**VPH Institute: Consultation on Consultation on directions for Future and Emerging Technologies (FET) research**

What does this topic address? What is the driving question, concept, challenge? Does it capitalise on a recent opportunity, a scientific breakthrough, a new idea or paradigm?

The Virtual Physiological Human (VPH) is a technology enabling a fully personalised and integrative investigation of human physiology in health and disease by means of computer modelling. The VPH is a unique tool that can be applied to help improve our understanding of health, support the exploration, testing and provision of personalised therapeutic approaches to patients, and thereby contribute to rationalising healthcare provision. Support for VPH through the Future and Emerging Technologies (FET) initiative will contribute to improvements in clinical practice, through a better ability to target more effectively the needs of patients and healthcare professionals alike, and thereby to make significant breakthroughs in the field of medical research and our understanding of human physiology.

The VPH capitalises on the relatively new advances in computer modelling, aiming to enable a fully personalised and integrative investigation of human physiology in health and disease through the application of advanced computer simulation and imaging systems. The application of these systems to rationalise and focus experiments will also contribute to the refinement, reduction and replacement of unnecessary animal testing. The acceptance, the adoption and the ultimate reduction to routine practice of in silico simulations will certainly take time. However with appropriate support from the Future and Emerging Technologies (FET) initiative, the Virtual Physiological Human concept and the application of advanced integrative modelling of human pathophysiology will facilitate a transition in current pharmaceutical development, from in vivo to in vitro and then to in silico clinical trials.

Such an investment to promote the VPH technologies will also contribute to delivering the goal of personalised medicine thanks to an improved understanding of the complex dynamics of disease and the ability to use model-based identification of biomarkers of therapeutic efficacy. Further, this improved understanding of disease mechanisms through the use of dynamic modelling systems within the VPH portfolio will support the identification of markers associated with the early onset of disease, offering the opportunity for early intervention. In other words, integrative modelling of complex systems will contribute to the improvement of preventive medicine with a consequent potential for a major positive impact on healthcare systems.

How does this go beyond established approaches? How does it compare to current practice, to the state-of-the-art? What are the structuring effects on the research and innovation landscape (e.g., new collaborations, new methodologies, new practices)?

The integration of a range of previously separate disciplines such as classical molecular and cellular biology, mathematical modelling and biomedical engineering is a brand new practice that requires collaboration across a range of scientific disciplines on a huge scale. The VPH if funded through the FET-proactive initiative will contribute to addressing the following three challenges:

- **Framing the complexity**: The VPH is a global reference frame that permits the organisation of data, information and knowledge accumulated about any biological system in a coherent and integrated
way. It also supports the translation of the observations and learning into an improved understanding of human pathophysiology.

- **Building the complexity**: by building a web of predictive models that can be composed, reused, updated and modified freely, we can bring a more comprehensively informed, better-structured and dynamic understanding of human pathophysiology.

- **Taming the complexity**: By collecting and integrating disparate data sets and information we can facilitate the creation of models that will help to rationalise and integrate the maze of knowledge on the health status of an individual.

These are the goals that the VPH community has set itself and aims to address in the coming years. The complexity being tackled requires extensive exploration, further development and integration of appropriate theoretical tools to achieve efficient model coupling and data assimilation for calibration and validation over multiple scales. Although simulation platforms based on simplified models will be exploited in the short-term, marking the entry of *in silico* medicine into the market, the full deployment of the VPH potential remains a long-term objective to be achieved through extensive basic research. We therefore call on the European Commission to support the Virtual Physiological Human through the FET initiative.

