Computational physiology from transcriptomics to tissue - modelling disease processes

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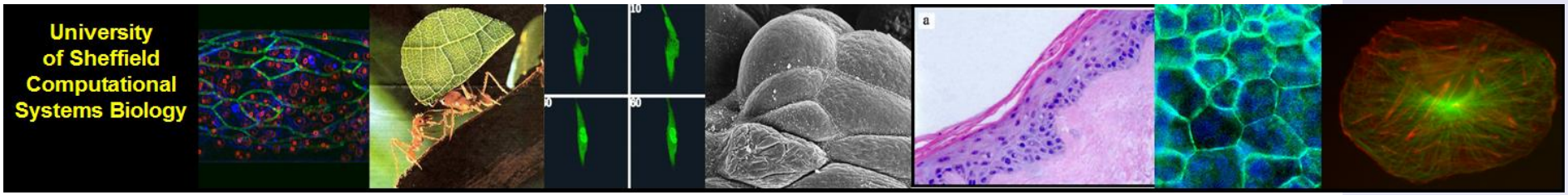

What do I mean by ‘Computational Physiology’?

Computational physiology is a tool to understand developmental changes and predict the medium to long term effects of our interventions:

- how did this particular individual reach this‘not normal’ state?
- if we intervene in some way, how will this ‘not normal’ state change in future?
- given this knowledge, can we rationally design prophylaxis and treatment?

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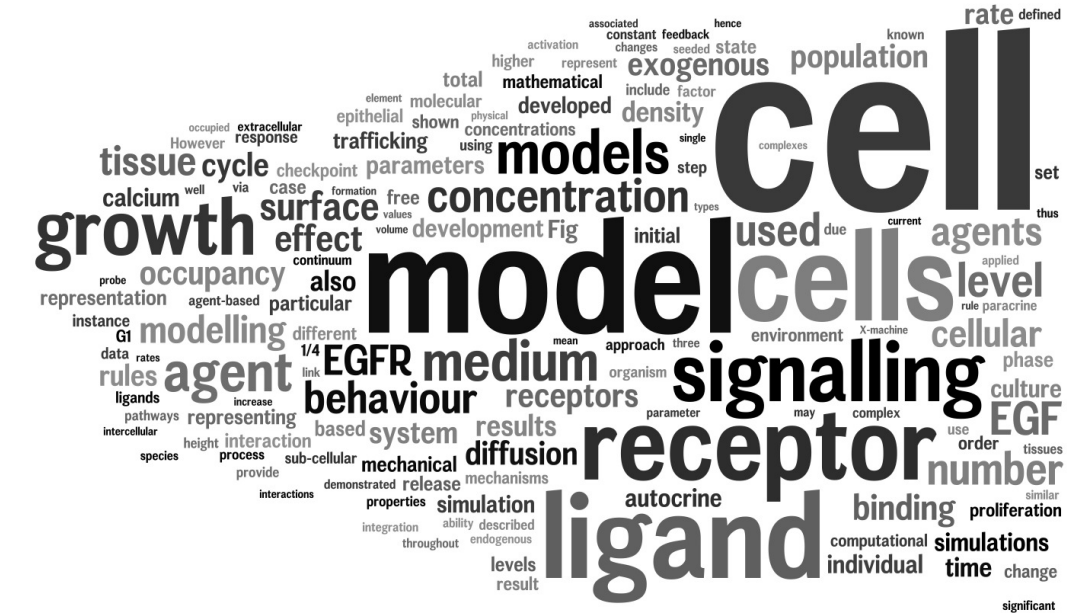
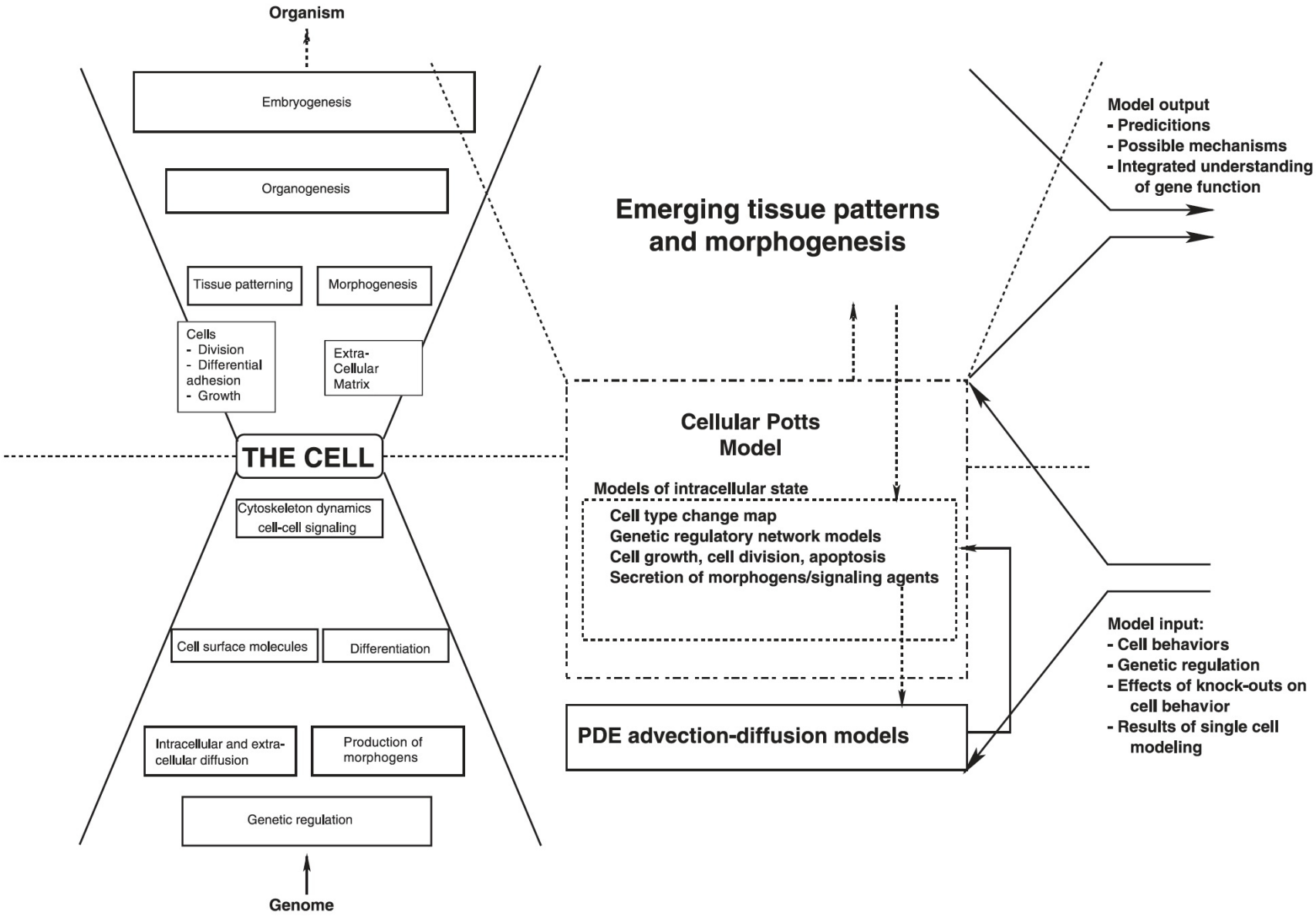
I will try to give you an idea of how this might be achieved by:

- making an assertion
- exploring the consequences of the assertion
- describing what we have done so far
- saying what we propose doing next

My assertion: if we want to be able to understand the route from ‘normal’ to ‘malignant’, and to be able to make some predictions about the medium to long term effects of our interventions, we need computational models in which the cell is central, and the information we can get from transcriptomics etc informs what the cells get up to.



http://www.dcs.shef.ac.uk/ rod/Integrative_Biology.html; Walker D et al (2006) J Theor Biol. 242:774-789; Maleki-Dizaji S et al (2009) Online Journal of Bioinformatics 10:51-59

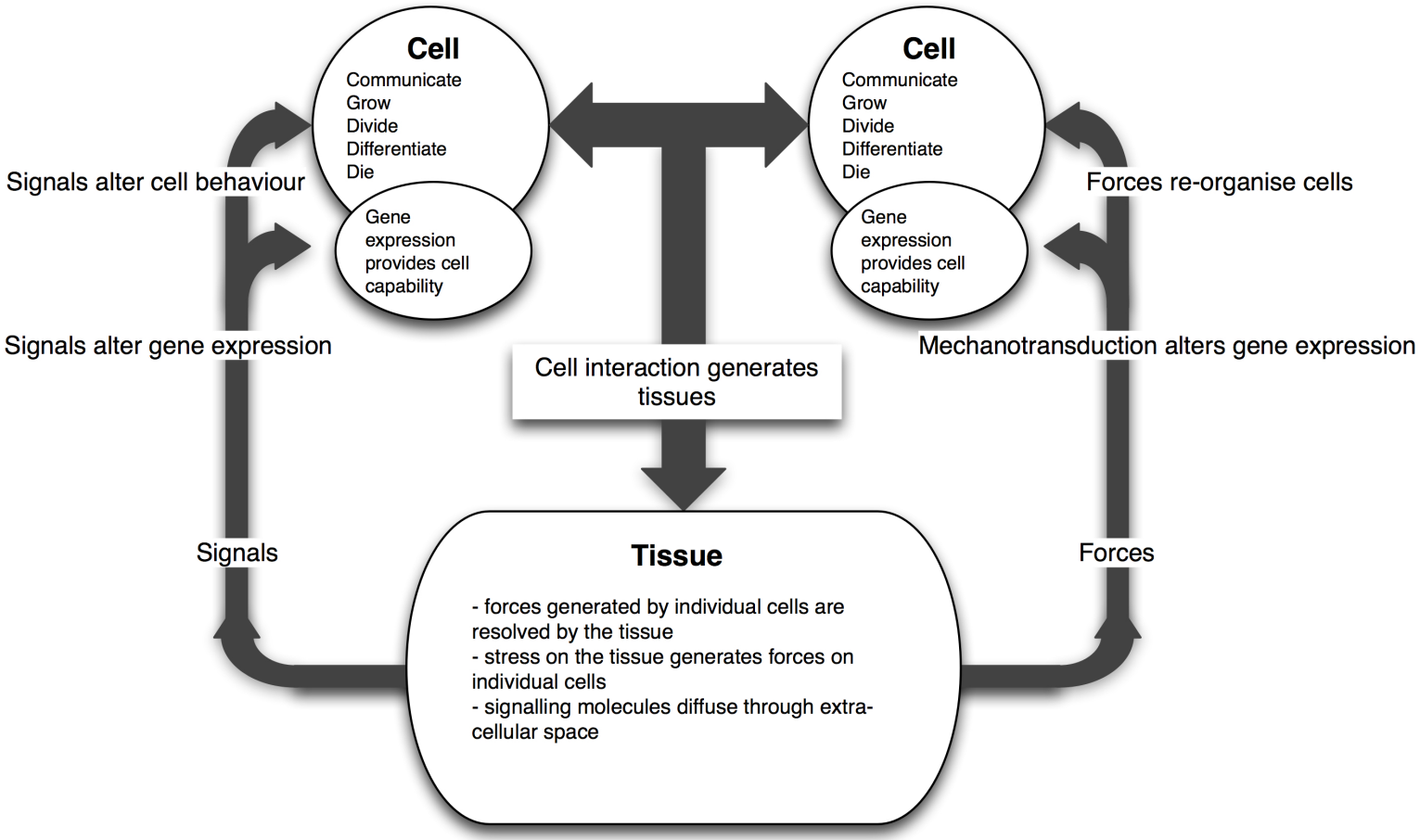

Organism
Embryogenesis
Organogenesis
Tissue patterning
Morphogenesis
Cells
- Division
- Differential adhesion
- Growth
Extra-Cellular Matrix
THE CELL
Cytoskeleton dynamics cell-cell signaling
Cell surface molecules
Differentiation
Intracellular and extra-cellular diffusion
Production of morphogens
Genetic regulation
Genome
Emerging tissue patterns and morphogenesis
Cellular Potts Model
Models of intracellular state
Cell type change map
Genetic regulatory network models
Cell growth, cell division, apoptosis
Secretion of morphogens/signaling agents
PDE advection-diffusion models
Model output
- Predicitions
- Possible mechanisms
- Integrated understanding of gene function
Model input:
- Cell behaviors
- Genetic regulation
- Effects of knock-outs on cell behavior
- Results of single cell modeling

The cell is central to any discussion of change - changes to tissues are the result of growth, division, differentiation and death of individual cells. These changes result in changes in the **organisation** and **behaviour** of the tissue.

Organisational change is driven by the forces that the cells exert as a result of size changes and the formation/breaking of bonds between cells and between cells and substrate/matrix.

Behavioural changes are driven by signalling - the production, transport (active and diffusive) and detection of chemical species. These processes can be initiated by forces applied to the cells (mechanotransduction).

Signalling may alter gene expression, giving rise to changes in cell type and behaviour.



(Some of) the issues:

Sub-cellular ('systems biology') and tissue-level ('computational physiology') modelling are not well connected

Techniques for incorporating the results of high-throughput screening (genomics, transcriptomics, proteomics) into computational models of physiology are in their infancy

Current physiome models provide a snapshot in time of the organism's behaviour. They do not include developmental processes ('how did the organism arrive at this state' and 'what is the prognosis')

Complexity (30,000 genes, 100 genes per biological function – 10^{289} combinations!)

Range of length scales (10^{-9}m to 1m)

