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Modelling the Virtual Physiological Human

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Abstract

The second half of the twentieth century can be regarded as the era of reductionism in biology, when, driven by revolutions in molecular biology and genomics, the dominant paradigm saw biology as the sum of its parts: the genes and proteins that make up each organism. Most biologists, however, now recognize that an integrative approach – an understanding of how these parts work together in a complex entity – is as important as a reductionist one. The relatively new discipline of systems biology combines this philosophy with an integration of experimental biology with computational biology. One of the most ambitious goals of systems biology is that of modeling the entire human physiology. Human body can be broken down into a series of interlocking organs and systems, with one of the most tractable to model being the heart. Simple mathematical models of cardiac ion channel action have developed over half a century into complex simulations that are being used successfully in drug discovery. Integrating models together, however, requires close international collaboration. Under Framework Six, the European Commission funded a few collaborative projects in human systems biology including ImmunoGrid, which set out, perhaps over-ambitiously, to model the immune system. Under Framework Seven, over €200 M has been channeled into research projects and networks under the umbrella of the Virtual Physiological Human. Projects funded under this initiative cover a large range of systems and disease states, with the cardio-vascular system and cancer dominating the first tranche of fifteen. This initiative is poised to further develop under the next framework programme (Horizon 2020), which will run for seven years from 2014.

Key words: systems biology, human physiology, modeling, heart, cancer

Introduction: Beyond Reductionism

We can assume – and the date is as good as any – that the era of modern biology can be dated from the publication of Darwin's *Origin of Species* in 1859. For about a century after that, most biology continued to be hypothesis-driven, as biology always had been before. The following half-century, however, saw the rise and apparent dominance of a reductionist approach to biology. The genome of the first free-living organism, the simple bacterium *Haemophilus influenzae*, was published in 1995 (Fleischmann et al., 1995); sequencing of the human genome took a mere eight years more, and the publication of new genomes is now becoming almost commonplace. In the genomics era, it has seemed as though the whole of biology would eventually be understood from the sum of its parts. Given enough time and enough – indeed, almost limitless – computer power, the complexity of all biological structure and function would be seen to arise from the genes and proteins, the "blocks" from which biology is built.

There is, however, another equally important way of looking at biology, which recognizes that not everything can be built from the bottom up. Sydney Brenner, one of the fathers of high-throughput genome sequencing and part winner of the Nobel Prize for Medicine, 2002, for his pioneering work in understanding the genetics of the nematode worm, wrote that "I know one approach that will fail, which is to start with genes, make proteins from them and try to build things bottom-up" (Brenner et al., 2001). Brenner and many other distinguished biologists have understood that reductionism must be complemented by integration, understanding how the parts work together to form a complete system. This is systems biology, which is more of a philosophical approach to biology than a single technique or techniques. It explicitly allows signals from "higher" or more complex levels

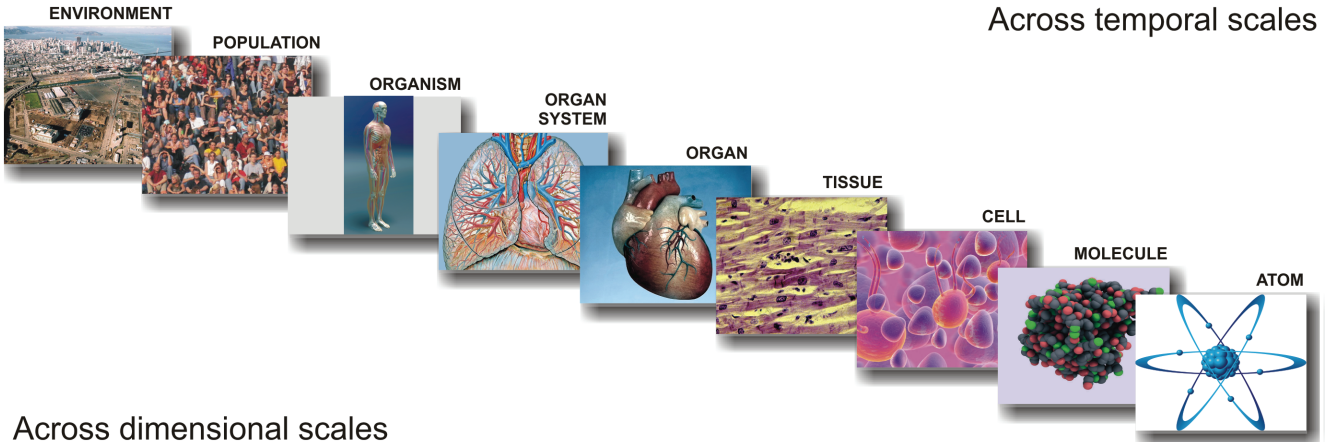

Fig. 1. A schematic diagram showing various scales over which human physiology can be modeled, ranging spatially from atoms and molecules through cells, tissues and organs to the individual and the community, and temporally from the nano- and microseconds of intermolecular interaction to the human lifespan. Figure © Peter Hunter, University of Auckland, New Zealand

to feed down to affect lower-level processes. For example, when an organism senses changes in its environment this automatically triggers changes to its signal transduction and gene expression patterns.

