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## From VPH and MSB to ITFoM

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# VPH, Molecular Systems Biology, and their ITFoM

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## Executive summary

The proposal for the European FET Flagship program called “IT Future of Medicine” or ITFoM for short, saw the convergence under the same initiative, of two research visions that have been running in parallel for quite some time in spite of considerable similarities and potential synergies: Molecular Systems Biology (MSB) and Virtual Physiological Human (VPH). This white paper describes the contributions of VPH and MSB to the ITFoM vision and the collaborations between the two founding streams. The key concepts of this document are:

1. The understanding of the human body and of its conditions and diseases cannot progress to its full potential if biomedical research does not recognise that the vast majority of biological processes are the result of complex interactions between phenomena often only observable at radically different space and time scales; some even occurring simultaneously across spatial scales.
2. There is no space-time scale that is inherently preferential; virtually every biological process of clinical relevance is caused by a cascade of interactions from the molecular level up to the whole organism, and from the organism back all the way down to molecules. Some researchers might start their investigation from the molecular scale and then work up, some other might start from the whole organism scale and then work down, but in the end they all aim to understand the whole cascade, across all scales.
3. Similarly, most biological processes involve interactions between different organ systems, and for these interactions to be fully understood this usually requires the combination of multiple domains of knowledge (biology, physics, chemistry, medicine, engineering, etc.). To advance biomedical research we need to integrate our knowledge across spatial-temporal scales, across organ systems, and across knowledge domains.
4. To make such integration practically possible we need to develop a whole new framework of methods and technologies that make possible to observe and quantify biological processes across radically different space-time scales; to develop reductionist hypotheses around every single set of observations, capturing this tentative knowledge into predictive models; develop information technology capable of executing hundreds or thousands of these reductionist models simultaneously and enable model interaction between each relevant sub-system, integrating the models into models of the whole, thereby dissolving antagonisms between reductionist and holist strategies.
5. This is a grand challenge for science as a whole, cutting across multiple knowledge domains. To tackle it effectively we need a proportionately grand science. We propose that the realisation of a global information technology framework for the integrative investigation of biological organisms, becomes the flagship of European research, a Grand Science project capable of catalysing the necessary critical mass in terms of human resources, public and private funding, clinical and industrial exploitation, and infrastructural resources.
6. If realised in full this information technology framework will make possible a medicine of the future where all our healthcare and lifestyle data are collected and managed with absolute confidentiality and under our complete control, and are constantly processed by accurate personalised predictive models that forecast our health and provide useful lifestyle and healthcare recommendation to us, to our carers, to our family doctor, or to the specialists in the hospital. This will be a medicine where the citizen-patient is at the centre, and where every clinical decision is personalised, takes into account the totality of the health status of the patient, and is capable of prediction, with reasonable accuracy, of the effect of every alternative treatment, so as to promote a patient-doctor interaction that is not only based on evidences, but that is also capable of providing explanations of why each treatment option is likely to produce certain effects. The impact such healthcare technology will have on prevention, risk reduction, management of chronic conditions, and on the self-aware management of our health status is so profound that it could change the face of modern medicine, and is today the only credible option to deal with the unsustainable growth of the cost of care for the ageing population.

## Introduction

Both the Virtual Physiological Human (VPH) initiative and a group of Molecular Systems Biologists (MSB) have developed the idea that it should become possible to make mathematical models of patients and that these models could help in preventing and/or curing diseases. A further approach, which the MSB strongly proposes, is the application of new ICT to integrate all biomedically relevant information into such models and thereby enable truly individualized medicine. This concept has made it to first-stage FET flagship status. The MSB group is now collaborating up with a VPH group to build an ICT for Future Medicine flagship (ITFoM) where the models can integrate the more molecular (MSB) aspects with the more physiological (VPH) aspects. This white paper constitutes a memorandum of understanding of how to proceed together on this avenue. It provides *the* common vision for both the VPH Institute and the ITFoM consortium and will be referred to as such by both groups.

