Cross-Validation of a Glucose-Insulin-Glucagon Pharmacodynamics Model for Simulation using Data from Patients with Type 1 Diabetes

Background:
Currently, no consensus exists on a model describing endogenous glucose production (EGP) as a function of glucagon concentrations. Reliable simulations to determine the glucagon dose preventing or treating hypoglycemia or to tune a dual-hormone artificial pancreas control algorithm need a validated glucoregulatory model including the effect of glucagon.

Methods:
Eight type 1 diabetes (T1D) patients each received a subcutaneous (SC) bolus of insulin on four study days to induce mild hypoglycemia followed by a SC bolus of saline or 100, 200, or 300 µg of glucagon. Blood samples were analyzed for concentrations of glucagon, insulin, and glucose. We fitted pharmacokinetic (PK) models to insulin and glucagon data using maximum likelihood and maximum a posteriori estimation methods. Similarly, we fitted a pharmacodynamic (PD) model to glucose data. The PD model included multiplicative effects of insulin and glucagon on EGP. Bias and precision of PD model test fits were assessed by mean predictive error (MPE) and mean absolute predictive error (MAPE).

Results:
Assuming constant variables in a subject across nonoutlier visits and using thresholds of ±15% MPE and 20% MAPE, we accepted at least one and at most three PD model test fits in each of the seven subjects. Thus, we successfully validated the PD model by leave-one-out cross-validation in seven out of eight T1D patients.

Conclusions:
The PD model accurately simulates glucose excursions based on plasma insulin and glucagon concentrations. The reported PK/PD model including equations and fitted parameters allows for in silico experiments that may help improve diabetes treatment involving glucagon for prevention of hypoglycemia.
Leveraging stochastic differential equations for probabilistic forecasting of wind power using a dynamic power curve

Short-term (hours to days) probabilistic forecasts of wind power generation provide useful information about the associated uncertainty of these forecasts. Standard probabilistic forecasts are usually issued on a per-horizon-basis, meaning that they lack information about the development of the uncertainty over time or the inter-temporal correlation of forecast errors for different horizons. This information is very important for forecast end-users optimizing time-dependent variables or dealing with multi-period decision-making problems, such as the management and operation of power systems with a high penetration of renewable generation. This paper provides input to these problems by proposing a model based on stochastic differential equations that allows generating predictive densities as well as scenarios for wind power. We build upon a probabilistic model for wind speed and introduce a dynamic power curve. The model thus decomposes the dynamics of wind power prediction errors into wind speed forecast errors and errors related to the conversion from wind speed to wind power. We test the proposed model on an out-of-sample period of 1 year for a wind farm with a rated capacity of 21 MW. The model outperforms simple as well as advanced benchmarks on horizons ranging from 1 to 24 h.

General information

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Simulating clinical studies of the glucoregulatory system: *in vivo meets in silico*

In this report we use a validated model of the glucoregulatory system including effects of insulin and glucagon for simulation studies in seven type 1 diabetes patients. Using simulations, we replicate the results from a clinical study investigating the effect of micro-doses of glucagon on glucose metabolism at varying ambient insulin levels. The report compares *in vivo* and *in silico* results head-to-head, and discusses similarities and differences. We design and simulate simple studies to emphasize the implications of some glucoregulatory dynamics which are ignored in most previous clinical studies: the effect of discontinuing insulin and glucose infusions prior to glucagon administration, the delayed effect of insulin, timing of data sampling, and carryover effects from multiple subcutaneous doses of glucagon. We also use simulations to discuss two hypotheses of how insulin and glucagon might interact in influencing the glucose response. Following the simulations we propose a study design that potentially could explore if the hypotheses are true or false.

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Organisations: Department of Applied Mathematics and Computer Science, Scientific Computing, Dynamical Systems, Copenhagen University Hospital, Zealand Pharma A/S, University of Copenhagen
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**Validation of a Simulation Model Describing the Glucose-Insulin-Glucagon Pharmacodynamics in Patients with Type 1 Diabetes**

Currently, no consensus exists on a model describing endogenous glucose production (EGP) as a function of glucagon concentrations. Reliable simulations to determine the glucagon dose preventing or treating hypoglycemia or to tune a dual-hormone artificial pancreas control algorithm need a validated glucoregulatory model including the effect of glucagon.

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Hidden Markov Models for indirect classification of occupant behaviour

Even for similar residential buildings, a huge variability in the energy consumption can be observed. This variability is mainly due to the different behaviours of the occupants and this impacts the thermal (temperature setting, window opening, etc.) as well as the electrical (appliances, TV, computer, etc.) consumption.

It is very seldom to find direct observations of occupant presence and behaviour in residential buildings. However, given the increasing use of smart metering, the opportunity and potential for indirect observation and classification of occupants’ behaviour is possible. This paper focuses on the use of Hidden Markov Models (HMMs) to create methods for indirect observations and characterisation of occupant behaviour.

