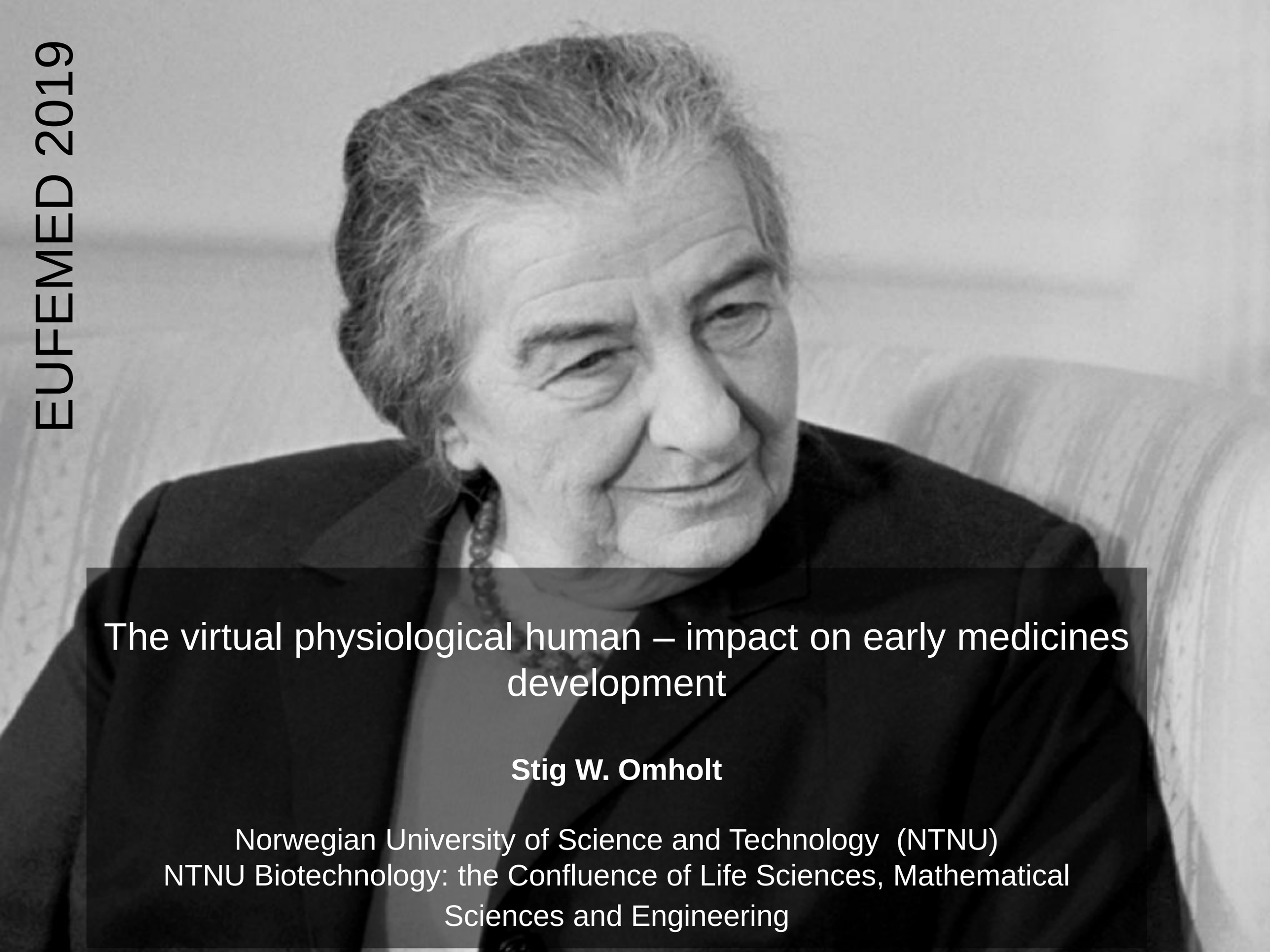
EUFEMED 2019

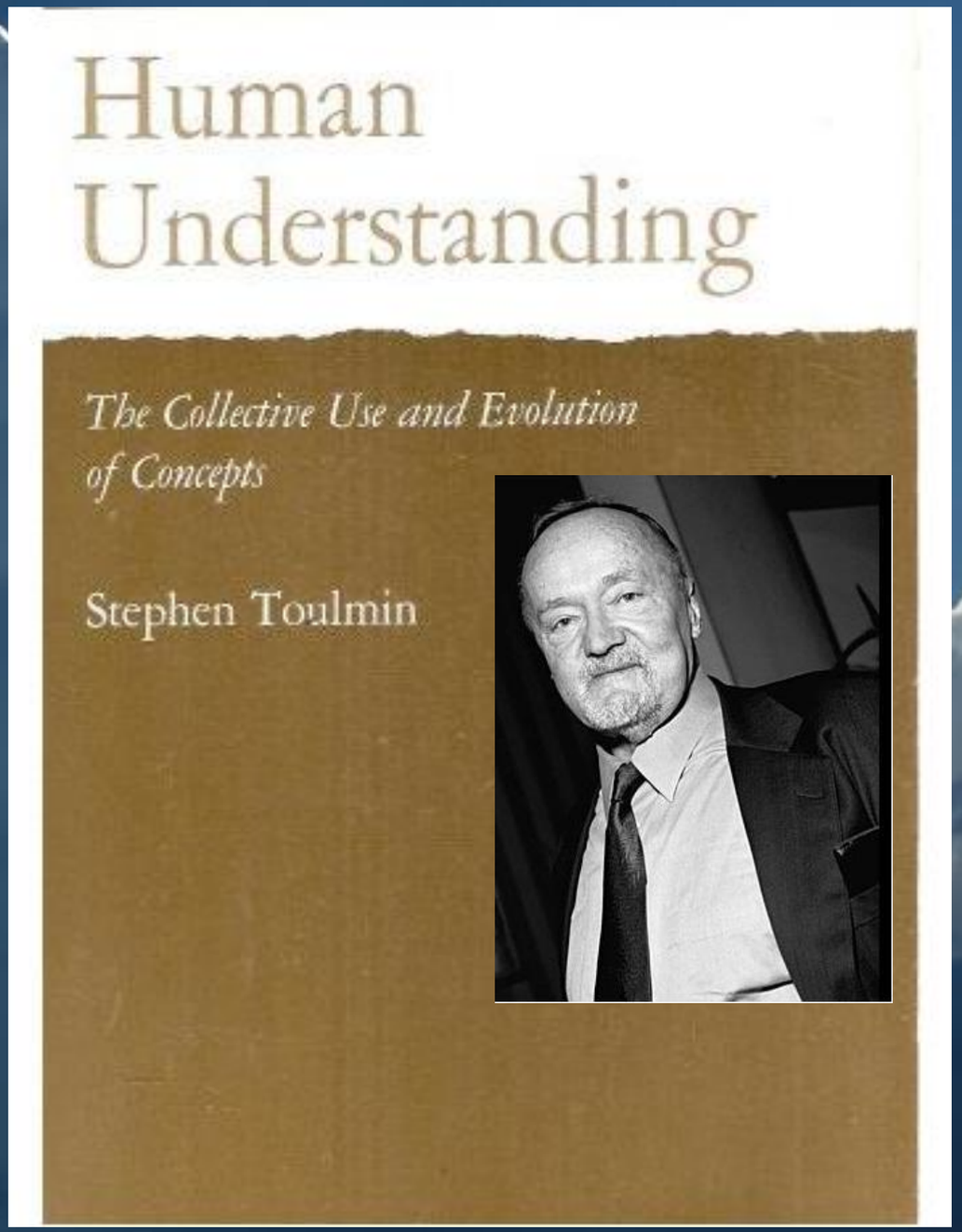


The virtual physiological human – impact on early medicines development

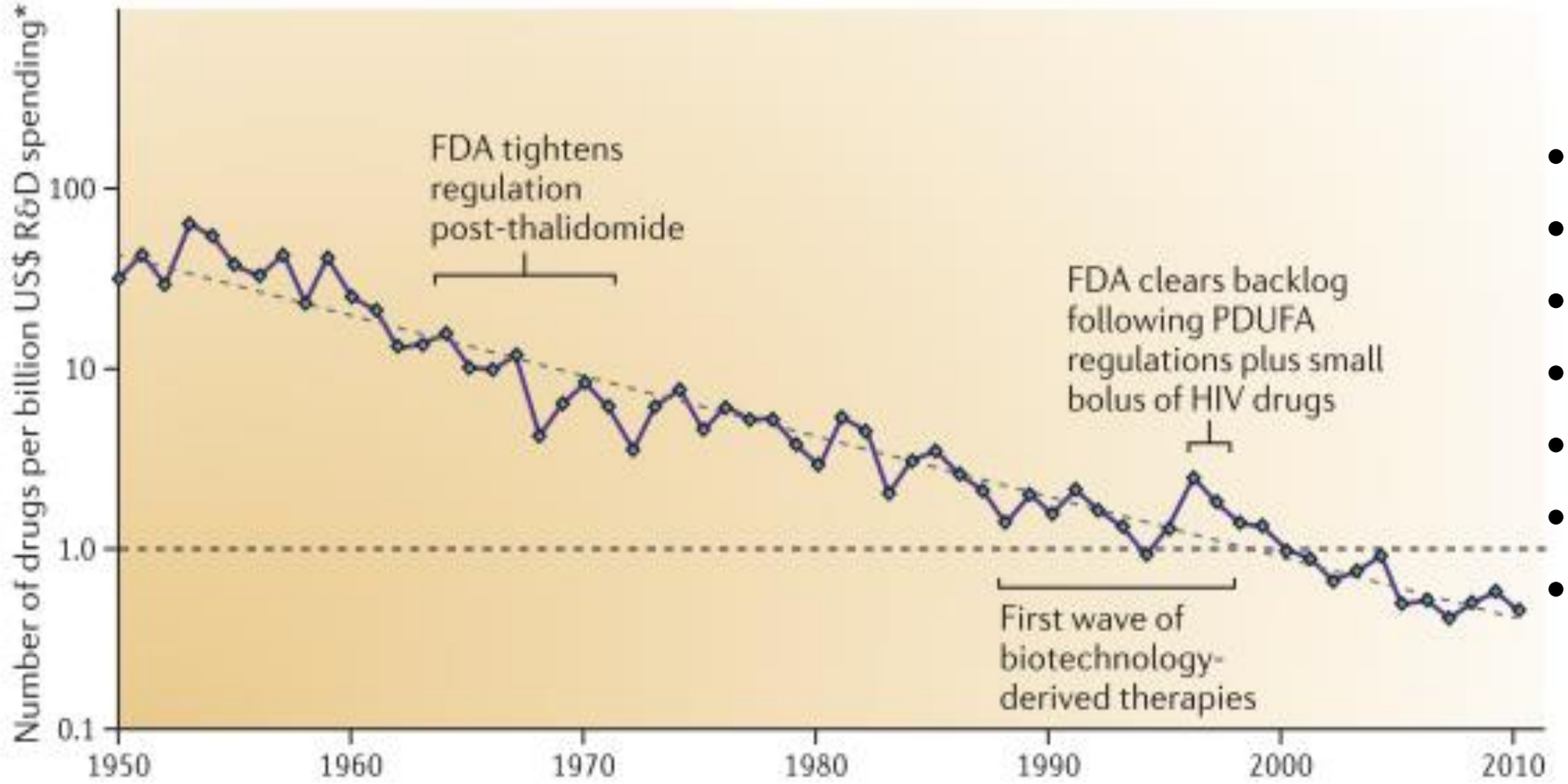
Stig W. Omholt

Norwegian University of Science and Technology (NTNU)
NTNU Biotechnology: the Confluence of Life Sciences, Mathematical Sciences and Engineering

Problems = Explanatory Ideals – Current Capabilities



Nat. Rev. Drug Disc. 11:191-200 (2012)



- Comb. chemistry
- DNA sequencing
- 3D protein str.
- Databases
- Transgenic mice
- HTP screening
- Management R&D

Eroom's Law in pharmaceutical R&D: The number of new drugs approved by the US Food and Drug Administration (FDA) per billion US dollars (inflation-adjusted) spent on research and development (R&D) has halved roughly every 9 years.

