Schedule for Summer School, Middelfart August 3 - 12

	Mon	Tue	Wed	Thu	Fri	Sat	Mon	Tue
7:30	Breakfast							
09:00-09:45 10:00-10:45	Gluc/Insulin De Gaetano	Theory Øksendal	Theory Øksendal	Theory Jacobsen	Theory Jacobsen	Contributed talks	Neurons Sacerdote	Neurons Pakdaman
	Coffee Break							
11:15-12:00	Nanda	Picchini	Picchini	Picchini	Statistics		PK/PD De	Gaetano
12:00-14:00	Lunch							
14:00-14:45 15:00-15:45	Theory Øksendal	Statistics Ditlevsen	Statistics Sørensen	Statistics Sørensen	Neurons Sacerdote		Neurons Pakdaman	Statistics Ditlevsen
	Coffee Break							
16:15-17:30	Exercises Nanda	Exercises UP, TG		Exercises UP, TG	Exercises UP, TG		Contributed talks	Contributed talks
18:30	Dinner							

Theory - Martin Jacobsen and Bernt Øksendal

Statistics - Michael Sørensen and Susanne Ditlevsen

Applications - Andrea De Gaetano, Seema Nanda, Umberto Picchini, Laura Sacerdote and Kashayar Pakdaman

Exercises - Seema Nanda, Umberto Picchini and Therese Graversen

Contributed talks

Schedule for Contributed Talks, Middelfart August 9, 11 and 12

Saturday, August 9

7:30	Breakfast
	Chair: Andrea De Gaetano
09:00-09:20	Christina Surulescu: A nonparametric approach to cell dispersal
09:20-09:40	Yanthe Pearson: A renewal process approach to growth cone kinematics in axonogenesis
09:50-10:10	Edmund Watson: Deconvolution of C-peptide to estimate insulin secretion and clearance in Han Wistar rats
10:10-10:30	Adnan Khan: Modeling water dynamics around a solute using stochastic differential equations
	Coffee Break
	Chair: Seema Nanda
11:00-11:20	Vladimir Jacimovic: Stochastic equilibrium and stochastic bifurcations
11:20-11:40	Amit Apte: Data assimilation and model error
11:40-12:00	Lukasz Szpruch: Simulating with the chemical Langevin equation
12:00-14:00	Lunch

Monday, August 11

	Chair: Umberto Picchini
16:15-16:35	Svetlana Azarina: On stochastic inclusions with mean derivatives
16:35-16:55	A.V. Obukhovski: On stochastic differential inclusions of Langevin type of Riemann manifolds

Tuesday, August 12

	Chair: Laura Sacerdote
16:15-16:35	Tiina Manninen: Stochastic methods for modeling neuronal signal transduction
16:35-16:55	Jukka Intosalmi: Stochastic modeling of neuronal IP3 receptor function

Abstracts for contributed talks

Saturday, August 9

9:00 – 9:20 Christina Surulescu

A nonparametric approach to cell dispersal

We propose a nonparametric approach to describe the evolution of cell population densities upon starting from the characterization of individual behavior. Owing to its flexibility, this technique opens the possibility to analyse very effectively more realistic models for cellular dispersal.

9:20 – 9:40 Yanthe Pearson

A renewal process approach to growth cone kinematics in axonogenesis

Studies in vivo and in vitro have demonstrated that ethanol disrupts axonogenesis. Current studies use time lapse microscopy of live embryonic rat hippocampal neurons growing in cell culture to study the dynamics of axonal growth and its disruption by ethanol. Thus far we can analyze axonal trajectory data based on cells growing in a homogeneous medium. This data is noisy due to the difficulties in tracking the growth cone coordinates as well as image/spatial resolution, pixel dependence and instabilities in the experimental apparatus. We develop algorithms to filter out noise while maintaining the underlying dynamics of the axon growth process. We propose a model for growth cone kinematics during axonogenesis without a gradient field. We propose a general model that can be extended to accommodate steering effects, a consequence of adding gradients. In this work we present a simple renewal process with the aim of reproducing certain path behaviors of the growth cone. Future development will include angle variability and gradients effects.

