MULTISCALE MODELING OF HUMAN PATHOPHYSIOLOGY

Marco Viceconti
INSIGNEO Institute for in silico medicine, University of Sheffield, UK

Keywords: Multiscale modeling, virtual physiological human, in silico medicine

Contents

Summary

In this chapter are presented some theoretical aspects of the multiscale modeling of pathophysiological processes in humans, and we identify some related research challenges that did not find a satisfactory answer, yet. First it is provided the rationale behind the Virtual Physiological Human initiative, and in particular on the role that modeling plays in it. Then it is explored in some depth the concept of scientific modeling, and some definitions are provided. In particular is defined a new class of models called integrative models, or also hypermodels, which are the primary tool for the multiscale investigation of human pathophysiology. Some of the open challenges in this research field are then briefly described: multiscale boundary conditions, non-periodic homogenization, strongly coupled hypermodels, under-identification, and estimation of confidence intervals. It is also briefly touched the more general problem of falsification and validation of hypermodels. Last, two major computational challenges (stochastic multiscale modeling and component models as reusable quantum of knowledge) are described.

1. The Blessing of Reductionism, the Curse of Reductionism

1.1. Reductionism

Faced with the infinite complexity of nature the human mind, in its finiteness, developed over time more and more complex strategies to investigate the world. One particularly effective is to decompose the problem at hand into much smaller (and confined) sub-problems, and to tackle them one by one.

Today in scientific research we call this approach *methodological reductionism*: “an approach to understanding the nature of complex things by reducing them to the interactions of their parts, or to simpler or more fundamental things” (2008).

Methodological reductionism is probably the most important "trick" that science has used over its few centuries of existence, and still today virtually every scientific investigation revolves around this fundamental idea.

1.2. The Limits of Reductionism

The problem is not reductionism, but how we have to use it in too many occasions. Even reducing a biological problem to the interaction of its parts is way too complex in most cases. Thus, we end up pretending that the parts in which we divide a process are independent one to each other. This is called *causal reductionism*, "which implies that the causes acting on the whole are simply the sum of the effects of the individual causalities of the parts" (Polkinghorne, 2007).

While in many cases even this brutal simplification makes possible the production of new knowledge, it is now becoming more and more evident that for a number of clinically relevant pathophysiological processes can seriously investigated only by taking into account the systemic interaction.

One particularly brutal form of causal reductionism is performed across space-time scales. For example, when we investigate the biochemical pathways with a single cell, the rest of the organism that surrounds that cell tend to disappear from our consideration, in spite the fact that most of what happen inside each cell is strongly regulated on its interactions with the other cells, the tissues, the metabolism, etc.

There is no investigation of the nature that does not involve some degree of approximation, some *idealization* in order to bring down the complexity to a manageable level. But causal reductionism, and in particular neglecting that most physiological and pathological processes occur across space-time scales, may introduce in some cases significant errors, and ultimately preventing us to truly understand such processes.

1.3. Integrationism

To exit such impasse we need to embrace the complexity of life. We must accept that most biological processes are the systemic emergence of complex interactions observable across radically different space-time scales, from the whole organism to the single molecule, and back to the organism.

It should be noted that this is much more that the concept of "hierarchical reductionism" proposed by Dawkins (Dawkins, 1986); Dawkins suggests that complex systems can be described with a hierarchy of organizations, each of which can only be described in terms of objects one level down in the hierarchy. To use the terminology of Donald T. Campbell, in the context of systems theory (Campbell, 1974): "the whole is to some degree constrained by the parts (upward causation), but at the same time the parts are to some degree constrained by the whole (downward causation)". If we pretend to explain organisms in terms of molecules (upward causation) we will surely miss a lot of important elements of the process we are investigating.

The observation that the whole might be more than the sum of its parts has been defined in philosophy with various terms, such as for example *emergentism*, a term frequently used in the philosophical debate around consciousness. With refer to natural systems the term *holism* is frequently used to suggest that natural systems should be seen as whole rather than sum of parts. While these terms generally mean pretty much the same thing, their use within specific debates has loaded them of associate meanings that are not appropriate here. For example holism is frequently used to indicate a complete rejection of reductionism, in all its forms. This is why we proposed the term *integrationism* instead (STEP Consortium, 2007).

