LIACS

Keywords for XJTU-Leiden joint Phd projects / own projects

We are looking for students already involved in a PhD process at XJTU and with relevant experience and publications in one or more themes as illustrated by the keywords below:

* Keywords: **Evolutionary computation, machine learning, and AI**  
  Contact: Prof. Dr. Thomas Bäck, Head (t.h.w.baeck@liacs.leidenuniv.nl)  
  Natural Computing Group  
  Leiden Institute of Advanced Computer Science (LIACS), Leiden University
* Keywords: **Artificial Intelligence, Intelligent Games, Symbolic Computations, Logic**   
  Contact: Dr. Alfons Laarman (a.w.laarman@liacs.leidenuniv.nl)  
  Theoretical Computer Science Group  
  Leiden Institute of Advanced Computer Science (LIACS), Leiden University
* Keywords: **Discovery of genome structure variants, pattern recognition, frequent pattern mining, genomes (Project in the area at the intersection of biology and computer science)**Contact: Dr. Walter Kosters (w.a.kosters@liacs.leidenuniv.nl)  
  Theoretical Computer Science Group  
  Leiden Institute of Advanced Computer Science (LIACS), Leiden University
* Keywords: **Deep learning, high throughput, segmentation, image analysis**Contact: Prof. Dr. Fons Verbeek, Head (f.j.verbeek@liacs.leidenuniv.nl)  
  Imaging & BioInformatics Group  
  Leiden Institute of Advanced Computer Science (LIACS), Leiden University

In life sciences, a lot of effort is put in getting large volumes of data in order to find potential candidates for drugs for various treatments. Effectiveness of drugs is tested on cells or zebrafish from which images are available. In order to measure effects, classification systems need be designed. Various CNN’s need to be tested, reconfigured, extended to find the best possible classifier.

* Keywords: **3D image analysis, deep learning, image restauration**Contact: Prof. Dr. Fons Verbeek, Head (f.j.verbeek@liacs.leidenuniv.nl)  
  Imaging & BioInformatics Group  
  Leiden Institute of Advanced Computer Science (LIACS), Leiden University

Classification of 3D images demands different approaches from the classifiers. Let alone because of the size of the images. Therefore, efficient strategies need be designed to investigate the relation of resolution and effectiveness of classification. The images are from microscopes that can produce 3D datasets. In general, a 3D image contains one 3D object. There are large sets of 3D objects available for classification tasks.

In some cases the 3D images need to be optimized; the effect of the optimization is transferred to the resolution and the effect of restauration (= optimization) on classification need be investigated.

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* Keywords: **3D image analysis, deep learning, image restauration**Contact: Prof. Dr. Fons Verbeek, Head (f.j.verbeek@liacs.leidenuniv.nl)  
  Imaging & BioInformatics Group  
  Leiden Institute of Advanced Computer Science (LIACS), Leiden University
* **Deep-learning-based image analysis and dynamic modeling of macrophage function in disease models**Keywords: deep learning, image analysis, mathematical modeling  
  Institute of Biology Leiden
* **Vertex-based modeling of transcription factor- and hormone-regulated stomatal patterning and development**  
  Plant Sciences, Institute of Biology Leiden
* **AI project on**  
  - **Imaging** (with NECEN), or   
  - **Genome Mining** (in collaboration with Marnix Medema)  
  Contact: Dennis Claessen, Microbial Biotechnology, Institute of Biology Leiden
* **Computational Bioscience, genome mining, scavenging of novel enzymes and/or novel synthetic clusters from one big database of mold genomes, as computational analysis and comparison of magaplasmids and transposable elements in control of conjugation and horizontal gene transfer of (antibiotics, chemicals, others) resistance development**

Contact: Arthur Ram, Han de Winde, together with Marnix Miedema), Industrial Microbiology, Institute of Biology, Leiden

* Keywords: **Machine learning, computational biology, antibiotics, natural products, antimicrobial resistance**

Contact: Institute of Biology Leiden

Mathematical Institute

**Towards extension of the 3D brain drug distribution model**

The development of drugs targeting the brain is very challenging. One of the reasons is a lack of quantitative understanding of the complex processes that govern the dynamics of a drug within the brain. While a number of models on drug distribution into and within the brain is available, none of these addresses the combination of factors that affect local drug concentrations in brain extracellular fluid (brain-ECF).

