In Silico Clinical Trials

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Outline

A. Introduction
- Clinical trials
- Limitations

B. In silico Clinical Trials
- what
- why
- how

C. Examples
- Clinical studies
- Precision dosing
- Research & Development
- Drafting a law

D. AI clinical trials
- AI synthesized patients
- Variational Autoencoders

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A. Introduction

- **Clinical trials**
- **Limitations**

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Clinical trial

- clinical investigation
- evaluates the **effect** (safety/efficacy) of a new drug/device/procedure) on human volunteers (healthy/patients)

The Code of Federal Regulations (21 CFR 312.3) defines a clinical trial as the **clinical investigation of a drug that is administered or dispensed to or used involving one or more human subjects**

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- Patients
- Pathological status
- Drug
- Clinical design

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Experiment: rules & luck

Statistical power

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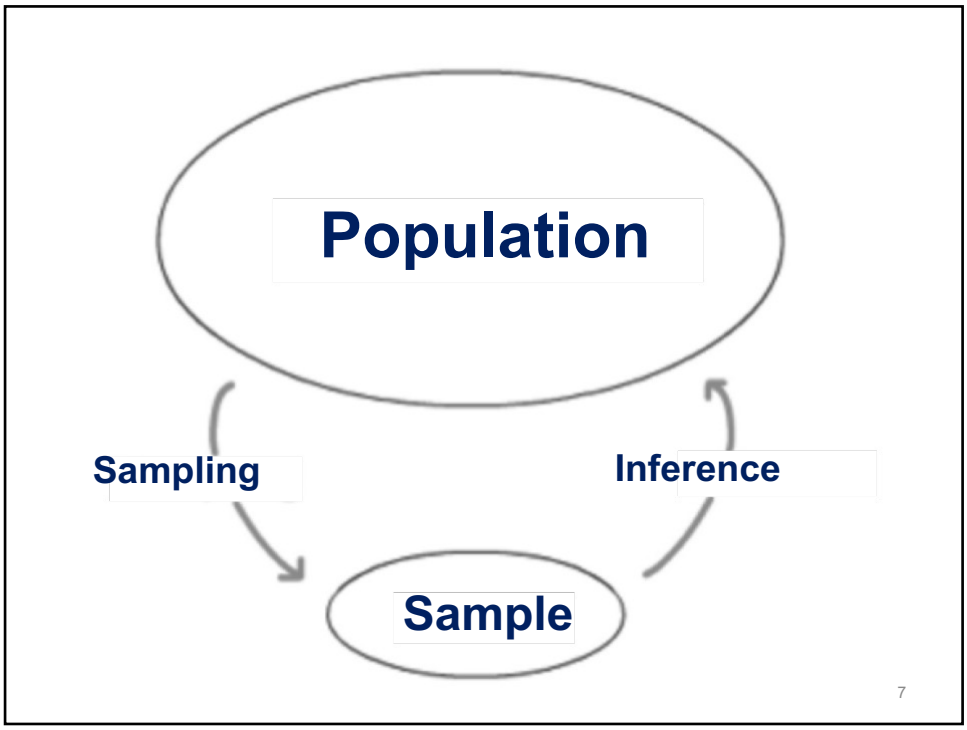

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Limitations/Bias/Errors

- **Time** consuming
- Not all **factors**
- **Drop outs**
- Patient/volunteer **compliance**
- Lack in **biomarker sensitivity**
- **Absence of optimization** in trial design
- **Confounding**
- **Cost**

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Journal of Health Economics 47 (2016) 20–33

Contents lists available at ScienceDirect

Journal of Health Economics

journal homepage: www.elsevier.com/locate/econbase

Innovation in the pharmaceutical industry: New estimates of R&D costs☆

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- The cost of bringing a new pharmaceutical product to the market has been increasing exponentially in the last decades, reaching the **$2.5** billion
- Of these, **$1.5** billion is due the clinical assessment

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- Difficult
- Time
- Cost

Can we find alternatives to predict the outcome of a clinical study?

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Albert Anker, Fortune Teller, 1880

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B. In silico Clinical Trials (ISCT)

- **what**
- **why**
- **how**

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In silico

… Pseudo-Latin for "in silicon", alluding to the mass use of silicon for computer chips

*… is an expression meaning "**performed on computer or via computer simulation**" in reference to biological experiments*

*… The phrase was coined in 1989 as an allusion to the Latin phrases **in vivo**, **in vitro**, and **in situ**, which are commonly used in biology*

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… what

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WIKIPEDIA
The Free Encyclopedia

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In silico clinical trials

From Wikipedia, the free encyclopedia

An ***in silico* clinical trial** is an individualised computer simulation used in the development or regulatory evaluation of a medicinal product, device, or intervention. While completely simulated clinical trials are not feasible with current technology and understanding of biology, its development would be expected to have major benefits over current *in vivo* clinical trials, and research on it is being pursued.

Contents [hide]
1 History
2 Rationale
3 Aim
4 See also
5 References
6 External links

History [edit]

The term *in silico* indicates any use of computers in clinical trials, even if limited to management of clinical information in a database.[1]

Rationale [edit]

The traditional model for the development of medical treatments and devices begins with pre-clinical development. In laboratories, test-tube and other *in vitro* experiments establish the plausibility for the efficacy of the treatment. Then *in vivo* animal models, with different species, provide guidance on the efficacy and safety of the product for humans. With success in both *in vitro* and *in vivo* studies, scientist can propose that clinical trials test whether the product be made available for humans. Clinical trials are often divided into four phases. Phase 3 involves testing a large number of people.[2] When a medication fails at this stage, the financial losses can be catastrophic.[3]

Predicting low-frequency side effects has been difficult, because such side effects need not become apparent until the treatment is adopted by many patients. The appearance of severe side-effects in phase three often causes development to stop, for ethical and economic reasons.[2][4][5] Also, in recent years many candidate drugs failed in phase 3 trials because of lack of efficacy rather than for safety reasons.[2][3] One reason for failure is that traditional trials aim to establish efficacy and safety for most subjects, rather than for individual subjects, and so efficacy is determined by a statistic of central tendency for the trial. Traditional trials do not adapt the treatment to the covariates of subjects:

- Taking account of factors such as the patient's particular physiology, the individual manifestation of the disease being treated, their lifestyle, and the presence of co-morbidities.[4][6]
- Compliance, or lack thereof, in taking the drug at the times and dose prescribed. In the case of a surgically implanted device, to account for the variability in surgeons' experience and technique, as well as the particular anatomy of the patient.[7] However, adjusting the evaluation of the study for noncompliance has proved difficult. Such adjustments often bias the results of the study, and so many health authorities mandate that clinical trials analyse the data according to the intention to treat principle.

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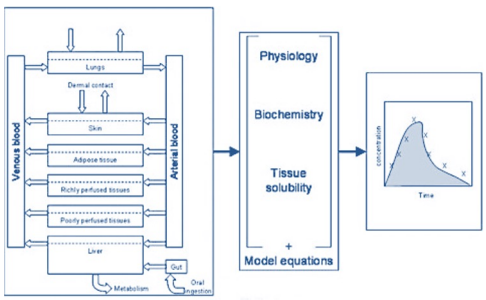
Components

Virtual subjects

adult, child, elder …



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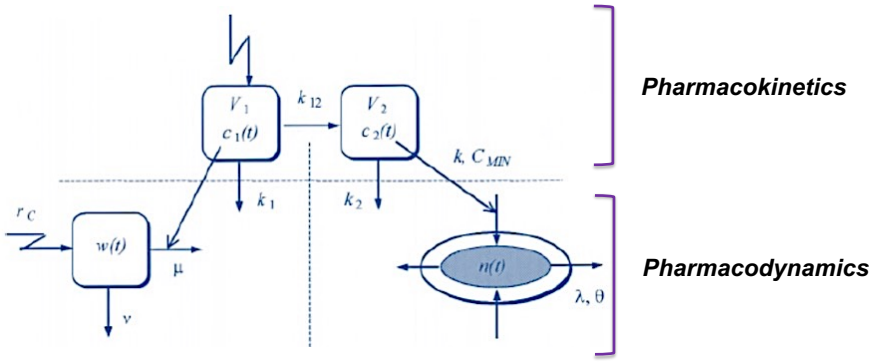
Drug

plasma levels, clinical response, adverse events…



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Pathological status / Disease progress

type of disease, status ..

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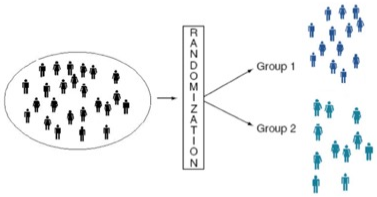
Trial design

type of design, number of arms, sample size, subject enrollment criteria, sampling scheme, dosage regimens…



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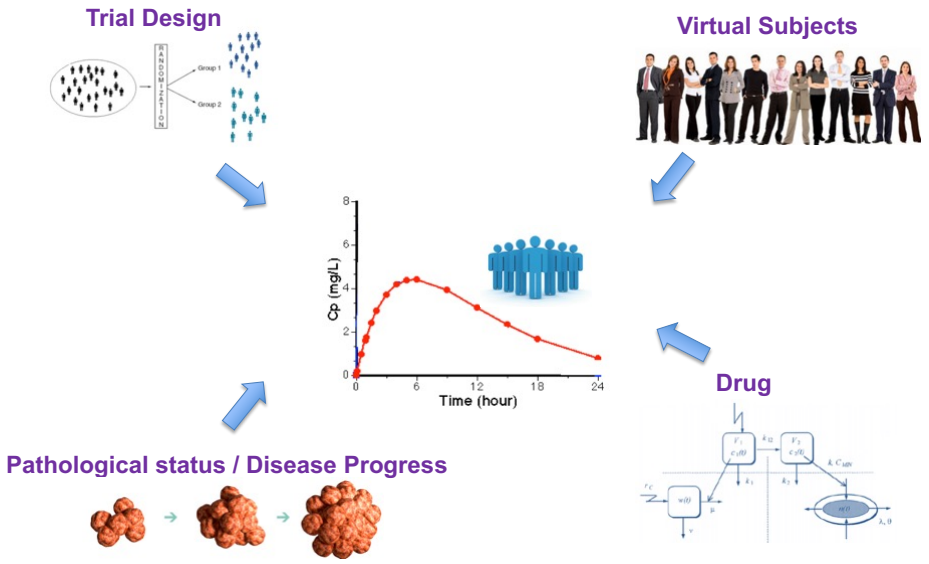
Overall: In silico clinical trials



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Allow **predicting the outcome of a clinical trial** and **testing any condition** that potentially affects the outcome, **without performing the actual study**

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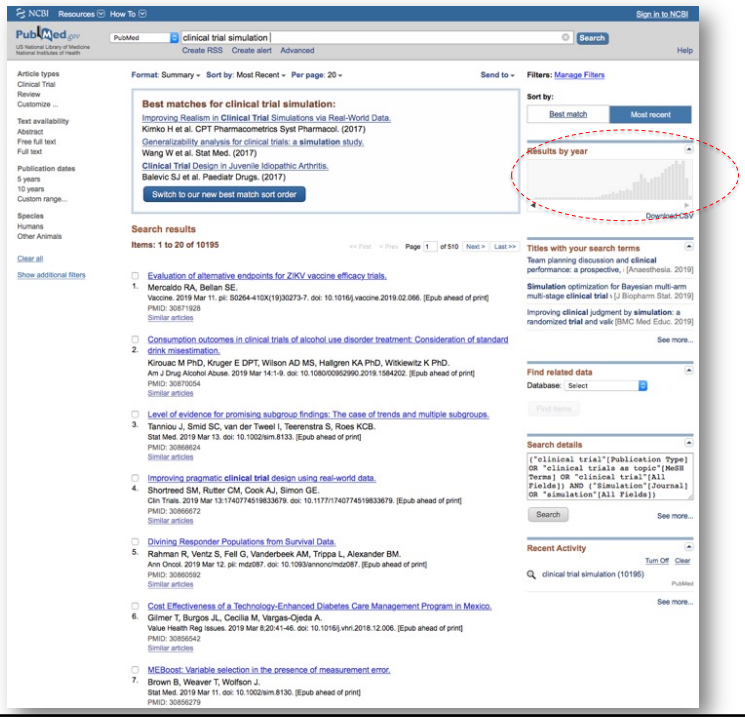

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… why

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Why use ISCT … advantages

- **Dosage** regimens & Dose selection
- **Study design** optimization
- Evaluate **different conditions**
- Investigate **cases not able to be tested in actual practice**
- Identify and quantify **sources of variability** (between- and within-subject, inter-occasion variability)
- Appropriate/reduced **sample size**
- Optimize benefit and minimize the **adverse events**
- **Predict in vivo** performance

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Why use ISCT … question to address

How likely is a trial to succeed?
What is the optimal dosing and treatment schedule for a particular indication?
What is the expected range of responses across doses?
How will a change in inclusion/exclusion criteria affect outcomes?
How frequently should the response be measured?
What is the impact of poor compliance or concomitant disease?
Should drug development be stopped if the results might not support a competitive drug?
Can we shorten Phase 1 and Phase 2 clinical trials?
Can we reduce the cost of the next trial?
Will the drug be successful in Phase 3?

