In Silico Medicine: The Practitioners' Points of View

Matteo Cerri [†]
matteo.cerri@unibo.it

Markus Reiterer [‡]
markus.w.reiterer@medtronic.com

Marco Viceconti [‡]
m.viceconti@sheffield.ac.uk

ABSTRACT

In this article, which is assembled from interviews, the main issues of *in silico* medicine, present and future, are discussed by three scientists who are directly involved in the implementation and development of *in silico* techniques.

keywords: In silico medicine, scientific practice, computational models, biological complexity, clinical trials, risk management, science training.

1. Introduction

Matteo Cerri (MC) graduated as an M.D., and then he left the clinical practice to enter a Ph.D. program in Neurophysiology. He started his research activity studying sleep and sleep regulation, with particular interest in REM sleep. He moved later to the field of autonomic neuroscience, mostly working on the neural control of thermoregulation. He is currently working on hibernation research. He tries to understand how the brain controls the hibernation process and how to replicate it in animals that don't hibernate, such as humans. His research is now supported by the European Space Agency and by the Ministero della Salute. He used a bit of computational modelling in trying to describe the general rules of interaction between body mass, metabolic rate and REM sleep regulation. For hibernation research, some modelling is being

[†] Alma Mater Studiorum - University of Bologna, Department of Biomedical and NeuroMotor Sciences.
[‡] Medtronic Inc., Minneapolis, MN, USA.
[‡] INSIGNEO Institute for *in silico* Medicine, The University of Sheffield, UK.

used to evaluate the amount of energy that a human could save if in a state of hybernation, especially in view of interplanetary travels.

Markus Reiterer (MR) holds a Dipl.-Ing. (M.S.) and a Doctor (Ph.D.) in materials science. For his Ph.D. thesis he has worked on sintering of ceramics (the process of compacting and forming a solid mass of material by heat and/or pressure without melting it to the point of liquefaction) in Austria, Germany and the U.S.. In 2006 he joined Medtronic, one of the largest companies in biomedical technology worldwide. He has worked in the battery research organization, then at the corporate research center where he has been involved in several high profile research projects supporting the market introduction of high revenue generating product lines. In the last two years he has been heavily involved in developing a company-wide strategy for modelling and simulation (M&S), and in the last year he has been leading the corporate strategy group for M&S. The objective of that group is to accelerate product development, make the regulatory process more predictable and cost effective and increase the predictability of the performance of Medtronic products in the field.

Marco Viceconti (MV) is an engineer by training, but he worked most of his career in medical research settings. He is a specialist of musculoskeletal biomechanics, and its application to develop devices and technologies to diagnose, prognose, and treat neuro-musculoskeletal diseases. In the last ten years he had a major leadership role in the *Virtual Physiological Human* initiative. He has an experimental research background, but in the last 15 years he used predominantly computational modelling techniques in his research, although most of the times in close collaboration with experimentalists.

Q: What are some concrete examples of *in silico* medicine?

MR: I will speak to the use of *in silico* medicine for medical device applications. In this domain, one example is *computational flow dynamics simulations*, which can be used to make a decision whether a cardiac stent should be delivered or not. These simulations are more accurate than imaging alone, and less invasive than a heart catheter procedure, that is used to determine the fractional flow reserve. In this first example, *in silico* medicine is used as a *clinical decision making tool*. Then, *finite element simulations* can be used to determine the correct size for a transcatheter heart valve or an abdominal stent graft. In this case, *in silico* medicine is used as a *surgical planning tool*. Finally, the FDA approval of conditionally MRI safe pacing systems heavily relied on multiphysics simulations to proof that they do no harm to the patient, when an MRI procedure

is conducted according to a defined protocol. *In silico* medicine can thus also be a *regulatory submission tool*.

