



ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

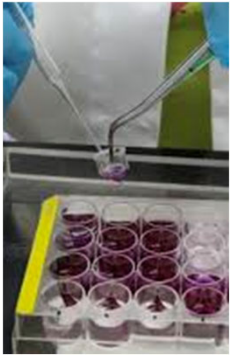
Special Presentation at
Virtual Human Global Summit II
Barcelona, 23 October 2025

From the Virtual Physiological Human to the Virtual Human Twin

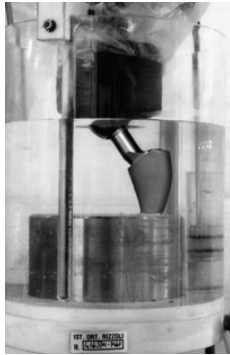
Marco Viceconti

Dipartimento di Ingegneria Industriale

1989: How to investigate living organisms



In vitro preclinical studies

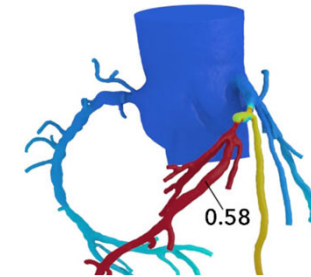


In vivo preclinical studies



In vivo clinical trials

And if you use computer
modelling & simulation?



***In silico* studies**

The expression *in silico* was first used to characterize biological experiments carried out entirely in a computer in 1989, in the workshop "Cellular Automata: Theory and Applications" in Los Alamos, New Mexico. (source: Wikipedia)

In Silico Medicine

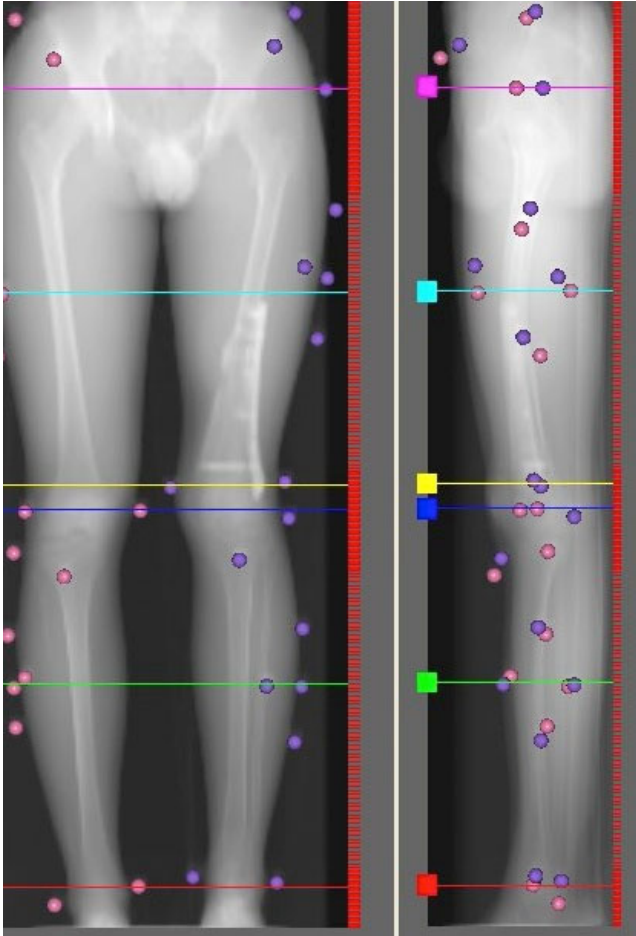
The Use of Computer Modelling & Simulation in Healthcare

We use the term to indicate when a computer model prediction supports a clinical decision relative to an individual patient

1993: The Physiome

- The Human Genome Project was launched in 1990
- A digital representation of the entire human physiology: “The physiome describes the physiological dynamics of the normal intact organism”.
- The idea was first proposed in 1993 but formalised in the IUPS Physiome project in 2001.

