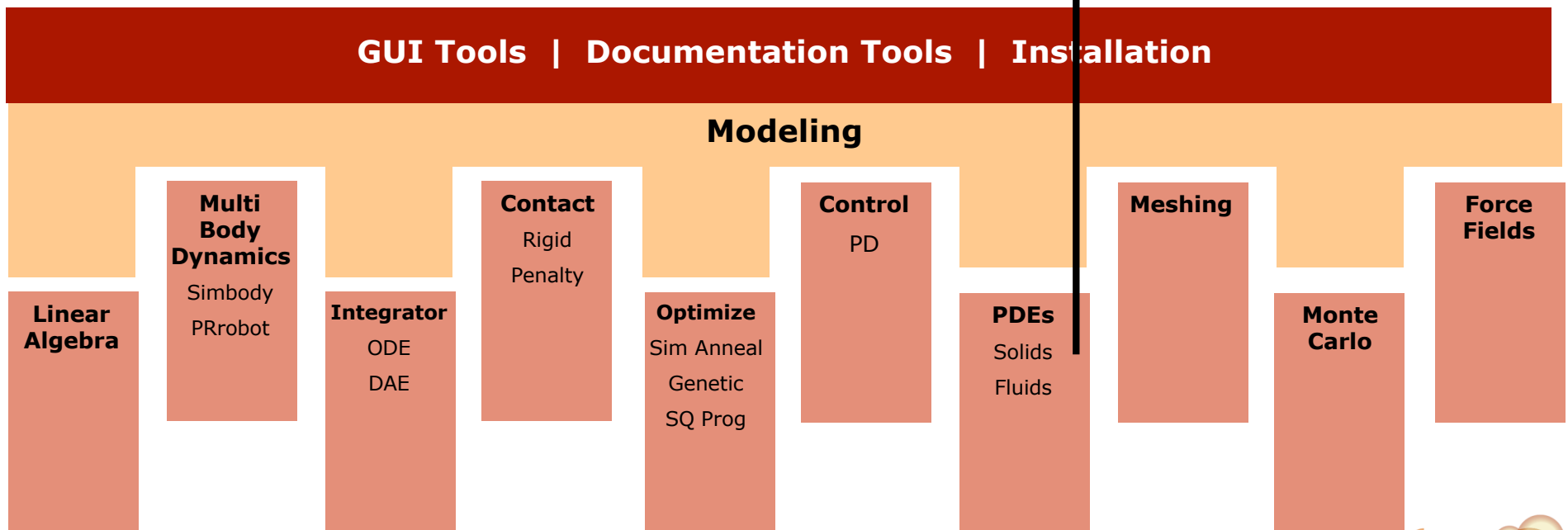
## Control Algorithms





# Simulation of structural dynamics

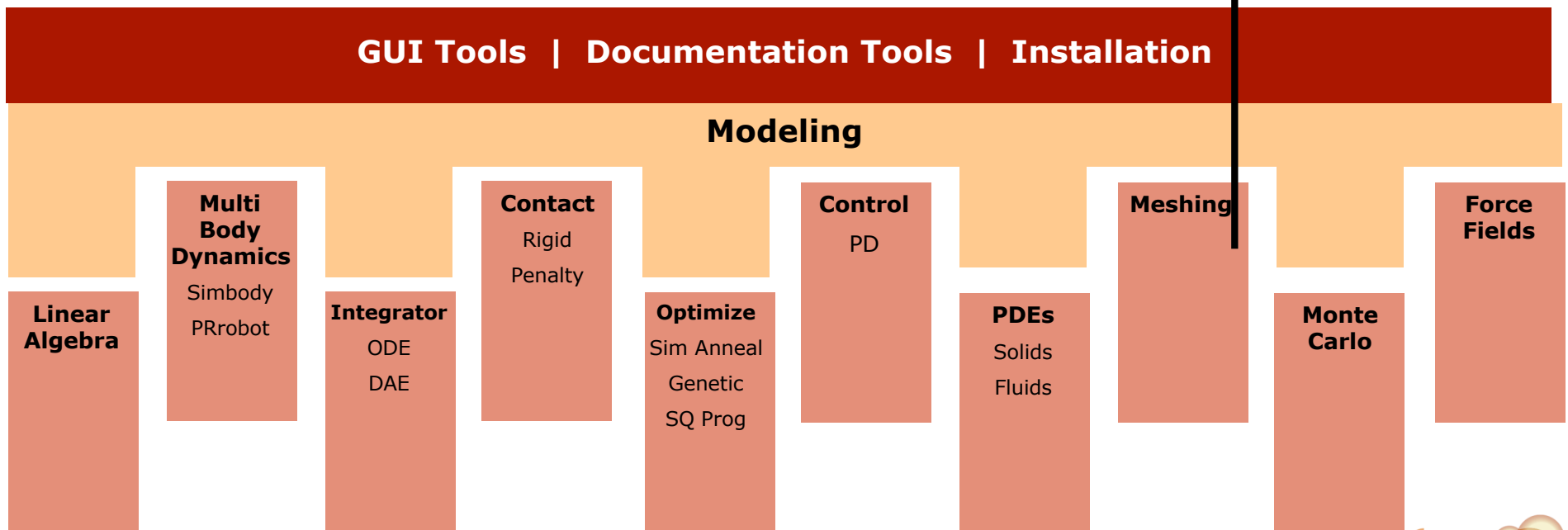
## Partial Differential Equations





# Simulation of structural dynamics

## Meshing algorithms

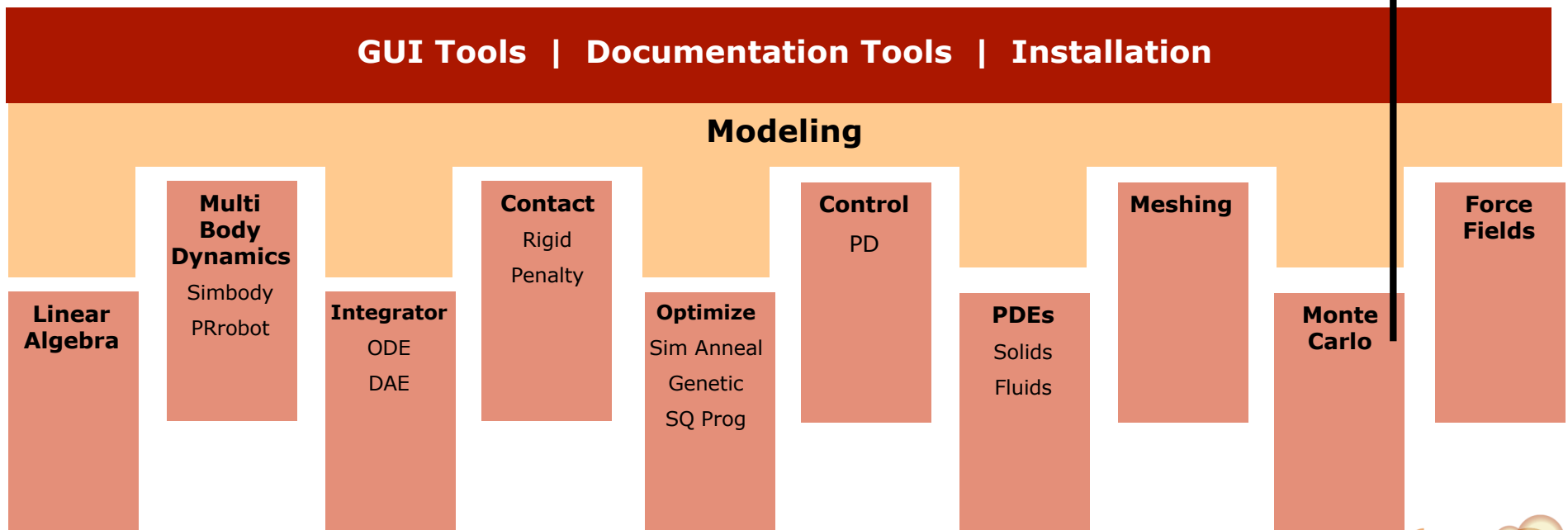






# Simulation of structural dynamics

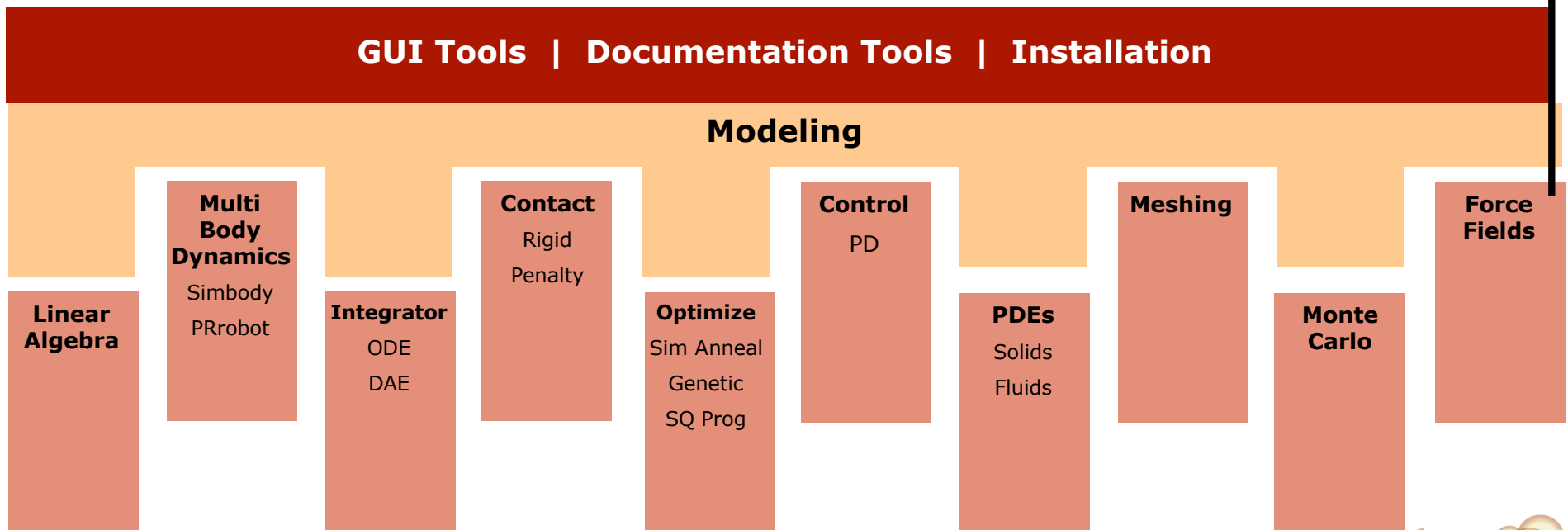
## Monte Carlo Methods





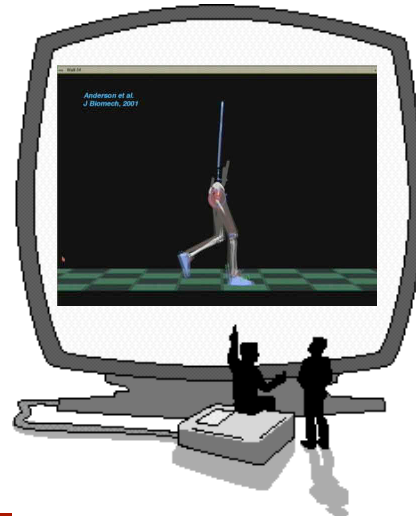
# Simulation of structural dynamics

## Force Fields



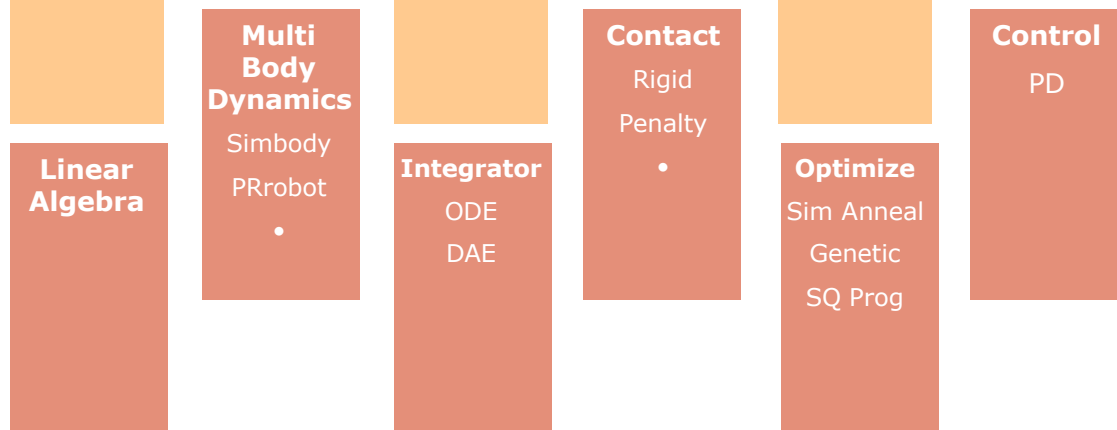


# Simulation Toolkit



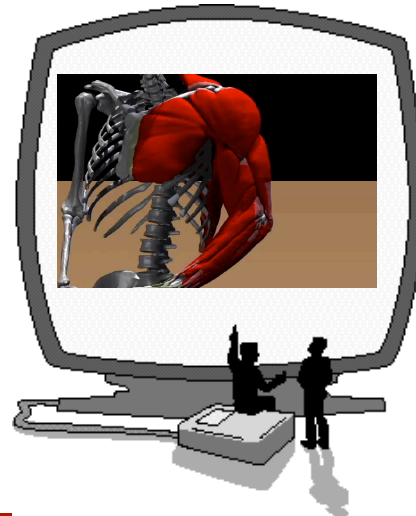
**GUI Tools | Documentation Tools | Installation**