The simple basic idea around integrationism, and at the basis of various initiatives in the biomedical research community such as systems biology, physiome, the virtual physiological human, is that after we have decomposed (reduced) a process into its parts, we need to capture the reductionist knowledge relative to each part and combine it that on the systemic interactions that link such parts toward the emergence of the process we are investigating. Thus, the integrationist agenda does not criticise methodological reductionism, but rather recognize the need for an additional step, to properly investigate complex biological processes.

1.4. Mechanistic Vs. Phenomenological

In philosophy the term phenomenology is used to define the direct investigation and description of phenomena as consciously experienced, without theories about their causal explanation and as free as possible from unexamined preconceptions and presuppositions. In science, the use of statistical methods, and more recently of machine learning techniques, has made possible the development of purely phenomenological theories, which can accurately predict some observable processes, without making any assumption whatsoever on why such processes as occurring in such fashion. Purely phenomenological theories are sometime misleading (See for example on the correlation between storks and birth rates: Hofer et al, 2004. New evidence for the theory of the stork. Paediatr Perinat Epidemiol 18(1), 88-92), but are unquestionably a powerful tool. Now one could wonder whether an integrationist approach could not be achieved simply by a holistic phenomenological investigation. My personal answer is no. As we wrote before, most biological processes span across radically different space-time scales. This implies that we simply cannot observe the process in all its parts simultaneously (This is a complex argument that would take us far away from the main scope of this chapter, but space-time scales are deeply connected to perception. Space is a continuum, and the quantization of space into spatial scales has mostly to do with our ability to perceive within given spatial limits.). So even if our investigation is phenomenological, most of the times we must cope with methodological reductionism.

In opposition a mechanistic theory aims to explain the observations in causal terms, providing a tentative answer to why such process occurs and is being observed. Some authors assume that all mechanistic theories are also deterministic, but this is a mistake. There are many cases where we can provide a perfectly detailed mechanistic explanation to a stochastic process. The opposition between mechanistic and phenomenological is not on whether they rely on statistics, but rather in the tension (or the lack of) toward a causal explanation of observations.

Another element worth noticing is that no theory can be completely and exclusively mechanistic. There is always a "phenomenological closure" somewhere. This typically corresponds to our attempt to bring into our theory the effects of processes occurring at a different space-time scale, effects that we represent as phenomenological manifestations at the scale of investigation.

1.5. The Need for Modeling: The VPH

A key passage in the idea of integrationism is that we can capture the knowledge we have accumulated over each sub-process in to containers that make it possible to systemically compose such knowledge. Now one possible way to capture what we know about a natural process is to encode such knowledge into a predictive model. Thus, predictive models can be seen as containers of reductionist knowledge.

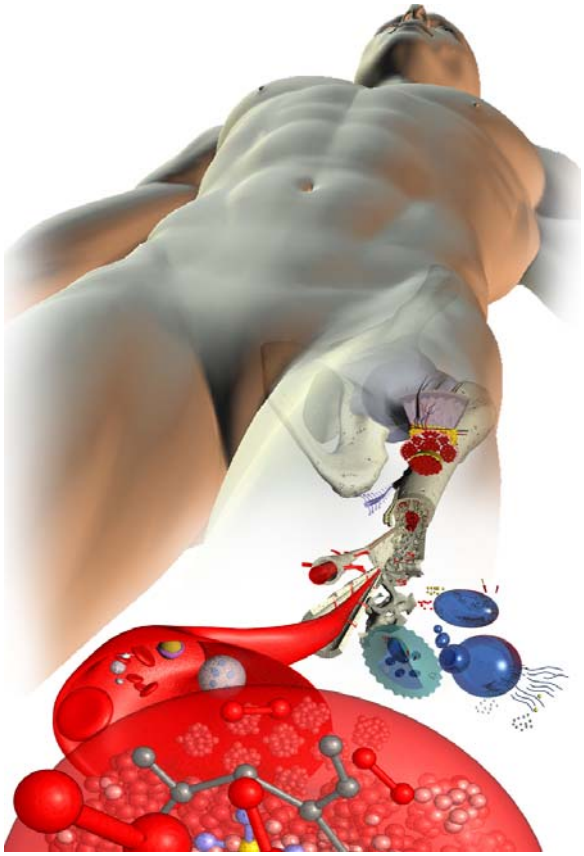

Figure 1. The multiscale nature of human pathophysiology. Pictorial representation: "From the atom to the whole body". Authors: Luigi Lena and Marco Viceconti. © 2011 VPH Institute, reprinted with permission.

