Systems biology

Bayesian ranking of biochemical system models

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ABSTRACT

Motivation: There often are many alternative models of a biochemical system. Distinguishing models and finding the most suitable ones is an important challenge in Systems Biology, as such model ranking, by experimental evidence, will help to judge the support of the working hypotheses forming each model.

Bayes factors are employed as a measure of evidential preference for one model over another. Marginal likelihood is a key component of Bayes factors, however computing the marginal likelihood is a difficult problem, as it involves integration of nonlinear functions in multidimensional space. There are a number of methods available to compute the marginal likelihood approximately. A detailed investigation of such methods is required to find ones that perform appropriately for biochemical modelling.

Results: We assess four methods for estimation of the marginal likelihood required for computing Bayes factors. The Prior Arithmetic Mean estimator, the Posterior Harmonic Mean estimator, the Annealed Importance Sampling and the Annealing-Melting Integration methods are investigated and compared on a typical case study in Systems Biology. This allows us to understand the stability of the analysis results and make reliable judgements in uncertain context. We investigate the variance of Bayes factor estimates, and highlight the stability of the Annealed Importance Sampling and the Annealing-Melting Integration methods for the purposes of comparing nonlinear models.

Availability: Models used in this study are available in SBML format as the supplementary material to this article.

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Supplementary information: Supplementary data are available at Bioinformatics online.

1 INTRODUCTION

One of the important challenges of Systems Biology is inferring the structure of biochemical systems from various experimental observations (Rubbeck and Jordan, 2006). Alternative models of a biochemical system can be used to describe different hypotheses about the system structure. For example, there are two alternative hypotheses about the topology of the Epidermal Growth Factor (EGF) activated MAPK pathway in PC12 cells (Roux and Blenis, 2004). The first one, supported by Brown et al. (2004) and Schoeberl et al. (2002), suggests that there is only one path involved in activating a protein named ERK when the system is stimulated with EGF. The second one, supported by Kao et al. (2001), suggests that there are two parallel paths involved in this process. These alternative hypotheses are described using systems of ordinary differential equations (ODE). The problem is to decide which of these two alternative hypotheses is more plausible. This can be achieved by performing experiments and collecting data, and then using a statistical inferential methodology to compare the a posteriori (after observing the evidence) probabilities of the alternative models.

In a diverse range of scientific disciplines, it has been shown that Bayesian Inference provides a consistent framework for knowledge updating and hypotheses testing, for example, Archaeology (Christen and Buck, 1998); Astrophysics (Brewer et al., 2007), Forensic Science (Dawid and Mortera, 1996), Bioinformatics and Computational Biology (Werhli et al., 2006; Wilkinson, 2007). In this article, we demonstrate how Bayesian hypotheses testing can be employed to rank ODE models of a biochemical system based on the evidential support they gain from experimental data and existing knowledge.

The research presented in this article is timely, as recent developments in molecular biology allow scientists to obtain more high-quality experimental data vital for consistent hypotheses testing, while at the same time, the research interest of the scientific community is being shifted to study more and more complex systems (Wang et al., 2007). It is important therefore to perform reliable hypotheses testing through consistent model ranking.

In this article, we assess several methods to estimate the marginal likelihood, a quantity which is required for Bayesian hypotheses testing. We consider methods that perform well on nonlinear ODE models using realistic amounts of experimental data.

Mendes et al. (2003) proposed to use artificial models for evaluation and comparison of optimization algorithms in a controlled context, where the correct result of the analysis is known. Such synthetically constructed models together with simulated data serve as a ‘gold standard’ with which to make comparison. The technique of using artificial models for testing methodology has been widely adopted, see for example (Husmeier, 2003; Hu et al., 2007), and as such, this approach will be used in this article.

2 APPROACH

Traditionally hypotheses about the structure of biological systems are expressed using mathematical models, typically (though not exclusively) nonlinear ordinary differential equations (de Jong, 2003; Voit, 2000). The parameters of such models...
are usually chosen in such a way that the predicted behaviours approach the mean of the experimental observations (Cho et al., 2003; Hoops et al., 2006; Schoeberl et al., 2002). The Bayesian literature (Bernardo and Smith, 1994; Jaynes, 2003; Neal, 1993) argues that using probability distributions over the parameter values is a more appropriate way of expressing the uncertainty inherent from the variability of observations. Distributions over the model parameters were successfully employed to express uncertain beliefs about parameter values by, for example, Brown et al. (2004), and more explicitly by Rogers et al. (2007) and Heron et al. (2007).

