# In memoriam Lambertus ("Bert") A. Peletier 29 March 1937–16 December 2023: furthering quantitative pharmacology through applied mathematics

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TRIBUTE

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## A LIFE DEVOTED TO SCIENCE AND COLLABORATION

On December 16, 2023, our respected, beloved colleague, and friend prof.dr.ir. Lambertus (*Bert) A. Peletier* passed away after a brief illness. Bert was an eminent mathematician with a broad interest in natural sciences. He received great international esteem for his fundamental research on partial differential equations. A list of his scientific publications can be found at https://scholargps.com/scholars/36194565598852/lambertus-a-peletier for further reading. Throughout his career as mathematician, several prestigious honors were bestowed upon him. He was elected as a member of the Royal Netherlands Academy of Arts and Sciences (KNAW) in 1999. In 2013, he received a knighthood in the Order of the Netherlands Lion (RNL).

In an interview with Ionica Smeets in 2015 ("Het keerpunt van Bert Peletier. De intellectuele bevrediging is anders, maar net zo groot." Nieuw Archief voor Wiskunde (in Dutch). https://www.nieuwarchief.nl/serie5/pdf/naw5-2015-16-3-213.pdf), Bert reflected on his academic career. As the son of an engineer, Bert had an innate interest in technology, fuelled by the ambition to engage in a study at the Technical University of Delft. On the recommendation of his math teacher, he chose to study theoretical physics rather than pure mathematics. The choice of physics was based on his belief that mathematics is best understood in the context of real-life examples. Throughout his academic career, Bert continued to seek out opportunities for discussion and debate with colleagues, adhering to the motto of one of his unknown American colleagues: Science is the pursuit of knowledge in the company of friends.

After his graduation, from the newly established Eindhoven University of Technology, Bert spent a year at the Massachusetts Institute of Technology (MIT) in Boston. It was the place where he became inspired by academic life and debate. It made him decide to pursue a career in academia rather than in industry. In 1967, he obtained his PhD at the Eindhoven University of Technology. The title of his thesis was "On a class of wave equations." After the completion of his PhD thesis and internships at the University of Sussex (UK) and the University of Minnesota (USA), he was appointed full professor of analysis and applied mathematics at Leiden University in 1977 from where he retired in 2002.

Just before his retirement from Leiden University, Bert accidentally met a pharmacist who had come across a publication by a group of Swedish researchers on mathematical modeling of drug effects. This pharmacist challenged Bert with the words: "If they can do this in Sweden, then you should be able to do this as well." The very next day, Bert called Meindert Danhof, Professor at the Leiden Academic Centre for Drug Research (LACDR). He learnt that LACDR had an active research program in pharmacokinetics and pharmacokinetic–pharmacodynamic (PK–PD) modeling and simulation with a unique infrastructure to generate high-density drug response over time data in vivo. At about the same time, postdoctoral fellow Piet Hein van der Graaf and two PhD students, Klaas Zuideveld and Sandra Visser, arrived in Leiden. This initiated what would become a long and fruitful collaboration around mechanism-based PK–PD modeling. Together with Bert,

they started reviewing high-density pharmacological response versus time profiles from LACDR's portfolio, discussing the underlying pharmacological mechanisms, generating new data, where appropriate, and scribbling out potential mathematical equations, where possible.

Upon his formal retirement from Leiden University in 2002, Bert remained active as a Professor Emeritus, enjoying the opportunity of expanding his research to a field that he had discovered by chance: mathematical pharmacology—the application of mathematical models to understand and explain the dynamic interaction of drug, biological system, and disease. This was what would become his "second career." In the 20+ years of this second career, Bert has impacted more than 60 publications at the interface between mathematics and pharmacology together with colleagues around the world.

In this "in memoriam," we attempt to highlight Dr. Peletier's contributions to mathematical pharmacology that furthered the science underlying modern model-informed drug discovery and development.

## CONTRIBUTIONS TO MATHEMATICAL PHARMACOLOGY

Bert Peletier brought mathematical rigor to the discipline of PK–PD at a time when increasingly more powerful computers and computing algorithms allowed for the identification of increasingly complex models, which are at risk of over-parametrization. He did this through the application of mathematical concepts that were new to PK–PD modeling, including but not limited to "phase-plane analysis" and "non-dimensionalisation." These methodologies provide unparalleled insights into the dynamics of complex systems, which enable convergence of curve fitting to otherwise over-parameterized models in various therapeutic areas.