9:50 – 10:10 Edmund Watson
Co-authors: M Chapell, SM Poucher, F Ducrozet, R Macdonald, A Yu

Deconvolution of C-peptide to estimate insulin secretion and clearance in Han Wistar rats

This presentation will demonstrate the application of deconvolution approaches performed on Han Wistar Rat data for both Intravenous Glucose Tolerance Test and hyperglycaemic clamp data in order to estimate the insulin clearance rate. Insulin clearance is known to be variable under different conditions. Endocrine output of the pancreas is delivered to the liver via the hepatic portal vein. Portal vein blood flow varies with physiological status so, since insulin is cleared in the liver, blood flow changes can affect insulin clearance. This means that measuring insulin peripherally leads to problems when modelling the glucose-insulin system. It is difficult to relate insulin secretion rate to glucose

concentration alone as the insulin observation varies with both glucose concentration and portal blood flow. Additionally, the quantity of insulin observed peripherally will be lower than the quantity of insulin actually present in the portal vein, leading to an inaccurate value for the insulin sensitivity. β-cells contain granules of pro-insulin, which cleaves into insulin and C-peptide in equal molar quantities when released. C-peptide is cleared via the kidneys, rather than through the liver. This means that measuring C-peptide can be used as a better peripheral biomarker of insulin secretion than insulin alone. The C-peptide model is a well-established 2-compartment model with first order elimination. An intravenous C-peptide pharmacokinetic study was performed in anaesthetised rats and used to obtain impulse response data for the system which allowed average parameters to be estimated. These parameters were then used to deconvolute the C-peptide secretion rate, which should be identical to that of the insulin. This in turn was used to relate the secretion rate to glucose concentration, as well as to determine insulin fractional appearance and insulin clearance. Two methods of deconvolution were used: WinNonLin and a Maximum Entropy approach using software developed previously at the University of Warwick. The WinNonLin method produced better results, however further work with the Maximum Entropy technique could lead to improvements in the resulting deconvolution. The Han Wistar rats studied were in different fasted states: free access to food, 4 hour fasted, 8 hour fasted or 16 hour fasted. The secretion rate of C-peptide was calculated for each animal and used to work out the insulin clearance rate and the fraction of insulin measured. It was discovered that fasting rats had a lower clearance rate of insulin and also a lower fraction of the secreted insulin was seen.

10:10 – 10:30 Adnan Khan

Modeling Water Dynamics Around a Solute using Stochastic Differential Equations

Protein molecules are the basic building blocks of biological organisms. The structure of proteins can be visualized using x-ray crystallography and MRI techniques. However their dynamic functioning is much harder to visualize experimentally as it is very difficult to make "protein movies" with the current technology. Because of these experimental limitations Molecular Dynamics (MD) simulations play a vital role in determining the functioning of a protein once its structure is known (bellisent2,bookschlick1). However the complexity of the dynamics severely limits the size and duration of real time over which such simulations can be done. Hence MD simulations, despite providing valuable information about the dynamics of proteins at the molecular level, are still quite limited in being able to simulate microbiological processes over biologically interesting times. A major obstacle in accelerating the MD simulations is the fact the solvent molecules surrounding the protein play a vital role in the dynamics and hence a large number of these solvent molecules must be included in the simulation As the actual dynamics of the water molecules is of secondary importance, one would like to represent the effects of water molecules on the protein dynamics without explicitly resolving the water dynamics. We consider stochastic models that capture the behavior of the solvent molecules without explicitly resolving their dynamics. As a first step towards modeling of solvent molecules around a protein we study a parameterization for the dynamics of water around a simple solute molecule.

We consider two models where we seek to parameterize the state of water near the solute surface through the drift and diffusion of the water molecules parallel and perpendicular to the solute surface. We compare our results to those obtained from MD data.

11:00 – 11:20 Vladimir Jacimovic

Stochastic Equilibrium and Stochastic Bifurcations

We state abstract mathematical theorem giving sufficient conditions for bifurcation and apply it to deterministic and stochastic dynamical systems. We use the theorem to investigate loss of stability and transition into (almost) periodic regime. Therefore, we can prove existence of (almost) periodical solutions for some values of parameters. In particular, we redefine Hopf bifurcation. This work is purely mathematical at the moment and we expect real applications in the future.

11:20 – 11:40 Amit Apte

Data assimilation and model error

Data assimilation is a powerful and versatile method for combining observational data of a system with its dynamical model to generate state estimates. I will briefly describe various data assimilation methods, such as Kalman filter and variational methods, used in weather prediction and in the study of atmospheric and ocean dynamics and also the Markov Chain Monte Carlo sampling methods we have developed. Then I will describe how "model error," the discrepancy between the actual dynamics of the system and our model for it, affects the data assimilation process. I will try to emphasize connections of this methodology with methods for parameter estimation and with observability and controllability.

