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Differential Equations arising from Organising Principles in Biology

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ABSTRACT. This workshop brought together experts in modeling and analysis of organising principles of multiscale biological systems such as cell assemblies, tissues and populations. We focused on questions arising in systems biology and medicine which are related to emergence, function and control of spatial and inter-individual heterogeneity in population dynamics. There were three main areas represented of differential equation models in mathematical biology. The first area involved the mathematical description of structured populations. The second area concerned invasion, pattern formation and collective dynamics. The third area treated the evolution and adaptation of populations, following the Darwinian paradigm. These problems led to differential equations, which frequently are non-trivial extensions of classical problems. The examples included but were not limited to transport-type equations with nonlocal boundary conditions, mixed ODE-reaction-diffusion models, nonlocal diffusion and cross-diffusion problems or kinetic equations.

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Introduction by the Organisers

Despite the immense progresses made over the last decades in mathematical biology, the multifaceted nature of biological processes still represents an enormous challenge for mathematical modeling. Technological advances lead to generation of massive data sets, which can then be used to improve the accuracy of modeling. This, in turn, contributes to a better understanding of the underlying complex biological processes. As a result, sophisticated mathematical methods have become

crucial for addressing the key questions and paradigms in diverse biological systems and for making predictions of the effects of system perturbations. In addition to providing an insight into the design principles of individual biological systems, mathematical modeling also allows comparative analyses across divergent systems and species, even in cases when direct molecular analogies are limited, such as when contrasting plants and animals.

This workshop brought together experts in modeling and analysis of organising principles of multiscale biological systems such as cell assemblies, tissues and populations. We focused on specific questions arising in systems biology and medicine and related to emergence, function and control of spatial and inter-individual heterogeneity in population dynamics. There were three main areas represented of differential equation models in mathematical biology. The first area involved the mathematical description and effective dynamics of structured populations. The second area concerned problems of control of the heterogeneity and synchronisation principles. The third area treated the evolution and adaptation of systems, following the Darwinian paradigm. This includes emergence and structure of the heterogeneity with their mathematical formulation using the selection-mutation models. These areas are intertwined and stimulated each other. They have contributed to progress in the fields of partial differential equations, asymptotic and multiscale analysis, singular perturbation methods, instability analysis, gradient flows, kinetic modelling, mean-field limits, cellular automata, hydrodynamic closures, entropy methods, semigroup theory and functional analytic methods.

One of the major aims of the workshop was an extensive exchange of ideas and techniques between experts from modeling and analysis of different self-organisation and structure formation mechanisms, as the corresponding mathematical problems are often tightly connected. This was very well accomplished as we corroborated with our colleagues that the activity level of information exchange during the workshop was quite high. We now elaborate a bit more in each of the subareas in which we focused during this workshop.

A.- Structured population dynamics: A typical feature of mathematical models based on biology is that multiple structuring variables appear, which are not only the spatial coordinates. Model equations typically describe the time dynamics of a population density $n(t, x)$ where x may represent a physiological, genetic or other characteristic of the individuals. The structure variables may be multidimensional, which leads to significant mathematical difficulties in model analysis and simulation, and often requires model reduction. Another challenge is understanding the difference between discrete and continuous structures, their impact and the choice of appropriate modeling approach.

A typical class of examples fitting into this area are the size-structured models and coagulation-fragmentation equations. They arise for instance in description of the dynamics of cluster growth, such as protein polymerization or in description of size distributions in bacterial populations. Structured population models also play an important role in mathematical epidemiology. Difficulties arise in linking the

dynamics in the environment to the within-host dynamics and accounting for processes taking place on very different time scales. Indeed, epidemiological processes run on a time scale of months or weeks, symptoms and infectiousness onset occur in few days, whereas the infection process at cellular level is usually completed within few hours from viral entry. Innovative modeling approaches accounting for the function of the immune system lead to new types of equations. The PDE for immune cell population couples a continuous transport process describing gradual decay of the immune status with jumps in the opposite direction modeling boosting of the immune system. Such reversible processes, often coupling continuous and jump-discontinuous transitions, appear also in cancer modeling due to the plasticity of cancer cells or in the modeling of tissue regeneration, *e.g.* when it is needed to take into account transitions between active and quiescent stem cells.

