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PERSPECTIVE

Lewis Sheiner ISoP/UCSF Lecturer Award: From Drug Use to Statistical Models and Vice Versa

F Mentré[1,2]

I was very honored to receive the University of California, San Francisco, and the International Society of Pharmacometrics Lewis Sheiner lecturer award in May 2013. In the present perspective, I outline the main points of my lecture at the American Conference of Pharmacometrics (slides in Supplementary Material 1). I first emphasize the scientific contributions of Lewis Sheiner as a quantitative pharmacologist toward the better use of drugs. I then focus on three statistical topics in pharmacometrics, describing Lewis Sheiner's impact and my own contributions and interactions with him.
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LEWIS SHEINER: A PIONEER

Prof Lewis Sheiner was an impressive scientist. Reviewing his publications, he can be described as (i) a physician who wanted better drug dosage regimens for patients, (ii) a quantitative scientist who advocated better use of computers in medicine, (iii) a clinical pharmacologist who sought better models to better understand drug action, (iv) a statistician who looked for better methods in clinical pharmacology, (v) a visionary who was driven to seek better methods in drug development. He was a pioneer in the use of nonlinear mixed-effect models (NLMEM) for better drug use, and he created the discipline of pharmacometrics. Prof Lewis Sheiner also had a huge impact on model-based drug development. He published 234 articles, which were cited over 13,070 times (Web of Science, May 2013; **Figure 1**).

I first met Lewis Sheiner at a meeting in 1991, and we subsequently enjoyed many stimulating discussions, mainly during the advanced pharmacokinetics/pharmacodynamics (PKPD) workshops where he lectured and I was a tutor from 1999 on. After his untimely death in 2004, with several colleagues, we took over the course to continue promoting his vision of quantitative pharmacology.

Lewis was for me a mentor and a friend who had a great impact on my career. He stimulated me to work in pharmacometrics, to become professor in a School of Medicine, to perform research in academia, to address unmet challenges and develop new methods, to (try) to report results intelligently and correctly, to develop international scientific collaborations and friendships, to learn from others and from interdisciplinary collaboration, and to teach and promote scientific and quantitative thinking.

CONTRIBUTIONS TO STATISTICAL METHODS IN NLMEM

Being a biostatistician, my main contributions in the field are the development of new statistical methods following the work of Lewis Sheiner. Here, I focus on three main statistical topics in NLMEM: parameter estimation, model evaluation, and optimal design. For these three topics, I have had scientific discussions and various interactions with Lewis Sheiner. Key references to Lewis's or my publications in those fields have been detailed in the slides (**Supplementary Material 1**).

Parameter estimation

The first, and most significant, contribution of Lewis Sheiner in the field of pharmacometrics was the introduction of NLMEM in pharmacokinetics for drug dosage individualization.[1,2] He introduced the concept of the "population approach" and developed the NONMEM software in 1980, implementing the FO estimation method. He later improved the methodology and expanded its scope, for instance, to discrete data.

I have contributed to this area through collaboration with colleagues for development and/or dissemination of several new estimation methods, specifically nonparametric maximum likelihood, iterative two-stage and SAEM. My involvement in stochastic EM approaches for NLMEM was triggered by Lewis Sheiner who asked me in 2001 to investigate the potential of MCPEM developed by Serge Guzy.

In an article in the special issue of *Journal of Pharmacokinetics and Pharmacodynamics* in honor of Lewis Sheiner, we describe the evolution of the estimation methods in NLMEM.[3] Mould and Upton[4] in their recent tutorial provided a list of all software developed since NONMEM. These improvements in estimation methods and software tools have contributed to the development and spread of pharmacometrics. Future developments are still needed to address faster algorithms, handling of more complex data or models, and better use of computers' capacities.

Model evaluation

Very early, Lewis Sheiner addressed the problem of evaluation, and his most quoted paper is on measurement of predictive performance.[5] He also introduced major concepts in modern model evaluation such as external validation, predictions errors, simulation-based diagnostic, and posterior predictive check.

My main contribution to this area has been the development of new "pseudo-residuals" that I later termed "prediction discrepancies" following long discussion with Lewis. The

