

End-to-End Infrastructure for Computational Science

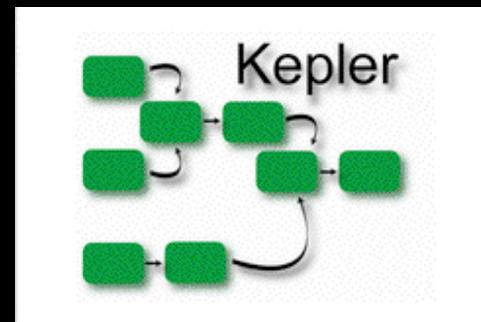
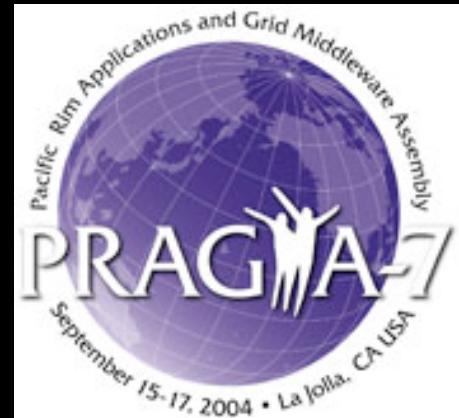
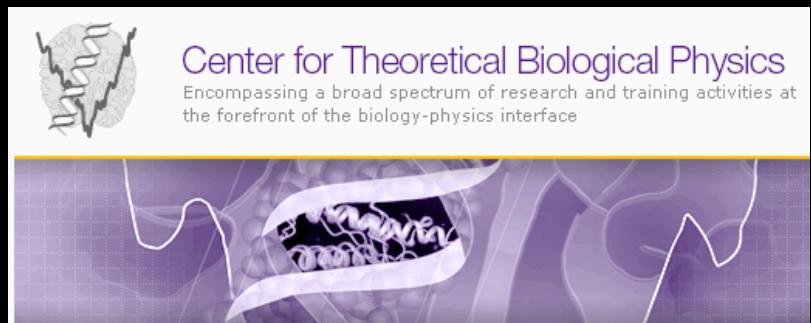
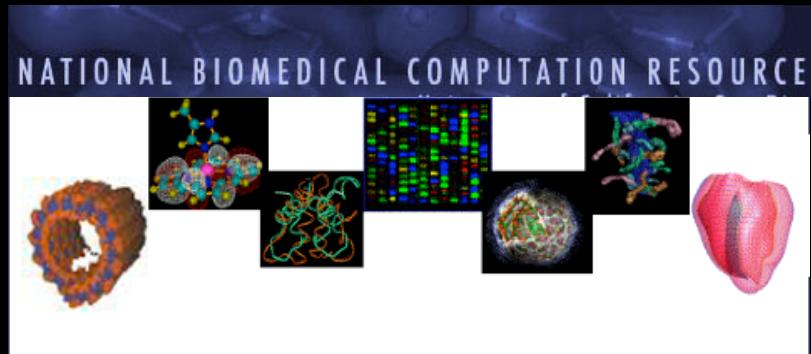
*GEMSTONE: Grid-Enabled Molecular Science
through Online Networked Environments*



Kim K Baldridge
Prof. of Theoretical Chemistry
University of Zürich
San Diego Supercomputer Center



Community Science Technology Driver Partnerships



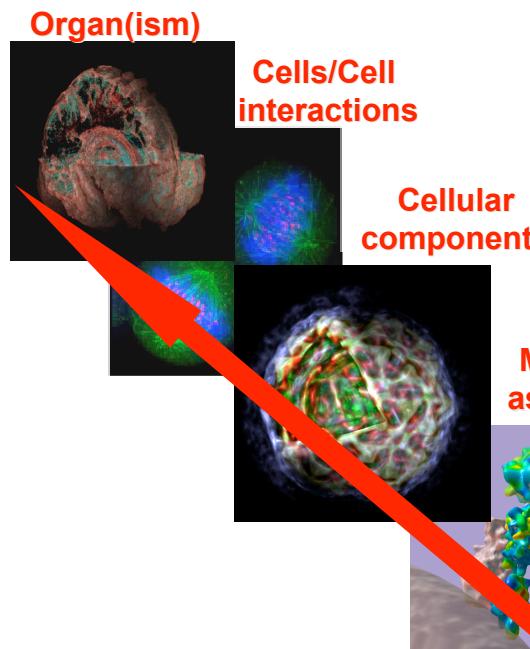
NIMROD
MONASH
UNIVERSITY

GEMSTONE

{ Grid Enabled Molecular Science Through Online Networked Environments }

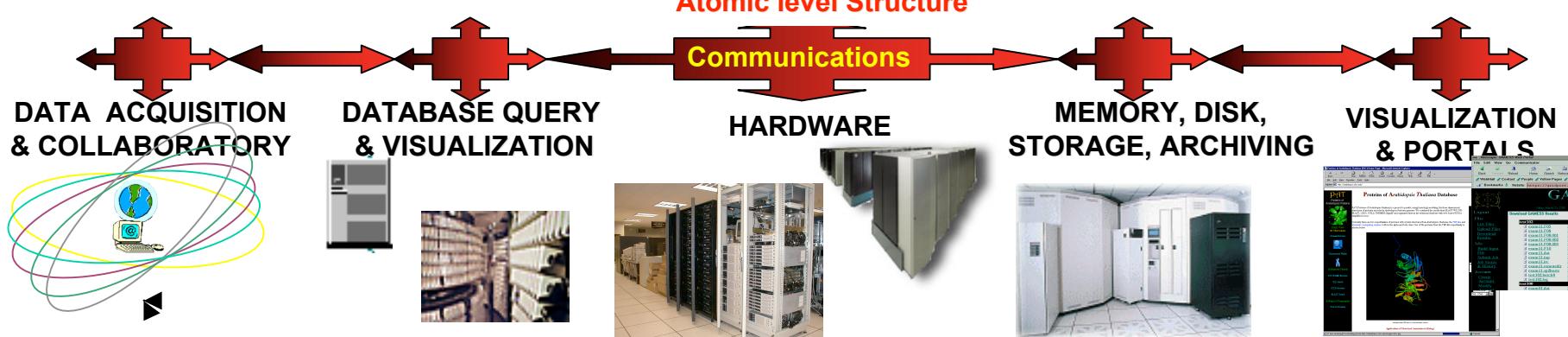
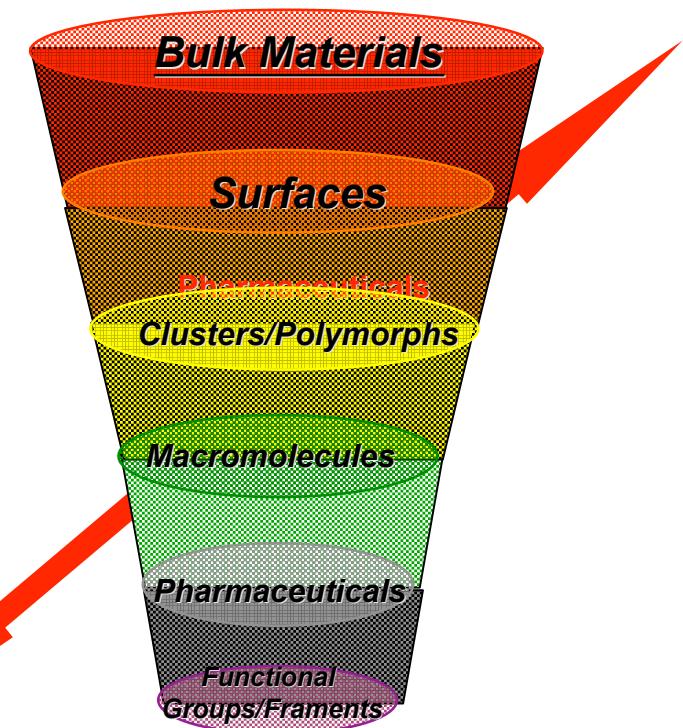
NMI

