In Silico Medicine: Social, Technological and Symbolic Mediation

Annamaria Carusi[†]
a.carusi@sheffield.ac.uk

ABSTRACT

In silico medicine is still forging a road for itself in the current biomedical landscape. Discursively and rhetorically, it is using a three-way positioning, first, deploying discourses of personalised medicine, second, extending the 3Rs from animal to clinical research, and third, aligning its methods with experimental methods. The discursive and rhetorical positioning in promotions and statements of the programme gives us insight into the sociability of the scientific labour of advancing the programme. Its progress depends on complex social, institutional and technological conditions which are not external to its epistemology, but intricately interwoven with it. This article sets out to show that this is the case through an analysis of the process of computational modelling that is at the core of its epistemology. In this paper I show that the very notion of 'model' needs to be re-thought for *in silico* medicine (as indeed, for most forms of computational modelling), and propose a replacement, in the form of the 'Model-Simulation-Experiment-System' or MSE-system, which is simultaneously an epistemological, social and technological system. I argue that the MSE-system is radically mediated by social relations, technologies and symbolic systems. We need now to understand how such mediations operate effectively in the construction of robust MSE-systems.

keywords: system medicine, philosophy of modeling and simulation, technological mediation.

1. Introduction

In silico medicine is still forging a road for itself in the current biomedical landscape. Its progress depends on complex social, institutional and

[†] Medical Humanities, University of Sheffield, UK.

technological conditions which are not external to its epistemology, but intricately interwoven with it. This article sets out to show that this is the case through an analysis of the process of computational modelling that is at the core of its epistemology. The analysis is based on combined philosophical and empirical methods, with extensive participant observation and immersion in computational or *in silico* modelling for biomedical purposes. This paper reports primarily on research conducted in the domain of computational cardiac electrophysiology; in the background are research conducted in the context of systems biological studies of cancer of the gastrointestinal tract, and more broadly in setting out principles for the use of *in silico* methods in the context of clinical trials. In this paper I show that the very notion of 'model' needs to be re-thought for *in silico* medicine (as indeed, for most forms of computational modelling), and propose a replacement, in the form of the 'Model-Simulation-Experiment-System' or MSE-system, which is simultaneously an epistemological, social and technological system.

In the first section, I discuss the origins of *in silico* medicine in the computational resources of systems biology, and discuss its rhetorical self-positioning, and my own positioning of it as a technoscientific domain that is radically socially and technologically mediated. The main thrust of my analysis is to show that *in silico* medicine, like other forms of technoscience, does not consist of a core of hard science, surrounded by facilitating or obstructing social relations and technologies; but rather that science, technologies, and social relations all play active roles in shaping, defining and characterising the domain that is labelled '*in silico*' medicine. Having introduced these terms in the background, I go on to demonstrate how they apply in the analysis of the modelling process.

2. Background

In silico medicine is the translational edge of systems biomedicine, that takes forward and develops further the computational resources associated with systems biology, rather than its focus on gaining understanding of complex systems. The computational resources of large data bases and supercomputing for data processing, modelling and simulation make it possible for science to consider systems characterised by dynamic non-linear causality, feedback, and cross-level networks of interactions. The programme of research and development that is

labelled '*in silico* medicine', however, comes out of essentially computational projects, such as the Virtual Physiological Human (VPH).

Initially funded by the European Commission ICT panel, the VPH has consistently described itself as a platform for developing methodologies and technologies 'to enable collaborative investigations of the human body as a single complex system'[1]. From the outset, potential medical applications were highlighted as motivations for investment in this area of technology development. From its first paragraph, the VPH White Paper published in 2005 presents itself as an initiative targeting healthcare, aiming to understand physiology not just for itself, but for 'its dysfunctions (diseases)', with impacts to be felt on diagnosis, treatment, drug and device development. Personalising medicine was identified as a potential area for development from the outset. Under the remit of the VPH Network of Excellence, the Discipulus project produced the Digital Patient Roadmap[2], setting out, step-by-step, what the VPH vision of personalised medicine would actually entail. '4P medicine', that is predictive, preventive, personalised and participatory medicine, is the centrepiece of the 2012 vision and strategy (Hunter et al. 2013), which culminated with the establishment of the VPH Institute. Developing the 'ICT and computational science framework' is seen as the main enabler of 4P medicine, while the main disablers – apart from scientific and technical challenges, are seen as existing ethical, legal, economic and regulatory frameworks. For example data sharing and integration face potential breaches of privacy and confidentiality; the economic framework in which drug development occurs does not easily make space for radically new methodologies that may disrupt ownership and patenting structures; and the regulations on drug and device safety testing will not easily make way for tests conducted *in silico* rather than on animals.[3]