By applying homogeneous HMMs on the electricity consumption of fourteen apartments, three states describing the data were found suitable. The most likely sequence of states was determined (global decoding). From reconstruction of the states, dependencies like ambient air temperature were investigated. Combined with an occupant survey, this was used to classify/interpret the states as (1) absent or asleep, (2) home, medium consumption and (3) home, high consumption. From the global decoding, the average probability profiles with respect to time of day were investigated, and four distinct patterns of occupant behaviour were observed. Based on the initial results of the homogeneous HMMs and with the observed dependencies, time dependent HMMs (inhomogeneous HMMs) were developed, which improved forecasting. For both the homogeneous and inhomogeneous HMMs, indications of common parameters were observed, which suggests further development of the HMMs as population models.

General information
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Modeling and Prediction Using Stochastic Differential Equations
Pharmacokinetic/pharmacodynamic (PK/PD) modeling for a single subject is most often performed using nonlinear models based on deterministic ordinary differential equations (ODEs), and the variation between subjects in a population of subjects is described using a population (mixed effects) setup that describes the variation between subjects. The ODE
setup implies that the variation for a single subject is described by a single parameter (or vector), namely the variance (covariance) of the residuals. Furthermore the prediction of the states is given as the solution to the ODEs and hence assumed deterministic and can predict the future perfectly. A more realistic approach would be to allow for randomness in the model due to e.g., the model be too simple or errors in input. We describe a modeling and prediction setup which better reflects reality and suggests stochastic differential equations (SDEs) for modeling and forecasting. It is argued that this gives models and predictions which better reflect reality. The SDE approach also offers a more adequate framework for modeling and a number of efficient tools for model building. A software package (CTSM-R) for SDE-based modeling is briefly described.

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**Modelling of glucose-insulin-glucagon pharmacodynamics in man**

The purpose is to build a simulation model of the glucoregulatory system in man. We estimate individual human parameters of a physiological glucose-insulin-glucagon model. We report posterior probability distributions and correlations of model parameters.

**General information**

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Main Research Area: Technical/natural sciences

**Model of the Glucose-Insulin-Glucagon Dynamics after Subcutaneous Administration of a Glucagon Rescue Bolus in Healthy Humans**

In healthy individuals, insulin and glucagon work in a complex fashion to maintain blood glucose levels within a narrow range. This regulation is distorted in patients with diabetes. The hepatic glucose response due to an elevated glucagon level depends on the current insulin concentration and thus endogenous glucose production (EGP) can not be modelled without knowledge of the concentration of both hormones in plasma. Furthermore, literature suggests an upper limit to EGP irrespective of glucagon levels. We build a simulation model of the glucose-insulin-glucagon dynamics in man including saturation effect of EGP.

Ten healthy subjects received a 1 mg subcutaneous (SC) glucagon bolus (GlucaGen®). Plasma samples were collected until 300 minutes post dose and analyzed for glucagon, insulin, and glucose concentrations. All observations were used to
fit a physiological model of the glucose-insulin-glucagon dynamics using the Hovorka model with a novel multiplicative
description of the effects of insulin and of glucagon on EGP.

Bayesian estimation by Maximum a Posteriori using prior knowledge reported in literature was used to estimate the model
parameters for each subject. Profile likelihood plots were used to investigate parameter identifiability. Unidentifiable
parameters were fixed at their prior mean values.

The new model enables simulations of the glucose-insulin-glucagon dynamics in humans at both low and high glucagon
concentrations (180-8000 pg/mL) and physiologic insulin concentrations
(1.2-81.9 mIU/L). The model can be used for simulation of glucagon bolus strategies for treatment of hypoglycemia and for
in silico simulation of dual-hormone artificial pancreas algorithms.

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Model of the Glucose-Insulin-Glucagon Dynamics after Subcutaneous Administration of a Glucagon Rescue Bolus In
Healthy Humans
In healthy individuals, insulin and glucagon work in a complex fashion to maintain blood glucose levels within a narrow
range. This regulation is distorted in patients with diabetes. The hepatic
glucose response due to an elevated glucagon level depends on the current insulin concentration and thus endogenous
glucose production (EGP) can not be modelled without knowledge of the
concentration of both hormones in plasma. Furthermore, literature suggests an upper limit to EGP irrespective of glucagon
levels. We build a simulation model of the glucose-insulin-glucagon
dynamics in man including saturation effect of EGP.

Ten healthy subjects received a 1 mg subcutaneous (SC) glucagon bolus (GlucaGen®). Plasma samples were collected
until 300 minutes post dose and analyzed for glucagon, insulin, and glucose concentrations. All observations were used to
fit a physiological model of the glucose-insulin-glucagon dynamics using the Hovorka model with a novel multiplicative
description of the effects of insulin and of glucagon on EGP.

Bayesian estimation by Maximum a Posteriori using prior knowledge reported in literature was used to estimate the model
parameters for each subject. Profile likelihood plots were used to investigate parameter identifiability. Unidentifiable
parameters were fixed at their prior mean values.