Facts do not cease to exist because they are ignored.

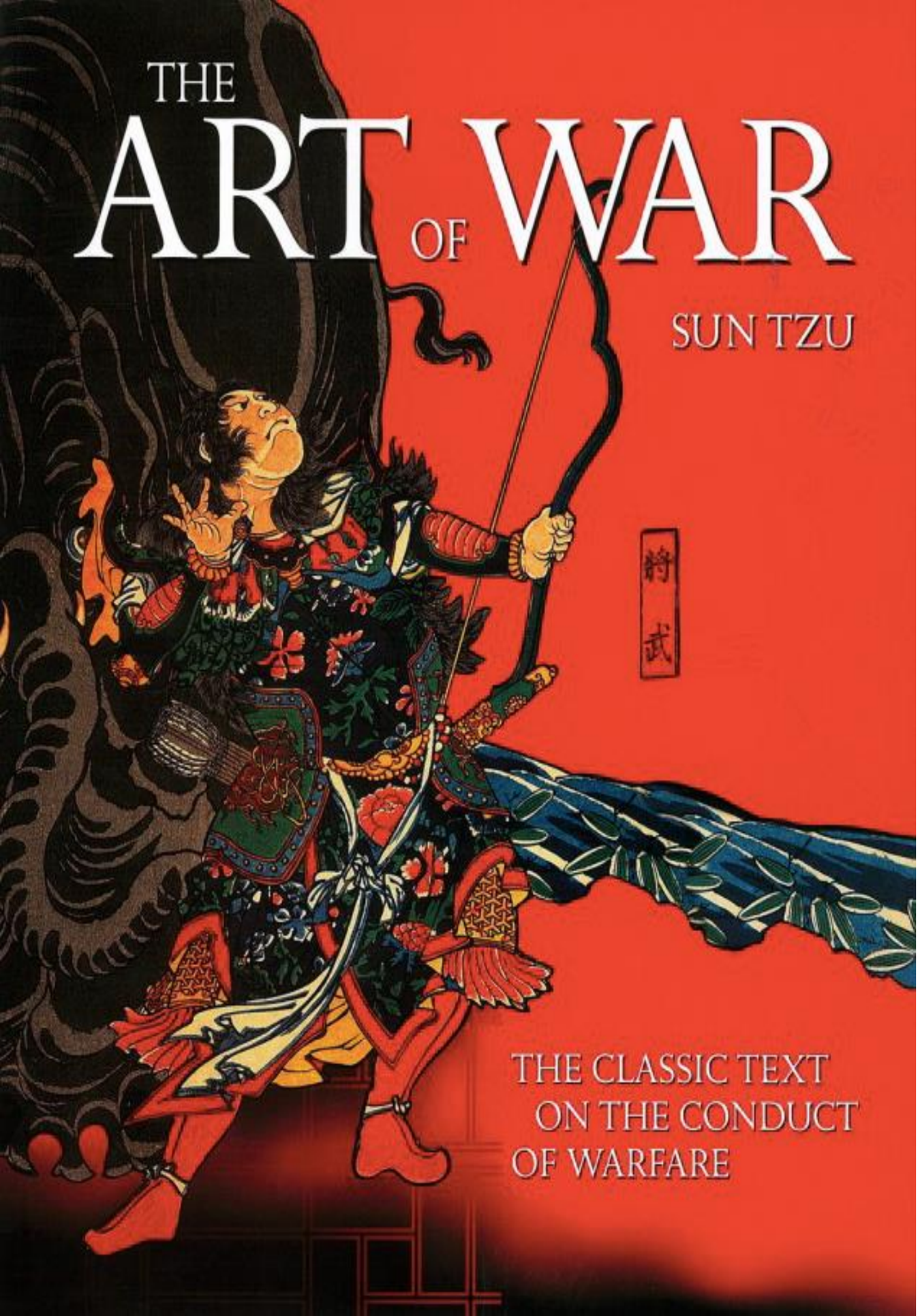
Aldous Huxley

The Darwinian theatre

Ecology

Almost nothing in biology makes sense except in the light of ecology!

Hunting the Cave Bear
Zdenek Burian, 1952



Take home message: 1

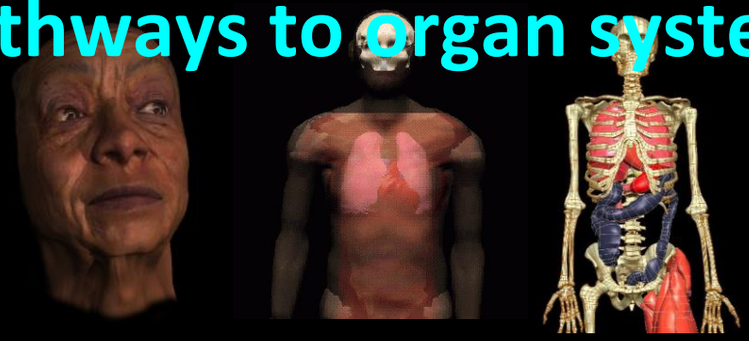
“If you know the enemy and know yourself, you need not fear the result of a hundred battles.

— Sun Tzu, The Art of War

IUPS Physiome: Molecular pathways to organ systems

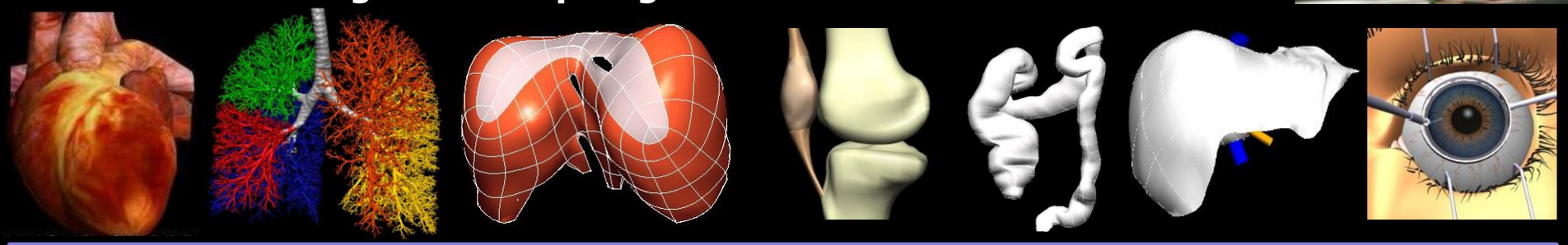
Environment

Organism



Organ system

Heart | Lungs | Diaphragm | Knee | Colon | Liver

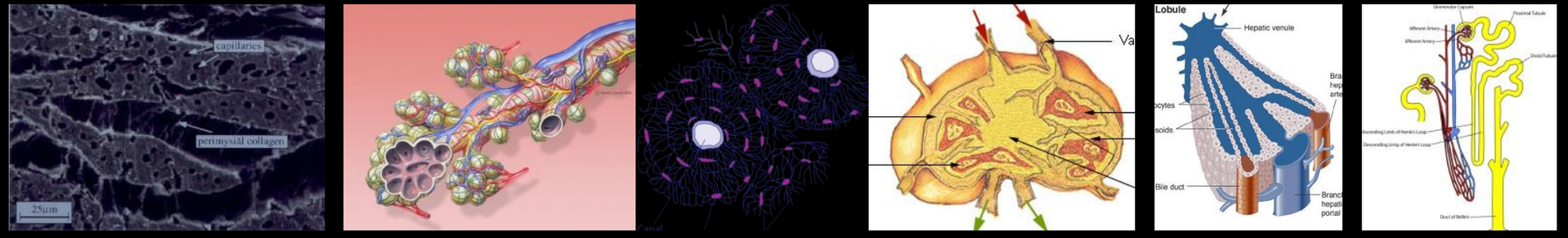


Organ

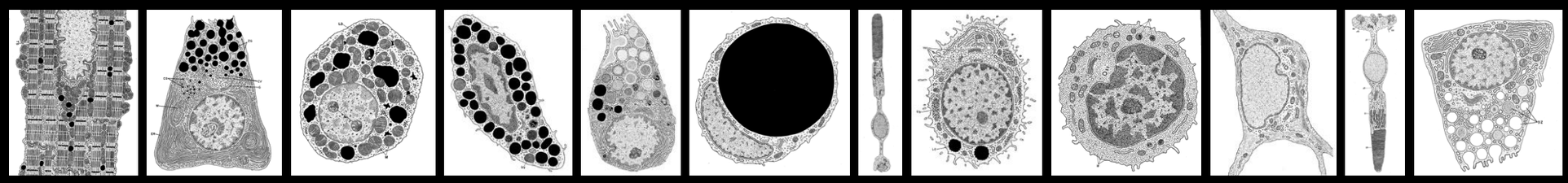
↑ x 1million ↓ 20 generations

Cardiac sheets | Acinus | Osteon | Lymph node | Liver lobule | Nephron

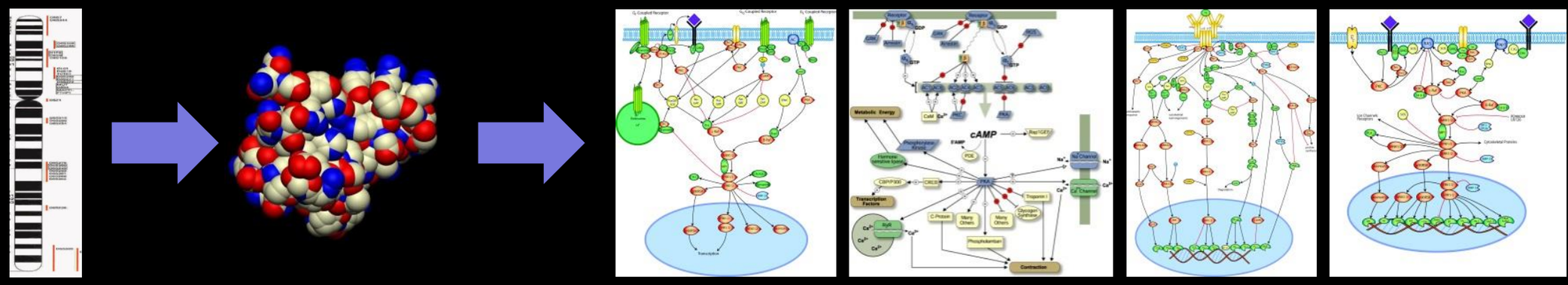
Tissue



Cell



Network
Protein
Gene
Atom



Continuum physics

Meter

- **Solid mechanics** (Finite elasticity)
- **Fluid mechanics** (Navier-Stokes eqns)

$$det\boldsymbol{F}^T\boldsymbol{F} = 0 \quad \tau^{ij}\Big|_i = f^j \quad \boldsymbol{\tau^{ij} = f(e_{ij})}$$

$$\nabla.\boldsymbol{u} = 0 \quad \frac{D\boldsymbol{u}}{Dt} = \frac{\partial \boldsymbol{u}}{\partial t} + \boldsymbol{u}.\nabla\boldsymbol{u} = -\frac{1}{\rho}\nabla p - \nabla.(-\nu\nabla\boldsymbol{u})$$

Entropy / Mole

- **Heat flow**
- **Reaction-diffusion**

$$\frac{DC}{Dt} = \frac{\partial C}{\partial t} + \boldsymbol{u}.\nabla C = f_s - \nabla.(-k\nabla C)$$

Coulomb / Candela

- **Electromagnetics** (Maxwell's eqns)

$$\nabla.\boldsymbol{E} = \frac{\rho}{\epsilon} \qquad \nabla.\boldsymbol{B} = 0$$

$$\nabla \times \boldsymbol{E} = -\frac{\partial \boldsymbol{B}}{\partial t} \qquad \nabla \times \boldsymbol{B} = \mu\left(\boldsymbol{J} + \epsilon\frac{\partial \boldsymbol{E}}{\partial t}\right)$$

Biology appears in the constitutive relationship. It is important that when these relationships are derived from the underlying physiological mechanisms, they obey conservation laws.