This makes possible to imagine an integrative research approach were all fragments of reductionist knowledge about a pathophysiological process are captured into predictive models, and these models are connected one to each other to represent the systemic nature of the process, and a complete multi-model simulation is run to predict the systemic emergence. The European research roadmap to Integrative Research (STEP Consortium, 2007) indicates the principal instrument for the practical realization of the

Integrative Research vision in the so-called *Virtual Physiological Human*, defined as "a methodological and technological framework that once established will enable the investigation of the human body as a single complex system" (Viceconti et al., 2006; Clapworthy et al., 2007; STEP Consortium, 2007; Clapworthy et al., 2008; Fenner et al., 2008; Kohl et al., 2008; Viceconti et al., 2008; Hunter and Viceconti, 2009; Thiel et al., 2009; Hunter et al., 2010; Kohl and Viceconti, 2010; Viceconti et al., 2010; Viceconti and Kohl, 2010).

The vision of Integrative Research (figure 1) will thus be possible when we shall be able to build models that accurately predict the human physiological and pathological processes at the various spatial and dimensional scales, and we shall be able to combine them so to explore the systemic behaviour that is at the basis of such processes. So at the basis of integrative research there is the ability to build accurate multiscale models of human pathophysiology. But before we proceed, it is necessary to answer to a fundamental question: what is a predictive model?

2. What Is a Model, Revised

2.1. Models are Cognitive Artifacts

With our mind we can imagine; it is hard to explain this concept, but every human being knows what this means. With our mind we imagine things that do not exist, but in some case we imagine reality. When we imagine portions of the reality we create representations of what we believe is real; in this sense imaginations of reality are the containers of our beliefs on the world. Another way to call an imagination of reality is *model*; thus a model is a cognitive artifact, build upon what we believe to be true, i.e. a container of our beliefs.

When we imagine the reality we are not recreating such reality inside our brains. Even the smaller portion of reality is infinitely complex, and we would need an infinitely large and complex brain to this purpose. Humans are limited creatures, so when we model the reality we need to simplify it; this process is called *idealization*. Every model involves idealization.

It is quite obvious why we image unreality; unreality by definition does not exist, so the only way we achieve it is to imagine it. But why we are compelled to image reality? A way to define our brain is to consider it as a thought processor. If you analyze this definition you will see that it is somehow recursive: a thought is what the brain produce, so we define the brain as the processor of what it produces. All the evidences we have suggest that the *human brain can understand only its own products*. Now if it is true that our brains understand only their own artifacts, then it becomes quite obvious why we need to model reality: *we imagine reality to conceive it*. From a cognitive point of view reality starts to exist only when we start to model it.

We model the reality to conceive it; so the first scope of modeling is representational. Representations are useful to many purposes, but probably the first is remembering. We create mental models of reality to remember it. The exact mechanism that provides memory is still under investigation, but we know that we remember a concept by

connecting it to a network of other memories; so as soon as we memorize a model this get connected to many other models. This is the second scope of modeling: to correlate portions of reality. But this makes possible to compare two portions of reality: so models are used also to compare. Comparison yield measurement, so models make possible to quantify and measure. Another scope of modeling is predicting. As soon as we discover regularities in the world, every time we notice that whenever we perceive a portion of reality sooner or later another connected portion of reality will also be perceivable, we are in the condition to make predictions. The last scope of modeling is simulation. Through prediction we can mentally explore which actions will transform portions of reality in the way we want.

So we have many reasons to model reality: *representation*, *correlation*, *quantification*, *prediction*, and *simulation*.

