Program Announcement
To DOE National Laboratories
LAB 01-21

Advanced Modeling and Simulation of Biological Systems

SUMMARY:
The Offices of Advanced Scientific Computing Research (ASCR) and Biological and Environmental Research (OBER) of the Office of Science (SC), U.S. Department of Energy, hereby announce interest in receiving proposals in support of computational 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. This goal will be achieved through the creation of scientific simulation codes that are high performance, scalable to hundreds of nodes and thousands of processors, and able to evolve over time and be ported to future generations of high performance computers. The research efforts being sought under this Program Announcement will take advantage of extensive information inferred from the complete DNA sequence, such as the genetics and the biochemical processes available for a well-characterized prokaryotic microbe; for example, *Escherichia coli* (*E. coli*). This Announcement encourages proposals from the disciplines of applied mathematics and computer science in partnership with microbiology, molecular biology, biochemistry and structural and computational biology to combine information available on a well characterized prokaryotic microbe with advanced mathematics and computer science to enable this new understanding. This announcement is being issued in parallel with Program Announcement 01-20, the Microbial Cell Project. Together, they represent a planned first step in an ambitious effort to understand the functions of the proteins in a prokaryotic microbial cell, to understand their interactions as they form pathways that carry out DOE-relevant activities, and to eventually build predictive models for microbial activities that address DOE mission needs.

SUPPLEMENTARY INFORMATION:
Extraordinary advances in computing technology in the past decade have set the stage for a new era in scientific computing. Within the next five to ten years, computers running at 1 to 10 trillion floating point operations per second (Tops) will become available. Using such computers, it will be possible to dramatically extend explorations of fundamental processes as well as advance the ability to predict the behavior of a broad range of complex biological systems.

The primary mission of the Office of Advanced Scientific Computing Research is to discover, develop, and deploy the computational and networking tools that enable researchers in the scientific disciplines to analyze, model, simulate and predict complex phenomena important to the Department of Energy. In carrying out this mission, ASCR:

- Maintains world leadership in areas of scientific computing research relevant to the missions of the Department of Energy;
- Integrates the results of advanced scientific computing research into the natural sciences and engineering;
- Provides world class supercomputer and networking facilities for scientists working on problems that are important to the missions of the Department.

The primary mission of the Office of Biological and Environmental Research is to advance environmental and biomedical knowledge connected to energy production, development, and use. In carrying out this mission, OBER:

- Contributes to the environmental remediation and restoration of contaminated environments at DOE sites through basic research in bioremediation, microbial genomics, and ecological science;
- Provides new knowledge that will widen DOE's options for clean and affordable energy through research in microbial genomics and bioinformatics;
- Advances our understanding of and finds solutions for the effects of energy production and use on the environment through research in global climate modeling and simulation, the role of clouds in climate change, carbon cycle and carbon sequestration, atmospheric chemistry, and ecological science;
- Helps protect the health of DOE workers and the public by advancing our understanding of the health effects of energy production and use through basic research in key areas of the life sciences including functional genomics and structural biology as well as low dose radiation research;
- Seeks to develop new applications of radiotracers in diagnosis and treatment and supports biomedical engineering research focused on fundamental studies in medical imaging, biological and chemical sensors, laser medicine, new biocompatible materials, informatics, and artificial organs.

The scope and complexity of the proposed projects will likely require close collaboration among researchers from the biological sciences, computational sciences, computer science, and applied mathematics disciplines. Accordingly, this solicitation calls for the creation of scientific simulation teams, or collaborations, as the organizational basis for a successful application. Partnerships among universities, national laboratories, and industry are encouraged but not required. A scientific

simulation team is a multi-disciplinary, and perhaps multi-institutional, group of people who will:

- create scientific simulation codes that take full advantage of terascale computers,
- work closely with other research teams and centers to ensure that the best available mathematical algorithms and computer science methods are employed, and
- manage the work of the team in a way that will foster good communication and decision making.

Biological systems and their regulatory and metabolic pathways are complex. The details of many biological processes are not well understood, and the resulting computations will require new algorithms, computational biology tools, and extraordinary computing resources. The successful development of the new tools will require the sustained efforts of multi-disciplinary teams, and applications of these tools will require Tops-scale and beyond supercomputers, as well as the considerable expertise required to use them. Although forms of these computational tools already exist, considerable research in mathematics and computer science remains to be done in order to develop reliable, robust, efficient, and widely applicable versions of these tools.