## Modeling



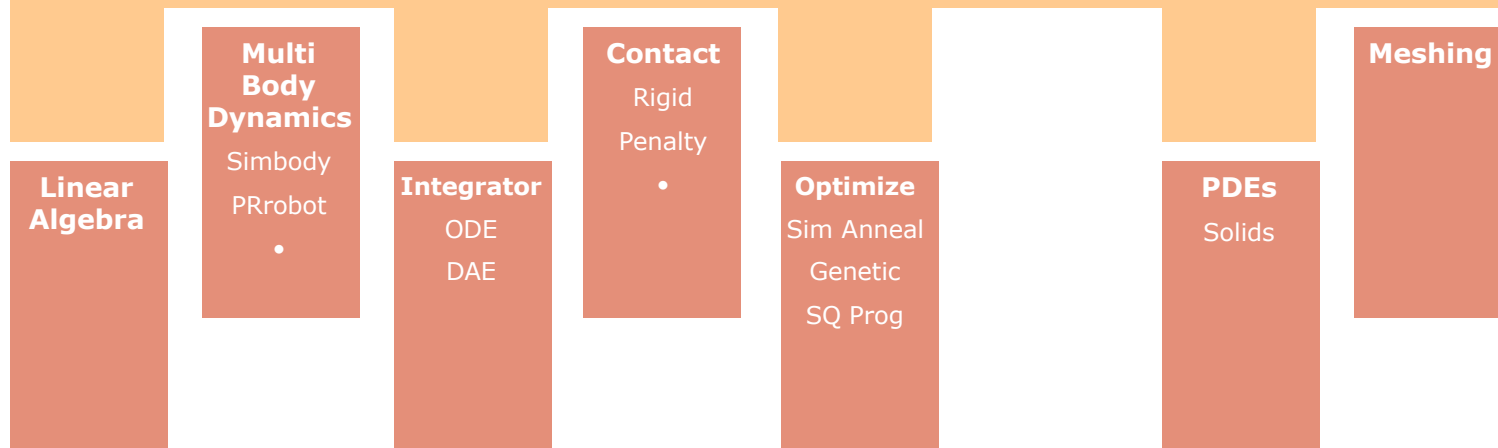


# Simulation Toolkit



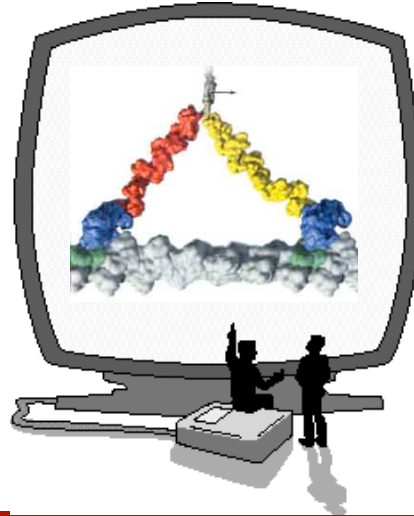
**GUI Tools | Documentation Tools | Installation**

## Modeling



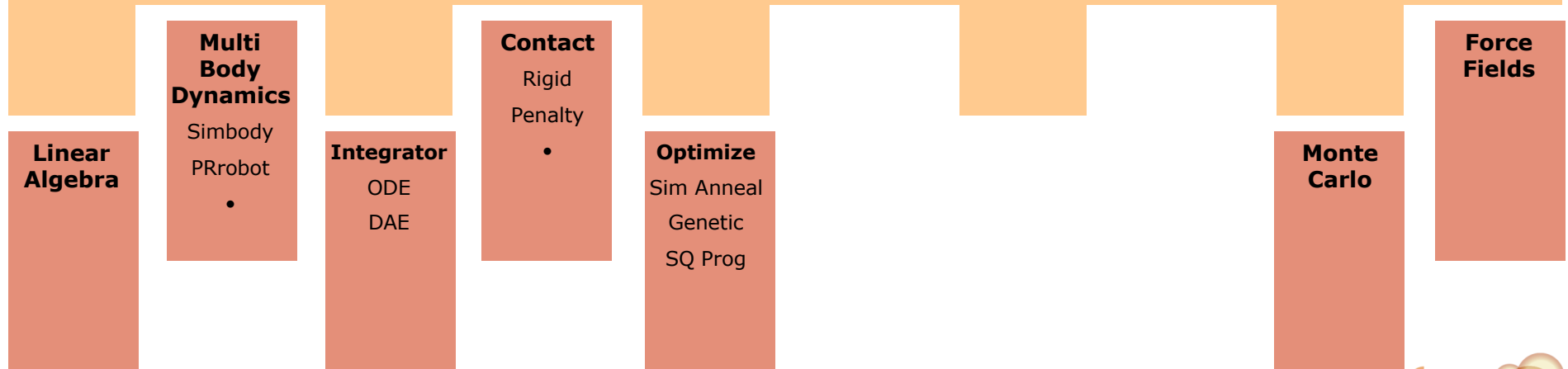


# Myosin-actin dynamics



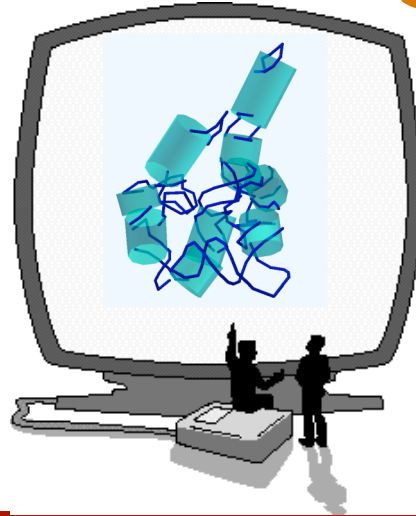
**GUI Tools | Documentation Tools | Installation**

## **Modeling**



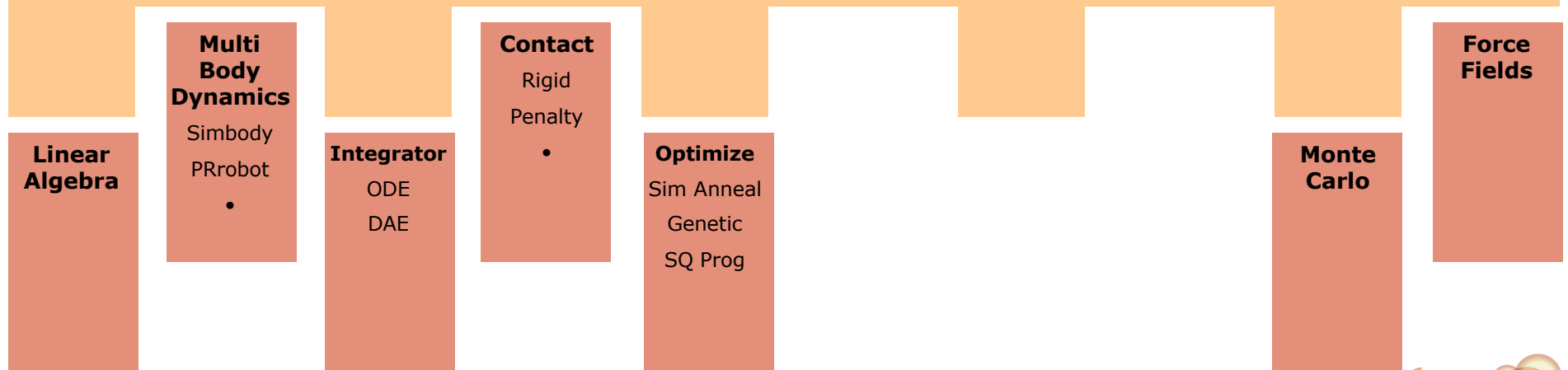


# RNA folding dynamics



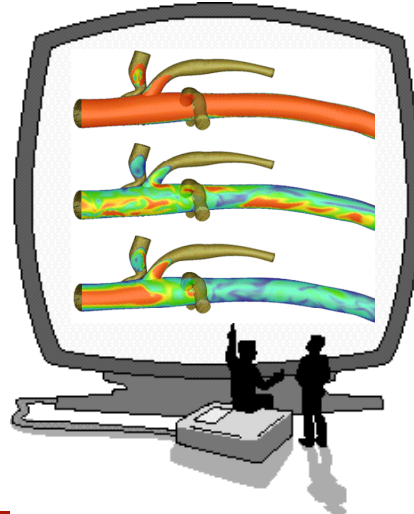
**GUI Tools | Documentation Tools | Installation**

## **Modeling**





# Cardiovascular blood flow



**GUI Tools | Documentation Tools | Installation**

## **Modeling**

**Linear  
Algebra**

**Integrator**  
ODE  
DAE

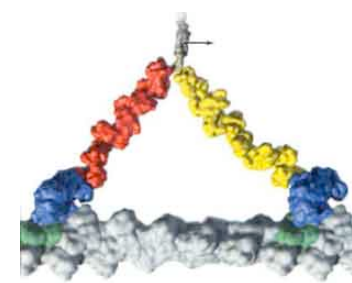
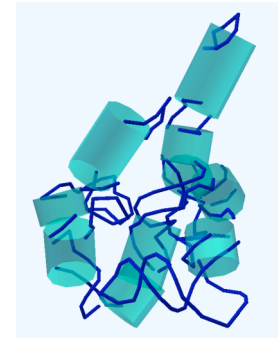
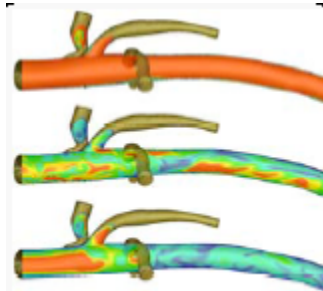
**Optimize**  
Sim Anneal  
Genetic  
SQ Prog

**PDEs**  
Solids  
Fluids

**Meshing**



# SimTK: Simulation Toolkit



**GUI Tools | Documentation Tools | Installation**

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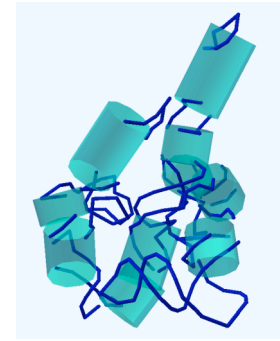
**PDEs**  
Solids  
Fluids







# SimTK: Simulation Toolkit



**GUI Tools | Documentation Tools | Installation**

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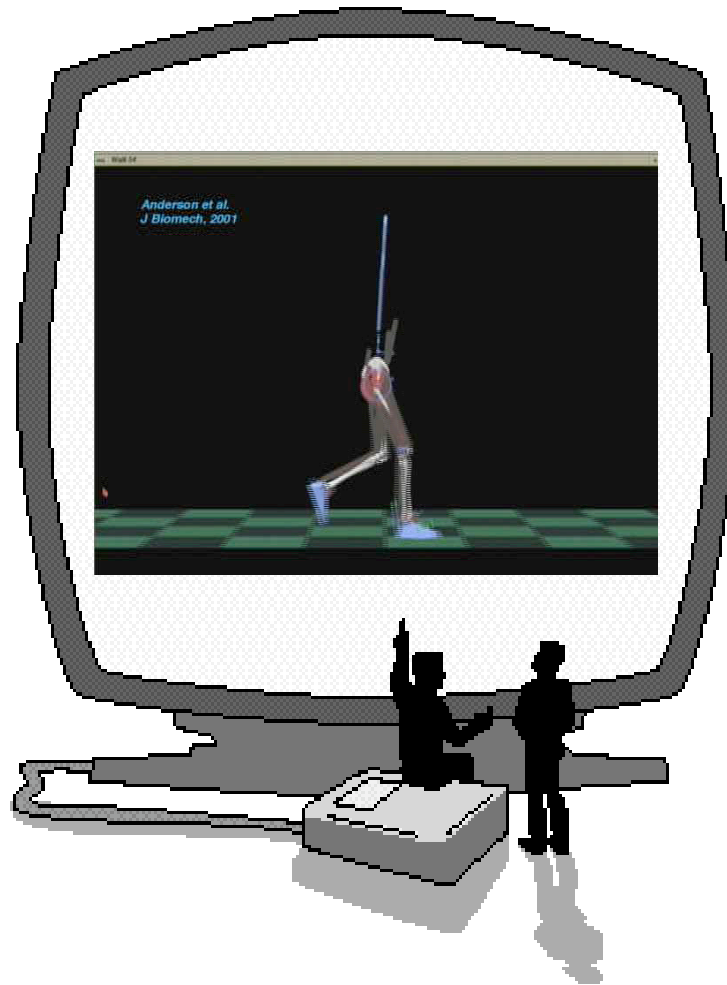
**Contact**  
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**Meshing**

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Solids  
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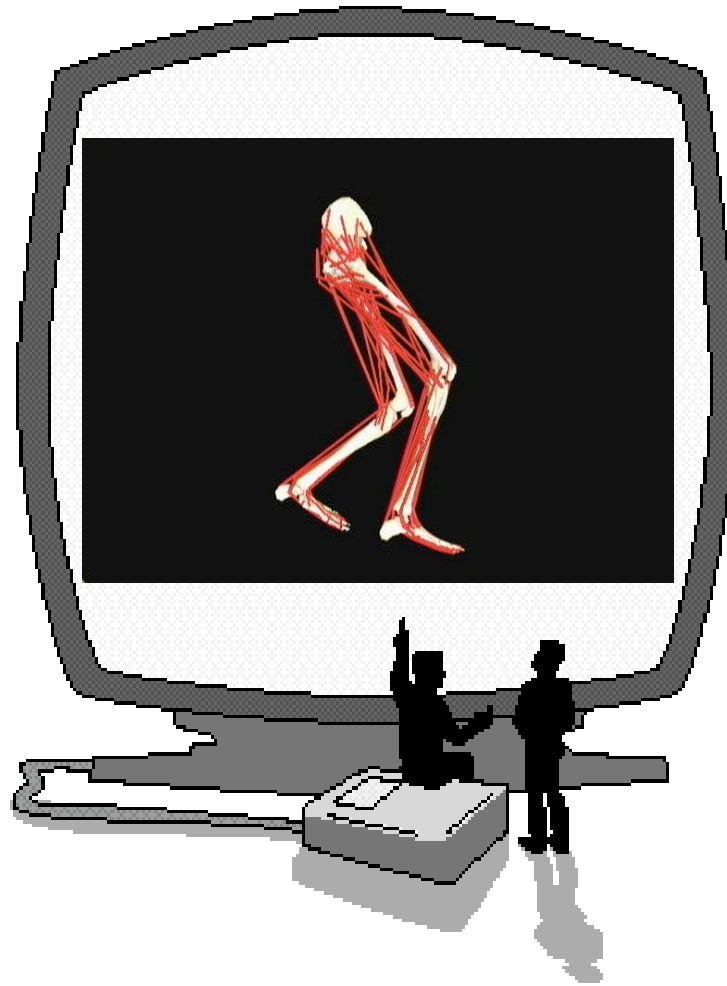


