The Lewis B. Sheiner Lecturer Award
International Society of Pharmacometrics
October 15, 2017

Theory, Empiricism, and a Vision for the Continued Growth of Pharmacometrics

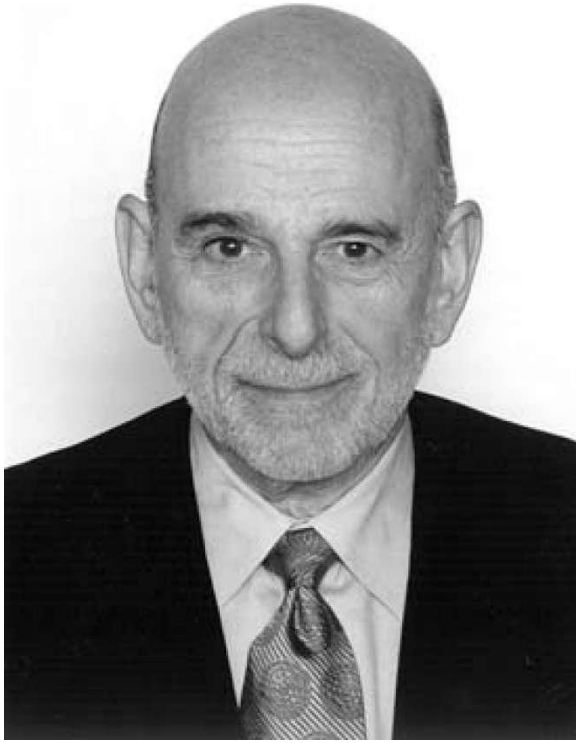
Marc R. Gastonguay, Ph.D., FISoP

Chief Executive Officer, Metrum Research Group LLC
Scientific Director, Metrum Institute

Acknowledgements

- Mentors
- Pharmacometrics Community
- Collaborators
  - Industry, Academia, Government
  - Students & Fellows
- METRUM RESEARCH GROUP
- Family

Dr. Lewis B. Sheiner

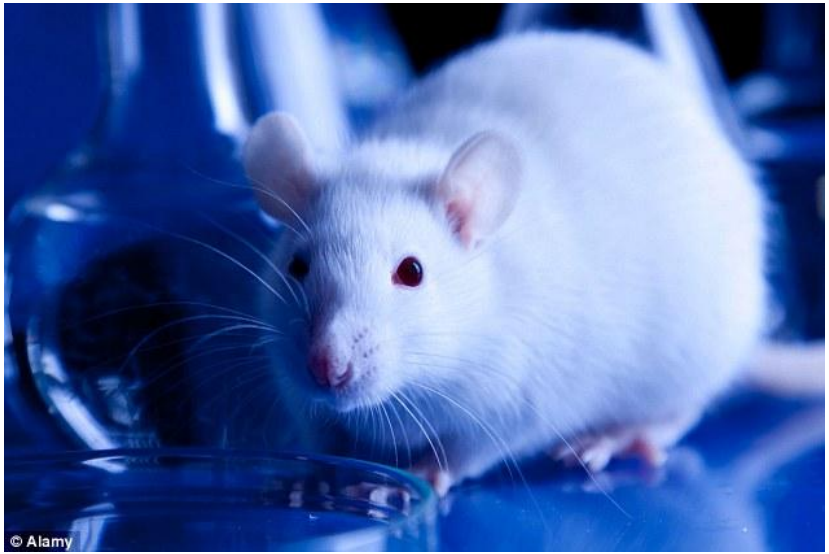


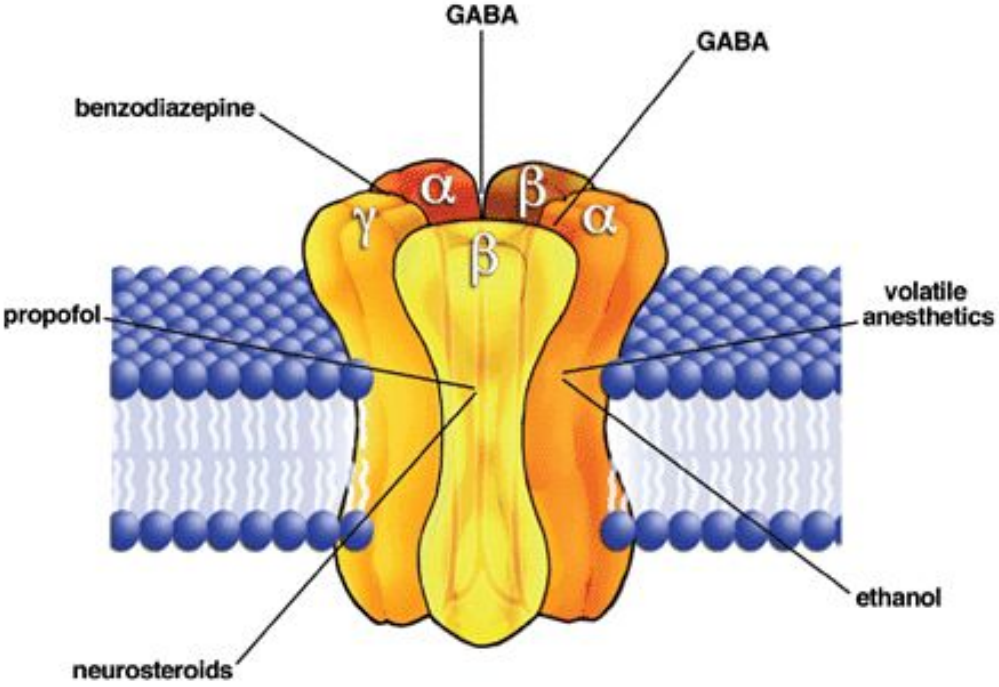
http://www.sfgate.com/bayarea/article/Lewis-Sheiner-expert-in-matching-drug-dose-to-2782937.php#photo-2202555

Defeating Disease

https://blog.chocchildrens.org/neurosciencethennow/

Defeating Disease: Neuroscience

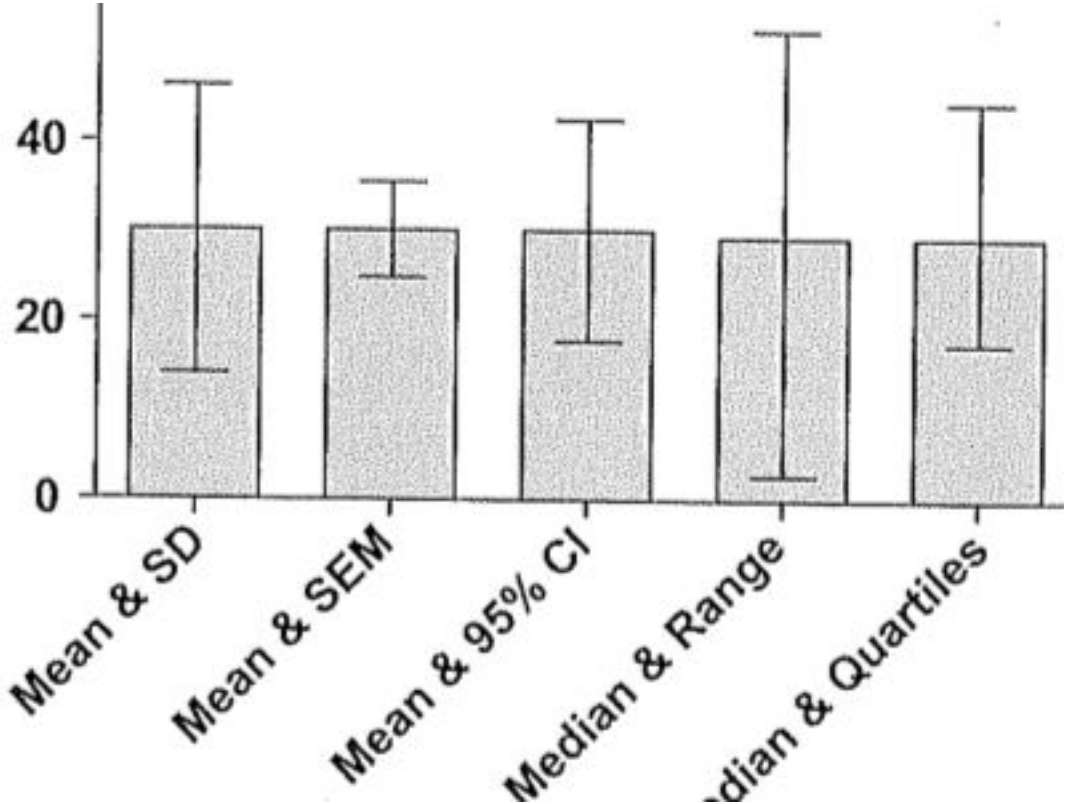




http://www.dailymail.co.uk/news/article-3072768/Alzheimer-hope-epilepsy-drug-Treatment-used-reduce-severity-seizures-reverse-memory-loss-tests-rats.html

