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IN SILICO ASSESSMENT OF BIOMEDICAL PRODUCTS: THE CONUNDRUM OF RARE BUT NOT SO RARE EVENTS IN TWO CASE STUDIES

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ABSTRACT

In silico clinical trials, defined as "The use of individualised computer simulation in the development or regulatory evaluation of a medicinal product, medical device, or medical intervention", have been proposed as a possible strategy to reduce the regulatory costs of innovation and the time to market for biomedical products. We review some of the the literature on this topic, focusing in particular on those applications where the current practice is recognised as inadequate, as for example the detection of unexpected severe adverse events too rare to be detected in a clinical trial, but still likely enough to be of concern. We then describe with more details two case studies, two successful applications of in silico clinical trial approaches, one relative to the Padova – UVA simulator that the FDA has accepted as possible replacement for animal testing in the pre-clinical assessment of artificial pancreas technologies, and the second an investigation of the probability of cardiac lead fracture, where a Bayesian network was used to combine *in vivo* and *in silico* observations, suggesting a whole new strategy of *in silico*-augmented clinical trials, to be used to increase the numerosity where recruitment is impossible, or to explore patients' phenotypes that are unlikely to appear in the trial cohort, but are still frequent enough to be of concern.

KEYWORDS

Medical devices, safety and efficacy, in silico clinical trials, computer modelling and simulation, regulatory science

INTRODUCTION

Computer modelling and simulation can be used in many ways to support product development, including the activities associated to the assessment of efficacy and safety (sometime referred as "de-risking") within their *context of use*: this term refers to the actual conditions under which a given product is or will be used. Hereinafter is used to indicate the use case scenarios for which safety and/or efficacy have been assessed. In the case of biomedical products these assessment activities are codified in regulatory evaluation frameworks, which are surveilled by agencies such as the Food and Drug Administration (FDA) in USA. Here we focus our attention on the so so-called *In Silico* Clinical Trials (ISCT), defined as "The use of individualized computer simulation in the development or regulatory evaluation of a medicinal product, medical device, or medical intervention" [1]. The keyword is "individualized". The idea is to recreate the concept of *in vivo* trial using an *in silico* approach, where a large number of individual patients is modelled by initializing a disease/intervention model with quantitative information either measured on an individual (subject-specific model), or sampled from population distributions of those values (population-specific model).

A 2014 report of the Tufts Center for the Study of Drug Development, USA suggests that the cost to bring to the market a new pharmaceutical product has been increasing exponentially in the last decades, reaching the $2.5bn [2]. Of these $1.5bn are due the clinical assessment, the so-called *clinical trials*. This poses a tremendous barrier to innovation, and makes more difficult to meet at reasonable prices the clinical needs posed by rarer conditions. In almost every other

industrial sector where the cost of de-risking for mission-critical products is an issue, *virtual prototyping* has become the best solution; but for biomedical products the use of computer modelling and simulation is still somehow limited. According to the recently published Avicenna Roadmap [1], there are three major barriers: i) cultural resistance from the content experts - mostly biologists, pharmacologists, and medics with limited background in mathematics and physics; ii) resistance of the regulators, who historically did not accept evidences obtained *in silico* for the certification process of new biomedical products, especially those in higher risk categories; and iii) the inherent complexity associated with the accurate quantitative modelling of living organisms. There are signals that this situation is changing, albeit not as quickly as it could.

The cultural barriers play an important role. The pharmaceutical industry is using more and more bioinformatics and molecular systems biology in the discovery phase, following the trends in molecular biology research [3, 4]. Because this area employs mostly biochemists, who have much greater familiarity with simulation technologies, there is substantial use of molecular dynamics simulation to define the mechanism of action of a new compound (i.e. [5]). And there is an extensive use of population pharmacokinetics and pharmacodynamics modelling (i.e. [6]), because it is based on a phenomenological statistical modelling reasoning that is familiar to clinical researchers. But the adoption of subject-specific modelling involving mechanistic, multiscale, physiology-based approach is still quite limited. Thus, it should not be a surprise if the medical device industry, where the R&D staff has more frequently an engineering and physical sciences background, is moving much faster in this direction.

After years of rejection, some regulators are now beginning to consider a possible role for computer modelling and simulation in the certification process for biomedical products. The United States Food and Drug Administration (US-FDA) is leading this trend, worldwide. In January 2014 they produced a draft guidance for FDA staff and industry on "Reporting of Computational Modeling Studies in Medical Device Submissions" [1]. In parallel they contributed to the establishment of an ASME Standardisation Committee V&V-40 "Verification and validation in computational modeling of medical devices" [7]. Additionally, FDA participated in formation of the Medical Device Innovation Consortium (MDIC) in 2012. The MDIC is a public-private partnership created with the sole objective of advancing medical device regulatory science, and has sponsored a working group focused on incorporating engineering data into clinical studies with a virtual patient framework [8]. The recently approved US Congress bill stating "urges FDA to engage with device and drug sponsors to explore greater use, where appropriate, of In Silico trials for advancing new devices and drug therapy applications" [9]. Only a few days later the European Parliament recommended the European Medicine Agency to "… develop a framework for the regulatory acceptance of alternative models and shall take into consideration the opportunities presented by these new concepts which aim at providing for more predictive medicines. These concepts may be based on human relevant computer or cellular models, pathways of toxicity, or adverse outcome pathways" [10].