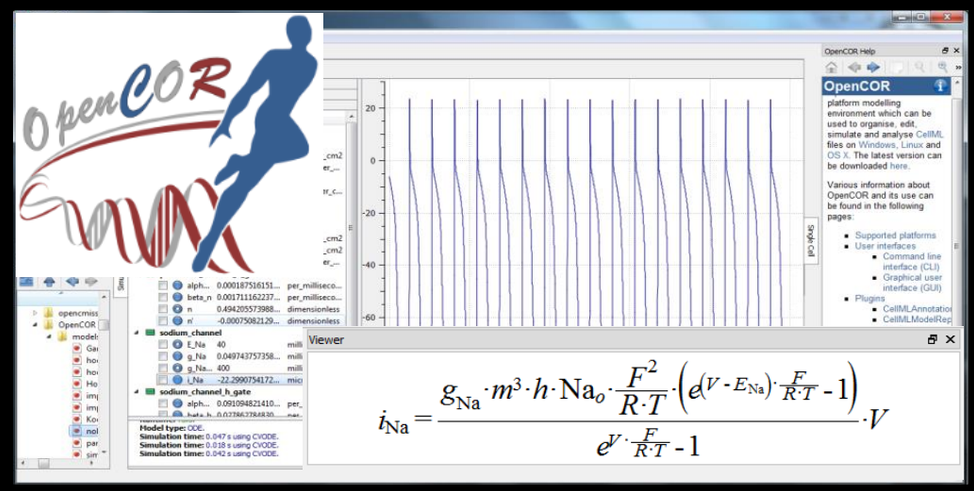
Markup Languages, PMR, OpenCOR

models.cellml.org

www.cellml.org

sed-ml.github.io

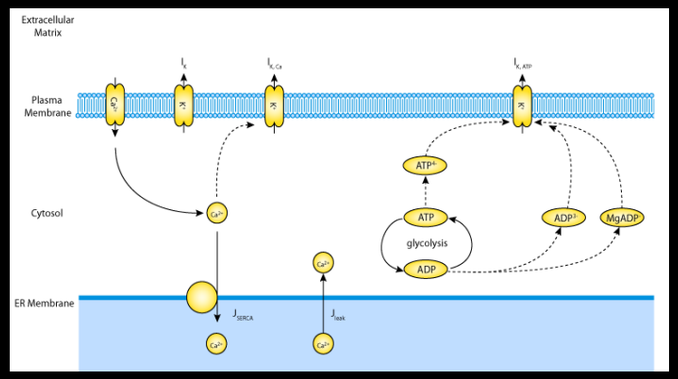
www.sbml.org



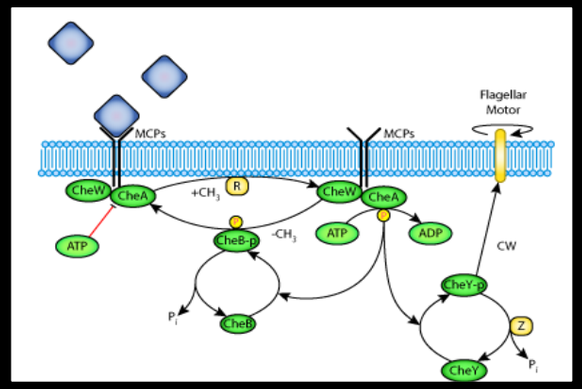
www.opencor.ws

The Physiome Repository (~1000 models)