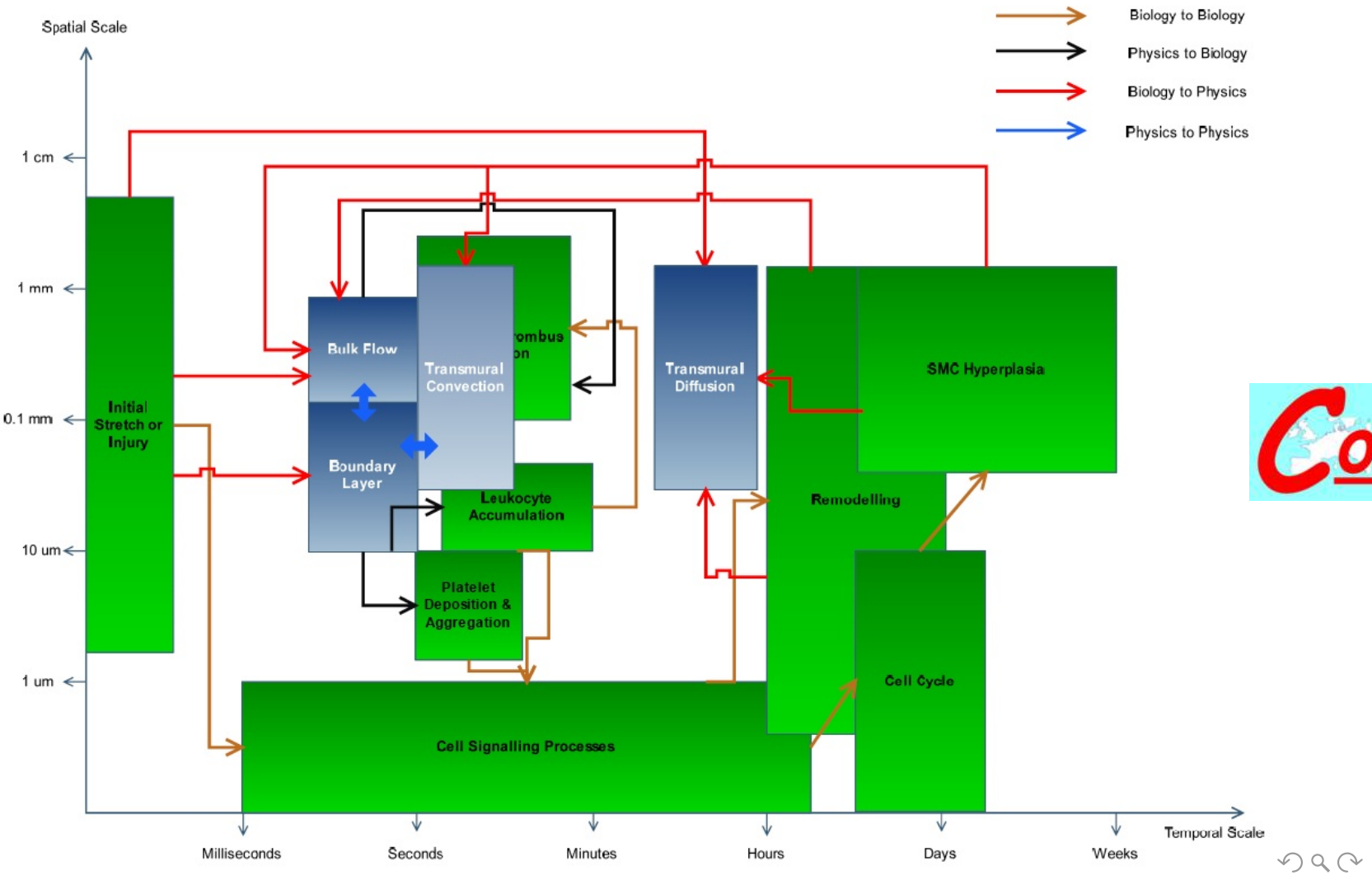
Range of time scales (10^{-6}s to 10^{9}s)

