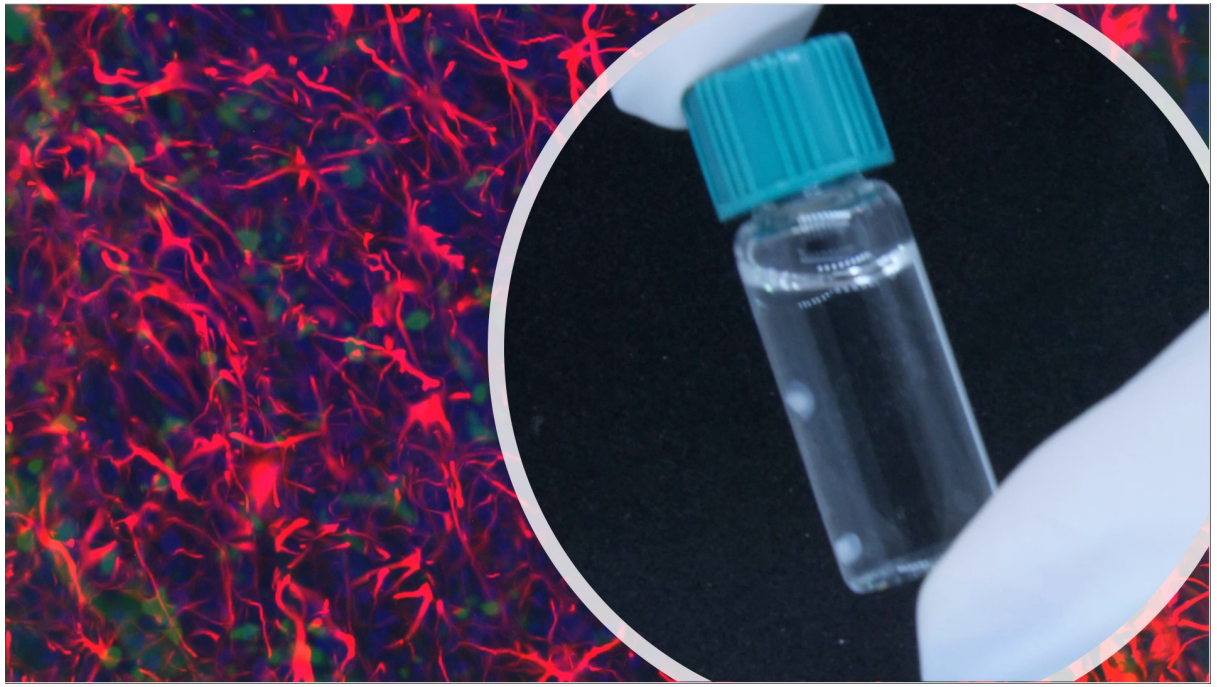
In silico approaches for cosmetics

Chiara Magliaro

My CV

- Biomedical Engineer, PhD
- Assistant Professor @DII, UNIPI

- Main research focus:
  - Imaging and image processing methods for neural tissue processing
  - Multi-physics and physics-based in silico modelling for experimental in vitro design



Outline of the course


Some useful definitions


Why in silico models?


In silico models in cosmetics


In silico models: fields of action


Some examples


Closing remarks

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Computational (in silico) tools

Matemathical models simulated using computational resources to study the behaviour (i.e., the dynamics) of complex systems

Computational (in silico) tools

Matemathical models simulated using computational resources to study the behaviour (i.e., the dynamics) of complex systems

Type of Algorithm

- Classical
- Emergent

Type of study

- Deterministic
- Stochastic

Type of dynamics

- Time-dependent
- Stationary

Type of discretization

- Structured grid
- Unstructured grid
- No grid
- Finite Elements

Scale

- Whole tissue
- Single cells

Environmental cues

- Chemical
- Mechanical
- ...

Computational (in silico) tools

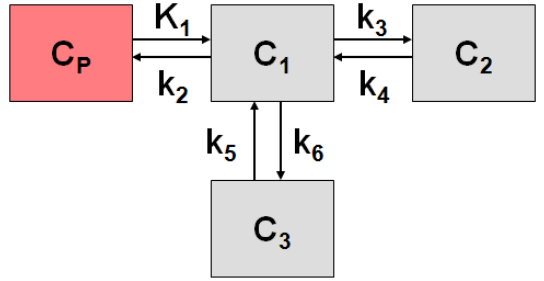
Type of Algorithm

- Classical
- Emergent

Differential equations

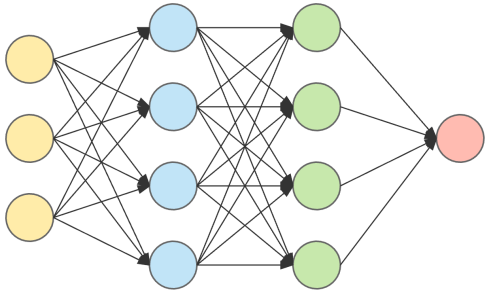
Standard statistical approaches

Compartmental models



Artifical-intelligent based methods

Data mining, machine learning, big data ...



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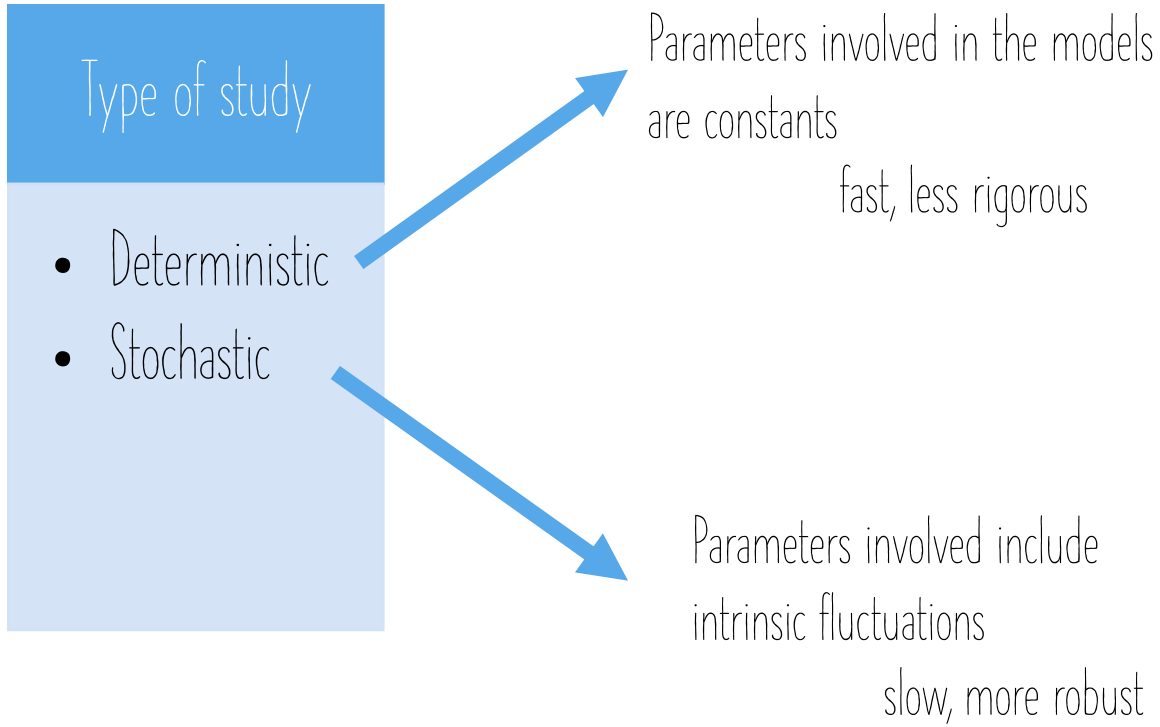

Matemathical models simulated using computational resources to study the behaviour (i.e., the dynamics) of complex systems

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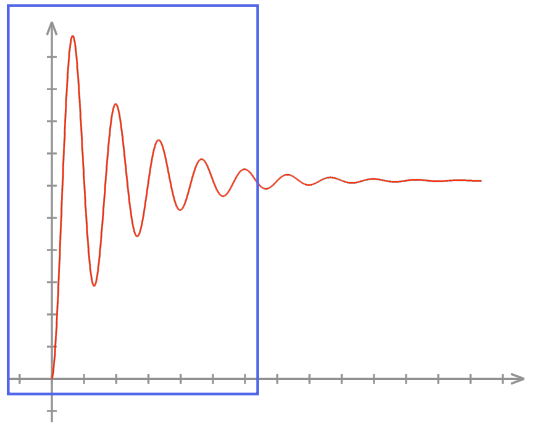
Matemathical models simulated using computational resources to study the behaviour (i.e., the dynamics) of complex systems

Type of dynamics

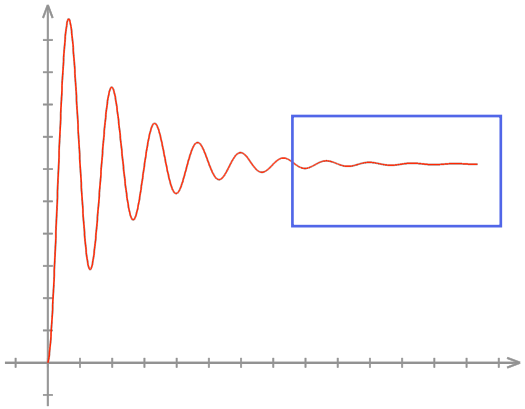
- Time-dependent
- Stationary

Dependent variable changes over time



Dependent variable does not change over time

Dynamic aequilibrium



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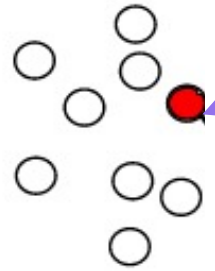

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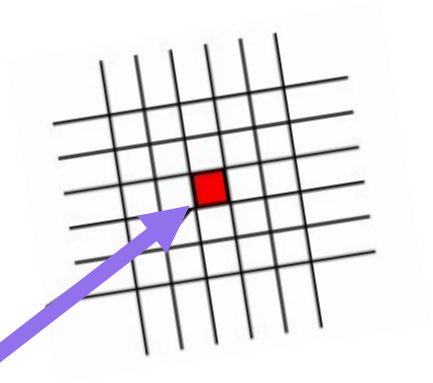