Data analysis, computational modeling and simulation will play critical roles in the future of biological research. Large sets of genomic data will be generated by the on-going DNA sequencing efforts at large genome centers around the world. These data will be analyzed and combined with different types of biological data, including information on structure, expression, and function to develop a more comprehensive understanding of biological systems. Homology-based protein structure correlations identified by pattern searches will be used to predict the structures of the proteins coded by the new genome sequences and will be invaluable for ascertaining protein function and for identifying more distant homologies than are possible by simple sequence comparisons. For selected biochemical processes, computational modeling will be used for a range of applications, from elucidating the mechanisms of enzymatic reactions to identifying the energetic principles underlying macromolecular interactions. Computer models of entire cells and microbial ecosystems will also use the understanding gained about biomolecular processes to predict likely behaviors of organisms under different conditions.

A goal for the research solicited here is to develop a predictive understanding of biological systems using a well characterized prokaryotic microbial cell, for example, *E. coli,* as a model system. Given the immense complexity of even the simplest microbes, fully predictive models that provide quantitatively accurate estimates of

each chemical component of a cell will remain a challenge for subsequent generations of researchers. Hence, in the foreseeable future, the modeling of cellular processes will instead be performed at a level beyond that of the individual chemical reactions, perhaps at the level of functional building blocks that can be pieced together or linked into higher order models. At this level, cellular pathways are described either qualitatively as being present or absent, or quantitatively, in terms of the average concentrations and rates of activity derived from experimental data. Despite their lack of chemical detail, such models will provide a powerful tool for integrating and analyzing the very large new biological data sets and, under some conditions, predicting cellular behavior under changing conditions. Just as importantly, these high level models will provide a means of inducing and testing the general principles of cellular function.

Three levels of modeling are included in this solicitation: (1) molecular simulations of protein function and macromolecular interactions, (2) semi-quantitative simulations of metabolic networks in whole cells, and (3) quantitative kinetic models of biochemical pathways. The latter simulations are much more demanding in terms of the empirical data and computer power required and therefore, will initially be limited to relatively small, well characterized pathways. Since both of these levels of modeling depend on having the (nearly) complete parts lists provided by the fully annotated genome sequences, combined with gene function, expression information and phenotypic data about an organism, the focus of this solicitation will be on *E. coli* or another well-characterized and studied prokaryotic microbe.

1) Molecular simulations of protein function and macromolecular interactions. The ultimate biological models would be molecular-level simulations of each biochemical process. There are many challenges to molecular-level simulations of biological processes, including the large size of biomolecules and the wide range of time scales of many biological processes, as well as the subtle energetics and complex milieu of biochemical reactions. Moreover, many biochemical reactions occur far from equilibrium and are regulated by both transport of the reactants and subsequent processing of the products. Finally, there remains a wide gulf between the detailed chemical data needed for initiating and validating biomolecular simulations and the data available on many biological processes and environments. Despite these challenges, there are a vast number of biochemical processes for which chemical simulations will have a major impact on our understanding. These problems include the elucidation of the energetic factors underlying protein-protein or protein-DNA interactions and the dissection of the catalytic function of certain enzymes. The promise of such modeling studies is rapidly growing as a result of the development of linear-scaling computational chemical methods and molecular modeling software for massively parallel computers. Additionally, molecular modeling will be used to

determine the principles that underlie protein-protein interactions, and ultimately to predict likely protein binding sites.

2) Semi-quantitative simulations of metabolic networks. This modeling approach follows the engineering tradition of making maximal use of limited information by combining highly simplified models with successive constraints to identify an "envelope" of expected behaviors of the system under different conditions. A fundamental tenet of such modeling is that the very complex molecular details of biology combine to form robust and relatively simple rules for behavioral responses. Such models are iteratively refined as more functional data and constraints become available from experiments that are themselves guided by the model's predictions.