Assume that alternative working hypotheses are expressed in a form of predictive parametric mathematical models. The likelihood of reproducing experimental data $D$, consisting of $N$ independent identically distributed data points, with model $M$ given a particular set of model parameters $\theta$, and assuming normal errors is defined as:

$$ p(D|M, \theta) = \prod_{i=1}^{N} N_D(\phi(M, \theta, x_i), \sigma), \quad (1) $$

where $x_i$ is the condition in which $D_i$ was measured, and $\phi(M, \theta, x_i)$ produces the value predicted with model $M$ using parameters $\theta$ in condition $x_i$. $N(\cdot, \cdot)$ is the normal probability density function, and $\sigma^2$ is the observation noise variance. Note, that a likelihood of this form is always strictly positive. This definition of the likelihood was chosen because it models the measurement noise. However, other likelihood definitions, for example Gaussian processes (Rasmussen and Williams, 2006), can be used if a more sophisticated model for the noise process is required.

In the case where a discrete set of competing hypotheses is considered, they can be ranked by the ratio of their posterior probabilities. A pair of hypotheses $H_1$ and $H_2$ can be represented with models $M_1$ and $M_2$ having parameters $\theta_1$ and $\theta_2$ correspondingly. Taking a prior distribution of beliefs in preference of each model $\pi$ into account, this ratio is:

$$ \frac{p(H_1|D)}{p(H_2|D)} = \frac{p(M_1|D)}{p(M_2|D)} \pi(M_1) \pi(M_2) B_{12}, \quad (2) $$

where

$$ B_{12} = \frac{p(D|M_1)}{p(D|M_2)} = \int p(D|M_1, \theta_1) \cdot p(\theta_1|M_1) d\theta_1 \int p(D|M_2, \theta_2) \cdot p(\theta_2|M_2) d\theta_2, \quad (3) $$

is called the Bayes factor for Models 1 and 2. Bayes factors are used to test competing hypotheses, and update corresponding beliefs using formula (2).

The Bayes factor is a summary of the evidence provided by the data in favour of one hypothesis, represented by a model, as opposed to another. Jeffreys (1961) suggested interpreting Bayes factors in half-units on the $\log_{10}$ scale. Pooling two of his categories together for simplification we demonstrate his scale in Table 1.

<table>
<thead>
<tr>
<th>$\log_{10}(B)$</th>
<th>$B$</th>
<th>Evidence support</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 1/2</td>
<td>1 to 3.2</td>
<td>Not worth more than a bare mention</td>
</tr>
<tr>
<td>1/2 to 1</td>
<td>3.2 to 10</td>
<td>Substantial</td>
</tr>
<tr>
<td>1 to 2</td>
<td>10 to 100</td>
<td>Strong</td>
</tr>
<tr>
<td>&gt;2</td>
<td>&gt;100</td>
<td>Decisive</td>
</tr>
</tbody>
</table>

Using the logarithms of the Bayes factors is often convenient, and $\log B_{12}$ is sometimes called the 'weight of evidence in favour of $H_1$'; while log likelihoods are sometimes called 'surprise values', 'log evidence' or 'information content' (MacKay, 2003). Logarithmic likelihoods are measured in units of information content which depend on the base of the logarithms used.

These categories are not a calibration of the Bayes factor, as it already provides a meaningful interpretation as probability, but rather a rough descriptive statement about standards of evidence in scientific investigation. In cases when data is uninformative due to, for example model overspecification, the Bayes factor will be close to 1 and thus the posterior odds do not deviate from the prior odds, thus highlighting that the experimental protocol has been uninformative.

Computing Bayes factors is challenging, as the marginal likelihoods for nonlinear models have to be evaluated to obtain these. The main problem is that the marginal likelihood

$$ p(D|M_i) = \int p(D|M_i, \theta_i) \cdot p(\theta_i|M_i) d\theta_i $$

can be evaluated analytically only in very special cases. The majority of biological models, however, are based on nonlinear ODEs. In such cases analytical integration of the marginal likelihood is impossible. Brute force numerical integration can be applied to low-dimensional problems. This approach, however, becomes computationally intractable as its complexity grows exponentially with the dimensionality of a problem.