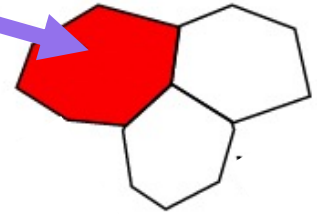

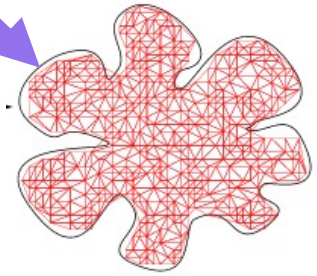

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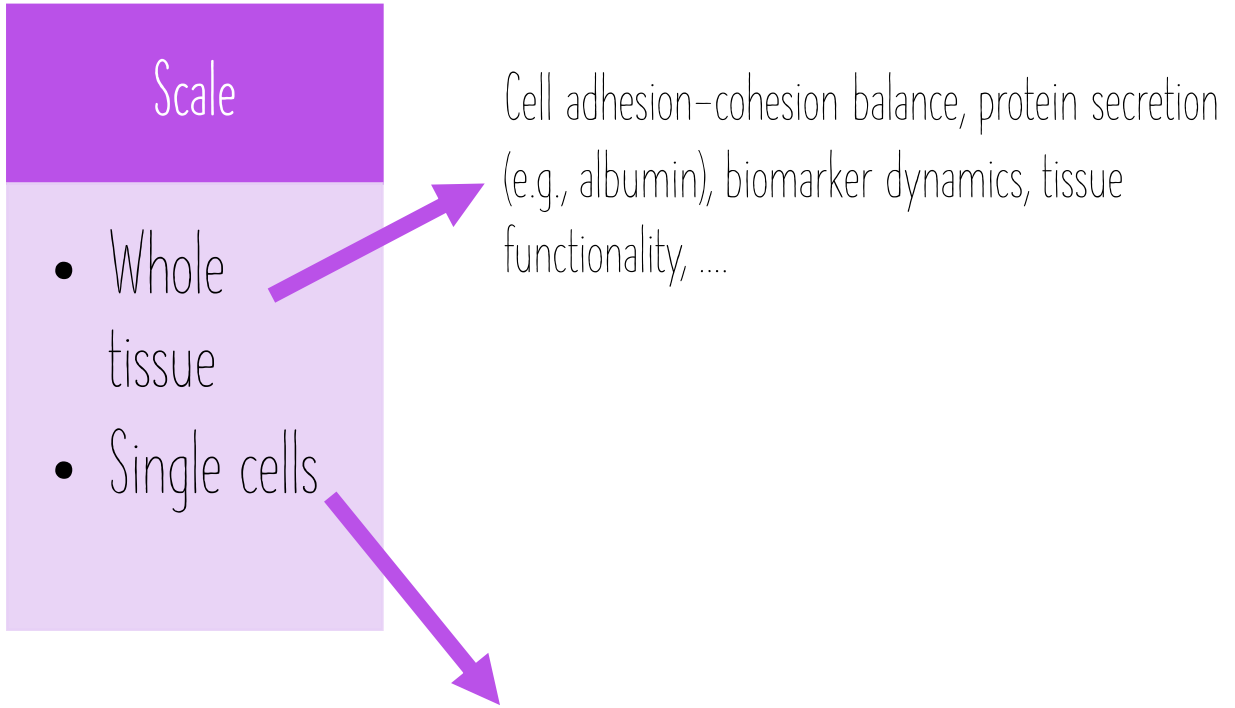

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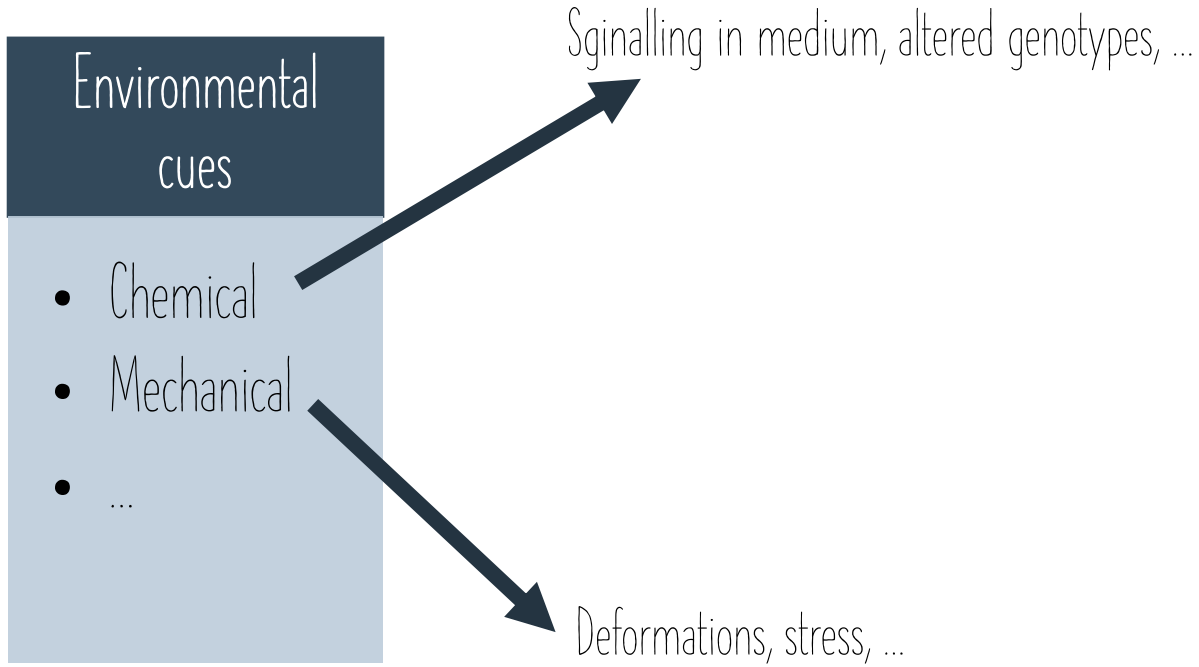

Matemathical models simulated using computational resources to study the behaviour (i.e., the dynamics) of complex systems

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In silico models: fields of action


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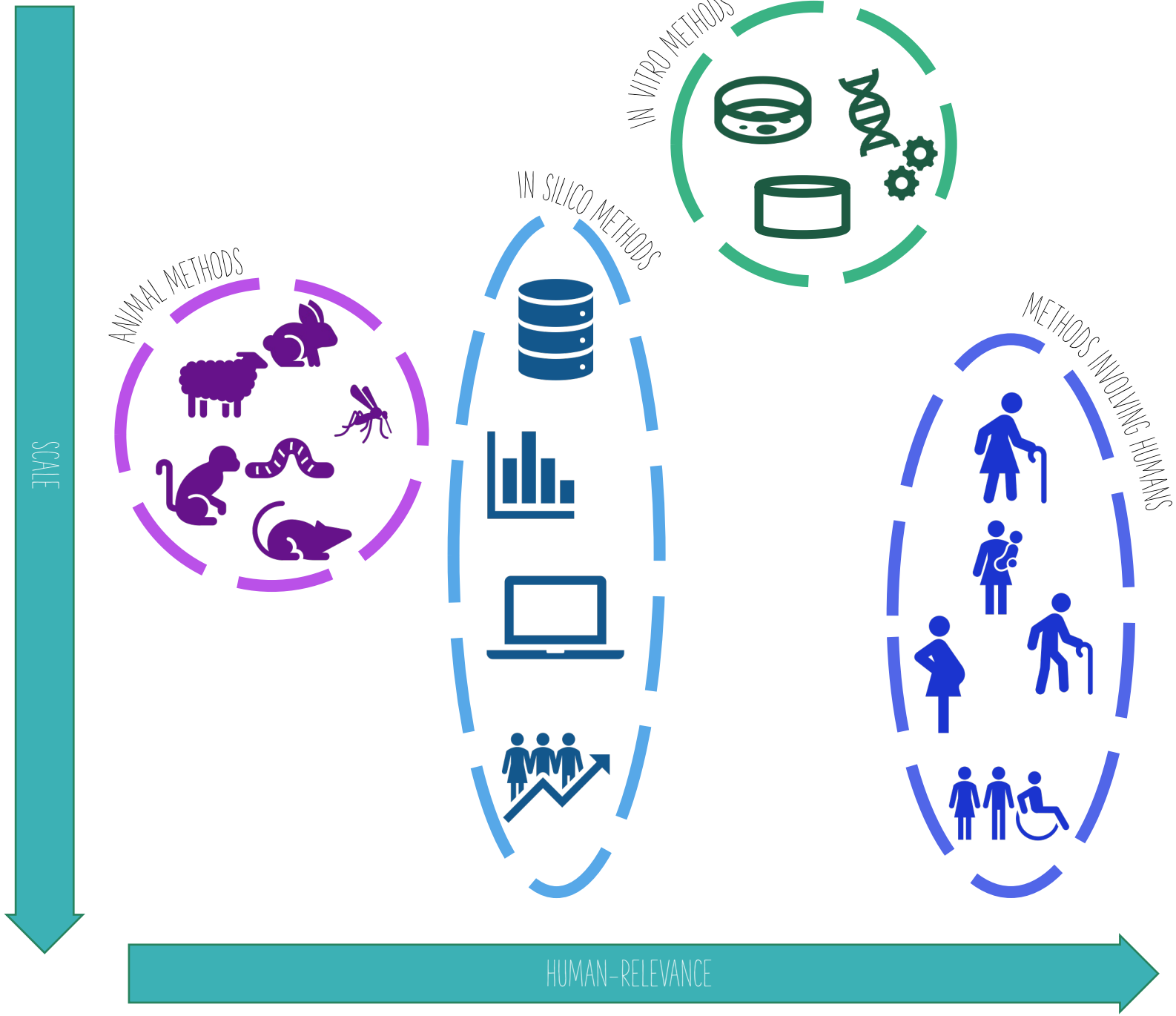
Which model?


SCALE
ANIMAL METHODS
IN SILICO METHODS
IN VITRO METHODS
METHODS INVOLVING HUMANS
HUMAN-RELEVANCE

Why in silico?

- .... Because they are cheap
- .... Because they easily allow high-throughput
- .... Because they give useful predictive information for experimental design
- ... Because they can give insights across scales
- ... Because they can give systemic info that cannot be obtained with non-invasive methods in humans or in vitro.

