Advances in Finite Time PK models, Fractal-Fractional PK-Pharmacometrics, MIDD Initiative, Chaotic models, the machine learning automated nonlinear mixed-effect model pyDarwin, and Boolean network modeling in Systems Pharmacology

SEMINAR: 25th June 2024, 9.00 am

THIS IS A SEMINAR OF THE 32nd PAGE MEETING: Welcome to the Population Approach Group in Europe (page-meeting.org)

Summary

This seminar is intended for Academics/students or scientists working in pharmaceutical industries, regulatory agencies, and contract research organizations.

The first talk will describe the science behind the Finite Absorption Time (F.A.T.) concept as well as the development/application of the pertinent Physiologically Based Finite Time Pharmacokinetic (PBFTPK) models. The models were built on two principles i) drugs are absorbed passively for a finite period and ii) time absorption constrains linked with the gastrointestinal transit times of drug in the stomach, the small intestines and the colon were applied. Relevant references: i) *Pharm Res* **37,** 187 (2020). https://doi.org/10.1007/s11095-020-02894-w ii) *Pharmaceutical Research* . 2022;39:. https://doi.org/10.1007/s11095-022-03230-0.

The second talk will focus on the re-interpretation of AUC and C_{max} under the prism of the F.A.T. concept as well as the modeling approaches for the assessment of bioequivalence. The pharmacokinetic approaches leading to estimates for the absorbed or the bioavailable fraction of dose from oral data exclusively will be described. These advances can abolish phase zero (microdosing) studies aiming at the estimation of absolute bioavailability in early drug development in big Pharma. Relevant reference: *Pharmaceutical Research* 38, 1345–1356 (2021) [DOI: 10.1007/s11095-021-03078-w]

The third talk will be centered on the implications associated with the finding of the bilinear character of oral drug absorption coupled with the recent revision of *in vitro in vivo* correlations (IVIVC) in accord with the Finite Absorption Time (F.A.T) concept. In principle, an *in vitro* two-phase system (n octanol-buffer) mimicking the *in vivo* conditions in line with the F.A.T principles will demonstrate high predictability of oral drug absorption diminishing thus the importance of PBPK studies in oral drug absorption. Relevant references i) *Pharmaceutical Research* 2023 Sep;40(9):2167-2175. doi: 10.1007/s11095-023-03578-x. Epub 2023 Aug 3. PMID: 37537424. ii) Pharm Res. 2024 Jan 8. doi: 10.1007/s11095-024-03653-x. Epub ahead of print. PMID: 38191705.

The fourth talk will be about the use of time coefficients (fractal kinetics) and not rate constants in biopharmaceutics-pharmacokinetics and the application of differential equations of non-integer order (fractional kinetics) to Pharmacokinetics and Pharmacometrics. Emphasis will be placed on the topology of the reactions and processes taking place under in vitro or in vivo conditions.

The fifth talk addresses challenges related to the application of the chaos synchronization technique when considering actual measurements that contain stochastic noise. Synchronization techniques work well in denoised settings but are challenged in settings with stochastic components.

The sixth talk will present multiple machine learning strategies for nonlinear mixed effects population pharmacokinetic model selection. These approaches include particle swarm, gradient boosted tree, random forest, gaussian optimization and genetic algorithms as implemented in the pyDarwin open source software developed in conjunction with the US FDA and Dr. Mark Sale at Certara Corporation.

The seventh talk is on Boolean network modeling, which serves as an initial foundation prior to the development of an ordinary differential equations-based model. Boolean network models have been shown to efficiently describe, in a qualitative manner, the complex behavior of signal transduction and gene/protein regulatory processes. In parallel, Boolean network models can also be utilized to discover novel therapeutic targets and combinatorial treatment strategies.

Programme

TIME	SPEAKER	**TOPIC**
8.55	Panos Macheras Department of Pharmacy, University of Athens. PharmaInformatics Unit, Research Center ATHENA, Athens, Greece	Welcome
9.00	Panos Macheras Department of Pharmacy, University of Athens. PharmaInformatics Unit, Research Center ATHENA, Athens, Greece	Fractal, fractional kinetics in Biopharmaceutics, Pharmacokinetics and Pharmacometrics
9.45	Panos Macheras Department of Pharmacy, University of Athens. PharmaInformatics Unit, Research Center ATHENA, Athens, Greece	Drugs are absorbed in finite time under sink conditions: The birth of finite absorption time (F.A.T.) concept and the physiologically based finite time pharmacokinetic (PBFTPK) models.
10.30	Panos Macheras Department of Pharmacy, University of Athens.	Moving MIDD to a Model-Informed Drug Development & Assessment (MIDDA) initiative: Can modeling approaches be applied for bioequivalence assessment

	PharmaInformatics Unit, Research Center ATHENA, Athens, Greece	and phase zero studies of big Pharma be abolished?
11.15	Coffee Break	
11.45	Panos Macheras Department of Pharmacy, University of Athens	The revised IVIVC pave the way for the replacement of PBPK studies by a dissolution/absorption apparatus mimicking the bilinear % absorbed -time profile.
12.30	Robert Bies School of Pharmacy and Pharmaceutical Sciences, University at Buflalo, USA	The chaos synchronization approach to parameter estimation
13.15	Robert Bies School of Pharmacy and Pharmaceutical Sciences, University at Buflalo, USA	pyDarwin: A machine learning enhanced automated nonlinear mixed-effect model selection toolbox
14.00	Donald Mager School of Pharmacy and Pharmaceutical Sciences, University at Buflalo, USA	Boolean Network Modeling in Systems Pharmacology
14.45-15.15		Discussion

Registration-Fees

- Industry, CROs : 300 €
- Academia-Government: 200 €
- Student: 100 €