Examples of pharmacometrics studies in preclinical and clinical oncology: mathematical models in concrete therapeutic applications

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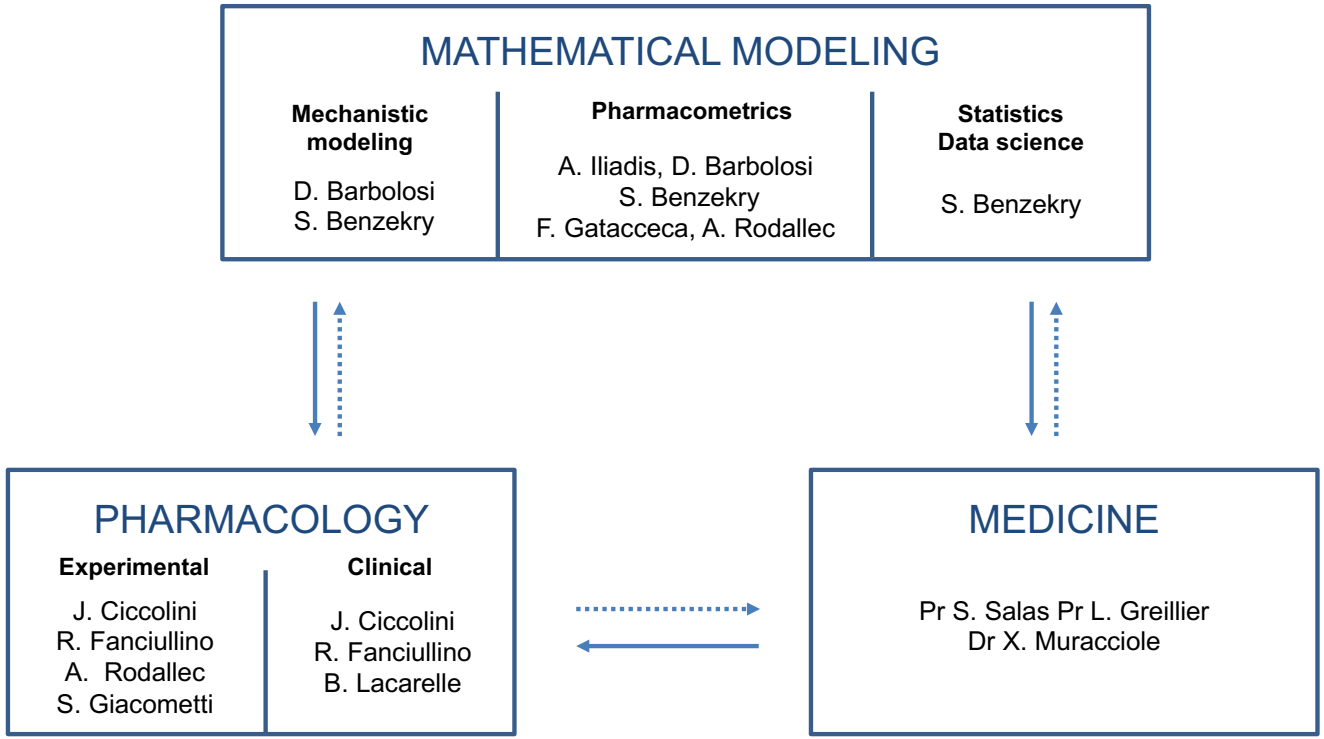
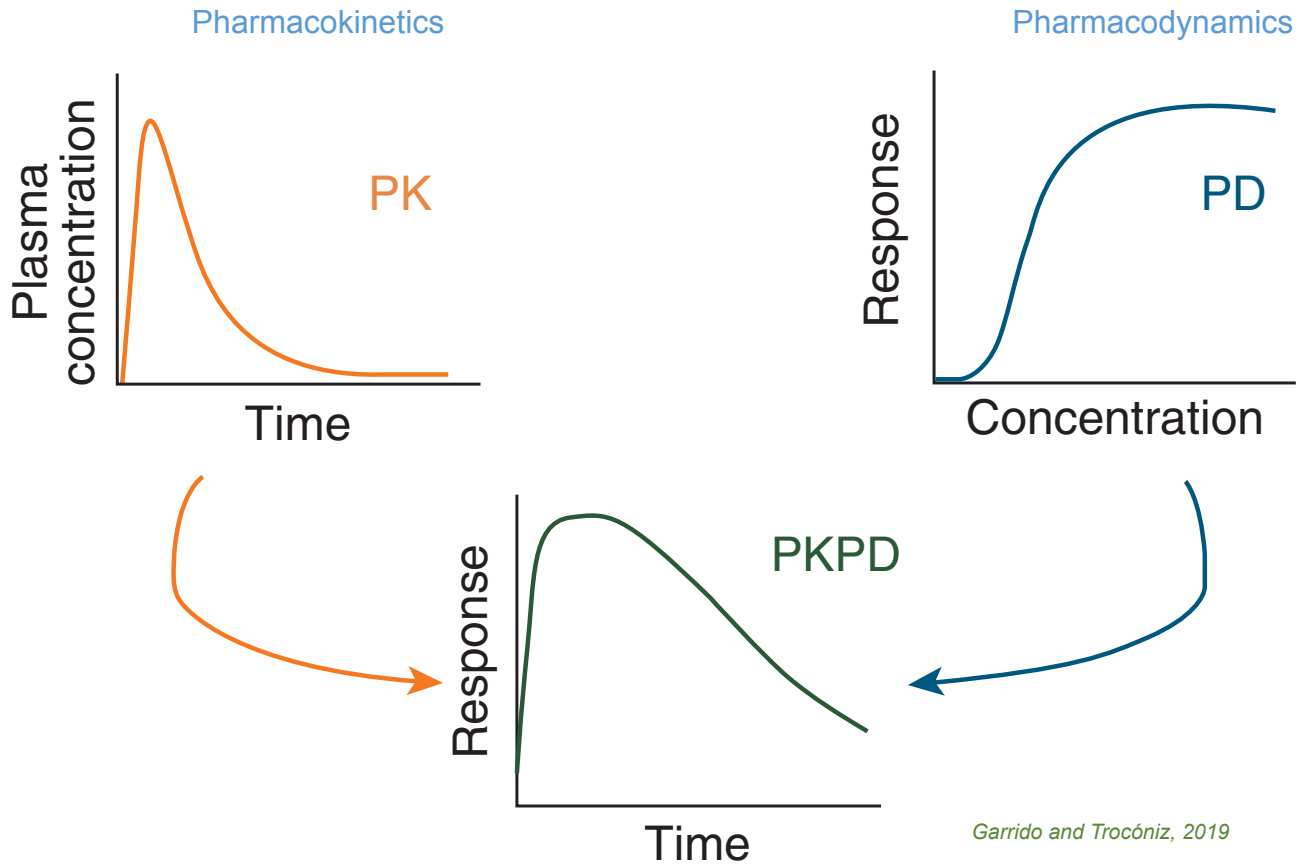
COMPO: COMPutational pharmacology and clinical Oncology