Incomplete knowledge

Variable quality data from multiple species

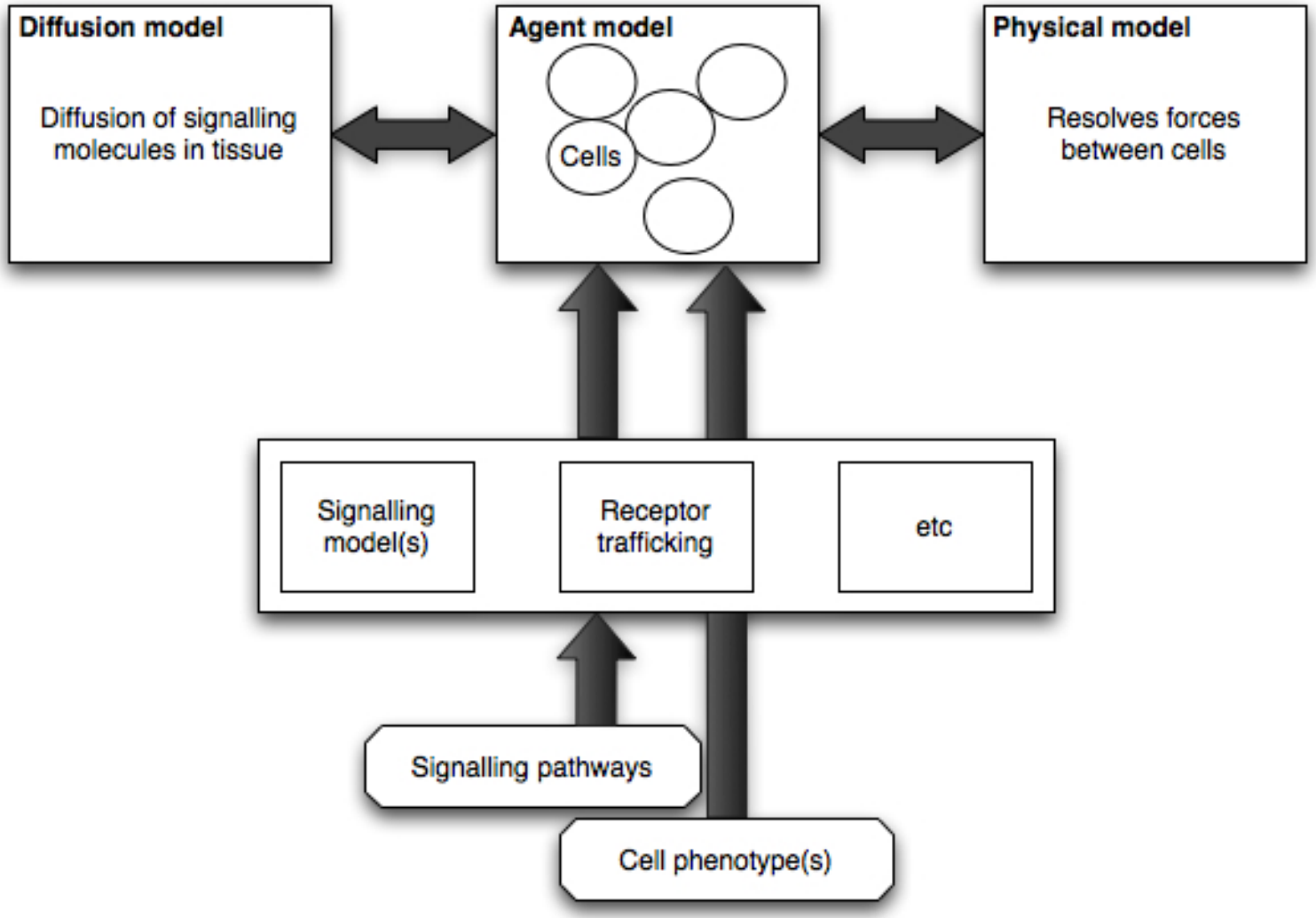
Multiscale issues: scale separation

The problem is multiscale in time and space. We have to reduce complexity by thinking