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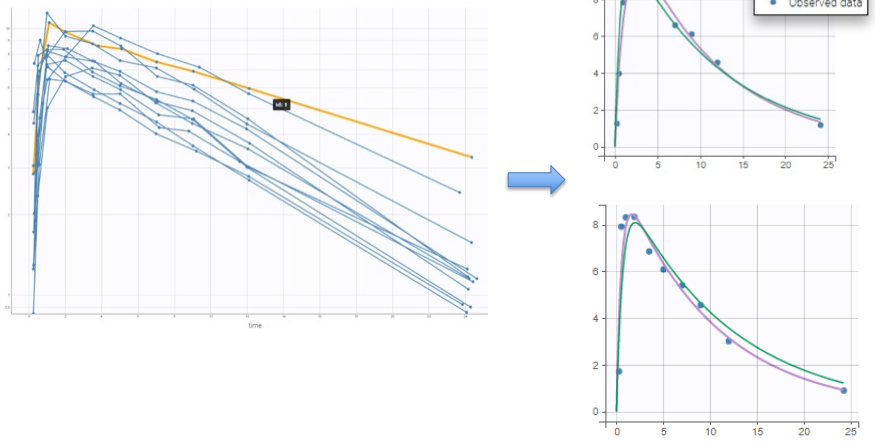
Why use ISCT … descritpion



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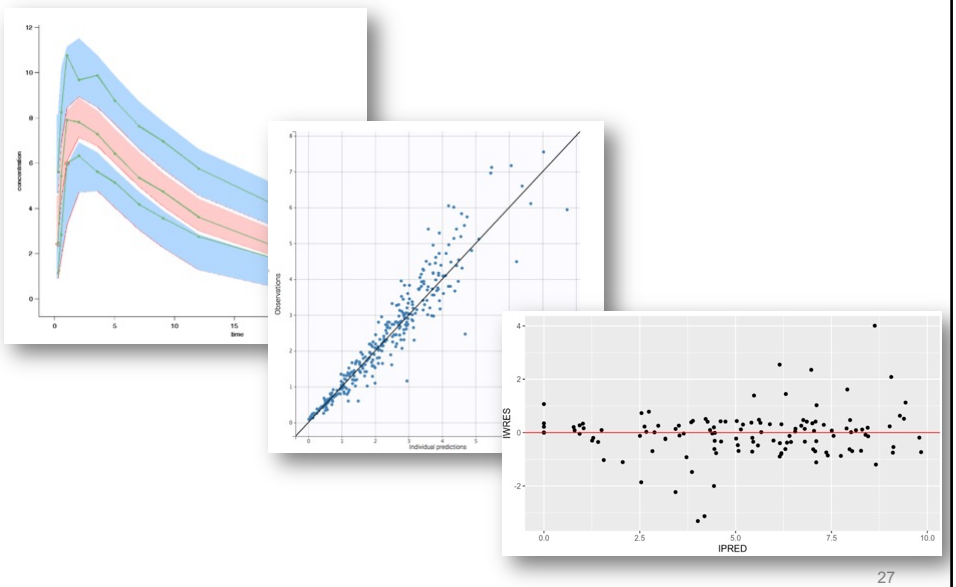
Why use ISCT … validation .. reproducibility



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… how

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The basic idea

- **Define** the situation (… clinical trial)
- **Describe** the system (… mathematics)
- **Simulate** the system (… in silico)

Predict the outcome

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Mathematical models

Model:
- a **miniature representation** of something
- a **system** of data, postulates, and inferences presented as a mathematical description

Mathematical model:
- a representation in **mathematical terms** of the behavior of real devices and objects

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Mathematical formula

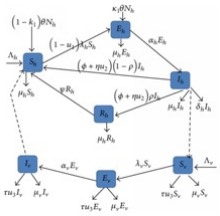
$$F_{\text{net external}} = ma$$

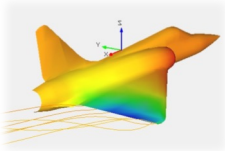
Net force on object = mass of object x acceleration

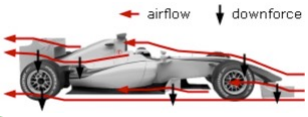
$$A + B \rightleftharpoons A' + B'$$

$$E + S \underset{k-1}{\overset{k+1}{\rightleftharpoons}} ES \underset{k-2}{\overset{k+2}{\rightleftharpoons}} E + P \longrightarrow V = \frac{V_{max}[S]}{K_m + [S]}$$

… a system of …







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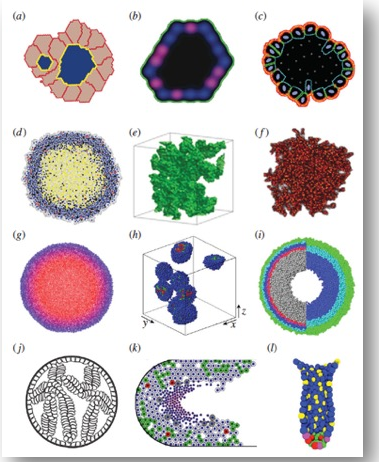
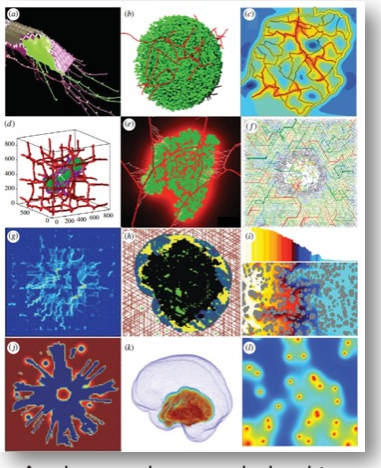
Model pathology

Mathematical models that explicitly take into account the **spatial architecture** of tumors and address tumor **development**, **progression** and **response** to treatments.



Organoids, multicellular spheroids and early tumor development.



Angiogenesis, vascularized tumor growth and tumor treatments

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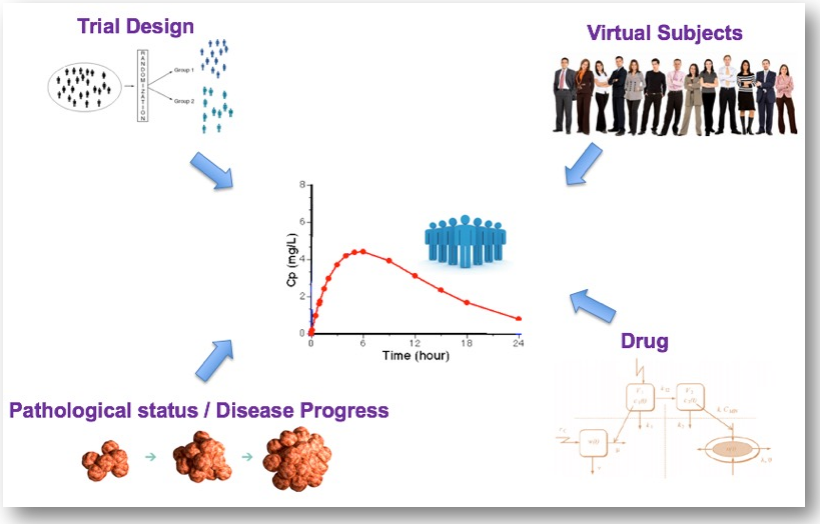
The purpose:



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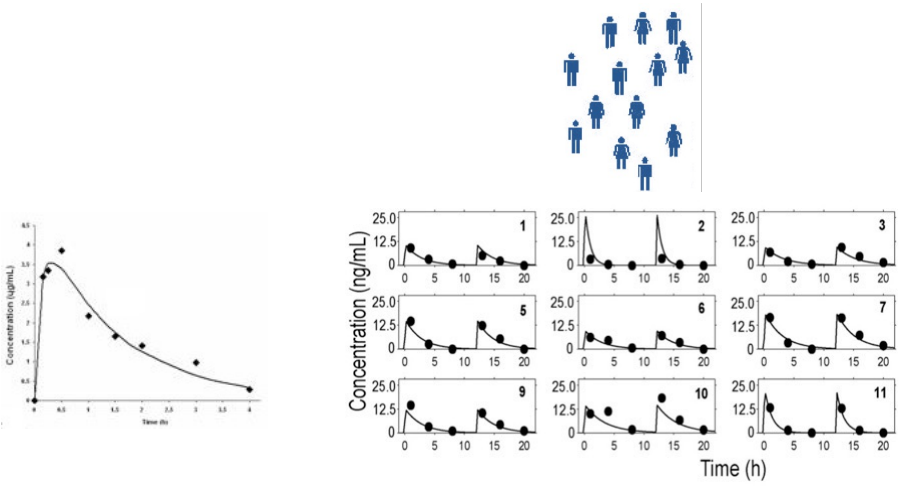
The beginning:
Model the 'average' and 'individual' drug performances



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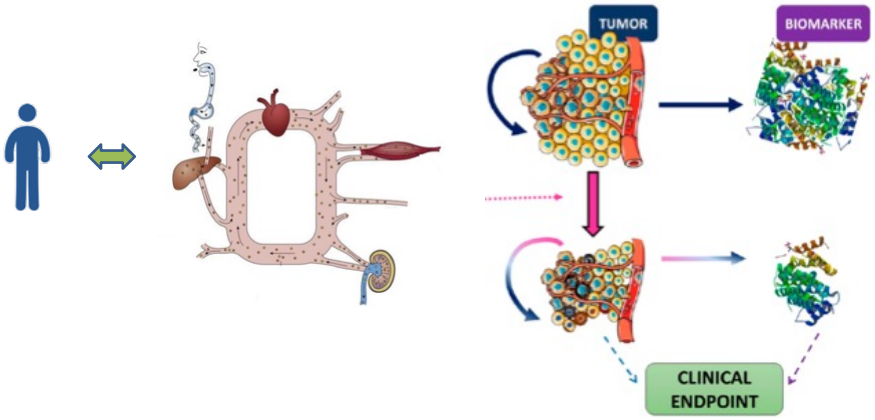
1. Virtual subject(s)

Imitate reality by creating a '**simpler**', but complete version

Drug kinetics | **Drug action**



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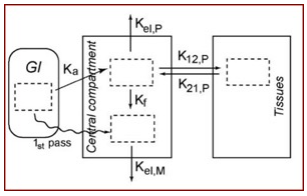
Mathematical description … Model parameters

(based on mass-balance ODEs)



GI: Parent drug

$$\frac{dM_{GI}}{dt} = -K_a \cdot M_{GI} - MM_0 \cdot \frac{M_{GI}}{MM_{50} + M_{GI}}$$

Central compartment: Parent drug

$$\frac{dC_{1,P}}{dt} = K_a \cdot \frac{M_{GI}}{V_{1,P}} - C_{1,P} \cdot (K_f + K_{el,P}) - K_{12,P} \cdot C_{1,P} + K_{21,P} \cdot \frac{M_{2,P}}{V_{1,P}}$$

Central compartment: Metabolite

$$\frac{dC_M}{dt} = K_f \cdot \frac{C_{1,P} \cdot V_{1,P}}{V_{1,M}} - K_{el,M} \cdot C_M + \frac{MM_0}{V_{1,M}} \cdot \frac{M_{GI}}{MM_{50} + M_{GI}}$$

Peripheral compartment: Parent drug

$$\frac{dM_{2,P}}{dt} = K_{12,P} \cdot C_{1,P} \cdot V_{1,P} - K_{21,P} \cdot M_{2,P}$$

$$\left.\begin{aligned} C_{1,P}(0) = C_M(0) = C_{2,P}(0) = 0 \\ M_{GI}(0) = F \cdot Dose \end{aligned}\right\}$$ **Initial conditions**

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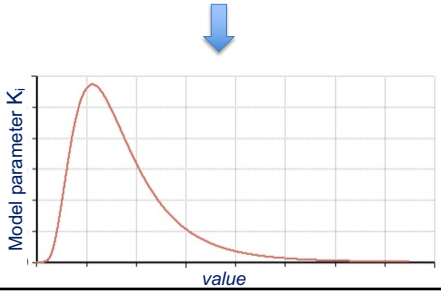
1. Between-Subject Variability