# Simulation-based treatment planning



Allison Arnold, Clay Anderson, Ayman Habib, Scott Delp

# Simulation-based treatment planning



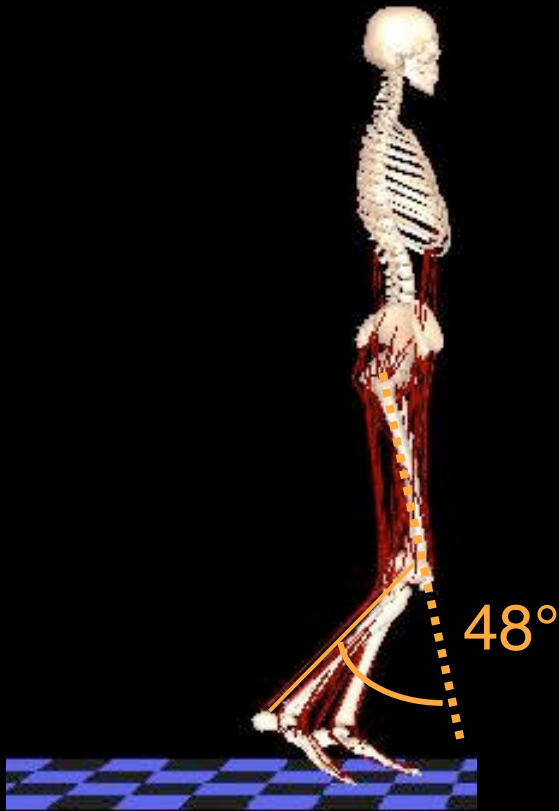
Allison Arnold, Clay Anderson, Ayman Habib, Scott Delp

