The Virtual Body Workshop: Current and Future Application of Human Biology Models in Environmental Health Research

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Biological modeling across the continuum from molecular to whole organisms has played and will continue to play an important role in understanding the effects of exposure to environmental agents on biological systems. A major element of many future research programs will be the development of a new generation of advanced biological models that closely couple high-performance computing with experimental research in an infrastructure that supports interactive, collaborative investigation. Environmental health researchers have often turned to computer models to help understand and predict how exposure to environmental agents affects human health. The need for modeling has grown as the problems we face in environmental health have become progressively more complex. Reliable, predictive biological models are required to handle this complexity, particularly as researchers struggle with limited resources and continued trends to reduce animal experimentation.

The National Institute of Environmental Health Sciences (NIEHS), in collaboration with universities and the Department of Energy national laboratories, is now pursuing these next-generation predictive models to meet the challenges of today's explosive rate of scientific knowledge acquisition. In June 2000, the first of two workshops jointly sponsored by NIEHS and the Pacific Northwest National Laboratory (PNNL) and organized by James Selkirk (NIEHS) and Ronald A. Walters (PNNL) was held at the NIEHS research campus. The organizers brought together a diverse group of scientists to help identify current needs and a future vision for the next generation of biologically based models.

As a first step, the symposium participants were asked to explore collectively what is technically feasible in developing the next generation of biological models and to identify the key research and infrastructure needs to advance the field. The overall objective of the workshop was to help identify potential approaches for developing more fully integrated anatomically and physiologically based models (for both animal and human systems) that could be incorporated into a framework that includes molecular, cellular, and whole-organ systems within a user-friendly simulation platform. It is envisioned that these advanced models will form the structural underpinnings of a more fully integrated biological model or "virtual body."

Workshop Overview

The symposium was organized around three major topic areas: environmental health effects of concern, current state-of-the-art modeling capabilities in environmental health, and new approaches and technologies in biological modeling. The format for the workshop incorporated both scientific presentations by leading experts in their fields and small, facilitated breakout group discussions. Participants brought many perspectives to these discussions, with participants having expertise in computational biology and modeling, biological imaging, and bioinformatics, as well as traditional areas of pharmacology, physiology, biochemistry, and molecular and structural biology. Group discussions focused on the value as well as the limitations of the current approaches, alternative directions and needs for future research, and an initial evaluation of how such advanced models would contribute positively to environmental health research. A list of the all the participating speakers, their presentation titles, and professional affiliations is presented in Table 1.

The first session brought together a diverse group of researchers within government (National Institutes of Health, U.S. Environmental Protection Agency), academia, and industry who highlighted the broad range of environmental health issues that would greatly benefit from predictive models that more fully address the complexity of biological responses in an integrated way. It was clear from the group dialogue following the presentations that virtually all health-related concerns, including carcinogenicity and reproductive, developmental, or neurological health effects, as well as specific organ responses to environmental insults, can take full advantage of advanced modeling approaches. For example, Barbara Davis (NIEHS) discussed how the impact of chemical contaminants on reproductive health is being advanced by having more predictive models of the hypothalamic-pituitary-ovarian axis. These models provide a more integrated understanding of how environmental stresses including chemical contaminants may or may not affect the reproductive endocrine system. It was clear that a broad range of environmental health researchers could more fully use advanced modeling approaches as an important tool to incorporate experimentally observed responses into integrated predictive modeling strategies.

The session on current state-of-the-art modeling capabilities in environmental health illustrated several modeling strategies that are being used today by environmental health researchers. Chris Portier and Michael Kohn (NIEHS) provided an overview of ongoing efforts to incorporate biologically based modeling into the overall NIEHS research strategy to predict cancer and noncancer responses. Mel Anderson (Colorado State University) illustrated important examples of how physiologically based pharmacokinetic and pharmacodynamic models are being used to link target tissue dosimetry with biological response. Likewise, Julie Kimbell (Chemical Industry Institute of Toxicology) provided an important illustration of how computational fluid dynamic modeling is being used to address upper respiratory–tract uptake of reactive vapors. All these modeling efforts focus on gaining a better understanding of dose–response relationships, cellular and biochemical dynamic responses, and functional alterations leading to adverse health effects such as cancer or developmental toxicity. In general, these modeling approaches were seen to have broad utility as research tools for integrating dosimetric and biological response data. They are also widely used by regulators who are charged with determining human health risk and setting appropriate exposure standards. It is clear that these current state-of-the-art models form a firm foundation for any future development of advanced biological models.

