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.
Nonlinear Stochastic Modelling of Antimicrobial resistance in Bacterial Populations

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Organisations: Mathematical Statistics, Department of Informatics and Mathematical Modeling
Authors: Philipsen, K. R. (Intern), Christiansen, L. E. (Intern), Madsen, H. (Intern)
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Modelling conjugation with stochastic differential equations

Conjugation is an important mechanism involved in the transfer of resistance between bacteria. In this article a stochastic differential equation based model consisting of a continuous time state equation and a discrete time measurement equation is introduced to model growth and conjugation of two Enterococcus faecium strains in a rich exhaustible media. The model contains a new expression for a substrate dependent conjugation rate. A maximum likelihood based method is used to estimate the model parameters. Different models including different noise structure for the system and observations are compared using a likelihood-ratio test and Akaike's information criterion. Experiments indicating conjugation on the agar plates selecting for transconjugants motivates the introduction of an extended model, for which conjugation on the agar plate is described in the measurement equation. This model is compared to the model without plate conjugation. The modelling approach described in this article can be applied generally when modelling dynamical systems.
Dynamics of extended-spectrum beta-lactamases in Escherichia coli: a mathematical model

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Organisations: Mathematical Statistics, Department of Informatics and Mathematical Modeling
Authors: Philipsen, K. R. (Intern)
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Dynamics of spread of intestinal colonization with extended-spectrum beta-lactamases in E.coli: a mathematical model

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Organisations: Mathematical Statistics, Department of Informatics and Mathematical Modeling, Utrecht University, University Medical Centre Utrecht
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Modelling bacterial growth in rich media with a non-parametric extension to an SDE based Model

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Parameter estimation for a discrete stochastic model of ESBL colonization in a human population

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Organisations: Mathematical Statistics, Department of Informatics and Mathematical Modeling
Authors: Philipsen, K. R. (Intern)
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Mathematical model for the growth of P. aeruginosa and four mutator strains in sub-MIC concentration of Ciprofloxacin

P. aeruginosa causes very critical and complicated infections, for which treatment is strongly dependent on successful antibiotic treatment. Therefore the evolution of antibiotic resistant P. aeruginosa does have serious consequences. Cystic fibrosis (CF) is characterized by the chronic P. aeruginosa lung infection. Intensive antibiotic treatment has improved the survival and clinical condition of CF patients, but development of resistance to antibiotics makes these infections difficult to treat efficiently. Ciprofloxacin is commonly used in the early and aggressive treatment. A hypothesis is that the presence of antibiotic results in selection of mutators in the lungs of CF patients, as these bacteria has a higher fitness under the presence of antibiotics. The goal of this study is to model the growth of P. aeruginosa and four different mutator strains (PAO1 mutT, mutY, mutM and mutM-mutY mutants) when growing under sub-MIC Ciprofloxacin concentration (0.1 μg/ml), in order to describe the growth pattern under the presence of antibiotic. Data available for the modelling process is bioscreen measurements of the bacterial content as a function of time for each bacteria strain growing in LB media with and without the presence of Ciprofloxacin. The growth of the bacteria strains is modelled with a continuous-discrete time stochastic state space model consisting of a continuous time state equation expressed as a system of stochastic differential equations and a discrete time measurement equation. The model parameters are estimated from data using a Maximum Likelihood approach. We introduce a new expression for multiple substrate dependent growth in LB media, which is identified by a method first introducing the growth as a random walk in the model. From the bioscreen measurement we found a change in the growth pattern under the presence of Ciprofloxacin. In most cases the presence of Ciprofloxacin resulted in a longer lag phase, a period of growth followed by a transition phase and then a second period of growth. We have developed a new mathematical model using a multi substrate approach, which will be able to describe this change in growth as a function of the Ciprofloxacin concentration. Following the determination of the growth pattern we wish to continue this study by modelling a competition experiment between PAO1 and each of the four mutator strains. The goal is to determine whether the mutator strain has an advantage in an environment with sub-MIC concentrate of Ciprofloxacin.

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Maximum Likelihood based comparison of the specific growth rates for P. aeruginosa and four mutator strains

The specific growth rate for P. aeruginosa and four mutator strains mutT, mutY, mutM and mutY–mutM is estimated by a suggested Maximum Likelihood, ML, method which takes the autocorrelation of the observation into account. For each bacteria strain, six wells of optical density, OD, measurements are used for parameter estimation. The data is log-transformed such that a linear model can be applied. The transformation changes the variance structure, and hence an OD-dependent variance is implemented in the model. The autocorrelation in the data is demonstrated, and a correlation model with an exponentially decaying function of the time between observations is suggested. A model with a full covariance structure containing OD-dependent variance and an autocorrelation structure is compared to a model with variance only and with no variance or correlation implemented. It is shown that the model that best describes data is a model taking into account the full covariance structure. An inference study is made in order to determine whether the growth rate of the five bacteria strains is the same. After applying a likelihood-ratio test to models with a full covariance structure, it is concluded that the specific growth rate is the same for all bacteria strains. This study highlights the importance of carrying out an explorative examination of residuals in order to make a correct parametrization of a model including the covariance structure. The ML method is shown to be a strong tool as it enables estimation of covariance parameters along with the other model parameters and it makes way for strong statistical tools for inference studies.

