

The SBML Discrete Stochastic Models Test Suite

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ABSTRACT

Motivation: Stochastic simulation is a very important tool for mathematical modelling. However it is difficult to check the correctness of a stochastic simulator, since any two realisations from a single model will typically be different.

Results: We have developed a test suite of stochastic models which have been solved either analytically or using numerical methods. This allows the accuracy of stochastic simulators to be tested against known results. The test suite is already being used by a number of stochastic simulator developers.

Availability: The latest version of the test suite can be obtained from <http://www.calibayes.ncl.ac.uk/Resources/dsmts/> and is licensed under GNU Lesser General Public License.

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1 INTRODUCTION

In recent years it has been increasingly recognised that mathematical modelling can help us to understand complex biological networks. As a result of this, the Systems Biology Markup Language (SBML) was developed as a standard format in which to represent the models (Hucka *et al.*, 2003). SBML is quickly becoming the lingua franca for the development and sharing of biochemical network models.

One popular modelling technique is to use a discrete stochastic kinetic framework. However, testing the correctness of the implementation of the underlying algorithm is difficult, since a stochastic simulator will by definition give you a different realisation for each run (for a different seed). This is especially problematic since it is possible for two exact algorithms, such as Gillespie's direct method (Gillespie, 1977) and the Next Reaction Method (Gibson and Bruck, 2000), to have different implementations and to use random number streams in an entirely different way.

A further complication in establishing the correctness of a simulator arises from issues of interpretation of the SBML model representation. The SBML specification contains little guidance relating to the proper procedures to be followed in encoding models intended for discrete stochastic simulation (though the latest specification does contain an example), leading to potential confusion. Indeed, SBML Level 1 was not capable of encoding discrete stochastic kinetic models in a correct, accurate and unambiguous way. Fortunately SBML Level 2 and beyond are quite capable in this regard. See the discussion in Chapter 2 of Wilkinson (2006) for further details.

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This paper describes how the SBML discrete stochastic models test suite (DSMTS) can be used to test a stochastic simulator. Versions of the test suite exist for SBML Level 2, versions 1 and 3.

2 TESTING A STOCHASTIC SIMULATOR

The only practical testing method is to run the simulator a large number of times and check that the distribution of outcomes is not significantly different from the true underlying distribution. This can only be tested in a probabilistic way. The test suite is a set of SBML models each with time course data for the means and standard deviations of the model species. Developers may use the suite to check that their simulators produce results that are consistent with the SBML standard. The test suite assumes that the simulator produces output on a regular time grid. Of course, exact stochastic simulators naturally produce output on a non-regular grid corresponding to individual reaction events (see Wilkinson (2006) for further details on stochastic simulators). However, this "step function" output is easy to map onto a regular time-grid either post-hoc, or during the simulation run itself.

In order to test the output from an exact stochastic simulator for a given SBML model (e.g. Gillespie (1977)), n independent simulation runs of the simulator should be performed. For the statistical tests to have reasonable power to detect subtle problems, n should be set to at least 10,000. The sample means and standard deviations of the species amounts from the simulation runs at $t = 0, 1, \dots, 50$ can be compared with the corresponding values in the test suite using the statistical tests described below. Figure 1 shows the mean and standard deviation over time for an example model which includes an event. By comparing the output of many simulations to the true value, we can test the stochastic simulator. The simulated values of a particular species, X , can be tested as follows: let $X_t^{(i)}$ be the value of X_t on the i^{th} run of the simulator, where X_t is the random variable representing X at time t . Put $\mu_t = E(X_t)$ and $\sigma_t = \sqrt{\text{Var}(X_t)}$. Assuming that simulator runs are independent, by the Central Limit Theorem we have

$$\bar{X}_t \sim N(\mu_t, \sigma_t^2/n), \quad \text{where } \bar{X}_t = \frac{1}{n} \sum_{i=1}^n X_t^{(i)},$$

giving

$$Z_t \equiv \sqrt{n} \left(\frac{\bar{X}_t - \mu_t}{\sigma_t} \right) \sim N(0, 1).$$

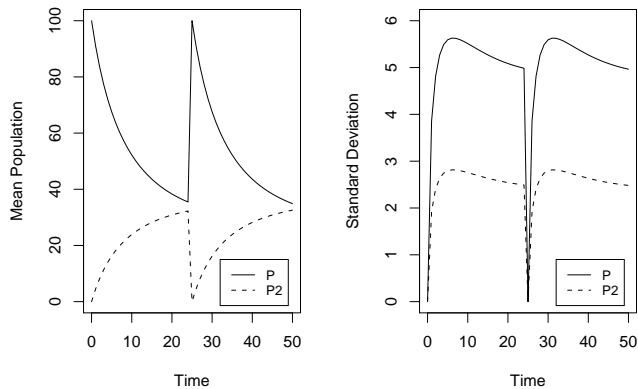


Fig. 1. This figure represents a simple dimerisation model including SBML “events”. When the time parameter t becomes greater than or equal to 25, the species populations are reset to $P = 100$ and $P2 = 0$.

So under the null hypothesis that the simulator is correct, the Z_t values should have a standard normal distribution. In this case, most values will lie in the range $(-3,3)$. Therefore, values of Z_t outside this range correspond to evidence that the simulator is in error. The DSMTS User Guide also describes a test for the standard deviation.

Although the test suite is designed primarily for rigorous testing of exact simulators, it should also prove useful to developers of approximate simulators (Gillespie and Petzold, 2003) or hybrid simulators (Kiehl *et al.*, 2004; Puchalka and Kierzek, 2004). For example, one way of using the test suite to assess the performance of an approximate simulator is to plot the means and standard deviations as percentages of their true values.

The DSMTS currently uses variations of three simple models:

- The birth-death process (see Cox and Miller (1965) for details);
- The dimerisation process (Wilkinson, 2006);
- The batch immigration-death process, of which the classic immigration-death process is a special case (Gillespie and Renshaw, 2005).

The models can be solved either analytically or, in the case of the dimerisation model, by using numerical linear algebra. At the time of writing there are 36 variations of the four models, and these test a variety of SBML features, such as units, rate law interpretation, events, and cell volumes. To run the entire test-suite takes approximately one hour, for $n = 10,000$ and a reasonably fast simulator.

3 CONCLUSION

The test suite is already being employed by a number of stochastic simulator developers. For example, the developers of the Systems Biology Workbench (Hucka *et al.*, 2002; Vallabhajosyula and Sauro, 2007), the BASIS system (Kirkwood *et al.*, 2003; Gillespie *et al.*, 2006) and COPASI (Hoops *et al.*, 2006) all use the test suite routinely. We have found the test suite to be invaluable when developing our own stochastic simulator, as it provides a simple and systematic means with which to test many aspects of the simulator behaviour.

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