The reasons of complexity leave us with the only practical option of considering methods for approximate evaluation of marginal likelihoods. Many of these approximate methods are limited by very strong conditions. For example, Laplace approximations (Bernardo and Smith, 1994) are large sample approximations around the maximum a posteriori parameter estimate. Such asymptotic approximations rely on the almost normal density of the posterior distribution, which is often not satisfied for nonlinear problems.

Two more methods which can be applied in a general case are importance sampling estimators (Newton and Raftery, 1994) and thermodynamic integration (Gelman and Meng, 1998; Ogata, 1989).

Four estimators from the above classes: the Prior Arithmetic Mean estimator, the Posterior Harmonic Mean estimator, Annealed Importance Sampling and the Annealing-Melting Integration are evaluated in this article. The first two were chosen because they are popular, straightforward to implement, and relatively inexpensive computationally. It will, however, be demonstrated in this article that estimates produced with these estimators have large variation, and therefore cannot be

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1 'Bit' corresponds to $\log_2 p$, 'nat' to $\ln p$, 'ban' to $\log_{10} p$ and 'deciban' to $10 \cdot \log_{10} p$. A historical overview for these names can be found in (MacKay, 2003).
used when comparing large nonlinear models. The latter two estimators are significantly more sophisticated, and have much higher computational complexity. The estimates produced with these methods are, however, significantly more stable than the ones produced with the importance sampling procedures.

Importance Sampling Estimators: Importance sampling estimation consists of generating a sample from an unnormalized density $\pi^*(\theta)$. Under quite general conditions, an estimate of the integral

$$p(D|M) = \int p(D|M, \theta) p(\theta|M) d\theta$$

is

$$\hat{p}(D|M) = \frac{\sum_{i=1}^{m} o_i \cdot p(D|M, \theta^{(i)})}{\sum_{i=1}^{m} o_i}, \text{ (4)}$$

where $o_i = p(\theta^{(i)}|M)/\pi^*(\theta^{(i)})$; the function $\pi^*(\theta)$ is known as the importance sampling function; and $\theta^{(i)}$ is sampled from $\pi^*(\theta)$.

The simplest application of this method is to use the prior as the importance sampling function $\pi^*(\theta) = p(\theta|M)$, in which case (4) produces the Prior Arithmetic Mean estimator (McCulloch and Rossi, 1991):

$$p(D|M) \approx \frac{1}{m} \sum_{i=1}^{m} p(D|M, \theta^{(i)}); \text{ } \theta^{(i)} \sim p(\theta|M). \text{ (5)}$$

A well-known problem with this estimator is that the high-likelihood region can be very small. Therefore, unless $m$ is very large, the sample drawn from the prior will contain virtually no points from the high-likelihood region, resulting in a very poor estimate of the marginal likelihood. The problem becomes aggravated in higher dimensions, as the relative size of the high posterior probability region tends to decrease as the dimension increases. Lewis and Raftery (1997) reference a study in which to reduce the standard error to an acceptable level, it was necessary to use a sample of roughly 50 million draws from the prior distribution.

An alternative application of importance sampling estimation, proposed by Newton and Raftery (1994), is to use the parameter posterior as the importance sampling function $\pi^*(\theta) = p(\theta|D, M)$. A sample from the parameter posterior can be obtained using Markov Chain Monte Carlo sampling. Such a sample should be significantly better in covering the high-likelihood region. Substituting the parameter posterior into (4) results in the Posterior Harmonic Mean estimator, we obtain:

$$p(D|M) \approx \frac{\left( \frac{1}{m} \sum_{i=1}^{m} \frac{1}{p(D|M, \theta^{(i)})} \right)^{-1}}{\theta^{(i)} \sim p(\theta|D, M). \text{ (6)}}$$

The main problem with this estimator is that sometimes its variance can become infinite (see the additional example provided in the Supplementary Material), because of the occasional occurrence of a value of $\theta^{(i)}$ with a small likelihood and hence a large effect on the final result. For vague prior distributions, parameters in regions of high posterior mass will have high-likelihood values, whilst parameters in the low posterior probability regions will tend to have low-likelihood values. As the likelihood appears as a reciprocal in (6) this implies that the salient contributions to the sum come from the tails of the posterior distribution, hence the possibility of huge variances. Raftery and Newton (2007) have also demonstrated that while being asymptotically unbiased, this estimator produces biased estimates in many practical cases when finite posterior samples are used, and tends to overestimate the real value of the marginal likelihood.

