Modelling and Biological Systems

Hyperboost Training Course Model-based Data Analysis for Clinical Applications

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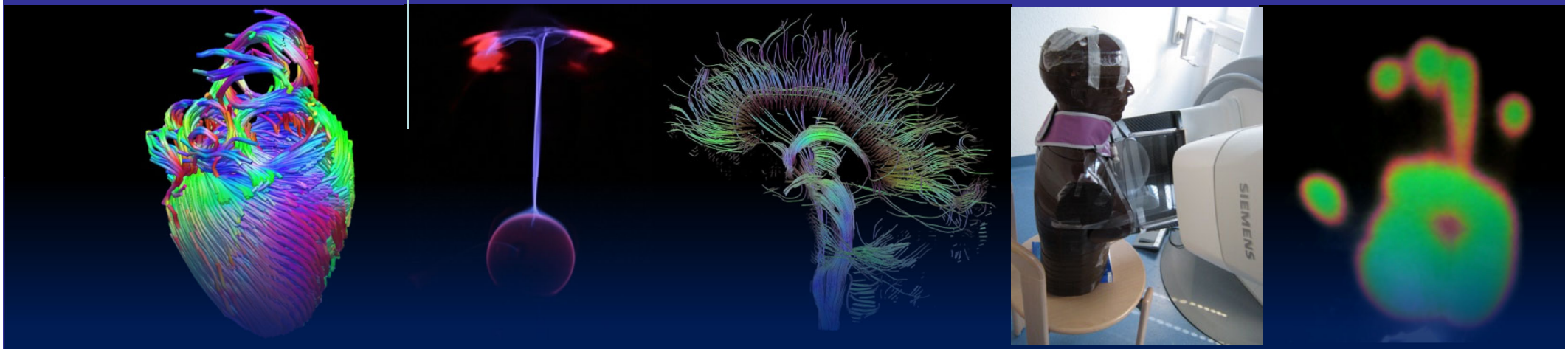
Medical Biophysics Group ZHAW
2024



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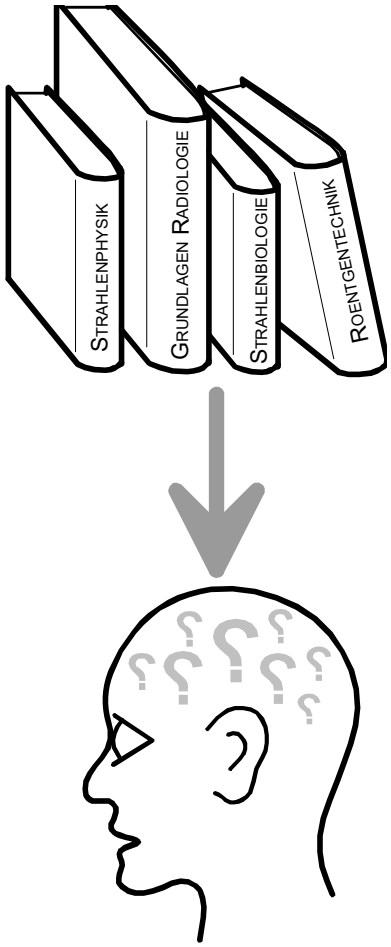


Model-based data analysis for clinical application – Modelling and Biological Systems:

Day 1

0920-1100: Modelling and Biological Systems

1320-1400: Using Graphical Model Editors

1400-1450: Using Python for Model Fitting

Day 2

1110-1200: Biokinetic / Biodynamic Modelling (→ Lab2: Model-based Data Analysis of PET Images)

Day3

0900-1100: Radiobiological Models

Learning Objectives

Students are able

- To be aware of the different purposes of modelling
- to explain the assumption for compartmental models
- to model compartmental biological systems and explore them by using computer simulations
- to use models for biological data analysis
- To use modelling and computer simulation as in silico lab tools

About Systems, Data & Models

Systems Biophysics – Systems Medicine – a Landscape

Concepts:
Illness, disease
Body as mechanism
Compartments
Life as process
emergence

Theory:
Physiology,
Pathophysiology
Systems theory of
- *Cancer*
- *Immune system*
- *…*

Math. Models:
Events, MC
Statistic mechanical
Compartmental
(neuronal) networks
Spatio-tempral

Data

Clinical observations

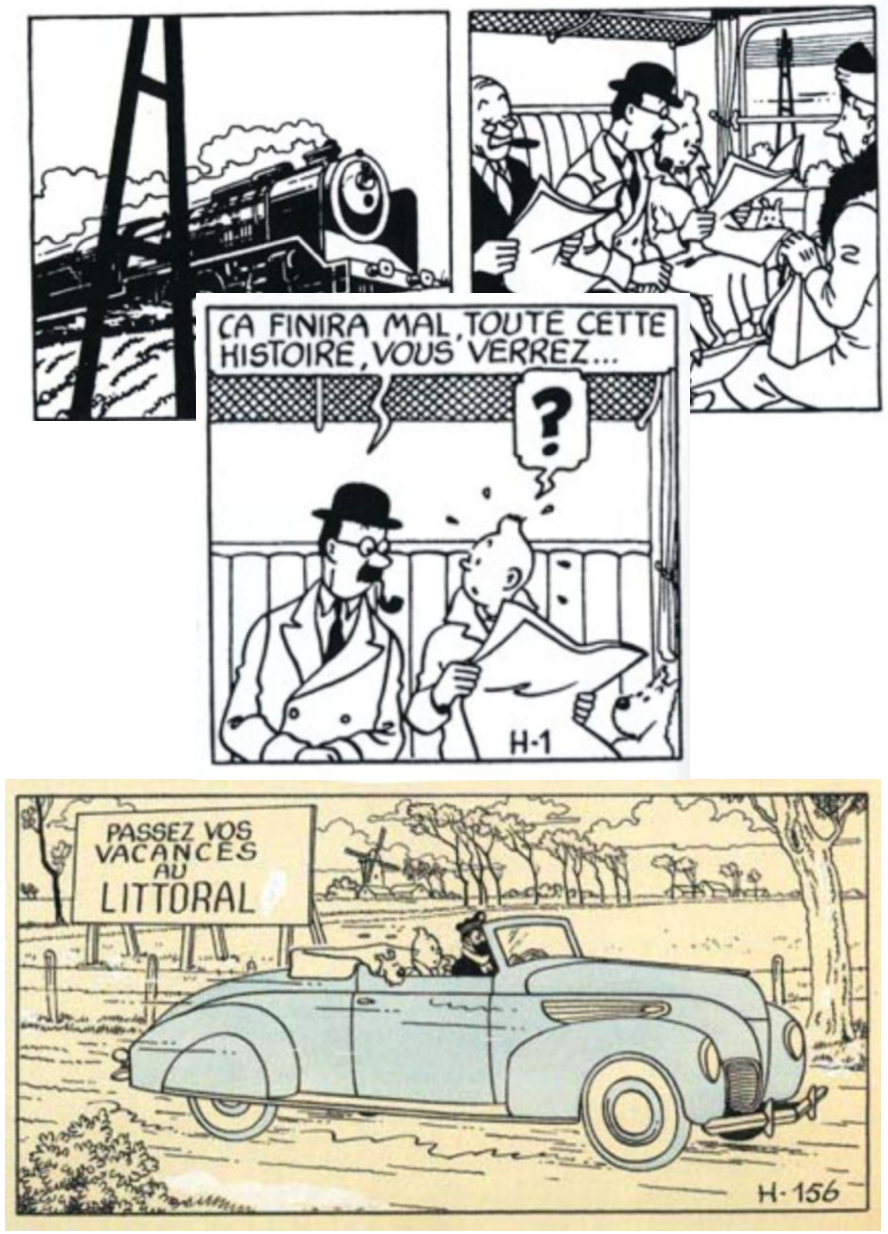
clinical trials

Experiments In vivo

Experiments In vitro

Experiments In silico

Biomedical Systems ?



Systems Science and Medicine…

- Do we have the adequate concepts to understand disease and treatment?
- Usually, clinical trials compare drug with placebo, before and after, but do not tell the story!
- Dynamics of involved processes (life!) are often not in the «field of view»
- How to catch the story …


JE COMPRENDS! C'EST NOTRE AMI RASCAR CAPAC QUI A EFFRAYÉ VOTRE CHIEN!... RASCAR CAPAC: CE LUI-QUI-DÉCHAÎNE-LE-FEU-DU-CIEL.
BANG
MON DIEU!... LA MOMIE!...
TIENS, TIENS, QU'EST-CE QUE C'EST QUE ÇA?...
UN BRACELET!... SAPRISTI! MAIS C'EST CELUI QUI SE TROUVAIT AU BRAS DE CETTE MOMIE!... C'EST CURIEUX... COMMENT CET OBJET EST-IL ARRIVÉ ICI?...

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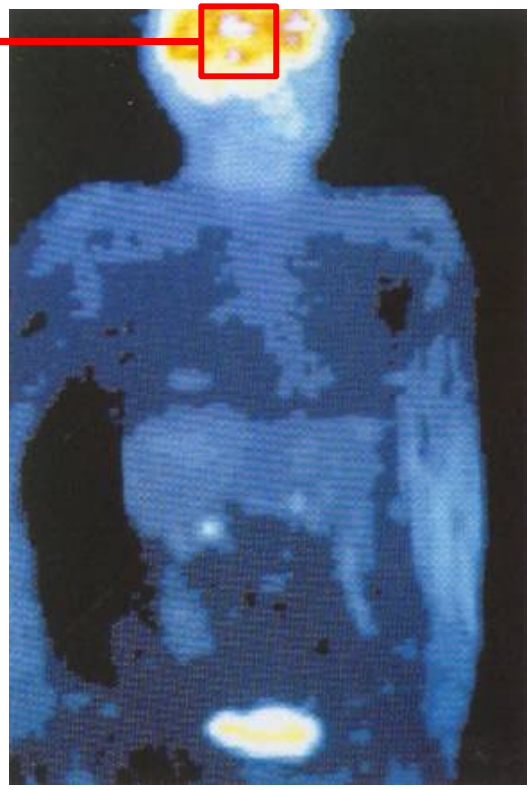
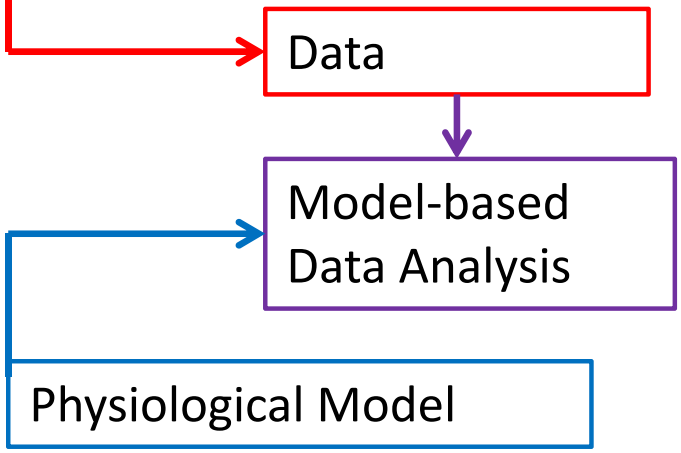




Catch the dynamics:

Model-based data analysis may reveal the processes responsible for outcome

- Example 1: Analysis of time-resolved biokinetic data (elimination)
- Example 2: Multi-process repair dynamics

Mechanism vs. process: Biological systems are not only dynamic but have high plasticity! Mechanistic or dynamic view?

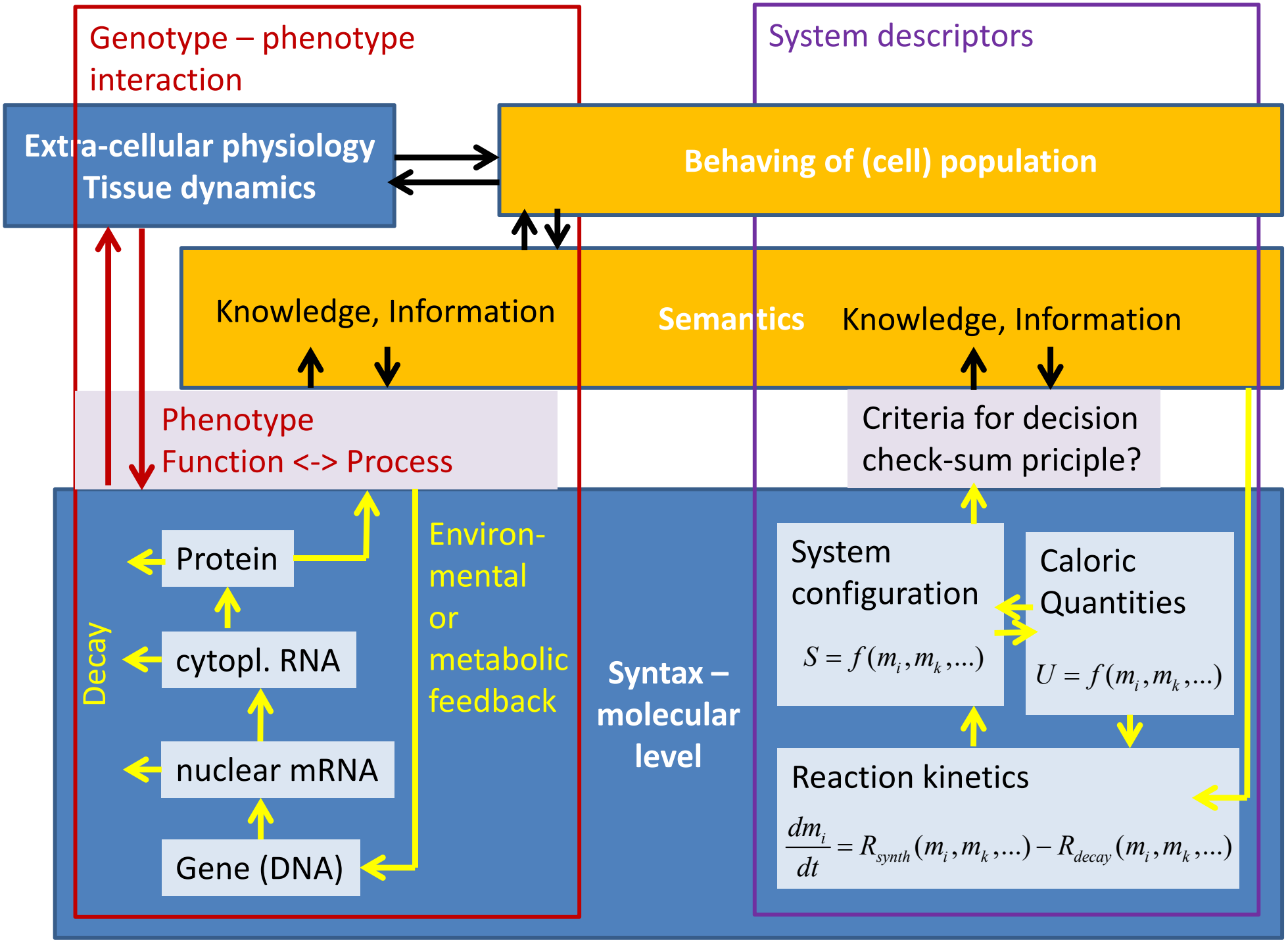
Comparison of outcomes may generate knowledge, but - in case of complex systems - not understanding!

