Computational Biology Discussion

Gary M. Johnson
Krell Institute

Prepared for:
Advanced Scientific Computing Advisory Committee Meeting
October 25 and 26, 2001
Crowne Plaza Hotel
14th and K Streets
Washington, DC
Outline of Discussion

1. Why are DOE, OBER and OASCR engaged in computational biology and systems biology research?
2. Specific research activities
3. Summary of GTL Program
4. Summary of FN 01-21 Awards
5. Agency funding levels
6. GTL program planning activities
7. Research opportunities in computational biology
8. Where should we go from here?
Systems biology is

- A systems analysis and engineering approach to biology to understand the workings of entire biological systems
- It requires the integrated application of methods from modern biology, computational science, and information science and technology
- It requires advanced measurement and analytical technologies
Systems biology provides biological solutions to DOE problems through understanding biological systems...

from the genome

to the proteome

to the cell and organism and microbial communities

The bridge between physical, computational and life sciences
Enabling scientific breakthroughs impacting DOE missions
Why Systems Biology and DOE?

• Only a systems approach can lead to biological solutions for complex energy and environmental problems.

• DOE is the only agency that can integrate the physical, computational and biological science expertise at a large scale and scope required for successful systems biology solutions to energy-related problems.
Payoffs in the near term

Significant savings in toxic waste cleanup and disposal

Bioremediation methods for accelerated and less costly cleanup strategies

Understanding metabolic pathways and mechanisms of native microbes

Improved diagnostics and standards for ecological and human health

Understanding responses of metabolic and regulatory pathways of organisms to environmental conditions

Sensors for detecting pathogens and toxins; strategies to enable strain identification; and improved vaccines and therapeutics for combating infectious disease

Investigating protein expression patterns, protein-protein interactions, and molecular machines

Improve the scientific basis for worker health and safety

Technologies and systems for detecting and responding to biological terrorism

Payoffs in the near term

Significant savings in toxic waste cleanup and disposal

Bioremediation methods for accelerated and less costly cleanup strategies

Understanding metabolic pathways and mechanisms of native microbes

Improved diagnostics and standards for ecological and human health

Understanding responses of metabolic and regulatory pathways of organisms to environmental conditions

Sensors for detecting pathogens and toxins; strategies to enable strain identification; and improved vaccines and therapeutics for combating infectious disease

Investigating protein expression patterns, protein-protein interactions, and molecular machines
Payoffs in the mid to long term

Enable independence of foreign oil

- Clean, efficient biological alternative to fossil fuels
- Harnessing metabolic pathways/mechanisms in H₂-producing microbes

Stabilize atmospheric carbon dioxide to counter global warming

- Designer plants for easily convertible biomass for fuels, chemical feed stocks, products
- Understanding metabolic pathways and networks, and cell wall synthesis

- Strategies and methods for storing and monitoring carbon
- Investigating enzymes, regulation, environmental cues, and effects
Specific research activities

• Joint OBER-OASCR program on Genomes to Life
• Joint OASCR- OBER project on Advanced Modeling and Simulation of Biological Systems
  – Office of Science Notice 01-21
• OBER Microbial Cell Project
  – Office of Science Notice 01-20
GTL Scientific Plan — To understand how genes, proteins, and cells work in intricate networks to form dynamic living systems exquisitely responsive to their environments.

**Cells** contain DNA—the hereditary material of all living systems.

**A genome** is an organism’s complete set of DNA.

**DNA** contains genes, whose sequence specifies how and when to build proteins.

**Proteins** perform most essential life functions, often working together in the cell as “protein machines.”

**Supercomputers** will analyze how protein machines interact through complex, interconnected pathways. Computer models of these life processes will be applied to help solve energy challenges.
DOE Cutting-Edge Facilities for Multidisciplinary Research

Production Sequencing Facility at DOE’s Joint Genome Institute

Beamlines at the National Synchrotron Light Source at Brookhaven National Laboratory and Stanford University’s Linear Accelerator

Advanced Light Source at Lawrence Berkeley National Laboratory

Advanced Photon Source at Argonne National Laboratory

Supercomputers at six national laboratories

Neutron sources at the High Flux Isotope Reactor at Oak Ridge National Laboratory and Los Alamos Science Center at Los Alamos National Laboratory. Under construction, the Spallation Neutron Source (site plan at left) at ORNL in collaboration with five other national laboratories.

Environmental Molecular Sciences Laboratory’s 800-MHz nuclear magnetic resonance spectrometer at Pacific Northwest National Laboratory
Supercomputers Will Decipher How Genes Work—This knowledge will aid development of new applications to solve energy and environmental challenges.