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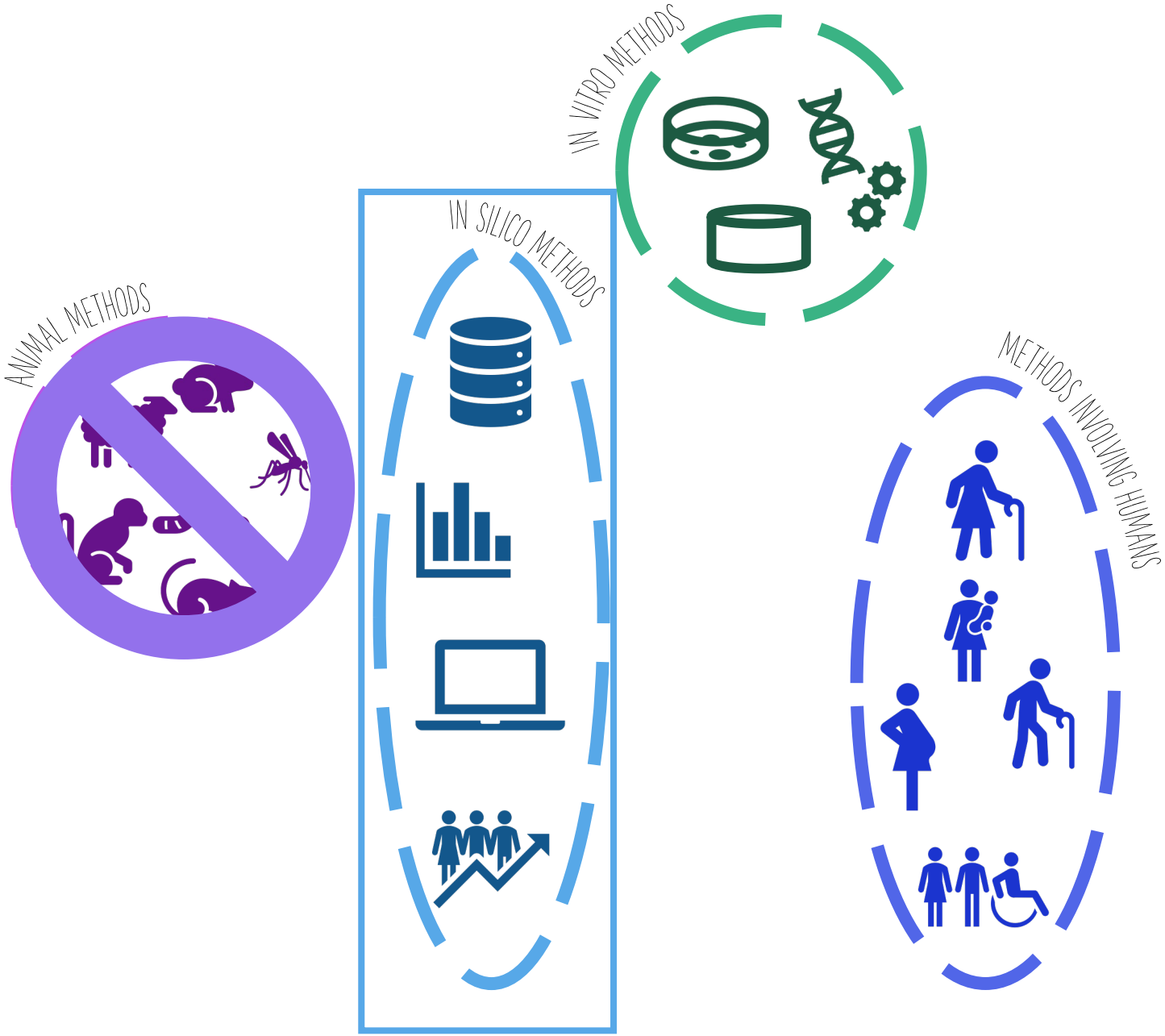
First documented application of in silico models in cosmetics '90s

The data obtained in the clinical studies aand those discussed in the nonclinical pharmacokinetic section of this FDA review were used to develop a physiologically based pharmacokinetic model. The model was used to estimate maternal and fetal plasma concentration of tretinoin and its metabolites in a theoretical abuse situation, i.e., after excessive application to face, lower arms, chest and neck and assuming exaggerated absorption of 10%. This model demonstrated that the systemic concentrations of tretinoin and potentially toxic metabolites achieved under such conditions remained several order of magnitude below endogenous concentration and minimally teratogenic dose of retinoic acid.

EU Cosmetics Directive banned animal-tested cosmetics after 2013



The European Commission funded research programmes in the area of alternatives in cosmetics for about 150 million € over the FP6 and FP7 framework programmes.

Some EU initiatives on the topic

Cosmetics Europe
the personal care association

The Cosmetics Europe (CosEu) ADME Task Force aims to evaluate and develop in silico skin penetration models using relevant measured values

COSMOS

Integrated *In Silico* Models for the Prediction of Human Repeated Dose Toxicity of COSMetics to Optimise Safety

The main aim of COSMOS was to develop freely available tools and workflows to predict the safety to humans following the use of cosmetic ingredients.

LIFE16
ENV/IT/000167
life vermeer

This platform will derive from an integrated combination of existing software, providing solutions for the Environmental and Human Health Risk Assessment.

One of the case-study for validating the platform is Cosmetics

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5 TOXICOLOGICAL AREAS OF INTERESTS*:

1. TOXICOKINETICS
2. REPEATED DOSE TOXICITY
3. CARCINOGENICITY
4. SKIN SENSITISATION
5. REPRODUCTIVE TOXICITY

* IDENTIFIED BY THE EU AS THE MOST CRITICAL AREAS IN THE LIGHT OF FULLY REPLACEMENT OF ANIMAL TESTS IN COSMETICS

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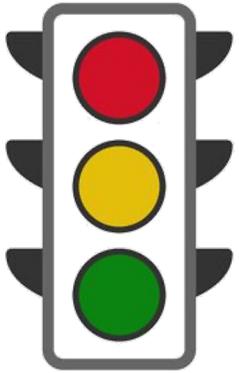


GENOTOXICITY, MUTAGENICITY

EYE IRRITATION, ACUTE TOXICITY, SKIN SENSITISATION

SKIN IRRITATION

* IDENTIFIED BY THE EU AS THE MOST CRITICAL AREAS IN THE LIGHT OF FULLY REPLACEMENT OF ANIMAL TESTS IN COSMETICS

If a cosmetic ingredient is bioavailable following dermal/oral/inhalation exposure, further tests on systemic/local toxicity are necessary.

The extent of such exposure is compared to the THRESHOLD OF TOXICOLOGICAL CONCERN (TTC), i.e., the dose which has a low probability to exert a toxic effect in humans.

TOXICOKINETICS

TOXICOKINETICS

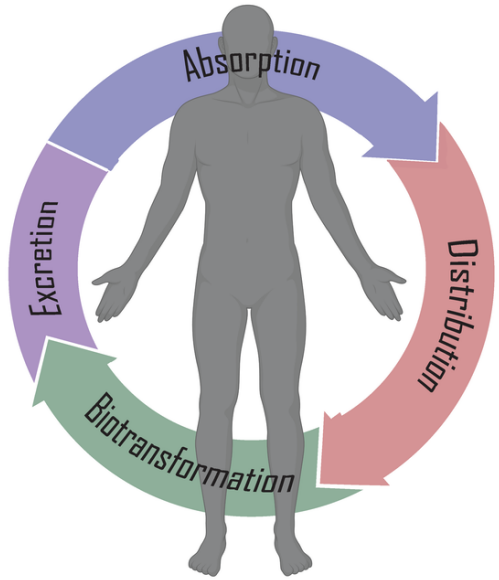
After a chemical compound (intentionally/unintentionally) penetrates into a living organism,

it is distributed to various tissues/organs by blood flow. D

it can bind to various receptors or target molecules. A

it can undergo metabolism B

it can be eliminated unchanged E



Effects occurring as a result of repeated daily dosing
with a substance for a part of the expected lifespan
or the major part of the lifespan*

REPEATED DOSE TOXICITY

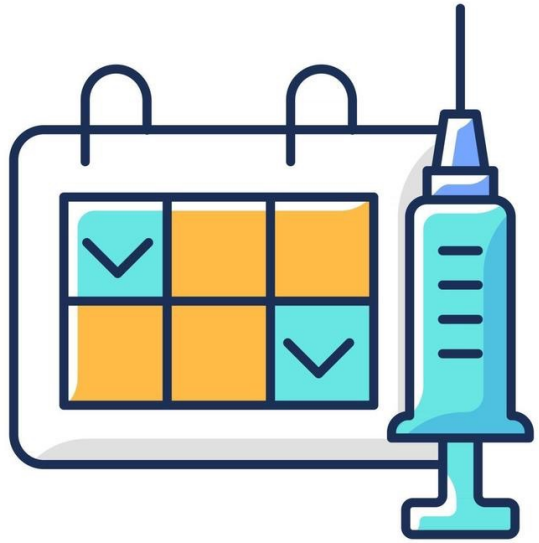
*The definition is very animal-related!

REPEATED DOSE TOXICITY

Deteriorating dysfunction of cells/organs/multiple organ systems

Including the concomitant contribution of toxicokinetics, hormonal effects, autonomic nervous system and immuno- systems

Sometimes modulated by feedback mechanisms



Complex long-term multifactorial process consisting in different stages, complex biological interactions and many different mode of action, which induces direct/indirect alterations in DNA

CARCINOGENITY

CARCINOGENITY

Gold standard: 2 year assay in rodents (usually not performed for cosmetics)

Not fully understood, so difficult to be mimicked by means of non-animal tests

The mode of action differs in different target organs, and in different species

Toxicological endpoint associated with chemicals that have intrinsic ability to cause skin allergy, termed allergic contact dermatitis, in humans

SKIN SENSITISATION

SKIN SENSITIZATION

Only after repeated exposure.

Complex mechanisms not well understood

- haptenation
- epidermal inflammation
- dendritic cell activation and migration
- T-cell proliferation

Models of the mechanisms and their interactions occurring in male/female fertility, and of the development of the human being during its prenatal life

REPRODUCTIVE TOXICITY

REPRODUCTIVE TOXICITY

- The most difficult to implement

  None yet gained regulatory acceptance

  - Lenghty research and development phase
  - Lack of understanding of the mode of actions of reproductive toxicants
  - Huge number of mechanisms involved in mammalian reproduction

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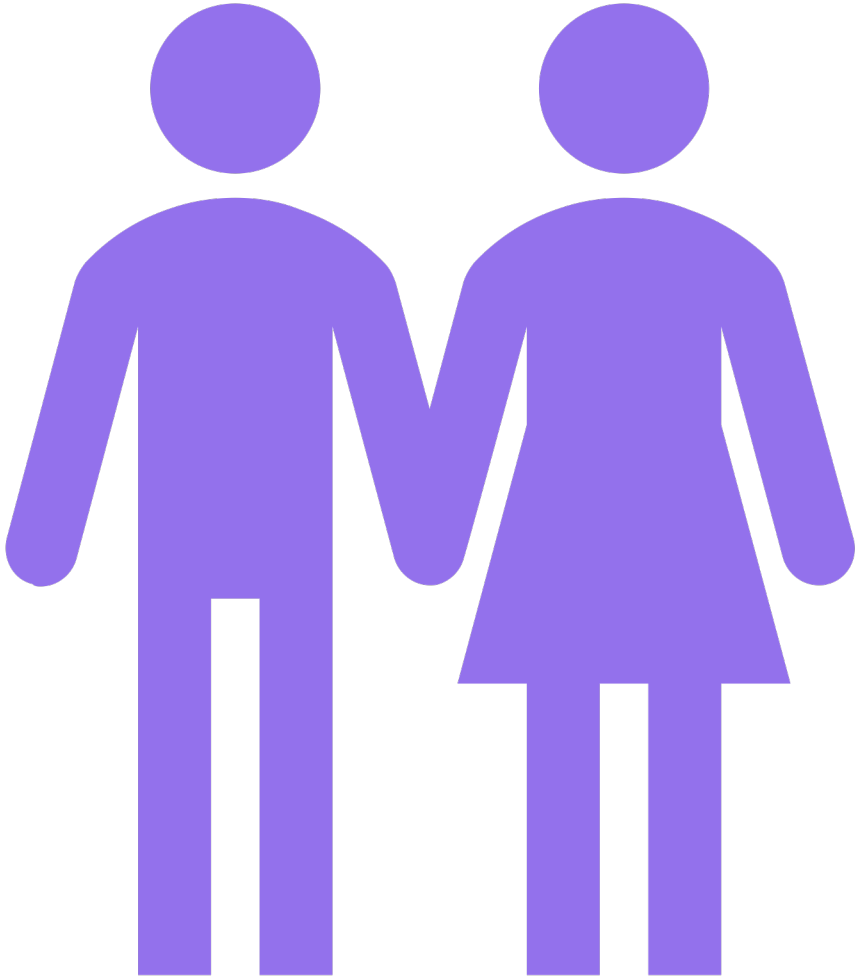
A) A very easy-to-use gold standard model

