Center for Biological Systems Architecture

Christina D. Smolke (PI)
Division of Chemistry and Chemical Engineering
1200 E. California Blvd., MC 210-41
California Institute of Technology
Pasadena, CA 91125
Phone: (626) 395-2460

Anand R. Asthagiri David Baltimore Michael B. Elowitz
John C. Doyle Grant Jensen Richard M. Murray
Dianne Newman Rob Phillips

California Institute of Technology

DRAFT. November 15, 2006

This cover page needs to be replaced with the NIH cover page. This is just a placeholder for the information that will be contained there.

- Box 1 (Title): Center for Biological Systems Architecture
- Box 2 (Reponse): Yes; RFA-GM-07-004
- Box 3 (PI): Christina D. Smolke
- Box 6 (dates): 1 July 2007–30 June 2012

Description *Applicants should describe concisely the mission of the proposed research center, the organizational structure, the goals of the research projects, and the plans for training and outreach activities.*

Performance Sites:

- California Institute of Technology, Pasadena, CA

Contents

Research Plan

The page limit for the Research Plan section of the application is 80 pages. Please note that there is no requirement to submit the maximum number of pages; instead, concise, articulate applications are desired. Applicants may submit CDs or DVDs as appendix material to illustrate some of the dynamic imaging or computational programs that do not convey well on paper.

Notes

- Instructions for the sections (from the NIH RFP) are in italics. These will be removed from the final version.
- Action items are shown in red, with someone's initials that we need to respond.

RMM: like this action item

- Comments are shown in blue, with the initials of the person who made the comments.

Like this comment (RMM)

- Current margins are narrower than the final versions will be (to leave room for marginal notes), so page counts are not quite as long as they appear. They will go down by 10-15% in the final formatting.

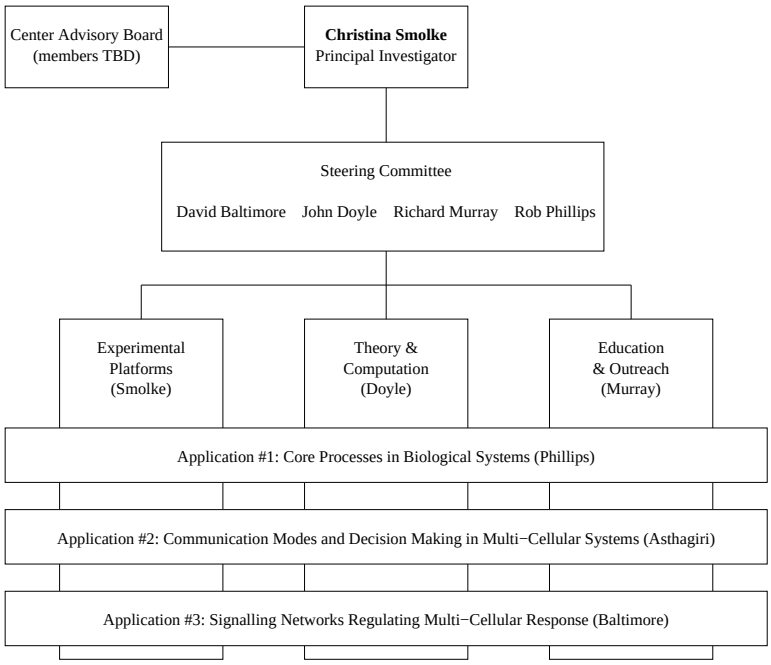

Figure 1: Center organizational chart.

2 Organizational Structure and Decision Making Plan

The center will be led by Christina Smolke, assisted by a steering committee consisting of David Baltimore, John Doyle, Richard Murray and Rob Phillips. The PI and the steering committee will be responsible for the success of the center and for insuring that the center evolves as needed to accomplish its mission. Figure 1 shows the structure of the center and the relationship between the major thrusts of the center. In the remainder of this section we describe the programmatic structure of the center as well as the decision making process.