2001: Patient-specific MSK models

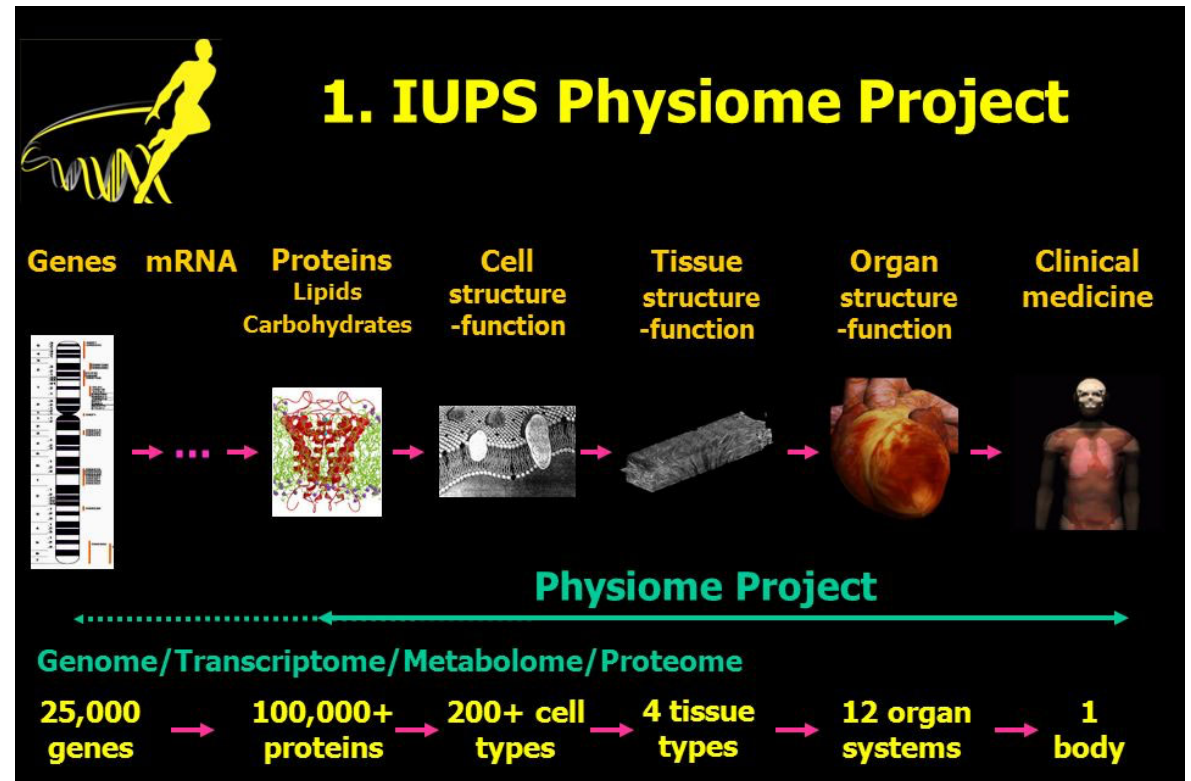


Taddei F, *et al.* Proc Inst Mech Eng H. 2002;216(2):95-104

2002: WCB 2002, Calgary



Prof Peter Hunter



4th World Congress of Biomechanics

The Virtual Physiological Human

- The VPH was born in 2005 as the UE version of the Physiome
- But from the beginning, the focus was on the clinical application, focusing on diseases and on using models as clinical decision support system

**TOWARDS VIRTUAL PHYSIOLOGICAL HUMAN:
MULTILEVEL MODELLING AND SIMULATION OF THE HUMAN ANATOMY AND
PHYSIOLOGY**

**Research challenges and intermediate steps to be addressed by future
interdisciplinary research programs**

DRAFT VERSION 2.8 of 4th November 2005



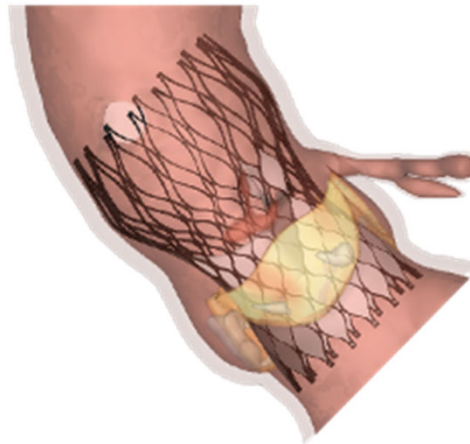
In Silico Medicine by end user



DIGITAL TWINS IN HEALTHCARE

Subject-specific predictions for decision-support, diagnosis, treatment planning, stratification

