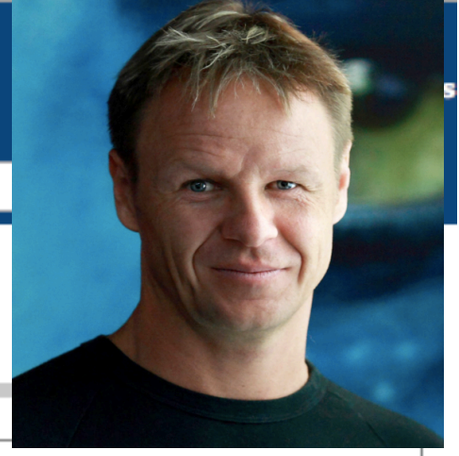
The Digital Salmon in the context of the Virtual Physiological Human

Stig W. Omholt
NTNU Biotechnology – the Confluence of Life Sciences, Mathematical Sciences and Engineering

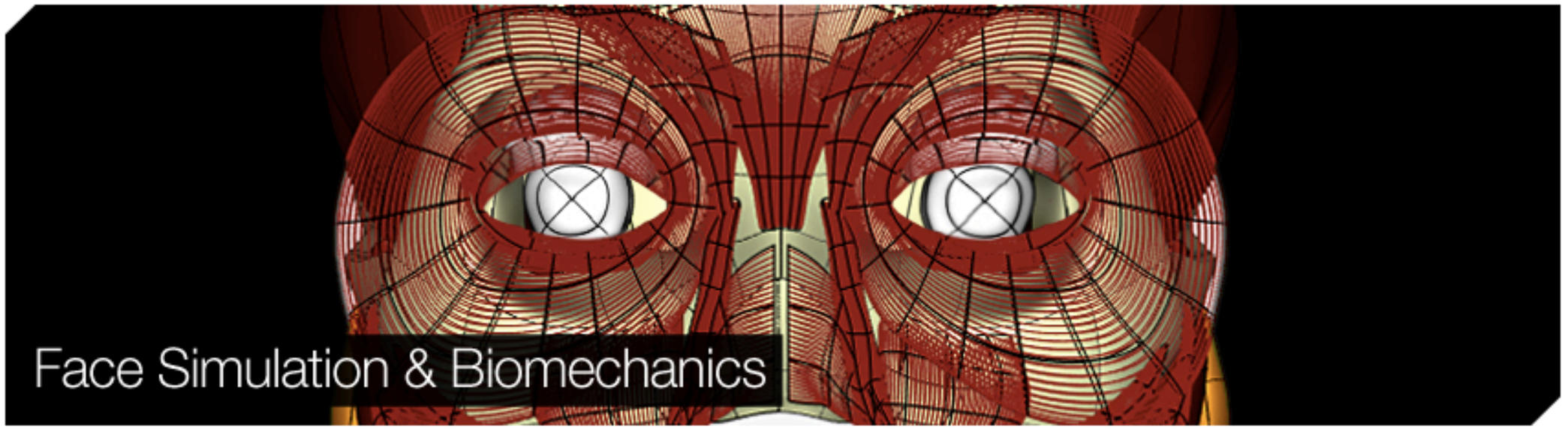


Auckland Bioengineering Institute

FOR
- Future postgraduates
- Current students
- International students
- The media

ABOUT
- Our Institute
- **Our research**
  - Bioinstrumentation Lab
  - Biomechanics for Breast Imaging
  - Biomedical Informatics
  - Biomimetics Lab
  - Cardiac and Cardiovascular research groups
  - CellML
  - Computational Fluid Mechanics
  - Development and Reproductive Health
  - Gastrointestinal System
  - Immune and Lymphatic System
  - Implantable Devices
  - Laboratory for Animate

LABORATORY FOR ANIMATE TECHNOLOGIES



K.G. Jebsen Center for Exercise in Medicine - Cardiac Exercise Research Group (CERG)

We aim to define optimal exercise programs for "most people" in order to increase the likelihood of development and preservation of good health throughout life.

More about CERG

High-intensity physical exercise will boost your health

NTNU Studies Life and housing Research About NTNU

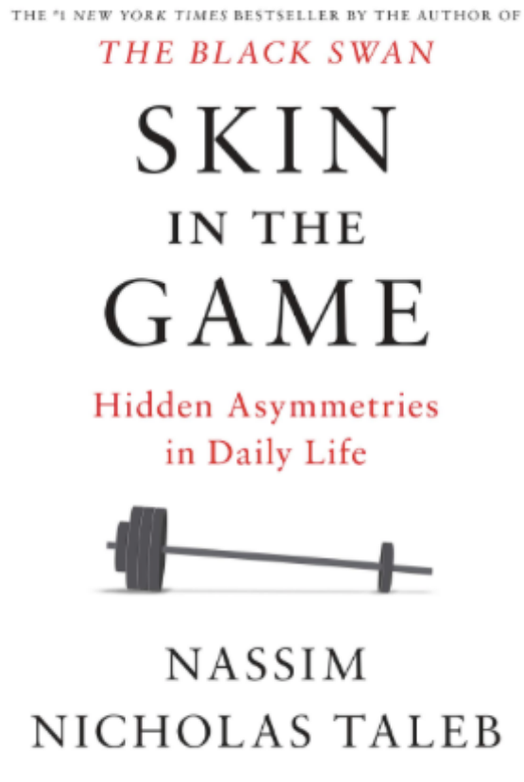
K.G. Jebsen Center for Genetic Epidemiology

