Schedule for Workshop, Middelfart August 13 - 15

Wednesday, August 13

7:30	Breakfast
	Chair: Susanne Ditlevsen, Uni Copenhagen
09:00- 09:45	Kashayar Pakdaman, ISC PIF Paris
09:45-10:30	Carlos Braumann, Universidade de Évora, Portugal: Stochastic differential equation models for population and individual growth and for harvesting in randomly varying environments
	Coffee Break
	Minisymposium: **Closed-loop estimation and control of blood glucose - from theory to practice**
	Chair and organizer: Michael Khoo, USC
11:00-11:05	Introductory Remarks by Session Chair
11:05-11:25	Cesar Palerm, Medtronic: Diabetes and technology: Managing a complex disease
11:25-12:00	Cesar Palerm, Medtronic: Diabetes and technology: Towards an “artificial pancrease”
12:00-14:00	Lunch
14:00-14:35	Robert Parker, Univ of Pittsburgh: Modeling for Diabetes Control - Beyond Insulin and Glucose
14:35-15:10	George D. Mitsis, National Technical University, Athens: Nonparametric (kernel-based) nonlinear modeling of glucose-insulin regulation
15:10-15:45	Michael Khoo, USC: Modeling the interactions between metabolic and cardiorespiratory control dysfunction
	Coffee Break
16:15-16:50	Jerry Batzel, Uni Graz: Parameter estimation issues in closed-loop modeling
18:30	Dinner

Thursday, August 14

7:30	Breakfast
	Chair: Franz Kappel, Uni Graz
09:00- 09:40	H.T. Banks, N.C. State Uni: Propagation of uncertainty in dynamical systems
09:40-10:20	Mathieu Kessler, Uni politecnica de Cartagena, Spain: An improved particle filter for Bayesian inference for diffusion processes
	Coffee Break
10:50-11:25	Umberto Picchini, Uni Copenhagen:
11:25-12:00	Adeline Samson
12:00-14:00	Lunch
	Chair: Michael Sørensen, Uni Copenhagen
14:00-14:35	Stefano Bonaccorsi, Uni Trento: Analysis of the stochastic FitzHugh-Nagumo system
14:35-15:10	Michelle Theiullen, Univ Paris 6: Random perturbation of a FitzHugh-Nagumo system
15:10-15:45	Henry Tuckwell: Some results for deterministic and stochastic nonlinear neurobiological systems
	Coffee Break
16:15-16:50	Marja-Leena Linne, Tampere Uni of Technology:
16:50-17:25	Helle Sørensen, Uni Copenhagen: SDE-analysis of growth and energy intake for pigs
18:30	Dinner

Friday, August 15

7:30	Breakfast
	Chair: Mathieu Kessler
09:00- 09:40	Petr Lansky, Academy of Sciences, Prague: Simple stochastic neuronal models and their parameters
09:40-10:20	Laura Sacerdote, Uni Torino: Parameter estimation problems for integrate and fire models
	Coffee Break
	Chair: Laura Sacerdote
10:50-11:25	Patrick Jahn: Statistical problems related to excitation threshold and reset value of membrane potentials
11:25-12:00	Renaud Jolivet, Uni Zurich: Predicting neuronal activity with simple models of the threshold type: Recent advances and benchmarks
12:00-14:00	Lunch
14:00-14:35	Antti Saarinen, Uni Tampere
14:35-15:10	Susanne Ditlevsen, Uni Copenhagen
15:10-15:20	Closing remarks
	Coffee Break

Abstracts for talks on Workshop

Wednesday, August 13

9:00 – 9:45 Kashayar Pakdaman, ISC PIF Paris

9:45 – 10:30 Carlos Braumann, Department of Mathematics and CIMA (Centro de Investigação em Matemática e Aplicações), Universidade de Évora, Portugal

Stochastic differential equation models for population and individual growth and for harvesting in randomly varying environments

The growth of a population living in a randomly varying environment (that affects birth and death rates) can be modelled by a stochastic differential equation (SDE) describing the dynamics of population size (number of individuals, biomass of a fishery,?). Stochastic differential equations can also be used to model the growth in size (weight, volume, length,?) from birth to maturity of individual animals or plants living in a randomly varying environment. Many SDE models have been proposed in the literature, some of them for both phenomena.

