Pharmacometricians and Statisticians

Can't We All Just Get Along??

Stacey Tannenbaum
Director, PK, Modeling, and Simulation
Astellas Pharma

Stacey.Tannenbaum@astellas.com

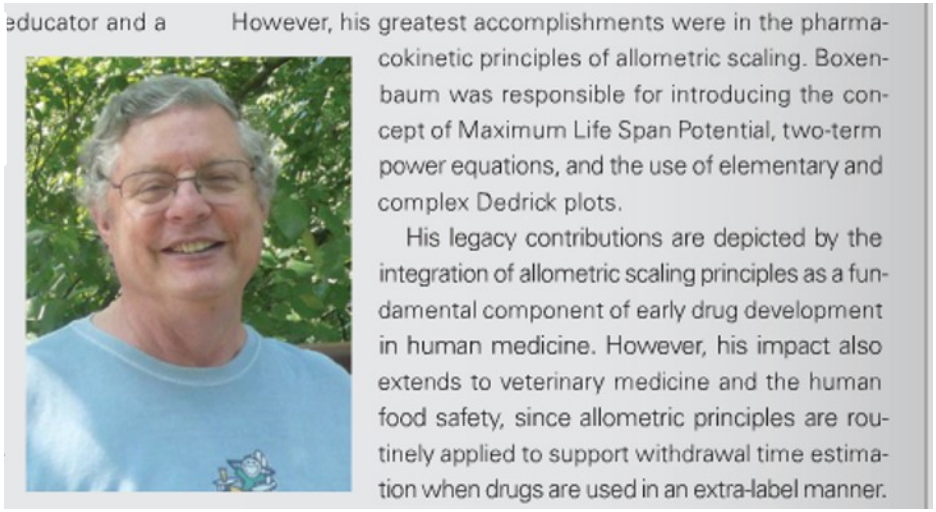
Note: portions of this content have been presented in previous venues

- Symposium: Bridging the Gap between Pharmacometricians and Statisticians
  - World Conference on Pharmacometrics (WCoP)
  - August 2016

- Workshop: Enabling Environments in Which Pharmacometrics and Biostatistics Help Produce Robust Development And Regulatory Strategies
  - American Conference on Pharmacometrics 6
  - October 2015

- BSE in Biomedical Engineering, Duke
- PhD in Pharmaceutical Sciences (PK) and Applied Mathematics at the University of Arizona, 2001

Harold Boxenbaum



educator and a

However, his greatest accomplishments were in the pharmacokinetic principles of allometric scaling. Boxenbaum was responsible for introducing the concept of Maximum Life Span Potential, two-term power equations, and the use of elementary and complex Dedrick plots.

His legacy contributions are depicted by the integration of allometric scaling principles as a fundamental component of early drug development in human medicine. However, his impact also extends to veterinary medicine and the human food safety, since allometric principles are routinely applied to support withdrawal time estimation when drugs are used in an extra-label manner.

- Post-doc at Center for Drug Development Science (CDDS), 2003

Carl Peck

- Novartis Modeling and Simulation (2003-2011)
- Astellas PK/M&S (2012-)

I identify as a pharmacometrician

pharmacometrician

English [edit]

Noun [edit]

pharmacometrician (*plural* **pharmacometricians**)

1. An expert at pharmacometrics.

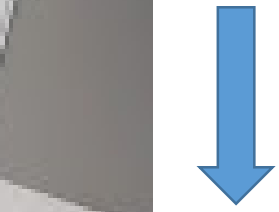
https://en.wiktionary.org/wiki/pharmacometrician

DISCLAIMER

All stereotypes are wrong, some are useful!

S. Tannenbaum, adapted from G. Box

This is Ted. Ted is an accountant.



2014

Income	
Service Fees	$ 25,692.00
Tangible Product Sales	$ 12,811.00
Intangible Product Sales	$ 55,852.00
Other Income/Revenue	$ 11,332.00
Large (Depreciated) Expenses	
Computers/Software	$ 2,415.00
Furniture & Decor (Office/Studio)	$ 8,655.00
Photography Equipment	$ 1,212.00
Backgrounds & Props	$ 892.00
"Disposable" Expenses	
Office Supplies	$ 3,441.00
Studio (or On Location) Supplies	$ 2,598.00
Maintenance	
Building Maintenance	$ 1,055.00
Equipment Maintenance	$ 432.00
Vehicle Maintenance	$ 750.00
Milage	
Vehicle Milage	2695
Physical Address	
Studio/Office Rent	$ 28,400.00
Utilities	
Gas/Oil/Electric	$ 3,569.00
Water	$ 250.00

Your Name Here
123 Four Five
Six, Seven 12345
123-456-7890
email@email.com

Communications/Presence	
Advertising/Promotional	$ 1,900.00
Website	$ 650.00
Phone	$ 2,520.00
Internet	$ 480.00
Product Related Costs	
Cost of Goods Sold	$ 2,566.00
Packaging	$ 850.00
Shipping/Postage/Freight	$ 600.00
Ongoing Education	
Tuition	$ 4,252.00
Books, etc.	$ 1,800.00
Miscellaneous Fees	
Bank Fees	$ 267.00
Credit Card Processing Fees	$ 6,285.00
Insurance	$ 450.00
Legal Fees	$ 1,450.00
Association Fees	$ 300.00
Subscription Fees	$ 120.00
Other	
Meals/Entertainment	$ 963.00
Travel	$ 950.00

Income | Lrg Exp | Disp Sups | Maint | Milage | Rent Util | Com Pres | Prod Rel Costs | Edu | Misc Fees | Other

	Statistics
Familiarity	Most science majors have taken at least one stats class
History	• Stats conferences: 1830s • First statistical society established 1834 • Statisticians in the Pharmaceutical Industry established 1977
Training	Statistics, mathematics, econometrics
Other disciplines	Actuarial sciences, economics, business, data mining, telecom, epidemiology, energy, image processing, medical, engineering, psychology, sociology, etc etc…
Models	“well” “understood”
Communication	Focus on results