# Subject-specific Simulation



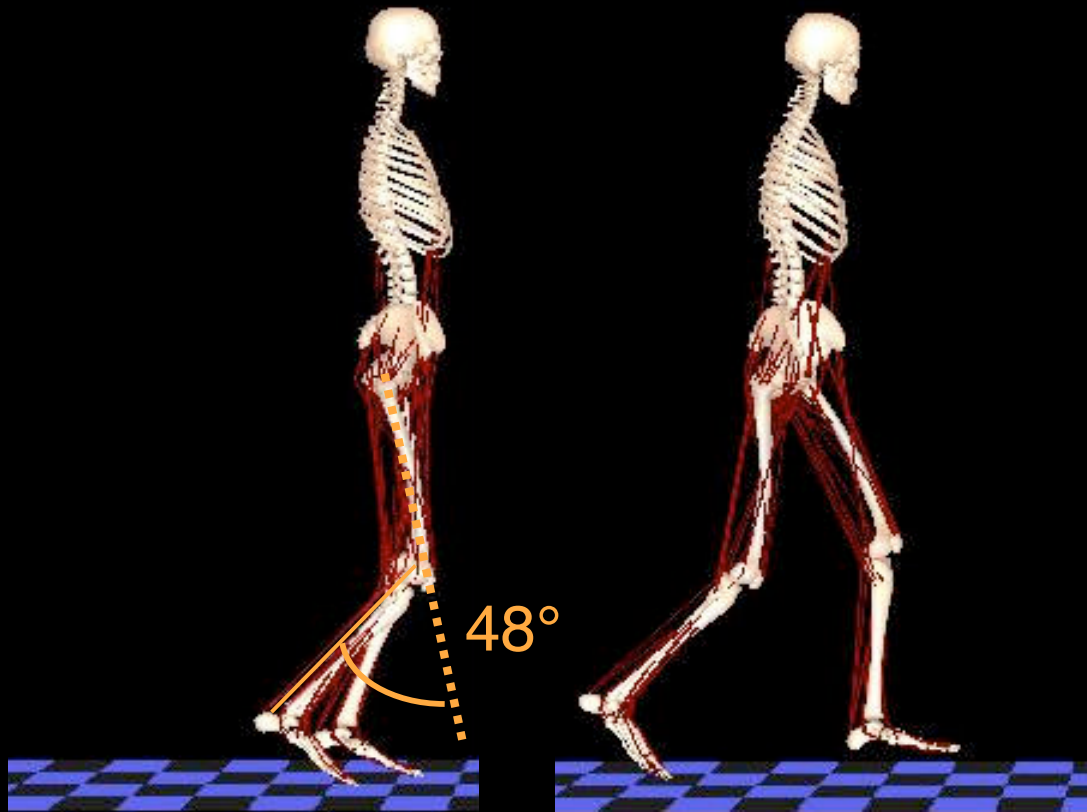
Original subject-specific simulation

# Subject-specific Simulation



Original subject-specific simulation

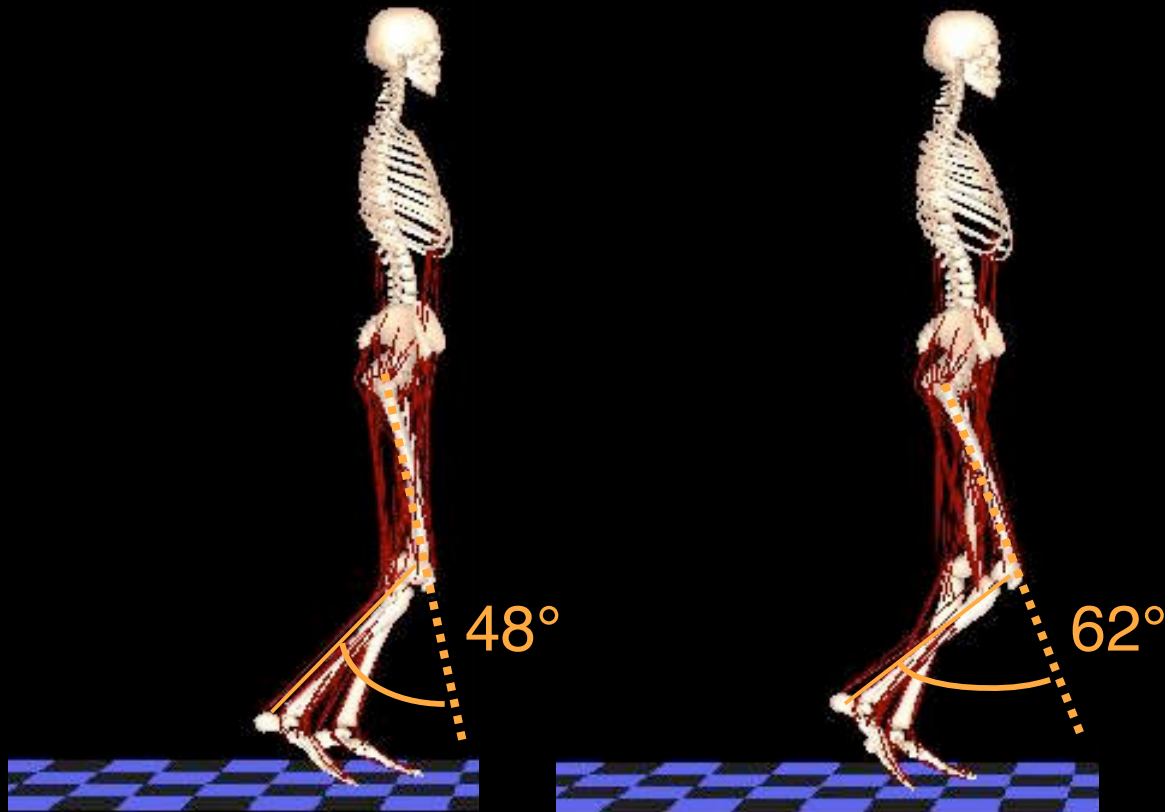
# Subject-specific Simulation



Original subject-specific simulation

Increase gastrocnemius force during double support

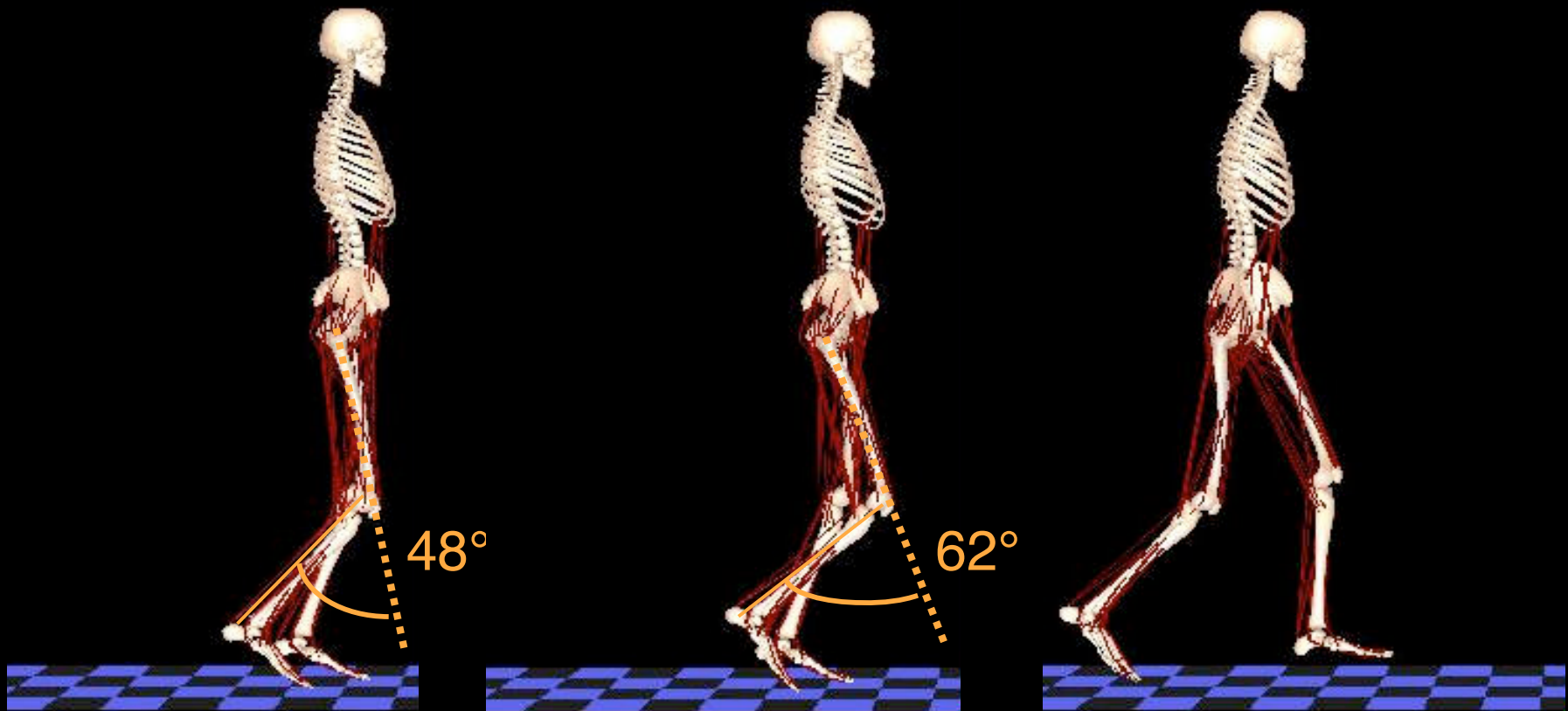
# Subject-specific Simulation



Original subject-specific simulation

Increase gastrocnemius force during double support

# Subject-specific Simulation



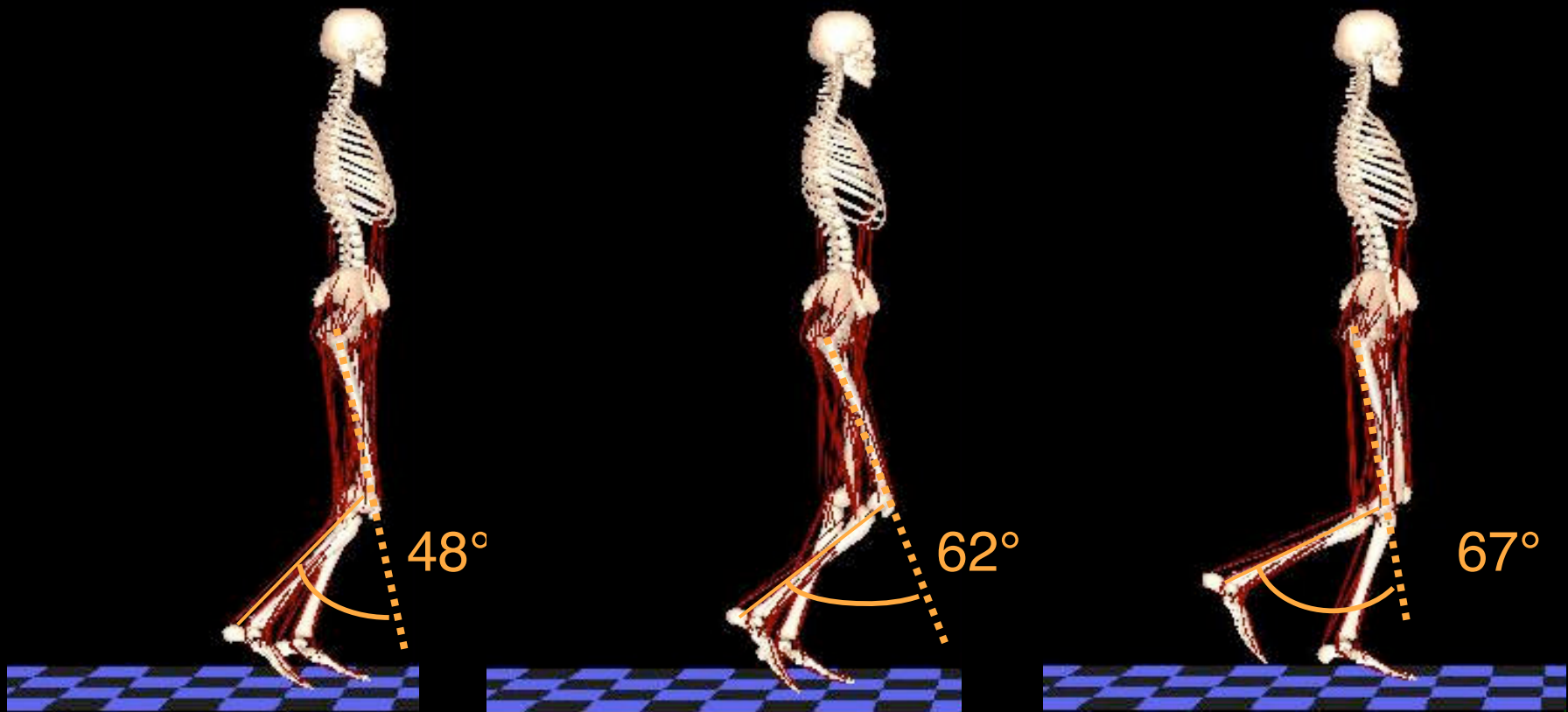
Original subject-specific simulation

Increase gastrocnemius force during double support

Decrease rectus femoris force during double support



# Subject-specific Simulation

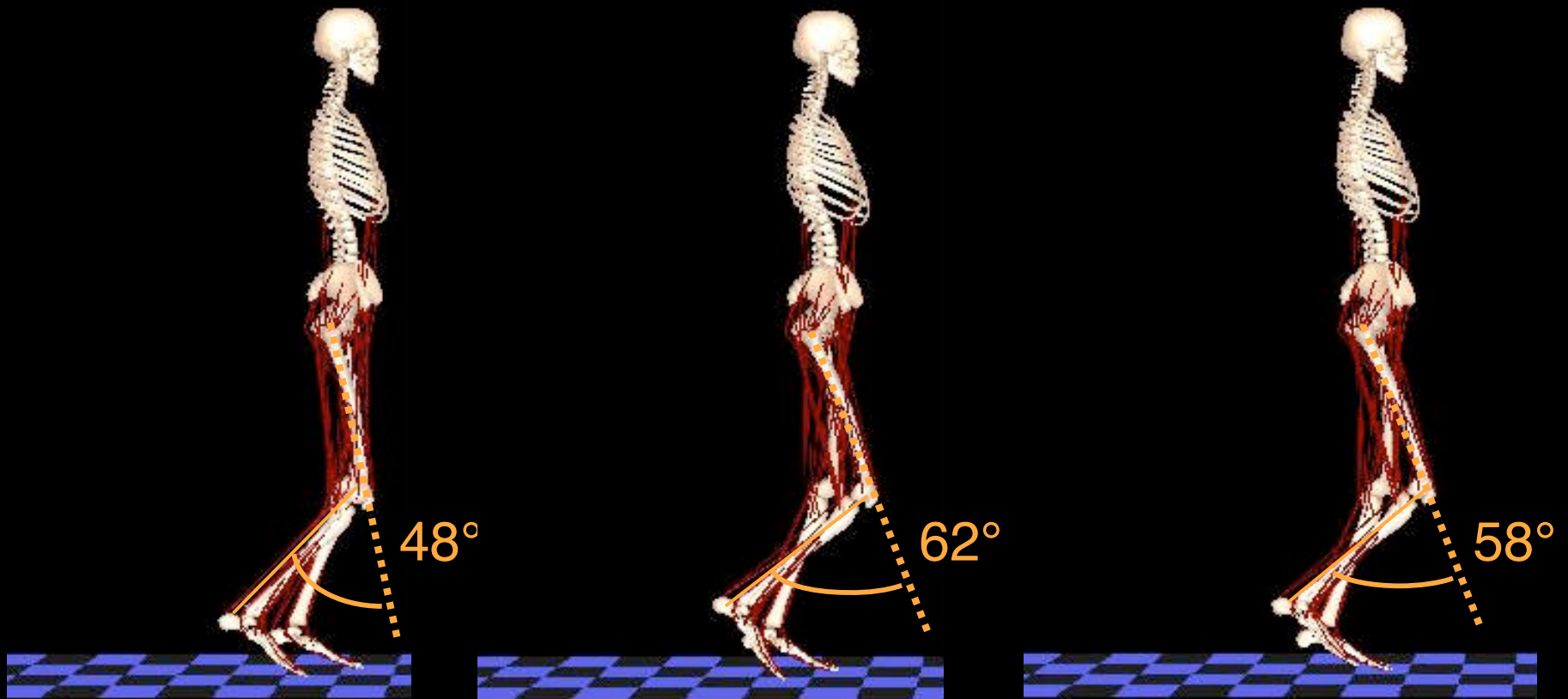


Original subject-specific simulation

Increase gastrocnemius force during double support

Decrease rectus femoris force during double support

# Subject-specific Simulation



Original subject-specific simulation

Increase gastrocnemius force during double support

Decrease rectus femoris force during double support

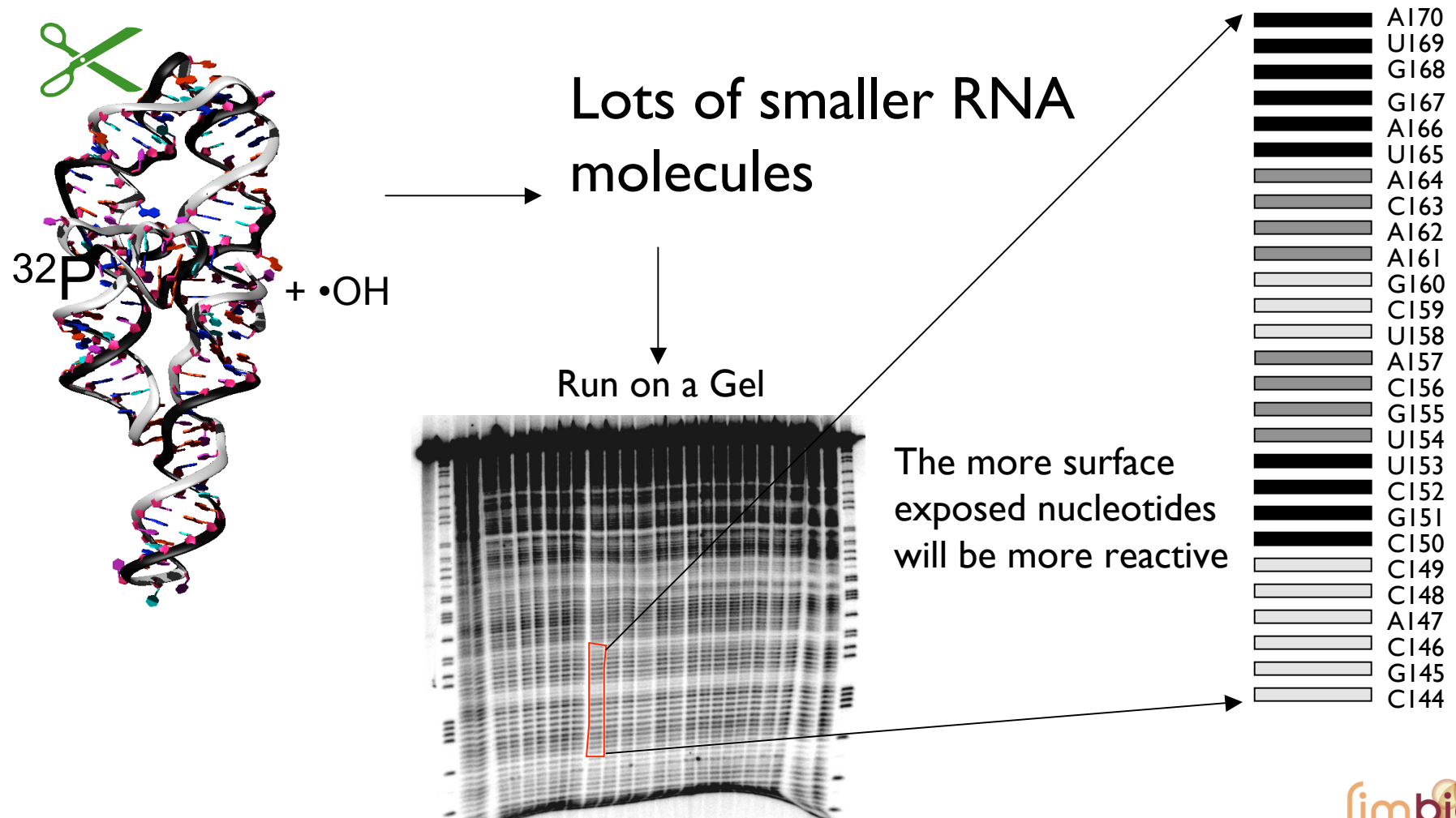


## RNA Folding Kinetics

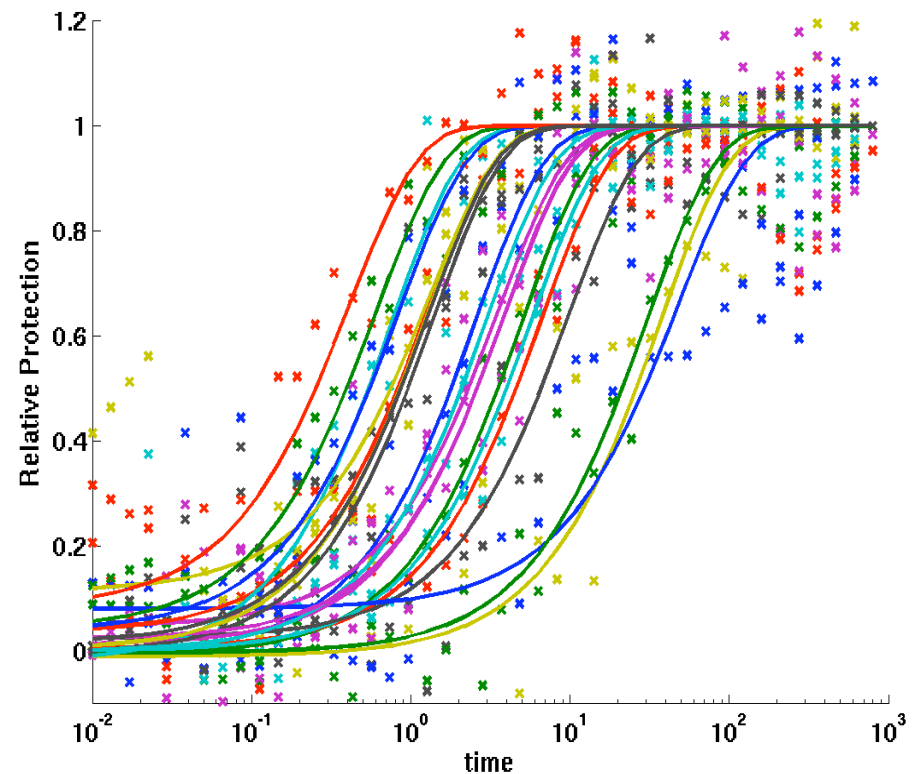
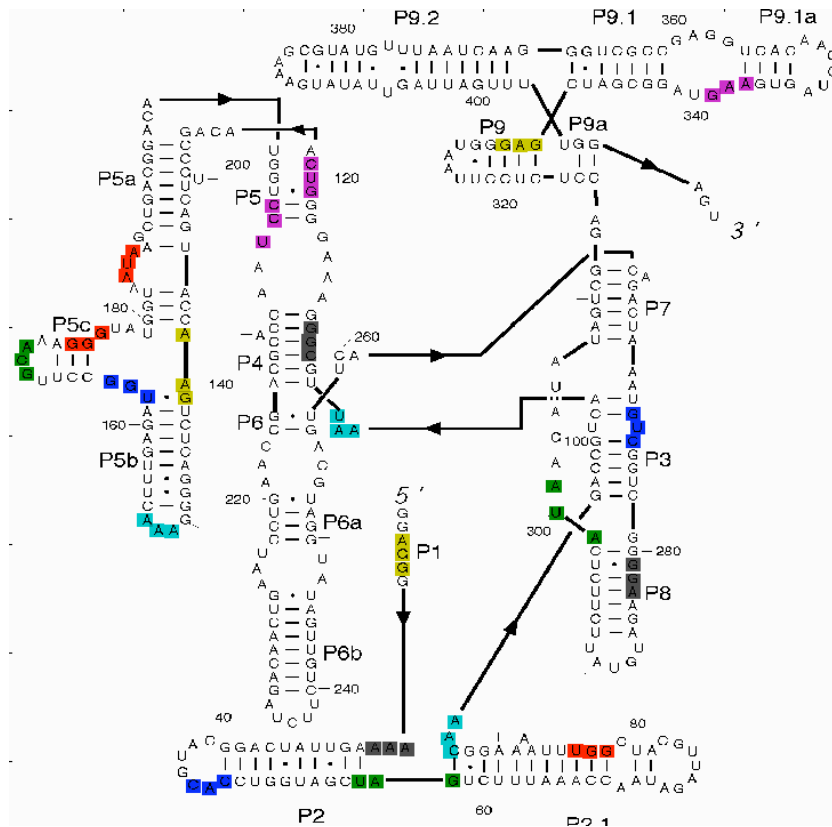
Alain Laederach, Magda Jonikas, Michael Brenowitz, Inna Shcherbakova, Mike Liang, Dan Herschlag, Russ Altman

J. Mol. Biol. 2006 (May 12) 358:4 p. 1179

# Hydroxyl Radical Footprinting



# Multiple Site Kinetics on the L-21 Tetrahymena group I intron

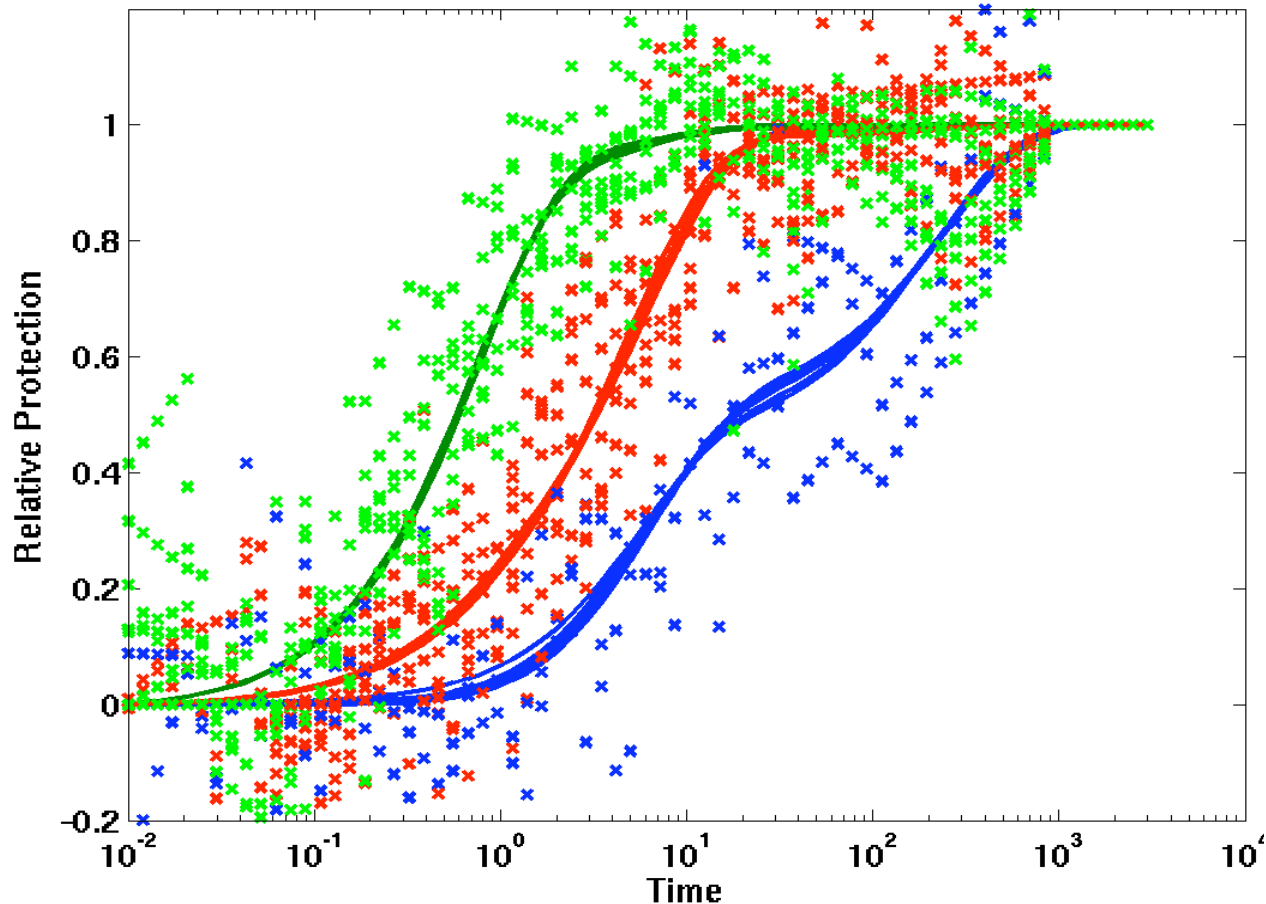


Time-resolved hydroxyl radical footprinting monitors the formation of tertiary contacts as the RNA folds.