2.2. Scientific Models

Every human being imagines the reality: the problem is that we all imagine it different. Now for a number of reasons humanity developed the need to have models of reality that where the same for all human been. Initially the reasons were practical: there are some models that are more effective than others in correlating, measuring, predicting, and simulating the reality. When we realize that we prefer to discard our own models, and replace them with these more effective one. It sounds easy but it is not: humanity struggled for centuries searching for the best way to identify among all possible models which one was the most effective to a certain cognitive scope. The best answer to this question so far is what we call the *scientific method*.

Scientists model the reality like any other human been. However, following the scientific method, we try to slowly develop *collective* models of reality that are found effective by the vast majority of scientists. The cognitive artifacts are scientific models, which are still models, i.e. imaginations of the reality and containers of our beliefs, but are formed through a collective and iterative process (the scientific method).

The reason for this very long introduction is that it may help us to start getting rid of some misconceptions that are besieging biomedical research. Modern biomedical research stands on two scientific traditions that are different, and even conflicting to a certain extent: biology and physics. For example biologists are fascinated by induction, and by observation that is its basis; physicists are fascinated by deduction, and by mathematics that is its basis. In addition, the scopes of biomedical research are largely defined by medicine, which like engineering is primarily a social demand, and only opportunistically becomes science, in the sense that uses scientific knowledge when it is useful to solve the problem. Medicine, like engineering, is strongly oriented toward *abduction*, intended as iterative process where observation is not used to create theories, but rather to test them.

Useless to say all these different perspectives are valid to a certain extend, but become invalid when pushed too far. The biological tradition drives many researchers to believe that only experimental observations are “true”, and substantially distrust any other approach, and models in particular. On the other side, the physics tradition drive others

researchers to pretend that only a deductive mathematical model makes sense, even if when in order to build it we have to push idealization too far. In between, the medical tradition that distrusts everything that did not yet proved to work in the clinical practice, but that is much less critical on how such efficacy is assessed. On the basis of what we wrote before we can make a few statements:

- Every scientific work is based on models; the experiment we design is just the materialization of a model we made of that portion of reality, a model we then use to interpret the results the experiment provides. Controlled experiments, like any other model, always involve some idealization.
- Also the use of mathematics and deductive reasoning in itself does not ensure greater truth content. A deduction is true only if the antecedents are true; if we use gross idealizations to make the problem mathematically treatable, the antecedents are false, and so is any deduction we can make from them.
- It is wrong to believe that a certain method of investigation is superior to the other *a priori*. How we probe reality in the end is not so important, what is important is the model we create, and the collective process that makes possible to share this model and repeatedly attempt to disproof its validity.

In this context we can define scientific models as: "*finalized cognitive constructs of finite complexity that idealize an infinitely complex portion of reality through idealizations that contribute to the achievement of knowledge on that portion of reality that is objective, shareable, reliable and verifiable*" (Viceconti, 2011).

Science pursues two distinct although related objectives: to solve concrete problems of humanity, and to increase our collective knowledge about the reality. This dichotomy is sometime represented with the terms applied and fundamental research. Now, when the scope is the production of knowledge, models become containers of our scientific beliefs, a.k.a. theories. According the classic Popperian conception of science, theories cannot be confirmed, but only disproved. Thus every model must be subjected to endless series of cleverly designed tests, aimed to falsify the theory, to prove it wrong. If all these attempts fail, we can consider for the time being that theory a scientific truth, and incorporate into our body of knowledge.

When we are engaged in problem solving, the story gets a bit more complicated.

2.3. Modeling and Problem Solving

In problem solving we are not particularly worried about the truth content of our models, but only to how good they are to absolve their scope. So the first step in this process is to define, explicitly and with the lowest possible level of ambiguity what is the *modeling scope*, i.e. the problem that the model is expected to solve. Above we listed five possible scopes for a model: representation, correlation, quantification, prediction, and simulation. These scopes should not be confused or mixed. A typical methodological error in models validation is to validate the model with respect to one scope, and then to use it for another. For example, if we prove that our model's predictions correlate with measurements obtained from controlled experiments this only validates the model for correlation purposes. If we want to use the model to make predictions, we first need to validate its predictive accuracy.