FOR THE DOCTOR



IN SILICO TRIALS

Virtual patient cohorts for 3R, surrogate outcomes, augmented clinical trials

FOR THE INDUSTRY



PERSONAL HEALTH FORECASTING

Subject-specific predictive models for mobile and digital health and wellness

FOR THE PATIENT - CITIZEN

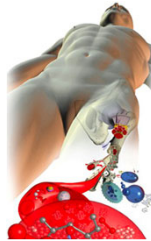


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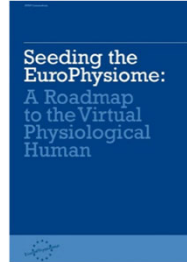
2001 – 2024: a journey



2001: IUPS Physiome



2005: VPH



2007: STEP
roadmap



VPH Institute
Building the Virtual
Physiological Human

2010: VPH
Institute



2015: Avicenna
roadmap



2016: Avicenna
Alliance



EDITH

2024: VHT Roadmap



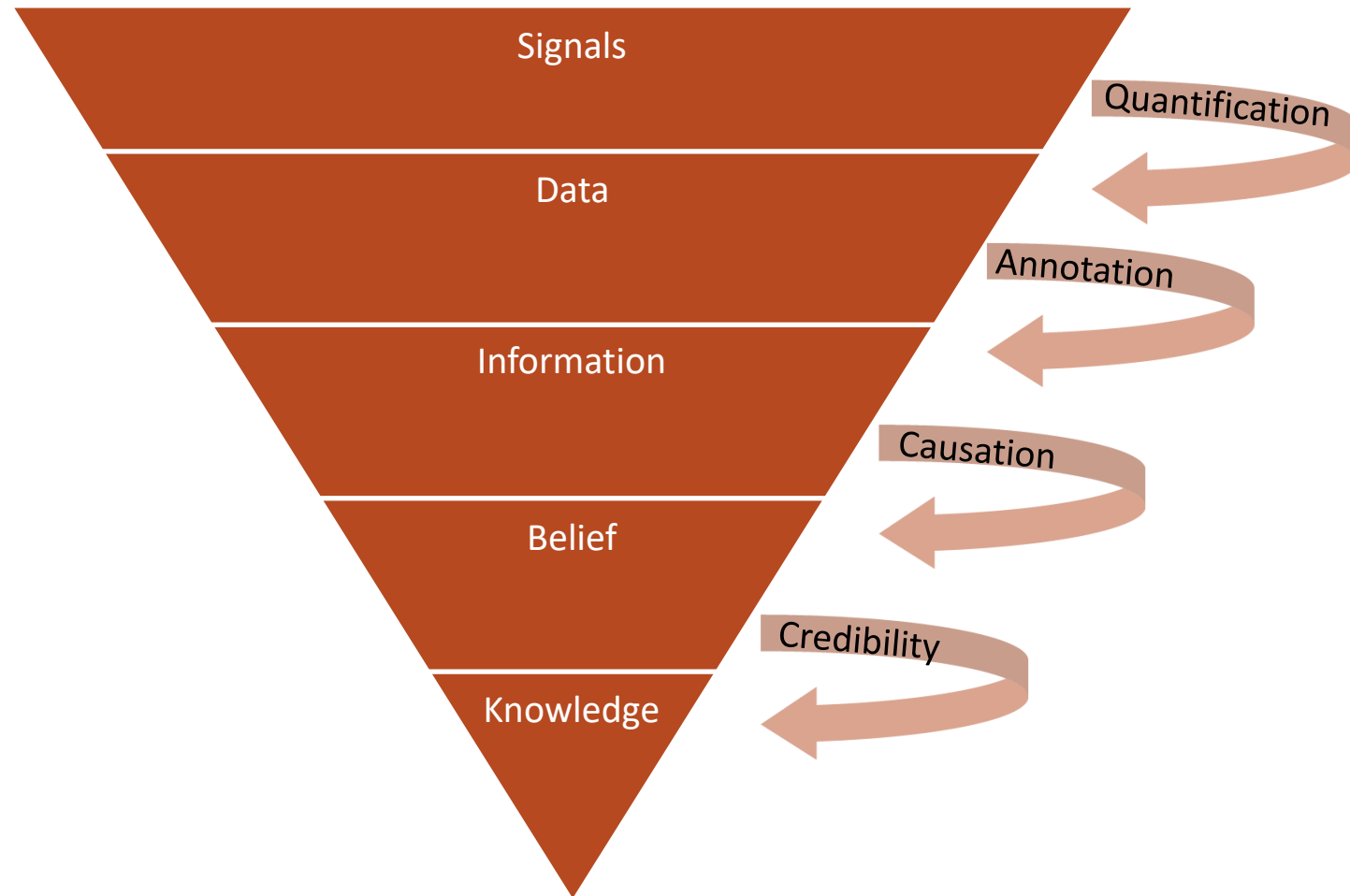
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In these 23 years, the idea of In Silico Medicine and In Silico Trials with Digital Twins for each patient has moved from science fiction to an industrial reality