**Living** systems are complex and not well understood.

**Computer** simulations and models have been used to understand many complex systems, such as nuclear reactions and global climate. DOE has much experience in fielding problems of this computational magnitude.

**BER and ASCR** of the Office of Science have formed a strategic alliance in GTL to develop the computational and mathematical capabilities to model living systems on the scale and complexity of living organisms.

**DOE** will discover how microbial genes, proteins, and microbial communities work together and will apply that knowledge to develop tools to solve energy and environmental challenges.

**Biological research problems will drive computer science for the coming decades.**
Systems Biology depends on high-performance computing

Problem size and complexity

- Thin film growth
- Nanoscale science
- Chemical reactions in solution

Computing requirements

Tera-scale

Peta-scale
Office of Science  
Notice 01-21  
Advanced Modeling and Simulation of Biological Systems

The goal of this program is to enable the use of terascale computers to explore fundamental biological processes and predict the behavior of a broad range of protein interactions and molecular pathways in prokaryotic microbes of importance to DOE.
FN 01-21 Awards

• 19 proposals received
• Proposals in areas of protein folding/docking and cell modeling
• 9+1 awards made
• First year awards totaled about $3M
### Computational Biology Portfolio
#### FN 01-21 Projects:

<table>
<thead>
<tr>
<th>ID</th>
<th>Institutions</th>
<th>Title</th>
<th>Total Funds Requested</th>
<th>2001 Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>83078</td>
<td>Scripps Research Institute</td>
<td>Biomolecular Simulation Using Amber and CHARMM</td>
<td>$673,464</td>
<td>$216,572</td>
</tr>
<tr>
<td></td>
<td><strong>Project Description</strong></td>
<td>Build on the existing CHARMM and Amber simulation packages, adapting them in novel ways to massively parallel architectures and high-performance CPUs.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>83086</td>
<td>Indiana University</td>
<td>Cyber Cell: Automated Physico-Chemical Cell Model Development Through Information Technology</td>
<td>$830,102</td>
<td>$268,340</td>
</tr>
<tr>
<td></td>
<td><strong>Project Description</strong></td>
<td>Integrate the comprehensive reaction-transport-genetic cell simulator, Cyber-Cell, with experimental data, resulting in an automated model development methodology. The model will be developed and tested using data on <em>E. coli</em>.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>83088</td>
<td>Columbia University</td>
<td>Computational Analysis and Simulation of Bacterial Molecular Networks</td>
<td>$1,461,968</td>
<td>$240,000</td>
</tr>
<tr>
<td></td>
<td><strong>Project Description</strong></td>
<td>The purpose of this project is to develop semi-quantitative models that capture the structure and function of the <em>E. coli</em> metabolism. The investigators plan to complement the purely topologic, pathway based methodologies with dynamical information quanti</td>
<td></td>
<td></td>
</tr>
<tr>
<td>83089</td>
<td>University of Notre Dame</td>
<td>Organization of Complex Metabolic Networks</td>
<td>$1,436,747</td>
<td>$331,509</td>
</tr>
<tr>
<td></td>
<td>Northwestern</td>
<td><strong>Project Description</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>The purpose of this project is to develop semi-quantitative models that capture the structure and function of the <em>E. coli</em> metabolism. The investigators plan to complement the purely topologic, pathway based methodologies with dynamical information quanti</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>83090</td>
<td>University of California, San Diego</td>
<td>Parallel Protein Docking and Interaction Dynamics with Adaptive Mesh Solutions to the Poisson-Boltzmann Equation</td>
<td>$1,900,200</td>
<td>$348,792</td>
</tr>
<tr>
<td></td>
<td>Scripps Research Institute</td>
<td><strong>Project Description</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>This project involves the improvement of tools for determination of the structures of protein complexes through docking with an energy function of high quality. Particular emphasis is given to electrostatic interactions, and much of the work involves need</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>83125</td>
<td>LLNL</td>
<td>Advanced Molecular Simulations of <em>E. coli</em> Polymerase III</td>
<td>$1,781,369</td>
<td>$446,612</td>
</tr>
<tr>
<td></td>
<td><strong>Project Description</strong></td>
<td>The project involves the use of advanced molecular simulation methods on terascale computers to improve understanding of bacterial multicomponent protein machines. The research will involve performing dynamical simulations of <em>E. coli</em> DNA polymerase III b</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### FN 01-21 Projects Continued:

<table>
<thead>
<tr>
<th>ID</th>
<th>Institutions</th>
<th>Title</th>
<th>Total Funds Requested</th>
<th>2001 Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>83136</td>
<td>PNNL</td>
<td>Computational Approaches and Framework for Microbial Cell Simulations</td>
<td>$1,470,000</td>
<td>$360,000</td>
</tr>
</tbody>
</table>