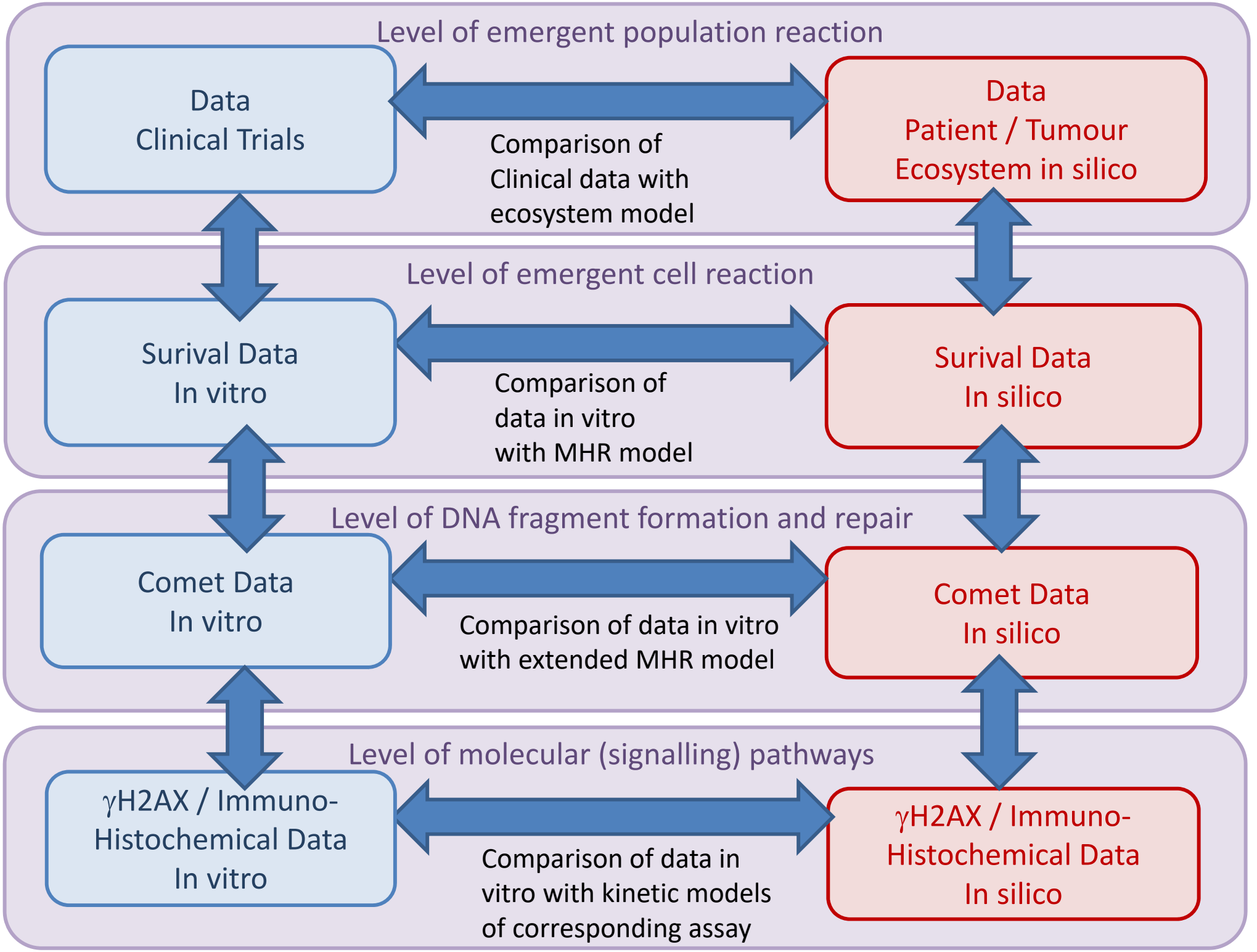
The Scales of Life

This is not a Teddy Bear – this is only a picture!

- Interpretation of colored patches requires semantics
- Semantics in living systems is an emergent phenomenon
- Emergence is a result of dynamics in a complex system!
  → without dynamics – no life!
- Syntax of life is more related to the molecular level

Fig.1. A sketch of a living system with some essential "sub-systems"


Genotype – phenotype interaction
System descriptors
Extra-cellular physiology
Tissue dynamics
Behaving of (cell) population
Knowledge, Information
Semantics
Knowledge, Information
Phenotype
Function <-> Process
Criteria for decision
check-sum priciple?
Protein
cytopl. RNA
nuclear mRNA
Gene (DNA)
Decay
Environ-
mental
or
metabolic
feedback
Syntax –
molecular
level
System
configuration
$S = f(m_i, m_k, ...)$
Caloric
Quantities
$U = f(m_i, m_k, ...)$
Reaction kinetics
$\frac{dm_i}{dt} = R_{synth}(m_i, m_k, ...) - R_{decay}(m_i, m_k, ...)$


Level of emergent population reaction
Data
Clinical Trials
Comparison of
Clinical data with
ecosystem model
Data
Patient / Tumour
Ecosystem in silico
Level of emergent cell reaction
Surival Data
In vitro
Comparison of
data in vitro
with MHR model
Surival Data
In silico
Level of DNA fragment formation and repair
Comet Data
In vitro
Comparison of data in vitro
with extended MHR model
Comet Data
In silico
Level of molecular (signalling) pathways
γH2AX / Immuno-
Histochemical Data
In vitro
Comparison of data in
vitro with kinetic models
of corresponding assay
γH2AX / Immuno-
Histochemical Data
In silico

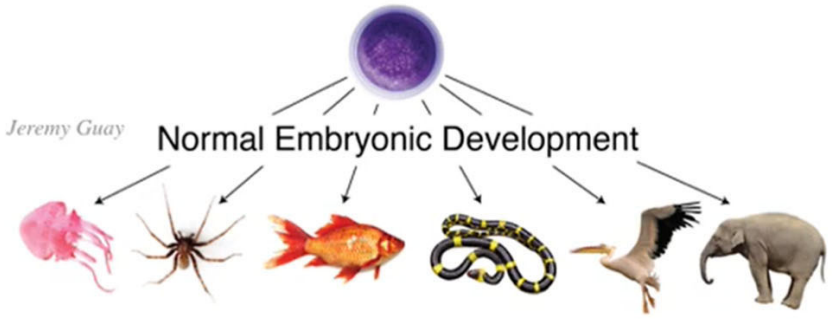
Anatomy and Function

Anatomy is evolved – design follows function.

- Biolgical systems have remarkable structural and functional plasticity and robustness ("anatomical homeostasis", top-down control of collective outcomes
- Bioelectric networks seems to be a way how evolution has expanded computational boundaries of cells into organisms (re-programmability: hardware vs. software!)
- Hypothesis (formulated by Michael Levin[1]): "multiscale autonomy of goal-seeking subunits while bringing the risk of cancer (!) is the key to adaptive function and evolvability"

[1]Levin M (2020): Key note lecture, Alife 2020 Conference

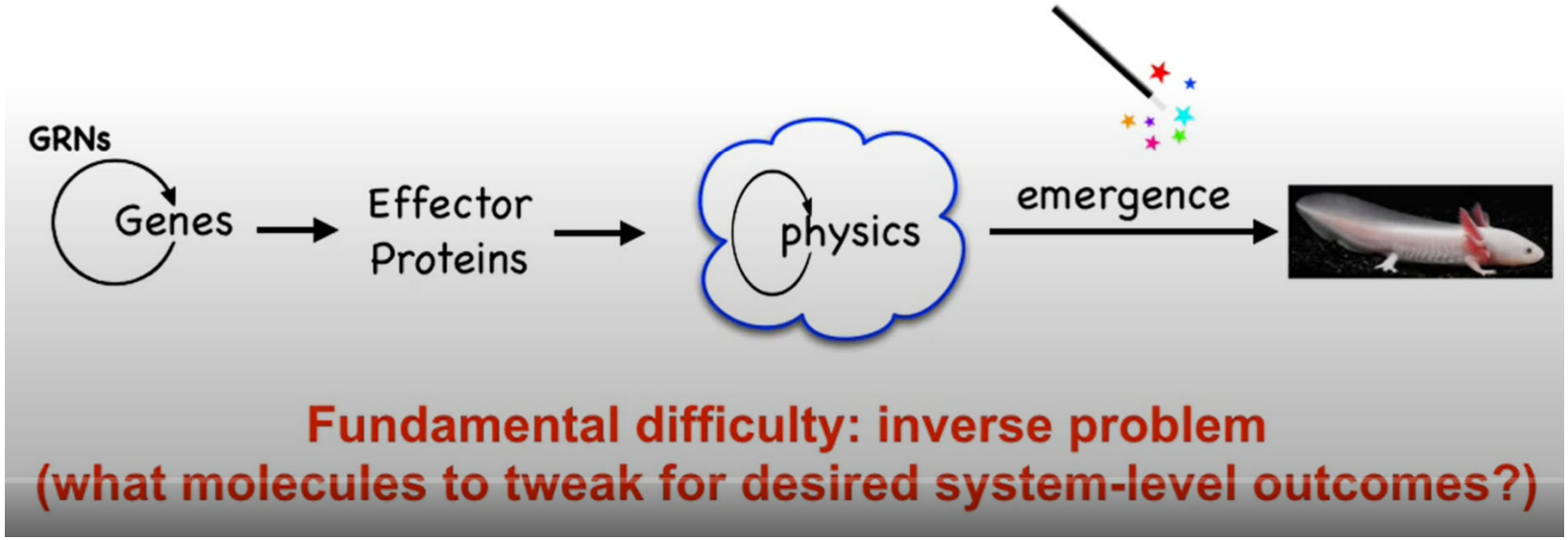
Current Paradigm of Anatomy



Tissues/organs emerge from
- cell differentiation
- cell proliferation
- cell migration
- apoptosis

under progressive unrolling of genome

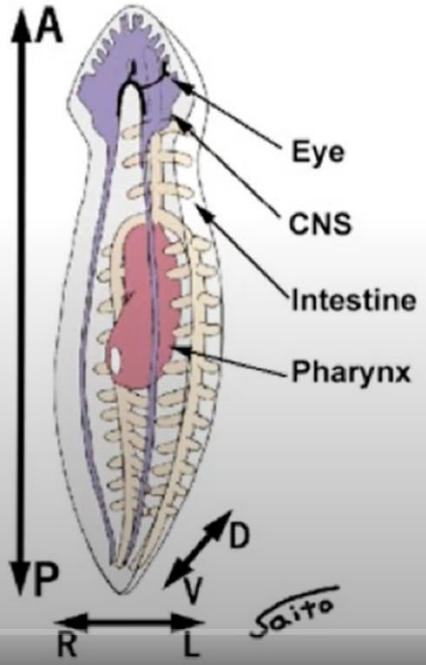
Open Loop system:

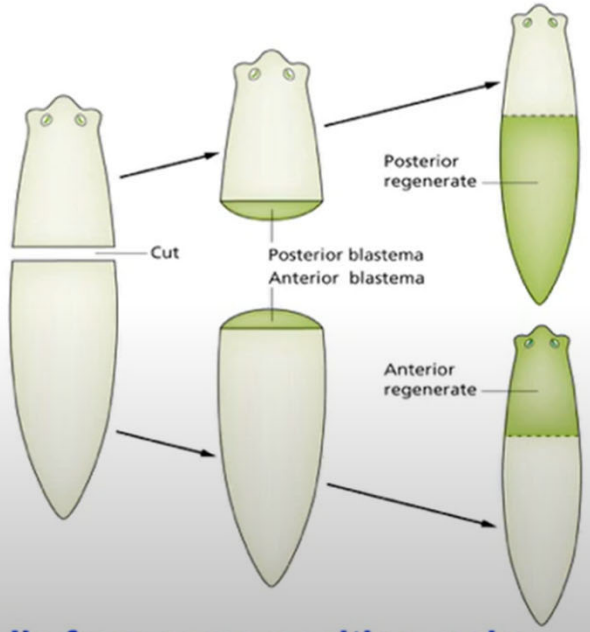


Fundamental difficulty: inverse problem
(what molecules to tweak for desired system-level outcomes?)

[1]Levin M (2020): Key note lecture, Alife 2020 Conference

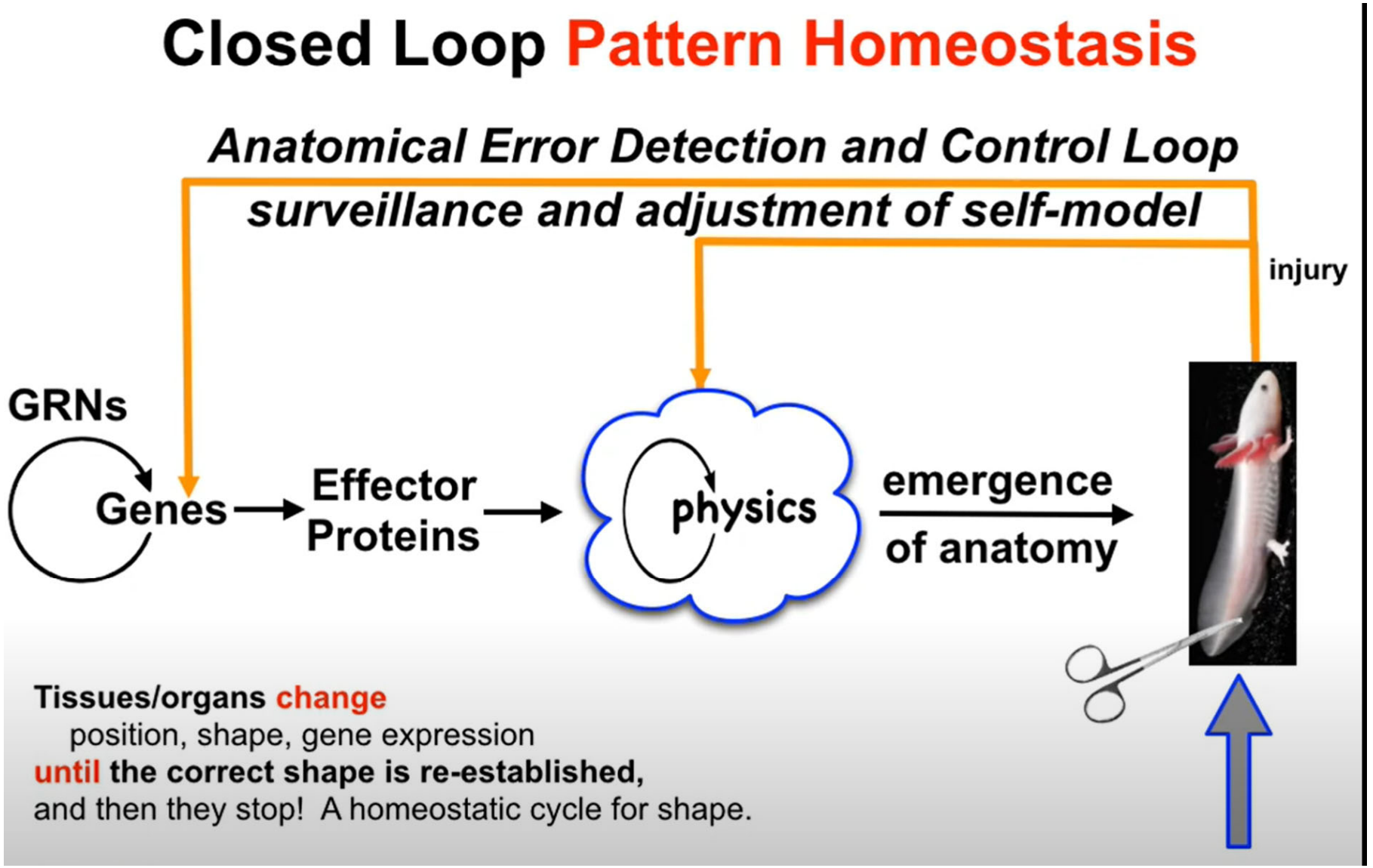
Planarian Regeneration: restoring global order





Cells from same position make radically different structures - non-local decision-making