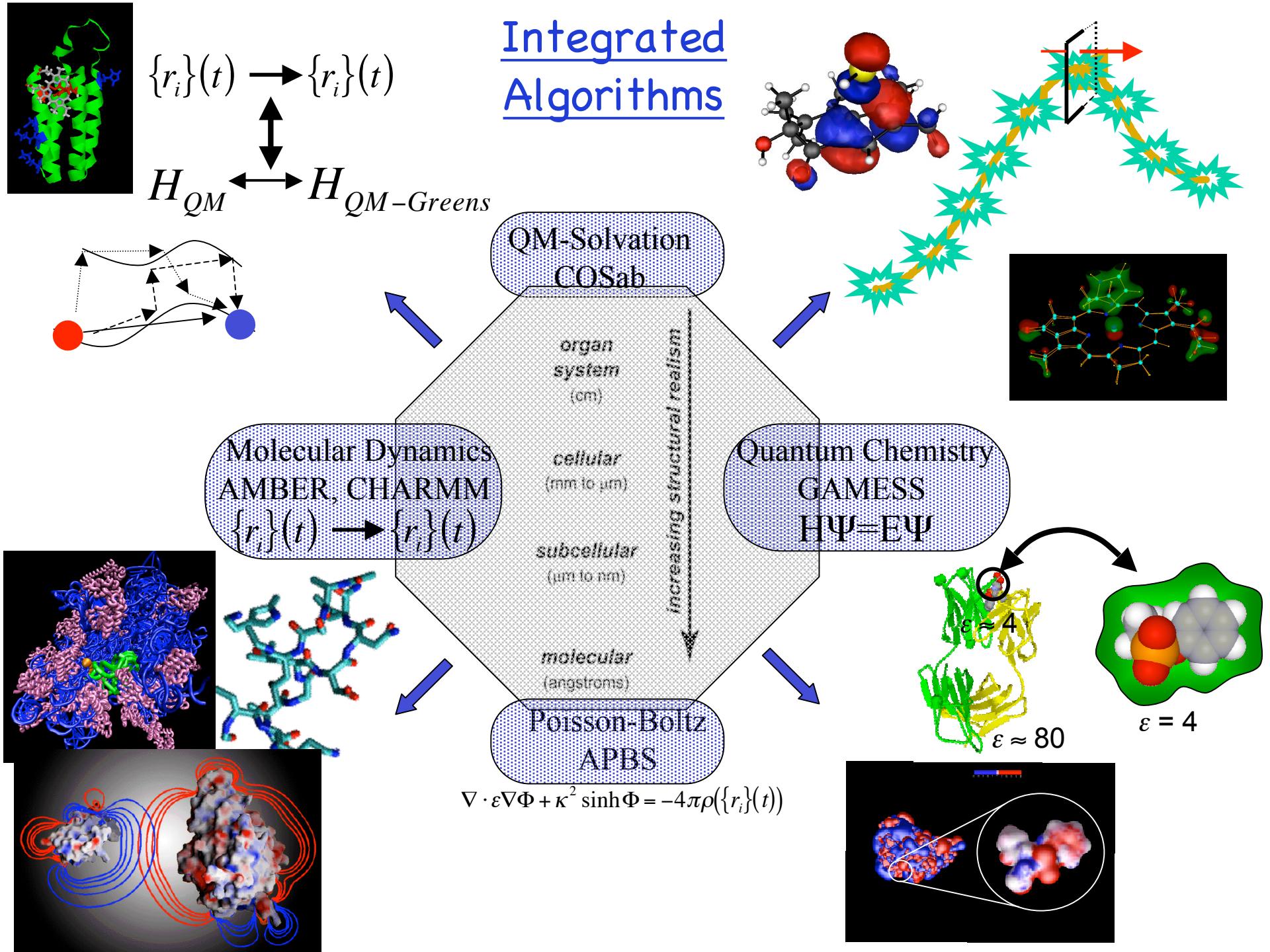
IT Challenges from a Scientific Perspective



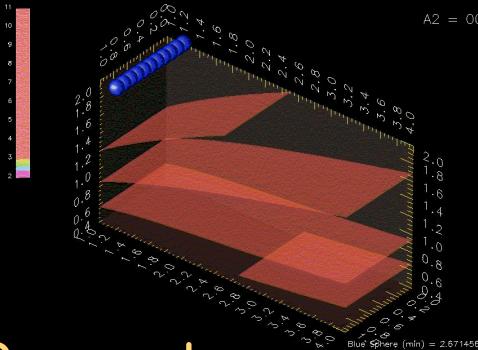
Integration Across Scale:

Data
Algorithms

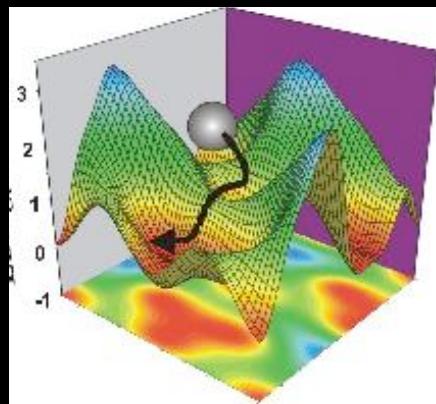




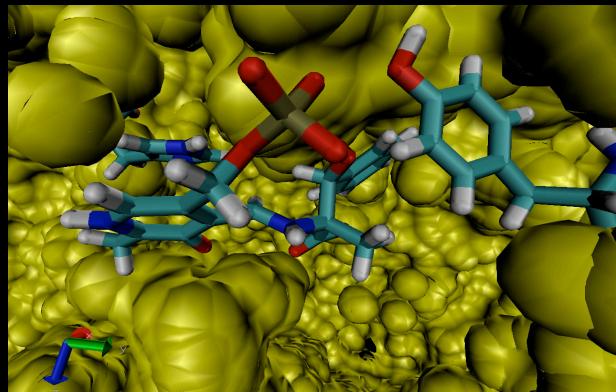
Grid Opportunities for Computational Chemistry



