Multiscale modelling to help making sense of dynamical multiscale resilience

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Two main messages

- Multiscale modelling of human physiology is has advanced a lot
  - but probably not enough for the topic of this workshop

- Multiscale modelling frameworks could contribute to deeper understanding of resilience in ageing

The Digital Twin

Virtual Physiological Human

- Dynamic multiscale models of human physiology and pathophysiology

Applications

- Digital Patients
- In-Silico Clinical Trials
- Personal Health Forecasting

The Virtual Physiological Human: Ten Years After

Marco Viceconti[1] and Peter Hunter[2]

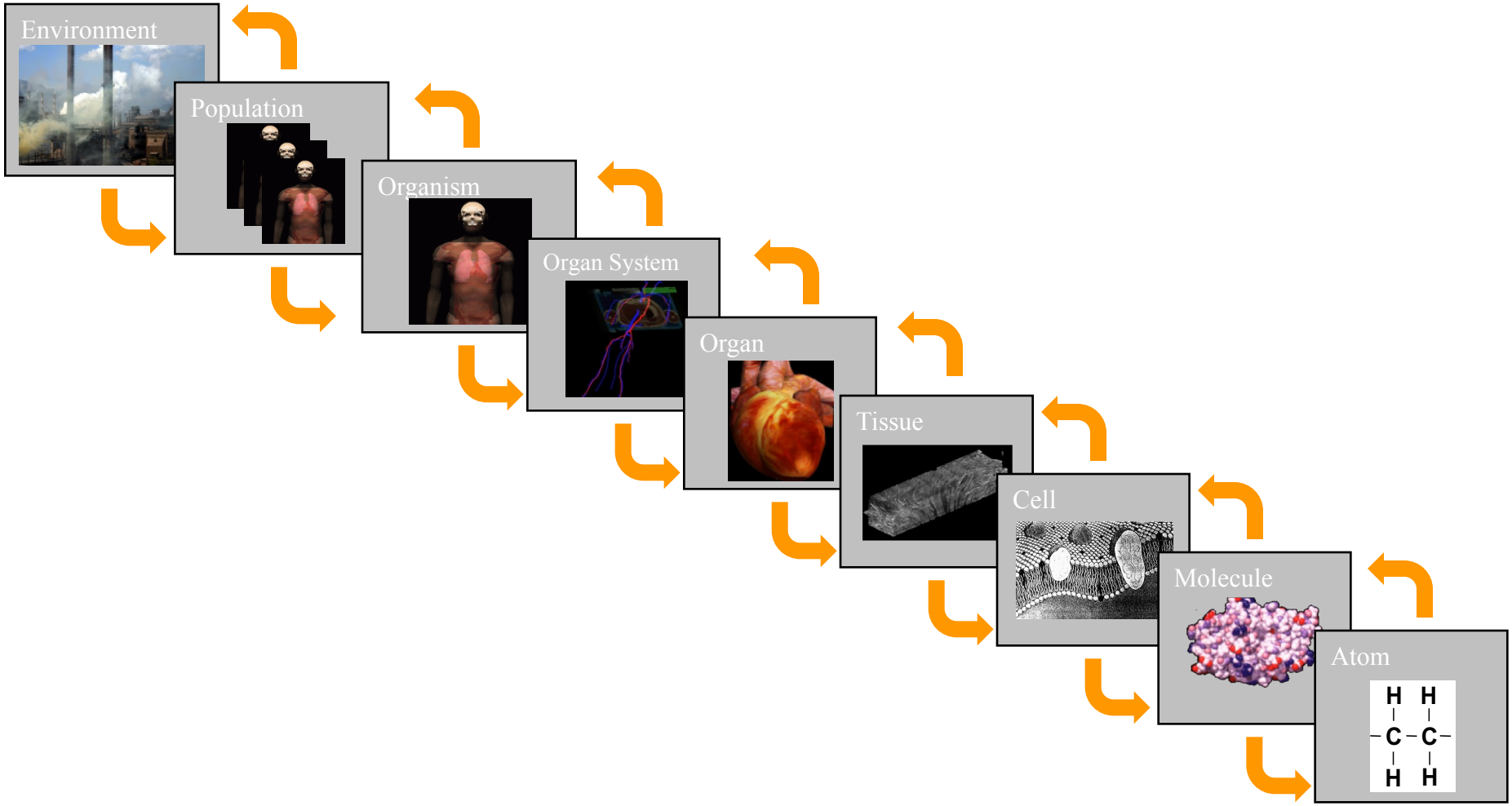
Annu. Rev. Biomed. Eng. 2016. 18:103–23

Virtual Humans film

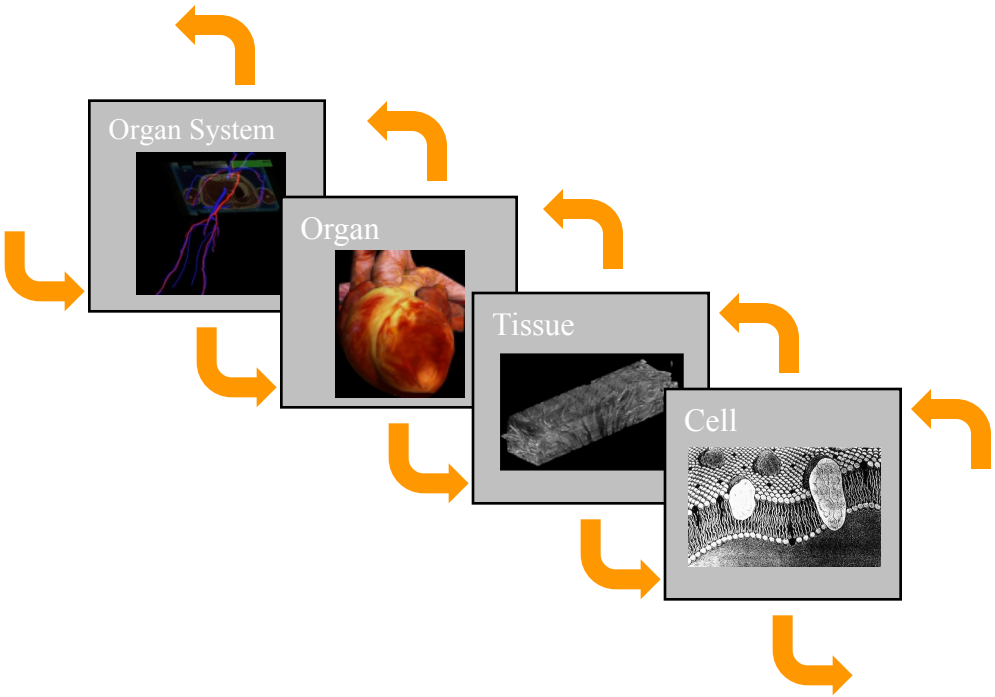
http://www.compbiomed.eu/home/how-to-build-the-virtual-human/

Multiscale Computational Biomedicine

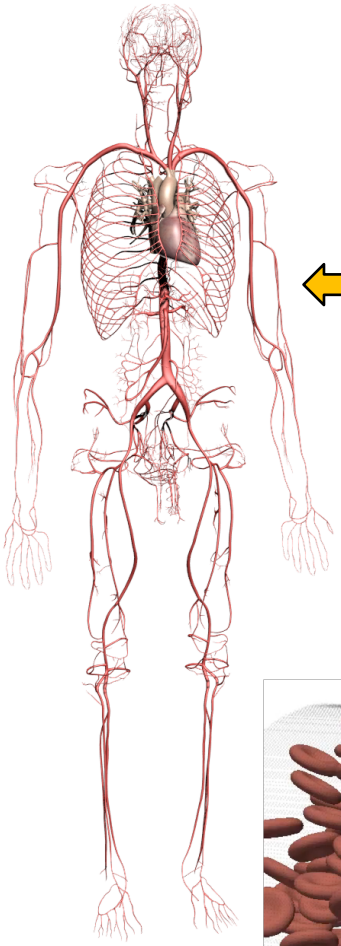
"from molecule to man"