The paper first describes the health (cost) problems of modern societies and the paradox that the sciences are both excellent (at measuring almost everything) and incapable (of reducing these problems significantly). It then identifies the cause of the paradox, i.e. the systemic nature of multifactorial diseases (i.e. dependence on many factors at the same time) and describes the resolution of such paradox, as proposed by the ITFoM flagship: to use new ICT replica-models of individual humans that organize all the extremely different types of information such that health, disease and therapy of the individuals become computable. It notes that both MSB and VPH are already engaged in complementary strategies for making such models, and describes how ITFoM entertains both types of strategies and particularly their integration. It also describes the proposed governance of ITFoM and particularly the roles of the MSB and VPH groups therein and in further collaborations.

## Science for Health: why doesn't it quite work yet?

Hygiene, education, nutrition and science have impacted human health tremendously, producing a strong increase in life expectancy. This has, in turn, resulted in other diseases, i.e. ones that cannot (yet) be prevented or cured by hygiene, nutrition and current antibiotics, becoming more noticeable, important and expensive for the health care systems of advanced economies. Most of these diseases are multifactorial. Consequently, the scientific paradigm of synthesizing a chemical molecule that targets and cures a single molecular cause of one of these diseases in all patients, is not as successful as one would have hoped: for this reason the impact of multifactorial diseases is constantly increasing, rather than being eradicated. They compromise human well-being, and in the long run may cripple the economy of developed countries.

Yet, the sciences and technologies have progressed enormously. At present one can determine the DNA sequence of an individual human at an affordable cost, and determine the concentrations of all mRNAs, many proteins and metabolites. Many of the macromolecules of our bodies have been characterized in terms of structure and function. The anatomy of the human body is largely understood and so are the physical forces that are at play in it.

If so many aspects of the human body are understood, why is it that we cannot understand health, disease and therapy and make the latter completely effective? The answer to this is that the

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functioning of the human body is brought about by the networking of its components and networking can be done in incredibly many and complex ways. Moreover, the networking proceeds at multiple spatial, temporal scales and organizational scales: two molecules may interact during 1 ms over 1 nm, whereas a heart and a liver interact during an hour over 1 m, and either metabolically or through hormone induced gene expression. In addition the networking is nonlinear, i.e. the networking of two components depends on the networking of these two and many other components. Last, but not least, the interaction across scales is not 'dictatorial' i.e. not unidirectionally hierarchical: it is true that molecular events such as gene expression affect cells, which affect tissues, which affect organs, which affect the organism (upward causation); but the opposite is also true, i.e. events affecting the organism propagate across scales to alter the genes' expression. Biology is organized hierarchically in the sense that different scales play different roles. Yet, these hierarchies are 'democratic' rather than 'dictatorial', many players at many levels co-determining each function. Because there is not a preferential scale at which all function is controlled, most clinically relevant processes involve complex interactions across radically different space-time scales, as well as across different sub-systems.

As a consequence the life sciences need to understand components not just in isolation, but rather in their natural context.

Most biological processes involve molecules that interact either as individual molecules or as higher order molecular consortia such as pathways or organelles, which in turn depend on intermolecular interactions for their existence. Similarly, most biological processes involve interactions between different organ systems, and to be fully understood usually require the combination of multiple domains of knowledge.

We need to develop a whole new framework of methods and technologies that enable us to observe and quantify biological processes across radically different space-time scales. We need to develop reductionist hypotheses around every single set of observations, capturing this tentative knowledge into predictive models. And then we need to develop information technology capable of executing hundreds or thousands of these reductionist models simultaneously and enable model interaction between each relevant sub-system. In this way the approach becomes integrative and leads to inferences at the holistic level. The resulting approach preserves the advantages of reductionism, but includes also a holistic understanding the traditional reductionist approaches miss.

In the area between macromolecule and pathway MSB has developed such integrative approaches. In the area between cells and tissues VPH has done the same. Therefore we anticipate that the grand challenge of doing it all, from molecule to whole human body, is not an impossible ambition. However, it is clearly still a grand challenge for science as a whole, cutting across multiple knowledge domains, and thus to tackle it effectively we need a proportionately grand science.