B) PBTK models

C) Emergent *in silico* models

D) In silico models supporting in vitro experimental design

A) Chemically-induced skin reactions



SKIN: THE LARGEST ORGAN → MOST PRONE TO EXPOSURE OF ORGANIC CHEMICALS

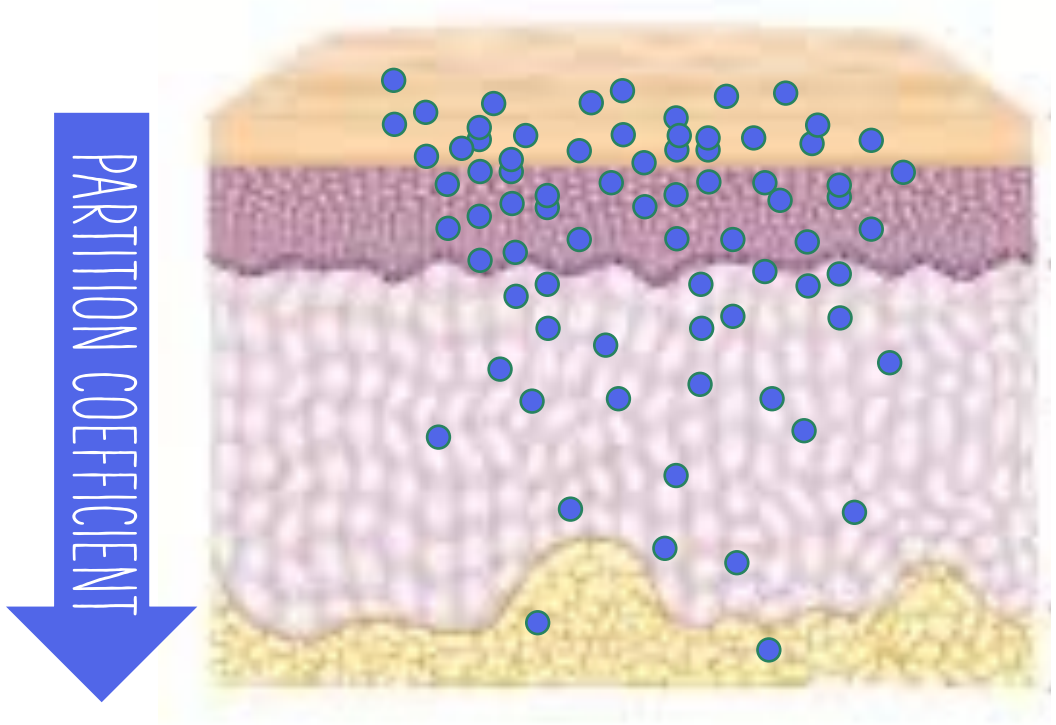
PERMEABILITY COEFFICIENT (K_p): KEY PARAMETER FOR THE ASSESSMENT OF DERMAL EXPOSURE

EXPERIMENTAL DATA OF K_p ARE LIMITED TO FEW HUNDRED ORGANIC CHEMICALS

- IN VITRO/IN VIVO METHODS ARE EXPENSIVE, LABORIOUS (AND HAVE ETHICAL IMPLICATIONS)

HOW DERMWIN* WORKS?

*PART OF THE EPI (ESTIMATION PROGRAM INTERFACE) SUITE SOFTWARE, USA



$$\log K_p = -2.80 + 0.66 \log K_{ow} - 0.0056\, MW$$

PERMEABILITY COEFFICIENT

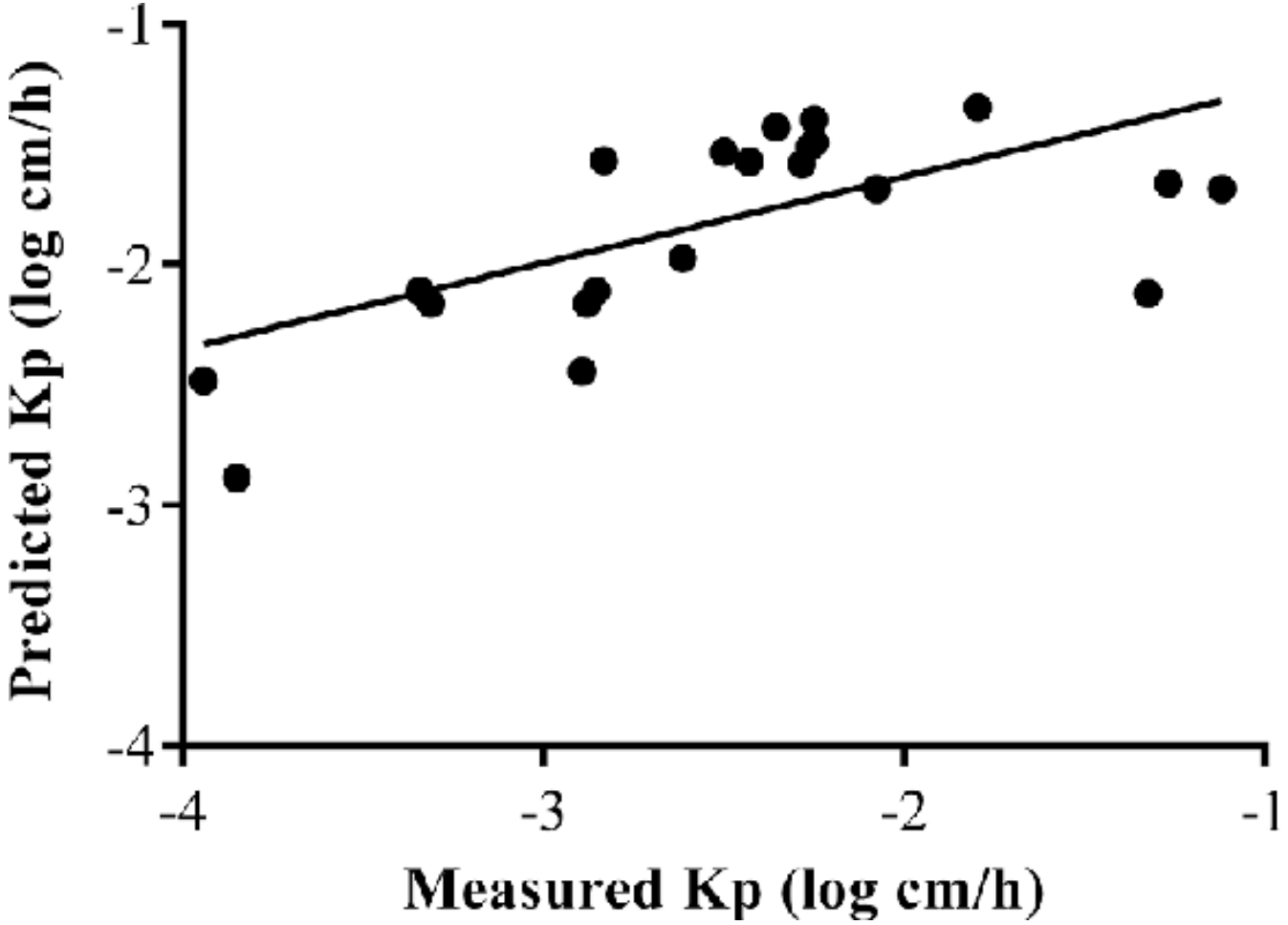
OCTANOL-WATER PARTITION COEFFICIENT → LIPOPHICILITY

MOLECULAR WEIGHT → DIFFUSIVITY

DermWIN model - PROS

- EASY TO IMPLEMENT
- GOLD STANDARD and widely considered a SAFETY ASSESSOR
- OPEN-SOURCE
- GRAPHICAL USER INTERFACE - USER FRIENDLY

DermWIN model - CONS

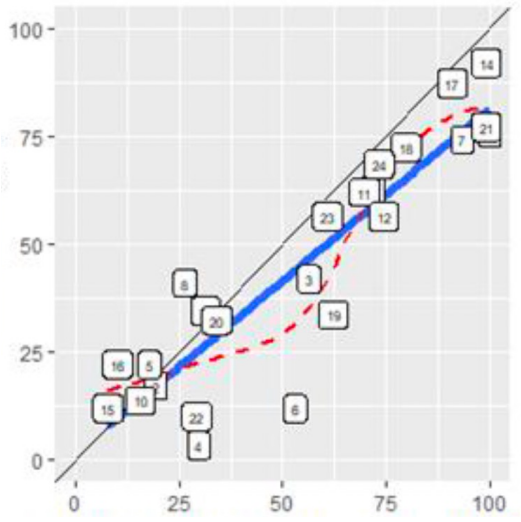


High errors in predicting K_p (R^2 =0.66)

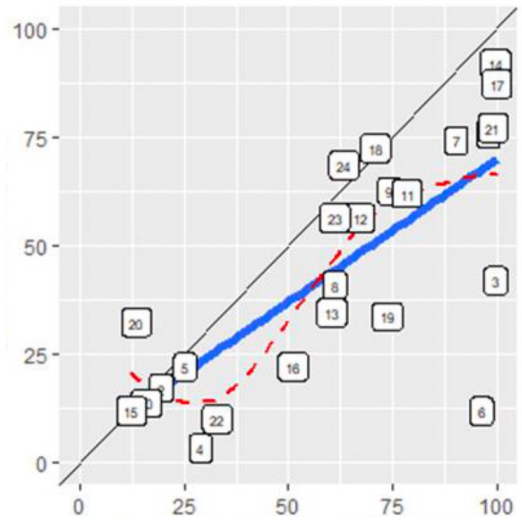
- Octanol is not an exact surrogate phase for the dermal lipid
- Octanol does not reflect all types of interactions that chemicals experience with the structural proteins on the skin