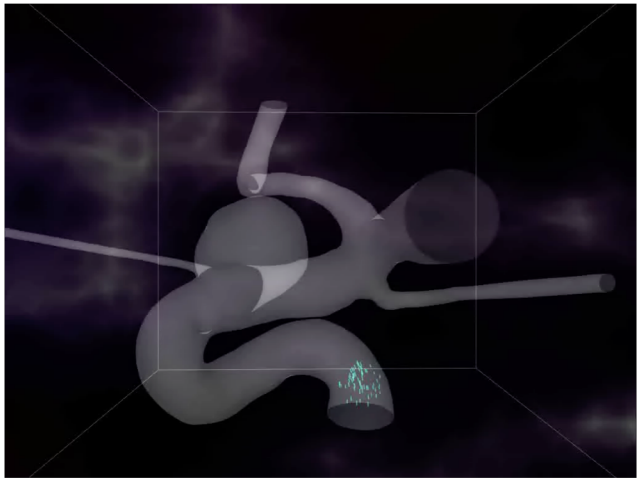


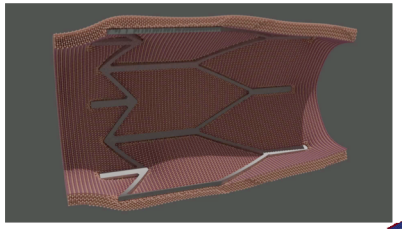
Middle Out Approach

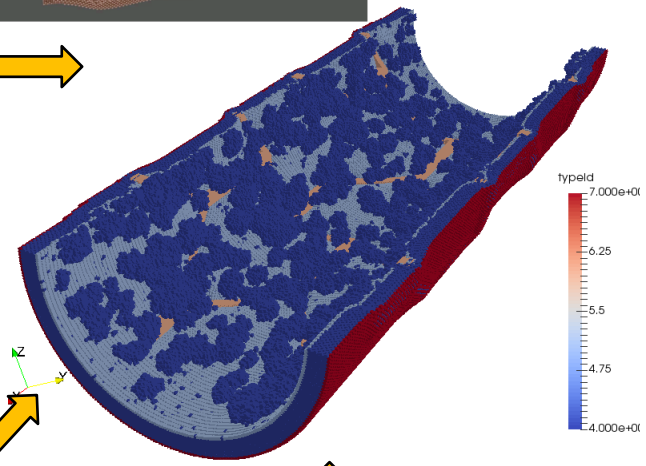


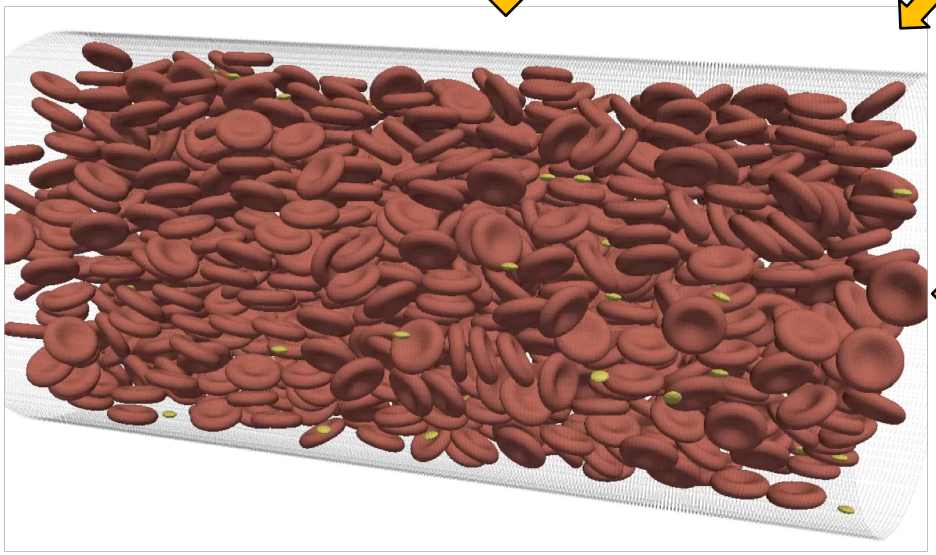
example, the virtual artery







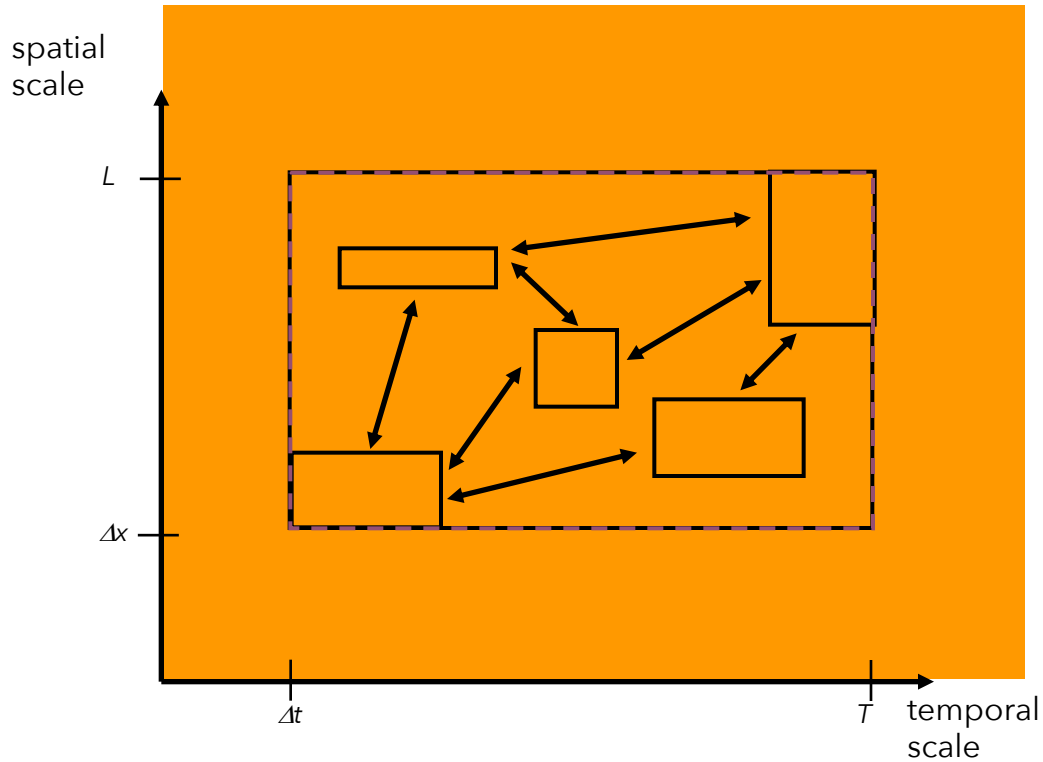




Molecular scales
- vWF
- Platelet aggregation
- Cellular regulation patheways

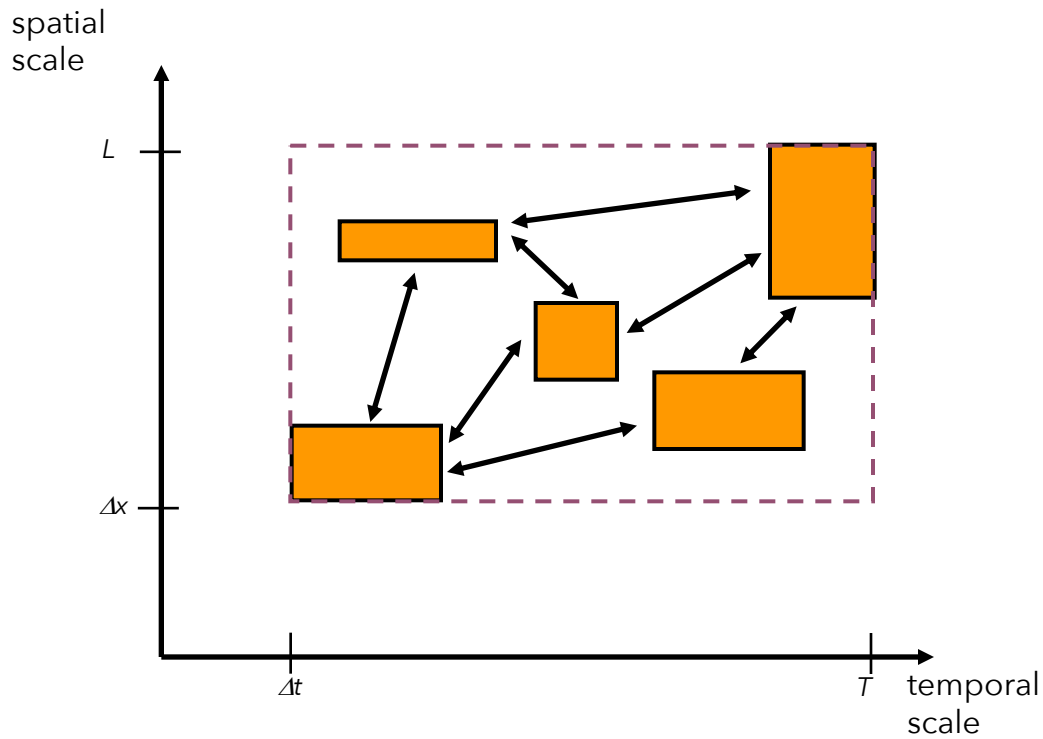
Multi-Scale modeling

- Scale Separation Map
- Nature acts on all the scales
- We set the scales
- And then decompose the multiscale system in single scale sub-systems
- And their mutual coupling