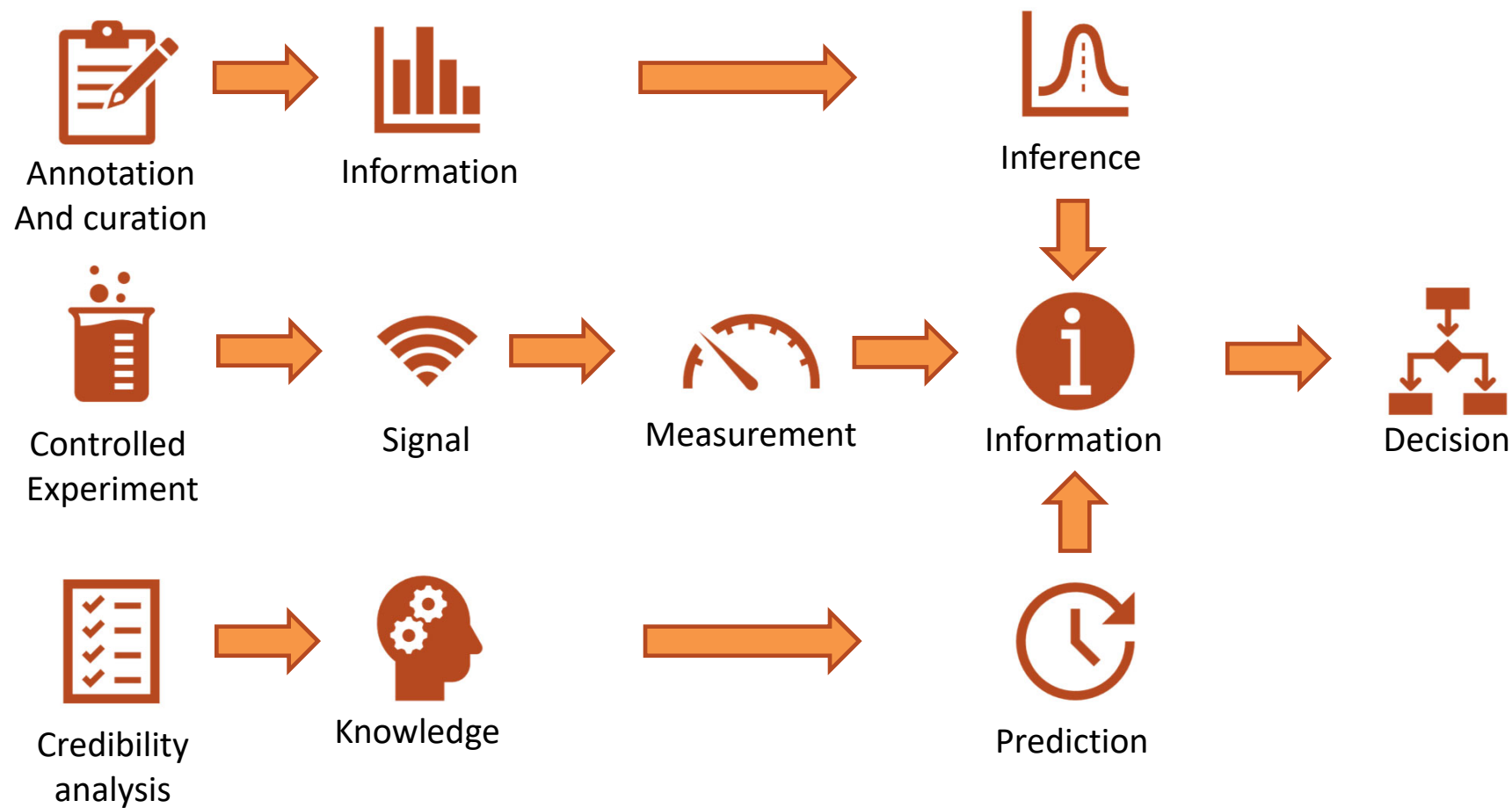
Can we predict life?