RNA folding initiated with 10 mM  $Mg^{2+}$  in CE buffer

(Sclavi, Sullivan, Chance, Brenowitz & Woodson, Science 1998, 279, 1940-3)

# Cluster time-evolution curves for local areas, define intermediates

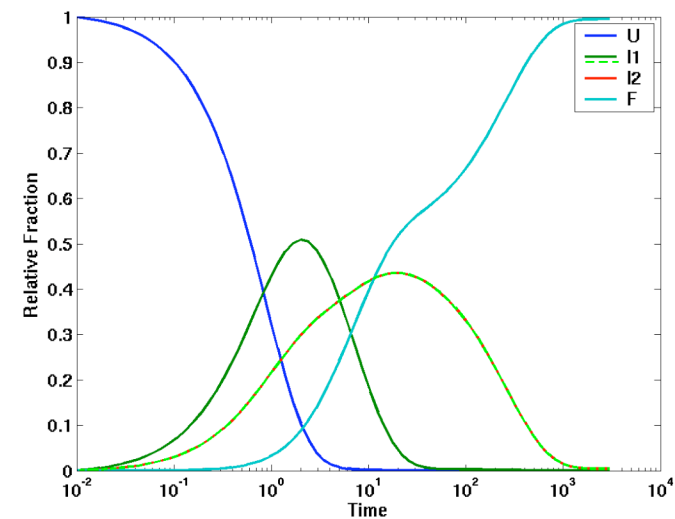
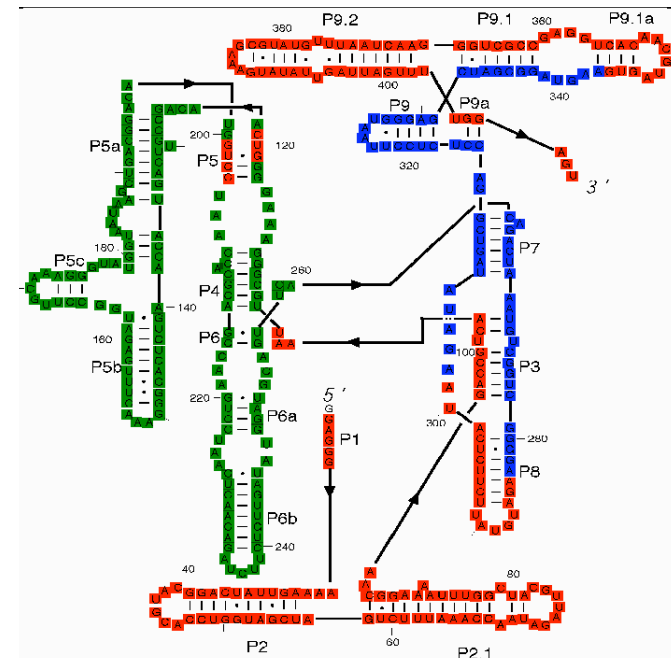
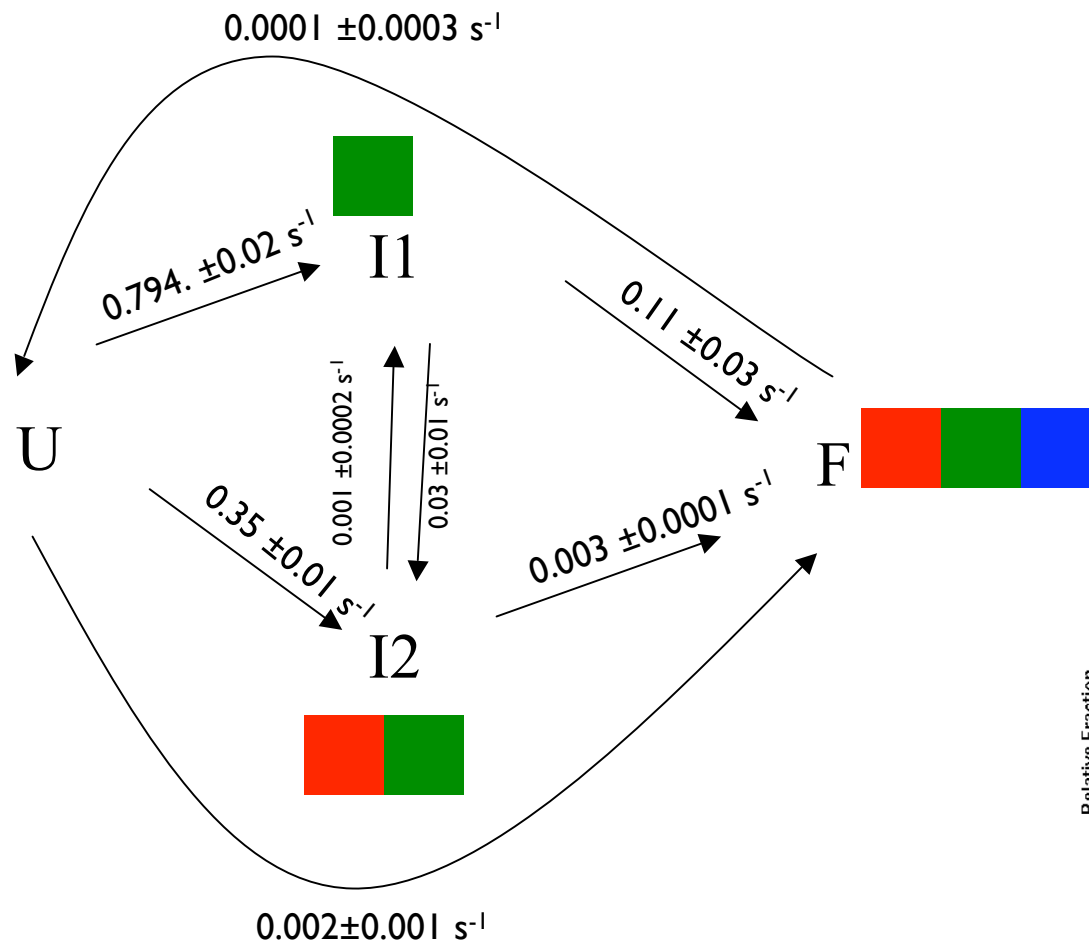


# Intermediates make sense

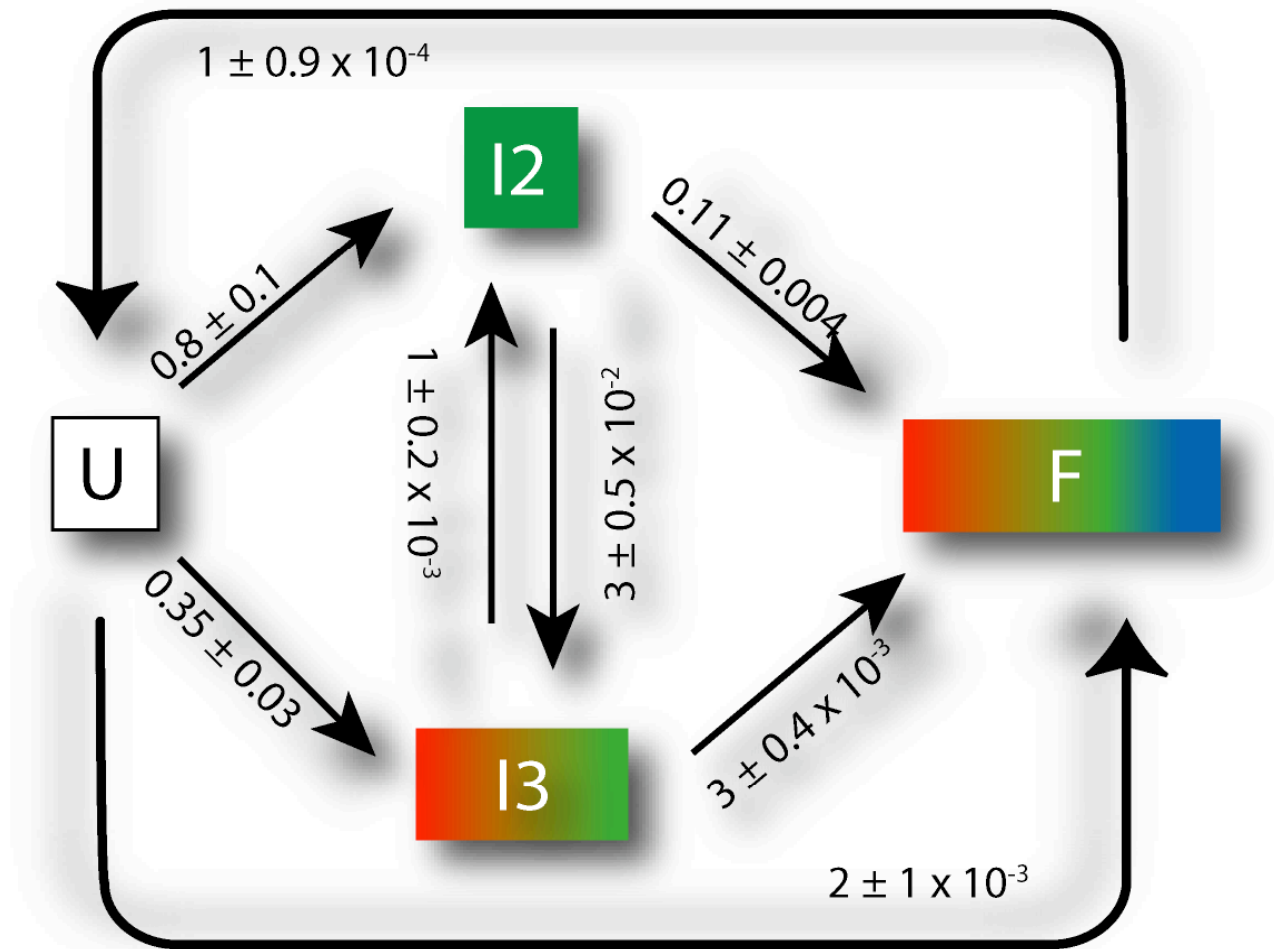
**P4P6 subdomain (Catalytic Core)**

**Red Cluster (Peripheral Region)**

**Blue Cluster (Catalytic Core)**

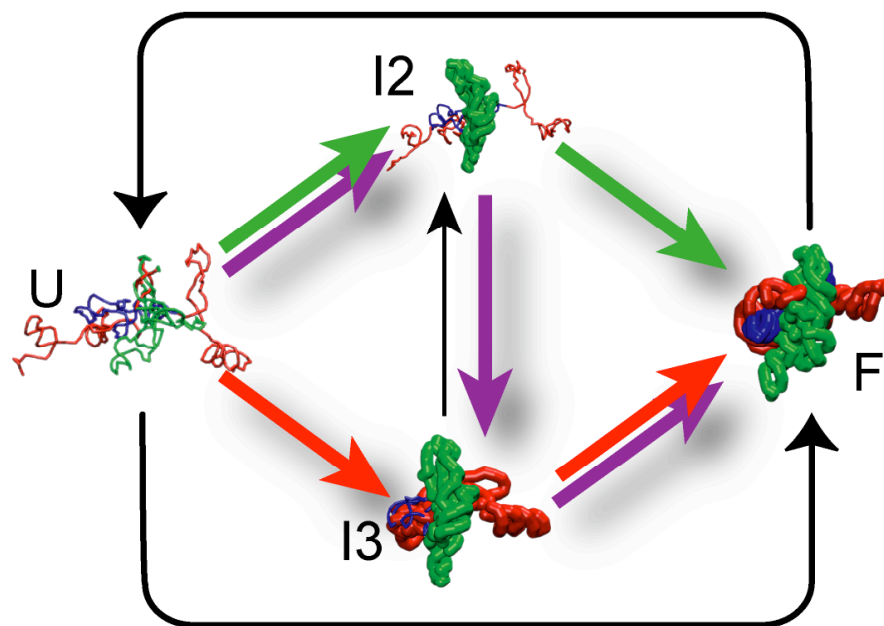
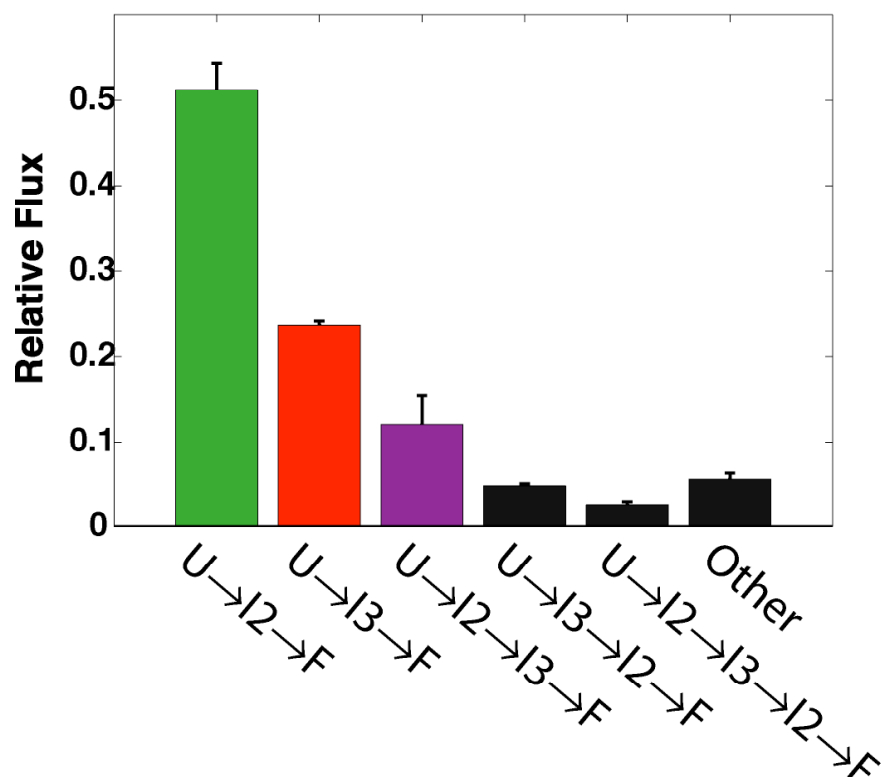