Patient *i*

Sample of patients



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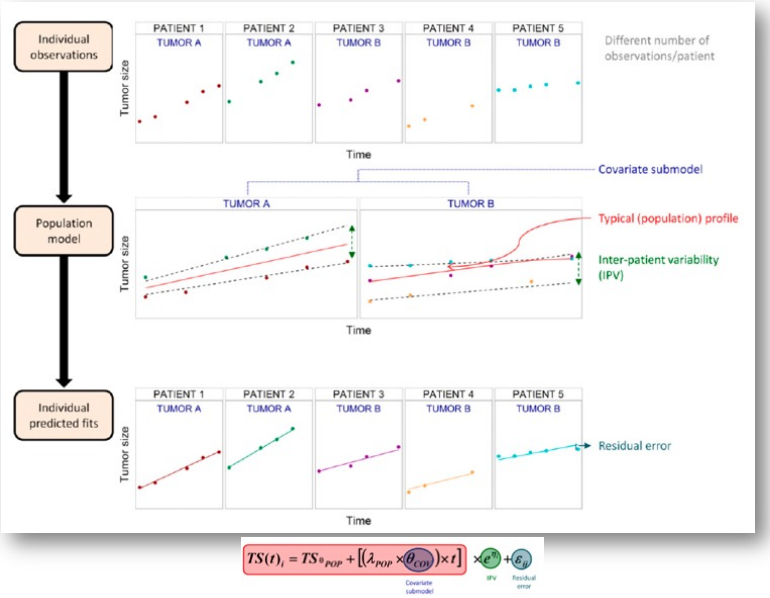
Describe the typical time course of **tumor size** and quantify the **interpatient variability**



$$TS(t)_i = TS_{0_{POP}} + \left[\left(\lambda_{POP} \times \theta_{COV}\right) \times t\right] \times e^{\eta_i} + \varepsilon_{ij}$$

Covariate submodel · IPV · Residual error

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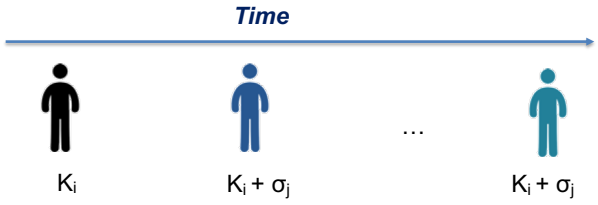
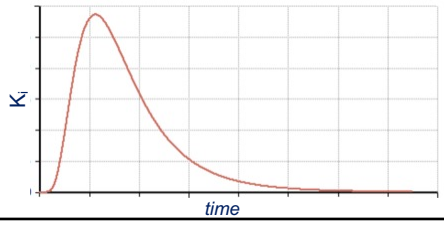
2. Within-Subject Variability

- Circadian rhythm
- Environment
- Physiology changes
- …





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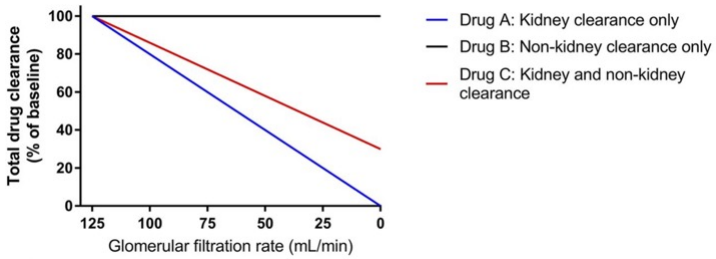
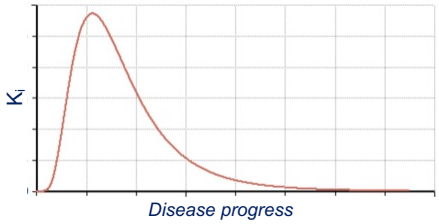
2. Pathological status / Disease progress





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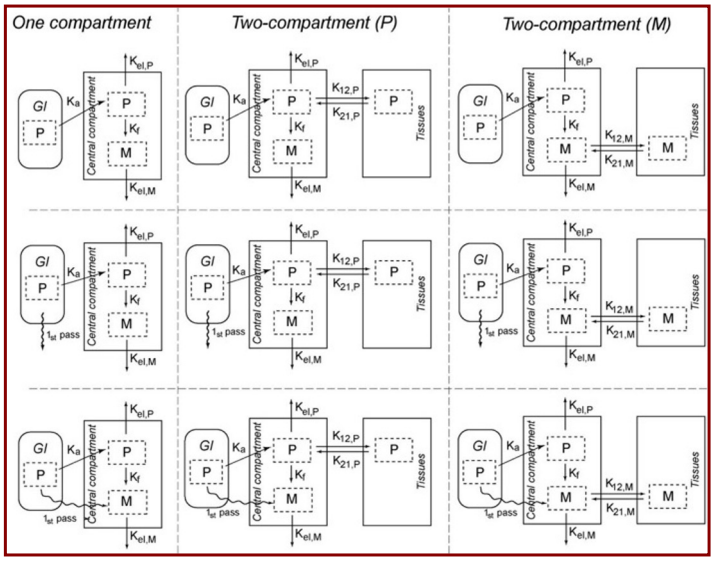
3. Drug

Different drugs ➔ Different models



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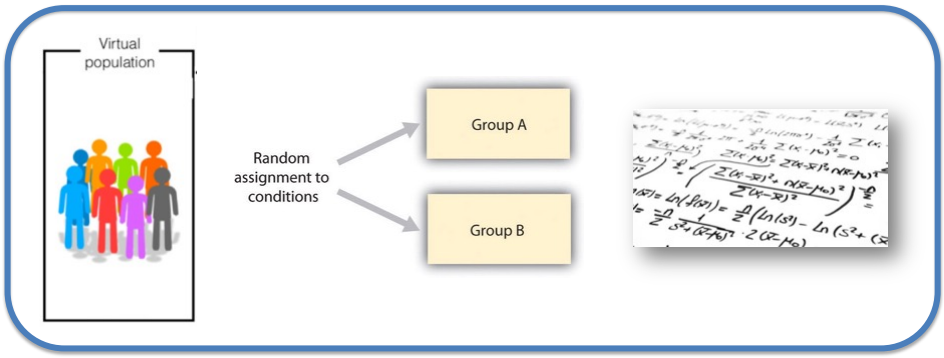
4. Trial design



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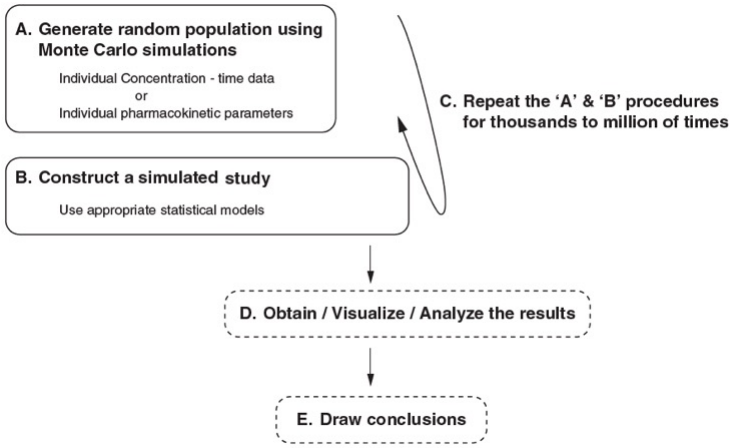
Overall: Schematic representation of the classical modeling and simulation methodology used in in-silico clinical trials



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Improving Realism via Real-World Data

Reality

Model

… Improved Realism

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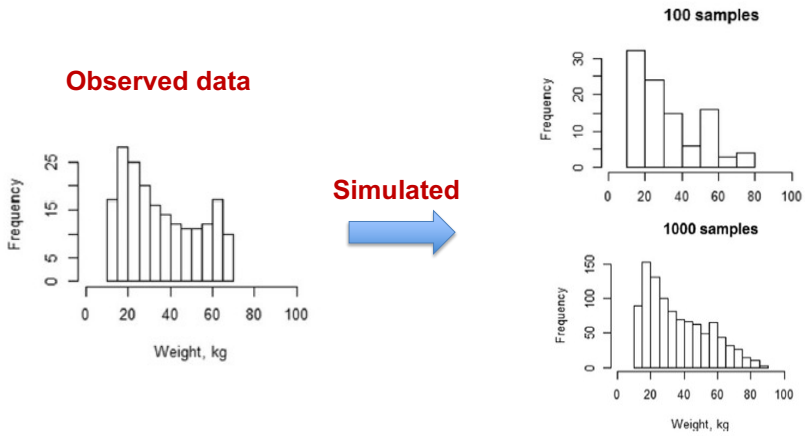
Example: simulations in pediatrics

- The models often include **body weight** as a covariate
- A certain number of **ages** are usually sampled **uniformly**



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Implementation

Software:

- Use **commercial** *or* **publicly available**

LIXOFT
NONMEM
The program for Nonlinear Mixed Effects Modeling
Phoenix WinNonlin
CERTARA

- User created **code**

R
MATLAB
python

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Modelling and Simulation Working Party

The Modelling and Simulation Working Party (MSWP) provides support to the European Medicines Agency's scientific committees and working parties on modelling and simulation relating to medicines, including the Committee for Medicinal Products for Human Use (CHMP), the Paediatric Committee (PDCO) and the Scientific Advice Working Party (SAWP). It also supports more general methodological discussions and qualification procedures regarding modelling and simulation.

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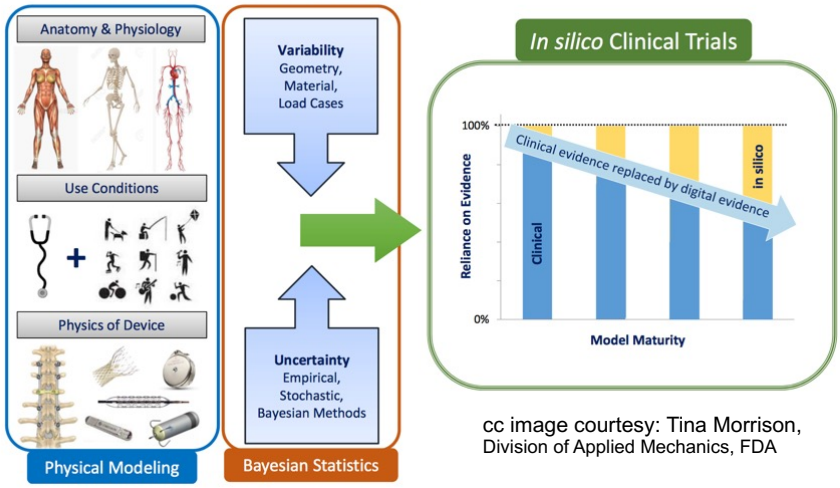
FDA U.S. FOOD & DRUG ADMINISTRATION

2019 Conference: The Role of *Digital Evidence* to Support Personalized Patient Healthcare.

Adapted from: Tina Morrison

Concept of "*In Silico* Clinical Trials"



cc image courtesy: Tina Morrison,
Division of Applied Mechanics, FDA

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C. Examples

- Clinical studies
- Posology
- Precision dosing
- Research & Development
- Drafting a law

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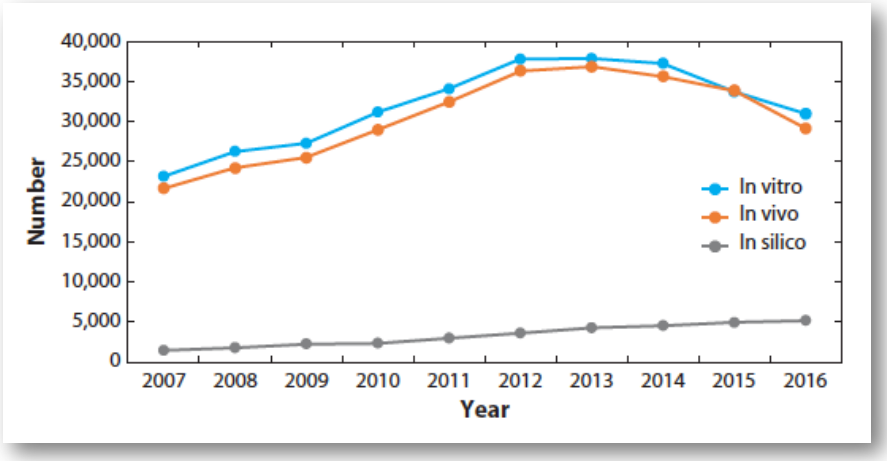
The number of in silico publications by year according to Google Scholar



