Future Trends in Mathematical Biology: In vitro, in vivo, and in silico

Department of Applied Mathematics and Computer Science

Technical University of Denmark, Kongens Lyngby, Denmark

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Abstracts

Mathematical modelling of life science problems

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Abstract:

In this talk I will discuss several spatio-temporal mathematical models arising in the modeling of life science problems. The main feature of these realistic life science models is based on the fact that their governing equations are characterized by highly-nonlinear density-dependent reaction-diffusion-transport systems comprising both porous media and singular diffusion type degeneracy as well as ODE-PDE type coupling. These kind of equations arise in particular, in the modelling of antibiotic disinfection of biofilms, biofilm growth in porous media as well as mitochondria swelling scenarios in vitro, in vivo. Well-posedness, long-time dynamics of solutions in terms of global attractors, and asymptotics of their Kolmogorov entropy will be treated.

System and Control Technologies for an Artificial Pancreas

John Bagterp Jørgensen, Department of Applied Mathematics and Computer Science, Technical University of Denmark, DK-2800 Kgs. Lyngby, Denmark

Abstract:

In this presentation we present mathematical modeling, simulation, estimation and control technologies for an artificial pancreas for people with type 1 diabetes (T1D). In healthy people the pancreas release insulin and glucagon to tightly regulate the blood glucose concentration. Insulin decreases the blood glucose concentration, while glucagon increases the blood glucose concentration. People with diabetes have reduced insulin sensitivity (type 2 diabetes, T2D), lack the ability to produce insulin (type 1 diabetes, T1D), or both (progressed T2D). Typical the glucagon response in people with diabetes is also reduced or suppressed. 415 mio people in the world suffers from diabetes. 90-95% of the diabetes population has T2D, while the remaining 5-10% has T1D. People with diabetes must administer insulin to control their blood glucose level. People with T1D and at least progressed T2D can benefit from an automatic control system

called an artificial pancreas (AP) that automatically administers insulin and in some cases glucagon based on continuous measurement of a signal related to the blood glucose concentration and possibly other signals as well. We discuss how mathematical and numerical technologies related to systems and control have been very successful in realization of an artificial pancreas for people with T1D.

Machine learning approach for drug candidate optimization

Kristian Moss Bendtsen, Novo Nordisk, Måløv, Denmark.

Abstract: Not available

Description and Comparison of Protein 3d-Structures with emphasis on (bio)-topology

Peter Røgen, Department of Applied Mathematics and Computer Science, Technical University of Denmark, DK-2800 Kgs. Lyngby, Denmark

Abstract:

The talk shortly introduces protein structure and present arguments why methods for comparing protein structures are need and are needed to be further developed. Structure comparison is fundamental for our understanding of proteins, specifically for studying their sequence and structural evolution and for guiding our efforts to predict their structures from their sequences of amino acids.

All methods for structural alignment of protein structures are based on a notion of geometric difference between two aligned substructures. Coordinate based structural alignment methods optimize a score based on the distances between aligned residue pairs after superposition. In a morph given by the linear interpolation between two superimposed structures the aligned residues, traverse these distances. Current alignment scores do not take into account if this implied morph is easy to perform, will cause steric clashes, or more severally, if it will cause (bio)-topological changes of the compared structures. I present novel algorithms designed to distinguish such cases buy applying an analogy of Reidemeister moves for protein structures.

Another strategy to separate protein fold-classes is by using sufficiently power full geometric invariants to describe protein chains or sub-sets of these. Usually the number of protein structures dominates the calculation time of a descriptor-based method. Therefor such methods are significantly faster than pair alignment methods. If time permits, I will present some descriptor families and results from applying them to search for both global (folds), intermediate (linking and poking) and local geometry in proteins.