To that end, we developed a mathematical model in which drug concentration varies in time and space (system of partial differential equations). First, we formulated a brain tissue unit containing 2 spatial dimensions, see [1], and recently we extended it to 3 spacial dimensions, see [2].

The 3D brain unit is a cube, in which the brain capillaries surround the brain-ECF. The drug concentration is described in both the blood-plasma-domain and in a brain-ECF-domain by a set of differential equations. The most advanced model consists of a network of 3x3x3 connected units and to each unit different parameter values can be assigned, see [3]. This current model is a first step towards a full brain model, however, not all physiological aspects of drug dynamics in the brain have been incorporated yet.

The new PhD project will deal with the next step: to extend the existing model with other properties of the brain that are essential in understanding drug dynamics in the brain. For example, cells have not yet been taken into account in the model explicitly and these do need to be added. After formulating the model, results need to be obtained by extending the existing numerical code.

References:

[1] E. Vendel, V. Rottschafer, E.C.M. de Lange (2018) Improving the Prediction of Local Drug Distribution Profiles in the Brain with a New 2D Mathematical Model, Bulletin of Mathematical Biology in the Special Issue: Mathematics to Support Drug Discovery and Development, 81(9), 3477 - 3507, <https://doi.org/10.1007/s11538-018-0469-4>

[2] E. Vendel (2019) Prediction of spatial-temporal brain drug distribution with a novel mathematical model, Doctoral Thesis https://openaccess.leidenuniv.nl/handle/1887/81579

[3] E. Vendel, V. Rottschafer, E.C.M. de Lange (2020) The 3D brain unit network model to study spatial brain drug exposure under healthy and pathological conditions, accepted in Pharmaceutical Research

Required background: Knowledge of ODEs and PDEs, Affinity with numerical simulation packages.

Contact: Vivi Rottschafer, Mathematical Institute, [vivi@math.leidenuniv.nl](mailto:vivi@math.leidenuniv.nl), Elizabeth de Lange, Leiden Academic Centre for Drug Research, ecmdelange@lacdr.leidenuniv.nl

**Theoretical statistics, martingales, reproducibility crisis, hypothesis testing**

Peter Grunwald's research is mostly in (mathematical, theoretical) statistics and machine learning; he is currently the 'president' of the Association for Computational Learning, which runs COLT, the world's main machine learning theory conference. But this project would be more statistical - it would be on the 'reproducibility crisis', looking for new types of hypothesis tests and confidence intervals that allow for effortlessly combining data from different studies. With the current, mostly p-value based methodology, it is almost impossible to meaningfully combine data from different tests (say different clinical trials), where the 2nd trial may have been performed because the first had a certain outcome, and the third because 1st two trials had certain outcomes, and so on. We have designed a new method which allows for generic combination of such tests while preserving error guarantees. This 'safe testing' methodology, introduced in 2019 (see this arxiv paper https://arxiv.org/abs/1906.07801), has already attracted considerable interest - we are organizing a workshop (https://www.eurandom.tue.nl/event/safe-anytime-valid-inference-savi/) on it in May, with speakers from various top universities such as Carnegie Mellon and Stanford. I am interested in Ph.D. students who would be willing to extend this work - both theoretically (there is a lot of math still to be done; this involves martingale theory but also e.g. minimax theorems and connections between statistics and group theory) and practically - we currently have R packages for 'safe' versions for the t-test and 2x2 testing, but we plan to extend this to many more standard testing/A/B-testing/optional stopping scenarios; also the corresponding theory for always-valid confidence intervals needs to be developed further. The ideal candidate should have an affinity with probability theory and/or theoretical statistics yet at the same time not shy away from programming; also expertise in optimization is useful. The precise division in rules between myself and the co-supervisor at XJTU is flexible, and we can discuss it later.