The ongoing VPH programme increasingly identifies itself with *in silico* medicine, and very skillfully positions itself relative to ongoing preoccupations in the biomedical arena. We see this in at least three key areas: First, it mobilises the discourse of personalised medicine that is closely associated with genomic medicine, and proposes to amplify and extend the 'gene by gene'

[1] https://en.wikipedia.org/wiki/Virtual_Physiological_Human#cite_note-10
[2] http://www.digital-patient.net/
[3] These challenges are set out in far more detail in the latest positioning document of the VPH Instititute (Viceconti, Henney and Morley-Fletcher 2016).

personalisation targeted by genomic medicine through an informational and computational infrastructure that would in principle at least, allow for the whole organism as system to become the basic 'unit' of personalisation. Second, as is demonstrated in a document such as the *Avicenna In Silico Clinical Trials Roadmap*[4], it reutilises the language of the 3Rs of animal research (reduction, refinement and replacement), in the context of clinical trials, and thereby creates a parallel between the use of animals and of humans in medical research, and the epistemological, pragmatic and ethical themes that arise from each. Third, the rhetorical parallelism of *in vivo, ex vivo, in vitro, in silico* places computational methods and models alongside experimental methods and models. This presents computational methods and models as further tools in the toolkit of biomedical sciences, along with others that are traditionally accepted, and lays the ground for reciprocal engagement between computational and experimental methods and models.

The rhetorical positioning that is evident in *in silico* medicine does not show it to be a kind of manipulative or empty public relations exercise; rather, it shows the social shaping and embedding of *in silico* medicine as it defines itself in relation to its potential contribution, capacities and other players in the biomedical domain – beginning with its very name[5]. Each of the three positionings are conversation openers with different audiences: funders, policy makers, industry partners, clinicians, cross-disciplinary researchers, especially experimentalists who do not currently engage with computational methods. The rhetoric here is in persuading these audiences to engage with *in silico* medicine, or to give it space enough to prove itself[6]. Rhetoric is a marker of the essential sociability of any sustained scientific programme of research, that comes out particularly prominently when that programme is at initial stages, as *in silico* medicine still is. Rhetoric is not an added extra aside from the 'actual' business of carrying out the research and development, confined to public discourse such as manifesto-like statements and position pieces. Instead (as in

[4] Viceconti M. et al, ibid.

[5] The label '*In silico'* medicine is fairly recent; it is associated with other labels such as 'systems biology', 'systems biomedicine', 'computational biology' or 'computational biomedicine', 'computational medicine'. The shifts in naming the set of computational resources, tools and techniques that loosely characterise the area mostly depend on the extent to which the labelled programmes are targetting medical audiences.

[6] It goes without saying that there are powerful social, economic and political shapers of the whole biomedical domain, but I do not address these here. I am talking about social issues that are closest to research cultures of disciplinary and sectorial groupings.

other sustained science and technology programmes), it is an indispensable element of the core business of *in silico* medicine, as it is that through which sociability expresses itself, shaping the epistemology as well as the communication of the programme of *in silico* medicine.

In this paper, I concentrate on showing how sociability and epistemology combine in the core business of the construction and validation of computational models and simulations in order to achieve biomedical ends of different types; and how this is sustained through the exchanges that occur through technological and symbolic mediation conjoining epistemic and communicative aspects of the different knowledge cultures involved in *in silico* medicine. By 'technologies' I mean all the different kinds of apparatus, instruments, equipment – mechanical, informational and computational – through which scientific research cultures of experimentation, modeling and simulation occur; by 'symbolic' I mean all the different means through which the inputs, outputs, and processes are rendered in order to make them communicable – be it through images, graphs, diagrams, information visualisations, and the symbolic systems of equations[7]. Any scientific domain is pervasively social, technological and symbolic.

