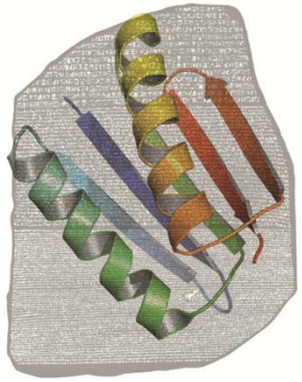
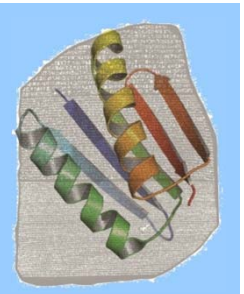
Efforts to establish a federally supported Rosetta center

Jens Meiler

Associate Professor
Vanderbilt University
Departments of Chemistry, Pharmacology, and Biomedical Informatics
Center for Structural Biology, Institute of Chemical Biology

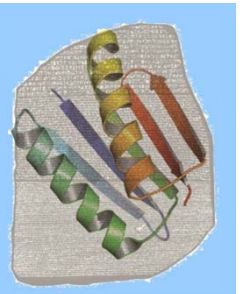


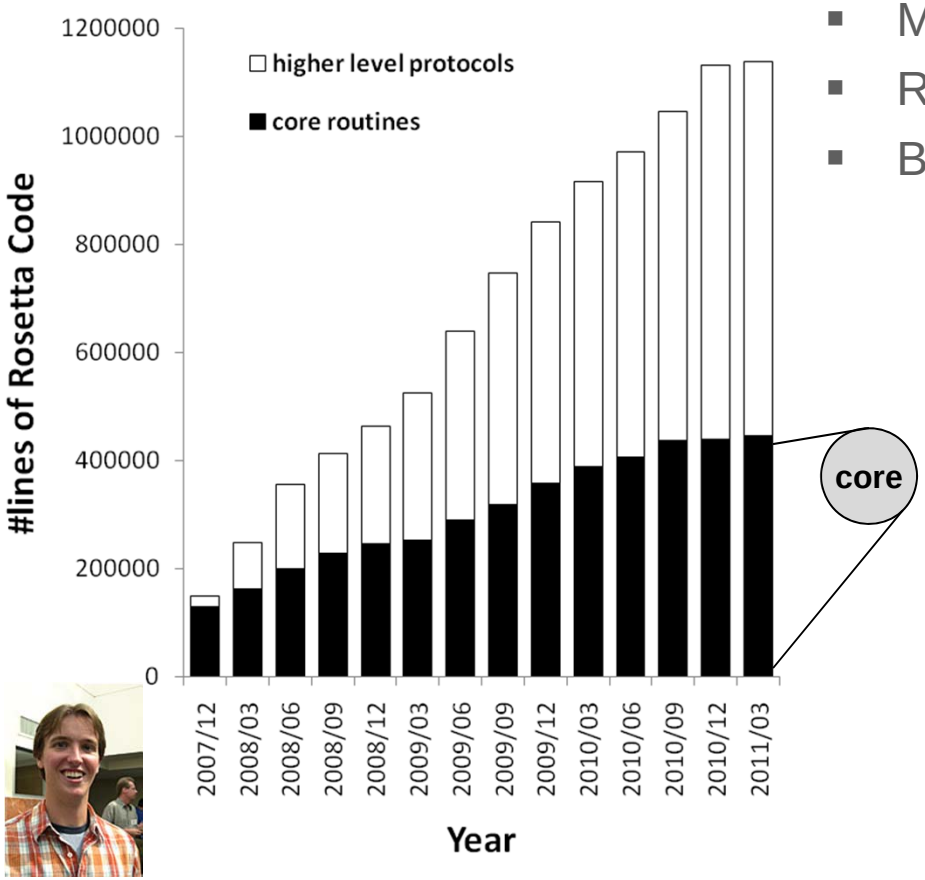
NIH Biomedical Technology Research Center (BTRC)



- 12/02/2008 – 1st pre-proposal submission
  - 20 pages of scientific and organizational description
  - Scored well but not yet invited for full application
- 10/08/2009 – 2nd pre-proposal submission
  - 23 pages of scientific and organizational description
  - Scored excellent and was invited for full application
- 09/28/2010 – 1st full proposal submission
  - 176 pages of 357 pages of scientific and organizational description
  - 03/22/2011 – NIH site visit
  - Scored mediocre and was not yet funded
- … more to come …

RosettaCommons Consortium of 16 Laboratories Maintains Rosetta Code





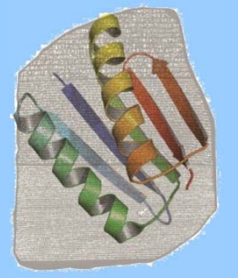
- Maintains core code functionality of Rosetta
- Releases software semi-annually
- Basis the BTRC will build upon

Andrew Leaver-Fay UNC

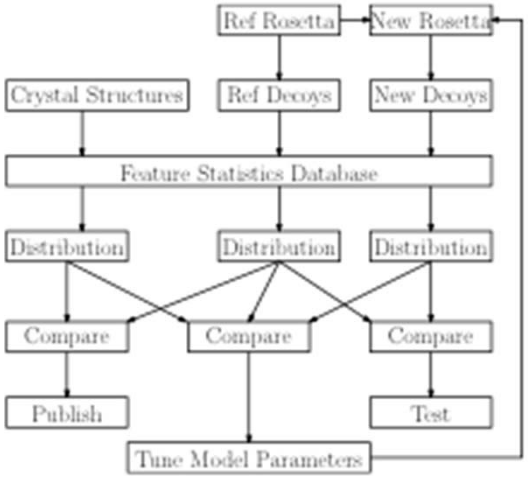
RosettaCon 2009, Leavenworth, WA, USA

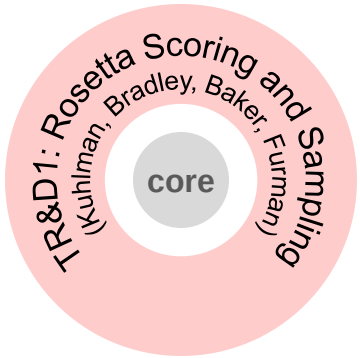
8:20 am 8:40 am Andrew Leaver-Fay: Rosetta software development

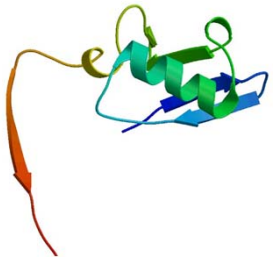
TR&D1: Develop, Integrate, and Test Rosetta Scoring and Sampling

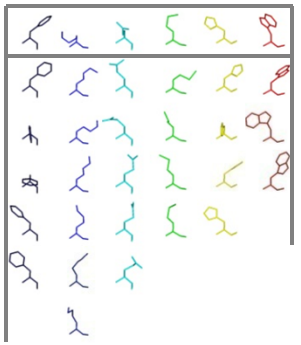


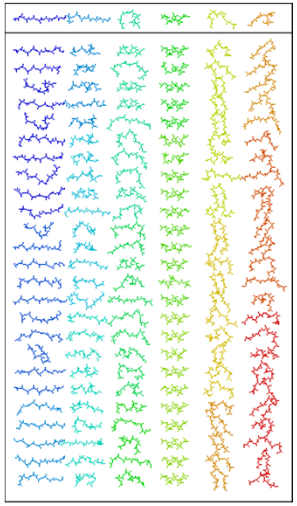
- Feature Database and Testing System for Energy Function Improvement
- Comparative analysis of Sampling Efficiency

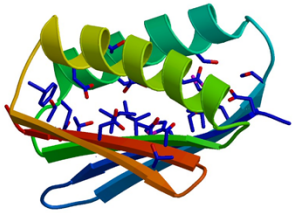




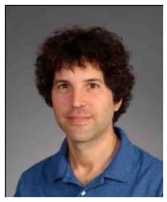









Phil Bradley, FHCRC

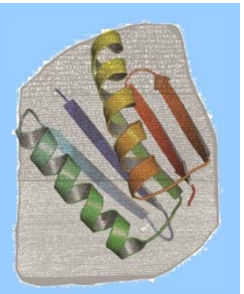

David Baker, UW


Brian Kuhlman, UNC

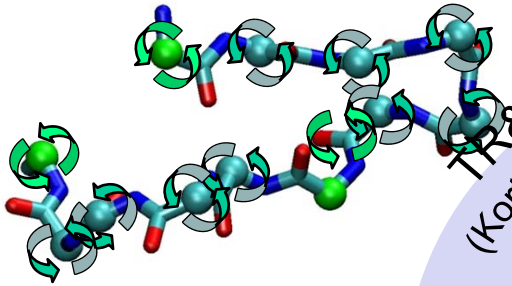

Ora Furman, HUJ

8:40 am 9:10 am Phil Bradley: TR&D1 -Rosetta scoring and sampling

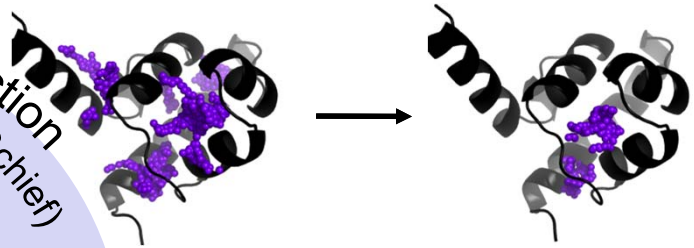
TR&D2: Integrate Novel Methods for Design of Biological Function