https://en.wikipedia.org/wiki/GABAA_receptor

Statistics and Modeling: My Early Impressions



http://www.personal.psu.edu/asb17/old/phs525/PHS_525_(old)/Course_Blog/Entries/2011/2/8_SD,_SEM,_Calculating_CI.html

http://www.tonybates.ca/wp-content/uploads/aha.jpg

CLINICAL PHARMACOLOGY & THERAPEUTICS
VOLUME 46 NUMBER 6 DECEMBER 1989

COMMENTARY

Clinical pharmacology and the choice between theory and empiricism

Lewis B. Sheiner, MD *San Francisco, Calif.*

Empiricism

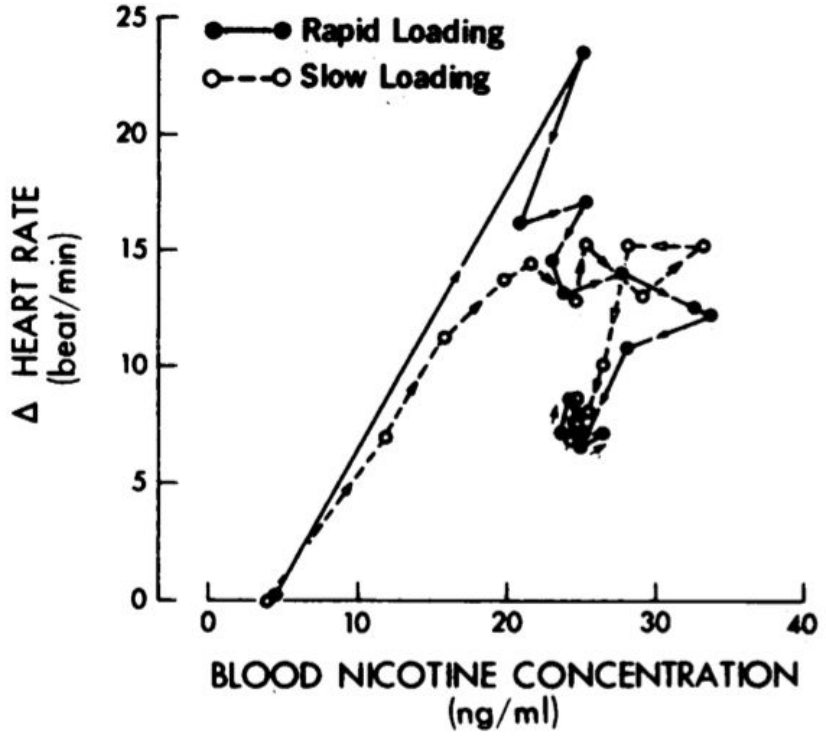
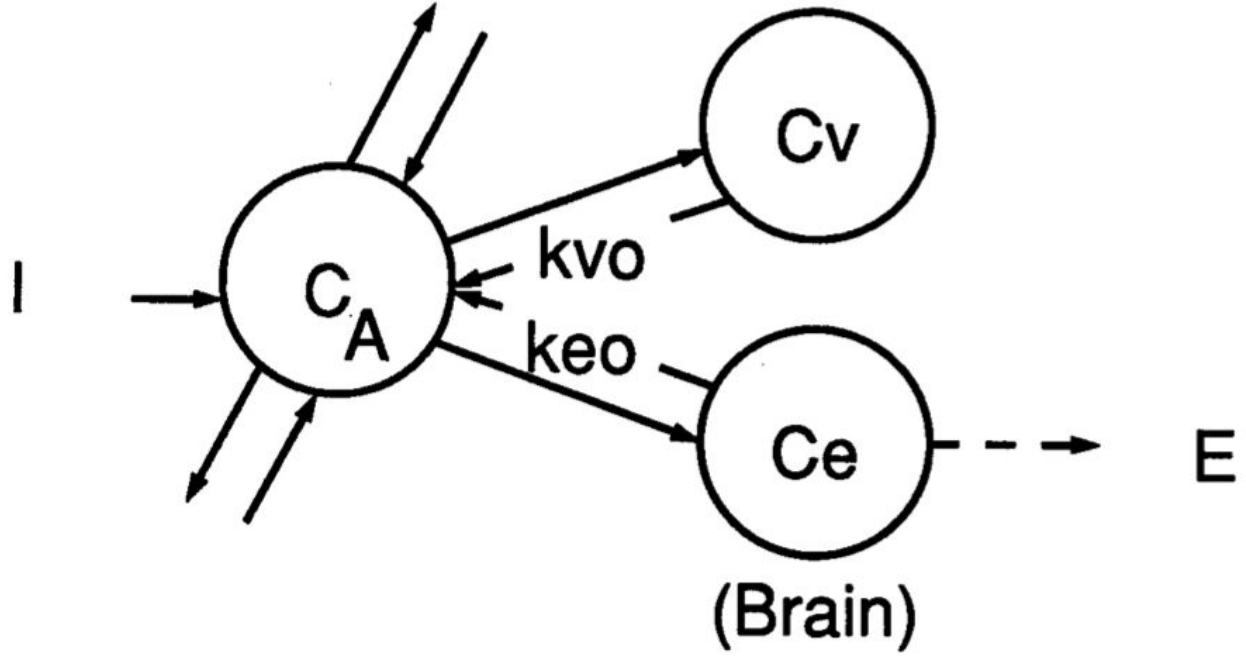


Figure 4. Average increase in heart rate plotted against the simultaneous mean forearm venous blood concentrations of nicotine for the two infusion protocols (see legend of Fig. 3). The points are connected in time order.

HC Porchet, NL Benowitz, LB Sheiner, JR Copeland. J. Clin. Invest. 80, 1466-1471, 1987.

Theory



LB Sheiner. Clin. Pharmacol. Ther. 46, 605-615, 1989.

Informed Empiricism

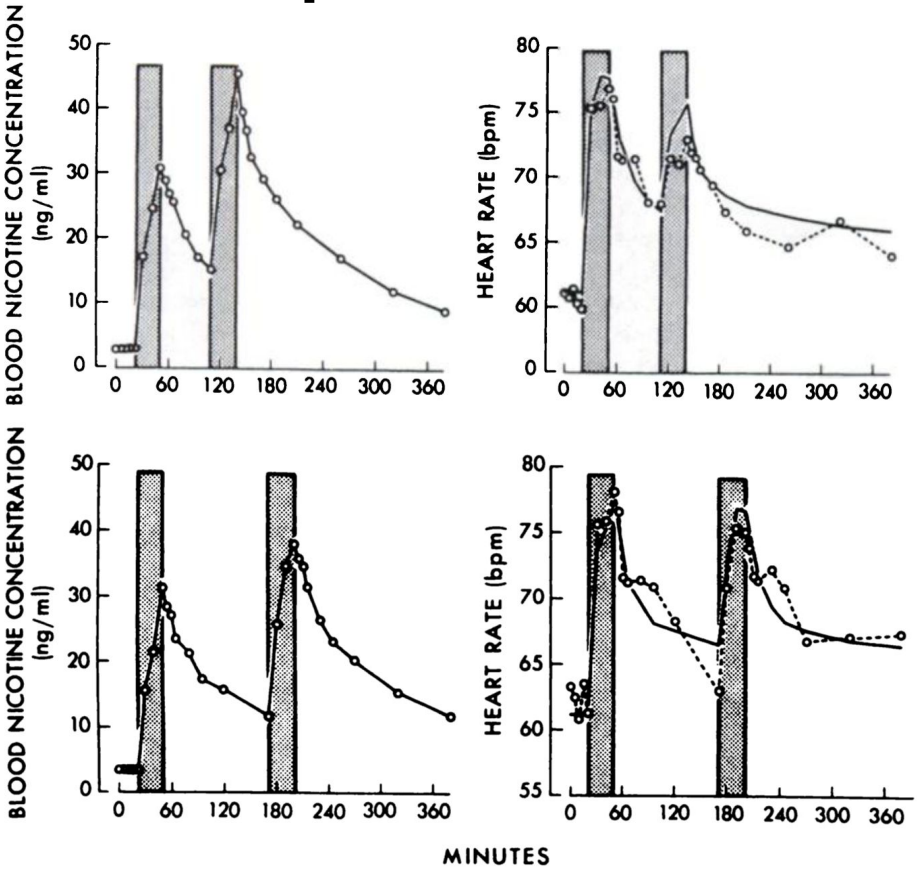


Fig. 2. Mean blood concentrations of nicotine (left panel) and the corresponding mean heart rate (right panel) in eight subjects after two 30-min i.v. infusions of 25 μg/kg/min of nicotine beginning 1 hr apart (treatment A; see text). The shadowed area indicates the periods during which nicotine was infused. The solid line in the right panel shows the fit of the model of figure 1 to the effect data.