Of course all this is driven by the growing capability of simulation technologies to accurately simulate complex physiological processes, such as the progression of a disease, the effect of interventions on such progression, and in some cases the manifestation of side effects and complications due to these interventions. This relies on significant pre-competitive research investments done in the last 10 years in the area of physiological modelling. Large scale research initiatives such as the Virtual Physiological Human [11] funded by the European Commission, or the portfolio of grants coordinated through the USA Interagency Modeling and

[1] http://www.fda.gov/RegulatoryInformation/Guidances/ucm371016.htm

Analysis Group (IMAG) [12]have driven a robust development of *in silico* technologies, in particular those capable of modelling individual subjects, that are particularly relevant here.

Some of these resources were used to develop modelling standards, aimed to simplify the exchange of models between researchers and users. The first of such modelling standards was CellML [13, 14], a mark-up language designed to handle any type of biophysical model. Another standard called FieldML is used to describe spatially varying structure and processes [15, 16].

The heart was one of the first targets of VPH researchers. From the seminal works linked to the *Cardiome Project* [17-19], researchers progressively focused more and more on clinical targets such treatment stratification for coronary stenosis patients [20, 21], better planning of cardiac re-synchronisation therapy [22, 23], or the personalisation of transcatheter valve implantation procedures [24, 25]. The FDA-approved HeartFlow service, using a patient-specific model generated from coronary computed tomographic angiography images, can predict the value of the FFR without any invasive procedure [26]. A similar application makes it possible to perform an accurate differential diagnosis of pulmonary hypertension [27]. Some notable results were obtained for abdominal aortic aneurysms [28].

Some applications for musculoskeletal pathologies are quite mature. Subject-specific models proposed to predict the risk of bone fracture in osteoporotic patients [29-31] achieved clinical accuracy of 75-85% [32, 33]. Whole body patient-specific models are also used in the treatment planning and functional grading of pediatric cerebral palsy patients [34-41], and in the analysis of the neuromuscular control. An interesting derivation of this research line is the stochastic modelling of neuromuscular control [42-44].

Multiscale approaches were used to investigate the role that molecular constituents in the macroscopic mechanical properties of tendons [45-48], bone [29, 49-52], muscles [46, 53-56], etc. Other interesting work has been done on the ethiopathogenesis of osteoarthritis [57], osteogenesis imperfecta [58], the biomechanics of parturition [59, 60], and on the response for individual patients with breast cancer undergoing neo-adjuvant therapy [61].

The general approach to establishment of credibility for *in silico* clinical trials revolves around the assumption that *in vivo* studies, whether on animals or on humans are the most reliable source of information, and any *in silico* approach should be "validated" against them. Thus, in the clinical assessment of subject-specific models, a group of patients is examined to collect quantitative information required to initialize the model, which is then used to predict one or more outcome biomarkers for each patient. The same outcome biomarkers are then observed experimentally, whether using an invasive technique or after enough time to make the direct experimental observation possible. For example, virtual Fractional Flow Reserve (vFFR) models, aimed to replace the direct invasive measurement of FFR with endovascular pressure probes, are validated against such measurements [21]. Models that predict the growth of solid tumors when treated with a specific chemotherapy are instead validated against the tumor size as measured through medical imaging, after the chemotherapy cycle has been completed [61].

All this is based on the assumption that *in vivo* clinical trials work fine, and the motivation for replacing them is related to the risk, duration or cost that the trial involves, but not to their ability to provide a reliable answer on the safety and/or efficacy of a new biomedical product. Unfortunately, this is not always the case. Below we present two real-world cases, both presenting success stories for ISCT, where the prime mover of the development were the shortcomings of the current *in vivo* trials. The problem is the numerosity (intended as the number of patients enrolled in the trial), or better its relation with the level of acceptable risk. A medical device in risk class III is typically tested in phase II clinical trials of over 100 patients. Trivializing the problem a bit, this leaves us with a 1% probability that something really wrong

could happen with our new device, but the clinical trials would not observe it. In practice the problem is more complex because any outcome depends on multiple factors, and it is the combination of infrequent unfavorable conditions that produces an adverse effect. While the probability of these adverse effects may be low, even a small percentage can be unacceptable if the effect is very serious. In these cases, *in silico* clinical trials can play an important role as the two following examples demonstrate.

THE PADOVA / UVA SIMULATOR

Two Nature reviews written a decade apart point to the rapidly increasing global prevalence of diabetes mellitus as a result of population ageing, urbanization and associated lifestyle changes [62, 63]. Between 1980 and 2010, the number of people with diabetes mellitus worldwide has more than doubled [64]. In 2010, an estimated 285 million people worldwide had diabetes mellitus, 90% of whom had type 2 diabetes (T2DM) and the rest had type 1 diabetes (T1DM). This number is projected to rise to 439 million by 2030 [65]. On March 6, 2013, the American Diabetes Association released data showing that the total costs of diagnosed diabetes in the U.S. have risen to $245 billion in 2012 from $174 billion in 2007, a 41 percent increase over five years. Hospital impatient days and emergency care account for 43 percent of this cost [66]. The only proven treatment of diabetes is the active maintenance of blood sugar levels within a target range [67, 68]. Thus, diabetes is a prime example of an enormous health care problem the only solution of which is integration of advanced technologies aiming personalized precise treatment, synergistic drug-device integration and, eventually, functional replacement of the failing beta cell.