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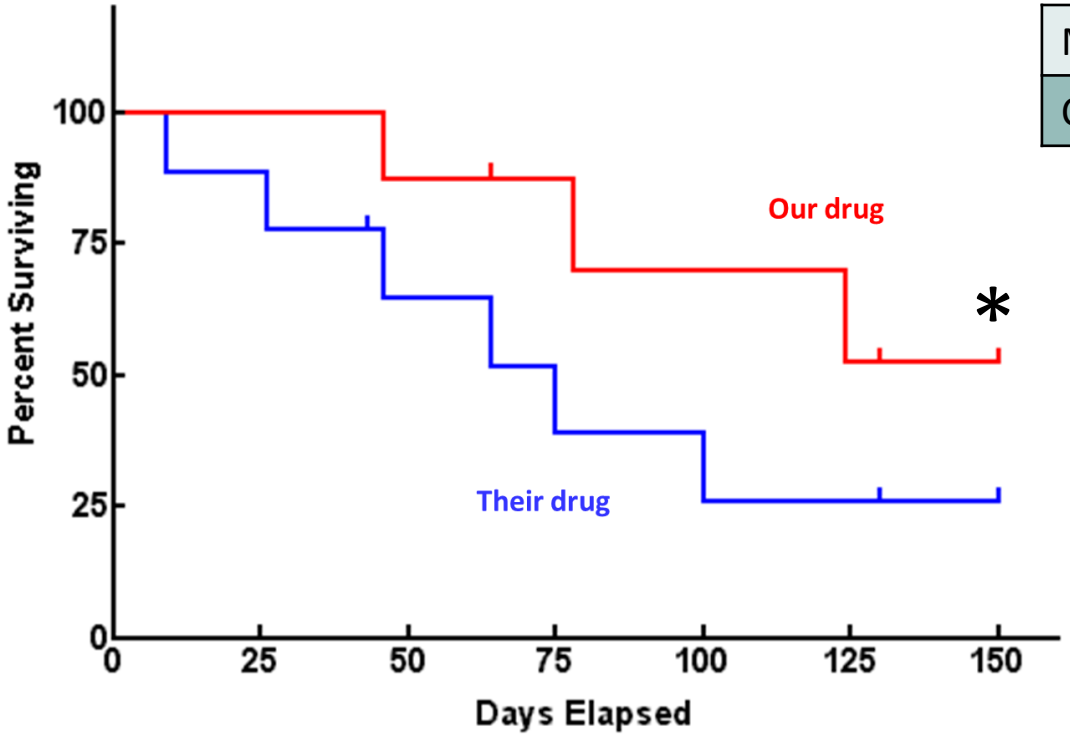
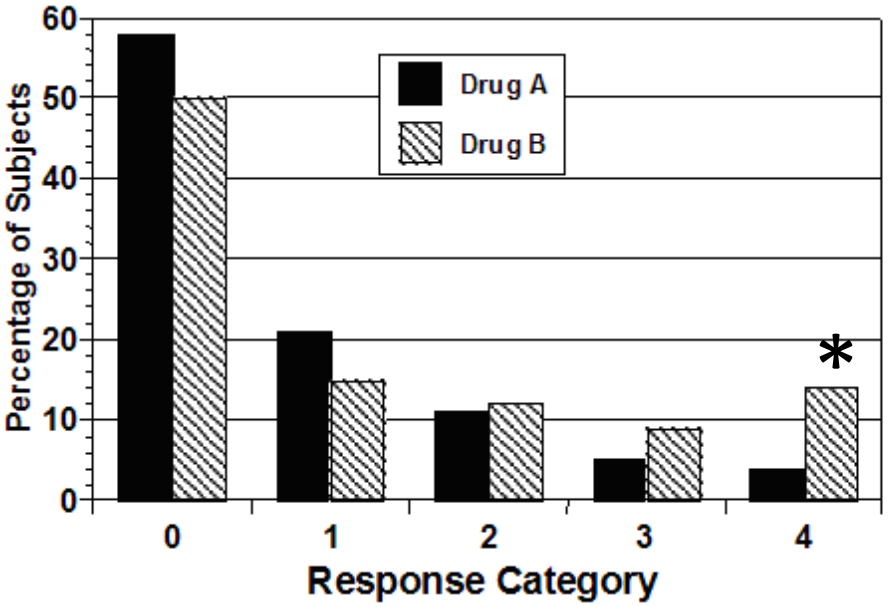
Communication	Focus on results



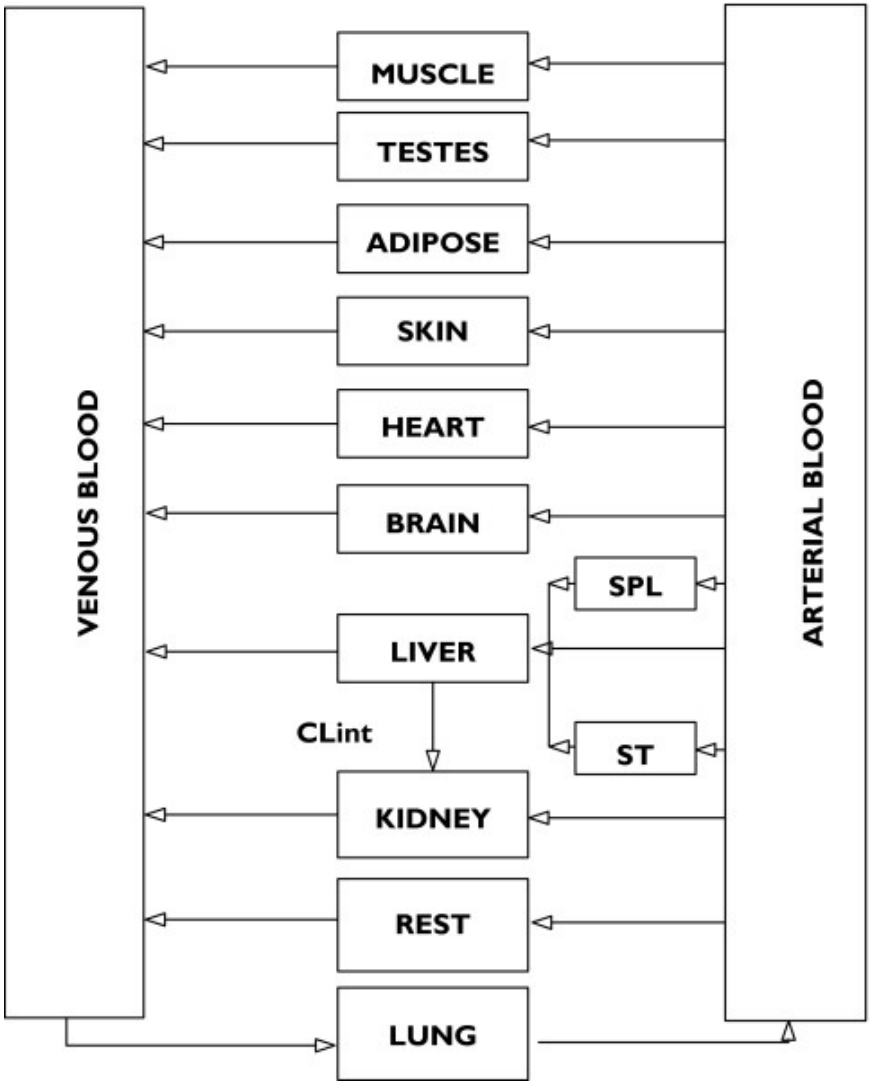



P<0.05!