**Project Description**

The investigators propose to develop a wide-ranging set of computational tools in support of intracellular model building. These tools will be applied to build computable representations of the core energy and material pathways in *Rhodobacter sphaeroides*

<table>
<thead>
<tr>
<th>ID</th>
<th>Institutions</th>
<th>Title</th>
<th>Total Funds Requested</th>
<th>2001 Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>83137</td>
<td>PNNL</td>
<td>Molecular Modeling of Complex Enzymatic reactions: The Respiratory Enzyme Flavocytochrome c, Fumarate Reductase of <em>Shewanella frigidimarina</em></td>
<td>$952,000</td>
<td>$313,000</td>
</tr>
</tbody>
</table>

**Project Description**

This project involves highly detailed simulations of complex reaction mechanisms in bacterial enzymes such as a flavocytochrome. It involves ongoing development of a program that permits such simulations, and specific application to the study of metal ion.

<table>
<thead>
<tr>
<th>ID</th>
<th>Institutions</th>
<th>Title</th>
<th>Total Funds Requested</th>
<th>2001 Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>83095</td>
<td>Genomatica, Inc.</td>
<td>Development of the Next Generation of Genome-scale Constraints-Based Cellular Models</td>
<td>$2,204,360</td>
<td>$0</td>
</tr>
<tr>
<td></td>
<td>Penn State University</td>
<td></td>
<td></td>
<td>$187,000</td>
</tr>
</tbody>
</table>

**Project Description**

The proposed research will extend the PI's work on a top-down approach to metabolic modeling, which begins with a stoichiometric network model and successively constrains the set of admissible solutions with conditions that are derived, for instance, from...

### FN 01-20 Projects:

<table>
<thead>
<tr>
<th>ID</th>
<th>Institutions</th>
<th>Title</th>
<th>Total Funds Requested</th>
<th>2001 Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>83108</td>
<td>Institute for Systems Biology</td>
<td>Interdisciplinary Study of <em>Shewanella putrefaciens</em> MR-1's Metabolism &amp; Metal Reduction</td>
<td>$4,498,512</td>
<td>$100,000</td>
</tr>
</tbody>
</table>

**Project Description**

The project is an integrated systems approach to study *S. putrefaciens* MR-1 in an attempt to delineate the organisms response to environmental perturbation. MR-1 is a suitable organism for this study because it can function in aerobic conditions, reduces...

### Grand Totals:

- Total Funds Requested: $17,208,722
- 2001 Funding: $2,811,825
FN 01-21 Distribution of Funds in 2001

- Labs: 41%
- Univ: 51%
- Other: 8%
Office of Science
Notice 01-20
Microbial Cell Project

The MCP is focused on fundamental research to understand those reactions, pathways, and regulatory networks that are involved in environmental processes of relevance to the DOE, specifically the bioremediation of metals and radionuclides, cellulose degradation, carbon sequestration, and the production, conversion, or conservation of energy (e.g. fuels, chemicals, and chemical feedstocks).
## Agency Funding Levels

<table>
<thead>
<tr>
<th>Agency</th>
<th>Funding Level</th>
<th>Focus Areas</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH</td>
<td>$50M to $100M</td>
<td>Human Health</td>
</tr>
<tr>
<td>NSF</td>
<td>$48M</td>
<td>Human, Animal, &amp; Plant Science</td>
</tr>
<tr>
<td>DARPA</td>
<td>$15M to $18M</td>
<td>Applications of Biotechnology to Defense</td>
</tr>
<tr>
<td>DOE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OBER</td>
<td>$9M</td>
<td>Systems Biology, GTL</td>
</tr>
<tr>
<td>OASCR</td>
<td>$3M</td>
<td>Systems Biology, GTL</td>
</tr>
<tr>
<td>USDA</td>
<td>$3M</td>
<td>Food Crops</td>
</tr>
</tbody>
</table>
GTL Program Planning Activities

August 2001 Workshop
  Computational Biology Workshop for the Genomes to Life Program
  Organizers Mike Colvin, LLNL & Reinhold Mann, ORNL
    username gtl
    password workshop

September 2001 Workshop
  Computational and Systems Biology: Visions for the Future
  Organizer Eric Lander, MIT
  Report pending
GTL Program Planning Activities

Future Workshops:

January 2002
  Computational Infrastructure for the Genomes to Life Program

February 2002
  Computer Science for the Genomes to Life Program

March 2002
  Mathematics for the Genomes to Life Program
Research Opportunities in Computational Biology

- Methods to model and simulate biological networks and pathways
- Methods to support the study of proteins, protein complexes, protein-protein interactions
- Methods to link models of biological processes and systems at various temporal and spatial levels of resolution
- Data management, access and analysis specifically focused on diverse data sets generated by modern biology experiments
- Tera-, peta-scale tool kits to support computational biology, e.g., pattern recognition algorithms, data mining, optimization, discrete math, multi-spectral image analysis, etc.
Biology is undergoing a major transformation that will be enabled and ultimately driven by computations.