generically; using scale separation to reduce model complexity; using black boxes in which detail is ignored; including only what is essential



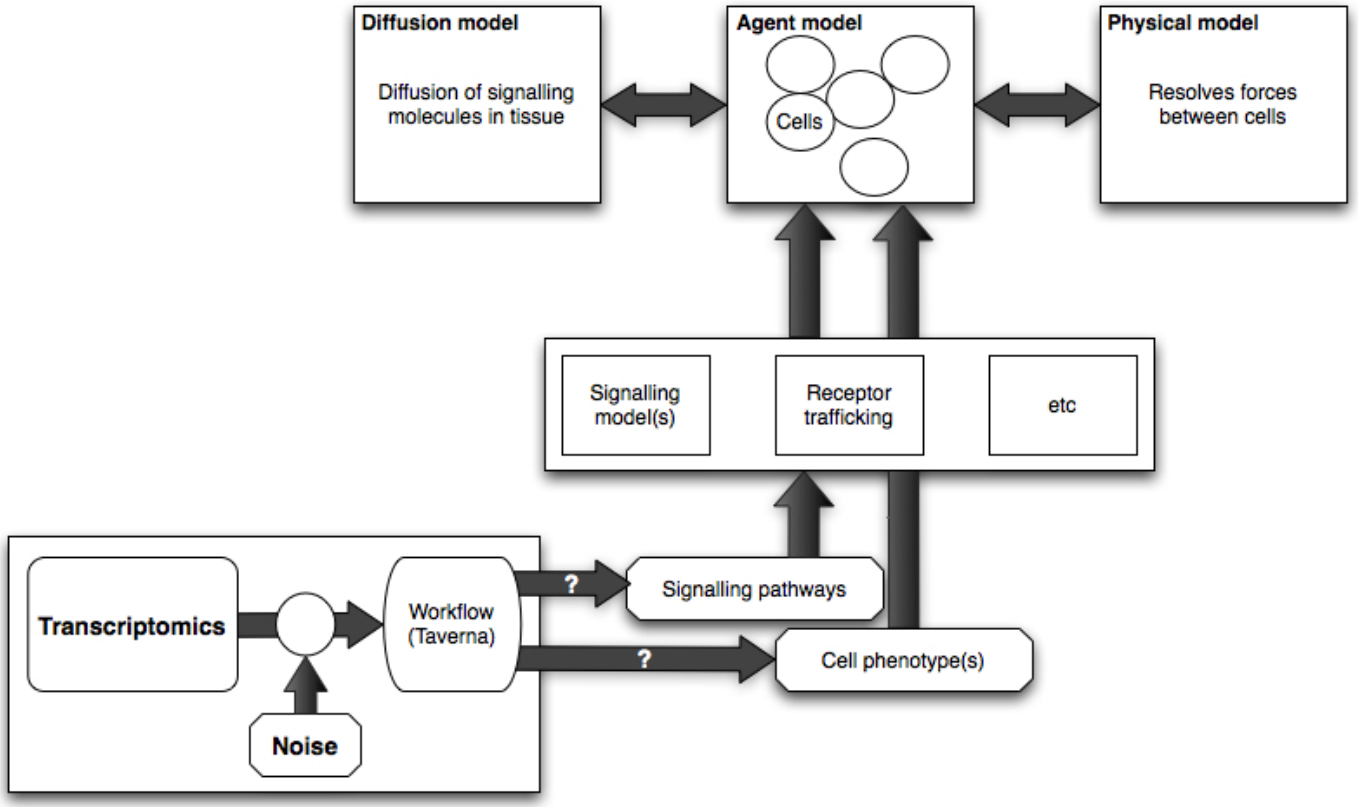
Getting 'omics into tissue models

What we want:



Getting 'omics into tissue models

In the SUMO (Systems Understanding of Microbial Oxygen Responses) project we have used Taverna workflows to identify up-regulated signalling pathways in E. coli under different environmental stress.



https://ptjapps.fz-juelich.de/sysmo/
Maleki-Dizaji S et al (2009) Online Journal of Bioinformatics 10:51-59

AirPROM - Airway Disease PRedicting Outcomes through Patient Specific Computational Modelling

Airprom WP5/6

Modelling and Measuring Gas exchange and flow in the airways over different length / time scales with 3He and 129Xe gas MRI

Generation

Conducting Airways: 0, 1, 2, 3, 4, 5 ⇩ 15

Respiratory Zone (Acini): 16 ⇩ 22, 23

Trachea

Bronchi

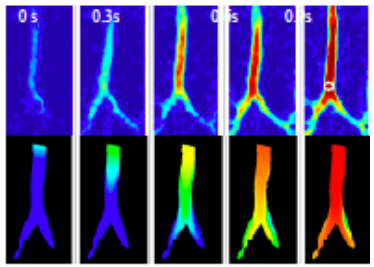
Bronchioles

Terminal Bronchioles

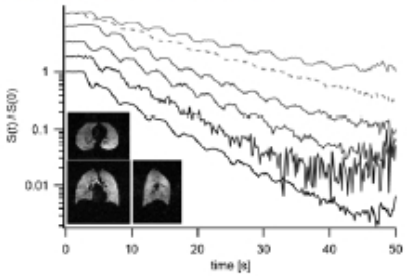
Respiratory Bronchioles

Alveolar Ducts

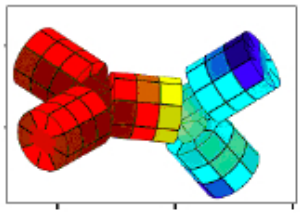
Alveolar Sacs



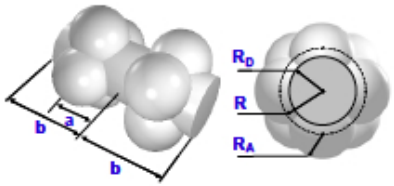
3He gas washout – obstruction at the bronchiole level reflected in 3He ventilation image heterogeneity and gas washout times Modelling with connected network models of resistance and compliance



3He dynamic imaging and CFD modelling of gas flow in the upper airways



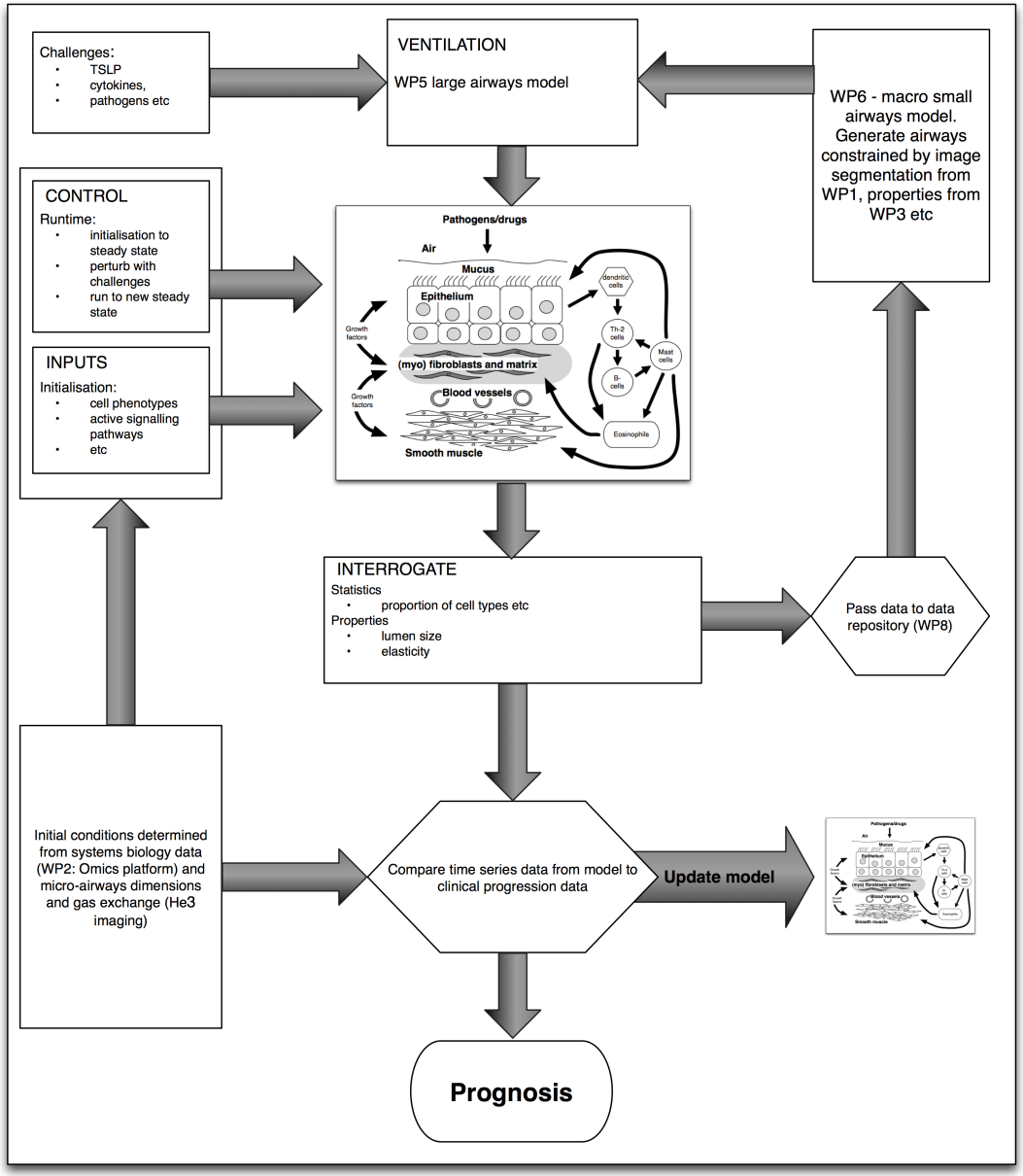
3He and 129Xe short range diffusion Coefficient – measures of alveolar duct geometry and finite difference Diffusion simulations