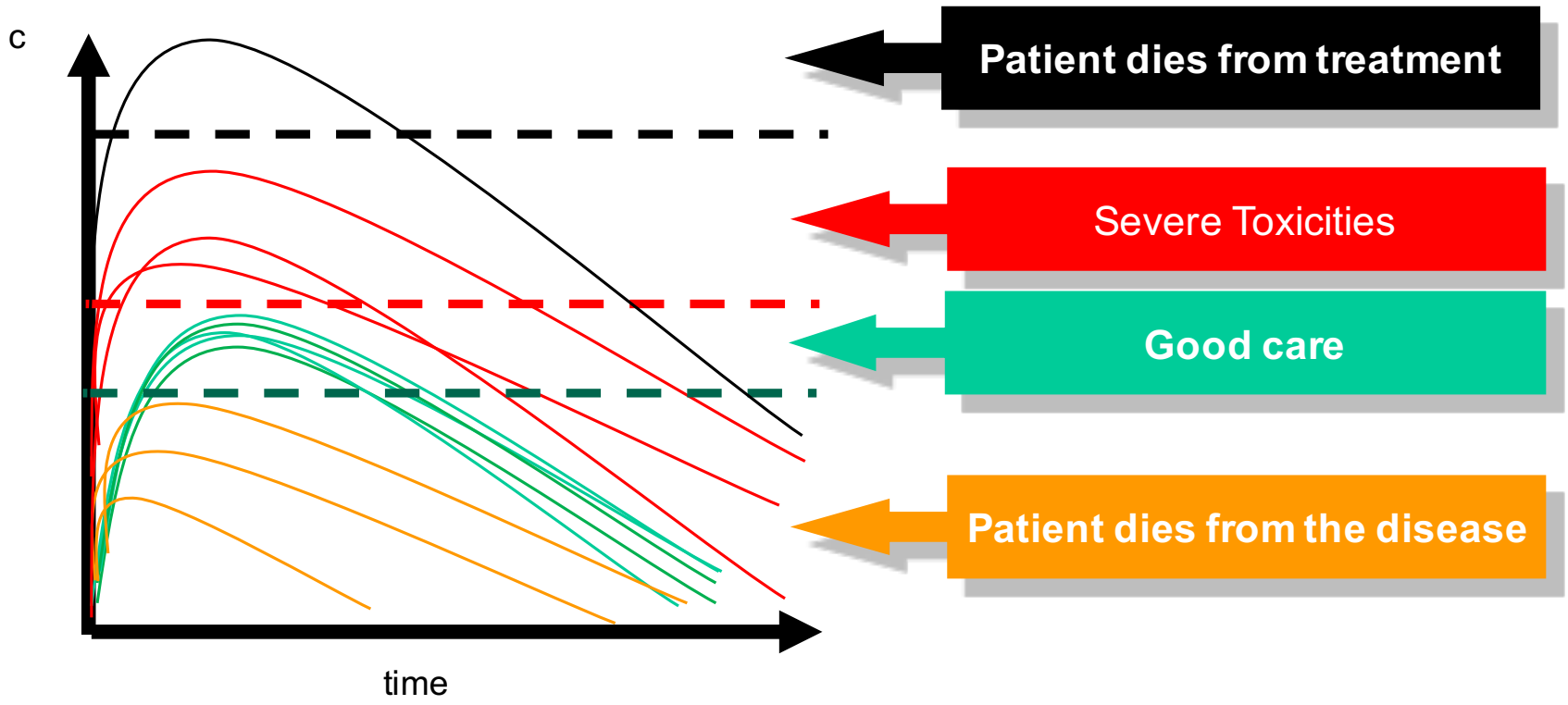


Pharmacometrics = the science of quantitative pharmacology



Garrido and Trocóniz, 2019

Inter-individual variability



Historical overview of PMX in oncology

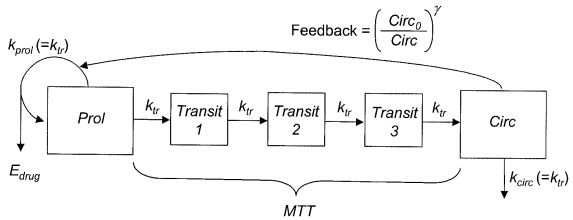
- 1980's: Principles of population PK modeling by Lewis Sheiner and Stuart Beal
- 1990's: pop PK models of cytotoxics
- 2000's: models of hematopoietic toxicity
- 2010's: tumor growth inhibition models

COMPUTERS AND BIOMEDICAL RESEARCH 5, 441–459 (1972)

Modelling of Individual Pharmacokinetics for Computer-Aided Drug Dosage*

LEWIS B. SHEINER, BARR ROSENBERG,† AND KENNETH L. MELMON

Departments of Medicine and Pharmacology, Division of Clinical Pharmacology, University of California San Francisco Medical Center, San Francisco, California 94122



Friberg et al., J Clin Oncol, 2002

VOLUME 27 · NUMBER 25 · SEPTEMBER 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Model-Based Prediction of Phase III Overall Survival in Colorectal Cancer on the Basis of Phase II Tumor Dynamics

Laurent Claret, Pascal Girard, Paulo M. Hoff, Eric Van Cutsem, Klaas P. Zuideveld, Karin Jorga, Jan Fagerberg, and René Bruno

How can standard dosing be part of personalized medicine?

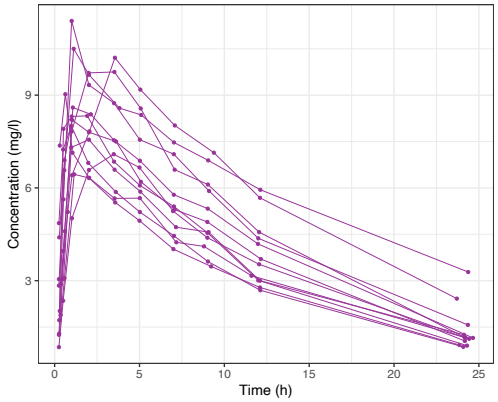
- Most anticancer agents are given as:
  - mg/m²
  - mg/kg
  - mg (flat-dose)

- Only carboplatin is given in a tailored fashion (i.e., AUC5 or AUC6 dosing).