Fig. 3. The same as figure 2 for two 30-min infusions of nicotine as for treatment A, but beginning 2 hr apart (treatment B).

HC Porchet, NL Benowitz, LB Sheiner. J. Pharmacol. Exp. Ther. 244, 231-236, 1988.

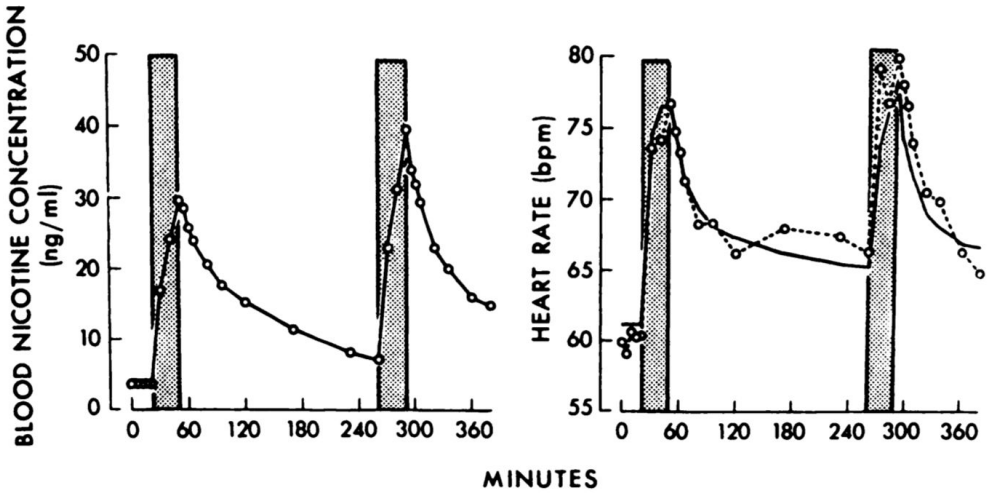


Fig. 4. The same as figure 2 for two 30-min infusions of nicotine as for treatment A, but beginning 3.5 hr apart (treatment C).

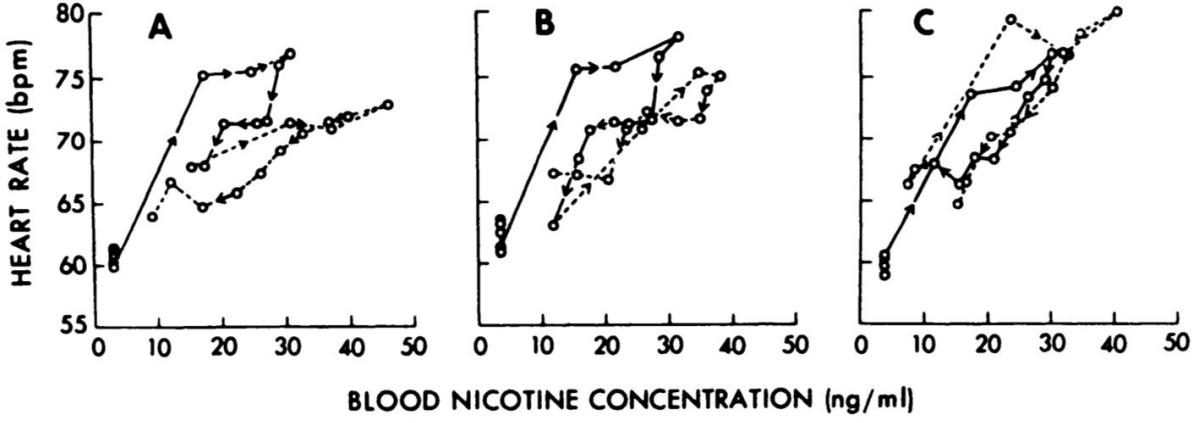
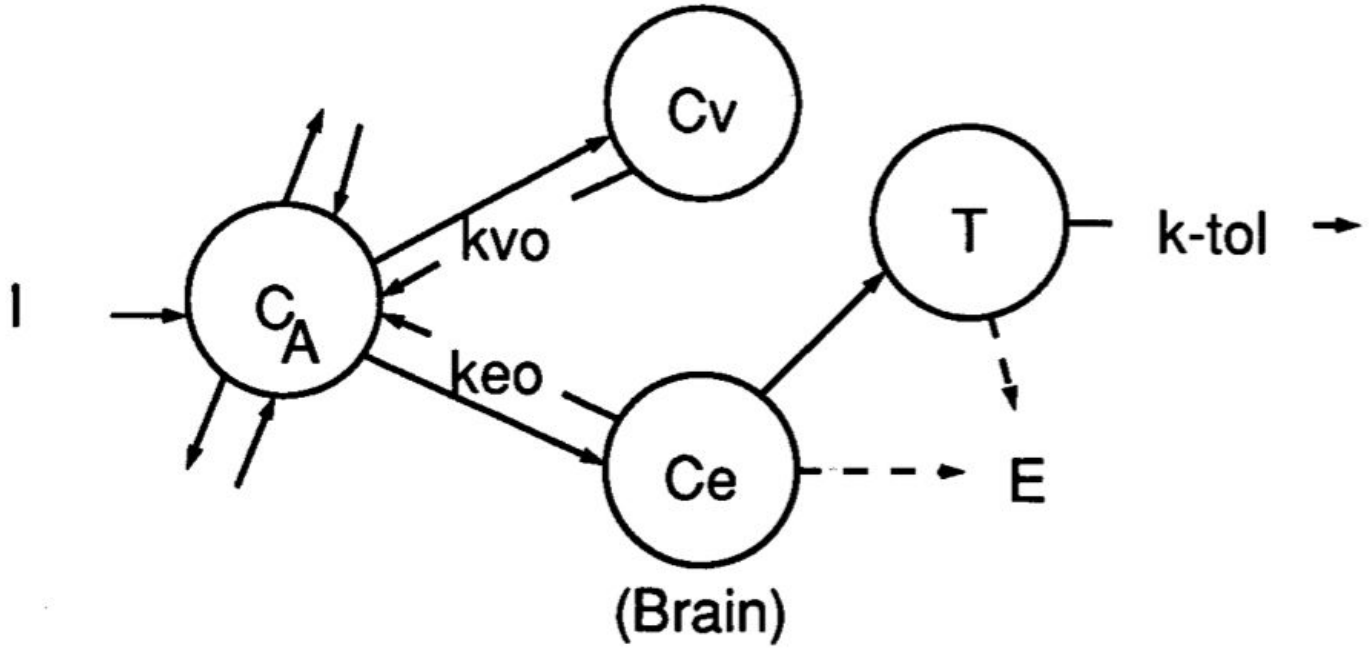


Fig. 5. Mean heart rate plotted against simultaneous mean blood concentrations of nicotine (hysteresis loops) for treatments A, B and C. The solid line correspond to the first infusions; the dashed lines correspond to the second infusions. Arrows indicate the progression of time during and after nicotine infusion.

HC Porchet, NL Benowitz, LB Sheiner. J. Pharmacol. Exp. Ther. 244, 231-236, 1988.

Revised Theory



LB Sheiner. Clin. Pharmacol. Ther. 46, 605-615, 1989.

Application of the Theory

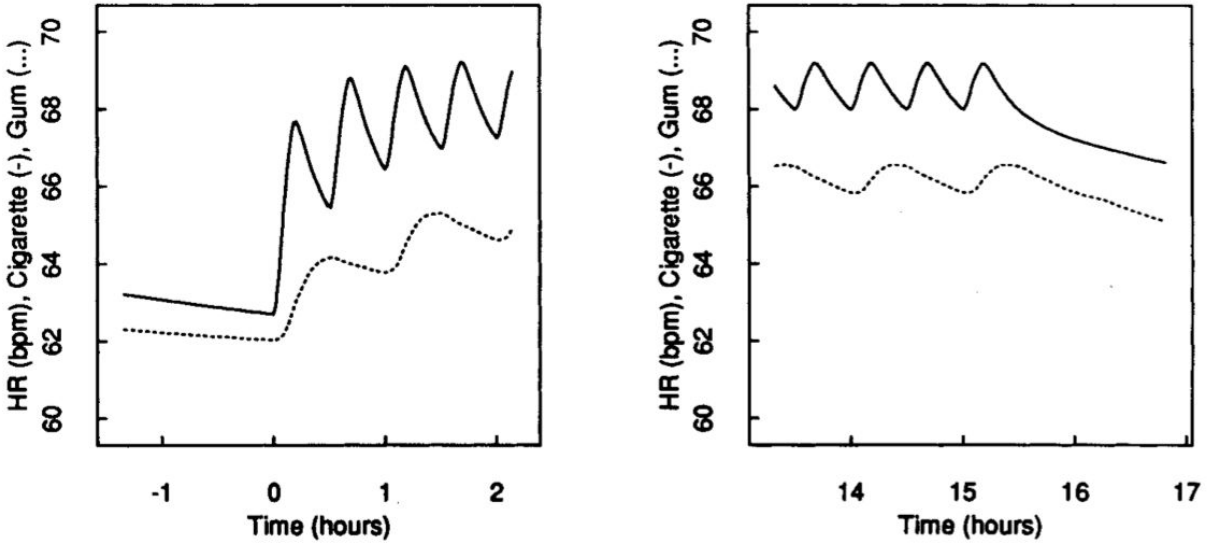


Fig. 9. Simulation of HR response (ordinate) to usual daily intake of cigarettes (——) or gum (- - -) versus time of day. Simulation with model of Fig. 4, fit of Fig. 5, and individual input functions from Figs. 7 and 8. **Left panel**, morning—intake begins after ovenight abstinence. **Right panel**, evening—input ceases for sleep.