Since such modeling depends only on the nature of the reactants and products (i.e., the stoichiometry) of the metabolic transformations, rather than the rates of these reactions (kinetics), most of the necessary data for building the model can be derived directly from annotated genomes, in some cases using artificial intelligence based pathway synthesis algorithms. These data are typically encoded in a "stoichiometry matrix" relating specific reaction products to metabolic reactions. Numerical analysis of this matrix can identify the entire repertoire of theoretically possible metabolic capabilities of a given genotype, for example, what nutrients are essential and what metabolic pathways are non-redundant. Such information, although qualitative, has enormous potential value. It will allow the inference of phenotypic properties directly from the functionally annotated genotype, help in the optimization of product yield in bio-reactors, and provide a predictive basis for engineering organisms with novel capabilities. Additionally, such analysis can be used to improve and validate tentative functional annotations. Even in the absence of stoichiometric data, mathematical analysis of metabolic networks can shed light on overall biological function. A number of successful models have already been developed for *E. coli* using both stoichiometric data, based on a network analysis, and constraint-based approaches.

Unlike the kinetic pathway described below, computing speed is not typically a limiting factor in molecular pathway analysis. Instead, the primary bottleneck to progress is the availability of functionally annotated genomes and the human talent trained in both the biological sciences and the art of developing and applying such mathematical models. The choice of a well-characterized prokaryotic organism as a model biological system for this solicitation minimizes the challenges associated with the first bottleneck.

3) Quantitative kinetic models of biochemical pathways. Although the metabolic network modeling described above can provide useful qualitative information on possible behavioral characteristics of organisms, a fully predictive understanding of biological processes will require quantitative information about the dynamics of each

sub-process. In other words, network analysis can suggest what metabolic transformations may be possible, but full kinetic details are required to determine which pathways are most important under the given conditions. Such models will require detailed empirical data, including *in vivo* reaction rates and substrate concentrations for each step in the biological system to be simulated. Additionally, these simulations are highly computationally demanding; for example, the simulation of a regulatory circuit involving only several dozen parameters required the use of a parallel supercomputer. These experimental and computational requirements will prohibit such quantitative simulations of whole cells in the foreseeable future. Nevertheless, for selected critical cell subsystems, such simulations offer the promise of quantitative predictions of cellular response and will constitute a rigorous validation of the completeness of our understanding the processes under investigation.

Kinetic models have been applied to a handful of specific cellular pathways that demonstrate both the benefits and technical challenges of such simulations. One of the most complex examples to date has been a full kinetic analysis of the lytic versus lysogenic pathways in phage lambda infected *E. coli* cells. The heart of the decision circuitry for this pathway contains only four promoter sites modulated by five gene transcripts, yet the kinetic model required nearly forty empirical rate constants and a number of other parameters. Additionally, to be computationally tractable, this model involved a number of simplifying assumptions, including approximating the cell as a well-stirred homogeneous mixture. Despite these assumptions and the large number of empirical parameters this model yielded reasonably accurate results for the lytic/lysogenic fractions at different levels of viral infection.

An important outcome of this previous work is to highlight the significant differences between the modeling methodologies necessary for biochemical pathways and those used for macroscopic chemical processes (e.g., in optimizing industrial chemical processes.) In the latter the chemical concentrations can be assumed to be continuous and therefore the kinetics can be simulated using ordinary differential equations. In contrast, the very small numbers of individual signaling molecules in biological regulatory pathways require the use of discrete stochastic simulations. Indeed, a number of seemingly non-deterministic features in gene expression have been ascribed to the inherently stochastic fluctuations in the concentrations of very small numbers of regulatory signals.

Overall, both the kinetic models and the metabolic network analysis will provide a means of combining and evaluating the consistency of large sets of biological data. Each requires detailed functional annotation of whole genomes and well as phenotypic data under a wide variety of conditions.

In a parallel solicitation, the Microbial Cell Project (see Program Announcement LAB 01-20) supports key DOE missions by building on the successful DOE Microbial Genome Program that has furnished microbial DNA sequence information on microbes relevant to environmental remediation, global carbon sequestration (e.g., CO2 fixation), complex polymer degradation (e.g., cellulose and lignins), and energy production (fuels, chemicals, and chemical feedstocks). These microbial genome sequences provide a finite set of "working parts" for a cell and the challenge now is to understand how these parts are assembled into functional pathways and networks to accomplish activities of interest to the DOE. The traditional reductionist experimental approach has defined specific steps or stages within many physiological processes; however, the availability of whole genomes affords the opportunity to integrate these individual pathways into a larger physiological or whole organism framework. The Microbial Cell Project seeks to integrate available information about individual processes and regulatory complexes to understand the intracellular environment, in which these pathways and networks exist and function. The DOE Microbial Cell Project is part of a coordinated Federal effort called the Microbe Project involving elements from several other Federal agencies. The long-term goal is that research funded in this program and in the Microbial Cell Project will converge so that simulations and models can be developed in organisms and for biochemical pathways important for the DOE mission.