Leadership Team To lead the center, we have brought together a collection of faculty who have a significant level of experience in scientific research, project management, and national leadership. The center will be led by Christina Smolke, who will commit 30% of her time to the center and who is a central participant in the technical activities of the center. To complement Smolke's skills, we have established a steering committee consisting of

David Baltimore, John Doyle, Richard Murray and Rob Phillips. Together, these faculty have substantial experience in leading scientific initiatives and running large scientific and engineering organizations. Together, the Center leadership will be able to provide the national scope, leadership experience, and scientific vision required for success.

David Baltimore

DB: 1 par bio

John Doyle

JCD: 1 par bio

Richard Murray is a Professor of Control and Dynamical Systems and the former Division Chair (dean) for Engineering and Applied Science at Caltech. Murray has had substantial experience in program and line management both in industry and university settings and has served as the PI on several multi-investigator AFOSR, DARPA and NSF grants.

Rob Phillips

RP: 1 par bio

Christina Smolke

CDS: 1 par bio

Program Management The center will be organized as a set of six interrelated research tasks:

- Driving Biological #1: Core processes in micro-organisms (Elowitz, Jensen, Phillips, Smolke)
- Driving Biological #2: Communication modes and probabilistic decision processes in multi-cellular systems (Asthagiri, Newman)
- Driving Biological #3: Signaling networks regulating multi-cellular response (Asthagiri, Baltimore, An/Csete)
- Foundational Technologies: molecular sensors (Smolke), spatial imaging (Jensen), single cell imaging (Elowitz)
- Computation and Theory: modeling, simulation, analysis and architecture (Doyle, Murray)
- Outreach and Training (All)

Figure 1 shows the relationship between these tasks. Within each, individual projects will be establish to pursue specific aims, as described in more detail below. Each of these projects will typically involve multiple faculty working together to solve a problem of relevance to the biological applications that are driving the activities of the center and the overall mission of the center.

Decision Making Process To manage the activities within the center, individual projects will be reviewed on an annual basis and funding decisions will be made based on the fit to the goals of Center and the degree of interaction with the key themes in the center.

Annual review: an annual workshop will be hosted by the center, in which all projects within the center will present their research results to the other members of the center, the advisory board, and the external scientific community.

Project continuation: based on the advise of the advisory board, the steering committee will evaluate whether individual projects should be continued under center funding. All projects will initially be funded for two years and annual requests for continuation beyond the currnet funding period will be solicited from the researchers working on each project. If the steering committee renews a project, an additional year of funding will be approved (providing two years of funding beyond the date of the renewal).

Project discontinuation: If the steering committee feels the project should *not* be continued under center funding, funding at the original level will be provided for the immediate year following the review, with half funding in the second year beyond the review. This allows for the possibility that a project could be renewed at full funding if new results or a new approach are presented in the following year. This all provides a graceful rolloff from center funding, to allow faculty to find other funding for graduate students or postdocs funded through the center.

While individual projects will be rotated in and out of the center over its lifetime, the overall thrusts will last for the duration of the center.

3 Center Development and Outreach Plans

The CBSA will support a number of development and outreach programs. The development programs will be designed to build, strengthen, and focus Caltech's efforts in molecular systems biology by interfacing the CBSA with existing institutes, centers, and programs on campus. The outreach programs will be developed to build knowledge, awareness, and interest in systems biology within K-12 students and the public. As possible the resources of the CBSA will be leveraged with other resources available to Caltech to maximize effectiveness and impact of the proposed programs.

3.1 Central Outreach Activities

CBSA website A CBSA website will be set up to support open dissemination of results, technologies, educational resources, and activities that are developed through the Center to a wider scientific audience and the general public. This website will be run through the Caltech server, have a dedicated systems administrator, and will be accessible to the general public and researchers across the world. It will also serve to organize the larger community structure and effort at Caltech in this area by linking to synergistic Centers and Institutes on campus (see Synergistic Activities).