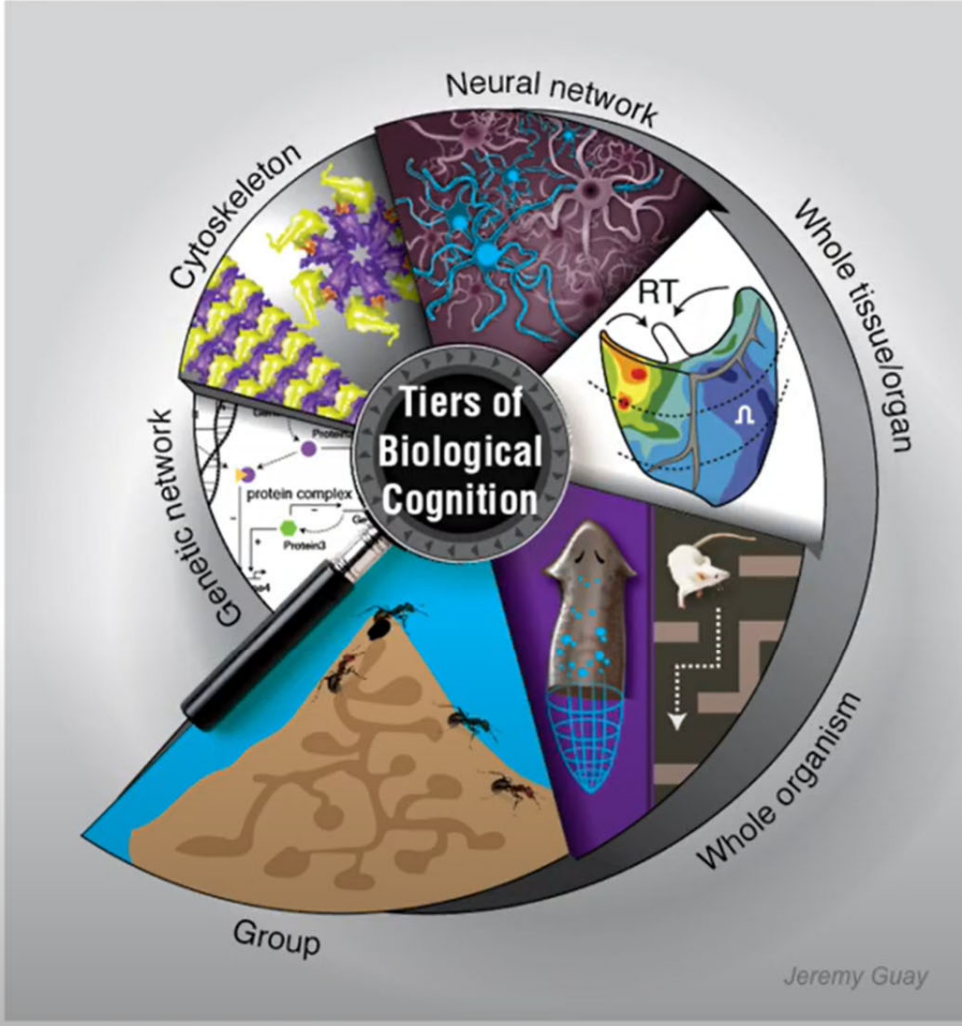
[1]Levin M (2020): Key note lecture, Alife 2020 Conference



[1]Levin M (2020): Key note lecture, Alife 2020 Conference

Developmental Biology <—> Basal Cognition <—> Comp Sci

- Complex decision-making at all levels of biology - **the parts are unreliable but smart**
- Cells and tissues compute during morphogenesis and repair
- Bioelectric networks underlie pattern memories and pattern homeostasis
- Combination of bottom-up emergence AND top-down representation, reprogrammability



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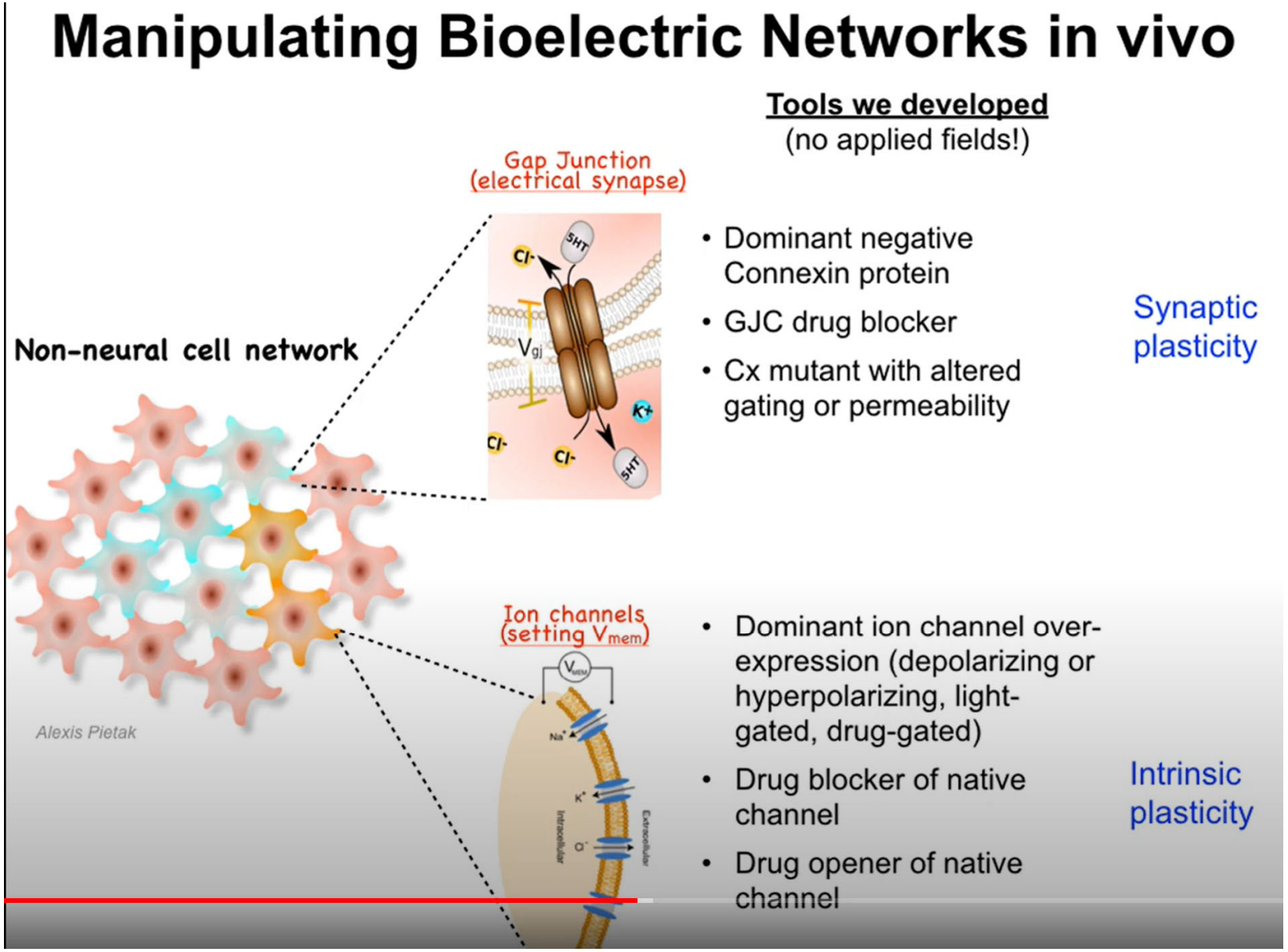
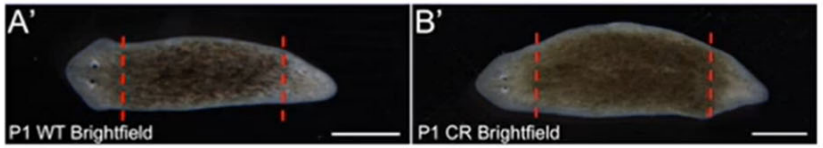
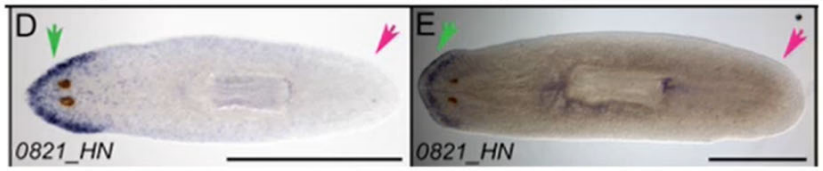


[1]Levin M (2020): Key note lecture, Alife 2020 Conference

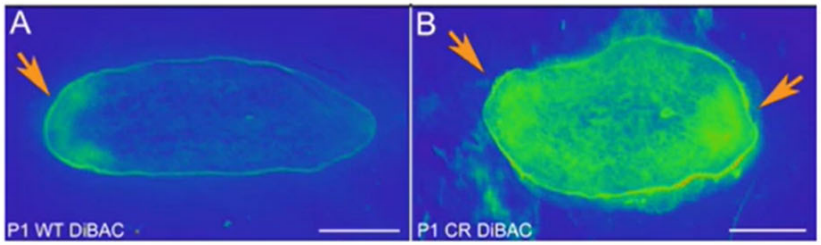
Bioelectrically-Encoded Pattern Memory



normal anatomy



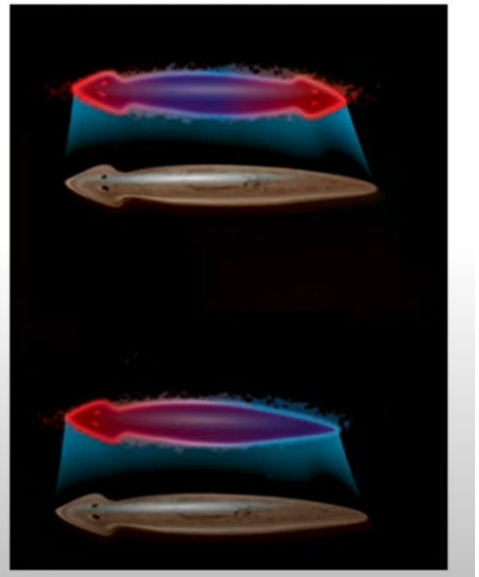
normal molecular histology



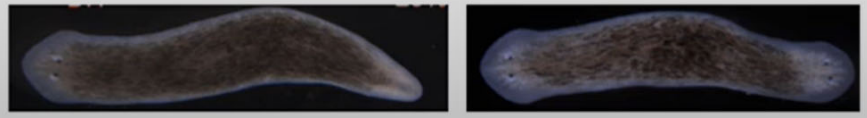
edited bioelectric pattern

We can now directly see the representation of large-scale goal states and re-write those memories!

The Same Body can Store different Electrical Pattern Memories



middle-third regenerates:



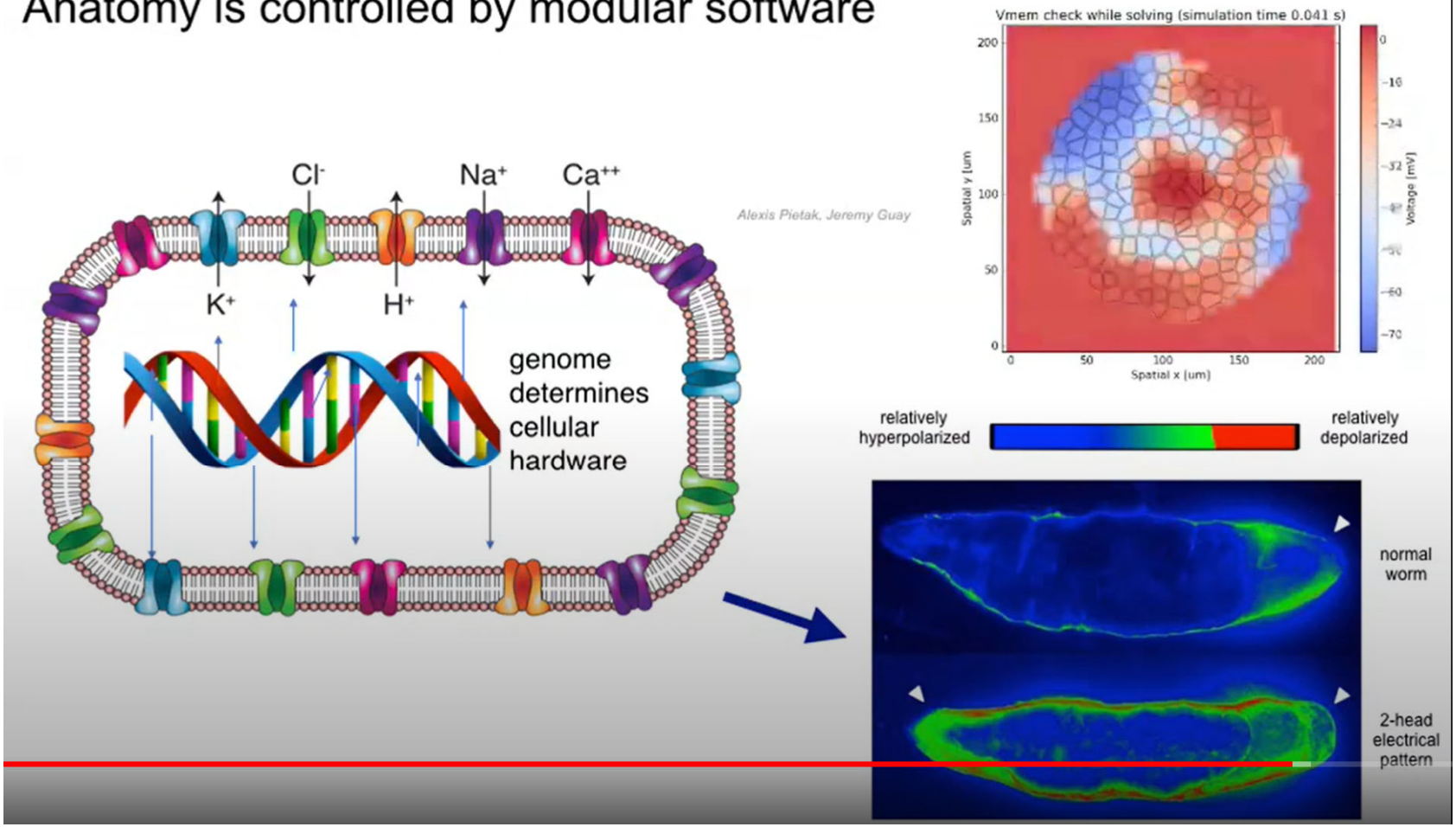
The bioelectric pattern doesn't indicate what the anatomy is now,
it encodes the pattern that will guide anatomy **if** it is cut at a future time

[1]Levin M (2020): Key note lecture, Alife 2020 Conference

A Better Metaphor:

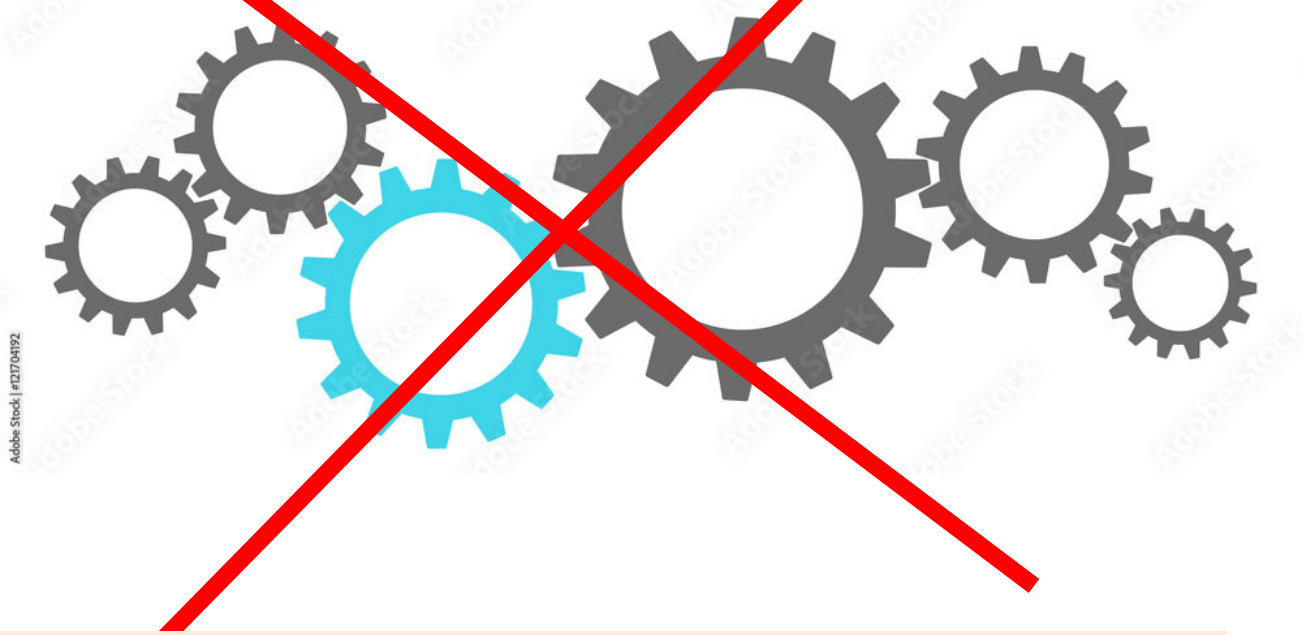
DNA encodes a versatile excitable medium with default symmetry-breaking dynamics and memory