This brings me to mediation. Technological and symbolic mediation of a scientific domain could mean different things: that technologies and symbols have an *epistemically instrumentalist role* as enablers, tools or instruments for the research questions and aims of scientists; or that they have a *communicatively instrumentalist role* as the go-betweeners for different research cultures coming together and exchanging tokens of their cultures, thereby being essential for setting up what Peter Galison calls the trading zone (Galison 1997). Clearly technologies and symbols play both these roles in *in silico* medicine. However, both of these roles still make it appear that technologies and their associated symbolic systems are somehow external to the research. For example, it might seem that as facilitators of knowledge, they make attaining knowledge *easier* (as though research could in principle still go on but with more difficulty without them) rather than actively shaping it. On this view, they are evidence providers rather than evidence shapers. There is a third sense of mediation that is applicable to *in silico* medicine, as it is to any similar scientific programme. This is 'mediation' that derives from the sense of

[7] On the symbolic and technological systems around equations, see for example studies of mathematicians' work practices in the context of computational biology (Mascord, Jirotka and Carusi 2006).

medium as the element in which something, such as an organism, art works, science etc., exist and develop, in inter-relationship with the social actors engaged in them[8]. *In silico* medicine is clearly a domain that is – or is being brought into being – through a combination of existing and emerging technologies and associated cultures, that define the environment in which it unfolds, in which it will thrive, or not. This third sense of mediation radically contextualises scientific programmes, positing them as always 'in the middle of' (*in medias res*) a social, technological and communicative interplay, which shapes the formation, significance, interpretation and weighting of every epistemic claim and statement made in it. This third sense of mediation sees technologies and symbols in a radically mediating role, whereby they are not only tools of the social actors, but active 'players' alongside them. This includes *all* the technologies involved in a programme such as that of *in silico* medicine, and not only the computational technologies. Crucially, mediation is by the whole range of technologies, experimental, computational and other[9], as it is by the whole range of social actors, and not only the engineers and computer scientists.

My aim in the rest of this paper is to show how radical mediation applies to *in silico* medicine as a programme of scientific research and development. As we know, this is a programme of enormous complexity, and it is difficult to generalise across the whole domain. I focus on an emblematic feature of the programme: the question of what a model is; and on what I hope will be a simple but key example of the interplay between the different cultures, symbols and technologies. In Section 1 I show that the distinction between model source and target does not work well in these contexts of modelling, and propose the notion of Model-Simulation-Experiment (MSE) system; in Section 2, I show that the process of development of MSE-systems is inherently mediated in the ways I have sketched out above; for MSE-systems to become robust enough to sustain medical and clinical decisions and consequences, there needs also to be awareness of that mediation, and attention paid to it in

[8] On this sense of mediation, see Hoel and Carusi (2016).

[9] How broadly these are defined depends on what specific area on is looking at: for example, there are also institutional and regulatory technologies.

order to ensure its effectiveness, both in the process of model development and in the process of translation to actual application[10].

3. From the Target-Source Distinction to the Notion of Model-Simulation-Experiment (MSE)

In silico medicine implies the use of computational approaches, among which are data processing techniques and computational simulation. In this paper, I focus on the latter, even though there is an overlap between them. Computational stimulations could be defined very narrowly as strictly consisting of the computational solution of mathematical models. At other times, 'computational simulation' is shorthand for modelling and simulation. In both of these cases, computational simulation stands apart from the laboratory experiments, which play two roles: they generate data that are used to parameterise the models, and they are used to validate the models. These two roles of experiments do not always go together[11]. But these roles, separately or together, often mean that experiments are seen as the target of computational simulation (narrowly or broadly defined). Figure 1 schematizes such traditional analysis of a modelling set up.

fig. 1

On this analysis the standard setters for computational simulation are experiments; computational simulations are successful or not depending on how well they stand in some relationship to experiments. Scientists most commonly use the term 'representation' for this relationship, but what is meant by this can vary across correspondence, description, reproduction, or

[10] For a fuller discussion of validation in contexts of application please see Carusi, Burrage and Rodriguez (in process).
[11] See Carusi (2014).