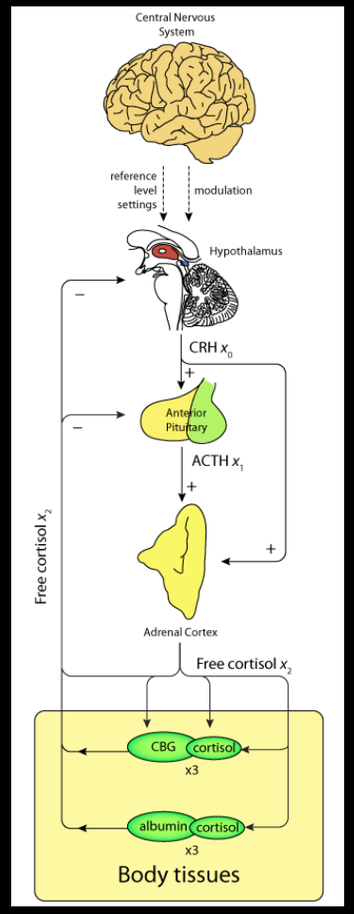
Calcium dynamics

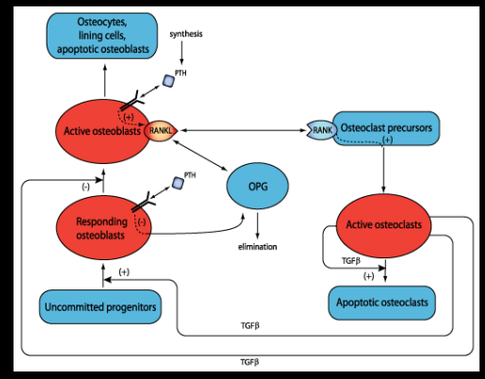


Cell migration



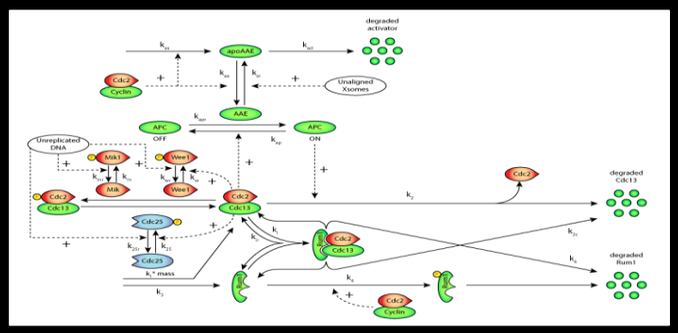
Endocrine system



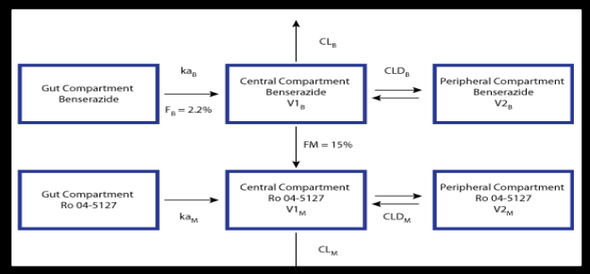


Material constitutive laws

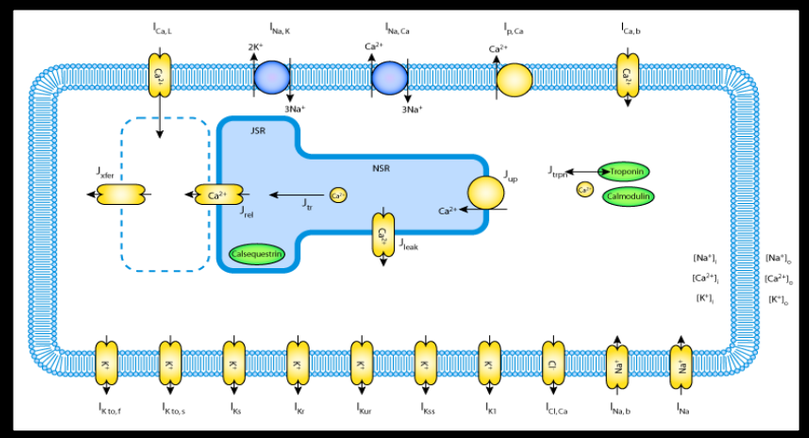
Cell cycle



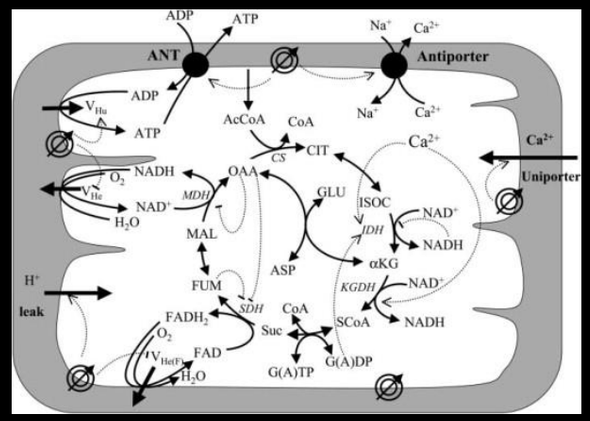
PKPD models



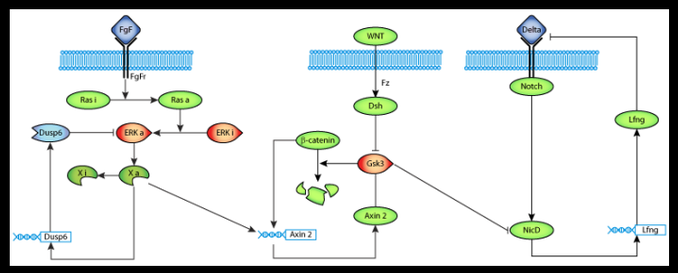
Electrophysiology



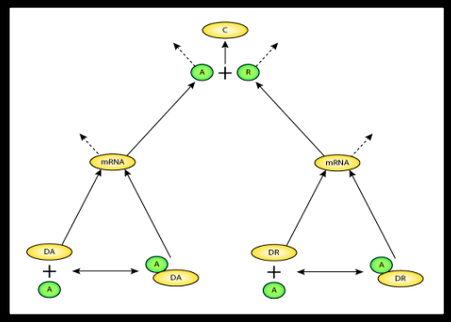
Metabolism

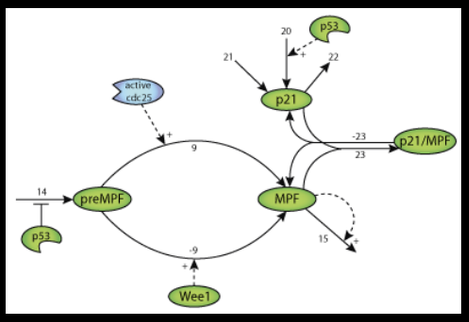


Circadian rhythms

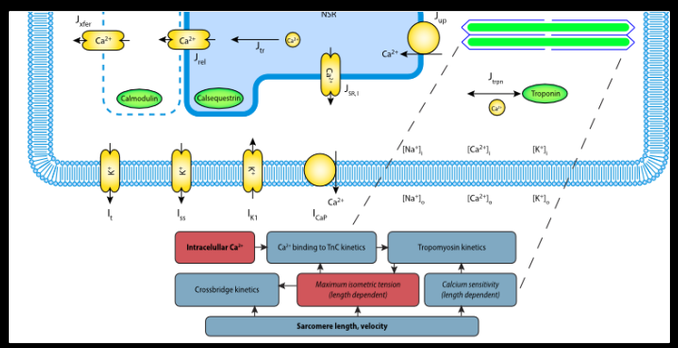


Gene regulation DNA repair

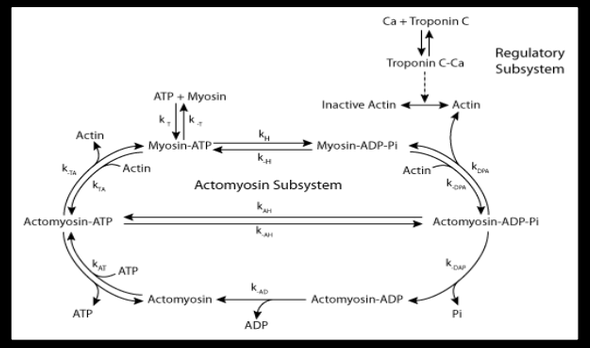




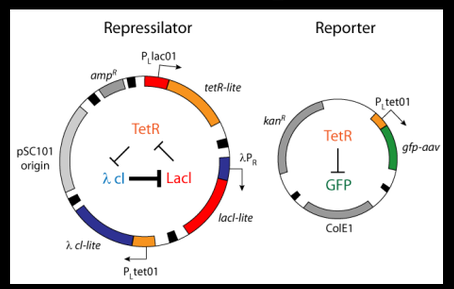
Excitation-contaction

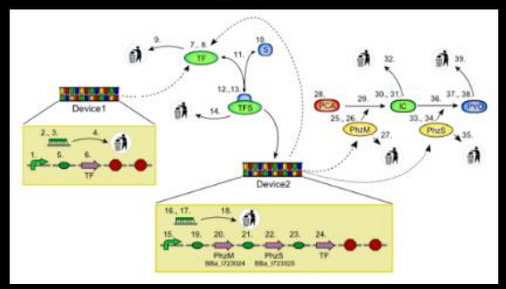


Myofilament mechanics



Synthetic biology





Most authors happy to have models ‘fixed’ ..

That's sounds wonderful, I'm glad you were able to get the code to match the published results. I'm also glad to hear about the student interested in our 2007 model, it's always nice to know that someone other than myself is interested in the models.

The value of 'a' was indeed missing, it is 2.5218 (at temp = 286K). Also note that the value of delta-H for gamma should be 200240 rather than 200.24, this is an error in the Table (the period should have been a comma).

Your guess is right: ko and k-o are 95 and 22/s, resp. They are not a function of voltage (as kv and k-v). I'll fix the bug in the table and make it clearer for the print version.

Thank you for your interest in our work and your careful reading of the paper. Eq. 7 was printed wrong. Whilst proofreading the article for publication we found several misprints but we missed this one (hopefully the only one). You are right, the last two iron terms in Eq. 7 should be in the ferrous form as in the pathway diagram (Fig. 1). Also, k8 and k8_ should have their units swopped over.

Units for biophysically based modelling

7 units:

- Joule (J)
- Second (s)
- Meter (m)

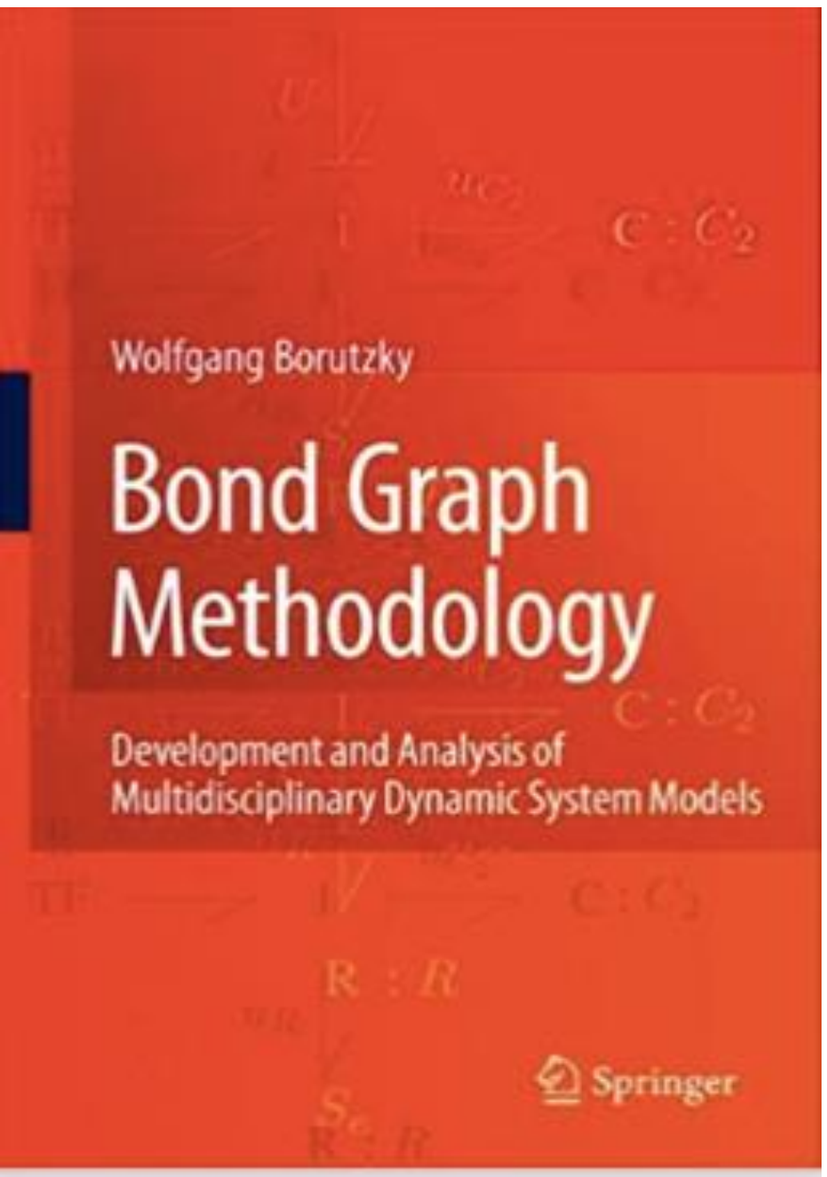
} space-time + energy

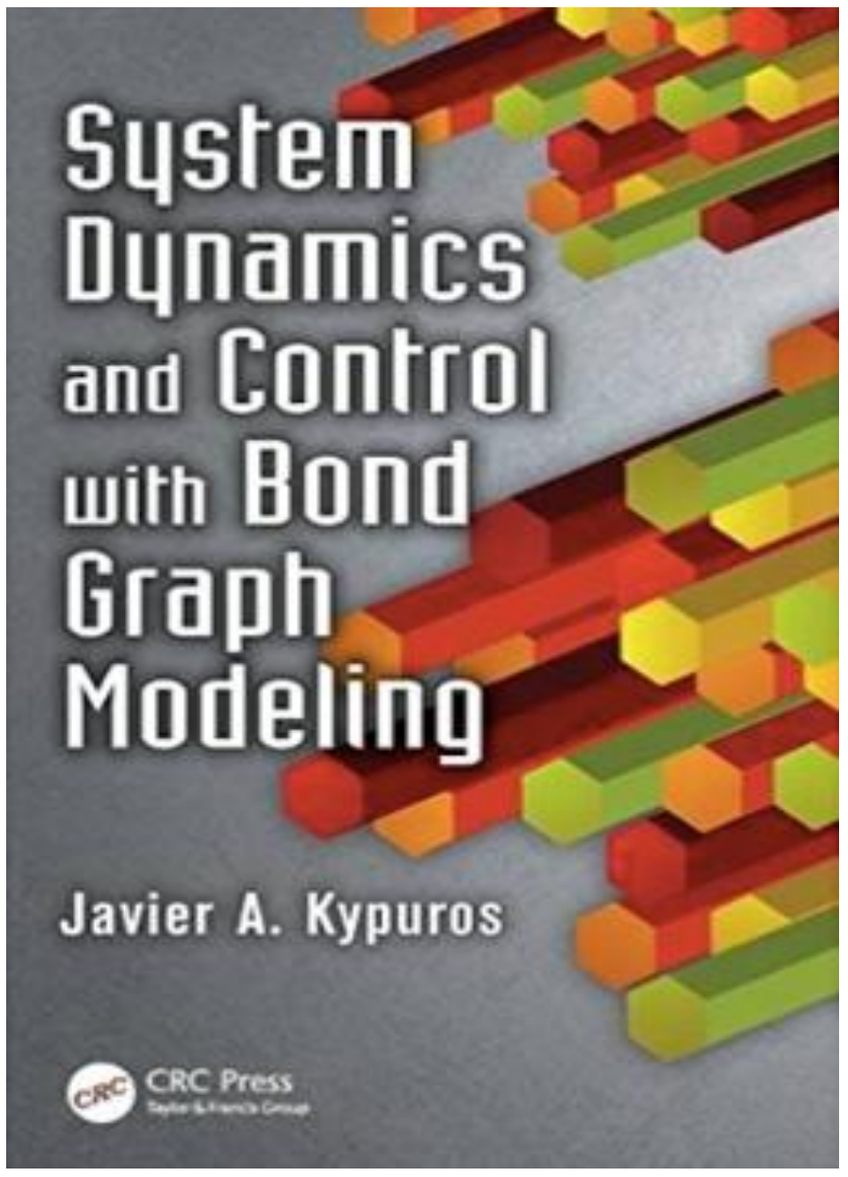
- Coulomb (C) - count electrons
- Candela (Cd) - count photons
- Mole (mol) - count atoms
- Entropy (e) - count probable states

