Virtual Tissues

a quantum leap in biomedical research

Position Paper of the v-Tissues 2009 Experts Panel

The First International Workshop on Virtual Tissues - April 21-22, 2009, EPA Campus, Research Triangle Park, North Carolina, USA

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Dr. Imran Shah is a scientist at the U.S. Environmental Protection Agency's (EPA's) National Center for Computational Toxicology (NCCT) where he provides leadership and guidance in the development of computational, systems-based models to support improved assessment of the public and ecological health implications of environmental stressors. Dr. Shah received a B.S. in Physics from the Imperial College of Science, Technology and Medicine in London, U.K., and a Ph.D. in Computational Biology from George Mason University. From 2001 to 2004, Dr. Shah was the director of the doctoral program in bioinformatics in the School of Medicine at the University of Colorado in Denver. Before joining EPA, he was employed at Icoria, a biotechnology company, where he led the development of computational systems approaches to discover biomarkers of liver toxicity from large-scale data streams. Dr. Shah is leading the NCCT Virtual Liver project, a multiscale computational model of chemical-induced chronic toxicity.

Marco Viceconti has a MS in engineering from the University of Bologna and a PhD from the University of Firenze. He started his research career in the USA, where he worked as visiting researcher at the University of Florida and at the University of Wisconsin. Since 1989 he works at the Istituto Ortopedico Rizzoli in Bologna, Italy, where he is currently the Technical Director of the Medical Technology Lab. He is also the Director of the BioComputing Competence Centre, a private no-profit organisation established in partnership with the CINECA supercomputing centre. His main research interests are related to the development and validation of medical technology. In his career he published over 200 papers, 160 of which are indexed in Medline. He serves as reviewer for 17 international scientific journals, including Journal of Biomechanics, Medical engineering & Physics, and Clinical biomechanics, for which he is also member of the Editorial Board, and for various grant agencies, including the European Commission. He served as President of the European Society of Biomechanics and as member of the Council of the European Alliance for Medical and Biological Engineering and Science (EAMBES). He is the promoter and animator of community initiatives such as the Europhysiome initiative, and the Biomed Town community. He is currently the coordinator of the VPHOP integrated project, a large European research consortium that is developing simulation-based technology for predicting the risk of bone fracture in osteoporosis patients. Dr. Viceconti is also leading the outreach program of the VPH Network of Excellence, and chairs the Board of Directors of the European VPH Institute.

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Executive Summary

The recognition of the importance of modelling in biomedicine is growing exponentially. The Virtual Physiological Human and the Integrative Biology initiatives in Europe, the coordination between US federal agencies made by the IMAG around the topic of modelling in biomedicine with the promotion of the Multi-Scale Modeling Initiative, the NIH call for proposals on Predictive Multiscale Models of the Physiome in Health and Disease are only a few examples of this increasing attention.

Tissue modelling is the missing link between basic research and clinical practice

In this context the Virtual Tissues conference organised by the US Environmental Protection Agency in collaboration with the European Commission and with the US Interagency Modeling and Analysis Group came at a perfect time. Indeed, it is becoming more and more evident that tissue modelling is the missing link:

- Tissue modelling is the missing link between the very large body of research done by biologists, bioinformaticians, and biomathematicians at the cell-molecule scales, and the equally large body of knowledge that we have accumulated at the body-organ scale both clinically and more recently through the physics based investigation using in bioengineering, biomechanics, and organs physiology.
- Tissue modelling is the missing link between the large body of work done in modelling the interaction between the environment the human pathogenesis, and the equally large body of work done in modelling the interaction between foreign chemical contaminants and the molecular and cellular responses these induce in the body.
- Tissue modelling is the missing link between the mechanist modelling approach that is becoming so popular recently the more phenomenological modelling approach that constitute the vast body of knowledge in many sub-domains of biomedical research.

Introduction

The present document represents the consensus of a panel of international experts working in USA and in Europe in research agencies or in various public and private research organisations.