Disease is experienced at the whole body level and even social level, rather than at the molecular level. Yet, diseases are sometimes caused by (toxins, carcinogens, lipids) and almost always influenced by (genes and their products, glucose, vitamin, calcium) molecules ('Nature'). Yet, they are sometimes caused by (obesity, alcoholism, UV irradiation) and almost always affected by (diet, exercise, lifestyle) behaviour ('Nurture'): neither health nor diseases are exclusively molecular or exclusively physiological; they are always both, although the contribution of Nature and Nurture may differ between diseases. To advance the impact of biomedical research we need to integrate

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molecular knowledge with whole-body knowledge. We need to integrate data and knowledge across space-time scales, across organ systems, and across knowledge domains. The information must be multi-faceted, and able to deal with the nonlinearities and with the extreme heterogeneity between the data types relevant at the various levels (e.g. from social interaction to binding affinity at the molecule level). Data have to be collected at the various levels and under the variety of conditions that are relevant of the living state. The data to be integrated are thereby more numerous, heterogeneous and significant than anything ever seen before.

### **ITFoM: the proposed solution**

VPH and MSB propose that the realisation of a *global information technology framework for the integration of information relevant for human health and disease in a predictive, individualized manner*, becomes a flagship of European research, a Grand Science project capable of catalysing the necessary critical mass in terms of human resources, public and private funding, clinical and industrial exploitation, and infrastructural resources.

This IT for the Future of Medicine (ITFoM) flagship will build the Information, Computation and Communication Technologies required to integrate all of the information necessary to diagnose and treat humans in an individualised way. The information to be integrated comes from at least six general directions: (i) from molecular analyses of human (patient) samples (e.g. genome sequencing, transcriptomics, proteomics, metabolomics, metagenomics), (ii) from technological developments in biomedical imaging, biomedical instrumentation and sensing, as well as clinical laboratory methods, (iii) from biosensors providing real-time information on dynamic molecular and physiological processes, (iv) from the vast body of medical knowledge and understanding by physicians, (v) from the underlying scientific knowledge in biology, chemistry and physics, (vi) from computer science and computational systems biology hardware, software and models and (vii) from the patient's needs and societal expectations including ethical and legal compliance. For all seven sources of information, new types of interface need to be formulated..

The way the information will be integrated is based on the concept that the complex properties emerging from the interactions between components can be understood by making a replica of the real system that is computable. The replica, what used to be called a 'mathematical model', will be realistic in the sense that it is both predictive and descriptive. Once the replica is realistic it can be interrogated in the ICT framework. This allows for the discovery of network mechanisms for health and disease. At present the computations are done using large, dedicated digital computers installed at the site of consumption, but this is changing rapidly, involving 'clouds', social networks and mobile phones; pervasive technologies will make possible scenarios of *Personal Health Forecasting*, where all personal health data are constantly processed in order to predict how the health status of the individual will evolve over time. The replica can also be treated with medicinal drugs or alterations in nutrition or behaviour to calculate what the effects will be of treating the corresponding real patient with the real drug (*in silico* clinical trials) or lifestyle change. Last, but not least, the replica can inform a *Digital Patient* environment, a digital avatar of the patient that the clinical specialist can use as support to his/her clinical decisions.

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If realised in full this information technology framework will enable a medicine of the future where all our healthcare and lifestyle data are collected and managed with absolute confidentiality and under our complete control, and are constantly processed by personalised predictive models that forecast our health and provide useful lifestyle and healthcare recommendations to us, to our carers, to our family doctor, or to the specialists in the hospital. A medicine where the citizen-patient is at the centre, and where every clinical decision is personalised, takes into account the totality of the health status of the patient, and is capable of prediction, with reasonable accuracy, of the effect of every alternative treatment. This will promote a patient-doctor interaction that is not only based on evidences valid for large groups, but that is also capable of providing explanations of why each treatment option is likely to produce certain effects in an individual. The impact such healthcare technology will have on prevention, risk reduction, management of chronic conditions, and self-aware management of our health status is so profound that it could change the face of modern medicine, and is today the only credible option to deal with the unsustainable growth of the cost of care in relation to the ageing population.