Parameter sweeps



Reaction
Processes

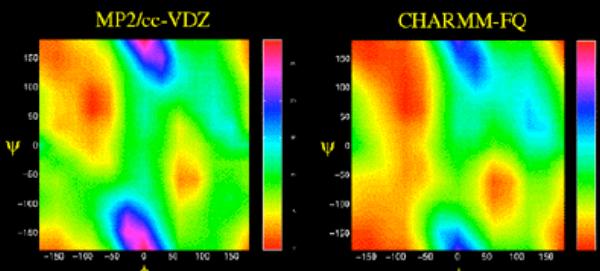


Ligand Docking



High through-put

Alanine ϕ - ψ Energetics



FF Parameterizations

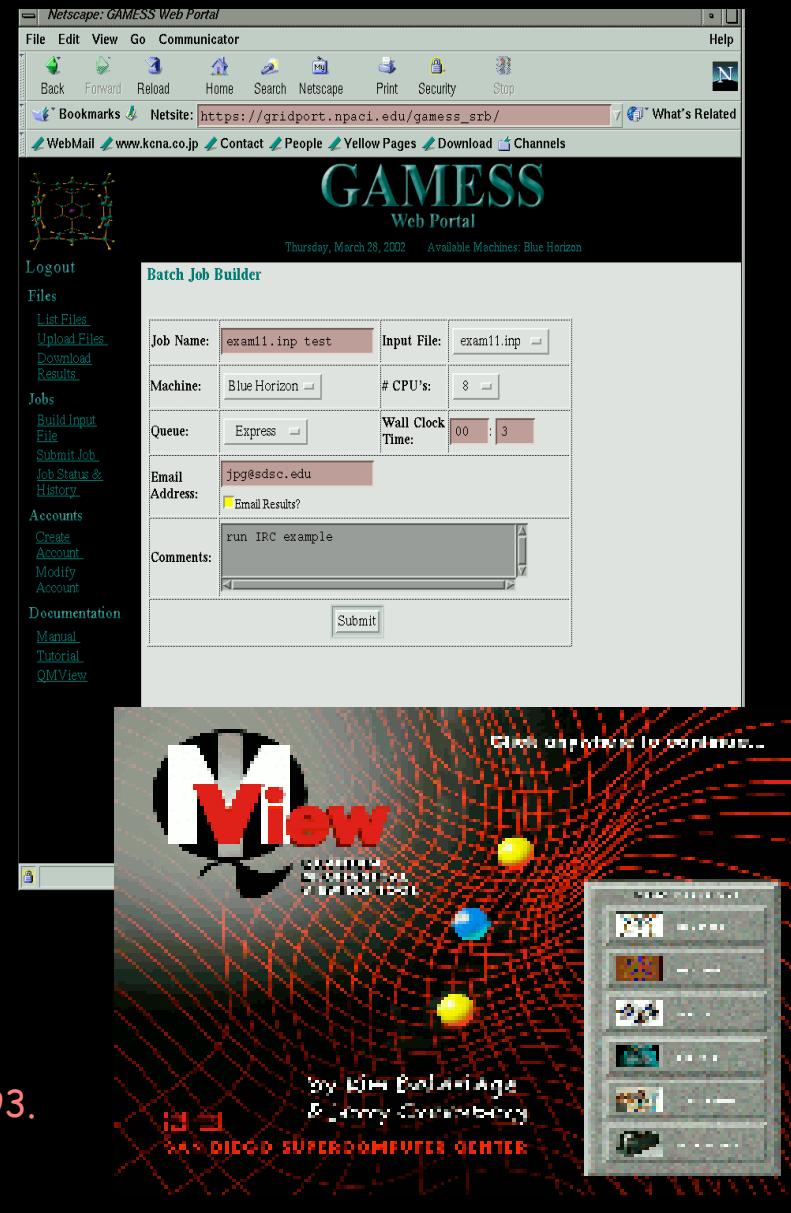
SHARED INFRASTRUCTURE

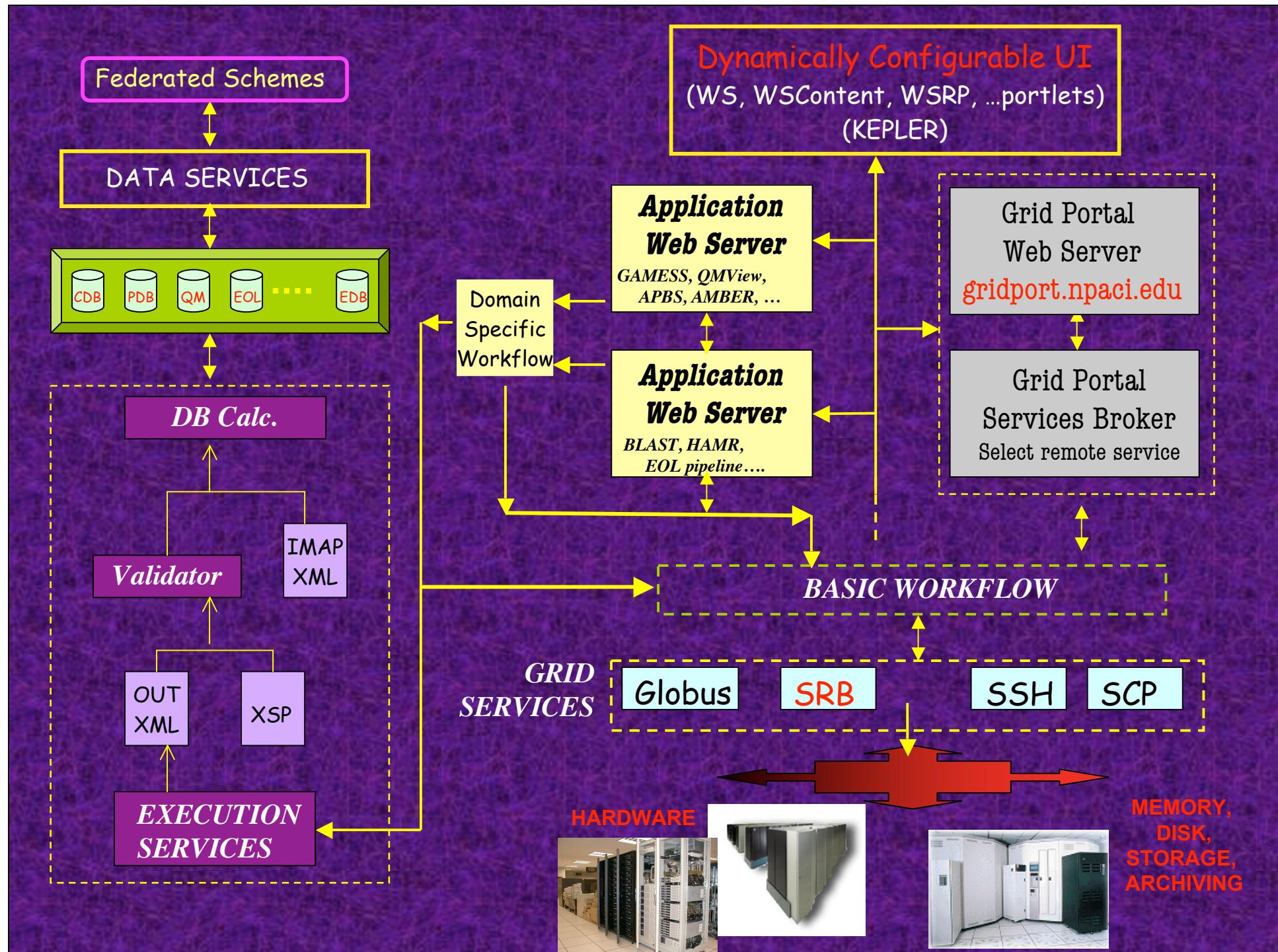
General Atomic Molecular Electronic Structure System GAMESS

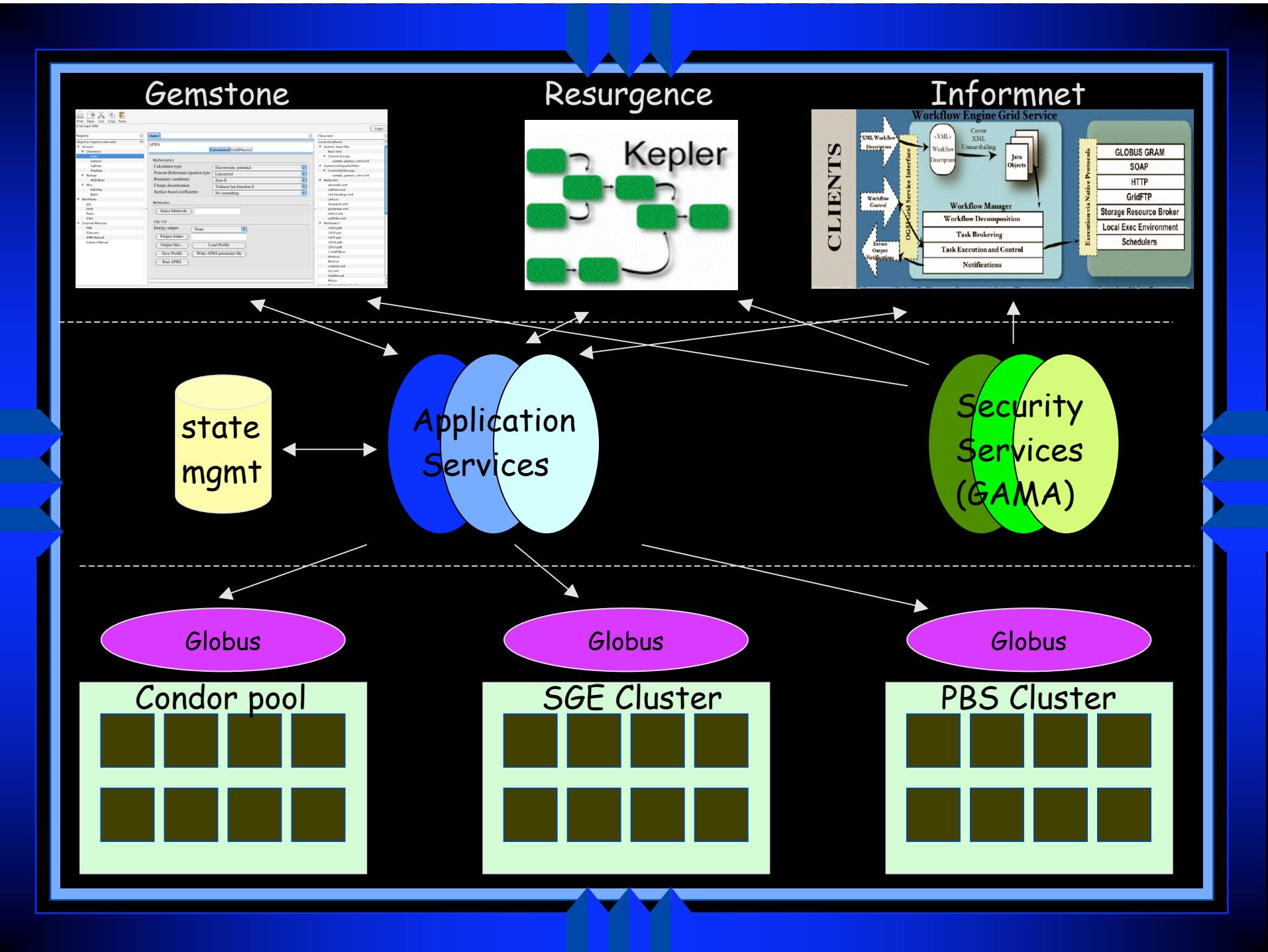
Schmidt, Baldridge, Boatz, Elbert, Gordon,
Jensen, Koseki, Matsunaga, Nguyen, Su, Windus
J. Comp. Chem, 1993

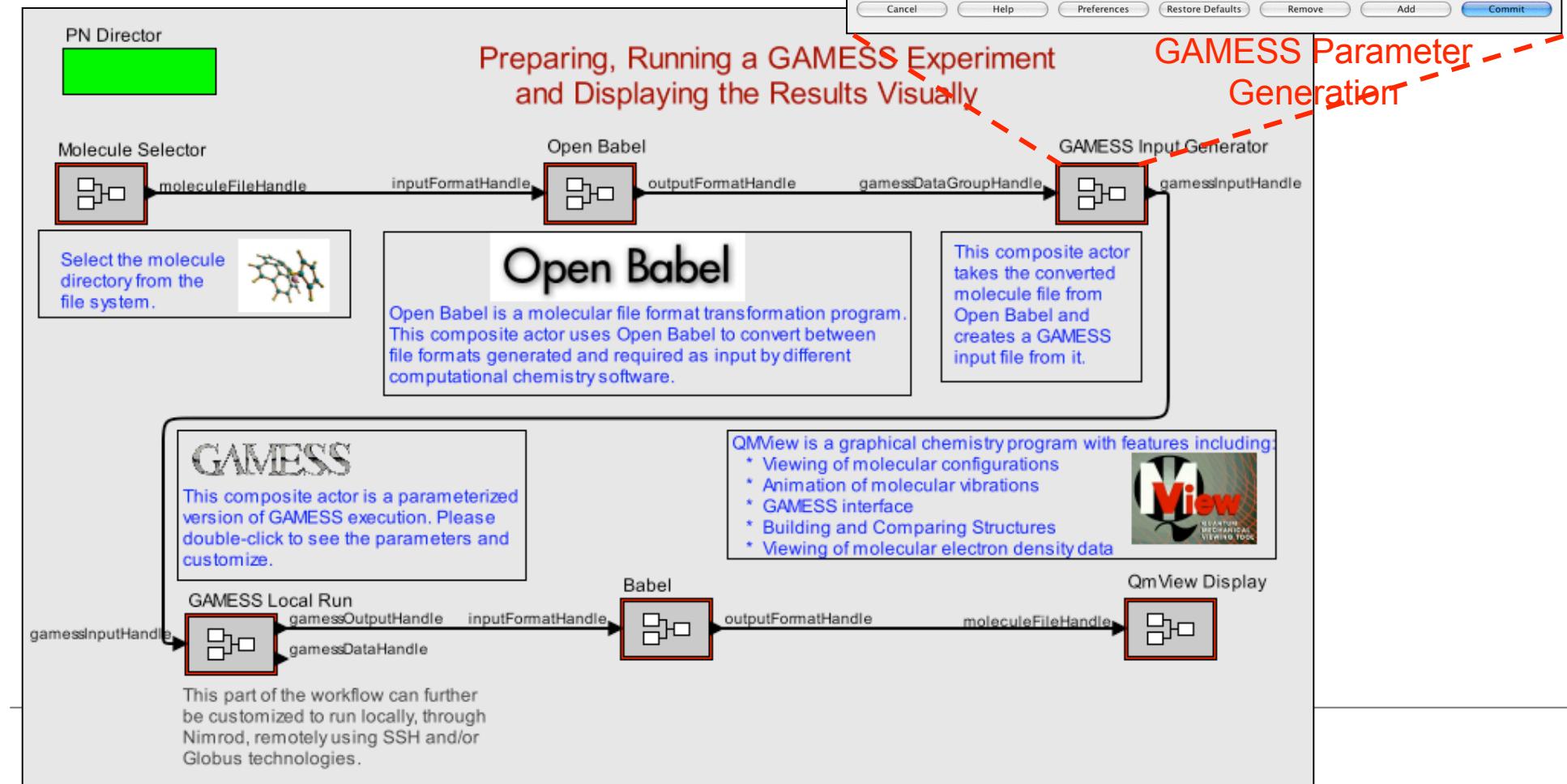
Open source QM code
(~400,000 lines of code)
Main group developers
Extensive international community
Supported on all current hardware
architectures