prediction. Here, I wish to explore the distinction between model source and target. This is important because it defines the appropriate relationship between computational methods and all the other methods commonly used in biomedical sciences. On the understanding of computational simulation as source and experiments as targets, computational simulations are secondary to experiments. *In vivo, ex vivo* and *in vitro* experiments are deemed to provide access to the phenomena 'in the world'. This assumes that experiments have epistemic priority over computational simulations. This is a position that is defended by several philosophers, on the basis of experiments and natural phenomena sharing the same matter[12]; on the basis of the causal interactions between experiment and natural phenomena (Giere 2009); or on the basis of experiment's ability to lead to the 'creation or isolation' of new phenomena, which simulations cannot do because they are based on models that set theoretical constraints on the behaviour of outcomes[13]. Other philosophers have argued against the epistemic priority of experiments (Parke 2014, Morrison 2009, Parker 2009, Giere 2009), but none has taken apart the distinction that leads to the issue of priority in the first place.

Whereas in many domains computational simulations do not sit side-by-side with experiments, in biological sciences they more often do. The reason may be that there are not relevant mathematically formulated theories in biology, as they are in physics, or that experiment is more of the normal way of conducting research in biology, in contrast with economics. At any rate, the models that drive simulations are not as theory driven as in other sciences (Keller 2002, Varenne 2010). In biomedical sciences with a real aspiration to translational impact in the clinic, in industry, and in other healthcare sectors, they *must* sit side by side with experiments, or fail to gain any traction in the area. In this situation, the driver of simulation research programmes is to become integrated with experiments. A viable biomedical programme to develop computational simulations that are useful (and will actually be used, which is just as important, but a separate matter) needs experimental data sets that are specifically produced for the purposes of model construction. The simulation techniques that are deployed need to be attuned to a deep knowledge of the biology and physiology of the phenomena in question, and

[12] For example, Guala (2002) and Morgan (2005).
[13] Morgan. 2005. op cit, 326.

can never simply be deduced for the model equations[14]. Parameter fitting and data calibration for the simulations need to be carried out in ways that are sensitive to experimental ranges[15]. The visualised outcomes of the simulation need to be rendered so as to be in visual affinity with the outcomes of experiments; if visualisation is deemed to be too 'subjective', validating metrics similarly need to be established in the interplay between model, simulation and experiment. Validating experiments need to be carried out in line with the requirements of the simulation. At this point, experiments are not autonomous but designed for the simulation, or there would not be criteria for comparing the computational simulation and the experiment, or for testing the predictions made by the simulations. Once these three elements become so closely intertwined with each other, they are no longer discrete entities, but rather interconnected parts of the system. Rather than a model source consisting of model and simulation on one hand, and experiment on the other, we have a model-simulation-experiment system, or MSE-system[16], in which each of the parts is defined in interrelationship with the others. What this means is that essential features of each, such as the research question addressed, the methods, the parameters and parameter ranges, the rendering of outputs, analysis and interpretation of outcomes, are defined in the inter-relationship. In such a system the question of epistemic priority falls away. It is the system as a whole that investigates the phenomenon or domain. Direct access is not reserved for experiments alone since the experiments are what they are in virtue of their relationship with models. Modeling and simulation can bring experiment into question as much as experiments can bring models into question; for example they can provoke a re-examination of research questions and hypotheses. M, S & E form an inter- connected system that must be holistically interpreted and evaluated.

4. Mediation and the Development of MSE-Systems

The MSE-system is not born all at of once; by virtue of being a system it takes time to develop. Iteration is a term that crops up often, underscoring the trial

[14] In this paper, I have not dealt with verification, under which the derivation of the simulation from the model equations is at issue. See Morrison (2015).
[15] Carusi, 2014, op cit.
[16] Carusi, Rodriguez and Burrage 2013.

and error nature of the process and crucially, its temporality. It is not only a matter of models, simulations, and experiments becoming hooked up into a system, but of modell*ers*, simulat*ors*, experiment*ers*. The following is an example of how this hooking up occurs. In cardiac electrophysiology, modellers and simulators are setting up collaborations with clinicians that will allow them to explore drug actions in a complementary way – that is, beginning to establish MSE-systems that will work across the academia / clinic boundary. As in academic laboratories, a typical methodology for clinicians in this domain are voltage clamp experiments, that control the flow of conductances across the ion channels of the cell membrane. Voltage experiments typically involve the kind of apparatus shown in Figure 2. Computational modelling and simulation instead typically involve apparatus such as PCs, software packages such as Matlab, Fortran, simulations packages such as CHASTE (http://www.cs.ox.ac.uk/chaste/); mark up software such as CellML, and depending on the complexity of the simulation, supercomputing resources. Just by the apparatus involved, it is clear that there is a huge difference in the research activities that the different people in this area undertake on a daily basis.