It is worth saying that the traditional regression models are appropriate to model observational errors but totally inadequate to model these phenomena. In fact, they do not keep memory of past sizes and a population (or individual) with a size substantially below model average has an equal probability of having a size above or below model average in the immediate future. This is clearly a non realistic property. SDE models, on the contrary, always consider the present situation and project it into the future using the dynamics of the growth process (and also how it is affected by the random environmental fluctuations).

Contrary to what is customary in the literature, instead of considered specific SDE models, we have obtained results on extinction and existence of a stationary density valid for a general class of SDE models (with mild assumptions mostly dictated by biological considerations). Such results are therefore model robust. Models for populations subjected to harvesting were considered as well. We have also studied the time to population extinction (for the population growth models) and the time to reach a maturity size (for the individual growth models). Here, we review those results.

Examples of application to real data (for specific models) will be shown, including the issues of parameter estimation and prediction.

11:05 – 11:25 Cesar Palerm, Medtronic

Diabetes and technology: Managing a complex disease

People with type 1 diabetes must frequently adjust their insulin dosing in order to maintain glucose levels as close to normal as possible. This represents a daily challenge, as many different forces influence glycemia, such as diet and meal composition, exercise and its intensity level, hormonal fluctuations, as well as stress, be it physical or psychological.

Technology has significantly improved the quality, and length, of life for those individuals with type 1 diabetes. Starting with the discovery and purification of insulin, on to home blood glucose meters, to designer insulins, subcutaneous infusion pumps, and more recently continuous glucose meters, each technology has had its impact. Nonetheless, these patients remain at increased risk for cardiovascular disease, increased morbidity and mortality when critically ill, and many other undesirable outcomes.

This talk will give an overview of type 1 diabetes and the challenges patients face in managing their glucose levels.

11:25 – 12:00 Cesar Palerm, Medtronic

Diabetes and technology: Towards an "artificial pancrease"

For people with type 1 diabetes the ultimate goal is complete normalization of blood glucose levels, as evidence suggests that even small deviations increase the risk of complications. While easy to say this is a formidable task, as patients need to frequently measure blood glucose levels, estimate meal carbohydrate content, and determine insulin dosing needs. Illness, exercise, stress and several other factors all affect glucose levels, making this a non-trivial problem.

Because of this, the holy grail in diabetes management has been the development of an artificial pancreatic β-cell. This is a fully automated closed-loop system which will use the signal from a continuous glucose sensor to adjust insulin infusion rates in real-time. Although significant progress has been made, many hurdles remain.

This talk will focus on the development of such a system at Medtronic Diabetes. Results from clinical trials will be presented, and an overview of the remaining challenges will be provided.

14:00 – 14:35 Robert Parker, University of Pittsburgh

Modeling for Diabetes Control - Beyond Insulin and Glucose

Since the discovery of insulin by Banting and Best, the primary foci of Diabetes diagnosis and treatment have been glucose and insulin. While this does encompass the minimum necessary set, as continued brain function requires adequate glucose supply, other endogenous and exogenous compounds and disturbances are of increasing importance. More than 20 years ago, glucagon, which is released from the alpha-cells of the pancreas, was incorporated into mathematical models of diabetic patients due to the upregulatory effect of glucagon on hepatic glucose release. This talk presents a view of metabolism that looks beyond the glucose-insulin relationship to encompass additional key variables, particularly fatty acids and exercise.

Fatty acids are the primary source of energy for the body, providing as much as 80% of the energy demand at rest. Interactions between fatty acids and glucose exist, as both are energy-providing substrates, and these interactions may impact both insulin demand and glucose control. In the case of a model-based control scheme, the choice to not account for fatty acid dynamics yields patient-model mismatch, which could impact the performance

of a closed-loop device. Exercise is commonly prescribed for glucose management in diabetic patients; the dynamics and intensity of exercise characterize this substrate sink that impacts insulin, glucose, and fatty acids. We model the response of glucose-insulin interactions based on physiological response to mild-to-moderate exercise (below the anaerobic threshold). This provides a complimentary disturbance to meal consumption, the most common disturbance explored in the literature, by challenging the patient model with a decrease in circulating substrate levels.