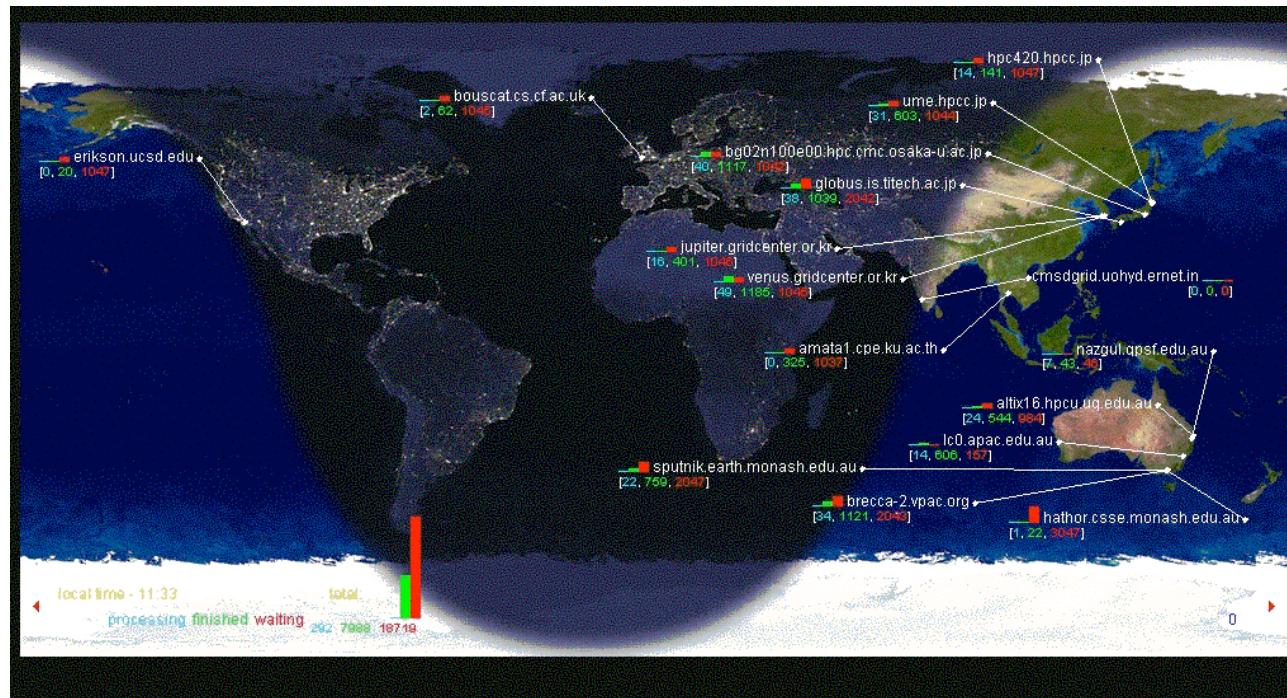
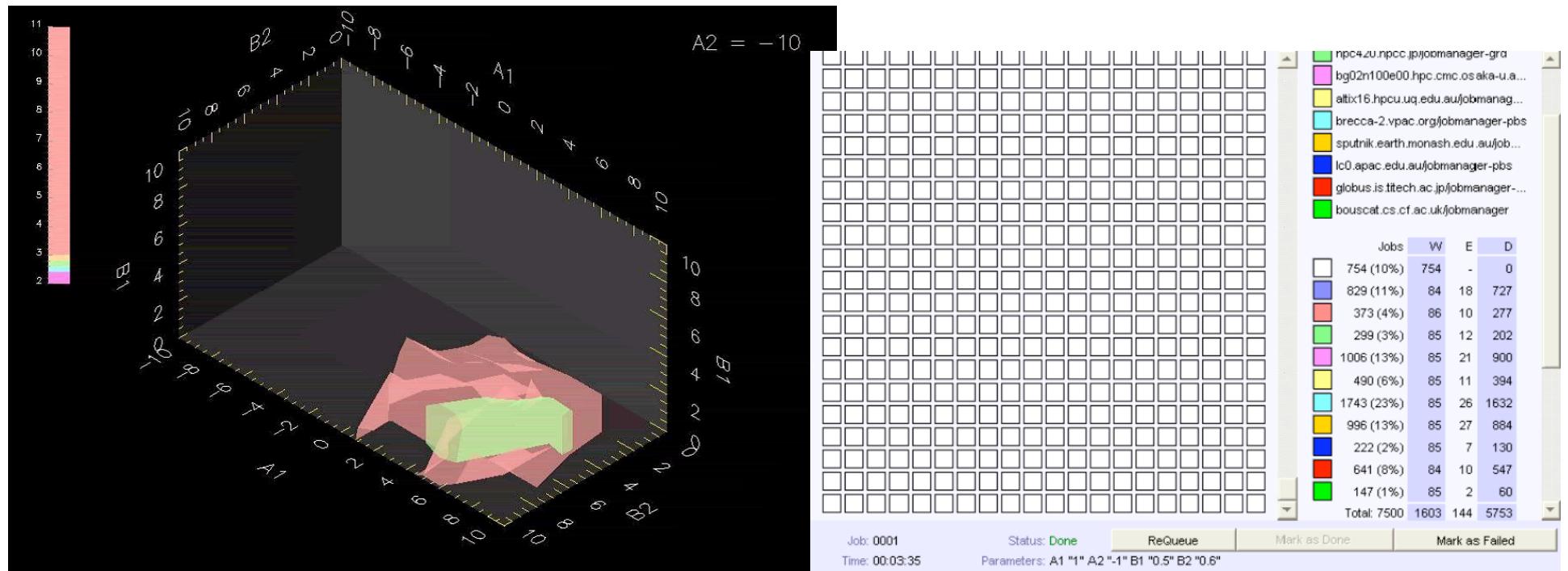
QMView - Viz/Analysis
Baldridge, Greenberg, J. Comp. Graphics, 1993.











•PRAGMA 4

-Large linear space,
original cost function
 $15,876 \times 4$ jobs

•Supercomputing 2003

-Large log space,
adapted cost function
 $53,361 \times 4$ jobs

-Small linear space,
adapted cost function:
 $60,016 \times 4$ jobs

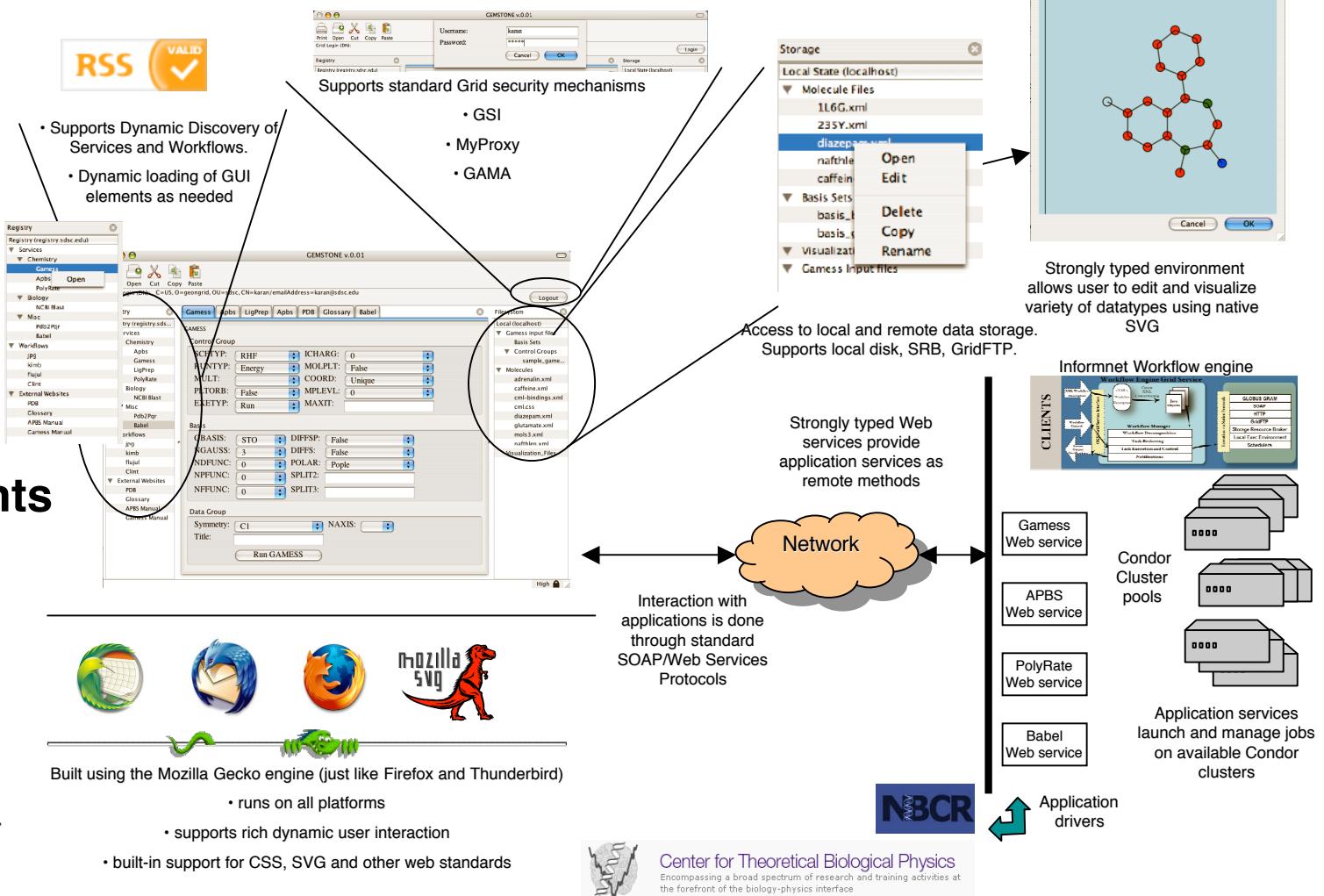


Grid Enabled Molecular Science Through Online Networked Environments

NSF Middleware
Grant SCI-0438430
PI: K. Baldridge
Co-PIs: K. Bhatia, J.
Greenberg

