*Sunrise session on hot PK/PD topics*

*Organized by <u>Pharma-Informatics Unit of the "Athena" Research and Innovation Center</u>, Athens, Greece*

June 11, 2019
Radisson Blu-Royal Viking Hotel Vasagatan 1 10124 Stockholm, Sweden

# ATHENA - Research and Innovation Center in Information, Communication and Knowledge Technologies

# https://www.athena-innovation.gr/en/

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The advancement of excellence, innovativeness and competitiveness in the crucial sector of Information and Knowledge Technologies lies at the center of the Athena Research and Innovation Center value system. Through national and international R&D projects, technological ecosystem development initiatives, innovative application activities and knowledge transfer to the social and economic environment, Athena RIC fulfills its mission to support the participation of Greece both in the "Europe 2020" strategy and the global movement towards smart and sustainable growth for all.

**Workshop summary**

This sunrise session is intended for scientists working in academia, pharmaceutical industries, regulatory agencies, and contract research organizations with interest on hot topics which might not be covered by main stream talks of the main event.

The first talk deals with the revision of oral drug absorption pharmacokinetic analysis. The heterogeneous character of oral absorption for drug classes II, III, and IV will be underlined. Monte Carlo simulations reveal that the processes are slowed down in heterogeneous media. The need for the use of time dependent coefficients instead of classical rate constants will be presented using specific drug examples. The notion of flip-flop kinetics will be questioned.

The second talk deals with the (ir)reproducibility of studies in biomedical sciences. The recent manifesto on reproducible science is built on the concept of noise and the objective analysis of the investigators who perceive patterns in random data. Irreproducibility in a system can arise from multiple sources of error including stochastic, deterministic, deterministic non-calculable or a combination of these. Of these three sources of error, the majority of concerns have been focused on issues related to stochastic processes. In this talk, the deterministic contributors to irreproducibility are considered. This issue is prominent in those disease processes that have nonlinear dynamic characteristic and are state dependent. The issue of irreproducibility is demonstrated by analyzing three nonlinear dynamic models that exhibit chaotic behaviors, using

three well-established models of tumor-immune cell interaction. These are the models proposed by Panetta et al(Kirschner & Panetta, 1998), Kuznetsov et al(Kuznetsov, Makalkin, Taylor, & Perelson, 1994) and Mehmet et al(Itik & Banks, 2010). Simulation studies and statistical tests demonstrate that slight changes in critical controlling parameters (i.e., model parameters) can cause a significant difference between the final states (tumor burden). This variability in parameter values may be attributed to different covariate effects, between subject variability and between occasion variability. Irreproducibility may thus arise from the inherent nature of the system and not necessarily be solely attributable to stochasticity.

The third talk will focus on demystifying ongoing debates regarding Local Sensitivity Analysis (LSA) vs Global Sensitivity Analysis (GSA), and throwing a new angle on a missing element regarding inter-correlation of parameters (which are often mistaken with "interaction" between parameters. Most GSA analysis consider the latter but ignore the former. Although global sensitivity analysis (GSA) allows simultaneously evaluating the relative contributions of each individual parameter to the model output variance by varying all parameters over the entire intended parameter space, there are only rare attempts to investigated the effect of correlations of input parameters on their rankings. This is a hot topic particularly due to the regulatory interest in applications of GSA for PBPK models submitted to the agencies.

Upon completion of the Human Genome Project, the next colossal effort can be the Human Homeostasis Model (HHM). The fourth presentation attempts to initiate a dialogue on the basic features of HHM. Although the exact structure and dimensionality of the homeostatic system are unknown, the system is obviously adaptive, extremely complex and nonlinear dynamically. Using one of the simplest non linear dynamical systems, the basic features of the chaotic homeostasis state during life are visualized. A chaotic aperiodic homeostasis state, which is synonymous with the healthy state, is generated using a specific value of the model control parameter. The importance of the initial conditions (birth), the uniqueness of the aperiodic curve for each individual during life, the loss of complexity because of aging or disease leading to periodic oscillations followed by fading oscillation leading to death (steady state) are visualized. Machine learning techniques can be used in the not too distant future for the development of the first real life HHM.

## Scientific Programme

| Time | Speaker | Topic |
|------|---------|-------|
| 07.00 am | Panos Macheras<br><br>Pharma-Informatics Unit of "ATHENA" Research Center, Athens, Greece | Welcome – |
| 07.05 am | Panteleimon Mavroudis<br><br>School of Pharmacy and Pharmaceutical Sciences, University at Buffalo, USA | Revising Oral Drug Absorption Analysis |

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| 7.30 am | Robert Bies, School of Pharmacy and Pharmaceutical Sciences, University at Buffalo, USA | Reproducibility: Stochastic and Deterministic Considerations |
| 8.00 am | Amin Rostami, Centre for Applied Pharmacokinetic Research, University of Manchester & Senior Vice President of R&D and Chief Scientific Officer, Certara <br> Nicola Melillo, PhD Candidate, Università degli Studi di Pavia, Italy | Complex Models, Sensitivity Analysis and Parameter Scanning vs Global Sensitivity Analysis: The Untold Story of Inter-Correlation of Model Parameters |
| 8.30 | Panos Macheras <br> Pharma-Informatics Unit of "ATHENA" Research Center, Athens, Greece | A First Step Towards a Colossal Effort: The Human Homeostasis Model |
| 8.45 am | End | |

Registration-Fees:

Early bird registration (up to May 15th 2019): ☐ Industry: 250 € ☐ Academia-Government: 200 € ☐ Student: 100 €

Late bird registration (up to May 31st 2019): ☐ Industry: 300 € ☐ Academia- Government 250 € ☐ Student: 150 €