The new model enables simulations of the glucose-insulin-glucagon dynamics in humans at both low and high glucagon
concentrations (180-8000 pg/mL) and physiologic insulin concentrations
(1.2-81.9 mIU/L). The model can be used for simulation of glucagon bolus strategies for treatment of hypoglycemia and for
in silico simulation of dual-hormone artificial pancreas algorithms.

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United States.
PK/PD modelling of glucose-insulin-glucagon dynamics in healthy dogs after a subcutaneous bolus administration of native glucagon or a novel glucagon analogue

Objective We aim to develop a simulation model of the complex glucose-insulin-glucagon dynamics based on physiology and data. Furthermore, we compare pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of marketed reconstituted glucagon with a stable liquid glucagon analogue invented by Zealand Pharma A/S.

Research Design and Methods We expanded a physiological model of endogenous glucose production with multiplicative effects of insulin and glucagon and combined it with the Hovorka glucoregulatory model. We used a Bayesian framework to perform multidimensional MAP estimation of model parameters given priors reported in the literature. We used profile likelihood analysis to investigate parameter identifiability and reduce the number of model variables. We estimated model parameters in pre-clinical data from one cross-over study with a total of 20 experiments in five dogs. The dogs received two subcutaneous (SC) bolus injections of low and high doses of glucagon and ZP-GA-1 (20 and 120 nmol/kg).

Results We report posterior probability distributions and correlations for all identifiable model parameters. Based on visual inspection and residual analysis, the PD model described data satisfactorily for both glucagon and the analogue. Parameter estimates of the PD model were not significantly different between the two compounds.

Conclusions The new PK/PD model enables simulations of the glucose-insulin-glucagon dynamics after a SC bolus of glucagon or glucagon analogue. The novel glucagon analogue by Zealand Pharma A/S shows PK and PD characteristics similar to marketed glucagon.

Probabilistic Approaches to Energy Systems

Energy generation from wind and sun is increasing rapidly in many parts of the world. This presents new challenges on how to integrate this uncertain, intermittent and non-dispatchable energy source. This thesis deals with forecasting and decision making in energy systems with a large proportion of renewable energy generation. Particularly we focus on producing forecasting models that can predict renewable energy generation, single user demand, and provide advanced forecast products that are needed for an efficient integration of renewable energy into the power generation mix. Such forecasts can be useful on all levels of the energy systems, ranging from the highest level, where the transmission system operator is concerned with minimizing system failures and is aided by wind power forecasts, to the end user of energy where power price forecasts are useful for users with flexible power demand.

The main contributions of this thesis lie in the realm of using gray box models to produce forecasts for energy systems.
Gray box models can be defined as a crossover between physical models (or white box models), that base their model on a physical understanding of the system at hand, and data driven models (or black box models) that focus on accurately describing the data without considering physical limitations of the system. Integrating these physical structures into a data driven approach allows for producing better forecasts with more accurate predictions. In this thesis we have developed and applied methodologies for gray box modeling to produce forecasts for vehicle driving patterns, solar irradiance, wind speeds, wind power, and solar power. The model for driving patterns has subsequently been used as input into an optimization algorithm for charging a single electric vehicle. In a subsequent study the behavior of a fleet of electric vehicles has been studied.

In the thesis we go through various examples of forecasts products and their applications. We emphasize that forecasting cannot stand alone and should be complimented by optimization and decision making tools for an efficient integration of renewable energy. Thus forecast products should be developed in unison with the decision making tool as they are two sides of the same overall challenge.

Probabilistic Forecasts of Wind Power Generation by Stochastic Differential Equation Models
The increasing penetration of wind power has resulted in larger shares of volatile sources of supply in power systems worldwide. In order to operate such systems efficiently, methods for reliable probabilistic forecasts of future wind power production are essential. It is well known that the conditional density of wind power production is highly dependent on the level of predicted wind power and prediction horizon. This paper describes a new approach for wind power forecasting based on logistic-type stochastic differential equations (SDEs). The SDE formulation allows us to calculate both state-dependent conditional uncertainties as well as correlation structures. Model estimation is performed by maximizing the likelihood of a multidimensional random vector while accounting for the correlation structure defined by the SDE formulation. We use non-parametric modelling to explore conditional correlation structures, and skewness of the predictive distributions as a function of explanatory variables.
Short-term Probabilistic Forecasting of Wind Speed Using Stochastic Differential Equations

It is widely accepted today that probabilistic forecasts of wind power production constitute valuable information for both wind power producers and power system operators to economically exploit this form of renewable energy, while mitigating the potential adverse effects related to its variable and uncertain nature. In this paper, we propose a modeling framework for wind speed that is based on stochastic differential equations. We show that stochastic differential equations allow us to naturally capture the time dependence structure of wind speed prediction errors (from 1 up to 24 hours ahead) and, most importantly, to derive point and quantile forecasts, predictive distributions, and time-path trajectories (also referred to as scenarios or ensemble forecasts), all by one single stochastic differential equation model characterized by a few parameters.