CWRES
THETA!
Objective function
FOCE-I
IPRED
shrinkage
pcVPC
Weibull
$COV

(Relatively New) Kids on the Block

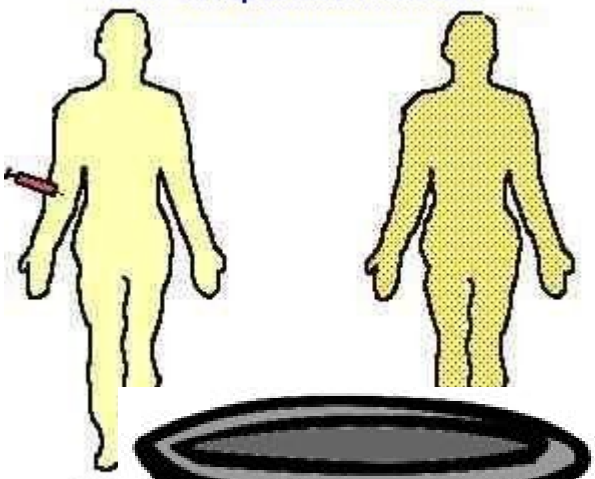
	Statistics	Pharmacometrics
Familiarity	Most science majors have taken at least one stats class	Unlikely to have much training in PMX/ PK / Clin Pharm
History	First statistical society established 1834 Stats conferences: 1830s Statisticians in the Pharmaceutical Industry established 1977	First pharmacometrics society (ISoP) established 2011 PAGE 1992, PAGANZ 1999, PAGJA 2006, PAGK 2007, PAGIN 2008, ACoP 2008, WCoP 2012 (PAGUSA?) Other CP/pharm sci organizations (ASCPT, ACCP, AAPS) 1950s-1970s
Training	Statistics, mathematics, econometrics	(Clinical) pharmacology, medicine, tox, PK, engineering, biology, mathematics, chemistry, statistics, computer science …
Other disciplines	Actuarial sciences, economics, business, data mining, telecom, epidemiology, energy, image processing, medical, engineering, psychology, sociology, etc etc…	**Pharmaco**…metrics *Modeling and Simulation, M&S, PK, PKPD, Quantitative Science, DMPK, Quantitative Decision Making, Quantitative [Clinical/Systems] Pharmacology, etc…* CMART
Models	“well” “understood”	**Not so much.**
Communication	Focus on results	Focus on the model/method

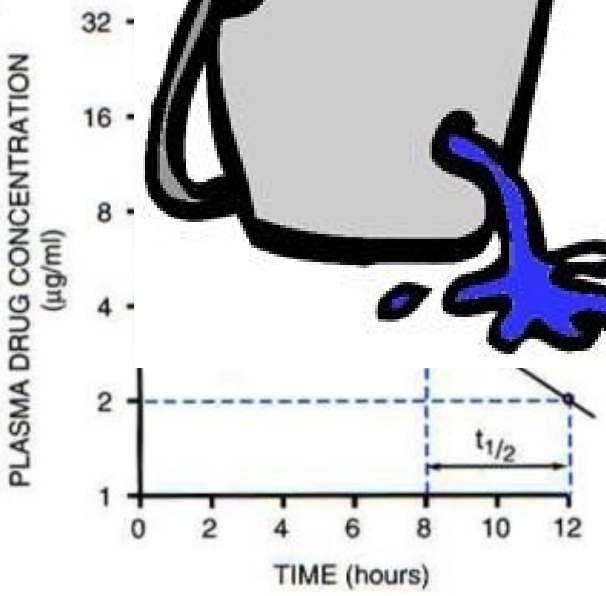


CREDIBILITY SCALE FOR PMX MODELS

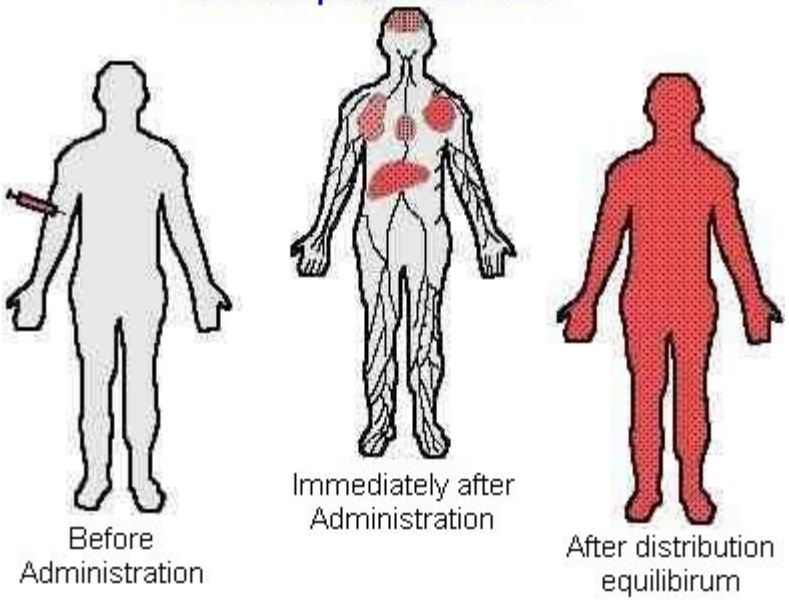
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1884881/

