Morphologie (2019) **103**, 127—130

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EDITORIAL

# Modelling towards a more holistic medicine: The Virtual Physiological Human (VPH)

## *Modélisation vers une médecine plus holistique : l'homme physiologique virtuel (VPH)*

**KEYWORDS**
Virtual Physiological Human;
VPH;
Holistic medicine;
Modelling

**Summary** The Virtual Physiological Human (VPH) is a European initiative, rooted in the international Physiome initiative, focusing on establishing a methodological and technological framework, enabling the collaborative investigation of the human body as a single complex system. This collective framework will facilitate the sharing of resources and observations formed by different institutions and organizations, and the creation of disparate but integrated computer models of the mechanical, physical and biochemical functions of a living human body. The VPH initiative has laid the foundation for integrating heterogeneous data sources into mechanistic computer models of most anatomical systems.


**Résumé** Le Virtual Physiological Human (VPH, ou en français, l'humain physiologique virtuel) est une initiative européenne, inspirée de l'initiative internationale Physiome, pour l'établissement d'une méthodologie et d'une infrastructure technologique permettant une analyse collaborative et multidisciplinaire du corps humain comme une entité unique et complexe. Cet effort collectif a pour but de faciliter le partage de ressources et d'observations acquises par différentes institutions et organisations (par exemple, des données provenant d'un dossier-patient et de la recherche fondamentale), et permettra la création de modèles digitaux intégrés à partir de données hétérogènes pour permettre une meilleure compréhension des fonctions mécaniques, physiques et biochimiques au sein du l'organisme humain. Le VPH a mis en place ces dernières années les fondations pour l'intégration de la plupart des systèmes anatomiques au sein de cette méthodologie. Ce numéro spécial illustre le paradigme derrière le VPH par le biais d'articles portant sur des recherches déjà appliquées en clinique ou encore au stade de la recherche fondamentale.


Fast-growing progress in medical research associated to continuous novel fundamental insights in human Anatomy and Physiology makes clinical activities more and more challenging. Nowadays it is estimated that each medical doctor should theoretically read thousands of scientific articles per year in order to remain informed of new clinically-relevant scientific findings. The platform Medline reports that more than 800k publications per year are published in several hundreds of journals of various levels of quality [1], covering multiple fields from good medical practices over drug development to biological discoveries. It is obviously a near impossible task and, therefore, knowledge uptake

https://doi.org/10.1016/j.morpho.2019.10.044
1286-0115/

occurs following one of two complementary paths. The first path consists of enabling specialists to gain high expertise in gross domains (e.g., neurology, orthopaedics, etc) and niche sub-domains (e.g., child brain neuro-surgery, vertebral reconstruction, etc). The flip side of this high specialisation is however that less and less individuals will keep an overall view on Medicine at large. Since today medical knowledge is rapidly growing, too quickly for most human capabilities, a second path should be available to enable a more integrative view of patient medical files and look at a patient as one living entity, instead of a collection of loosely linked anatomical systems.

The Virtual Physiological Human (VPH) is a European initiative, rooted in the international Physiome initiative, focusing on establishing a methodological and technological framework, enabling the collaborative investigation of the human body as a single complex system. This collective framework will facilitate the sharing of resources and observations formed by different institutions and organizations, and the creation of disparate but integrated computer models of the mechanical, physical and biochemical functions of a living human body. The VPH initiative has laid the foundation for integrating heterogeneous data sources into mechanistic computer models of most anatomical systems.

## The virtual physiological human—the origin

Modern medicine is unfortunately often lacking true multidisciplinary collaboration between medical specialties. Often, a patient suffering from some health disorders is facing a long way to find the proper medical support because of an organizational shortage in Clinics. For example (real example), a 42-year-old woman, several times national long jump champion is suffering from severe limping. Because of her high-level sport history, her general practitioner logically thought about a mechanical problem and sent the patient to an orthopaedist. After several months of physical therapy, the surgeon decided to remove a part of her meniscus that showed some limited damage. Almost 15 months after her first consultation, the patient was still suffering from limping, and the limping gradually worsened. She then also complained of loss of balance and reduced grip strength. Her physical therapist thus advised her to see a neurologist. Neurological examinations showed that she was suffering of multi system atrophy (or MSA), a very aggressive form of Parkinson disease [2]. This patient lost several months of MSA-targeted treatment [3] because of the lack of a holistic approach that should have been adopted by the medical professionals whom she contacted.