### **The originators of ITFoM: MSB and VPH**

#### **Molecular Systems Biology (MSB)**

Molecular Systems Biology is one area of science where such realistic models are made. Molecular systems biology has become a scientific field with substantial annual international conferences and funding. It studies how biological function emerges from the interactions of macromolecules. It has two roots (Westerhoff & Palsson, 2004): on the one hand molecular biology ultimately leading to genome sequencing and functional genomics and bioinformatics, and on the other hand biochemistry, (bio)physics and mathematical biology. Top-down molecular systems biology measures the amounts of all molecules of a certain type expressed from the genome and tries to find patterns of behaviour and hence mechanisms of regulation. Bottom-up systems biology typically starts with a small subset of molecules and examines how they together can already account for part of the cell's function. The MSB community has developed many standards at the molecular level such as gene ontologies, genome wide metabolic maps, standards for measuring, quantifying and storing molecular properties, and live repositories for models.

Most molecular systems biology acts at the level between macromolecules and whole cells. It rarely addresses tissues or the whole body. Since health and disease span scales from molecules all the way to the entire patient, MSB in its present approach may not suffice to fulfil the ambition of ITFoM of making all-encompassing, molecule-based replica models of the patients and their disease. This is not to say that MSB alone could not make significant progress in identifying drug molecule combinations that work on intracellular networks of diseased cells. Those combinations could well have a substantial therapeutic benefit. However, an MSB-only approach would not be quite as powerful as an integrated all-level approach.

#### **The Virtual Physiological Human (VPH)**

Whereas MSB vision undersigns a bottom-up approach, the VPH vision promote the so-called *middle-out* approach: the biological process is first modelled at the scale where it is observed

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clinically; the integrative model is then extended upward and downward across scales, until it achieves the predictive accuracy that is necessary for that specific clinical application. Similarly, VPH integrative models first capture the biophysical process that produces the clinical presentation (mechanical in a bone fracture, electrical in fibrillation, chemical in a dismetabolism) and then expands to complex multi-physics simulations in order to capture all different mechanisms that are relevant to the process. No predictive model of a real-world complex system can be entirely mechanistic: VPH integrative models are no exception, and they usually combine sub-models that are purely phenomenological and sub-models that are highly mechanistic. However, the VPH vision recognises that the more mechanistic a model is, the greater is its knowledge content; thus, whenever possible mechanistic models are preferred, being formulated as validated relationships between observable properties, such as action potentials, time, and space. Because they have been validated, the relationships are realistic at the physiological level of VPH. Exemplary for VPH are the models for cardiac arrhythmias where one sees the action potential spreading across the myocardium based on ion channel electrophysiology at the cell level and reaction-diffusion equations that express conservation of charge at the tissue level. VPH has a strong component of modelling the spatial-anatomical structures at the level of cells, tissues and organs, and then of solving the laws of physics on these structures in the same way as engineers do for man-made structures such as cars and aeroplanes.

The VPH is also dealing with the issue of model reproducibility by developing standards for model and data encoding (via XML mark-up languages) and 'minimum information' standards, as well as metadata standards for linking model components to genomics, proteomics and metabolomics databases via the bio-ontologies such as GO, Biopax, FMA, etc. (mostly managed by EBI and BBMRI). Model repositories based on these standards are being developed and address issues of curation, annotation and provenance.

Most VPH activities focus on the level of tissues and only occasionally descend to the macromolecules. Since health and disease span scales from the entire patient all the way to molecules, VPH in its present approach would not suffice for the ambition of ITFoM of making all-encompassing, molecule-based replica models of the patients and their disease. This is not to say that VPH could not by itself yield to important approaches to disease. Examples are cases where the effects of both drugs and devices on electrocardiograms (perhaps for unknown molecular reasons) have been explained and optimised respectively using VPH models for treating heart failure, and cases where physical exercise of a muscle may cure muscle ache. However, the VPH approach alone may not be as powerful and robust as an integrated all-level approach.

### VPH and MSB are complementary

VPH is primarily **Physiology** interested in the integrated modelled organism based on the laws of physics, as well as the IT problem of applying these models in the clinic. Very frequently, the VPH speaks in terms of tissues, arteries, and electric potentials across an entire epithelium. MSB is primarily **Biochemistry** and **Molecular Biology** interested in integration using the laws of molecular biochemistry and biophysics. VPH starts its models from the human **macro-anatomy** (organ structure) while MSB starts its models from flux anatomy. VPH is associated intimately with biomedical imaging and sensing, and its most recent developments aimed to provide a quantitative representation of most physiological processes. VPH talks in terms of volumes, blood flow, or of macroscopic forces. MSB is associated intimately with functional genomics and its most recent



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developments such as the thousand genomes project, and deep sequencing. MSB talks in terms of genes, mRNAs, proteins, smaller molecules and how they network all together to produce living systems.