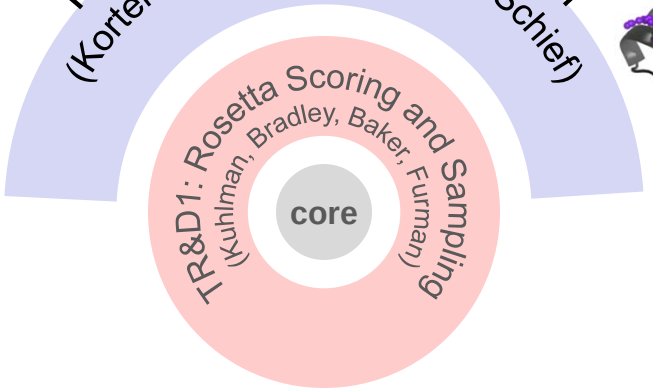


- Robotics-Inspired Conformational Sampling

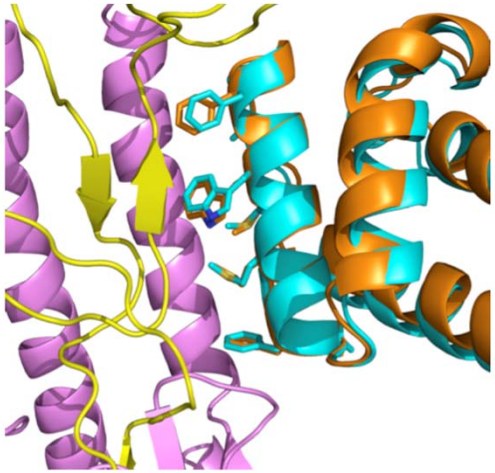


- Problem-Targeted Refinement of Designs with High-Order Energy Functions





- Scaffolding Epitopes and Binding Sites




Tanja Kortem-me, UCSF

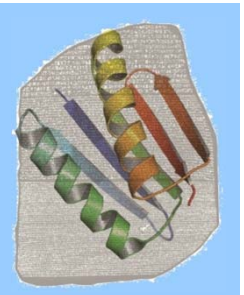

Bill Schief, SCRIPPS


Jim Havranek, Wash U

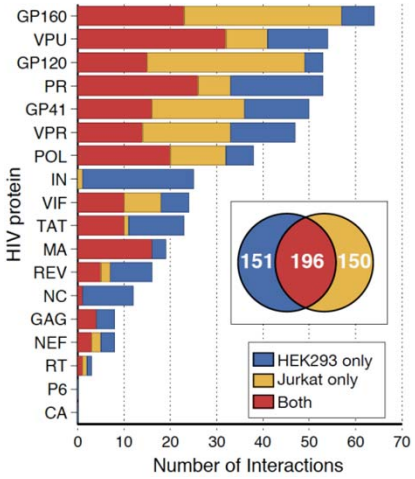

Jeff Gray, JHU

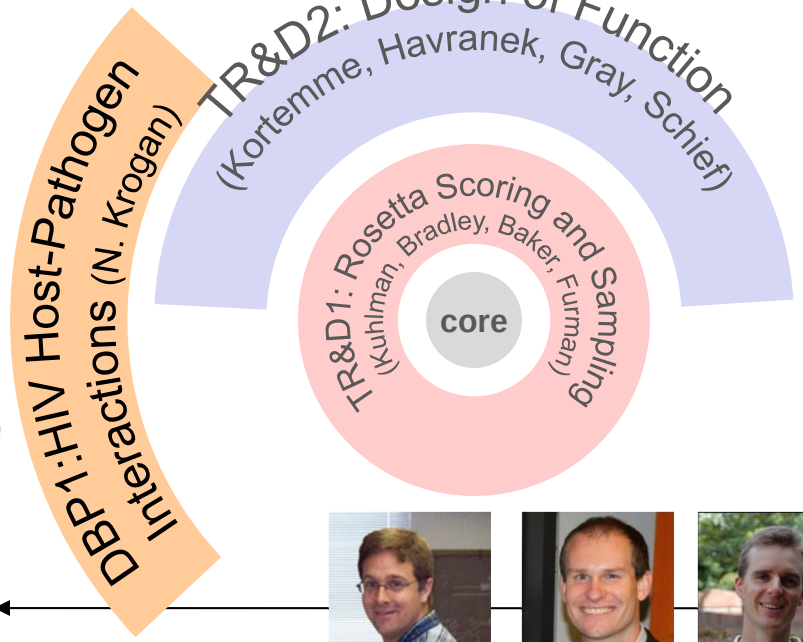
9:10 am 9:30 am Jim Havranek: TR&D2 -Design of Function

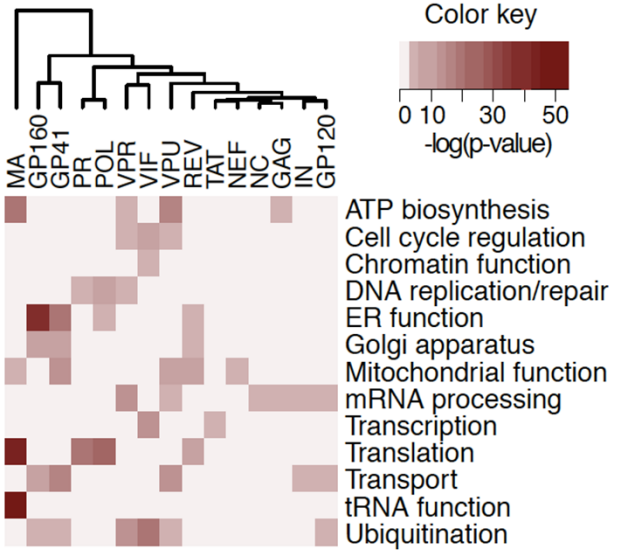
DBP1: HIV Host-Pathogen Interactions, Nevan Krogan, UCSF



- Prediction and Design of HIV Host-Pathogen Interactions to Generate Hypotheses and Plan Biomedically Informative Experiments





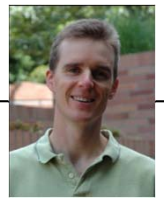


Nevan Krogan, UCSF

Tanja Kortem-me, UCSF

Jim Havranek, Wash U

Jeff Gray, JHU



Phil Bradley, FHCRC

David Baker, UW

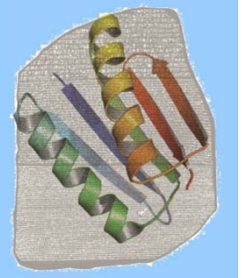
Brian Kuhlman, UNC

Ora Furman, HUJ

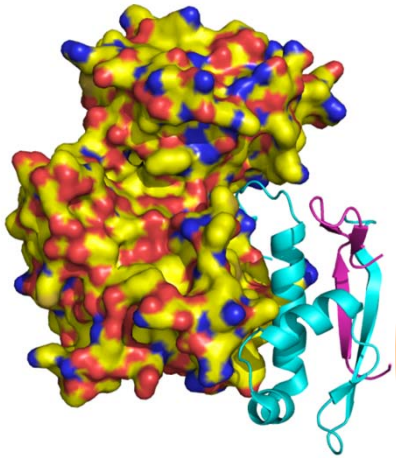
9:30 am 9:40 am Jim Havranek: DBP1 - HIV Host-Pathogen Interactions

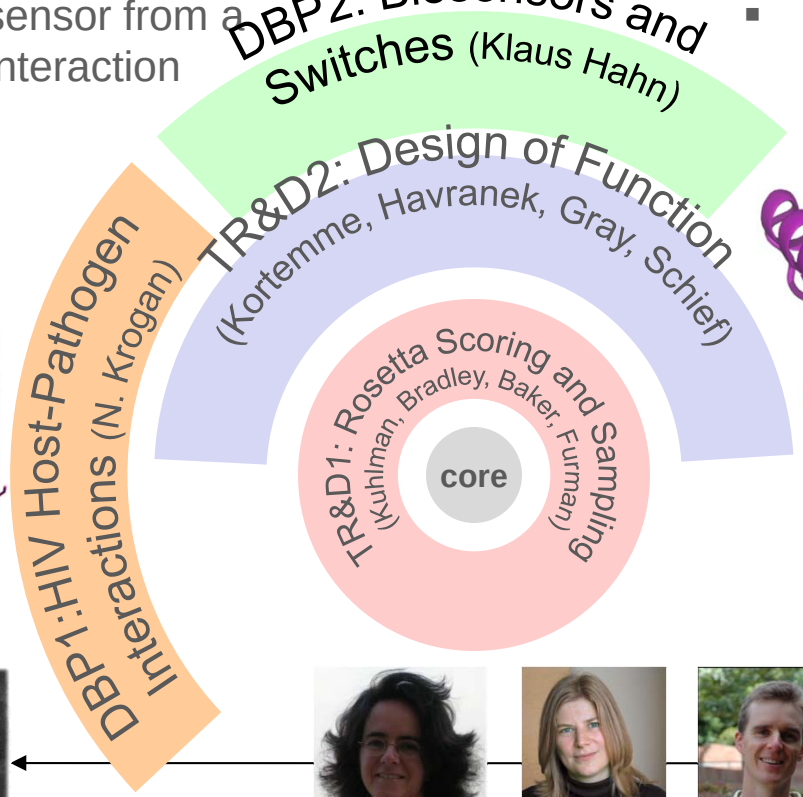
P01 AI090935 / P50 GM082250

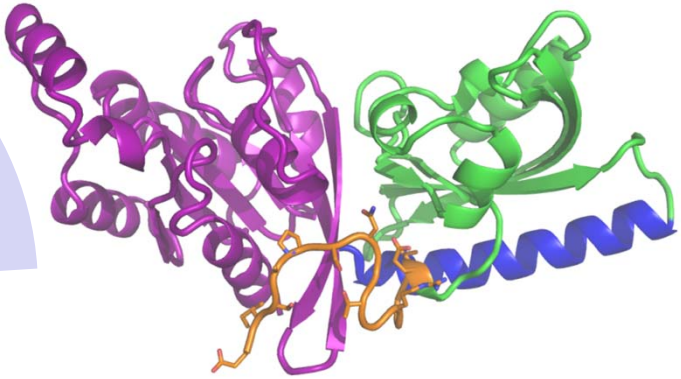
DBP2: Biosensors and Switches, Klaus Hahn, UNC



