Computer simulations can replace in-vivo experiments for implantable medical devices

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Introduction and overview: Clive Baldock, moderator

Since the time of Leonardo da Vinci in the sixteenth century, researchers have endeavoured to understand the structure of the human body and how it functioned. Early investigators used an in-vivo approach in undertaking experiments on both living and deceased subjects. Such early investigations led to the discovery of new knowledge resulting in innovations in medical and surgical practice. By the time of the nineteenth century, an in-vitro approach was also being adopted in which experiments were undertaken in test tubes and petri dishes as a precursor to innovations in pharmaceuticals. Subsequent innovations and developments in computing have led to the present day in which much research, known as in-silico, is undertaken computationally. This approach has the potential to transform our understanding of biological systems and the human body and its associated diseases. In this timely debate Drs Esra Sorguven and Selim Bozkurt discuss whether computer simulations can replace in-vivo experiments for implantable medical devices.¹

Arguing for the Proposition is Esra Sorguven PhD. Dr Sorguven was born in Istanbul, Turkey, and received her BSc in Chemical Engineering at Bogazici University. She earned her MSc and PhD in Germany from University of Erlangen-Nuremberg (FAU), and University of Karlsruhe (now KIT), respectively. After receiving her PhD in 2004, she returned to Istanbul and worked at the Department of Mechanical Engineering, Yeditepe University for 12 years. In 2016, she

moved to UK to join the University of Sussex as a Senior Lecturer based at the Thermo Fluid Mechanics Research Centre (TFMRC). Since 2004 Dr Sorguven has been teaching modules in thermo-fluid area both in undergraduate and graduate levels. Her research interests are numerical modelling, analysis and design of fluid mechanic and thermodynamic systems. Her work is interdisciplinary and encompasses mechanical and biological applications. Her work on design of turbomachinery and biomedical devices, and developing high-fidelity numerical methodologies for use-inspired research has attracted funding both from industry and research councils. She has led over a dozen academic and industrial projects, which resulted in numerous invited talks and refereed publications. She has also co-authored the book *Biothermodynamics: Principles and Applications*.

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Arguing against the Proposition is Selim Bozkurt PhD. Dr Bozkurt received his undergraduate degree in Mechanical Engineering from Eskisehir Osmangazi University in Turkey. He subsequently received his Master's degree in Mechanical Engineering from Yeditepe University where

¹ Contributors to Topical Debates are selected for their knowledge and expertise. Their position for or against a proposition may or may not reflect their personal opinions.

he also worked as a research assistant in a project aiming to design, analyse and prototype production of a miniature implantable rotary blood pump. He undertook his PhD research at the Department of Biomedical Engineering of the Eindhoven University of Technology in the Netherlands and did research on arterial pulsatility and aortic valve function to evaluate continuous-flow left ventricular assist device support. In his PhD study, he developed varying speed CF-LVAD support algorithms to increase arterial pulsatility and improve aortic valve function. He showed the beneficial effects of pulsatile CF-LVAD support over constant speed pump support on aortic valve behaviour and perfusion rates using in-silico, in-vitro and ex-vivo techniques. After receiving his PhD degree in 2014, Dr Bozkurt joined the Department of Mechanical Engineering at University College London where he worked as a research associate. There, he designed and optimised the metallic wireframe of a novel bi-leaflet transcatheter mitral valve. He has worked at the Institute of Cardiovascular Science of University College London, and Craniofacial Unit of Great Ormond Street Hospital for Children since 2017 and developed patient-specific computational models which simulate spring-assisted craniostylosis correction in paediatric patients.

Selim Bozkurt

For the proposition: Esra Sorguven

Opening Statement

Computer simulations are already an integral part of the design, analysis and implementation of medical devices. Yet, is it possible for simulations to replace in-vivo experiments? This might still sound like science fiction, since it means to have a virtual tool that faithfully mimics all aspects of the medical device and the living system: from biochemical reactions occurring at cellular levels to the biomechanics of individual organs. Despite the many difficulties this endeavour encompasses, I am, for the reasons I have put forward below,

convinced that simulations will replace in-vivo experiments for implantable medical devices.