Annealed Importance Sampling: Neal (2001) proposed to combine importance sampling principles with the Simulated Annealing heuristic (Kirkpatrick et al., 1983).

The Annealed Importance Sampling estimator can be designed to draw samples $\theta^b_j$ approximately from a series of unnormalized distributions

$$q_b(\theta) \propto p(D|M, \theta)^b p(\theta|M); \text{ } 0 \leq b \leq 1,$$

which form a path in the probability density space connecting the prior (when $b=0$) and the posterior (when $b=1$). The important feature for this estimator is that $\theta^b_j$ only need to be drawn approximately; thus, when using a Markov chain for producing these, the convergence of the chains to the stationary distribution is not generally required. This is a very attractive property for integrating the likelihoods of nonlinear models, as in such cases achieving convergence of the Markov chains to their stationary distributions is a very challenging problem.

The following quantities are estimated from such samples:

$$Z_b = \int q_b(\theta) d\theta.$$  

The marginal likelihood is then expanded as

$$p(D|M) = \frac{Z_1}{Z_0} = \frac{Z_{\beta_0}}{Z_{\beta_0}} \frac{Z_{\beta_{0-1}}}{Z_{\beta_{0-1}}} \ldots \frac{Z_{\beta_1}}{Z_{\beta_1}}, \text{ (7)}$$

where $0 = \beta_0 \leq \beta_1 \leq \ldots \leq \beta_{n-1} \leq \beta_n = 1$. Each term in (7) is approximated using importance sampling based on samples from $q_b(\theta)$. The logarithm of the marginal likelihood is then estimated as:

$$\ln p(D|M) \approx \ln \left[ \frac{1}{M} \sum_{j=1}^{M} \tilde{I}_j \right]. \text{ (8)}$$

$$\tilde{I}_j = \exp \left[ \sum_{i=1}^{n} (\beta_{i-1} - \beta_i) \ln p(D|M, \theta^{(i)}_j) \right],$$

where $\theta^{(i)}_j, j = 1, \ldots, M$ are sampled from $T_{\beta_{i-1}}(\theta|\theta^{(i-1)}_j)$, where $T_{\beta_{i-1}}$ is a Markov transition kernel that has $q_{\beta_{i-1}}(\theta)$ as its stationary distribution.

Neal (2001) showed that Annealed Importance Sampling produces unbiased estimates of the marginal likelihood.

Thermodynamic Integration: The logarithm of the marginal likelihood can be represented in terms of the integral

$$\ln p(D|M) = \int_0^1 E_{\beta_0\theta}\left[ \ln p(D|M, \theta) \right] d\beta.$$  

This integral can be approximated by numerical integration (as in Friel and Pettitt, 2006; Larzillotte and Philippe, 2006). As with Annealed Importance Sampling, this method relies on samples from unnormalized ‘bridging’ distributions $q_b(\theta)$.
that link the prior and the posterior. In the case of thermodynamic integration, a Markov chain Monte Carlo simulation is usually run for particular values of $\beta$, in which $q_\beta$ is used as an unnormalized density in the Metropolis–Hastings ratio. The average of the logarithmic likelihood is then estimated on this sample. This computation is repeated for a series of values of $\beta$ partitioned between 0 and 1, which implies running a separate chain for each value of $\beta$. There are a number of ways to select a schedule for $\beta$ to estimate this integral. Lartillot and Philippe (2006) use $\beta$ values equally distributed between 0 and 1, whilst Friel and Pettitt (2006) use a different schedule, selecting these values as 

$$\beta_i = a^*_i, \quad a_i = i \frac{c}{N}, \quad i = 0, \ldots, N,$$

with $N=40$ and $c=4$. In the example described in this article, the latter one will be used as it produces lower variance estimates. Though, this schedule was shown to be theoretically suboptimal in general by Gelman and Meng (1998); its variance is superior to a uniform spacing.

3 METHODS AND RESULTS

Here we consider four alternative models of a biochemical system, with an additional example provided in the Supplementary Material. The models are artificially constructed to demonstrate the essence of the proposed methodology and demonstrate its main points and advantages on an example with a known result.