K.G. Jebsen Center for Genetic Epidemiology

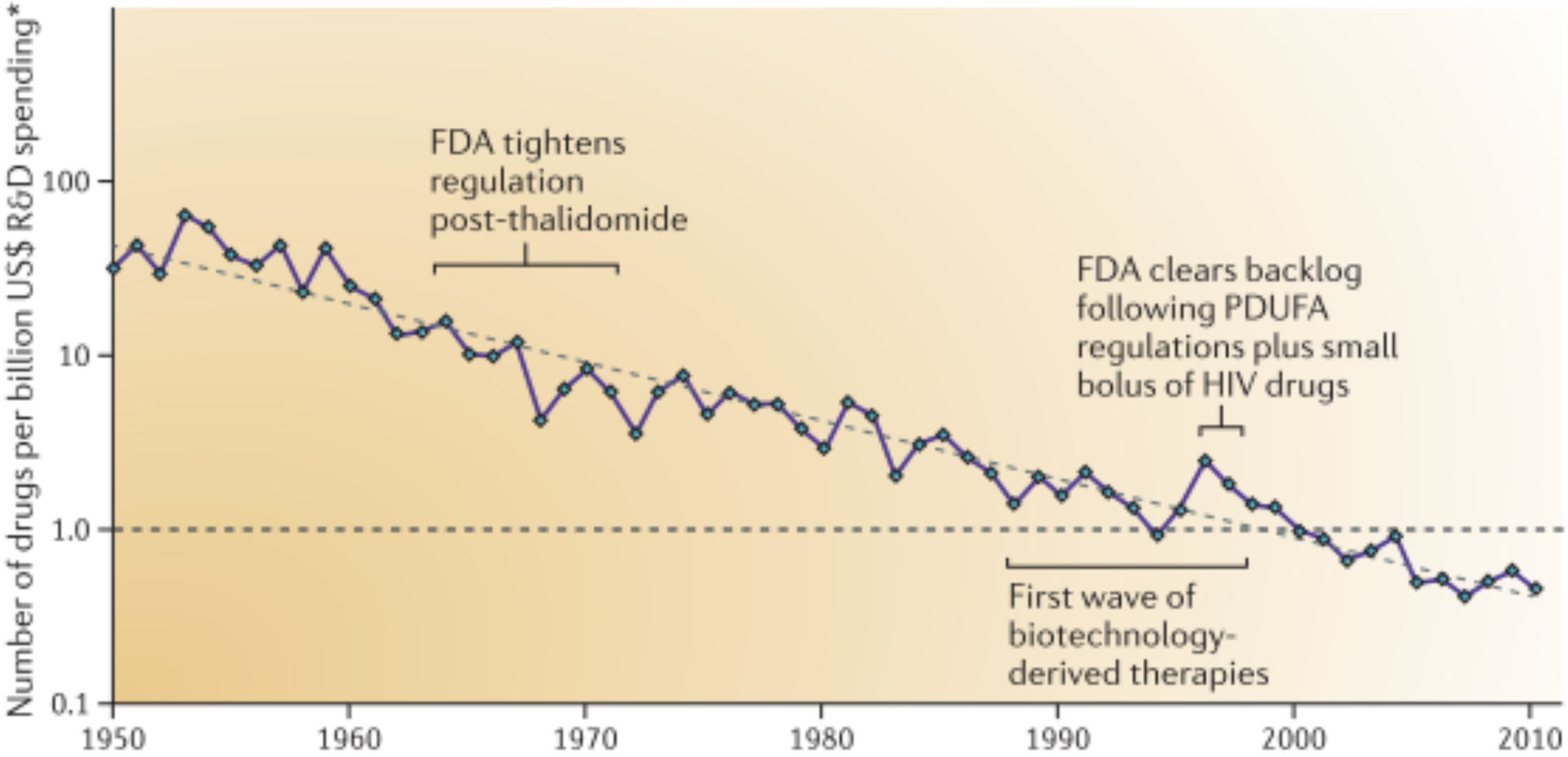
About Publications Tag cloud Network

Network

Personalised mathematical models of the effect of exercise > 10 000 individuals



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

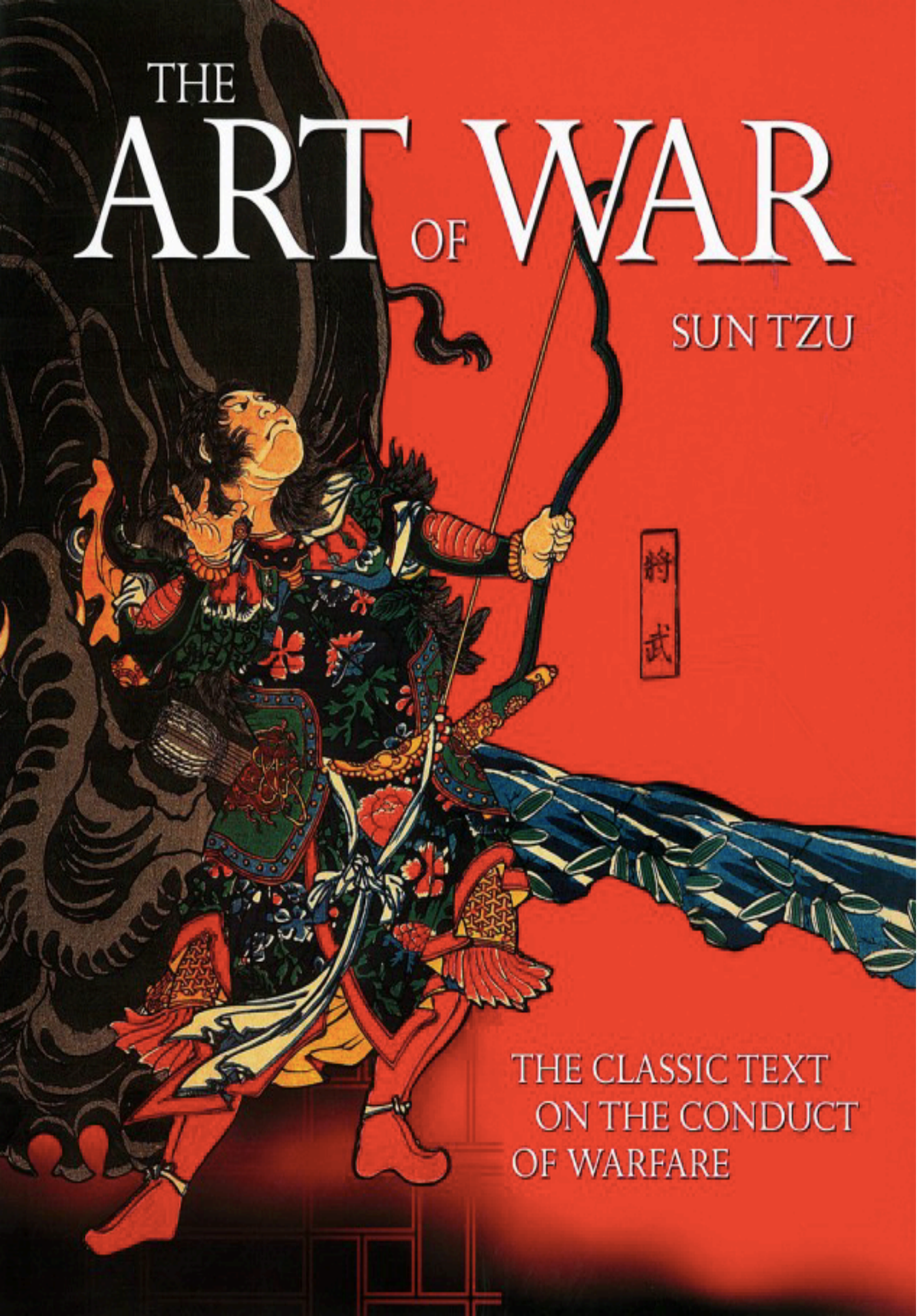


Eroom's Law in pharmaceutical R&D: The number of new drugs approved by the US Food and Drug Administration (FDA) per billion US dollars (inflation-adjusted) spent on research and development (R&D) has halved roughly every 9 years.

EUFEMED EUROPEAN FEDERATION FOR EXPLORATORY MEDICINES DEVELOPMENT

15-17 MAY 2019 –

SESSION 1: CURRENT AND FUTURE OPTIONS FOR VIRTUAL TRIALS IN EARLY MEDICINES DEVELOPMENT Chairs: Eric Legangneux, France and Georg Wensing, Germany	
09.00	Keynote lecture **The potential role of virtual trials in early medicines development: Beyond pharmacology to mechanisms** Adriano Henney, UK
09.20	**The in silico paradigm: understanding the potential of mechanistic models and their limitations, adapting organizations and building the necessary expertise** François-Henri Boissel, France
09.40	**The virtual physiological human – impact on early medicines development** Stig Omholt, Norway
10.00	**Open forum discussion** With session chairs, speakers, and Ingrid Klingmann, Belgium



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

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

› ABOUT
› GOVERNANCE
› MEMBERSHIP
› COLLABORATIONS
› RESOURCES
› MEDIA

VPH Conference >
AVICENNA ALLIANCE >

> The Virtual Physiological Human will revolutionise the way health knowledge is produced, stored and managed as well as the way in which healthcare is currently delivered
>
> European Commission

‹ HIGHLIGHT ›

05/04/2018

VPH2020 IN PARIS

The VPH Institute is happy to announce that VPH2020, the next VPH conference on in silico medicine, will be in Paris, organised by Inria and partners.

WELCOME TO THE VPH INSTITUTE

We are an international non-profit organisation incorporated in Belgium, whose mission is to ensure that the Virtual Physiological Human is fully realised, universally adopted, and effectively used both in research and clinic.

READ MORE

NEWS

VPHi history

2007

STEP VPH RESEARCH ROADMAP

"Seeding the EuroPhysiome: A Roadmap to the Virtual Physiological Human"

2008

VPH NOE VISION AND STRATEGY

A concrete implementation plan on the incorporation of the VPH Institute is proposed

2009

PUBLIC PETITION

300 experts supported the creation of the Institute

PRO-TEMPORE BOARD

The BoD drafts the VPHi statute and follows its approval

2010

CONSTITUTION MEETING

1st meeting of the Founding members

INCORPORATION

The VPHi gets officially incorporated

2011

2011

PAWG
Establishment of the Policy Affairs Working Group
Position statement
Why we need a strategy for health research in Europe

2012

Incorporation
The VPHi gets officially incorporated

2013

Parliament & EC
Following an official parliamentary request the EC ensures continued funding to VPH
Strategic policy docs
3Rs, big data...

Digitial Patient
Relased Roadmap for the Digital Patient
Parliament event
Organised event at the European Parliament

2014

Avicenna Roadmap
Released Roadmap for in silico Clinical Trials

2015

Avicenna Alliance
Created an Industry-Academia Association.
e-Health Stakeholder group
EC appointed VPHi as one of its 30 members

2016

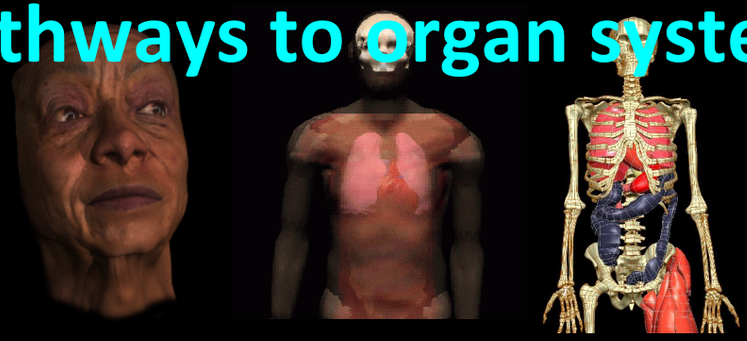
FDA
The FDA signed a Memorandum of Understanging with AA
Digital Health Society Declaration

2017

IUPS Physiome: Molecular pathways to organ systems

Environment

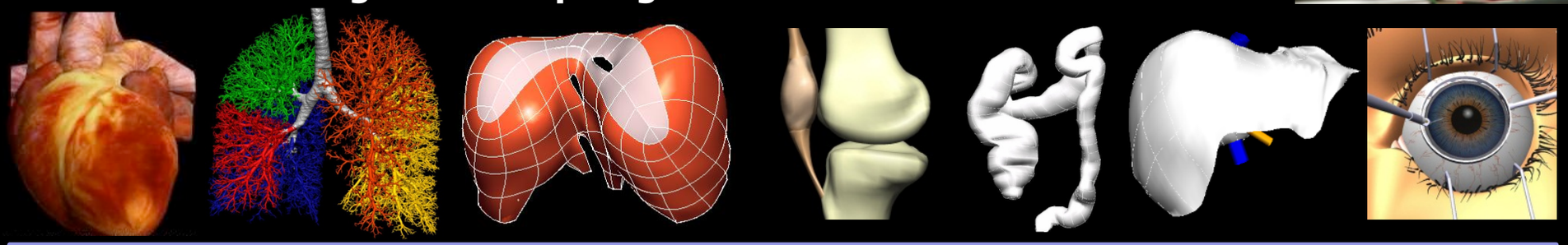
Organism



Organ system

Organ

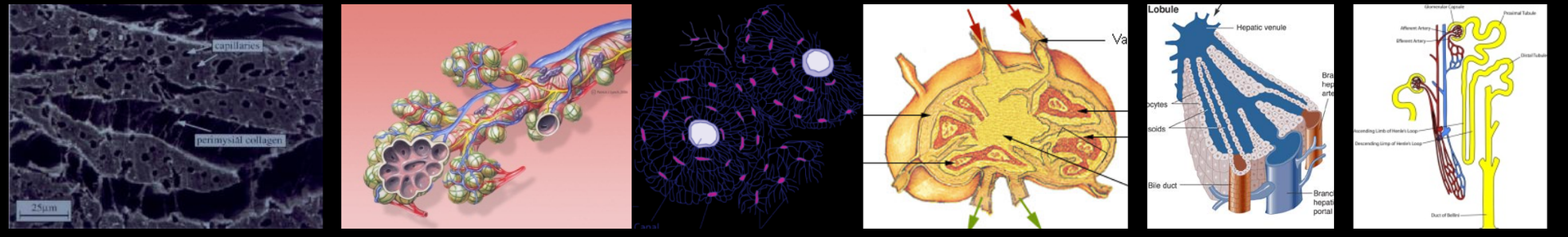
Heart | Lungs | Diaphragm | Knee | Colon | Liver