Anatomy is controlled by modular software



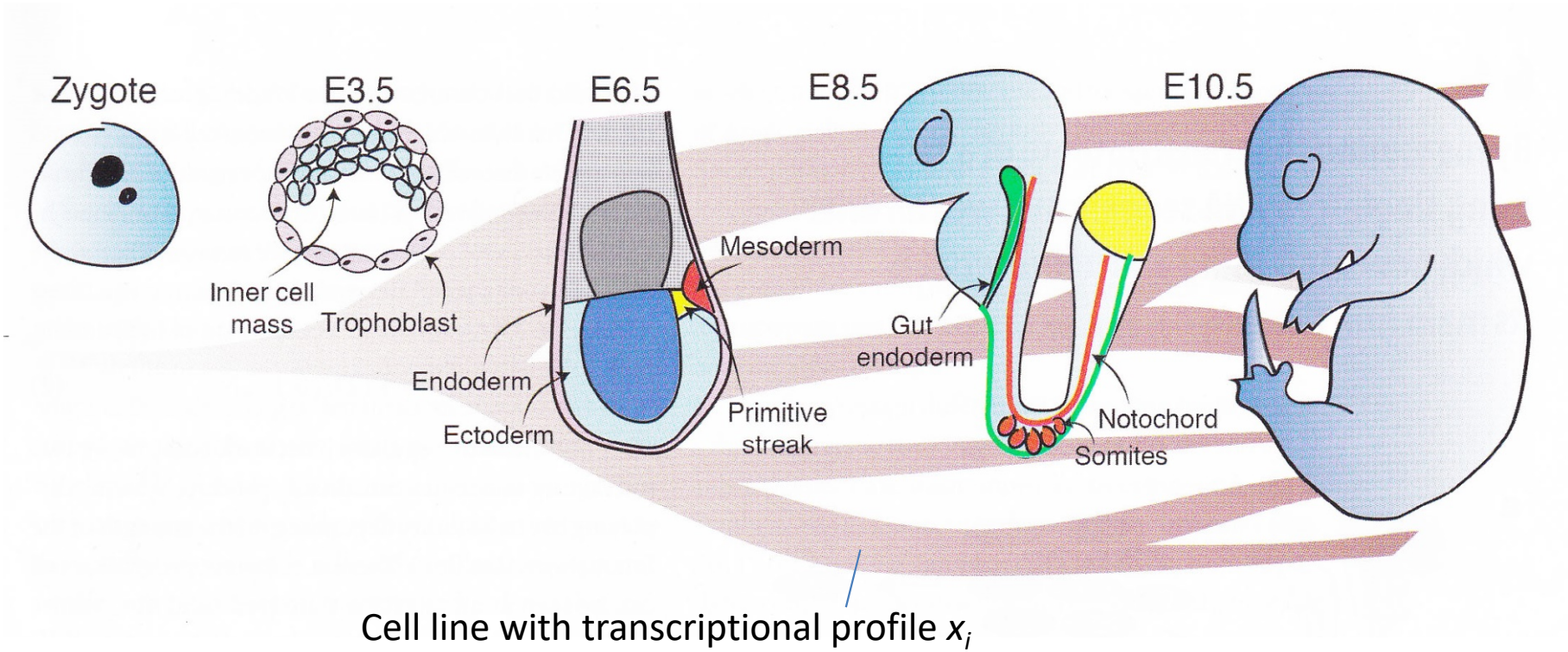
[1]Levin M (2020): Key note lecture, Alife 2020 Conference

Mechanism?
Molecular Machinery?
Biological systems as a Gearbox?



Biological systems are different!
Complex dynamics, emergence, plasticity, redundancy!

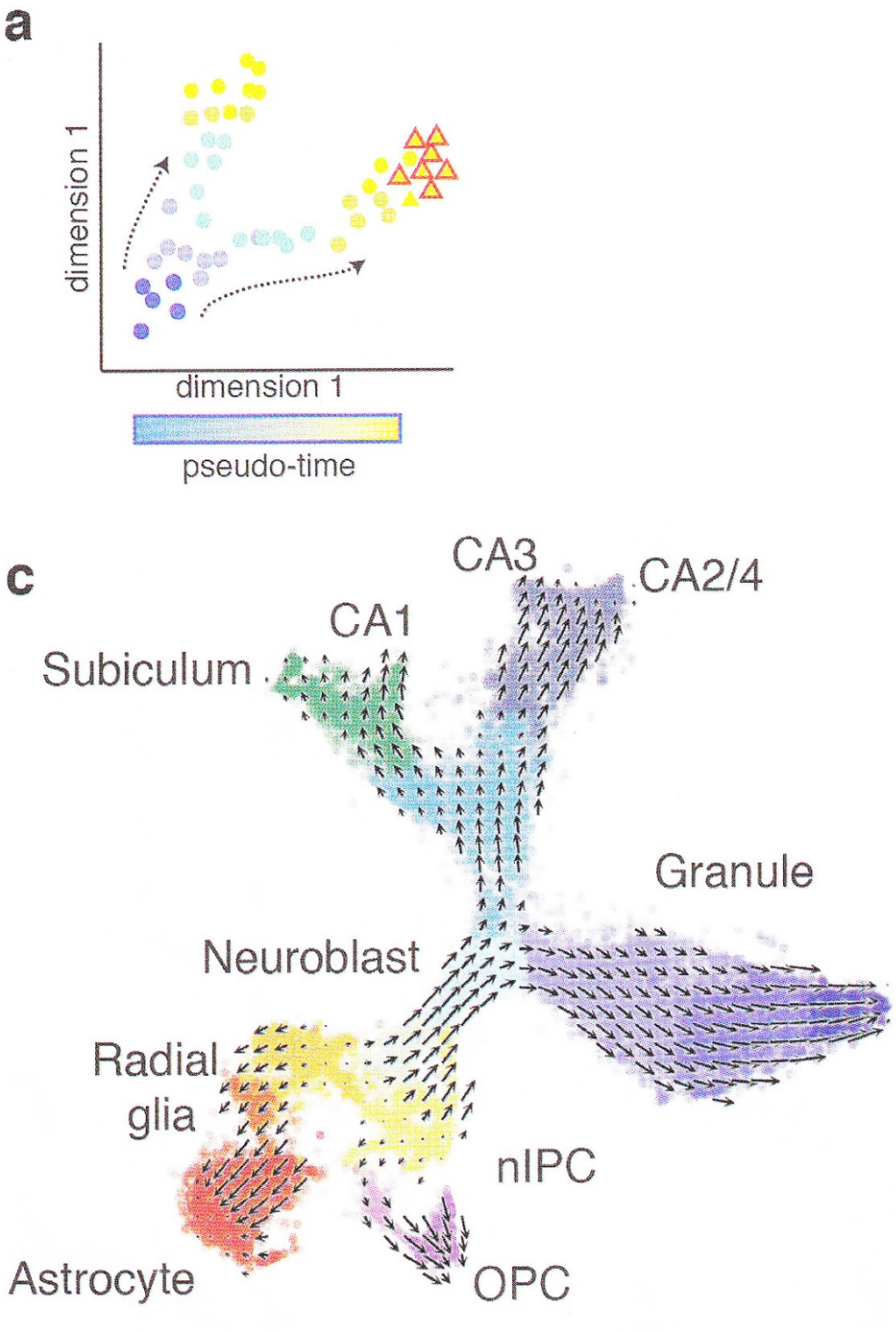
Advanced Modelling of Cell Differentiation



Cell line with transcriptional profile x_i
and cell fate probability $P = P(x_i, t)$

Fig.1. Differentiation pathways and cell fate (Alemany A, https://doi.org/10.1051/epn/2020505)

Cell Differentiation

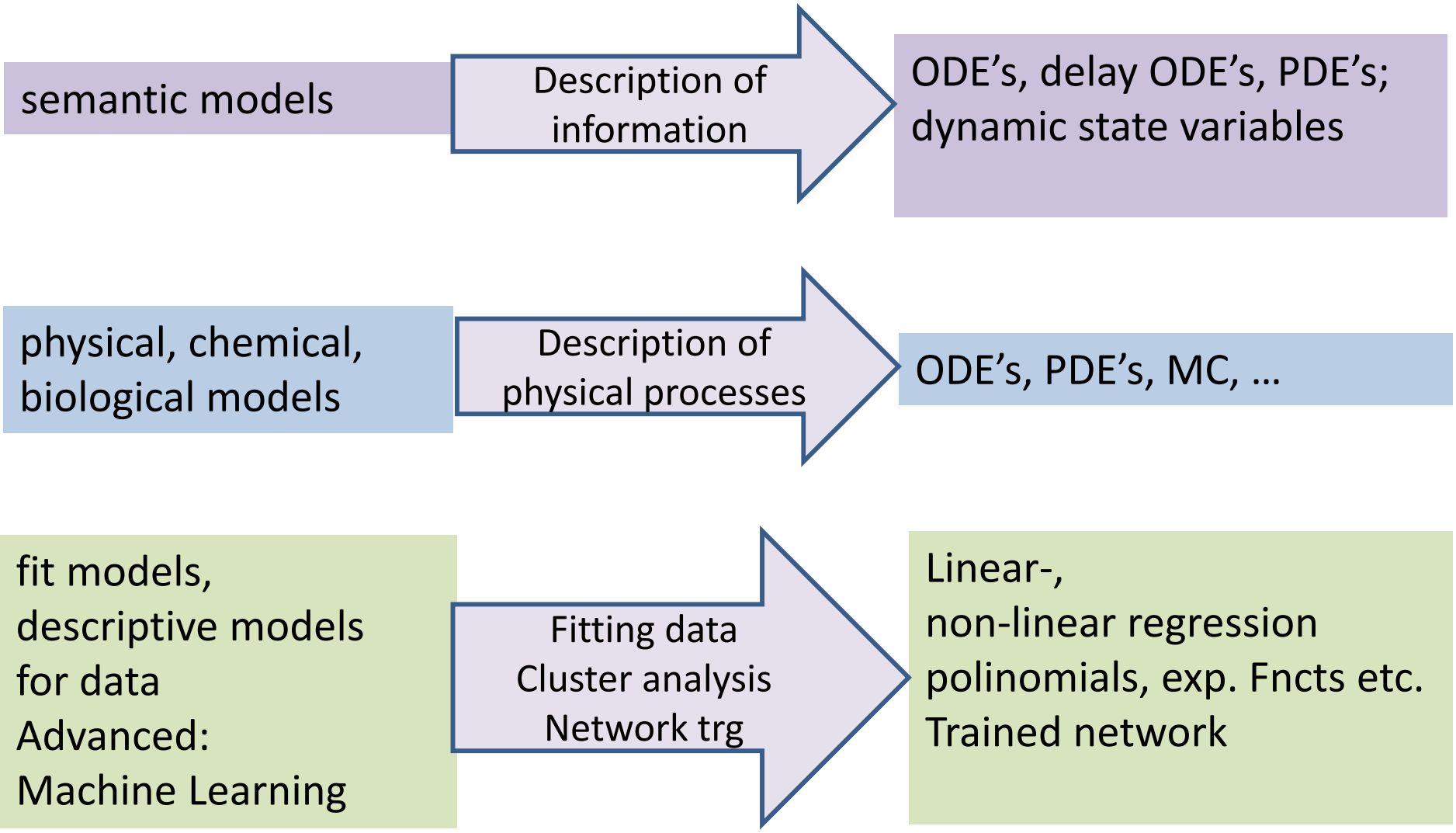


Description of cell fate probability P by directed diffusion (Fokker-Planck Equation); **F** denotes a vector with functions governing the transcription (corresponding to the transcriptome vector)

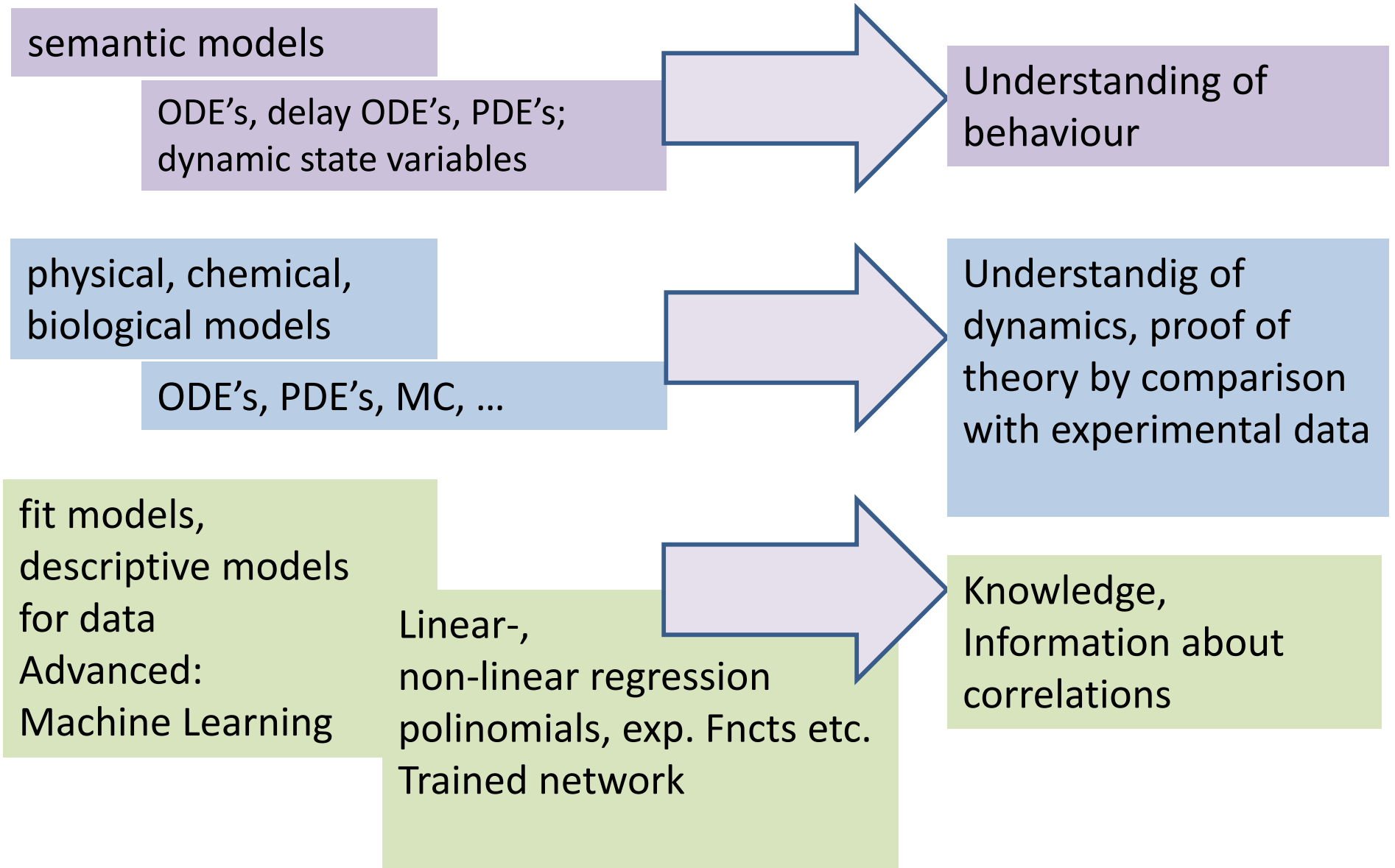
$$\frac{dP}{dt} = \Delta\left[DP\right] - \nabla \bullet \left[\vec{F}P\right]$$