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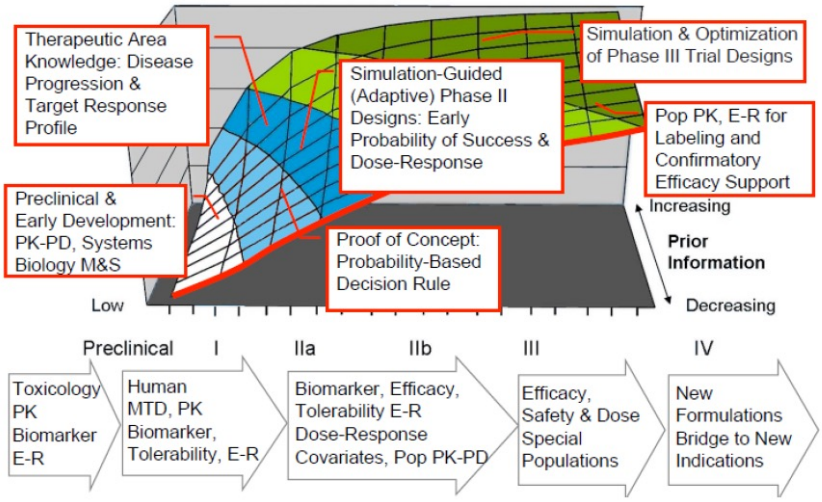
In silico trials in drug development process



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C1. Clinical studies

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Applications

- Suggest the appropriate **Clinical design**
- **Sample size** estimation
- Waive the need of many clinical studies: **Study extrapolation**

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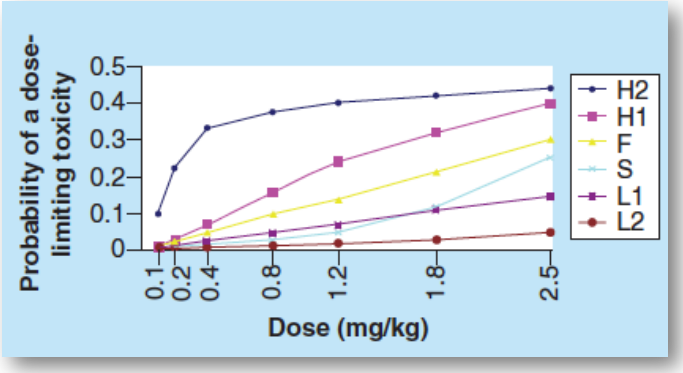
Phase I study:
Simulations to determine MTD

Simulations were conducted on **six** potential dose–toxicity curves



1. **F**: Flat slope at maximum tolerated dose
2. **H1**: High-toxicity profile 1
3. **H2**: High-toxicity profile 2
4. **L1**: Low-toxicity profile 1
5. **L2**: Low-toxicity profile 2
6. **S**: Steep slope at maximum tolerated dose

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Phase II study:
Simulations to better define dose–response relationships

To estimate the **probability of success** for **five** different **study designs**

Design	Design options			
	Dose–response model	Response adaptive randomization	Arm dropping	Early stopping criteria†
Design A	No	No	No	No
Design B	Yes	No	No	No
Design C	Yes	Yes	No	No
Design D	Yes	Yes	Yes	No
Design E	Yes	Yes	No	Yes

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Probability of success

Design	Dose–response curves			
	Null	C1	C2	U-shaped
Design A	0.15	0.62	0.73	0.83
Design B	0.15	0.61	0.72	0.82
Design C	0.04	0.56	0.73	0.88
Design D	0.13	0.60	0.71	0.82
Design E	0.05	0.58	0.71	0.89

Mean sample size

Design	Dose–response curves			
	Null	C1	C2	U-shaped
Designs A/B/C†	640	640	640	640
Design D	554	590	585	614
Design E	444	549	520	492

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Phase III study:
Guide group sequential designs

To test an investigational women's therapy **against an active comparator**, using a **non-inferiority design** with **90% power** and a **one-sided 2.5% significance level**

Simulations were performed to allow decision making on:

- What **stopping rules** should be used?
- **How many interim analyses** should be conducted and when they should take place?
- How the **robustness** of the design would be affected by various assumed response rates?

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The impact of two possible stopping rules for **futility** (*inability to demonstrate noninferiority*)

- The **O'Brian-Fleming** rule requires strong evidence for stopping early, but has a smaller impact on the maximum sample size.
- The **Pocock rule** more easily allows for stopping early, but tends to lead to a larger maximum sample size

Planned sample sizes and numbers of interim analyses

Number of interim analyses	Analysis	O'Brien–Fleming		Pocock	
		30% response rate	40% response rate	30% response rate	40% response rate
Two	Interim 1	465	531	509	582
	Interim 2	697	797	764	872
	Final	929	1062	1018	1163
Three	Interim 1	376	429	416	476
	Interim 2	563	644	624	713
	Interim 3	751	858	832	951
	Final	939	1073	1040	1189

59

C2. Posology

60

60

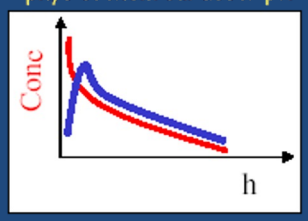
Physiologically Based PharmacoKinetic models, PBPK

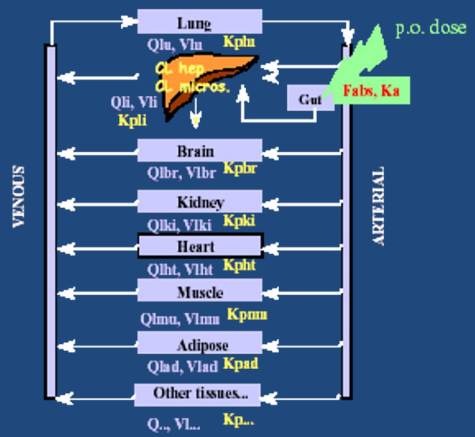
61

Input Parameters Required in PBPK Models

Species specific
- tissue volume (V)
- Flow rates (Q)

Compound specific
- tissue partitioning (Kp)
- CL (hep, microsomes)
- protein binding
- physicochemical descript.





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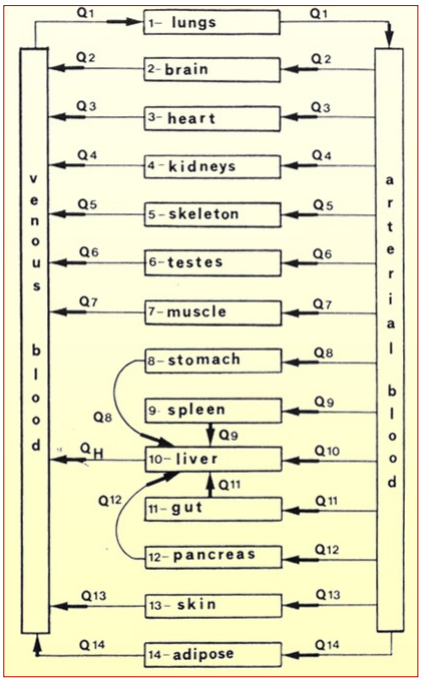


63

Blood flow

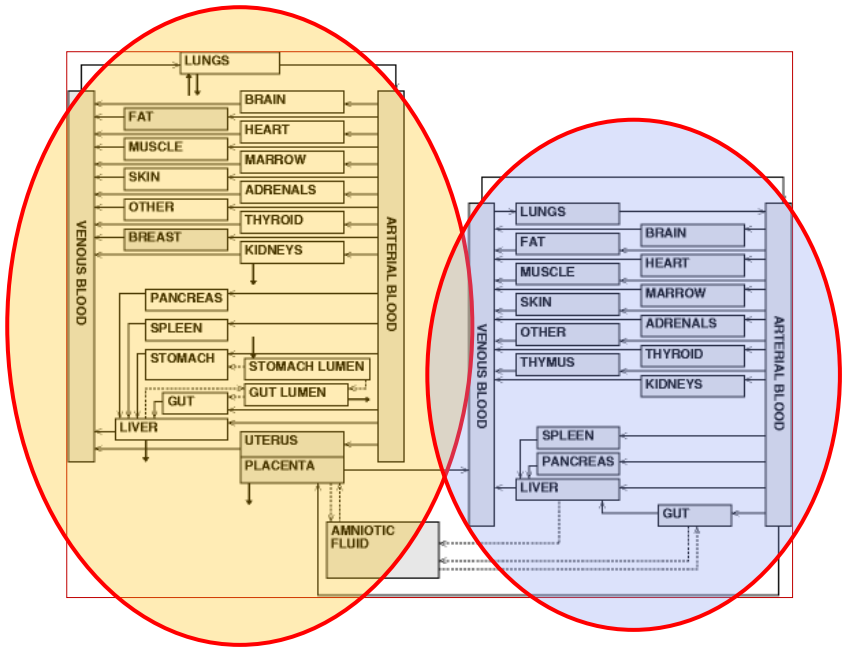
Blood flows	Mouse	Rat	Rabbit	Monkey	Dog	Human
Brain	-	1.3	-	72	45	700
Liver	1.8	13.8	177	218	309	1450
Kidneys	1.3	9.2	80	138	216	1240
Heart	0.28	3.9	16	60	54	240
Spleen	0.09	0.63	9	21	25	77
Gut	1.5	7.5	111	125	216	1100
Muscle	0.91	7.5	155	90	250	750
Adipose	-	0.4	32	20	35	260
Skin	0.41	5.8	-	54	100	300
(mL/min)						

64

Organ volumes

Organ volumes	Mouse	Rat	Rabbit	Monkey	Dog	Human
Brain	-	1.2	-	-	72	1450
Liver	1.3	19.6	100	135	480	1690
Kidneys	0.34	3.7	15	30	60	280
Heart	0.095	1.2	6	17	120	310
Spleen	0.1	1.3	1	-	36	192
Lungs	0.1	2.1	17	-	120	1170
Gut	1.5	11.3	120	230	480	1650
Muscle	10.0	245	1350	2500	5530	35000
Adipose	-	10.0	120	-	-	10000
(mL)						

65



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C3. Precision dosing

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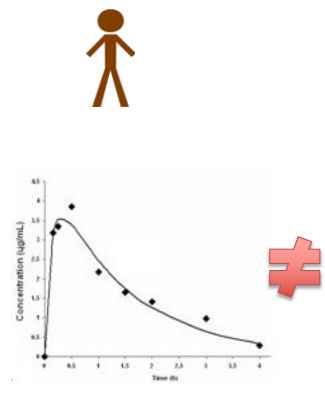

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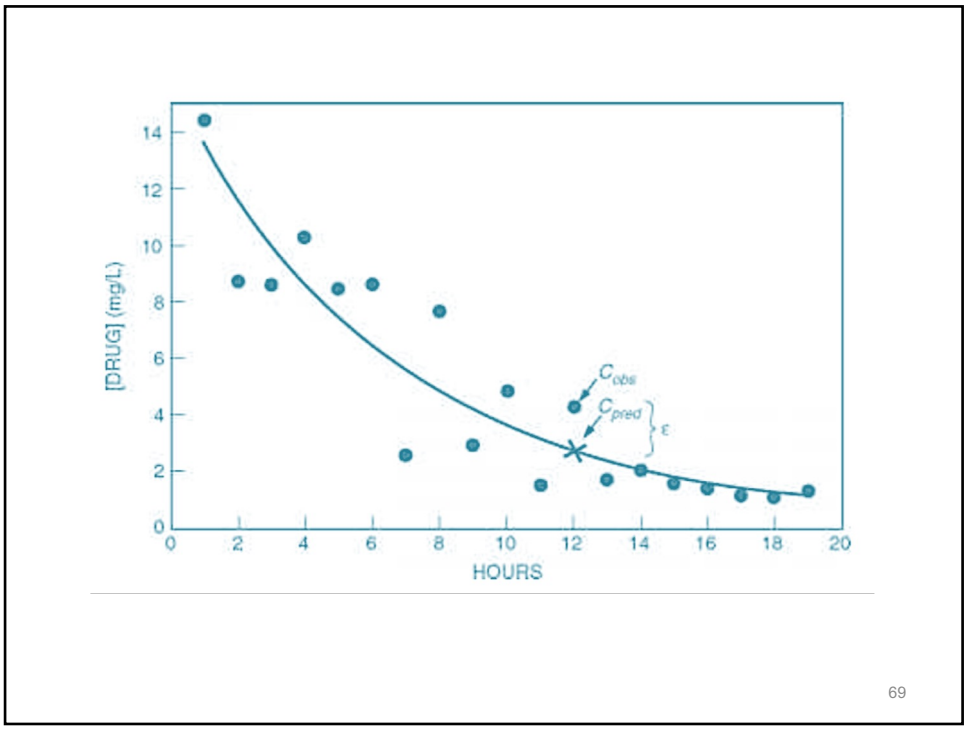