This Announcement takes advantage of decades of research on *E. coli* (or a similarly well characterized prokaryotic microbe) providing much of the biological information needed to begin developing more comprehensive models of biological systems. It is anticipated that the applied mathematicians and computer scientists will need to partner with biologists in the initial phases of algorithm development, as well as in the design of biological tests to validate models that are developed, including predictions made using these models. Links to some of the vast amount of information available on *E. coli* can be found at http://genprotec.mbl.edu/start and http://web.bham.ac.uk/bcm4ght6/res.html.

The mathematical and computer science challenges in this effort span a broad range of the current research topics in both fields. A few examples of possible areas include: advanced techniques for data fusion; algorithms for solution of low dimensional dynamical systems in the presence of uncertainty; applications of computational geometry and topology to pattern recognition and analysis; advanced concepts in discrete state machines; and control theory. It must, however, be emphasized that the preceding list is only a list of possible examples and does not reflect any prioritization of areas. Collaboration and Coordination

Proposers are encouraged to collaborate with researchers in other institutions, where appropriate. Further information on preparation of collaborative proposals is available

in the Application Guide for the Office of Science Financial Assistance Program that is available via the World Wide Web at: http://www.science.doe.gov/production/grants/Colab.html.

DATES: Preproposals referencing Program Announcement LAB 01-21 should be received by February 21, 2001. Earlier submissions will be gladly accepted. A response to timely preproposals will be communicated to the proposer by March 9, 2001.

Formal proposals in response to this Announcement should be received by 4:30 p.m., E.D.T., April 24, 2001, to be accepted for merit review and funding in FY 2001.

ADDRESSES: Preproposals referencing Program Announcement LAB 01-21 should be sent to Dr. Walter M. Polansky, Office of Advanced Scientific Computing Research, SC-32, Office of Science, U.S. Department of Energy, 19901 Germantown Road, Germantown, MD 20874-1290; e-mail is acceptable for submitting preproposals using the following address: walt.polansky@science.doe.gov.

Formal proposals referencing Program Announcement LAB 01-21, should be forwarded to: U.S. Department of Energy, Office of Science, Grants and Contracts Division, SC-64, 19901 Germantown Road, Germantown, MD 20874-1290, ATTN: Program Announcement LAB 01-21. This address must be used when submitting proposals by U.S. Postal Service Express Mail or any commercial mail delivery service, or when hand-carried by the proposer.

FOR FURTHER INFORMATION CONTACT:
Dr. Walter M. Polansky, Office of Advanced Scientific Computing Research, SC-32, Office of Science, U.S. Department of Energy, 19901 Germantown Road, Germantown, MD 20874-1290; telephone: (301) 903-5995, e-mail: walt.polansky@science.doe.gov.

Dr. John Houghton, Office of Biological and Environmental Research, Office of Science, U.S. Department of Energy, 19901 Germantown Road, Germantown, MD 20874-1290; telephone: (301) 903- 8288, e-mail: john.houghton@science.doe.gov.

Preproposals

Potential proposers are strongly encouraged to submit a brief preproposal that consists of two to three pages of narrative describing the research objectives, the technical approach(es), and the proposed team members and their expertise. The intent in requesting a preproposal is to save the time and effort of applicants in preparing and submitting a formal project proposal that may be inappropriate for the program.

Preproposals will be reviewed relative to the scope and research needs outlined in the summary paragraph and in the SUPPLEMENTARY INFORMATION. The preproposal should identify, on the cover sheet, the title of the project, the institution, principal investigator name, telephone, fax, and e-mail address. No budget information or biographical data need be included, nor is an institutional endorsement necessary. A response to each timely preproposal will be communicated to the Principal Investigator by March 9, 2001.

Program Funding

It is anticipated that up to $2 million will be available for all awards in Fiscal Year 2001. Multiple year funding is expected, also contingent on availability of funds and progress of the research; pending the availability of future funding, it is anticipated that this initiative will reflect a long term commitment to understanding the workings of a microbial cell. Awards are expected to range from $250, 000 to $600,000 per year with terms of one to three years. The DOE is under no obligation to pay for any costs associated with the preparation or submission of an proposal. DOE reserves the right to fund, in whole or in part, any, all, or none of the proposals submitted in response to this Announcement.