Can we predict changes in the health status of individual patients based on causal knowledge of human physiology and the specific diseases that affect such patients?

The Knowledge pyramid



To decide we need information



1000 years using the same experimental approach

- In 1025, Ibn Sina (Avicenna) completed his Canon of Medicine, which provided the basis for randomised clinical trials, assessing the efficacy of a new treatment through experimentation.
- In these 1000 years, while the details became much more sophisticated, the essence of the method remains the same.
- At the core of Avicenna's approach, there is a pure frequentist worldview.



Two conflicting worldviews

Frequentist inference



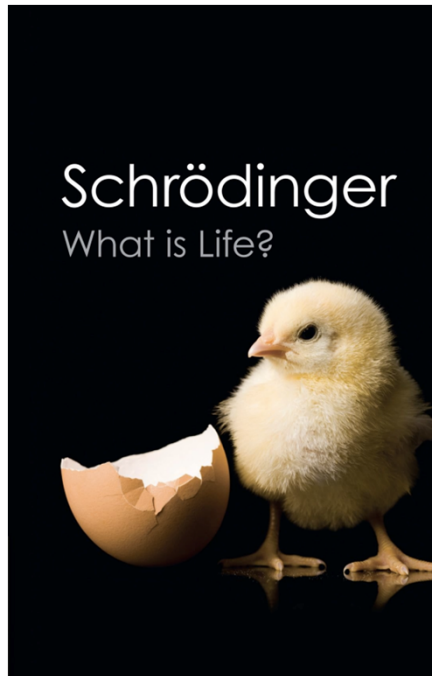
- Used in social and life sciences
- Semi-quantitative and biased observations are expected
- It postulates that truth exists but is hidden
- Observations are reliable (even if biased), but a priori knowledge is unreliable
- The decision starts from a default hypothesis (H_0), which we would choose in the absence of observations
- We can choose the opposite of H_0 (H_1) only if there are sufficient observations that, even taking into account bias, falsify H_0 .

Bayesian inference



- Used in the physical sciences (including engineering)
- Quantitative observations are expected and almost free from systematic errors
- The truth does not exist; there are beliefs (hypotheses that someone believes are true) that are more or less probable
- Every hypothesis has a posteriori probability, which is the product of the probability derived from the a priori knowledge available (prior) and that derived from observations (likelihood)
- The hypothesis with the highest probability is used to make a decision.

The thermodynamics of life



What Is Life? The Physical Aspect of the Living Cell (1944)

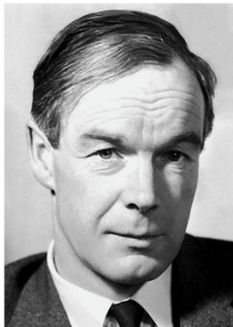
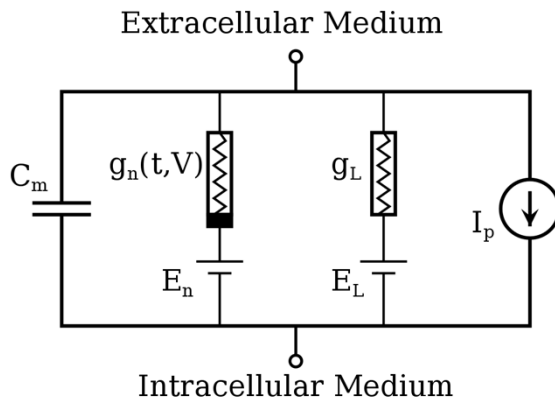
Based on a course of public lectures delivered in February 1943, at Trinity College, Dublin.



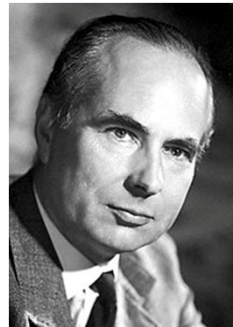
Erwin Schrödinger (1887-1961)

1958: Model of action potential in neurons

Nobel Prize 1963



Alan Hodgkin
(1914-1998)



Andrew Huxley
(1917–2012)

500

J. Physiol. (1952) 117, 500–544

A QUANTITATIVE DESCRIPTION OF MEMBRANE CURRENT AND ITS APPLICATION TO CONDUCTION AND EXCITATION IN NERVE

By A. L. HODGKIN AND A. F. HUXLEY

From the Physiological Laboratory, University of Cambridge

(Received 10 March 1952)

This article concludes a series of papers concerned with the flow of electric current through the surface membrane of a giant nerve fibre (Hodgkin, Huxley & Katz, 1952; Hodgkin & Huxley, 1952 a-c). Its general object is to discuss the results of the preceding papers (Part I), to put them into mathematical form (Part II) and to show that they will account for conduction and excitation in quantitative terms (Part III).