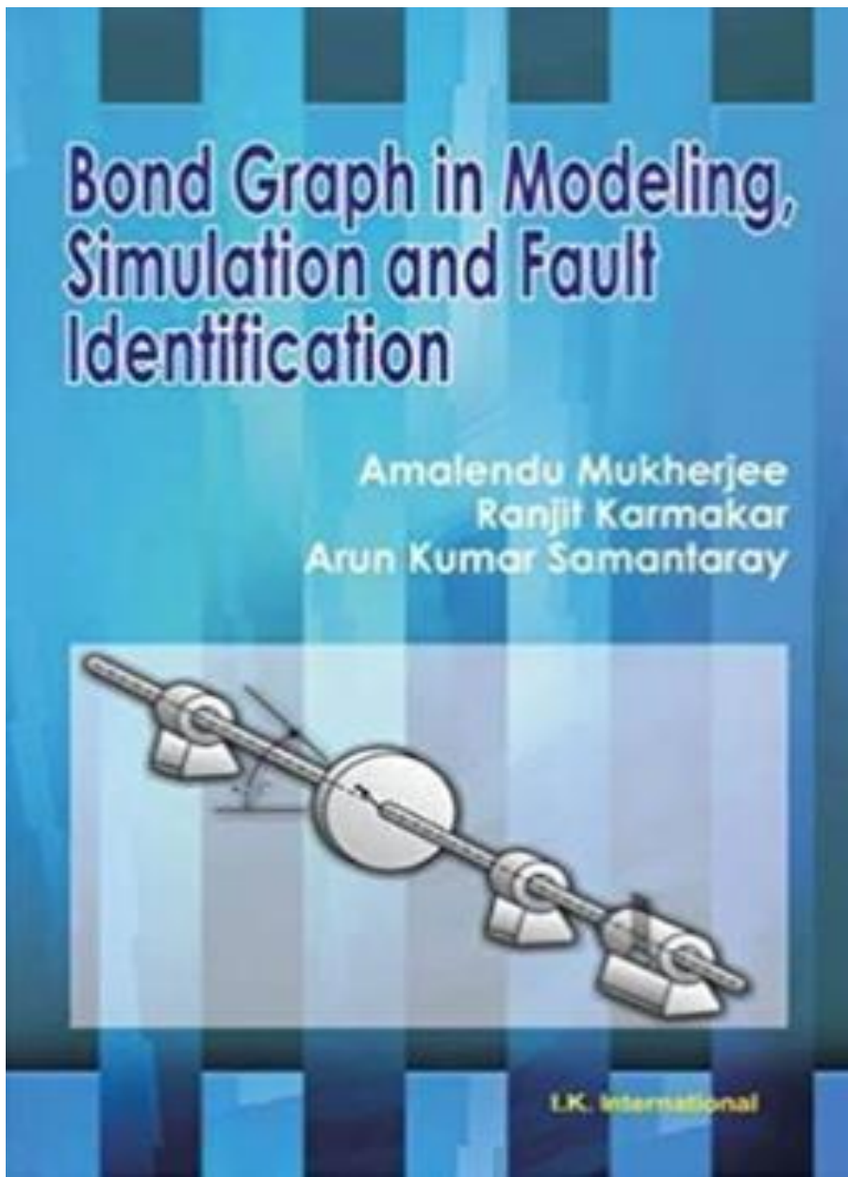
1. Mechanics (J,s,m,e): (i) Solids; (ii) Fluids
2. Electro-physiology (J,s,C)
3. Heat transfer (J,s,e)
4. Signalling pathways (J,s,b,e)
5. Metabolic pathways (J,s,mol)
6. Membrane transporters (J,s,mol,C): (i) neutral; (ii) electrogenic; (iii) ATPase
7. Electro-magnetic (J,s,C,Cd)

"Bond graphs deal with energy transfer between different physical systems and make a distinction between the supply, storage, transmission and dissipation of energy. "

Henry M. Paynter
(1923 –2002)







Bond graphs

Potential u $(J.quantity^{-1})$

Flow v $(quantity.s^{-1})$

u x v = Power ($J.s^{-1}$)

quantity is

- *m or m^3*
- *Coulomb (C)*
- *candela (cd)*
- *mole (mol)*
- *entropy (e)*
- *bits (b)*

Mechanical system

u is **force** (*Newtons* or $J.m^{-1}$) or **torque** (***N.m/rad***) or **pressure** (*kPa* or $J.m^{-3}$)

$v = \dot{q}$ is **velocity** ($m.s^{-1}$) or **angular vel.** ($rad.m^{-1}.s^{-1}$) or **volume flow rate** ($m^3.s^{-1}$)

Electrical circuit

u is **electrical potential** (*Volts* or $J.C^{-1}$)

$v = \dot{q}$ is **current *flow*** (*Amps* or $C.s^{-1}$)

Biochemical reaction

u is **chemical potential** ($J.mol^{-1}$) or ($J.mM^{-1}$)

$v = \dot{q}$ is **molar flow rate** ($mol.s^{-1}$) or ($mM.s^{-1}$) .

Heat flow

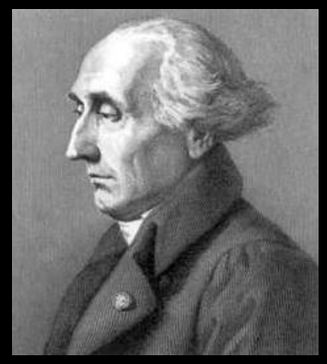
u is **temperature** (*deg K*)=**entropic potential** ($J.e^{-1}$)

$v = \dot{q}$ is **entropy flow rate** ($e.s^{-1}$).

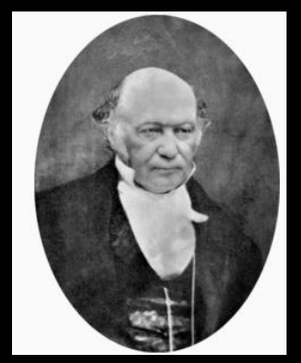
Information flow

u is **information potential** ($J.b^{-1}$)

$v = \dot{q}$ is **information flow rate** ($b.s^{-1}$).



Joseph-Louis Lagrange
(1736-1813)



William Rowan Hamilton
(1805 – 1865)

Take home message 2

Physiology is the place in the known universe where we see the most sophisticated inter-twined exploitation of electro-magnetism, fluid mechanics, mechanical behaviour of solid materials and the principles governing the change in space and time of the concentration of chemical substances.

Can we dramatically improve drug development without making use of tools that are designed for taming such complexity?

James W. Black 1924-2010

- Propanolol
- Cimetidine

“Myocardial oxygen consumption is determined by the work of the heart and is a function of arterial blood pressure and heart rate. Lowering blood pressure by systemic vasodilatation might dangerously reduce the perfusion pressure and blood flow through disease-narrowed coronary arteries. Indeed, hypotension was known to be able to induce a heart attack. Heart rate, on the other hand, is largely determined by the cardiac autonomic nervous system. Heart rate would thus be reduced by cardiac sympathetic blockade. In addition, there was much discussion in those days about a postulated “anoxiating” action of adrenaline, proposing that the price of rapidly increasing cardiac power was a decrease in cardiac metabolic efficiency.”

“These clinical, therapeutic and physiological features of hearts coping with coronary artery disease all seemed to point to the potential advantage of annulling the actions of the sympathetic hormones, noradrenaline and adrenaline, on the heart. “

Nobel Lecture, December 8, 1988

Putting the James Black approach on steroids by use of multiscale physiological modelling

$$\begin{Bmatrix} a_{11} \\ a_{12} \\ \ldots\ldots \\ a_{1n} \end{Bmatrix} = \overline{a_1} \rightarrow M_1 \rightarrow \overline{P_1} = \begin{Bmatrix} P_{11} \\ P_{12} \\ \ldots\ldots \\ P_{1m} \end{Bmatrix}$$

↓

Multidimensional sensitivity analysis (S($\overline{a_1}, \overline{P_1}$))

↓

Identify putative drug targets (a_{1j}, a_{1k})

↓

Construct lower-level model M_2

$$\begin{Bmatrix} a_{21} \\ a_{22} \\ \ldots\ldots \\ a_{2z} \end{Bmatrix} = \overline{a_2} \rightarrow M_2 \rightarrow \overline{P_1} = \begin{Bmatrix} P_{21} = a_{1j} \\ P_{22} = a_{1k} \\ \ldots\ldots \\ P_{2v} \end{Bmatrix}$$

↓

Multidimensional sensitivity analysis (S($\overline{a_2}, \overline{P_2}$))

↓

Identify putative drug targets (a_{2i}, a_{2l})

↓

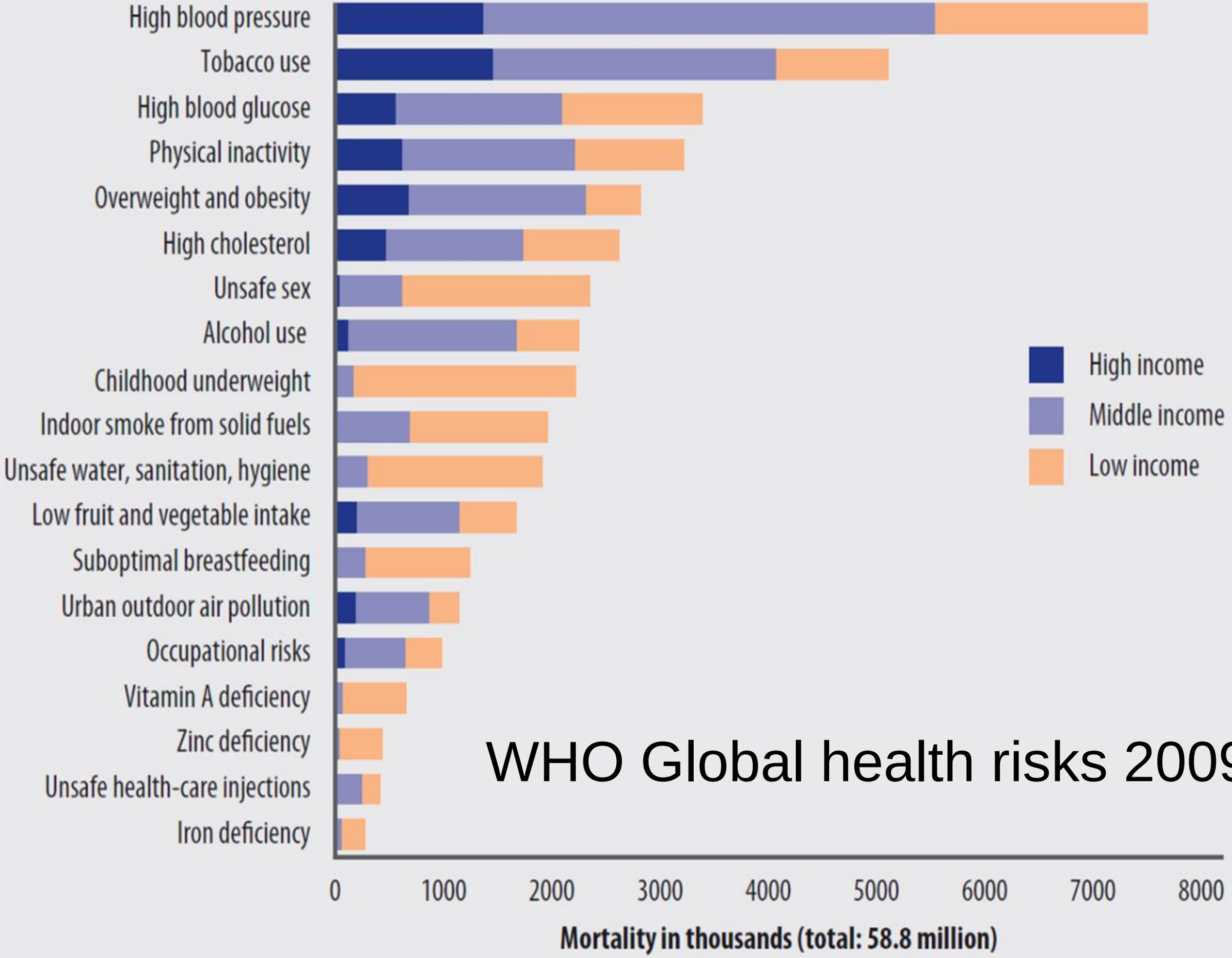
.....