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Organisations: Department of Applied Mathematics and Computer Science, Dynamical Systems, Centre for IT-Intelligent Energy Systems in Cities
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Main Research Area: Technical/natural sciences
Statistical modelling using CTSM-R

The ability to forecast the future of a system is more important than ever. Countless of applications require precise forecasting models to make smarter decisions in real time. Practitioners need software tools allowing an easy, quick and accurate implementation of their ideas. This thesis shows our software CTSM-R, which means: Continuous Time Stochastic Modelling in R. CTSMR provides the ability to implement statistical models and estimate unknown parameters. Thus allows modellers to model and understand the physical system of interest.

The main contributions of this thesis are the development of a generic software tool for grey box modelling. Grey box models use knowledge about the physical system of interest in combination with data to create models that accurately
explain the data. The thesis will demonstrate how to implement linear and nonlinear models. These two model classes then serve as a building block for population models and spatiotemporal models. Population models known from the pharmaceutical industry where nonlinear population modelling has been long used in the industry to analyse trial data from many subjects. Spatiotemporal modelling extends CTSM-R to model complex correlations in space and time. This thesis demonstrates how to use spatio-temporal models for solar power forecasting.

CTSM-R is built in R using fast computations in Fortran when needed. CTSMR provides a simple interface which is quickly learned through our examples on our website http://ctsm.info.

Finally, this thesis demonstrates the importance of identifiability. A model is just a representation of the physical reality and such a representation is not guaranteed to be unique. Identifiability and the use of profile likelihood figures should be a standard tool of any modeller to verify the uniqueness of the solution.
Probabilistic Forecasts of Solar Irradiance by Stochastic Differential Equations

Probabilistic forecasts of renewable energy production provide users with valuable information about the uncertainty associated with the expected generation. Current state-of-the-art forecasts for solar irradiance have focused on producing reliable point forecasts. The additional information included in probabilistic forecasts may be paramount for decision makers to efficiently make use of this uncertain and variable generation. In this paper, a stochastic differential equation framework for modeling the uncertainty associated with the solar irradiance point forecast is proposed. This modeling approach allows for characterizing both the interdependence structure of prediction errors of short-term solar irradiance and their predictive distribution. Three different stochastic differential equation models are first fitted to a training data set and subsequently evaluated on a one-year test set. The final model proposed is defined on a bounded and time-varying state space with zero probability almost surely of events outside this space.

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Authors: Iversen, J. E. B. (Intern), Morales González, J. M. (Intern), Møller, J. K. (Intern), Madsen, H. (Intern)
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Inhomogeneous Markov Models for Describing Driving Patterns

It has been predicted that electric vehicles will play a crucial role in incorporating a large renewable component in the energy sector. If electric vehicles are integrated in a naive way, they may exacerbate issues related to peak demand and transmission capacity limits while not reducing polluting emissions.

Optimizing the charging of electric vehicles is paramount for their successful integration. This paper presents a model to describe the driving patterns of electric vehicles, in order to provide primary input information to any mathematical programming model for optimal charging. Specifically, an inhomogeneous Markov model that captures the diurnal variation in the use of a vehicle is presented. The model is dened by the time-varying probabilities of starting and ending a trip and is justified due to the uncertainty associated with the use of the vehicle. The model is tied to data collected from the actual utilization of a vehicle. Inhomogeneous Markov models imply a large number of parameters. The number of parameters in the proposed model is reduced using B-splines.
A formal statistical approach to representing uncertainty in rainfall-runoff modelling with focus on residual analysis and probabilistic output evaluation - Distinguishing simulation and prediction

While there seems to be consensus that hydrological model outputs should be accompanied with an uncertainty estimate the appropriate method for uncertainty estimation is not agreed upon and a debate is ongoing between advocates of formal statistical methods who consider errors as stochastic and GLUE advocates who consider errors as epistemic, arguing that the basis of formal statistical approaches that requires the residuals to be stationary and conform to a statistical distribution is unrealistic. In this paper we take a formal frequentist approach to parameter estimation and uncertainty evaluation of the modelled output, and we attach particular importance to inspecting the residuals of the model outputs and improving the model uncertainty description. We also introduce the probabilistic performance measures sharpness, reliability and interval skill score for model comparison and for checking the reliability of the confidence bounds. Using point rainfall and evaporation data as input and flow measurements from a sewer system for model conditioning, a state space model is formulated that accounts for three different flow contributions: wastewater from households, and fast rainfall-runoff from paved areas and slow rainfall-dependent infiltration-inflow from unknown sources. We consider two different approaches to evaluate the model output uncertainty, the output error method that lumps all uncertainty into the observation noise term, and a method based on Stochastic Differential Equations (SDEs) that separates input and model structure uncertainty from observation uncertainty and allows updating of model states in real-time. The results show that the optimal simulation (off-line) model is based on the output error method whereas the optimal prediction (on-line) model is based on the SDE method and the skill scoring criterion proved that significant predictive improvements of the output can be gained from updating the states continuously. In an effort to attain residual stationarity for both the output error method and the SDE method transformation of the observations were necessary but the statistical assumptions were nevertheless not 100% justified. The residual analysis showed that significant autocorrelation was present for all simulation models. We believe users of formal approaches to uncertainty evaluation within hydrology and within environmental modelling in general can benefit significantly from adopting the evaluation measures applied here, so the probabilistic performance of their models can be assessed properly. (C) 2012 Elsevier B.V. All rights reserved.
Conceptual urban drainage model, Infiltration inflow, Maximum likelihood estimation, Output error method, Stochastic differential equations, Interval skill score