DermWIN model - IMPROVEMENTS

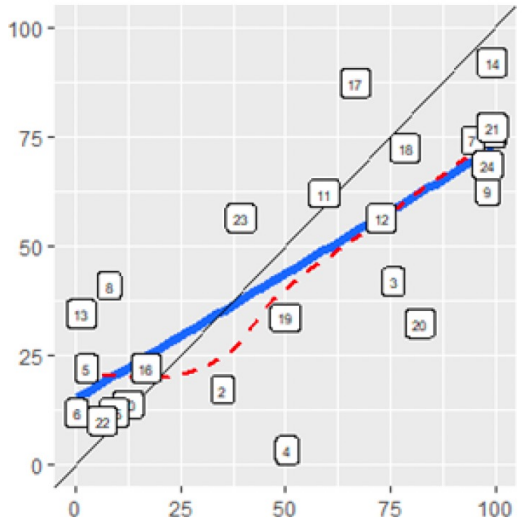
TCAT™



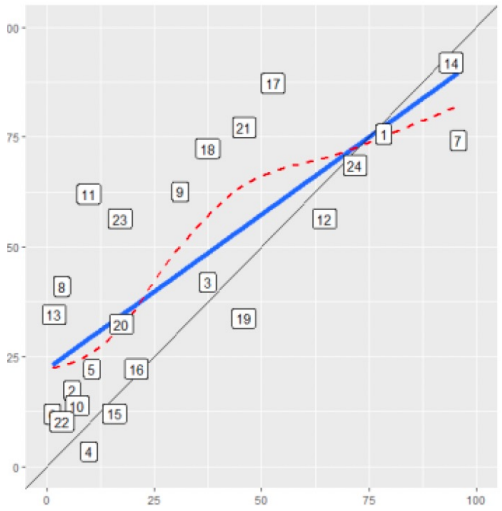
Simcyp



DSkin



CDC



Dermal delivery (%)

Predictive dermal delivery (%)

linear regression

Non-linear regression

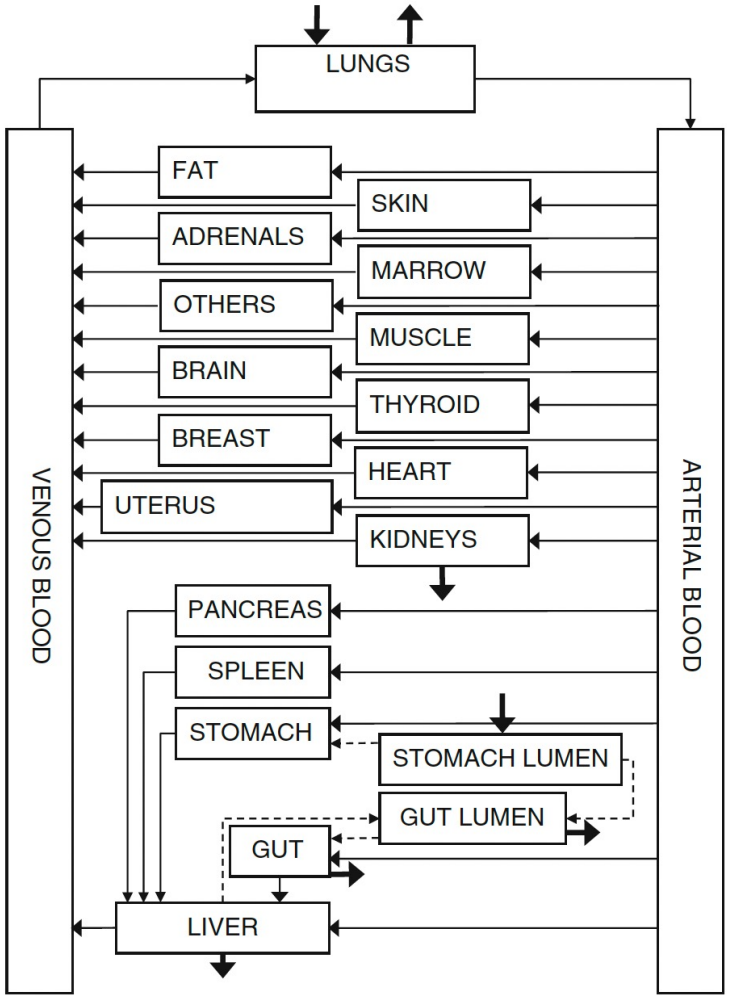
B)

PBTK models

PBTK: physiologically-based toxicokinetic models

DIFFERENT COMPARTMENTS DIRECTLY CORRESPONDING TO A SPECIFIC ORGAN/TISSUE OF THE HUMAN BODY, CONNECTED VIA CARDIOVASCULAR SYSTEM

MODELS OF MASS TRANSPORT, FLUID DYNAMICS and BIOCHEMISTRY



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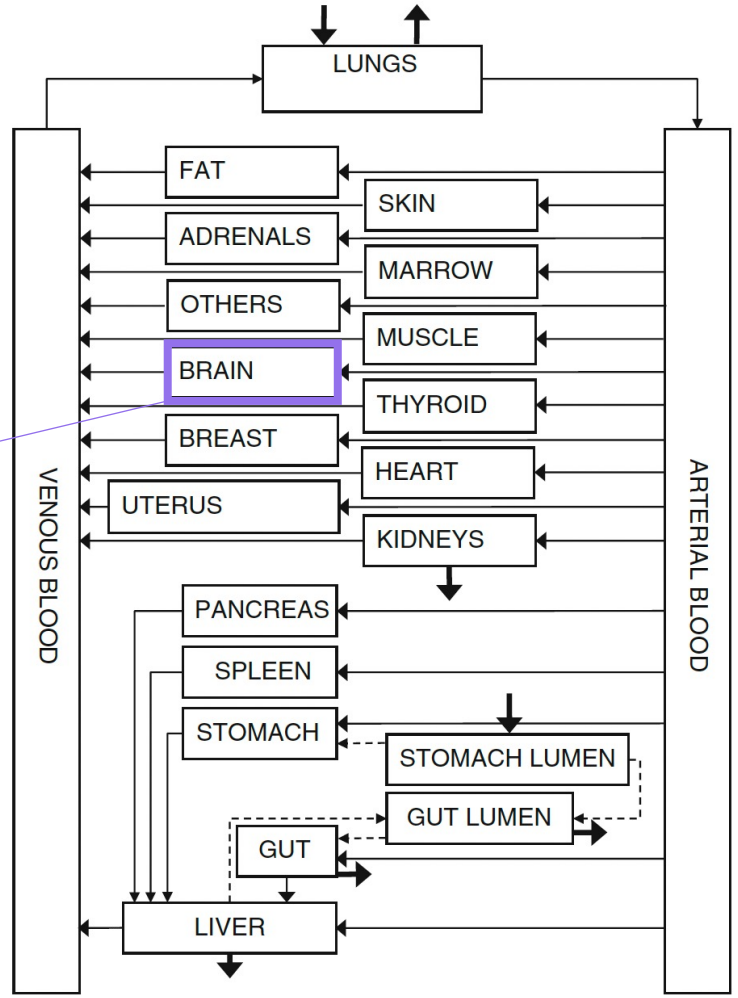
$$\frac{dQ_b}{dt} = F_b\left(C_{art} - \frac{Q_b}{P_b V_b}\right)$$

- $\frac{dQ_b}{dt}$: CHEMICAL CONCENTRATION
- F_b: BLOOD FLOW
- C_{art}: CHEMICAL CONCENTRATION WITHIN THE ARTERIA (INPUT)
- $\frac{Q_b}{P_b V_b}$: RATIO OF TISSUE/VENOUS CHEMICAL CONCENTRATION AT EQUILIBRIUM
- V_b: VOLUME OF THE COMPARTMENT



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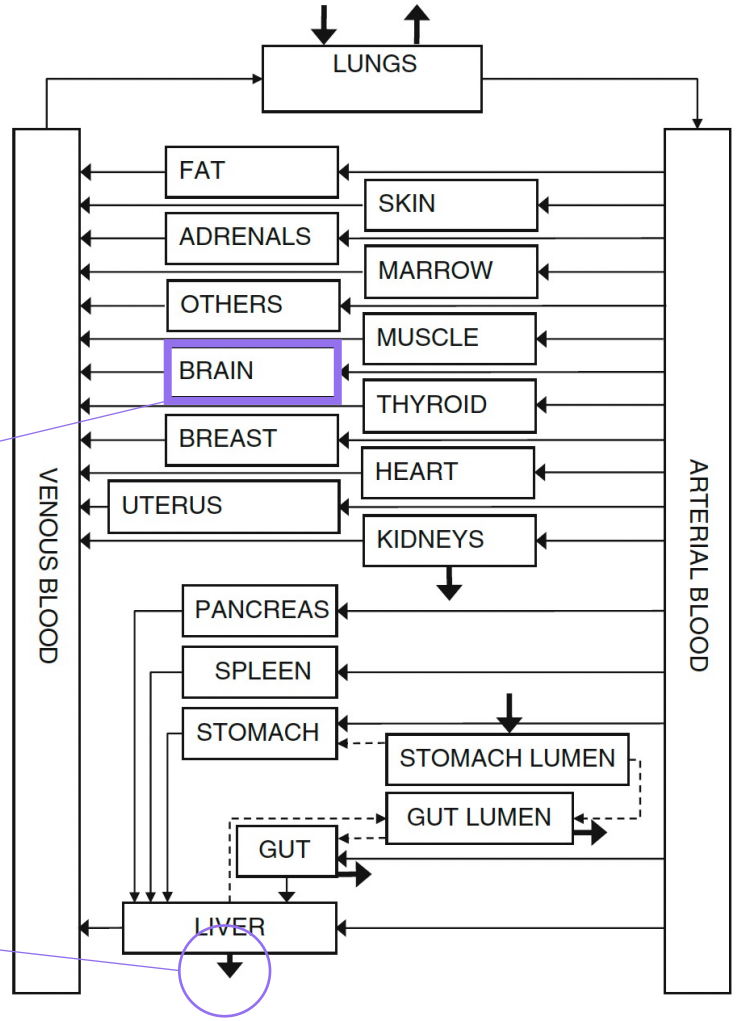
$$v = \frac{d[P]}{dt} = \frac{V_{MAX}[S]}{K_m + [S]}$$