Then we need to choose in which ways we want to materialize the model; we can implement it as a mathematical model, and a numerical model, as an animal model, as an experimental model, as an epidemiological model, etc. Depending on the type of implementation we use, we need to complete the *verification* process (figure 2). This process aims to exclude or quantify the deviations from the modeling scope that are not due to the model, but to the concrete implementation we choose. This implies that the verification is very different depending on the type of implementation we use. A mathematical model might have to be verified for existence and uniqueness of the solution; a numerical problem for the numerical errors; a controlled experiment for the accuracy and repeatability of the measurements involved. Verification is based on experience: we cannot investigate a type of deviation that we are not aware of. For each method we use to implement the model there is a body of knowledge that tells us to verify that method. When such body of knowledge does not exist, or it is incomplete, then the method is unverified, and should not be used.

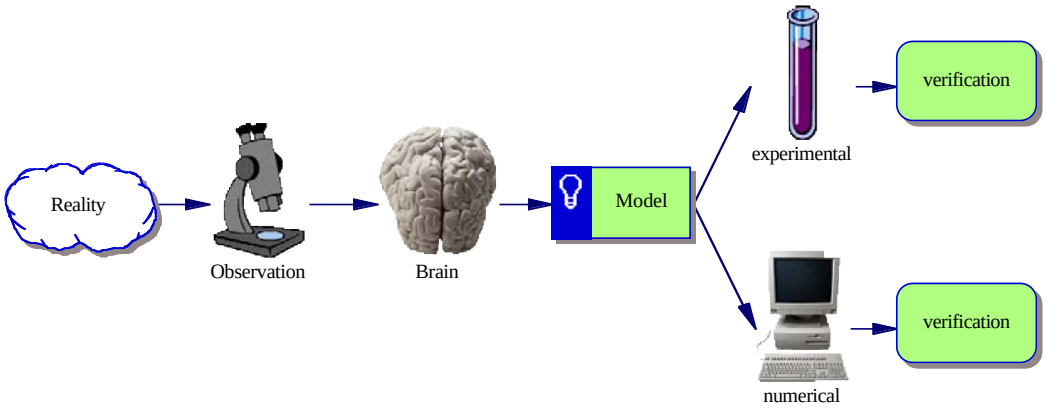

Figure 2. From reality to verification.

Once the implementation method is verified the model can be validated. Validation is very delicate process: in order to quantify the ability of the model to fulfill the modeling scope, we usually need to create another model, with a separate implementation, and use this to verify the first one (figure 3). I am sure many think this description is wrong, as it does not fit the validation of models with direct observation *in vivo*. Accept this fact: everything we do is a model. Say that we want to validate a sugar metabolism model, with an experiment *in vivo*. Still the decision to measure a certain quantity in the patients, or to induce a certain metabolic condition by injecting a certain substance, implies a model that is then implemented into an experiment *in vivo*.

In some cases there is the concrete risk that the two models involved in the validation process, one of which is frequently defined only implicitly through its experimental implementation, might have conflicting idealizations. To avoid this, a good approach is to derive from the model to be validated, another model whose idealization set is somehow orthogonal to that on the model to be validated, and in general not in conflict. Such model usually requires a different implementation method. The construction of the orthogonal idealization set is not a trivial operation; thus, the most effective operation is to use the model in a numerical implementation to design the experimental implementation that is then used to validate the model.

-

-

-

Bibliography

2008. Reductionism. Wikipedia, The Free Encyclopedia, http://en.wikipedia.org/wiki/Reductionism. [Excellent definition of reductionism].

Brenner, S., Noble, D., Sejnowski, T., Fields, R., Laughlin, S., Berridge, M., Segel, L., Prank, K., Dolmetsch, R., 2001. Understanding complex systems: top-down, bottom-up or middle-out? In Novartis Foundation Symposium: Complexity in Biological Information Processing. Chichester, John Wiley. [Reflection of the development of multiscale models].

Calve, S., Simon, H. G., 2011. High resolution three-dimensional imaging: Evidence for cell cycle reentry in regenerating skeletal muscle. Dev Dyn 240(5), 1233-9. [Example of serial sectioning].