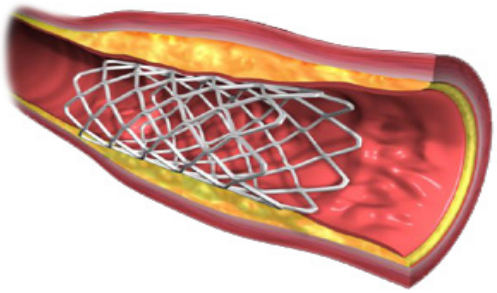


From a Multi-Scale System to many Single-Scale Systems

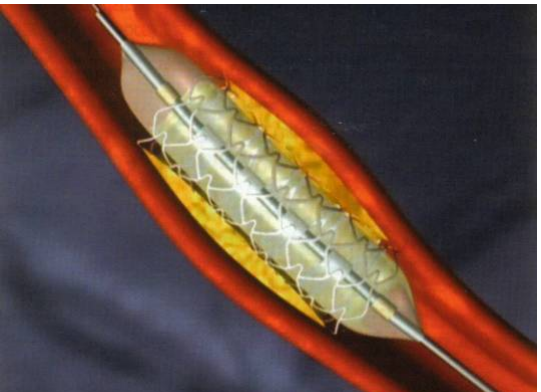
- Identify the relevant scales
- Design specific models which solve each scale
- Couple the subsystems using a coupling method

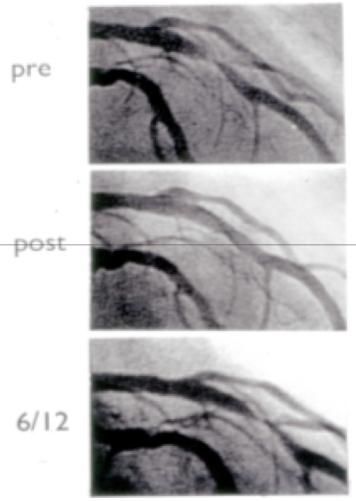


Example, In-Stent Restenosis



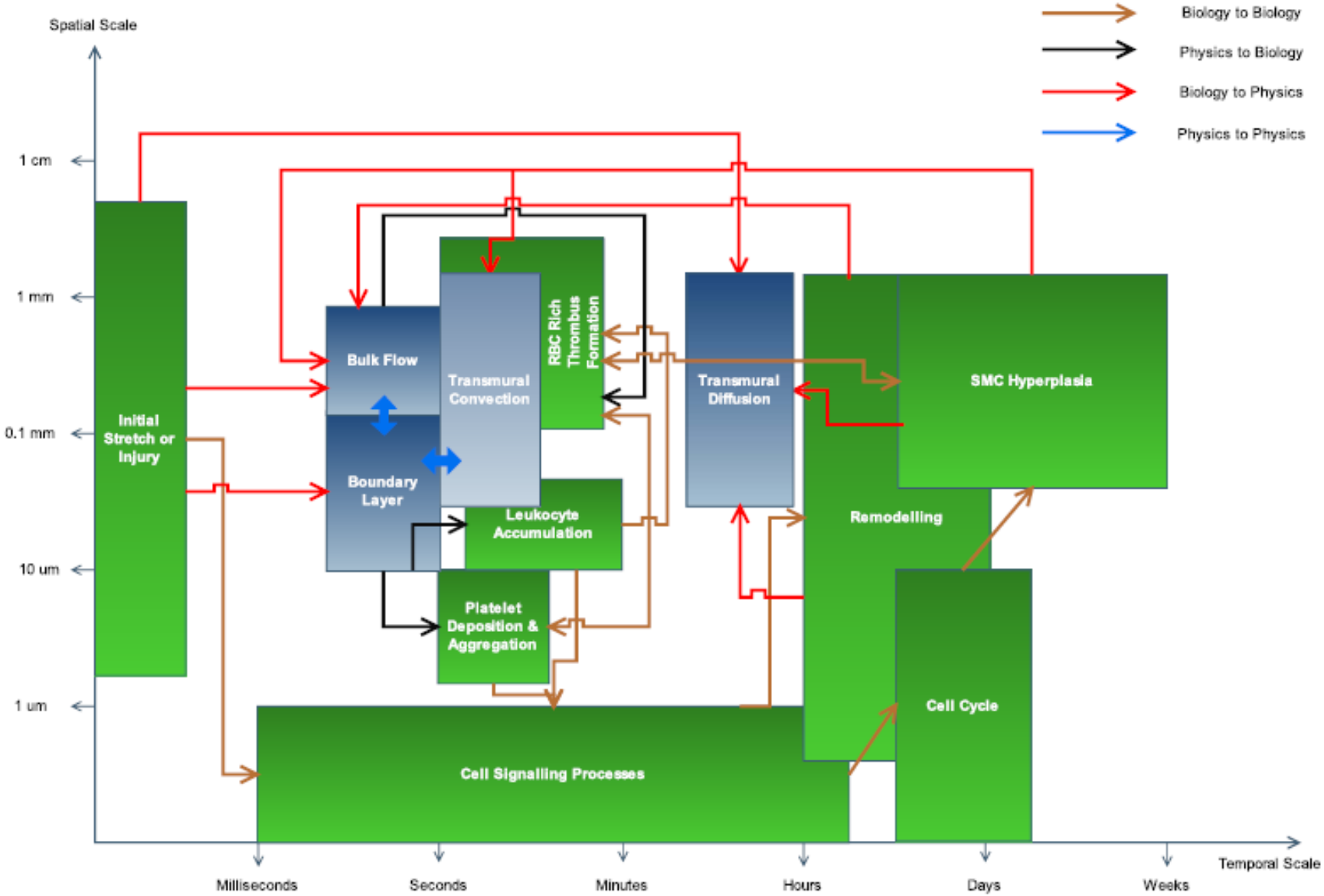
- Adverse response after treatment of coronary artery stenosis
- Restenosis
  - Development of a new stenosis after angioplasty
  - Caused by excessive proliferation of smooth muscle cells