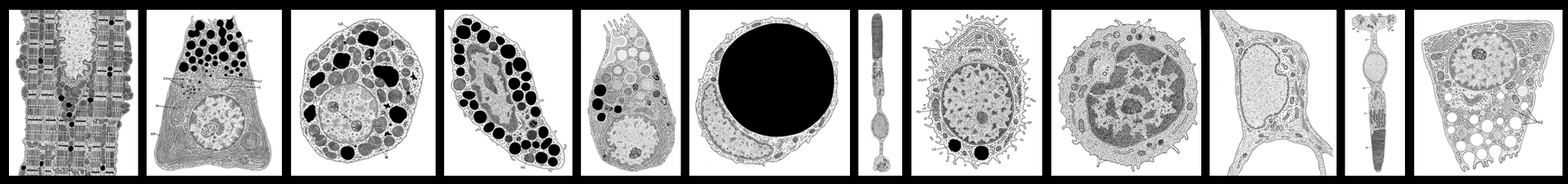
↑ x 1million ↓ 20 generations

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

Tissue



Cell

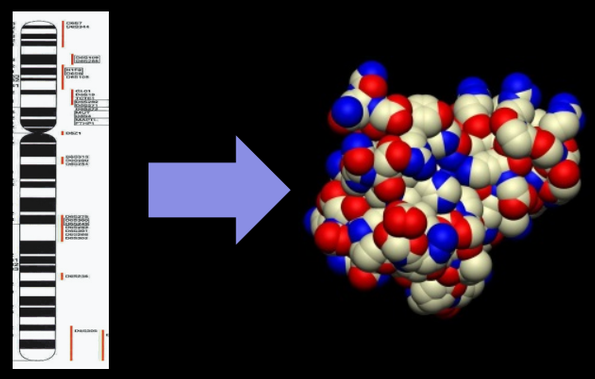


Network

Protein

Gene

Atom



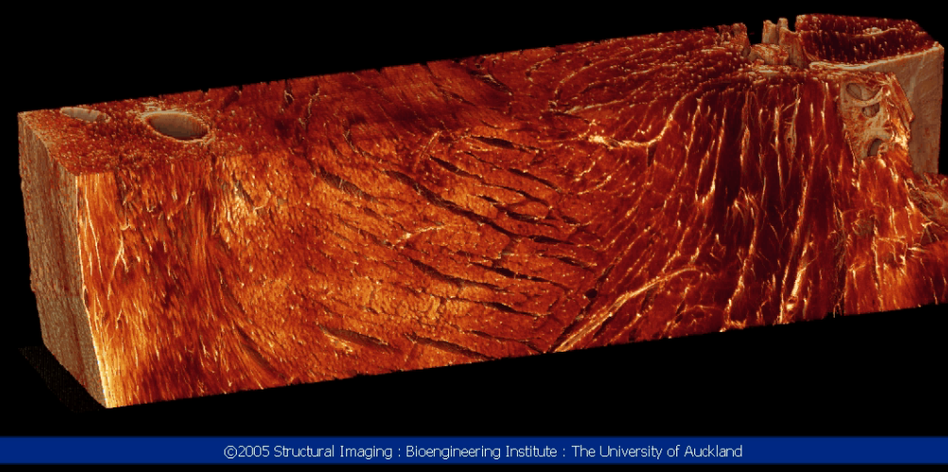
The heart physiome

m
$=10^9$nm

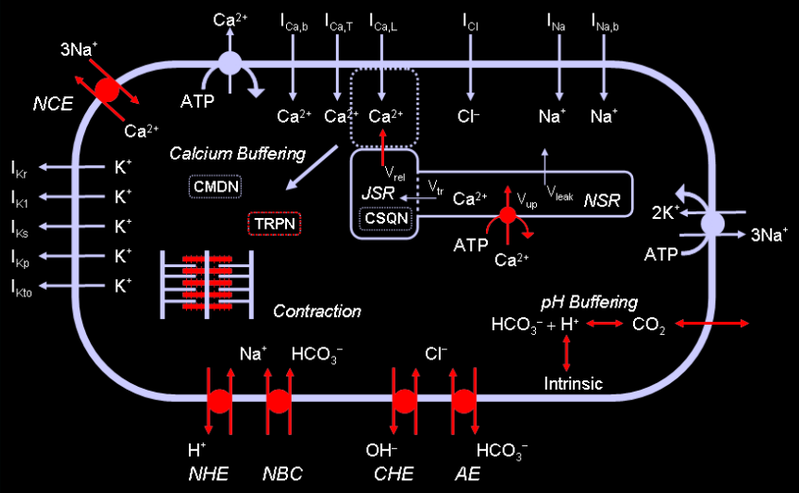
torso

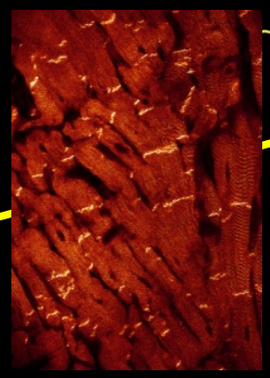
heart

tissue



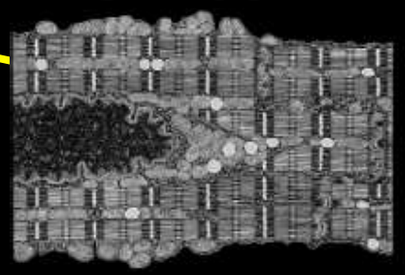
cellular processes



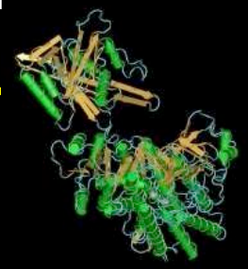


cell-cell connections

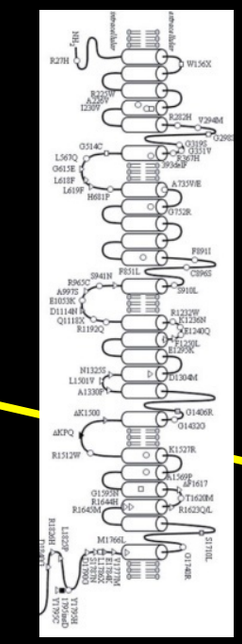
3D cell



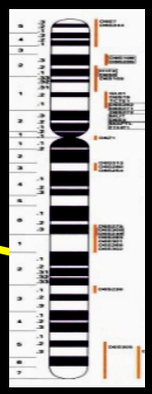
proteins



amino acid sequence



genomic sequence



nm

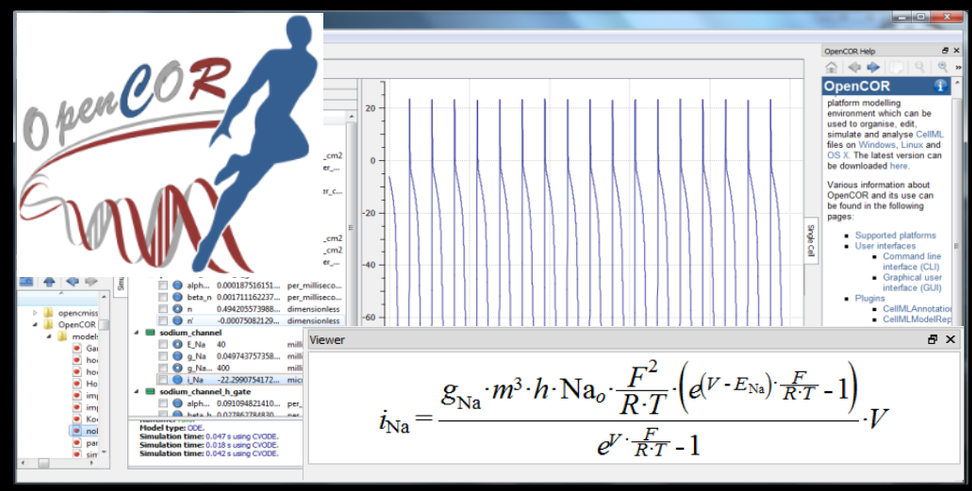
Markup Languages, PMR, OpenCOR

models.cellml.org

www.cellml.org

sed-ml.github.io

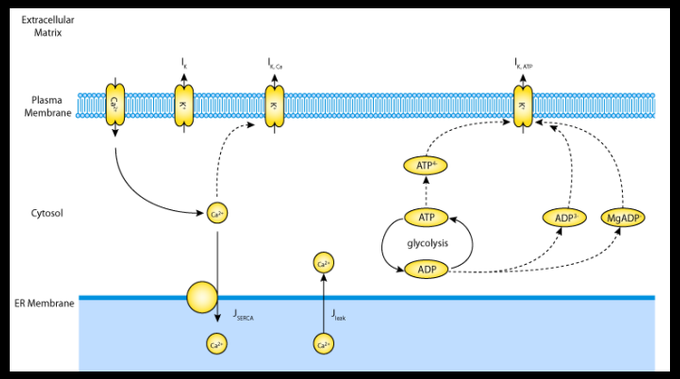
www.sbml.org



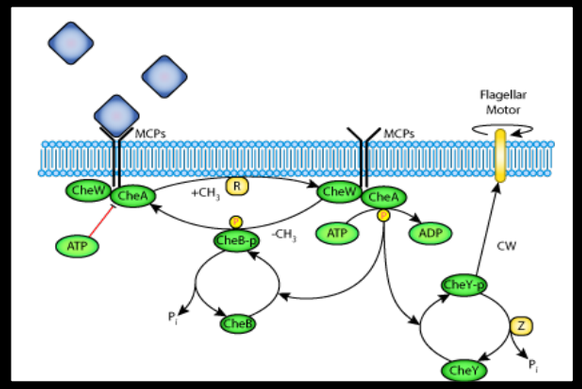
www.opencor.ws

The Physiome Repository (~1000 models)