The schematic diagrams for the models are depicted in Figure 1a–d. The entities in circles represent proteins, while arrows correspond to biochemical reactions. Enzymatic behaviour is indicated by an arrow with a circle as head. For example, see Figure 1b where $S$ is an enzyme for activation of $R$. Kinetic parameters of the reactions are depicted as text beside the arrows e.g. $k_1$, $V_1$. These networks represent realistic networks, and they all have a structure which is very common in nature (Han et al., 2007).

The proposed approach, however, is not limited to signal transduction applications. In the Supplementary Material, we additionally consider the Repressilator (Elowitz and Leibler, 2000) that includes gene regulation processes, and utilizes data measured in a biochemical laboratory.

Model 1: This model defines a common motif of signalling pathways that is a stage in a signal transduction cascade, for example this motif is repeated several times in Schoeberl et al. (2002). The input signal is represented by the concentration of protein $S$ depicted in the top left of the diagram (Fig. 1a). This protein activates the next stage of the cascade by binding to protein $R$ forming complex $RS$, and activating $R$ into its phosphorylated form Rpp. Protein Rpp can then be deactivated. Model 1 also defines input signal degradation by converting protein $S$ into its degraded form $dS$.

All the proteins used in this model will be represented as dependent variables in our ODE model. As we are interested in modelling and analysis of temporal behaviour, the independent variable is time. The dephosphorylation reaction $Rpp \rightarrow R$ is defined using the Michaelis–Menten kinetic law, while the rest of the reactions (arrows in Fig. 1a) are defined using the Mass Action kinetic law with parameters depicted as textual remarks beside the arrows in the model diagram (e.g. $k_1$, $k_2$). The system of ODEs which defines this model can be found in the Supplementary Material. This model has six kinetic parameters: $k_1$, $k_2$, $k_3$, $V$, $K_m$.

Model 2: The model depicted in Figure 1b was constructed as a simplified representation of the signal transduction cascade stage.

Model 3: a biochemical model which is significantly different to the rest of the models considered in this article. This model does not describe degradation of protein $S$. (d) Model 4: a more complex version of Model 1. This model mechanistically describes how protein $Rpp$ is deactivated by phosphotase $PhA$.

It essentially represents the same system as defined with Model 1, but uses the Michaelis–Menten kinetic law to define phosphorylation of $R$.

The system of ODEs used in this model can be found in the Supplementary Material. The model has five kinetic parameters: $k_1$, $k_2$, $k_3$, $V_1$, $V_2$.

Model 4: The model depicted in Figure 1d is a more complex version of Model 1. Phosphatase $PhA$ depicted in the bottom of the diagram deactivates protein $R$. All the reactions are defined using the mass action kinetic law. This model was constructed to demonstrate how it would be penalized for complexity according to Occam’s razor concept (Jaynes, 2003) in Bayesian hypotheses testing.

The system of ODEs used in this model can be found in the Supplementary Material. This model has seven kinetic parameters: $k_1$, $k_2$, $k_3$, $k_4$, $V$, $K_m$.

The initial values for all of the models can be found in SBML files provided as the Supplementary Material to this article.

Data generation: For this study, we use data generated from Model 1. To generate the data we simulated the behaviour of Model 1 with the following values for kinetic parameters:

$$k_1 = 0.07, \quad k_2 = 0.6, \quad k_3 = 0.05, \quad k_4 = 0.3, \quad V = 0.017, \quad K_m = 0.3$$
by solving an initial value problem, and generated the time series of variable values (protein concentrations).

We decided to generate a data set for the experiments as a set of three replicates of a time series of $R_{pp}$ values, measured at the following time points: $t \in \{2s, 5s, 10s, 20s, 40s, 60s, 100s\}$. We added observation noise with variance 0.01 to the simulated values at each of the time points. The data set $D$ contains twenty one samples. The obtained values are depicted in Figure 2.

**Overall statistical models:** The definition of the likelihood (1) has been used as described in Section 2. Only one additional noise parameter $\sigma$ has been added to each of the models, as the same noise value was used when the data was generated. The same noise parameter will be substituted to the normal distributions placed at each of the time points when evaluating the likelihood (1).

More sophisticated models of experimental noise can be considered if required. For example, using immunoblotting data may require a separate noise parameter for different experiments due to different affinities of the labelling antibodies; and using microarray data may require considering a log-normal distribution for experimental noise due to the saturation properties of the microarray probes.