PART I. DISCUSSION OF EXPERIMENTAL RESULTS

The results described in the preceding papers suggest that the electrical behaviour of the membrane may be represented by the network shown in Fig. 1. Current can be carried through the membrane either by charging the membrane capacity or by movement of ions through the resistances in parallel with the capacity. The ionic current is divided into components carried by sodium and potassium ions (I_{Na} and I_K), and a small 'leakage current' (I_l) made up by chloride and other ions. Each component of the ionic current is determined by a driving force which may conveniently be measured as an electrical potential difference and a permeability coefficient which has the dimensions of a conductance. Thus the sodium current (I_{Na}) is equal to the sodium conductance (g_{Na}) multiplied by the difference between the membrane potential (E) and the equilibrium potential for the sodium ion (E_{Na}). Similar equations apply to I_K and I_l and are collected on p. 505.

Our experiments suggest that g_{Na} and g_K are functions of time and membrane potential, but that E_{Na} , E_K , E_l , C_m and $\bar{g}$ may be taken as constant. The influence of membrane potential on permeability can be summarized by stating: first, that depolarization causes a transient increase in sodium conductance and a slower but maintained increase in potassium conductance; secondly, that these changes are graded and that they can be reversed by repolarizing the membrane. In order to decide whether these effects are sufficient to account for complicated phenomena such as the action potential and refractory period, it is necessary to obtain expressions relating



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It was a long and winding road ...



2025: Plenty of causal knowledge

- In the last 60 years, the technological advancement of experimental and computational methodologies has made it possible to accurately and reproducibly quantify many manifestations of the health status of individual persons.
- A vast body of causal knowledge about human pathophysiology has been produced, which has resisted extensive falsification attempts.
- In addition, biochemists, biophysicists, and bioengineers have successfully applied fundamental laws of chemistry and physics to the causal explanation of specific aspects of human health.

Can we predict life? Yes, we can

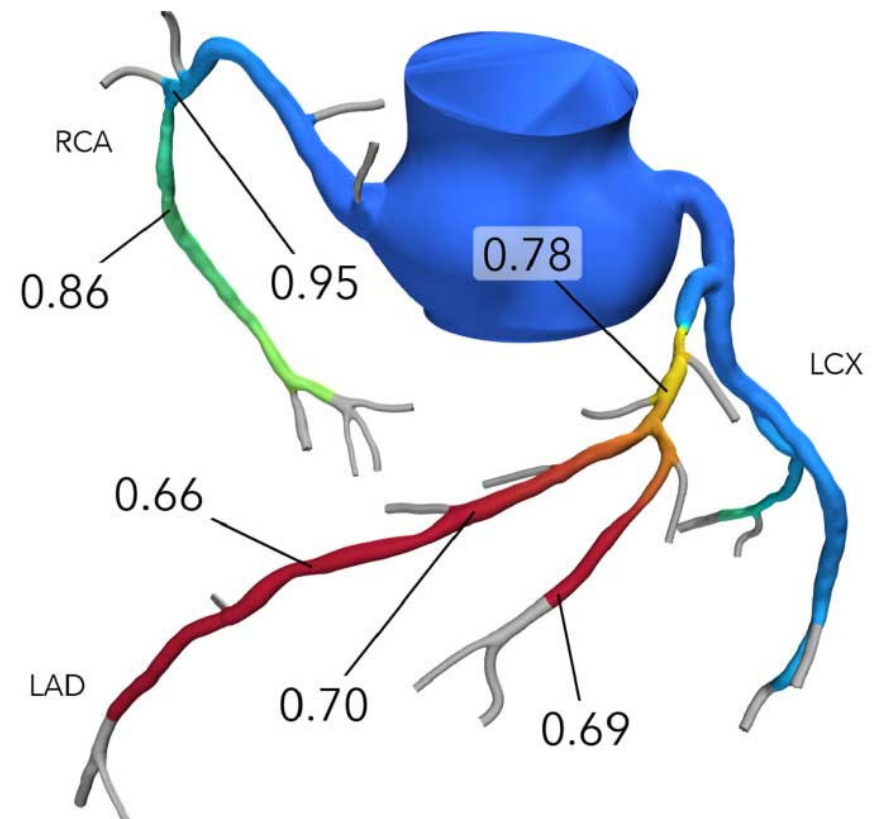
- Today, we know that:
 - If a clinical decision requires the estimate of information (quantity of interest, QI) that cannot be easily observed, with an estimation error smaller than ε
 - If we do have sufficient causal knowledge of which observable quantities (features) cause that QI to assume a particular value in a specific location in the body of a specific subject at a specific time
 - If such causal knowledge makes it possible to predict the QI value in controlled validation experiments with accuracy smaller than ε
- I can take that clinical decision using the predicted information in all situations not too different from those of the validation experiments