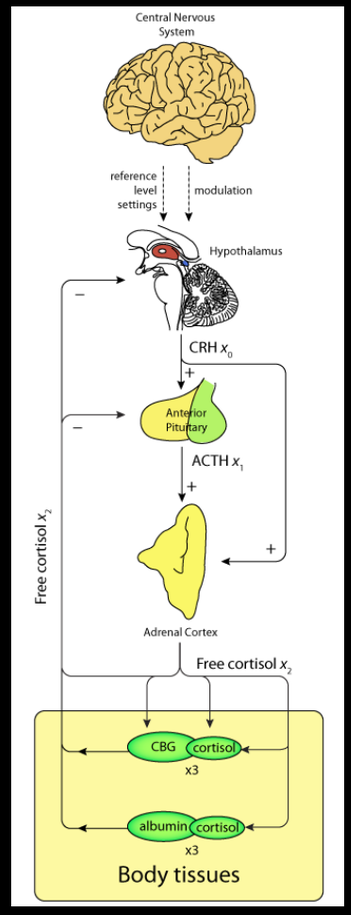
Calcium dynamics

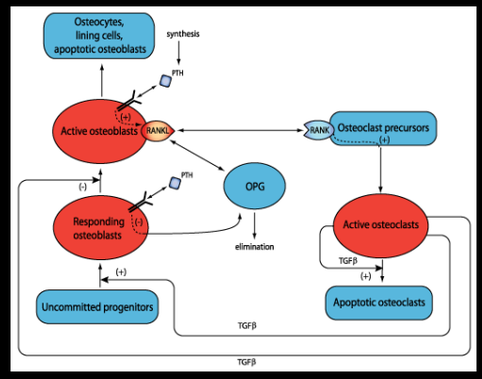


Cell migration



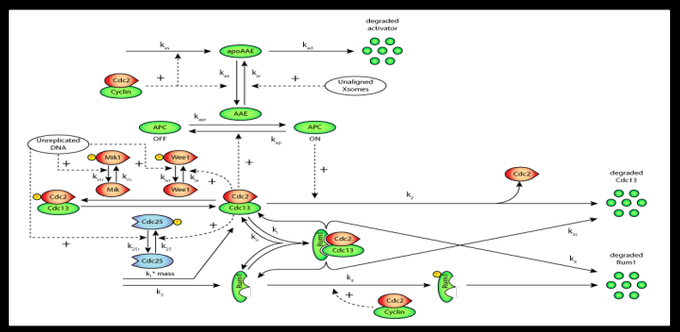
Endocrine system



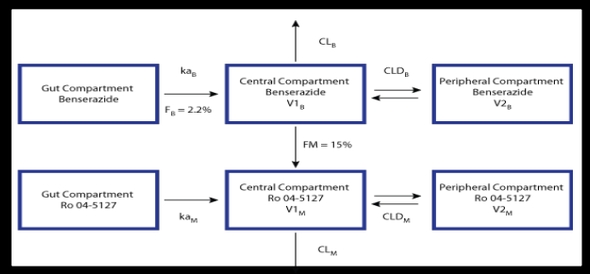


Material constitutive laws

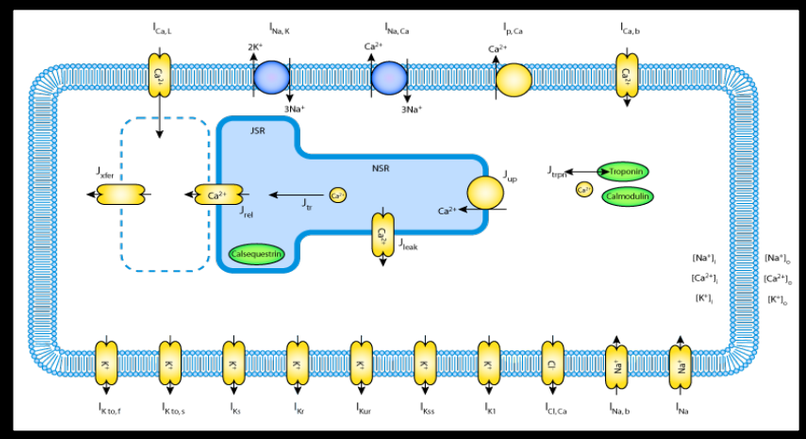
Cell cycle



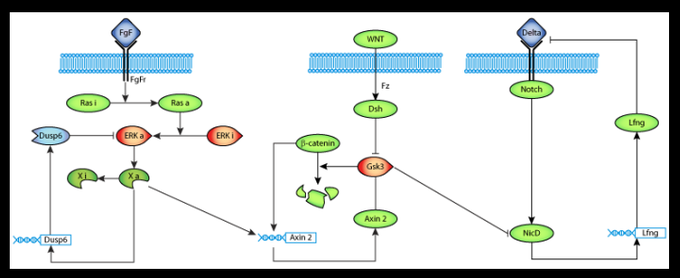
PKPD models



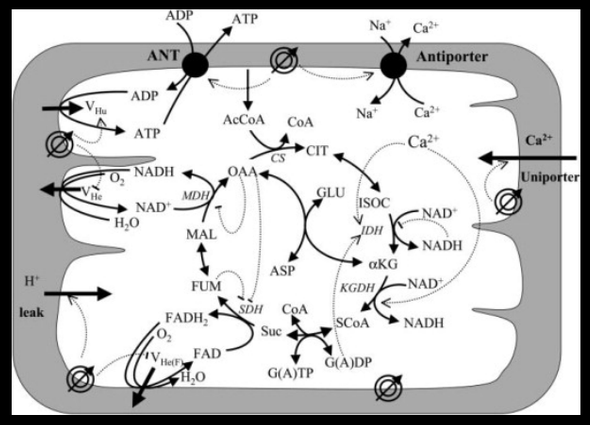
Electrophysiology



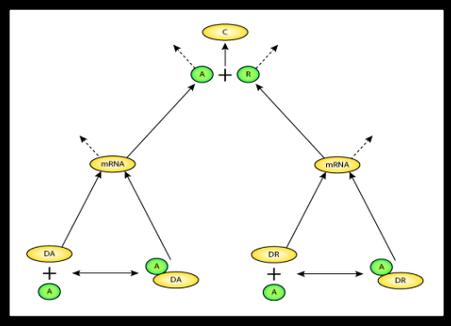
Circadian rhythms

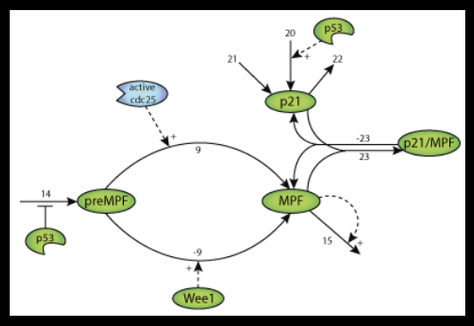


Metabolism

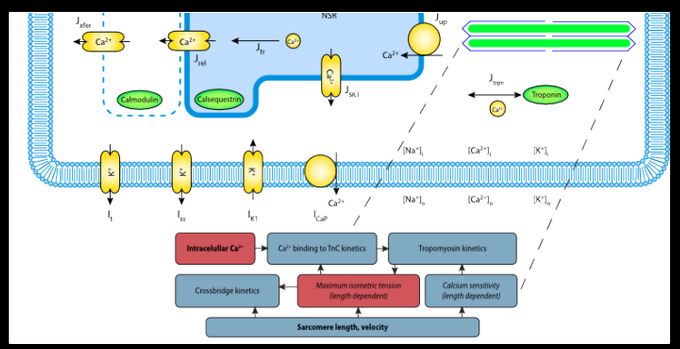


Gene regulation DNA repair

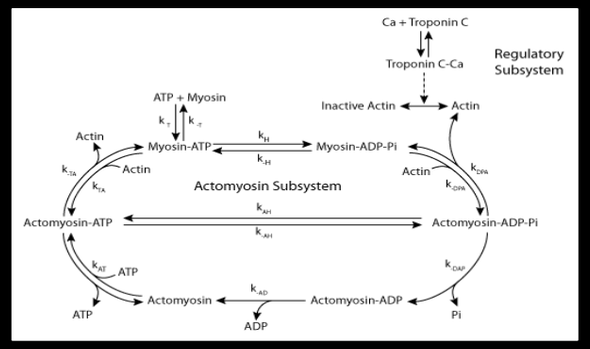




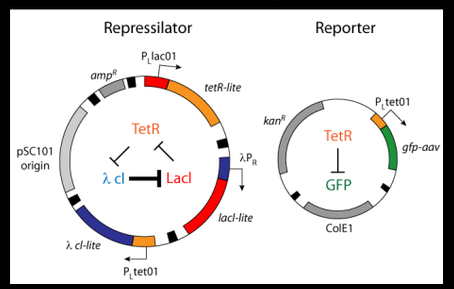
Excitation-contaction

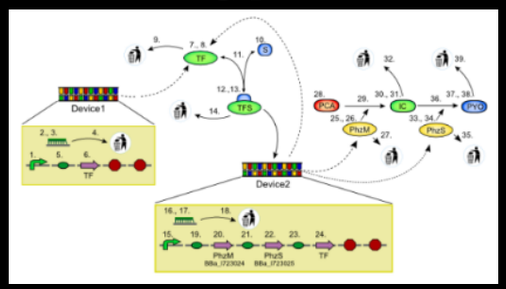


Myofilament mechanics



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.

Continuum physics

Meter
- **Solid mechanics** (Finite elasticity): $det\boldsymbol{F}^T\boldsymbol{F} = 0 \quad \tau^{ij}\Big|_i = f^j \quad \boldsymbol{\tau^{ij}} = f(\boldsymbol{e_{ij}})$
- **Fluid mechanics** (Navier-Stokes eqns): $\nabla.\boldsymbol{u} = 0 \quad \frac{D\boldsymbol{u}}{Dt} = \frac{\partial \boldsymbol{u}}{\partial t} + \boldsymbol{u}.\nabla\boldsymbol{u} = -\frac{1}{\rho}\nabla p - \nabla.(-\nu\nabla\boldsymbol{u})$

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): $\nabla.E = \frac{\rho}{\epsilon} \quad \nabla.B = 0$

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

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

Units for biophysically based modelling

7 units:

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

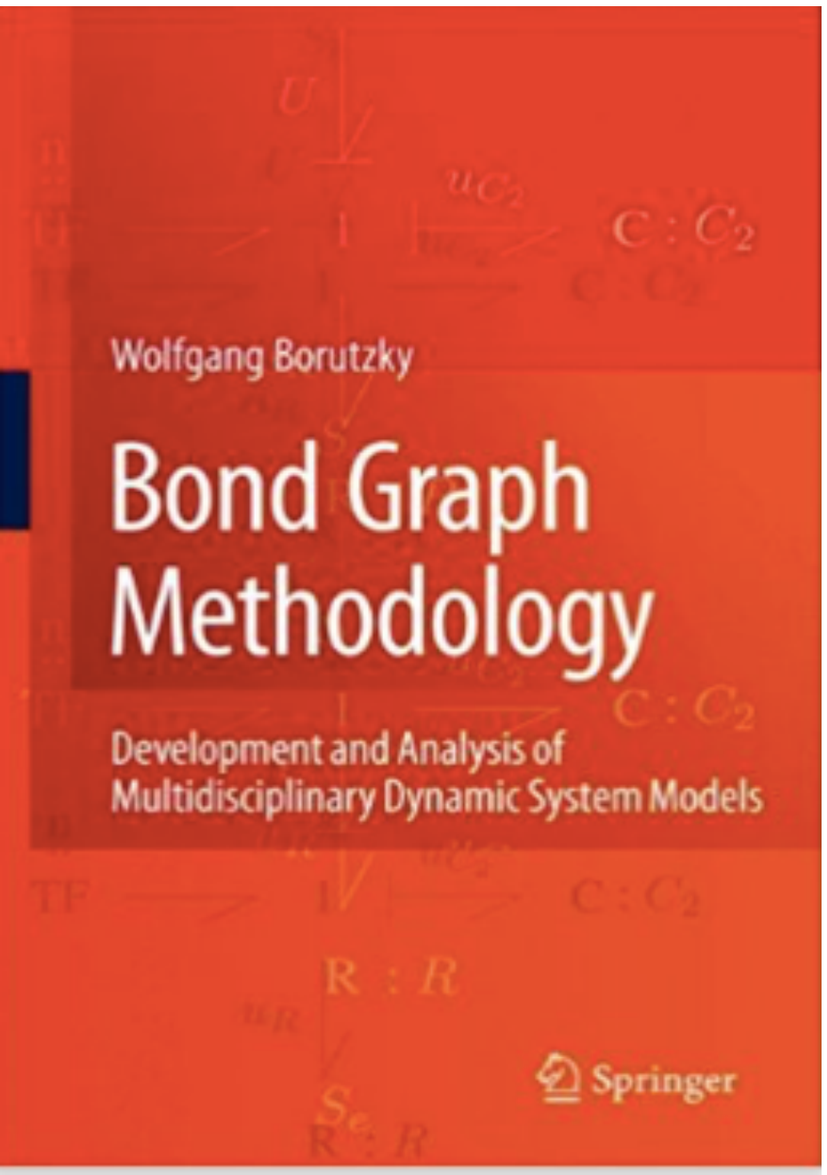
} space-time + energy

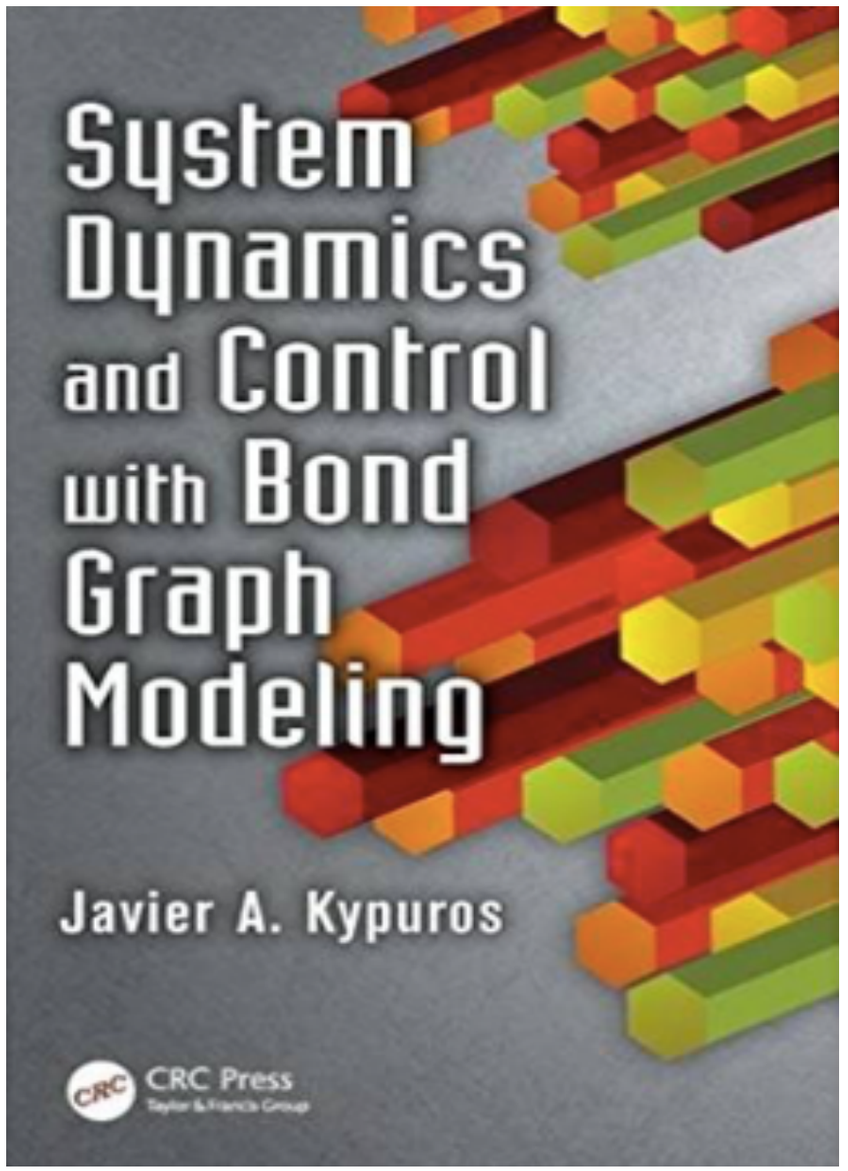
- Coulomb (C) - count electrons
- Candela (Cd) - count photons
- Mole (mol) - count atoms
- Entropy (e) - count probable states