GEMSTONE

<http://grid-devel.sdsc.edu/gemstone>



Center for Theoretical Biological Physics
Encompassing a broad spectrum of research and training activities at
the forefront of the biology-physics interface

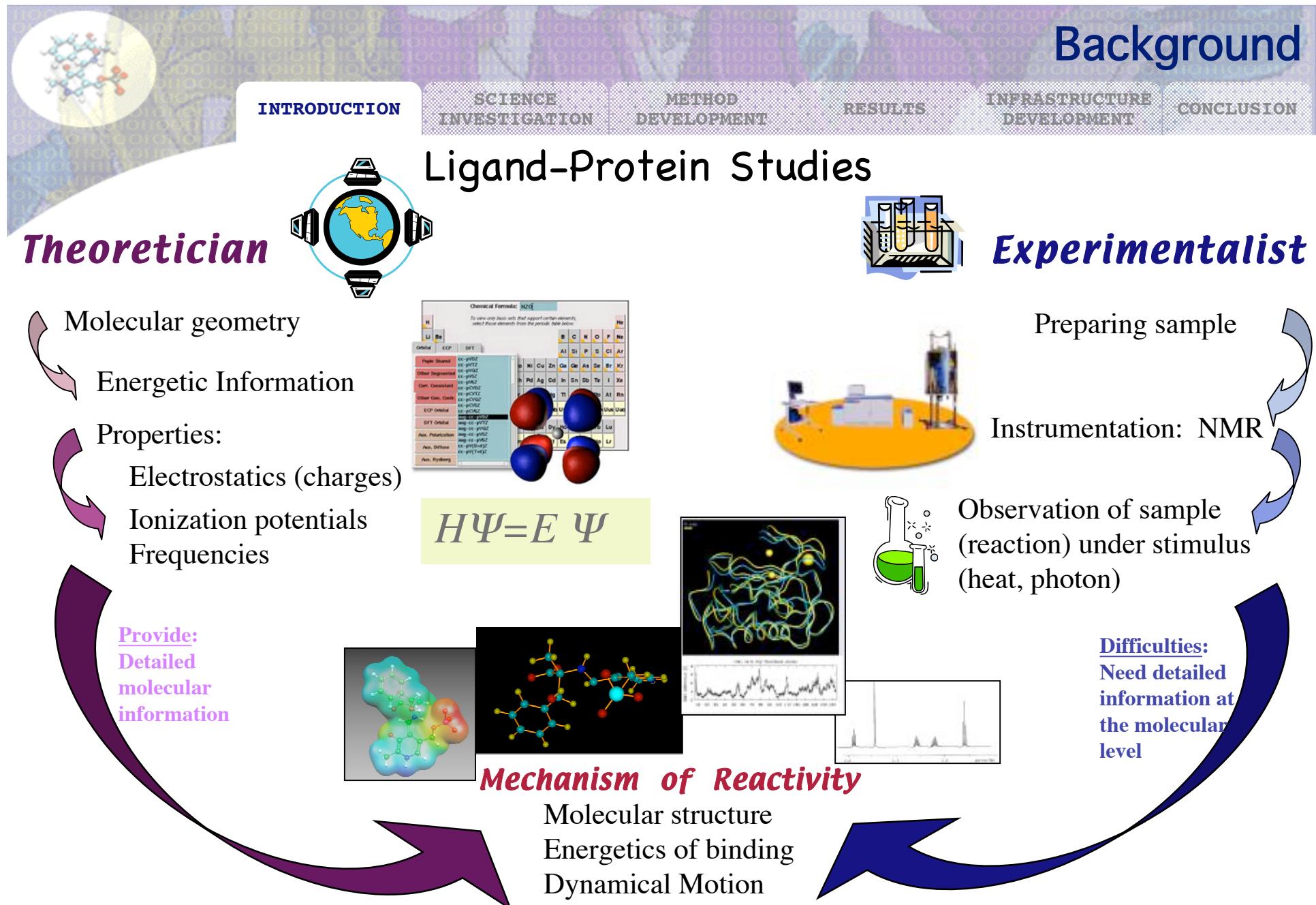
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Some services

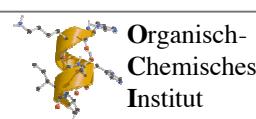
◆ APBS, GAMESS, QMView, LigPrep

- Definition of data types and APIs
 - Data passed around as XML documents using Web service technology (SOAP/HTTP)
- Implementation of the services
 - Services wrap scientific codes
 - No (or minimal) modifications required to these codes
- Implementation of clients in Java and Python
 - Java clients used by workflow tools
 - Python clients used by rich clients, e.g. PMV/Vision

Background

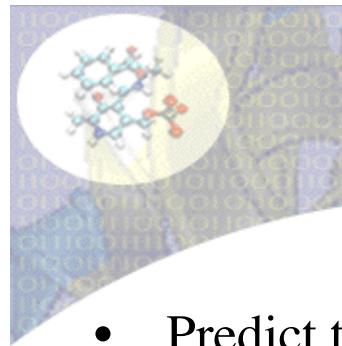


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Combination QM/MM



INTRODUCTION

SCIENCE
INVESTIGATION

METHOD
DEVELOPMENT

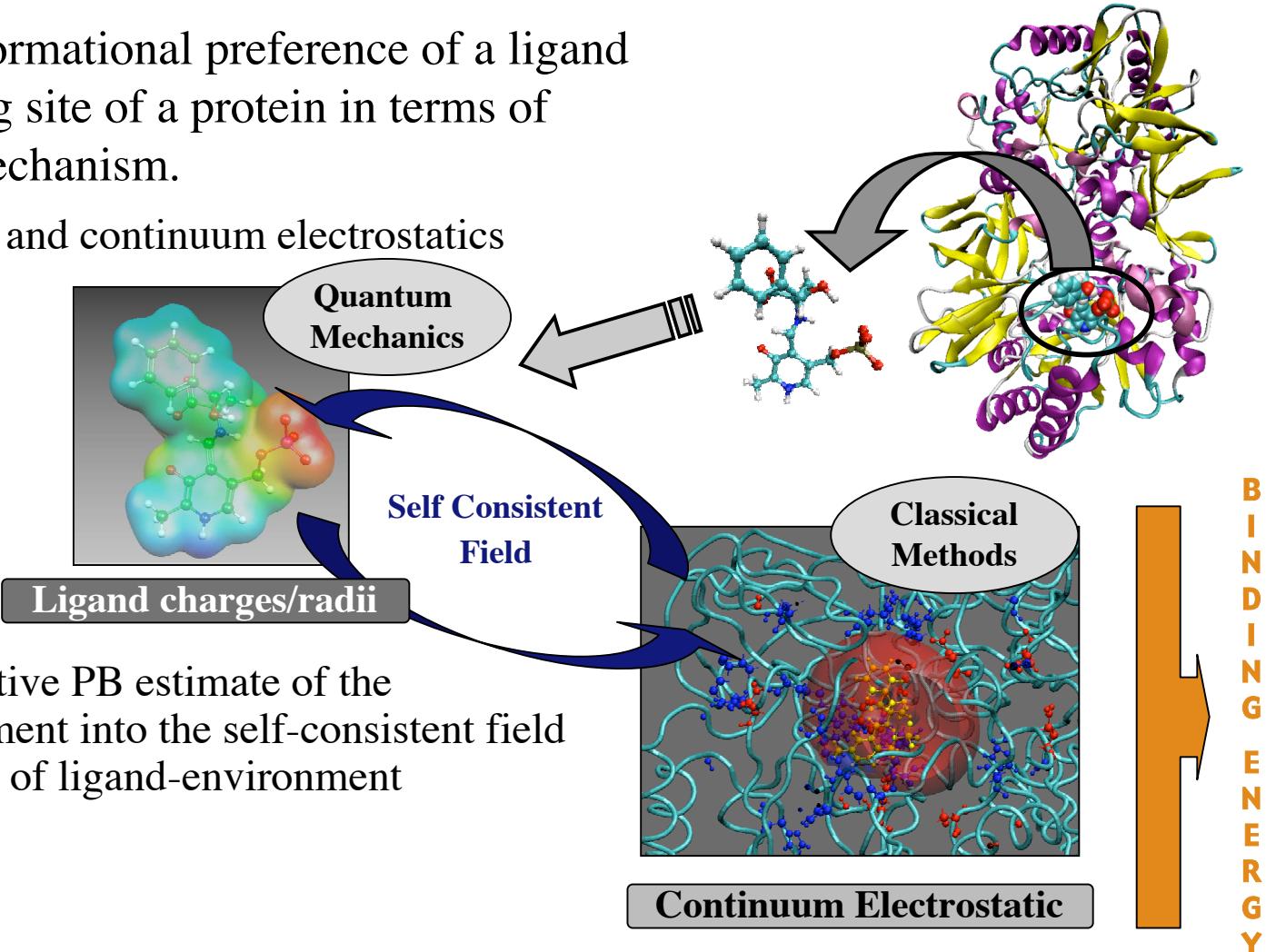
RESULTS

INFRASTRUCTURE
DEVELOPMENT

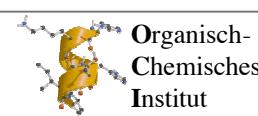
CONCLUSION

Protein-ligand complex

- Predict the conformational preference of a ligand to fit in a binding site of a protein in terms of energetic and mechanism.
 - Combine QM and continuum electrostatics



