Ethics Involved in Simulation-Based Medical Planning

Anthony Tongen
Program in Applied Mathematics
University of Arizona

Mary Adam
Department of Pediatrics
University of Arizona College of Medicine

Abstract: Computational biology, including simulation and modeling, is a burgeoning field with a recent influx of mathematicians, computer scientists, and engineers. With this recruitment, significant advancement has been made in numerous biological areas. However, as is the case in almost any rapidly evolving field, innovation can move beyond ethical considerations. We discuss one specific example of a simulation-based model that impacts surgical decision making on human patients. We then discuss a recent code of ethics for simulationists and its inadequacy in addressing issues relating to human subjects research. Finally, we recommend a system of validations for computational simulations involved in research applied to human subjects.

Introduction

With the fairly recent influx of data in the areas of biology and genetics, there has been enormous growth in the field of computational biology and genomics. The National Institute of Health has promoted this growth by opening major avenues of funding to disciplines like mathematics, computer science, and engineering to augment the already well established field of computational biology. With the influx of researchers, much progress is being made as they collaborate to answer questions about human disease processes. However, in some cases ethical considerations become a background rather than a foreground issue.

First, we will discuss and define computational biology; this will lead to our focus on simulation-based medical planning. We will then discuss a fairly recent code of ethics for simulationists, which is intended to address general ethical questions for those involved in simulation. Finally, we will make suggestions of a verification procedure for those interested in computational simulations that apply to human subjects.

Computational Biology and Simulation

Computational biology is an emerging field of research for both biologists and non-biologists and includes areas such as anthropology, genomics, physiology, ecology, and evolutionary biology. Computational biology encompasses all areas of biology where computational modeling and simulation are used. In this arena of research, simulations are goal-driven experiments with models that vary in time;[1] and simulationists are professionals who are involved in these modeling activities.[2] Simulationists develop computational models and use these models to study and predict the behavior of physical systems. This focus on simulation and modeling has resulted in

an influx of mathematics and mathematicians into the biological sciences. A good illustration of the influx of mathematicians into the area of computational biology is the work of James Keener and James Sneyd. They wrote a book in 1998 titled Mathematical Physiology.[3] This work exemplifies the tremendous diversity in computational biology. We would like to specifically examine one application of computational biology that relates to research on clinical decision making in human subjects.

The application of computational biology to clinical decision making in human subjects is in need of a more reflective process. Simulationists may be familiar with modeling applications that involve human physiology; however, their experience with research that directly involves human subjects may be limited. Also, while many human physiological systems are understood as mechanistic processes, humans cannot be reduced to mechanistic processes alone. Simulationists often collaborate with experts in other fields, i.e. physicians, utilizing their mathematical and programming expertise to answer important clinical questions. In these situations, simulationists may rely on physicians to deal with the ethical considerations in the interdisciplinary research involving human subjects. However, as the research advances and the mathematical and programming aspects of the simulation move beyond most physicians' abilities to assess correct methodology, it becomes important for simulationists to consider ethical issues in human subject research. Physicians - who have as their primary concern the welfare of their patients – should not be expected to shoulder this responsibility alone.

The ability to further inform physicians' clinical decisions by way of simulations is potentially beneficial for physicians and patients. This collaboration of simulationists and physicians requires a level of trust and integrity that is similar to specialty referral in the clinical setting. However, it differs in that the domains of expertise of the clinician and the simulationist are completely independent. Physicians would rarely have the expertise needed to determine if the level of accuracy of the mathematical model or the computational method utilized for a simulation is sufficient. It is imperative that the simulationist and the physician understand the advantages as well as the limitations of simulations or patients' care may suffer. We will discuss a specific example of a simulation that assists surgical decision making regarding positioning of grafts in vascular disease.

Simulation-Based Medical Planning

The simulation of blood flow in arterial bypass grafts strives to identify the optimal placement of the bypass grafts in order to improve blood flow for patients with end stage vascular disease.[4] The techniques for this type of simulation-based medical procedure include constructing a geometric model of the blood flow obstruction from three-dimensional magnetic resonance imaging (MRI) and computed tomography (CT) data. The simulationist extracts preoperative patient specific physiologic data from cine phase contrast MRI data and builds a model of the patient's current blood flow. Then the simulationist develops models corresponding to differing bypass graft positions and estimates how the different positioning of the graphs impacts blood flow distal to the obstruction. The surgeon can utilize the models to choose the preferred location or positioning of the bypass graphs using simulation data calculated from the pre-operative MRI.