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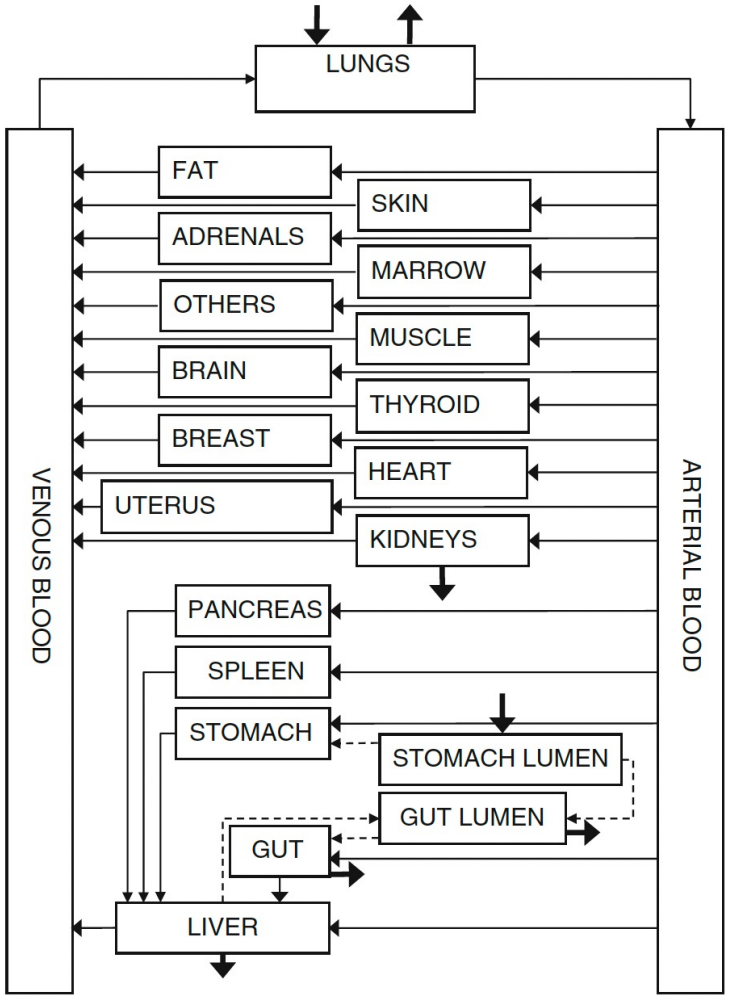
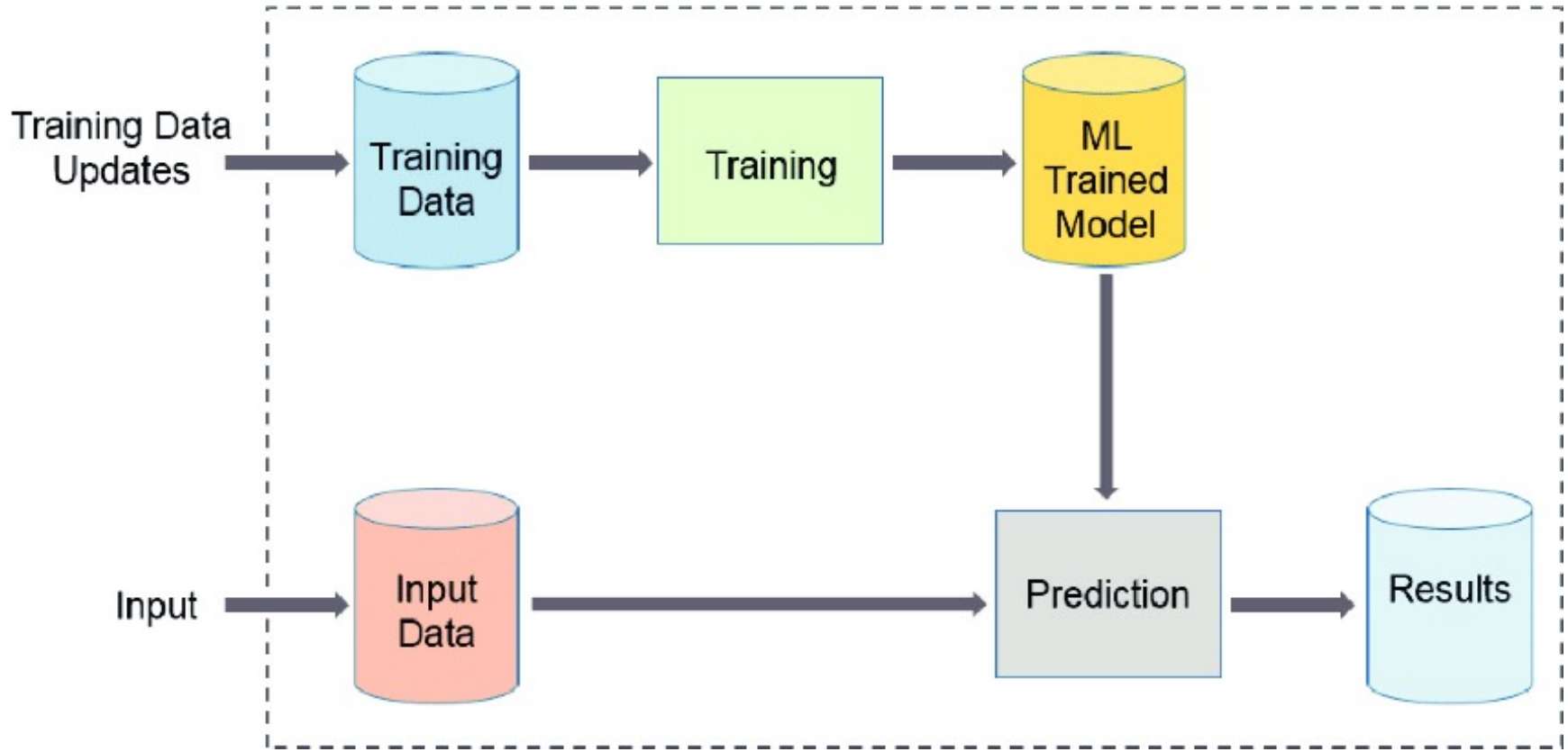
PARAMETERS OF THE MODEL DETERMINED BY MEANS OF

- in vitro data
- human data
- scientific literature
- available databases



C) THE NEW ERA: MACHINE LEARNING

NEW STATISTICAL METHODS ATTEMPTING TO FIND PATTERNS WITHIN DATA

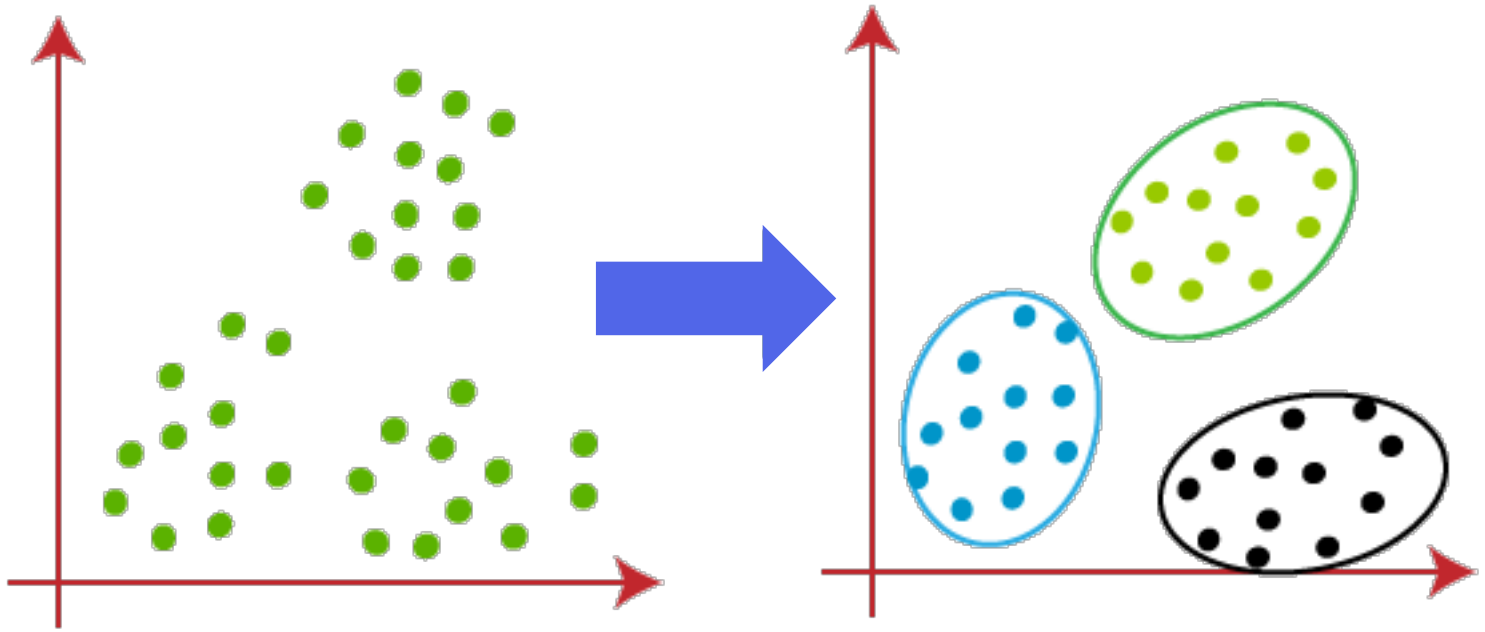


C) THE NEW ERA: MACHINE LEARNING

NEW STATISTICAL METHODS ATTEMPTING TO FIND PATTERNS WITHIN DATA

USED FOR DRUG TOXICITY MORE THAT FOR COSMETICS

NOT ALREADY FOR REGULATORY ENDPOINTS PER SE, BUT RATHER FOR ASSESSING SOME SPECIFIC EFFECTS, E.G., ORGAN TOXICITY



C)

Quantitative Structure Activity Relationship (QSAR) model

1. EXPERIMENTAL DATA or DATABASE
2. EXTRACT MOLECULAR DESCRIPTORS
3. MODELLING
4. MODEL APPLICATION
   (PREDICT THE BEHAVIOUR OF SIMILAR CHEMICALS)