Campbell, D. T., 1974. Downward causation in hierarchically organized biological systems. In: Ayala, P. J., Dobzhansky, T. (Eds.), Studies in the philosophy of biology and related problems. University of California Press, pp. 179-186. [Definition of upward and downward causation].

Christie, G. R., Nielsen, P. M., Blackett, S. A., Bradley, C. P., Hunter, P. J., 2009. FieldML: concepts and implementation. Philos Transact A Math Phys Eng Sci 367(1895), 1869-84. [Introduction to FieldML].

Clapworthy, G., Kohl, P., Gregerson, H., Thomas, S., Viceconti, M., Hose, D., Pinney, D., Fenner, J., McCormack, K., Lawford, P., Van Sint Jan, S., Waters, S., Coveney, P., 2007. Digital Human Modeling: A Global Vision and a European Perspective. In: Digital Human Modeling. pp. 549-558. [One of the first positions papers on the Virtual Physiological Human vision].

Clapworthy, G., Viceconti, M., Coveney, P. V., Kohl, P., 2008. The virtual physiological human: building a framework for computational biomedicine I. Editorial. Philos Transact A Math Phys Eng Sci 366(1878), 2975-8. [Opening editorial of the first special issue of the Royal Society on the VPH; first volume].

Dawkins, R., 1986. The Blind Watchmaker. W. W. Norton & Company, Inc., New York. [Where Richard Dawkins introduces the concept or hierarchical reductionism, which implies that only upward causation is active].

Erturk, A., Bradke, F., 2012. High-resolution imaging of entire organs by 3-dimensional imaging of solvent cleared organs (3DISCO). Exp Neurol. Apr;242:57-64. [Another example of serial sectioning].

Fenner, J. W., Brook, B., Clapworthy, G., Coveney, P. V., Feipel, V., Gregersen, H., Hose, D. R., Kohl, P., Lawford, P., McCormack, K. M., 2008. The EuroPhysiome, STEP and a roadmap for the virtual physiological human. Philos Transact A Math Phys Eng Sci. Sep 13;366(1878):2979-99. [Paper summarizing the STEP research roadmap for the VPH].

Fujimura, A., Nozaka, Y., 2002. Analysis of the three-dimensional lymphatic architecture of the periodontal tissue using a new 3D reconstruction method. Microsc Res Tech 56(1), 60-5. [Another example of serial sectioning].

Halloran, J. P., Erdemir, A., van den Bogert, A. J., 2009. Adaptive surrogate modeling for efficient coupling of musculoskeletal control and tissue deformation models. J Biomech Eng 131(1), 011014. [Example of multiscale coupling issue solved with surrogate modeling].

Heino, J., Tunyan, K., Calvetti, D., Somersalo, E., 2007. Bayesian flux balance analysis applied to a skeletal muscle metabolic model. J Theor Biol 248(1), 91-110. [Introductive paper for the Metabolica code].

Hofer, T., Przyrembel, H., Verleger, S., 2004. New evidence for the theory of the stork. Paediatr Perinat Epidemiol 18(1), 88-92. [About false hypotheses from statistical analyses].

Hoffpauir, B. K., Pope, B. A., Spirou, G. A., 2007. Serial sectioning and electron microscopy of large tissue volumes for 3D analysis and reconstruction: a case study of the calyx of Held. Nat Protoc 2(1), 9-22. [Another serial sectioning paper].

Hucka, M., Finney, A., Sauro, H. M., Bolouri, H., Doyle, J. C., Kitano, H., Arkin, A. P., Bornstein, B. J., Bray, D., Cornish-Bowden, A., Cuellar, A. A., Dronov, S., Gilles, E. D., Ginkel, M., Gor, V., Goryanin, II, Hedley, W. J., Hodgman, T. C., Hofmeyr, J. H., Hunter, P. J., Juty, N. S., Kasberger, J. L., Kremling, A., Kummer, U., Le Novere, N., Loew, L. M., Lucio, D., Mendes, P., Minch, E., Mjolsness, E. D., Nakayama, Y., Nelson, M. R., Nielsen, P. F., Sakurada, T., Schaff, J. C., Shapiro, B. E., Shimizu, T. S., Spence, H. D., Stelling, J., Takahashi, K., Tomita, M., Wagner, J., Wang, J., 2003. The systems biology markup language (SBML): a medium for representation and exchange of biochemical network models. Bioinformatics 19(4), 524-31. [Basic reference for the SBML language].