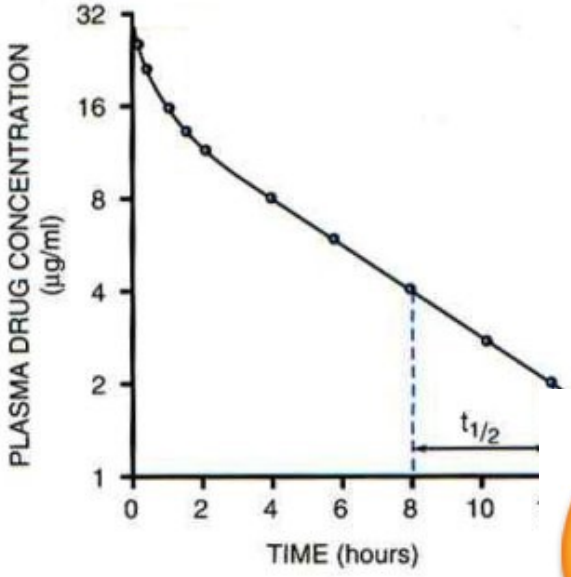
One compartment model



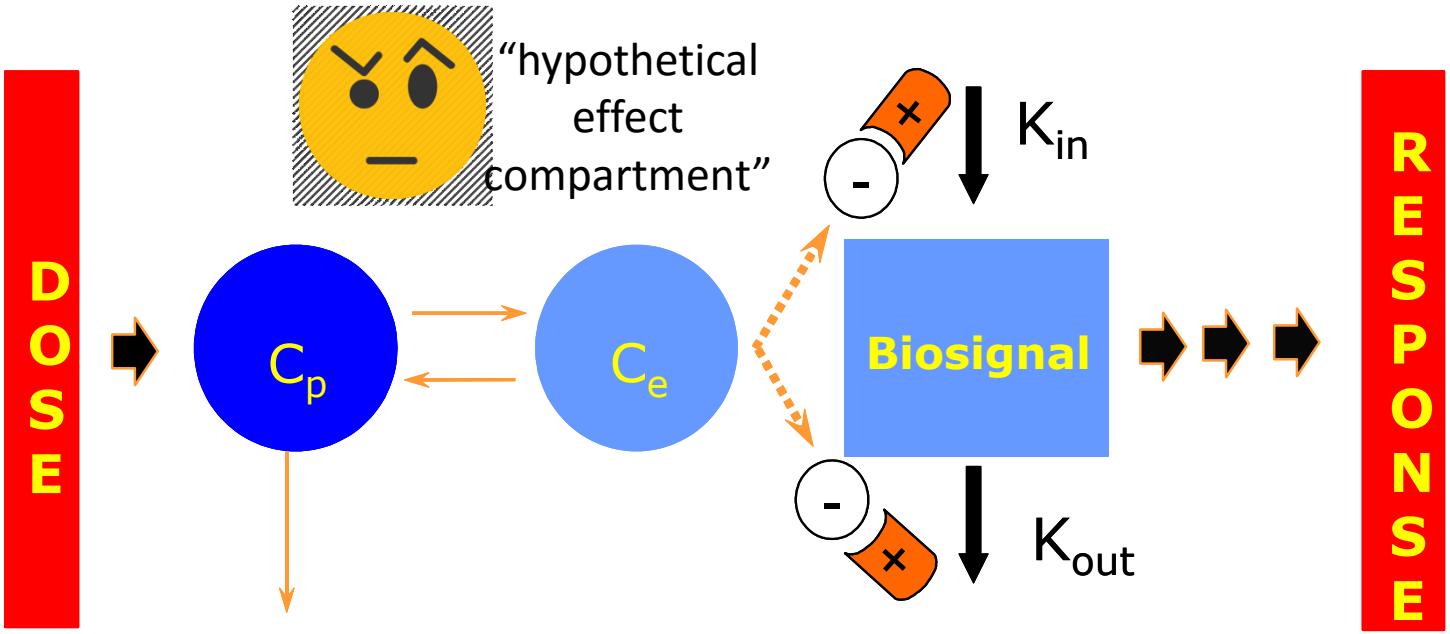


Two compartment model

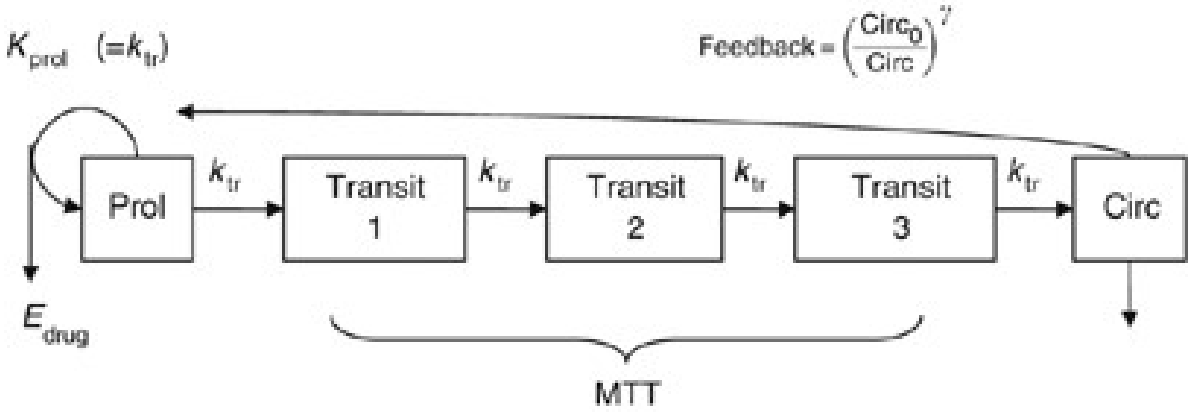




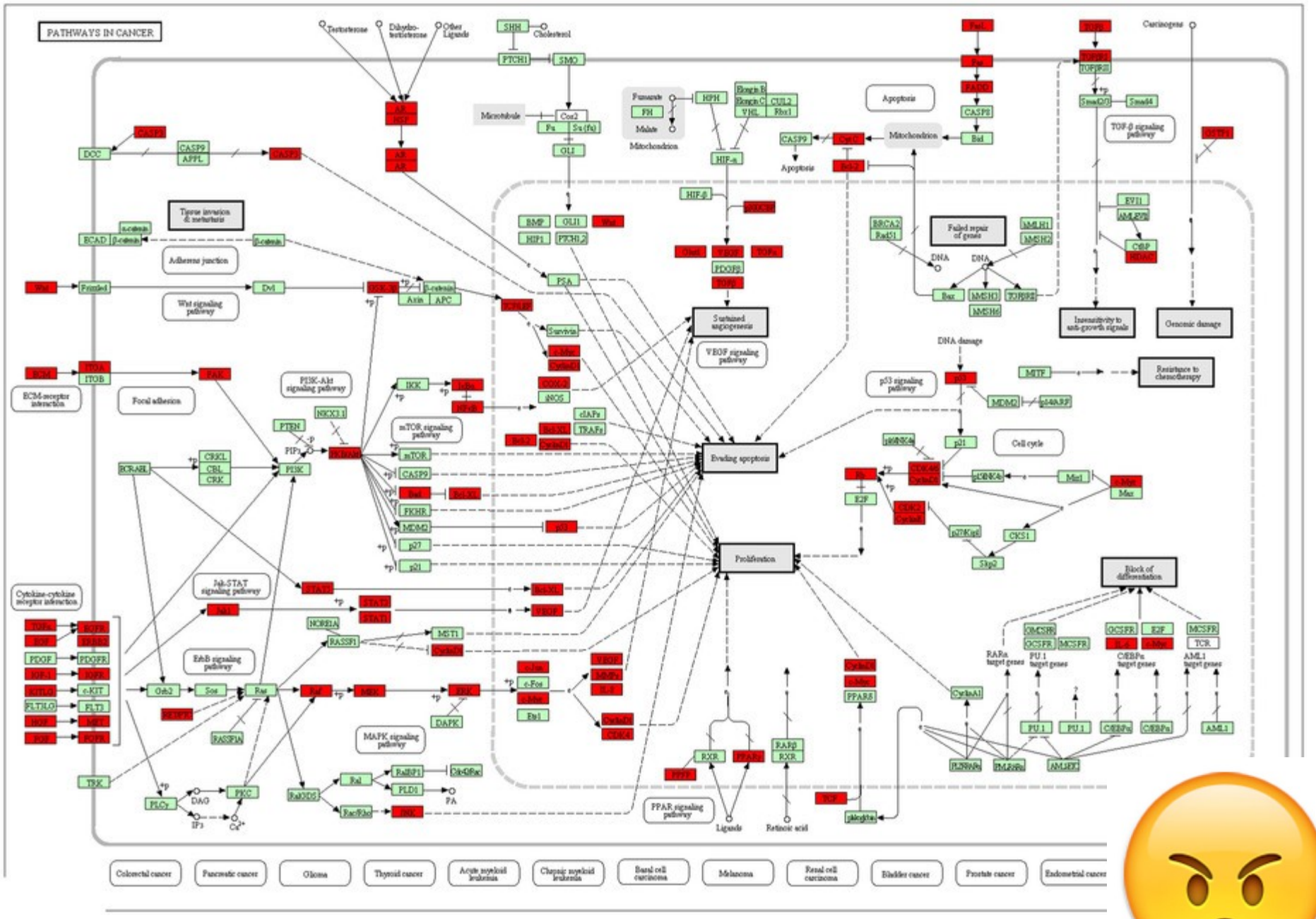
http://www.rxkinetics.com/pktutorial/1_5.html



Jusko et al, *JPB (1995)*



Puisset et al, *Br J Cancer* (2007)



Systems pharmacology of mifepristone… Yu et al. Scientific Reports 5 (2015)

Be a Model Communicator

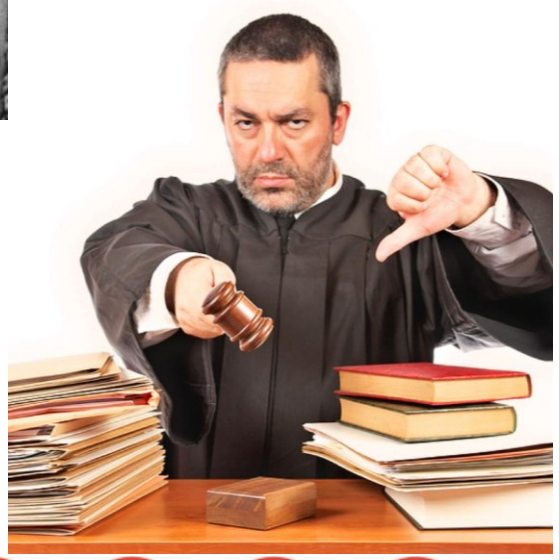
and Sell Your Models to Anyone

Peter L. Bonate, PhD

My boss!


Just the
facts,
ma'am.


THOMPSON
U.S.ARM



INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

STATISTICAL PRINCIPLES FOR CLINICAL TRIALS
E9

"The extent to which the procedures in the protocol are followed and the primary analysis is planned a priori will contribute to the degree of [redacted] in the final results and conclusions of the trial."

https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073137.pdf

Medical Statistician - One who won't accept that Columbus discovered America because he said he was looking for India in the trial plan

http://www.senns.demon.co.uk/wdict.html


N
VANDEVALL


123RF

Guidance for Industry

Population Pharmacokinetics

In contrast to traditional pharmacokinetic evaluation, the population PK approach encompasses some or all of the following features (3):

- The collection of relevant pharmacokinetic information in patients who are representative of the target population to be treated with the drug.
- The identification and measurement of variability during drug development and evaluation.
- The explanation of variability by identifying factors of demographic, pathophysiological, environmental, or concomitant drug-related origin that may influence the pharmacokinetic behavior of a drug.
- The quantitative estimation of the magnitude of the unexplained variability in the patient population.

https://www.fda.gov/downloads/drugs/guidances/UCM072137.pdf

Guidance for Industry

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Population PK data analysis, as a modeling exercise, cannot be planned to the fullest detail. However, as mentioned above, the protocol should include study objectives; patient inclusion and exclusion criteria and pharmacokinetic evaluability criteria; sampling design; data handling and checking procedures; initial assumptions for modeling; a list of possible covariates to be investigated and the rationale for choosing them; and whether a sensitivity analysis and a validation procedure are envisioned. In addition, the proposed method of model building, critical for covariates inclusion and exclusion, should be described.