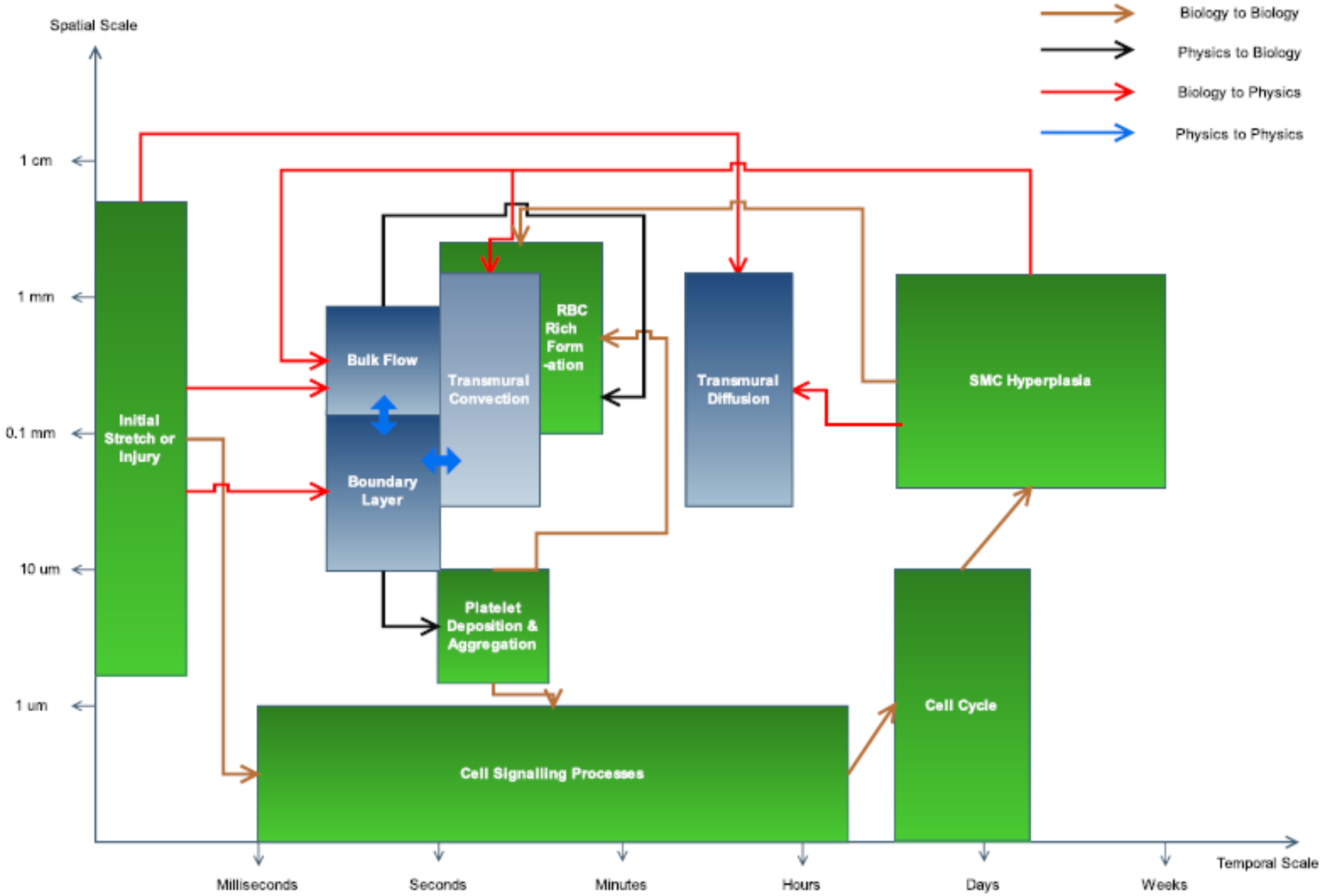


Human angiogram depicting restenosis six months post-PCI

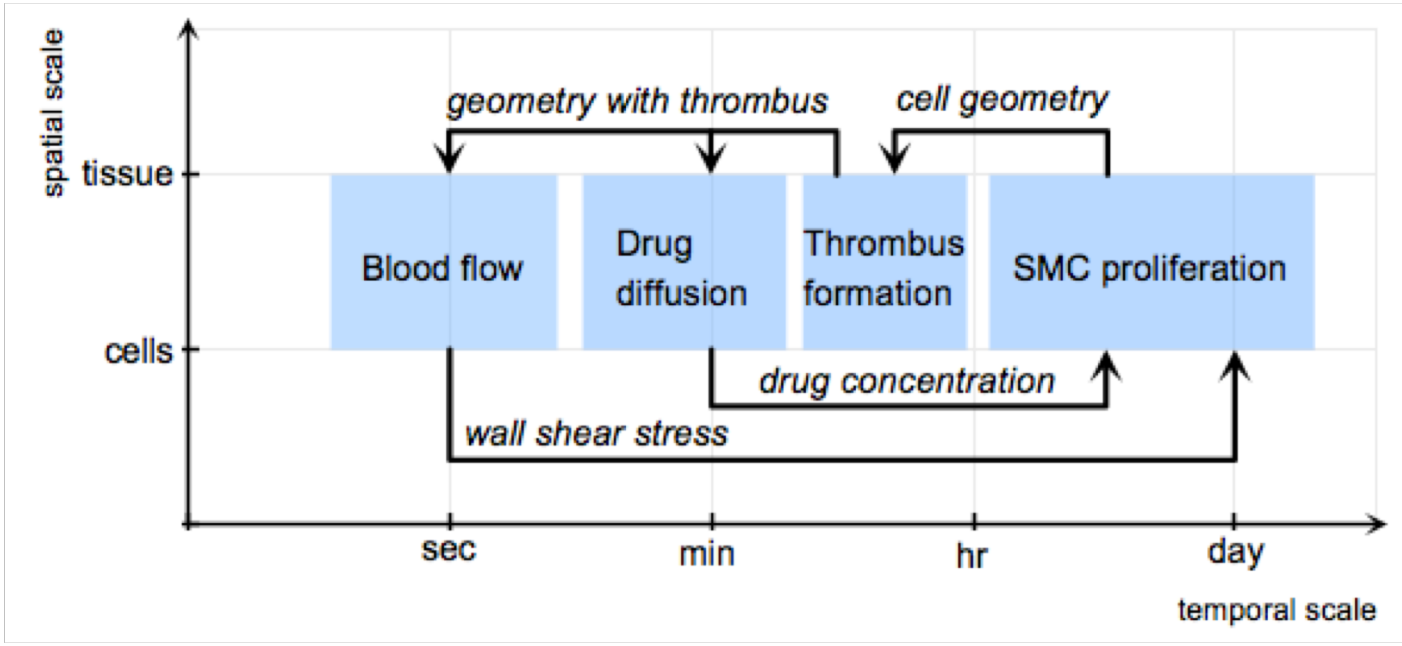
Example - Comprehensive Scale Separation Map