A typical systems biology approach involves both experimental and computational or theoretical biologists working together to understand and model a biological system at a number of levels of both space and time (Fig. 1). A "system", similarly, can be defined as any complex biological entity that is made up of simpler, interacting parts: an organism is a system, but so is an organ, a tissue and even a single cell. In fact, some of the most important successes of the systems biology approach so far have been in developing and validating extremely detailed and complex computational models of single-celled model organisms such as yeasts (see Castrillo et al., 2007).

Modelling Human Systems

One of the systems biologists' most ambitious goals is the modeling of human physiology. The reductionist way of looking at this involves building upwards from an understanding of the structure, function and role of each of our genes and proteins, or, at most, at a few closely connected parts such as those involved in a single signaling pathway. An integrative systems approach involves linking those pieces together with the eventual, if breathtakingly ambitious, aim of completing the "jigsaw" to form a mathematical avatar of a human. For this, the human body will need to be modelled at all scales from nanometers (molecules) to meters (the body) and from nanoseconds to the human lifespan, and these models will need to be integrated together. Even if the "virtual human" is ever to be feasible, it is clearly many decades away. However, significant progress has been made in modeling individual organs and systems, although some are much more tractable to work with than the others.

Perhaps surprisingly, one of the simplest of all human organs to study, in terms of systems, is the heart. The first research papers in human physiology that fit clearly into the current systems biology paradigm were published as long ago as the early 1960s, and these are concerned with the mathematical modeling of cardiac electrophysiology. The movement of ions into and out of cardiac muscle cells through channels in the cell membranes gives rise to the tiny currents that control the heartbeat. Denis Noble, then a PhD student at University College London, UK, initially used differential equations to model the current through just four differential equations (Noble, 1960). Since then, Noble and his group have continually extended and improved these models, which now use several hundred simultaneous differential equations to model over 50 types of ion channels and pumps now known to be found in heart cell membranes, as well as many other processes that occur in these cells. Working in collaboration with bio-engineer Peter Hunter and his group in Auckland, New Zealand, they have ordered the cell models into a three-dimensional array that simulates the structure of a mammalian ventricle (Fig. 2). Simulating ion movement in and out of these

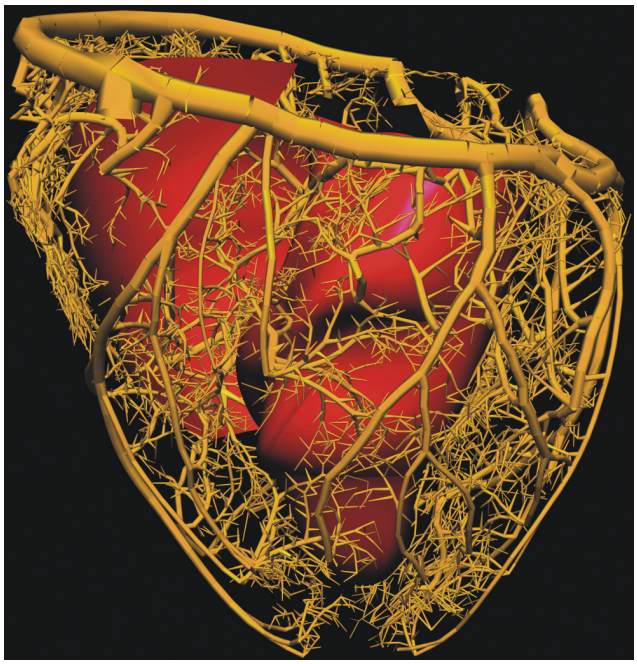

Fig. 2. A computational model of heart physiology showing the mesh of coronary arteries. The diameter of the arteries is shown exaggerated as gold cylinders, and the inner surface of the ventricles is shown in red. Figure © University of Auckland, New Zealand

cells forms a remarkably accurate model of cardiac physiology, incorporating genetic differences, which can be used to predict the effects of candidate drug molecules on the heart (Bassingthwaite et al., 2009).