Fighting Fires Forth and Back in Time -- Modelling and First Indicative Results

Florian Rupp, Faculty of Mathematics, Technical University of Munich, Germany

Abstract:

Globally ascending temperature extremes combined with long lasting droughts increase probability and extend of large scale wild-land fires; just think of the almost yearly re-occurring disasters in Australia, California or Mediterranean countries like Spain or Greece. This raises the urgency for effective and efficient extinction strategies. Such strategies are in the focus of our work. Here, we start by establishing a coupled PDE-ODE model for the spread of flame fronts subject to anisotropic effects due to different vegetation zones and wind effects as well as the renewal of ignitable fuels. Next, based on these state equations an optimal extinction strategy is derived by means of the corresponding adjoint PDE-ODE equations and non-linear optimization with on-the-fly grid construction on the whole space-time domain. They yield statements on what optimal extinction strategies would look like if the fire fighters were omnipresent. As they run backward in time, they are typically difficult and expensive to solve; in particular in terms of memory. Our approach combines spacetree data structures with space-time grids, i.e. it resolves the whole computational domain throughout the whole observation time at once. We will conclude by providing indicative numerical results on the simulation of the PDE-ODE state equations and the corresponding optimal extinction controls. (Joint work with T. Weinzierl, Durham University.)

Closed-loop control applications in biomedicine: Perspectives for the treatment of epilepsy

Dimitri Boiroux, Department of Applied Mathematics and Computer Science, Technical University of Denmark, DK-2800 Kgs. Lyngby, Denmark

Abstract:

Epilepsy is a neurological disorder affecting around 40 million people worldwide, and is characterized by sudden occurrences of seizures. Currently, the main treatment is anti-epileptic drugs, but these drugs do not work for about a third of the patients. Neuromodulation, i.e. the alteration of neuronal activity through external stimuli, may be an alternative to drugs. The aim of this talk is to present the perspectives of closed-loop neuromodulation for epilepsy. I will provide a review of the models used for simulations of a single neuron and a network of interconnected neurons. I will also present the state of the art of treatments using open- and closed-loop control and discuss the possible future trends for the treatment of neurological disorders.

Substrate-depletion oscillators: Canards without attracting slow manifolds

Kristian Uldall Kristiansen, *Department of Applied Mathematics and Computer Science, Technical University of Denmark, DK-2800 Kgs. Lyngby, Denmark*

Abstract:

In this talk, I will present joint work with Peter Szmolyan on the substrate-depletion oscillators. This planar system is not slow-fast yet numerical computations show a canard-like explosion of limit cycles. Using geometric singular perturbation theory, with blowup as the main technique, we perturb away from a singular, piecewise smooth limit and uncover a new type of canard explosion occurring without the presence of an attracting slow manifold. Instead we find that this canard explosion is due to the intersection of another (nonunique) invariant manifold with a repelling slow manifold. The invariant manifold collapses in the singular limit to a weak direction of a stable node. We provide a complete rigorous description of the bifurcation diagram and identify en route further canard phenomena where relaxation oscillations can be created or destroyed in homoclinic bifurcations.

Numerical Simulation of growing and harvesting cells on electromechanical resonator sensors

Bolaji James Adesokan, Department of Applied Mathematics and Computer Science, Technical University of Denmark, DK-2800 Kgs. Lyngby, Denmark

Abstract:

Centrifugal microfluidics systems have several advantages compared to other conventional microfluidic platforms. One of the advantages of using centrifugal platforms is the elimination of an external pumping which means minimal load for liquid transport and the removal of bubbles, which effectively minimize dead volumes. In this talk, we shall model the centrifugal microfluidics platform for perfusion cell cultures by solving multiphase Navier-Stokes problem and investigate parameters such as flowrate, rotation speed and channel dimension such that low amount of shear stress are delivered to the cells on the microfluidic platform.

Excitation induced shape transformations in semiflexible biopolymer rings

Yuri B. Gaididei, Bogolyubov Institute for Theoretical Physics, Metrologichna str. 14 B, 03680 Kiev, Ukraine

Abstract:

Shape transformations in driven and damped molecular filaments are considered. Closed chains of weakly coupled molecular subunits under the action of spatially homogeneous time-periodic external field are studied. The coupling between the internal excitations and the bending degrees of freedom of the chain modifies the local bending rigidity of the chain. In the absence of driving the array takes a circular shape. When the energy pumped into the system exceeds some critical value the chain undergoes a non-equilibrium phase transition: the circular shape of the aggregate becomes unstable and the chain takes the shape of an ellipse or, in general, of a polygon. The excitation energy distribution becomes spatially nonuniform: it localizes in such places where the chain is more flat. The weak interaction of the chain with a flat surface restricts the dynamics to a flat manifold.