The V-Tissues initiative was intended as an effort to better understand and provide integrative models of human function accounting for the multi-scale phenomena involved (from sub-molecular to environment and population).

The term *virtual tissues* (v-Tissues™) embody innovative paradigms for understanding disease progression via *in silico* cross-scale models of cellular organization and emergent functions. Tissues are the clinically relevant level for diagnosing and treating the transition from normal to adverse states in chemical-induced toxicities leading to cancer, immune dysfunction, developmental defects, and more. Currently in vivo rodent experiments are used to evaluate tissue-level effects of altered molecular and cellular function; however, the extrapolation of animal models to humans is often uncertain. v-Tissues™ aim to computationally simulate key molecular and cellular processes in the context of normal tissue biology to: (a) help understand complex physiological relationships, and (b) to predict adverse effects due to chemicals. As the number of chemicals in consumer products, the workplace and the environment continues to rise, v-Tissues™ offer the promise of a more efficient, effective and humane approach for evaluating their impact on human health.

A prime reason for the event was the growing awareness that such integrative approach to biomedical research requires an intense international cooperation, as it will only be through the collaboration of researchers from all over the world that such huge endeavour will be tackled. In consideration of the long history of cooperation between Europe and the United States of America on various matters including research, it was quite natural to start the exploration of these new cooperation scenarios from this bilateral meeting.

The consensus process that produced this document revolved around a set of charge questions:

I. Virtual Tissues Objectives: Translational Goals
   a) What are the overall objectives of Virtual Tissues and which specific translational goals can they address?
   b) How can these goals be packaged and prioritized in terms of short-term (1-5 years), medium-term (5-10years) and the long-term (10-15 years)?

II. Virtual Tissues: Cross-scale modelling issues
   a) Why are tissue-level models necessary? What are the unique translational opportunities that Virtual Tissues might provide?
   b) What are the differentiating factors between Virtual Tissues and related biological modelling efforts?
   c) What specific clinical endpoints / phenotypic outcomes will Virtual Tissues predict? Can they be prioritized?
   d) How will Virtual Tissues be developed? What are the fundamental challenges in modelling the interaction between molecules, cells, tissue, and the microenvironment?
   e) Who is going to do it? What are the new needs in term of interdisciplinary training / re-training does tissue modelling require?

III. Data generation requirements for Virtual Tissues

a) What specific types of molecular/cell/tissue data are needed for calibrating / evaluating Virtual Tissues?

b) Are additional data necessary for Virtual Tissues? What specific predictive goals support the need for new experimental methods linked to tissue modelling?

c) How can we get these data? Are the in vitro / in vivo models and the available instrumentation sufficient?

d) Who is going to do it? What are the new needs in term of training and re-training that these experimental activities impose? Is the separation between modellers and experimentalist still justified?

These charge questions are also the basis of this document, where they have been re-organised under five major headings:

- Where: the V-Tissues 2009 workshop
- Why: fundamental and transitional goals of virtual tissues
- What: modelling technologies and methods
- What: data collection, management and sharing
- Who: specific training and re-training actions

Where: the V-Tissues 2009 workshop

The First International Workshop on Virtual Tissues: v-Tissues 2009, was held in April 21-22, 2009, at the EPA Campus in Research Triangle Park, NC, USA. Sponsored by EC-US Joint Task Force on Biotechnology and hosted by U.S. EPA's National Center for Computational Toxicology, the workshop aimed to bring together academic, government and industry experts from the United States (US) and the European Union (EU) to: (a) discuss key biological and computational challenges in applying v-Tissues™ for chemical-induced toxicity, and (b) to highlight synergies and gaps between US and EU projects. The key topics included:

- Case studies on target organs: liver, development, immune system and lung
- Data requirements for v-Tissues™ applications: Large-scale data sets including, -omics, in vitro high-content screening (HCS) and high-resolution in vivo imaging
- Cross-scale computational approaches: simulating biological process at the molecular, cellular and tissue levels.