Fig.1. Differentiation pathways and cell fate (Alemany A, https://doi.org/10.1051/epn/2020505)

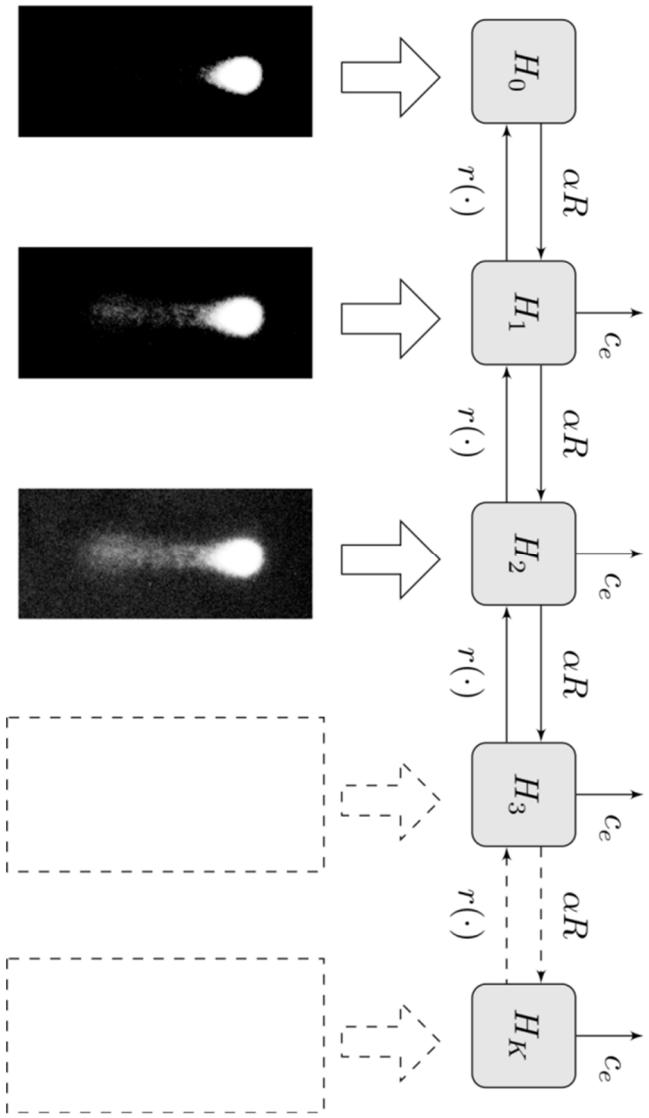
Catching the Real World in Models



What We Can Learn form Models



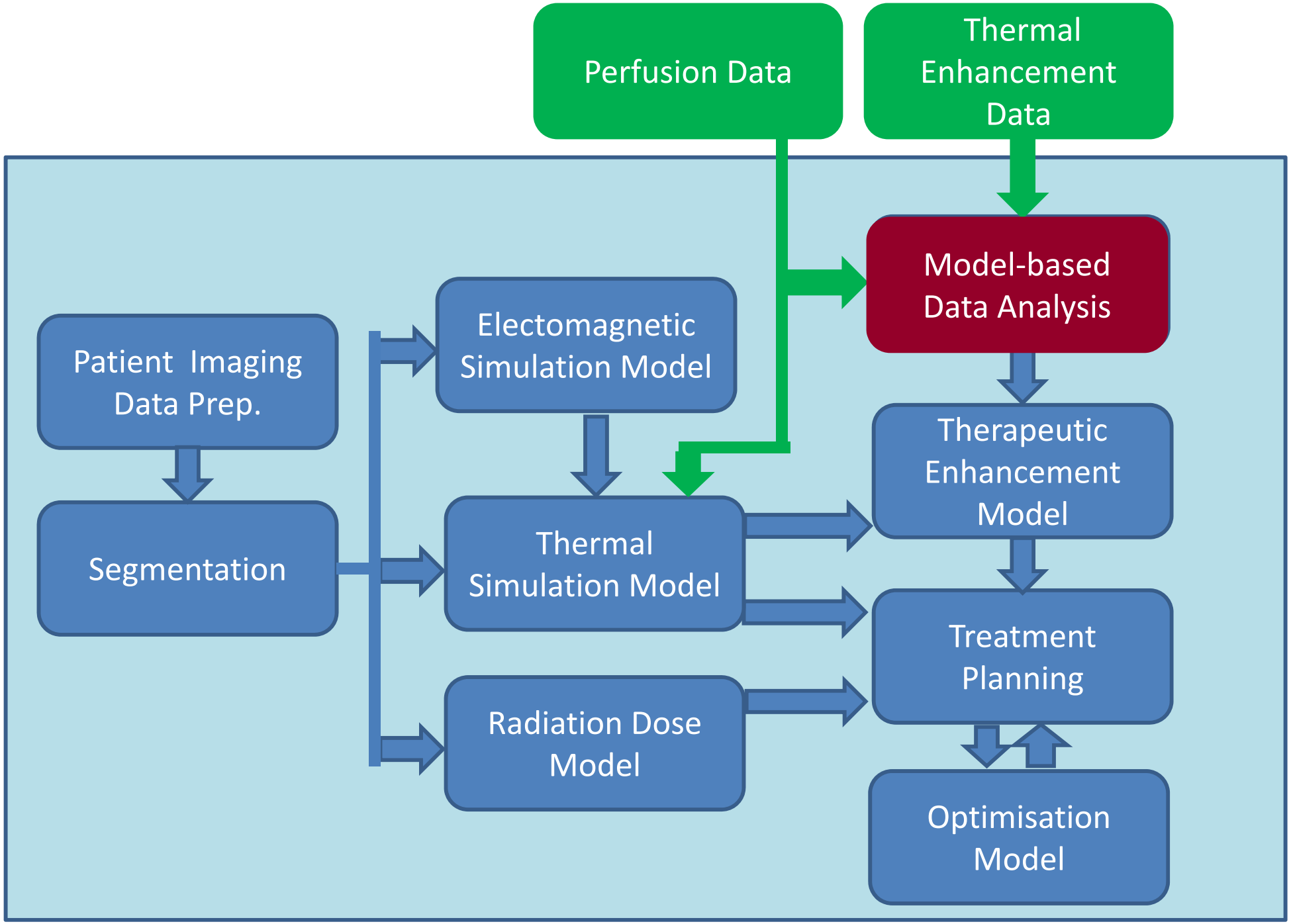
Aims of Modelling



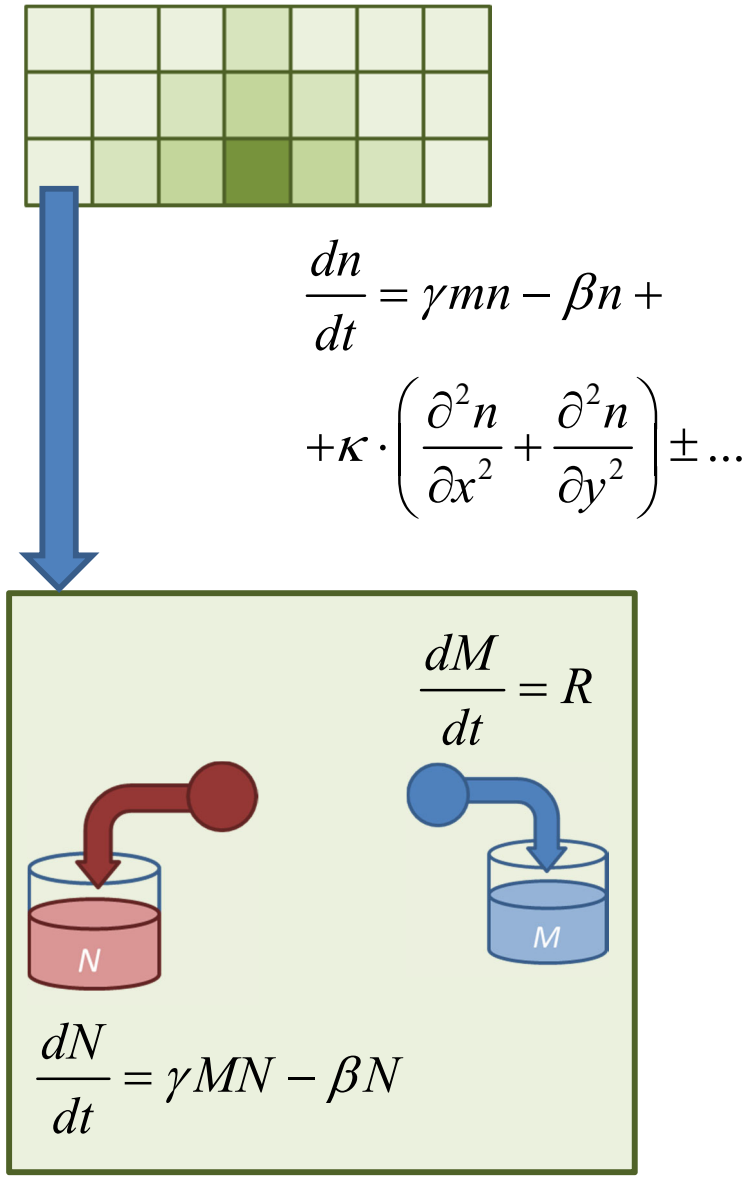
The way of modelling a biological system is dependent on the purpose:

- Models for treatment planning have to be predictive (weather forecast)
- Models for model-based data analysis must be comparable to the data
- Models for investigating dynamics in biological systems must represent the relevant aspects of the system behaviour

Fig.1. Mapping of the Multi-Hit-Repair (MHR) model to Comet assay data (DNA damage)


Perfusion Data
Thermal Enhancement Data
Model-based Data Analysis
Patient Imaging Data Prep.
Electomagnetic Simulation Model
Therapeutic Enhancement Model
Segmentation
Thermal Simulation Model
Treatment Planning
Radiation Dose Model
Optimisation Model

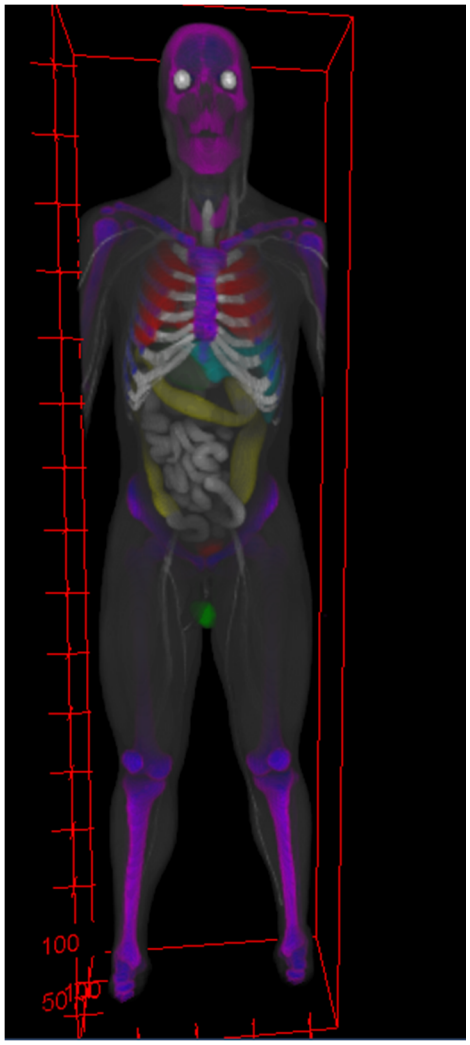
Modelling Approaches and Techniques



Depending on the purpose, different modelling approaches can be useful:

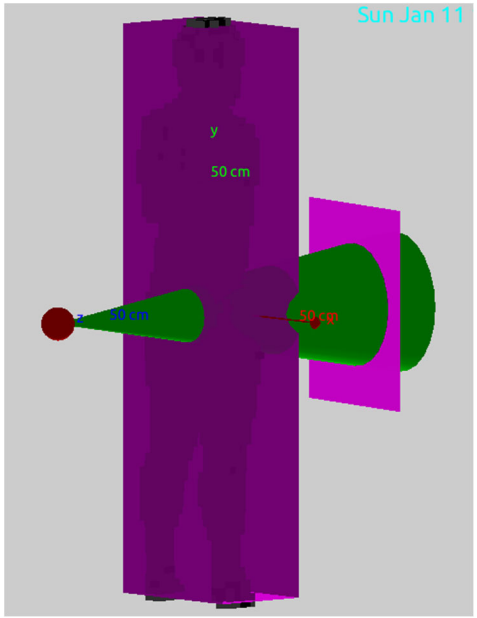
- Compartmental models: Mathematical description by ordinary differential equations (ODE) or delay differential equations (DDE); simulation using finite difference methods
- Spatio-temporal models: Mathematical description by partial differential equations (PDE), simulation using time-domain finite difference (TD-FD) methods or finite elements methods (FEM)

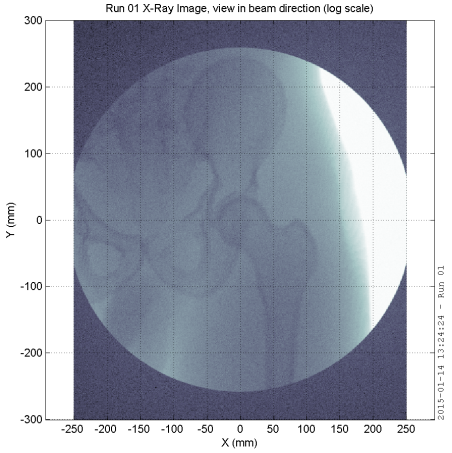
Modelling Approaches and Techniques

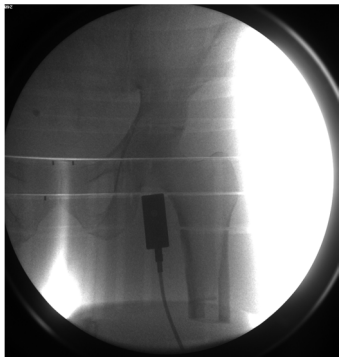


Non-differential equation-based methods:

- Cellular automaton
- Agent-based models
- Monte-Carlo (MC) simulations

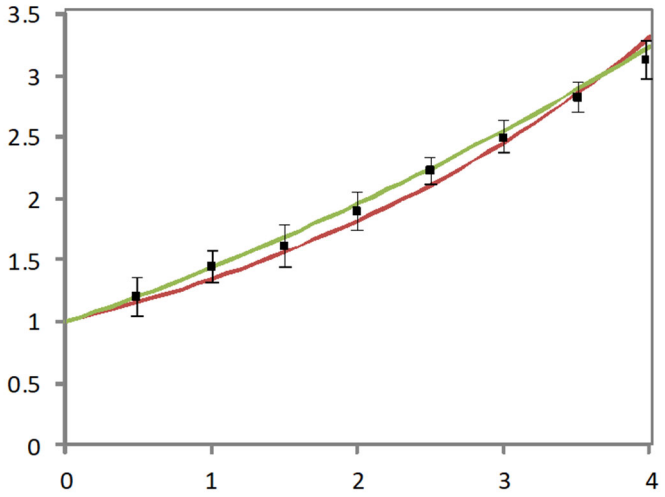






MC Model, calculation and images by Patrik Eschle

Modelling and Computer Simulation



Does a model work correctly?

