The Use of Computational Modeling and Simulation to Create Virtual Patients: Application to Cardiac Pacing and Defibrillation Systems

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Computational models have long been used in engineering applications and are increasingly being used in medical device design. Physics-based equations describe simple structures and field problems such as the bending of a beam or the electrical field gradient across conducting material. For more complex problems, techniques such as finite element analysis (FEA) are used to discretize a structure of interest into smaller domains that are coupled together to solve the entire problem. Statistical Monte Carlo simulation methods can be used to solve similar problems many times with the addition of random variability. It is straightforward to imagine parallels between medical devices and engineering applications. For example, consider the flexing of a stent graft and the flexing of a reinforced gasoline hose. Another example is the similarity between a suspension link in an automobile and an artificial implanted joint. Continuing the automotive theme, compare the electronic cables on a steering wheel to an implanted pacemaker lead. Despite differences in physical environment between biomedical and industrial applications, the fundamental engineering principles behind performance and reliability are the same.

Although there are applications for computational modeling across all parts of the biomedical industry, there are often aspects of medical device design that make them ideal for the use of computational models. For example, devices typically act in a specific physical and local manner (e.g., structural support, electrical stimulation, measurement for diagnostic purposes). In contrast, drugs often act in a systemic fashion with complex pharmacological interactions [1]. The local action of a device enables a much simpler path for simulating the engineering mechanisms required for successful operation, as

compared to the systemic mechanism of action for drugs. For example, placement of a stent will not affect hair growth. Another distinguishing feature of medical devices is that they are often evolutionary in nature, with successive models differing only slightly from a predecessor. This enables the validation of engineering simulations on the predecessor device, providing confidence for predicting the performance of a new device.

When clinical outcomes can be directly simulated in a computational model, the result can be thought of as a virtual patient [2]. If sufficiently credible, virtual patient models can inform or even replace human clinical evaluation in some applications. The entire anatomy and physiology of a patient does not need to be included in the simulation, but rather only those aspects which are needed for the clinical outcome of interest. For example, a simulation that predicts the structural integrity of the femoral stem of a hip prosthesis would incorporate the kinetic activities of daily living and force transmission through the hip joint, and would not use a parameter such as blood pressure. A virtual patient model of closed-loop blood glucose control systems for diabetes would focus on metabolic parameters and would not need information about gait and posture. Establishing virtual patient model credibility is vital to the use of such models and needs to be performed with a high level of rigor, commensurate with human clinical studies. Evaluation of virtual patient model credibility requires input from both engineering and clinical professionals.

To properly represent the wide variation in clinical outcomes that would occur in an actual human study, the virtual patient model must include both patient-to-patient variability and the inherent device-to-device manufacturing variation. The inclusion of variability means that the simulation must be statistical as well as physics-based. For the example of a hip implant, patient variability would include activity level and patient weight, while manufacturing variability would represent the difference in size and strength across the

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population of implanted devices. An important attraction of virtual patient modeling is that cases that are rare or difficult to study in clinical practice can be evaluated, such as highly active patients with unusual anatomy, pediatric patients, or frail patients.

Two recent examples of virtual patient modeling have been applied to cardiac rhythm devices: magnetic resonance imaging (MRI) safety and lead fracture. In both cases, the virtual patient application was for an anatomically local and specific physical action. These two examples also highlight the important role that clinicians and regulatory agencies play in the emerging use of virtual patient modeling for medical device development.

In the first example, MRI safety evaluation includes evaluation of induced heating of a cardiac lead due to magnetic fields. Excessive temperature rise at the interface between the lead and tissue can cause damage to the tissue, which may result in reduced ability to pace the heart. The large number of combinations of patient anatomy, positioning in the MRI system, and lead implant path makes characterization of impact to performance very expensive, if not practically impossible in a clinical setting. Wilkoff et al. [3] performed computer simulations that involved two parts: (1) electrical field simulation to determine the power dissipated in the lead electrode and (2) pre-clinical studies in canines to determine the effect of power dissipation on the voltage required to pace the heart, pacing capture threshold. By incorporating variability in human anatomy, MRI coil, position in the MRI coil, and lead path, the authors simulated approximately 2.4 million unique cases. The model was validated by comparing outputs to empirical measurements in a body phantom filled with a homogeneous saline solution. The change in pacing capture threshold was studied in vivo by applying RF power to a population of leads chronically implanted in canines. A statistical model was then used to predict safety of pacing performance for the expected implant population. Subsequent clinical study supported the expected safe performance and found no adverse effect on the electrical performance of implanted cardioverter defibrillators (ICD) after MRI scanning [4].