- Designing a Biosensor from a Protein-Protein Interaction
- Tuning Protein Switches through Computational Design





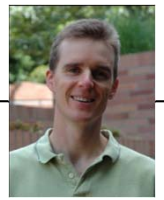



Klaus Hahn, UNC


Brian Kuhlman, UNC

Ora Furman, HUJ

Tanja Kortem-me, UCSF


Phil Bradley, FHCRC


Jeff Gray, JHU

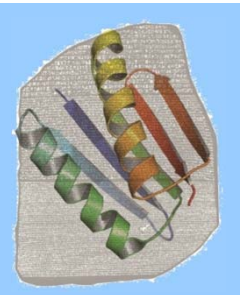

Jim Havranek, Wash U


David Baker, UW

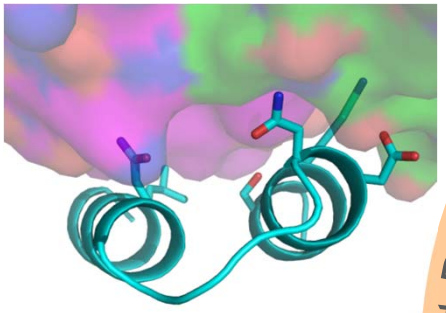
9:40 am 10:00 am Brian Kuhlman: DBP2 -Biosensors and Switches

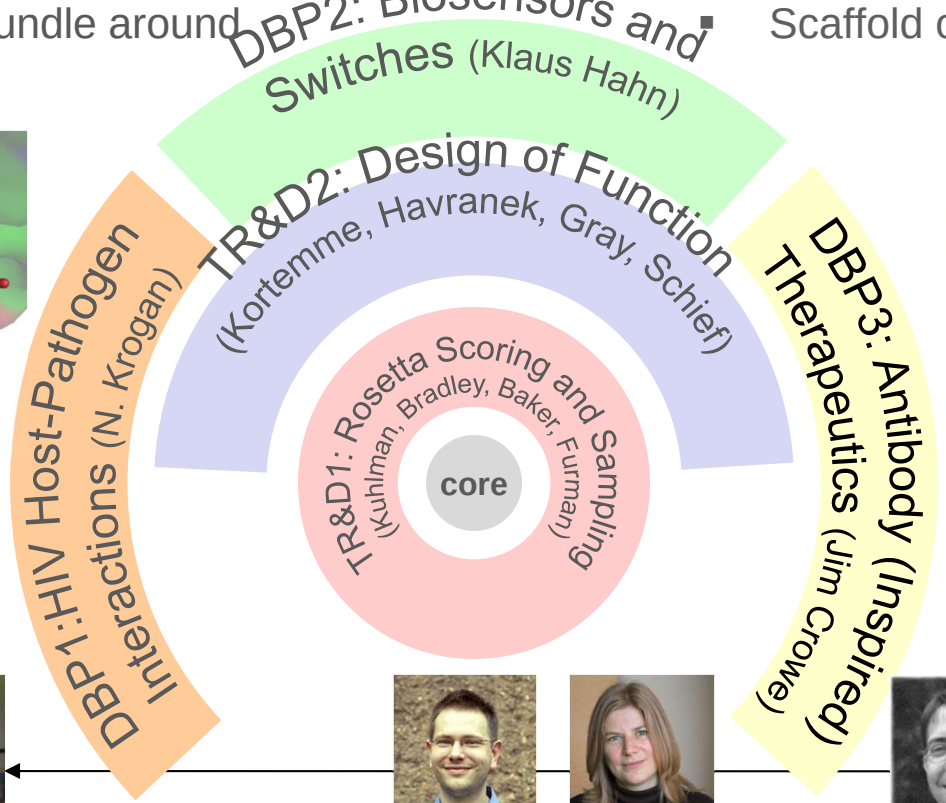
R01 AG015430 / R01 OD006169

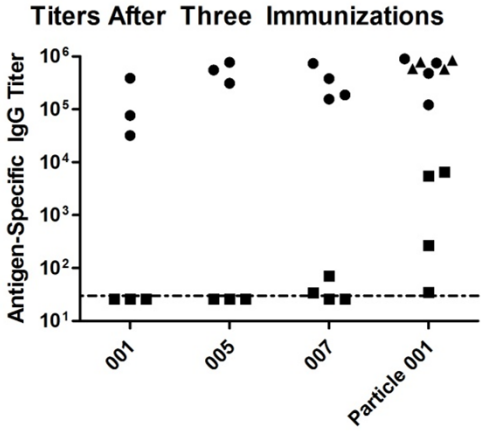
DBP3: Design of Antibody (Inspired) Therapeutics, Jim Crowe, Vanderbilt



- Folding helical bundle around epitopes
- Scaffold on virus-like particle elicits specific Abs in mice







BAA AI2008031


Jim Crowe, Vanderbilt


Bill Schief, SCRIPPS

Jens Meiler, Vanderbilt

Tanja Kortem-me, UCSF

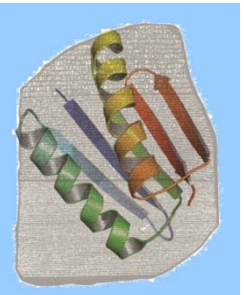

Brian Kuhlman, UNC


Jeff Gray, JHU

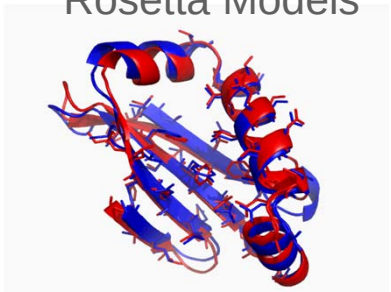

David Baker, UW

10:10 am 10:40 am Bill Schief and Jim Crowe: TR&D2 and DBP3 - Design of Antibody Inspired Therapeutics

