

## Report Lorentz Workshop on “Mathematical Pharmacology”

**Description and motivation.** High rates of attrition in drug development are limiting the development of novel drug treatments. Quantitative models have already shown their use in rationalizing drug development and optimizing drug treatment in patients. However, major challenges remain in the effective development and application of these mathematical models in drug development and specifically pharmacology. Mathematical model development and analysis could further address the challenges in this area.

**Aim.** This Lorentz workshop aimed to assess if and how a stronger involvement of mathematicians in the area of pharmacology, i.e. mathematical pharmacology, can move forward the effective application of mathematical approaches in this area. A mix of early career and established mathematicians and pharmacologists from both academia and industry was brought together, and through a combination of lectures with case examples and group discussions the key challenges and opportunities were explored. Specifically the workshop focused on three major challenges:

**Theme 1: Multiple scales and the integration between those scales.** Talks focused on i) time delays in cell maturation, ii) individual cell behaviour in tissues, and iii) spatio-temporal models to describe drug concentration gradients in organs such as the liver. The talks were followed by group discussions which underlined the potential for multi-scale models and identified the challenges in and need for making such models useful for a pharmacological context.

**Theme 2: Integration of modelling approaches outside differential equation-based models.** Talks about the use of agent-based models and network-based Boolean logic models provided input on the use of model formalisms other than the commonly used differential equation based methods. The group discussions clarified the complimentary character of those approaches and the need to combine and integrate them better.

**Theme 3: Bridging between highly mechanistic models that are too complex to apply in drug development.** One major challenge for pharmacologists is how to integrate and apply large systems biology models towards key questions in drug development. The talks on various model reduction techniques received strong interest and the group discussions concluded that those techniques have a huge potential for further collaboration between disciplines.

**Outcomes.** Until now, there has been only very limited interaction between pharmacologists and mathematicians. However, at the end of this meeting a clear consensus was reached that further interactions between (quantitative) pharmacologists and mathematicians will be valuable, and the development of a novel specific sub-field of mathematical pharmacology should be stimulated. In order to achieve this, raising further awareness of a field of mathematical pharmacology in both pharmacologist and mathematics audiences is of importance. To this aim, a session on the theme of mathematical pharmacology are proposed at three major conferences: the American Conference on Pharmacometrics (ACOP), the European Conference on Mathematical and Theoretical Biology (ECMTB), and the Conference on Complex Systems (CSS). The ECMTB and CCS proposals are accepted. Furthermore, a website is created ([www.mathematical-pharmacology.org](http://www.mathematical-pharmacology.org)). Finally, we are preparing the submission of a Perspective to CPT: Pharmacometrics & Systems Pharmacology to summarize the specific outcomes of this Lorentz workshop and raise further interest.

Future plans are a European Study Group on Mathematical Pharmacology and a follow-up meeting on a specific pharmacological problem to explore contrasting and integrating the various approaches.

**Structure of program, lectures, discussion time.** The first day was an introductory day, followed by 3 days with the different themes, ending Friday with a wrap-up/conclusions day. The division of mornings with talks and most of the afternoon with group discussions (distributed into 3 groups) worked well.

**Other comments, suggestions and criticisms.** It turned out to be a major challenge for industrialists to commit a full week at a workshop. Unfortunately a few industrial participants had to cancel their participation at short notice because of urgent project commitments at their company and a few others could attend a few days only. Although the Lorentz Center prefers participants to attend all days, a greater industrial input might have been achieved if we had been more flexible about participation for a few days only.

One of the participants was invited to give a presentation at the Leiden University series “This Week’s Discoveries” during lunch on Tuesday. This was an exciting opportunity to promote our activities. A slight point of improvement could have been the communication with organisers of this series so it would have been less disrupting and confusing for our program.

The support of the Lorentz Center has been crucial for the success of our meeting, Many thanks for this!