The workshop was open to scientists in academia, industry and government, as well as graduate students and postdoctoral researchers. Registration is required as seats are limited.

At the end of the workshop, the panellists listed above had a closed doors meeting, where through a consensus process the positions summarised in the present document were reached.

Why: fundamental and transitional goals of virtual tissues

a) What are the overall objectives of Virtual Tissues and which specific translational goals can they address?

VT can be used to solve concrete problems (clinical, environmental, public health), to generate new knowledge, and to organise and integrate existing knowledge. The discussion showed a greater interest in the problem-solving aspect in the EU experts, and a greater attention to the production and integration of knowledge in the US experts.

b) How can these goals be packaged and prioritized in terms of short-term (1-5 years), medium-term (5-10years) and the long-term (10-15 years)?

We simply separated between low-risk medium-yield (low hanging fruits) and high-risk /high yield (killer applications) goals.

Low hanging fruits => moderate effort can produce intermediate results that already can have significant impact, although the complete unravel of these problems will require considerable effort.

- Diseases where the main outcome (bone fracture, vessel rupture, vessel flow, etc.) can be fully explained with the fundamental laws of physics.
- Skin permeability to chemical and chemical damage to skin.
- Regenerative medicine, stem cell research, VT to predict the direction of differentiation Target the functional modules, such as nephron, liver lobule, bone osteon, lymph node, etc.
- VT as tools to interpret and quantify outcomes in clinical trials.
- Directly link tissue models to exposure data of drugs and chemicals.

Killer application => significant effort and serious risk toward goals with great impact potential.

- Environmental research: multi-chemicals targeting a single tissue, single chemical targeting multiple tissues
- Drug development: VT as tool to interpret clinical results. Patient-specific drug resistance, or more accurate assessment of the clinical end points; major impact in cancer drugs.
- Drug development: use VT to screen candidate compounds in term of outcome on the true clinical endpoint (regeneration, healing, functional recovery, etc.)
- Drug development: use VT to facilitate screening candidate compounds in terms of mechanistic consequences
- Drug development: knowledge of causal mechanistic cascades will help in finding better targets
- Clinical: toward quantitative evidence-based medicine.

What: modelling technologies and methods

a) Why are tissue-level models necessary? What are the unique translational opportunities that Virtual Tissues might provide?

- The development of VT is starting as an evolution of state of the art computational biology, but as it takes momentum and consolidate methodologically it will become revolutionary with respect to the current practice.
- Start from well defined problems so that we can verify progresses, and the let the process slowly become combinatory, it will reach naturally the tipping point where the critical mass shows up, like happen to internet.
- In the conference speakers showed how VT could link, within integrative models, two set of modelling components that are traditionally separated (molecule-cell Vs organ-organism), and components build over different epistemologies (phenomenological Vs. mechanistic).
- The panel stressed how system biology MUST extend its attention outside the single cell and recognise the systemic interplaying between tissues, cell networks, and the genetic/molecular biology processes inside each cell. System biology emerge form the recognition of the limits of the traditional reductionist approach that always pretend to explain the big from the small (organism from the molecules); it is paradox that some system biology does not recognise the importance of downward causation between tissues, cell networks, and the molecular events.
- VT will make possible to integrate knowledge currently spread over too many "knowledge pools"

b) What are the differentiating factors between Virtual Tissues and related biological modeling efforts?

- Construct and understand cellular networks; VT are necessary because the classic single gene approach to perturbing pathways does not work in too many cases.
- Manage downward causation from tissue/networks down to molecules.
- Integrate dispersed knowledge.

c) How will Virtual Tissues be developed? What are the fundamental challenges in modelling the interaction between molecules, cells, tissue, and the microenvironment?