- **Verification**: equilibrium levels, initial rates, frequencies, dynamic behavior under controlled conditions
- **Calibration**: use of observed data for fitting
- **Validation**: use of observed data for comparison with model prediction
- **Certification**: needed e.g. for medical products

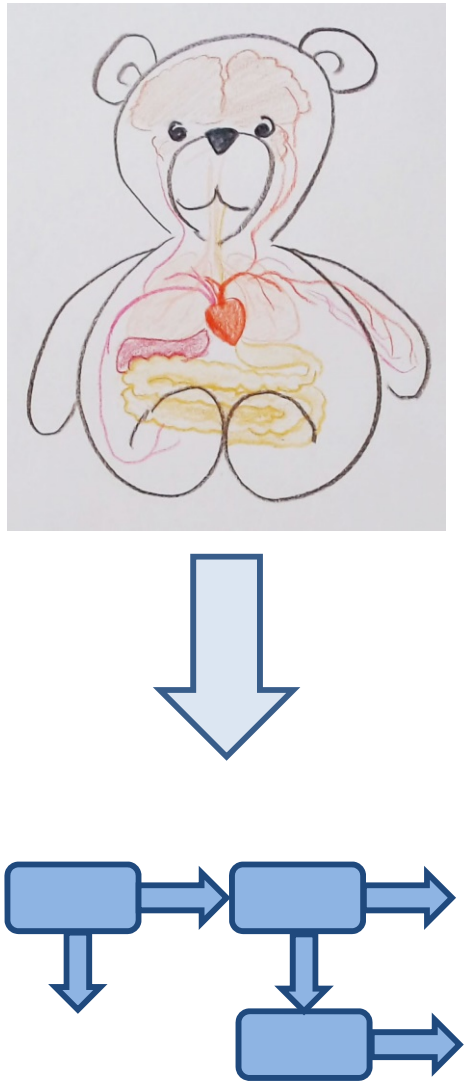
$$\frac{dN}{dt} = \alpha N$$

???

$$\frac{dN}{dt} = \alpha \sqrt{N}$$

Approaches to Stock & Flow – and Compartmental Modelling

Compartmental and ODE-based Models

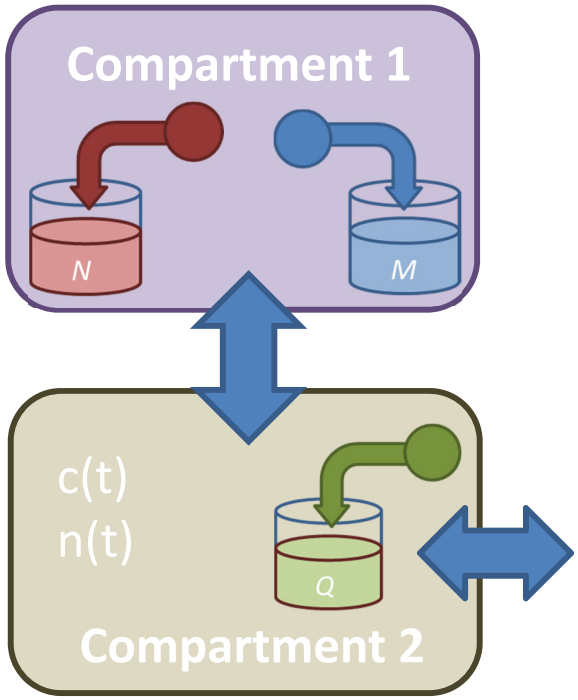


In a first step, we start with simplistic compartmental models to introduce fundamental concepts of modelling. Compartmental modelling can be applied to:

- Populations and ecosystems
- Epidemiological problems
- Physiological processes
- Drug distribution (biokinetics)
- Therapy optimizations
- …

Fig.1. Mapping of a living system to a compartmental model

Compartments and Stock & Flow - Models



$$N = N(t);\ M = M(t);\ Q = Q(t)$$
$$n(t);\ c(t);\ldots$$

$$J_c = -\kappa_c \nabla \varphi;\ J_n = -\kappa_n \Delta n$$
$$J_{N1} = f(N,\ldots;t);\ J_{N2} = h(N,\ldots;t)$$

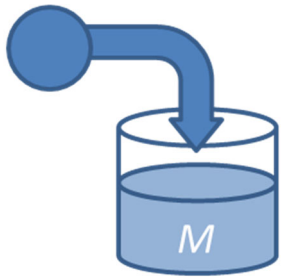
$$\frac{dc}{dt} = J_c = -\kappa_c \Delta c;\ \frac{dn}{dt} = J_n = -\kappa_n \Delta n$$
$$\frac{dN}{dt} = J_{N1} - J_{N2};\ \frac{dM}{dt} = \sum_k J_K$$

A recipe:

- Topology of the system? Define compartments and / or stocks
- Quantities describing the system? Define numbers of cells, densities, amount of drugs, concentrations etc.
- These quantities are considered as functions of time: To describe the dynamics, we need the first derivative in time (why?)
- To get the flows, describe the driving forces leading to the (ex)change of the aforementioned quantities.
- Formulate the flow balance

Population Models

$$\frac{dM}{dt} = R$$



$$M(t) = \int R dt$$

Given the population size (number of individuals, organisms) $N = N(t)$, the system can be described mathematically by the first derivative with respect to time t:

- The temporal change in the system is equal to the balance of birth – and death rate

$$\frac{dN}{dt} = \dot{N}$$

$$\frac{dN}{dt} = birthrate - deathrate = \sum_i R_i$$

Population Models

$$\frac{dN}{dt} = \alpha N$$

$$\int \frac{dN}{N} = \ln|N|$$

$$= \int \alpha dt = \alpha t + const.$$

$$N(t) = N_0 \cdot e^{\alpha t}$$

$$\frac{N(T_2)}{N_0} = 2 = e^{\alpha T_2} \rightarrow T_2 = \frac{\ln 2}{\alpha}$$

Example: exponential growth. Even in this case, solution can be found easily by

- Separation
- Integration

Population Models

$$\frac{dN}{dt} = \alpha\sqrt{N}$$

$$\int \frac{dN}{N^{0.5}} = \int N^{-0.5} dt = 2N^{0.5}$$

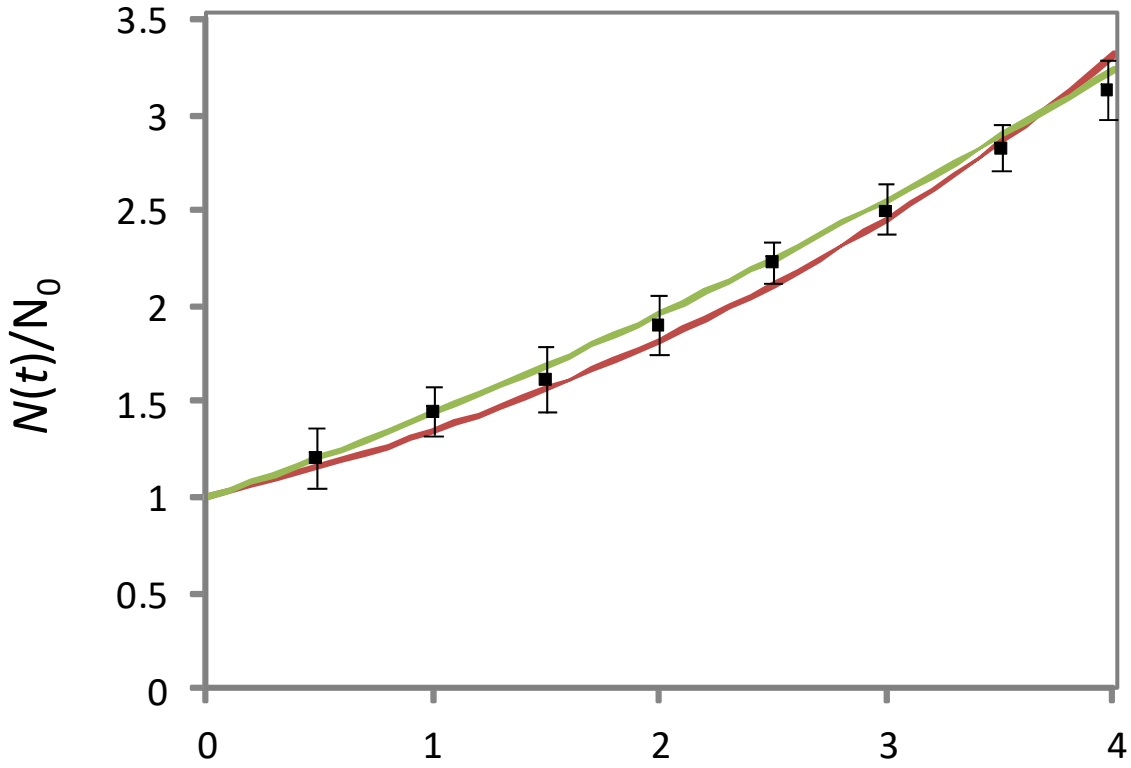
$$= \int \alpha dt = \alpha t + const.$$

$$N(t) = \left(\frac{1}{2}\alpha t + \sqrt{N_0}\right)^2$$

Exponential growth is only possible as long as nutrients (resources) are unlimited. A model for planar growth (cell cultures etc.) can be found by the following assumptions:

- Nutrient limitation leads to growth inhibition within the populated area
- only at the rim of the populated area, growth is possible (new substrate)
- The circumference is proportional to the square root of the area, therefore the growth rate is proportional to the square root of the population size.

Population Models: Model-based Data Analysis



$$N(t) = N_0 e^{\alpha t}$$

$$N(t) = \left(\frac{1}{2}\alpha t + \sqrt{N_0}\right)^2$$

Data Analysis

Fitting Model

$$\frac{dN}{dt} = \alpha N$$

$$\frac{dN}{dt} = \alpha\sqrt{N}$$

Population Models

$$\frac{dN}{dt} = \alpha N - \beta N^2$$

Many observations of growth in biological systems indicate a logistic growth:

- with an exponential growth
- Inhibition proportional to N^2
- Equilibrium level is given by the ratio of growth- and inhibition constants

$$\alpha N_{eq} - \beta N_{eq}^2 = 0$$

$$N_{eq} = \frac{\alpha}{\beta}$$

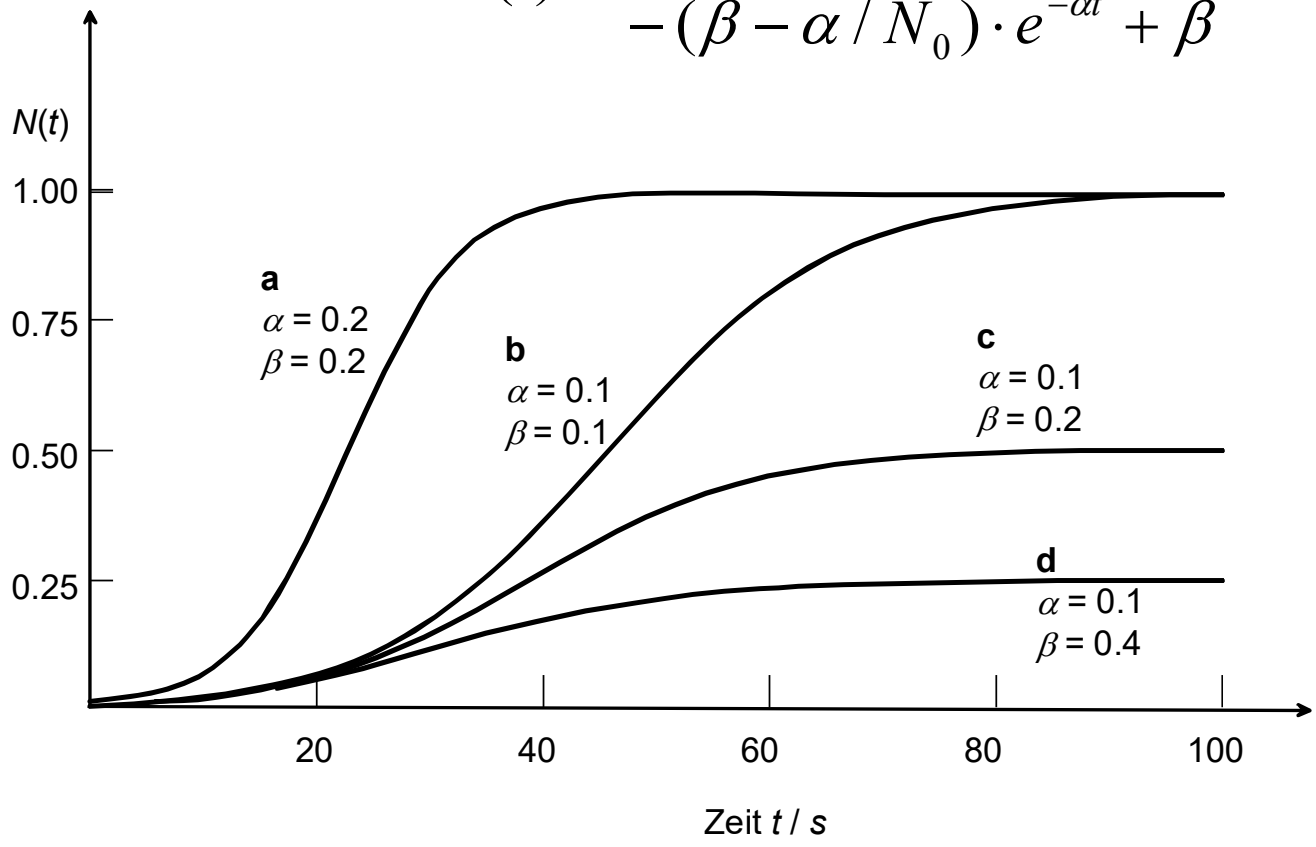
Population Models

$$\frac{dN}{dt} = \alpha N - \beta N^2$$

$$\int \frac{dN}{\alpha N - \beta N^2} = \int dt$$

Solution can be found by partial fraction separation, expansion / decomposition and integration:

$$N(t) = \frac{\alpha}{-(\beta - \alpha / N_0) \cdot e^{-\alpha t} + \beta}$$



Combined Population Models

$$\frac{dc}{dt} = \text{inflow} - \text{outflow}$$

$$\frac{dc}{dt} = k_1 \cdot (c_{ref} - c) - k_2 N$$

$$\frac{dN}{dt} = \alpha(c) \cdot N$$

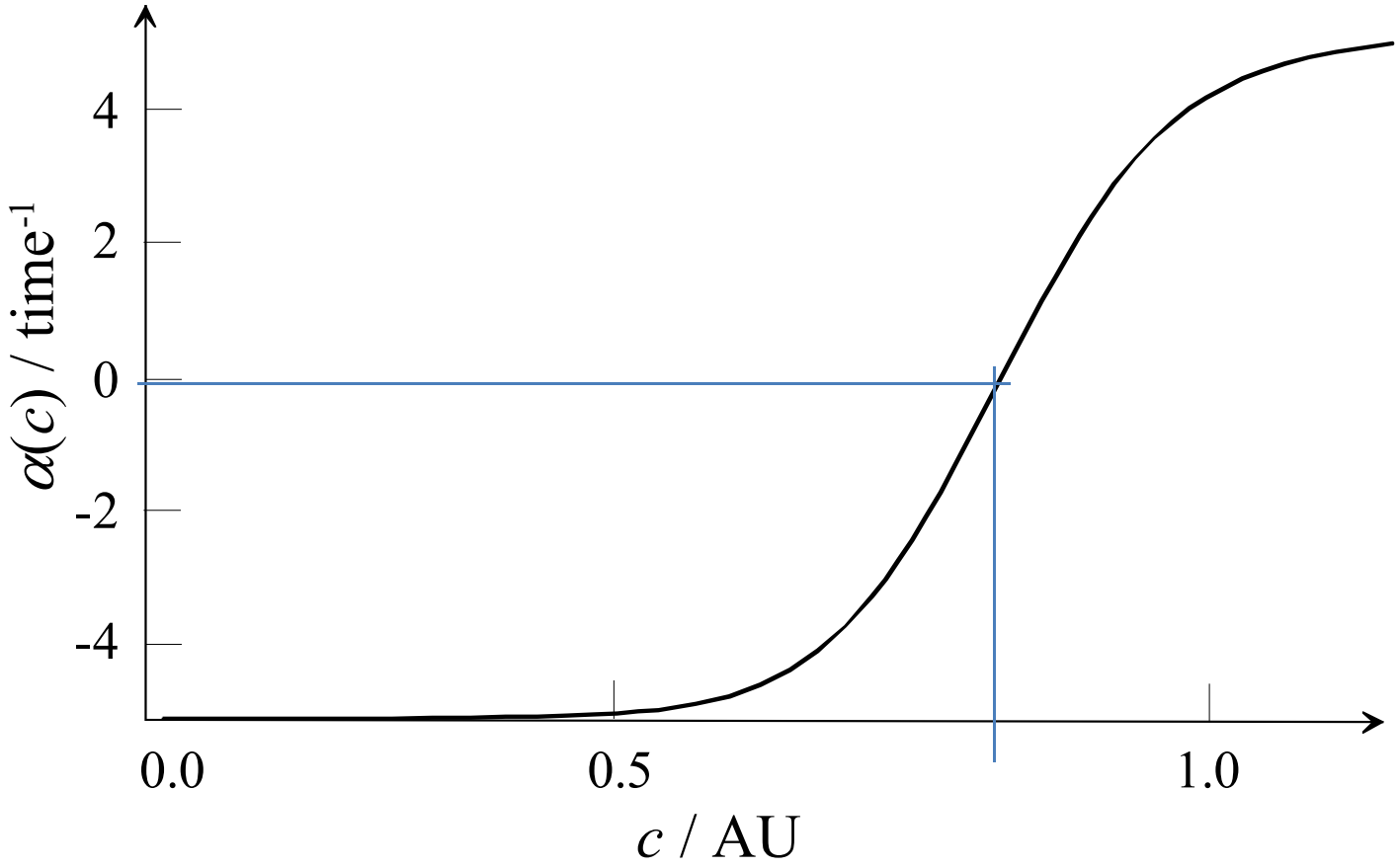
$$\alpha(c) = \frac{\lambda_1}{-(\lambda_2 - \lambda_1 / \alpha^*) \cdot e^{-\lambda_1 c} + \lambda_2} - \frac{\lambda_1}{2\lambda_2}$$