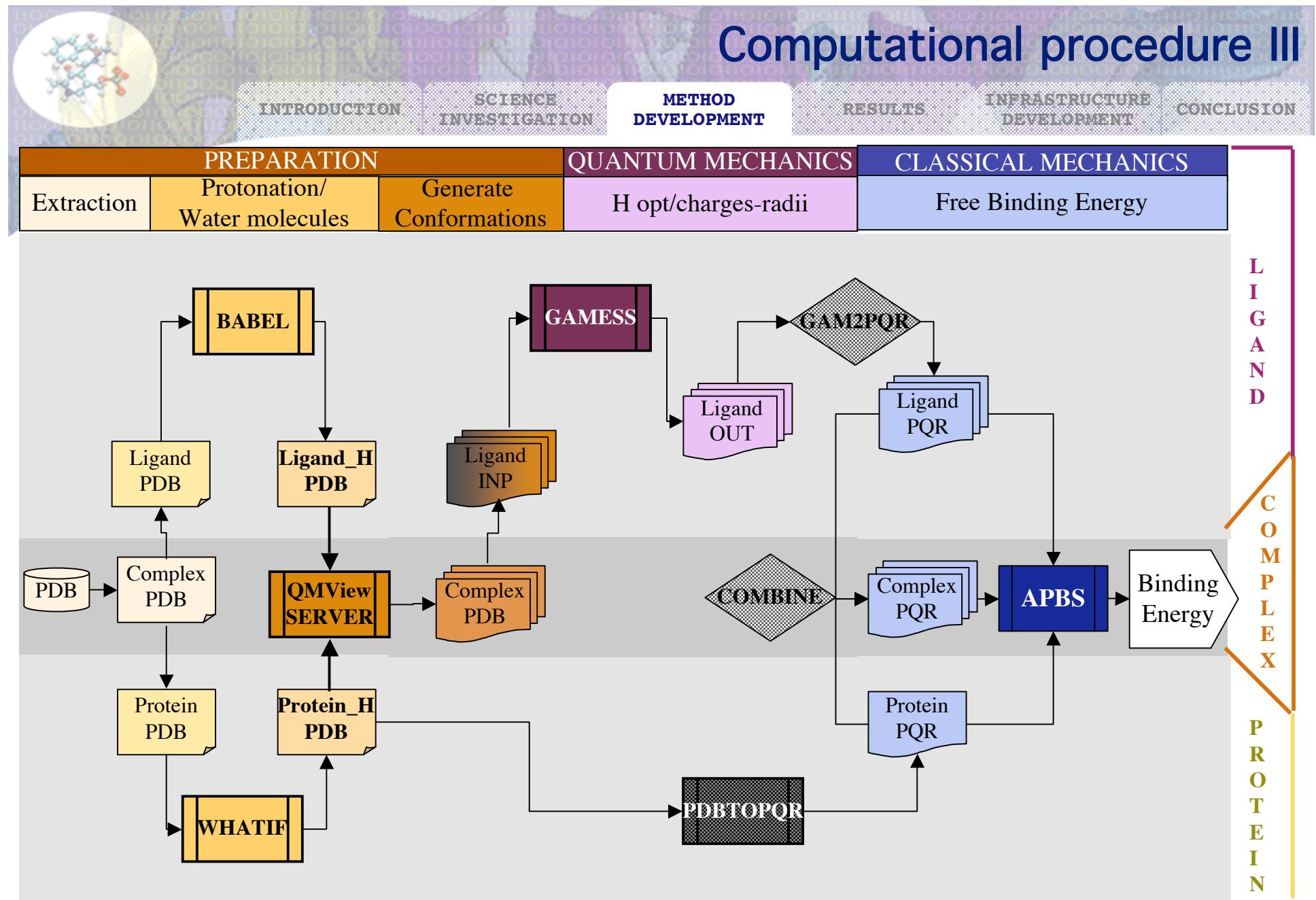
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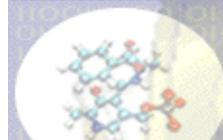


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MOVIE

Computational procedure III





Conformational checking 2R3R

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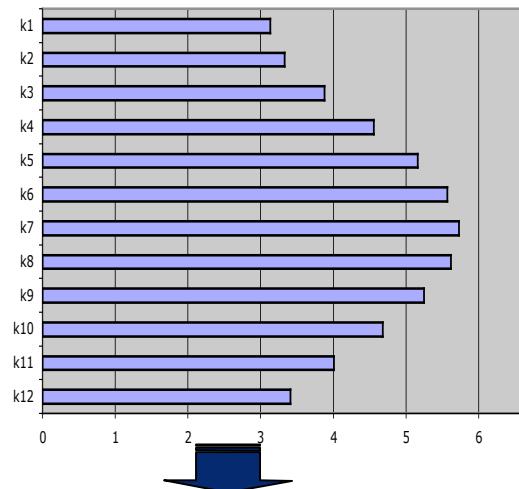
RESULTS

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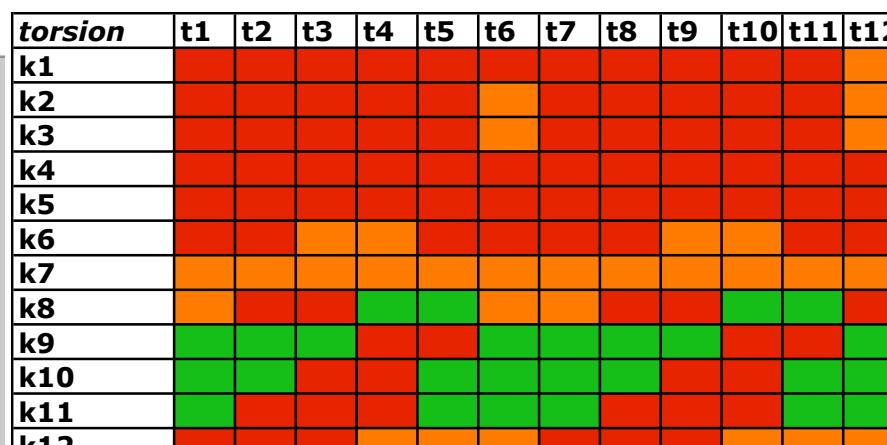
- Conformation Accessibility of 2R3R
 - Replace the ligand into the protein with a rigorous alignment with PDL (144 conformations)
 - Legend: intra/intermolecular intermolecular no atomic clash

Distance estimation in angström: HO-OP



Short distance => k11-k3

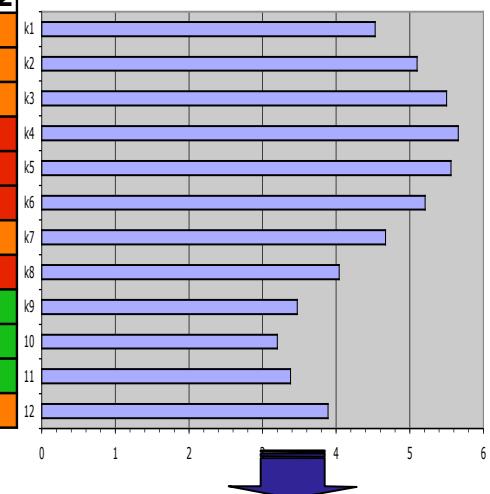
2R3R



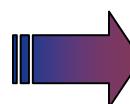
Windows between k8-k11 => good conformation

Periodicity in the results => rotation Phenyl ring

Distance estimation in angström: HO-NE2(H166)



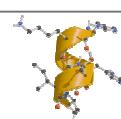
Short distance => k8-k11



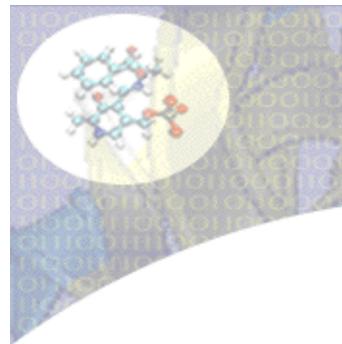
Favorable to react with Hist / reasonable structures k9 k10 k11



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Conformational checking 2R3S

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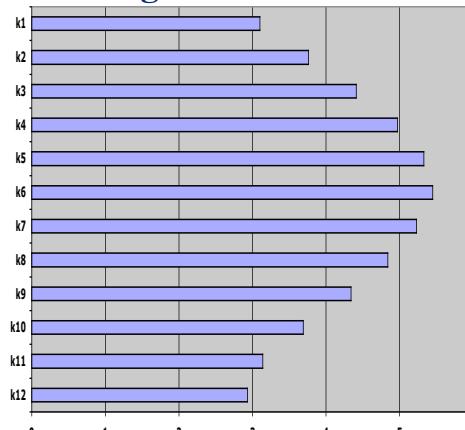
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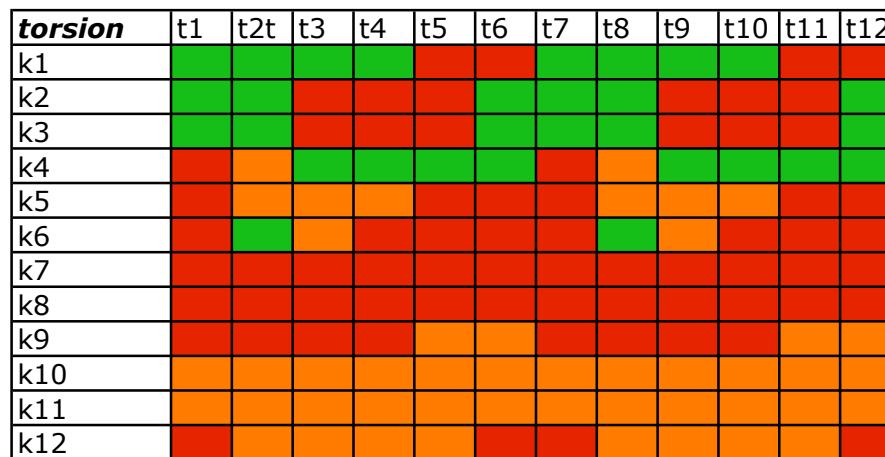
CONCLUSION