Modeling the heart has proved quite successful largely because of this organ's relatively simple construction. It consists of a limited number of cell types, with cells arranged in an ordered fashion and with one regular function. The immune system, in contrast, is one of the most complex systems in the human body. It is extremely dynamic, with many different types of immune cell distributed throughout the body in response to foreign molecules and invading pathogens. An immune response typically involves the differentiation and distribution of a wide range of cells and molecules throughout the body to the site of infection, over different time-scales and in response to different signaling pathways. Furthermore, each individual has a different complement of immune cells that depends not only on their genetics but on the pathogens that they have come in contact with. However, bioinformatics and computational biology have been successful in modeling many of the individual processes involved.

The ImmunoGrid project (Lollini et al., 2006) was set up with funding from the European Commission's Framework Programme 6 to develop a natural-scale model of the human immune system that would be complex enough to reflect its diversity, adaptability and dynamic nature. This ambitious project linked scientists from four European countries and Australia, with expertise in bioinformatics, cell modeling and experimental immunology and immunotherapy. Noble's heart cell models primarily use relatively simple ordinary differential equations, whereas the cellular models developed by the ImmunoGrid project were "agent-based" stochastic models, using probability to describe a population of individual agents (cells and molecules of the immune system) interacting together using a series of simple rules. This method is increasing in popularity, although it is arguably more successful in developing descriptive (qualitative) than predictive (quantitative) models. The consortium developed descriptive models of HIV, Epstein-Barr virus infection and cancer immunotherapy, and a predictive model of a preventative vaccine for breast cancer that has had some success in mice (Halling-Brown et al., 2010). These, however, represent only a fraction of the immunological processes that could, theoretically, be usefully modeled. A complete, fully functional "natural scale" model of the immune system represents a much more ambitious project and would require a concerted effort by many more international and inter-disciplinary groups.

ImmunoGrid was one of a handful of projects funded by Framework Programme 6 under the banner of the "Virtual Physiological Human". This, in turn, built on early efforts to coordinate human systems biology internationally through the Physiome Project, run by the International Union of Physiological Societies and championed by Noble, Hunter and other pioneers (Hunter and Borg, 2003).

The Virtual Physiological Human

Under Framework 7, which runs from 2007 to 2013, the European Commission is investing a total of approximately € 207 million in projects under the *Virtual Physiological Human* umbrella (Viceconti et al., 2008). The lar gest part of this funding is invested in large and medium-sized collaborative research projects with practical applicability to clinical medicine: it is a requirement of the calls that project teams include clinicians. There are