Traveling pulse solutions in the FitzHugh-Nagumo equations

Paul Carter, Department of Mathematics, University of Arizona, Tucson, Arizona, USA

Abstract:

In this talk I will describe methods for analyzing nonlinear waves in multiple timescale reaction-diffusion systems. I will focus primarily on the construction of single and double pulse solutions in the FitzHugh—Nagumo equations of mathematical physiology, which serve as a simplified model of nerve impulse propagation. The main techniques involve reduction to a traveling wave ordinary differential equation and exploiting the slow/fast timescale separation through the use of geometric singular perturbation theory and blow-up desingularization methods.

Interdisciplinary teaching of mathematical biology

Ken Haste Andersen, National Institute of Aquatic Resources, Technical University of Denmark, DK-2800 Kgs. Lyngby, Denmark

Abstract:

Teaching mathematical biology represents some unique challenges. First of all, the topic attracts students from very different backgrounds, from bachelors in: biology, environmental engineering, mathematics, and physics. Further, the models in mathematical biology are predominantly nonlinear, barring much standard analysis. Fortunately, the models are conceptually simple, making numerical analysis straight-forward. Here I report on the development of the course “mathematical biology” at DTU. By trial and error over the last 10 years we have develop a concept where students from the different backgrounds all obtain significant

learning, though on different fronts. The key is a focus on model assumptions and development and on communication of model results in the context of the biological reality that the models represent.

Optimality and games in behavioural ecology: Vertical strategies of marine predators and prey

Uffe Høgsbro Thygesen,

Abstract:

One axiom in biology is that of evolution, and "nothing in biology makes sense except in the light of evolution" (Dobzhansky). Here, I will present examples of how fitness maximization leads to predictions about behaviours of animals. The examples involve the vertical behaviour of foraging tuna, migrating eels, and the games played between oceanic predators and prey that lead to the diel vertical migration of the deep scattering layer. I will discuss the different mathematical formalisms that can be used to study these phenomena as well as the ecological motivations and implications of the studies.

Why math matters?

Johnny T. Ottesen, Roskilde University, Denmark

Abstract:

Math is fun, fun is living, and living is math. Mathematicians know this, but non-mathematicians do not, and even worse, most people do not believe in this claim and physicians are no exception! To fake-quote a former president, “Do not ask what medicine can do for math – ask what math can do for medicine.” Thus, we need a long list of good stories illustrating how important math is to biology and medicine, how mathematics may make the inaccessible accessible, and why math matters.

In my talk I will give some examples from my own research showing how mathematical skills may contribute to bio-medicine, in silico and in vivo, by achieving insights biologist and physicians typically would not obtain without mathematics. This will be illustrated by examples, e.g. by a controversy in blood pressure regulation methodology, a potential cure for type-1 diabetes, a diagnostic tool for depression as an endocrine disease, and the role of inflammation in development and treatment of the pre-leukemic disease, the JAK2-positive myeloproliferative neoplasm (MPN). The examples will demonstrate how mathematical skills and competences mostly related to solid mechanisms based mathematical modeling bridging the fields, advance analysis of dynamical systems and modern methods of parameter estimation can make a difference for understanding, diagnoses and treatments of diseases.

Modelling vector distribution and abundance using environmental predictors and machine learning techniques

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Abstract:

Vectors are organisms, usually arthropods, which can transmit pathogens from reservoir to host. Examples of vector-borne diseases are Bluetongue and Schmallenberg transmitted to livestock via biting midges, malaria or Zika transmitted to humans via mosquitoes, and Lyme disease and tick-borne encephalitis transmitted to humans via ticks. Many of these diseases have become more common in recent decades and present a real public health problem in many parts of Europe. Risk assessment, risk based surveillance, control, and prevention of these diseases require a better understanding of vector abundance as well as risk factors determining vector exposure. The spread of these diseases depends largely on vector distribution and abundance, which is highly influenced by the dynamics of their host species as well as the climate, the actual weather and the environment in which they live. There is a great need for analyses and models that can predict how vectors and their associated pathogens are distributed in time and space, how it varies from year to year and how this relates to high risk areas for human and animal exposure. Often, extensive data on host species can be difficult to obtain, whereas environmental, weather, climate and climate change data are more readily available. In the vector group, we combine field data, satellite imagery, and environmental data with machine learning techniques and mathematical transmission models to predict spatio-temporal distribution and abundance of vectors in Europe and to quantify disease transmission potentials for the various infections transmitted by these vectors. This also includes modelling emerging diseases that we have no prior experience with (ex. Schmallenberg, when it emerged in Germany in 2011). These techniques allow us to predict for larger areas without having to perform extensive sampling all over the region in question, and enable us to produce models and maps with high predictive value. The results from these models can help us pinpoint areas with high risk of vector exposure and thus potentially vector-borne diseases and target costly surveillance and preventive measures to these areas.

Time and cluster effects of antibiotics on resistance genes in the pig gut

K. Græsbøll, A.C. Birkegård, MiniResist project, 'Vet Forlig II' participants, A. Folkesson, N.Toft.
Department for Diagnostics and Scientific Advice, National Veterinary Institute, Technical University of Denmark, Copenhagen, Denmark

Abstract:

Two studies of Danish pigs have given us unique knowledge on the temporal dynamics and clustering of resistance genes in the pig gut. The first study sampled 1200 nursery pigs prior to treatment with tetracycline, two days after treatment, and finally when exiting the stable in 5 farms. The second study sampled slaughter pigs from 680 farms at the slaughterhouse, and antibiotic use for each farm was matched using the Danish VetStat database.

Results show that treatment with tetracycline increases the level of resistance genes. However, the baseline level of genes is not constant; even on the same farm the levels change significantly over time for many of the genes observed. The cross sectional study showed that many of the resistance genes cluster, and not just in clusters with similar resistance profile.

The implications of these findings are that the composition of resistance genes in a batch of pigs influence on the response to antibiotics. Furthermore, gene clusters may be used to give farms a risk score based on composition of genes. To exemplify this: blaTEM that code for penicillin resistance was in cluster with some of the tetracycline resistance genes, and while blaTEM is present in such low levels that it is often difficult to detect with a few samples from each farm, the tetracycline resistance genes are often highly expressed making them indicator bacteria for much more problematic genes.

Speed of Evolution in Spatially Extended Populations

Erik Andreas Martens, Department of Applied Mathematics and Computer Science, Technical University of Denmark, DK-2800 Kgs. Lyngby, Denmark

Abstract:

How fast do species adapt to a given environment? This is one of the most fundamental questions in evolutionary biology. Many theoretical models are restricted to the case of well-mixed populations. To characterize the speed of evolution in spatially extended populations, it is necessary to consider the wave-like spread of evolutionary novelties. The presence of such wave-like sweeps reduces the speed of evolution for two reasons. First, the waves are slower than the exponential spread of beneficial mutations known from well-mixed populations. Second, because these sweeps are slower, spatially extended populations are more prone to be in a state where multiple beneficial mutations sweep si- multaneously. This problem of clonal interference has been demonstrated in microbial experiments and has recently gained strong interest. We simulate the spread of mutations in spatial dimensions using computer simulations, where we include effects of recombination and long-range migration. We find that 1) the adaptation rate obeys robust power laws, which 2) are independent of the particular choice of selective fitness distributions (”universality”), 3) that spatial populations experience clonal interference over a broader range of parameters, and 4) that the effects of clonal interference can be mitigated by recombination and long-range migration. We therefore speculate that both processes are selectively favorable. Furthermore, if time allows, I will briefly outline possible applications of the results to cancer progression models of pre-malignant tissues (neoplasms).

[1] Martens, E. A., & Hallatschek, O. (2011). Interfering Waves of Adaptation Promote Spatial Mixing. Genetics, 189(November), 1045–1060. http://doi.org/10.1534/genetics.111.130112

[2] Martens, E. A., Kostadinov, R., Maley, C. C., & Hallatschek, O. (2011). Spatial structure increases the waiting time for cancer. New Journal of Physics, 13, 115014. http://doi.org/10.1088/1367-2630/13/11/115014