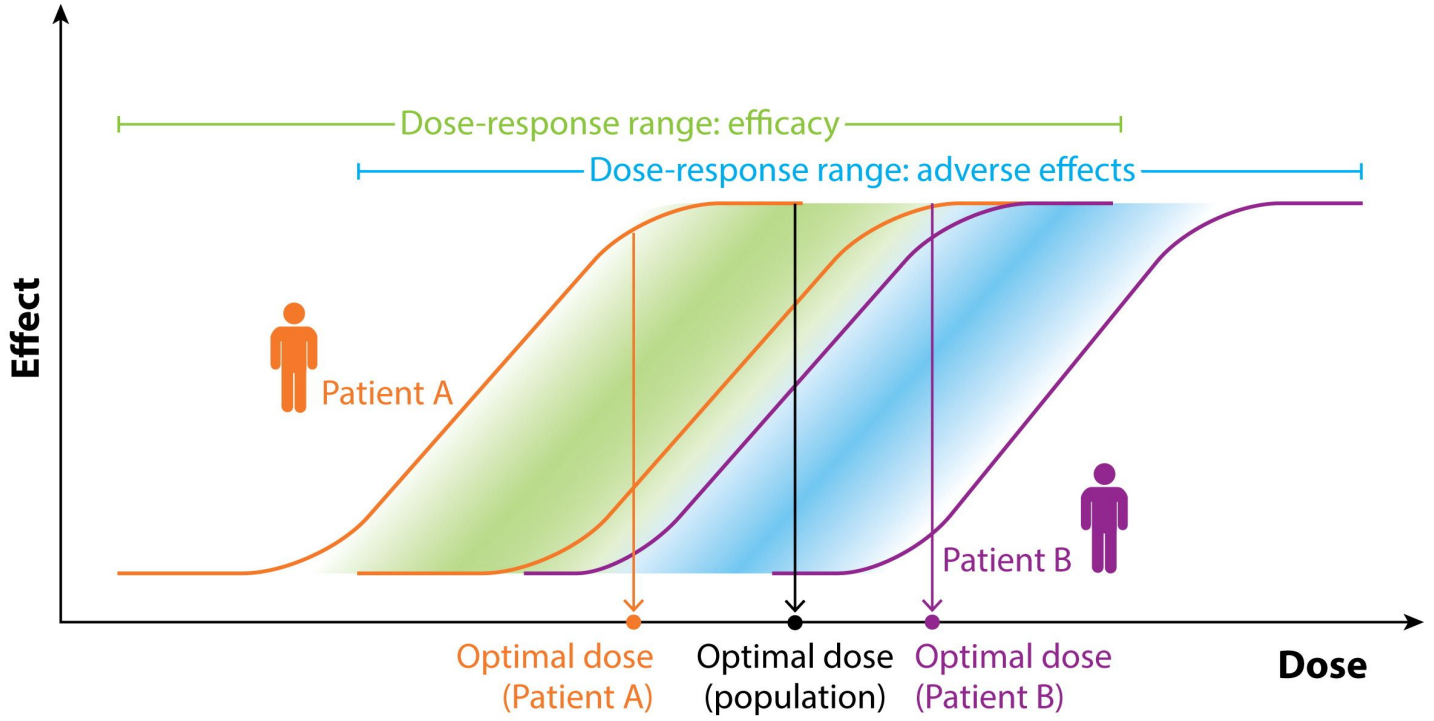
AMIDD Lecture 9: Population Modelling and Clinical Trials



Peck RW. 2018.
Annu. Rev. Pharmacol. Toxicol. 58:105–22

Peck, Richard W. 2018. "Precision Medicine Is Not Just Genomics: The Right Dose for Every Patient." Annual Review of Pharmacology and Toxicology 58 (1): 105–22.