C) DEREK NEXUS

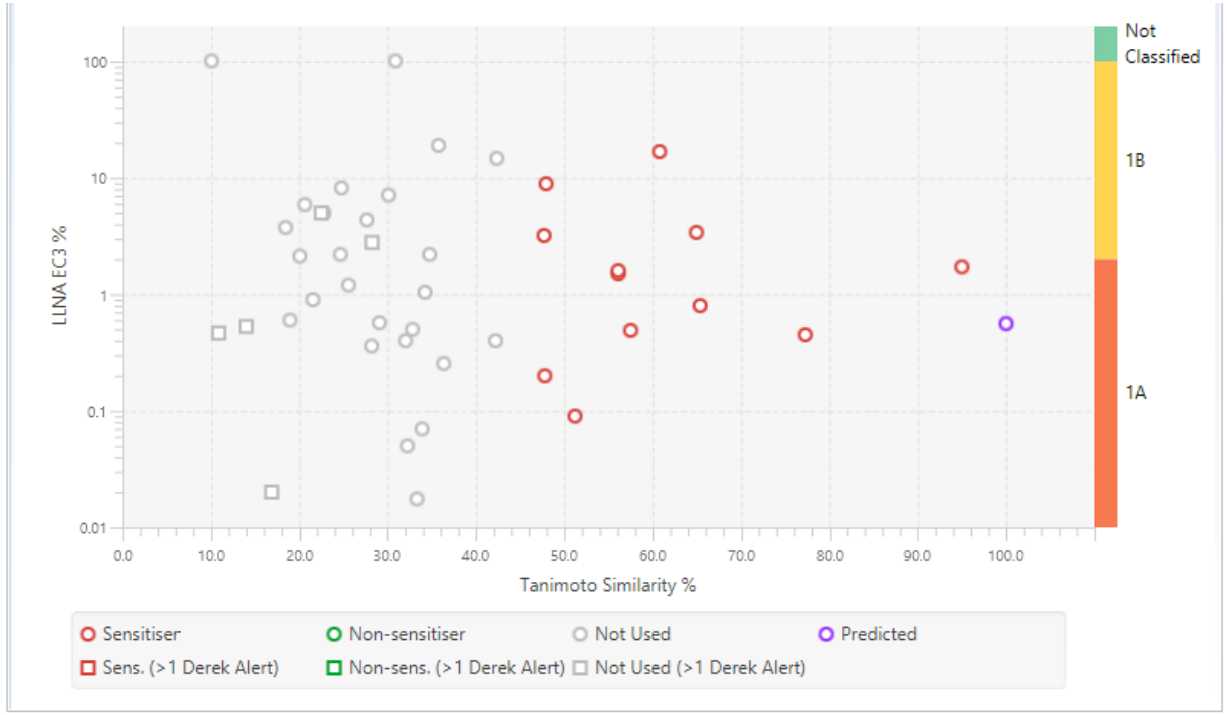
Different tools available online

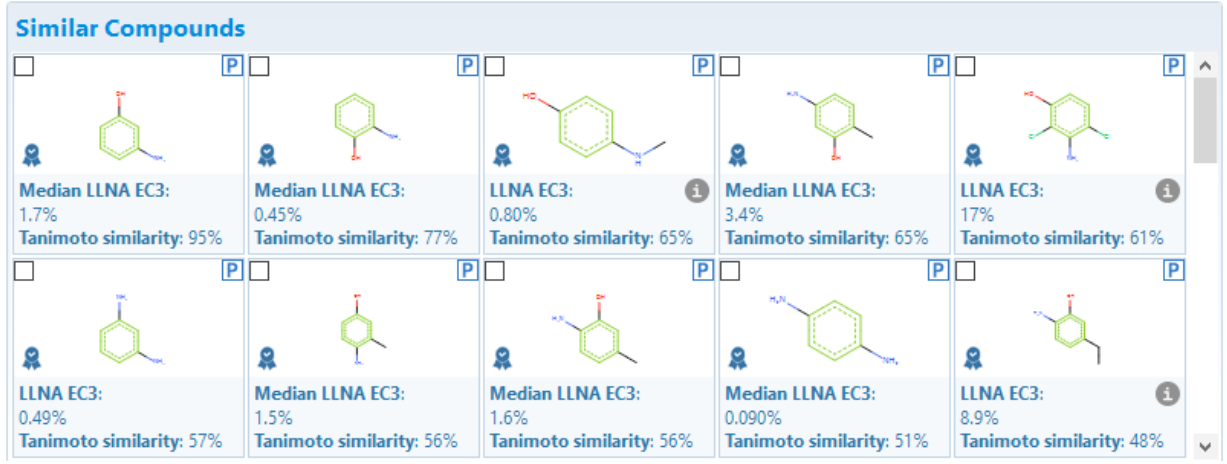
K Nearest Neighbour is a simple algorithm that stores all the available cases and classifies the new data or case based on a similarity measure

EC3 prediction (Effective Concentration required to induce a 3-fold upregulation of lymph node cell proliferation)

Used for skin sensitization

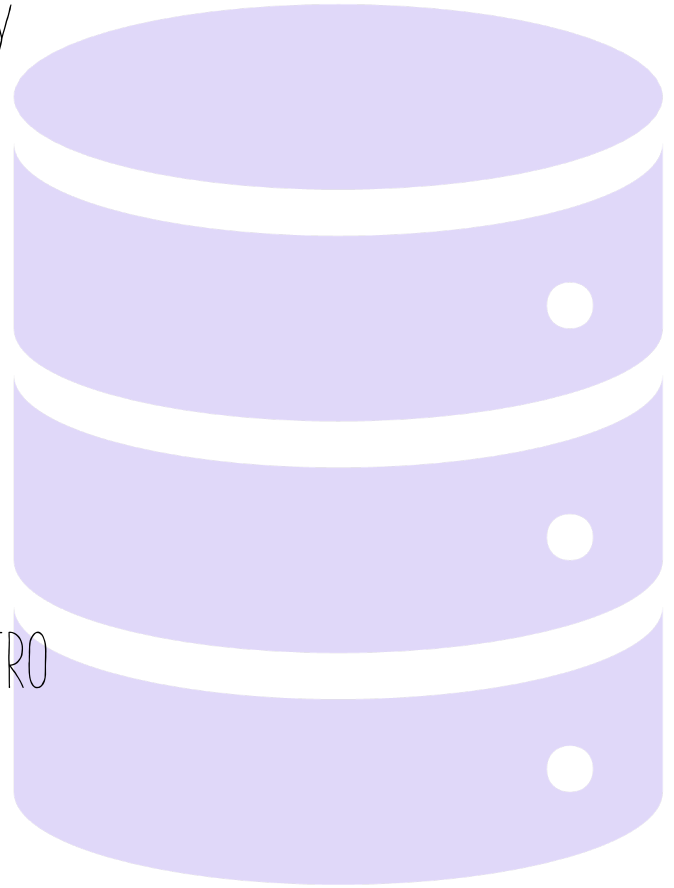
Predicted EC3 for 3,5-diaminophenol:



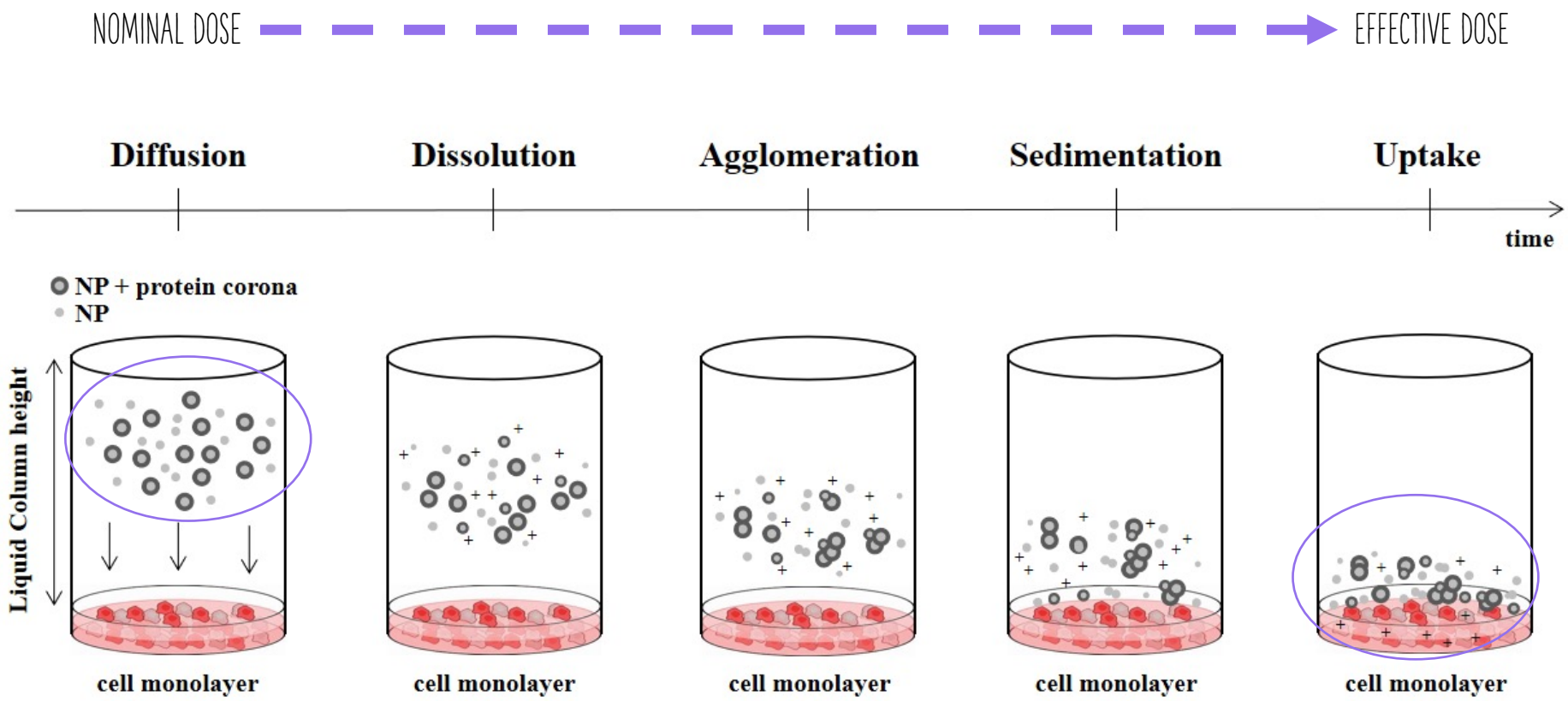


DATABASES

- ALLOWING IDENTIFICATION OF SIMILAR MOLECULES OR GROUPS OF MOLECULES THAT MAY SHARE SIMILAR PROPERTIES
- ALLOWING FOR AN ANALYSIS OF THE PROPERTY SPACE (very broad, giving a chance for developing new computational strategies) OCCUPIED BY COSMETIC INGREDIENTS IN COMPARISON TO PHARMACEUTICAL, BIOCIDES, OTHER INDUSTRIAL CLASSES
- PROVIDING A MEANS TO SELECT CHEMICALS FOR TESTING, E.G., AS A PARTE OF AN IN VITRO TESTING STRATEGY