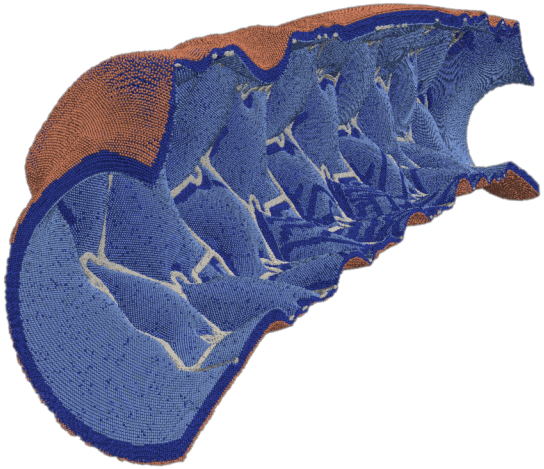
Simplified Scale Separation Map

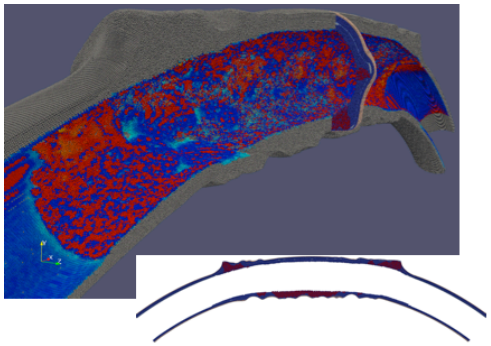


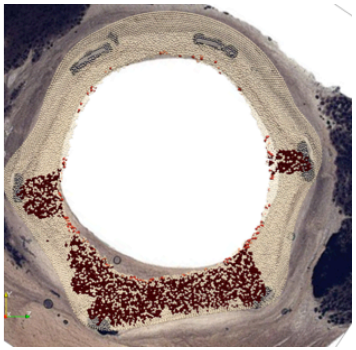
even simpler …

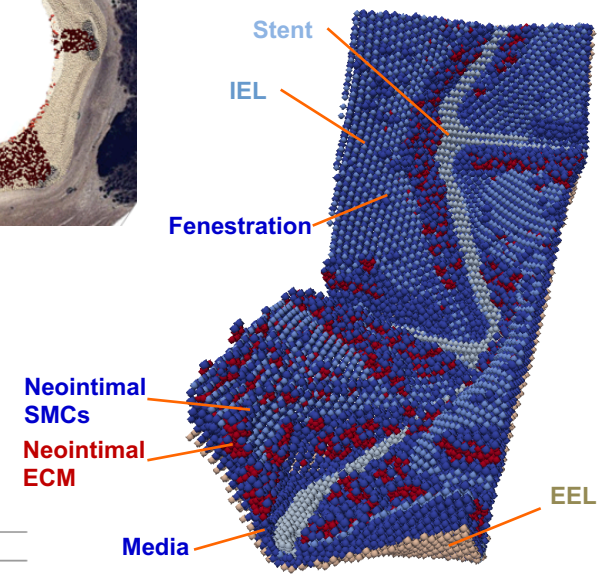


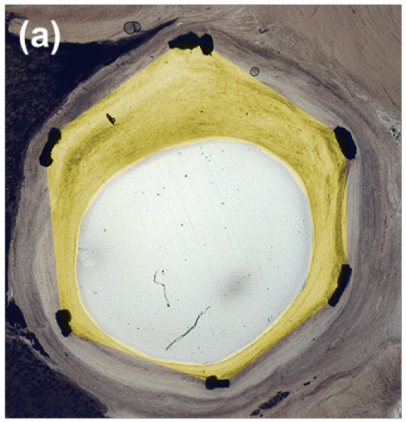
Model is validated against in-vitro and in-vivo data

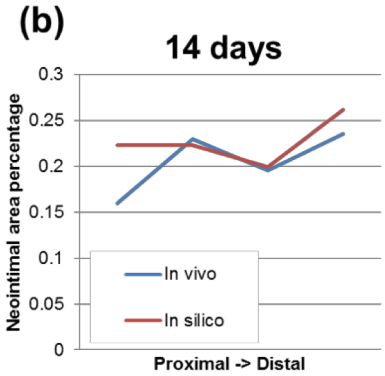


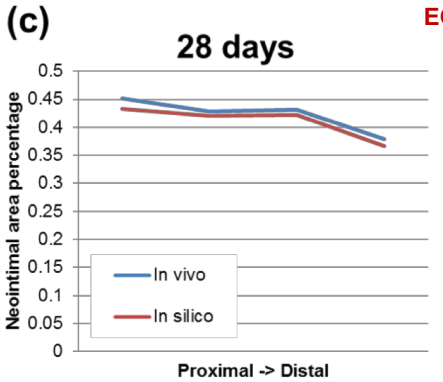




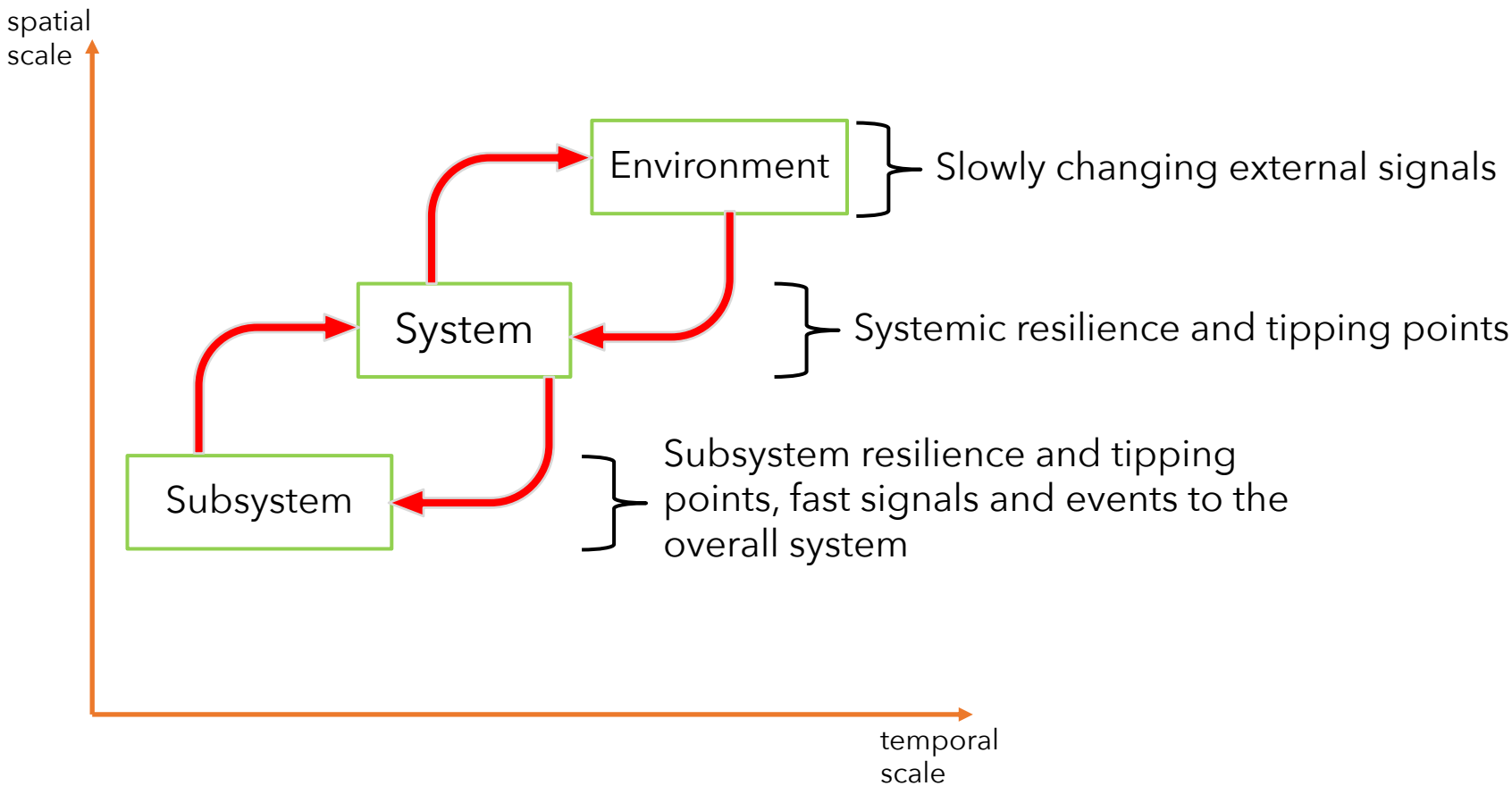








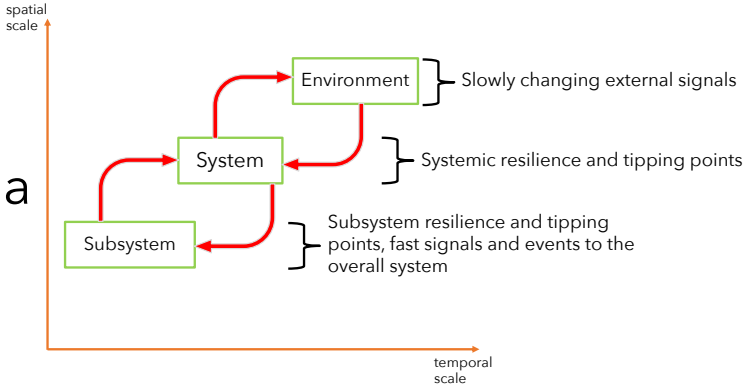
Multiscale resilience



- A slow process on a larger scale could provide a signal to a faster process, and could push this process over a tipping point, no matter how resilient it is.
- Another process on the same scales or smaller scales could also provide signals or events (sub systems tipping points) that could move the systems towards a tipping point.