https://www.fda.gov/downloads/drugs/guidances/UCM072137.pdf

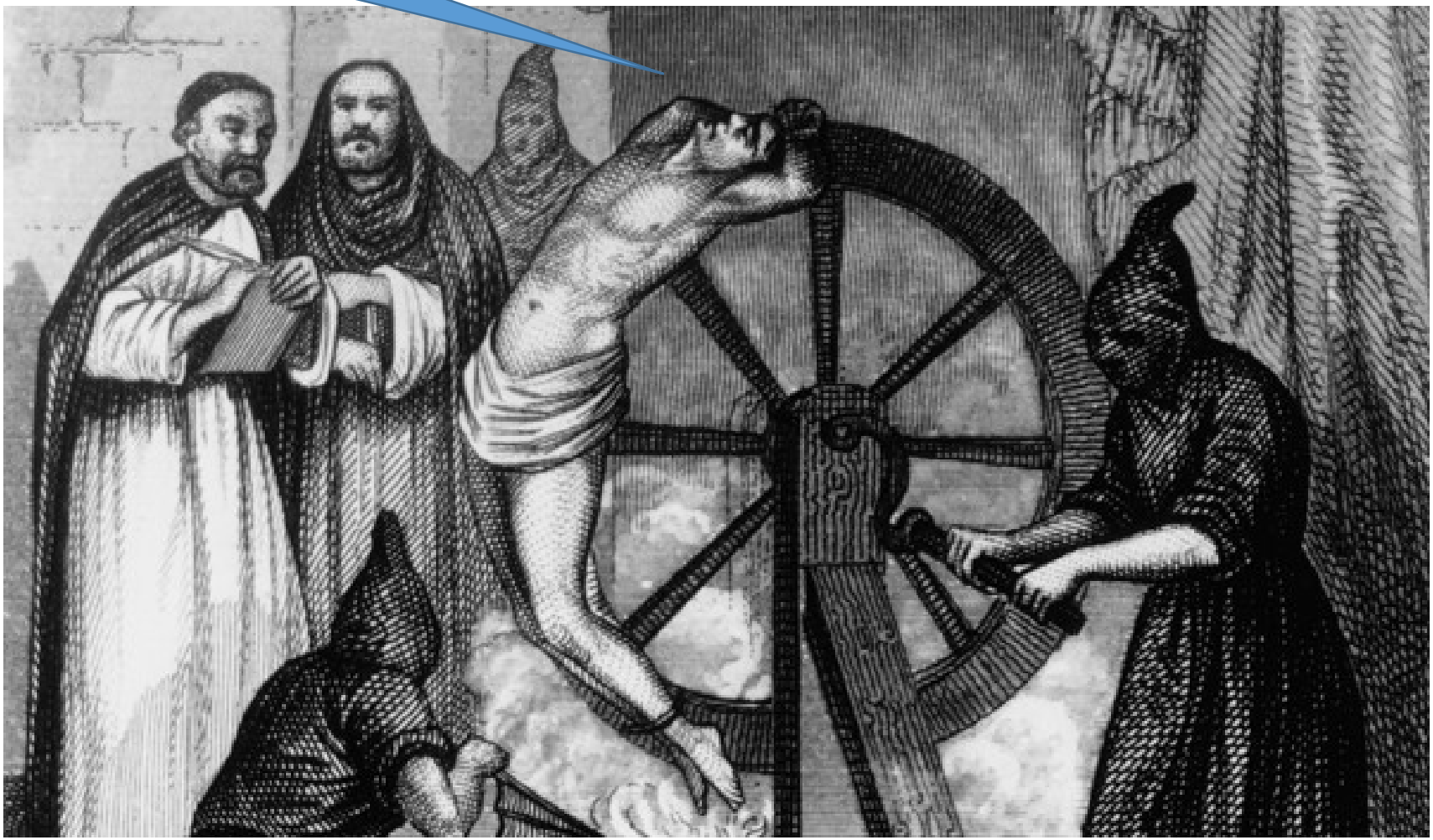

WENT ON WILD GOOSE CHASE
CAUGHT WILD GOOSE
memegenerator.net


OMG
SHINY OBJECT


SQUIRREL!

Shoe size is a significant covariate!

"If you torture the data long enough, it will confess."
Ronald H. Coase

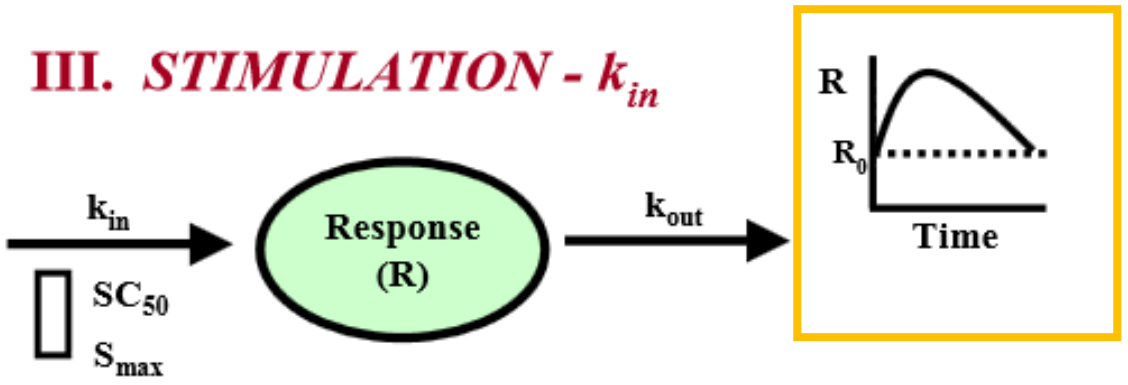


Tension between PMX and Stats

Kowalski (2015), "**My Career as a Pharmacometrician and Commentary on the Overlap Between Statistics and Pharmacometrics in Drug Development**", *Statistics in Biopharmaceutical Research*, 7:148-159.

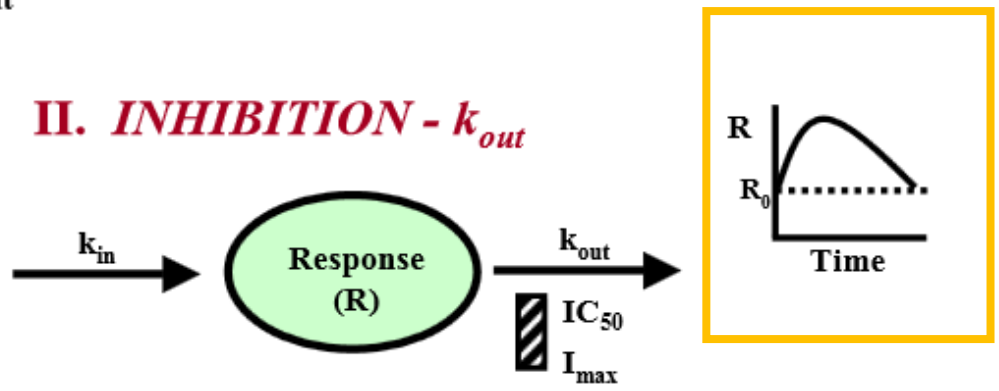
- Mechanistic versus empirical models
- Adequacy of the model fit and predictive performance
- Exposure-response relationships
- Exposure versus dose
- Inadequate understanding of statistics
- Use of assumption-rich models
- Drawing confirmatory conclusions from exploratory data analysis

Mechanistic versus empirical models



$$\frac{dR}{dt} = k_{in}\left(1 + \frac{S_{max} \cdot C_p}{SC_{50} + C_p}\right) - k_{out} \cdot R$$