LB Sheiner. Clin. Pharmacol. Ther. 46, 605-615, 1989.

“Thus, by going beyond empiricism and stressing understanding, not data collection, we not only answer our first question, but we also gain far more. For clinical pharmacology, as for all other sciences, the goal is theory, not data. The pursuit of theory involves both induction (imagination) and deduction (with subsequent empiric verification); one is useless without the other. If theory is kept as the goal, it will not only be more aesthetically satisfying, but will inevitably lead to insight and technique applicable far beyond the original locus of study. In short, and in truth, there is nothing so practical as a good theory.”

LB Sheiner. Clin. Pharmacol. Ther. 46, 605-615, 1989.

Diagnostics for Time-Variant Pharmacodynamics

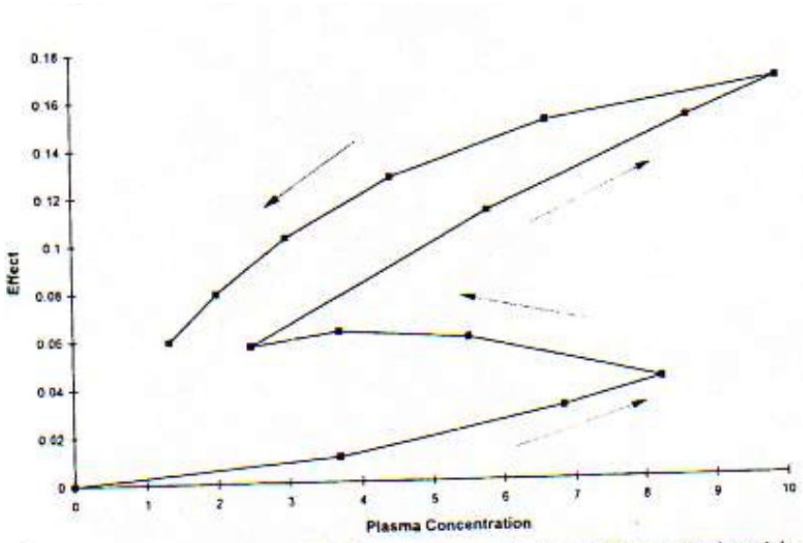


Figure 1: Model-simulated plasma concentration-effect relationship of a multiple infusion experiment showing sensitization. The pharmacodynamic model in this simulation generated an effect which was proportional to plasma drug concentration and sensitized with time. Effect and concentration are expressed in arbitrary units. Arrows indicate the sequence of events over time.

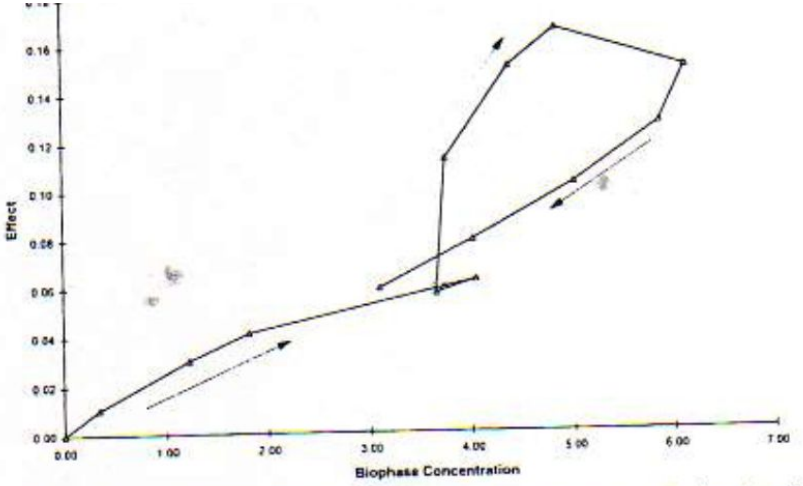


Figure 3: Pharmacodynamic system analysis of the model-simulated multiple infusion experiment with sensitization. The entire data set (0 to 50 minutes) from the multiple hysteresis simulation shown in Figure 1 was analyzed with ATTRACT. The resulting biophase concentration-effect relationship is shown. Effect and concentration are expressed in arbitrary units. Arrows indicate the sequence of events over time.

MR Gastonguay, SL Schwartz. Pharm. Res. 11, 1825-1828, 1994.

Theory-Driven Science: Influence on My Work

Bayesian Modeling Methods and Tools	Pediatric Dosing, Trial Design, and Extrapolation	Simulation with Uncertainty & Global Sensitivity Analysis	Big Data and Causal Inference in Pharmacometrics
Nonlinear Dynamics in PKPD Modeling	Covariate Modeling	Missing Data in Pharmacometric Analyses	Dose Selection and Trial Designs in Rare Diseases

Design & Empirical Data: Non-Random Dropout

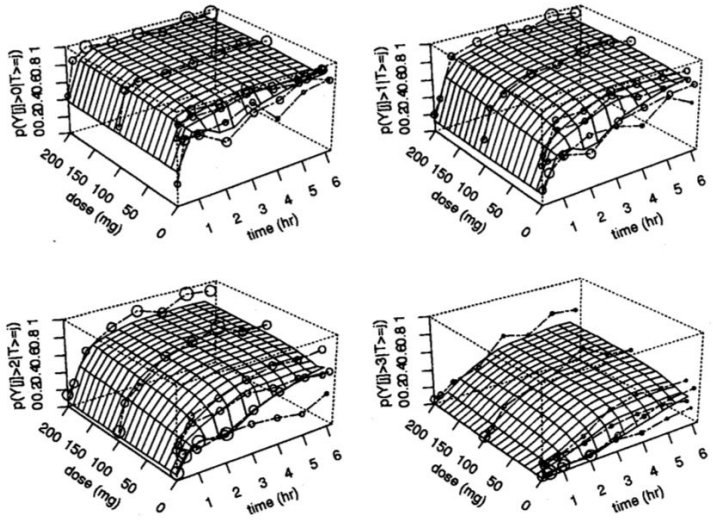


Figure 5. $p(Y_j > m | T \geq j)$, Denoted by $p(Y[j] > m | T >= j)$, Versus Dose and Time for m = 0 (Upper Left), 1 (Upper Right), 2 (Lower Left), and 3 (Lower Right). Data-based estimates of the appropriate quantities, obtained as described in the legend to Figure 4, are shown in all panels. As for Figure 4, the circles are proportional to the reciprocal standard errors of the data-based estimates.