Any information about the parameter values used to generate data for our experiments with Model 1 has been discarded; and the prior for model parameters was defined. As none of the parameters can take a negative value, we defined the priors for all of the parameters of all the model parameters was defined. As none of the parameters can take a

### Table 2. Estimates of $\ln p(D|M_i)$

<table>
<thead>
<tr>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAM</td>
<td>9.6 ± 5.5</td>
<td>11.8 ± 3.8</td>
<td>-1.1 ± 0.1</td>
</tr>
<tr>
<td>PHM</td>
<td>71.0 ± 2.2</td>
<td>44.6 ± 0.8</td>
<td>1.9 ± 0.7</td>
</tr>
<tr>
<td>AIS</td>
<td>44.6 ± 0.8</td>
<td>28.9 ± 0.3</td>
<td>-1.1 ± 0.1</td>
</tr>
<tr>
<td>AMI</td>
<td>45.8 ± 0.2</td>
<td>29.2 ± 0.1</td>
<td>-1.1 ± 0.1</td>
</tr>
</tbody>
</table>

PAM row corresponds to the estimates obtained with the Prior Arithmetic Mean estimator, PHM corresponds to the Posterior Harmonic Mean estimator, AIS corresponds to the Annealed Importance Sampling and AMI corresponds to the Annealing-Melting Integration. The Posterior Harmonic Mean estimator, the Annealed Importance Sampling and the Annealing-Melting Integration methods produce the following ranking of the models: Model 1 > Model 4 > Model 2 > Model 3. The Prior Arithmetic Mean estimates are not sufficiently separated to produce a meaningful ranking.

### Table 3. The obtained Bayes factors

<table>
<thead>
<tr>
<th>$\log_{10} B_{12}$</th>
<th>$\log_{10} B_{13}$</th>
<th>$\log_{10} B_{14}$</th>
<th>$\log_{10} B_{24}$</th>
<th>$\log_{10} B_{34}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.209</td>
<td>20.370</td>
<td>4.763</td>
<td>2.446</td>
<td>13.161</td>
</tr>
</tbody>
</table>

`‘decisive’` `‘decisive’` `‘decisive’` `‘decisive’` `‘decisive’`
According to the evidence support categories by Jeffreys (1961) defined in Table 1, the evidence suggests a ‘decisive’ preference of the original Model 1 over the rest of the models. Interestingly, if the true model, Model 1, is not in the set being considered, we see that Model 4 > Model 2, though the log $B_{42} = 2.446$ is only just decisive. This suggests both models may be considered as plausible explanation of the observed data.

4 DISCUSSION

We perform Bayesian hypothesis testing for a selection of biochemical models by computing Bayes factors. An alternative approach to this is based on the maximum $a$ posteriori point estimates of the model parameters. Such estimates can be produced using, for example, the Simulated Annealing algorithm (Hoops et al., 2006; Kirkpatrick et al., 1983). Once such point estimates are found, the alternative models are compared by the maximized value of the corresponding posterior densities. The main problem with using maximum $a$ posteriori estimates for model comparison is their common trend to prefer more complex models over simpler ones due to the ability of more complex models to provide a better fit to data.

The main problem with a more general non-Bayesian hypotheses testing framework using frequentist significance tests is the obscurity of meaning for the $P$-values (Goodman, 1999). The smaller the $P$-value is, the more significant the result is said to be. This value, however, is not the probability of an error. Moreover, non-Bayesian tests tend to reject null hypotheses in very large samples, whereas Bayes factors do not. An example with a number of samples $n = 113,566$ was discussed by Raftery (1986), where a meaningful model that explained 99.7% of the deviance was rejected by a standard $\chi^2$ test with a $P$-value of about $10^{-120}$ but was nevertheless favoured by the Bayes factor.

Akaike (1983) proposed yet another criterion for model comparison, which takes the complexity of the models into account. This criterion suggests choosing the model which minimizes AIC (Akaike information criterion): $AIC = -1 \log$ maximum likelihood + 2(number of parameters). Akaike (1983) claimed that model comparisons based on the AIC are asymptotically equivalent to those made with Bayes factors. But this is true only in the situations when predictions of the prior are compatible to those of the likelihood, and not in the more usual situation when prior information is small in comparison to the information provided by the data. Additionally, using Akaike information criterion, or similar methods, e.g. the deviance information criterion (Spiegelhalter et al., 2002), may not always provide reliable results, as these methods are justified only for the cases when parameter posteriors are unimodal and almost multivariate normal. This is a very rare case in modelling biological systems, for example, the models considered in this study are nonlinear.