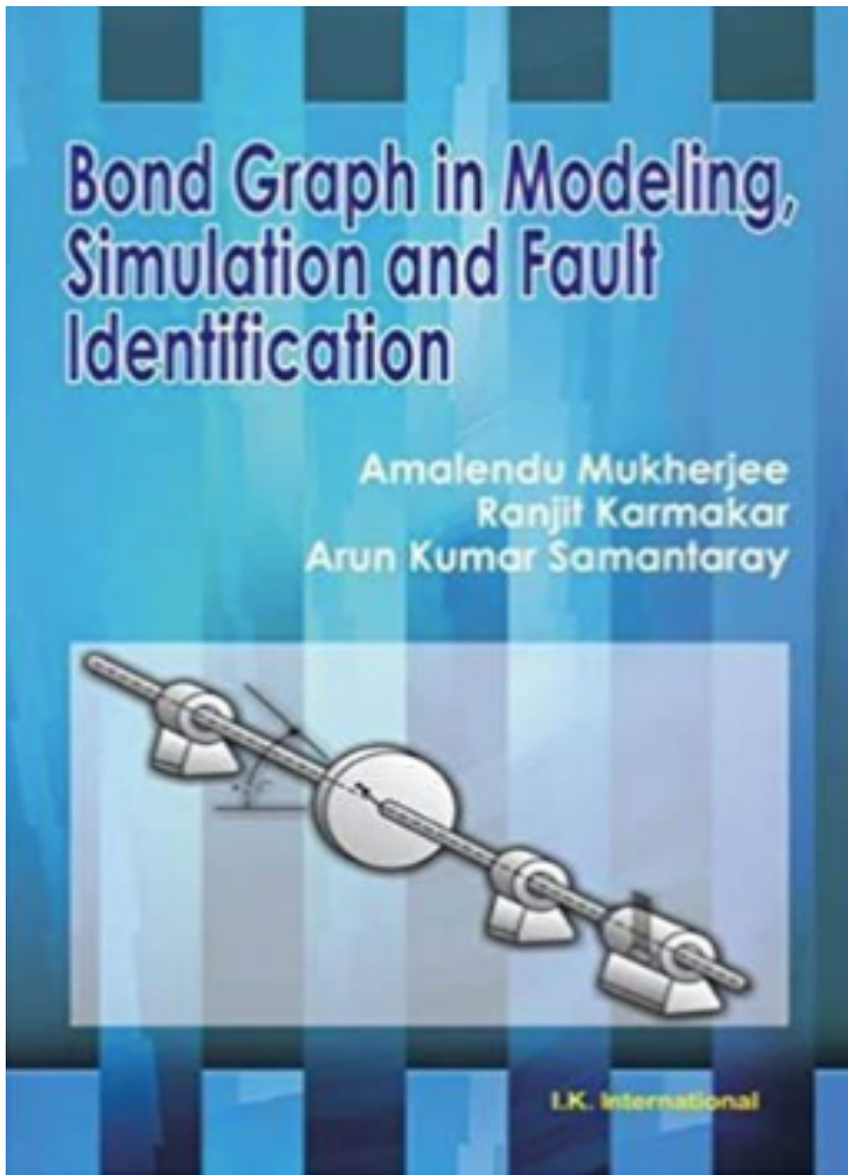
1. Mechanics (J,s,m,e): (i) Solids; (ii) Fluids
2. Electro-physiology (J,s,C)
3. Heat transfer (J,s,e)
4. Signalling pathways (J,s,b,e)
5. Metabolic pathways (J,s,mol)
6. Membrane transporters (J,s,mol,C): (i) neutral; (ii) electrogenic; (iii) ATPase
7. Electro-magnetic (J,s,C,Cd)

"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

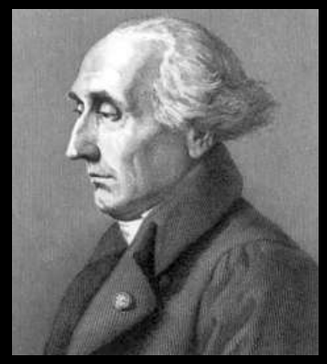
u is **temperature** (*deg K*)=**entropic potential** ($J.e^{-1}$)

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

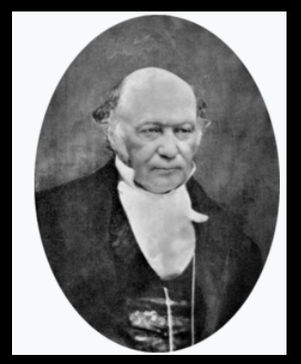
Information flow

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

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



Joseph-Louis Lagrange
(1736-1813)



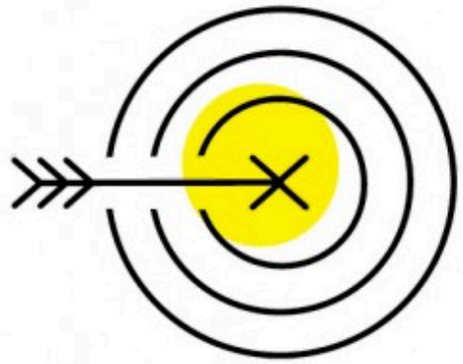
William Rowan Hamilton
(1805 – 1865)

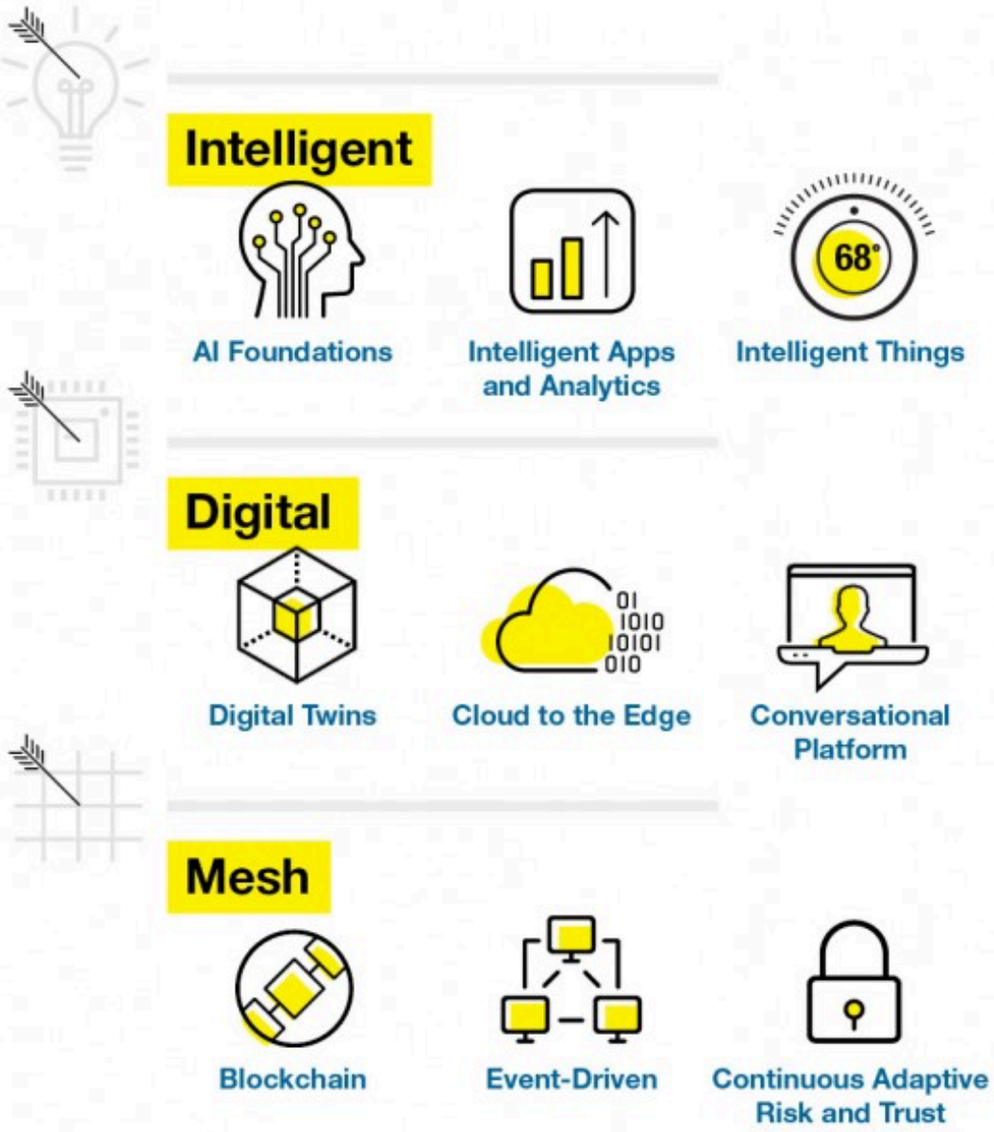
Take home message 2

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 our understanding of the salmon without making use of tools that are designed for taming such complexity?