RMM: We either need to budget for the sysadmin or host this on existing server that is covered by someone else

One role of the CBSA website will be to encourage the dissemination and sharing of technologies and research resources that come out of Center activities. Specific technology and design resources will be made available to the larger scientific community through this website. As one example, a sensor design tool will be made available through the website to assist researchers in designing molecular sensors for new molecules and biological systems.

Say more about what this means? (CDS)

Another role of the CBSA website will be to support open dissemination of education resources that are developed through the Center. Unique education resources will be developed through the CBSA and will be made accessible to other institutions and colleges through this website. For instance, the portable research-based learning modules developed by Center members as part of the CBSA's educational activities (see below) will be available through the website. In addition, links to course websites for all courses supported through the CBSA (see below) will also be available through this website.

RMM: Add something here about computational tools (MATLAB toolboxes); talk about SBML as a model.

The CBSA website will also include information regarding general educational and training activities supported through the Center. For instance, information regarding the training programs supported through the CBSA

(see Training Programs), such as the postdoctoral fellows program and the undergraduate training program, will be available on the website. Training program pages will include information on the program, application procedures, and activities of current and past trainees. Information regarding the educational programs supported through the CBSA (see below), such as the workshops and summer schools offered to researchers in this area, will also be available on this website. Educational program pages will include information on the program, application procedures, and resources and information from past events. Finally, information regarding the outreach programs and activities to both K-12 students and the general public will be available on the CBSA website. This will include general information and advertising for field trips, symposiums, lectures, and workshops geared towards younger students and the public supported through the CBSA and through the larger Caltech community.

Finally, the CBSA website will serve to highlight exciting research and educational activities of its Center members and the Center as a whole. On the Center home page there will be a section highlighting recent exciting work in these areas (both research and education) by team members, which will be updated monthly. In addition, recent speakers in the seminar series will be highlighted on the Center home page, including links to the dedicated seminar page which will contain general information about the seminar series, links to past speakers, and web streams of past seminars supported through this program.

Systems biology K-12 outreach programs Effective outreach programs that target younger students (high school and middle school), particularly those in underrepresented populations such as women and minorities, are critical to developing and cultivating deep interests in science, math, and technology. The CBSA will leverage its resources to develop and disseminate effective, high impact outreach programs by teaming with the Caltech Classroom Connection (CCC), a new outreach program at Caltech (of which Smolke is a Director). The CCC creates partnerships between Caltech student and researcher volunteers and participating K-12 science and math teachers in public schools within the Los Angeles area. This public school system is underfunded and serves a higher percentage of students from lower income families and minority backgrounds. Therefore, outreach programs targeting this school district have the potential to make significant impact on the interests of a significant number of students in science, math, and engineering as they enter college. The Caltech volunteers team with their teacher

partners to bring exciting, cutting-edge science and technology-based learning strategies into the classroom to cultivate the interests of students in these areas. Each partnership is provided a stipend, which they can use to develop effective and innovative science and math educational modules in a manner appropriate for the particular class. The CBSA will partner with the CCC to assist in developing innovative systems biology educational modules, which can then be used by student-teacher partnerships as appropriate for a given class. As an example, the distilled research-based learning modules will be ideal portable demos and instructional tools for participating classes in physics, chemistry, mathematics, and biology. In addition, Center members will work with the CCC to organize an annual systems biology field trip day, where approximately 75 high school students will be brought onto Caltechs campus for a series of lab tours/demos in systems biology and listen to presentations by Center members and other expert faculty with the aim of providing students with a foundational understanding of systems biology and the impacts, in terms of capabilities, risks, and ethics, that this interdisciplinary field will have on our society.