C) IN SILICO MODELS FOR *IN VITRO* DESIGN

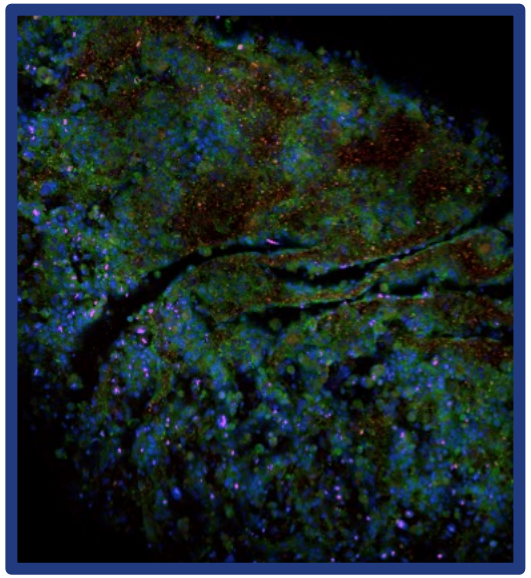


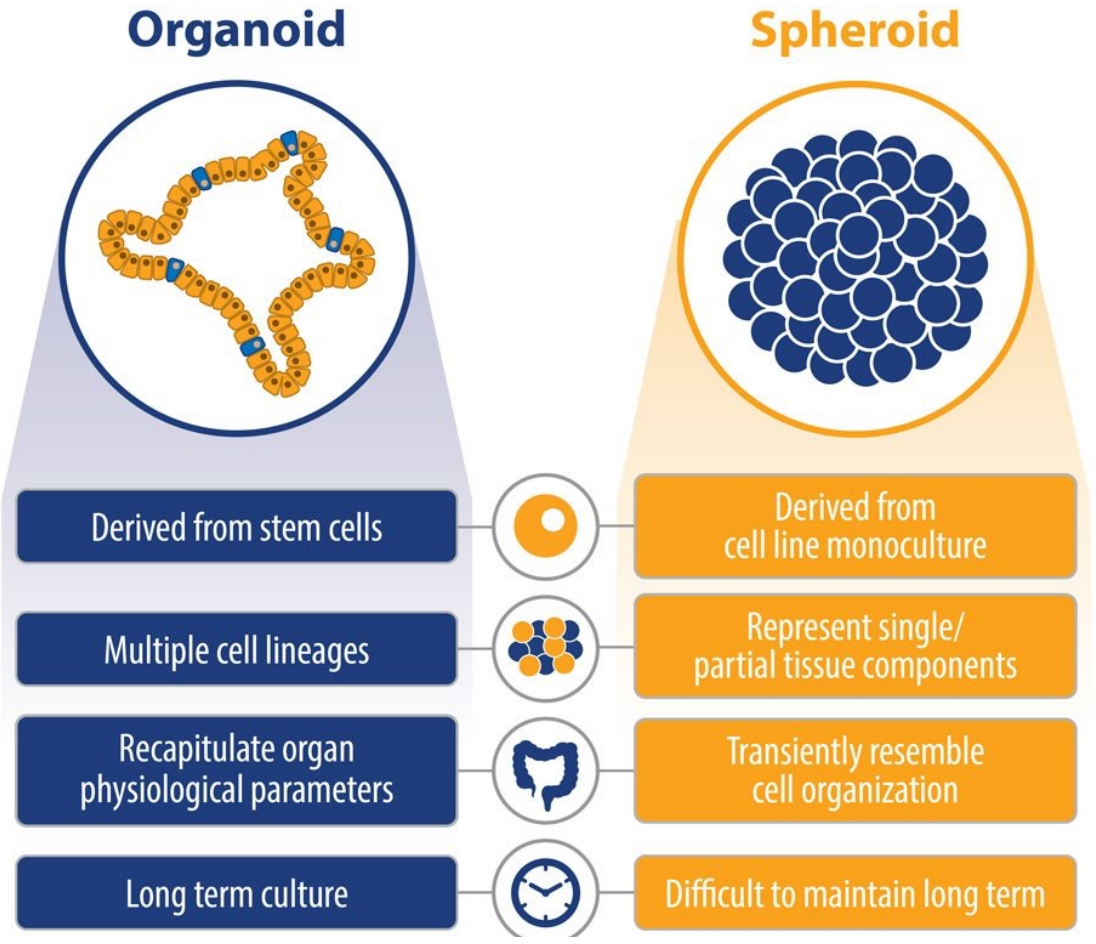
PATROLS
Advanced Tools for NanoSafety Testing

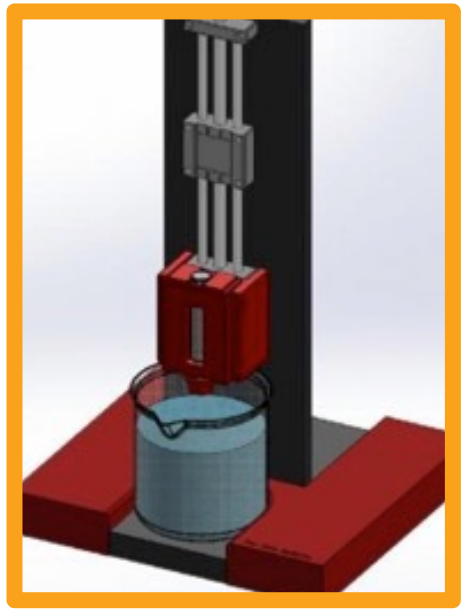
C) IN SILICO MODELS FOR IN VITRO DESIGN

3D STRUCTURES RESEMBLING THE MAIN STRUCTURE AND FUNCTION OF AN ORGAN

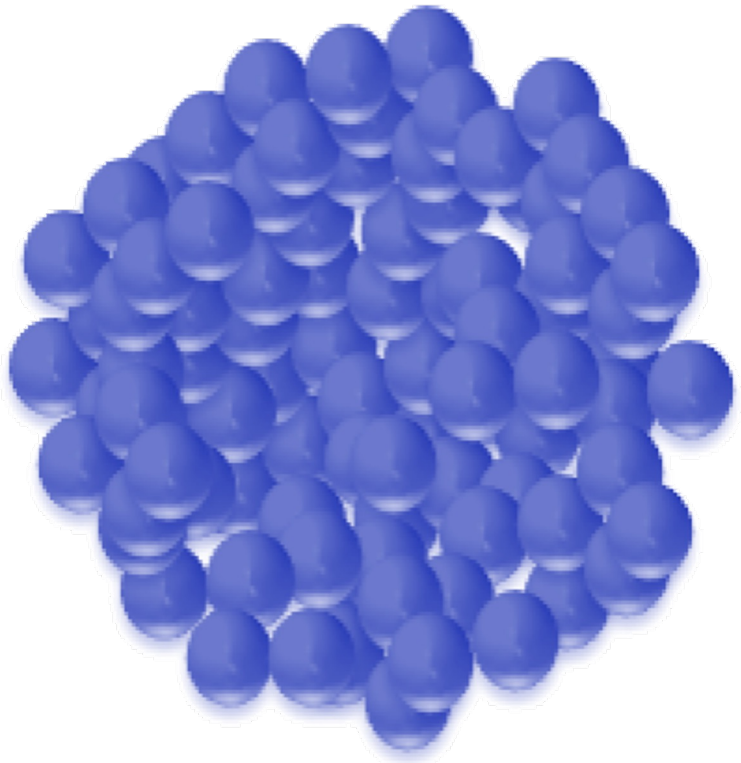
- DIFFERENT GENERATION PROTOCOLS
- VESSEL-FREE
- NECROTIC CORE







C) IN SILICO MODELS FOR IN VITRO DESIGN



$$\frac{\partial[O_2]}{\partial t} = \nabla^2[D_{org}O_2] - \frac{V_{\max}[O_2]}{k_m + [O_2]}$$

↑ OXYGEN DIFFUSION

↑ OXYGEN CONSUMPTION (Michaelis–Menten kinetics)

AFTER EXPOSURE....
ALTERATIONS IN METABOLISM
INFO ABOUT CELL VITALITY

Outline of the course

Some useful definitions

Why in silico models?

In silico models in cosmetics

In silico models: fields of action

Some examples

Closing remarks

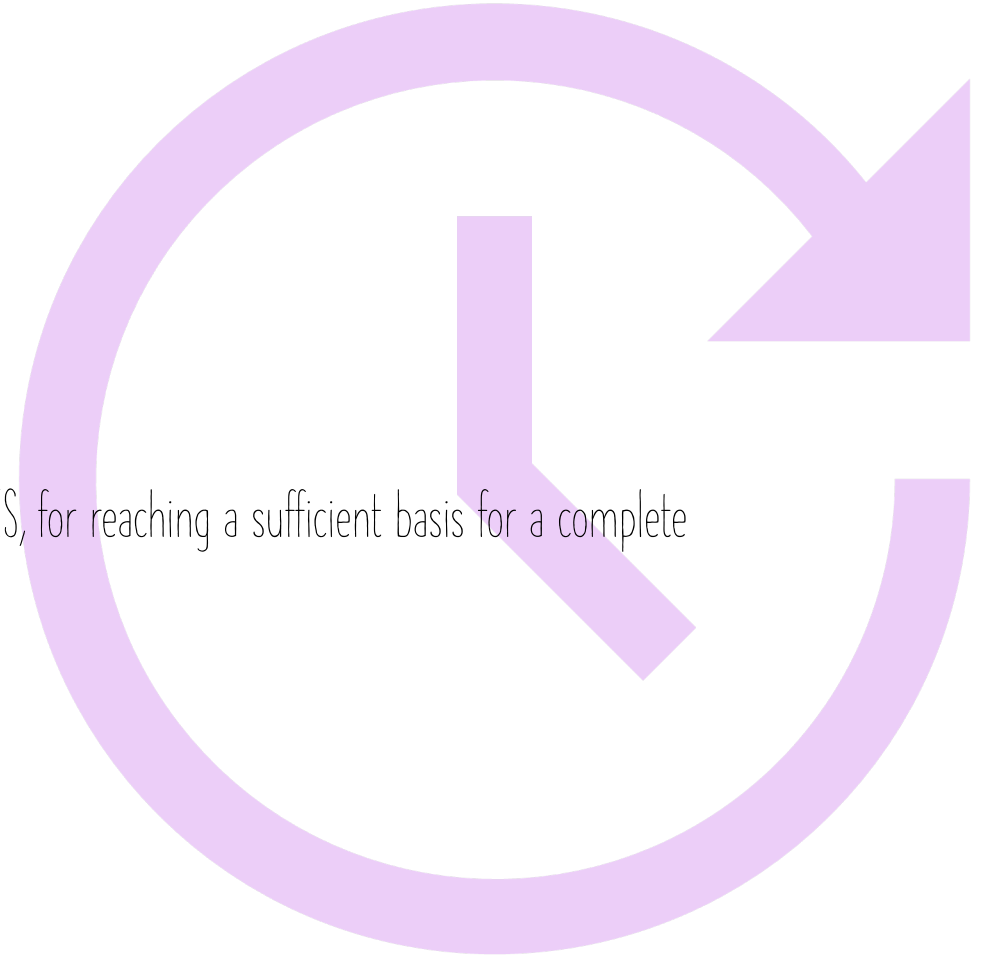
CONCLUSIONS & FUTURE PROSPECTS

- In silico methods:
  - Good descriptors of the toxic effects of a chemical on a biological system
  - Promising predictors of risk assessment

- A trade-off between accuracy and reproducibility to be found

- Integration of different methods for implementing the so-called INTELLIGENT TESTING STRATEGIES, for reaching a sufficient basis for a complete safety assessment
- Exploitation of **databases** (even from animal-based research)!!!!!

- Progresses made will be useful in other regulatory contexts (food, environment)



Thank you

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Research Center E. Piaggio
University of Pisa

DIPARTIMENTO DI
INGEGNERIA
DELL'INFORMAZIONE