Theoretical Framework for studying multiscale - multisystem Resilience?

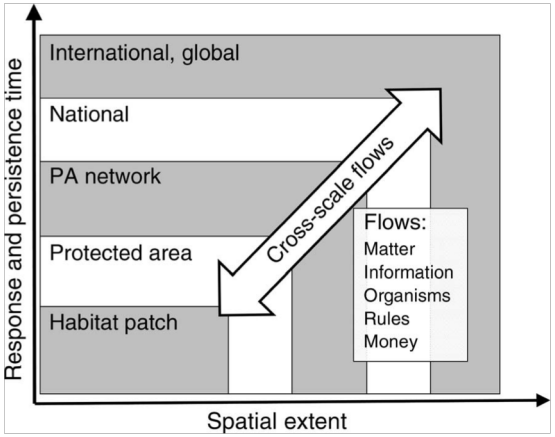
- Could we create a coupled model
  - With the system, it's environment, and a few subsystems
- where we can mimic sub-system resilience and tipping points,
- and signals from the environment,
- and then theoretically study systemic resilience and tipping points?



Ecological Applications, 25(2), 2015, pp. 299–319

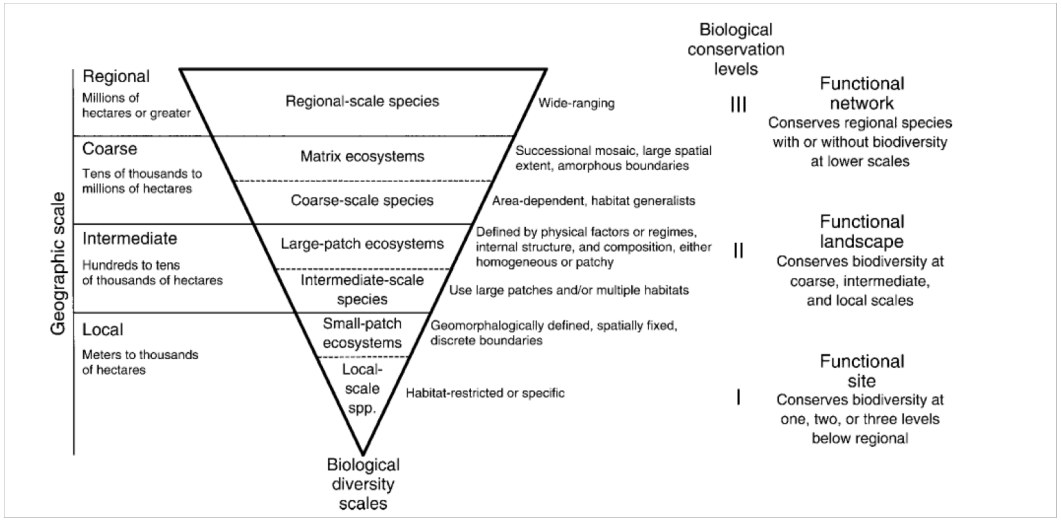
Understanding protected area resilience: a multi-scale, social-ecological approach

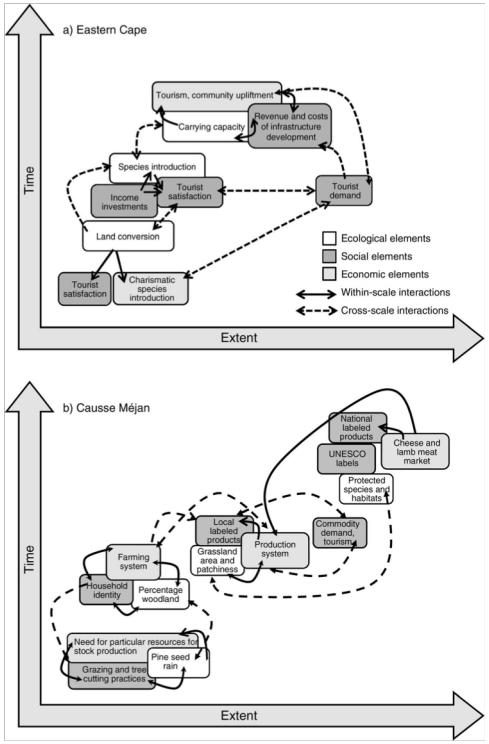
Graeme S. Cumming,[1,11] Craig R. Allen,[2] Natalie C. Ban,[3] Duan Biggs,[4] Harry C. Biggs,[5] David H. M. Cumming,[1] Alta De Vos,[1] Graham Epstein,[6] Michel Etienne,[7] Kristine Maciejewski,[1] Raphaël Mathevet,[8] Christine Moore,[1] Mateja Nenadovic,[9] and Michael Schoon[10]



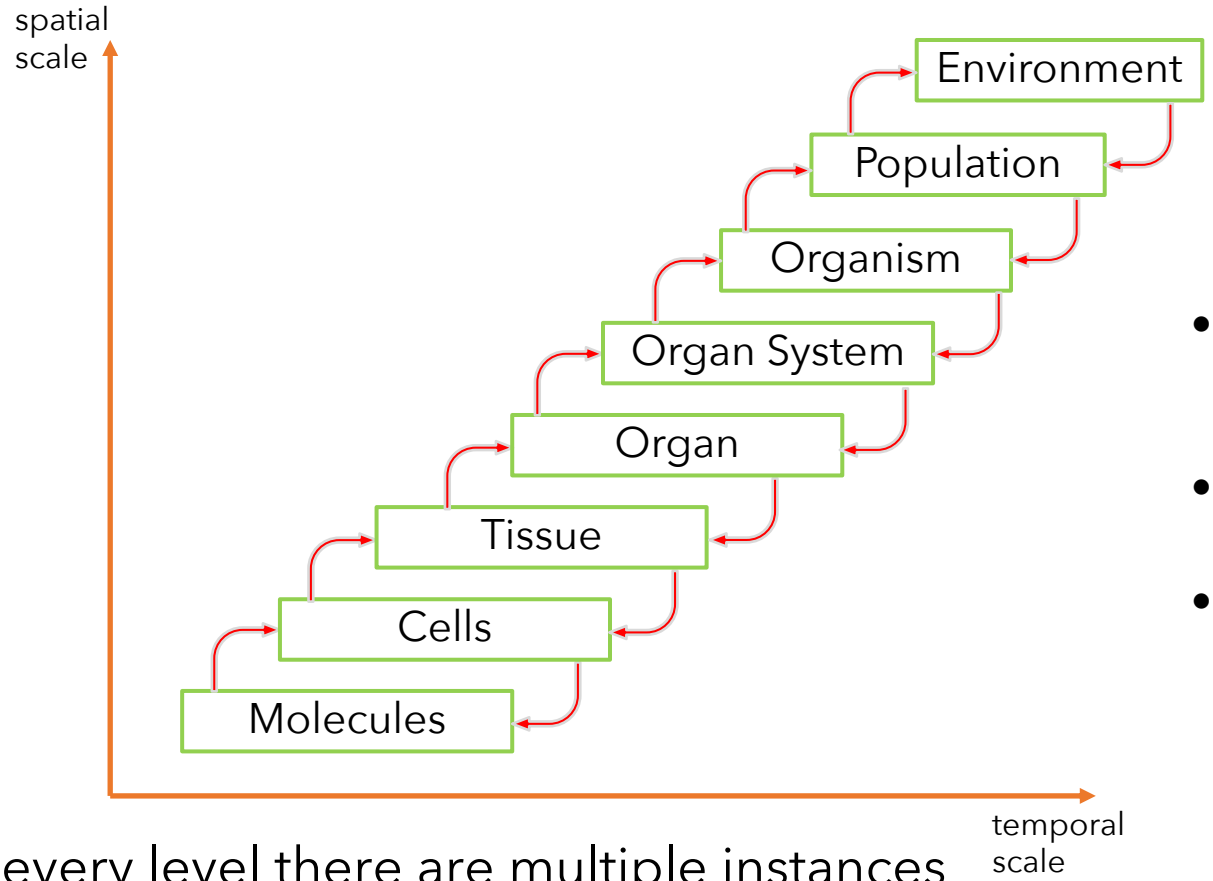
"Analysis of the resilience of PAs requires a hierarchical, cross-scale and multilevel framework in which different scales and institutional levels are connected by a set of interactions between different actors, resources, and processes."