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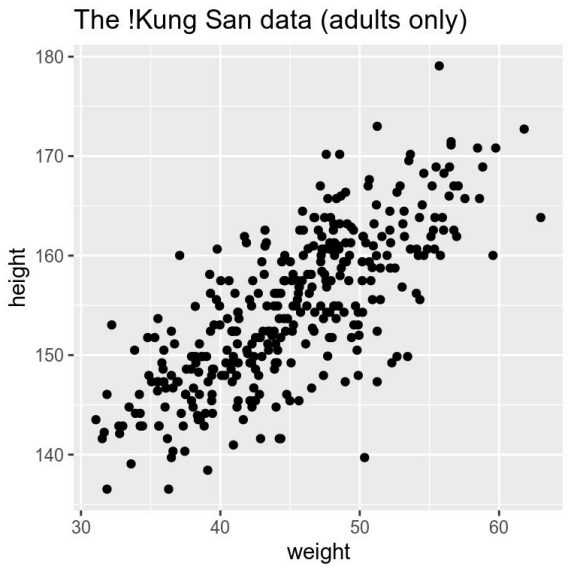
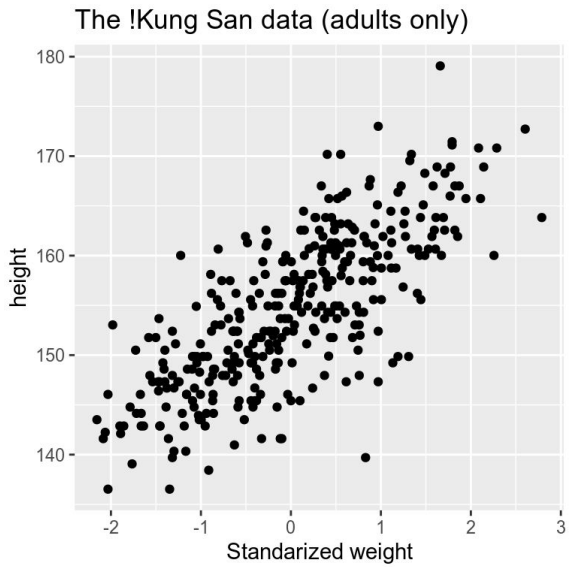
A linear model has one level of variability



variable scaling

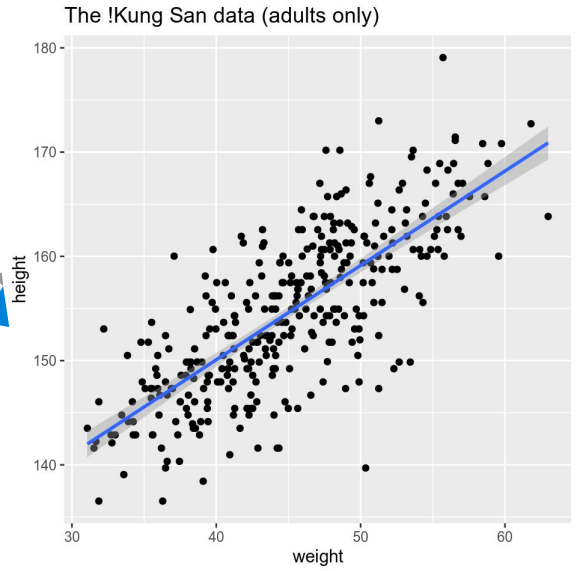


The Frequentist language

$$y_i = f(x) + \epsilon$$
$$f(x) = \alpha + \beta x$$
$$\epsilon \sim \mathcal{N}(0, \sigma)$$

The Bayesian language, with some personal priors

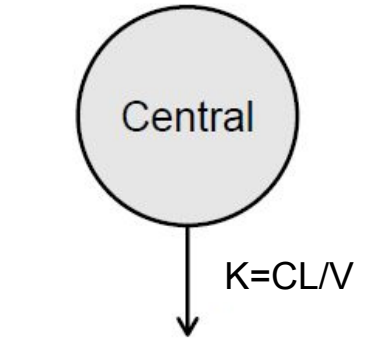
$$y_i \sim \mathcal{N}(\mu_i, \sigma)$$
$$\mu = \alpha + \beta x_i$$
$$\alpha \sim \mathcal{N}(169, 20)$$
$$\sigma \sim \text{Unfoirm}(0, 50)$$