In the second example, cardiac lead fracture is a failure mode that can be caused by patient movement or heart motion inducing a critical number of bending cycles in a lead, ultimately causing fatigue of the metal conductors. The failure mode of fatigue fracture is a highly local phenomenon, usually affected only by the conditions at the site of the fracture. Like the MRI case, there is a large amount of variability in the implanted population that can affect device performance, specifically patient activity and in vivo lead path. Additionally, the fatigue strength of the conductors within a lead is subject to manufacturing variability. Haddad et al. incorporated patient activity, in vivo extracardiac lead path, and bench measurements of fatigue strength to generate populations of virtual patients for two market-released lead models [5]. Important

aspects of the model included replicating the in vivo mode of deformation in the bench tests, selecting the proper statistical model for fatigue survival, and availability of prior data for patient activity and implanted lead path. The authors compared the fracture survival in the virtual patient models to the observed field performance for two market-released products having different levels of performance. The product that had better field performance also had better performance in the virtual patient model. Additionally, the risk of fracture over time was found to agree between the virtual patient models and field performance.

When good prior information on clinical use of a device exists, Bayesian methods may enable this information to be incorporated into the statistical analysis of a trial [6]. This prior information typically has been historical data from use in a different patient population or geography, or from a highly similar device. With a Bayesian approach, the analysis of the final study objective would include information from both the current study and the prior data. Virtual patient models can be incorporated into some studies in the same way as historical data, providing benefits of reduced trial size and duration while still controlling the study operating characteristics [2]. This practice will involve collaboration between engineers, statisticians, clinicians, and regulators. To provide a venue and demonstration vehicle for this type of collaboration, the Medical Device Innovation Consortium (MDIC) has sponsored a mock investigational device exemption (IDE) submission that evaluated the pre-clinical analysis and clinical study design for a hypothetical ICD lead [7]. MDIC is a public-private partnership among industry, nonprofit organizations, and federal agencies (including the FDA). The mock IDE submission followed the typical pre-submission communication process, with a sponsor team formed of FDA and industry participants and a review team formed from employees at the FDA Center for Devices and Radiological Health. The clinical study application utilized a discount function to weight the influence of the virtual patients according to how well they agree with data collected from human patients in the hypothetical study, thus maintaining study power while controlling type I error to an acceptable level. A summary of the project is available at <http://mdic.org/computer-modeling/virtual-patients/>, and future publication of the proceedings is expected.

The increasing influence of computational models in the product development and regulatory approval processes requires an increasing level of rigor in the verification and validation (V&V) of these models [8]. Verification and validation can be considered as methods to answer the questions: “was the model used correctly?” and “was the correct model used?” V&V has been formalized by working groups within the American Society of Mechanical Engineers (ASME) for applications such as nuclear systems and advanced manufacturing. The ASME V&V40 committee is currently developing a standard for computational modeling of medical devices.

Computational modeling is increasingly being adopted for the development of medical devices, opening the possibility for developing virtual patient models that can directly simulate clinical outcomes. Virtual patient models can efficiently provide insights that are difficult or impossible to achieve with human clinical evaluation, such as performance in rare populations or direct simulation of failure conditions. Two applications of modeling for cardiac leads were presented in this report: MRI safety and fatigue fracture. Establishing model credibility through appropriately rigorous verification and validation processes is a necessary component to the use of a computational model to assure safety and efficacy for manufacturers, regulators, physicians, and patients. As the experience with modeling as a source of evidence grows, virtual patient outcomes may augment or even supplant clinical study for some future devices [9].

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