A Deconvolution Method for Linear and Nonlinear Systems based on Stochastic Differential Equations

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Introduction

Deconvolution techniques are often applied to characterize fluxes of endogenous and exogenous substances in physiological systems, because they can be used for reconstruction of unknown input rate profiles from plasma concentration data using a model of the disposition kinetics of the substance. Examples of profiles include:

- Secretion rate profiles for hormones and other substances.
- Production rate profiles for endogenous substrates.
- Appearance rate profiles for extravascularly administered drugs.

Common deconvolution techniques can be applied to linear time-invariant systems, i.e. systems with linear disposition kinetics for the investigated substance. A variety of such techniques are available:

- Parametric (profile determined by a number of parameters).
- Nonparametric (profile determined by a penalty on a derivative).
- Stochastic (profile determined by a simple stochastic model).

Deconvolution techniques for nonlinear systems are uncommon, but a new technique based on stochastic differential equations (SDEs)[1] provides sufficient flexibility to be applicable to nonlinear systems.

Objectives

For linear time-invariant systems the new SDE-based deconvolution technique is theoretically equivalent to a conventional stochastic deconvolution technique[2] (see Table 1), and the objectives of the analysis therefore are to investigate the new technique in terms of:

- Practical equivalence with the conventional technique for linear time-invariant systems (using simulated as well as real data).
- Applicability to nonlinear systems (using only simulated data).

Table 1. Comparison of deconvolution methods

	Conventional	SDE-based (New)
Model of disposition	Impulse response*	State space**
Stochastic model	(Int.) Random walk	(Int.) Random walk
Criterion of fit	Maximum likelihood	Maximum likelihood
Algorithm of solution	Regularization	EKF smoothing
Software implementation	WinStoDec	CTSM

*: Discrete time input-output model, **: Continuous time stochastic state space model

Methods

Data and model assumptions

For the analysis of the equivalence between the two techniques for linear-time invariant systems, two different examples are used:

- An example of reconstruction of the disposal rate of glucose during a euglycaemic clamp, using simulated plasma glucose data.
- An example of reconstruction of the secretion rate of C-peptide during free-living conditions, using real plasma C-peptide data.

For each of the two examples, the same assumptions with respect to the model of disposition kinetics and with respect to knowledge of the measurement noise level are used with both techniques.

For the analysis of the applicability of the new SDE-based technique to nonlinear systems, a single simulated example is used:

- An example of reconstruction of the rate of appearance of an extravascularly administered drug with nonlinear disposition kinetics (Michaelis-Menten), using plasma concentration data.

Knowledge of the nonlinear model of the disposition kinetics and of the measurement noise level is assumed for the analysis.

Software and data analysis

The following software is used for the reconstruction of the profiles:

- The new SDE-based deconvolution technique is applied as implemented in CTSM[1], a stand-alone GUI-based software for SDE modelling, i.e. with state space models of disposition kinetics.
- The conventional stochastic deconvolution technique is applied as implemented in WinStoDec[3], a GUI-based toolbox for MATLAB, i.e. with impulse response models of disposition kinetics.

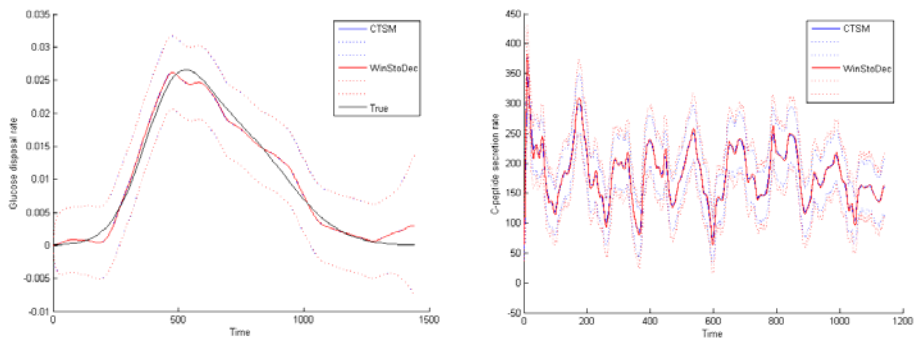
MATLAB is used for visualization of all of the reconstructed profiles.