"The kinds of interactions and feedback loops in which PAs participate may have different consequences for system resilience, particularly in relation to the spatial and temporal scales of different actors and interactions."





Multiscale view of Physiology



- On every level one could define a "level resilience",
- with a higher level environment,
- and a lower level subsystem resilience and tipping points.

- On every level there are multiple instances
  - One individual has 10 organ systems
  - Every organ system has several organs, etc …
- All the instances are in some way coupled
  - On the same scale/level
  - Or multiscale coupling

Network View of Physiology

IOP Publishing New J. Phys. 18 (2016) 100201 doi:10.1088/1367-2630/18/10/100201

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EDITORIAL

Focus on the emerging new fields of network physiology and network medicine

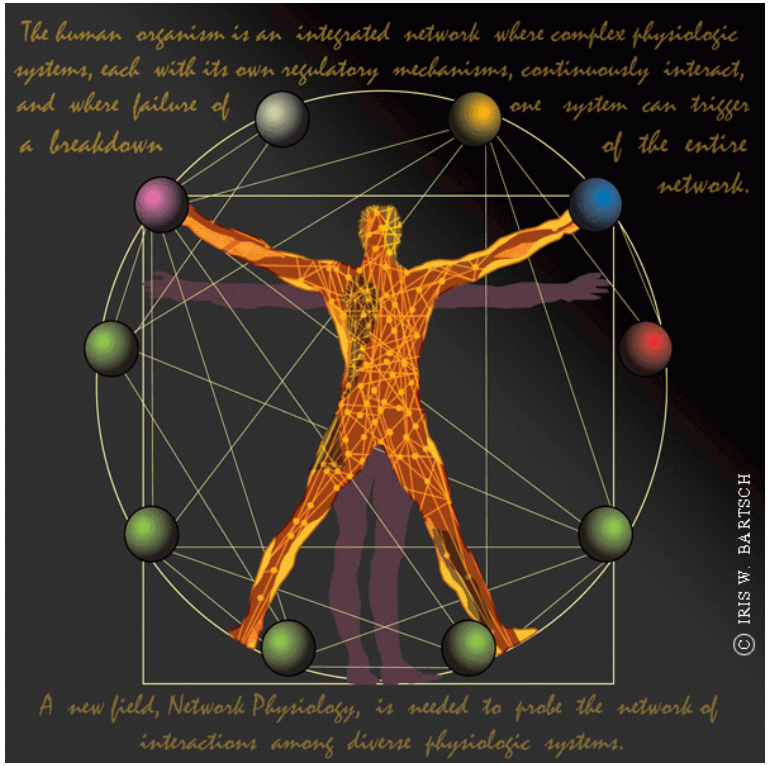
Plamen Ch Ivanov[1,2,3,6], Kang K L Liu[1,4] and Ronny P Bartsch[5]

1 Keck Laboratory for Network Physiology, Department of Physics, Boston University, Boston, MA, USA
2 Harvard Medical School and Division of Sleep Medicine, Brigham and Women Hospital, Boston, MA 02115, USA
3 Institute of Solid State Physics, Bulgarian Academy of Sciences, Sofia 1784, Bulgaria
4 Department of Neurology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts, USA
5 Department of Physics, Bar-Ilan University, Ramat Gan, 5290002, Israel
6 Editor of the 'focus on' issue.

"While systems biology and integrative physiology have focused on the *vertical integration* from the sub-cellular and cellular level to tissues and organs, "

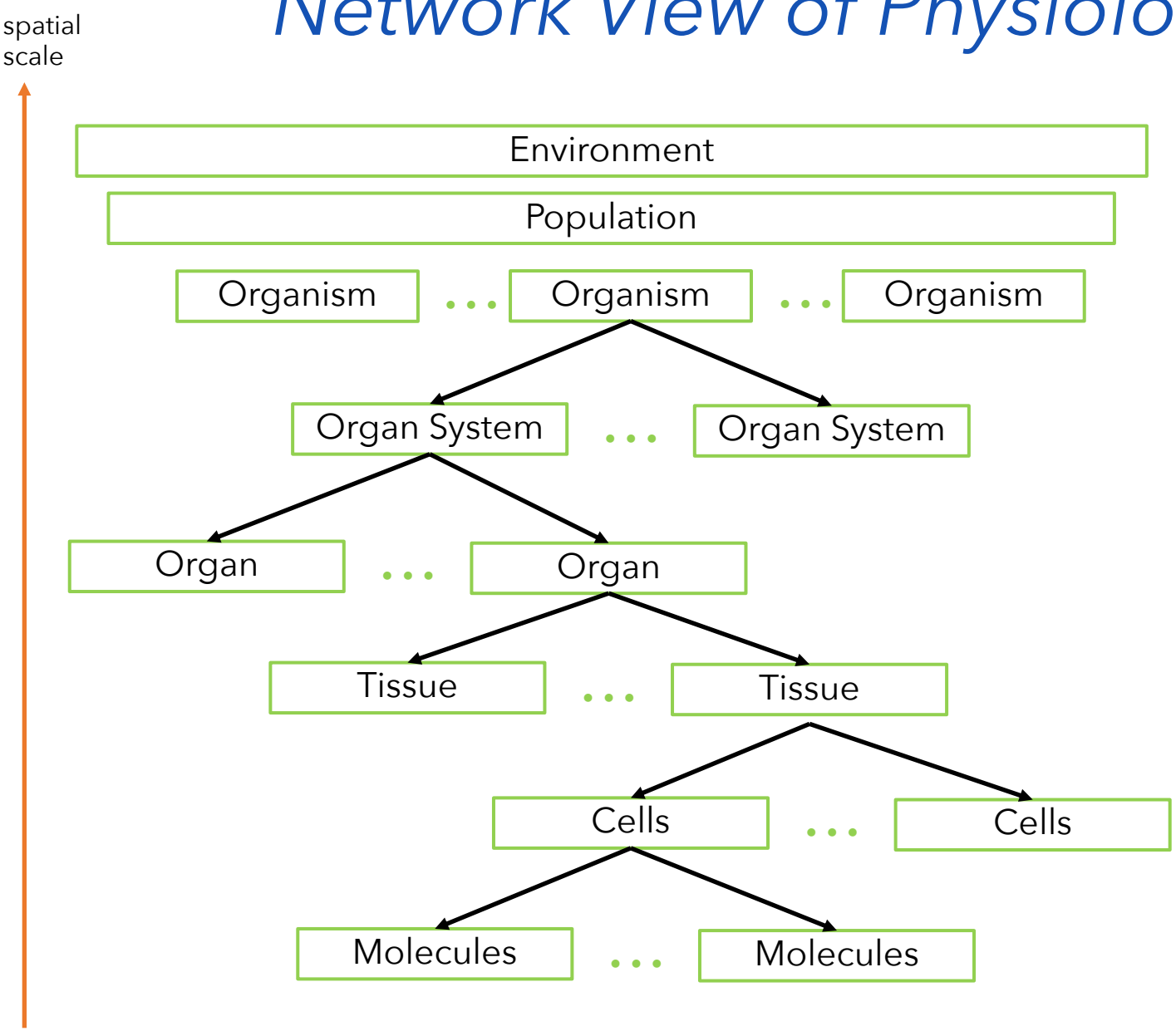
"there is a wide gap of knowledge in the direction of *horizontal integration* at the level of organ-to-organ interactions. "

"A new field, network physiology, has emerged to fill this gap and to address the fundamental question of how physiological systems coordinate, synchronize and integrate their dynamics to optimize functions and to maintain health."