3He and 129Xe long range diffusion coefficient – measures of alveolar duct interconnectivity and gas mixing

Jim Wild, University of Sheffield, 6/6/2010

AirPROM - Airway Disease PRedicting Outcomes through Patient Specific Computational Modelling



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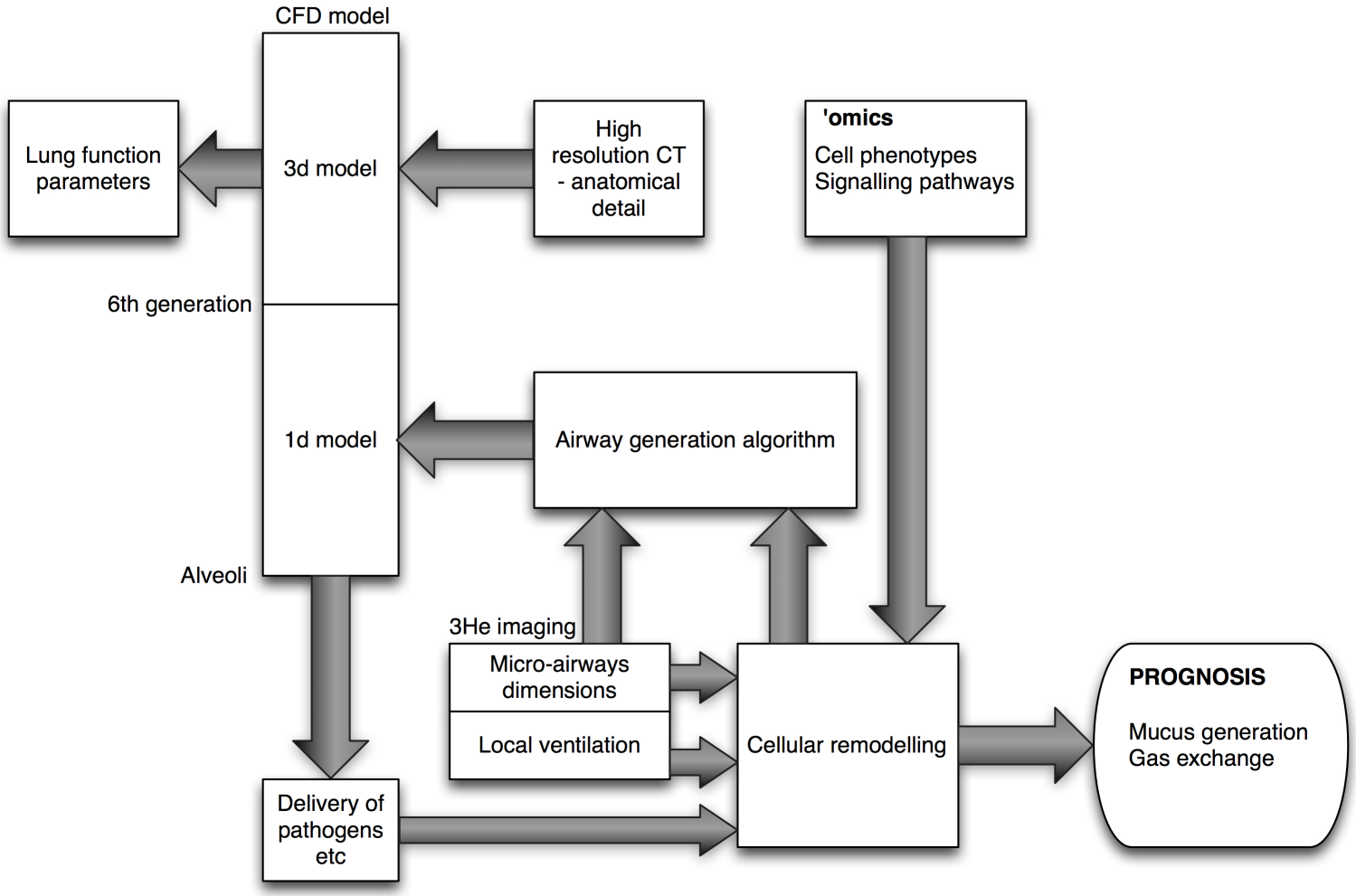