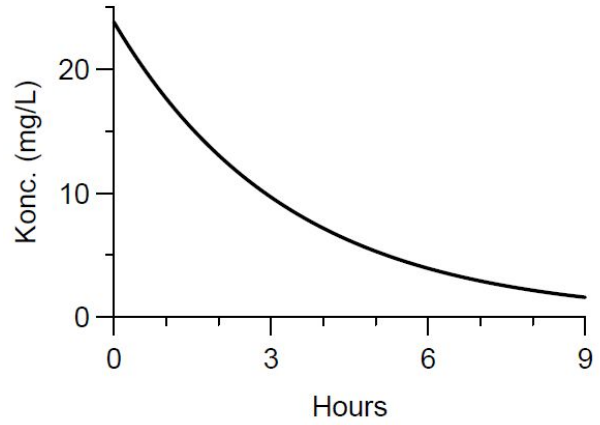
Example inspired by the *Statistical Rethinking* book by Richard McElreath

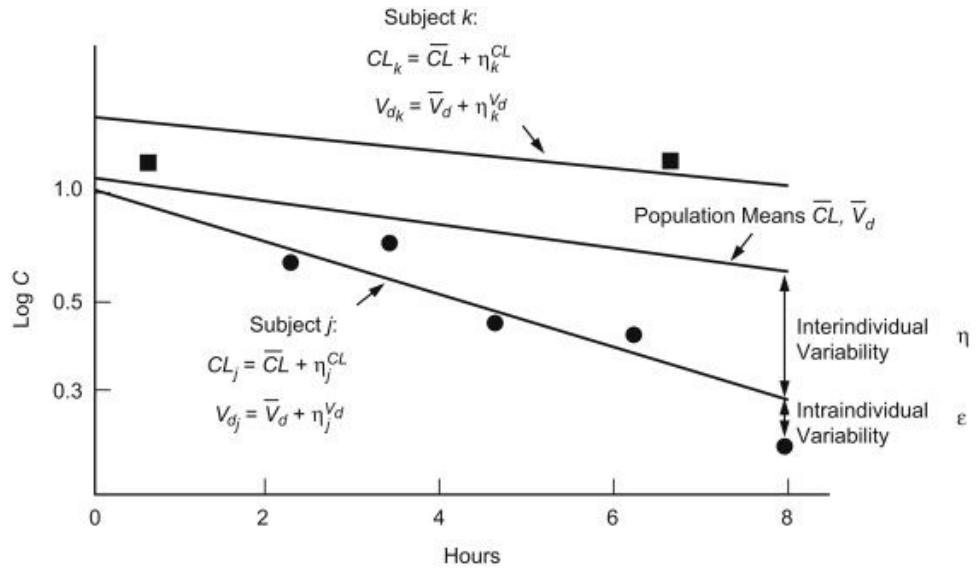
In population modelling, we deal with two levels of variability, which calls for mixed-effect models

- Consider a simple one-compartment model, with an intravenous bolus dose (right).
- **Two types of variability**
  - **Between-subject variability**, *e.g.* the differences in clearance rate among patients
  - **Between-occasion variability**, *e.g.* the differences from one time point to the other within each patient.
- A **mixed-effect model** (mixed=fixed+random effect model, a type of hierarchical model or *multilevel model*) is needed to model such data.
- If we assume that V_D is a constant value that is the same for all subjects, but clearance varies between subjects (for instance due to ethnicity), then V_D is a fixed-effect parameter and *CL* is a random-effect parameter.
- If we assume that both V_D and *CL* vary between subjects, then both are random-effect parameters.



$$C(t) = \frac{\text{Dose}}{V} e^{-\frac{CL}{V}t}$$





Bottom figure: Raymond Miller, in Principles of Clinical Pharmacology (Third Edition), 2012

A general form of nonlinear mixed-effect models

The Bayesian language

$$y_{ij} \sim \mathcal{N}(\mu_{ij}, \Sigma_i)$$
$$\mu_{ij} = f(t_{ij}, \beta_i, d_i)$$
$$\beta_i \sim \mathcal{N}(\beta, D)$$

- y_{ij} is the j^{th} response for the i^{th} subject
- f is a scalar function nonlinear with regard to β
- β is a $k \times 1$ parameter vector, giving PK parameters such as absorption, V_D, and CL.
- t_{ij} is the j^{th} time of measurement for the i^{th} subject
- d_i is the dose of the i^{th} subject
- j ranges from 1 to n_i
- D is a $k \times k$ covariance matrix
- Σ_i is an $n_i \times n_i$ covariance matrix