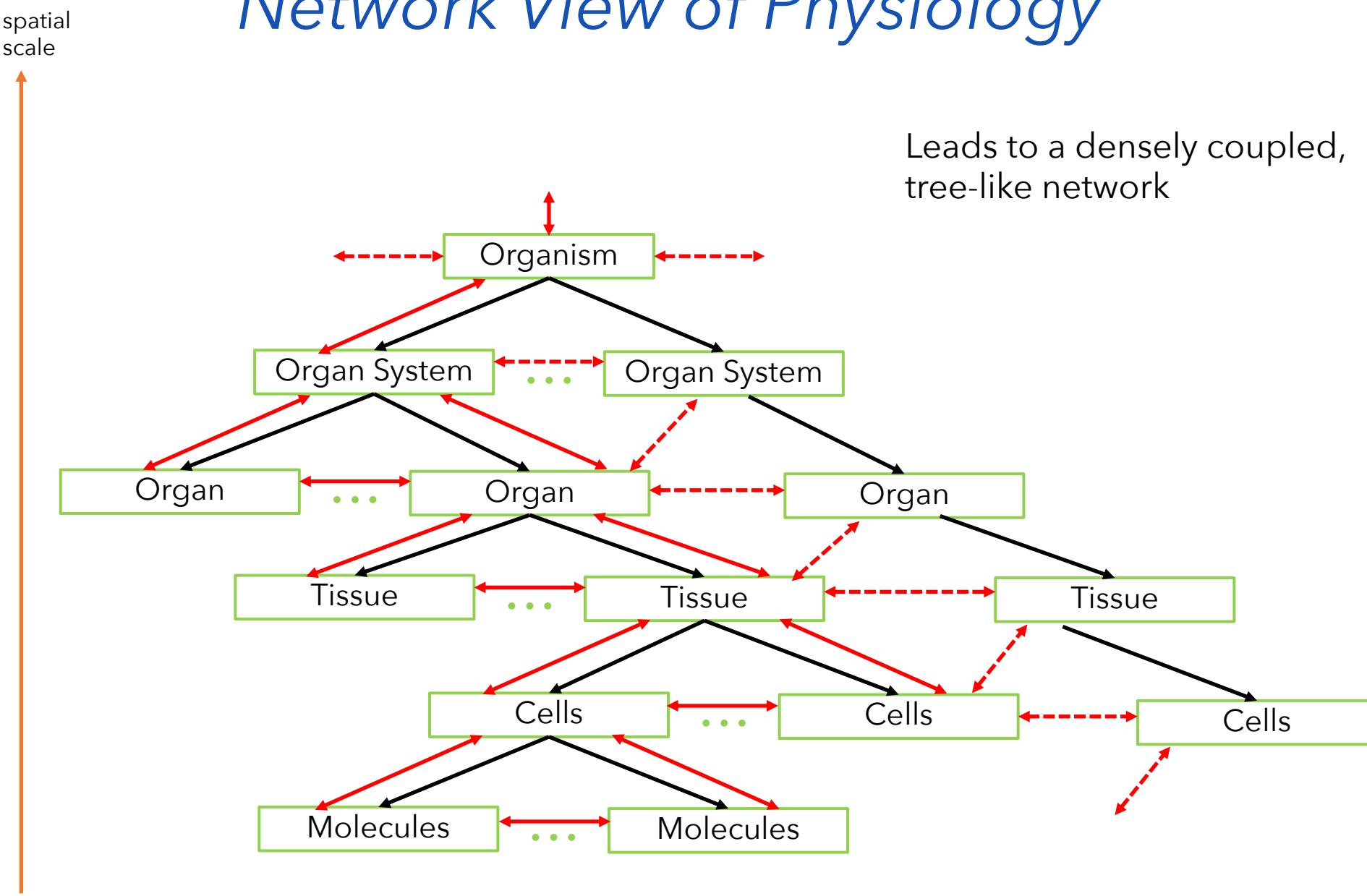


"The human organism is an integrated network where complex physiologic systems, each with their own regulatory mechanisms, continuously interact, and where the failure of one system can trigger a breakdown of the entire network. A new field, network physiology, is needed to probe the network of interactions among diverse physiological systems. (Image copyright: Iris W Bartisch.)"

Network View of Physiology



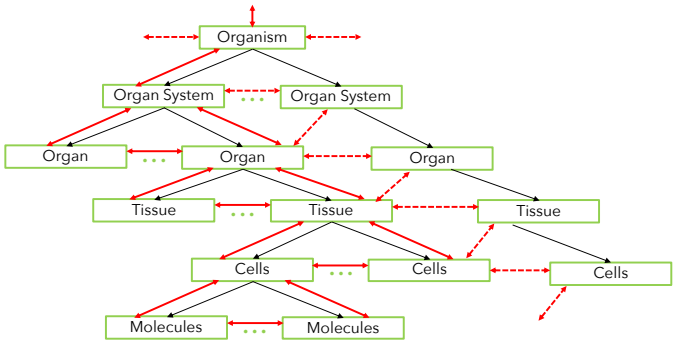
Network View of Physiology



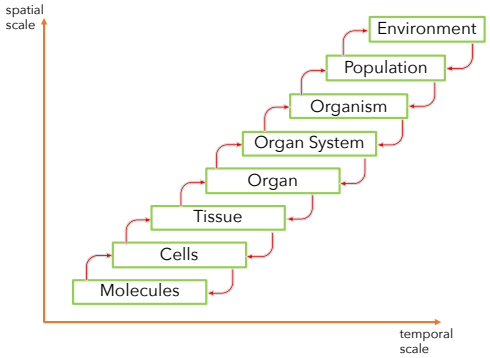
Leads to a densely coupled, tree-like network

Combine both views

- Lay out the network view in the multiscale view
- Quickly grows out of hand, so pruning of graphs is needed
  - Middle out approach



- Could subsystem TPs be understood in a multilevel cell-tissue-organ sense, but systemic resilience requires the network physiology approach?



From our 'homework' reading

- To gain more understanding of the underlying physiology of systemic resilience in man, it is best to properly define systemic resilience in humans, as the whole persons' capacity to recover from challenges, and regain the previous levels of physical and mental condition, and of autonomy in activities of daily living, ultimately determining the chances of survival.

- Complementary, subsystem resilience refers to the recovery potential of physiological subsystems such as postural balance, blood pressure, cerebral perfusion or mood.

- Either the person may recover from the perturbation induced by such a subsystem TP and the balance of the whole system is restored, or the TP may set in motion a cascade of events driving the system down to a state of more decline, ultimately leading to death.

- By generating dynamic measures of systemic resilience over various organ systems we may subsequently model resilience generically across many chronic diseases, affecting different organ systems.

Two main messages

- Multiscale modelling of human physiology is has advanced a lot.
  - But probably not enough for the topic of this workshop.

- Multiscale modelling frameworks could contribute to deeper understanding of resilience in ageing.

Some relevant papers

A few relevant publications:

1. P.M.A. Sloot, A.G. Hoekstra, Multi-scale modelling in computational biomedicine, Br. Bioinform. 11 (2010) 142–152. doi:10.1093/bib/bbp038.
2. B. Chopard, J. Borgdorff, A.G. Hoekstra, A framework for multi-scale modelling, Philos. Trans. R. Soc. A. 372 (2014) 20130378. doi:10.1098/rsta.2013.0378.
3. A.G. Hoekstra, S. Alowayyed, E. Lorenz, N. Melnikova, L. Mountrakis, B. van Rooij, et al., Towards the Virtual Artery: a Multiscale Model for Vascular Physiology at the PCB Interface, Phil. Trans. R. Soc. A. 374 (2016) 20160146. doi:http://dx.doi.org/10.1098/rsta.2016.0146.
4. P.S. Zun, T. Anikina, A. Svitenkov, A.G. Hoekstra, A Comparison of Fully-Coupled 3D In-Stent Restenosis Simulations to In-vivo Data, Front. Physiol. 8 (2017) 284. doi:10.3389/fphys.2017.00284.

Full list, see https://publications.computationalscience.nl/author/aghoekstra/

Thank you

Computational Science

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