One approach to modeing is the so-called "Minimal" approach of Cobelli and co-authors. Their 3-state mathematical model of glucose-insulin interactions, which includes a remote insulin action compartment, is perhaps the most well-studied diabetes model in the literature. Following their philosophy, we synthesized an extended minimal model that includes fatty acid dynamics. The result is a moderately-sized ODE-based model that includes mixed meal consumption. Alternatively, one can model based on the physiology of the system. Detailed models of glucose, insulin, and fatty acids were constructed based on mass balances around physiological tissues of interest (brain, heart/lungs, gut, liver, kidney, muscle, adipose tissue). Subcompartments were included as required to capture tissue dynamics (based on the capillary/interstitial diffusion resistance), and interactions between circulating insulin, glucose, and fatty acids were included with saturating hyperbolic tangent functions. This model also captured available literature data, and it provides a biologically-motivated structure from which additional characterization and validation studies can be designed as well as a platform for closed-loop algorithm synthesis and testing.

14:35 – 15:10 George Mitsis, National Technical University, Athens

Nonparametric (kernel-based) nonlinear modeling of glucose-insulin regulation

The dynamic relationship between insulin and glucose has been examined extensively using compartmental models, which usually assume the form of nonlinear differential equations. These models are based on prior assumptions about the underlying physiological mechanisms and are often combined with specific experimental protocols, such as glucose tolerance tests, to extract parameters of clinical importance. However, it remains questionable whether they accurately describe the dynamic effects of insulin on glucose (and vice versa) under more general operating conditions. With the advancement of continuous glucose sensor and programmable insulin micropump technology, the application of more general, data-driven approaches in modeling insulin-glucose interactions has become possible. Therefore, in the present work we will initially compare compartmental (differential equation) and Volterra (data-driven/nonparametric) models of the dynamic effects of variable infusions of insulin on blood glucose concentration in humans analytically. With respect to compartmental models, we consider the widely accepted "minimal model" and an augmented form of it, which incorporates the effect of insulin secretion by the pancreas, in order to represent the actual closed-loop operating conditions of the system. With respect to data-driven models, we consider the class of Volterra-type models that are estimated from input-output data, which describes a very broad class of dynamic nonlinear systems. We demonstrate the equivalence between the two approaches analytically and derive re-

lations between the descriptors of the Volterra models, i.e., the Volterra kernels, in terms of the compartmental model parameters. We subsequently demonstrate the feasibility of obtaining accurate Volterra models from insulin-glucose utilizing both simulated data generated from the aforementioned compartmental models, as well as experimental data of frequently sampled spontaneous insulin and glucose variations in a fasting dog. The results corroborate the proposition that it may be preferable to obtain data-driven models in a realistic operating context, without resorting to the restrictive prior assumptions of model structure that are necessary for the compartmental (parametric) models. These prior assumptions may lead to results that are improperly constrained or biased by preconceived (and possibly erroneous) notions - a risk that is avoided when we let the data guide the inductive selection of the appropriate model within the general class of Volterra-type models.

14:35 – 15:10 Michael Khoo, USC

Modeling the interactions between metabolic and cardiorespiratory control dysfunction

Obesity and insulin resistance are highly prevalent in subjects diagnosed with sleep-disordered breathing (SDB). One factor common to obesity, SDB and insulin resistance is sympathetic nervous system overactivity. Although the causal links among these factors are not well understood, it is likely that the vicious cycle of interplay among these factors predisposes to the emergence of "metabolic syndrome", a convergence of obesity, hypertension, insulin resistance and dyslipidemia that is appearing in epidemic proportions in the United States and other countries.

In this talk, we will discuss the experimental and modeling studies currently underway in our laboratory, aimed at further elucidating the nature of the relationships among autonomic dysfunction, insulin resistance and severity of SDB in overweight subjects. To quantify autonomic dysfunction, we employ a closed-loop minimal model of cardiorespiratory control which has been tested extensively over a variety of conditions and subject groups over the past several years. In one of our ongoing studies, we estimate the parameters of the closed-loop model from human subjects under baseline conditions, and also under orthostatic stress and cold face stimulation. We subsequently determine the relationship of these model parameters to the parameters estimated from the Bergman minimal insulin-glucose model using data obtained from the frequently sampled intravenous glucose tolerance test performed on the same individuals. In a separate study, we are determining how autonomic function, as reflected in indices derived from heart rate variability and pulse transit time variability, in various sleep-wake stages is associated with measures of glucose metabolism based on the oral glucose tolerance test. Alongside these studies, we are also starting to explore the potential mechanisms for autonomic-metabolic interactions by developing a simulation model of metabolic control and linking it to a comprehensive model capable of simulating cardiorespiratory and sleep-wake control.