- **« One dose fits all » (standard dosing)**

Mixed-effects modeling

Population data

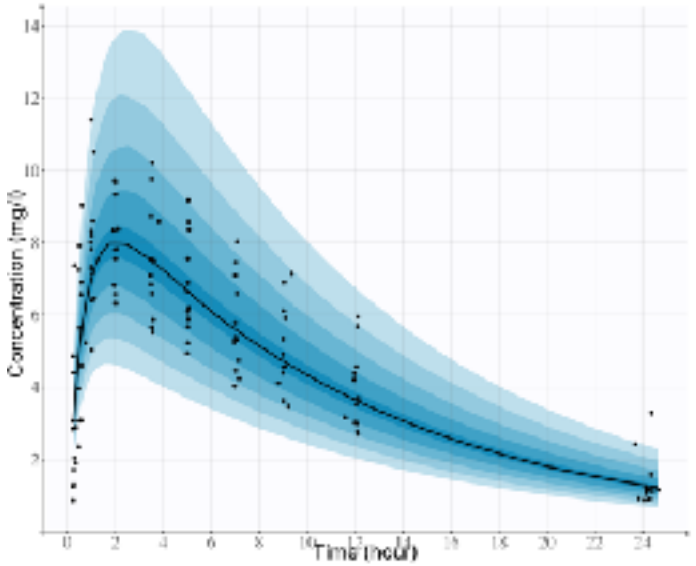


$$\psi^i = \psi_{pop} + \eta^i, \quad \eta^i \sim \mathcal{N}(0, \Omega)$$

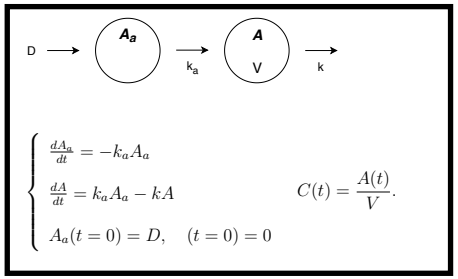
fixed effects

random effects

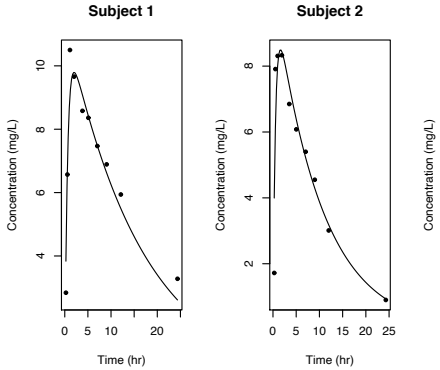
Population fit (MLE)



Individual structural model



Individual fit

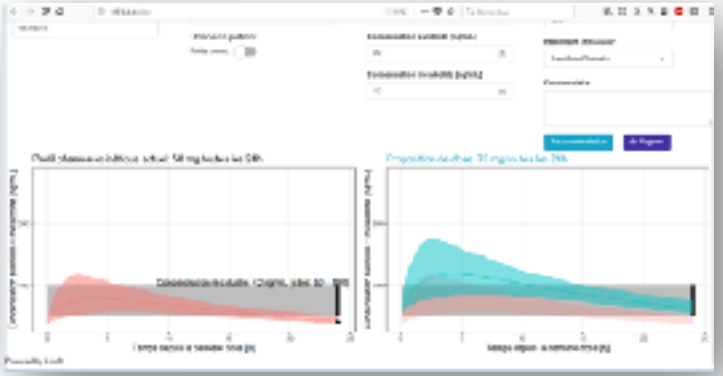


Precision and adaptive dosing of TKIs

Population prior + Sparse measurements from therapeutic drug monitoring

Bayesian estimation

$$p\left(\psi^i \mid y^i\right) \propto p\left(y^i \mid \psi^i\right) p\left(\psi^i\right)$$