In some applications drugs and devices are similar in others very different. In some devices only the part of the body that is affected needs to be simulated (orthopedics), whereas for most drug scenarios multiple organs or the whole body need to be accounted for. In cases where the device regulates a physiological phenomenon, the complexity is higher than in others, where the therapy is, i.e., purely mechanical. There are more similarities between devices that regulate physiology and pharma, than with orthopedic implants.

A crucial notion used in my strategic work is that of *virtual patients*. In our definition, a virtual patient consists of the constitutive model and the variability and uncertainty. The deterministic and the probabilistic components together can describe the behaviour of an implant in a certain patient population. Smart combination of experiments and simulation can not only reduce the effort to achieve a certain performance level, but there is also a realistic opportunity to achieve better performance. The argument is fairly trivial: virtual prototypes can be built and tested a lot faster and cheaper than the physical equivalent, hence more instances can be tested out. In addition, in virtual prototypes variabilities can be controlled tighter and numerical experiments can be run, which wouldn't be possible in the real world. In some cases the associated experiments are physically impossible, practically unfeasible or, in the case of medical devices, unethical. For example it is unethical to test thresholds of patient harm for certain procedures. A good computer model can give a more realistic insight of the performance of a device in the field, than a reasonably large human clinical trial. Due to the higher efficiency of a computer model, the extremes of the population can be studied, patients that would have been excluded from the trial can be studied and a more realistic care environment can be investigated (Haddad, et.al., *Reliability Engineering and System Safety*, 123, 2014).

In the long run, computer models may be better suited to predict the effectiveness of certain treatments than pre-clinical studies or human clinical trials. All kinds of models have limitations. Human clinical trials are conducted under idealized circumstances, cover only a subset of the total populations, and cover only a significantly shorter time. The time acceleration of human clinical trials is not possible. At least theoretically, *in silico* clinical trials can investigate larger cohorts, cover patients at the edge of the population and can

be used for acceleration. Animal trials have other problems, the results are only partially applicable to humans. A computer model offers the advantage that the idealization can be carefully designed, versus in human or animal trials the idealization if mostly predetermined. *In silico* clinical trials are thus very important for the handling of the largest medical challenges that we face as a society, both in the US and abroad. We need to figure out how to significantly reduce the effort of product development and the associated raise in human clinical cost in order to bring new, better medical devices to the patients. Numerical simulation can make a positive impact on both.[1]

MC: there has been progress in the modelization of cell functions. Systems biology and synthetic biology are now entangled in a positive reciprocal loop that allows scientists on one side to make deeper discovery into cell biology, and, on the other, to generate better modelling of the same biology. 'Primordial creatures' may present a degree of complexity that could eventually be treated. Such is the case for instance of the attempt to simulate the behavior of the *C. elegans*, a small warm with a approx 300 neurons nervous system. Of this animal, the entire connectome is known, and, even if a still complete simulation has yet to come, it may be under way. A third layer of complexity lays in the interaction of an organism with the environment, including other organisms. This layer may be indeed more complex for humans than for other species, especially in the organism-to-organism relationship.

2. How is Scientific Practice Changing?

Q: So, how are *in silico* modelling methods transforming practices in biology with respect to more traditional experimental and trialling methods? Does the advent of large scale *in silico* modelling imply that research will become more automated and computer-driven in the place of traditional practices?

MC: In systems physiology, the use of *in silico* modelling is still limited. Such limitation is mostly caused by the limited knowledge we have of the physiological regulation of the body and by the complexity of the interactions between systems. Moreover, even within the same system, there are many layers that can have causal explanatory power. The simulation of a whole mammalian organism described accurately both within the horizontal

[1] Stefan Thomke, "Enlightened experimentation: The new imperative for innovation", Harvard Business Review 79.2 (2001): 66-75.

interactions, as the interactions occurring within the same explanatory layer, and the vertical ones, as the interactions occurring between different explanatory layers, is, for now, in my opinion, beyond the current possibility. What would be interesting to examine is if it will remain so in the future. In other terms, the question is whether complexity, beyond a certain degree, may be un-simulable, at least within the current frame of mathematics and computer science. A further reason for reflection is that most of physiology is still investigating the unknown. In other terms, since the events and the agents that make up our body function are not still completely known, a large part of the experimental work is aimed at finding these events and agents, even within the still limited simulation power of our years.