Now, is it the fault of the medical staff she encountered? Yes and no. Yes, because they could probably have thought about potential problems outside their area of expertise; it is clear than limping is not a specific orthopaedic problem and that it is also frequently caused by some neurological disorders. On the other hand, as above-mentioned, the amount of knowledge and treatment collected the last decades makes it very difficult for medical staff to remain up-to-date (especially for rare diseases similar to MSA) and to read all possible publications that could be useful for their practice. It is humanly impossible to track all this information, sort it, extract the useful elements for daily clinical practice and integrate these elements in usable clinical protocols, while also keeping an eye on other medical specialties focusing on patients with similar clinical signs (e.g., the above example of limping that could be caused by either an orthopaedic or neurological problems).

The Virtual Physiological Human Initiative (VPHi) was created exactly to meet that purpose: to build tools and organize Science in order to enable medical professionals practicing a more holistic approach of their patients.

## The virtual physiological human—the vision [4]

The VPH is a methodological and technological framework that, once fully established, will enable collaborative investigation of the human body as a single complex system. The VPH is not one single ''super computer model'' that will explain all possible aspects of human physiology or pathology. It is a way to share observations, to derive predictive hypotheses from them, and to integrate them into a constantly improving understanding of human physiology/pathology, by regarding it as a single system. Computer models and simulations are frequently indicated by the term 'in silico' tools. 'In silico' refers to silicon, the main component of computer chips, and is chosen in analogy to the well-known terms for the other tools used in biomedical sciences, namely in vitro ('in glass' or in the laboratory) and in vivo (in living beings).

Today, biomedical research faces many problems similar to the one above and involves a complexity for which the traditional approach is inadequate. This approach is based on the subdivision of biological systems in some way—by dimensional scales (body, organ, tissue, cell, molecule), by scientific disciplines (biology, physiology, biophysics, bioengineering), or by anatomical sub-systems (cardiovascular, musculoskeletal, gastrointestinal, etc.). But these artificial subdivisions make it impossible to unravel the systemic nature that governs many of the physical manifestations of the human body. To continue the scientific exploration of the human body that has already so dramatically improved the length and quality of life for a major section of mankind, it has become apparent that it will be necessary to complement this traditional approach with an integrative approach that makes it possible to combine observations, theories and predictions across the temporal and dimensional scales, the scientific disciplines, and anatomical sub-systems, all of which currently create the rather artificial divisions described. This realization, shared by the vast majority of experts in the field, has given rise to a number of initiatives such as integrative biology, system biology, physiome, etc. This integrative approach requires a radical transformation in the way biomedical research is conducted. It is necessary to have a framework within which observations and measurements from a variety of sources can be collected, shared and combined in many different ways. This framework should allow experts from a variety of disciplines to work collaboratively to analyse these observations and to develop systemic hypotheses. It should also make it possible to combine predictive models defined at different scales, with different methods or with different levels of detail, in order to make the hypotheses tangible, and to allow their validity to be tested against existing results. Currently, we

are investigating the human body by pretending that it is a jigsaw puzzle made up of a trillion pieces and we are trying to understand the whole picture by looking only at a single piece (see the above example of the limping patient) or, maybe, a few closely interconnected pieces; it should be no surprise that we are having a hard time. The scope of the Virtual Physiological Human is to propose a methodological and technological framework that will enable investigations of the human body as a single (though hugely complex) system. The VPH is the framework within which we can finally start to put all of the pieces together and it is also the glue that can connect them. The VPH will not represent, per se, the whole picture, but it does represent our best pathway towards forming that picture at some time in the future.

The VPH has been started in 2008, but the road is still long to achieve it fully as explained below.

## The Virtual Physiological Human—A path to a holistic medicine?

For many years, researchers realized that focusing on very specific research topics from a very limited and specialized point of view could not lead to important breakthroughs a more holistic health care system would requires [5,6].

In 2005, a group of 20 researchers wrote a common White Paper [7], which goal was to shape a clear overview of ongoing VPH-related activities, to build a consensus on how they can be complemented by new initiatives for researchers in the European Union and to identify possible mid-term and long-term research challenges. This initiative was an add-on to the existing scientific areas already supported by the European Commission. Activities identified spanned from better use of existing data and tools to the development of new methods, libraries and tools. Examples of these specific VPH activities were to address the need to further development of numerical modelling, and simulation, address the need for innovative imaging processing methods to make use of them, the multidisciplinary dimension, the infrastructure needed and finally the acceptance issue. It is important to underline that these areas were already being developed also in a more specific content but new needs were identified in the realm of the VPH.

In 2007, a group of more than 300 international researchers from a large variety of fields (medicine, engineering, biology, etc.) gathered in Brussels to produce and to co-sign a roadmap that includes their vision about how to achieve the VPH goals. This roadmap [4] was given to the European Commission in order to receive their support.