Individual prediction

New patient

Unknown PK parameters

Pop-PK

One observation

Ct

Bayesian Estimation

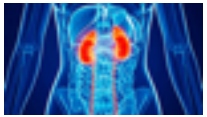
PK identification

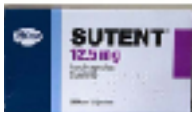
Simulations

J. Ciccolini

Sunitinib in metastatic kidney cancer

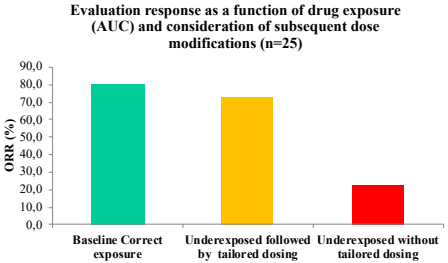
Patient #	Starting Dose (mg)	Total Su + met (ng/ml)	Sampling Time	Simulated Trough Level (ng/ml)	Proposed Dose (mg)	% change
1	50	195	5H30	161	25	-50
2	50	55	23H00	56	62,5	25
3	50	37,4	24H15	40	87,5	75
4	50	40	23h45	42	75	50
5	50	166	22H20	158	25	-50
6	50	161	4H45	136	25	-50
7	50	70	24H00	73	50	no change
8	50	161	4h45	136	25	-50
9	50	17,1	24H00	18	100	**100**
10	50	170	12H30	149	25	-50
11	50	90	24H00	90	37,5	-25
12	50	44,3	24H00	47	75	50
13	50	88	2H15	76	50	no change
14	50	106	19H00	100	37,5	-25
15	50	54,2	6H00	42	87,5	75
16	50	141	1H30	81	37,5	-25
17	50	128	24H00	106	37,5	-25
18	50	118,9	1H00	81	50	no change
19	50	145	19H00	115	37,5	-25
20	50	87	9H30	72	50	no change
21	50	104	3H20	90	37,5	-25
22	50	125	24h00	112	37,5	-25
23	50	62	19H00	58	62,5	25
24	50	246	24H00	231	12,5	**-75**
25	50	150	24H00	143	25	-50
26	50	83	12h00	71	50	no change
27	50	216	24h00	204	12,5	-75
28	50	197	24h00	192	25	-50
29	50	116	8H30	97	37,5	-25
30	50	78	24H00	71	50	no change





Standard dose: 50 mg

80% of AP-HM patient have dose modification of Sutent® 12.5 <>100 mg (-75% ⇨ + 100%!)



Unpublished data - do not post

J. Ciccolini

Model-based dosing regimen for a phase I/II clinical trial

Goal: safe densification of docetaxel (DTX) + epirubicin (EPI) in metastatic breast cancer

PK models

PK DTX

PK EPI

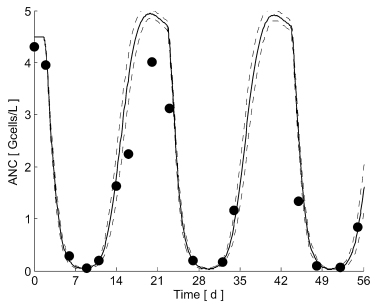
Interface model

(+ G-CSF rescue)

PD models

TOXICITY

(Friberg-like)



EFFICACY

(Gompertz-like)