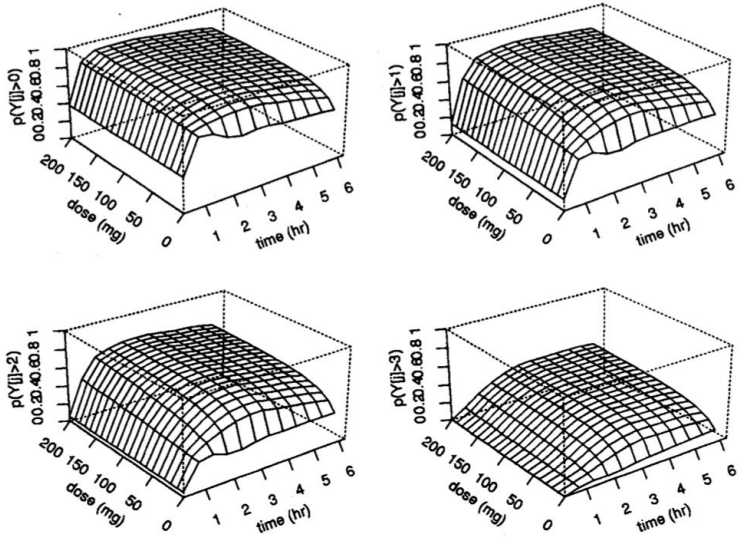
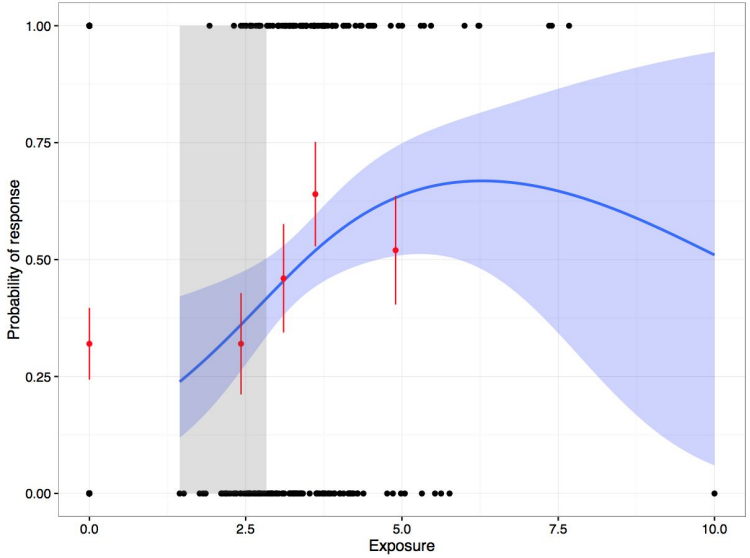


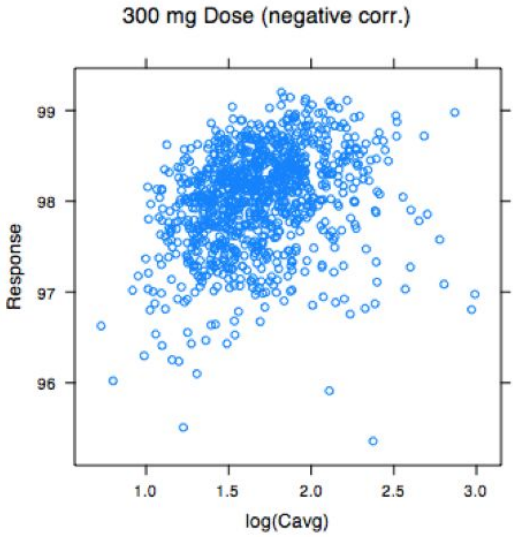
Figure 6. $p(Y_j > m)$, Denoted by $p(Y[j] > m)$, for m = 0–3 Versus Dose and Time. See the legend to Figure 5.

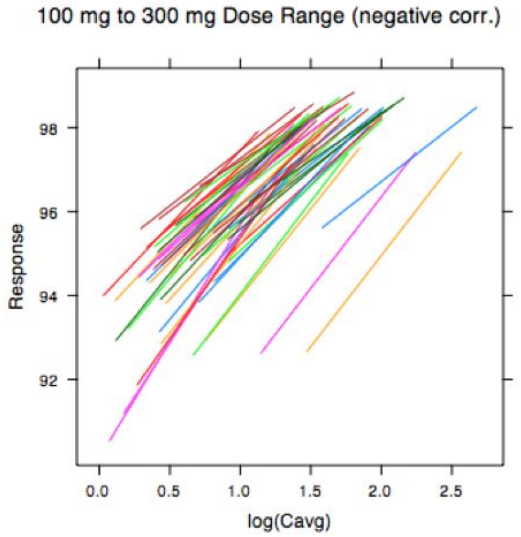
LB Sheiner, SL Beal, A Dunne. JASA, 92, 1235-1244, 1997.

Design & Empirical Data: Confounded E-R



J French. ACOP 2016.





MR Gastonguay. IMMPACT-VIII Workshop, 2008.

Design & Empirical Data: Confounded E-R

Pitfalls in Retrospective Analysis in Search of Concentration-Effect Relationships

Carl Peck, Tom Ludden

Leiden University, The Netherlands, and CDER, FDA, USA

PAGE 3 (1994) Abstr 867 [www.page-meeting.org/?abstract=867]

1994

Intention-to-treat analysis and the goals of clinical trials

Lewis B. Sheiner, MD, and Donald B. Rubin, PhD[a]

San Francisco, Calif. and Cambridge, Mass.

Clin. Pharmacol. Ther. 57, 6-15, 1995.

1995

Diagnostics for confounding in PK/PD models for oxcarbazepine

Jerry R. Nedelman[1,*,†], Donald B. Rubin[2] and Lewis B. Sheiner[3,✠]

Stat. Med. 26, 290-308, 2007.

2007

Design & Empirical Data: Big Data

British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2016) **81** 804–806 804

EDITORIAL

Big Data: Challenges and opportunities for clinical pharmacology

Received 29 January 2016; **accepted** 29 January 2016

David Flockhart[1], Robert R. Bies[2], Marc R. Gastonguay[3] and Sorell L. Schwartz[4]

Big Data: Correlation vs. Causation

Scientists are trained to recognize that correlation is not causation. Petabytes allow us to say: ‘Correlation is enough’.

Chris Anderson, 2008

In hiring decisions, what if algorithm predicts that males will be better employees?

“Models that ignore causation can add to historical problems instead of addressing them.”

R. Schutt & C. O’Neil. Doing Data Science. 2013.

http://www.nytimes.com/2015/06/26/upshot/can-an-algorithm-hire-better-than-a-human.html

Pharmacometrics: Learning from Other Disciplines

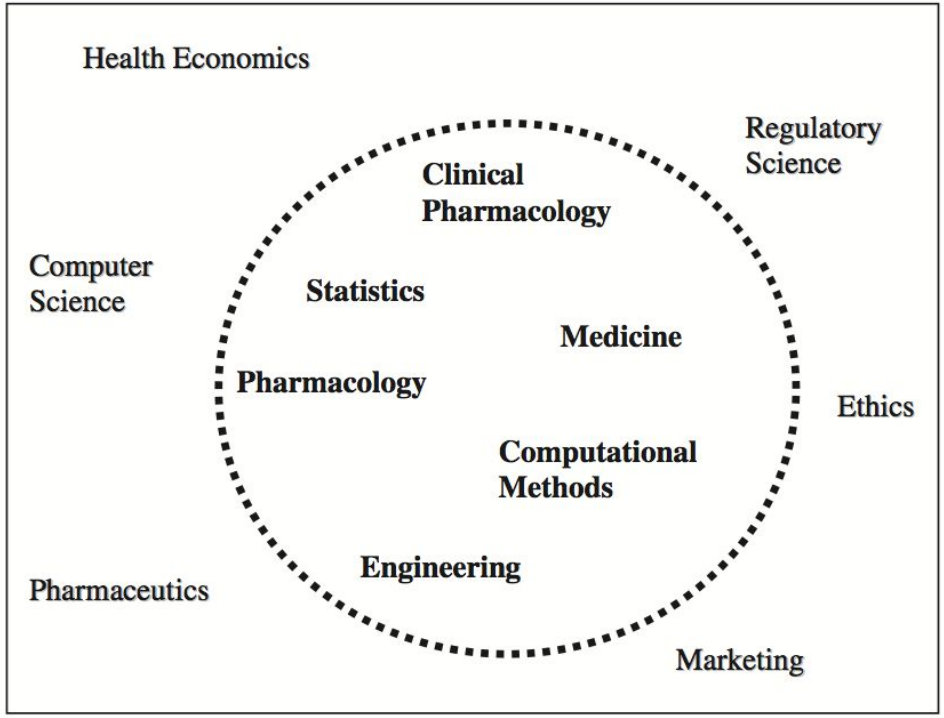


Figure 1. Multidisciplinary influence on the field of pharmacometrics.

JS Barrett, MJ Fossler, KD Cadieu, MR Gastonguay. J. Clin. Pharmacol. 48, 632-649, 2008.

Growing the Science: LBS

From: LSheiner <lewis@c255.ucsf.edu>

Subject: Re: BQLs

Date: Tue, 26 Jun 2001 09:32:34 -0700

This has been discussed before ...

First, let's be clear on what is the "right" thing to do in principle. If you are using ML, then the right thing to do is use the marginal likelihood, integrating out the "missing value", that is, if the usual likelihood contribution for datum y is L(y) = p(y|params), and y is censored (i.e., known to be < QL, but not known further), then the likelihood contribution should be L*(y) = p(y<=QL|params) = Integral[p(y|params)dy], where the integration is from -infinity to QL. In the case of normal residual noise with var = sigma**2, this would be the CDF of a Standard Normal density (i.e. with mean = zero and variance = 1) evaluated at (QL-yhat)/sigma, where yhat = E(y|params) -- in fact the "Y" usually defined in $ERROR.