TR&D3: Protein Structure Prediction



- Molecular Replacement with Rosetta Models

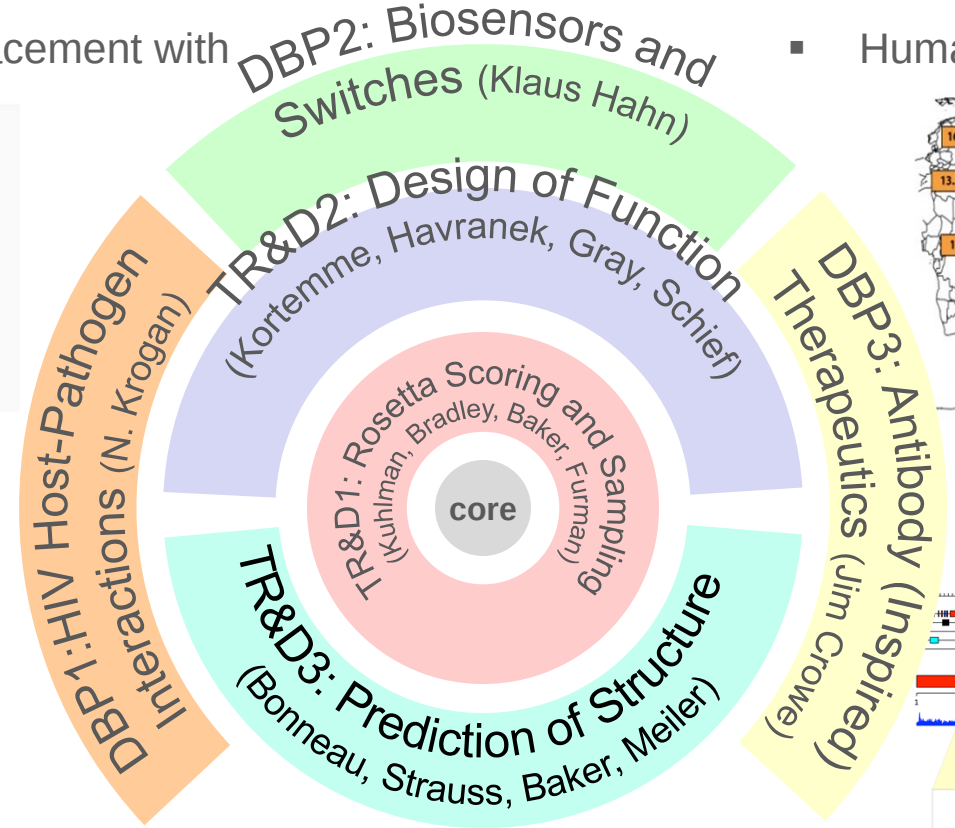


Rich Bonneau, NYU

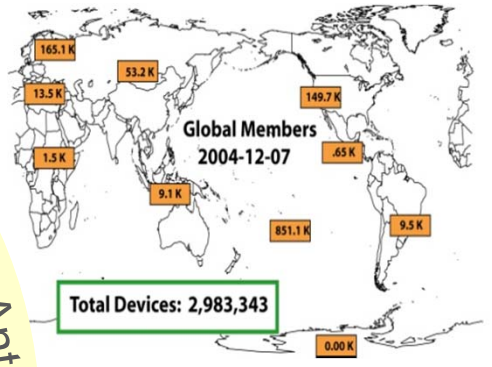
Charlie Strauss, LANL

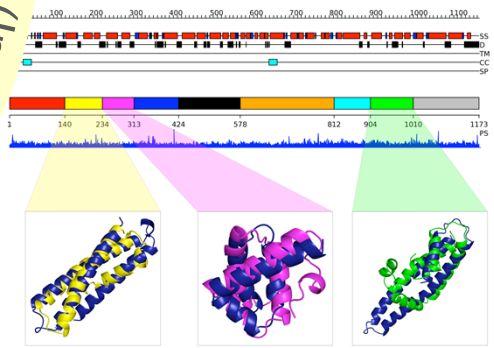
Jens Meiler, Vanderbilt

David Baker, UW



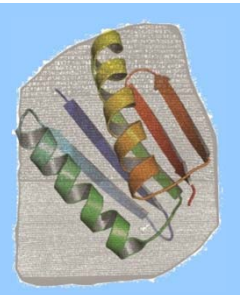
- Human Protein Folding Project



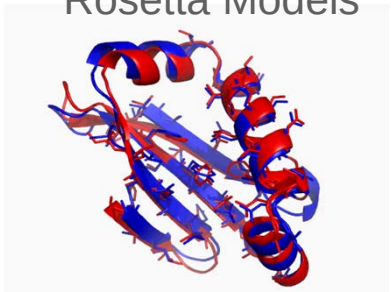


10:40 am 11:10 am Rich Bonneau and Guy Montelione: Protein Structure Determination from Sparse Data

TR&D3: Protein Structure Prediction



- Molecular Replacement with Rosetta Models

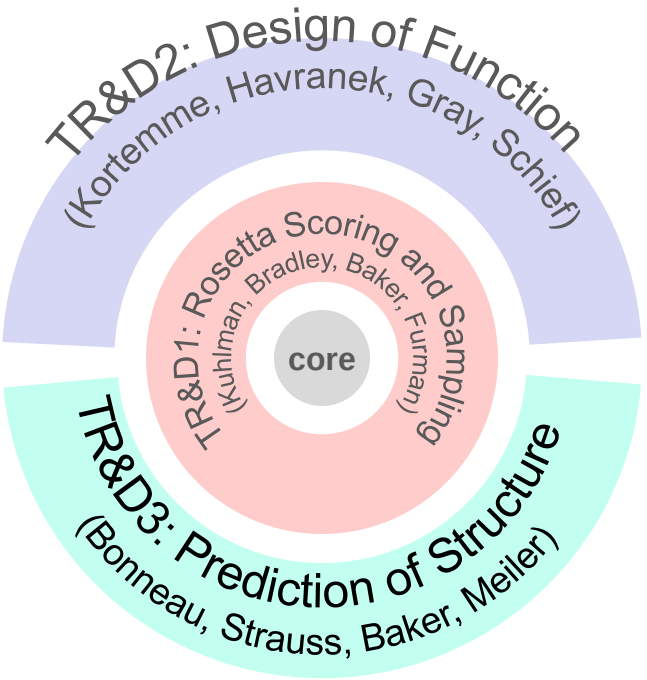


Rich Bonneau, NYU

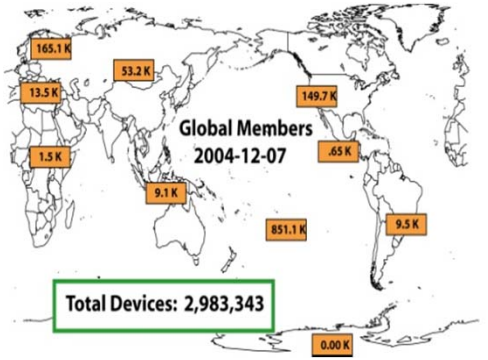
Charlie Strauss, LANL

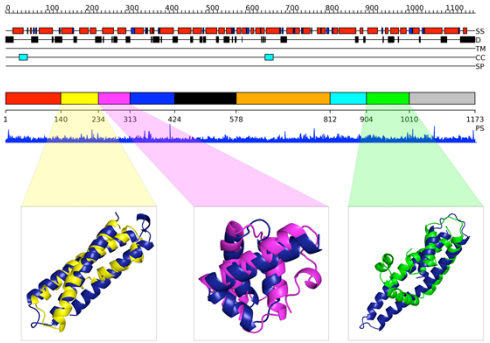
Jens Meiler, Vanderbilt

David Baker, UW



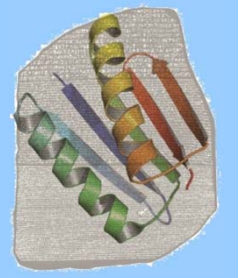
- Human Protein Folding Project



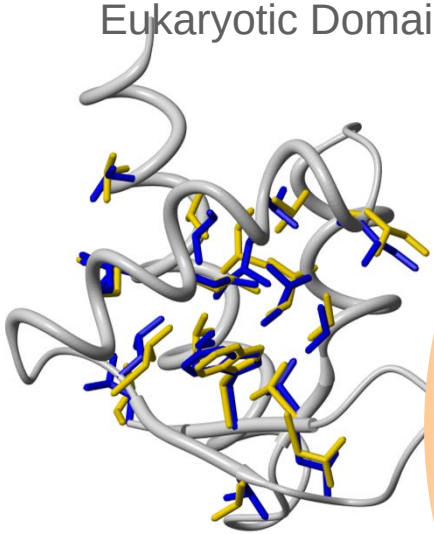


10:40 am 11:10 am Rich Bonneau and Guy Montelione: Protein Structure Determination from Sparse Data

DBP4: Protein Structure from Sparse Data (G. Montelione, Rutgers)



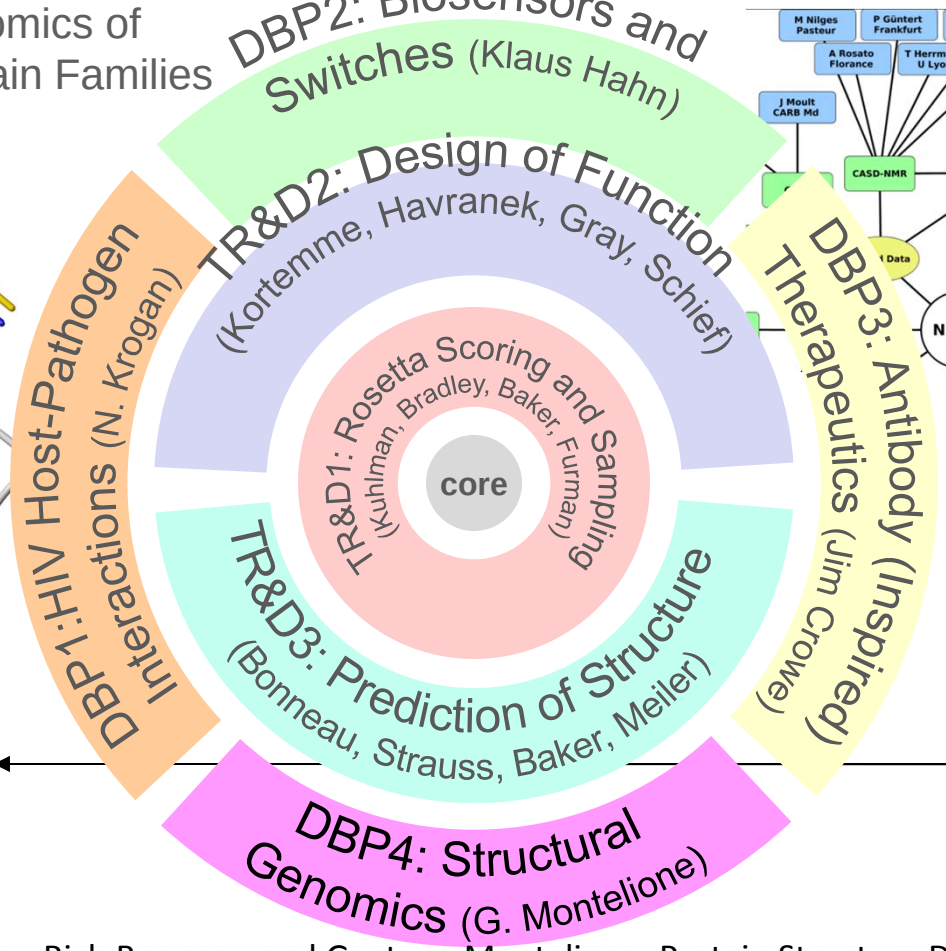
- Structural Proteomics of Eukaryotic Domain Families