1: Kristensen et al., "CTSM – Continuous Time Stochastic Modelling", Http://www.imm.dtu.dk/ctsm
2: De Nicolao et al., "Nonparametric Input Estimation in Physiological Systems: Problems, Methods and Case studies", *Automatica*, 33 (5), pp. 851-870, 1997
3: Sparacino et al., "WinStoDec: A Stochastic Deconvolution Interactive Program for Physiological and Pharmacokinetic Systems", *Computer Methods and Programs in Biomedicine*, 67, pp. 67-77, 2001

Results

Figure 1 shows reconstructed rate profiles (with confidence intervals) from CTSM and WinStoDec for the two linear time-invariant systems and demonstrates the equivalence between the two techniques.

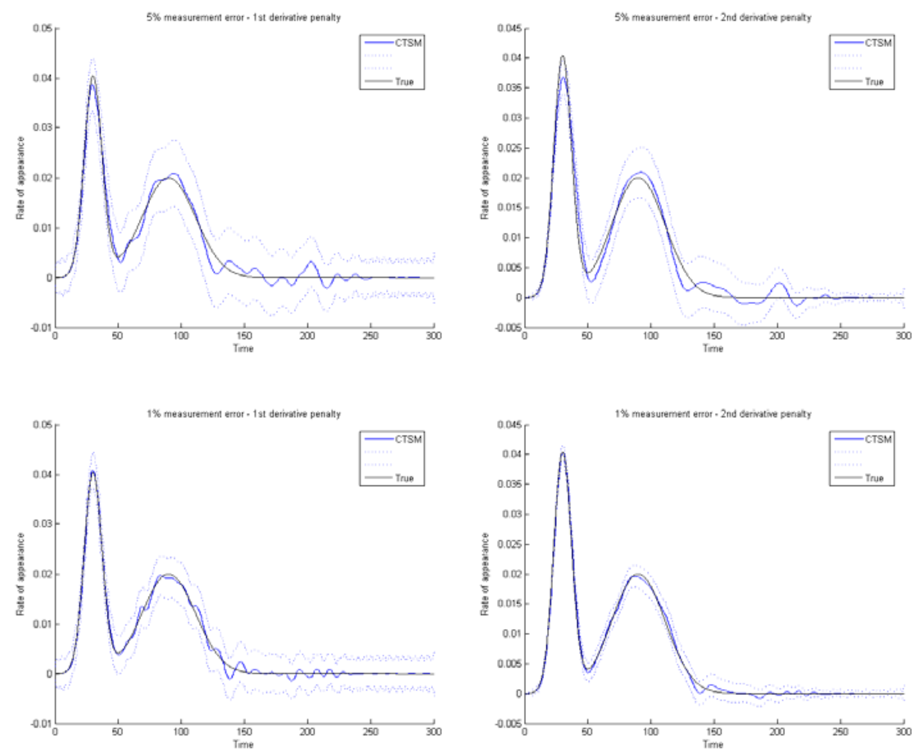
Figure 1. Equivalence with conventional method



Demonstration of the equivalence between CTSM and WinStoDec for linear time-invariant systems. Left: Simulated data (glucose disposal rate reconstructed from plasma glucose data). Right: Real data (C-peptide secretion rate reconstructed from plasma C-peptide data). Solid lines: Mean values, dotted lines: 95% CI.

Figure 2 shows reconstructed rate profiles (with confidence intervals) from CTSM for the nonlinear system, using two different levels of measurement noise for the simulated plasma concentration data.

Figure 2. Deconvolution for a nonlinear system



Reconstruction of the rate of appearance for a drug with nonlinear disposition kinetics (Michaelis-Menten), using simulated plasma concentration data with two different levels of measurement noise, and using different assumptions for the smoothness of the reconstructed profile. Solid: Mean values, dotted: 95% CI.

Being based on a continuous time stochastic state space model, the new SDE-based deconvolution technique provides additional benefits compared to common deconvolution techniques, which are based on discrete time input-output models. More specifically, arbitrarily irregularly sampled plasma concentration data can be used and arbitrarily fine discretization of the reconstructed profile can be obtained to give any desired level of continuity of the profile.

Conclusions

- A new deconvolution technique, which is based on stochastic differential equations, has been investigated in practice.
- The new technique is equivalent to a conventional stochastic deconvolution technique for linear time-invariant systems.
- Unlike common techniques, the new technique can also be applied to nonlinear systems, and it provides additional flexibility by allowing arbitrarily irregularly sampled data and arbitrarily fine discretization of the reconstructed profile.