The Reinhart-Heinrich Doctoral Thesis Award 2019

The winner of the ESMTB Reinhart-Heinrich Doctoral Thesis Award for 2019 is **Lisa Maria Kreusser**, for the thesis **Anisotropic nonlinear PDE models and dynamical systems in biology**. The award will be formally given in a ceremony at the ECMTB conference in Heidelberg in 2021. The awarding committee made the following statement: *The thesis by Lisa Maria Kreusser is very comprehensive and voluminous. [...] In summary, Kreussers thesis is very beautiful work, especially on the maths side, and is outstanding both in quality and quantity. Each of the two parts would have been excellent PhD theses on their own. The dissertation is appealing by its mathematical depth, exact and detailed presentation, and the biological applications and interpretation.* She did her PhD at the Department of Applied Mathematics and Theoretical Physics (DAMTP) and at the Cambridge Centre for Analysis (CCA), within the University of Cambridge, UK, under the supervision of Professor Peter A. Markowich and Professor Carola-Bibiane Schönlieb. We congratulate her for her excellent and exciting work! First, she presents herself, and then follows an extended abstract of the thesis.

Lisa Maria Kreusser Personal statement

Since my undergraduate studies at the University of Kaiserslautern, Germany, I have been very interested in partial differential equations due to their wide range of applications in biology, physics, engineering, and socio-economics. This was further enhanced by research projects I have been involved in at the Fraunhofer Institute for Industrial Mathematics ITWM and at Imperial College London. My research internship at Imperial College not only sparked my curiosity in interacting particle models which are prevalent in biological applications, but also convinced me to move to the UK for my PhD. I completed my PhD at the Department of Applied Mathematics and Theoretical Physics at the University of Cambridge in 2019.

During my PhD, supervised by Prof. Peter Markowich and Prof. Carola-Bibiane Schönlieb, I have worked on mathematical models with diverse biological applications, including the simulation of fingerprint patterns and the simulation of biological transport networks such as leaf venation or blood circulation systems. Since October 2019, I have been a Nevile Junior Research Fellow at Magdalene College, Cambridge. This independent research fellowship allows me to build my own research programme in the field of partial differential equations in biology and data science.

The research area of mathematical biology fascinates me because it is a highly interdisciplinary area where I can work at the intersection of significant mathematical problems and fundamental questions in biology. Driven by my desire to pursue biological applications in interaction with biologists, I investigate new and challenging mathematical models. For this research, I use a wide range of mathematical tools including mathematical modelling, numerical analysis, scientific computing and analysis of partial differential equations. This work gives new insights into the properties of the models and results in a better understanding of the underlying biological processes such as biological pattern formation.

Thesis summary: 'Anisotropic nonlinear PDE models and dynamical systems in biology' by Lisa Maria Kreusser

Overview The recent, rapid advances in modern biology heavily rely on fundamental mathematical techniques and, in particular, on partial differential equations, an essential tool for the mathematical modelling of biological, socio-economic and physical processes. The thesis deals with the analysis and numerical simulation of anisotropic nonlinear PDEs and dynamical systems in biology. It is divided into two parts:

- Part I is motivated by the simulation of fingerprint patterns and deals with a class of anisotropic interaction equations, based on the work in [1, 2, 3, 4, 11].
- Part II focuses on mathematical models for biological transportation networks describing living systems such as leaf venation in plants, blood circulatory systems, and neural networks, and is based on the research in [5, 6, 7, 12].

Through mathematical analysis and computer simulations, we have gained new insights into the qualitative properties of the underlying mathematical models which have resulted in a better understanding of complex phenomena in biology such as biological pattern formation. Equally important, these new and challenging PDE models have led to intra-disciplinary research, involving modelling, PDE theory, dynamical systems, graph theory and numerical simulations. This research has opened up a whole new range of fascinating mathematical problems, which we have studied by developing new mathematical tools.

Simulation of fingerprint patterns

In Part I of the thesis, we focused on modelling fingerprint patterns which is not only of great interest in the biological community, but also in forensic science and increasingly in biometric applications where large fingerprint databases are required for developing, validating and comparing the performance of fingerprint identification algorithms. Besides, similar models have proven to be very useful for modelling swarming in nature, including flocks of birds or colonies of bacteria/cells, and have received significant attention in the scientific community recently due to their great practical relevance in biological applications.

One of the key features of many of these models is the social communication between individuals at different scales, i.e. each individual can interact not only with its neighbours but also with individuals further away. This can be described by short- and long-range interactions. An example of this class of models is the Kücken-Champod model [13] for describing the formation of fingerprint patterns.