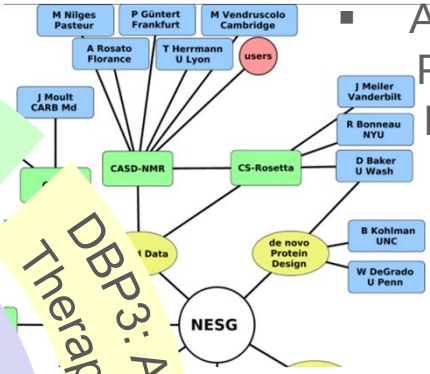
U54 GM094597

G. Monetlione, Rutgers

Rich Bonneau, NYU



- Align Structure Prediction and Determination Pipelines



Jens Meiler, Vanderbilt

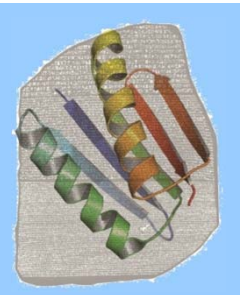
Charlie Strauss, LANL

Brian Kuhlman, UNC

David Baker, UW

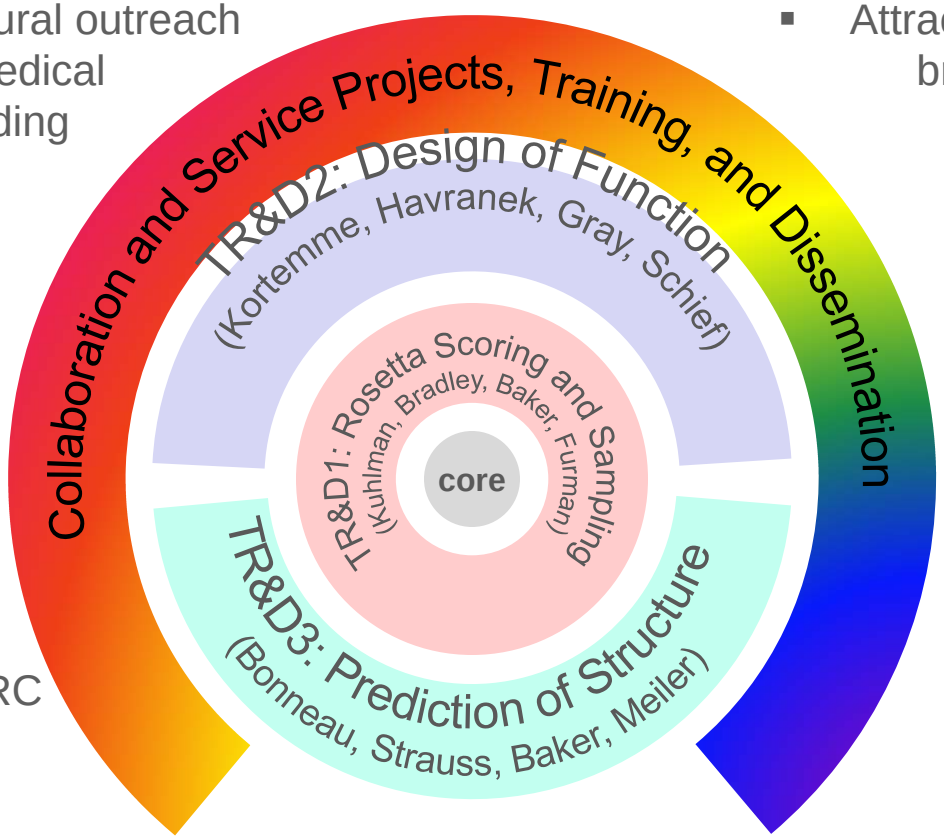
10:40 am 11:10 am Rich Bonneau and Gaetano Montelione: Protein Structure Determination from Sparse Data

C&STD: Empower the Biomedical Research Community to use Rosetta

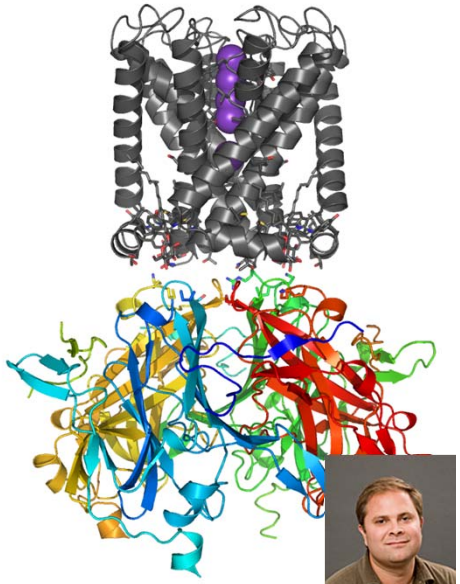


- PI directs intramural outreach program to biomedical community including collaborations, workshops, and tutorials
  - 100 Interactions
  - 13 Publications
  - 22 Proposals
- Framework, expertise, and personnel to kickoff the RosettaBTRC

Jens Meiler, Vanderbilt



- Attract junior investigators with bright ideas and interesting problems to use Rosetta

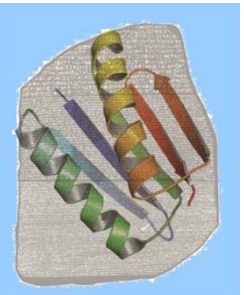


R01 DK082884

Jerod Denton, Vanderbilt

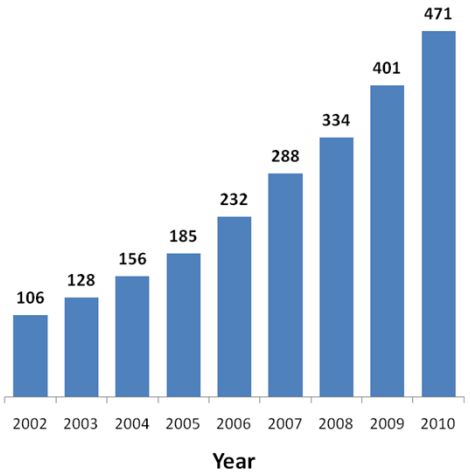
12:45 pm 1:25 pm Jens Meiler & Jerod Denton: Collaboration and Service, Training, and Dissemination

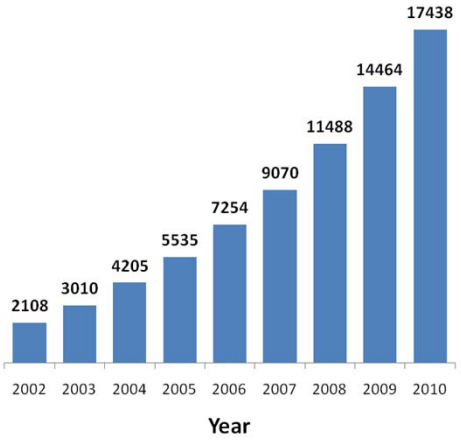
Significant Impact on Structure Prediction and Protein Design Field



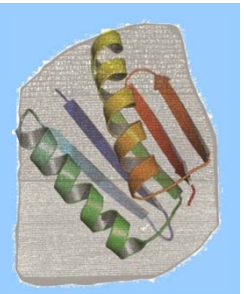
- 471 papers | 17,438 citations | 71 h-index

- Examples of high-impact publications:
  - Simons, K. T.; et al. **"Assembly of Protein Tertiary Structures from Fragments with Similar Local Sequences using Simulated Annealing and Bayesian Scoring Functions"** J. Mol. Biol. 1997, 268, 209-225. *(496 citations)*
  - Kuhlman, B.; et al. **"Design of a Novel Globular Protein Fold with Atomic Level Accuracy"** Science 2003, 302, 1364-1368. *(440 citations)*
  - Gray, J. J.; et al. **"Protein-protein docking with simultaneous optimization of rigid-body displacement and side-chain conformations"** J Mol Biol 2003, 331, 281-99. *(263 citations)*
  - Kortemme, T.; et al. **"A simple physical model for binding energy hot spots in protein-protein complexes"** PNAS 2002, 99, 14116-21. *(255 citations)*
  - Jiang, L.; et al. **"De novo computational design of retro-aldol enzymes"** Science 2008, 319, 1387-91. *(179 citations)*