The Frequentist language

$$y_{ij} = f(t_{ij}, \underline{\beta}_i, d_i) + \varepsilon_{ij}$$
$$\underline{\beta}_i \sim N(\underline{\beta}, D)$$
$$\underline{\varepsilon}_i \sim N(\underline{0}, R_i)$$

y_{ij} is the jth response for the ith subject

f is a scalar function nonlinear in $\underline{\beta}$

$\underline{\beta}$ is a $k \times 1$ parameter vector

t_{ij} is the jth time for the ith subject

d_i is the ith subject's dose

j ranges from 1 to n_i

ε_{ij} is residual error

D is a $k \times k$ covariance matrix

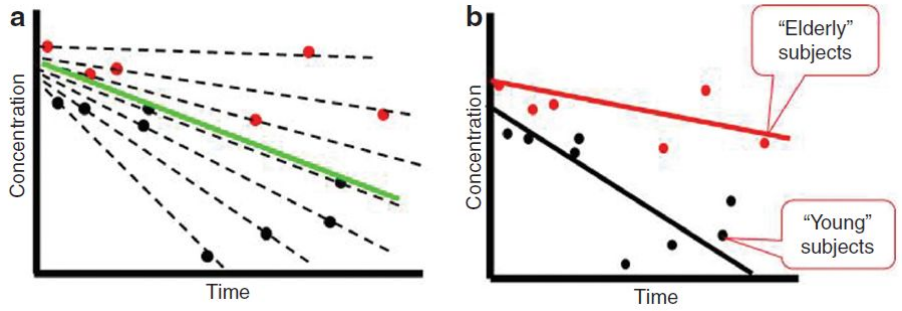
R_i is an $n_i \times n_i$ covariance matrix

In practice, maximum-likelihood estimation (MLE) based modelling fitting is performed by numerical methods including *Laplace approximation* and *Gaussian quadrature*.

One of the mostly used software is **NONMEM** (non-linear mixed effects modeling), a commercial software. Other platforms are being actively developed, for instance GTS and ITS.

Further reading: Introduction to PK/PD Modeling for Statisticians by Alan Hartford (AbbVie), ASA Biopharm FDA-Industry Statistics Workshop. The Frequentist language was adapted from it.

NLME modelling helps understanding clinical PK-PD parameters



	Vemurafenib			
	240 mg bid	**480 mg bid**	**720 mg bid**	**960 mg bid**
Day 1	*n* = 12	*n* = 12	*n* = 12	*n* = 16
AUC_8 (μg·h/mL)	8.3 ± 6.13 (73.9)	13.8 ± 7.72 (55.8)	21.9 ± 12.97 (59.3)	27.0 ± 18.87 (69.9)
AUC_{24} (μg·h/mL)	40.9 ± 23.43 (57.3)	62.4 ± 35.71 (57.2)	111.6 ± 34.22 (30.7)	130.6 ± 71.78 (55.0)
C_{max} 0–8 h (μg/mL)	1.9 ± 1.66 (85.3)	2.6 ± 1.56 (60.5)	4.4 ±1.98 (44.6)	4.8 ± 3.34 (69.8)
t_{max} 0–8 h (h)	4.0 (1.92–8.00)	4.0 (1.95–5.00)	5.0 (2.00–8.08)	5.0 (2.00–8.00)
Day 15	*n* = 10	*n* = 10	*n* = 9	*n* = 11
AUC_8 (μg·h/mL)	117.8 ± 50.52 (42.9)	233.8 ± 106.93 (45.7)	343.3 ± 151.23 (44.1)	392.2 ± 126.37 (32.2)
AUC_{168} (μg·h/mL)	920.3 ± 538.35 (58.5)	2243.5 ± 1336.15 (59.6)	3127.1 ± 1789.97 (57.2)	3530.3 ± 1811.43 (51.3)
C_{max} 0–168 h (μg/mL)	17.2 ± 7.43 (43.1)	35.4 ± 17.44 (49.2)	52.7 ± 22.40 (42.5)	61.4 ± 22.76 (37.1)
$t_{½}$ (h)	31.5 ± 19.05 (60.4)	38.4 ± 24.18 (63.0)	34.9 ± 19.48 (55.9)	34.1 ± 19.66 (57.7)
Accumulation ratio (AUC_8 on day 15/day 1)	24.9 ± 29.4 (118)	23.3 ± 16.0 (68.7)	18.8 ± 12.4 (66.0)	23.2 ± 16.5 (71.1)

Top: Mould, D R, and R N Upton. 2012. "Basic Concepts in Population Modeling, Simulation, and Model-Based Drug Development." CPT: Pharmacometrics & Systems Pharmacology 1 (9): 1–14.

