EC-US Workshop on Virtual Tissues

www.epa.gov/ncct/virtual_tissues

Patrik Kolar and Elaine Francis

19th EC-US Task Force on Biotechnology Meeting
June 25 - 26 2009
Importance & Potential of Virtual Tissues

• to efficiently evaluate human health risk for thousands of environmental chemicals and pharmaceuticals

• to predict adverse health outcomes (e.g., oncogenic, chronic disease, developmental & reproductive) using:
  – high-throughput data-streams collected on *in vitro* systems
  – bioassays sensitive to environmental-relevant (low) exposures
  – experimental models relevant to human biology and toxicities
  – *in silico* models to extrapolate low-dose and cross-species
  – systems to evaluate genomic variation in response

• reduce dependence on animal testing
  – extrapolation from *in vitro* to *in vivo* biology
  – alternative model systems (lower model organisms, stem cells)
What are Virtual Tissues?

**Motivation:** computational (*in silico*) models to navigate the complexity of biological systems and phenotypes

**Goal:** simulate ‘real’ tissues reacting to perturbation across agents, system, life-stage, genetics, dose and time

**Inputs:** detailed knowledge of molecular targets, toxicity pathways, cellular networks and disease phenotypes

**Outputs:** working models of ‘functional modules’ and *in silico* reconstruction of tissues and organs
Virtual Tissues – why?

- practical support of systems biology effort to link molecular defect with clinical phenotype (cross-scale models)

- the interface between state-of-the-art experimental biology and computational (in silico) modeling

- comprehensive exploration of complex cellular fabrics during normal and adaptive responses of tissues / organs

- virtual tissues will be needed to build in vitro data onto an in vivo architecture: how can we best leverage EU-US collaborations to get there?
Workshop Preparation Timeline

- **Spring 2007**: EPA proposal accepted by EC-US Joint Task Force on Biotechnology.

- **Summer 2008**: EU-US Organizing Committee established.

- **Fall 2008**: US-EU expert panel began monthly meetings to develop workshop agenda and organizational tasks.

- **21 – 22 April 2009**: Workshop held at EPA in Research Triangle Park, NC.

- **Summer 2009**: Workshop report draft.
Workshop organizers

Organisational / Funders & Policy Makers

- EPA (E. Francis, I. Shah)
- Other US Funding agencies (NIH / NIBIB, DoE, NSF)

Scientific Co-chairs

- US: I. Shah (EPA)
- EU: M. Viceconti (Inst. Ortopedico Rizzoli, Bologna)

+ most of the speakers contributed to the agenda – preparation process
Scientific focus: “driver” questions

• What are the ‘translational research’ gaps that can be bridged by a Virtual Tissues paradigm?

• What are the short-term products and long-term applications of the tools and technologies?

• What computational and experimental bottlenecks must be overcome to meet these products & applications?

• How can EU-US international collaborations help to advance these goals?
Virtual Tissues (VT): Meeting Format

Conference on VT: Plenary sessions (public)

- Overview & Objectives
- Why Virtual Tissues?
- Virtual Tissues in Practice
- Tissue Modeling Today

Focused Workshop on VT: Discussion (by invitation)

- Breakout group discussions (charge questions)
- Report from two breakout groups & joint conclusions
- Discussion on International collaboration issues
Conference on VT (overview)

Introduction

L. Bochereau, E. Francis, R. Kavlock, R. Connoly, M. Viceconti

Why Virtual Tissues?

E. Mosekilde, A. Hunt, A. Schuppert, J. Glazier, D. Drasdo

Virtual Tissues in Practice

R. Corley, R. Superfine, F. Castiglione, T. Keppler, O. Lorentz, T. Otter, T. Knudsen, I. Shah, V. Cristini, K. Marias

Tissue Modelling Today

Conference wrap-up

• CULTURAL ISSUES

– EU-US should tackle complex problems of broad international significance
– VT challenge: biologists (problem identification) + engineers (problem-solving)
– need to address VT time-frame and how to manage VT expectations
– confidence vs skepticisim, simplicity (abstraction) vs complexity (detail)
– resource for sharing models, ontologies, computational toolbox

• IDENTIFYING KEY ATTRIBUTES

– VTs are subset of MSMs that simulate tissue function through cellular fabric
– bridges molecules → phenotype across technology platforms and time-scales
– computational models execute modular processes
– explore hypotheses for missing information via computer simulation
– modularity allows ‘living’ VT models that are integrative, extensible and evolvable
– enables emergence of phenotypic outcomes through aggregate cellular behaviors
DATA STREAMS

