In silico clinical trials: A grand challenge for IMI2

Proponent: VPH Institute for Integrative Biomedical Research

Step #1: The VPH

To be able to cure diseases using innovative therapies, we need to understand how they work.

On the one hand we have a large body of observational knowledge: millions of digital records of medical images, biomedical signals, laboratory exams, and clinical reports that describe the *Disease Phenotype*, i.e. how the phenotype of the healthy individual is transformed by the disease over time, and also how this phenotype responds to interventions. In general this knowledge is phenomenological (it does not explain *why*) and is affected by a large number of errors and biases.

On the other hand we have a very large, and constantly growing body of mechanistic knowledge of how certain processes work in a living organism, under physiological and pathological conditions. In general this knowledge is fragmentary and incomplete. More importantly, this mechanistic knowledge is built through reductionism and assumes each process is independent, despite growing evidence that processes in living organisms are interdependent (life is entangled).

In the last 20 years, a growing community of biologists, physiologists, clinicians, pathologists, mathematicians, biophysicists and bioengineers has started to explore the possibility of using computer models to recompose this fragmentary mechanistic knowledge, and to feed it with the observational knowledge obtainable for each patient, in order to predict the development of their health status over time, as a result of disease progression, and in relation to possible interventions.

In the last 10 years the focus has primarily been on the technological challenges of this idea, such as the adoption of standards and workflows that ensure reproducibility of model simulations and the development of modular and semantically-annotated modelling frameworks. We call this challenge the *Virtual Physiological Human*, and it is intended as a framework of methods and technologies that, once established, will make possible the creation of *in silico* patient-specific representations that are descriptive, predictive, and integrative. Today a number of prototypes designed around these principles are being tested clinically; preliminary results show considerable prognostic value for patient-specific computer models in areas such as osteoporosis [Keaveny 2010], coronary stenosis [Morris 2013], corneal surgery [Sinha Roy 2013], cancer [Graf 2009; Stamatakos 2011], etc.

Step #2: From VPH to Design

In silico methods are also being adopted in the population-based design and pre-clinical testing of new biomedical products. Interesting results were obtained for orthopaedic devices [UNMC OBAS Tech Lab Nebraska; Wake Forest Preclinical Translational Services]. Similarly, VPH-like approaches are being used to investigate animal models better [Cambridge Healthtech Institute; EC REACH Initiative, Basel]. Also PK/PD has a good number of examples where computer models of physiological processes are used effectively to explore the pharmacodynamics of a molecule [Virtual Tumor; GastroPlus; QSAR techniques].

Step #3: From VPH to *IS*CT

Avicenna, a Persian physician and philosopher (980-1037), in his Canon of Medicine, first gave a formal structure to the process of evaluating the effect of a treatment on a disease. Since then, the fundamental nature of clinical trials has changed surprisingly little. Today, a new biomedical product is still developed and tested with an empirical approach that fundamentally relies only on knowledge resulting from direct observation.

The fact that biomedical products are heavily regulated reinforces a conservative attitude in this industrial sector. As a result, the cost associated with the development and assessment of new

products has been steadily increasing, and the rate of effective innovation has been decreasing. In other industrial sectors, such as aerospace and nuclear power, where similar trends were observed, the optimum approach to keeping the cost and complexity of safe product development at bay has been computer simulation, usually referred to as Virtual Product Development (VPD); the adoption of VPD in the development and assessment of biomedical products has, however, so far been frustratingly slow.

Recent results from the use of VPH models to make clinically relevant predictions for individual patients, the progressive expansion of *in silico* methods in the design phase, and the extension of the VPH approach to animal models suggests, at least for certain diseases and for certain treatments, a new approach to biomedical product development and assessment that we refer to as ***in silico clinical trials* (*IS*CT)**.

Proposal: *IS*CT - a Grand Challenge for IMI2

We therefore propose *IS*CT for consideration as a Grand Challenge within IMI2, with these targets:

1. Production of validated anatomo-functional statistical atlases for selected populations, to create *in silico* cohorts of virtual patients without ethical and legal constraints. Industrial partners could contribute with anonymised patient data collected in clinical trials.
2. Production of validated stochastic models for daily life history of physiological and life style parameters (including treatment compliance), relevant to inter-subject variability of response to treatment. Industrial partners could again contribute with anonymised patient data collected in clinical trials or ad hoc studies.
3. Co-development of validated identification and modelling processes for the large scale production of patient-specific computer models of specific biological/physiological processes.
4. As item 3, but for commonly used animal models. Industrial partners could develop 'benchmark problems' where a relevant biological process is measured in a given animal model under controlled conditions, to be used to assess the model's predictive accuracy.
5. Co-development of validated identification and modelling processes related to the fundamental biological and physiological processes underlying families of treatments (drug transport, accumulation and release).
6. Development of advanced inter-species translational models based on large collections of patient-specific and animal-specific models, to predict more accurately how the effects of a new treatment on an animal model will translate into humans. Industrial partners could contribute with bodies of pre-clinical and clinical data relating to well-known treatments, which could be used to verify the predictive accuracy of such translation models.
7. Use of validated patient-specific modelling processes to produce reliable surrogate end points that reduce the size and duration of clinical trials, and allow for digital transparency of outcomes to avoid publication bias distorting the accrued evidence. Industrial partners could augment clinical trials with arms aimed at validating such surrogate end points.
8. A multiscale systemic representation of the causation and maintenance of complex disease states as we age. The goal is a new drug-targeting paradigm in which interconnected modelling enables an integrated understanding of disease, from high-level phenotype to molecule, so facilitating a completely systematic approach to drug design. This would provide a seamless link to the *in silico* clinical trial process, where the outcome of drug candidates addressing a wide range of targets would be predicted. Industrial partners could guide the selection of pathophysiologies, assist with drug design expertise, and provide empirical testing.

For such a Grand Challenge we nevertheless suggest that tangible outcomes could be achieved with moderate investment, for pathologies affecting organ systems already investigated extensively within the VPH initiative: the cardio-vasculo-respiratory system, the endocrine system, the immune system, and the neuro-musculo-skeletal system.

About the VPH Institute

'One Life, One Knowledge: Technology to Integrate'

Despite the human need to reduce everything to its component parts in order to understand it, life is the result of an intricate interaction between many processes occurring at radically different spatial and temporal scales. Every day worldwide, biomedical research and clinical practice produce a huge amount of information on such processes, but this information is highly fragmented, and its integration is largely left to the human actors, who find this more and more difficult as the breadth and depth of information available increases exponentially. We therefore need to develop a new approach, to make possible the integration of this information, and to simplify its transformation into integrated knowledge. The Virtual Physiological Human (VPH) is a framework of methods and technologies that, once fully established, will make it possible to investigate the human body as a whole.

The Virtual Physiological Human Institute for Integrative Biomedical Research, in short the VPH Institute, is an international non-profit organisation incorporated in Belgium, whose mission is to ensure that the Virtual Physiological Human initiative is fully realised, universally adopted, and most-effectively used, both in research and in the clinic. For more information, please see http://www.vph-institute.org/

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