In silico experiments are of enormous value to accelerating diabetes technology development and drug design. It is often not possible, appropriate, convenient, or desirable to perform an experiment on human subjects because it cannot be done at all, or it is too difficult, too dangerous, or unethical. In such cases, simulation offers an alternative way of experimenting in silico with the system. Several simulation models have been published since the 1960's, mostly in biomedical engineering journals [69-75], but their impact in the field has been modest. The reason is that all of these models were average models and, as a result, their capabilities were generally limited to predicting a population average that would be observed during a clinical trial. However, given the large observed inter-individual variability, an average model approach cannot describe realistically the variety of individual responses to diabetes treatment. Thus, to enable realistic in silico experimentation, it is necessary to have a diabetes simulator equipped with a cohort of in silico "subjects" that spans sufficiently well the observed inter-individual variability of key metabolic parameters in the general population of people with type 1 and type 2 diabetes.

A Serendipitous Beginning

The story of the FDA accepted UVA/Padova Type 1 simulator began largely by chance. In 2006 as part of a NIH program project studying the effects of two-year administration of "youth pills" in elderly men and women, physiological performance, body composition, and bone density were measured in 204 nondiabetic individuals [76]. These subjects underwent a triple tracer meal protocol which provided, in addition to plasma glucose and insulin concentrations, model-independent estimates of fundamental fluxes of the glucose system, including the rate of appearance in plasma of ingested carbohydrates, endogenous glucose production, glucose utilization and insulin secretion [77]. This rich flux & concentration portrait was key to developing a large-scale glucose-insulin model, which was impossible to build from only plasma glucose

and insulin concentrations. A model including 18 differential equations with 42 parameters, 33 of which were free and 9 were derived from steady-state constraints, was identified in each individual by using a Bayesian forcing function strategy [78, 79]. From the model parameter estimates of the 204 subjects participating in this study, the inter-individual variability was described in a nondiabetic population. From there, using the joint multivariate probability distribution of the model parameters, any number of virtual subjects could be generated by random sampling, thereby producing a virtual "population".

Simultaneously with the events above, and thanks to the advent of minimally-invasive subcutaneous (s.c.) continuous glucose sensors (CGS), increasing academic, industrial, and political effort has been focused on the development of a s.c.-s.c. closed-loop control systems for diabetes, which became known as the Artificial Pancreas (AP). Generally, the AP uses a CGS coupled with a s.c. insulin infusion pump, and a control algorithm directing insulin dosing in real time.

Accelerating Artificial Pancreas Research: the FDA accepted Type 1 Diabetes Simulator

In September 2006, the Juvenile Diabetes Research Foundation (JDRF) initiated the Artificial Pancreas Project and funded a consortium of university centers in the US and Europe to carry closed-loop control research. At the time, the regulatory agencies mandated demonstration of the safety and feasibility of AP systems in animals, e.g. dogs or pigs, before any testing could begin in humans. This approach was reported in two papers showing the use of the Medtronic AP system first in 8 dogs [80] and then, later, in 10 people [81]. However, it also became evident that animal studies were slow and cumbersome, and that a simulator of T1DM would allow a cost-effective preclinical testing of AP control strategies by providing direction for subsequent clinical research and ruling out of ineffective control scenarios. We argued that a reliable large-scale simulator would account better for inter-subject variability than small-size animal trials, and would allow for fast and extensive testing of the limits and robustness of AP control algorithms.

We therefore set to build a simulation environment based on the data and the expertise accumulated at the University of Padova and the University of Virginia – two groups that were already collaborating on several aspects of diabetes technology. A first necessary modification of the existing models [79] was the substitution of endogenous insulin secretion subsystem with an exogenous s.c. insulin delivery, i.e. an insulin pump. This required describing insulin absorption with a two-compartment model approximating non-monomeric and monomeric insulin fractions in the s.c. space. Given the absence in 2006 of tracer studies in T1DM similar to those described above for healthy subjects, a more difficult task was the description of inter-person variability. In order to obtain the joint model parameter distributions in T1DM we introduced certain clinically relevant modifications to the models developed in health. The resulting T1DM simulation model included 13 differential equations and 35 parameters, 26 of which were free and 9 were derived from steady-state constraints (Figure 1). Once the T1DM model was built, its validity was tested using number of T1DM data sets including adults, adolescents, and children. Now the Padova-UVA simulator is equipped with 300 virtual "subjects": 100 adults, 100 adolescents, and 100 children, spanning the variability of the T1DM population observed in vivo. In addition, the simulator is equipped with models of CGS and insulin pumps. With this technology, any meal and insulin delivery scenario can be tested efficiently in silico, prior to its clinical application (Figure 2) [82].

After extensive testing, in January 2008, this simulator was accepted by the U.S. Food and Drug Administration (FDA) as a substitute to animal trials for the preclinical testing of control

strategies in artificial pancreas studies and has been adopted by the JDRF AP Consortium as a primary test bed for new closed-loop control algorithms. The simulator was immediately put to its intended use with the in silico testing of a new model predictive controller, and in April 2008 an investigational device exemption (IDE) was granted by the FDA for a closed-loop control clinical trial. This IDE was issued solely on the basis of in silico testing of the safety and efficacy of AP control algorithm, an event that set a precedent for future clinical studies [83]. In brief, to test the validity of the computer simulation environment independently from the data used for its development, a number of experiments were conducted, aiming to assess the model capability to reflect the variety of clinical situations as closely as possible. These experiments included:

A. Reproducing the distribution of insulin correction factors in the T1DM population of children and adults, which tests that the variability in the action of insulin administered by control algorithms will reflect the variability in observed insulin action;

B. Reproducing glucose traces in children with T1DM observed in clinical trials performed by the Diabetes Research in Children Network (DirecNet) consortium;

C. Reproducing glucose traces of induced moderate hypoglycemia observed in adults in clinical trials at the University of Virginia, which provides comprehensive evaluation of control algorithms during hypoglycemia.