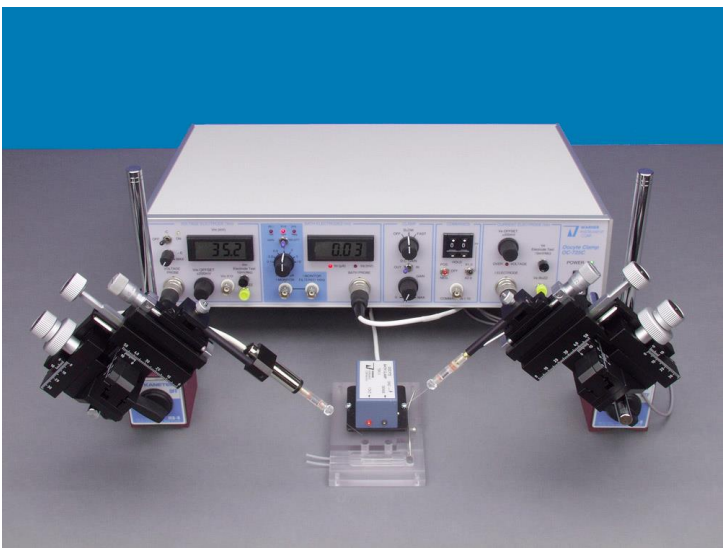

Figure 2: Voltage Clamp Apparatus Two Electrode Voltage Clamp Apparatus. From https://www.warneronline.com/product_info.cfm?name=TEV-700+Two+Electrode+Voltage+Clamp+Workstation&id=170.

The following is an extract from my fieldwork in this area; a doctoral student co-supervised by a clinician and a computational modeller, the co-supervision itself being one of the building blocks of the collaboration. The co-supervision provides the institutional infrastructure for the exchange between clinical laboratory and computational laboratory to occur; and itself emerges out of many discussions and social interactions. We are very much 'in the middle' of MSE development, already mediated.

Excerpt 1
Research Participant [RP] Because in this model, after 100 or 200 beats of pacing there was a drift in these concentrations. So the very first beat may look like this, and second like that ... there's substantial drift. So there was a suggestion to clamp those concentrations and I said to myself why not? And I did. [laughs]
AC: so how do you clamp? This comes from experimental protocols doesn't it [...]
RP: What I mean by that .. there is as set of equations whereby if you write down the derivative of any of these concentrations, there is something here, usually some sort of expression, but if you set that to 0 –[see figure 3] sorry, at that point this concentration has to be constant– ... so that's what I did

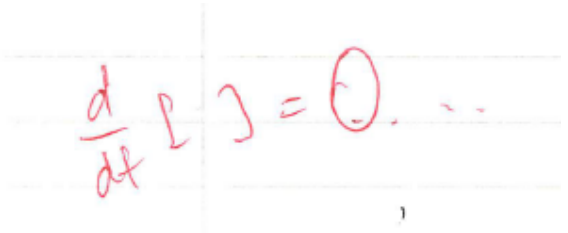

Figure 3: The equation written down in the context of interview, relating to how the model equations convey voltage clamp experiment.

AC: so that's what constitutes clamping?
RP Yes.
AC: And *is* it an equivalent of clamping in an experiment? Does it map onto the clamping in an experiment? ..... Is it to say, this is as though I were clamping in the experiment?
RP: [referring to another researcher] thinks yes, I think no, and we disagree on that [laughs] ... so I disagree with it personally because, you know, when I