Top 10 Strategic Technology Trends for 2018

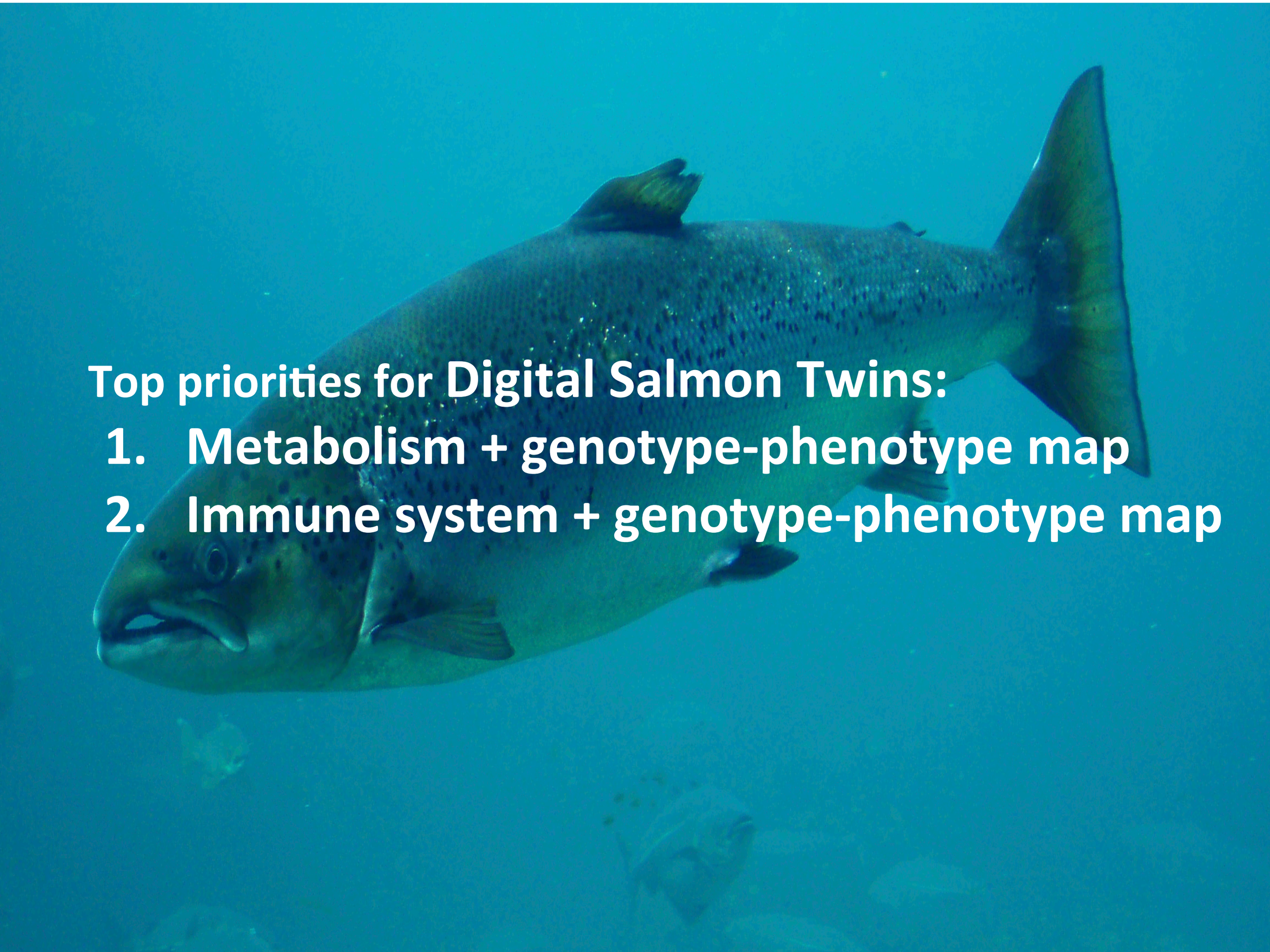




gartner.com/SmarterWithGartner

Gartner

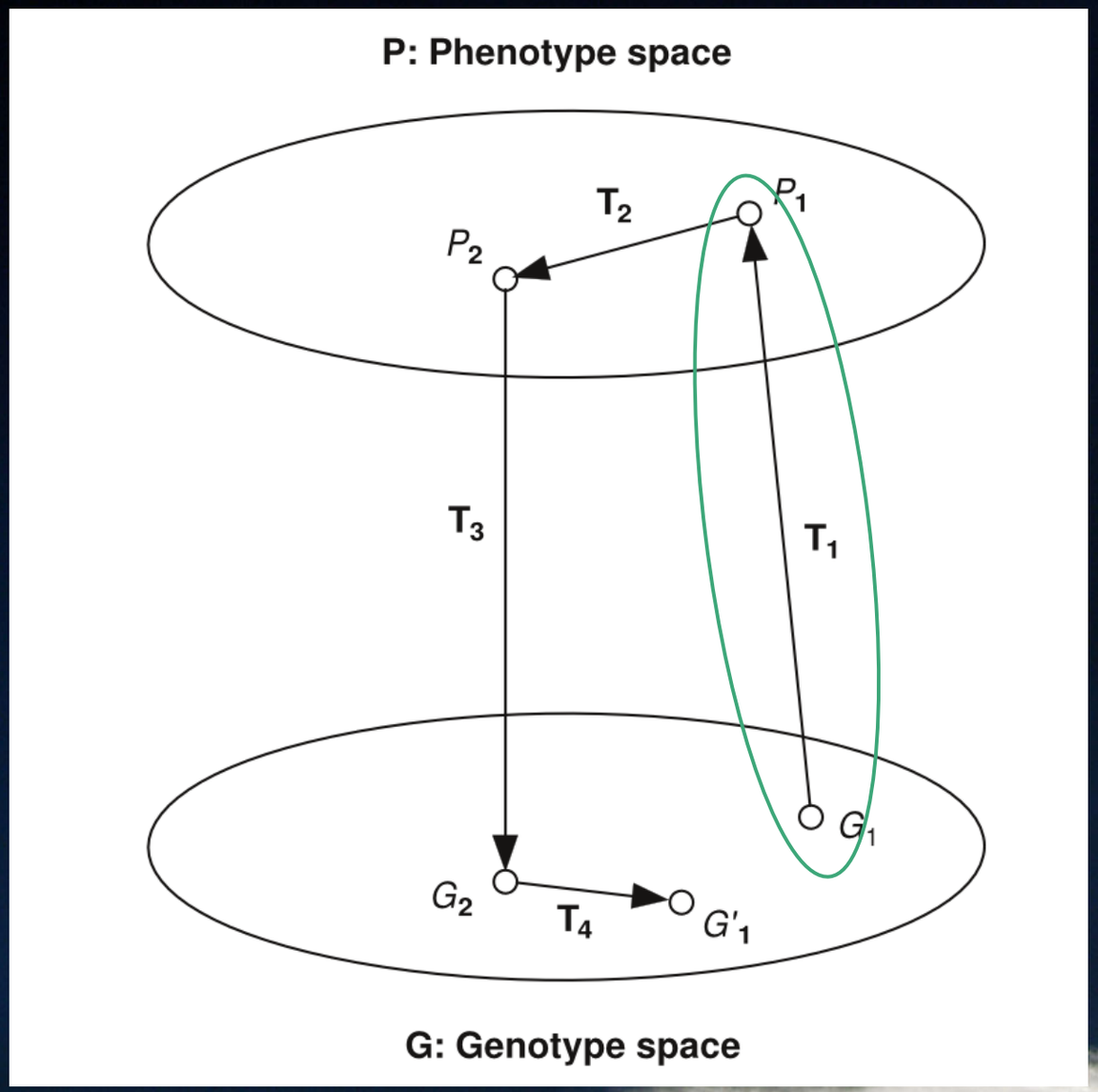
"A Digital Twin is a dynamic software model of a physical thing or system"



Top priorities for Digital Salmon Twins:

1. Metabolism + genotype-phenotype map
2. Immune system + genotype-phenotype map

Structure of genetic theory



R. C. Lewontin (1974): The genetic basis of evolutionary change

DOI: 10.1534/genetics.108.087064

When Parameters in Dynamic Models Become Phenotypes: A Case Study on Flesh Pigmentation in the Chinook Salmon (*Oncorhynchus tshawytscha*)

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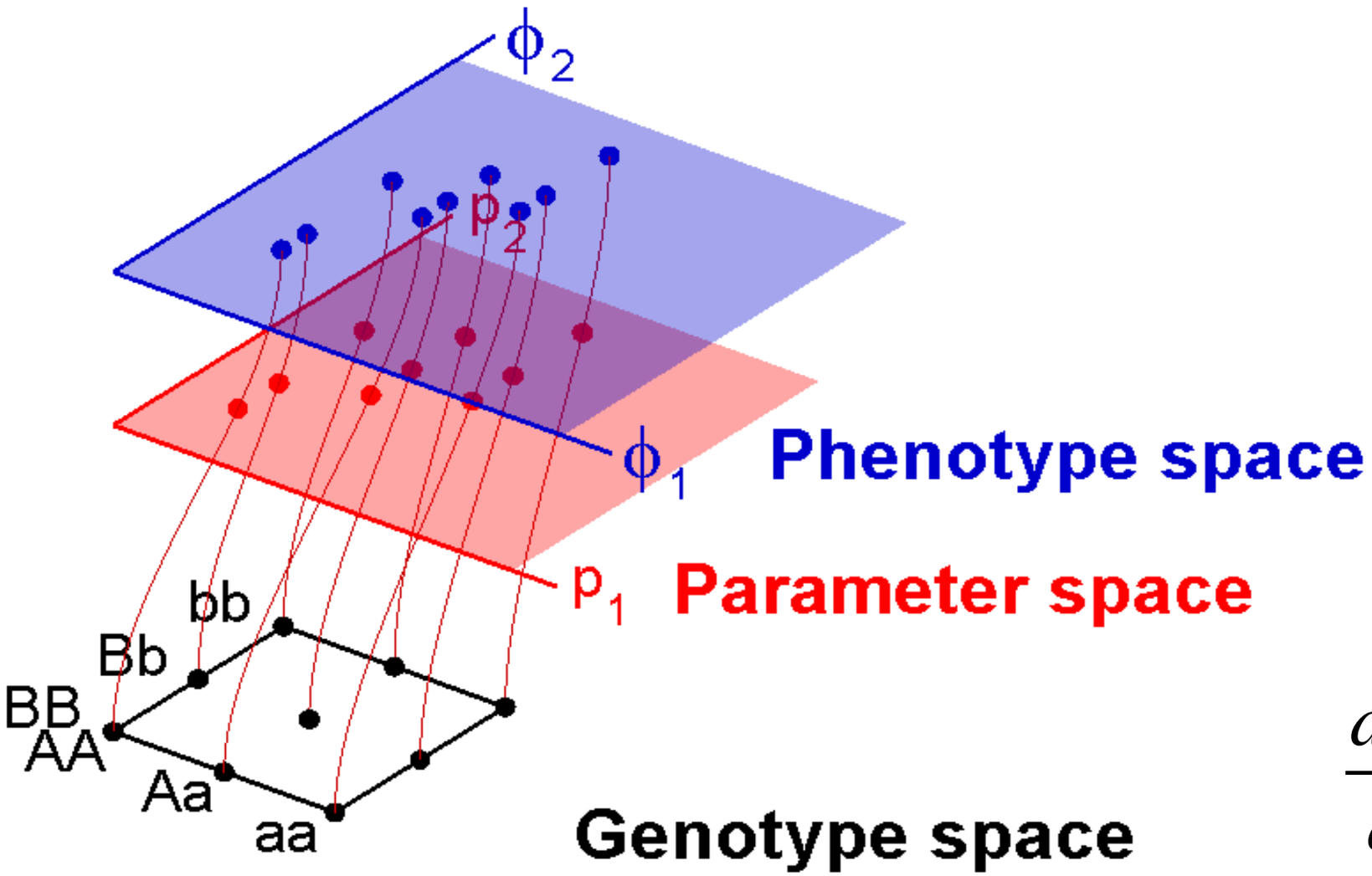
Centre for Integrative Genetics (CIGENE) and Department of Animal and Aquacultural Sciences, Norwegian University of Life Sciences, N-1432 Ås, Norway



$$\frac{d\phi_1}{dt} = p_1\phi_2 - \beta_1\phi_1$$

$$\frac{d\phi_2}{dt} = p_2\phi_1 - \beta_2\phi_2$$

Causally cohesive genotype-phenotype models

- Mathematical models describing how phenotypes arise from lower level processes in a causally cohesive way
- Genetic variation tied to model parameters
- Population of dynamic systems connected to genetic maps

The excuse…

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The genotype-phenotype map for a given environment is incredibly predictable!

