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Technical note

Validation of Bayesian analysis of compartmental kinetic models in medical imaging

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ABSTRACT

Introduction: Kinetic compartmental analysis is frequently used to compute physiologically relevant quantitative values from time series of images. In this paper, a new approach based on Bayesian analysis to obtain information about these parameters is presented and validated.

Materials and methods: The closed-form of the posterior distribution of kinetic parameters is derived with a hierarchical prior to model the standard deviation of normally distributed noise. Markov chain Monte Carlo methods are used for numerical estimation of the posterior distribution. Computer simulations of the kinetics of F18-fluorodeoxyglucose (FDG) are used to demonstrate drawing statistical inferences about kinetic parameters and to validate the theory and implementation. Additionally, point estimates of kinetic parameters and covariance of those estimates are determined using the classical non-linear least squares approach.

Results and discussion: Posteriors obtained using methods proposed in this work are accurate as no significant deviation from the expected shape of the posterior was found (one-sided $P > 0.08$). It is demonstrated that the results obtained by the standard non-linear least-square methods fail to provide accurate estimation of uncertainty for the same data set ($P < 0.0001$).

Conclusions: The results of this work validate new methods for a computer simulations of FDG kinetics. Results show that in situations where the classical approach fails in accurate estimation of uncertainty, Bayesian estimation provides an accurate information about the uncertainties in the parameters. Although a particular example of FDG kinetics was used in the paper, the methods can be extended for different pharmaceuticals and imaging modalities.

1. Introduction

Kinetic compartmental analysis is frequently used to compute physiologically relevant quantitative values from time series of medical images. Traditionally, methods based on nonlinear least squares parameter optimization are used to estimate the values of kinetic parameters and their asymptotic covariance matrix. Although the use of nonlinear least squares optimization is ubiquitous in science, it is not often well suited to estimation of kinetic parameters from clinical data with low signal-to-noise-ratio (SNR) where the classical analysis may erroneously result in variations in parameter values which are outside the known physiological range. Furthermore, the classical approach is rooted in the idea of steady state systems and it is not easily generalized to the analysis of temporal perturbations, such as the effect of amphetamine on dopamine release. These issues are not merely intellectual and conceptual, the limitations have profound effect on the design of experiments and hypothesis test.

Bayesian analysis, among other advantages listed in the discussion, provides the range of probable values. The main difference between the classical approach and the method investigated here is that the result of the Bayesian analysis (BA) is a probability distribution and not a point estimate. This is schematically illustrated in Fig. 1(A and D). In addition to providing accurate representation of the precision, the Bayesian analysis has an intuitive means of displaying the result, schematically shown in Fig. 1(C and D) which increases a confidence in the analysis.

The actual shape of the posterior distribution can be visualized, providing a diagnostic tool for determination of which parameters are estimable and which are not. If a parameter is not estimable that will be indicated by a wide 1D posterior (Fig. 1D). In general, the more information is contained in the prior and the data the narrower the posterior and therefore the method provides a reliable and intuitive tool for visualization of