imagine a cell and I know that even if the cell, well you know, in experiment what you typically do is you do a voltage clamp. At that point you hold the voltage constant and then you apply some rapid steps to the voltage. And I can also do that with my simulations, I've done that with my simulations [...] so when it comes to voltage clamping I can do that very easily, and there's a direct match between experiments and simulations. But with concentrations, I am less inclined to say so. The main reason being that I don't know if that's what is actually happening in cells. I don't think it can be happening in the cells. Because, essentially, what happens when you record action potentials, from cells, in a whole cell patch clamp scenario, you've got a cell, right, and you're piercing it with a pipette, and there is some solution that you stick into the pipette, and there is also some solution that you have outside. And then you apply a small ... you inject a small current in here and you hope that that's going to trigger the action potential.
AC: Have you ever done this, yourself?
RP: I have seen it done. I would not have the patience to do that myself, because I've seen the pain that it requires. Because if your cells die midway your whole experiment is ruined. Which is why I'm a computational researcher ... so this is kind of speculation essentially, we don't really have information about what is happening to these ionic concentrations inside of the cell and outside of the cell. We have a reasonable idea of what's happening outside of the cell, because you have the cell, and it's sitting in this bath, and you constantly pass this liquid through this bath making sure to wash out whatever the cell is excreting. So you're trying to have the constant concentration outside of the cell, that's what you're trying to do with this wash, which would actually correspond to clamping the sodium and potassium and calcium outside of the cell, right? I don't think you can do that inside of the cell even though I've done it
AC: you mean even though you did it in your model?
RP: Yes

[...]

AC: [...] How important was it for you to go and see how they are doing it?
RP: Actually very important because there were things that I, well, I'm not an experimentalist and I needed to understand what they were doing in the lab so I could to the best of my ability here
[...] So I create these models and then I simulate them in conditions as closely resembling experiments as possible. So I match the concentrations of ions outside, I match the temperature ... I've been trying to match as much as possible between experiments and simulations.

From these excerpts it is clear that there is labour involved in establishing how models correspond to experiments, what in the experiments they correspond to in the experiments, a labour that includes within it agreement and disagreement with others. The experimental set up, with its apparatus, solutions, combinations of organic matter (cells) and inorganic tools (pipettes through which solutions conveying conductances pass into the cell) are foreign to modellers. Frequently, we hear comments about personal characteristics required in order to *be* an experimentalist – such as patient, or a modeller – such as analytic; yet they attempt to grapple with it so as to be able to 'do the best of [their] ability' in reproducing, not just the data, but the experiments in the models and simulation. The modeller re-enacts voltage clamp in the model, including even such details as temperature; but even in so doing, is not certain that it *is* a re-enactment of voltage clamp. Whether it will or will not be depends on the ongoing iterations of the model and simulation, relative to experiments; it depends on whether clinicians, mathematicians and other computational researchers accept it as being such, or are not convinced. The group spends a great deal of time in discussions among different combinations of people defining what is 'close enough', 'good enough', 'of interest'.

The output of the experiments using techniques like voltage clamp is commonly in graphical form, produced through a recording of action potentials measured by the apparatus on a vertical scale for amplitude and a horizontal scale for time. These graphical renderings are also the way in which the outcomes of the simulations are rendered. This is ensured by the software that already bridges between the experiments and the simulations, setting the interpretive frame that makes the outputs of the simulations interpretable as graphs of action potentials. These graphs are public renderings of experiments and of simulations, and constitute an essential equivalence generator between experiments and simulations. They are also a mediating step between other visualisations of the simulations, which otherwise do not have any resemblance to any visual output from experiments (see Figure 4).

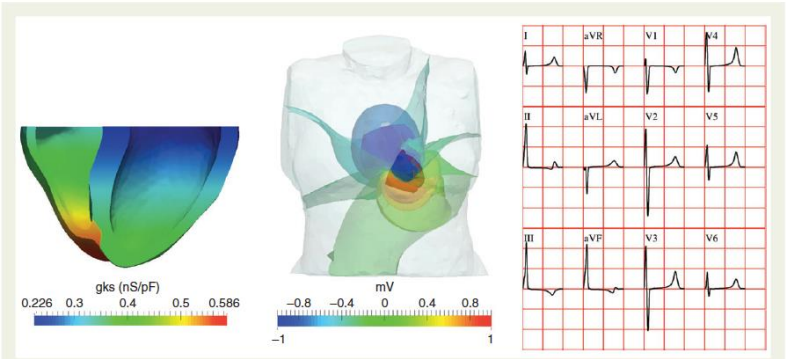

Figure 4: These are all visualisations produced by computational simulations, but the two visualisations on the left have no equivalent in experiments; the ECG mediates between the computational visualisation and the visual output of experiments.