Can fit clusters to topology of intermediates AND time constants



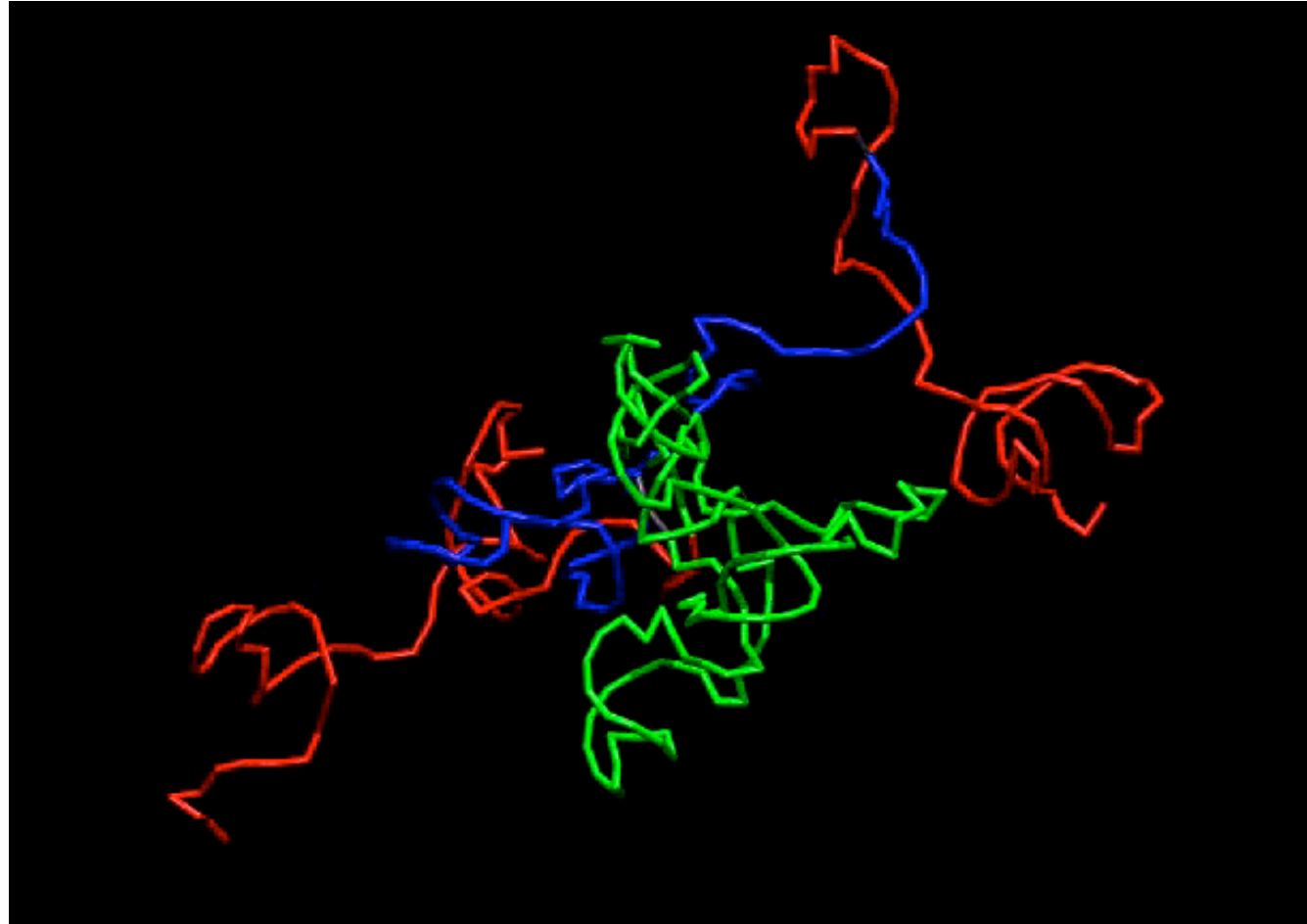


# Monte Carlo simulation of flux through intermediates



P4P6 then (periphery and core)

51%

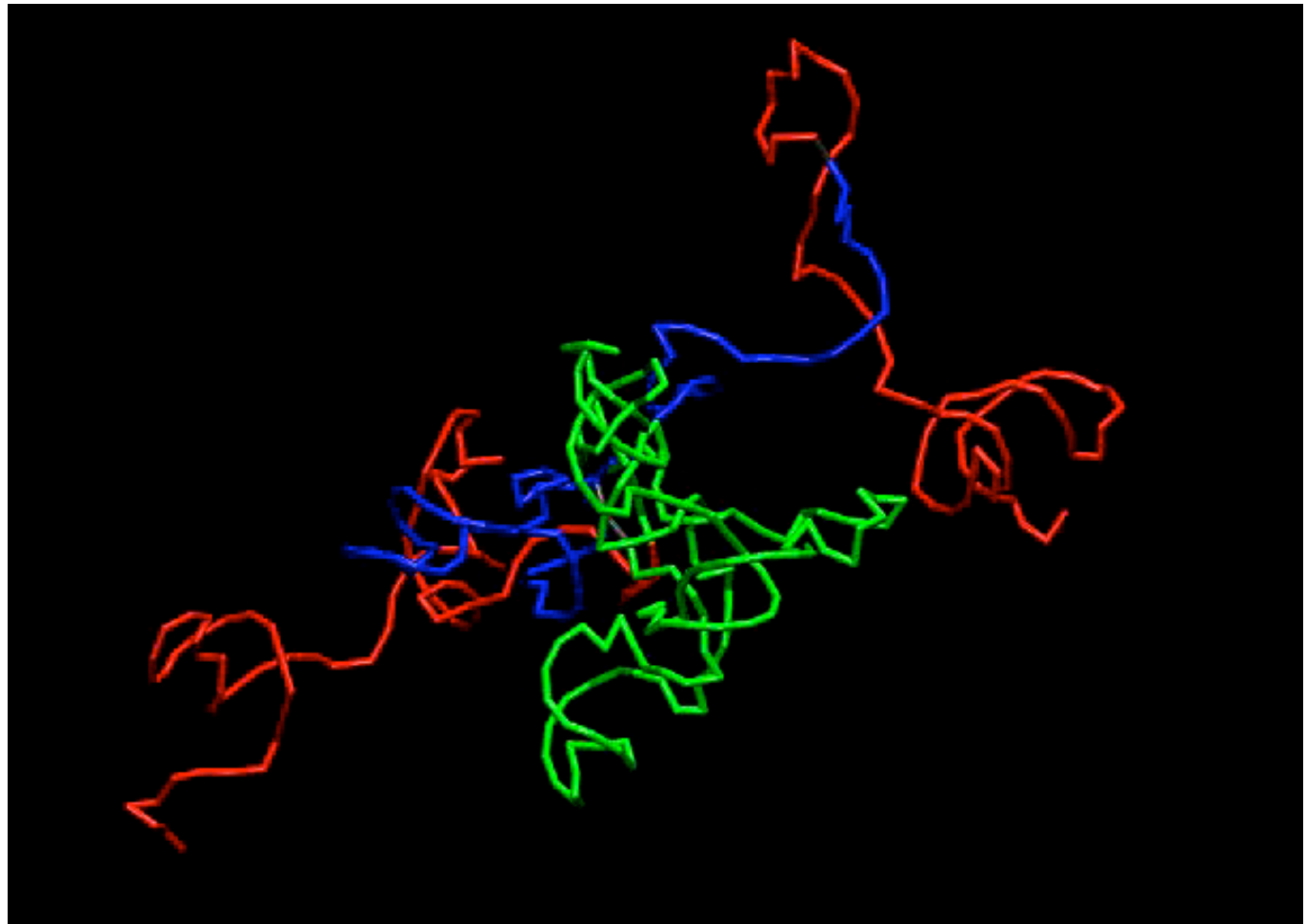


Magda Jonikas and Randy Radmer



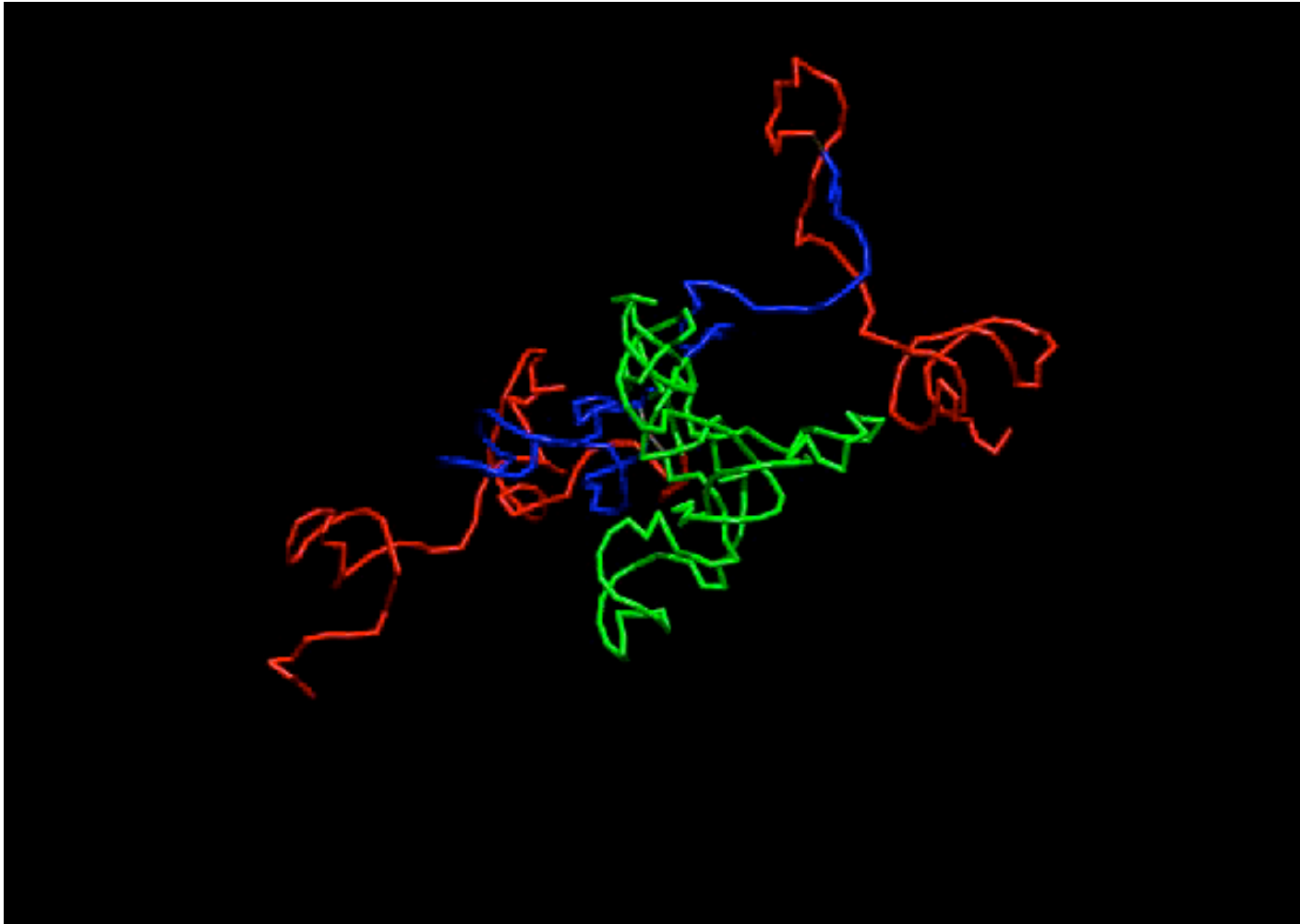
(P4P6 and Periphery) then core

24%



P4P6 then periphery then core

12%



# Summary

- Hydroxyl radical local probes tell us how local regions evolve from Unfolded to Folded
- We can cluster these regions to define intermediates with structural features
- We can model the folding pathways kinetically and structurally
- Allows us to explore different conditions, effects of mutations, etc...