The development of fingerprints can be described by three phases [13]. In the first phase, growth forces in the epidermis and shrinkage of volar pad create compressive mechanical stress, modelled by Kücken and Newell [14, 15]. The second phase consists of the rearrangement of Merkel cells from a random configuration into parallel ridges along the lines of smallest compressive stress, cf. Figure 1. This phase can be regarded as the actual pattern forming process and was first modelled by Kücken and Champod [13]. In the third phase, the primary ridges are induced by the Merkel cells.

Since the first phase of the fingerprint devel-

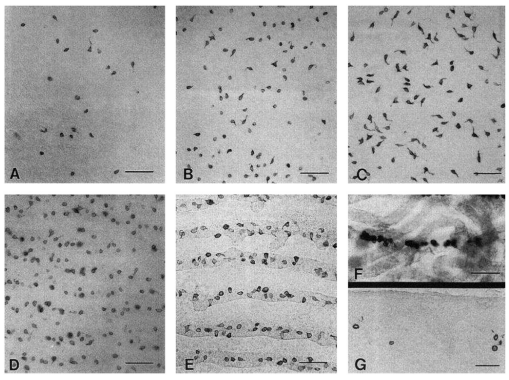


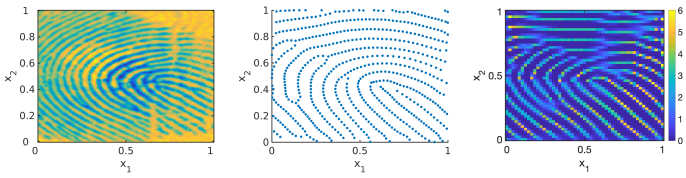
Figure 1: Development of Merkel cell distribution by Kim and Holbrook: Merkel cells appear at about the 7th week of pregnancy, multiply and arrange in lines at about the 10th week. Figure from [10].

opment has already been successfully modelled [14, 15] and the third phase can easily be modelled based on the second phase, we focus on the second phase where the stress field from the first phase is assumed to be a given input. Mathematically, the formation of fingerprints can then be described as a large system of interacting Merkel cells [13], which align themselves according to certain interaction forces and form our fingerprint lines.

Part I of the thesis deals with a class of interacting particle models with anisotropic repulsive-attractive interaction forces motivated by anisotropic pattern formation in nature. In most existing models, the forces are isotropic and particle models lead to non-local aggregation PDEs with radially symmetric potentials. The central novelty in the models we consider is an anisotropy induced by an underlying tensor field, cf. Figure 2(A). This innovation does not only lead to the ability to describe real-world phenomena more accurately, but also renders their analysis significantly harder compared to their isotropic counterparts. Due to the non-existence of an interaction potential and a gradient flow formulation, much of the existing analytic theory does not apply to these anisotropic interaction models and new methods are required for studying these models rigorously.

We studied the role of anisotropic interaction in these biological models by considering both the particle model and its continuum counterpart. This allowed us to propose a bio-inspired model to simulate realistic fingerprint patterns, cf. Figure 2(B) for simulation results of the discrete model, featuring important properties of a biologically meaningful fingerprint development model. We also gave a rigorous proof of the stability of line patterns. Moreover, we investigated the role of nonlinear diffusion on the widening of line patterns both analytically and numerically, and simulated realistic fingerprint patterns efficiently with the continuum model, cf. Figure 2(C). In the following, we describe the results of Part I in more detail.

Anisotropic pattern formation [1]: A crucial step towards understanding anisotropic pattern formation in nature is to investigate the role of the anisotropy which can be characterised by one parameter in the model. We studied the variation of this parameter, describing the transition between the isotropic and the anisotropic model, analytically and numerically. We analysed the equilibria of the corresponding mean-field partial differential equation and investigated pattern formation numerically in two dimensions by studying the dependence of the parameters in the model on the resulting patterns.



(A) Anisotropy (B) Particle model (C) Mean-field model

Figure 2: Numerical simulation results for fingerprint patterns.

Simulation of fingerprint patterns [4]: Evidence suggests that both the interaction of Merkel cells and the epidermal stress distribution play an important role in the formation of fingerprint patterns during pregnancy [9]. To model the formation of fingerprint patterns in a biologically meaningful way these patterns have to become stationary. For the creation of synthetic fingerprints it is also very desirable that rescaling the model parameters leads to rescaled distances between the stationary fingerprint ridges. Based on these observations, as well as the model introduced by Kcken and Champod [13] we proposed a new model for the formation of fingerprint patterns during pregnancy. In this anisotropic interaction model, the interaction forces not only depend on the distance vector between the cells and the model parameters, but additionally on an underlying tensor field, representing a stress field. This dependence on the tensor field leads to complex, anisotropic patterns. We studied the resulting stationary patterns both analytically and numerically. In particular, we showed that fingerprint patterns can be modelled as stationary

solutions for an appropriate choice of the underlying tensor field.