Currently, we rely on in-vivo experiments for the final testing of implantable medical devices. However, in-vivo experiments come at a high cost: They are expensive, time-consuming and raise a series of ethical questions. Furthermore, if an in-vivo experiment gives a negative result, the exact origin of the failure remains usually unknown and only limited insight can be gained. This initiates a rather long and laborious phase of iterative improving-and-testing. The motivation to reduce the number of in-vivo experiments is so strong that governmental regulations and extended funding opportunities are now in place. A sizable decline in animal testing was achieved in the latter part of twentieth century, and focus shifted from in-vivo towards in-silico experiments [1]. Digital twinning of biological systems attracts attention both from academia [2] and industry [3]. So we have the motivation and opportunity; do we have the means?

Recently considerable advancements have been made in simulations of thermodynamic [4], biomechanic [5], and hemodynamic [6] states in living organisms. Mature simulation methods are now available to predict time-dependent changes in microscopic processes at the cellular level, as well as changes in macroscopic scales within one organ, their interactions with mechanical devices or the whole body. The next steps in research will be to couple these models to predict the three-way interactions between the cellular metabolism, organ functionality and physiological environment.

Undoubtedly, this involves challenges. Some are easier to overcome, such as the requirement of powerful computational resources with advanced parallel computing and massive data transfer capabilities. Some are more challenging, such as modelling the complicated and evasive interactions between the microscopic states that define cellular metabolism, bioprocesses within an organ coupled with the medical device, and the behaviour of the whole body. Fortunately, artificial intelligence and machine learning can prove to be extremely useful in developing sophisticated models to mimic not-well-understood real-life interactions. We see examples of these readily in aerospace engineering [7].

These recent advances in technology, alongside the strong motivation and opportunities in this research direction, make me confident that soon we will have mature computational models that replace in-vivo experiments for implantable medical devices.

Against the proposition: Selim Bozkurt

Opening Statement

Pre-clinical tests and clinical trials are essential steps in medical device development to collect information about

the feasibility of a new medical device [8]. In-vivo models allow collecting exploratory, explanatory and predictive information. For instance, large animal models are used to collect information about device safety, reliability, and biocompatibility in Left Ventricular Assist Device (LVAD) research, where simulations cannot provide adequate details [9]. Although computational models have been utilised to simulate physiological systems and evaluate the effects of new therapies, they have limitations such as being based on assumptions or only simulating described physiological mechanisms. However, physiological systems are highly complex, and specific complications may occur in patients after implantation of the medical devices such as LVADs [10]. Moreover, complications that develop in patients are diverse and depend on several factors. Generic models are capable of simulating generalised physiology and do not provide patient-specific information. Prediction of developing complications in the patients require numerical models which can simulate the interaction among the physiological systems, long term adaption mechanisms in the body, the connection between the different scales from the cellular level to organ level and the models must be patient-specific. Increasing complexity of numerical models to simulate the involving mechanisms in the developing complications may not always yield realistic results [11]. Moreover, assumptions made in a numerical model may also influence the simulations results. For instance, using Newtonian blood properties in a simulation may overstate the risk of thrombosis or blood clot in a blood pump [12]. Therefore, the reliability of the numerical models needs to be improved before simulating complex physiological systems and patient-specific problems. Here it should be noted that there are already ongoing efforts to Reduce, Refine and Replace (3R) in-vivo trials by developing in-silico tools, and funding programmes support such efforts. Roadmaps already exist to increase the use of in-silico models to achieve 3R and simulate patient-specific physiology [13]. Indeed, computational models will play a significant role in the pre-clinical assessment of implantable medical devices in the future. They will transform the research and medical device industry, reduce the need for in-vivo tests and be a complementary part of the product life cycle. However, computer models need to be verified, validated, and analysed for uncertainties [14]. There are still challenges in computer models such as scaling and merging to describe an entire organism or at least a significant part of it before we can use them to as pre-clinical test tools [15]. Therefore, pre-clinical in-vivo tests and clinical trials will continue to be part of the total product life cycle in implantable medical devices.