Workshops Annual workshops on systems biology tools will be held through the CBSA and will be open to graduate students and postdoctoral researchers. For instance, a two-day workshop on Computational Tools for the Systems Biologist will be held at Caltech every two years. This workshop will provide attendees with an introduction to the use of new computational tools and strategies in systems biology, with a particular emphasis on tools being developed through this Center. Topics covered in this workshop would include . As another example, a two-day workshop on Design Principles in Biological Systems will be held at Caltech every two years. This workshop will provide attendees with an introduction, overview, and discussion of the regulatory architectures guiding dynamic systems behaviors. Topics covered in this workshop would include: . Workshops will be open to approximately 30 to 60 researchers from across the country.

Summer school A Molecular Systems Biology summer school open to advanced undergraduate students and more advanced researchers will be run out of Caltech every two years. The summer school will run for a four-week period, during which one week will be spent in an intensive research-based boot camp training program. Instructors for this summer school will be Center members, with guest lectures provided by leading researchers from across the country in the areas of systems biology. Material covered in this

summer school will include . A boot camp training program will provide attendees with an intensive hands-on research experience in systems biology and will take place during the second week of the school. The experimental training program will be organized to provide attendees with a more open-ended research-based framework and topics will include: . Thes topics will interplay with the research-based learning modules described above and be modfications of the larger modules. During the summer school attendees will also gain experience in the application of computational tools to systems biology problems. In week three of the summer school, attendees will be given several research-based computational systems biology problems, based on the systems that they examined during the week two boot camp training program. Attendees will be asked to apply different computational tools to analyze the given research problems. Each summer school session will be open to approximately 30 students and researchers from across the country.

RMM, JCD: Fill out. Provide hands on training in computational tools.

30 may be too many for boot camp (RMM)

Web-based seminar series Approximately ten seminar speakers will be co-sponsored annually through the CBSA and the Center for Biological Circuit Design (CBCD) (see Synergestic Activities) at Caltech. These seminars will be videotaped and made available through web-cast on the CBSA website so that they may be viewed remotely by researchers and students across the world. Speakers will be selected by Center members and will be leading researchers in the area of systems biology.

Research-based learning modules in systems biology Center members will develop portable research-based learning modules that will be targeted to advance undergraduate laboratories. Initial research-based modules will be developed in several core research areas supported by the CBSA: . These modules will be developed by Center members as portable, self-contained, research-based laboratory projects that span approximately 2-4 weeks of an advanced undergraduate laboratory course. These projects will emphasize the creative and open-ended nature of research.

As one example, an educational research module in Control systems in metabolism will be developed and made available through the CBSA website. This module will examine the effects of different biological control systems on metabolic flux, or metabolite levels, through a simple, synthetic metabolic pathway in a host microorganism, such as yeast. A synthetic pathway will be used for this module to create a model system, isolated from the endogenous control systems and metabolic pathways of the cell host,

thereby enabling a cleaner implementation of the control systems and analysis of the resulting effects on information flow through this pathway. The module will examine the effects of biological control loops acting through different regulatory mechanisms, such as transcriptional, post-transcriptional, and post-translational mechanisms, both through theory and experiment. The effects on the dynamical and steady-state behavior of pathway metabolite levels in response to perturbations to the system as compared to the open loop systems will be characterized. System analysis will be performed using standard techniques such as LC-MS and the newer technologies made available through the CBSA, such as the molecular sensor platforms, paired with population imaging tools such as flow cytometry to monitor fluctuations in metabolite levels. Models of the system will be built and analyzed in Matlab.

To effectively disseminate these learning modules to other institutions, all material necessary to run the module, including syllabus, laboratory methods and infrastructure, and source code, will be made available through the CBSA website. In addition, distilled versions of each module, appropriate for high school students will be developed and made available through the CBSA website as shorter demos that can be imported into high schools (see above). During the initial five year funding of the CBSA it is anticipated that other modules will be developed in appropriate areas associated with products from research efforts supported by the Center. It is anticipated that these dedicated modules will provide additional flexibility for teachers at various educational levels to incorporate cutting-edge systems biology educational tools into existing laboratory courses or they can be combined to develop new interdisciplinary undergraduate research-based laboratories in systems biology. These research-based learning modules will highlight the exciting science, mathematical, and engineering challenges emerging in the field of systems biology with the intent to excite the interest of the next generation of scientists and engineers.