Contact: Peter Grunwald, Mathematical Institute

**Waves and patterns in random and/or structured media**

Basic patterns such as waves, spots and spirals can be readily observed in many natural systems and their analysis has been a driving force in the fields of dynamical systems and differential equations during the past decades. Indeed, one of the main success stories in the field of PDEs is that such patterns can be reproduced and shown to be robust in a wide range of models – allowing them to be used as fingerprints and/or building blocks to shed light on the global behaviour of the underlying system.

However, the vast majority of work in the broad area of pattern formation is focused on homogeneous systems posed on continuous spatial domains. The goal of this PhD project is to go beyond this setting and consider pattern formation in environments that are noisy and/or spatially structured – which appear naturally in many applications.

The specific direction that we will take is highly flexible and depends on the background and interests of the PhD candidate. Three example projects are outlined below.

* Basic reaction-diffusion equations such as the Nagumo equation, the FitzHugh-Nagumo equation and the Fisher-KPP equation admit travelling wave solutions, which are known to survive in a suitable sense if noise is added to the coefficients. In a recent PhD project we pioneered a framework to analyze the limiting speed and shape of such stochastic waves in several basic situations (such as the presence of a spectral gap for the linearized system). We here continue this work by looking at more general scenario’s. A basic knowledge of stochastic differential equations would be helpful. See <https://pub.math.leidenuniv.nl/~hupkeshj/trnsinv.pdf> for an introduction and an overview of the main ideas and questions.
* Lattice differential equations are widely used to model dynamics taking place in discrete media such as crystals, granular materials or biological cells. The broken translational and rotational symmetries lead to highly complex behaviour that cannot be observed in the natural PDE counterparts. In this project we will investigate the 2d curvature-driven spreading behaviour of compact disturbances, which can be described by using planar travelling waves as building blocks. Basic dynamical systems knowledge is a prerequisite here. For a recent introductory survey, see <https://pub.math.leidenuniv.nl/~hupkeshj/ldervw.pdf>.
* Reaction-diffusion equations on infinite graphs are almost completely unexplored. The goal here is to analyze nonlinear spreading phenomena on (random) graphs by building a bridge between the theory of travelling waves and recent progress in the probabilistic description of random walks in random environments. Some background in probability and/or networks would be useful. Alternatively, such questions can be pursued by functional-analytic techniques, see sections 5.2 and 5.3 from the survey above.

Contact: Hermen Jan Hupkes, Mathematical Institute, [hhupkes@math.leidenuniv.nl](mailto:hhupkes@math.leidenuniv.nl)

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* Keywords: **data mining / statistical modelling, structure-based drug discovery / molecular modeling, proteochemometrics, computational chemical biology, molecular dynamics, medicinal chemistry, cheminformatics, bioinformatics, machine learning, artificial intelligence, dimensionality reduction**Contact: Dr. G.J.P. van Westen, [gerard@lacdr.leidenuniv.nl](mailto:gerard@lacdr.leidenuniv.nl)
* Keywords: **image analysis, mathematical modeling, cell-based modelling**  
  Contact: Dr. J.B. Beltman, [j.b.beltman@lacdr.leidenuniv.nl](mailto:j.b.beltman@lacdr.leidenuniv.nl)
* Keywords: **pharmacometrics, quantitative systems pharmacology modeling, PK-PD modeling**Contact: Dr. J.G.C. van Hasselt, [coen.vanhasselt@lacdr.leidenuniv.nl](mailto:coen.vanhasselt@lacdr.leidenuniv.nl)

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