Stability analysis of line patterns [3]: Stable line patterns play a crucial role in the pattern formation of the anisotropic interaction model and are also important for the simulation of fingerprint patterns. For a given spatially homogeneous tensor field, we showed that there exists a preferred direction of straight lines, i.e. straight vertical lines can be stable for sufficiently many particles, while many other rotations of the straight lines are unstable steady states, both for a sufficiently large number of particles and in the continuum limit. For straight vertical lines we considered specific force coefficients for the stability analysis of steady states, showed that stability can be achieved for exponentially decaying force coefficients for a sufficiently large number of particles, and relate these results to the Kücken-Champod model for simulating fingerprint patterns. The mathematical analysis of the steady states is completed with numerical results.

Role of nonlinear diffusion on pattern formation [2]: For simulating fingerprint patterns with a finite width an additional nonlinear diffusion term can be considered in the mean-field model resulting in an anisotropic, nonlocal aggregation equation with nonlinear diffusion which does not possess a gradient flow structure. We studied the equilibria of this model by deriving equilibrium conditions for stationary line patterns which can be reformulated as the minimisers of a regularised energy functional if the underlying tensor field is spatially homogeneous. For this case, we showed the existence of energy minimisers, established Γ-convergence of the regularised energy functionals as the diffusion coefficient vanishes, and proved the convergence of minimisers of the regularised energy functional to minimisers of the non-regularised energy functional. Finally, we proved weak convergence of a numerical scheme for the numerical solution of the model with any underlying tensor field, and showed numerical results. This numerical scheme allowed us to simulate fingerprint patterns using the mean-field modelling approach. The resulting patterns are better than for the associated particle model. In particular, by rescaling the forces we could vary the distances between the fingerprint lines.

Formation of biological transport networks Part II of the thesis deals with transportation networks which are ubiquitous in living systems such as leaf venation in plants, blood circulatory systems, and neural networks. Understanding the development, function, and adaptation of biologic transportation networks has been of long-standing interest in the scientific community due to their complexity. Inspired by the complex biological phenomena, mathematical models and methods have recently been developed for adaptive transportation networks.

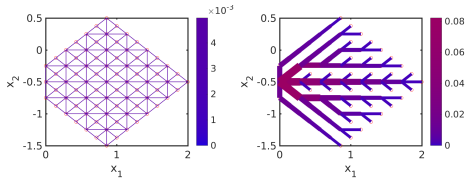
Mathematical modeling of transportation networks is traditionally based on discrete frameworks, in particular mathematical graph theory and discrete energy optimization, where the energy consumption of the network is minimized under the constraint of constant total material cost. However, networks and circulation systems in living organisms are typically subject to continuous adaptation, responding to various internal and external stimuli. For instance, for blood circulation systems it is well known that throughout the life of humans and animals, blood vessel systems are continuously adapting their structures to meet the changing metabolic demand of the tissue. In particular, it has been observed in experiments that blood vessels can sense the wall shear stress and adapt their diameters according to it. Consequently, dynamic models are required for modelling biological transport networks accurately.

Motivated by this observation, a new discrete dynamic modelling approach on a graph has recently been introduced by Hu and Cai [8] to describe the formation of biological transport networks. The main mathematical interest of this dynamical model stems from the highly unusual coupling of a system of ODEs whose solution is defined on the edges of a graph to a linear system on the nodes of the graph. In particular, the linear system is only solvable under certain conditions and due to the coupled defining equations on both nodes and edges of the graph

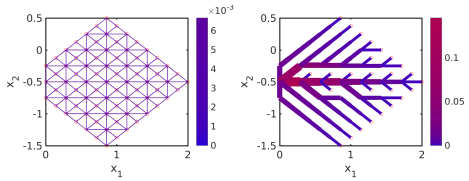
it is not clear under which assumptions a limit model can be derived.

The aim of Part II is to get a better understanding of the Hu-Cai model [8] for generic biological transport networks and adapt it to the cellular context for leaf venation. Using methods from various fields within mathematics, we investigated the global existence of solutions of the microscopic and the associated macroscopic models, which can be written as the unusual coupling of a linear system and a system of ordinary differential equations on a graph and its continuum counterpart. Moreover, we proved the rigorous limit between the microscopic and macroscopic model for the two-dimensional regular setting which required the formal derivation of an appropriate macroscopic model. These analytical results were complemented by numerical simulations of the discrete model (cf. Figure 3) illustrating the convergence to steady states, their non-uniqueness as well as their dependence on initial data and model parameters. Based on this model, we proposed an adapted model in the cellular context for leaf venation, investigated the model analytically and showed numerically that it can produce branching vein patterns (cf. Figure 4). In the following, we discuss our results in more detail.