Different mechanism, same shape → different predictions



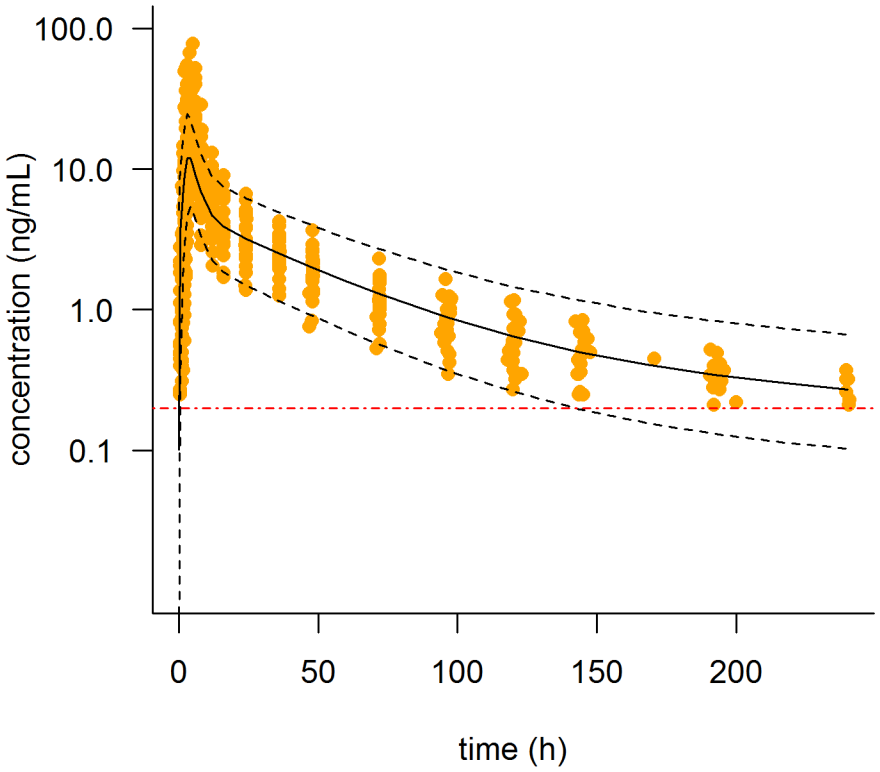
$$\frac{dR}{dt} = k_{in} - k_{out}\left(1 - \frac{I_{max} \cdot C_P}{IC_{50} + C_P}\right) \cdot R$$

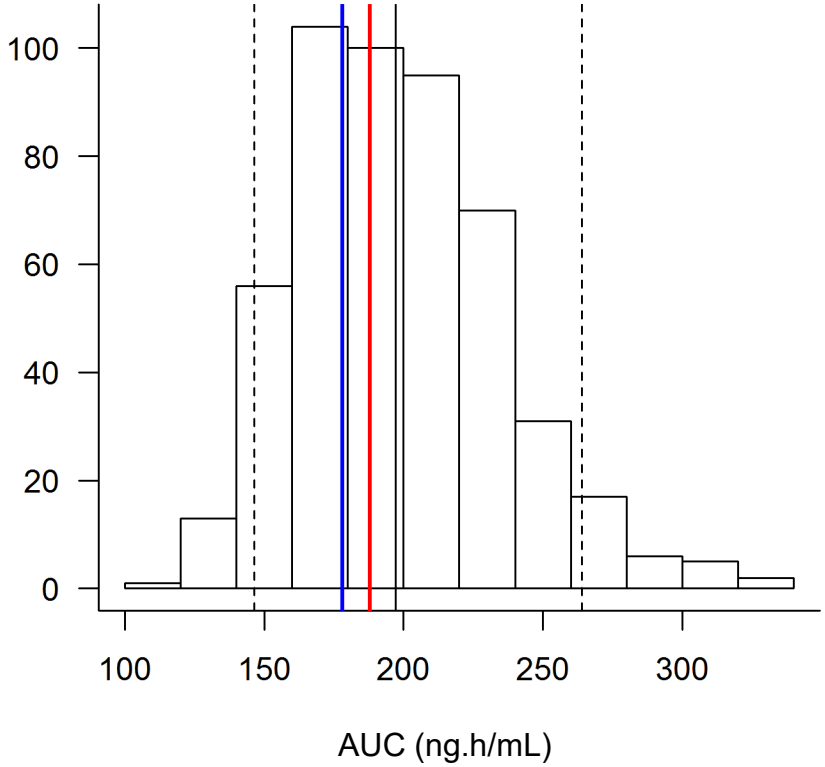
"competing … models and their predictions should be brought forward as part of a sensitivity assessment to select designs that are robust to this model uncertainty….. predictions are *hypothesis-generating*"

Sharma and Jusko, *Br. J. Clin. Pharmacol.* 45: 229 (1998)