The final session on new approaches and technologies for biological modeling provided an enticing glimpse into the future possibilities. For example, The Physiome Project, led by James Bassingthwaighte of the University of Washington in Seattle, is a public–private consortium project to establish a modeling

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The workshop was held 22–23 June 2000 at the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Received 27 October 2000; accepted 20 November 2000.

infrastructure for developing and applying advanced computational and simulation tools to integrate biological models from the molecular level to the whole organism. These researchers have established a long-term goal to understand and describe the human organism, its physiology, and its pathophysiology by providing a functional description of all human biological systems in healthy as well as disease states. Charles Timchalk presented an overview of a complementary effort, ongoing within the Virtual Biology Center, at PNNL, to develop an advanced three-dimensional dynamic model of the human and rodent respiratory tracts to quantitate the complete fate of inhaled particulate matter pollutants and the associated pathophysiological response within the respiratory tract. This "virtual lung" incorporates realistic lung geometry, bidirectional airflow, and tissue visco-elastic properties. It is envisioned that once the biological and mathematical underpinnings of the model have been established, the virtual lung will provide a unique tool for assessing the effect of airborne pollutants on potentially sensitive human populations such as asthmatics or individuals with chronic obstructive pulmonary disease. The discussion groups within this session explored the possibilities that these advanced models could be developed in ways that bridge both animal and human systems to develop an integrated biological model.

The virtual body is a grand concept and is a framework for integrating and understanding the complexity of human life. The virtual body should have broad applications across scientific disciplines, from basic researchers trying to unravel the effects of chemicals and drugs on biological systems at the molecular level to physicians using the virtual body to facilitate disease diagnosis and cure. Such a model could be used to recognize and identify complex interaction patterns that would not be intuitively obvious, and guide research and experimentation beyond traditional linear approaches. As a formal statement of human biological knowledge, the virtual body would be used to predict health impacts and assist in the prevention of adverse disease, thereby protecting and enriching human health.

The group also reinforced the point that for these advanced models to be of value, they must be readily accessible by a broad segment of the scientific research community, including both modelers and experimentalists who are interested in applying modeling approaches to test their hypotheses. Richard Ward highlighted efforts underway by a group led by Clay Easterly of the Oak Ridge National Laboratory to develop an integrated architecture for linking various models and databases as an important example of what is needed by researchers. The project, called the "virtual human," aims to develop an integrated simulation resource that incorporates a large number of biophysical models and links to required databases and advanced computational algorithms, and is coupled to three-dimensional geometrical models of the human anatomy. The modeling platform would be designed to provide a user-friendly interface that is readily accessible to all interested researchers through the World Wide Web.

Results

The consensus of the workshop participants was that biological modeling, from the molecular to whole-organism level, will continue to play a major role in environmental health research. The advances being made in modeling, with innovative programs such as those described at this workshop, must be integrally linked with experimental research. Concepts such as the Physiome Project and the virtual lung/body/human are extremely important for enabling researchers and regulators to address the complex effects of environmental agents on biological systems. Existing models and concepts provide a strong foundation for the work that needs to be done to achieve a long-term goal of developing predictive models that accurately reflect biological response. Workshop participants felt that this is an important goal and, as part of their small-group discussions, began to formulate a road map and a set of priorities for how these efforts should move forward. Four major areas were identified as important: the need to acquire and develop modeling databases; the development and integration of modeling software into common platforms; the development/acquisition of virtual organ and system models; and the establishment of an infrastructure for developing a virtual body architecture. This framework was used to facilitate discussion of both short-term (1–3 year) and long-term (5–8 year) project goals.

Databases. A fundamental feature of a virtual body program is ease of use by the scientific community. There is a need to consolidate the vast amount of experimental data needed for model parameterization and validation into a format that is publicly accessible and easy to retrieve and use by those interested in building and running these models. We anticipate that these types of data will come from both peer-reviewed and non-peer–reviewed sources; therefore a process for accessing the quality and applicability of the data for specific modeling purposes must be in place.

Table 1. Program for Human Biology Models for Environmental Health Effects.