Non-invasive FFR HeartFlow®

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La Barbera M. Noninvasive Cardiac Imaging: Coronary CT Angiography
<https://www.clinicalcorrelations.org/?p=679>



HeartFlow FFRCT. Courtesy of HeartFlow Inc.



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Step by step guidance with GSP

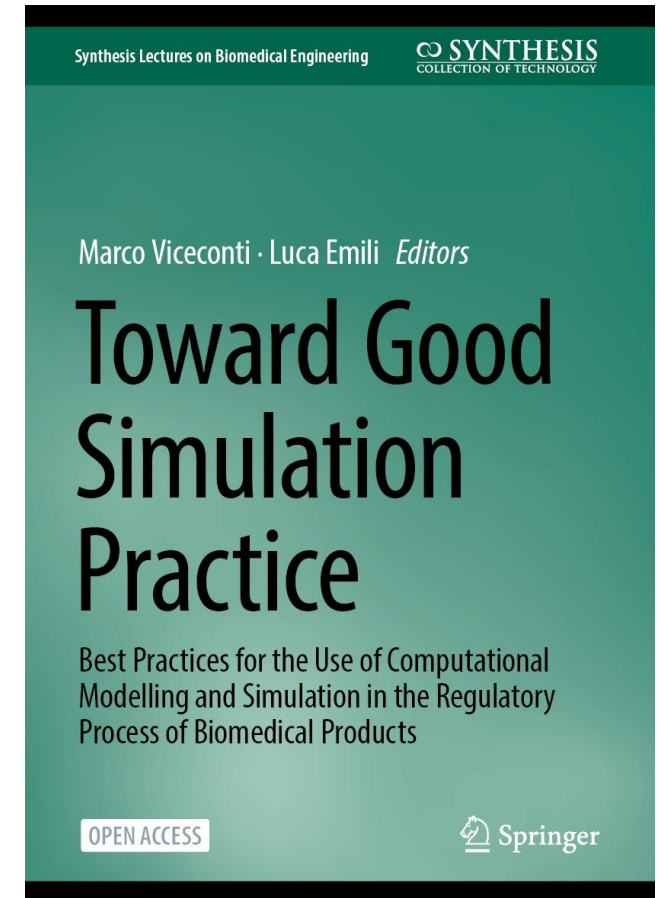
Open Access book:

Toward Good Simulation Practice

Best Practices for the Use of Computational
Modelling & Simulation in the Regulatory
Process of Biomedical Products

<https://link.springer.com/book/9783031482830>

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The barriers to the adoption of In Silico Medicine /1



Frequentist worldview

- Frequentists simply do not trust any prior knowledge and thus fundamentally reject the idea that a piece of information can be predicted by assuming causal knowledge.
- Models can be, at most, used to make inferences from observational data, such as regressions.
- Frequentist inference is widely used in social science and also in the drug regulatory world because they assume that the most pessimistic view is also the safest.