Meille et al. (Iliadis), Clin Pharmacokinet, 2016

Scheduling optimization

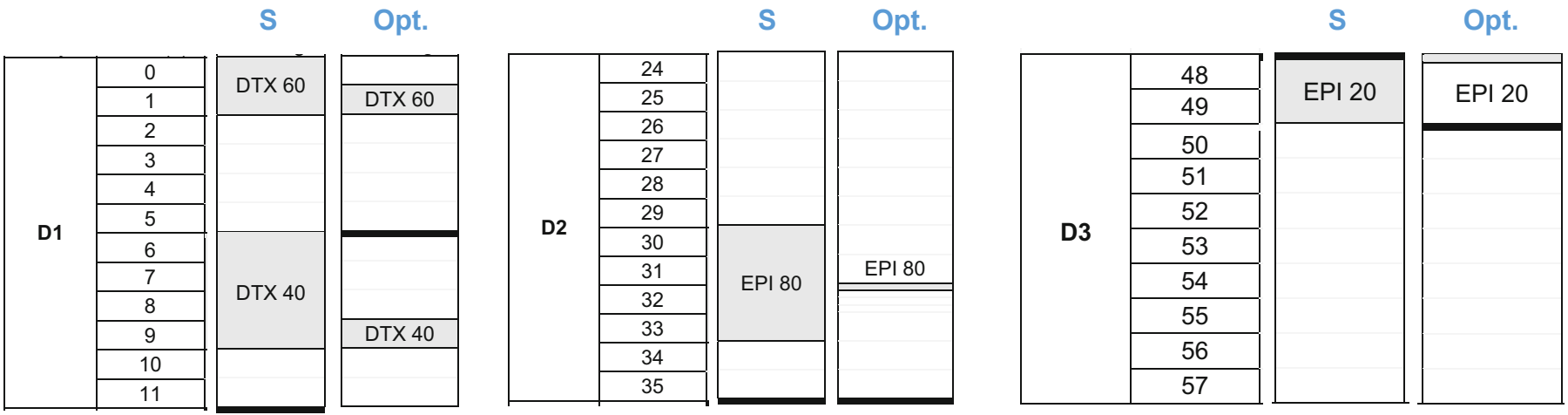
Parameter estimation

- PK: popPK previous studies
- PD toxicity: estimated from previous phase I study
- PD efficacy: *in vitro* cytotoxicity + fit to previously published clinical studies

Optimization

$$\underline{d}^* = \arg\min \left[\frac{1}{T} \int_0^T n(t, \underline{d}, \underline{t}^*) \cdot dt \right]$$

under toxicity constraints



S = standard, Opt = optimized

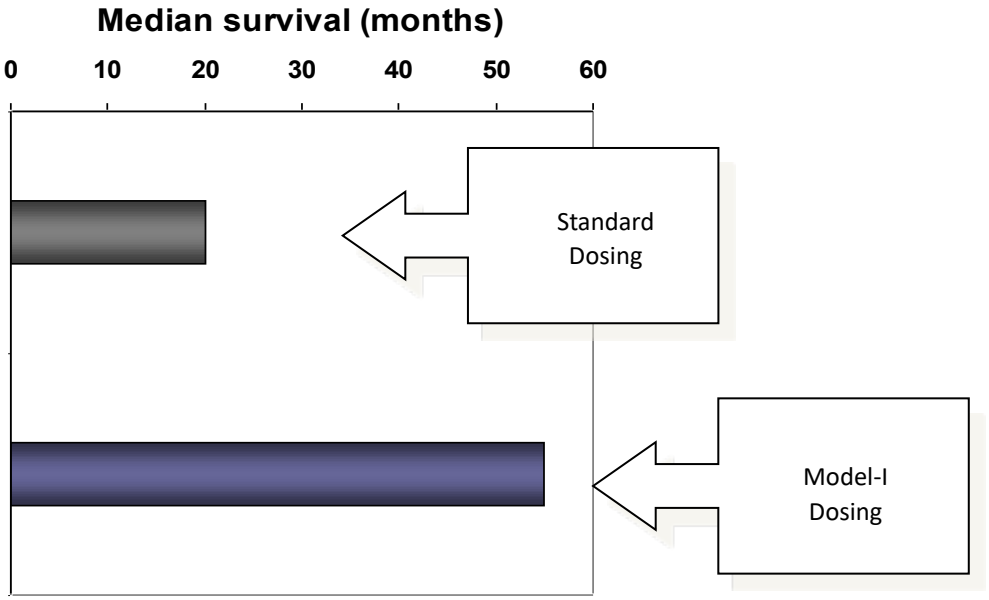
Meille et al. (Iliadis), Clin Pharmacokinet, 2016

MODEL1 clinical results

Previously: life-threatening toxicities
- 100% grade ≥ 3 neutropenia
- **1 death**