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Evolution of antibiotic resistance in bacterial populations is an increasing problem having fatal consequences for treatment of diseases. Therefore it is very important to understand this evolution. Traditionally evolution is considered to happen by single point mutations, where each mutant must have a growth advantage over the parent strain and grow to a sufficient number before a second mutation can occur. However, when multiple mutations are necessary for development of resistance, single mutations occurring with a normal mutation rate can not always explain the observed resistance. We introduce an alternative hypothesis by which a subpopulation of mutators drives the evolution process. Resistance is acquired by a subpopulation of mutators, for which the mutation rate is much higher than the wild-type. If the resistance is located on a transferable plasmid it can subsequently be transferred to the wild-type population by conjugation. To examine whether this pathway will in fact speed up evolution, we perform a simulation study, where bacteria are simulated to grow in a chemostat environment, such as the intestine of a human. Since mutation events are stochastic processes, we model the system by a discrete Markov process with the possibility of changes in each state given by a Poisson distribution. Parameters for growth, mutation and conjugation rates used in the simulation study resemble those of E.coli with a mutator obtained with the XL1-red mutator strain having a 5000 times higher mutation rate than the wild-type. We simulate the process for 24 hours and perform 1000 repetitions, which correspond to considering 1000 people with the same initial bacterial population in the intestine. In none of the repetitions a double mutation occurs in the wild-type population, but in almost 300 cases a double mutated strain has been conjugated to the wild-type bacterial population. To confirm these results future work should include an experimental study of the hypothesis.
Using random walk in models specified by stochastic differential equations to determine the best expression for the bacterial growth rate

In this presentation we consider a new method first introduced by Kristensen et al. [1] to improve the model for bacterial growth. Traditionally the substrate dependent growth rate $\mu(S)$ is modeled using the Monod expression, however it fails to describe the growth of bacteria in rich media. For P. aeruginosa we observe a growth pattern far from Monod growth. Therefore a reformulation of the growth expression is necessary. Without any pre-knowledge about the functional dependence between the growth rate and the substrate content and with only limited experimental resources necessary, the proposed method allows us to develop a new expression for the growth rate. The method is based on the stochastic continuous-discrete time state-space model, with a continuous-time state equation (a stochastic differential equation, SDE) combined with a discrete-time measurement equation. In our study the SDE contains two state variables, the bacterial and substrate densities. To improve the growth model we initially allow the growth rate $\mu(S)$ to vary as a random walk, i.e. we reformulate the SDE model to include $\mu(S)$ as an extra state variable which change is described by the Wiener process. We use data from Optical Density bioscreen measurements of P. aeruginosa to perform a Maximum Likelihood estimation of the model parameters and subsequently obtain a smoothing estimate for the model state variables by means of a nonlinear smoothing algorithm based on the extended Kalman filter, using an implementation described by Kristensen et. al [2]. The resulting time series allows us graphically to inspect the functional dependence of the growth rate on the substrate content. From the method described above we find three new plausible expressions for $\mu(S)$. Therefore we apply the likelihood-ratio test to compare the expressions which are nested. Additional inferens concerning the best expression is performed by considering the incremental variance $\sigma^2$ of the Wiener process. The best expression is found to be $S(a/(1 + b(1 − S)^2) + c)$ with $\sigma^2 = 3.46 \cdot 10^{-4}$, which is one order of magnitude lower than the incremental variance for the Monod expression. Thus, the method was applied to successfully determine a significant better expression for the substrate dependent growth expression, and we find the method generally applicable for model development. References [1] Kristensen NR, Madsen H, Jørgensen, SB (2004) A method for systematic improvement of stochastic grey-box models. Computers and Chemical Engineering 28:1431-1449. [2] Kristensen NR, Madsen H, Jørgensen, SB (2004) Parameter estimation in stochastic greybox models. Automatica 40:225-237.

Stochastic differential equations used to model conjugation

Stochastic differential equations (SDEs) are used to model horizontal transfer of antibiotic resis-tance by conjugation. The model describes the concentration of donor, recipient, transconjugants and substrate. The strength of the SDE model over the traditional ODE models is that the noise can be split into measurement noise and system noise. The system noise is used to compensate for those biological processes not explicitly described by the model. Many authors model conjugation by a simple mass action model first proposed by Levin et al. (1979). Also Michaelis-Menten dependence on the recipient concentration has been used to mathematically describe conjugation (Andrup et al. (1998)). We find that it is important to include substrate depletion to model conjugation for a system with exhaustible media and implement the substrate dependence as a Michaelis-Menten expression. This is supported by an experiment conducted with E. faecium. In addition, we suggest that a 3rd order time-delay must be included in the model to account for the delay before a newly conjugated plasmid is expressed. A ML estimate of the parameters based on experimental data is found using the software CTSM. The conjugation rate is estimated to $1.4e^{-9} \pm 0.38e^{-9}$ 1/h.
Projects:

Nonlinear Stochastic Modelling of Antimicrobial resistance in Bacterial Populations

Department of Informatics and Mathematical Modeling
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