Here are the two approximations Pete discusses: [*detail omitted*]

LBS.

http://www.cognigencorp.com/nonmem/nm/99jun262001.html

Growing the Science: LBS

COURSES ON POPULATION PHARMACOKINETIC DATA ANALYSIS USING THE NONMEM SYSTEM

BASIC COURSE

Kyoto, Japan (1989),
San Franciso, CA (1990,92,93,95,97)
Lyon, France (1991,93,97,01),
Uppsala, Sweden (1995,99)
Rockville, MD (1998).

INTERMEDIATE WORKSHOP

San Francisco, CA (1992,93,95,97),
Lyon, France (1993,97,01),
Uppsala, Sweden (1995, 99),
Rockville, MD (1998).

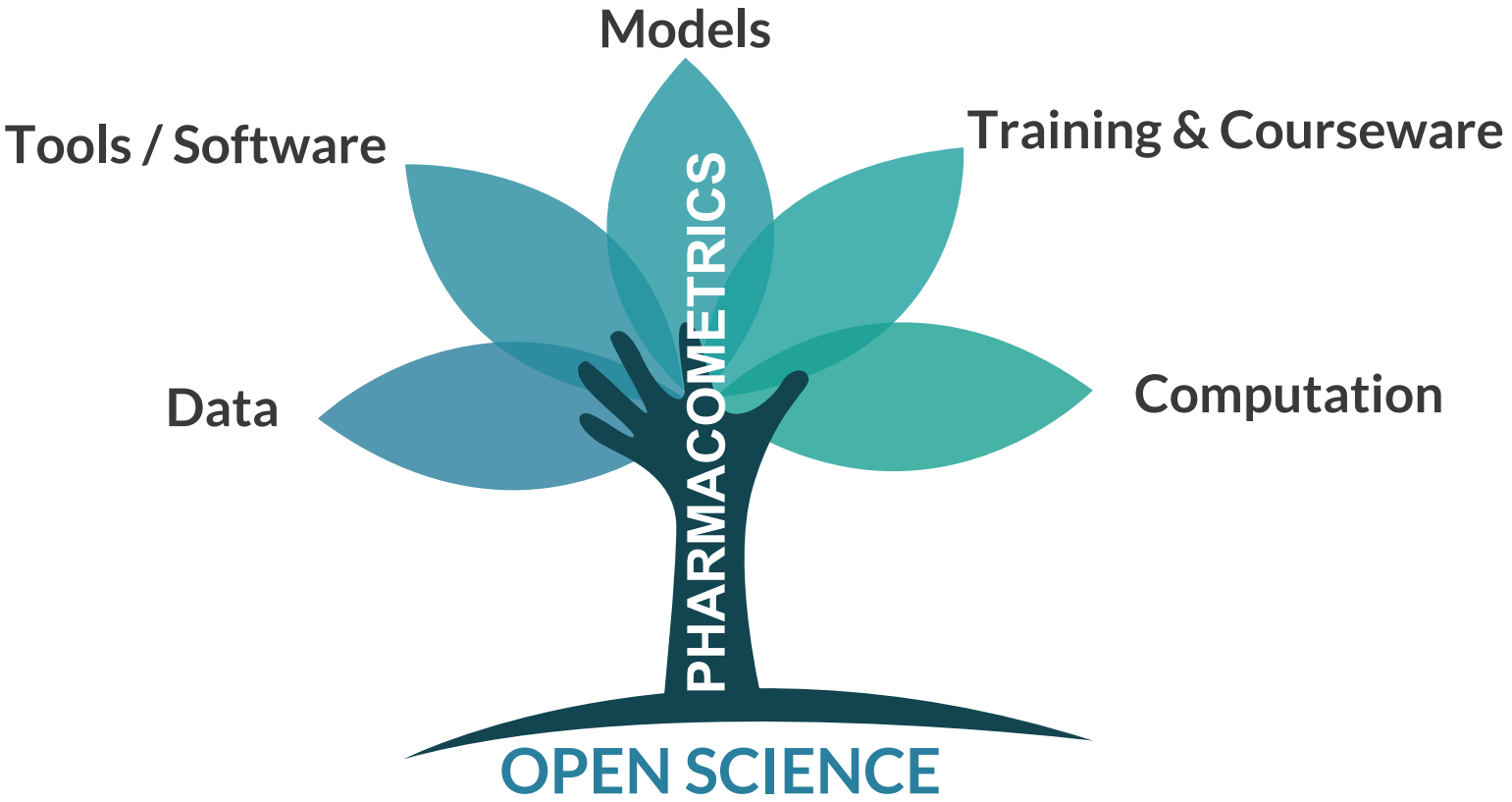
BASIC AND INTERMEDIATE LEVEL SHORT COURSE
Uppsala, Sweden (2003)