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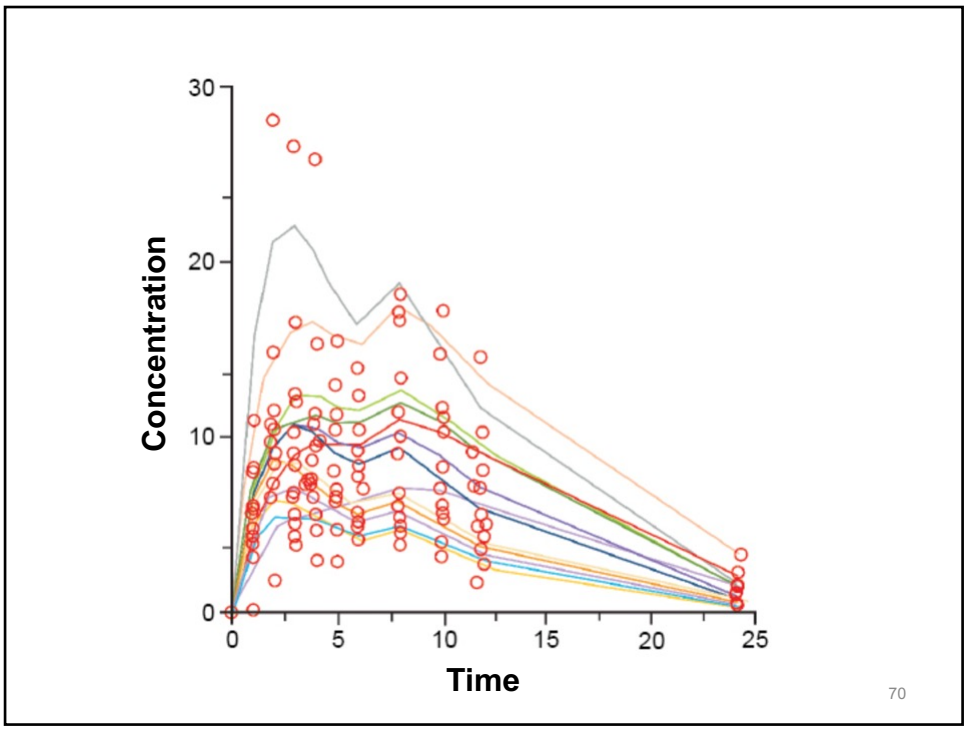

70

Optimizing dosage regimen in cancer chemotherapy

to:

- minimize the tumor burden during the treatment period
- while maintaining the WBC population above a lower level as a limit of toxicity

71

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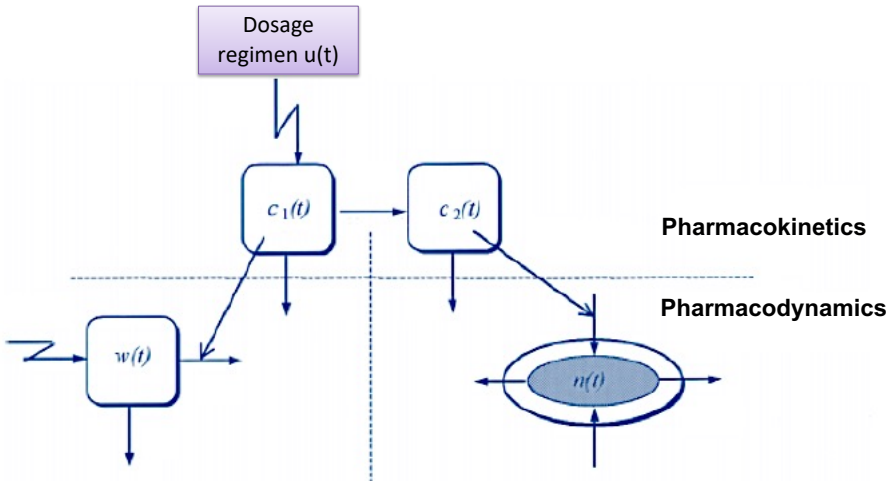
The (etoposide) model



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Pharmacokinetic modeling

Determine the optimal **dosage regimen u(t)**

$$\frac{dc_1(t)}{dt} = -(k_1 + k_2)\cdot c_1(t) + \frac{u(t)}{V_1} \qquad c_1(0) = 0.$$

$$\frac{dc_2(t)}{dt} = k_{12}\cdot\frac{V_1}{V_2}\cdot c_1(t) - k_2\cdot c_2(t) \qquad c_2(0) = 0$$

Pharmacodynamic-Efficacy Modeling

Although clinical tumors are ***heterogeneous***, herein they were considered ***homogeneous***, not only throughout their growth but also after being perturbed by an anticancer drug. Then, we assumed that this **tumor grows according to a Gompertz-type** growth equation and that the cell loss term, due to the action of cytotoxic drug, depends on the effective drug concentration in the tumor site:

$$\frac{dn(t)}{dt} = \lambda\cdot n(t)\cdot\ln[\theta/n(t)] - k\cdot[c_2(t) - C_{MIN}]\cdot n(t)\cdot H[c_2(t) - C_{MIN}] \qquad n(0) = n_0$$

n(t) denotes the number of tumor cells at time *t*, and n_0 denotes the initial size of the tumor at $t = 0$.

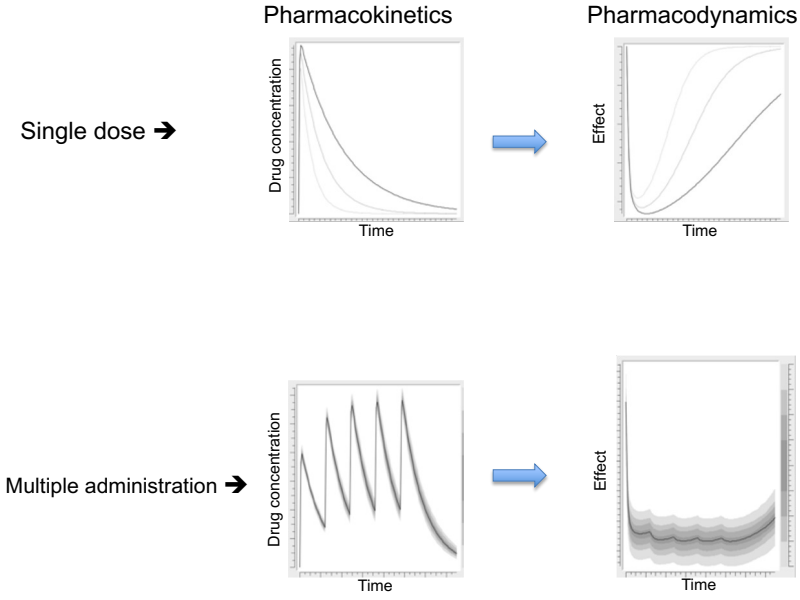
Pharmacodynamic-Toxicity Modeling

The **WBC count** differential equation becomes:

$$\frac{dw(t)}{dt} = r_C - v\cdot w(t) - \mu\cdot w(t)\cdot c_1(t-\tau) \qquad w(0) = w_0$$

73

Simulate different dosage regimens



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C4. Research & Development

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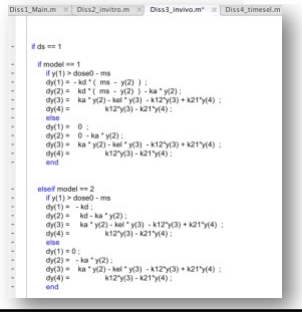
Bridge the gap

Available evidence

Marketing Authorization

MS methods



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Predict the probability of success of a BE study relying on in vitro data (IVIVS)

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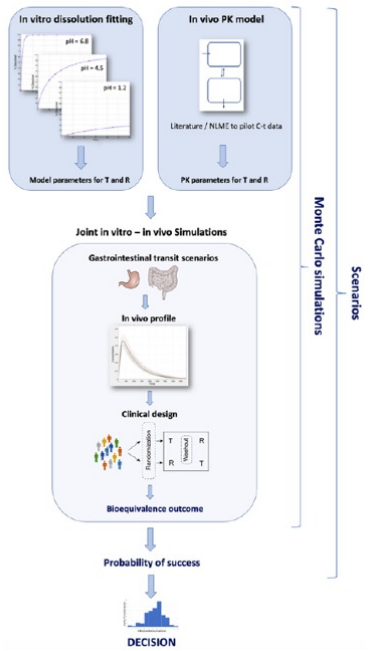

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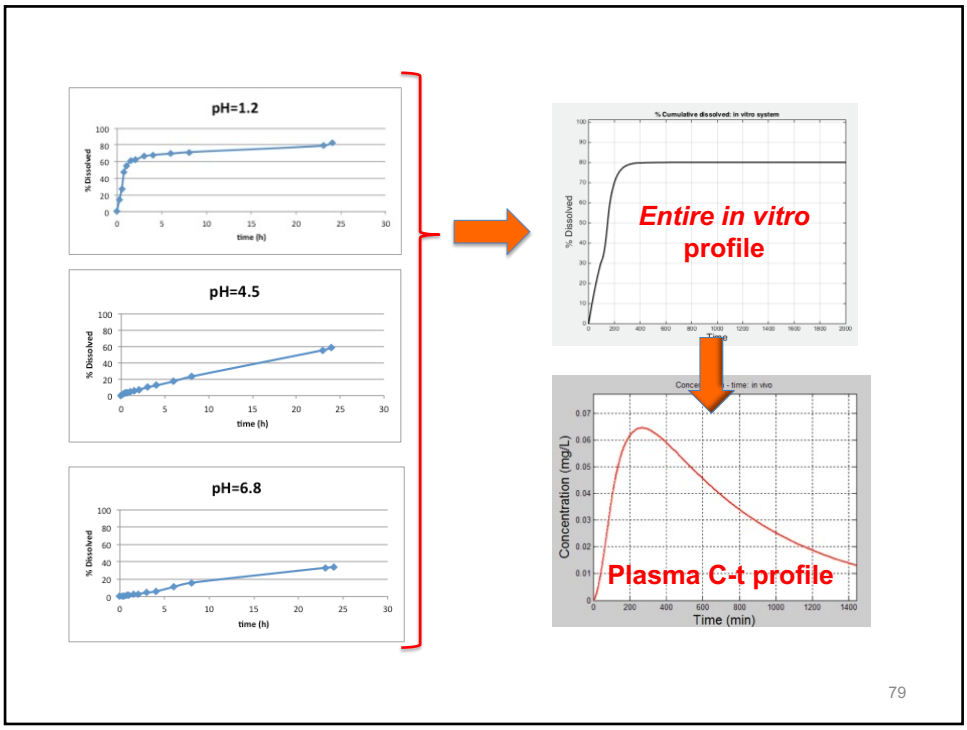
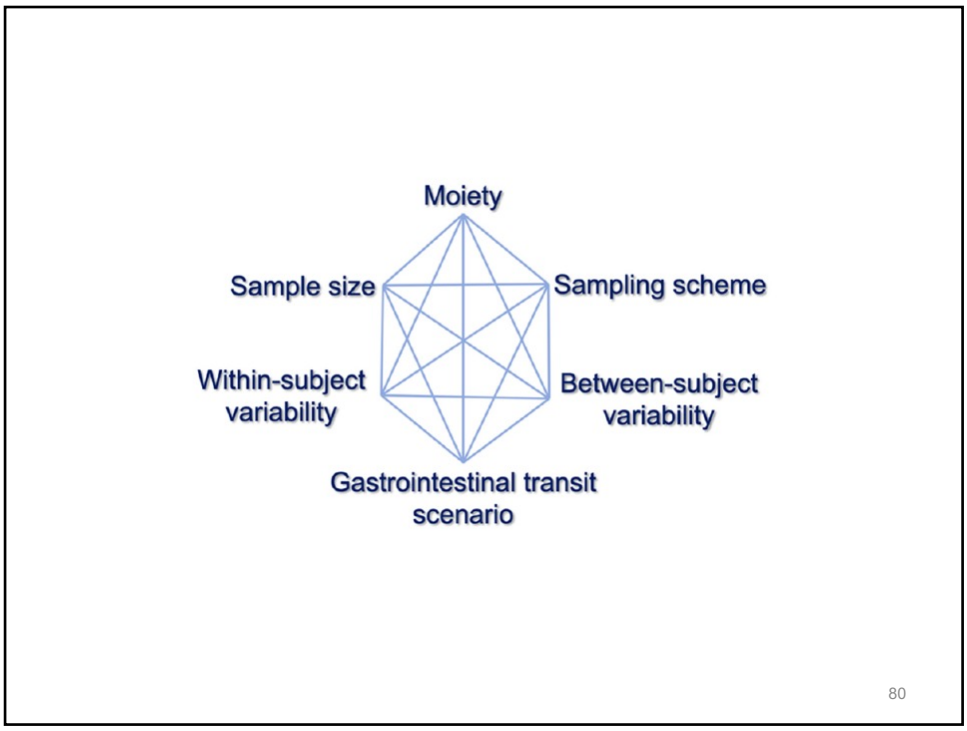
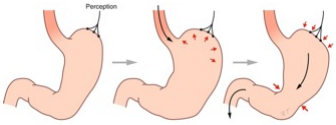

pH=1.2
% Dissolved
time (h)
pH=4.5
% Dissolved
time (h)
pH=6.8
% Dissolved
time (h)
% Cumulative dissolved: in vitro system
% Dissolved
Time
Entire in vitro profile
Concentration (mg/L)
Time (min)
Plasma C-t profile
79