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Development of a restricted state space stochastic differential equation model for bacterial growth in rich media

In the present study, bacterial growth in a rich media is analysed in a Stochastic Differential Equation (SDE) framework. It is demonstrated that the SDE formulation and smoothened state estimates provide a systematic framework for data driven model improvements, using random walk hidden states. Bacterial growth is limited by the available substrate and the inclusion of diffusion must obey this natural restriction. By inclusion of a modified logistic diffusion term it is possible to introduce a diffusion term flexible enough to capture both the growth phase and the stationary phase, while concentration is restricted to the natural state space (substrate and bacteria non-negative). The case considered is the growth of Salmonella and Enterococcus in a rich media. It is found that a hidden state is necessary to capture the lag phase of growth, and that a flexible logistic diffusion term is needed to capture the random behaviour of the growth model. Further, it is concluded that the Monod effect is not needed to capture the dynamics of bacterial growth in the data presented.

General information
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Organisations: Mathematical Statistics, Department of Informatics and Mathematical Modeling
Authors: Møller, J. K. (Intern), Philipsen, K. R. (Intern), Christiansen, L. E. (Intern), Madsen, H. (Intern)
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Scopus rating (2016): SJR 0.918 SNIP 0.932 CiteScore 2.16
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BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.084 SNIP 1.017 CiteScore 2.21
Web of Science (2015): Indexed yes
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Scopus rating (2014): SJR 1.07 SNIP 1.048 CiteScore 2.25
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BFI (2013): BFI-level 1
Scopus rating (2013): SJR 1.04 SNIP 1.044 CiteScore 2.44
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BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.134 SNIP 1.081
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 2
Scopus rating (2008): SJR 0.87 SNIP 1.088
Scopus rating (2007): SJR 1.269 SNIP 1.104
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 1.108 SNIP 1.054
Evaluation of probabilistic flow predictions in sewer systems using grey box models and a skill score criterion

In this paper we show how the grey box methodology can be applied to find models that can describe the flow prediction uncertainty in a sewer system where rain data are used as input, and flow measurements are used for calibration and updating model states. Grey box models are composed of a drift term and a diffusion term, respectively accounting for the deterministic and stochastic part of the models. Furthermore, a distinction is made between the process noise and the observation noise. We compare five different model candidates’ predictive performances that solely differ with respect to the diffusion term description up to a 4 h prediction horizon by adopting the prediction performance measures; reliability, sharpness and skill score to pinpoint the preferred model. The prediction performance of a model is reliable if the observed coverage of the prediction intervals corresponds to the nominal coverage of the prediction intervals, i.e. the bias between these coverages should ideally be zero. The sharpness is a measure of the distance between the lower and upper prediction limits, and skill score criterion makes it possible to pinpoint the preferred model by taking into account both reliability and sharpness. In this paper, we illustrate the power of the introduced grey box methodology and the probabilistic performance measures in an urban drainage context.

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Organisations: Mathematical Statistics, Department of Informatics and Mathematical Modeling, Urban Water Engineering, Department of Environmental Engineering, Krüger A/S
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Grey Box Modelling of Flow in Sewer Systems with State Dependent Diffusion

Generating flow forecasts with uncertainty limits from rain gauge inputs in sewer systems require simple models with identifiable parameters that can adequately describe the stochastic phenomena of the system. In this paper, a simple grey-box model is proposed that is attractive for both forecasting and control purposes. The grey-box model is based on stochastic differential equations and a key feature is the separation of the total noise into process and measurement noise. The grey-box approach is properly introduced and hypothesis regarding the noise terms are formulated. Three different hypotheses for the diffusion term are investigated and compared: one that assumes additive diffusion; one that assumes state proportional diffusion; and one that assumes state exponentiated diffusion. To implement the state dependent diffusion terms Itô's formula and the Lamperti transform are applied. It is shown that an additive diffusion noise term description leads to a violation of the physical constraints of the system, whereas a state dependent diffusion noise avoids this problem and should be favoured. It is also shown that a logarithmic transformation of the flow measurements secures positive lower flow prediction limits, because the observation noise is proportionally scaled with the modelled output. Finally it is concluded that a state proportional diffusion term best and adequately describes the one-step flow prediction uncertainty, and a proper description of the system noise is important for ascertaining the physical parameters in question.
Parameter estimation in a simple stochastic differential equation for phytoplankton modelling