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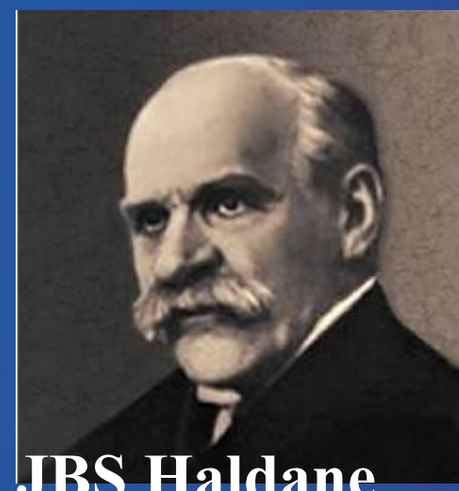
Heritability concept

$$R = h^2 S$$

Ronald Fisher (1890-1962)



JBS Haldane (1892-1964)

Sewall Wright (1889-1988)

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Effect of Regulatory Architecture on Broad versus Narrow Sense Heritability

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Genetics (CIGENE), Department of Mathematical Sciences and Technology, Norwegian University of Life Sciences, Ås, Norway, **3** NTNU Norwegian Uni
and Technology, Department of Biology, Centre for Biodiversity Dynamics, Realfagsbygget, NO-7491 Trondheim, Norway