↓

Drug design targeting parameters (a_{ji}, a_{jl})

Causally cohesive prediction of drug effect

Drug targeting becomes a merge between multiscale physiological modelling + nonlinear control engineering + deep phenotyping


High blood pressure
Tobacco use
High blood glucose
Physical inactivity
Overweight and obesity
High cholesterol
Unsafe sex
Alcohol use
Childhood underweight
Indoor smoke from solid fuels
Unsafe water, sanitation, hygiene
Low fruit and vegetable intake
Suboptimal breastfeeding
Urban outdoor air pollution
Occupational risks
Vitamin A deficiency
Zinc deficiency
Unsafe health-care injections
Iron deficiency
High income
Middle income
Low income
0
1000
2000
3000
4000
5000
6000
7000
8000
Mortality in thousands (total: 58.8 million)
WHO Global health risks 2009

OPEN ACCESS Freely available online

PLOS | COMPUTATIONAL BIOLOGY

Arterial Stiffening Provides Sufficient Explanation for Primary Hypertension

Klas H. Pettersen[1]*, Scott M. Bugenhagen[2], Javaid Nauman[3], Daniel A. Beard[2], Stig W. Omholt[3]

1 Department of Mathematical and Technological Sciences, Norwegian University of Life Sciences, Ås, Norway, **2** Department of Physiology, Medical College of Wisconsin, Milwaukee, Wisconsin, United States of America, **3** Department of Circulation and Medical Imaging, Cardiac Exercise Research Group, NTNU Norwegian University of Science and Technology, Trondheim, Norway

Abstract

Hypertension is one of the most common age-related chronic disorders, and by predisposing individuals for heart failure, stroke, and kidney disease, it is a major source of morbidity and mortality. Its etiology remains enigmatic despite intense research efforts over many decades. By use of empirically well-constrained computer models describing the coupled function of the baroreceptor reflex and mechanics of the circulatory system, we demonstrate quantitatively that arterial stiffening seems sufficient to explain age-related emergence of hypertension. Specifically, the empirically observed chronic changes in pulse pressure with age and the impaired capacity of hypertensive individuals to regulate short-term changes in blood pressure arise as emergent properties of the integrated system. The results are consistent with available experimental data from chemical and surgical manipulation of the cardio-vascular system. In contrast to widely held opinions, the results suggest that primary hypertension can be attributed to a mechanogenic etiology without challenging current conceptions of renal and sympathetic nervous system function.

Citation: Pettersen KH, Bugenhagen SM, Nauman J, Beard DA, Omholt SW (2014) Arterial Stiffening Provides Sufficient Explanation for Primary Hypertension. PLoS Comput Biol 10(5): e1003634. doi:10.1371/journal.pcbi.1003634

Editor: Feilim Mac Gabhann, Johns Hopkins University, United States of America

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Competing Interests: The authors have declared that no competing interests exist.

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Observations

The aorta gets stiffer with age

Baroreceptors are strain sensitive

Hypothesis

stiffening of the arterial wall with age

↓

constitutively reduced signaling from the baroreceptors to the sympathetic nervous system

↓

misinformation of the autonomic nervous system about the actual blood pressure

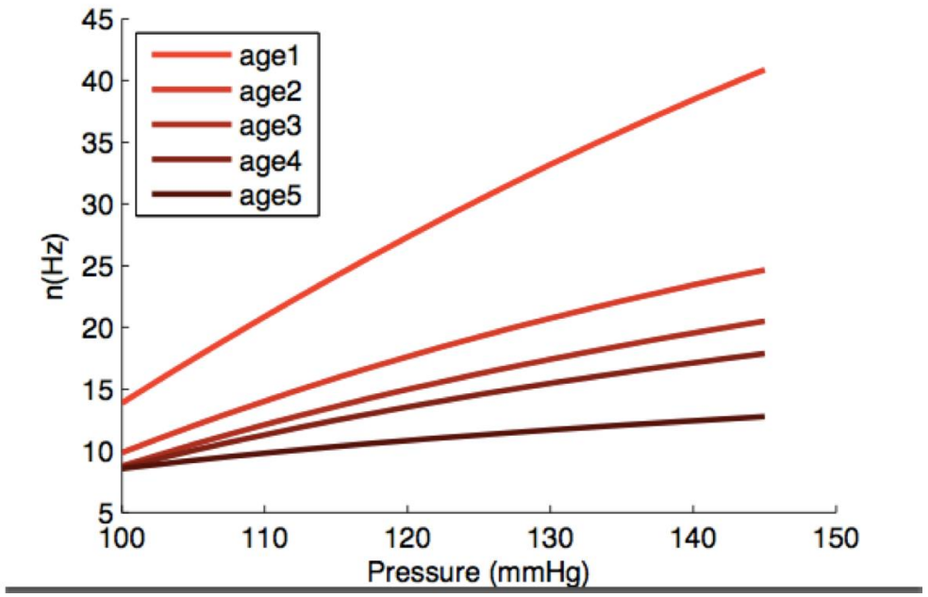
↓

prevention of a proper negative feedback response through regulation of the heart rate, vasculature and renal system

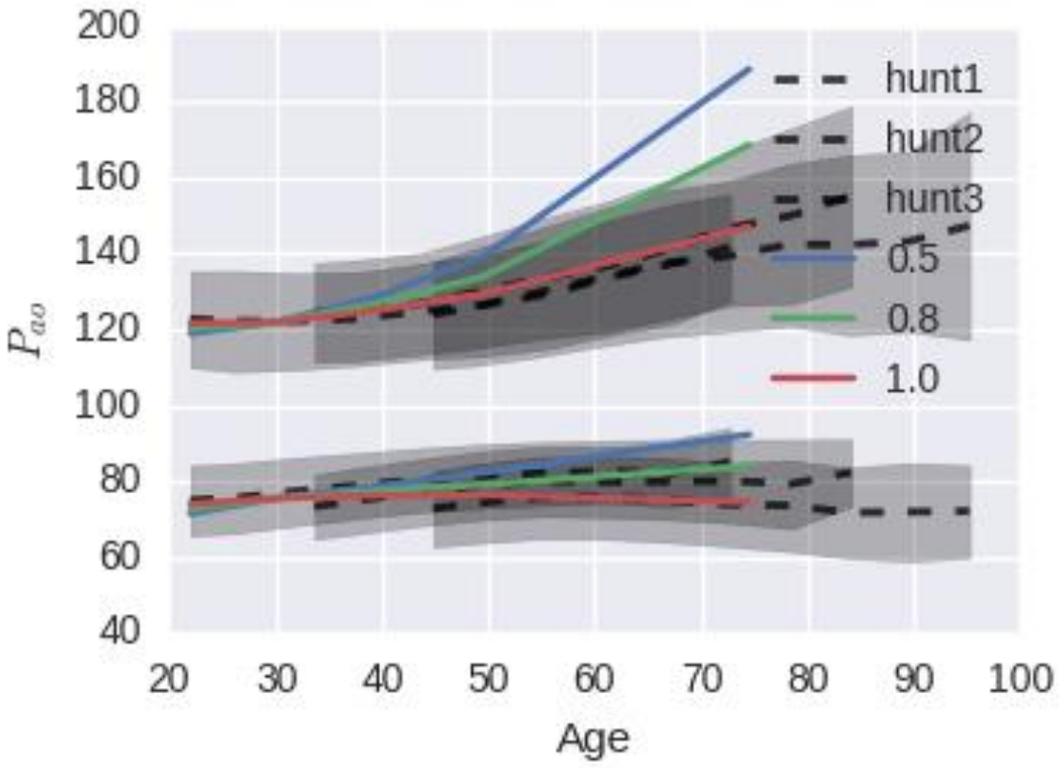
↓

hypertension

Pressure firing relation



Predictions on 65000 people



Phenomics: the next challenge

David Houle, Diddahally R. Govindaraju‡ and Stig Omholt§||*

Abstract | A key goal of biology is to understand phenotypic characteristics, such as health, disease and evolutionary fitness. Phenotypic variation is produced through a complex web of interactions between genotype and environment, and such a 'genotype–phenotype' map is inaccessible without the detailed phenotypic data that allow these interactions to be studied. Despite this need, our ability to characterize phenomes — the full set of phenotypes of an individual — lags behind our ability to characterize genomes. Phenomics should be recognized and pursued as an independent discipline to enable the development and adoption of high-throughput and high-dimensional phenotyping.

Phenomics: The acquisition of high-dimensional phenotypic data on an organism-wide scale.

Model-guided phenomics: encapsulate what you know in mathematical descriptions → identify phenotypic data that will advance understanding

Hypertension model example: blood volume

Take home message: 3

There is always a grey zone between a grand vision and a plain hallucination. But can we afford not to check it out?