These graphical renderings are a typical symbolic mediation in this context. They are of course tightly connected with their respective technologies. These renderings mediate the interactions around experiments and models in various ways: different features of the curve are pointed to in order to draw out similarities and differences; at times the quantitative measures are considered, for example the exact time for the curve to reach a particular amplitude; at other times qualitative features of the curve are focused on, and attention is drawn to the shape of the curves. There is negotiation about which points of the curve might be used as the basis for making predictions. From such negotiations, the design of ongoing work in experimentation and modelling takes shape.

From the preceding, it is clear that the environment of *in silico* modelling is populated by people from many disciplines entering into relationships whereby they agree to undertake joint activities, the outcomes of which need to persuade all involved that it is worthwhile continuing on the iterative cycle of the research. For example, experimentalists (including clinicians) need to be persuaded to conduct experiments with a view to modelling and simulation; mathematicians and computer scientists need to be persuaded to fit models to specific biological and physiological phenomena of interest to experimentalists or clinicians. These different communities often have very different conceptions of what the validation process consists in and what counts as

validation[17]. Margaret Morrison discusses the crucial role of validation experiments in assessing whether simulations are accurate representations of the target (in the form of experimental data). Although her formulation remains within the paradigm of source and target that I have sought to displace towards a more systems way of thinking, validation experiments are certainly a key component of the construction of a robust system. Morrison points out that validation experiments are independent of the data used to construct the model. She goes on to say:

> Validation experiments are designed specifically so that data are sufficiently related to code calculations in a specific domain. Unlike traditional experiments, where the emphasis is on measurement of processes in a controlled environment, in validation experiments the emphasis is on the characterisation of the experiment itself, that is, measuring the various characteristics of the experiment that are needed for the simulation. Controlling the environment is less important than being able to accurately specify the surroundings in a precise way so that all the relevant features of the simulation model are contained in the experiment. (Morrison, op cit, 272)

In a translational biomedical programme, there can be no doubt that these experiments must be carried out by regular experimentalists and not by modellers with their experimentalist cap on, because they need the results to be accepted by those who are able to bring these modelling techniques and resources into biomedical contexts. However, conducting such validation experiments geared towards simulations may be far from the interest or priority of researchers in clinics or in pharmaceutical companies. Ensuring that these experiments are actually carried out requires an enormous amount of social investment in time spent demonstrating the utility and value of collaborating with the simulation programme. This is a process of persuasion in which, for example, modellers tailor their models to experimentalists' interests and try to communicate them in the terms (and through the symbolic systems) familiar to experimentalists[18]. It takes time and negotiation on both sides to arrive at a commonly agreed set of criteria for validation experiments. The labour of MSE-system construction is only indirectly that of constructing and testing models and simulations; the nitty-gritty of the labour in developing the MSE-

[17] As amply demonstrated at the recent 'Models and Validation in Computational Biomedical Sciences: Philosophy, Science, Engineering' workshop, held in Sheffield, December 2015.
[18] See for example, as described in Carusi 2014, op cit.

system is actually that of constructing a system of equivalences between M, S and E, that form them into a closely interconnected system; it is on the basis of this system of equivalences binding the elements together that, paradoxically, comparisons between apparently independent models and simulations, on one hand, and experiments on the other, are made and interpreted[19].

To continue the example of voltage clamp experiments: this technique also disturbs the cell membrane and its effects have to be taken account of in the simulation techniques and importantly in the interpretation of the outcomes. Thus, not only in the equations but in the simulation too, it is not a given, nor an assumed accepted fact, how voltage clamping is reenacted. A system of equivalences needs to be *established* for voltage clamping across model, simulation and experiment. The system of equivalences allows for a series of exchanges of data, methods, and questions, that are as much as feature of the social interactions amongst the research cultures as they are of the MSE-system. The social interactions are not predicated upon any one set of actors in the research culture knowing which is the right way; which then must be transmitted (in a unidirectional way) to the others. Instead, in order for the iterative process of developing the MSE-system to continue, they most together establish what counts as equivalent to an experimental technique such as voltage clamp, for a simulation to have successfully solved the equations including the zero parameter value that re-enacts voltage clamp; for simulation interpretation and comparison with validating experiments to have successfully accounted for ulterior effects of voltage clamp. Before it is possible to make judgements of accuracy, cast in terms of comparisons between outcomes of simulations and experiments (see for example, Morrison, op cit, 276), it is necessary to agree on what can be deemed equivalent to what. Through the 0 in a model equation being deemed equivalent to voltage clamp in experiments, model equations and experiments exchange the feature of controlling membrane excitability. This is a two-way exchange over the long-haul of MSE-system construction, as experiments can also take on the voltage clamp features of the models and simulations when they are designed with a view to the MS part of the system.