Submission Information

The Project Description in the formal proposal must be 25 pages or less, exclusive of attachments. It must contain an abstract or project summary on a separate page with the name of the proposer, mailing address, phone, FAX and E-mail listed. The proposal must include letters of intent from collaborators (briefly describing the intended contribution of each to the research), and short curriculum vitaes, consistent with NIH guidelines, for the proposer and any co-PIs.

DOE policy requires that potential proposers adhere to 10 CFR Part 745 "Protection of Human Subjects" (if applicable), or such later revision of those guidelines as may be published in the Federal Register.

The Office of Science requires organizations performing research involving recombinant DNA molecules and/or organisms and viruses containing recombinant DNA molecules shall comply with the NIH "Guidelines for Research Involving Recombinant DNA Molecules," which is available via the World Wide Web at: http://www.niehs.nih.gov/odhsb/biosafe/nih/rdna-apr98.pdf, (59 FR 34496, July 5, 1994), or such later revision of those guidelines as may be published in the Federal Register.

Other useful web sites include:

MCP Home Page - http://microbialcellproject.org

Microbial Genome Program Home Page - http://www.er.doe.gov/production/ober/microbial.html

DOE Joint Genome Institute Microbial Web Page - http://www.jgi.doe.gov/JGI_microbial/html/

GenBank Home Page - http://www.ncbi.nlm.nih.gov/

Human Genome Home Page - http://www.ornl.gov/hgmis

The instructions and format described below should be followed. Reference Program Announcement LAB 01-21 on all submissions and inquiries about this program.

OFFICE OF SCIENCE
GUIDE FOR PREPARATION OF SCIENTIFIC/TECHNICAL PROPOSALS TO BE SUBMITTED BY NATIONAL LABORATORIES

Proposals from National Laboratories submitted to the Office of Science (SC) as a result of this program announcement will follow the Department of Energy Field Work Proposal process with additional information requested to allow for scientific/technical merit review. The following guidelines for content and format are intended to facilitate an understanding of the requirements necessary for SC to conduct a merit review of a proposal. Please follow the guidelines carefully, as deviations could be cause for declination of a proposal without merit review.

1. Evaluation Criteria

Proposals will be subjected to scientific merit review (peer review) and will be evaluated against the following evaluation criteria which are listed in descending order of importance:

1. Scientific and/or Technical Merit of the Project;
2. Appropriateness of the Proposed Method or Approach;
3. Competency of the Personnel and Adequacy of Proposed Resources;
4. Reasonableness and Appropriateness of the Proposed Budget.

In addition to the above evaluation criteria, proposals will also be evaluated on the following:

5. The robustness of the organizational framework if a consortium is proposed;

The evaluation under item 2, Appropriateness of the Proposed Method or Approach, will also consider the following elements:

a) clarity of the plan in detailing areas of work to be addressed by biologists, computational scientists, applied mathematicians, computer scientists and computer programmers;
b) quality of the plan for effective collaboration among participants;
c) viability of the plan for verifying and validating the models developed, including verification using experiment results; and
d) quality and clarity of the proposed work schedule and project deliverables.

The evaluation will include program policy factors such as the relevance of the proposed research to the terms of the announcement, the uniqueness of the proposer's capabilities, and demonstrated usefulness of the research for proposals in other DOE Program Offices as evidenced by a history of programmatic support directly related to the proposed work.

2. Summary of Proposal Contents

Field Work Proposal (FWP) Format (Reference DOE Order 5700.7C) (DOE ONLY)
Proposal Cover Page
Table of Contents
Abstract
Narrative
Literature Cited
Budget and Budget Explanation
Other support of investigators
Biographical Sketches
Description of facilities and resources
Appendix

2.1 Number of Copies to Submit

An original and seven copies of the formal proposal/FWP must be submitted.

3. Detailed Contents of the Proposal

Proposals must be readily legible, when photocopied, and must conform to the following three requirements: the height of the letters must be no smaller than 10 point with at least 2 points of spacing between lines (leading); the type density must average no more than 17 characters per inch; the margins must be at least one-half inch on all sides. Figures, charts, tables, figure legends, etc., may include type smaller than these requirements so long as they are still fully legible.