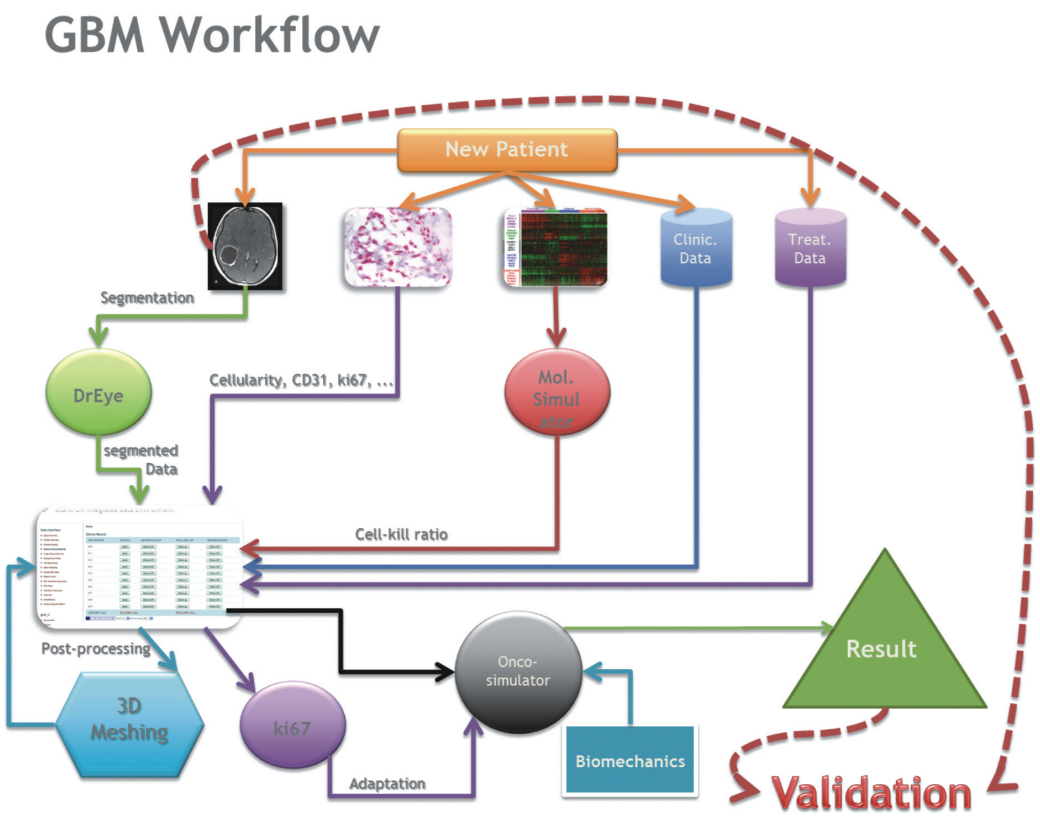

Fig. 3. A schematic diagram of the workflow used to simulate the response to treatment of a particular patient with the brain tumour glioblastoma multiforme (GBM), illustrating the data input to the OncoSimulator. Figure © ContraCancrum, Foundation for Research and Technology Hellas (FORTH), Greece

also a number of smaller coordinating projects, including INBIOMEDvision, which promotes and monitors the development of the related field of biomedical informatics throughout Europe. A total of 27 of the larger research projects have been funded so far in two competitive rounds, and there will be one further round with a deadline early in 2012.

The multi-scale modeling approach being pursued in these projects requires access on demand to high performance computational facilities that may not be locally available to each participating researcher. The Virtual Physiological Human Network of Excellence, set up to support Vph-related research within and beyond Europe, is also charged with helping to coordinate researcher access to supercomputer facilities. It has achieved through establishing a VPH Virtual Community on the DEISA supercomputing grid (www.deisa.eu).

The Network of Excellence is coordinated by Peter Coveney at University College London, UK; it has thirteen core partners and a growing list of institutions associated with it as general members. It supports systems biology researchers in all member institutions through small "pump-priming" grants, conferences and training courses, and promotes and disseminates VPH-funded work throughout the research community and beyond. It also aims to address important issues of standardization. Any research project involving multiple, interdisciplinary groups can only succeed if all groups use a standard nomenclature and a standard set of tools. The Network maintains a "toolkit", a curated set of programs developed by members that are designed to be flexible and interoperable and that can be built into user-friendly solutions for clinicians (Cooper et al., 2010).

VPH Projects

The large and medium-sized collaborative research projects funded by VPH initiative are modeling a wide range of human organs and systems in both healthy and diseased state, and each involves experimental and clinical research as well as mathematical and computer modeling. However, some systems stand out as being parti-

cularly well covered. Not surprisingly, five of the first 15 projects to be funded concern the cardiovascular system and a further four are concerned with cancer. Diseases of ageing such as osteoporosis and Alzheimer's disease are also being targeted.

Each of the four cancer projects funded in the first VPH round addresses a different aspect of the disease using a range of experimental and computational techniques. The largest and most ambitious of these is Contra-Cancrum (Latin for "against cancer"), coordinated by the Foundation for Research and Technology Hellas (FORTH) in Greece. The eight groups involved in this project are collaborating to develop multi-scale models of tumor development and of the response of tumor and normal tissue to drugs that are collectively termed the Onco-Simulator (May et al., 2011). Their initial models use data from lung cancer and glioblastoma patients (Fig. 3), but this approach could be adapted for other types of tumor as well. Other projects address single tumor types. NEOMARK is developing profiles for different types of oral cancer and using these profiles to construct tools that can predict which tumors are most likely to recur. The HAMAM project, coordinated from Austria, is combining breast images with other clinical data into a tool for early breast cancer diagnosis, and scientists involved in IMPPACT are developing a complex physiological model of the liver to aid in planning minimally invasive surgery to remove tumorous tissues.

Collaborative investigation of the human body as a single complex system is set to continue after Framework 7 comes to an end in 2013. The new framework program, which has been newly renamed *Horizon 2020*, is set to run from 2014 through 2020. Negotiations over its nature are bound to be protracted, but many VPH researchers are working to keep these ideas at the forefront of the Commission's thinking. It is certain that, in the current financial climate, nothing can be guaranteed. However, the VPH approach is closely allied to the EU's stated aim of enabling "personalized, predictive and preventative medicine" throughout Europe by 2020 and this may be a good sign for success in future funding initiatives (http://ec.europa.eu/information_society/ activities/health/docs/projects/istresults/201006-ictresults-policy-report-health.pdf)

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