14:35 – 15:10 Jerry Batzel, University of Graz

Parameter estimation issues in closed-loop modeling

Physiological models can be of various complexity. Global models have been developed to summarize current knowledge, study interactions of various mechanisms, and consider causes of various clinical and health problems. Because of advances in computing power and numerical methods models of ever greater complexity can be studied. However, such models cannot usually be adapted to study the physiological features of a particular individual (or patient in the clinical setting) as the number of parameters to be estimated for the individual are too large given the available data. As new techniques for data measurement are developed the number of parameters that can be estimated should in principle increase but there is always a boundary where the modeler must decide how to simplify his or her model to match the level of system information contained in the available data. This leads necessarily to issues of model validation. An important conflict arises in modeling for clinical application because models need sufficient complexity to represent the system interactions directly or indirectly implicated in system dysfunction but in the clinical setting the ability to measure key states is either not possible or restricted by cost, time, and the desire for non- or minimally invasive testing procedures. This represents an important limiting factor for applications. The presentation will seek to familiarize the listener with current methods and computational techniques for validation of complex physiological models. We will examine physiological models and describe how to approach the parameter estimation process using several methods generally referred to as sensitivity analysis and exhibit how the information provided by these methods can aid in analyzing the problem of estimating key parameters. A special emphasis will be placed on the problem of only having access to data restricted to clinical sources. Applications will be drawn from modeling important control mechanisms of the human cardiovascular-respiratory system, glucose-insulin models, as well as anti-HIV treatment. Sensitivity analysis refers to the study of how variations in model parameters influences model output. This analysis can be used to provide insight into the parameter estimation process. Classical and generalized sensitivity analysis, as well as eigenvalue grouping, will be used to develop information on how the model-specific structure and limited data availability influence the parameter estimation process. Such information can improve the well-posedness as well as the numerical implementation of the estimation process. Such analysis can provide insight on the relevance of the data of various outputs for the estimation process and hence give ideas for improved experimental design to access the most important data. This is especially relevant for data collected in the clinical setting where cost and practicality are central concerns. For this talk, the constraint on the data is that it be collected only from non- or minimally invasive measurements in conjunction with specialized tests.

Thursday, August 14

9:00 – 9:40 H.T. Banks, Center for Research in Scientific Computation, N.C. State University, Raleigh, NC

Propagation of Uncertainty in Dynamical Systems

After discussing the shortcomings of a crypto-deterministic formulation, we compare two other approaches for inclusion of uncertainty/variability in modeling growth in size-structured population models. One entails imposing a probabilistic structure on growth rates in the population that leads to random differential equations while the other involves formulating growth as a stochastic Markov diffusion process, resulting in forward Kolmogorov or Fokker-Planck equations. We present a theoretical analysis that allows one to include comparable levels of uncertainty in the two distinct formulations in making comparisons of the two approaches. Computational aspects of the approaches are also discussed.

9:40 – 10:20 Mathieu Kessler, Departamento de Matemática Aplicada y Estadística, Universidad Politécnica de Cartagena, Spain
Co-authors: Diego Salmerón (Murcia) and Juan Antonio Cano (Murcia)

An improved particle filter for Bayesian inference for diffusion processes

Bayesian inference for partially observed diffusions models requires computational intensive methods which result specially difficult to implement when the process is multidimensional and observed with measurement error and/or when some coordinates are unobserved. In this work, we choose the particle filter approach to propose an efficient method to obtain Monte-Carlo realizations of the posterior distribution of the parameters of interest. We suggest an improvement of the standard particle filter which is specifically adapted to diffusions context and reduces the impact of the well known problem of particles impoverishment.

10:50 – 11:25 Umberto Picchini, University of Copenhagen, Denmark

Fast estimation of a time-inhomogeneous stochastic differential model of glucose dynamics

Stochastic differential equations (SDEs) are assuming an important role in the definition of dynamical models allowing for explanation of internal variability (stochastic noise). SDE models are well-established in many fields, such as investment finance, population dynamics, polymer dynamics, hydrology and neuronal models. The metabolism of glucose and insulin has not yet received much attention from SDE modellers, except from a few recent contributions, because of methodological and implementation difficulties in estimating

SDE parameters. Here we propose a new SDE model for the dynamics of glycemia during a euglycemic hyperinsulinemic clamp experiment, introducing system noise in tissue glucose uptake. We estimate the new model parameters using a computationally efficient approximate maximum likelihood approach, where a closed-form Hermite expansion of the transition densities of the solution process is computed as proposed in [1]. By comparison with other currently used methods, the estimation process is very fast, obviating the need to use clusters or expensive mainframes to obtain the quick answers needed for everyday iterative modeling. Furthermore, it can introduce the demonstrably essential concept of system noise in this branch of physiological modeling.