The use of stochastic differential equations (SDEs) for simulation of aquatic ecosystems has attracted increasing attention in recent years. The SDE setting also provides the opportunity for statistical estimation of ecosystem parameters. We present an estimation procedure, based on Kalman filtering and likelihood estimation, which has proven useful in other fields of application. The estimation procedure is presented and the development from ordinary differential equations (ODEs) to SDEs is discussed with emphasis on autocorrelated residuals, commonly encountered with ODEs. The estimation procedure is applied to a simple nitrogen-phytoplankton model, with data from a Danish estuary (1988-2006). The resulting SDE is simple enough to have a well-known stationary distribution and this distribution is presented.
Stochastic State Space Modelling of Nonlinear Systems - With Application to Marine Ecosystems

This thesis deals with stochastic dynamical systems in discrete and continuous time. Traditionally, dynamical systems in continuous time are modelled using Ordinary Differential Equations (ODEs). Even the most complex system of ODEs will not be able to capture every detail of a complex system like a natural ecosystem, and hence residual variation between the model and observations will always remain. In stochastic state-space models, the residual variation is separated into observation and system noise, and a main theme of the thesis is a proper description of the system noise. Additive Gaussian noise is the standard approach to introduce system noise, but this may lead to undesirable consequences for the state variables. In biological models, where the state-space generally contains positive real numbers only, modelling in the log-domain ensures positive state variables, however, this transformation is likely to conflict with the concept of mass balances. One of the central conclusions of the thesis is that the stochastic formulations should be an integral part of the model formulation. As discrete-time stochastic processes are simpler to handle numerically than continuous-time stochastic processes, I start by considering discrete-time processes. A novel approach combining multiplicative and additive log-normal noise has been developed in discrete time, and used to demonstrate the effect of stochastic forcing in simple discrete-time regime shift models. An approximate maximum likelihood estimation procedure based on the second order moment representation of the multiplicative and additive log-normal noise model was developed and tested in simulation studies. The transition to continuous-time stochastic models (here Stochastic Differential Equations (SDEs)) offers the opportunity of embedding parts of the ODE processes into the stochastic part of the model (the diffusion term). The estimation method we use here (maximum likelihood and the Extended Kalman Filter (EKF)) rely on state-independent diffusion, but for a wide class of SDEs there exist an alternative description (given by the Lamperti transform) of the input-output relation, where the diffusion term is independent of the state. This alternative description is used to develop better parametric descriptions of the diffusion term, while maintaining the opportunity of estimation by standard software. Additionally, the state-space formulation facilitates estimation of unobserved states. Based on estimation of random walk hidden states and examination of simulated distributions and stationarity characteristics, a methodological framework for structural identification based on information embedded in the observations of the system has been developed. The applicability of the methodology is demonstrated using phytoplankton and nitrogen data from a Danish estuary as well as bacterial growth data from a controlled experiment. In summary, the novelty of the work presented here is the introduction of more appropriate stochastic descriptions in non-linear state-space models, which can include combinations of additive and multiplicative noise components under various distributional assumptions. A model identification and estimation framework for working with such models has been developed and tested using data from biological and ecological systems typically characterised by non-linear and non-Gaussian responses.

General Information
State: Published
Organisations: Mathematical Statistics, Department of Informatics and Mathematical Modeling, Department of Environmental Science and Engineering
Authors: Møller, J. K. (Intern), Carstensen, N. J. (Intern), Madsen, H. (Intern)
Publication date: 2011

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Place of publication: Kgs. Lyngby, Denmark
From State Dependent Diffusion to Constant Diffusion in Stochastic Differential Equations by the Lamperti Transform

This report describes methods to eliminate state dependent diffusion terms in Stochastic Differential Equations (SDEs). Transformations that leave the diffusion term of SDEs constant is important for simulation, and estimation. It is important for simulation because the Euler approximation convergence rate is faster, and for estimation because the Extended Kalman Filter equations are easier to implement than higher order filters needed in the case of state dependent diffusion terms. The general class of transformations which leaves the diffusion term independent of the state is called the Lamperti transform. This note gives an example driven introduction to the Lamperti transform. The general applicability of the Lamperti transform is limited to univariate diffusion processes, but for a restricted class of multivariate diffusion processes Lamperti type transformations are available and the Lamperti transformation is discussed for both univariate and multivariate diffusion processes. Further some special attention is needed for time-inhomogeneous diffusion processes and these are discussed separately.