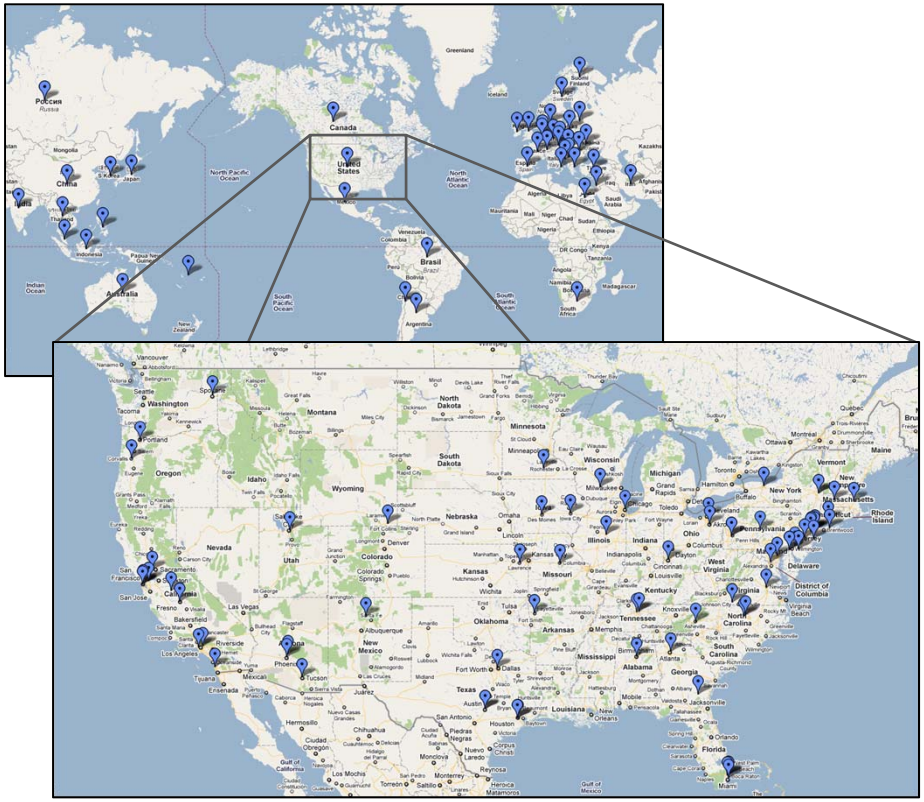


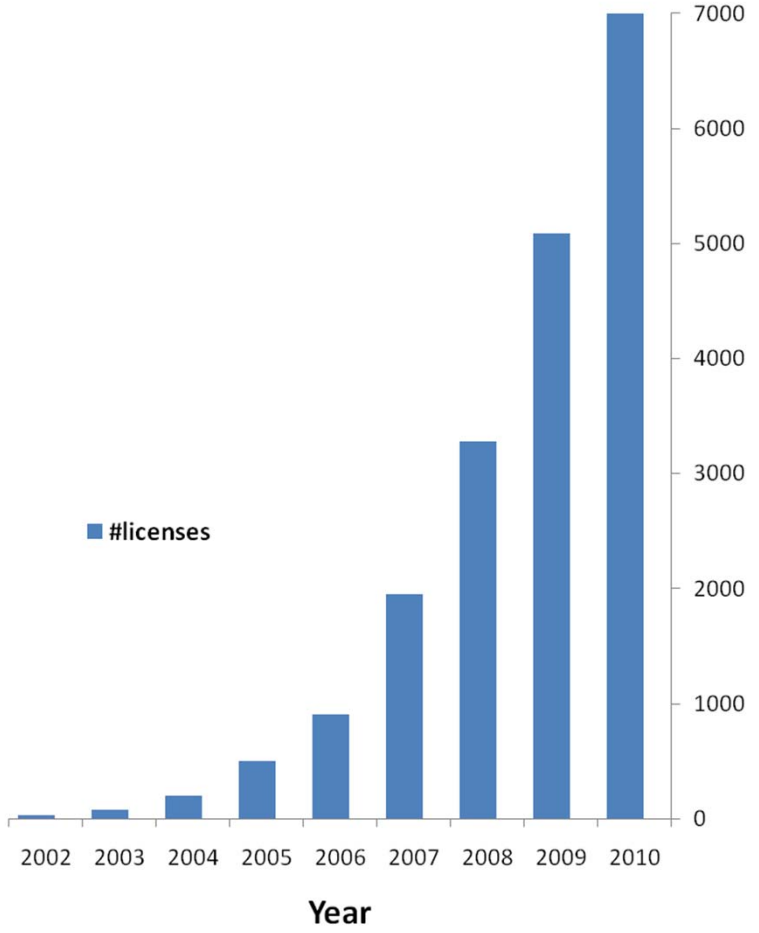


Number of Rosetta Licenses Reached 7000 at the End of 2010

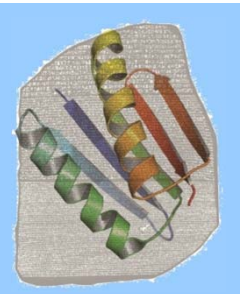


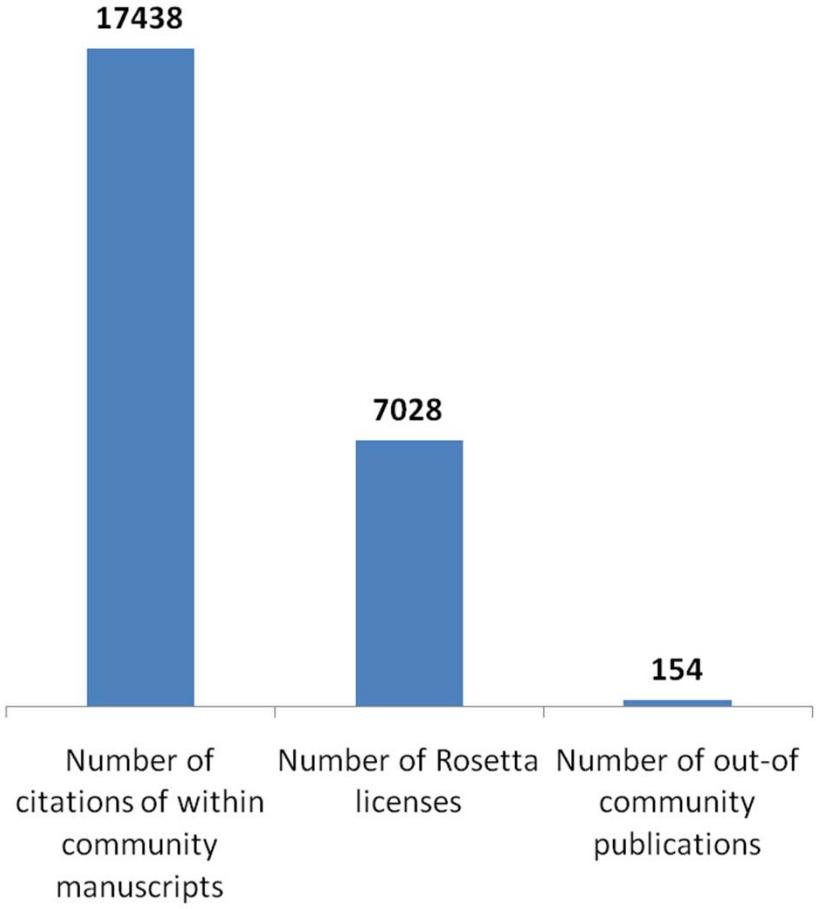
- 249 Organizations in the US
- Licensees in 61 countries





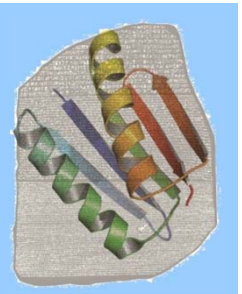
BTRC: Empower the Biomedical Research Community to use Rosetta





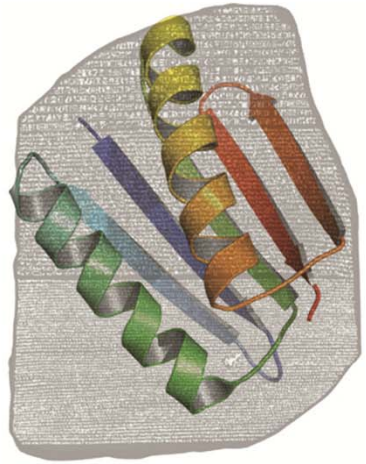
- Collaboration and service projects will attract junior investigators with bright ideas and interesting problems to use Rosetta (~100 interactions over 5 years)
- Tutorials and workshops (~480 interactions over 5 years) will disseminate state-of-the art protocols on a regular basis.
- Help desk will provide immediate expert feedback on problems (~1,000 interactions over 5 years including tutorial download).

Tutorials Make Rosetta Review Most Read Article in past 12 Months



ACS Publications
MOST TRUSTED. MOST CITED. MOST READ.

50th Anniversary BIOCHEMISTRY
including biophysical chemistry & molecular biology



Practically Useful: What the ROSETTA Protein Modeling Suite Can Do for You

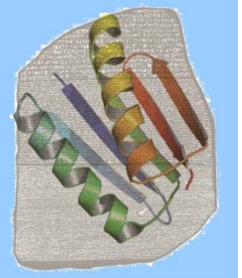
Kristian W. Kaufmann, Gordon H. Lemmon, Samuel L. DeLuca, Jonathan H. Sheehan and Jens Meiler

2010, *49* (14), pp 2987-2998

Publication Date (Web): March 17, 2010 (Current Topic)

DOI: 10.1021/bi902153g

“Local” 1.5 Day Rosetta Workshop March 11&12 at Vanderbilt University



- 24 slots were filled within a week of opening registration
- Over 200 requestors had to be turned down
- Rosetta Hands-On Training using Biochemistry Tutorials

Folding Tutorial

ROSETTA Folding Tutorial – Step- by-step Instructions

*** BLUE text means that these files and/or this information is provided.**
*** RED text means that this material will NOT be conducted during the workshop**
*** If you want to try making files that already exist (e.g., input files), write them to a different directory!**

1. Prepare your input files
a. FASTA file of your sequence
- Get sequence in FASTA format from NCBI
- The `2LZM_.fasta` file is already provided for you in the `$WORKSHOP_ROOT/tutorials/folding/1-input_AbinitioRelax` directory

⋮

2. Run ROSETTA AbinitioRelax application
a. Make sure all the filenames and paths in the options file are correct!
b. Go to the folding tutorial main directory
c. Type the following command line. It is also found in the command file in `$WORKSHOP_ROOT/tutorials/folding/2-command_AbinitioRelax`

```
-$ROSETTA_BIN/AbinitioRelax.$ROSETTA_SUFFIX
@$WORKSHOP_ROOT/tutorials/folding/1-
input_AbinitioRelax/2LZM_abrlx.options >& $WORKSHOP_ROOT/
tutorials/folding/3-analyze_AbinitioRelax/abrlx.log &
```