Right: Zhang, Weijiang, Dominik Heinzmann, and Joseph F. Grippo. 2017. "Clinical Pharmacokinetics of Vemurafenib." Clinical Pharmacokinetics 56 (9): 1033–43. AUC_8 and AUC_{168}: AUC from time zero to 8h or 168 h.

Clinical studies and clinical trials

- A **clinical study** is research using human volunteers (*i.e.* participants), with the intention to add to medical knowledge.
- Two main types of clinical studies: **clinical trials** (also called interventional studies) and observational studies. In clinical trials, participants are assigned to specific **interventions** by the investigator, which is not the case in observational studies.
- **Most drug and vaccine candidates fail**.
- Only drugs undergoing successful clinical studies are approved by regulatory agencies. For instance, FDA usually requires that a drug must show statistical significance in two 'adequate and well-controlled' pivotal Phase III studies as a precondition of its approval.

Probability of Success[2] by Clinical Trial Phase and Therapeutic Area

	P1 to P2	*P2 to P3*	*P3 to Approval*	*Overall*
Oncology	57.6	32.7	35.5	3.4
Metabolic/Endocrinology	76.2	59.7	51.6	19.6
Cardiovascular	73.3	65.7	62.2	25.5
Central Nervous System	73.2	51.9	51.1	15.0
Autoimmune/Inflammation	69.8	45.7	63.7	15.1
Genitourinary	68.7	57.1	66.5	21.6
Infectious Disease	70.1	58.3	75.3	25.2
Ophthalmology	87.1	60.7	74.9	32.6
Vaccines (Infectious Disease)	76.8	58.2	85.4	33.4
Overall	66.4	48.6	59.0	13.8
Overall (Excluding Oncology)	73.0	55.7	63.6	20.9

Source: Chi Heem Wong, Kien Wei Siah, Andrew W Lo. "Estimation of clinical trial success rates and related parameters." *Biostatistics* 20(2): April 2019, Pages 273-286. Published online: 31 January 2018. DOI: 10.1093/biostatistics/kxx069

Data between 2000 and 2015 of 406,038 trials (of which 185,994 were unique) and well over 21,000 compounds were collected. The table was formatted by ACSH.

Phases of clinical trials prior to approval

- **Aim:** To get PK data and to verify the drug behaves as expected.
- **Dose:** *Microdosing e.g. <= 1/100 NOAEL (no observed adverse effect level) or pharmacologically active dose.*
- **Subjects:** Usually <15 healthy subjects
- **Time:** A few weeks

- To find a safe dose range and optimal dosing region and identify safety profile. Further PK and PD data are collected.
- Subtherapeutic single and multiple ascending doses
- Usually 20-100 healthy volunteers, in certain indications (e.g. cancer) patients can participate.
- Usually a few months

- To assess efficacy and side effects of the drug, and determine dosing regimen
- Therapeutic dose
- Usually 100-300 patients with a specific disease
- At least a year and longer

- To test efficacy, effectiveness, and safety profiles in a large number of patients, compared with standard-of-care treatment option
- Therapeutic dose
- Usually 300-3000 patients
- Usually several years

* Since early 2000. See an update-to-date review by Burt, Tal, Graeme Young, Wooin Lee, Hiroyuki Kusuhara, Oliver Langer, Malcolm Rowland, and Yuichi Sugiyama. 2020. "Phase 0/Microdosing Approaches: Time for Mainstream Application in Drug Development?" Nature Reviews Drug Discovery 19 (11): 801–18.