79


Moiety
Sample size
Sampling scheme
Within-subject variability
Between-subject variability
Gastrointestinal transit scenario
80

80

Gastric emptying and GI transit times



Location	Mean Transit Time (Minutes)				
	1	*2*	*3*	*4*	*5*
Stomach	10	20	30	45	60
Small intestine	180	200	215	240	265
Large intestine	1970	1940	1915	1875	1835

81

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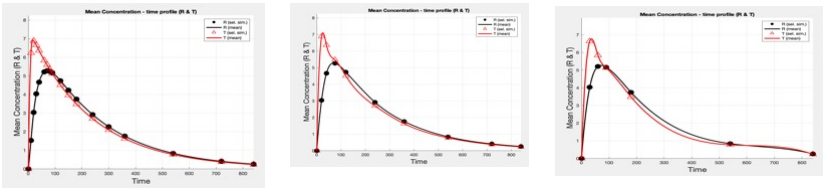
Sampling scheme



Design	Sampling Times (in Minutes)															
Sparse	0	10	40	60	90	160	240	480	720	1440						
Typical	0	10	20	40	60	90	120	180	240	360	480	720	960	1440		
Dense	0	10	20	40	60	80	100	120	150	180	240	360	480	600	720	960	1440

82

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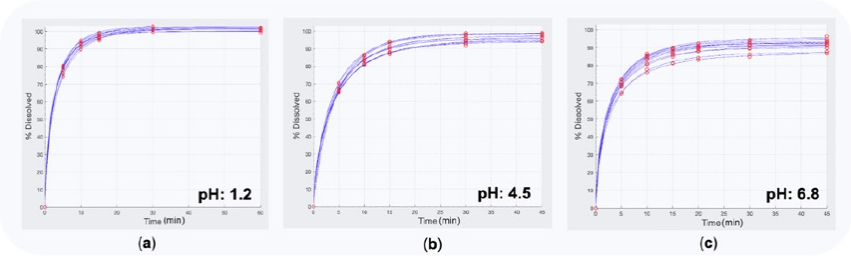
In vitro dissolution fittings



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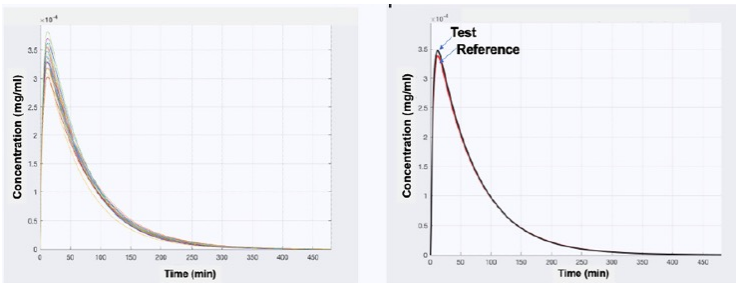

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Backward methodology

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Backward methodology:

Start from:
Literature C-t data
➔
Set/Suggest:
- the appropriate *in vitro* dissolution profile
- **Dose selection** (if different salt/ester)

86

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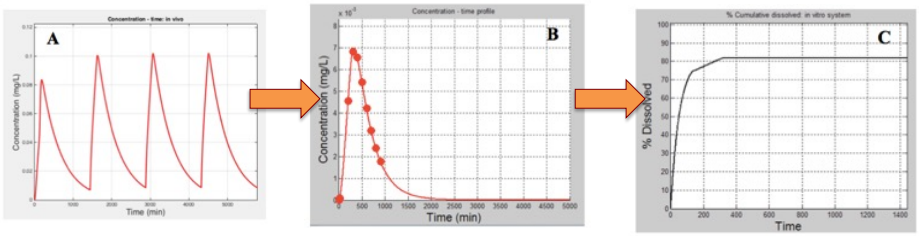
For example:

Start from C-t data at steady state (after multiple dosing)



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Applications:

Assist the RD department to develop a product with the **appropriate dissolution characteristics**, <u>when</u> **in vitro data** of a **comparator** product are **not available**.

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Reveal the “hidden” in vitro performance

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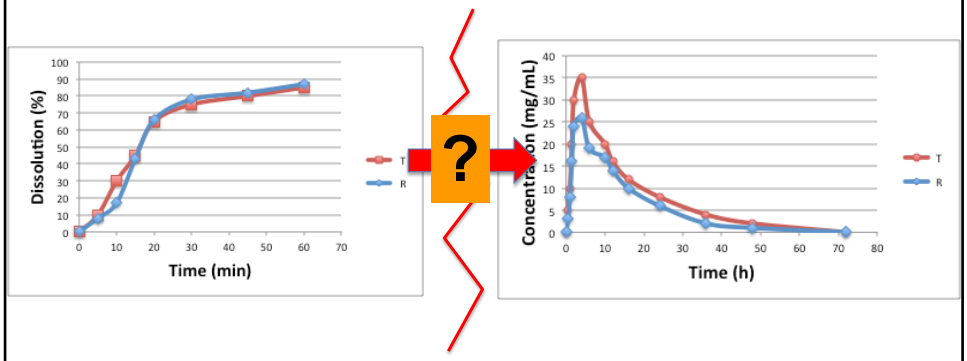
In vitro: Almost identical

In vivo: Large discrepancy



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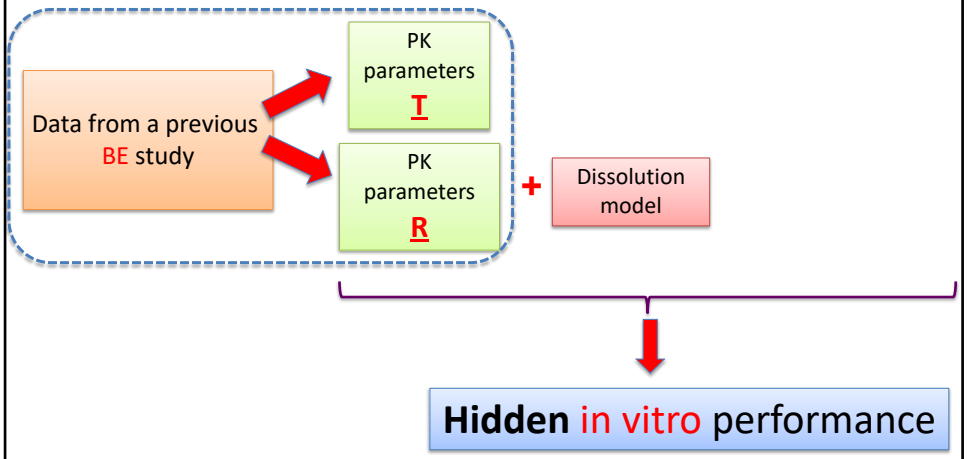
Modeling framework



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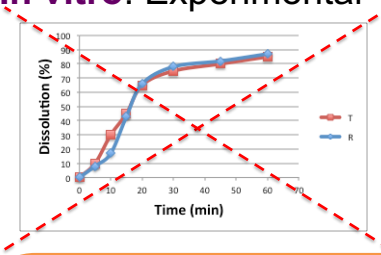
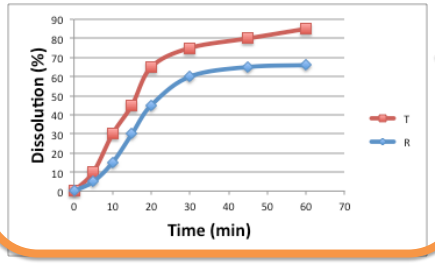
… what happened:

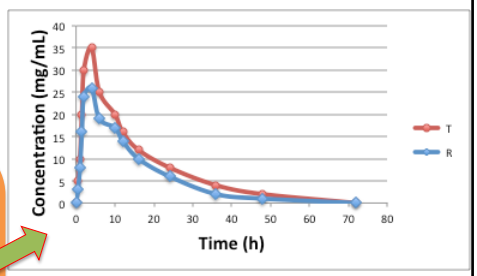
In vitro: Experimental



In vitro: Modeled (hidden)



In vivo



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Applications:

In situations where:

A. The application of the **typical in vitro tests** (e.g., at pH: 1.2, 4.5, and 6.8) showed high level of **similarity** between the T and R products

BUT:

The in vivo data, showed a **high level of discrepancy**.

B. During **drug development** (in collaboration with the RD group) to assess the anticipated in vivo performance ➔ **suggest an appropriate**

93

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Waive the need of clinical/PK studies: Study extrapolation

94

94

Applications:

For example:

A. MR products:

A variety of studies are required (fasting, fed, steady-state, dose-proportionality etc.)

➔

The use of modeling/simulation can **waive the need of performing** all or part of the required studies

95

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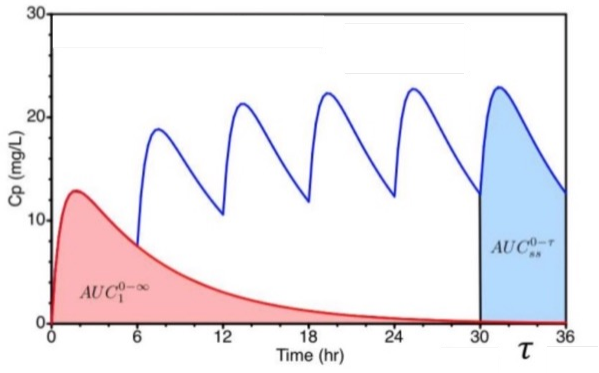
Study extrapolation:

Perform a Single dose study ➔ simulate multiple-dose studies



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96

Applications:

For example:

A. If in vivo data are available only in case of single dose studies, **BUT:** Regulations require **further** knowledge/assessment at the **steady-state**.