MV: I do not work in biology, strictly speaking. If we are talking about biomedical research in a broader sense then I can try to answer. Information technologies have impacted all human activities including biomedical research, introducing digital representations, automation, reproducibility, etc. But *in silico* research is a lot more than this.

There are two trajectories that are happening in parallel; in one *in silico* technologies are seen as enabling technologies that support but do not alter traditional research. We make the same research questions; we build confidence in specific answers in the same way. *In silico* technologies only help us to do this better and faster. A typical example is the most orthodox bioinformatics, where *in silico* technologies help the biologist to handle a deluge of data, but the discovery process is not radically changed.

The other in my opinion challenges the most traditional epistemology of biomedical sciences. Historically biomedical research, challenged by tremendous complexity, was forced to develop epistemologies that either provided mechanistic theories by aggressive reductionism, or approached systemic processes only phenomenologically. In this second trajectory *in silico* technologies are used to develop more mechanistic and less reductionist explanations of the observations we make. That is radical transformation, that impacts on the fundamental approach to research, and that goes beyond the mere technologies, although those technologies make it possible.

Normally science is a self-regulating process, so eventually who is right will win, but the funding and research careers models overload these confrontations, exasperating the scientific debate. "Keeping a cool mind and use measured words, avoid overhype whenever possible is something I

recommend to all *in silico* practitioners, mostly for the good of science in general; we need to fight the good fight, that required to establish scientific truth, and be gentle and respectful of our peers in any other situation".

MR: *In silico* methods have the big advantage that the systems can be tightly controlled. In any type of test (experimental of numerical) an idealized model of the instance of interest has to be developed. However, with any kind of model a compromise between simplicity and accuracy has to be found.

The lab or *in silico* representation may not accurately describe the behaviour of the system of interest under the specified condition, but the researcher can understand the system well enough to gain insights of the underlying processes. This understanding may be of fundamental nature or phenomenological. The big down side of this approach is that the applicability can always be questioned.

On the other end of the spectrum is a trial that is directly conducted on the specimen of interest, in our case a human (model). Here, there are only few questions about the applicability of the model, but the opportunity to tightly control the experiments is limited. The convoluted nature of the test will often not allow the development of scientifically based theory. The observations are then of purely mathematical/statistical nature, which allows us to describe the correlation between input and output variables, but not to make any conclusion about the causality of our observations. If my learning is only of statistical and not of causal nature, I cannot transfer my learnings from one situation to the next. The same is true for interpolation vs. extrapolation. Without a solid causal model, extrapolation is a dangerous game.

Variability is something that a computer can better deal with, as statistical methods can be used to assess a very large variety of use cases. The danger of creating purely data driven models, is that the true physical causations are very hard to determine. In an ideal world we would use a lot of mechanistic models to simulate the human biology. However the trend is to rely more on strong statistical correlations and not so much on weaker mechanistic explanations. These simplifications need to be assessed in a systematic way.

MV: First, in many cases the complexity is structural: providing an accurate mechanistic explanation of the observations made at a characteristic space-time scale is still a grand challenge in many problems. Then, we need to release the reductionist constrains and observe the same phenomenon at multiple space-time scales, typically from the scale of intervention (which for a drug is molecule) to the scale of clinical manifestation (that depending on the diseases

is tissue, organ or organism). Once we have accurate mechanistic models at each scale, we need to understand those various single scale models relate one to each other, for example how changes at the tissue scale manifest into the biomarkers we observe the organ scale. Then we need to put everything together, which is both a scientific and technological challenge, in many cases. It is a long way to go, although some low-hanging fruits exist.