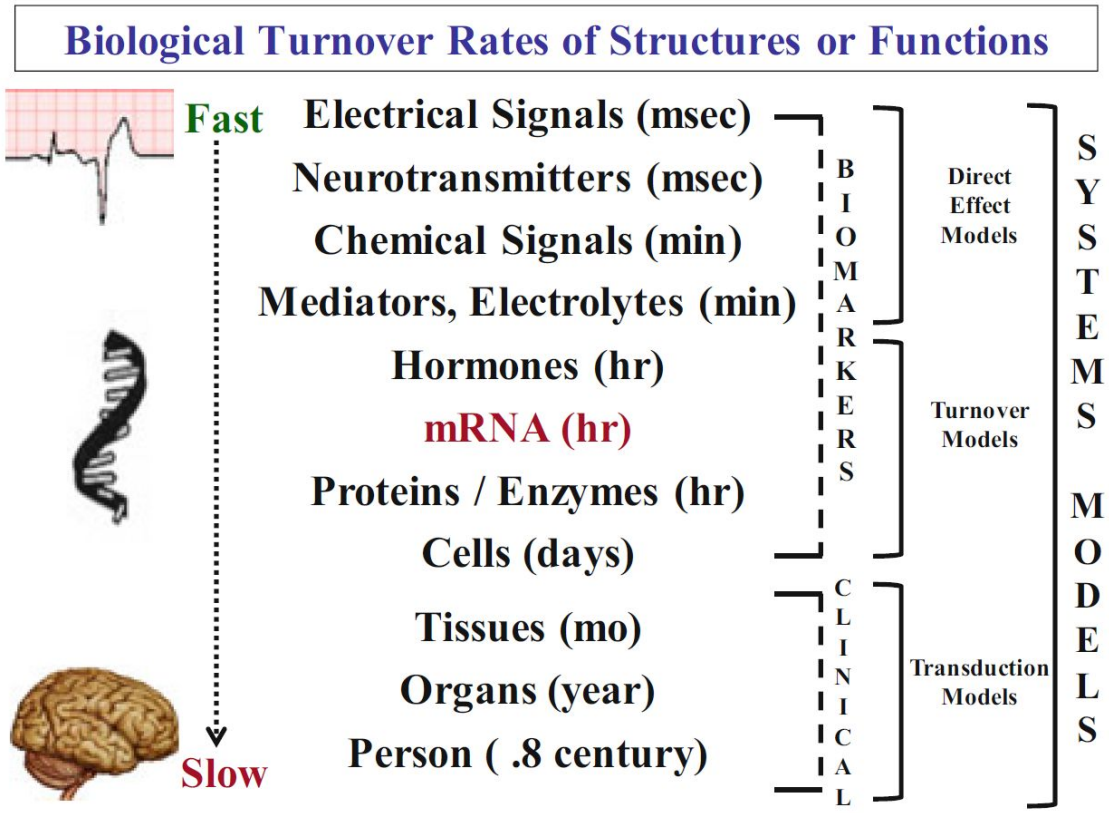
We use clinical endpoints, biomarkers, and surrogate endpoints to judge whether a drug works or not

• **Clinical endpoints:** direct evidence of clinical outcome, reflecting how a patient feels (*e.g.* relieve of anxiety and depression), functions (*e.g.* hospitalization), responds to pathogens (*e.g.* infection rate), or how long a patient survives (*e.g.* progression-free survival, overall survival). It can be expensive and take long to measure them.

• **Biomarkers**: objectively measured and evaluated as an indicator of normal biological, pathogenic processes or pharmacological response to a drug, which can take many forms

- **Biochemical**, *e.g.* alanine aminotransferease (ALT), CD4+, cholesterol
- **Anatomical/morphological**, *e.g.* tumor Size, artery diameter, and imaging results of PET, CT-Scan, MRI, *etc.*
- **Histological**, *e.g.* biopsy pathology, whole blood count (WBC)
- **Other measurements**, *e.g.* Blood pressure, pain relief, QT interval in electrocardiogram, *etc.*

• **Surrogate endpoints**: biomarkers supported by strong evidence so that they may substitute a clinical end point when obtaining registration, *e.g.* neutralising antibodies against spike proteins of the coronavirus in the plasma as a surrogate of reduced rate of infection.