Thus, the following paradigm has emerged: 1) in silico modelling could produce credible preclinical results that could substitute certain animal trials and 2) in silico testing yields these results in a fraction of the time and the cost required for animal trials. This was a paradigm change in the field of T1DM research: for the first time a computer model has been accepted by a regulatory agency as a substitute of animal trials in the testing of insulin treatments. Since its introduction, this simulator enabled an important acceleration of AP studies, with a number of regulatory approvals obtained using in silico testing. A total of 140 candidate control algorithms have been formally evaluated from March 2008 to August 2014: 4 in 2008, 86 in 2009, 32 in 2010, 2 in 2011, 6 in 2012, 3 in 2103, and 7 in 2014. These 140 evaluations represented 16 AP projects, which typically resulted in IDEs being submitted to FDA after final algorithm validation. However, one needs to emphasize that good in silico performance of a control algorithm does not guarantee in vivo performance; it only helps to test the stability of the algorithm in extreme situations and to rule out inefficient scenarios. Thus, computer simulation is only a prerequisite to, but not a substitute for, clinical trials.

Further Developments of the Padova-UVA Type 1 Diabetes Simulator

Since 2012, the AP studies successfully moved to outpatient free-living environment and became longer, with durations of up to several weeks [84-87]. These trials are collecting large amounts of data, typically including closed-loop control and an open-loop mode as a comparator. New data became available on hypoglycemia and counter-regulation as well, which allowed an update of the in silico model in the 2014 [88]. This new version has been proven to be valid on single-meal scenarios: in fact, it has been shown that the simulator was capable of well describing glucose variability observed in 24 type 1 diabetes subjects who received dinner and breakfast in two occasions (open- and closed-loop), for a total of 96 postprandial glucose profiles [89]. The simulator domain of validity was then extended by the introduction of diurnal patterns of insulin sensitivity based on data in 19 T1DM subjects who underwent a triple-tracer study [90]. This has allowed the incorporation of a circadian time-varying insulin sensitivity into the simulator, thus making this technology suitable for running multiple–meal scenarios and enabling a more robust design of AP control algorithms [91].

Finally, another validation of the simulator was done by comparing in silico output to data of 47 T1DM subjects from 6 clinical centers, who underwent three randomized 23-hour admissions, one open-loop and two closed-loop. The protocol approximated real life with breakfast, lunch and dinner and collected 141 daily traces of glucose and insulin concentrations. We used Maximum a Posteriori Bayesian approach, which exploited both the information provided by the experimental data and the a priori knowledge on model parameters represented by the joint parameter distribution incorporated in the simulator. Plasma insulin concentrations were used as model-forcing functions, i.e. assumed to be known without error. The identification of the simulator on a specific person provided an in silico "clone" of this person; thus, the possibility emerged to clone a large number of T1DM individuals and to move from single-meal to breakfast/lunch/dinner scenario, thus accounting for intra-subject variation in glucose absorption and insulin sensitivity [92] . These enhanced versions of the T1DM simulator have been, and still are, extensively used in designing and testing the new generation of closed-loop control algorithms, in particular those aiming at individualization, i.e. tuning the control algorithm to a specific person [93], and those making the AP adaptive, i.e. learning from the behavior in time of a specific person [94].

The Type 1 Diabetes Simulator: New Applications

The Padova-UVA simulator has been used in a variety of contexts by 32 research groups in academia, by companies active in the field of diabetes pharma and technology and has led to 63 publications in peer reviewed journals (data updated to 2013). Here we briefly discuss the use of the simulator in two important diabetes technology areas, CGS and inhaled insulin.

Glucose sensors

In the past 10 years, the accuracy of s.c. glucose sensing has moved from MARD (Mean Absolute Relative Difference, a common metric used to compare CGS to reference blood glucose) of 19.7 % of the Medtronic RT-Guardian to a 9% of the Dexcom G4 Platinum (with software 505). Does this improved accuracy make s.c. glucose sensors reliable for insulin treatment decisions in place of self-monitoring of blood glucose? A clinical trial addressing this question would be almost impossible since the required number of patients to ensure exploration of the tail of the sensor MARD distribution would be huge. Also, retrospective data are not too useful because it is impossible to see what would have happened of the insulin dosing was based on CGS rather than self-monitored blood glucose. Determining if CGS is safe and effective enough to substitute self-monitoring of blood glucose in diabetes management has therefore become a hot topic of investigation for the diabetes research community and regulatory agencies. Computer simulation is of critical importance because it allows to perform in silico clinical trials (see also the outcome of a recent FDA panel meeting [95] and commentary [96]. The simulator used in this case is in the context of a patient decision-making model (Figure 3). By describing the blocks B, C and D and defining in silico scenarios to recreate real-life conditions, e.g. 100 adults and 100 paediatric patients, 3 meals per day with variability in time & amount and meal bolus behaviour, we have evaluated standard outcome metrics, e.g. time in severe hypo, time in hypo, time in target, hypo- or hyperglycemic events, for both CGS and self-monitored blood glucose scenarios. Our preliminary results based on 40,000 simulated virtual subjects in adults support the non-inferiority of CGS vs. self-monitored blood glucose; moreover, time below 50 mg/dl and time below 70 mg/dl are significantly improved, time between 70 and 180 mg/dl and time above 180 mg/dl are slightly improved, and the number, extent, and duration of hypoglycemic events are significantly reduced [97].