Distance estimation in angström: HO-OP

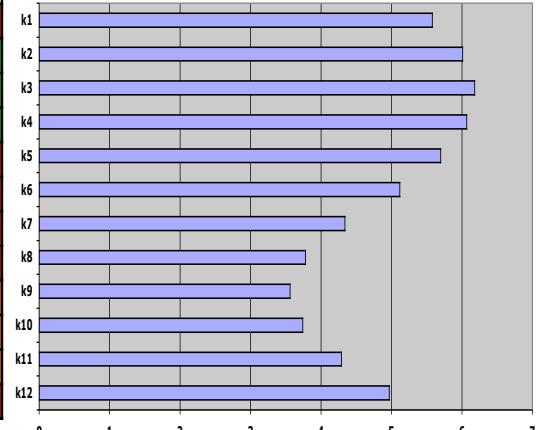


Short distance => k10-k2

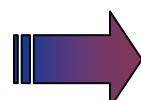
2R3S



Distance estimation in angström: HO-NE2(H166)



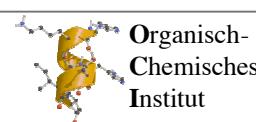
Short distance => k8-k11



Favorable to react with Phosphate group / reasonable structures k1 k2 k3

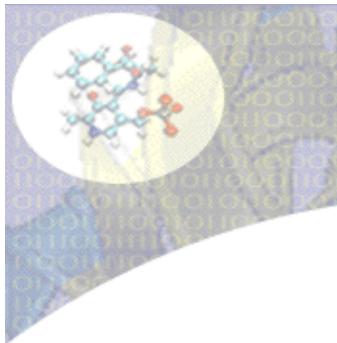


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QM Results



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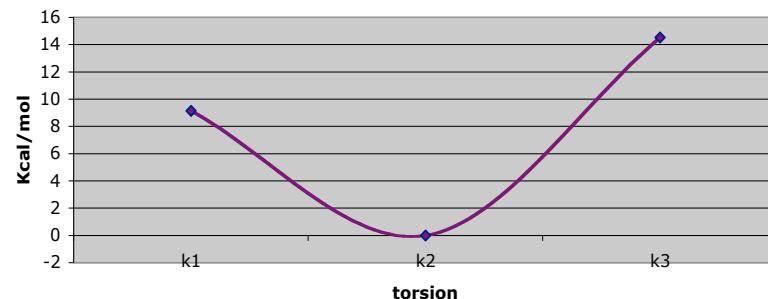
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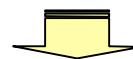
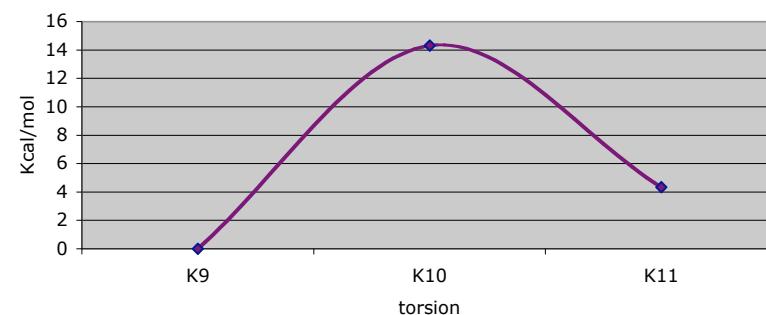
2R3S

Internal Energy evaluated by QM methods
(B3LYP/DZV(d,p))



2R3R

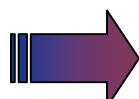
Internal Energy evaluated by QM methods
(B3LYP/DZV(d,p))



K2 most stable structure



K9 K11 most stable structures

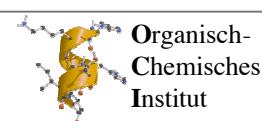


QM results:

- Prediction of most reasonable H-atom positions => H optimization
- Prediction of accurate charge values at atomic positions => CHELPG
- Prediction/Assessments of internal energy of ligand

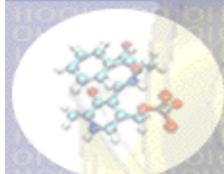


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Electrostatic study results



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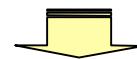
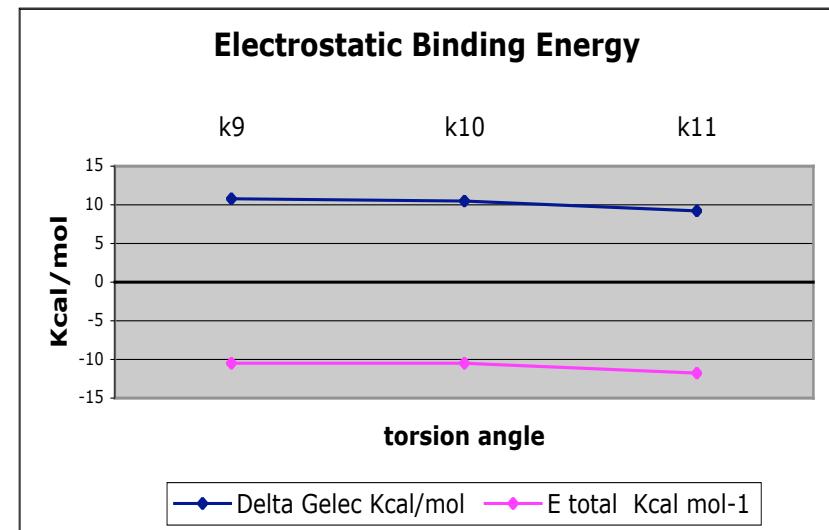
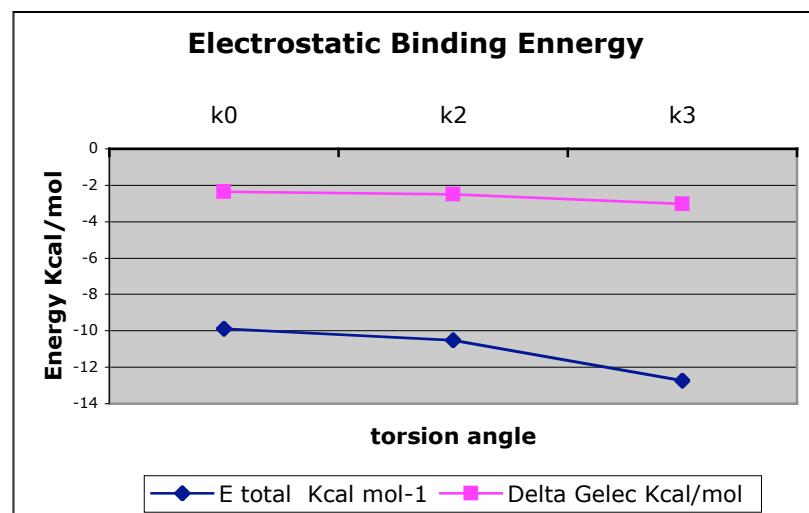
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- Electrostatic binding energy: $\Delta G = \Delta G_{\text{complex}} - \Delta G_{\text{protein}} - \Delta G_{\text{ligand}}$
- Add the apolar contribution: $\Delta G_{\text{tot}} = \Delta G + \gamma \Delta S_{\text{ASA}}$



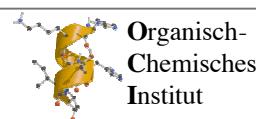
K3 the most favorable



K11 the most favorable

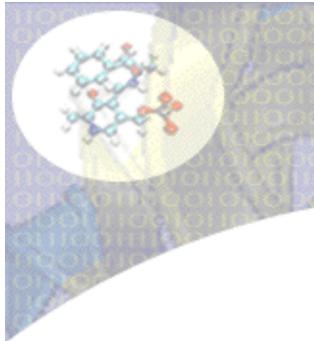


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Total Energy



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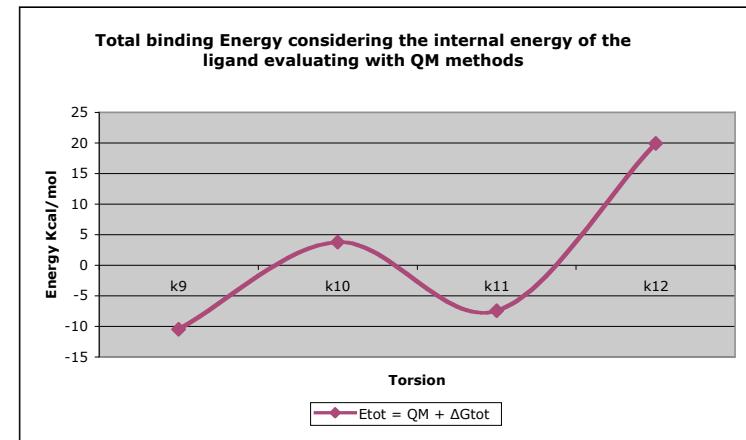
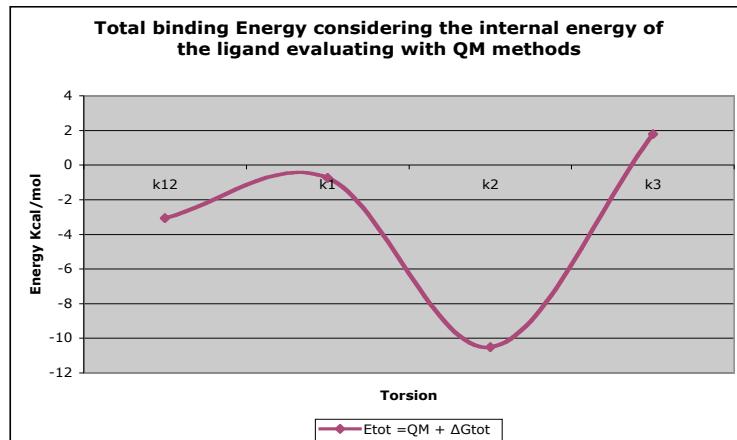
INFRASTRUCTURE
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$$E_{tot} = \Delta G_{tot} + QM_{internal-Energy}$$