[19] The notion of 'system of equivalences' is derived from Merleau-Ponty's philosophy, arising in many of his works, including the essay on algorithms in Merleau-Ponty (1973). See also Carusi 2014, op cit.

Establishing a system of equivalences means that discussion of epistemic priority between experiments and models/simulations falls away. We can reformulate this as follows: the extent to which epistemic priority is still discussed among possible collaborators is inversely proportional to the likelihood that robust MSE-systems will develop and be capable of becoming absorbed into biomedical implementation settings. In addition, talk of replacement of experiments by models and simulations falls away: rather there is far more of an emphasis on bridging, connecting, creating complementarity between different methods. An example is in a recent community-wide discussion to develop a vision of how computational methodologies could contribute to the further development of human-based approaches, thereby obviating several of the problems (mainly epistemological but also ethical), with experiments using animals in pre-clinical studies. One of the key challenges identified is:

> Complementarity between different approaches requires input and investment from the scientific community, who are key to defining the criteria to be met for the assessment of drugs and models, through establishing benchmarks, as well as through a reconsideration of different methods and approaches to model validation. A consensus for how the pharma and biotech industry should respond is required and ideally supported by compelling data that draw on a retrospective analysis supporting the reasons to change (Rodriguez, Carusi et al. 2015).

I am a co-author of this paper; however my role at the workshop which the paper describes was observer only. These points regarding the need to establish community based criteria and benchmarks that would enable the different methodologies described to be interconnected was a constant theme throughout, articulated by the scientists and industry participants. It is this kind of work that I understand as that of establishing a system of equivalences that engenders MSE-systems.

In this section, I have argued that the construction of the MSE-system is inherently social; what counts as validation, for example, is something that is essentially outward looking to people in other research cultures who need to recognise the value or potential in some aspect of the other's practices sufficiently to engage with it and get it to the next iteration; this is particularly evident in a translational programme such as *in silico* medicine. Continuing development of a MSE-system therefore ensures that the different research cultures – including their priorities and concerns – are inscribed into the

system via nitty gritty details of practice, such as voltage clamp experiments. Establishing equivalences between experiments and models and simulations on something like the voltage clamp technique enables these to exchange features, and to repeat them across the system, despite their very different technologies. The symbolic renderings of the different technologies are an essential mediation for these equivalences to be established.

In summary: the *in silico* medicine programme of research, development and implementation of computational approaches – especially modelling and simulation – into biomedical domains depends upon the construction of MSE-systems, consisting of interwoven models, simulations and experiments. MSE-systems are hybrid systems connecting up many different forms of research activities, and their associated technologies and apparatus. An MSE-system is constructed through the labour of establishing equivalences that operate systematically across the different modalities of experimenting and simulating, bringing them together – we would say, interweaving them into a system. In the opening paragraphs of this paper, we saw how the work of inter-relating *in silico* methods with other methods is already evident in the discursive rhetoric of the programme, as evidenced in examples taken from the Virtual Physiological Human project. It is evident also at the level of scientific labour in the form of establishing a system of equivalences between the different modalities, which when interconnected, all begin to be co-defined and co-shaped in relation to each other. The system of equivalences is highly social and mediated by the symbolic systems and technologies of the domain. It is produced, not found, given or discovered. Indeed it must be co-produced by representatives of the different research cultures involved in it, because otherwise it will not be *accepted*. Acceptance is key; without it *in silico* medicine will never develop into anything but the name of a mode of doing medicine that might have been. The robustness of *in silico* medicine is not only a matter of following good scientific methods and sound epistemologies; indeed there is nothing like 'good' and 'sound' in this domain independently of the communities that form it. Robustness therefore requires attention to be paid also to the social, technological and symbolic mediation of *in silico* medicine, in order to understand what are the ways of acting on and through mediation that result in greater robustness. This is not something that has yet been undertaken in a systematic way.

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