Inhaled insulin

The delayed onset of action inherent to the current s.c. injected insulin analogues makes their optimal administration difficult, particularly in the presence of real-life perturbations, such as meals. Inhaled prandial insulin with rapid kinetics may overcome some of these delay, but also introduces new challenges. Technosphere® insulin (TI) (MannKind Corporation, Valencia, CA) is a dry powder formulation of recombinant human insulin adsorbed onto Technosphere microparticles [98]. Upon inhalation, these microparticles can reach the deep lung allowing absorption into the systemic circulation with a time to maximum serum insulin concentration of 12–15 min [99]. In a phase III trial in T1DM, TI demonstrated non-inferiority to s.c. prandial insulin Aspart (Novolog®) [100]. However, because of the fast onset and short duration of action, the dosing regimen of TI in this study may have been suboptimal. Designing a clinical trial to identify the optimal dosing regimen and the optimal titration rule would be prohibitively expensive because countless combinations would need to be tested. Thus, we performed in silico trials translating the known pharmacokinetic profile of TI (and insulin Lispro as comparator) into the expected post-prandial glucose response following a meal tolerance test [101]. The simulations suggested that post-meal dosing (at 15 or 30 min after start of the meal) and split dosing (with 15 or 30 min split times) results in a flatter post-prandial glucose profile than at-meal dosing (Figure 4). In several virtual patients the flatter profile allowed for a higher TI dose without increasing the risk for hypoglycemia events. In addition, the simulations revealed that the selection of the titration rule is crucial to achieve optimal treatment benefit. Simulated up-titrations using 20 titration rules identified that the best time to measure post-prandial glucose is 150 min after the meal and the upper threshold for the glucose target should be 150 to 160 mg/dL. These optimized titration rules can considerably improve the efficacy of TI on post-prandial glucose control. Clinical studies are currently planned to validate the results from these in-silico meal test simulations.

IN SILICO-AUGMENTED CLINICAL TRIAL OF DEFIBRILLATOR LEADS

When it occurs, conductor fracture is widely recognized as a failure mode that can have serious implications [102]. Recent advances in test methods, numerical simulation, and in-vivo imaging have enabled more thorough methods of cardiac lead fracture analysis [103, 104]. A Bayesian Network methodology has been developed that integrates in-vivo measurements of device loading with in-vitro measurements of fatigue strength to simulate fatigue lifetime [105]. Many plausible combinations can be simulated within this framework to generate a family of fatigue fracture survival curves, enabling sensitivity analyses and the construction of confidence bounds on survival.

Since the fracture model predicts the same endpoint that would be observed in clinical practice with the same population variability, we use the term virtual patients to refer to these simulations.

The methodology is given below and in [105]:

1. Measure representative use condition and lead fatigue strength to inform estimates for population statistics
2. Estimate posterior parameter distributions for inputs
3. Randomly generate use conditions
4. Randomly generate fatigue strength
5. Calculate time to fracture and survival curve

6. Repeat from step 2 to simulate multiple virtual patient cohorts

A Bayesian framework was utilized to estimate all of the parameters for the distributions used in the simulation. This approach accounts for uncertainty due to sampling. For example, small sample sizes result in large uncertainty, which is reflected in high variability between virtual patient cohorts.

This approach was developed for fatigue of conductors within cardiac leads, specifically for conductor coils. Coil fatigue is governed by the magnitudes and frequency of bending cycles. Previous work [106] has shown that curvature of a coil is related to stress and strain, so we adopt curvature as a fatigue stressor variable. When coupled with the highly mobile anatomical structures around the shoulder, cardiac leads can encounter potentially large amplitudes of bending. Both curvature and frequency are statistical in nature, reflecting variability between implanted shapes and patient activity. To account for the wide span of patient age and associated activity level, we adjust the cycle count distributions according to the patient demographics.

With input parameters for cycle counts, curvature amplitude and fatigue strength, a Monte Carlo simulation can be performed to simulate many possible fatigue experiences, generating a survival curve. Repeating the process with a new set of parameter estimates enables the generation of a family of predicted survival curves, which can be used to generate confidence bounds, reflecting uncertainty in the input data.

The virtual patients can be implemented as prior knowledge in a Bayesian clinical trial. The statistical framework leverages FDA guidance for the use of Bayesian statistics in medical device clinical trials [104]. This approach can have benefits of decreased sample size and trial length while minimizing impact to study endpoints, type I error, and type II error. The methods described here are currently being evaluated in a mock IDE submission as part of a collaborative FDA-industry working group within the Medical Device Innovation Consortium (MDIC).

There are two elements that may be novel to the statistician implementing or reviewing this method, discussed briefly below.

1. Many cohorts of virtual patient outcomes will be incorporated via a modified version of the power prior method. Cohort differences represent model uncertainty.
2. The number of virtual patients will be controlled by a loss function, which bases the number of virtual patients on the agreement between real and simulated data.

Incorporation of each cohort of virtual patient data is based on the method of power priors [107]. In this method, a discount value between 0 and 1 is applied to prior data, where 0 indicates no borrowed information and 1 indicates full borrowing. Unlike historical data, there is not a finite limitation on the number of virtual patients that can be simulated. Therefore, in order to better express variability, it is desirable to simulate a large number. However, the number of virtual patients incorporated into the study is subject to constraints driven by desired power and type I error. The modification developed by the working group converts the potentially large number of virtual patients to an effective number for incorporating into the study data. With this approach, the number of simulated patients can be kept large enough to capture the tails of the distribution, and will be down-weighted to a level that does not overwhelm the clinical data, thereby protecting against a type I error. Integration across the multiple virtual patient cohorts accounts for engineering model uncertainty.