3. Analyze your data
a. Score and extract PDBs

⋮

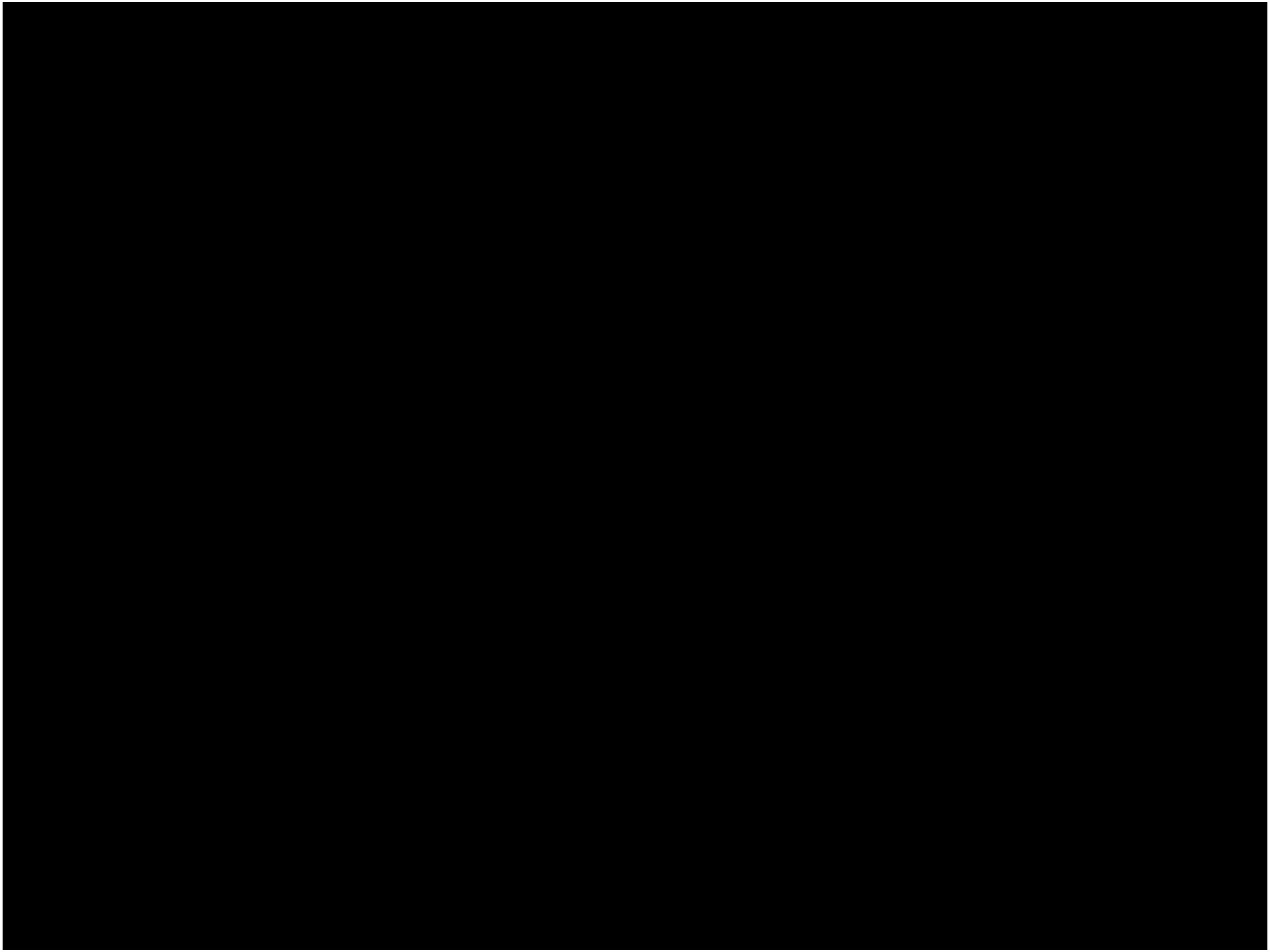
Interactive, Hands-On Training Experience

Jonathan Sheehan (Vanderbilt), James Zhu (USDA)

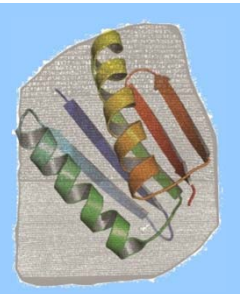
Serdar Durdagi (University of Calgary), and Jarrod Smith (Vanderbilt)

Fangyu Ding (Vanderbilt), Roman Pleskot (Institute of Experimental Botany, Czech Republic), Sam DeLuca (Vanderbilt) and Jordan Willis (Vanderbilt)

Gordon Lemmon (Vanderbilt), Michael Sellers (US Army), Alexander Johs (Oak Ridge)



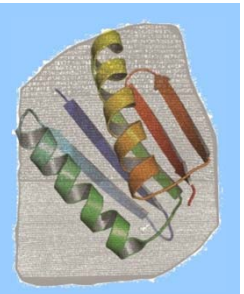
What will happen in 2012?

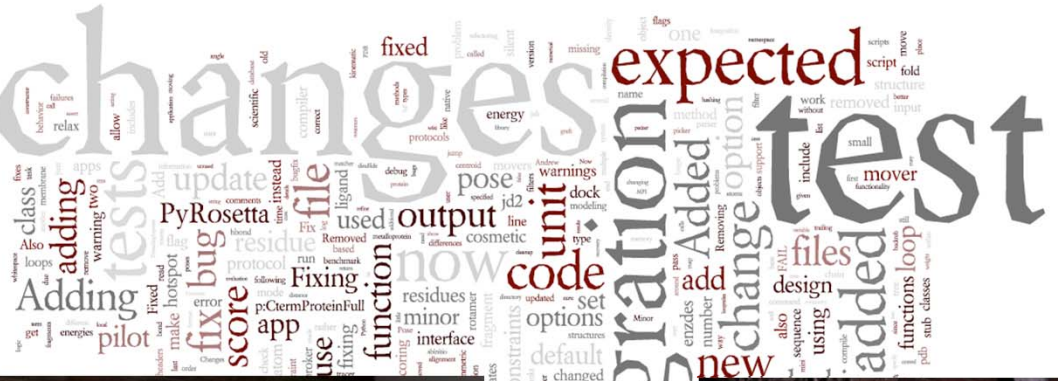


- Resubmission of revised BTRC application?!
  - NCRR dissolves this fall
  - proposal moves to NIGMS
  - Might improve funding chances

- NSF Software Infrastructure for Sustained Innovation (SI2)
  - long-term hubs of excellence in software infrastructure and technologies
  - research community of substantial size and disciplinary breadth
  - while contributing to the education of next generation researchers and creators of future cyberinfrastructure

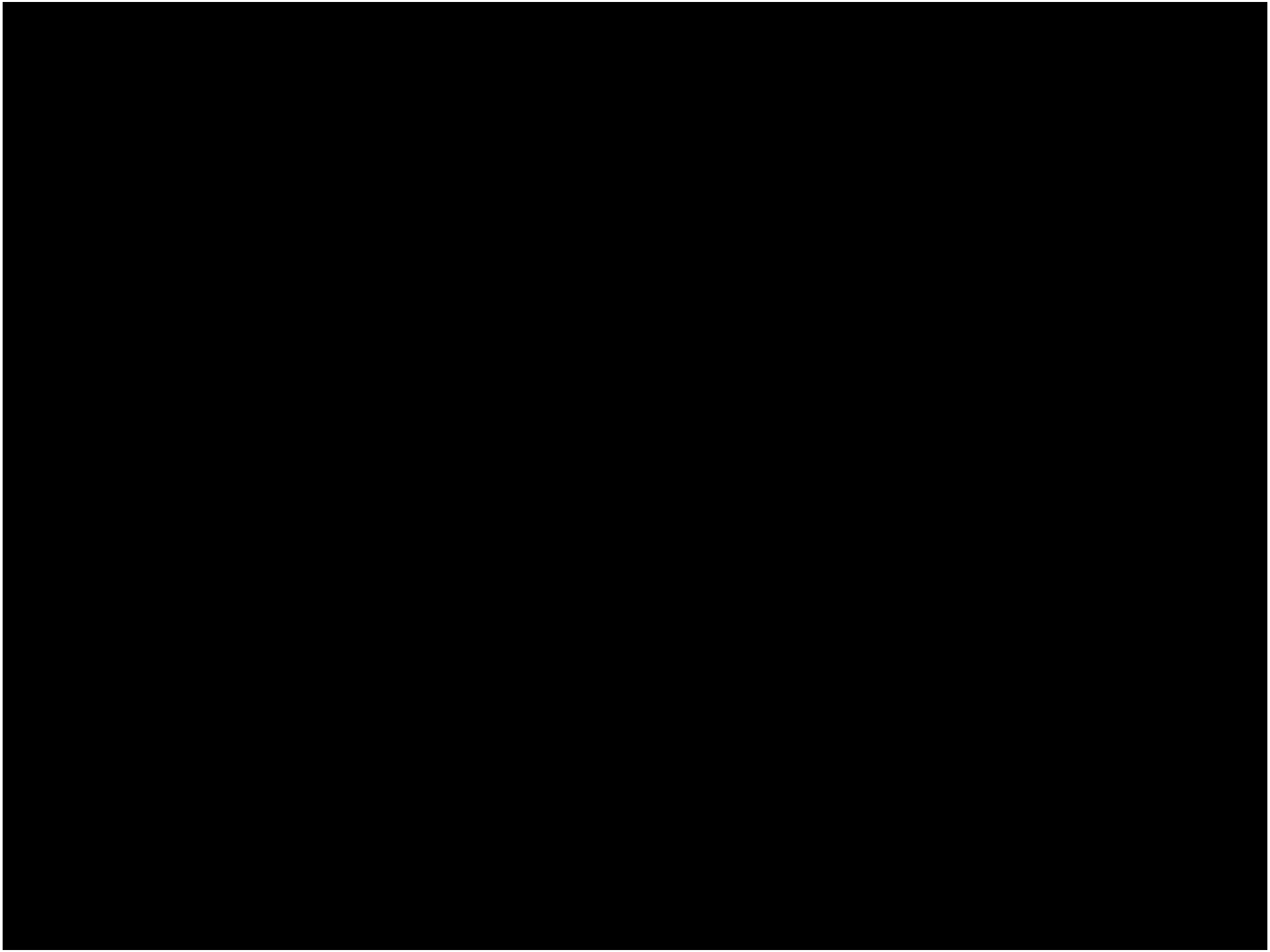
More than 50 Developers Actively Improve the Code at any given Time