Simbios Resources:

SimTK

Simbiome

Biomedical Computation Review

# Simbios Resources

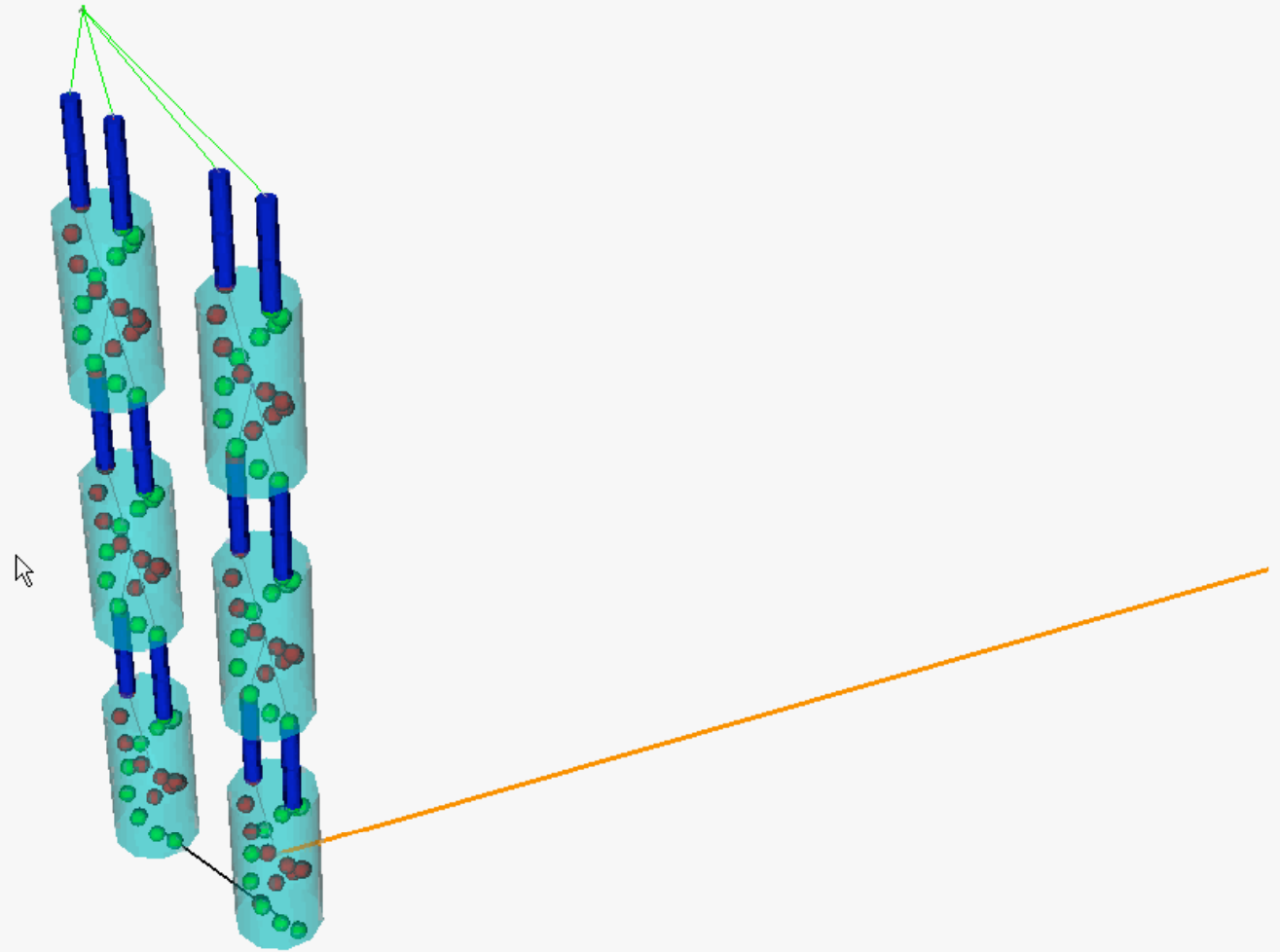
- SimTK: tool kit with freely available tools and models for building physics-based simulations
- SimTK.org: website and federated infrastructure
  - promotes collaborative environment for user communities of physics-based modeling
- Simbiome: “yellow pages” with trusted information on resources for the community
- Biomedical Computation Review
  - Magazine of biomedical computation with a focus on cross cutting issues that are important to the entire community.

# SimTK component: Simbody

- Multi-body dynamics code
  - Define structural components, degrees of freedom, mass properties
  - Supports all joint types
  - Compatible with multiple integrators
  - Can add relevant forces
  - (Cf SD/Fast)
- Open source



# Simbody: Connected RNA cylinders



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**Enabling groundbreaking biomedical research by providing open access to high-quality simulation tools, accurate models and the people behind them.**

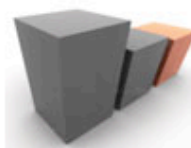
### About SimTK

SimTK, the Simulation Toolkit, is part of the **Simbios** project funded by the National Institutes of Health. [Learn more.](#)

### Simbios Sites



NIH Center for  
Physics-based Simulation



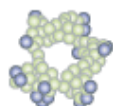
Simbiome



Biomedical Computation  
Review

### Biological Application Areas

#### Biomolecular Simulation - Current Emphasis



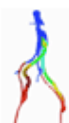
##### RNA Folding

RNA, even more than DNA, implements its functions using complex structural strategies.



##### Myosin Dynamics

Myosin is the fundamental source of motive force in many living systems.



##### Cardiovascular Dynamics

The dynamics of fluid flow through the human cardiovascular system has many clinical applications, including surgical bypass planning.



##### Neuromuscular Biomechanics

The modeling of human motion has applications in the planning of interventions to assist patients with abnormal movement dynamics, resulting for example from cerebral palsy.

### Simulation Applications

Free downloadable stand-alone simulation software

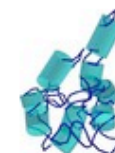
### Simulation Technology

The underlying algorithms and computational tools applicable to a variety of biological application areas.

### How to Contribute



### Featured Project



**SimTK  
ToRNADo RNA  
3D Structure  
Morphing and  
Visualization  
Application**

SimTK ToRNADo is a dynamic visualization tool for coarse grain (lumped) representations of RNA and/or protein structure.

[Feedback](#) | [Simbios](#) | [BCR](#) | [Our Pledge Your Responsibility](#)

SimTK, the Simulation Toolkit, is a part of the Simbios project funded by the National Institutes of Health through the NIH Roadmap for Medical Research, Grant U54 GM072970. Information on the National Centers for Biomedical Computing can be [obtained here](#).



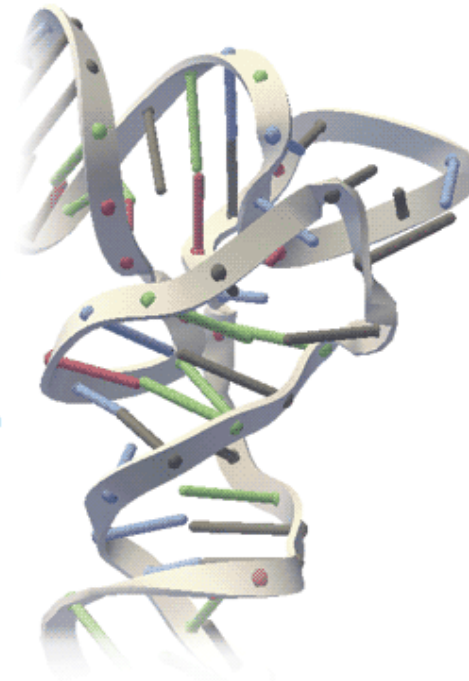
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# RNA Folding



## Key Simtk.org Projects

[SimTK ToRNADo](#)

RNA 3D Structure

Morphing and

Visualization Application

[SimTK Ion Simulator](#)

Interface

Interface to ISIM Grand

Canonical Monte Carlo

Ion Simulator

[NAST](#)[KinFold](#)[SAFA](#)

## Individual Participants

Dan Herschlag

Russ Altman

Yu Bai

Nathan Boyd

Chris Bruns

Mark Engelhardt

Magda Jonikas

Sophie Liu

Alain Laederach

Vijay Pande

Manisha Paul

Randy Radmer

Bernie Sattin

Jeanette Schmidt

Segey Solomatin

## Consultants

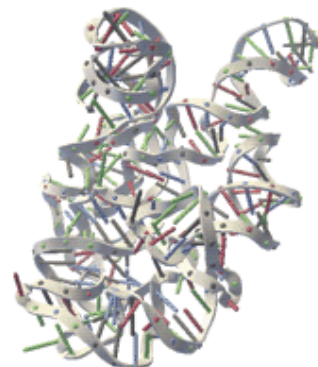
Sebastian Doniach

(Applied Physics)

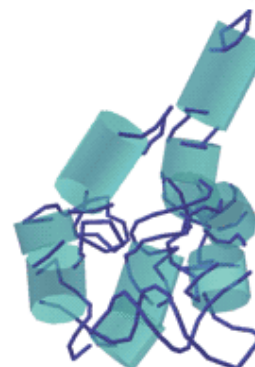
Steve Block

(Physics)

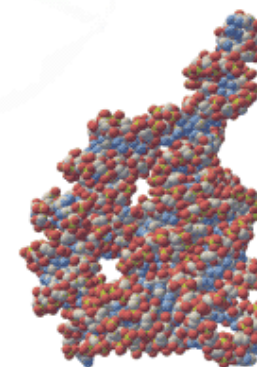
This driving biological problem investigates the mechanism of RNA folding through the integrated application of experimental and computational approaches. The focus is on the folding Tetrahymena thermophila self-splicing group I intron ribozyme, with a relatively well-understood structure, folding and catalytic mechanism. Although the primary scale of the RNA work is at the atomic level, certain computations are too expensive to perform atomistically. Thus, this project requires coarse-grain models in which, for example, an A-form duplex is represented as a cylinder. The information obtained from this project will allow comparison with the folding behavior of proteins. Dr. Herschlag and Prof. Altman are the lead investigator of this project working with a world-class team from the Stanford Departments of Biochemistry, Genetics, Physics, and Applied Physics.



Tetrahymena ribozyme (ribbon representation, pdb entry 1GRZ)



Tetrahymena ribozyme (rope and cylinder representation, pdb entry 1GRZ)



Tetrahymena ribozyme (space filling representation, pdb entry 1GRZ)

## How were these figures generated?

You can generate these figures with [Tornado](#), an interactive visualization tool under development for coarse grain (lumped) representations of RNA and protein structure.



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## Overview

[Statistics](#)  
[Geography of use](#)

## Team

## Downloads

## Documentation

## Advanced

### Project Administrator

[Christopher Bruns](#)  
[Contact](#)[Mark Engelhardt](#)  
[Contact](#)

### Team

[6 members](#)

# SimTK Ion Simulator Interface

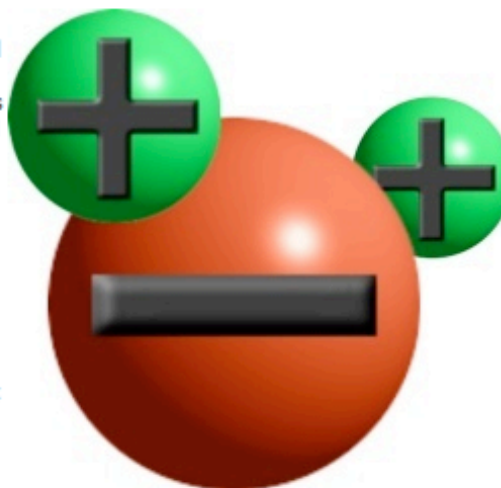
## Overview

ISIM interface a simple Java graphical user interface for running the programs APBS and ISIM. ISIM is package that simulates the thermodynamic ensemble of ions around a macromolecule using a grand canonical monte carlo scheme and simple hard sphere ion models. It is meant to provide an alternative mechanism to mean field approaches to allow the calculation of ion distributions around a highly charged molecule using a simple model that takes into account ion-ion correlations and steric interactions. The original source was created in the McCammon group at UCSD (<http://mccammon.ucsd.edu/isim/>). The version of ISIM used is available in the ISIM project on simtk.org.

**Purpose** ISIM interface provides a simple graphical interface for running the programs APBS and ISIM. This is closely related to the ISIM project on simtk.org.

**Audience** Researchers interested in simulating the ionic environment around macromolecules.

**Long Term Goals and Related Uses** Provide a simple interface to guide users through the process of preparing a structure file, running APBS, running ISIM, and examining the results.



### Project Administrator

[Christopher Bruns](#)  
[Contact](#)[Mark Engelhardt](#)  
[Contact](#)

### Principal Downloads

[isim\\_interface](#)[See All Downloads](#)

### News

[No News](#)

### Driving Biological Problems

[This project is part of RNA Folding](#)





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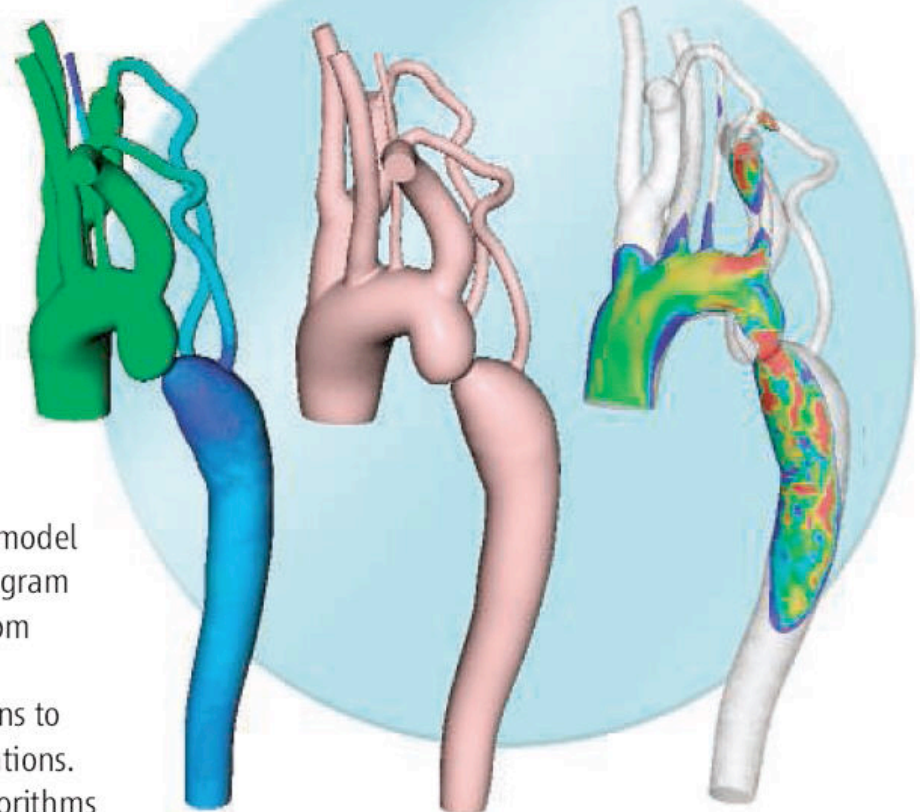
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## TOOLS

### Bodily Functions >>

Don't fret if you can't get your simulation of aortic blood flow to work. Download one of the models available at SimTK. The site, hosted by researchers at Stanford University, is part of a project to devise and share "physics-based" models and software that emulate how force and motion affect a range of biological processes. Visitors can take home code that mimics RNA folding, blood dynamics, and ions jostling a large molecule. Plenty more projects are under way, including a model of the colon lining and SimBody, a dynamics program that can help researchers studying everything from molecular shape to walking. The site also offers modules that you can plug into your own creations to perform tasks such as rapidly solving linear equations. Researchers can contribute their models and algorithms to the site. At right, a simulation to gauge blood pressure and velocity in coarctation of the aorta, a congenital narrowing of the vessel. >>