These types of three-dimensional models make many assumptions that influence the accuracy of the predictions. One assumption of the current simulation methodology that has received significant criticism is the assumption that blood vessels have rigid walls. This assumption is valid for high velocity flows, but it becomes a less suitable assumption at lower velocities. Researchers have responded to these criticisms by implementing a one-dimensional model where the blood vessels have elastic walls. Data from simulations using the one-dimensional elastic arterial wall assumptions found that the flow rates are similar to the three-dimensional rigid wall results. This is encouraging, but concern remains about what margin of error is acceptable given differing sets of assumptions.

A variety of potential sources of error highlight the importance of determining what margin of error is acceptable. Another source of potential error is the accuracy of the geometric model developed from MRI data. The procedure for obtaining detailed structural information from MRI data is still in its infancy and is being refined. Error related to geometric models developed from MRI data hopefully will continue to be minimized. That said, it is accurate to assume some small amount of initial error due to inaccuracies in the geometric models. The physician must be concerned with whether this error is significant enough to distort the potential improvement in blood flow for different placement of the bypass graft. Practically, the physician needs to be assured that a given bypass graft placement site will improve blood flow in the patient and not just in the simulation.

Many researchers and physicians believe that the benefits of simulation-based medical planning far outweigh the few concerns. The biggest potential advantage is the opportunity to assist doctors in the decision making process with pseudo-surgery that does not physically affect the patient at all. Simulations can be used as an experimental lab that may allow for innovative surgical advancement without any threat of harm to the patient. However, if physicians are to make clinical decisions based on simulations, it is of paramount importance that the simulations be carried out in a manner which maintains the highest standards of professional and ethical conduct.

Code of Professional Ethics for Simulationists

Simulationists have begun to recognize and write about the importance of ethical practice within their field. The Code of Professional Ethics for Simulationists is available in its entirety in *Proceedings of the 2002 Summer Computer Simulation Conference*.[5] The code addresses five areas: personal development and the profession; professional competence; trustworthiness; property rights and due credit; and compliance with the code.

The personal development section includes professional obligations such as acquiring and maintaining professional competence. The fair treatment and encouragement of newcomers is emphasized; in addition, it suggests supporting members in simulation and promotion of the credible use of modeling and simulation.

The professional competence section includes a discussion of proper methodologies and technologies, the use of critical professional review, the stipulation of proper and achievable goals for any project, and the proper documentation of simulations. Full disclosure of assumptions and known limitations is discussed as well as specification

about the conditions of applicability of models and results. The code cautions against acceptance of results without proper verification and unbiased interpretations of results.

The trustworthiness section includes a commitment to honesty about possible conflicts of interest and discusses the importance of honoring agreements and contracts. It identifies responsibilities and accountabilities and highlights how organizational settings should be conducive to ethical behavior. This section also calls for support of studies which will not harm humans and the environment.

The property rights and due credit section includes a call to fully acknowledge other's contributions and give proper credit for intellectual property, honoring property rights including patents and copyrights; and honoring privacy rights and confidentiality of data and knowledge.

The section on compliance with the code addresses the importance of adhering to the code and encouraging others to adhere to the code. It calls simulationists to treat violations of this code as inconsistent with being a simulationist and to seek advice from professional colleagues in ethical dilemmas. In addition, the authors advise any professional society which supports this code to be aware of updates.

The current formulation of the code represents an excellent move toward identifying professional and ethical scientific behavior for simulationists. However, it lacks any specific discussion of issues that arise when simulations are used in medical decision making for human subjects. This omission is understandable, since the domain of simulationists is only just beginning to include research that involves human subjects. It may also be the case that where there has been work with applications for human subjects it was assumed that physicians would be responsible for ethical research standards with human subjects.

We appreciate the call for input to this code, because it recognizes that in a rapidly evolving area, ethical reflection and input from many can enhance the applicability of such a code. Therefore, we will suggest additions to the code specifically in areas where simulations are a part of clinical decision making and we will discuss the possibility of verification systems for simulations that affect clinical decision making in human subjects.

Verification Procedure for Simulation-Based Medical Planning

We propose that a system of verifications is needed for simulations that seek to direct clinical decision making. The discussion on validation of predictive tools or simulations is not entirely new in medical ethics literature. The Handbook of Medical Informatics[6] has a chapter devoted to predictive tools for clinical decision support and a more recent book concerning ethics, computing and medicine has a chapter devoted to decision-support software.[7] In both of these examples, the discussions emphasize statistical data related to past medical decisions. However, statistical comparisons and simulation-based medical planning are significantly different approaches. We think that there needs to be a new system of validation for simulations.