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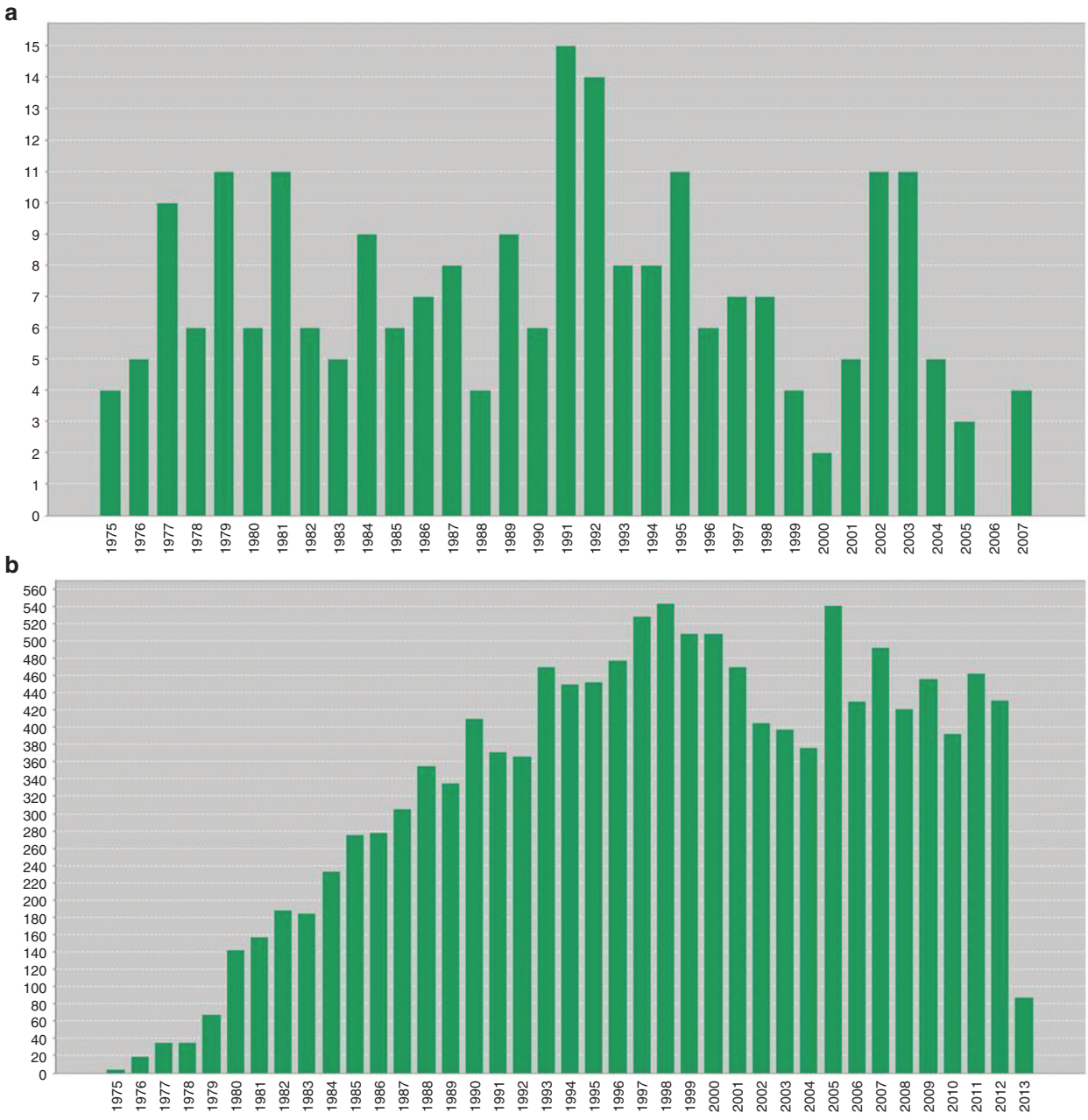

Figure 1 Histograms of the number of Prof Lewis Sheiner's publications (total = 234, top) and number of citations (total = 13,070, bottom) per year (Web of Science, May 2013).

NPDE metric is now implemented in several software, and a specific R package was developed (http://www.npde.biostat.fr). Future research is needed in this area. The main topics are: external vs. cross-validation, prediction-corrected visual predictive check vs. transformed npde, extension of simulation-based diagnostics for complex data and/or complex designs, summary statistics to quantify predictability of a model, and so on.

Model evaluation is a crucial step in pharmacometrics, and it is still lacking standardization and/or consensus. In 2014, at the American Conference of Pharmacometrics, I chaired the first meeting of the International Society of Pharmacometrics working group for model evaluation in pharmacometrics which is part of the Standard and Best Practice Committee.

Optimal design

With the increased ability to apply NLMEM to PKPD and clinical data, the problem of designing good studies emerged. In 1991, after work on design for dose ranging studies, Lewis Sheiner published the first simulation study to compare and evaluate several designs in PKPD, showing the importance in the balance between number of samples and number of patients.[6]

Evaluation of population designs by simulation is time consuming and is not suited for design optimization. That