MSB is close to functional **genomics**. It associates state of the art genome sequencing, deep sequencing information, proteomics and metabolomics, and therewith engages with the moving interface between genomics and society. VPH builds up from cells and tissue and thereby associates with the developing biological understanding of organ function.

MSB focuses on **pathways** and molecular interaction networks, whereas the VPH focuses on the **spatial structure** of cells, tissues and organs and uses the laws of physics to understand phenotype.

MSB tries to encompass the entire field of **molecular biology** and genome-wide detail, whilst VPH starts from **engineering and computer science** principles and uses multi-scale modelling to link to molecular biology.

**MSB's** funding history lies in molecular genetics, **molecular genomics** and the systems biology of pathways and **model organisms** (yeast, *T. brucei*, *E. coli*), which testify to its focus on understanding systems in molecular terms. **VPH** funding's history lies in the anatomy, **physics** and **physiology** based modelling of whole human organ **function** (e.g. the heart). Only with the flagship ITFoM the consortium is able to address the extreme challenge of doing the same for the entire human as an integrated biological system. This is of importance because most diseases (particularly diseases associated with ageing societies, such as metabolic, cardiovascular diseases and cancer) do not affect a single biological process or a single organ, but rather involve multiple organs and have to integrate genetic and physiological alterations with environmental and societal factors.

### ITFoM integrates MSB and VPH approaches.

The above shows that MSB and VPH are not just different approaches that could be competitive. They are almost completely complementary: Each lacks what the other approach leads and offers. Together the two approaches would come close to all that is needed, as far as they can be integrated with enough information technology and medical knowledge. ITFoM is a major mechanism to synergize VPH and MSB in this sense, and to connect with Medicine. Both VPH and MSB will become much more powerful and useful through the synergy that ITFoM will catalyse (see fig. 1).



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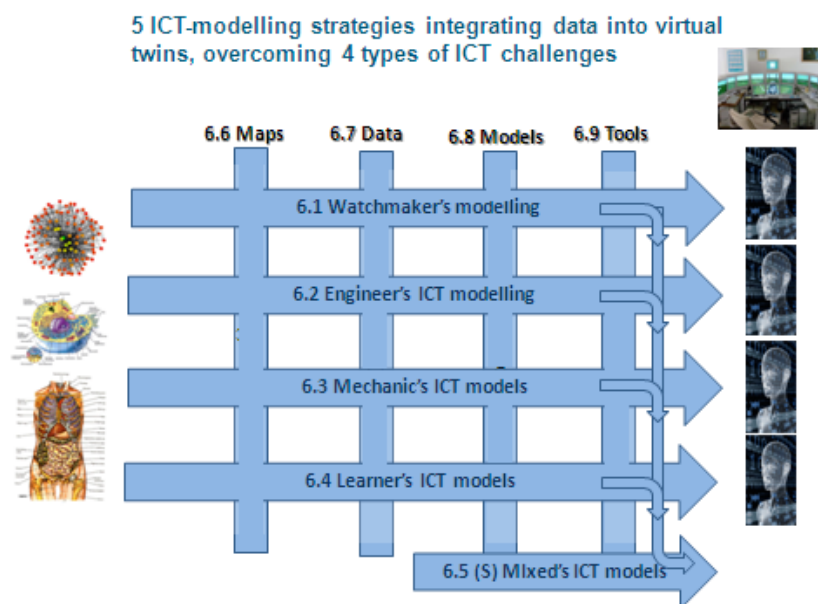


Figure 1. The ICT integration strategies of ITFoM in WP6: booths 6.6-6.9 making consensus maps, data, models and tools; and 5 strategies integrating data dynamically into predictive models. 6.3 and 6.5 are VPH led, 6.1 and 6.2 MSB led, while the others are integrating VPH and MSB.