11:40 – 12:00 Lukasz Szpruch

Simulating with the Chemical Langevin Equation

Markov jump processes can provide accurate models in many applications, notably chemical and biochemical kinetics. Stochastic differential equations offer a computationally efficient way to approximate these processes. It is known that the jump and diffusion models agree, in a well defined sense, in the thermodynamic limit. However, there seems to be little practical guidance available concerning the range of parameter values and the types of behavior for which the diffusion process captures features of the underlying jump process. We will look at some very simple reactions where analysis and detailed simulation is viable.

Monday, August 11

16:15 – 16:35 Svetlana Azarina

On stochastic inclusions with mean derivatives

Consider an Euclidean space $\mathbb{R}^n$ and a stochastic process $\xi(t)$ with values in $\mathbb{R}^n$ given on some probability space $(\Omega, \mathcal{F}, \mathsf{P})$. Denote by E_t^ξ the conditional expectation with respect to σ-algebra generated by preimages of the mapping $\xi(t) : \Omega \to \mathbb{R}^n$. Edward Nelson defined the mean forward derivative as follows:

$$D\xi(t) = \lim_{\triangle \to +0} E_t^\xi \Big(\frac{\xi(t+\triangle t) - \xi(t)}{\triangle t} \Big).$$

It gives information about the drift of stochastic process. Introduce the so called quadratic mean derivative by the formula

$$D_2\xi(t) = \lim_{\triangle \to +0} E_t^\xi \Big(\frac{(\xi(t+\triangle t) - \xi(t)) \otimes (\xi(t+\triangle t) - \xi(t))}{\triangle t} \Big).$$

It is shown that it gives information about the diffusion coefficient of $\xi(t)$.

We show that under some natural hypotheses $\xi(t)$ can be rocovered from its forward and quadratic mean derivatives.

Consider set-valued mappings $\mathbf{a}(\mathbf{t}, \mathbf{x})$ and $\boldsymbol{\alpha}(t, x)$ from $[0, T] \times \mathbb{R}^n$ to $\mathbb{R}^n$ and to the space of symmetric positive semidefined $n \times n$ matrices respectively. The system of the form

$$\begin{cases} D\xi(t) \in \mathbf{a}(\mathbf{t}, \mathbf{x}), \\ D_2\xi(t) \in \boldsymbol{\alpha}(t, x). \end{cases}$$

is called inclusion with mean derivatives. Such inclusions naturally arise in many applications. We prove some existence theorems for this inclusion for different righthand sides.

16:35 – 16:55 A.V. Obukhovskiĭ

On stochastic differential inclusion of Langevin type on Riemann manifolds

A new type of stochastic differential inclusions on Reimannian manifolds is investigated. It is a set-valued analogue of the well-known Langevin equation that describes motion under both deterministic and stochastic forces (e.g., the motion of physical brownian particle). The inclusions arise in systems with control, with discontinuous forces, etc., the use of Riemannian manifolds allows one to cover the case of non-linear configuration spaces.

The mathematically well-posed description of the above inclusions is done in integral form through integrals with Riemannian parallel translation constructed by means of Cartan's development. Several theorems on existence of weak and strong solutions are proved under various conditions on the set-valued forces.

Tuesday, August 12

16:15 – 16:35 Tiina Manninen

Stochastic methods for modeling neuronal signal transduction

Mathematical modeling and simulation of dynamic biochemical systems are receiving considerable attention due to the increasing availability of experimental knowledge and computing power. In addition to deterministic approaches, several stochastic approaches have been developed. The problem with most of the stochastic approaches, however, is the larger computational time compared to deterministic approaches, especially when large-scale systems are simulated. It is therefore necessary to study alternative ways to incorporate stochasticity and to seek approaches that reduce the computational time needed for simulations, yet preserve the characteristic behavior of the system in question. Computational framework based on the Itô stochastic differential equations is developed for neuronal signal transduction networks. Several neuronal signal transduction networks are used as test cases in method development.

16:35 – 16:55 Jukka Intosalmi

Stochastic modeling of neuronal IP3 receptor function

The time evolution of chemical systems is traditionally modeled using deterministic ordinary differential equations. Chemical reactions, however, are random in nature, and the deterministic approach is valid only for a restricted class of systems. Stochastic models take random fluctuations into account and are thus more realistic. In this work, we simulate an inositol trisphosphate receptor model using ordinary differential equations, stochastic differential equations, and the Gillespie stochastic simulation algorithm. The main goal of this work is to study the applicability of these methods for a system containing small numbers of molecules and ions. We concentrate especially on the SDE approach and investigate how well it models systems with small numbers of chemical species.