[simtk.org](http://simtk.org)



#### Overview

[Statistics](#)  
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#### Team

#### Downloads

#### Documentation

#### News

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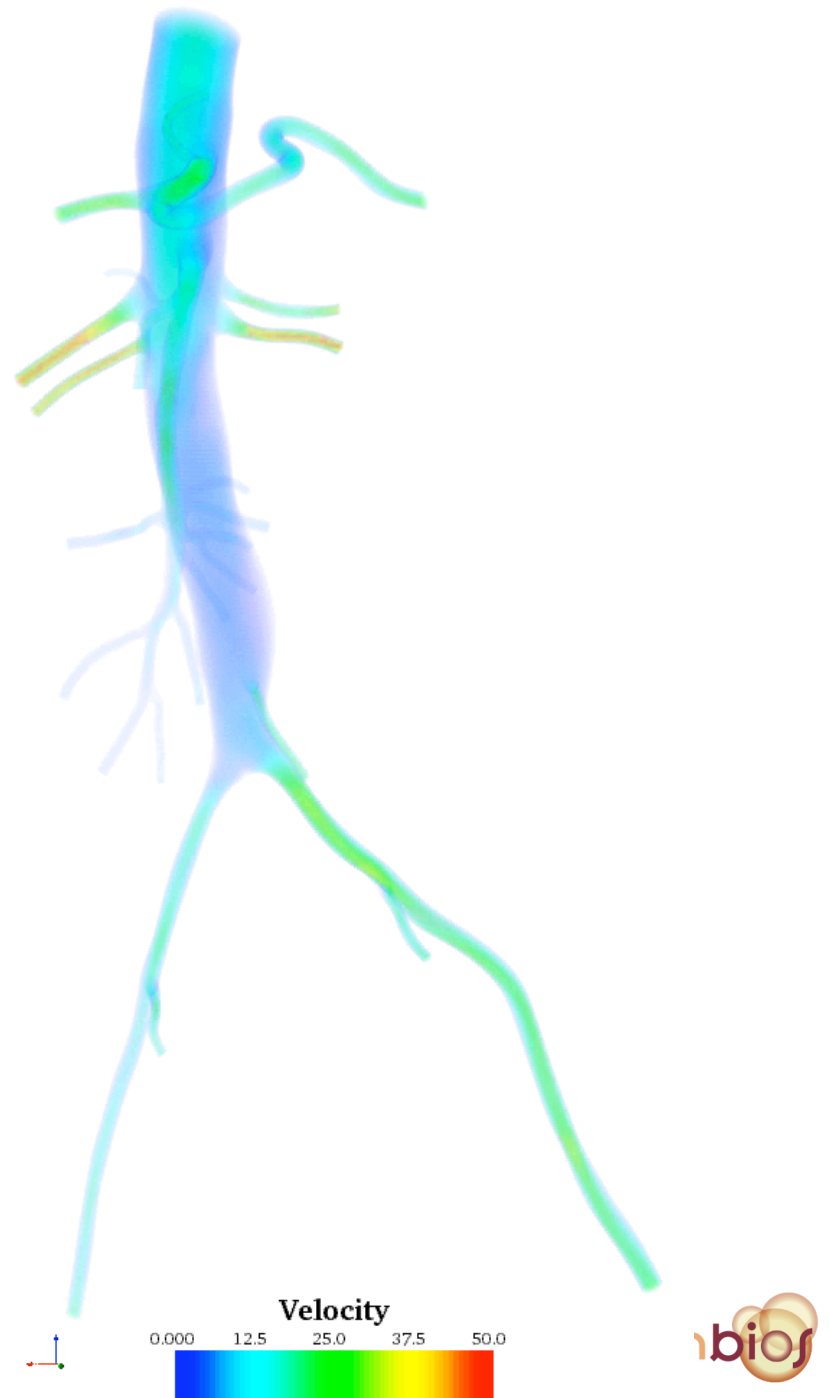
#### Project Administrator

[Christopher Bruns](#)  
[Contact](#)

#### Team

[10 members](#)

# Cardiovascular blood flow simulations (Charles Taylor Lab)



# SimTK/SimTK.org uses and users

Repository of  
advanced algorithms



for computer scientists,  
applied mathematicians,  
etc.

Modeling



for modelers such as  
engineers, physicists,  
bio-physicists

Applications with  
easy-to-use GUI



for end users, such as  
clinicians or bench  
scientists



Simbiome: Curated portal to  
all available simulation-  
related resources (NOT just  
SimTK/Simbios...)

Jon Dugan, Bill Katz,  
Jeanette Schmidt



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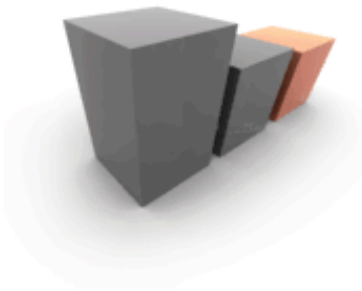
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Simbiome, the Resource Inventory for Simbios



## Welcome to Simbiome!

Simbiome has recently been updated. We appreciate your feedback: please send comments to: [feedback@simbiome.org](mailto: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.

<http://www.simbiome.org/>



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## GROMACS

*Stockholm Bioinformatics Center, Stockholm University*

### Molecular Dynamics Simulation

<http://www.gromacs.org/>

#### *Summary Assembled by Curation Team*

Software: Simulation Application

GROMACS is a versatile package to perform molecular dynamics, i.e. simulate the Newtonian equations of motion for systems with hundreds to millions of particles.

It is primarily designed for biochemical molecules like proteins and lipids that have a lot of complicated bonded interactions, but since GROMACS is extremely fast at calculating the nonbonded interactions (that usually dominate simulations) many groups are also using it for research on non-biological systems, e.g. polymers.

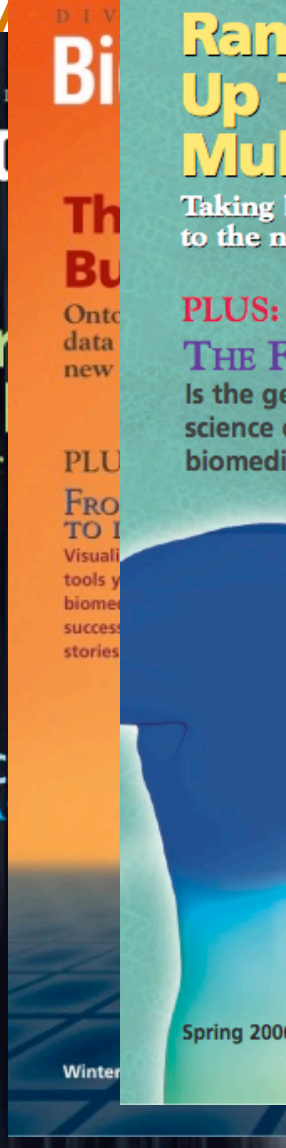
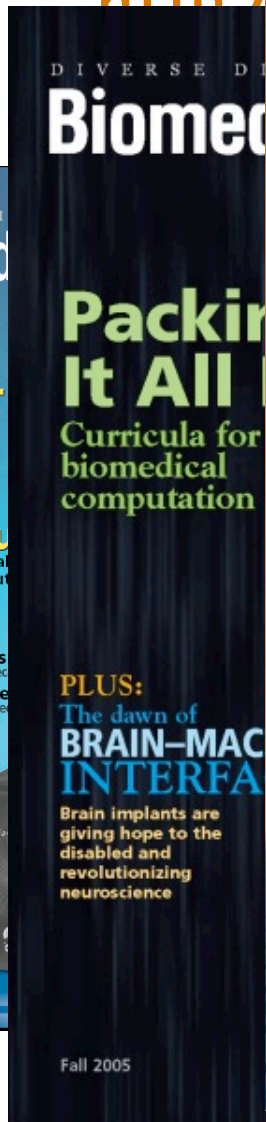
Development Stage	5 - Production/Stable
Keywords	
Size Scale	1 - Atomic / Molecular
Support	2 - Organized User base / Mailing lists



# Biomedical Computation Review

Biomedical

http://





# Simbios Collaborators



James Spudich



David Paik



Leonidas  
Guibas



Pat Hanrahan



Chris Bruns



Osussama  
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Rachel  
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David Parker



Paula Petrone



Russ Altman



Scott Delp



Padma  
Sundaram



Peter Pinsky



Michael  
Levitt



Alex Labute



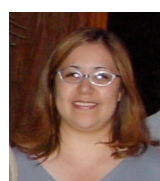
Alain Laederach



Clay Anderson



Silvia Blemker



Blanca Pineda



Ron Fedkiw



Peter  
Feenstra



Bryan Keller



Jack Middleton



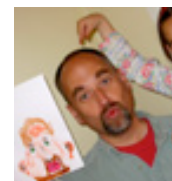
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Ayman Habib



Randy Radmer



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Michael Sherman

# Contacts

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Supported by NIH Roadmap for Medical Research U54GM072970

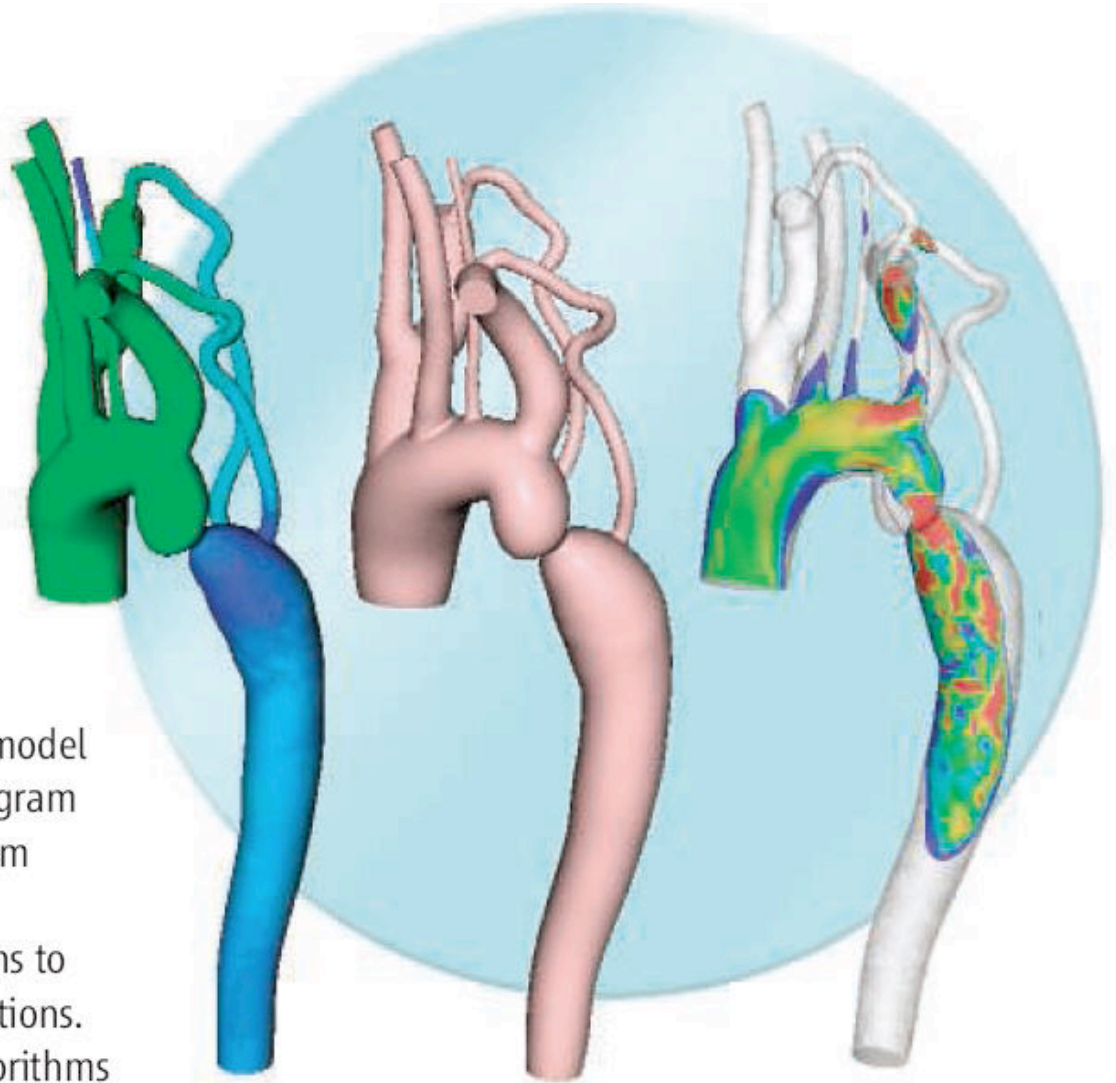


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# Simbios Resources



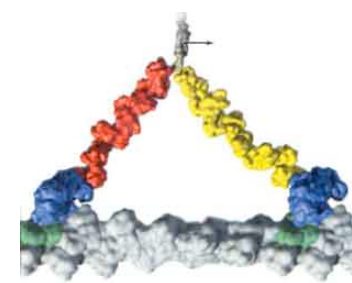
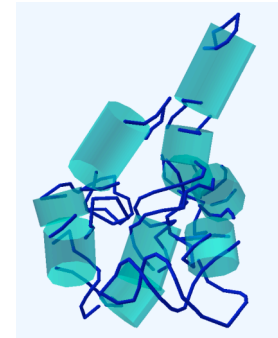
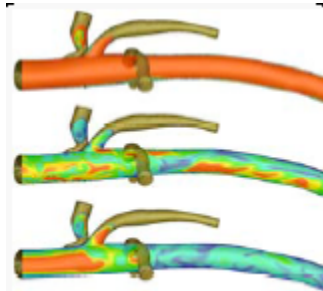
## SimTK

- tools for building physics-based simulations:
  - robust, high performance, pre-built binary computational methods
    - Linear algebra, numerical integration, multibody dynamics, molecular force fields, finite element solvers, *etc.*
  - shareable models
  - application building tools
  - narrow, domain targeted applications
  - all open source and available in [SimTK.org](http://SimTK.org)





# Simulation Toolkit



**GUI Tools | Documentation Tools | Installation**

## Modeling

**Linear Algebra**

**Multi Body Dynamics**

Simbody  
TAO  
•

**Integrator**

ODE  
DAE

**Optimize**

Sim Anneal  
Genetic  
SQ Prog

**Monte Carlo**

**Force Fields**

**Control**  
PD

**Contact**

Rigid  
Penalty  
•

**Meshing**

**PDEs**

Solids  
Fluids

