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Biomechanics–based In Silico Medicine: the manifesto of a new science

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Biomechanics–based *In Silico* Medicine: the manifesto of a new science[1]

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> « La filosofia è scritta in questo grandissimo libro che continuamente ci sta aperto innanzi a gli occhi (io dico l'universo), ma non si può intendere se prima non s'impara a intender la lingua, e conoscer i caratteri, ne' quali è scritto. Egli è scritto in lingua matematica, e i caratteri son triangoli, cerchi, ed altre figure geometriche, senza i quali mezzi è impossibile a intenderne umanamente parola; senza questi è un aggirarsi vanamente per un oscuro laberinto.» *(Galileo Galilei, Il Saggiatore, Cap. VI)*

Abstract

In this perspective article we discuss the role of contemporary biomechanics in the light of recent applications such as the development of the so-called *Virtual Physiological Human* technologies for physiology-based *in silico* medicine. In order to build Virtual Physiological Human (VPH) models, computer models that capture and integrate the complex systemic dynamics of living organisms across radically different space-time scales, we need to re-formulate a vast body of existing biology and physiology knowledge so that it is formulated as a quantitative hypothesis, which can be expressed in mathematical terms. Once the predictive accuracy of these models is confirmed against controlled experiments and against clinical observations, we will have VPH model that can reliably predict certain quantitative changes in health status of a given patient, but also, more important, we will have a theory, in the true meaning this word has in the scientific method. In this scenario, biomechanics plays a very important role: biomechanics is one of the few areas of life sciences where we attempt to build full

[1] Some of the concepts exposed here were first presented at the 7th World Congress of Biomechanics, held in Boston (USA) in July 2014, in the plenary lecture entitled:" To Infinity and Beyond Musculoskeletal Biomechanics in the Age of the Virtual Physiological Human".

mechanistic explanations based on quantitative observations; in other words, we investigate living organisms like physical systems. This is in our opinion a Copernican revolution, around which the scope of biomechanics should be re-defined. Thus, we propose a new definition for our research domain: “Biomechanics is the study of living organisms as mechanistic systems”.

Keywords

Biomechanics, Virtual Physiological Human.

In silico medicine (ISM) is usually defined as the use of computer simulation in the provision of healthcare (Wikipedia contributors, 2014). In this sense, ISM appears primarily an engineering challenge, where existing knowledge about the physiology and the pathology of the human body is captured in computer models, combined with specific quantitative data about the anatomy, physiology, pathology, and biology of the patient, and used to make predictions useful in prevention, diagnosis, prognosis, treatment planning, rehabilitation planning, and monitoring (Bassingthwaighte, 1997; Popel *et al.*, 1998; Hunter *et al.*, 2002; STEP Consortium, 2007).

While this perspective is essential, and it defines the path to translate this research into true socioeconomic impact (Thiel *et al.*, 2009; Viceconti, M., and McCulloch, 2011; Thiel *et al.*, 2013), it tends to hide a much more fundamental perspective: that *in silico* medicine is a new science.

Admittedly, this status emerges somehow from necessity. In order to build *Virtual Physiological Human* (VPH) models, computer models that capture and integrate the complex systemic dynamics of living organisms across radically different space-time scales, we need to re-formulate a vast body of existing biology and physiology knowledge so that it is formulated as a *quantitative hypothesis,* which can be expressed in mathematical terms. Some physiologists pioneered this approach: for example Noble's seminal work in cardiac electrophysiology (Noble, 1960), or Guyton' model for circulatory control (Guyton *et al*., 1972).

We then need to attempt the falsification of these quantitative hypotheses by means of *quantitative experiments*. However, due to the complexity of living organisms, each experiment must trade complexity (some authors refer to this as *realism*) with controllability. If we experiment with an intervention on a patient or a volunteer, there are limited possibilities to control a number of co-factors that can influence the outcome; in other words our ability to *control* the experiment is somehow limited. So we resort to experimental models: the simpler is the model, the higher is the level of control we can have on it. So an animal model is much more complex (and difficult to control) than a *ex vivo* tissue culture model, which in turn is much more complex and much less controllable than an *in vitro* experiment. This is why in the most advanced VPH models we falsify our hypotheses by using progressively more complex experimental models (or progressively reduced controllability), typically starting *in vitro*, then move to animal models, and then last to human experimentation. In this process our understanding of the limitations of the theory at hand increases, we unravel the co-factors that interfere with the observations, and we are thus in a much stronger position to interpret the outcomes of clinical experimentation.