Identification of ecosystem parameters by SDE-modelling

Stochastic differential equations (SDEs) for ecosystem modelling have attracted increasing attention during recent years. The modelling has mostly been through simulation experiments in order to analyse how system noise propagates through the ordinary differential equation formulation of ecosystem models. Estimation of parameters in SDEs is, however, possible by combining Kalman filter techniques and likelihood estimation. By modelling parameters as random walks it is possible to identify linear as well as non-linear interactions between ecosystem components. By formulating a simple linear SDE describing interactions between phytoplankton and water-column nitrogen with light as forcing, using data form a Danish estuary covering a 16 years period (1988-2003), and modelling primary production as a random walk, it is demonstrated how non-linear relationships between states can be identified by plotting the (random) production parameter as a function of the states in the system and global radiation. The resulting SDE model (that does not contain random walks), is analysed by simulation studies, to determine the properties of the seasonal distribution of phytoplankton.
Dynamic two state stochastic models for ecological regime shifts
A simple non-linear stochastic two state, discrete-time model is presented. The interaction between benthic and pelagic vegetation in aquatic ecosystems subject to changing external nutrient loading is described by the nonlinear functions. The dynamical behavior of the deterministic part of the model illustrates that hysteresis effect and regime shifts can be obtained for a limited range of parameter values only. The effect of multiplicative noise components entering at different levels of the model is presented and discussed. Including noise leads to very different results on the stability of regimes, depending on how the noise propagates through the system. The dynamical properties of a system should therefore be described through propagation of the state distributions rather than the state means and consequently, stochastic models should be compared in a probabilistic framework.
Parameter Estimation in State Space Models with Multiplicative Noise - Examples

General information
State: Published
Organisations: Mathematical Statistics, Department of Informatics and Mathematical Modeling, Department of Environmental Science and Engineering
Authors: Møller, J. K. (Intern), Carstensen, N. J. (Intern), Madsen, H. (Intern)
Publication date: 2009

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Place of publication: Kgs. Lyngby
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Publication: Research › Journal article – Annual report year: 2009

Combined Forecast and Quantile Regression for Wind Power Prediction

General information
State: Published
Organisations: Mathematical Statistics, Department of Informatics and Mathematical Modeling
Authors: Møller, J. K. (Intern), Madsen, H. (Intern), Nielsen, H. A. O. T. 3. (Intern)
Publication date: 2008

Publication information
Place of publication: Lyngby
Publisher: Technical University of Denmark, DTU Informatics, Building 321
Original language: English
Number: 2007-19
ISSN: 1601-2321
Time-adaptive quantile regression
An algorithm for time-adaptive quantile regression is presented. The algorithm is based on the simplex algorithm, and the linear optimization formulation of the quantile regression problem is given. The observations have been split to allow a direct use of the simplex algorithm. The simplex method and an updating procedure are combined into a new algorithm for time-adaptive quantile regression, which generates new solutions on the basis of the old solution, leading to savings in computation time. The suggested algorithm is tested against a static quantile regression model on a data set with wind power production, where the models combine splines and quantile regression. The comparison indicates superior performance for the time-adaptive quantile regression in all the performance parameters considered.
Predictions of wind power production for horizons up to 48-72 hour ahead comprise a highly valuable input to the methods for the daily management or trading of wind generation. Today, users of wind power predictions are not only provided with point predictions, which are estimates of the most likely outcome for each look-ahead time, but also with uncertainty estimates given by probabilistic forecasts. In order to avoid assumptions on the shape of predictive distributions, these probabilistic predictions are produced from nonparametric methods, and then take the form of a single or a set of quantile forecasts. The required and desirable properties of such probabilistic forecasts are defined and a framework for their evaluation is proposed. This framework is applied for evaluating the quality of two statistical methods producing full predictive distributions from point predictions of wind power. These distributions are defined by 18 quantile forecasts with nominal proportions spanning the unit interval. The relevance and interest of the introduced evaluation framework are consequently discussed.

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Organisations: Mathematical Statistics, Department of Informatics and Mathematical Modeling
Authors: Pinson, P. (Intern), Møller, J. K. (Intern), Nielsen, H. A. O. 3. (Intern), Madsen, H. (Intern), Kariniotakis, G. N. (Ekstern)
Publication date: 2007

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Publication: Research - peer-review › Report – Annual report year: 2007

**Non-parametric probabilistic forecasts of wind power: required properties and evaluation**
Predictions of wind power production for horizons up to 48-72 hour ahead comprise a highly valuable input to the methods for the daily management or trading of wind generation. Today, users of wind power predictions are not only provided with point predictions, which are estimates of the conditional expectation of future generation for each look-ahead time, but also with uncertainty estimates given by probabilistic forecasts. In order to avoid assumptions on the shape of predictive distributions, these probabilistic predictions are produced from nonparametric methods, and then take the form of a single or a set of quantile forecasts. The required and desirable properties of such probabilistic forecasts are defined and a framework for their evaluation is proposed. This framework is applied for evaluating the quality of two statistical methods producing full predictive distributions from point predictions of wind power. These distributions are defined by a number of quantile forecasts with nominal proportions spanning the unit interval. The relevance and interest of the introduced evaluation framework are discussed.