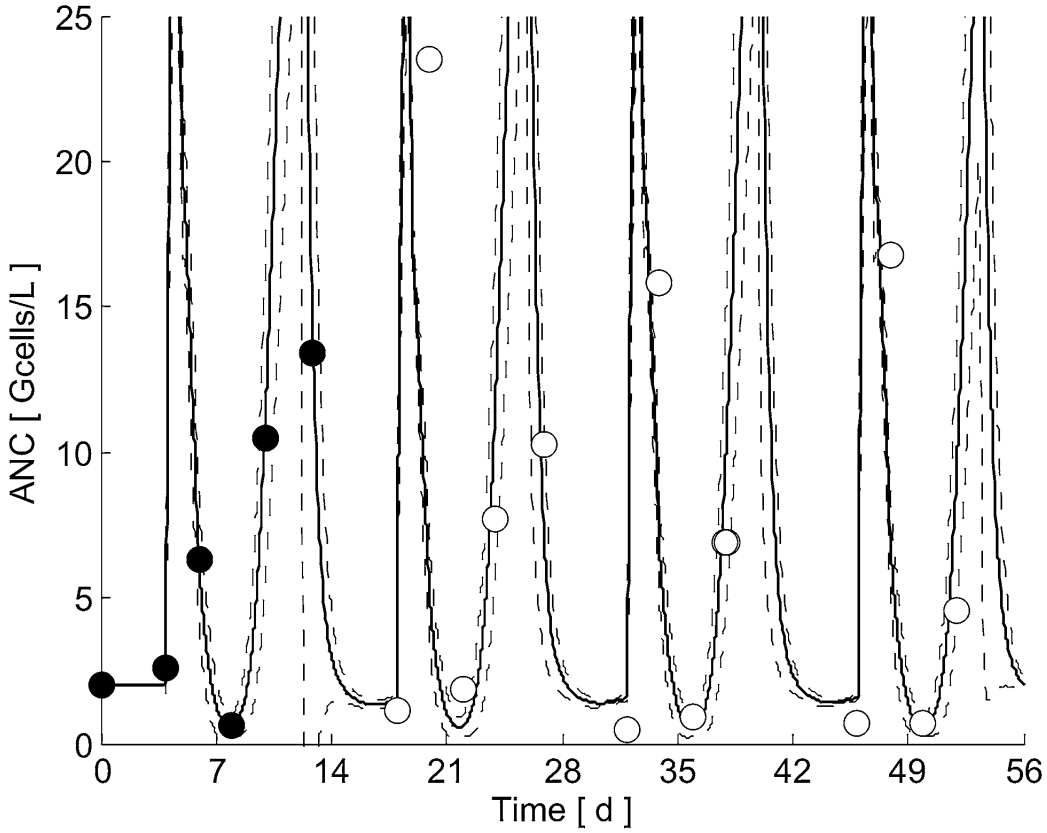
Viens et al., J Clin Oncol, 2001

MODEL1: no lethal toxicities
- **0% grade ≥ 3** neutropenia

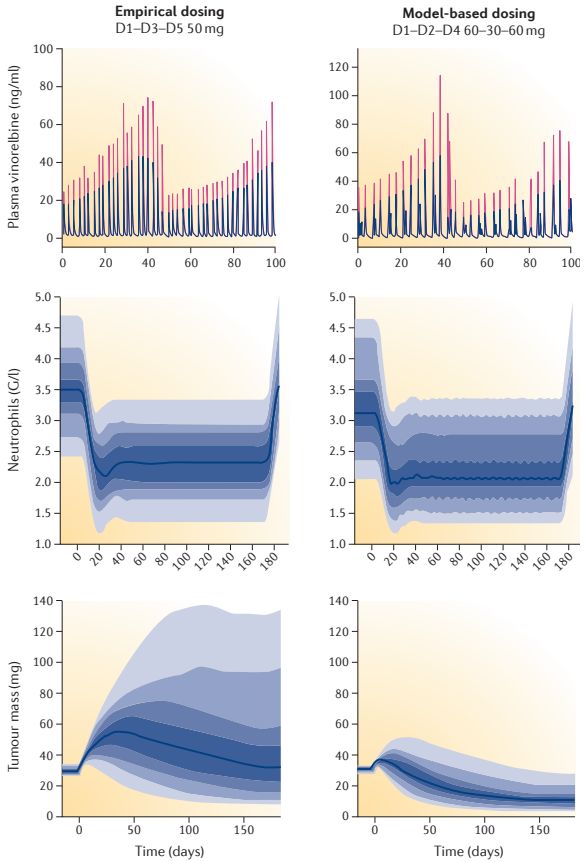


Hénin et al. (Iliadis, Freyer), Breast Cancer Res Treat, 2016

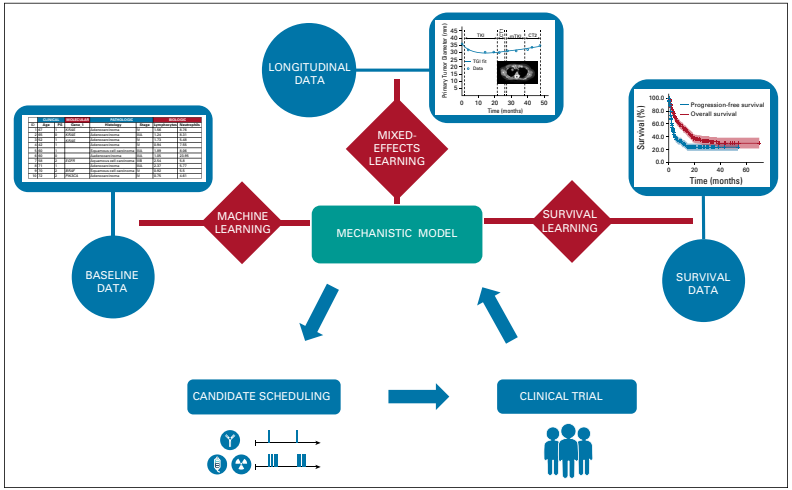
Individualization of parameter estimates



Other model-based trials



- Metronomic vinorelbine in NSCLC (NCT02555007)
- Combination of radiotherapy and immune-checkpoint inhibition (NCT03509584)



Barbolosi et al., Nat Rev Clin Oncol, 2016
Ciccolini et al. (Benzekry), J Clin Oncol: Precision Oncology, 2020

The QUANTIC Project

QUANTitative modeling combined to statistical learning to understand and predict resistance to Immune-checkpoint inhibition in non-small cell lung Cancer

Conclusions

- Pharmacometrics is an important field with demonstrated clinical utility of mathematical/ statistical models
- Often neglected and not sufficiently appreciated
- Advanced statistical techniques of parameter estimation
