Using random walk in models specified by stochastic differential equations to determine the best expression for the bacterial growth rate.

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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 σ^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 grey-box models. Automatica 40:225-237.