These verifications should include, but not be limited to: (1) proper verification of the mathematical model, (2) proper understanding of the relationship between the model and actual human physiology, (3) proper verification of margins of error, and (4) proper verification of the risks and benefits of the new technology in sufficient numbers of human subjects to confirm usefulness and expose unanticipated outcomes.

Our four-fold suggestion for verification of new simulation technologies applied to human subjects is partially discussed in the current code of professional ethics for simulationists. Proper verification of the mathematical model and proper understanding of the relationship between the model and actual human physiology, (1) and (2) above, are the primary responsibility of the simulationist and they are addressed in the professional competence section of the code. There needs to be a comprehensive explanation by the simulationist of all of the basic assumptions and limitations of the model, as well as the end goals and prior applications of similar models. While these issues are addressed in the professional competence section of the code, they are not elucidated in regard to the importance in applications which involve human subjects.

The code does not discuss the margin of error of simulations or the verification of the risks and benefits of simulation technology in human subjects research. We would like to address these two issues in more detail.

Margin of Error

Despite the usefulness of simulations, an important concern is that these models are approximations based on inexact measurements. Therefore, it is extremely important to have a discussion about how much error is acceptable for simulations applied to human subjects. In the aforementioned simulation-based medical planning research, Ku et al[8] had blood flow predictions that were within 10.6% of the experimental data with an average absolute error of 5-6% for bypass-to-inlet and aorta-to-inlet blood flow ratios. Is this an acceptable error tolerance when computing future blood flow rates in humans? For these results, it is argued that when the computed pre-operative results are low, then a similar correlation is seen in post-operative results. This correlation highlights the importance of refining the accuracy of the geometric model, but does not completely answer the question of how much error tolerance is acceptable.

The potential of compounding error is another cause for concern. The error in the initial MRI data results in error in the simulation's preoperative and postoperative results. The MRI data is important, because the accuracy of the geometric model has a significant impact on the resulting computational flows.[9] When you add the error implicit in a mathematical model due to simplifications and assumptions, add the possible error from MRI and CT data, and add the margin of error of the surgeon during the procedure, there are numerous areas where the simulator can over or under approximate certain components. Therefore, a serious discussion about an acceptable margin of error is necessary when this technology is applied to human subjects.

In Vivo Validation and Clinical Trials

Simulation-based medical decision making should be subject to validation protocols which could include both in vitro and in vivo trials for each element of the simulation process. Mathematical models tend to be static and may not be able to adequately approximate dynamic physiological processes. By their nature, simulations can only estimate the real world setting. This fact represents an acknowledgment of both the assets and limitations of simulation methodology, one better understood by simulationists than practicing physicians. Since simulation-based medical planning is so new, physicians may be at risk for embracing these simulation options prior to sufficient examination. The necessary level of certainty can only be gained through extensive

clinical trials. Physicians are familiar with protocols used to validate new drugs and devices such as those utilized by the Food and Drug Administration (FDA). In order for a medical device to be authorized for use in humans in the United States, a system of tests must be completed and the safety and reliability of the device must be demonstrated. We propose the development of validation protocols including clinical trials for simulation-based medical decision making so that simulations can be evaluated as thoroughly as other treatments and therapies.

The first level of validation we recommend for simulation-based medical planning is to do post hoc testing.[10] For instance, the patients' MRI and CT data can be used, both preoperative and postoperative, to evaluate the numerical results of the blood flow calculations. Post hoc testing has the advantage of causing no additional harm to the patient, limited inconvenience, no additional surgical procedures, but some increased costs.

The second level of validation would be clinical trials where simulations are used to predict and affect medical decision making. Experimental protocols with sufficient numbers of patients are needed to confirm the usefulness of simulations and expose any unanticipated outcomes. At present, there are limited protocols for these types of clinical trials and few Institutional Review Boards have experience in assessing the ethical dimensions of this type of research.

Conclusions

We desire to open the discussion about the development of validation protocols where mathematical simulations are utilized in clinical decision making. We believe the best way to verify simulations are both in vitro and in vivo validation protocols as well as clinical trials.

We propose expanding the code of ethics for simulationists to include some of the issues raised by human subjects research. The proper verification of margins of error for the specific simulation is a very important discussion that needs to be held. We also suggest having additional items which specifically address research on human subjects. The additions should include a discussion of the value of post hoc testing as well as the importance of participating in clinical trials in which simulations are used in clinical decision making.

The goal of this paper has been to educate those in the medical community about innovative applications of computational biology which are on their way to a hospital near you. Now is the time for simulationists to address the need for a fully orbed ethical reflection on the implications of their exciting technology. The time is ripe for a discussion of the proper means of verification and validation of simulation-based medical devices.

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