Heavy use of M&S is indeed a paradigm shift in the medical device industry. In order to achieve our objective to reduce the time and cost associated with the introduction of new therapies to the market, the M&S specialists need to work with the regulatory affairs specialists. This is different than in the past, where design and test engineers were the partners for the M&S experts.

3. Computational Power and Biological Complexity

Q: There is something of an expectation that greater computer power and computation can overcome any problems of biological complexity and biological variability by simply scaling it up. How subtle and clever however do we have to be in our use of computation in order to overcome complexity and variability? How much additional work and understanding needs to go into modelling in order to get computation to work as well as it might?

MV: In a few lucky cases it is possible that the complexity is only combinatory, and in those cases computational models can help to "scale up" our ability to handle such combinatory complexity. But in general I think this is an oversimplification of the challenges ahead.

MR: For sure it is current understanding that a large enough computer will be able to solve most of our problems of interest. I believe, however, that for conventional computers a physical limit for the size of the problems they can solve exists. I don't think that any extrapolation of today's technology (e.g., quantum mechanical *ab initio* methods) will enable us to build a functional computational equivalent of the human body. Consequently, all computer models of the human body and its interactions with therapies need to rely on simplifications to reduce the complexity of a biological system. Should we even be able to create very complex replicas of the human biology, we need to be able to comprehend the results in order to act accordingly. We also need to be aware that for most models we cannot learn anything that wasn't included in the modelling framework. I don't know to which extent modern analytical methods

(Big Data) can be used to truly learn something from a model that was not included originally.

MC: Big data could highlight useful correlation, that may help orienting research activity towards the unexpected. I think the current idea of interactome goes in this direction, creating a useful conceptual frame that can successfully orient basic biological research

I fear the possibility that even with a scaling up of computational power, physiology may still be too complex to be simulated in a useful way. This, of course, if a complete simulation, from molecules to systems is the *desideratum*.

I can be more optimistic for simulations that are contained to a more limited domain, and that can definitely have in a big data approach a powerful support. There are three different levels of complexity that appear to overlap in a description of modern life: cells, multicellular organisms, and organisms-environment assemblages. The arena of the simulation, in terms of which layer is the target of the simulation, has therefore to be carefully picked at the moment, to put the computational power at our disposal to the best usage. The relationship between complexity and modelling is thus to be contextualized into the evolutionary path of complexity, something we could call comparative complexity.

MR: For me complexity means that a system has multiple interactive dependencies. This is definitely the case with the human body. If we bring the human mind into consideration then the complexity increases even more dramatically. Is the interdependency of mind and body what we should understand as the human factor? Other systems, i.e., computers, transportation networks, etc. don't have this interplay between body and mind. How do we need to understand this interplay in animals?

In contrast to my statement above, human factors means something completely different to industrial engineers, who try to understand how the way a human being interacts with a technology influences the outcome. Examples are how are people using a drill or a computer program.

4. Clinical Setting and Research Setting

Q. How might clinical or other applied or decision-making settings differ from research settings when thinking about the proper roles of *in silico* models and how they might be applied responsibly?

MR: In my understanding medicine shall improve the wellbeing and/or happiness of a human being. I think that practitioners need to support and respect the objectives of the patients. What is the purpose of diagnosis without a treatment? Some patients don't what to know the diagnosis and prognosis, whereas others will benefit from the knowledge of the diagnosis, even of the prognosis is devastating. In some cases a diagnosis is nearly a verdict.

The patient needs to be at the center of all medical practice and research. The concept of an empowered patient is a difficult concept for some (or many) physicians. One can be surprised how much 7 year old patients with diabetes type 1 understand about their health issue, or how much an elderly person with Parkinson's disease understands about the interactions between all the medications she is taking for her co-morbidities. On the other hand how shall the physician deal with patients, who don't have the capability to comprehend their situation or are not interested in their wellbeing?

In most cases medical devices provide restorative rather than regenerative therapies. For the benefit of patients and society, there should be a stronger focus on regenerative therapies. There are not many therapies for chronic disease that are truly healing.