[1] A.V. Egorov, H. Li and Y. Xu (2003). Maximum likelihood estimation of time-inhomogeneous diffusions. Journal of Econometrics 114, 107 – 139.

11:25 – 12:00 Adeline Samson

14:00 – 14:35 Stefano Bonaccorsi, University of Trento, Italy

Analysis of the stochastic FitzHugh-Nagumo system

In this talk we aim to study a system of stochastic differential equations with dissipative nonlinearity which arise in certain neurobiology models. Besides proving existence, uniqueness and continuous dependence on the initial datum, we shall be mainly concerned with the asymptotic behaviour of the solution. We prove the existence of an invariant ergodic measure ν associated with the transition semigroup P_t; further, we identify its infinitesimal generator in the space $L^2(H;\nu)$.

14:35 – 15:10 Michele Thieullen, Labo. de Probabilites et Modeles Aleatoires, Univ. Paris 6, France
Co-author: Catherine Doss (Labo. J.-L. Lions, Univ. Paris 6, France)

Random perturbation of a FitzHugh-Nagumo system

Deterministic FitzHugh-Nagumo system is a simple model for neuronal activity exhibiting possible periodic behaviour. We are interested in periodic behaviour and equilibrium points of the stochastic FitzHugh-Nagumo system obtained by submitting the neuron to a white noise current.The main tool is the theory of large deviations developped by Freidlin and Wentzell.

15:10 – 15:45 Henry Tuckwell

Some results for deterministic and stochastic nonlinear neurobiological systems

We consider briefly several nonlinear systems which are used to describe the properties of neurons and neural populations. For the latter a multi-component reaction-diffusion model is used to portray the propagation of waves of spreading cortical depression. Such waves spread across gray matter at speeds of a few mm/minute and are strongly implicated in migraine and other pathogies such as stroke and spinal injury. Phenomena such as spiral and reverberating waves are analyzed. For single neurons, we consider firstly the spatial Fitzhugh-Nagumo model driven by two-parameter white noise.Simulation results give excellent agreement with analytical ones when the noise is small. The success or failure of the propagation of action potentials is examined for various spatial distributions of noise. Finally, the noisy Hodgkin-Huxley model is shown to exhibit silencing and inverse stochastic resonance when repetitive firing is subjected to noise.

16:15 – 16:50 Marja-Leena Linne, Tampere University of Technology, Finland

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16:50 – 17:25 Helle Sørensen, University of Copenhagen, Denmark

SDE-analysis of growth and energy intake for pigs

Data on growth and energy intake for pigs is analyzed simultaneously with a new SDE-model. The dataset is unusual for animal nutrition science because the pigs are followed from birth until maturity and because of the simultaneous measurements of weight and energy intake. Simple biological assumptions on maintenance and allometry are used to define the SDE-model, hence the model has biologically interpretable parameters. Estimation is performed with the extended Kalman filter (using the program CTSM). The analysis leads to a discussion of various topics: model validation and transformation; parametrization; incorporation of correlation between the two diffusion terms; distinction between diffusion noise and measurement noise; model validation using a test data set.

Friday, August 15

9:00 – 9:40 Petr Lansky, Academy of Sciences, Prague, Czech Republic

Simple stochastic neuronal models and their parameters

Many stochastic models of neurons have been proposed and deeply studied in the last forty years. They range from simple statistical descriptors to sophisticated and realistic biophysical models. On their basis, properties of neuronal information transfer are deduced. The present talk aims to review the simple models. The difference between their parameters and the signal, which formally may also appear as a parameter, is stressed.

9:40 – 10:20 Laura Sacerdote, University of Torino, Italy

Parameter estimation problems for integrate and fire models

Integrate and fire models benefit of a large popularity due to their mathematical manageability and to their ability to qualitatively reproduce experimentally observed features. A first step to check also quantitatively this ability requests the estimation of the model parameters from experimental data.

Two types of data are involved in the model description: the first group contains parameters related with intrinsic properties of the cells and we assume that can be deduced from some direct measurements due to their direct biological interpretation. Parameters belonging to the second group are determined by the properties of the input signal to the cell and request specific methods of estimation.