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Organisations: Mathematical Statistics, Department of Informatics and Mathematical Modeling
Algorithms for Adaptive Quantile Regression - and a Matlab Implementation

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State: Published
Organisations: Mathematical Statistics, Department of Informatics and Mathematical Modeling
Authors: Møller, J. K. (Intern), Nielsen, H. A. O. 3. (Intern), Madsen, H. (Intern)
Publication date: 2006

Publication information
Original language: English
Main Research Area: Technical/natural sciences
Electronic versions:
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imm4727.pdf
Source: orbit
Source-ID: 191725
Publication: Research - peer-review › Report – Annual report year: 2006

Regime Shift Models for Simulation of the Interaction between Benthic and Pelagic Production

General information
State: Published
Organisations: Mathematical Statistics, Department of Informatics and Mathematical Modeling, Department of Environmental Science and Engineering
Authors: Møller, J. K. (Intern), Carstensen, N. J. (Intern), Madsen, H. (Intern)
Publication date: 2006

Publication information
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Original language: English
Main Research Area: Technical/natural sciences
Electronic versions:
imm5203.pdf
Source: orbit
Source-ID: 200972
Publication: Research - peer-review › Report – Annual report year: 2006

Projects:

Stochastic Predictive Control of Wastewater Treatment Processes

Department of Applied Mathematics and Computer Science
Period: 15/09/2017 → 14/09/2020
Number of participants: 6
Phd Student:
Stentoft, Peter Alexander (Intern)
Supervisor:
Madsen, Henrik (Intern)
Mikkelsen, Peter Steen (Intern)
Munk-Nielsen, Thomas (Ekstern)
Stochastic grey-box models for marine ecosystems

Department of Applied Mathematics and Computer Science
Period: 01/08/2017 → 31/07/2020
Number of participants: 4
PhD Student:
Moazzami, Hamidreza (Intern)
Supervisor:
Carstensen, Niels Jacob (Intern)
Møller, Jan Kloppenborg (Intern)
Main Supervisor:
Christiansen, Lasse Engbo (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: Industrial PhD
Project: PhD

Datadriven models for energy advising leading to behavioural changes in SMEs and residences

Department of Applied Mathematics and Computer Science
Period: 15/05/2016 → 14/05/2019
Number of participants: 4
PhD Student:
Liisberg, Jon Anders Reichert (Intern)
Supervisor:
Bacher, Peder (Intern)
Madsen, Henrik (Intern)
Main Supervisor:
Møller, Jan Kloppenborg (Intern)

Financing sources
Source: Internal funding (public)
Name of research programme: Samfinansieret - Andet
Project: PhD

Enhanced Subsea Acoustically Aided Inertial Navigation

Department of Applied Mathematics and Computer Science
Period: 15/12/2011 → 24/02/2016
Number of participants: 6
PhD Student:
Jørgensen, Martin Juhl (Intern)
Supervisor:
Larsen, Mikael Bliksted (Intern)
Main Supervisor:
Poulsen, Niels Kjølstad (Intern)
Examiner:
Møller, Jan Kloppenborg (Intern)
Harbo, Anders la Cour (Ekstern)
Pascoal, António M. (Ekstern)
**Financing sources**  
Source: Internal funding (public)  
Name of research programme: Institut, samfinansiering

**Relations**  
Publications:  
Enhanced Subsea Acoustically Aided Inertial Navigation  
Project: PhD

**Multivariate Probabilistic Forecasting for Energy Systems**  
Department of Applied Mathematics and Computer Science  
Period: 01/10/2011 → 21/09/2015  
Number of participants: 7  
Phd Student:  
Iversen, Jan Emil Banning (Intern)  
Supervisor:  
Morales González, Juan Miguel (Intern)  
Møller, Jan Kloppenborg (Intern)  
Main Supervisor:  
Madsen, Henrik (Intern)  
Examiner:  
Pinson, Pierre (Intern)  
Dent, Chris (Ekstern)  
Lindström, Erik (Ekstern)

**Financing sources**  
Source: Internal funding (public)  
Name of research programme: Institut stipendie (DTU) Samf.  
Project: PhD

**Identification of Ecological Thresholds of Sustaniability in Marine Ecosystems**  
Department of Informatics and Mathematical Modeling  
Period: 01/08/2006 → 25/05/2011  
Number of participants: 6  
Phd Student:  
Møller, Jan Kloppenborg (Intern)  
Supervisor:  
Carstensen, Niels Jacob (Intern)  
Main Supervisor:  
Madsen, Henrik (Intern)  
Examiner:  
Nielsen, Bo Friis (Intern)  
Ditlevsen, Susanne (Ekstern)  
Guttorp, Peter (Ekstern)

**Financing sources**  
Source: Internal funding (public)  
Name of research programme: 1/3 DTU-stip, 2/3 FUR/andet  
Project: PhD

**Activities:**

**A Stochastic Method to Manage Delay and Missing Values for In-Situ Sensors in an Alternating Activated Sludge Process**  
Period: 13 Jun 2017  
Peter Alexander Stentoft (Speaker)  
Jan Kloppenborg Møller (Other)  
Henrik Madsen (Other)
Peter Steen Mikkelsen (Other)
Thomas Munk-Nielsen (Other)
Department of Applied Mathematics and Computer Science
Dynamical Systems
Department of Environmental Engineering
Urban Water Systems

Description
Oral Presentation
Degree of recognition: International

Related event
12th IWA Specialized Conference on Instrumentation, Control and Automation
11/06/2017 → 14/06/2017
Quebec, Canada
Activity: Talks and presentations › Conference presentations