The VPH-Network of Excellence (VPH-NoE) was officially launched in June 2008 with EU investment of €8 million under the FP7 European funding programme. The aim of this NoE was to organise and promote the VPH vision through Europe, to convince researchers to join the effort, to convince clinicians to adopt the VPH holistic paradigm when dealing with patients, and to help SMEs access clinical knowledge to reach markets. Clinical practice included many categories of diseases and disorders. A certain number of diseases had a relatively simple aetiology and did not present major challenges for clinicians. Others, however, like cerebral palsy, osteoporosis and heart valve failure, are still challenging because they involved several anatomical and physiological levels. Focusing on the ICT tools used in the development and use of the VPH, it must be stressed again that VPH is not ''the creation of non-realistic or clinically non-relevant technologies, or the creation of a super-clinician.'' The VPH is about the creation of integrative technology used to answer specific clinical questions. For example, cerebral palsy (CP) is a good example of a neurological disorder with a complex aetiology. Overall, there are three challenges for these complex aetiology disorders. Firstly, diagnosing the primary disorder through performing clinical analysis such as medical imaging, motion capture, etc. The CP aetiology is a perinatal brain lesion that leads to numerous clinical signs such as muscle disorders including spasticity, weakness and poor coordination. The long-term effect is member misalignment, joint overuse, psycho-social troubles and lower professional opportunities. The second challenge is the clinical quantification and follow-up of the patient progresses. This requires understanding the patient data, which can be addressed by using in silico modelling methods and bio-statistics. Finding the best ''specific treatment'' is the third challenge. Current CP clinical treatment often involves a series of treatments, such as: drugs (orally and intrathecal bacloflen); neuromuscular blocks; phenol or botulinum toxin A; selective dorsal rhizotomy; tendon transfer; and bone correction [8]. In future, it is necessary to find ''clinical consensus'' on the best treatment option, and VPH technologies could help achieving this consensus. Meeting these three challenges combined are the goals for the Virtual Physiological Human initiative. It must be stressed that by combining clinical and anatomical knowledge with practical expertise, system development and analysis, the proper problem formulation and modelling methods can then be identified. The focus of the VPH initiative is to improve the European healthcare system and the prevention, diagnosis, treatment and care of patients with numerous conditions, including cardiovascular disease, osteoporosis, oncology, liver disease, Alzheimer's disease and breast cancer. The prediction of cancer reoccurrence should also be possible by developing specific ICT technology in the Virtual Physiological Human.

Since the launch of the VPH-NoE project more than 100 VPH-related projects have been funded by the European Union and other funding agencies. Most of these efforts are associated to the VPH-Institute (www.vph-institute.org).

## The Virtual Physiological Human—Where are we now?

Since its inception, the VPH Institute has worked not only on supporting researchers developing their VPH technologies, it has also actively worked on preparing the path for said technologies to clinical uptake. In a series of roadmaps developed by the VPH community, the different challenges are identified and possible solutions are proposed [9,10]. Besides the technical aspects, these challenge are related to regulatory approval, need for appropriate policies, patient acceptance and clinical uptake. The last five years, major steps have been taken related to the implementation of appropriate policies. Rather than developing specific policies related to in silico tools, we have worked on incorporating the use of in silico tools in existing policies.

The acceptability of evidence generated by in silico tools is now explicitly acknowledged in the new EU Medical Device Regulation, the legal framework of EMA and the EU eHealth Action Plan. On the regulatory side, the USA-FDA has been leading the way for the use of in silico technologies in medical devices by publishing guidelines detailing what technical model-related information should be included in the dossier submitted for regulatory consideration [11]. Recently, in a collaborative effort with industry and ASME, a standard was published, the V&V40, detailing how much Verification and Validation ought to be done when including digital evidence (i.e. evidence resulting from the use of in silico models) in regulatory submissions [12]. On the European side, VPHi and EMA are drafting a white paper providing guidelines on the validation of in silico tools in the context of drug design and development. With the path towards clinical implementation cleared from the perspective of the policy makers and regulators, it is crucial to work on uptake by the clinical community. All of the VPH technologies are developed in close collaboration with clinicians, but these are only a small fraction of all clinicians. In the coming years, the VPHi will focus on informing the clinical community about the possibilities and benefits of incorporating in silico models in their clinical practice, as an additional tool to help in the diagnosis, treatment and follow-up of their patients.

This special issue of Morphologie presents the results of several VPH-related projects. Some of them are already well established in clinical settings, others are still at fundamental levels. All of them are based on a sound knowledge of human anatomy and physiology, and demonstrate as such that in order to be effective in Medicine, novel technological developments must be supported by strong fundamental research as well as by appropriate training. Research in Anatomy and Physiology is therefore more then never required to feed these promising developments in order to lead to a more integrative and holistic Medicine.

## Disclosure of interest

The authors declare that they have no competing interest.

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Available online 8 November 2019