Another large class of structured population models appears in computational neuroscience. For instance voltage and conductance are typical structured variables in models of neural networks such as the integrate-and-fire neuron models. Among the different modeling approaches, the mean-field theory has proven to play a crucial part in investigating neural networks' dynamics. This leads to a formulation of population dynamics in terms of the Fokker-Planck type equations. However, the Fokker-Planck equations arising are far from standard since they frequently have atypical boundary conditions or stiff right-hand sides to take into account the firing and relaxation of neurons beyond voltage threshold values. The nonlinearity enters through the drift caused by the flux of neurons at the firing voltage. This nonlinearity and the firing mechanism are main challenges in the mathematical analysis of these models. There are clearly two future directions in this field that need to be addressed. On the one hand finding periodic solutions to some of the models will clarify the questions of synchronization in neuron models. Regularizing some of these models based on the biological observations including time delays and relaxation may lead to existence proofs of the sustained oscillations. There are other models which involve relaxation times and more classical structured population models such as age-structured equations. These connections should also be explored further. Spatial versions of the models with neurons labeled according to their location in the cortex constitute another interesting direction where interaction with groups working in synchronization might be interesting.

B.- Invasion, pattern formation and collective dynamics: At a certain scale, the spatial-temporal dynamics of biological populations can be modelled by a reaction-diffusion equation

$$\partial_t u - a_{i,j}(x,t)\partial_{i,j}u - b_i(x,t)\partial_i u = f(x,u).$$

In case of constant coefficients, these equation have interesting particular solutions, so-called travelling waves. Their level-sets move at constant speed and can be interpreted as an invasion front. Showing existence of traveling waves when the coefficients depend on (x,t) and characterising their speed are challenging mathematical problems.

In case of systems of reaction-diffusion equations or their shadow type limits leading to equations with nonlocal terms, the lack of maximum principle leads to a complex dynamics. Different diffusion rates or nonlocal terms may lead to diffusion-driven instability (Turing mechanism) and emergence of asymptotically stable spatially heterogeneous patterns (Turing patterns), while a lack of diffusion in a subsystem may induce formation of non-Turing patterns in the form of asymptotic spikes or transition layers with jump-discontinuities. Such systems arise from modeling of interactions between cellular processes and diffusing signaling factors. They proved to be very different from the classical reaction-diffusion models. Since stationary solutions for the non-diffusing variables are discontinuous, linearised stability analysis cannot be directly applied. Another problem encountered is that of existence of an infinite number of solutions with changing connecting point. Such problems and models are important in developmental biology. Moreover, there are crosslinks to the models of tumour growth and invasion of surrounding tissue.

Another well-established discipline, which generates interesting nonlinear mathematical problems is spatial ecology. This research is usually interdisciplinary and involves a variety of approaches, ranging from model analysis to field work. It is of immense practical importance, since it involves modeling of movements of populations and their interaction, under changing environmental conditions. Examples include invasion of aquatic species under pressure from ocean warming. Mathematically, it includes systems of nonlinear differential equations, which may or may not involve structure. Behaviors of interest include extinctions, periodicity and chaotic behavior.

By including velocity as a structure variable, we arrive at models for populations structured by position and velocity. They can be used to explain self-organized dynamics of agents and their tendency to align. Dynamics of such systems are governed solely by interactions among individuals or agents, with the tendency to adjust to their environmental averages. This, in turn, leads to the formation of clusters, such as colonies of ants, flocks of birds, parties of people, *rendezvous* in mobile networks, and so forth. A natural question which arises in this context is when and how clusters emerge through the self-alignment of agents, and what types of rules of engagement influence the formation of such clusters. Of particular interest are cases where the self-organized behavior tends to concentrate into a single cluster, reflecting a consensus of opinions, flocking of birds, fish, or cells, rendezvous of mobile agents, and, in general, concentration of other traits intrinsic to the dynamics.

This area has been particularly active in the last decade using models ranging from transport equations, kinetic equations, to parabolic Fokker-Planck equations such as the famous Keller-Segel system. The extremely rich qualitative behaviours, including clustering and concentration, has led to a variety of mathematical methods adapted to each particular situation, including gradient flows, entropy methods, and self-similar solutions. In addition to that, hierarchies of models are also crucial because of the many scales, from the individual to the population and

multiscale analysis plays an important role in this field. The tools connecting the different levels of description such as mean-field limits or closure assumptions will be explored and expanded in other directions such as cell polymerization and cell movement.

The case of cells within a tissue is particularly relevant for this field but also much more challenging. A major outcome of this workshop will be to orient a part of the community to this important challenge for medical science including topics such as tumor growth, tissue repair and cell adhesion. Several species interaction is another major topic of expansion with very interesting biological implications in organogenesis such as neural crest or lumen formation, or in developmental biology such as stripe patterns organization by pigment cells in zebra fish. Here models for cell adhesion or pattern formation may be stimulated by feedback from groups working in collective behavior of animals. Taking into account nonlocal cell-to-cell interactions may bring new concepts and insights into the tissue self-organisation and patterning.