$$V_P = V_G + V_E$$

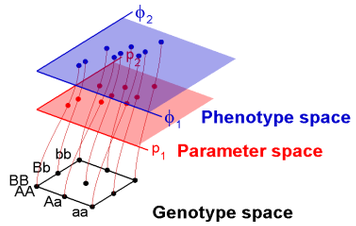
$$V_G = V_A + V_D + V_I$$

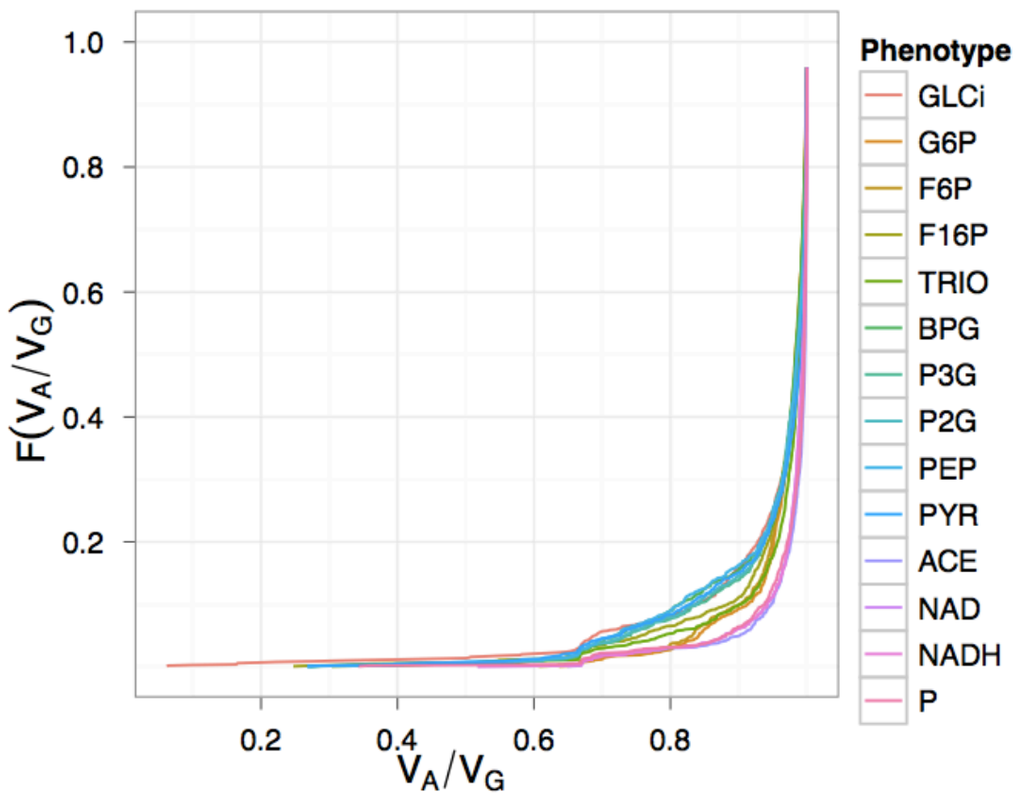
$$h^2 = \frac{V_A}{V_P}$$

$$H^2 = \frac{V_G}{V_P}$$

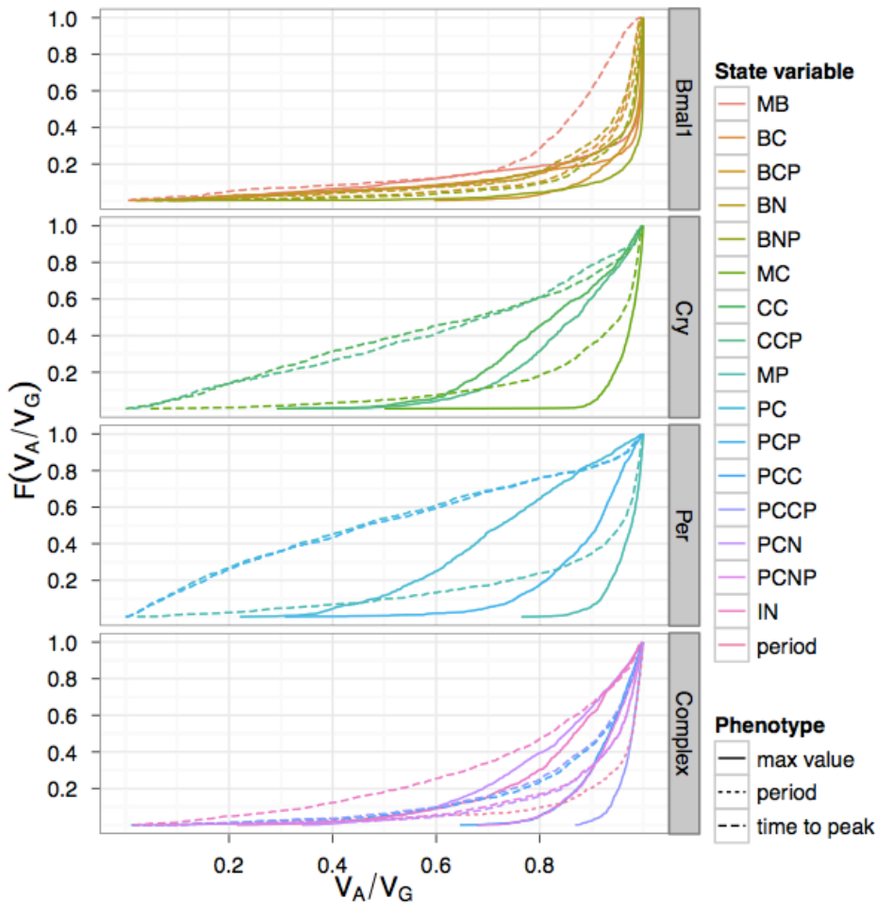
$$\frac{h^2}{H^2} = \frac{V_A}{V_G}$$

Glycolysis

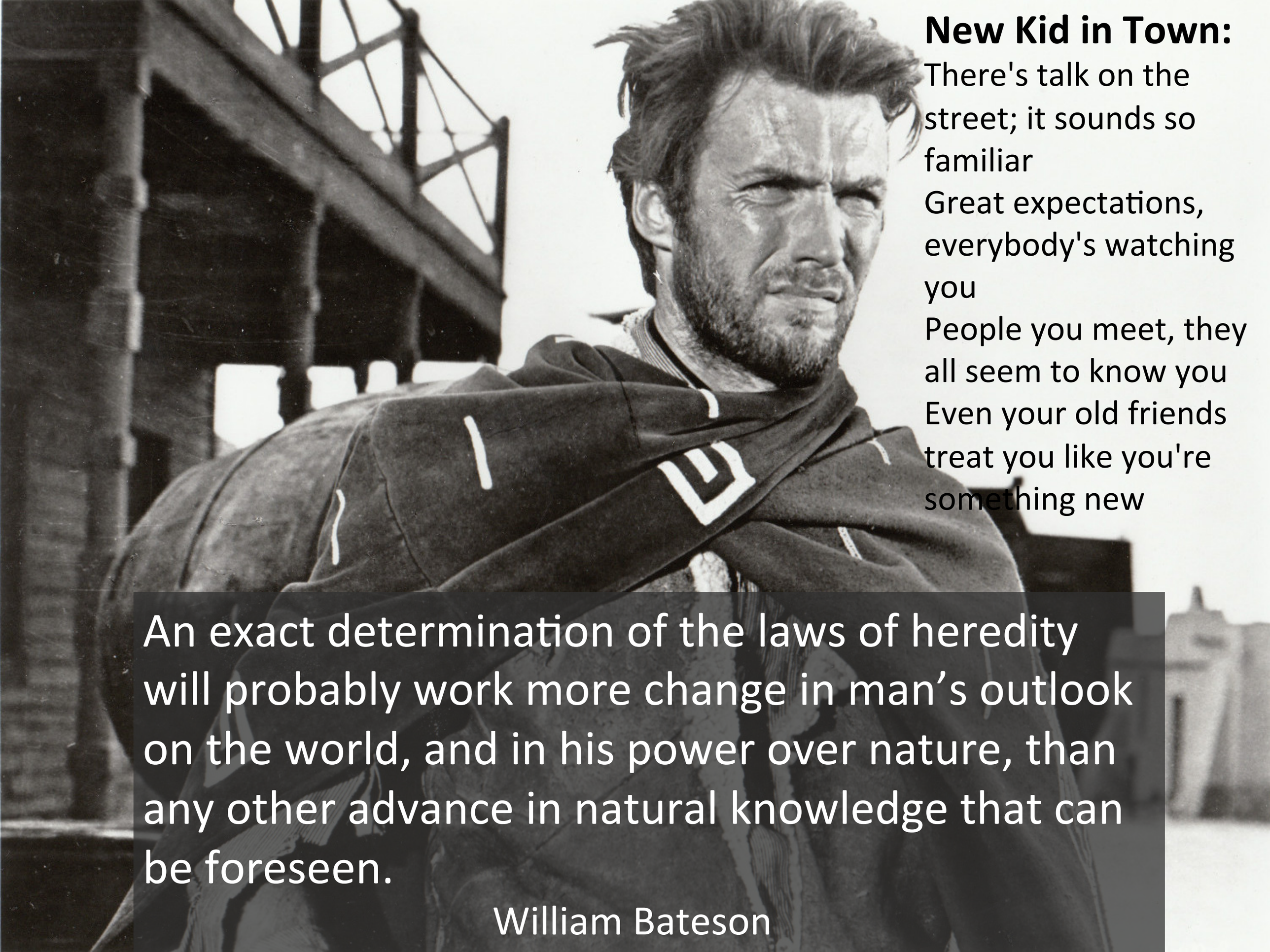




Circadian clocks



Nature, nurture, dynamics and monotonicity

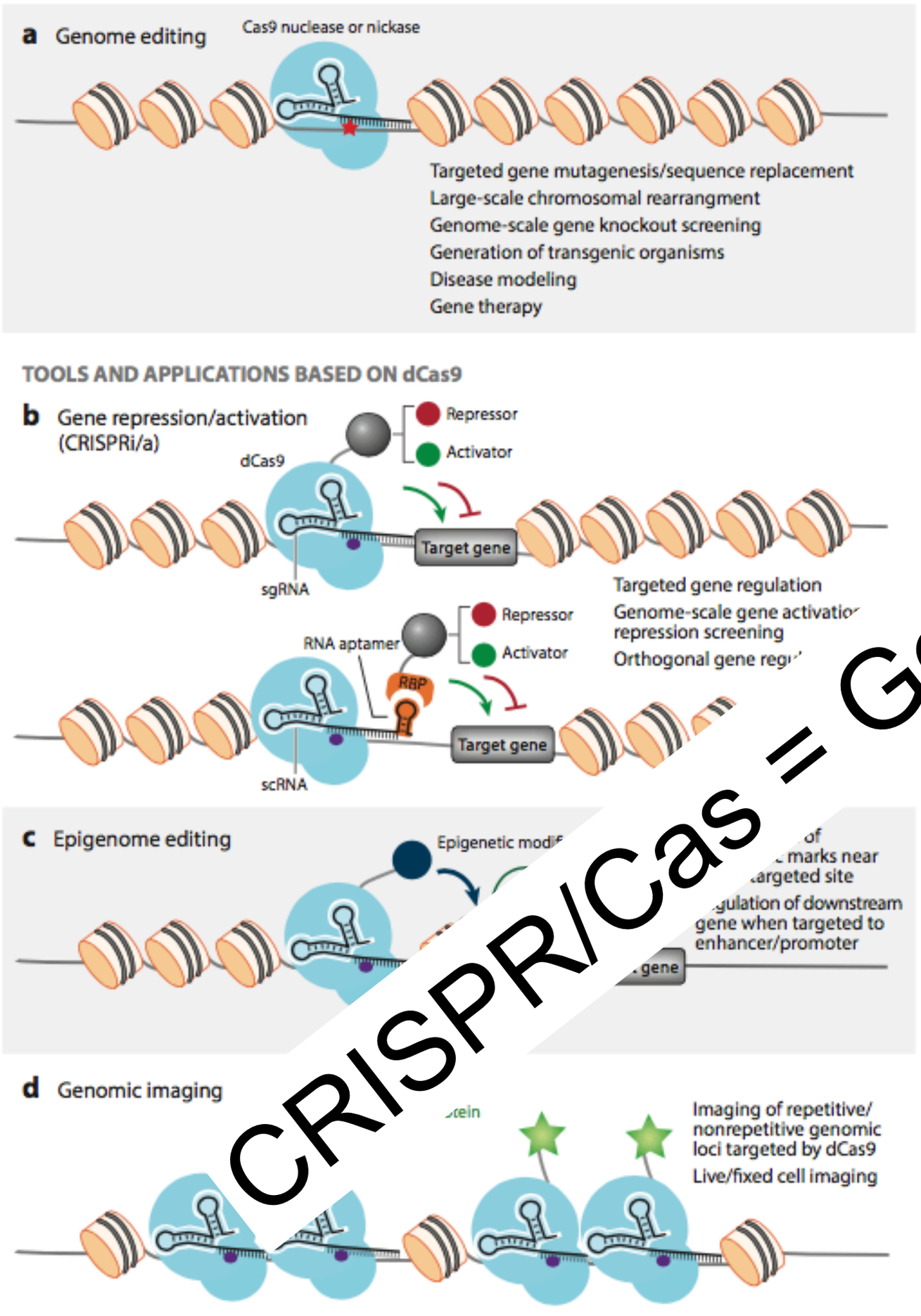


New Kid in Town:

There's talk on the street; it sounds so familiar
Great expectations, everybody's watching you
People you meet, they all seem to know you
Even your old friends treat you like you're something new

An exact determination of the laws of heredity will probably work more change in man’s outlook on the world, and in his power over nature, than any other advance in natural knowledge that can be foreseen.

William Bateson



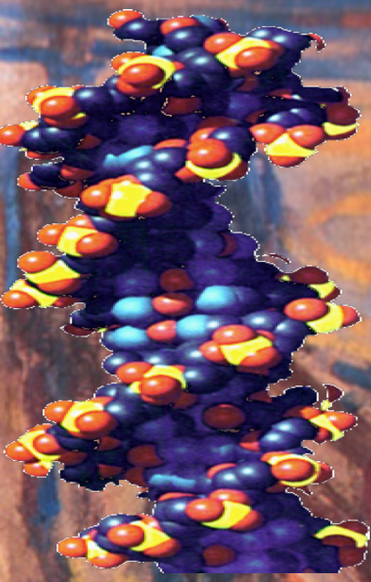
CRISPR (clustered regularly interspaced short palindromic repeats)/Cas (CRISPR-associated protein)

Annu. Review, 2016, 85:227

CRISPR/Cas = Genome editing

CRISPR GENOME EDITING

- Cas9 FOR GENE REGULATION
- Cas9 FOR EPIGENOME EDITING
- Cas9 FOR GENOMIC IMAGING
- Cas9 FOR STUDYING ENDOGENOUS PROTEIN–GENOME INTERACTIONS AT SPECIFIC LOCI



Is there a neat genetic solution to the sea louse problem?

'Mindblowing . . .
a masterpiece'
Chris Anderson,
author of The Long Tail

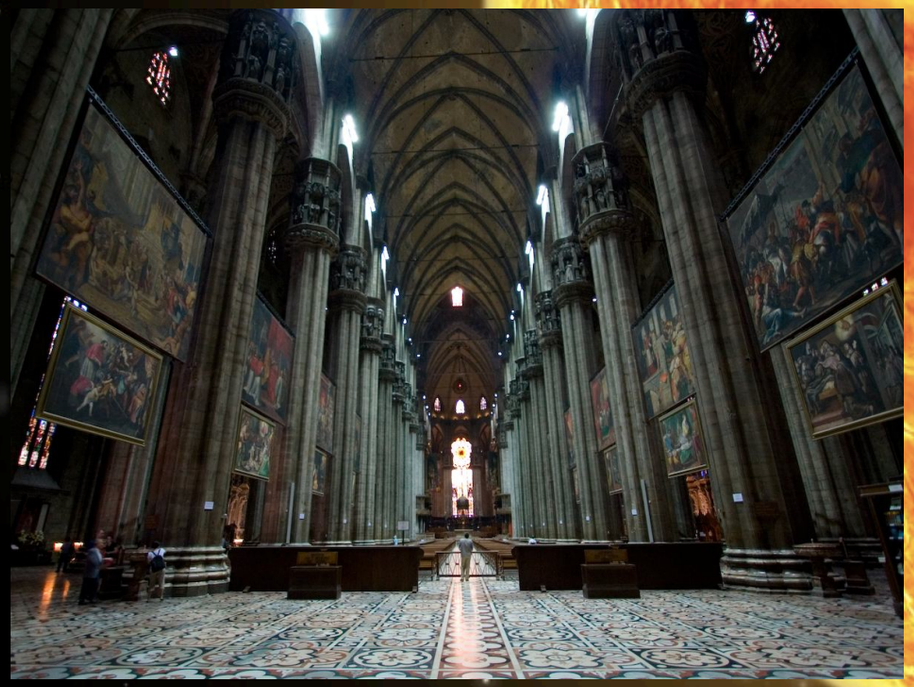
'Hugely enjoyable –
compelling'
Financial Times

The Black Swan

The Impact of the Highly Improbable

Nassim Nicholas Taleb

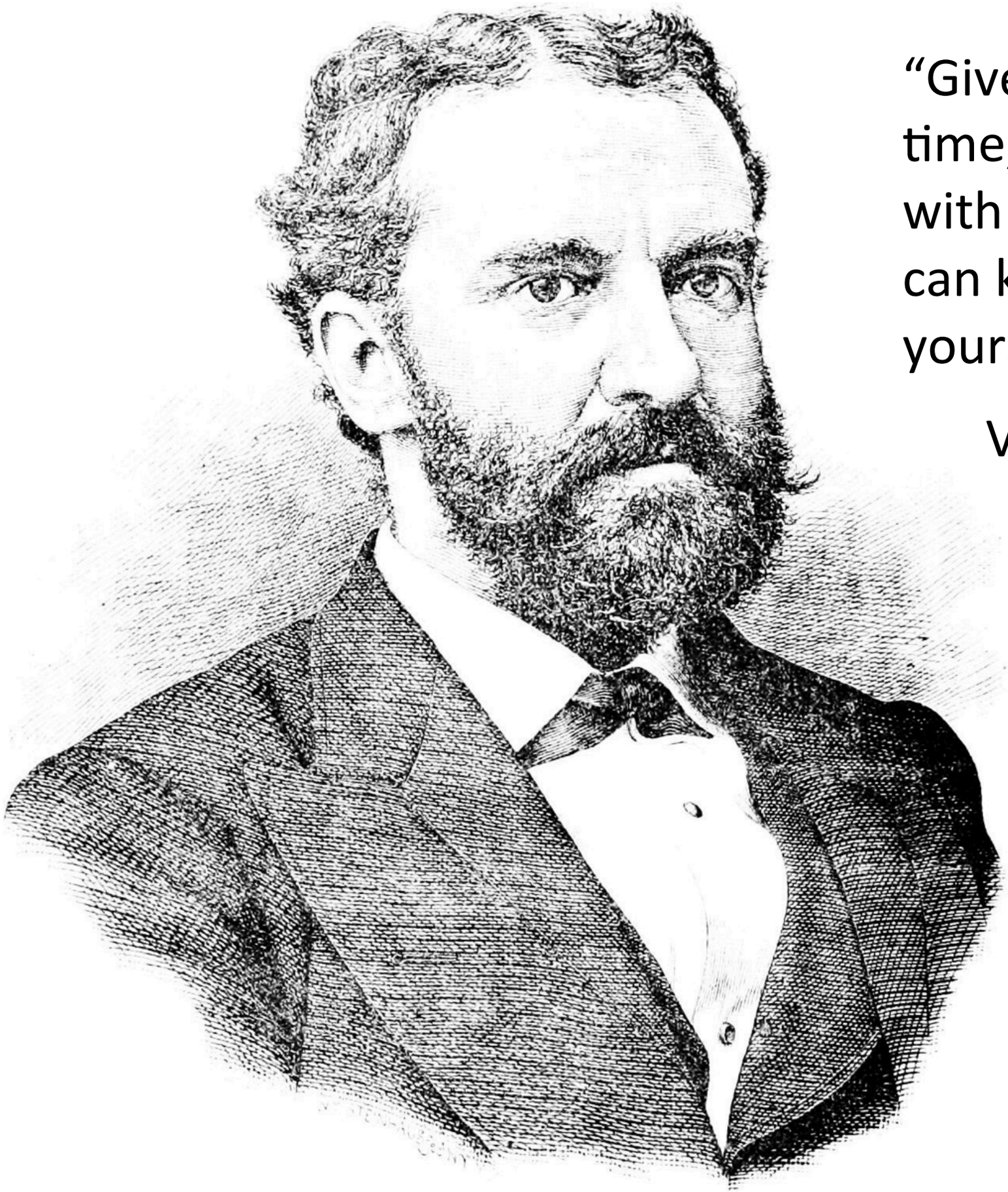

BØRSEN



Take home message: 3

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 by computational physiology
- Remember old Norwegian saying