3.1 Field Work Proposal Format (Reference DOE Order 5700.7C)
(DOE ONLY)

The Field Work Proposal (FWP) is to be prepared and submitted consistent with policies of the investigator's laboratory and the local DOE Operations Office. Additional information is also requested to allow for scientific/technical merit review.

Laboratories may submit proposals directly to the SC Program office listed above. A copy should also be provided to the appropriate DOE operations office.

3.2 Proposal Cover Page

The following proposal cover page information may be placed on plain paper. No form is required.

Title of proposed project
SC Program announcement title
Name of laboratory
Name of principal investigator (PI)
Position title of PI
Mailing address of PI
Telephone of PI
Fax number of PI
Electronic mail address of PI
Name of official signing for laboratory*
Title of official
Fax number of official
Telephone of official
Electronic mail address of official
Requested funding for each year; total request
Use of human subjects in proposed project:
    If activities involving human subjects are not planned at any time during the proposed project period, state "No"; otherwise state "Yes", provide the IRB Approval date and Assurance of Compliance Number and include all necessary information with the proposal should human subjects be involved.
Use of vertebrate animals in proposed project:
    If activities involving vertebrate animals are not planned at any time during this project, state "No"; otherwise state "Yes" and provide the IACUC Approval date and Animal Welfare Assurance number from NIH and include all necessary information with the proposal.

Signature of PI, date of signature
Signature of official, date of signature*

*The signature certifies that personnel and facilities are available as stated in the proposal, if the project is funded.

3.3 Table of Contents

Provide the initial page number for each of the sections of the proposal. Number pages consecutively at the bottom of each page throughout the proposal. Start each major section at the top of a new page. Do not use unnumbered pages and do not use suffices, such as 5a, 5b.

3.4 Abstract

Provide an abstract of no more than 250 words. Give the broad, long-term objectives and what the specific research proposed is intended to accomplish. State the hypotheses to be tested. Indicate how the proposed research addresses the SC scientific/technical area specifically described in this announcement.

3.5 Narrative

The narrative comprises the research plan for the project and is limited to 25 pages. It should contain the following subsections:

Background and Significance: Briefly sketch the background leading to the present proposal, critically evaluate existing knowledge, and specifically identify the gaps which the project is intended to fill. State concisely the importance of the research described in the proposal. Explain the relevance of the project to the research needs identified by the Office of Science. Include references to relevant published literature, both to work of the investigators and to work done by other researchers.

Preliminary Studies: Use this section to provide an account of any preliminary studies that may be pertinent to the proposal. Include any other information that will help to establish the experience and competence of the investigators to pursue the proposed project. References to appropriate publications and manuscripts submitted or accepted for publication may be included.

Research Design and Methods: Describe the research design and the procedures to be used to accomplish the specific aims of the project. Describe new techniques and methodologies and explain the advantages over existing techniques and

methodologies. As part of this section, provide a tentative sequence or timetable for the project.

Subcontract or Consortium Arrangements: If any portion of the project described under "Research Design and Methods" is to be done in collaboration with another institution, provide information on the institution and why it is to do the specific component of the project. Further information on any such arrangements is to be given in the sections "Budget and Budget Explanation", "Biographical Sketches", and "Description of Facilities and Resources".

3.6 Literature Cited

List all references cited in the narrative. Limit citations to current literature relevant to the proposed research. Information about each reference should be sufficient for it to be located by a reviewer of the proposal.

3.7 Budget and Budget Explanation

A detailed budget is required for the entire project period, which normally will be three years, and for each fiscal year. It is preferred that DOE's budget page, Form 4620.1 be used for providing budget information*. Modifications of categories are permissible to comply with institutional practices, for example with regard to overhead costs.

A written justification of each budget item is to follow the budget pages. For personnel this should take the form of a one-sentence statement of the role of the person in the project. Provide a detailed justification of the need for each item of permanent equipment. Explain each of the other direct costs in sufficient detail for reviewers to be able to judge the appropriateness of the amount requested.

Further instructions regarding the budget are given in section 4 of this guide.

* Form 4620.1 is available at web site:
http://www.sc.doe.gov/production/grants/forms.html

3.8 Other Support of Investigators

Other support is defined as all financial resources, whether Federal, non-Federal, commercial or institutional, available in direct support of an individual's research endeavors. Information on active and pending other support is required for all senior personnel, including investigators at collaborating institutions to be funded by a subcontract. For each item of other support, give the organization or agency, inclusive

dates of the project or proposed project, annual funding, and level of effort devoted to the project.