For the proposition: Esra Sorguven

Rebuttal statement

I am pleased to see that my esteemed friend and colleague Selim Bozkurt agrees with me in that “computational models will play a significant role in the pre-clinical assessment of implantable medical devices”. Our main disagreement is on the extent to which simulations will replace in-vivo experiments. His case is built upon two important issues: the necessity of verification, validation and uncertainty quantification and the challenges in modelling an entire organism with all its complexity.

On the first point, I simply agree with him. A thorough assessment of the credibility of any numerical model is a must; and indeed a strong headway is made to assess the risk-informed credibility, especially via the standards and guidelines formed by ASME [16] and FDA [17].

His second point, i.e. complexity, deserves a nuanced discussion on both the model itself and the goal of the experiment. Firstly, to deal with the complexity of the entire organism, multiscale simulations are necessary that describe the physiological processes with the fundamental equations of physics and biochemistry, as well as statistical models, employing a large collection of clinical and genomic data. Once credibility of each model is assessed, we achieve a reliable virtual tool. Already, there are examples of such virtual tools, such as the diabetes simulator [18] or virtual trials for implantable cardiac devices [19].

Secondly, the goal of the experiment is as important as the capabilities of the computational model. When the goal is to ensure that a new device does not manifest a known side effect or failure mode, then the computational model (trained with the existing clinical data containing adverse effects already observed in similar devices) is well within the limits of its validity range. Thus, in-silico experiments can successfully replace in-vivo experiments. However, when the goal is to determine any unexpected adverse effects of a novel medical device, then computational results will inevitably have a high uncertainty. Yet, even under these conditions, numerical results are valuable, because sufficiently complex non-linear models can make clinically-yet-unobserved predictions and help to reduce the number of in-vivo experiments and clinical trials.

To summarize, computer models have already begun replacing in-vivo experiments. This trend will continue to accelerate. We will witness the emergence of a new generation of virtual tools in biomedical applications.

Against the proposition: Selim Bozkurt

Rebuttal statement

Indeed, animal experiments are costly and raise ethical questions; therefore, there is a need for reduction. They may yield negative results as well. However, negative results are equally important in clinics, and they are published by the journals increasingly. The scientific community can benefit from negative results because they help to interpret positive results better and adjust research plans accordingly to reduce a laborious phase of iterative improving-and-testing. Moreover, funding agencies can distribute funds that goes to research more selectively after evaluating the published data with negative results [20].

Long term in-vivo tests are time-consuming; however, they can reveal long term effects of the implantable medical devices in the patients. Moreover, different guidelines such as ARRIVE (Animal Research: Reporting In-Vivo Experiments) have been published to improve the reliability of the in-vivo experiments [21].

Modelling and simulation of the physiological mechanisms still involve challenges. Time-dependant models simulating physiological mechanisms are used to have a global outlook of the dynamic events in physiological systems. However, there is no consensus on how these mechanisms interact. For instance, the cerebral blood flow rate is regulated by complex interactions of time-dependent mechanisms and interaction among these mechanisms remains controversial. Under CF-LVAD support during exercise, cerebral blood flow rate may remain insufficient and the pump operating speed may need to be increased [22]. A computational model describing the blood flow rate and regulatory mechanisms in the cerebral circulation must simulate dynamic events accurately with sufficient detail before it can be used as a pre-clinical tool. Identification of the interaction among these mechanisms may require performing experiments.

Artificial intelligence is a powerful technology and has a potential in medicine. However, issues need to be solved before it can be used with full capacity. In some cases, it might be challenging to identify the set of features describing the problem. The output of the data-driven artificial intelligence algorithms depends on the input data. Input biases may be amplified by the algorithm and lead to wrong conclusions [23]. Large datasets are required to train artificial intelligence algorithms and make them work efficiently.

There is a declining trend in animal testing, and computational models will play a significant role in reducing the in-vivo experiments. However, it is still a question whether the computational models will completely replace the in-vivo experiments.

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