MV: The distance from pre-clinical research to clinical practice is huge. If we refer to *in silico* technologies that have been successfully used in clinical research, their translation to the clinical practice is a challenge, which is getting a bit simpler as we go. Let us focus on *in silico* medicine technologies that are to be used as decision-support systems for diagnosis, prognosis, or treatment planning. After you have completed your development you have to challenge these technologies like any other healthcare technology: run a *phase I* clinical trial aimed to test feasibility, impact the hospital setting, and safety (where relevant); then run a *phase II* clinical trial aimed to assess the efficacy; and then run a *phase III* multi-centric clinical trial to evaluate the cost-benefit and risk-benefit ratio. Until recently there were no regulatory pathways defined for such predictive medicine technologies, anywhere in the world. In 2014 the USA Food and Drug Administration approved the first *in silico* technology based on patient-specific modelling; this is a fundamental step because it provides, at least for the USA market, a pathway for the certification of *in silico* technologies required for widespread adoption. We can only hope Europe will follow soon.

MR: Researchers have the responsibility to provide evidence that their models are applicable and the verification and validation process is suitable for the intended context of use. I think that openness and transparency are very important to convince the user of the model of the applicability of the model. The user or recipient of the model or simulation can be a reviewer at a notified body such as TUV or the FDA. On the other hand, a user could be a clinician, who has in my opinion just as much responsibility only to rely on models that are appropriate for the context of use. Let me give you an example: A doctor, who decides on a cancer treatment strategy, has the responsibility to be informed about the evidence behind different options. It is the obligation of the industry or the researchers to provide the evidence.

The danger with CM&S models is the illusion of the pretty picture. Another danger is that simulations in many cases are carried out in a deterministic, rather in a probabilistic way, and in reality most results are not just yes or no answer. However, if a simulation is set up a certain way, it can leave the impression that one obtains a clear yes or no answer. I wish that people are aware that models in general are simplifications of reality. That is true for computational models, animal models, and also for clinical trials, which are also not a full representation of reality. Clinical trials are conducted on a carefully selected patient population, for a shortened period of time, and the best care situation, which is not realistically achievable for the whole patient population.

People often say that CM&S is too complicated and only true experts can understand the risks. Experiments that replicate complex situations or behaviours are also very complicated and cannot be judged by lay men. Why is there more scepticism towards CM&S? One reason is that realistic human simulation is fairly young and many of the key opinion leaders and teachers in academia are not trained in CM&S. As a result we are not disseminating realistic human simulation at the pace that would be needed to initiate a big change.

I believe that surgical planning tools or medical decision making tools that have a well-defined context of use and have been validated accordingly can provide better advice to a physician than his experience alone. Simulations are wonderful tools to test different scenarios, when many factors play a role.

MC: Clinical decisions do not necessarily need an explanatory level behind them to support them and make them effective. Semmelweiss's famous case of washing hands before gynecological procedures clearly shows that medically effective procedures don't require an underlying causal explanation. While this can be accepted, it is also clear that a randomized clinical trial (RCT) cannot be

conducted for all the possible clinical activity. For this reason, an effective simulation to support clinical decision making may receive more effective input from basic science than from RCT. The building of a mechanistic model after all may be imperfectly adherent to the complex reality of each patient, but could be easier to develop and averagely effective in supporting the doctor's activity.

In a research setting, for now and for what the field of physiology is, simulation may help in designing experiments, especially experimental conditions. Less in showing the path to new findings, this latest part still being the most prominent.

5. Risks and Responsibilities

Q: Do you see any particular risks associated with the use and advocacy of *in silico* models and methods? What kind of responsibilities does research have when representing the effectiveness of *in silico* models and computational methods in research and clinical settings, particularly given expectations about the effectiveness of computation in general?

MV: With respect to the clinical application, I do not believe there is anything special that separates *in silico* technologies form any other health technology in this regard. Developed countries have robust and widely tested processes to ensure that only safe and effective technologies are used, and while there are some problems once every while, overall these processes work. And around these processes the clinical users builder their trust in using complex technologies. The tension is more within the research community. As I said before there is a trajectory of introduction of *in silico* methods that is incremental on the current research methods, and another that is disruptive.