Speaker	Title	Affiliation
I. Environmental Health Effects of Concern		
C. Barrett	Carcinogenic health effects	National Cancer Institute
B. Davis	Realities of reproduction for the virtual human	NIEHS
J. Rogers	Development of a biologically based dose–response model for the model teratogen 5-fluorouracil	NHEERL- U.S. Environmental Protection Agency
J.Mattsson	Neurological health effects and the dilemma of randomization and double-blinding	Dow AgroSciences
J. Brain	Modeling respiratory health effects: linking exposure with lung dose	Harvard School of Public Health
II. Modeling Examples in Environmental Health		
C. Portier	Stochastic modeling in carcinogenesis and developmental toxicology	NIEHS
J. S. Kimbell	Respiratory tract fluid dynamic modeling	Chemical Industry Institute of Toxicology
M. Anderson	Environmental exposure to biological dose: the environment–organism interface, pharmacokinetics, and biochemical interactions	Colorado State University
M. Kohn	Effect of increasing biological realism on predictions of dose–response models implications for TCDD risk assessment	NIEHS
W. Suk	NIEHS extramural research overview	NIEHS
III. New Approaches to Biological Modeling		
J. Bassingthwaighte	Strategies for large–scale modeling in the physiome project	University of Washington
R. Ward	Virtual human concepts for integrated modeling of the human body	Oak Ridge National Laboratory
C. Timchalk	Development of a 3-dimensional virtual respiratory tract for studying the health effects of airborne particulate matter	Pacific Northwest National Laboratory

Modeling environment. Linking of databases, model parameters, and models will require reliable and readily accessible platforms that can be accessed by multiple end users and model developers. A broad range of modeling software is currently being used to develop and run model codes. We must develop a software platform architecture that will facilitate model integration and cross-model communication. Likewise, a user-friendly interface must be an essential element of the modeling environment because software and models are useful only when both modelers and nonmodelers alike feel comfortable using them.

Virtual organ and system model development. The current state of the art in biologically based modeling will form the underpinnings for development of more fully integrated virtual organ and system models that are the building blocks to a virtual body. As a first step we must inventory and collect relevant models and critically evaluate these models to understand their utility and limitations and the extent to which they have been validated against experimental data. To develop the virtual organ and system models, we must link models hierarchically so that it is feasible to integrate across scales from molecules to cells to organs and systems as well as across species. Finally, we must initiate efforts to address current modeling gaps and to develop new modeling strategies that have as a primary goal the support of a more fully integrated systems approach.

The virtual body program. To achieve the grand vision of developing a virtual-body, we must develop an administrative infrastructure to champion and clearly articulate the goals and objectives of the program. It was envisioned that eventually the virtual body program would result in the development of National Institutes of Health centers of excellence and the establishment of educational programs to provide the needed training and technical expertise to build and operate this next generation of biological models.

Future Direction

The scope and breadth of such a program, representing national and even international research interests, will require a strong champion with the interest and ability to develop a large, complex program. The development of a virtual body program, for instance, will require significant guidance and cooperation. A multiagency, multi-institution team should be established to oversee the guidance and coordination of such a program. NIH/NIEHS and the Department of Energy are ideally suited for organizing such a program, given their experience leading other complex projects like the Human Genome Program and their ability to work across multiple agencies and institutions. Given the growing support and activities related to the development of integrated biological models, participants at this workshop believe that now is the time for an interagency plan to be developed.

Details of the research to be conducted in this program still need to be developed. A leadership team should be established to clearly define the mission, goals, approaches, and outcomes of the program. This team—which should include leaders from the primary ongoing efforts as well as agency leaders—should also identify the short- and long-term goals and outcomes expected to keep the virtual body program on target. They will also need to define and specifically communicate the size, scope, duration, and cost of the program and identify other key researchers both from the experimental and the modeling communities that will be needed to develop the plan and conduct the necessary research.

Conclusion

There is a great need for predictive models to address complex problems in environmental health. This workshop, by identifying and evaluating the current state of the art and various emerging concepts for models that can integrate the various scales and levels of biological systems, has crystallized the importance and timeliness of moving forward with these concepts. The virtual body, for instance, is a grand concept and neither a simple nor a short-term endeavor. However, the development of a framework that all researchers can use to target their contributions to this larger goal can give us incremental gains that will have important implications for human health. The engineering and physical sciences all have effectively developed and used computationally based models that simulate highly complex integrated systems. The biological sciences are advancing rapidly in this direction as well. A future vision of a predictive model that can simulate the effects of environmental agents, medicines, or by-products of energy production on biological systems is one that is achievable and will allow us all to understand better the intricacies of how the human body functions and, most important, how to prevent and mitigate human disease.