- should define modeling objectives in light of what clinical data we can get
- define how complex models must be to have useful and confident application
- technologies are now capable of generating ample quantitative data
- databases hold information for relevant knowledgebase development
- bottom-up versus top-down approaches for data collection meet at tissue-scale

MODEL PERFORMANCE

- evaluate VTs with reference ‘clinical’ data and knowledge
- consistency of predictions with data and knowledge of normal biology
- predictive utility: ‘what if’ questions to exercise VTs across complex perturbations
- objective criteria needed for assessing model fitness and emergent behaviors
Workshop Charge Questions

1. What are the short-term (1-5y), medium-term (5-10y) and long-term (10-15y) goals?

2. What modeling paradigms will be most suited to accomplish these goals and how can they be "phased-in" practically?

3. What levels of biological organization need to be interrogated/perturbed in order to obtain the relevant data to develop/ calibrate/ evaluate these models?

4. What biological assay technologies exist / will be required to accomplish this?
Workshop conclusions

Translational goals

**short-term:** map cellular dynamics in simpler research models and model systems (*in vitro* → tissues)

**intermediate:** model local movements of small molecules in tissues, including extracellular matrix

**long-term:** understanding mechanisms of *in vivo* tissue endpoints, predicting from micro-heterogeneity that drives progression from normal → abnormal states
Modeling issues

Functional unit of a tissue:

- this should be more precisely defined
- needed to understand and predict impact from collective cell behavior
- scale of a functional unit = “larger than a single cell”
- *in vivo* architecture and *in vitro* replication of physical space

Measurement: *use important lessons learned from*

- systems biology: limitation is ability to make the right measurements, despite the availability of new tools
- PBPK: limitation not in the measurements or tools, but how to understand the target-level (tissue) microdosimetry.
Modeling Issues (contd.)

Global Research Network:
– focus in silico reconstruction on well-understood systems
– engineered tissues should display well-defined features
– parameterization, kinetic constants from best practices
– automated pattern recognition diagnostic of histopathology
– compare VT model fitness with physiological outcomes
– VTs should predict endpoints not explicitly encoded in model

Data Sharing:
– community of practice for data & model sharing
– comprehensive map of gene expression across systems
– more attention to cellular networks (including ECM)
– HTP/HCS data for self-adjusting, organotype in vitro models
– quantitative 3D histomorphometry (patients, animals)
Data & Computational Requirements

• **Data/Experimental requirements**
  – define organ/functional units → tissue context
  – need *in vivo* cell/tissue data/histomorph
  – develop *in vitro/organotypic* cultures/

• **Computational requirements**
  – need different modeling & simulation formalism:
    • encapsulate complexity: inside cells / between cells
    • micro-anatomic transport / micro-dosimetry
    • generate emergent responses from cells

  – cell/tissue-level *knowledge* integration: ontologies to capture *meaning* / reduce ambiguity:
    • structure/components: cells, cell-cell, cell-ecm
    • function/behaviors: molecular → cell, cell → phenotype
International Collaboration

- "Combat specialisation"
  Biologists, clinicians and modellers to speak the same language
  (EU-US trainings needed)

- Involve "bench scientists" into preparation "VT agenda"

- Establish "Transatlantic Community of Practice in VT"
  (Meeting regularly as satellite to existing meetings or in separate forum)

- Develop "Transatlantic Roadmap on VT"
  (This Conference a first step)

- Journal Editors to become more aware of the recognition of the potential in new emerging field

- Funders to explore further possibilities of funding the preparation of a roadmap (CA / SA) and research
  (Coordinated calls: US: NIH, EPA, EC –Health, eHealth)
Musings from a Virtual World

Building models for complex tissues seems harder today. Oh, so many issues.

Problems too complex for biology’s history require engineers to solve the mystery.

In silico solutions and deciphering code can loosen the grasp of molecules’ fold,

but electrons pumped by a virtual heart: is this engineering (or really great art)?

Only 20 minutes to cover immunity? No way! Proclaimed with impunity …

… just 3 more minutes, please and you’ll see how it all works, whether T or B.

Humans? Too tall for testing these drugs. Let’s treat the computer and see what it does …
Musings from a Virtual World

Who needs those expensive hospital halls when we can trial behind firewalls,
and ask this machine to predict from a map what chemicals do while real people nap.

It’s all so confusing, this virtual world, how kidneys pulse and cilia hurl …

I thought that Henle combed the blood …
But a molecular comb for ciliary mud?

How complex these diverse tissues can be, the sorting and movements of cells in a sea …

leading some to insist that livers MUST rule
but for me, the embryo is what is MOST cool.

Alas, we’ll capture these cells in a stream, as computers enable reality’s dream,
predicting cell function will not escape reason:
Virtual Tissues have now come in-season (☺).

-TB Knudsen, 2009