B. Examine if '**steady-state**' conditions are **reached**.

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C5. Drafting a law

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

FDA

98

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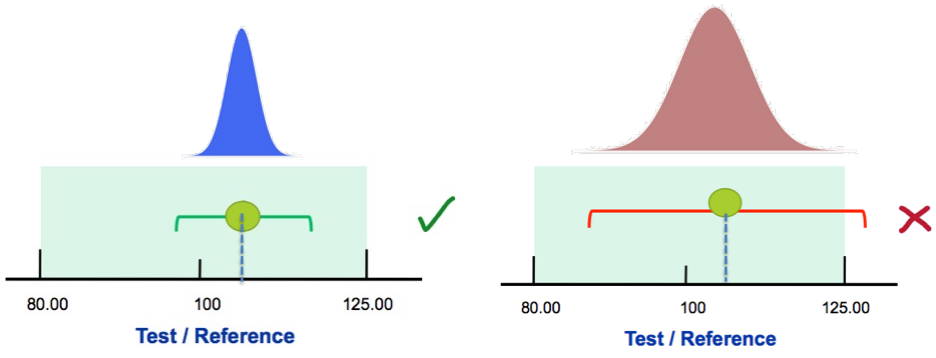
The impact of variability on BE acceptance

Greater variability → More difficult to prove BE



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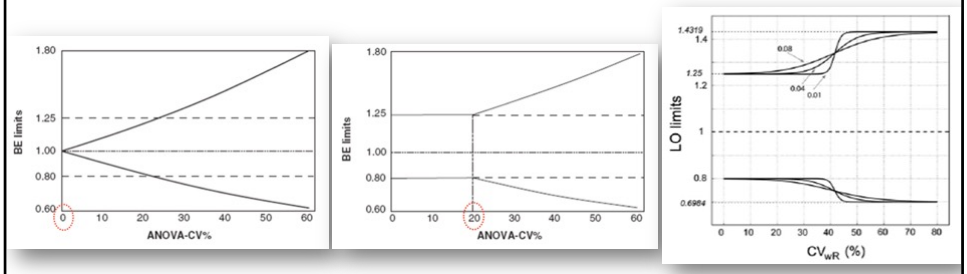
A solution: Scaled BE approaches

The BE limits are not constant any more

$$\text{BE limits} = f(\textit{variability})$$



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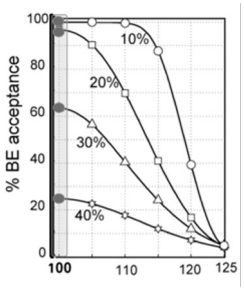
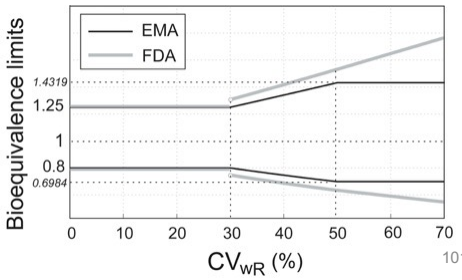
1. Highly variable drugs - Scaled bioequivalence limits



Greater variability → Less statistical power

Scaled approaches of the EMA and FDA



101

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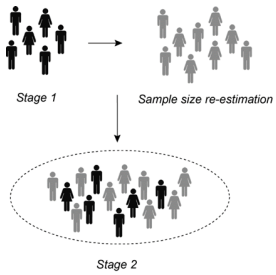
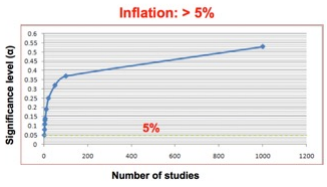
2. Study the properties of clinical designs

Sample size re-estimation designs





An 'ideal' design:

- should not lead to **inflation** of the type I error
- exhibit the highest possible **statistical power**

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D. AI clinical trials

- AI synthesized patients
- Variational Autoencoders (VAEs)
- Generative Adversarial Networks (GANs)

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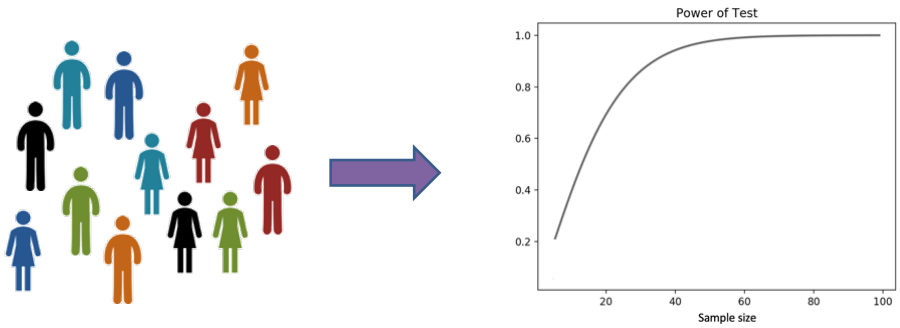

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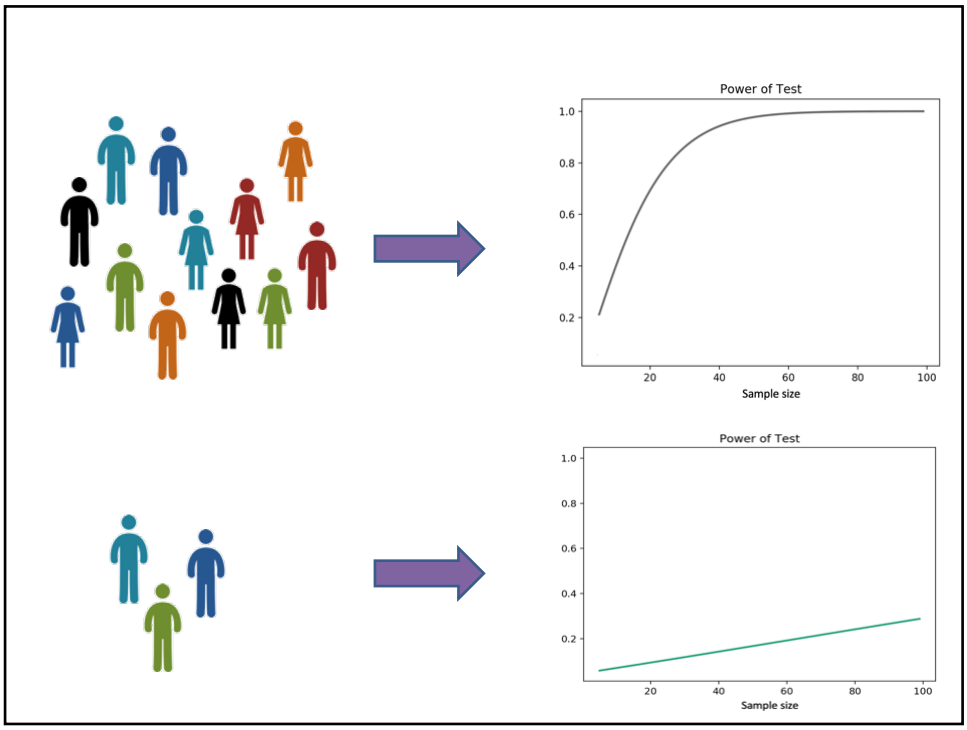
Power of Test
1.0
0.8
0.6
0.4
0.2
20
40
60
80
100
Sample size
Power of Test
1.0
0.8
0.6
0.4
0.2
20
40
60
80
100
Sample size

105


CGI (Computer-generated imagery)
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Create virtual subjects from the available data

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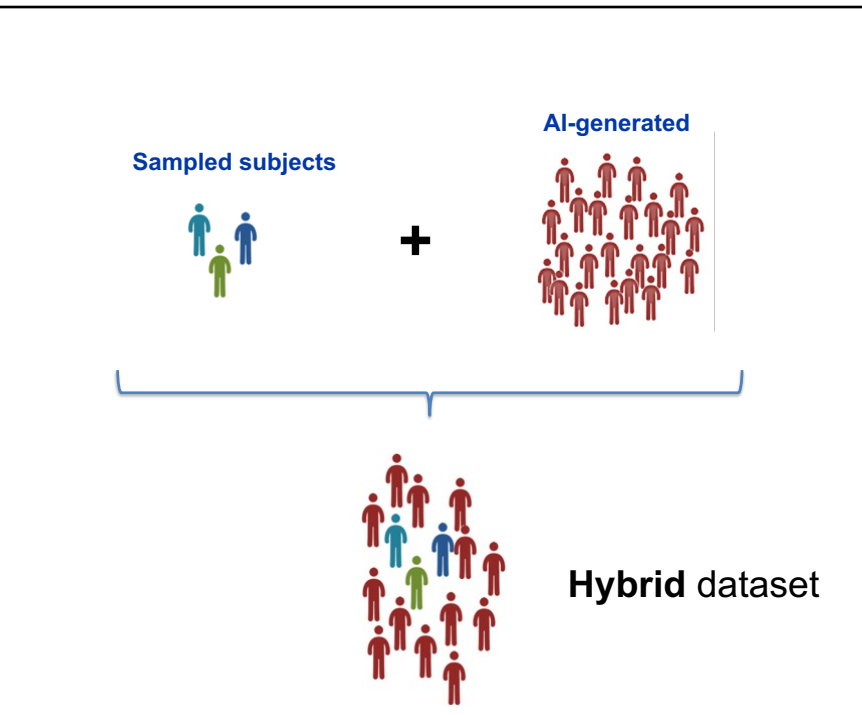

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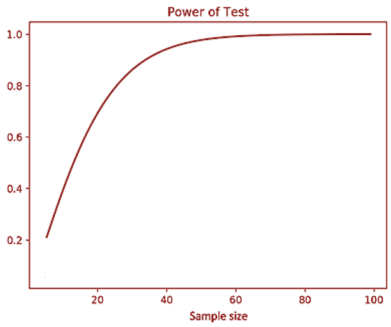

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How it is done

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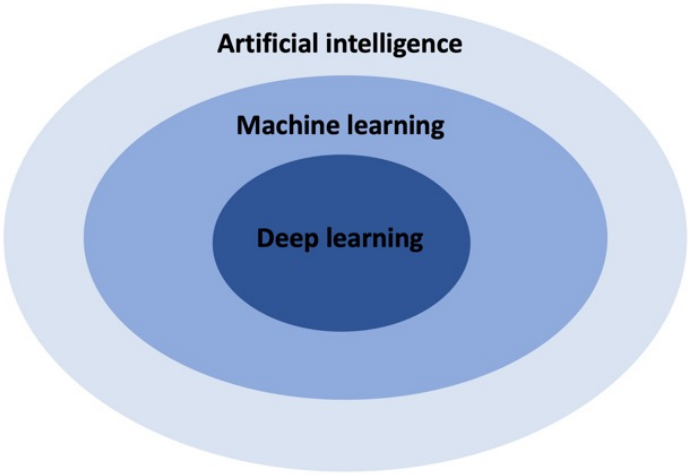
AI / ML / DL



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Machine learning

- Supervised learning
- Unsupervised learning
- Reinforcement learning
- …

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Supervised	Unsupervised	Reinforcement
Linear regression	Principal Component Analysis	Q-learning
Logistic regression	K-means clustering	SARSA
Linear discriminant analysis	KNN (k-nearest neighbors)	Policy iteration
Decision trees	Hierarchal clustering	Monte Carlo tree search
Naive Bayes	Anomaly detection	Bellman Equations
Support-vector machines	Neural Networks	Markov Decision Process

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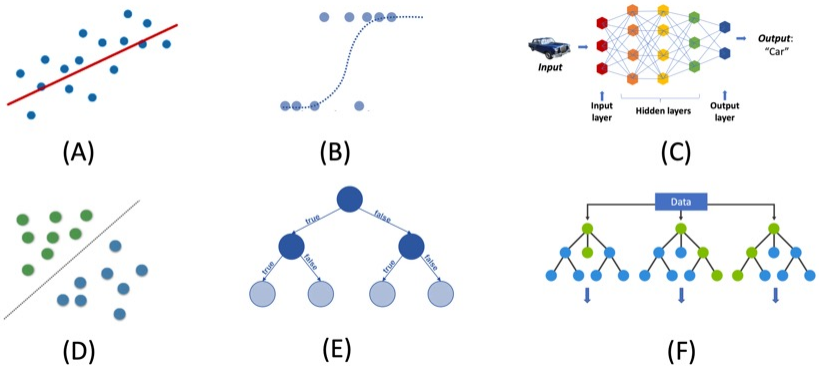
Supervised learning



(A) (B) (C)

(D) (E) (F)

A) linear regression, B) logistic regression, C) deep neural network, d) support vector machine, e) decision tree, f) random forest

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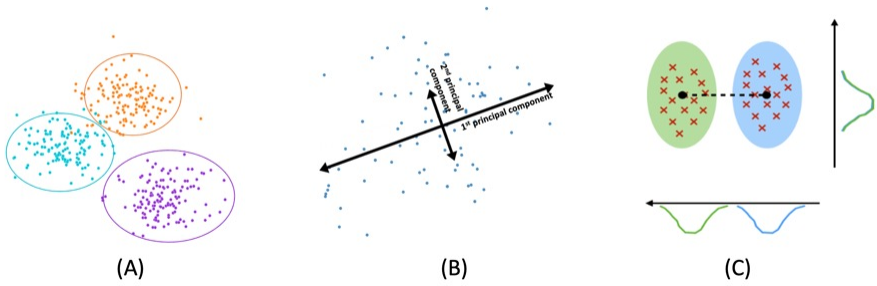
Unsupervised learning



(A) (B) (C)

A) k-means cluster analysis, B) principal component analysis, C) linear discriminant analysis

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Reinforcement learning

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"Machine Learning is a new technology"

Logistic regression -1958
Hidden Markov Model -1960
Stochastic gradient descent -1960
Support Vector Machine -1963
k-nearest neighbours -1967
Artificial Neural Networks -1975
EM algorithm-1977
Decision tree -1986
Random forest -1995