The ITFoM consortium aims to enable integral approaches that span from few molecules to the organism and populations and back, with a clear focus on improving both quality and quantity of human life. Even more so, it has the aim of making all its approaches integral in this sense: even though approaches may well begin as MSB or VPH, ITFoM will work to integrate each MSB approach with a VPH approach and *vice versa*. Figure 1 is the description of work package 6 of the ITFoM long-term plan. Four modelling approaches will begin to be used, including the Mechanic's approaches, which are mostly VPH and the Engineer's and Watchmaker's approaches which are mostly MSB type. ITFoM will try out all four approaches and will integrate what works best of each of these, thereby achieving a fifth *amalgam*. The integration will take place at the vertical rectangles in figure 1 at which integration of maps, data, models and tools between all five approaches can be achieved.

Together these approaches will extend from molecules to individual patients. Some of the ITFoM researchers will therefore start their investigation at the molecular scale and work up; some others will start from the whole organism scale and work down, but in the end they all aim to understand the whole cascade, across all scales.

The models made by the integrated activities of VPH and MSB will serve to integrate the data of individual patients into replica models of those individuals. The models can then be interrogated. This integration will be brought about by the massive implementation of new ICT. Figure 2 shows that ITFoM will thereby not only integrate VPH and MSB but also their combination with ICT and with substantial inspiration from Medicine.

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Fig.2. ITFoM integrates Molecular Systems Biology and the Virtual Physiological Human. It also integrates the resulting integral with the relevant ICT and Medicine.

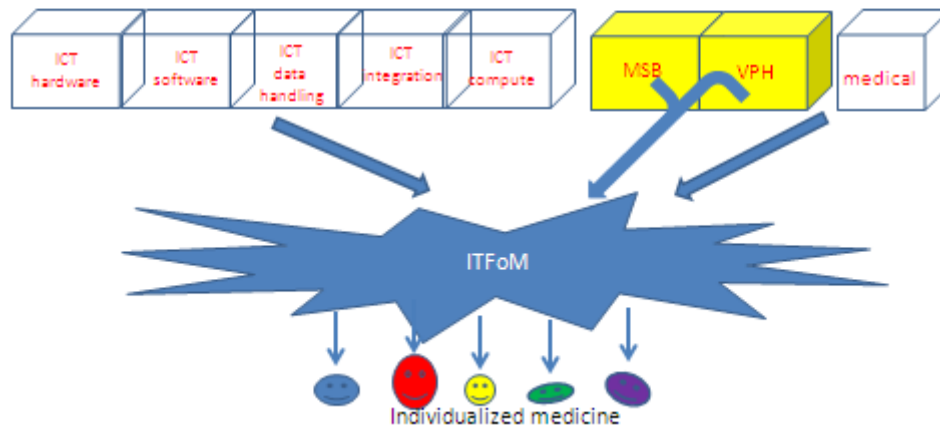


Figure 2. ITFoM integrates MSB and VPH with medical and with much new ICT to make a splash towards new, truly individualized medicine.

Within this integration there lay some grand challenges for Information Technology in itself, such as:

- 1) The process of model personalization, which requires not only the extraction of specific measurements on individuals, but also the capacity to adjust the models so that they can explain the measurements. This requires developing new expertise in inverse problem solving or data assimilation for huge systems having a very large number of parameters and variables. As many of the measurements come from bio-signals, most of them being medical imaging from the whole body to subcellular levels, this also requires the mastering of new forms of biomedical image analysis and simulation.
- 2) The statistical analysis on measurements made over populations to constrain the range of possible parameters on anatomical, physical or physiological models. This is of utmost importance for the resolution of the above-mentioned personalization problems, but also to improve computer-aided diagnosis, prognosis, therapy planning and guidance from computational models of organs and pathologies.
- 3) As MSB and VPH models integrate, covering from the molecule up to the organism, they become complex in their mathematical representations, frequently highly non-linear, and include essential stochastic processes. The computational weight and the computational complexity involved can be project well beyond the capabilities of the biggest computing systems currently available.
- 4) The data range from functional genomics deep sequencing data, through kinetic properties of macromolecules and physiological properties of organs, to patient opinions and epidemiological quantities. The digital patient will need to be readily accessible to molecular geneticists, databases,

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individual patients, physiologists and physicians, all with their own, optimal reversible interfaces. The maps produced will be highly diverse (from anatomy, through pathways, to geographical disease distributions) as will be the models (from stochastic through deterministic differential equations through Bayesian to pictorial and associative). The ICT needs to provide for maximum integration of data, maps, models and tools, which is an enormous challenge in view of their heterogeneity.