I²AGE
Transforming the challenge of ageing into an age of opportunity

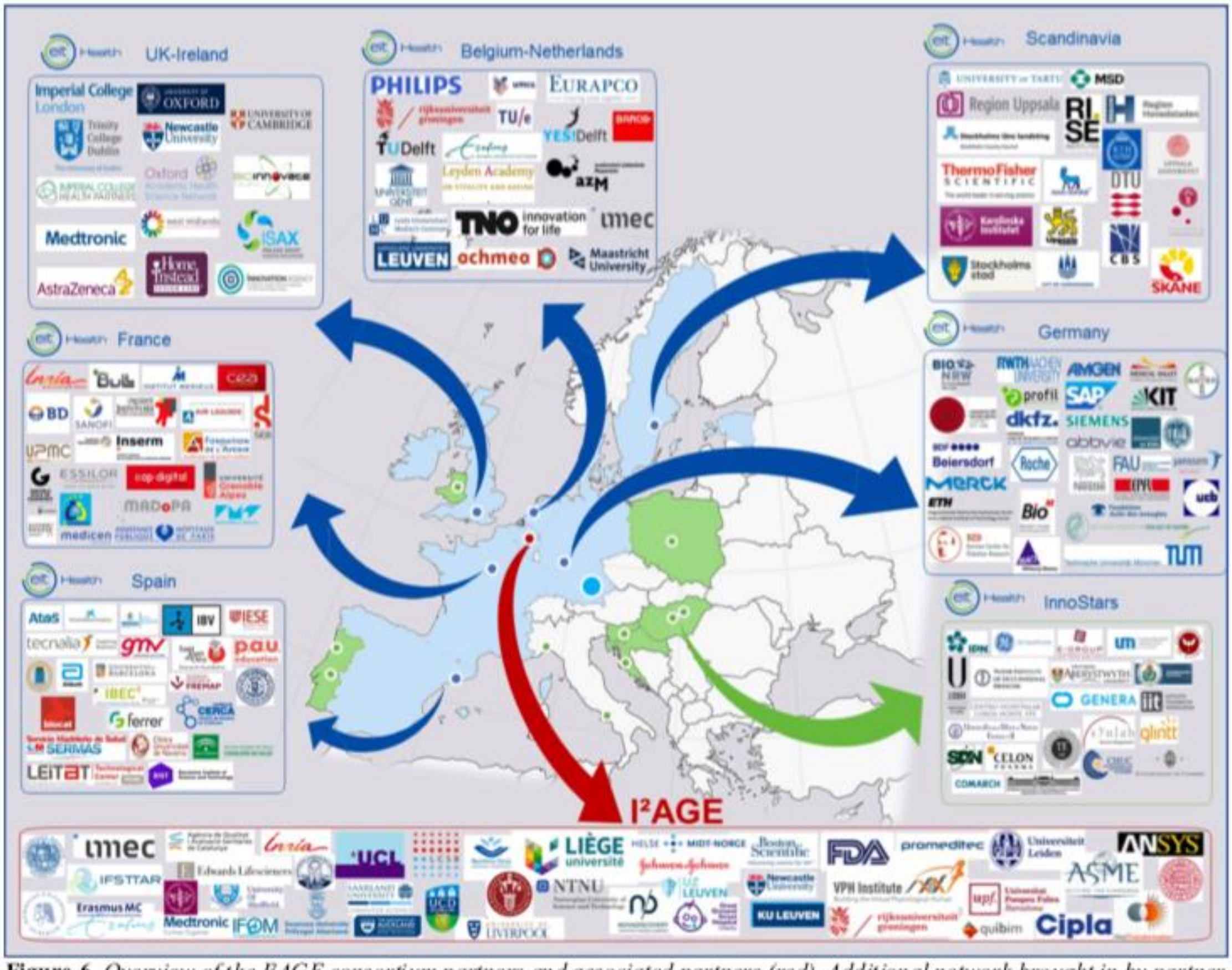
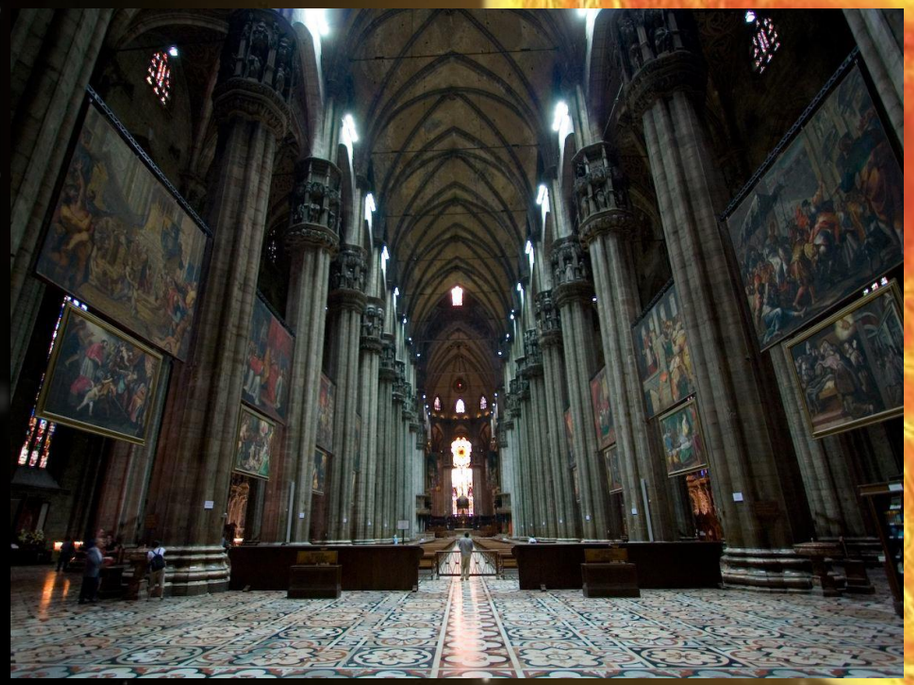


Figure 6. *Overview of the I²AGE consortium partners and associated partners (red). Additional network brought in by partner EIT Health (blue & green). Several consortium partners are also partners in EIT.*


BØRSEN



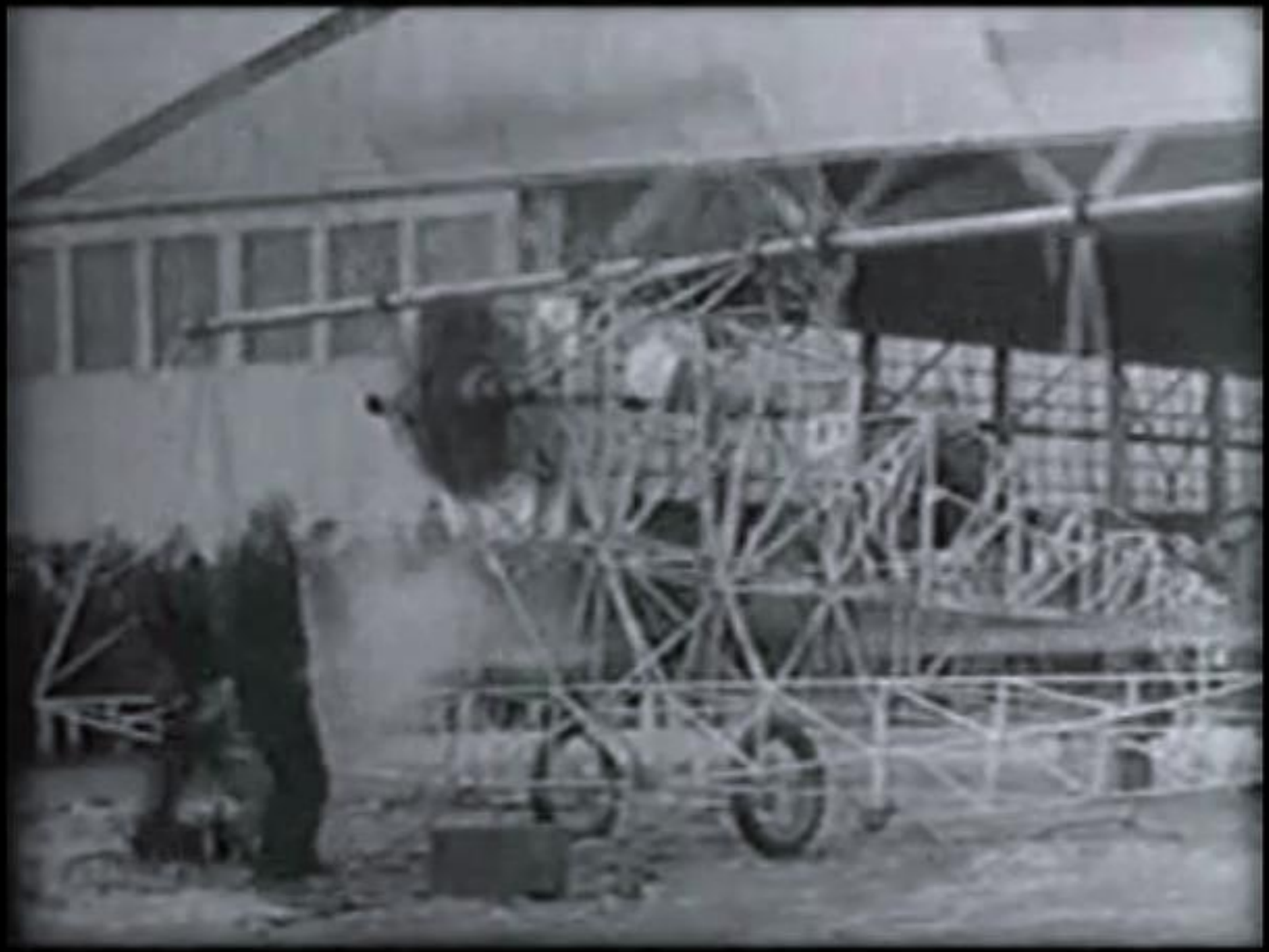
Horizon Europe funding opportunities

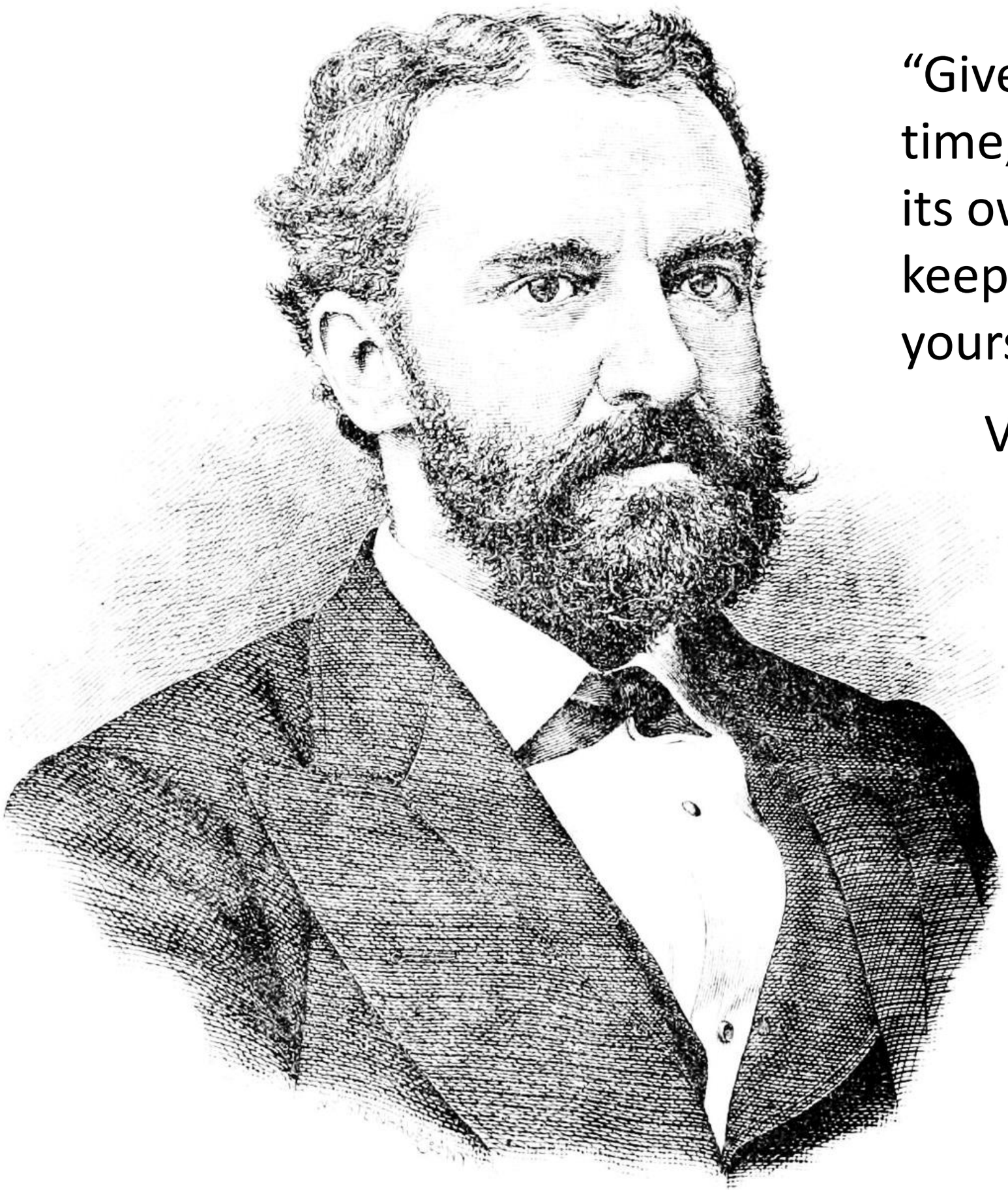
	Preliminary list of candidates for European Partnerships in Pillar II, III and cross-pillar, and short description of what the partnership stands and aims for	Currently envisaged implementation mode(s)	Predecessors	Composition of partners	Relevance for clusters/ pillars
Health	**1. EU-Africa Global Health Partnership** Increase health security in sub-Saharan Africa and Europe, by accelerating the clinical development of effective, safe, accessible, suitable and affordable health technologies as well as health systems interventions for infectious diseases in partnership with Africa and international funders.	Article 185 or Article 187 or Co-programmed or co-funded	EDCTP2 (Art.185)	MS/AC and 3rd countries (i.e. sub-Saharan African countries) Foundations/industry on an ad-hoc basis	Cl.1
	2. Innovative Health Initiative A collaborative platform bringing the pharmaceuticals, diagnostics, medical devices, imaging and digital sectors together for precompetitive R&I in areas of unmet public health need, to accelerate the development and uptake of people-centred health care innovations.	Article 187 or Co-programmed	IMI2 (Art.187)	Industry, other organisations on an ad hoc basis	Cl.1
	3. European partnership for chemicals risk assessment Bring together the European risk assessment and regulatory agencies to implement a joint research agenda, to ensure their capacity to deal with persistent or emerging challenges. It will promote the uptake of new methods, tools, technologies and information in chemical hazard identification and risk assessment and as part of this, sustain the development and use of human biomonitoring capacities in Europe.	Co-funded	Human Bio-monitoring and a number of other actions	MS/AC, National agencies, tbd the role of the corresponding EU agencies	Cl.1, 4, 6
	4. Pre-clinical/clinical health research The partnerships aims for establishing and implementing a strategic research agenda and joint funding strategy between major European public funders in health research.	Co-funded	Around 10 previous and current ERA-NET actions	MS / AC / 3rd countries	Cl.1, 6
	5. Large-scale innovation and transformation of health systems in a digital and ageing society Improving health and care models in an ageing, data-driven and digital society, shifting to holistic health promotion and person-centred care approaches through health policy and health systems research.	Co-funded	AAL2 (Art.185), JPI 'More Years, Better Lives' and others	MS / AC Civil Society organisations	Cl.1
	6. Personalised Medicine To align national research strategies, promote excellence, reinforce the competitiveness of European players in Personalised Medicine and enhance the European collaboration with non-EU countries	Co-funded	ERA-PerMed and actions in support of ICPerMed	MS / AC	Cl.1
	7. Rare Diseases To improve the integration, the effectiveness, the production and the social impact of research on rare diseases through the development, demonstration and promotion of Europe/ world-wide production, sharing and exploitation of research and clinical data, materials, processes, knowledge and know-hows.	Co-funded	EJP Rare diseases (until 2023)	MS/AC /3rd countries, civil society organisations, EU research infrastructures	Cl.1