The barriers to the adoption of In Silico Medicine /2



Frequentist worldview

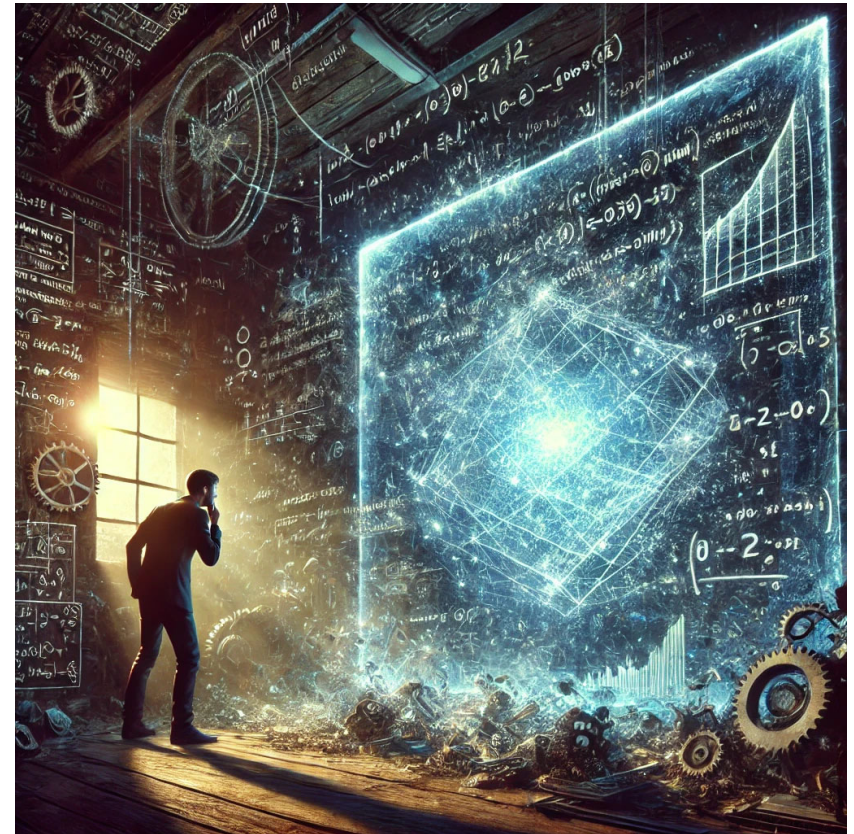


AI confusion

- The hype around AI, combined with the frequentist worldview, is creating the legend that data-driven models do not use prior knowledge, and thus are “safer”.
- Every prediction requires causal knowledge, which can be explicit or implicit. In the latter case, you need to demonstrate not only the credibility of your predictions but also the validity of your implicit knowledge.

Non-technical stakeholders mistrust *in silico* method

- The unquestionable complexity surrounding *in silico* medicine, especially about credibility, is discouraging.
- Even most stakeholders with a technical background need retraining, as core concepts are not yet in the study curricula.
- However, to non-technical stakeholders, all this sounds much like a mumbo-jumbo, and they do not trust it.



The barriers to the adoption of In Silico Medicine /3



Frequentist worldview



AI confusion



Investors trust

- The frequentist worldview, the hype around AI, and the mistrust of non-technical stakeholders raise the third barrier: private investments in *in silico* methodologies are growing slower than we hoped.
- This is amplified by the defensive attitude that large biomedical companies have toward methodologies that in principle could lower the access barriers to the remunerative niche market of healthcare.
- All this take the shape of ROI arguments.

EDITH: Ecosystem Digital Twins in Health Coordination and Support Action 2022-2024

Coordinator: VPH Institute (Director: Prof Liebet Geris)



EDITH is a coordination and support action funded by the Digital Europe
program of the European Commission under grant agreement n° 101083771.



Conclusions

- In Silico Medicine is ready for prime time. Its broader adoption is limited by the frequentist worldview, the confusion around AI, and the need for investments. My recommendations are:
 - Private and public stakeholders should lobby for a single regulatory scientific advice for drugs and devices. Now that the FDA is in trouble, it's up to Europe to drive.
 - Empower the VPH Institute to drive a systematic layperson information campaign on In Silico Medicine, which leverages the AI hype but clarifies.
 - Lobby the EC for more research funding on this topic. The European Virtual Human Twin is the future of In Silico Medicine, but only if the EC invests in projects aimed at populating the VHT federated repository infrastructure.
 - Lobby the management of biomed companies to ramp up private investments.

A pixelated version of Mickey Mouse dressed as the Sorcerer's Apprentice. He wears a blue wizard's hat with a crescent moon and stars, a red robe with a gold belt, and stands on a dark, rocky outcrop. He has a mischievous expression, with one hand pointing upwards and the other extended outwards. The background is a dark blue night sky filled with white stars.

Your purpose in life is
to find your purpose

Fake Buddha quote



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Thank You!

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