**Why does this require a dedicated (FET-proactive) initiative, i.e., beyond the level of a single project?**

Some European Commission Directorates-General have recognised the potential that VPH can bring to scientific knowledge, to the medical community and to European society as a whole, by previously funding some projects within the VPH. The combined potential delivery from across the VPH community of approaches is very much in line with the FET objective of “fostering novel non-conventional approaches, foundational research and supporting initial developments on long-term research and technological innovation in selected themes”\(^1\). We therefore believe that proactive support for this highly innovative and groundbreaking area, under a dedicated FET initiative, will enable the European Commission to achieve its challenging long-term goals. It will also permit the Commission to continue with its tradition of supporting ICT-based tools for better understanding of the human pathophysiology and for the facilitation of approaches to personalised and predictive healthcare.

**What time scale do you envisage before this could lead to first results and what could these results be?**

The VPH is composed of a variety of different areas that will have different timelines for delivery and the generation of tangible impact. Therefore it is highly likely that results and evidence of potential utility in some scientific areas will emerge long before the final completion of the VPH itself. As an example, increased research into imaging technologies, which is a core theme of VPH, will also lead to the delivery of enhanced diagnostic tools to frontline services. Further, modelling and simulation will be used to identify potential biomarkers and rationalise frontline candidates from amongst many alternatives, which is likely to support the emergence of new revolutionary approaches in personalised medicine. While the goal of the realisation of the Virtual Physiological Human model is a long term one, the milestones that must be met along the road to eventual delivery will have immediate practical applications in the broad field of medicine and healthcare.

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Does it tackle a great societal challenge, like global warming, energy supply, pollution, ageing of society, global crisis, peace, democratic deficit, etc.)? Does it open up radically new possibilities for humanity? Who would be ultimately benefiting from this, and how?

Ageing societies have been identified as one of the major challenges Europe is currently facing. As highlighted in the launch of the European Innovation Partnership on Active and Healthy Ageing, Europe is at a crossroads that requires integrated and more innovative solutions to ageing societies and healthcare requirements.

A new generation of multidisciplinary science fields is emerging at the junction of information technology, medicine and biology that provide approaches in in silico multi-scale modelling and simulation in medicine and biology that are optimally placed to meet this challenge. For example, patient-specific computer models of human cells or organs can bring new understanding of disease, support the discovery of new drugs or can help explore the effects of different choices of treatments before any experimental or clinical investigations are undertaken. If targeted drugs and well-being management are to be developed for personalised medicine in order to improve the management of old age, then the development and application of enhanced modelling systems that enable a greater understanding of the complex dynamics of disease must be a priority. Frameworks like VPH are needed to make this a reality, by giving researchers and healthcare workers a tool box of innovative approaches to identify effective leverage points for specific actions that can heal or, at least, reduce the symptoms of disease and patient morbidity. This would be a huge step forward towards affordable, predictive and personalised healthcare.

Does it relate to / compete with other initiatives worldwide?

Already in the first decade of the 21st century, the National Science Foundation and the National Institutes of Health in the United States started to support actively the development of complex models in biology, an area that was recognized as one of the major 21st century challenges to improve healthcare. Indeed, the United States has already been working since 2011 on supporting a competing Virtual Physiological Patient model, recognising that such modelling systems are key to ensuring the advancement of future healthcare technologies. Given that the US, a prime driver in healthcare technologies, has already begun work on this topic, there is an urgent need to fund research here in Europe to ensure that our healthcare technologies can remain internationally competitive.

Why is it important to do it now? What would happen if we don’t?

Without initiatives such as the VPH there will never be a transition to in silico clinical trials or truly patient-specific medicine. Without it our understanding of diseases, human pathophysiology and our ability to address the major healthcare imperatives imposed by the ageing population will eventually be subject to diminishing returns, and we will lose the opportunity to manage well-being by positively modifying patient-behaviour in modern society (which is a key for inclusion and healthy ageing). The critical healthcare challenges cannot be addressed effectively by continued application of 20th century technologies; they require the application of ground-breaking, innovative strategies reflecting cutting edge 21st century multidisciplinary science. Such ambitious goals can only be sustained in the long-term by politicians that are willing to focus on supporting highly skilled, productive and committed European resources in the Virtual Physiological Human initiative that have the proven ability to deliver future impact in this area.