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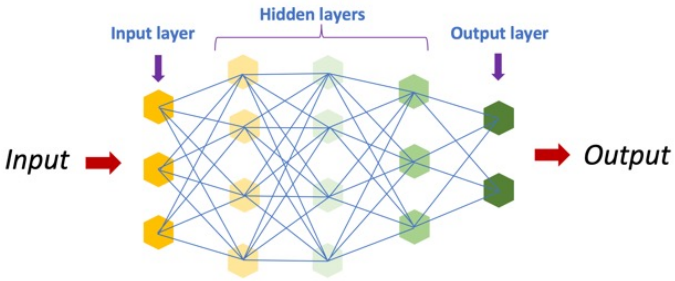
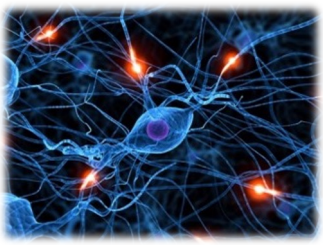
Deep learning





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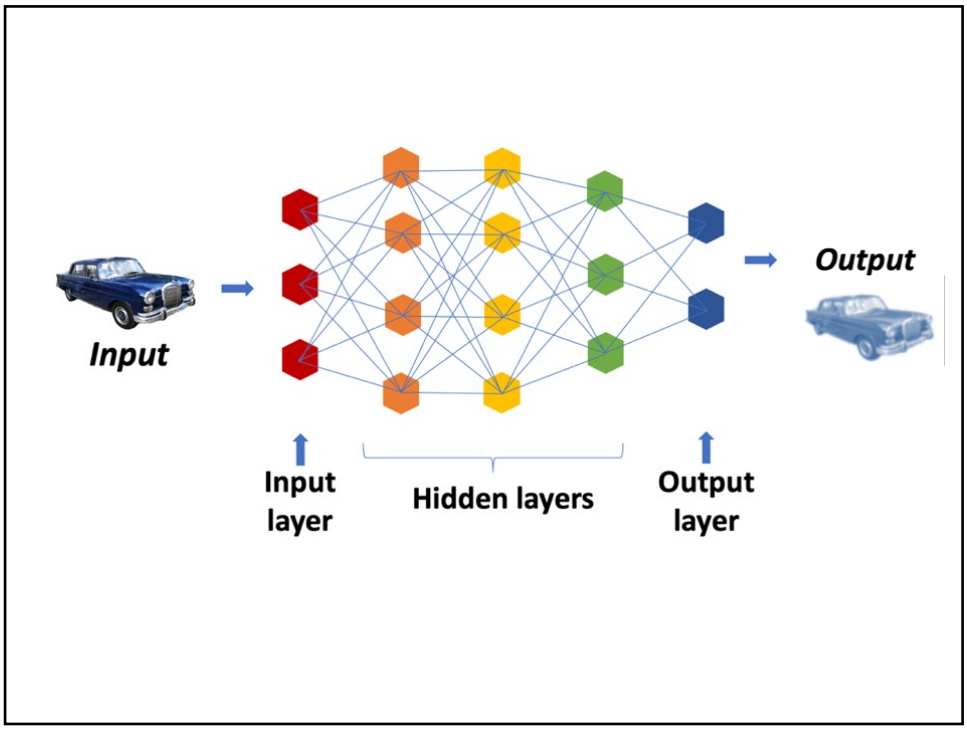
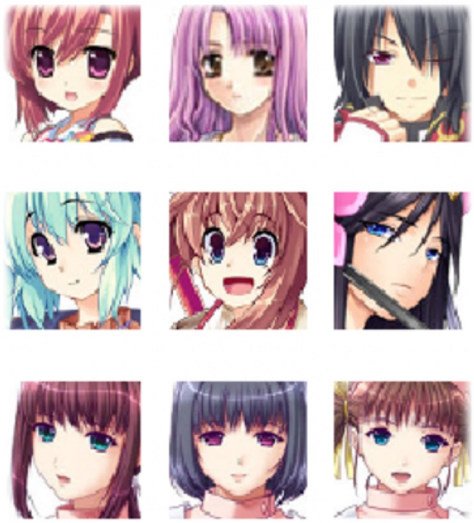


119

VAEs

(Variational Autoencoders, 2013)

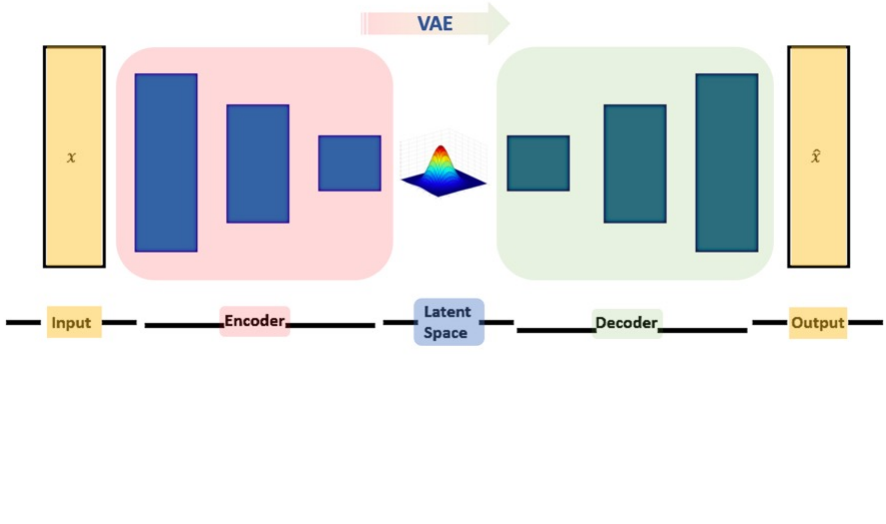


120

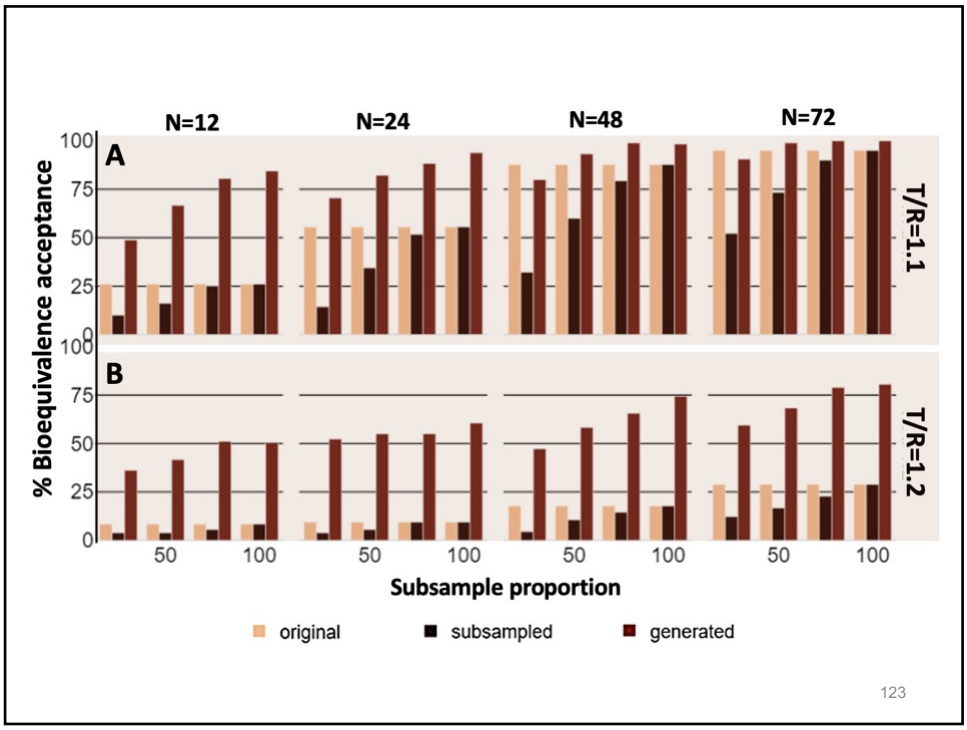
GANs

(Generative Adversarial Networks, 2014)

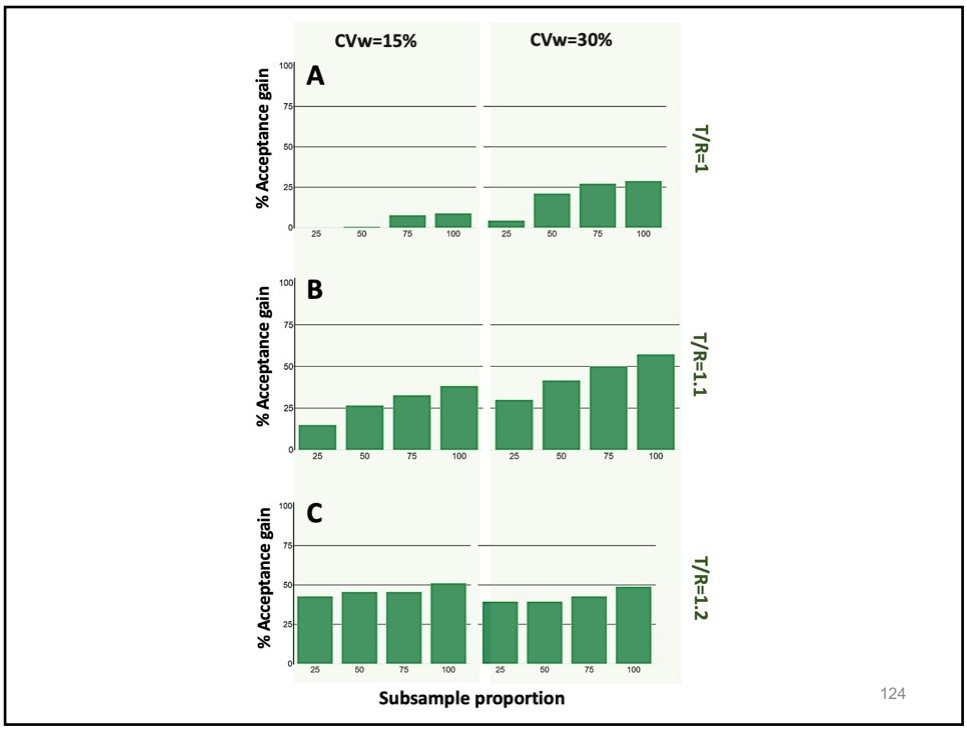
121



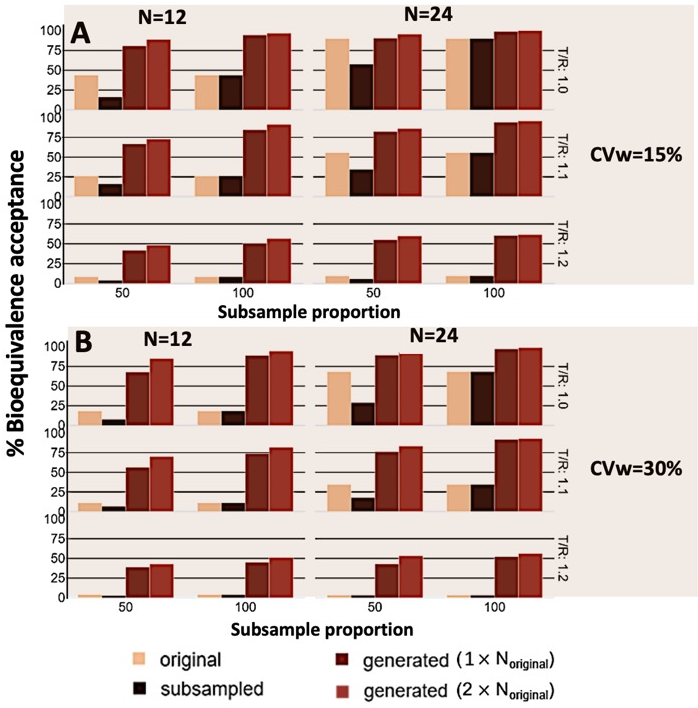
122


N=12
N=24
N=48
N=72
A
B
T/R=1.1
T/R=1.2
% Bioequivalence acceptance
100
75
50
25
0
50
100
Subsample proportion
original
subsampled
generated
123

123


CVw=15%
CVw=30%
A
B
C
T/R=1
T/R=1.1
T/R=1.2
% Acceptance gain
25
50
75
100
Subsample proportion
124

124



125

125

Less actual human data can be used to achieve similar, and even better, results

- decrease in human exposure
- reduction in dropouts
- significantly shorter study completion times
- lower complexity in the clinical trial
- reduced workload for physicians and clinics
- significantly lower costs for sponsors or health agencies.

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126

Ben-Hur (1959, 11 Oscars)

Actual

The Lord of the Ring III (2003, 11 Oscars)

Generated

127

127