Hunter, P., Coveney, P. V., de Bono, B., Diaz, V., Fenner, J., Frangi, A. F., Harris, P., Hose, R., Kohl, P., Lawford, P., McCormack, K., Mendes, M., Omholt, S., Quarteroni, A., Skar, J., Tegner, J., Randall Thomas, S., Tollis, I., Tsamardinos, I., van Beek, J. H., Viceconti, M., 2010. A vision and strategy for the virtual physiological human in 2010 and beyond. Philos Transact A Math Phys Eng Sci 368(1920), 2595-614. [Update of the vPH NoE roadmap].

Hunter, P. J., Viceconti, M., 2009. The VPH-Physiome Project: Standards and Tools for Multiscale Modeling in Clinical Applications. Biomedical Engineering, IEEE Reviews in 2, 40-53. [Position paper on the VPH/PHysiome tools].

Itu, L., Sharma, P., Ralovich, K., Mihalef, V., Ionasec, R., Everett, A., Ringel, R., Kamen, A., Comaniciu, D., 2012. Non-Invasive Hemodynamic Assessment of Aortic Coarctation: Validation with In Vivo Measurements. Ann Biomed Eng. Apr;41(4):669-81. [Example of reduced order model usage in VPH application].

Kohl, P., Coveney, P., Clapworthy, G., Viceconti, M., 2008. The virtual physiological human. Editorial. Philos Transact A Math Phys Eng Sci 366(1879), 3223-4. . [Opening editorial of the first special issue of the Royal Society on the VPH; second volume].

Kohl, P., Noble, D., 2009. Systems biology and the virtual physiological human. Mol Syst Biol 5, 292. [Poition paper on the relation between systems biology and the VPH].

Kohl, P., Viceconti, M., 2010. The virtual physiological human: computer simulation for integrative biomedicine II. Philos Transact A Math Phys Eng Sci 368(1921), 2837-9. . [Opening editorial of the second special issue of the Royal Society on the VPH; second volume].

Kroese, D. P., Taimre, T., Botev, Z. I., 2011. Handbook of Monte Carlo Methods. Wiley. [Essential textbook for Monte Carlo methods].

Lloyd, C. M., Halstead, M. D., Nielsen, P. F., 2004. CellML: its future, present and past. Prog Biophys Mol Biol 85(2-3), 433-50. [Presentation of the CellML language].

Machiels, L., Maday, Y., Oliveira, I. B., Patera, A. T., Rovas, D. V., 2000. Output bounds for reduced-basis approximations of symmetric positive definite eigenvalue problems. Comptes Rendus de l'Academie des Sciences - Series I - Mathematics 331(2), 153-158. [Model order reduction using reduced bases].

Mayerich, D., Abbott, L., McCormick, B., 2008. Knife-edge scanning microscopy for imaging and reconstruction of three-dimensional anatomical structures of the mouse brain. J Microsc 231(Pt 1), 134-43. [Another example of serial sectioning].

Mishchenko, Y., 2009. Automation of 3D reconstruction of neural tissue from large volume of conventional serial section transmission electron micrographs. J Neurosci Methods 176(2), 276-89. [Another example of serial sectioning].

Polkinghorne, J. C., 2007. Reductionism. Interdisciplinary Encyclopedia of Religion and Science, http://www.disf.org/en/Voci/104.asp. [Philosophical treaty on the role of reductionism in science].

Santos, V. J., Bustamante, C. D., Valero-Cuevas, F. J., 2009. Improving the fitness of high-dimensional biomechanical models via data-driven stochastic exploration. IEEE Trans Biomed Eng 56(3), 552-64. [Application of Markov-Chain Monte Carlo to physiological modeling].

Sargent, R. G., 1994. Verification and validation of simulation models. In Proceedings of the 26th conference on Winter simulation, Society for Computer Simulation International. [Paper on the general problem of V&V].