- As VT progress is made, a consequence will be the development of math that is better adapted to biology. We need to team-up with applied mathematicians and computer scientists to capitalise their huge body of knowledge into well-targeted methods and tools, whose aim emerge form the application.
- As VT progress is made, a consequence will be math that is better at coping with the peculiar mesoscale of tissues, not continua, not discrete.
- A consequence of advances in VT research will be new methods, which cope with the combinatory nature of integrative models. Pure combinatory approach would scale the complexity up dramatically; we need special approaches to manage the combinatory explosion.
- Standardization is happening (cell ML, SMBL), but at the cell balance model (ODE), whereas cell-tissue interaction (PDE) does not have any standard mature enough, although some

promising efforts are emerging. The mechanical industry experience with standards like STEP, which in spite of their huge complexity failed to ensure true interoperability across CAD-CAE software vendors, should be taken into consideration, in order to avoid the same mistakes. We recommend that at the present stage we do not aim to true standards, but rather ensure the Good Practices are established locally within each research consortium, and all these GP are periodically revised in GP events, where also specific aspects such as concrete interoperability between software artefacts is tested (such as *Integrating Healthcare Enterprise Connectathons*).

What: data collection, management and sharing

a) What specific types of molecular/cell/tissue data are needed for calibrating / evaluating Virtual Tissues?

b) Are additional data necessary for Virtual Tissues? What specific predictive goals support the need for new experimental methods linked to tissue modelling?

- Modelling and measuring need to be designed together, and the funding models should make this possible. Data collection is vital and cannot be separated from the modelling effort. Complementarily between data collection and VT helps to interpret what you collected, and see what you need to collect more. Data Driven modelling, but also model driven data collection.
- Data collection and modelling should be coupled; as data validate the model, sometime the model help to spot a major issue with the data. This is especially important in some molecular biology measurement, which accuracy is not always defined.
- VT related data collection should cover, in vitro, as well as in vivo human and animal. Animal to human extrapolation is an opportunity for VT, as you can use modelling to understand what are correct translations across species. Synergy with histology and cell cultures in producing mechanistic hypotheses to experimental observations.
- Mapping proteomic information, and in general multiple molecular information, over volumes of tissues. VT requires redundant experiments, measure the same thing at lest two dimensional scales, microarray, vs. whole organ. High throughput methods require the development extreme automation, which is a technological challenge.
- Good reproducible data. Fully qualified measurements with variance, and inherent accuracy assessed. Some of these repeated measurements are not something wet lab researchers will do spontaneously; collaborative projects must support this.
- Some data are available but not accessible to those who would need them. Data sharing infrastructures and protocols, while leveraging on existing experiences (BIRN, PhysiomeSpace) should be made available to ensure that precious data are capitalised.
- Validation: quantity and quality of the data to validate depend on the model. Effective validation requires good data, but better models have lesser requirements to be validated.

c) How can we get these data? Are the in vitro / in vivo models and the available instrumentation sufficient?

- Intercellular localization and dynamics, including molecular mapping over large volumes of tissues.
- Automate histopathology, make it 3D, multimodal.
- Drive the imaging development also in the perspective of generating useful data for VT
- Coordinate data collection: shared datasets for benchmarking, accumulative programs, etc.
- Quality assurance: develop methods and protocol that document the quality of the data collected, and for measurements the interval of uncertainty associated to them.

Who: specific training and re-training actions

d) Who is going to do it? What are the new needs in term of training and re-training that these experimental activities impose? Is the separation between modellers and experimentalist still justified?

- Fight specialization at the undergraduate level. Develop team science skills and then drill down in grad studies. However, there is a risk that these students are less competitive in the job market.
- Introduce simple modelling activities as instruments to sharpen reasoning & analytical skills, perhaps as early as high school
- Consider the support of fellowship for PhD and post-doc on tissue modelling as a new discipline on its own, that requires appropriate vocational training.
- Include in PhD training specific elements oriented to the of effective interdisciplinary team building.
- A retraining week where the goal is to bring all to a certain level of generalisation, executive business schools can be used as a model for generalist retraining of highly skilled seniors. Collaborative projects could start with such retraining weeks where each partner contributes with his/her own expertise. Sometime more broader VT retraining weeks could be organised jointly US-UE. Future workshops should involve more biologists.