Models closely related to those of swarming and chemotaxis cell movement that have been used for the activation/deactivation of actine-myosin polymers in cells to model their movement. Cytoskeleton dynamics are usually modelled by gradient flows of energies involving the cross linking of polymer fibers. The mathematical analysis and modelling of these phenomena has been recently tackled and the cross fertilization of these ideas with modern techniques in simulation/understanding of steepest descent settings and kinetic approaches will certainly lead to further advances.

C.- Dynamics of adaptation: Models for population dynamics are motivated, in part, by the desire to understand how species evolve. This fascinating research area aims to understand Evolution, which is one of the fundamental principles in nature. At the same time, it has promising applications, including a better understanding of the emergence of resistance to antibiotics, chemotherapy or insecticides.

To build a model of evolution that includes selection and mutations, we start with a population structured by a physiological characteristic $x \in \mathbb{R}^d$. We assume that this characteristic confers a fitness advantage, and directly influences the competitiveness of an individual in the population.

We refer to this characteristic as a phenotypic trait. The population density $n(t, x)$ provides the number of individuals with trait x at time t . The population density changes over time by a growth/death term selecting for the fittest trait and a mutation term, leading to the following equation

$$\partial_t n(t, x) = \overbrace{n(t, x)R(x, I(t))}^{\text{growth/death}} + \overbrace{\Delta n(t, x)}^{\text{mutations}},$$

with the total number of individuals defined as

$$I(t) := \int_{\mathbb{R}^d} n(t, x) dx.$$

The trait changes due to mutations are given by the Laplace operator. The growth/death term R models competition for a common resource, such as food or nutrients. The availability of the common resource depends on the total number $I(t)$ of individuals. In particular, the net growth rate $R(x, I)$ can become negative for I large enough. A typical example is $R(x, I(t)) = p(x) - d(x)I(t)$, where $p(x)$ models proliferation and $d(x)I(t)$ death/competition for a common resource. The question “what is the selected trait?” corresponds to the long-time behaviour of the equation. A Gaussian-like concentration effect arises which leads to the so-called constrained Hamilton-Jacobi equations

$$\begin{cases} \frac{\partial}{\partial t} u = R(x, \bar{\rho}(t)) + |\nabla u|^2, \\ \max_x u(x, t) = 0, \end{cases}$$

The selection-mutation models can be further generalized to account for more realistic description of the mutation process, such as in case of genetic mutations which take place during DNA replication. Such description is based on integral operators or infinite systems of ordinary differential equations, which lead to new challenges in mathematical analysis. New biological insights into the mutation process may also suggest a new generation of models defined on a metric space reflecting geometry of the space of mutations.

Another direction of further developments of selection-mutation models is related to coupled systems of equations accounting for a competition and cooperation among different populations. For systems, the classical approach to prove long-time behaviour is not feasible. Difficulty of the analysis is caused by the specific nonlinearities in the model, which do not allow for component-wise estimates. Entropy methods work only in some cases due to the lack of a rich class of entropies. We need, therefore, novel approaches to establish long-time behaviour for these coupled systems.

Final Outcome and Participants: The organizers were very positively surprised by the great thrive and enthusiasm that the conference produced in the international mathematical biology community based on PDE models. It has been several years that there were no conferences in the subject in Oberwolfach. This occasion, in the framework of the Year of Mathematical Biology 2018 organized by the EMS and the ESMTB, has served to structure a community of researchers with common goals and clear agendas in the use of mathematical modelling based on differential equations in the increasingly important area of Mathematical Biology. This is one of the most positive outcome of the meeting.

We had plenty of excellent talks given by senior and junior speakers with a high percentage of female and young participants. We had the participation of biologists and physicists interested in the mathematical modelling based on differential equations, this is essential for an interdisciplinary area to be able to overcome barriers and setting a common language of interaction. We made use of the Simons Program for Visiting Professors and the US Junior Oberwolfach fellows for Shigeru Kondo and Alexandria Volkening respectively.

The quality of the mathematical techniques used in the talks was very high and diverse using techniques of upscaling, mean-field limits, stochastic processes, kinetic theory, statistical mechanics, probability theory, numerical analysis apart from the obvious ones in differential equations such as bifurcation theory, long time asymptotics, pattern formation, travelling waves, concentrations, entropies, modelling, numerical simulations, and qualitative behavior tools.

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