3.9 Biographical Sketches

This information is required for senior personnel at the laboratory submitting the proposal and at all subcontracting institutions. The biographical sketch is limited to a maximum of two pages for each investigator.

3.10 Description of Facilities and Resources

Describe briefly the facilities to be used for the conduct of the proposed research. Indicate the performance sites and describe pertinent capabilities, including support facilities (such as machine shops) that will be used during the project. List the most important equipment items already available for the project and their pertinent capabilities. Include this information for each subcontracting institution, if any.

3.11 Appendix

Include collated sets of all appendix materials with each copy of the proposal. Do not use the appendix to circumvent the page limitations of the proposal. Information should be included that may not be easily accessible to a reviewer.

Reviewers are not required to consider information in the Appendix, only that in the body of the proposal. Reviewers may not have time to read extensive appendix materials with the same care as they will read the proposal proper.

The appendix may contain the following items: up to five publications, manuscripts (accepted for publication), abstracts, patents, or other printed materials directly relevant to this project, but not generally available to the scientific community; and letters from investigators at other institutions stating their agreement to participate in the project (do not include letters of endorsement of the project).

4. Detailed Instructions for the Budget

(DOE Form 4620.1 "Budget Page" may be used)

4.1 Salaries and Wages

List the names of the principal investigator and other key personnel and the estimated number of person-months for which DOE funding is requested. Proposers should list the number of postdoctoral associates and other professional positions included in the proposal and indicate the number of full-time-equivalent (FTE) person-months and

rate of pay (hourly, monthly or annually). For graduate and undergraduate students and all other personnel categories such as secretarial, clerical, technical, etc., show the total number of people needed in each job title and total salaries needed. Salaries requested must be consistent with the institution's regular practices. The budget explanation should define concisely the role of each position in the overall project.

4.2 Equipment

DOE defines equipment as "an item of tangible personal property that has a useful life of more than two years and an acquisition cost of $25,000 or more." Special purpose equipment means equipment which is used only for research, scientific or other technical activities. Items of needed equipment should be individually listed by description and estimated cost, including tax, and adequately justified. Allowable items ordinarily will be limited to scientific equipment that is not already available for the conduct of the work. General purpose office equipment normally will not be considered eligible for support.

4.3 Domestic Travel

The type and extent of travel and its relation to the research should be specified. Funds may be requested for attendance at meetings and conferences, other travel associated with the work and subsistence. In order to qualify for support, attendance at meetings or conferences must enhance the investigator's capability to perform the research, plan extensions of it, or disseminate its results. Consultant's travel costs also may be requested.

4.4 Foreign Travel

Foreign travel is any travel outside Canada and the United States and its territories and possessions. Foreign travel may be approved only if it is directly related to project objectives.

4.5 Other Direct Costs

The budget should itemize other anticipated direct costs not included under the headings above, including materials and supplies, publication costs, computer services, and consultant services (which are discussed below). Other examples are: aircraft rental, space rental at research establishments away from the institution, minor building alterations, service charges, and fabrication of equipment or systems not available off-the-shelf. Reference books and periodicals may be charged to the project only if they are specifically related to the research.

a. Materials and Supplies

The budget should indicate in general terms the type of required expendable materials and supplies with their estimated costs. The breakdown should be more detailed when the cost is substantial.

b. Publication Costs/Page Charges

The budget may request funds for the costs of preparing and publishing the results of research, including costs of reports, reprints page charges, or other journal costs (except costs for prior or early publication), and necessary illustrations.

c. Consultant Services

Anticipated consultant services should be justified and information furnished on each individual's expertise, primary organizational affiliation, daily compensation rate and number of days expected service. Consultant's travel costs should be listed separately under travel in the budget.

d. Computer Services

The cost of computer services, including computer-based retrieval of scientific and technical information, may be requested. A justification based on the established computer service rates should be included.

e. Subcontracts

Subcontracts should be listed so that they can be properly evaluated. There should be an anticipated cost and an explanation of that cost for each subcontract. The total amount of each subcontract should also appear as a budget item.

4.6 Indirect Costs

Explain the basis for each overhead and indirect cost. Include the current rates.