ODE- and PDE-based modelling [6]: To get a better understanding about the dynamics

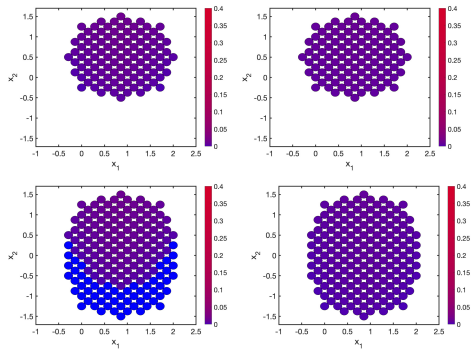


(A) Full graph

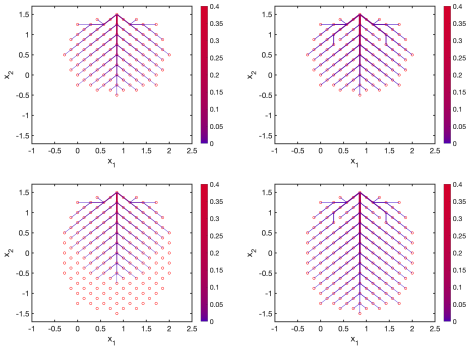


(B) Perturbed full graph

Figure 3: Steady states for full graph and perturbed full graph



(A) Auxin concentration



(B) Transport activity

Figure 4: Steady states for auxin concentration and transport activity for different background source strengths and different grid shapes (round, oval).

in the Hu-Cai model [8], we studied the global existence of solutions of a discrete (ODE based) model on a graph. We proposed an adaptation of this model so that a macroscopic (PDE based) system can be obtained as its formal continuum limit. We proved the global existence of weak solutions of the macroscopic PDE model. Finally, we presented results of numerical simulations of the discrete model, illustrating the convergence to steady states, their non-uniqueness as well as their dependence on initial data and model parameters.

Rigorous continuum limit [7]: For the analysis and simulation of complex dynamical systems in biology, it is often very useful to consider the associated continuum limit which may given additional insights about the biological transport and allows us to include additional modelling assumptions such as network growth.

This motivated our study of the rigorous limit of the discrete model. For the spatially two-dimensional rectangular setting we proved the rigorous continuum limit of the constrained energy functional as the number of nodes of the underlying graph tends to infinity and the edge lengths shrink to zero uniformly. The proof is based on reformulating the discrete energy functional as a sequence of integral functionals and proving their Γ-convergence towards the continuum energy functional.

Application to auxin transport in leaf venation [5]: The plant hormone auxin controls many aspects of the development of plants. One striking dynamical feature is the self-organisation of leaf venation patterns which is driven by high levels of auxin within vein cells. The auxin transport is mediated by specialised membrane-localised proteins. Many venation models have been based on polarly localised efflux-mediator proteins of the PIN family. We investigated a modelling framework for auxin transport with a positive feedback between auxin fluxes and transport capacities that are not necessarily polar, i.e. directional across a cell wall. Our approach is derived from a discrete graph-based model for biological transportation networks, where cells are represented by graph nodes and intercellular membranes by edges. The edges are not a-priori oriented and the direction of auxin flow is determined by its concentration gradient along the edge. We proved global existence of solutions to the model and the validity of Murray's law for its steady states. Moreover, we demonstrated with numerical simulations that the model is able connect an auxin source-sink pair with a mid-vein and that it can also produce branching vein patterns. A significant innovative aspect of our approach is that it allows the passage to a formal macroscopic limit which can be extended to include network growth. We also performed mathematical analysis of the macroscopic formulation, showing the global existence of weak solutions.

Conclusion In the thesis, we studied two complex PDE models arising in biological applications. Part I, motivated by the simulation of fingerprint patterns, is mainly based on four papers [1, 2, 3, 4] which are among the first works on the analysis of anisotropic interaction models. Using innovations on the modelling, analysis, and computational methods, this research on anisotropic interaction is a crucial step towards the accurate description of real-world phenomena. Part II is motivated by the formation of biological transport networks and is mainly based on three journal articles [5, 6, 7]. This research resulted in a better understanding of the Hu-Cai model for biological transport networks and its continuum counterpart, and led to an adapted model in the cellular context for leaf venation.

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