But at the end of this tortuous and incredibly challenging process not only we will have a VPH model that can reliably predict certain quantitative changes in health status of a given patient, but also, more important, we will have a *theory*, in the true meaning this word has in the scientific method. This is a new science where researchers trained in biology, physiology, chemistry, mathematics, physics, engineering, and medicine work together sharing this epistemology.

It is a new science where the methods of synthetic biology, cellular biology, tissue engineering, animal experimentation, or experimental biophysics (biomechanics, bioelectricity, biochemistry, etc.) are used not as an end but as a mean to inform and validate new quantitative hypotheses, and the computer models that embody them. In this sense ISM is not a computational science, nor an experimental science; it is in the continuous exchange between models and experiments that this new science manifest itself.

In this scenario, biomechanics plays a very important role, much more important than it was recognised so far. First, biology has historically privileged the chemical side of all processes, neglecting the role that mechanical factors play in most physiological and pathological processes; we need a lot more of biomechanical knowledge at all space-time scales, from the whole body neuromuscular coordination to the effect of nucleus deformation on the synthesis of proteins within a single cell.

But the potential role that biomechanics can play in this context is much broader. Traditionally biomechanics is defined as " […] the study of the structure and function of biological systems by means of the methods of mechanics" [Hatze, 1974]. This reflects an old academic subdivision of physical sciences around the fundamental types of energy (mechanical, chemical, electromagnetic); but as biomechanics develop its research agenda also at organ, tissue, and cell scales, the separation of mechanical factors from the chemical or electrical ones becomes arbitrary, to say the least.

So what is the role of biomechanics in the 21st century? It is interesting to notice that many VPH specialists emerged from biomechanics, and that the musculoskeletal and cardiovascular systems (historically the most biomechanics-intensive) are the two organ systems where the use of VPH approaches has yield the best results so far. The reason is simple: biomechanics is one of the few areas of life sciences where we attempt to build full mechanistic explanations based on quantitative observations; in other words, we investigate living organisms like physical systems.

In the past the idea that living organisms could be reduced to physical systems has been debated, for example by Ernst Mayr (Mayr, 2004), claiming that biology could not be reduced to physics and chemistry, and had its own unique epistemological space. Most of the arguments of this thesis are based on limitations, in the sense that they suggest that the complexity of living organisms prevents to investigate them as physical systems, and thus a new epistemology must be used, that of biology. It is unquestionable that there are broad areas such as evolution (Mayr himself was an evolutionary biologist) where this is true; but the constant improvement of experimental and computational technologies is expanding the territory of biological problems were a full mechanistic approach is viable. An evidence of this is the appearance of *Systems Biology*, where a bottom-up mechanistic approach is advocated.

And here is, in our opinion, the unique space for biomechanics research: where a mechanistic approach is possible, who better than a biomechanician can pick up this challenge? This is in our opinion a Copernican revolution, around which the scope of biomechanics should be re-defined. Thus, we propose a new definition for our research domain: "**Biomechanics is the study of living organisms as mechanistic systems**". Wherever there is space for a mechanistic investigation, biomechanics steps in, with its quantitative observations made over space and time and across space-time scales, with its mechanistic theories, and with its progression of experimental falsifications from the most controllable experiments to the clinical experimentation.

In conclusion, biomechanics-based *in silico* medicine is a new science of life, based on the conviction that the book of nature, including living organisms, is written in the language of mathematics, and on the arrogance that we can eventually, one day, understand that book.

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Conflict of interest statement

The author declares he has no conflicts of interest to disclose in relation to this manuscript.

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