Data poor

Data rich

Qualitative

Quantitative & predictive

“It’s time for biologists to graduate from cartoons to a real understanding of each protein machine.”

– Bruce Alberts, 9/6/01 (paraphrased)
Simulation and modeling are rapidly emerging as ways to explain biological data and phenomena.

However, the field is still awaiting a major biological breakthrough achieved by supercomputer simulations.
What capabilities are needed to be a leader in the emerging field of systems biology?

**Strong experimental biology program**

**Theory and simulation**

\[
\sum_i \left( \frac{-m_i}{2} \nabla_i^2 + \sum_{j \neq i} \frac{q_i q_j}{r_{ij}} \right) \Psi = E \Psi
\]

\[
k \left[ \frac{\partial^2 T}{\partial x^2} + \frac{\partial^2 T}{\partial y^2} + \frac{\partial^2 T}{\partial z^2} \right] = \rho c_p \frac{\partial T}{\partial t}
\]

**High performance computing**
Where should we go from here?

• Plan R&D agenda with components in:
  - Mathematics and statistics
  - Computer science
  - Informatics
  - Hardware and networking infrastructure

• Focus it on DOE mission opportunities to:
  - Use biological data to enable scientific discovery
  - Determine the structural details of biological “parts”
  - Model whole cells and microbial communities
Report on the
Computational Biology Workshop
for the
Genomes to Life Program
Summary of Recommendations

Modeling of Cells and Microbial Communities
• DOE should support a program of research aimed at accelerating the development of high-fidelity models and simulations of metabolic pathways, regulatory networks, and whole-cell functions.

Biomolecular Simulations
• DOE should ensure that advanced simulation methodologies and petaflop computing capabilities be available when needed to support full-scale modeling and simulations of pathways, networks, cells, and microbial communities.
• DOE should provide a software environment and infrastructure that allow for integration of models at several spatial and temporal scales.
Report on the
Computational Biology Workshop
for the
Genomes to Life Program
Summary of Recommendations

Functional Annotation of Genomes:
• DOE should support the continued development of automated methods for the structural and functional annotations of whole genomes, including research into such new approaches as evolutionary methods to analyze structure/function relationships.

Experimental Data Analysis and Model Validation:
• DOE should develop the methodology necessary for seamless integration of distributed computational and data resources, linking both experiment and simulation.
• DOE should take steps to ensure that high-quality, complete data sets are available to validate models of metabolic pathways, regulatory networks, and whole-cell functions.
Report on the  
Computational Biology Workshop  
for the  
Genomes to Life Program  
Summary of Recommendations

**Biological Data Management:**

- DOE should support the development of software technologies to manage heterogeneous and distributed biological data sets, and the associated data-mining and visualization methods.
- DOE should provide the biological data storage infrastructure and the multiteraflop-scale computing to ensure timely data updates and interactive problem-solving.
- DOE should set a standard for open data in its GTL program and demonstrate its value through required universal use.
Report on the
Computational Biology Workshop
for the
Genomes to Life Program
Summary of Recommendations

General Recommendations:

• Continue the development of the GTL computational biology plan through a series of workshops focused on informatics, mathematics, and computer science challenges posed by the GTL systems biology goals;

• Ensure that the computing, networking, and data storage environment necessary to support the accomplishment of GTL goals will be available when needed. This environment should include computing capabilities scaling up through the multiteraflop and into the petaflop range; as well as a storage infrastructure at the multipetabyte level; and a networking infrastructure that will facilitate access to heterogeneous distributed biological data sets by a geographically dispersed collection of investigators. Further definition of this environment should be pursued through a dedicated workshop;
Report on the Computational Biology Workshop for the Genomes to Life Program
Summary of Recommendations

**General Recommendations:**

- Establish policies for distribution and ownership of any data generated under the GTL program, prior to commencing peer review of GTL proposals or making any awards that would lead to the creation of such data; and

- Support sufficient scope of research to assemble the cross-disciplinary teams of biologists, computational biologists, mathematicians, and computational scientists that will be necessary for the success of GTL.