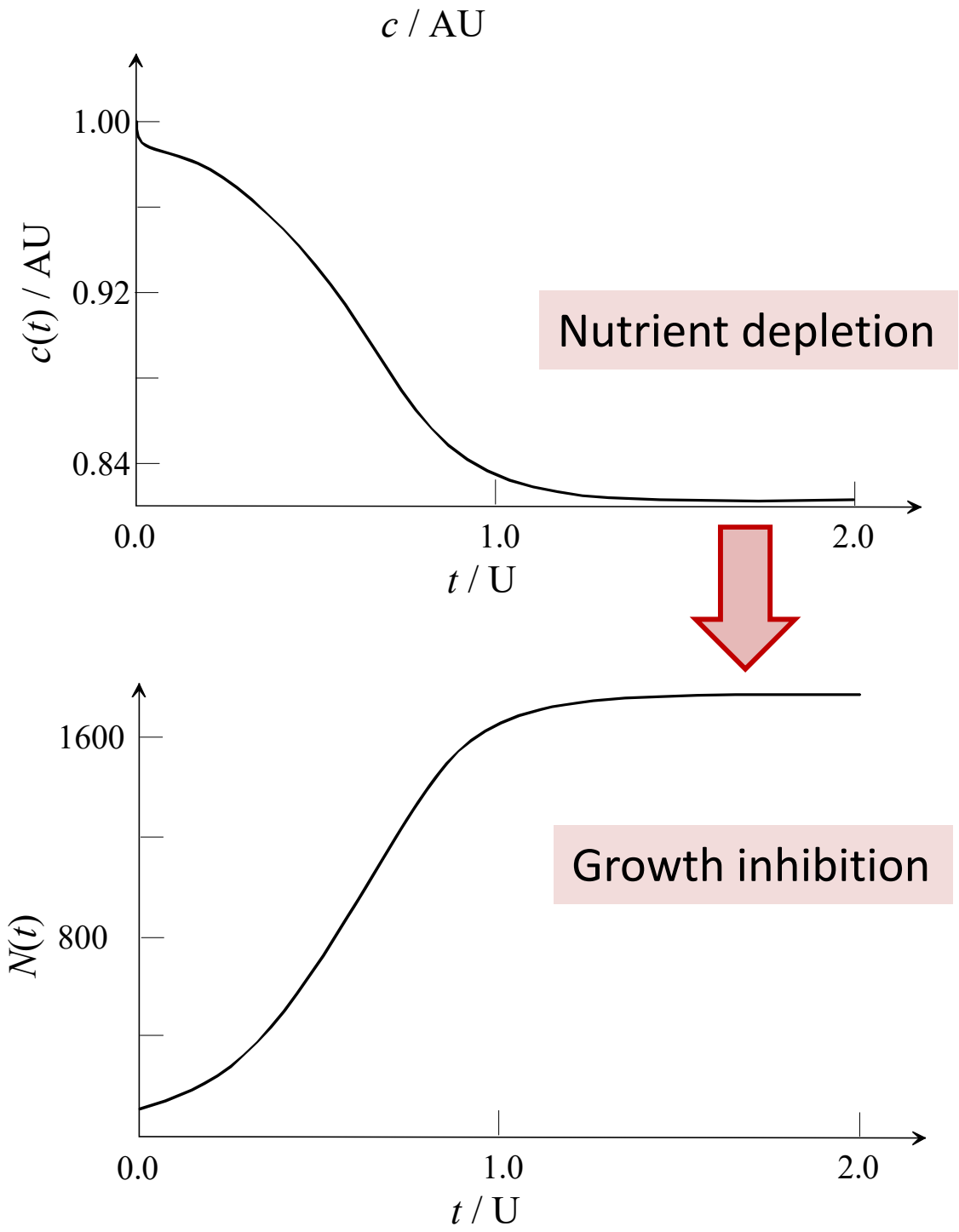
Growth inhibition may be introduced by nutrient limitation:

- Modelling of nutrients (concentration *c*) is similar to our general modelling approach (balance of flows)
- The coupling of the population model and the nutrient model is possible via nutrient-dependent growth constant and population-size dependent consumption rate

Combined Population Models

$$\alpha(c) = \frac{\lambda_1}{-(\lambda_2 - \lambda_1 / \alpha^*) \cdot e^{-\lambda_1 c} + \lambda_2} - \frac{\lambda_1}{2\lambda_2}$$

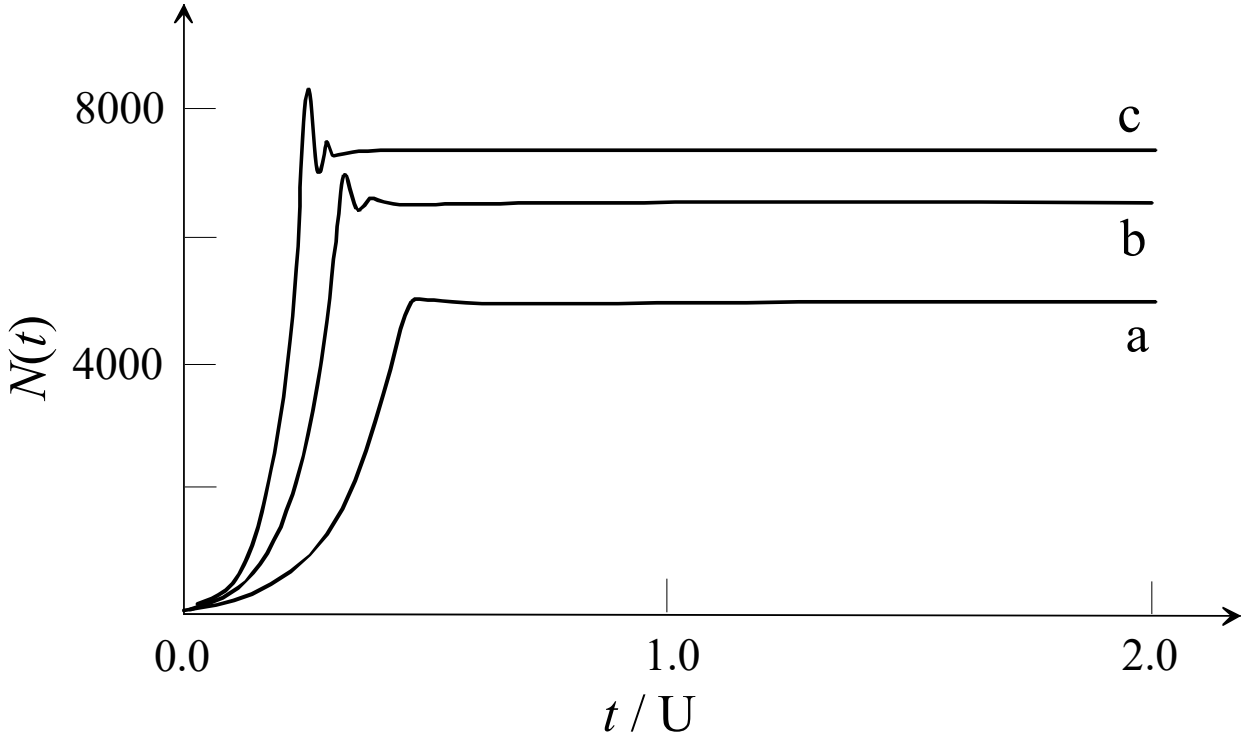



c / AU
1.00
0.92
0.84
c(t) / AU
0.0
1.0
2.0
t / U
Nutrient depletion
1600
800
N(t)
0.0
1.0
2.0
t / U
Growth inhibition

Combined Population Models

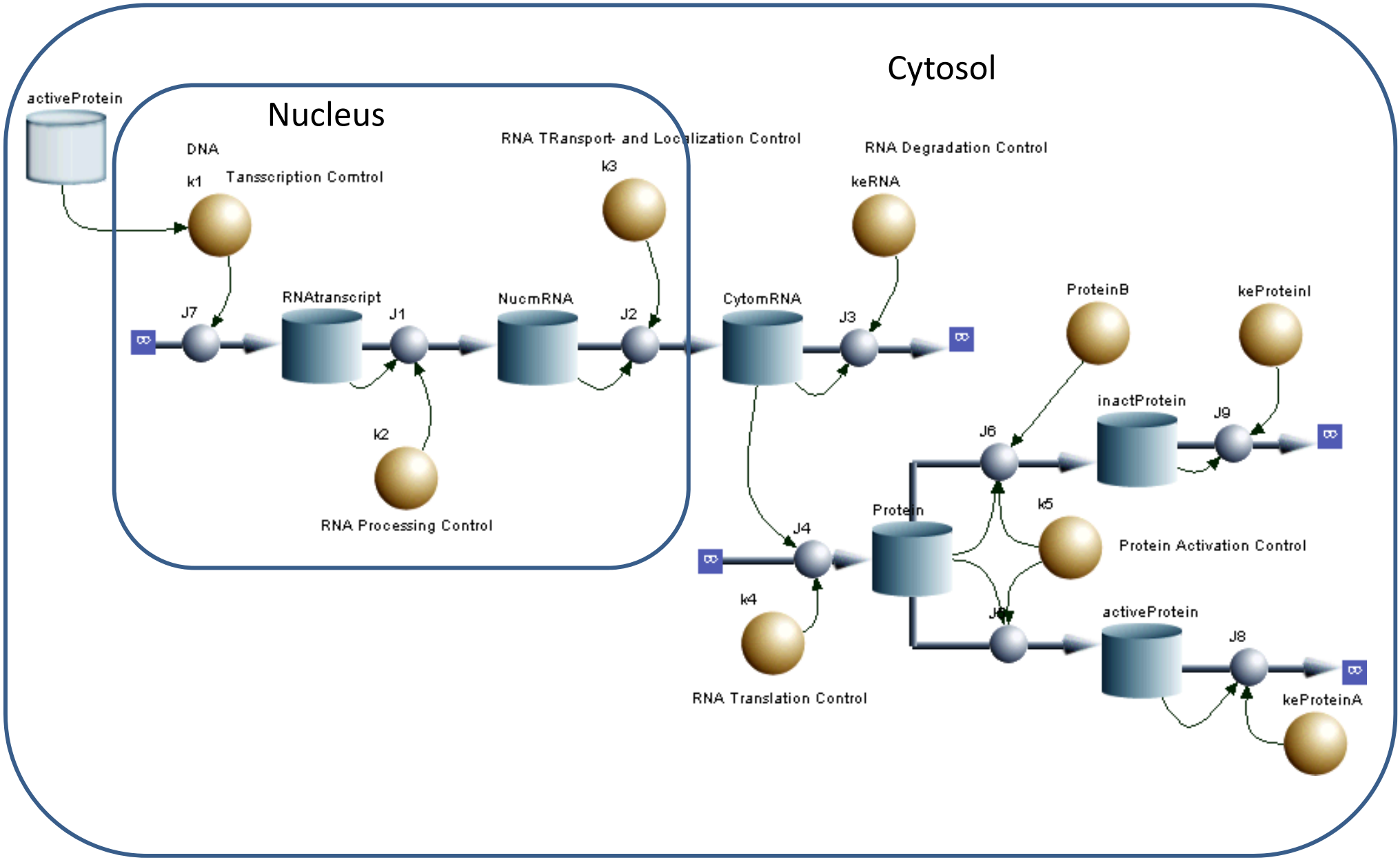
Combined growth – nutrient models can replicate the logistic growth, but depending on the parameter values, the model exhibit more versatile behavior:

- Models should be as complex as required!

