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Dizzy-Beats: a Bayesian Evidence analysis tool for systems biology

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ABSTRACT

Motivation: Model selection and parameter inference are complex problems of long-standing interest in systems biology. Selecting between competing models arises commonly as underlying biochemical mechanisms are often not fully known, hence alternative models must be considered. Parameter inference yields important information on the extent to which the data and the model constrain parameter values.

Results: We report Dizzy-Beats, a graphical Java Bayesian evidence analysis tool implementing nested sampling - an algorithm yielding an estimate of the log of the Bayesian evidence Z and the moments of model parameters, thus addressing two outstanding challenges in systems modelling. A likelihood function based on the L1-norm is adopted as it is generically applicable to replicated time series data.

Availability: http://sourceforge.net/p/bayesevidence/home/Home/

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1 INTRODUCTION

Bayesian methods provide a sound basis for ranking alternative systems biology models and for characterising the extent to which parameters are constrained by models and data (Kirk et al., 2013). Markov Chain Monte Carlo (MCMC) methods have been applied to model selection (Schmidl et al., 2012) and to parameter inference in systems biology (Hug et al., 2013; Kanodia et al., 2014), but often require considerable algorithmic and conceptual development. Nested sampling promises to ease these complex computational tasks: Recent biological applications include (Aitken and Akman, 2013; Kirk et al., 2013; Pullen and Morris, 2014).

General purpose code for nested sampling is available in R (Skilling, 2006; Aitken and Akman, 2013), and biological applications of the MultiNest tool (Feroz et al., 2013) have been reported (Kirk et al., 2013; Pullen and Morris, 2014). A C-based command-line application implementing nested sampling and providing an SBML interface has recently been released (Johnson et al., 2014), but no graphical tool is currently available. Thus we sought to add nested sampling to the widely-used Dizzy chemical kinetics simulation tool (Ramsey et al., 2005) (over 200 citations as of November 2014). While doing so we also added an optimisation function and SBML 3.1 compatibility. However, as Dizzy’s command language has operators that cannot be captured in MultiNest, this feature is restricted to the intersection of the modelling languages.

2 METHODS

Nested sampling calculates two of the central results of Bayesian inference: the posterior distribution X(θ) of the parameters θ, and the evidence P(D|H), that is, the posterior probability of model H (Skilling, 2006), through a sampling strategy. A selection between two alternative models H0 and H1 can be made by calculating the ratio of their posterior probabilities (1), a calculation that can be decomposed into the Bayesian evidence (Z0 and Z1) and the prior probability of the respective hypotheses.

P(H1|D) P(H0) dθ
P(H0|D) P(H1) P(H0) = Z1 P(H1)
Z0 P(H0) (1)

The evidence (2) is a scalar quantity that can be viewed as an integral of the likelihood (L) over the elements of mass (dθ = θdθ) associated with the prior density π(θ). The prior mass can be accumulated from its elements (dθ) in any order. The enclosed prior of likelihood > λ can be defined (3), and this allows the evidence to be written as a one-dimensional integral of the (inverse) likelihood L(X) over the unit range (taking the enclosed prior mass X to be the primary variable) (4) (Skilling, 2006).

X(λ) = ∫L(θ)>λ
Z = ∫L(X) dX
L(X(λ)) ≡ λ (4)

Given a sequence of decreasing values 0 < Xm < … X2 < X1 < 1 where the likelihood L = L(Xi) can be evaluated, the evidence can be approximated numerically as a weighted sum. Inferences about the posterior can be obtained from the sequence of m discarded points generated by sampling, P. Each point is assigned the weight pi = L(θi)wi/Z, from which the first and second moments of each parameter in θ can be estimated - for more details see Skilling (2006) and Aitken and Akman (2013). The size of the population of active points (points θi within the evolving constraint X(λ) > λ used to sample the parameter space is the only

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3 DISCUSSION

Dizzy-Beats is a graphical application for simulating and optimising systems models based on an established simulator (Ramsey et al., 2005) and its simple textual model syntax, to which we have added SBML 3.1 import/export functionality. Uniquely, Dizzy-Beats provides model comparison and parameter inference functions through the nested sampling algorithm in a graphical application. Comparable functions are implemented in BioBayes (Vyshemirsky and Girolami, 2006), however, users must edit the XML representation of the model should they wish to make modifications. SYSBIONS (Johnson et al., 2014) implements nested sampling but all interaction is via the command-line. The use of a likelihood based on the \( L_1 \)-norm derived from biological replicate data makes fewer assumptions than a Gaussian error model (Vyshemirsky and Girolami, 2008; Johnson et al., 2014), and is less computationally complex than a transitional likelihood function derived from reaction propensities (Heron et al., 2007; Aitken and Akman, 2013).

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