5) The total capacity needed for data storage, for communication and for model calculations vastly exceeds what is possible at the moment even with the fastest supercomputers and largest data storage systems available. New, intelligent ICT solutions will need to be developed for the massive storage, communication and computation required.

### A new anthropomorphic ICT for individualized medicine, through ITFoM

With the ITFoM inclusive strategy, the integration of the information and approaches will take place in an IT environment that has a structure that reflects the functional processes/fluxes in the modelled object, i.e. the human's pathways, making the human body work on the basis of its molecular and physiological activities. For each metabolic pathway, for each flux network, for each gene-cluster's processes, for each cell type's functioning, etcetera, a consortium of research groups will be responsible. Such a group will work to collect all data relevant to their topic and integrate all this information into a 'process model' for that object (e.g. pathway). This 'model' is not 'just' a differential equation model, but a model in the complete systems IT sense, i.e. with a scaffold associating all relevant data, able to predict ultimately through network-causality, behaviour and effects of drugs. The 'model' as defined here is a new type of IT tool for data integration, as it is process based. Because the ICT is organized following the IT organization of the human body, physiology and molecular biology, we call this an anthropomorphic ICT (figure 3).

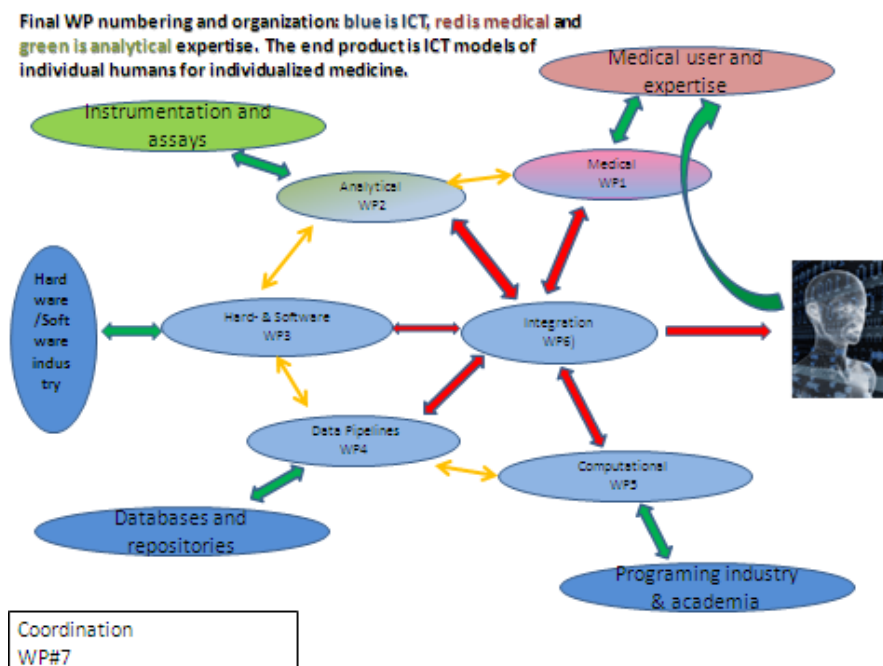


Figure 3. The overall organization of ITFoM in terms of 7 workpackages. Blue refers to ICT activities, red to medical activities and green to analytical activities. 'Medical user includes health care and society and refers to the medical expertise needed by the users.

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A second integrative aspect is the integration of all models to produce a molecule-up integral model of human individuals, one for each individual (and for each tumour cell), each of which will be a variant of a common blueprint model. A third aspect then goes back from the models to the five interfaces, i.e. to the analytics required for further analysis (and better information technology), to the clinic to request additional human diagnoses and interaction with the patient, to hardware/software industry to request more refined ICT enablers, to the information industry to request improved data from model repositories and pipelines, and to the software industry to request better computing and statistical analyses.