https://www.page-meeting.org/page/page2006/AlisonBoeckmann.pdf

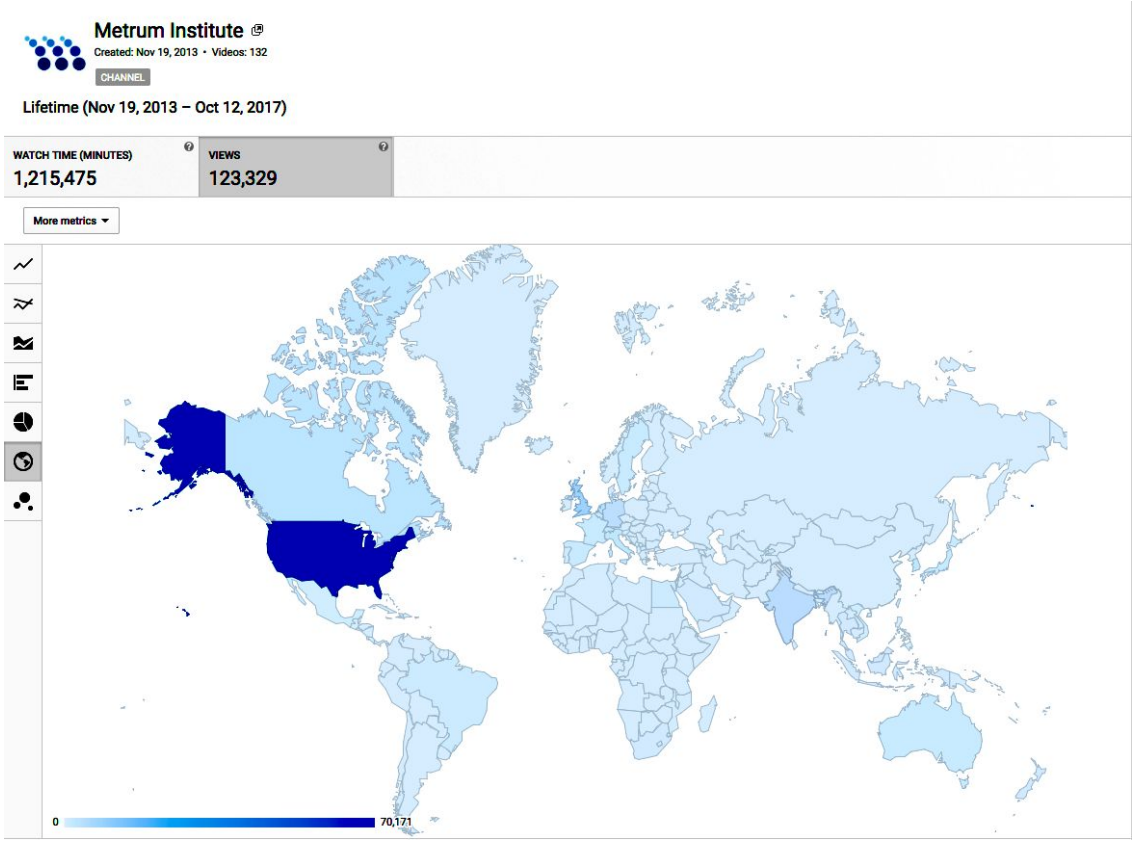
Growing the Science: LBS

http://www.acop7.org/

Growing the Science: A Community Responsibility



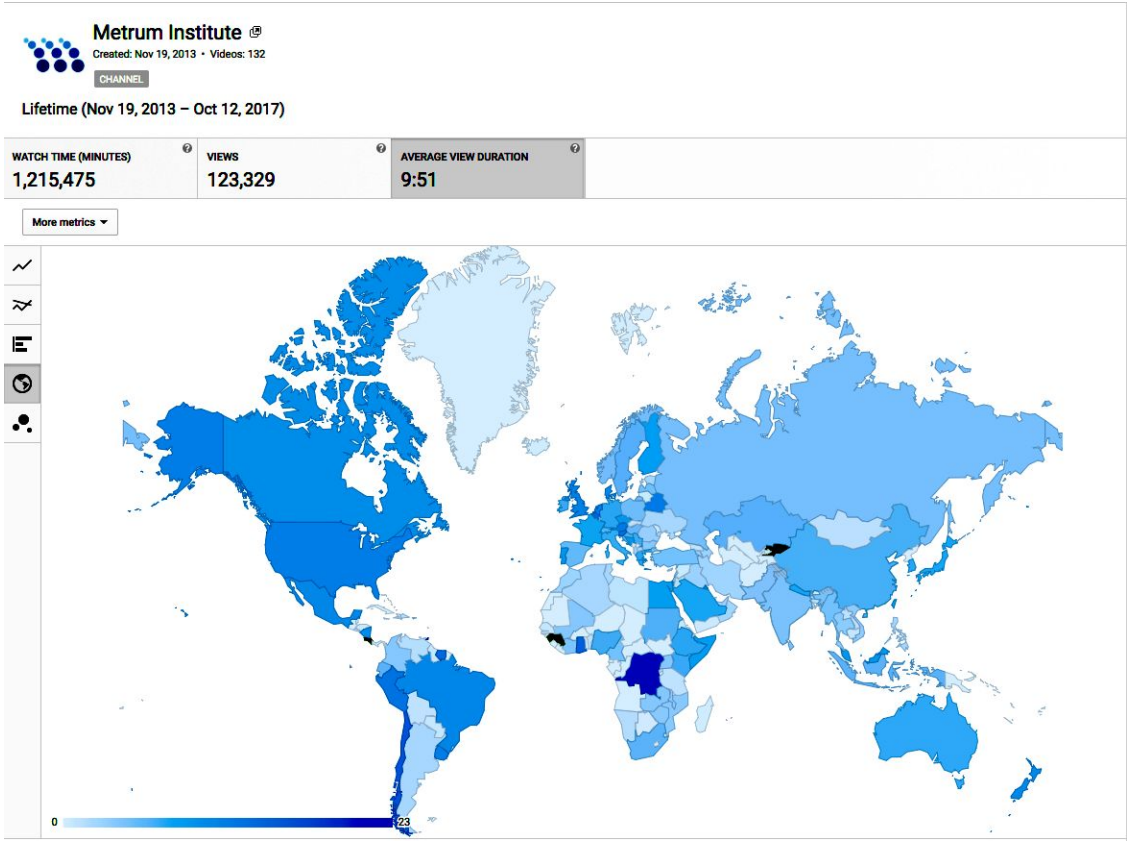
Growing the Science: Open Courseware



- 920 subscribers
- > 350 hours of training material with examples
- Topics:
  - R Programming
  - Population PKPD (continuous and odd-type data)
  - Model-Based Meta-Analysis
  - Bayesian Models/Methods (BUGS, Stan)

https://www.youtube.com/user/metruminst

Growing the Science: Open Courseware



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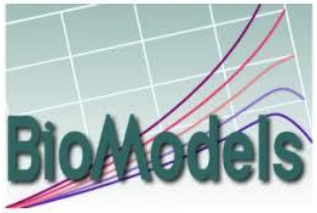
  - R Programming
  - Population PKPD (continuous and odd-type data)
  - Model-Based Meta-Analysis
  - Bayesian Models/Methods (BUGS, Stan)

https://www.youtube.com/user/metruminst

Open Model Repositories

A few examples...



http://biomodels.caltech.edu/static-pages.do?page=ModelMonth%2F2016-07

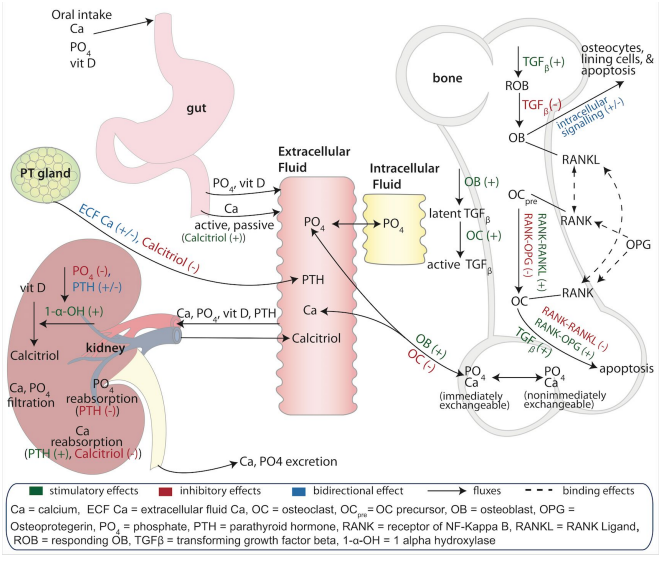
http://repository.ddmore.eu/models

https://github.com/Open-Systems-Pharmacology/Suite

https://github.com/metrumresearchgroup/OpenBoneMin

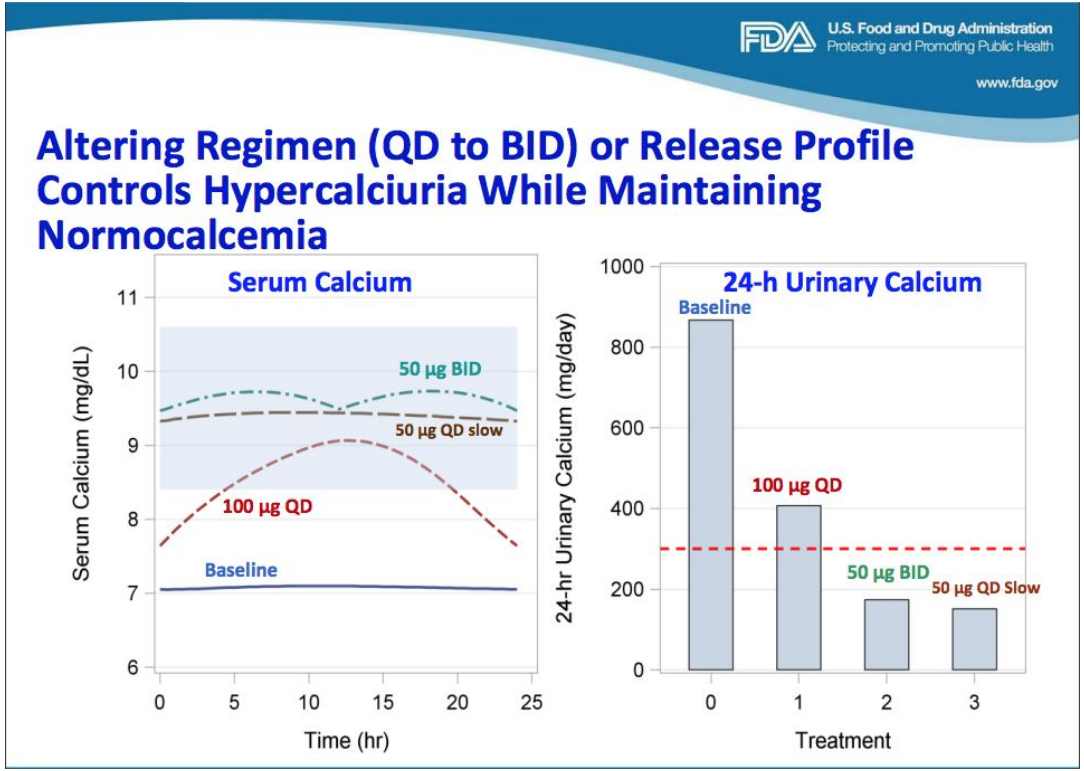
https://bitbucket.org/metrumrg/alzheimers-disease-progression-model-adascog/wiki/Home

Open Model Utility & Impact



https://github.com/metrumresearchgroup/OpenBoneMin

"Using systems pharmacology model we showed that control on hypercalciuria is feasible with more frequent regimen or a slow release PTH profile at lower systemic exposure than 100 µg QD"