The nonlinearity of models employed to describe alternative hypotheses is due to the fact that, in biological research, mechanistic models based on the laws of chemical kinetics are widely used. In the case when experimental data is available for only a few of the model variables (e.g. chemical species), these systems of ODEs collapse into high-order differential equations, which may cause complex nonlinear likelihoods.

Nonlinearity of the models poses the biggest challenge for computing the marginal likelihoods required to calculate the Bayes factors, as simple methods of computing these can fail dramatically (see PAM in Table 2 and PHM in the Supplementary Material). In this article, we have demonstrated that such methods produce very unstable or biased results when applied to nonlinear models of biochemical systems. The reliability of such estimates will be even smaller if the parameter posterior is distributed in multiple equiprobable modes, as sampling from such distributions is very difficult.

On the other hand, the methods based on the principles of path sampling, for example the Annealing-Melting Integration discussed in this article, overcome the problem of integrating difficult distributions by linking the prior, which is usually very simple to sample from, and the posterior with a path in the probability densities space. Moving along such a path helps to overcome so-called energy barriers which separate local modes, and prevent Markov chains used for sampling from convergence to the true posterior distribution. These methods, however, are computationally more expensive, as Markov chains at each of the intermediate steps must converge to their stationary distributions, which may require millions of ‘burn-in’ samples to be discarded first. We provide a comparison of the computational time required to produce one marginal likelihood estimate for Model 4 using a computer with Intel Core 2 Duo processor, PAM $= 92$ s, PHM $= 145$ s, AIS $= 2187$ s, AMI $= 28703$ s. The problem of convergence becomes more and more challenging as the complexity and the size of models grow. This is a potential limitation of the applicability of the Annealing-Melting Integration estimator to only small- to medium-sized problems.

The Annealed Importance Sampling method provides a very attractive feature that the chains do not have to converge to the stationary distributions to be useful in producing the estimates. We have demonstrated that the variance of the estimates produced with the Annealed Importance Sampling method is only marginally worse than the stability of Annealing-Melting Integration estimates, while promising faster estimation and better scalability to larger problems.

5 CONCLUSION

In this article we considered four alternative hypotheses about the structure of a biological system defined with four realistic ODE models. All the models were artificially constructed to allow testing of the proposed methodology on an example with a known result.

We simulated the experimental data from one of the suggested models; selecting the original model as the most probable one at the model comparison stage, was a crucial result to demonstrate the correctness of the approach. We demonstrated how the principle of Occam’s razor works in this framework, as the overly complex model was not preferred to the original one despite it being capable of reproducing the experimental data precisely enough. At the same time, the framework does not blindly select the simplest model. The control experiment using a structurally different model which was not capable of reproducing the general trends of system behaviour was also successful.
Bayesian ranking of biochemical system models

as we demonstrated that this model was rated significantly lower as compared to the rest of the alternatives.

We estimated the marginal likelihood for each of the models using four different estimators: the Prior Arithmetic Mean estimator, the Posterior Harmonic Mean estimator, the Annealed Importance Sampling and the Annealing-Melting Integration method. The estimates produced with the Prior Arithmetic Mean estimator are very unstable, while the estimates of the marginal likelihoods produced with the Posterior Harmonic Mean estimator are biased to larger values, though still capable of producing a correct ranking in this study. This demonstrates that in the cases when complex nonlinear models are employed in a study, the traditional methods of marginal likelihood estimation with importance sampling procedures may fail to provide reliable results. At the same time Annealed Importance Sampling and Annealing-Melting Integration methods provide low variance estimates. We propose to use the Annealed Importance Sampling or Annealing-Melting Integration methods in the cases when hypotheses are expressed with nonlinear ODE models. The Annealed Importance Sampling method is usually faster, as it does not require the samplers to converge when sampling from distributions bridging the prior and the posterior. At the same time, the Annealing-Melting Integration produces smaller errors of the estimates. We highlight the stability of the estimates obtained using annealing-related methods, and foresee the potential of these methods to scale to more complex applications.

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