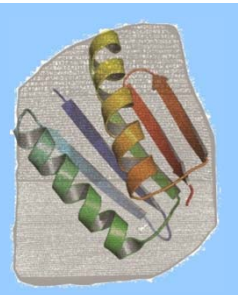


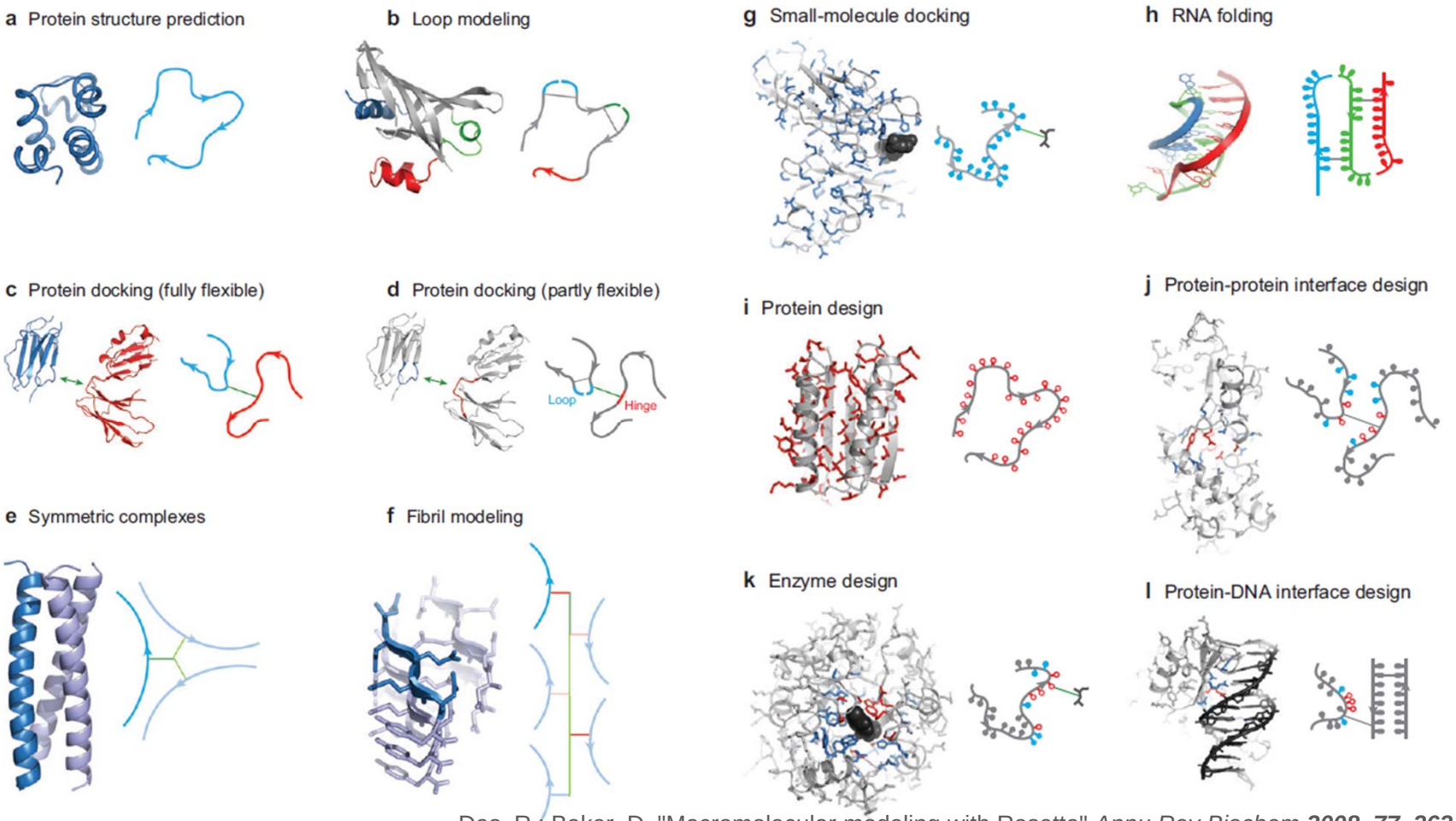
Andrew Leaver-Fay (UNC), Brian Weitzner (Johns Hopkins), and Steven Lewis (UNC)

Christopher Miles (UW), Matt O'Meara (UNC), Sam DeLuca (Vanderbilt) and Brian Weitzner (Johns Hopkins)



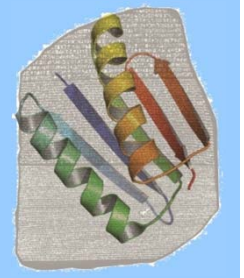
Rosetta: A Unified Framework for Structure Prediction and Design



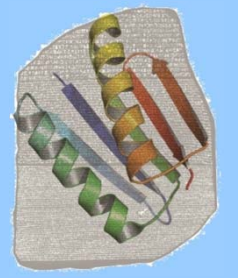


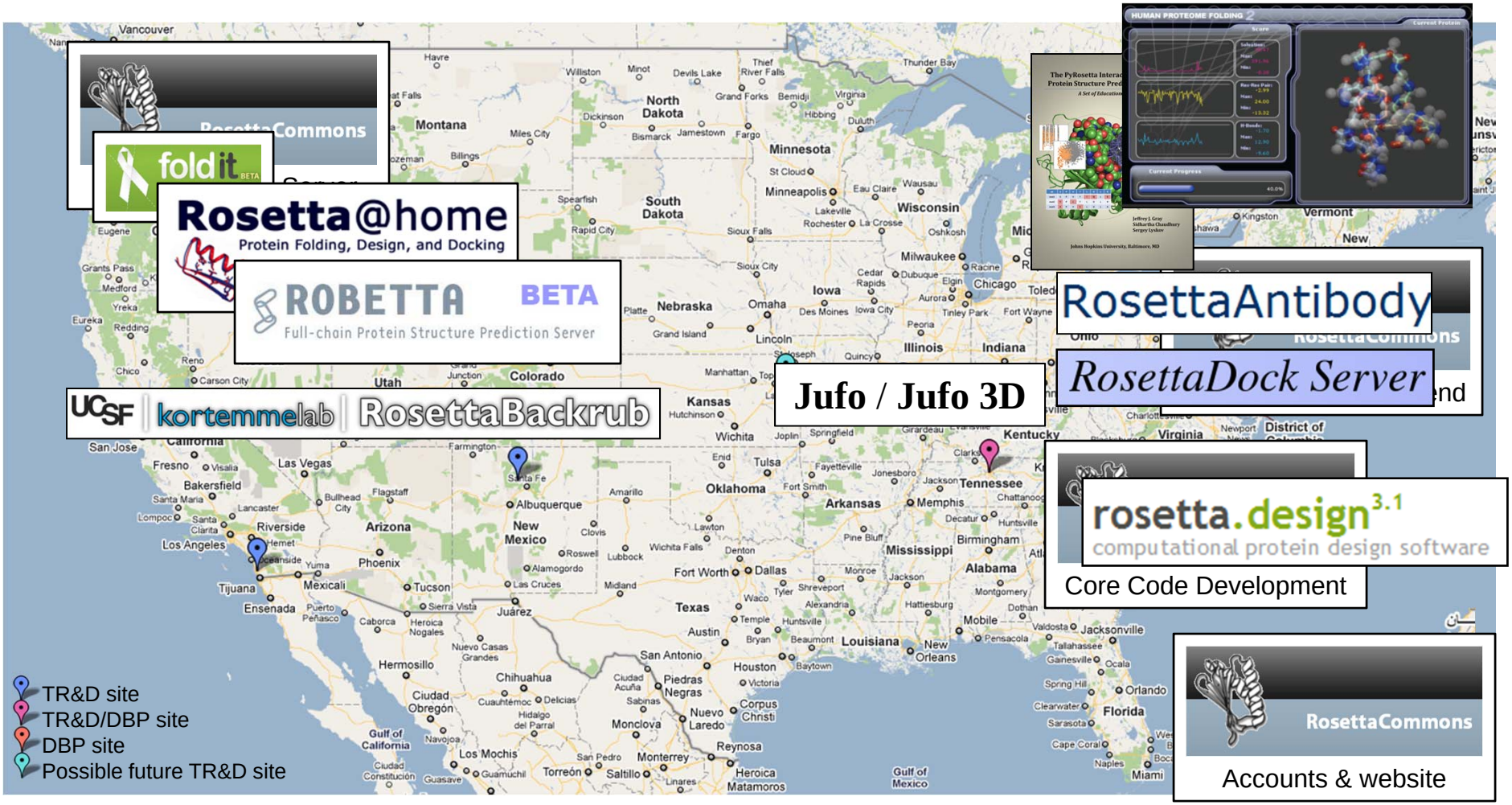
Das, R., Baker, D. "Macromolecular modeling with Rosetta" *Annu Rev Biochem* ***2008, 77, 363-82.***

Rosetta Technology is Developed at more than Ten Laboratories



Shared Development Platform with Distributed Responsibilities





BTRC: Integrate and Focus Sampling and Scoring Technologies