CBSA team research meetings The CBSA will organize and support two different research meetings for Caltech graduate students and postdoctoral researchers and fellows conducting research in systems biology. A Systems Biology Supergroup meeting will be held once a month. Researchers working within Center members laboratories in related project areas will be expected to attend. The format of the Supergroup meetings will be to have two researchers from different laboratories give approximately 40 minute presentations covering their research project and findings to the

larger group, comprised of faculty, postdoctoral fellows and researchers, graduate students, and undergraduate students associated with the Center. The Systems Biology Supergroup research meeting is expected to provide an environment in which researchers can present their work to a larger, more broad audience in systems biology and receive feedback and constructive questioning regarding methodology, data, and conclusions. In addition, this meeting format will provide these researchers with an environment in which they can discuss openly work-in-progress or data in unpublishable forms. These research meetings will be targeted mainly to the laboratories of Center members; however, Caltech laboratories not part of the CBSA or individual researchers may also participate in these meetings.

A monthly Systems Biology journal club will also be organized through the CBSA for graduate students and postdoctoral researchers in this area. Every month a different Center member will select a recent, topical, cutting-edge article in the systems biology field for the group to critically read and discuss. It is expected that this meeting will train researchers in scientific critical thinking and analysis skills. As such, at least two faculty Center members will be present at each journal club to lead, promote, and direct discussion among the group. It is also expected that this journal club format will encourage discussion and exchange of ideas between Center members.

New advanced courses in systems biology

3.2 Synergistic Activities

The CBSA will interface with a number of existing Institutes and Centers on campus for the purpose of building synergistic activities within molecular systems biology at Caltech.

Institute for Collaborative Biotechnology (ICB) **RMM:** Write up RMM
1 pargraph summary

Beckman Institute Biological Networks Modeling Center (BNMC)
Mike Hucka: One paragraph summary Mike Hucka

Center for Advanced Computing Research (CACR) The Center for Advanced Computing Research (CACR) exists to ensure that Caltech is at the forefront of computational science and engineering (CSE). CACR's

strategy is to bridge the semantic gap between scientific domains and the computational substrate to make e-Science easier and more effective. CACR provides an environment that cultivates multidisciplinary collaborations. Our researchers take an applications-driven approach to CSE, and currently work with Caltech groups in aeronautics, applied mathematics, astronomy, biology, computer science, engineering, geophysics, gravitational physics, high-energy physics, and neutron science, as well as NASA's Jet Propulsion Laboratory.

Center for Integrative Study of Cell Regulation The Gordon and Betty Moore Foundation has awarded $5.6M to Caltech for the creation of the Center for Integrative Study of Cell Regulation. This center is a joint effort between Caltech's Biology Division and CACR. The goal is to develop new computational methods for understanding how the many genes and proteins that make up individual cells work together to carry out specialized functions of different cell types, including neurons, plant cells, and bacteria. The Center will provide computational and programming expertise to cell biological projects carried out by faculty and students at Caltech. It will also provide equipment and help with methods to measure parameters for quantitative analyses and simulations.

Mark Stalzer: Can you get me a summary here? Mark Stalzer

Information Science and Technology (IST) Center for Biological Circuit Design (CBCD) **RMM:** Write up 1 paragraph summary RMM

4 Research Projects and Preliminary Studies

This section is currently being written in sections. Here is a rough sketch of the contents:

- Foundational Technologies (Owner: Smolke)
  - Modular sensors (Smolke)
  - Spatial imaging (Jensen)
  - Single cell imaging (Elowitz)
- Driving Biology Problems
  - Core Processes in Micro-Organisms (Owner: Smolke)
  - Communication modes and probabilistic decision processes in multi-cellular systems (Owner: Smolke)
  - Signaling networks regulating multi-cellular systems response (Owner: Doyle, w/ Baltimore, Covert)
- Theory and Computational Tools (Owner: Doyle with Murray, Phillips)