MR: If the funding for the creation of *in silico* clinical trial data comes from public sources, the full content, including models, simulation input, etc., should possibly made available for the interested public. If the funding comes from private sources, then the intellectual property, related to the models, resides with the company or sponsor.

Now, however, let's assume we can predict the outcome of a therapy for severe chronic or potentially fatal diseases by personalized computer modelling. In case there is no successful therapy, the hope of the person is diminished. Does that mean we shouldn't try to cure that person and only use palliative care? What is the confidence level we need to have in such a computer model?

MC: The main risk I can see for research settings is that the *in silico* modeling could be seen as a complete replacement for experimental research. In biology,

animal research and actual laboratory activity is still necessary at this stage of development of this science. In clinical settings, *in silico* model could provide a great support to the activity of doctors, possibly increasing the level of care pro patients and reducing the cost of the health system.

6. Collaboration or Hybrid Specialization?

Q: What is the best model of researcher and research going forward? Is it the hybrid researcher trained substantially in both experimental biology and mathematical methods and computation, or is it the collaborator, who is solely specialized in one of these areas, but has the knowledge nonetheless for working across disciplinary borders? What implications does your answer have for education?

MC: This is a hard question to answer. I am personally in favour of a combined training in both biological science and mathematical methods. But also in embracing the combination of training, great care would have to be directed on how to combine them. My personal opinion is that the peculiarities of biology, which I like to remember, is a science that still is in the age of exploration, appears sometimes alien to students trained in more formal sciences. I would therefore design a combined education to have biology at the base.

MR: I don't think anybody has resolved the old education problem of how to deal with the ever growing amount of information and knowledge in medical sciences and related fields. I don't think that a person can learn all what it takes to conduct multi-disciplinary studies in a 4 year college program. Most likely it will take someone with a PhD and several years of work experience to become proficient in matters of *in silico* clinical trials. As an alternative, multi-disciplinary cells need to be formed to address the pervasive problems.

Benchtop experiments and computer simulation as well as computer simulations and human clinical trials have to be used together to maximize the learning benefit. Bayesian statistical methods provide the mathematical means to combine different sources of evidence.[2]

In silico clinical trials are inherently multi-disciplinary, which makes the learning problem more difficult. I think that the researchers participating in *in silico* clinical trials need to be informed enough to understand the bordering

[2] Haddad, et.al., *Reliability Engineering and System Safety*, 123, 2014.

knowledge domains without the need to be an expert in all disciplines. The appreciation for other methods and the basic understanding of the other person's discipline needs to be brought to the students.

The application of good scientific or engineering practices is very important. It consists of applicable statistical methods, domain knowledge, and critical thinking. The more potent the tools are, the more important are skills of critical thinking. The challenge with critical thinking is that these skills cannot really be taught in a class room setting, there is no recipe for critical thinking. Education in this subject is more an awareness exercise as the application is very situational.

MV: We live in a splendid time where in developed countries the educational offer is extraordinarily variegate, and thus our researchers in training do have very different profiles, which I think is a good thing. Everyone who really does interdisciplinary research will tell you that we need vertical and horizontal, people with in depth understanding of a specific narrow area, and people trained to work across areas, with a wider although more shallow preparation. The only recommendation I want to make is that we need to progressively increase in all biomedical degrees, even the most traditional ones, the amount of Mathematics, Physics, and Engineering teaching. The traditional vision that if you were good in math you would go study engineering, and if not you would study medicine, has in my opinion damaged the development of biology and medicine in the last decades. There is so much technology in every hospital, in every biology lab nowadays, that such radical positions are now unacceptable, in my opinion. Every student in science, including biology and medicine students, must have a minimum training in math, physics, and engineering, to cope with pervasive technological presence.

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