The Watchmaker and Engineer's strategies of ITFoM start with the huge complexity of the vast intracellular networks and then build upward to the integral human. The total amount of data involved far exceeds that seen in previous megaprojects such as putting a man on the moon and sequencing the human genome. ITFoM's Mechanic's strategy starts from the more macroscopic physics-based physiological description of the body's functioning and builds downward to the molecules. The Learner's approach starts at the empirical level of data and through machine learning approaches finds mechanisms that it then interprets in collaboration with the other approaches.

ITFoM will focus on this challenge and will not address the problems of today as described in the e-Health field other than by integrating the results and data of the latter into its models and making its models useful for the e-Health field. ITFoM will solve the fundamental questions how genes and (molecular) information defines biological processes and in consequence human health. This will be done through the development of comprehensive models – in ICT terminology the firmware and operating systems – of human individuals. Such a model will be a technological breakthrough, which will dramatically change the future of medicine.

### **Attachment 1: The 20110905 meeting in Brussels and its recommendations**

On September 5<sup>th</sup>, 2011 Representatives of the VPH and MSB communities and the European Commission met in Brussels to discuss the VPH-MSB collaborations in the context of ITFoM. The meeting participants formulated six recommendations. Below we discuss how this white paper has followed the recommendations.

**Recommendation 1:** *the agreed strong cooperation between the two initiatives is to be fully supported by all relevant parties, as it will greatly propel the proposed integrative approach.*

It is impossible to speak for the entire VPH and MSB communities. However, the formulation of the 10-year plan ('report submitted April 30<sup>th</sup>, 2012) of ITFoM has depended much on three members of the VPH community, (Coveney, Henney, Viceconti), on two members of the MSB community (Lehrach and Westerhoff) and on many more others stemming from the ICT (Birney, Benhabiles, Girolami, Mencer), medical (Zatloukal) or mixed communities, where Lehrach was responsible for the final formulation. ITFoM will function as a catalyst of strong collaboration between the MSB and VPH communities. However, the MSB community is not sufficiently organized for the MSB members of the focus group to be able to drive integration of the whole MSB community with VPH.

**Recommendation 2:** *A focus group should be set-up aiming at bridging the two communities and identifying topics of cooperation.*

This focus group has been instated, and has been active in formulating this white paper and helping formulate the ITFoM 10-year plan.

**Recommendation 3:** *a white paper on initiatives integration (synergizing MSB and VPH) should be produced within 2 months.*

Because it became clear quite rapidly that bringing about the collaboration between VPH and MSB vis-à-vis ITFoM was facile, more immediate and much simpler than sorting out the other aspects of the organization of ITFoM, the precise formulation of this white paper has been postponed until after the submission of the ITFoM report by April 30<sup>th</sup>, 2012.

**Recommendation 4:** *A governance model for the integrated/integrative ITFoM will be defined by the end of April 2012.*

This model has been defined in Annex 1

**Recommendation 5:** *ITFoM to perform an inventory of existing infrastructures and to identify relevant elements/components to be integrated.*

A European Strategy Forum on Research Infrastructures-inspired Infrastructure for Systems Biology (ISBE) will soon begin its preparatory phase, where such an inventory will be made. ITFoM is directly connected with ISBE (personal union of a WP coordinator) and the inventory will be made together in an (open) ISBE working group in which MSB and VPH members will participate.

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**Recommendation 6:** *By the end of the ITFoM preparatory action, a roadmap for integrating all relevant infrastructures and research initiatives will be produced.*

This roadmap requires a professional and comprehensive approach and could not be completed at a sufficient level of quality by the focus group. In the October 2012 application of ITFoM for actual support there will be an application for a CSA to produce this roadmap.

### Colophon

*This white paper is based on contributions from Peter Hunter, Marco Viceconti, Adriano Henney, Peter Coveney, Stig Omholt, Nicholas Smith, Nour Shublaq, and Hans Westerhoff, and inspired by various colleagues. Westerhoff and Viceconti have taken final editorial responsibility.*