A loss function controls the number of virtual patients incorporated into the study data. This approach utilizes a function that scales the virtual patient number based on the agreement with the study data. In the approach developed by the working group, a Weibull cumulative

distribution function is constructed that uses a Bayesian p-value as an input. When the clinical and virtual data are highly similar, the p-value approaches 1 and the full amount of virtual patients can be incorporated. Likewise, when the clinical data diverges from the virtual data, the p-value approaches zero and the number of virtual patients also approaches zero. The Weibull parameters control the relationship between p-value and fraction of virtual patients allowed. The loss function parameters and the maximum number of virtual patients allowed in the study are items to be agreed upon prior to starting the study.

There are two ways in which this method is suitable for a Bayesian adaptive design with interim looks. First is the traditional case where we adapt the trial based on the clinical endpoint response variable. Second, we adapt the trial based on input data used in the engineering model, collected from the (real) enrolled patients. Both cases can be used for sample size re-estimation or stopping the trial early for success or futility.

The mock IDE submission process is a novel means of demonstrating the statistical methods and considerations associated with using this framework for a clinical trial designed with virtual patients. The activity started in 2014, sponsored by MDIC, and is expected to complete in mid-2016. Two pre-submission meetings were held at FDA in 2015 to introduce the concept and discuss the virtual patient model. A final pre-submission meeting is planned for 2016 to discuss the clinical statistical methods. Updates from the work have been given in conference presentations, and a complete review of the method and mock submission process will be given in a future FDA workshop.

DISCUSSION

Although very different, these two examples illustrate the concept of using subject-specific computer simulations to generate "Virtual Patients" that can replace animal experimentation, or supplement human clinical trials.

With respect to replacement of animal experimentation, it is important to acknowledge that in the context of product de-risking, animal models are based on organisms different, sometimes significantly different, from humans. In addition to differences in biology, anatomy, and physiology between the selected animal model and humans, it is typically necessary to develop a disease model, by intervening on the animal in various ways (genetic manipulation, surgery, environmental control, exposure to exogenous agents such as viruses or bacteria, etc.). In the end the "reality distance" between an ovariectomized mouse and a post-menopausal woman may be as large as the difference between the same woman and a computer model of bone remodeling based on data of individual patients. Simply because it involves a living organism, the animal model is not necessarily "more real". Like with any other model, we need to compare to what extent each model accurately predicts the effect the product being tested will produce in humans, regardless of whether the model is in vivo, in vitro, or in silico.

In many cases, it is difficult if not impossible to conclusively demonstrate the accuracy of a pre-clinical model (again whether based on in vivo, in vitro, or in silico methods); in these cases, it is important to acknowledge the role that patients organizations, such as the JDRF in the case of the Padova-UVA Type 1 Diabetes Simulator, can play in representing in a fully unbiased way, the balance between the need for surveillance and that for innovation. While, in principle, the regulators are also supposed to represent both sides of this equation, in practice in most countries regulators are put under pressure by the public opinion if an authorized product fails, and are under much less pressure if innovation is slow. Patient's organizations can thus play a vital role in the regard.

The second project we presented pioneers the use of subject-specific models in the clinical assessment of medical devices. There are essentially three groups of motivations that drive this type of exploration. The first is to overcome limitations associated to specific products/diseases where a reliable clinical assessment is impossible. The most obvious example is the testing of products to treat rare diseases, where the difficulty is enrolling enough patients to achieve statistical power.

The second is linked to the need to test for a rare but severe failure scenario in a class of products that are normally trialed clinically with a cohort size that makes very unlikely to observe that failure mode. The most common scenario is that produced by the interaction of multiple factors, when each can assume a fairly unlikely value, for example a patient who is severely overweight, and conducts a very active lifestyle.

The third group of motivations is related to the cost and duration of clinical trials. While the cost of innovation in the biomedical industry has reached levels that concern most analysts and pose a serious threat to the long-term sustainability of universal healthcare systems, it is unquestionable that the idea of replacing, even only partially, a clinical trial with a computer simulation, would raise many eyebrows. Thus, we recommend to begin using in silico clinical trials for evaluation of technologies targeting rare conditions, where no viable statistically significant trial design is possible, and to test the occurrence of rare failure scenarios.