The very first model in this context was an application to serotonin 5-$HT_{1A}$ receptor agonists and their effect on body temperature. Physiology teaches us that body temperature is controlled by a body-temperature set-point located in the hypothalamus, and this was implemented in the model as such. The model was informed by data generated in rats, which yielded high-density profiles of the effects on body temperature. Depending on the 5-$HT_{1A}$ agonist, the dose, and the rate of administration, distinctly different response profiles were observed. Fast administration of high doses resulted in a gradual lowering of body temperature followed by a gradual return to the baseline. In contrast, lower doses of the same 5-$HT_{1A}$ agonists or partial agonist yielded a fluctuating repose pattern. Bert and colleagues managed to explain this behavior using those advanced mathematical methods. In a second application, Bert contributed to the establishment and understanding of a simple, identifiable yet fundamentally mechanistic model for characterizing "bell-shaped" drug response patterns. This model allowed the simultaneous description of several $GABA_A$ receptor modulators based on their intrinsic affinity for the receptor and a single and unique transducer function, identifying benzodiazepines as $GABA_A$ receptor partial agonists. This concept has since successfully been applied to several other therapeutic areas. In a third application, Peletier and Post were able to characterize processes related to bone turnover and disease progression that occur on vastly different timescales ranging from days or weeks (bone turnover) to years (fracture) via mathematical model reduction. This analysis was later formalized and ultimately enabled fitting of a mechanistically complex model to clinical data.

One of the most important conceptual contributions of Bert to the field of PK–PD modeling has been the introduction of the concept of a pharmacological validation. In practice, the validity of a PK–PD model is commonly assessed using a predictive validity check, that is, a comparison of model-based simulated data and experimentally observed data. This approach is limited by the fact that it is an internal validation procedure, which is based on data from a limited number of nearly identical studies. Pharmacological validation, on the other hand, relies on the use data for comparison that has been obtained under entirely different experimental conditions. This concept was applied in a study of multiple antagonist concentrations on an agonist pharmacological response, essentially performing a comprehensive "Schild analysis" in vivo.

## IMPACT ON DRUG DISCOVERY AND DEVELOPMENT

Bert's capabilities and enthusiasm to work across multidisciplinary teams had a significant impact on our understanding of PK-PD and on why some subjects may differ in their demand of drug. Although most of his work was focused on formalizing and advancing fundamental insights into the mathematical behavior of PK–PD models, Bert also collaborated with several pharmaceutical companies to address actual drug discovery and development project questions. This quest started when Bert dissected the basic turnover model (known as the indirect response model) from a mathematical perspective. Different topics, such as dose–response–time data analysis, physiological limits, turnover taxonomy, and more in-depth characterization of functional adaptation, were rapidly chiseled out

in collaboration with Bert. He gave unprecedented support to project teams who struggled with deriving the concentration–response relationship at equilibrium based on new "open" model expressions of in vivo potency, efficacy parameter, and clearance. This step-change was anchored onto experimental data and comprehensive literature reviews showing that target turnover rate varies with age, species, tissue or subregion, treatment, disease, hormonal and nutritional state, day–night cycle, etc., beyond drug-target binding. The concepts initially established for small molecules were later expanded to monoclonal antibodies in an attempt to strike a balance between capturing data and model complexity. His work on translating a systems biology model of cross-membrane signal transduction of receptor tyrosine kinases to a systems pharmacology model has been used in more than five drug discovery and development programs for the treatment of pain to select targets and clinical candidates (PHvdG, personal communication). Another example is the framework for the impact of plasma-protein binding on receptor occupancy that Bert developed that provides guidance to medicinal chemists and PK–PD scientists at the stage of compound design in early discovery.

## TEACHING AND MENTORSHIP

Bert's scientific curiosity was paired with his seemingly natural ability to teach and mentor. He often penciled down ideas on yellow pieces of paper and took his time to get it right. While doing so, Bert paid great attention to detail and was meticulous about the use of punctuation marks, periods, and commas when detailing mathematical equations in manuscripts. To him, mathematics was a language that could be read like books or sheets of music and applied to provide answers to questions. "Mathematics is a language," he would say and, in a text, "has to be an integral part of the sentence or paragraph."

Over the years, Bert organized a number of mathematical conferences at Leiden University to which he would sometime invite his pharmacology students to present. While pharmacological and medical conferences follow a certain protocol, with short, often parallel presentations, Bert's conferences were completely different, in duration of the conference as well as lectures, with fewer presentations per day and ample time to discuss with the presenters after the sessions. This cross-fertilization of scientific disciplines inspired among other things the use of for example 3D animations of mathematical models in PK–PD lectures, enabling visualization of both the drug response in time as well as the underlying effect on the control or feedback function.

Bert was transitioning back and forth between two worlds: the world of mathematics and the world of applied mathematical pharmacology. He jokingly mentioned that "generally pharmacologists have actual data and are less strong in mathematical theory, while mathematicians have less data and actual theory. It can be either boring or fun depending in which world you live." His love for science was contagious and his gentle nature made him easy and fun to work with. Bert helped many of his younger colleagues to make first decisive steps in their own careers and was always open to listening and providing advice. Bert's passing leaves a hole in the lives of many people, but his spirit lives on in the ones he touched. For that, we are grateful!

We conclude with a personal anecdote from Bert: "In my high school we had a rather wordy physics teacher who did fantastic experiments and explained in elegant though slightly opaque terms the underlying phenomena. However, some of us did not always get it. Then after class, we went straight to the math teacher, who subsequently formulated the material in a few simple transparent mathematical expressions, and the clouds lifted."


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