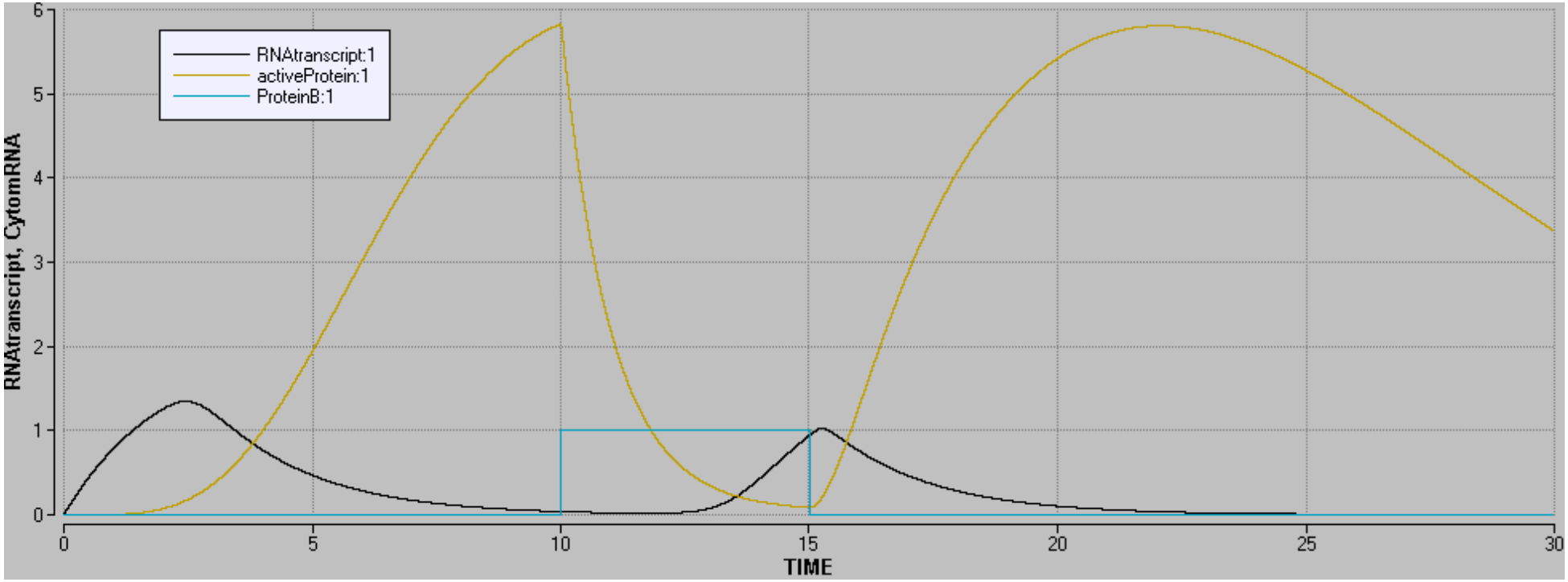


Some Examples …

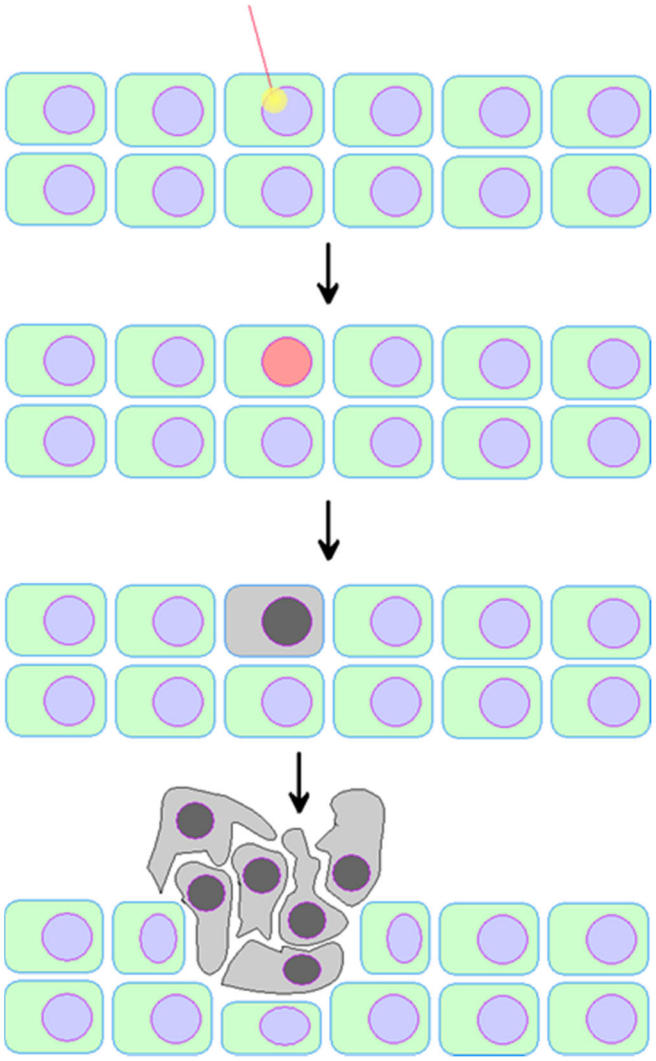
Modelling Transcription and Translation



Modelling Transcription and Translation



Population Models



Medical applications of population models:

- Epidemiology
- Tumour growth and anti-cancer treatment
- Immunology
- Ecosystem dynamics and system medicine

Fig.1. Cancerogenesis in host tissue (green cells)

Tumour Translation / Transformation and Progression

Adenoma model for colo-rectal cancer

- *N*: Host tissue (epithelial cells)
- *A*: adenoma cells
- *C*: carcinoma cells

$$\frac{dN}{dt} = (\alpha_N - \beta_N N) \cdot N - \gamma_{NA} N$$

$$\frac{dA}{dt} = \gamma_{NA} N + (\alpha_A - \beta_A A) \cdot A - \gamma_{AC} A$$

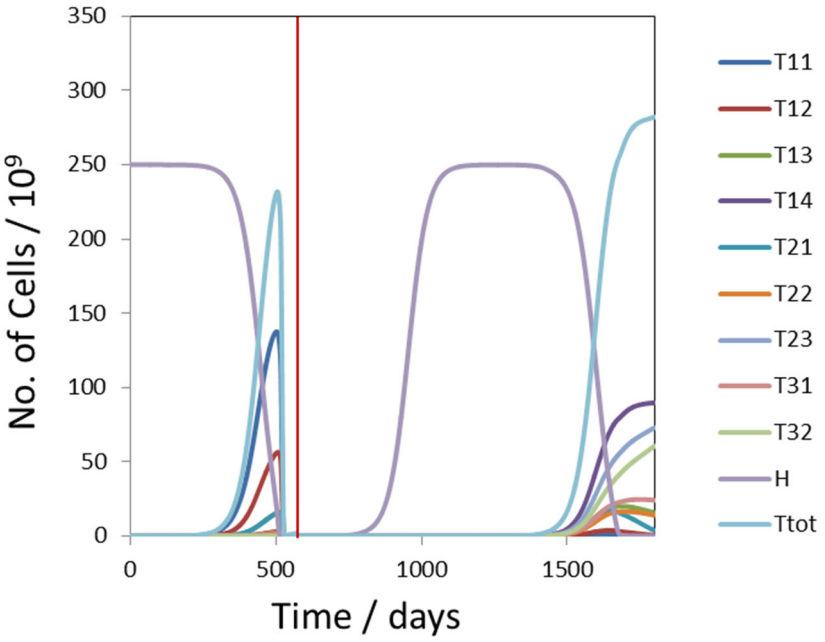
$$\frac{dC}{dt} = \gamma_{AC} A + \alpha_C C$$

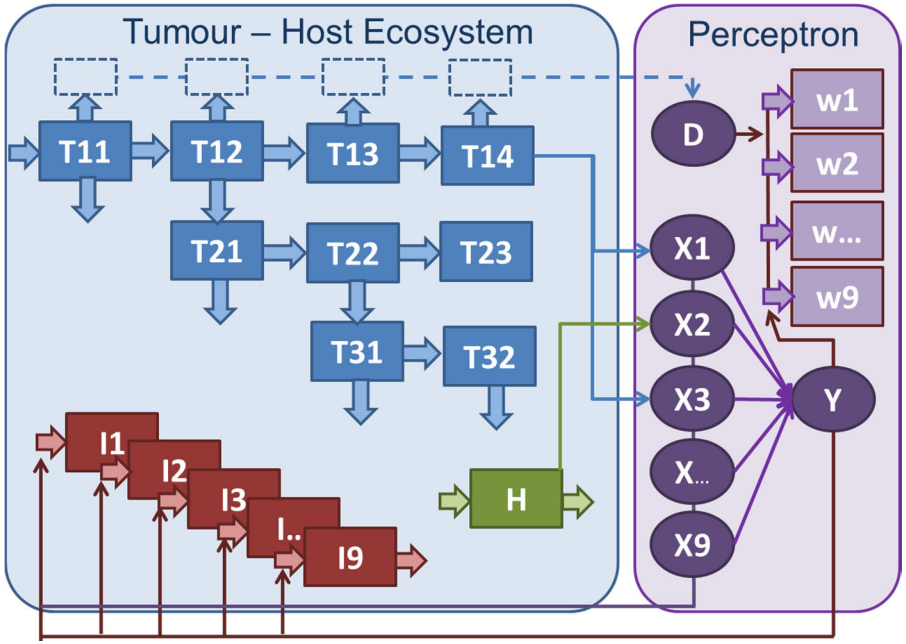
Tumour – Host –Immune Ecosystems

Tumours are fast-evolving ecosystems

→ Interactions (competition, commensalism and synergism) with cellular environment are essential for disease progression!

→ Spatial information processing seems also to influence immune response





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Scheidegger et a. (2023), The MIT Press Journals: Alife 2023, article in press.

Epidemiological Models

$$\frac{dS}{dt} = -\alpha SI$$

$$\frac{dI}{dt} = \alpha SI - \beta I$$

$$\frac{dR}{dt} = \beta I$$

Kermack – McKendric (SIR) model (1927):

- *S*: number of susceptible individuals
- *I*: number of infected individuals
- *R*: number of recovered (immune) individuals
- $S + I + R = N$

Epidemiological Models

More complex nCoV model based on SIR approach:

$$\frac{dS}{dt} = -\alpha SI$$

$$\frac{dI}{dt} = \alpha SI - \beta I$$

$$\frac{dR}{dt} = \beta I$$

$$\frac{dS}{dt} = -\sum_n k_{an} S I_{a,n} - k_v S + k_{idv} V + \sum_n k_{id} R_n$$

$$\frac{dI_{a,n}}{dt} = (k_{an} S - k_{rn} - k_{sn}) \cdot I_{a,n}$$

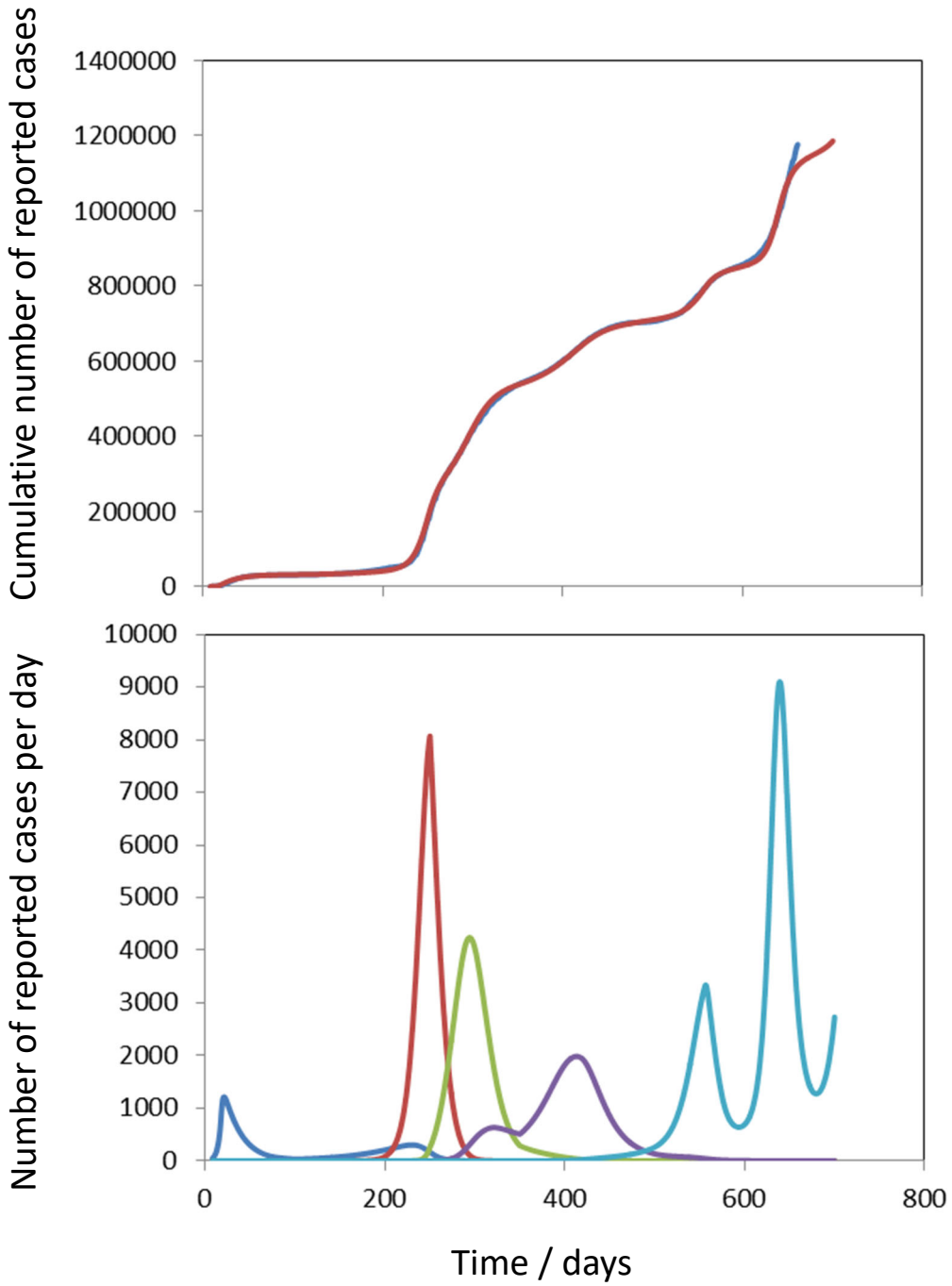
$$\frac{dI_{s,n}}{dt} = k_{sn} I_{a,n} - (k_{en} + k_{dn}) \cdot I_{sn}$$

$$\frac{dR_n}{dt} = k_{rn} I_{a,n} + k_{en} I_{sn} - \sum_n k_{id} R_n$$

$$\frac{dD}{dt} = \sum_n k_{dn} I_{sn}$$

$$\frac{dV}{dt} = +k_v S - k_{idv} V$$

Ecosystem Dynamics and Compartmental Models

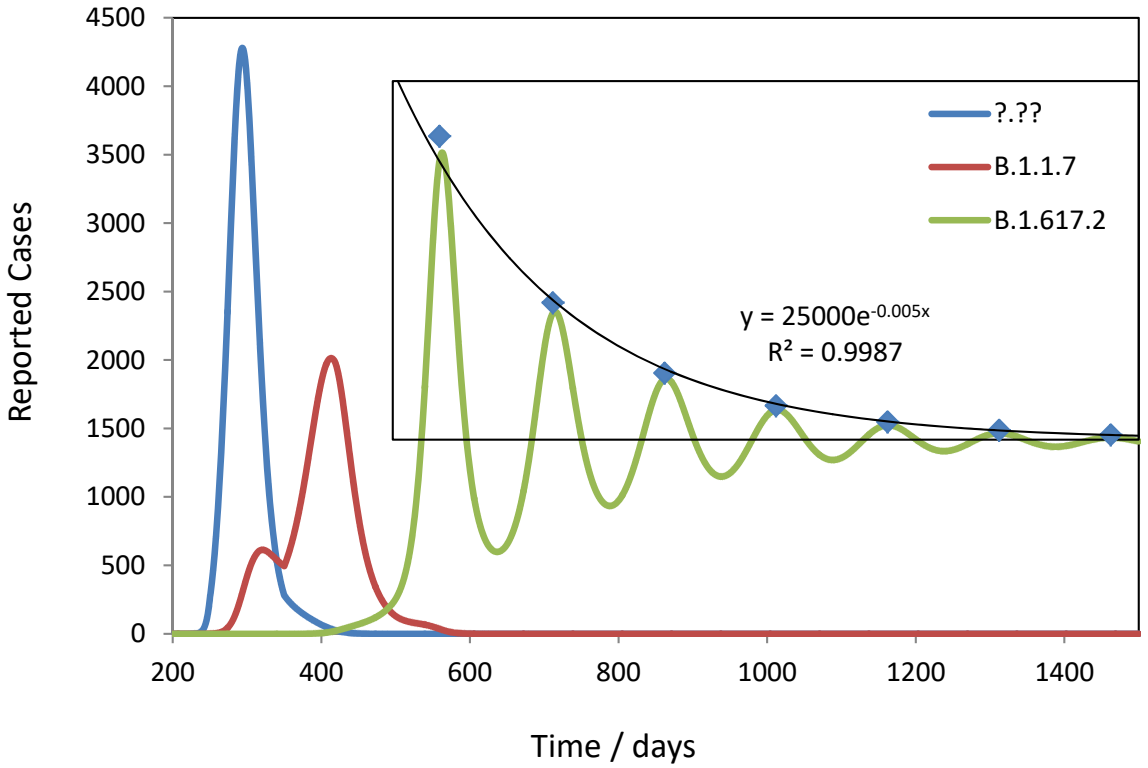


Reported by FOPH
Model

wt (?)
?
?
α (B.1.1.7)
δ (B.1.617.2)

Competition between 5 nCoV-2 – sub-types with different virulence

Modelling SARS CoV-2 Pandemics



Oscillations in a system with waning immunity encodes information about half-life of immunity.

Comming Soon

Application of dynamic models

- Biokinetic modelling and PET data analysis (Day 2)
- Radiobiological models (Day 3)