We focus here on this second group of parameters and we illustrate the estimation problem in two different experimental frames, i.e. when one observes the membrane potential evolution at regular time intervals or when the sample is constituted by Interspikes Intervals (ISIs). In the first case we outline the difficulties in the estimation procedure for the input parameters related with the presence of the firing threshold that determines a systematic bias on the estimated parameter while in the second we illustrate difficulties that prevent from using likelihood method and we discuss some properties of moment estimators.

10:50 – 11:25 Patrick Jahn, University of Mainz, Germany

Statistical Problems Related to Excitation Threshold and Reset Value of Membrane Potentials

In real data it is not obvious at all to determine the exact value of an excitation threshold or a reset value for the neuron under observation. Assume the membrane potential between spikes follows a known SDE. Assume further that we dispose of observation of the spike times and/or of certain level crossing times between the spikes. Minimum Dis-

tance Estimation, Maximum Likelihood Estimation and LAN theory is used to find a most probable location for an excitation threshold and a reset value.

11:25 – 12:00 Renaud Jolivet, University of Zurich

Predicting neuronal activity with simple models of the threshold type: Recent advances and benchmarks

As large-scale, detailed network modeling projects are flourishing in the field of computational neuroscience, it is more and more important to design single neuron models that not only capture qualitative features of real neurons but are quantitatively accurate in silico representations of those. Recent years have seen substantial effort being put in the development of algorithms for the systematic evaluation and optimization of neuron models with respect to electrophysiological data. I will briefly review these recent developments and present how two simple deterministic neuron models of the integrate-and-fire type - namely the Spike Response Model and the adaptive Exponential Integrate-and-Fire model - can be systematically constructed from intracellular recordings. I will show that despite being very simple, these models reach a significant level of correct predictions. I will then discuss a stochastic extension of the former as well as an extension towards input scenarios more realistic than current injection. This approach allows one to determine the minimal level of description needed to account for the large variety of observed neuronal behaviors. Finally, I will present recent efforts at setting benchmarks for neuron models under the form of a yearly challenge similar to the ones which have been present in the machine learning community for some time. I will give a brief account of the first two challenges which took place in 2007 and 2008 and discuss future directions.

14:00 – 14:35 Antti Saarinen, Tampere University of Technology, Finland

In recent years the study of stochastic phenomena has gained more interest in many fields of research. Also in the fields of neuroscience and computational neuroscience, stochastic phenomena shaping the dynamic behavior of a neuron are considered more when modeling the electroresponsiveness of neurons. In this talk, we introduce an SDE model of a single cerebellar granule cell where the description of the ion channel kinetics incorporate the natural stochasticity observed in the dynamic behavior of these channels. We present also ways of incorporating stochasticity to the well-known Hodgkin-Huxley (HH) model of action potential generation in a squid axon and a methodology for fitting these stochastic models to irregular current-clamp data. This kind of fitting and the use of irregular data have been challenging with the existing deterministic models and deterministic parameter estimation techniques. We show that we are able to obtain accurate Maximum Likelihood (ML) estimates for the selected model parameters based on the learning data. In conclusion, the use of SDEs in neuronal modeling enables more accurate reproduction of the irregular electrophysiological activity of a neuron. The presented estimation method offers also an attractive way to perform parameter estimation in situations where it has not been possible with the deterministic models and methods.

14:35 – 15:10 Susanne Ditlevsen, University of Copenhagen, Denmark

Parameters of stochastic diffusion processes estimated from observations of first hitting-times

The first hitting-time to a constant threshold of a diffusion process has been in focus for stochastic modeling of problems where a hidden random process only shows when it reaches a certain level that triggers some observable event. Applications come from various fields, e.g. neuronal modeling, survival analysis and mathematical finance. In many applications where renewal point data are available, models of first hitting-times of underlying diffusion processes arise. Despite of the seemingly simplicity of the model, the problem of how to estimate parameters of the underlying stochastic process has resisted its solution. The few attempts have either been unreliable, difficult to implement or only valid in subsets of the relevant parameter space. In this talk a newly developed estimation method that overcomes these difficulties is presented, it is computationally easy and fast to implement, and also works surprisingly well on small data sets. It is a direct application of the Fortet integral equation. The method is illustrated on simulated data and applied to recordings of neuronal activity.