2R3S

2R3R



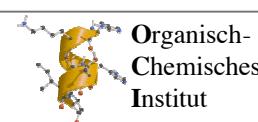
K2 lowest total Energy
Stable and favorable range of good conformations around this position



K9 K11 lowest total Energy
Stable and favorable set of conformations around these 2 torsions to fit into the protein



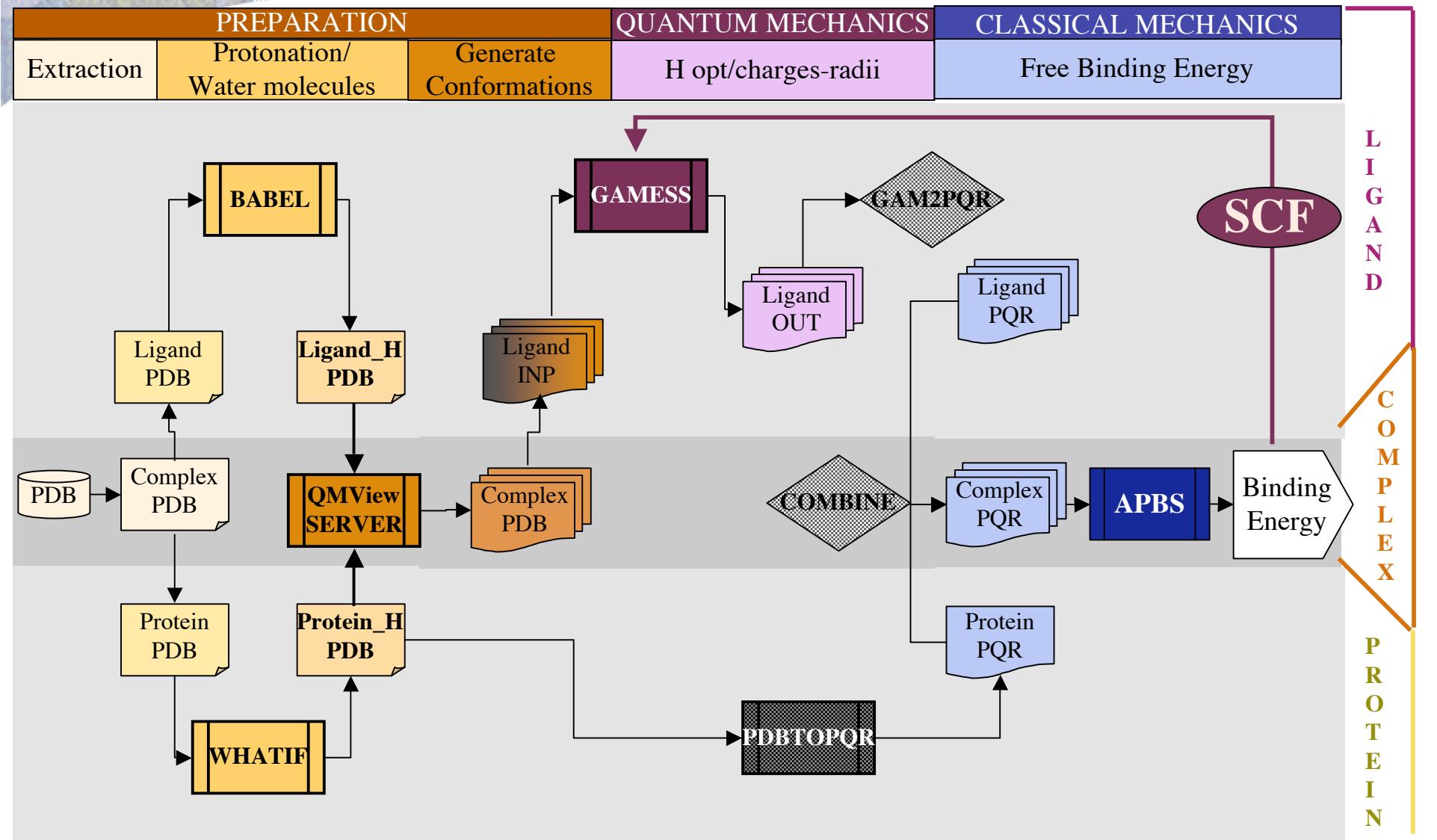
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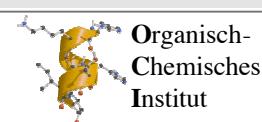
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Computational hybrid method

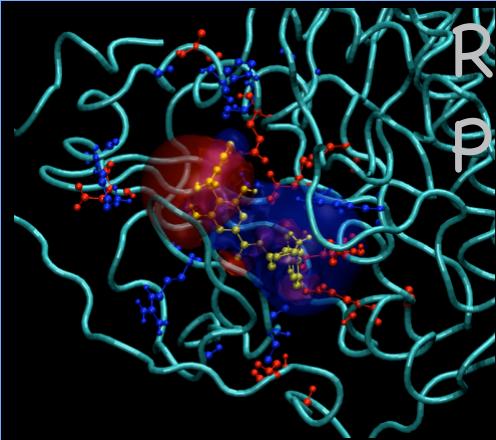
INTRODUCTION SCIENCE METHOD RESULTS INFRASTRUCTURE CONCLUSION



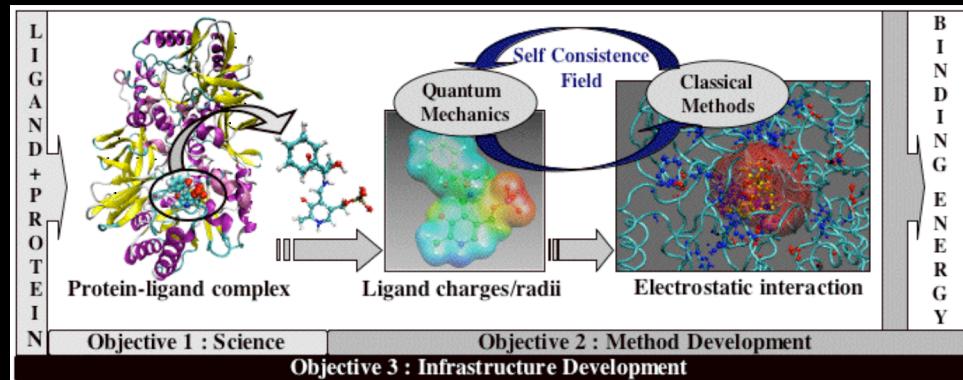
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Recent Projects



- ◆ Coordination of chemistry code (GAMESS/APBS) with optimization code (Nimrod)
- ◆ More substantial testing of a newly designed framework for ligand-protein interactions using GAMESS/APBS tools (quantum mechanics plus continuum electrostatics strategy)
- ◆ Comparison of ligand docking strategies used in GAMESS/APBS and current community docking code, AUTODOCK.

QMView

APBS

GAMESS

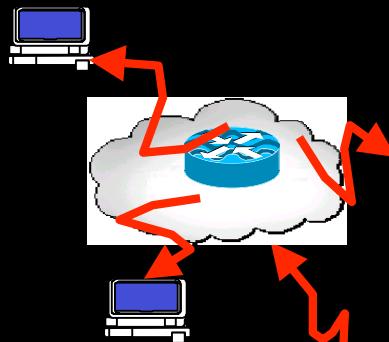
VMD

AutoDock

Celine Amoreira

Chris Kondric
Duy Nyguyn
Laura Berstis
James Wang

Towards the Grid...



UZ



GAMESS@HOME



ROCKS:
Papadopoulos; Bruno; Katz
rocks.npac.i.edu



7 institutions in 1 country
6 institutions in 2 countries
27 institutions in 10 countries

Karan Bhatia

Jerry Greenberg

Steve Mock

Brent Stearn

Sriram Krishnan

Michela Taufer
Ilkay Altintas

Middleware Efforts



Wibke Sudholt

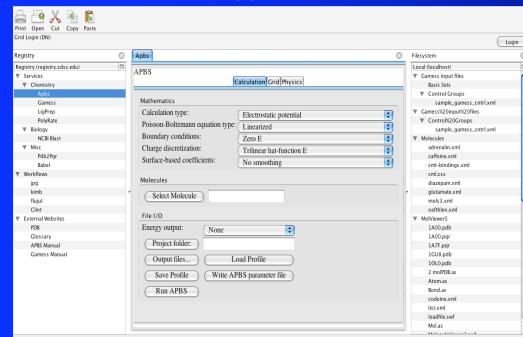
Celine Amoreira

Anne Bowen

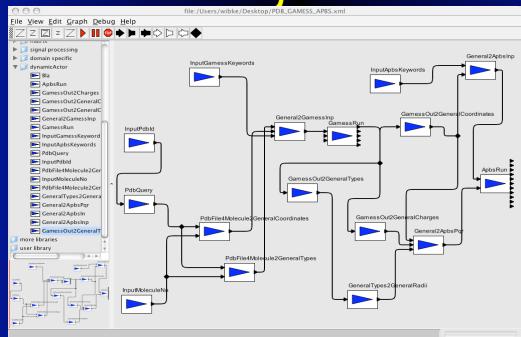
Richard Zamudio

Chris Kondric
Duy Nguyen
Becky Abramson

Gemstone



Resurgence



Informnet