- Model-based adaptive dosing is routinely done for some cytotoxics (e.g. Busulfan, cisplatin) and most TKIs
  - Not for all (under development: immune-checkpoint mAbs)
  - Limitation: needs PK measurements
- First model-driven phase I/II dose-escalation study
  - Shows encouraging results
  - Limitation: small number of patients, not randomized

We have open positions!!

- **Full research tenure**
- Postdoc
- Engineer

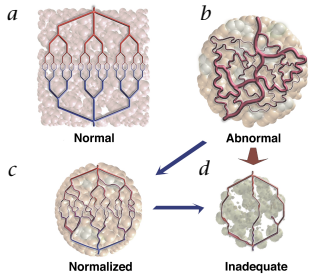
sebastien.benzekry@inria.fr

Axis 2: Optimizing combinatorial strategies
Cytotoxics + antiangiogenics

Therapeutic question

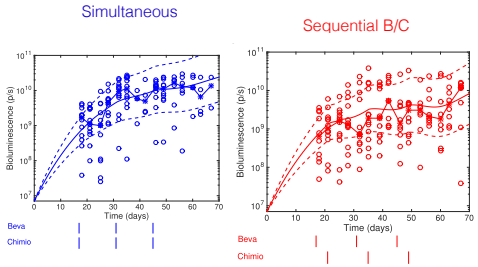
What is the **optimal time gap** between administration of bevacizumab and cytotoxic chemotherapy?

Biological rationale

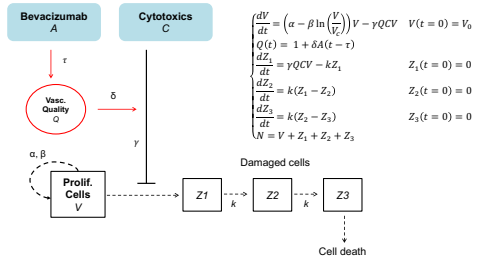


Jain, Nat Med, 2001

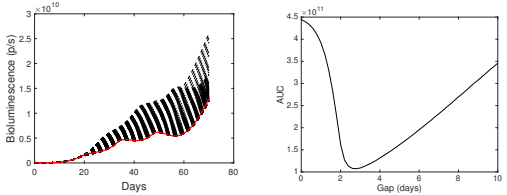
Calibration



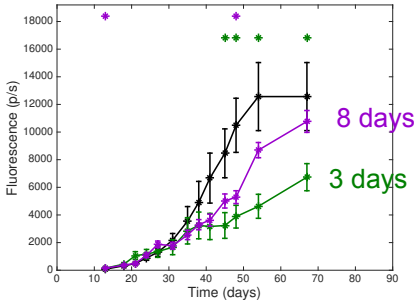
Modeling



Prediction



Validation



Imbs et al., Benzekry, CPT: Pharmacometrics and Systems Pharmacology, 2017