5 Core Facilities

All: We need to figure out what to put in this section. The center itself does not have any core facilities, but there are many Caltech facilities that we will use. Let Christina and Richard know if you have any thoughts. All

6 Training and Educational Plans

The CBSA will support a number of training and educational programs that target researchers at various levels in their training careers. These programs will be designed to bring talented young researchers in the area of systems biology to Caltech to provide them with opportunities to interact with Center members and cultivate their development as independent, talented, creative, cutting-edge researchers in systems biology. The Postdoctoral Fellows Program will also be used to bring new expertise and research ideas into the CBSA through the talented fellows participating in this program. The educational programs will be developed to provide innovative teaching tools, strategies, and curriculum to train the next generation of scientists and engineers able to drive forward and define the field of systems biology. As possible, the resources of the CBSA will be leveraged with other resources available to Caltech to maximize effectiveness and impact of the proposed training and educational programs.

6.1 Postdoctoral Fellows Program in Systems Biology

The CBSA will support a postdoctoral fellows program in systems biology. Applicants will apply for fellows positions within the CBSA. These positions will support creative, talented postdoctoral researchers that will work independently through the CBSA with two or more Center members. Fellow positions will be awarded annually for two-year periods and applicants will be required to submit a curriculum vitae, a five page independent research proposal that addresses how the proposed research ties in with and extends current Center interests, and letters from two Center members supporting the applicant. It is anticipated that 1-2 fellow positions will be awarded each year and that at any given time the CBSA will support 3-4 fellows. Fellows will sit within one or more Center member's laboratories, although the Principal Investigators of the laboratories are expected to act as faculty sponsors rather than traditional faculty mentors. The positions will support the fellow's salary and benefits, as well as award each fellow a $25,000 direct costs research supply fund.

The systems biology fellows will be required to participate in a number of activities associated with the CBSA, in addition to their proposed research program. For example, fellows will teach at least one lecture in the summer school program and will develop a discussion section for the workshop. In addition, by the end of their two-year appointment fellows will be expected to develop a new research-based learning module associated with

RMM: We should increase this to the level used for projects.

What sort of activities should we include here? Suggestions? (CDS)

their research.

6.2 Graduate Training in Systems Biology

The CBSA will support graduate training through developing an effective educational program in systems biology for Caltech graduate students. In order to recruit and attract intelligent, talented, and motivated graduate students interested in pursuing training in systems biology, Caltech needs to develop and organize focused and effective training and educational programs in this area. The CBSA will work with other appropriate Centers and Institutes (see above) and with the Bioengineering Graduate Option at Caltech to develop a track program within this graduate option in Molecular Systems and Synthetic Biology. The track program will consist of core curriculum requirements for bioengineering graduate students who select to minor in this track area. Center members will develop and instruct (see above) many of the core classes in this track. In addition, students participating in this track will be expected to attend the monthly CBSA-sponsored Supergroup meetings (see above), in which researchers from Center members' laboratories present their research to the larger group, and the monthly CBSA-sponsored journal clubs (see above), in which recent papers in the field are critically reviewed and discussed. It is anticipated that once this track program is in place, the CBSA will organize efforts to acquire dedicated funding for graduate students participating in this program by applying for separate graduate student training grants in this area.