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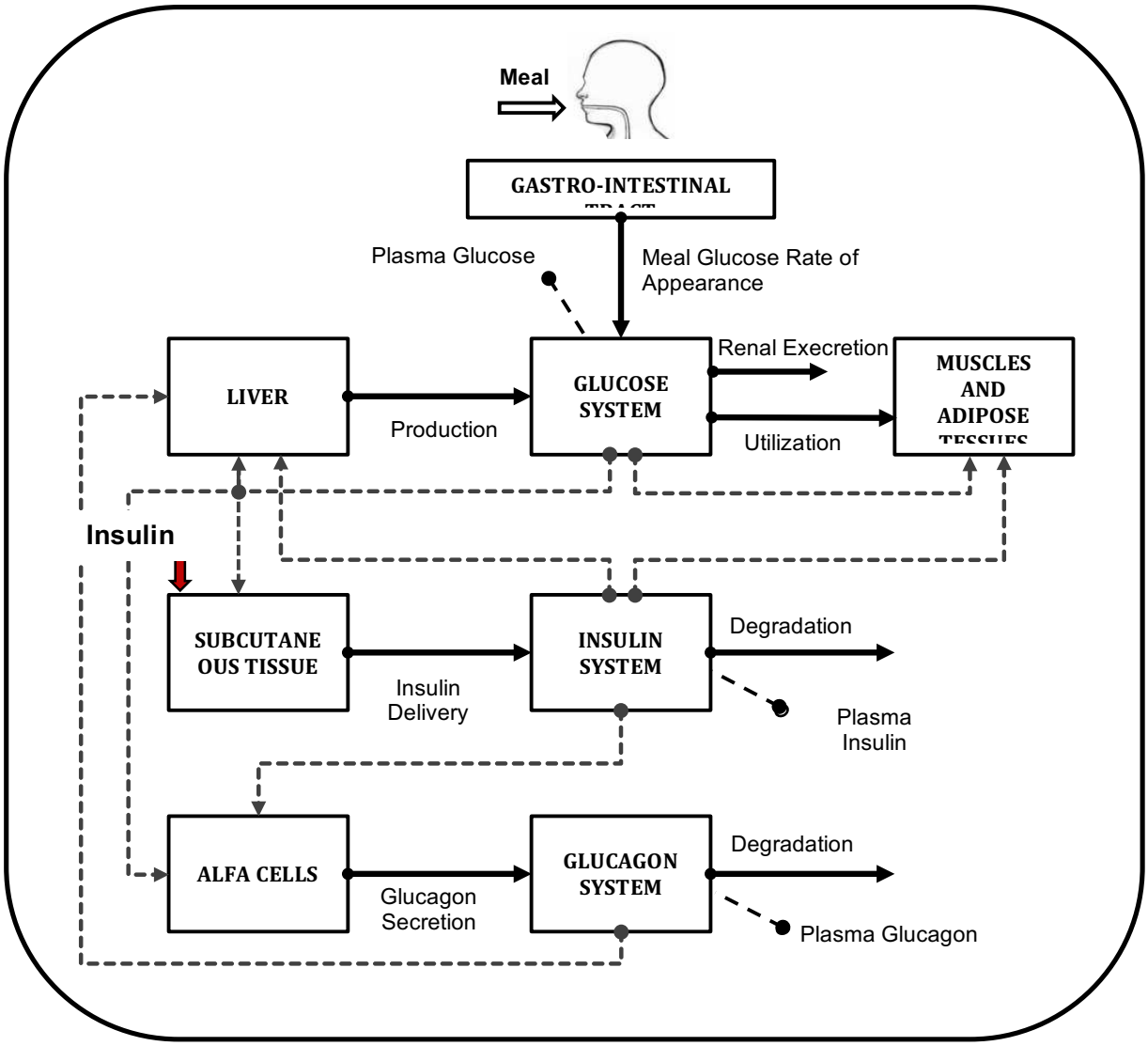
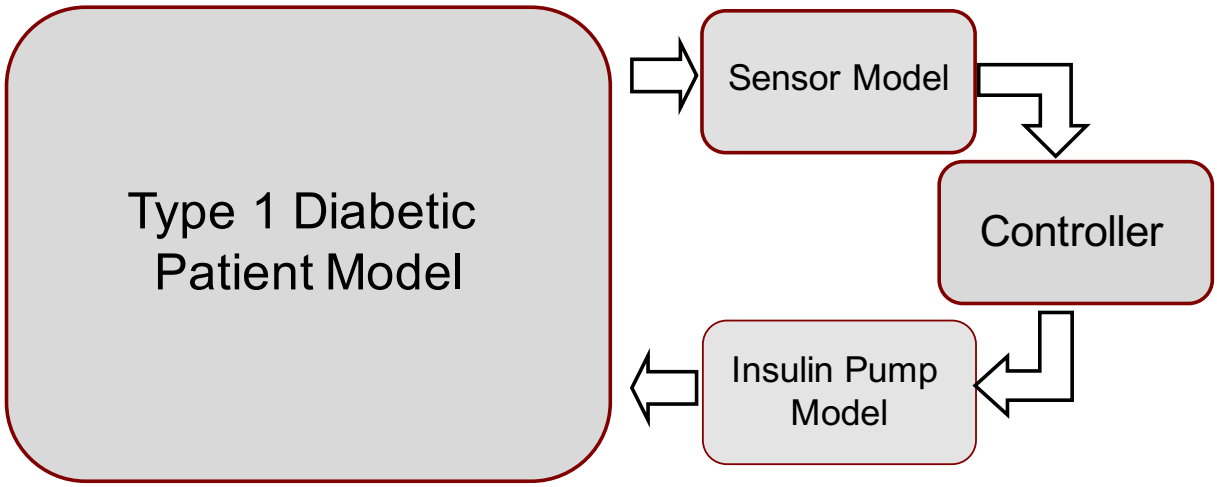


Figure 1: Scheme of the glucose metabolism model included in the FDA-accepted T1DM simulator [82,88].

Use of the Type 1 Diabetes Simulator



- Controller design, testing & validation
- In silico trials for regulatory purposes
- Glucose sensors & insulin analogues

Figure 2: Three uses of the T1DM simulator.