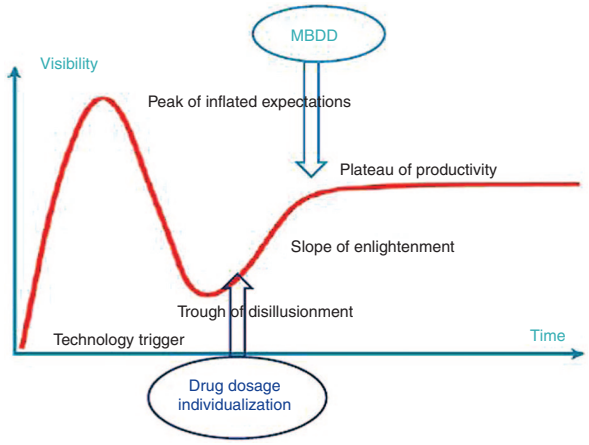

Figure 2 The Gartner hype cycle (en.wikipedia.org/wiki/Hype_cycle) for model-based drug development (MBDD) and drug dosage individualization (adapted from an idea of Steve Kern, World Conference on Pharmacometrics, 2012).

is why, with Alain Mallet, we developed an expression of the Fisher Information Matrix (FIM) for NLMEM using FO.[7] My main contribution in pharmacometrics is certainly all the work I perform with my team on optimal population designs. Since that first paper, we have extended the expression of the FIM for more complex cases. In 2001, we developed the first R function with evaluation of the Population FIM (PFIM; http://www.pfim.biostat.fr), and the latest version was released in April 2014. Several academic teams started working on those topics and made significant improvements. Other software tools have been developed in the field (PopED, PopDes, POPT, and PkStamp), and a comparison of the results for design evaluation in a PK example and in a more complex pharmacokinetic/viral kinetic model was recently performed.[8]

In 2006, Basia Bogacka (University of London) and I founded the multidisciplinary group Population Optimum Design of Experiments which has met every year since. The highlight was in 2011, where the meeting was held in Cambridge in the Isaac Newton Institute for Mathematical Sciences, uniting pharmacometricians and statisticians working in designs for mixed or generalized models.

All the work and simulations performed for design in NLMEM showed that design considerably affects precision of estimation. With the increased use of the results in drug development or use, designs leading to small estimation errors are needed. Especially for sparse designs, the best information is needed out of each sample. Of course, prediction of standard error via the expected FIM can be optimistic for design of small sizes as it will provide a lower bound of the variance, so that clinical trial simulation is important to evaluate strategic designs.

Future work in that area involves FIM for more complex data or design, evaluation of FIM without linearization, adaptive designs, model-averaging approaches, design for individual predictions, and dosage individualization. More collaboration between statisticians and pharmacometricians is needed to help design clinical studies that provide meaningful results with feasible sample sizes.

CONCLUSION

Although pharmacostatistical models were first developed for improvement of dosage in patients, their main area of application nowadays is in drug development. In the framework of the "hype cycle" (**Figure 2**), we can view pharmacometrics in model-based drug development as having reached its plateau of productivity; however, there are still too few applications in clinical routine for patients' treatment. For instance, the first paper by Sheiner on computer-aided dosage of warfarin was in 1969,[1] and as late as 2013, papers are still published addressing that question. With new tools (smartphones and tablets) and clever implementation of Bayesian forecasting, use of models for helping decision making under uncertainty should be more developed in clinical routine.

Another point of discussion is the relationship between pharmacometricians and statisticians, leading Stephen Senn[9] to write in 2010: "the battle lines were clear." It is time to bridge the gap through a better understanding of model-based approaches by statisticians and by more rigor in selecting data and models by pharmacometricians.

Most deaths in the world (57 million in 2002; http://www.worldmapper.org) are preventable deaths (19 million in 2002), among which 11 million are from infectious and parasitic diseases. Pharmacometricians should "redirect their expertise to focus on the disease burden affecting the developing world"[10] and work on the several important challenges in this area.

To conclude, following the inspiration of our mentor, I hope that pharmacometricians and statisticians will work together and will develop (i) model-based analysis of pivotal trials, (ii) model-based treatment individualization, and (iii) model-based evaluation of treatments in the developing world.

I wish and hope that the development of pharmacometrics will contribute to decrease disease burden in the word by using better treatments better targeted to each patient.

Acknowledgments. I thank the University of California, San Francisco, and the International Society of Pharmacometrics for selecting me for this award. I sincerely thank David D'Argenio for giving me the award and for his (too) nice introduction (See **Supplementary Material 2**). I was very honored and moved as I first met David when I was a PhD student and he was working on optimal design. I wish to thank Jean-Louis Steimer (my Master's supervisor) and Alain Mallet (my PhD supervisor) who introduced me to the field of pharmacometrics and taught me statistics. I thank my research team in Paris and all my PhD students for their energy and contribution to my work. I also thank all members of PODE for the healthy competition on optimal design. Warm thanks to Malcolm Rowland who, with Lewis Sheiner, asked me to become a tutor at the "Silsmaria advanced PKPD workshop." Thanks to both of you for the discussions and advice on my career while walking around Sils' lake. Thank you to my colleagues and friends, Leon Aarons, Steve Duffull, Mats Karlsson, and Nick Holford, with whom we pursued the "Sheiner/Rowland Advanced Course in PKPD," for all the scientific discussions and beyond. And thank you, Lewis.

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