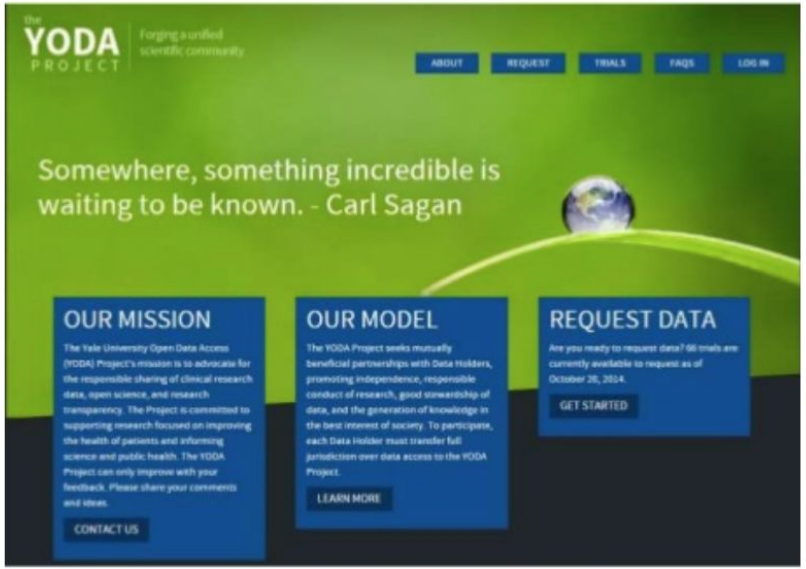


https://wayback.archive-it.org/7993/20170405215559/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM416168.pdf

Open Data

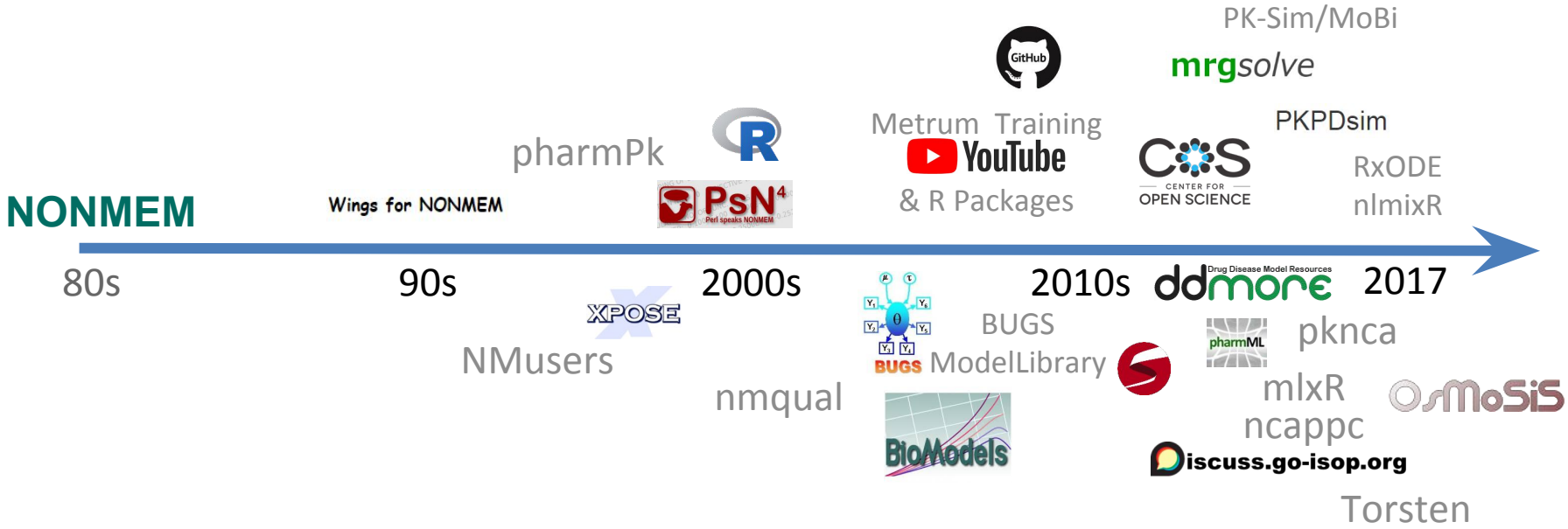
OpenTrials
All the Data, on All the Trials, Linked

Project Data Sphere®



Courtesy Vijay Ivaturi, ACoP 2016.

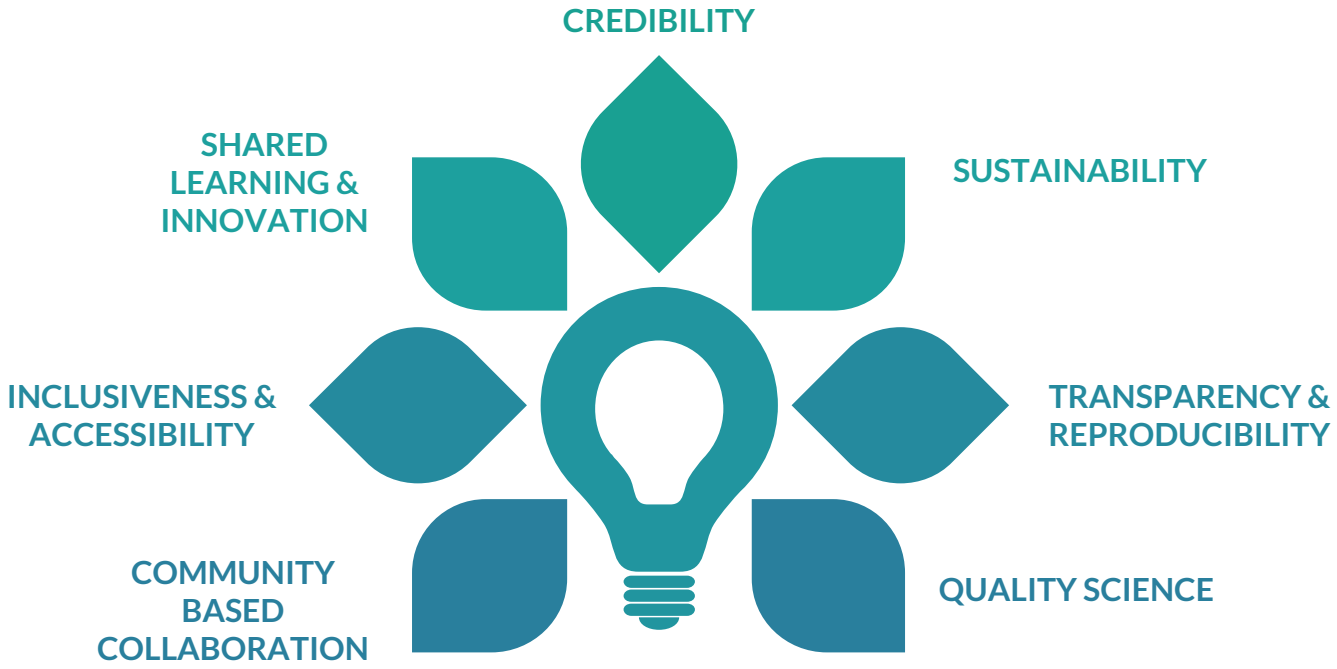
Proud History of Open Tools & Open Science



…in large part supported by single individuals or institutions

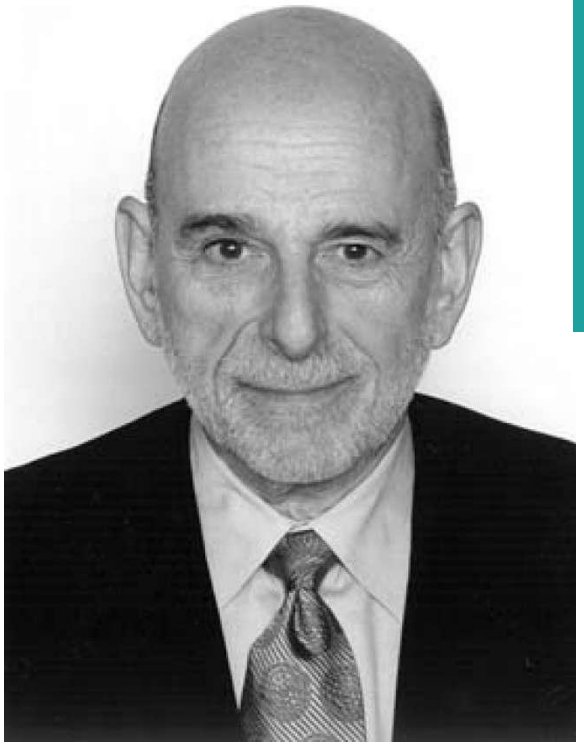
Adapted from: Brian Corrigan, ACoP 2016.

Why Open Science in Pharmacometrics?



Dr. Lewis B. Sheiner: Learnings

Focus on Theory as the Goal



Inform Empiricism with Theory

Learn from Other Disciplines

Grow the Science

http://www.sfgate.com/bayarea/article/Lewis-Sheiner-expert-in-matching-drug-dose-to-2782937.php#photo-2202555

Why?

https://www.dchsystem.com/sites/www/Uploads/wf%20pediatric%20nurse.png

http://www.ascseniorcare.com/wp-content/uploads/2014/10/bigstock-Happy-senior-citizen-woman-at-58893383.jpg

Thank You