Sloot, P. M., Hoekstra, A. G., 2010. Multi-scale modeling in computational biomedicine. Brief Bioinform 11(1), 142-52. [Paper that introduces the scale separation map].

STEP Consortium, 2007. Seeding the EuroPhysiome: A Roadmap to the Virtual Physiological Human. http://www.europhysiome.org/roadmap. [Research roadmap of the VPH initiative].

Taddei, F., Martelli, S., Reggiani, B., Cristofolini, L., Viceconti, M., 2006. Finite-element modeling of bones from CT data: sensitivity to geometry and material uncertainties. IEEE Trans Biomed Eng 53(11), 2194-200. [Sensitivity analysis of subject-specific finite element models].

Thiel, R., Stroetmann, K. A., Stroetmann, V. N., Viceconti, M., 2009. Designing a socio-economic assessment method for integrative biomedical research: the Osteoporotic Virtual Physiological Human project. Stud Health Technol Inform 150, 876-80. [Cost-benefits analysis for VPHOP Technology].

Viceconti, M., 2011. A tentative taxonomy for predictive models in relation to their falsifiability. Philos Transact A Math Phys Eng Sci 369(1954), 4149-61. {Reflection on models in sciences, and on their classification in relation to their falsifiability].

Viceconti, M., Brusi, G., Pancanti, A., Cristofolini, L., 2006. Primary stability of an anatomical cementless hip stem: a statistical analysis. J Biomech 39(7), 1169-79. [Stochastic modeling used to evaluate the effect of inter-subject and inter-surgery variability on the clinical outcome of new medical device].

Viceconti, M., Clapworthy, G., di Tecnologia Medica, L., Rizzoli, I. O., Bologna, I., 2006. The virtual physiological human: challenges and opportunities. In Biomedical Imaging: Macro to Nano, 2006. 3rd IEEE International Symposium on. pp.812,815, 6-9 April 2006. doi: 10.1109/ISBI.2006.1625042. [First position paper on the VPH].

Viceconti, M., Clapworthy, G., Testi, D., Taddei, F., McFarlane, N., 2010. Multimodal fusion of biomedical data at different temporal and dimensional scales. Comput Methods Programs Biomed. 102(3):227-237. [Interactive visualization of multiscale data].

Viceconti, M., Clapworthy, G., Van Sint Jan, S., 2008. The Virtual Physiological Human - A European Initiative for In Silico Human Modeling. J Physiol Sci. Dec;58(7):441-6. [Another position paper on the VPH].

Viceconti, M., Kohl, P., 2010. The virtual physiological human: computer simulation for integrative biomedicine I. Philos Transact A Math Phys Eng Sci 368(1920), 2591-4. [Opening editorial of the second special issue of the Royal Society on the VPH; first volume].

Viceconti, M., Taddei, F., Cristofolini, L., Martelli, S., Falcinelli, C., Schileo, E., 2012. Are spontaneous fractures possible? An example of clinical application for personalised, multiscale neuro-musculo-skeletal modeling. J Biomech 45(3), 421-6. [Invited plenary lecture at the XXIII conference of the International Society of Biomechanics, July 2011 Brussels].

Biographical Sketch

Marco Viceconti is Scientific Director of the Insigneo Institute for in silico Medicine and full Professor of Biomechanics at the Department of Mechanical Engineering at the University of Sheffield. Before he was the Technical Director of the Medical Technology Lab at the Rizzoli Orthopaedic Institute in Bologna, Italy. He is currently President of the European Alliance of Biomedical Engineering (EAMBES). His main research interests are related to the development and validation of medical technology, especially that involving simulation, and primarily in relation to musculoskeletal diseases. He has published over 200 papers, mostly indexed in Medline, and serves as reviewer for many international funding agencies and peer-reviewed journals. Marco Viceconti is one of the key figures in the emerging Virtual Physiological Human (VPH) community. Co-author of the first white paper on VPH, scientific coordinator of the seminal VPH research roadmap, "VPH ambassador" for the VPH Network of Excellence, Coordinator of one the VPHOP integrated project, he is also currently chairing the Board of Directors of the VPH Institute.