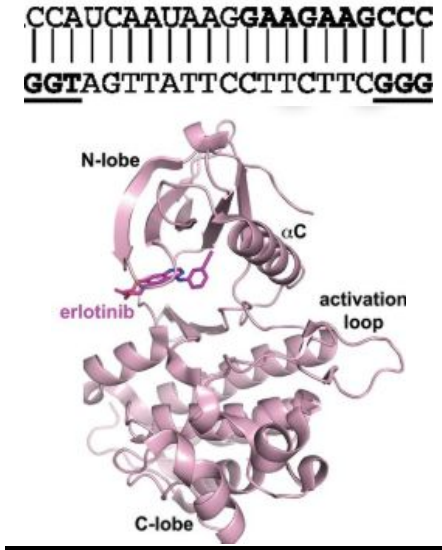


Jusko, William J. 2016. "Foundations of Pharmacodynamic Systems Analysis." In Systems Pharmacology and Pharmacodynamics, edited by Donald E. Mager and Holly H.C. Kimko, 161–75. AAPS Advances in the Pharmaceutical Sciences Series. Cham: Springer International Publishing.

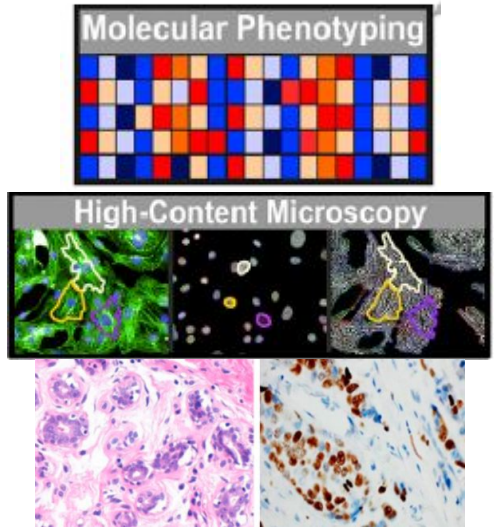
Conclusion of the course

Multiscale Modelling of Drug Mechanism and Safety

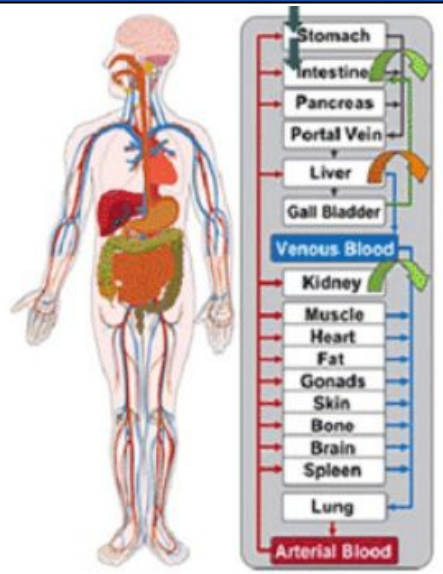
Forward translation



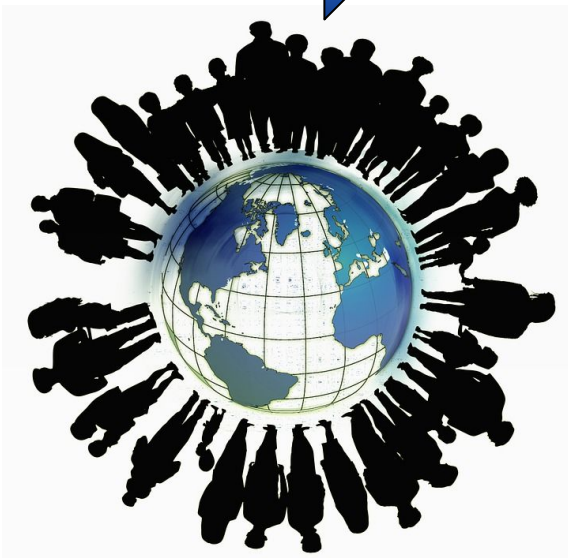
Molecular modelling



Omics & cellular modelling



Organ & system modelling



Populational modelling

Reverse translation

Principles that we covered: molecular biology (the central dogma), bioinformatics (DP and MC/HMM), chemoinformatics and CADD (molecular descriptors, QSAR, docking), omics (RNA sequencing), pharmacology (PK, PD, PBPK), population modelling (NLME), ...

Thank you for...

- Attending the course virtually;
- Giving me and the course feedback;
- Hopping between disciplines together with me;
- Reading (maybe too) much material;
- Taking time for offline activities;
- Asking and answering questions;
- Googling strange terms that you have never heard of;
- Bearing with my accent, speaking speed, and poor drawing;
- Being interested in applied mathematics and informatics in drug discovery.

Backup

Increased success rate in since 2014?