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1120-1797/

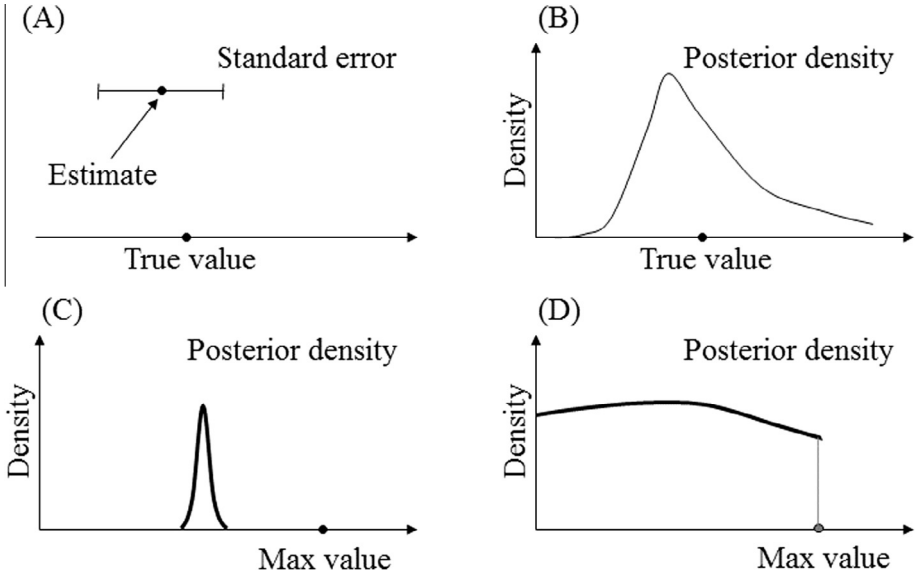

Fig. 1. Standard analysis (A) provides a point estimate of the true value of a parameter and the standard error indicated by the bar. Bayesian approach provides a posterior density distribution estimate (B) indicative of the beliefs that a given parameter value is true. (C) and (D) present examples of an informative narrow posterior and non-informative posterior indicating non-estimable parameter, respectively. Max value is the known upper limit value for a given parameter.

the precision of the estimate represented by the width of posterior distribution.

The classical applications of kinetic compartment modeling is well researched and we briefly describe a general theory in Section 2.1. A more complete description is covered in [1]. The Bayesian analysis is a very rich area with many theoretical and computational innovations discovered over the years. Bayesian analysis is applied in many areas of science, engineering, finance, and others [2–4].

The literature on Bayesian approach to analysis of kinetic models in medical imaging is relatively sparse and recent. In [5] the investigators use estimated posterior for the compartment model-selection task. This approach is useful if the underlying model of the time series is unknown and the most probable model is sought. The method presented in [5] is an approach to find the best model and best parameters corresponding to this model that are consistent with the observed time series. In another application [6] authors investigate Bayesian model of one-compartment data where they model the statistics in the data as well as in the input function. The novelty in this paper, aside from use of Bayesian approach, is the modeling of the noise in the input function. In the overwhelming majority of applications of the compartment modeling in medical imaging the noise in the input function is ignored because of difficulties in incorporating the noise in the statistical model. In the work presented in this paper, the normality of the data is assumed. In some alternative approaches the Bayesian analysis, the analysis can be performed without the knowledge of the noise model using approximate Bayesian computing (ABC) [7].

In this paper, we focus on how the limitations of the classical approach to modeling stationary systems can be mitigated with Bayesian analysis. We discuss, illustrate and validate a method of Bayesian analysis with simulated data, exemplifying the strengths of the Bayesian approach. In the following sections we detail the implementation of Bayesian methods for two-compartment model and provide validation of the resulting posterior densities. In general, the validation of the posterior is a more difficult task than the validation of the point estimate because the correctness of the entire shape of the distribution needs to be evaluated.

2. Materials and methods

The mathematical description of the compartmental model and the derivation of the closed form of the posterior distribution from the normal model data and Bayes theorem is given in Section 2.1. In Section 2.3 we briefly describe the approach for validation of the posterior density distributions which is based on [8]. The numerical Markov chain Monte Carlo (MCMC) methods used to find the approximations of the posterior distributions are given in the Appendix A.

Note that we use two different approaches for the validation of posteriors (results of Bayesian methods, Section 2.3.1) and for the validation of point estimates (results of classical analysis, Section 2.3.2). This is done out of necessity, as the statistical meaning of the results differs for those two approaches.

2.1. Compartment model

We define the instantaneous concentration of tracer in a volume of interest (VOI) as described by a function $C_T(t)$. The tracer molecule may be in different biochemical states (different compartments) in a biological system. Furthermore, we assume that tracer movement between compartments is governed by first-order kinetics. Accordingly, the transfer rates of a tracer molecule from compartment a to a compartment b is linearly proportional to the concentration of the tracer in compartment a and independent of the concentration in compartment b and in any other compartment. The proportionality coefficients between transfer rates and concentrations are referred to as *kinetic parameters*.

In compartment models discussed here, we consider a single mechanism for input of tracer. This will usually be the concentration in the arterial plasma, as it enters the capillary bed. Following the convention frequently used by others we assume the concentration of tracer in the plasma to be known or measurable but we do not require the plasma concentrations to obey compartment definitions. The concentration of the tracer in the plasma is referred to as *input function*. Although in theory the number of compartments can be infinite, the low signal-to-noise of medical imaging data coupled with relatively short measurement periods

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