Name any other suggestions? (CDS)

Don't know how useful this one might be?? (CDS)

6.3 Undergraduate Research-Based Educational Opportunities

Caltech provides opportunities for undergraduates to conduct mentored research in Institute laboratories through the existing SURF (summer undergraduate research fellowship) program. In addition, Caltech offers research opportunities targeted for underrepresented student populations through the existing MURF (minority undergraduate research fellowship) program. The CBSA will team with the SURF/MURF programs to offer a team-based summer research opportunity for six SURF/MURF students to conduct research in Center members' laboratories over the summer. The summer research program will be advertised on the CBSA website and the SURF/MURF fellowship program website. Interested students will be required to submit a pre-proposal to the CBSA six weeks before the standard SURF deadline, including a curriculum vitae and statement of research in-

terests. Six students will be selected from this applicant pool to participate in the systems biology summer research program. These students will then apply for a summer fellowship through the standard SURF/MURF application process, which will require them to work with Center members to develop a ten-week summer research proposal. On the application the students will indicate their interest in this particular research opportunity. Efforts will be made to include students from outside institutions and from underrepresented groups. The CBSA will leverage resources for supporting this program with resources available through the SURF/MURF program.

The purpose of this program is to provide a research-based educational opportunity for talented undergraduate students in systems biology. Participating students will be presented with a larger team-based challenge in systems biology and will be placed primarily within one of the Center-associated laboratories to conduct focused research on an element of the larger project. Through this program students will gain experience in conducting systems biology-related research and will be introduced to interdisciplinary research and team-based efforts. In addition to performing independent research, students will receive training in technical writing and will be required to present their research findings in a number of different environments including Caltech-wide undergraduate research symposia and weekly undergraduate group meetings held through the CBSA. Furthermore, these students will attend the monthly CBSA-sponsored Supergroup meetings (see above). A bi-monthly CBSA-sponsored summer undergraduate researcher journal club, similar to the year-long journal club described previously, will be run over the summer for those undergraduate students participating in this program. At least two senior Center members, either faculty or postdoctoral fellows, will be present at each journal club to assist in leading article discussions. A separate journal club will be run for the undergraduate researchers to provide a smaller, more comfortable environment in which they can have a greater level of participation in the discussion and critical review of recent, cutting-edge research in systems biology.

RMM: We should say something about HHMI. CDS says "I don't know if we can say anything about this since it is really synthetic biology but maybe we can leverage it. Let me know what you think... Maybe we can dicuss how best to leverage it."

Budget

This funding opportunity uses the just-in-time budget concepts. It also uses the non-modular budget format described in the PHS 398 application instructions (see `http://grants.nih.gov/grants/funding/phs398/phs398.html` *). A detailed categorical budget for the "Initial Budget Period" and the "Entire Proposed Period of Support" is to be submitted with the application.*

An applicant may request a project period of up to five years and a budget for direct costs up to $2 million per year. Funds for initial large equipment may be requested in excess of the $2 million limit if prior approval is obtained from staff responsible for Scientific/Research issues, listed in Section VII.1. The fifth year support of new awardees is conditional on a successful administrative site visit in the third year. The earliest anticipated start date is July 1, 2007.

We plan to break the budget down into 7 primary "tasks". Each of the tasks will correspond to the technical activities listed in the body of the proposal, but we are not pulling out specific amounts for specific groups at this point. Within each task there are some number of projects (the things we are all writing up). Roughly, if there N projects in a task, anticipate $1/N$ funding for that project based on the support levels. listed below:

- DBP #1 (core processes): 2 students, 2 postdocs
- DBP #2 (multi-cellular): 2 students, 1 postdoc
- DBP #3 (NFkB, sepsis, MODS): 1 students, 1 postdoc at Caltech + $130K to Emory and Northwestern (tie to clinical)
- Experimental platforms: 3 students, 3 postdocs
- Theory and computation: 4 students
- Training: 4 "center" postdocs (ala BI fellows)
- Administration: 50% assistant, small supplies, etc

For supplies, we put in $25K per researcher (student or postdoc) on experimental projects and $5K per researcher on computational/theory projects. We also included $2K/researcher for travel and office supplies. Finally, we put down $10K per faculty member in salary support, an additional $8K for faculty on the steering committee and some additional support on top of that for Christina (who has to commit 30% time to the project).