THE T1DM PATIENT DECISION-MAKING MODEL

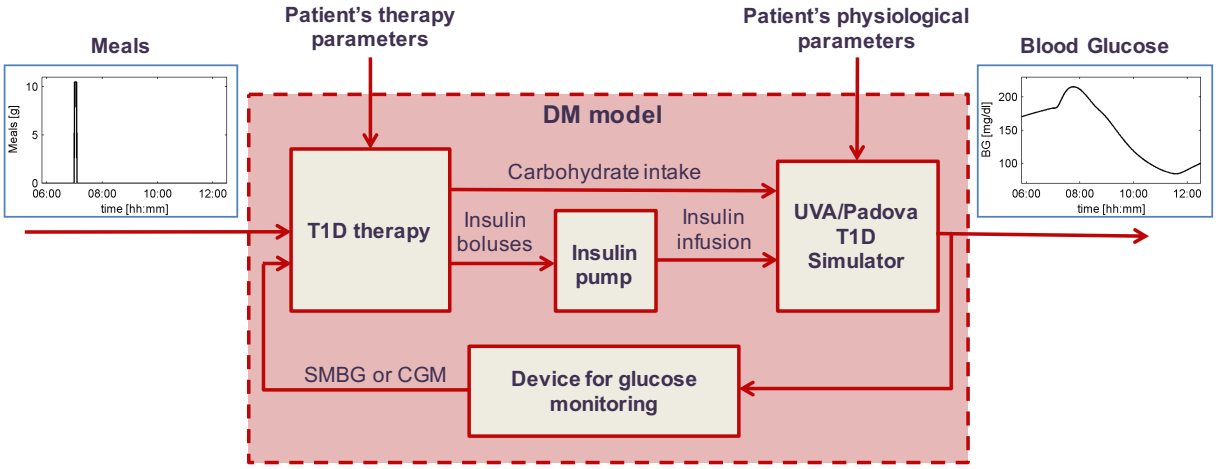


Figure 3: The T1DM patient decision-making model [96].

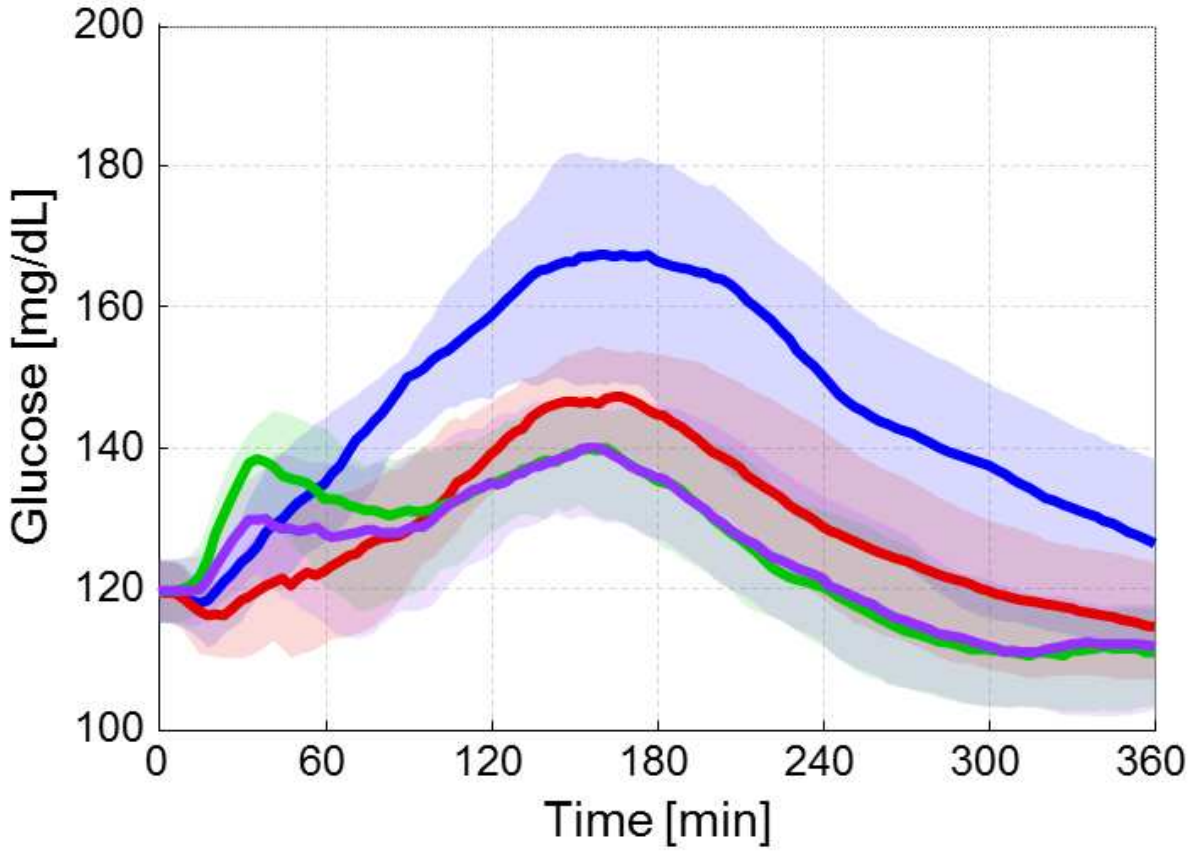


Figure 4: Glucose time courses obtained by simulating meal test in 100 virtual subjects receiving an individualized at-meal dose of TI selected by titration rule based on PPG90<160mg/dL condition (A), or an individualized at-meal dose of TI selected by titration rule based on PPG150<160mg/dL condition (B), or an individualized post-meal dose (Δt=15 min) of TI selected by titration rule based on PPG150<150mg/dL condition (C), or an individualized split dose (Δt=15 min) of TI selected by titration rule based on PPG150<150mg/dL condition (D). A comparison of the mean glucose profiles for at-meal targeting PPG90<160 mg/dL (blue), for at-meal dosing targeting PPG150<160 mg/dL (red), post-meal dosing targeting PPG150<150 mg/dL (green) and split dosing targeting PPG150<150 mg/dL (magenta) is shown in (E) [92].