http://accp1.org/pharmacometrics/pkpdcourse2006/lecs/lec2/IDR.pdf

Adequacy of the model fit and predictive performance



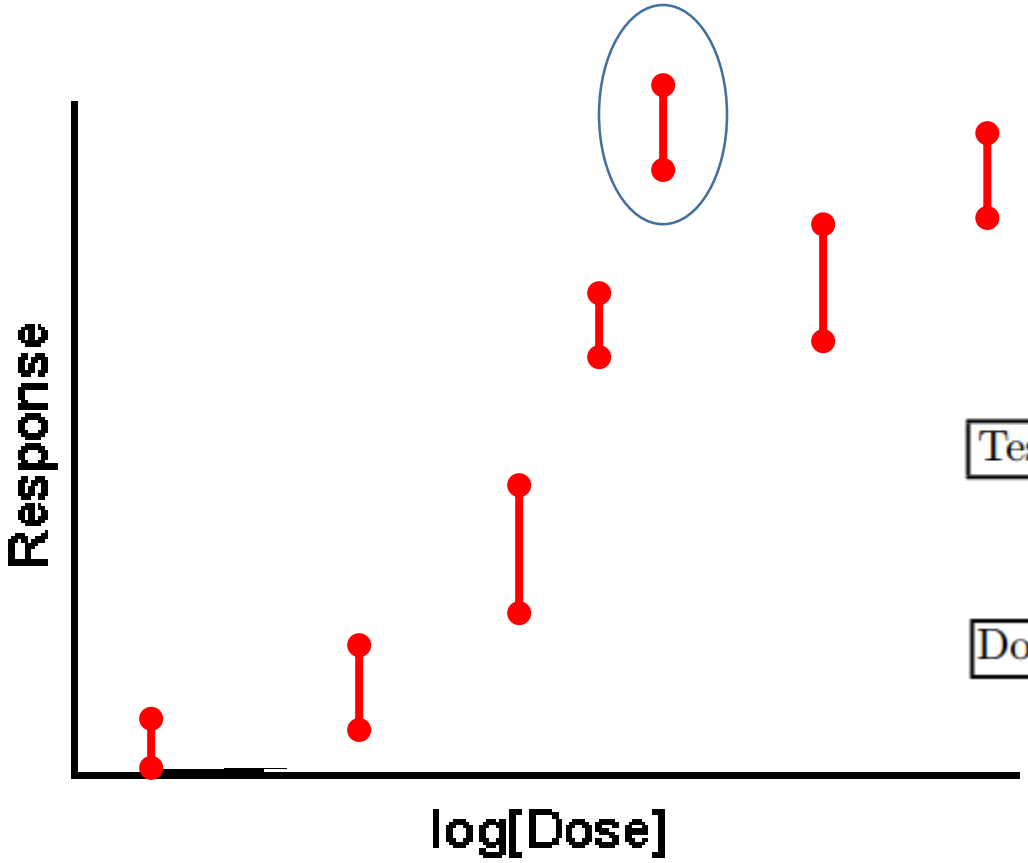


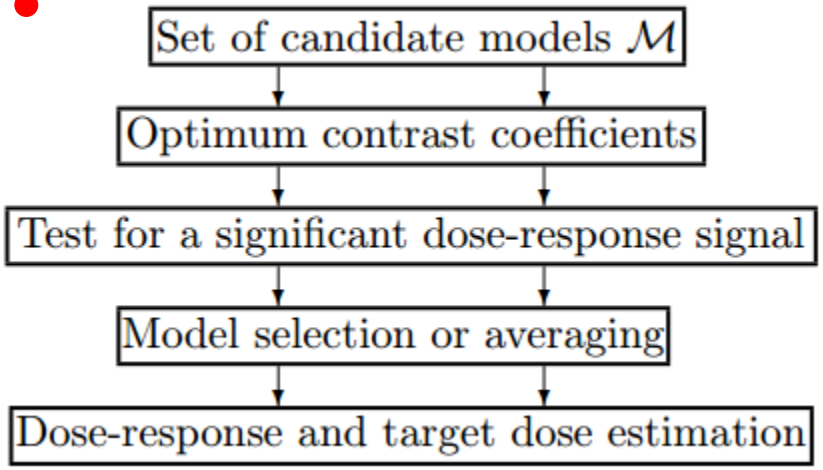
AUC targeted by dosing regimen

Median AUC in simulated data

Exposure-response relationships

MCP vs Mod





https://www.jstatsoft.org/article/view/v029i07/v29i07.pdf
FDA qualification ; EMA qualification

“I know nothing about statistics”

- Most Pharmacometricians

But you’re fitting **nonlinear mixed effect models** using **maximum likelihood**, **SAEM** or **MCMC**, using **likelihood ratio tests** to determine **significance**, **covariate search techniques**, considering **collinearity**, performing **model diagnostics**, **simulating** new outcomes, evaluating **decision criteria**, using **optimal design** theory…

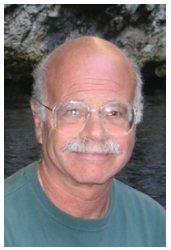
Most of these topics would **scare the living crap** out of a graduate statistician.

Courtesy Mike K. Smith, Pfizer

Inadequate understanding of statistics

“Big cheeses” of PMX

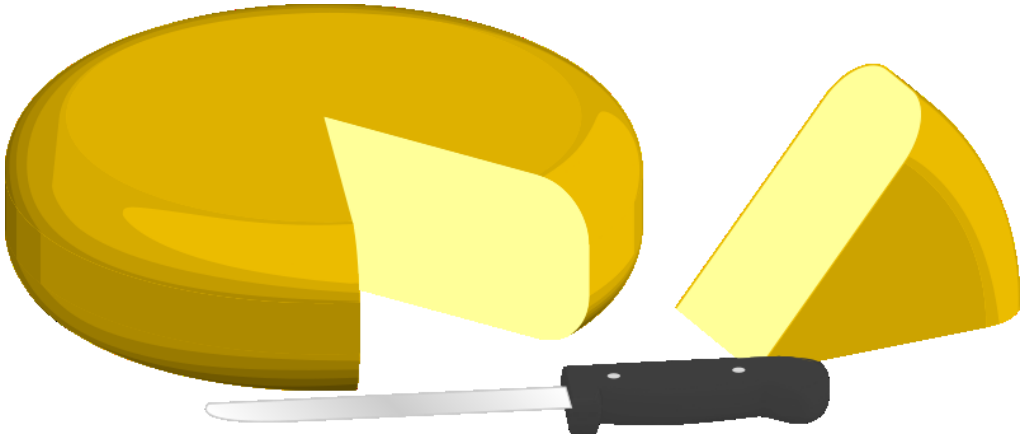
Beal



Mentre

Weiner

Steimer



I don't care about PK, I just care if we meet our endpoint with statistical significance!

All statisticians care about are p-values!


MEL GIBSON DANNY GLOVER
and Joe Pesci
The magic is back again.
LETHAL WEAPON 3


STOP
COLLABORATE AND
LISTEN

Statisticians and pharmacokineticists: what can they learn from each other?

Senn, SJ; (1997) Statisticians and pharmacokineticists: what can they learn from each other? In: Aarens, EA, (ed.) **COST B1 Medicine: The population approach: measuring and managing variability in response, concentration and dose,.** European Commission: Brussels.

STATE OF THE ART nature publishing group

Statisticians and Pharmacokineticists: What They Can Still Learn From Each Other

S Senn[1]

Examples are given of how the practice of statistics could be improved if statisticians showed a greater awareness of pharmacokinetic and pharmacodynamic modeling. Some examples are also given where a wider appreciation of statistical theory would improve current approaches to pharmacometrics. Areas in which the two disciplines are in agreement but have failed to have as much influence on others in drug development as they ought are also considered. It is concluded that there would be much benefit in increasing collaboration between these disciplines.

http://bookshop.europa.eu/en/cost-b1-pbCGNA17611/
https://www.ncbi.nlm.nih.gov/pubmed/20613721

Courtesy Mike K. Smith, Pfizer
[slide adapted]

http://www.go-isop.org/asa-sig ; http://community.amstat.org/sxp/home

Collaboration and cooperation

- Understand and agree what the quantitative analyses need to support
  - What are the key development questions?
  - What are the decision criteria?
  - Who is doing what? Don't work in parallel!

- Build a relationship
  - Teach about your discipline/language
  - Acknowledge what you don't know
  - Leverage your partner's strengths and ask for help
  - Support each other at team meetings
  - Debate and disagreement can be healthy but keep it friendly!
- Find commonalities → learn R
- Identify champions in both camps to set the tone
  - Influential leaders → acceptance trickles down from the top
- Work together on an analysis
  - Clinical trial simulations, quantitative decision making

Thank you to my statistician friends! [practice what you preach]

- Ken Kowalski
- Mike K. Smith
- Donna Kowalski [no relation!]
- Kevin Chartier
- Axel Krebs Brown
- Matthias Stolzel
- David James
- Guenter Heimann
- Peter Bonate
- To Rosa for the opportunity!
- To YOU for attending!