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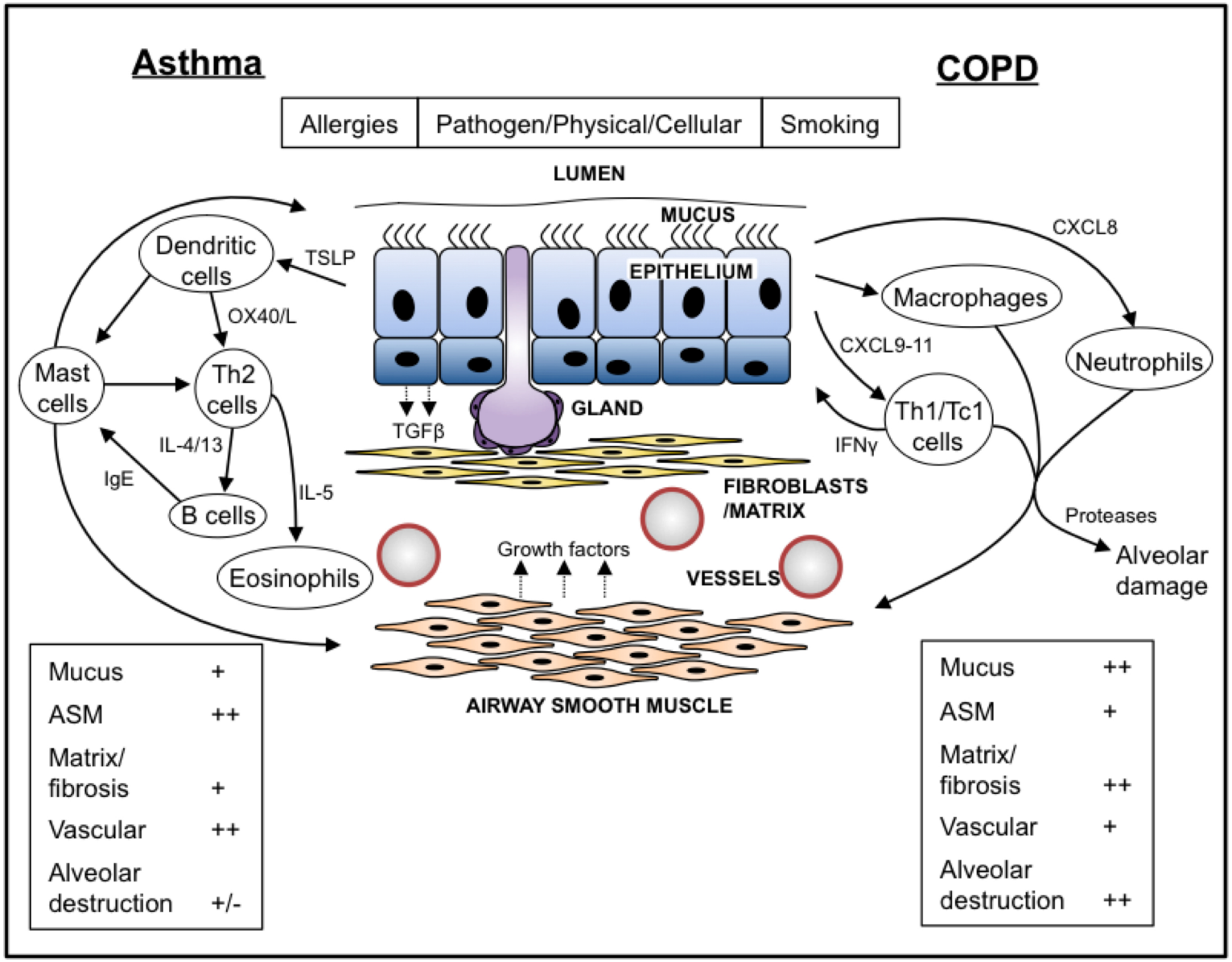

What are the challenges?

- generating usable information on cell phenotype and signalling pathways from genomic and transcriptomic data
- coupling a disparate array of measurements and models
- validation, validation, validation!
- describing individual models, boundary conditions, coupling methods, processes
- the range of timescales (signalling event to cell cycle time to lifetime)
- developing a metamodel that can be used in the clinic

Acknowledgements

The opinions expressed are my own, but have benefited from discussions with and work by:

- Jenny Southgate (urothelial cell biology)
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- Pat Lawford (numerate biology)
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