Take home message: 4

A log's flame leaps to another. Fire kindles fire. A man listens, thus he learns. The shy stays shallow.

Hávamál



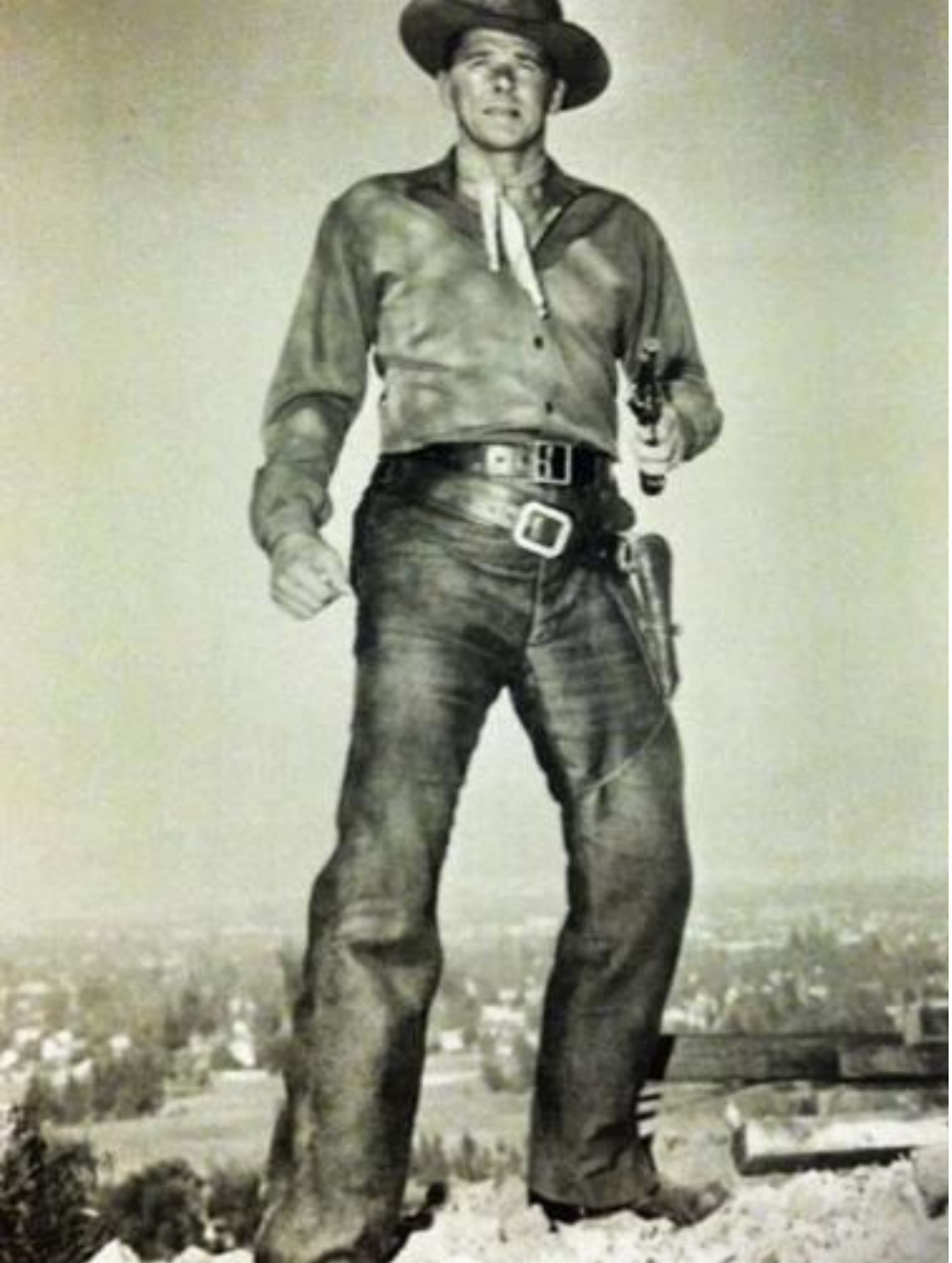


"Give me the fruitful error any time, full of seeds, bursting with its own corrections. You can keep your sterile truth for yourself."

Vilfredo Pareto (1848-1923)

Take home:

- Remember Sun Tzu
- Taming complexity
- New drug targeting paradigm – PG/PK/PD
- Remember old Norwegian saying



“New technologies are seldom created by luck; they are instead the result of private and public sector investments of time, money and effort.”

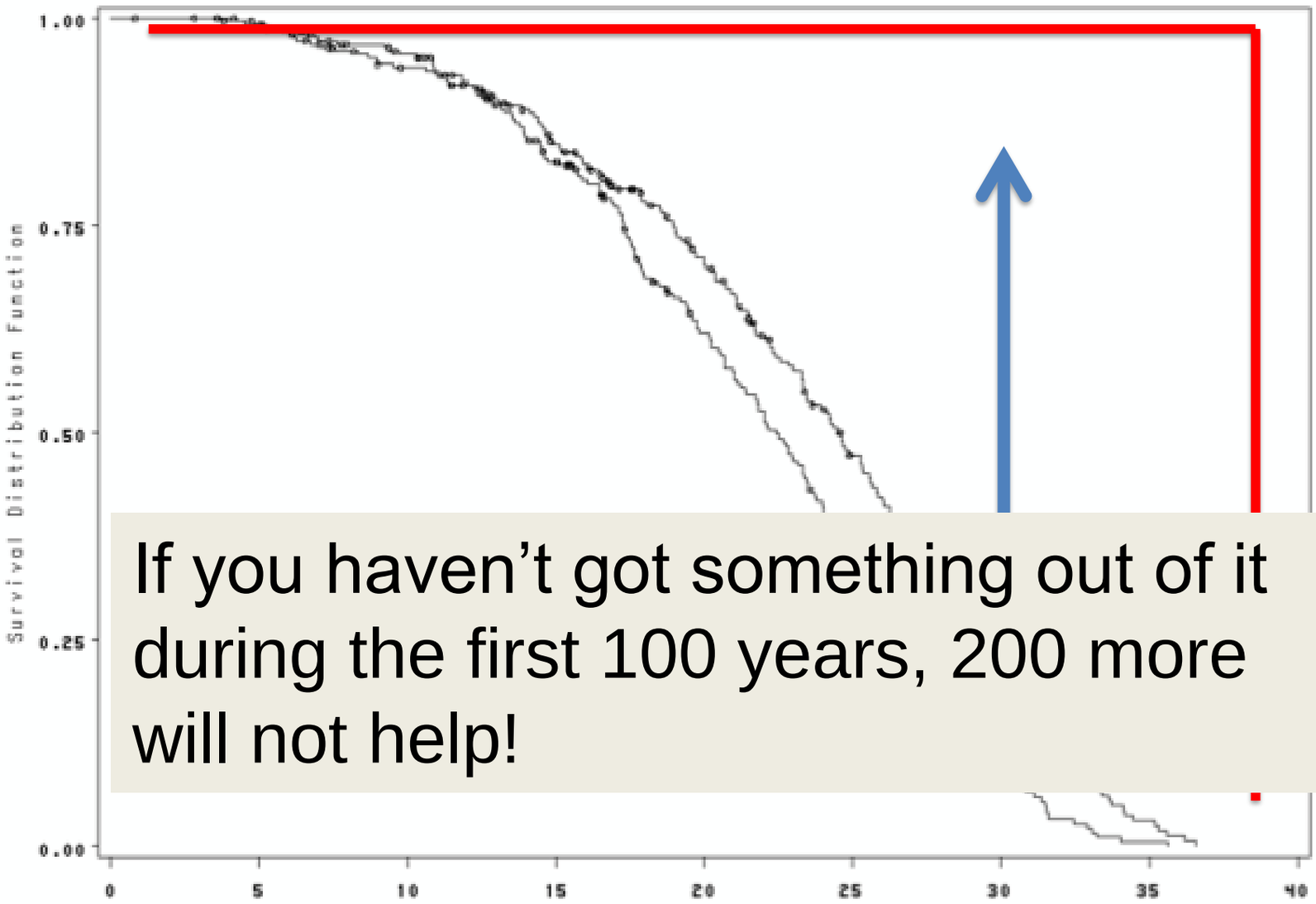
Ronald Reagan, 1983

Physiology

“the study of the functions and activities of living matter (as of organs, tissues, or cells) as such and of the physical and chemical phenomena involved”

Webster's Third New International Dictionary

Is it possible to rectangularise the intrinsic mortality curve?



If you haven't got something out of it during the first 100 years, 200 more will not help!

European Psychologist 2006; Vol. 11(3):204–223

Take home message: 4