matLeap: A fast adaptive Matlab-ready tau-leaping implementation suitable for Bayesian inference

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Abstract

Background: Species abundance distributions in chemical reaction network models cannot usually be computed analytically. Instead, stochastic simulation algorithms allow sample from the system configuration. Although many algorithms have been described, no fast implementation has been provided for τ-leaping which i) is Matlab-compatible, ii) adaptively alternates between SSA, implicit and explicit τ-leaping, and iii) provides summary statistics necessary for Bayesian inference.

Results: We provide a Matlab-compatible implementation of the adaptive explicit-implicit τ-leaping algorithm to address the above-mentioned deficits. matLeap provides equal or substantially faster results compared to two widely used simulation packages while maintaining accuracy. Lastly, matLeap yields summary statistics of the stochastic process unavailable with other methods, which are indispensable for Bayesian inference.

Conclusions: matLeap addresses shortcomings in existing Matlab-compatible stochastic simulation software, providing significant speedups and summary statistics that are especially useful for researchers utilizing particle-filter based methods for Bayesian inference. Code is available for download at https://github.com/claassengroup/matLeap.

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1 Background

Chemical reaction networks (CRNs) provide a quantitative description of the probabilistic evolution of systems of interacting molecules, and are

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frequently used to model biological systems such as gene regulatory or signaling networks. However, CRNs are not generally solvable in closed form. One may instead produce sample trajectories of the stochastic process dependent on initial conditions, reaction stoichiometry and parameters using the Stochastic Simulation Algorithm (SSA) \[5\] and related algorithms. However, SSA is prohibitively expensive for systems with disparity in relevant time scales \[7\]. Algorithms exist for exploiting the difference in time scales including \(\tau\)-leaping algorithm and variants \[6\], which reduce computational effort by approximating the Markov jump process by a Poisson process over intervals for which reaction probabilities are approximately constant. The jump intervals are chosen to bound the expected change (and variance) in reaction probabilities, providing a tunable control for accuracy \[3\].

Several implementations of stochastic simulation algorithms are available, often combined with extensive graphical environments for creating, simulating and analyzing the results, see e.g. Systems Biology Toolbox \[12\], or Matlab SimBiology. However, they are limited to either explicit or implicit \(\tau\)-leaping and do not adaptively change in response to dynamic system stiffness. To address this gap we developed matLeap, a fast C++ based implementation of the adaptive explicit-implicit \(\tau\)-leaping algorithm \[4\]. matLeap adapts between \(\tau\)-leaping algorithms with the stiffness of the system, and ensures non-negativity of species by using critical reactions and switching to SSA when required. Unlike most available packages, we focus on a minimalistic interface-free implementation which integrates directly with Matlab, using models provided as SBML files and a few tuning parameters to perform simulations.

For Bayesian parameter inference of CRNs, one is often interested in inferring the posterior distribution of the reaction constant \(\theta_i\) of reaction \(i\). Assuming mass action kinetics, the reaction propensity at time \(t\) is given by \(a_i(X_t) = \theta_i g_i(X_t)\), where \(g_i(X_t)\) is a function of the reaction educt copy numbers and \(X_t\) is the state of the system. Inference is simplified if one assumes gamma-distributed reaction constants, i.e. \(\pi_i(\theta_i) = \Gamma(\theta_i; \alpha_i, \beta_i)\) with hyperparameters \(\alpha_i, \beta_i\). In this case the posterior distribution for a trajectory with \(r_i\) firings of reaction \(i\) and integral \(G_i = \int g_i(X_s)ds\) of the function \(g_i\) is given by \(\Gamma(\theta_i; \alpha_i + r_i, \beta_i + G_i)\) \[8\]. matLeap provides the summary statistics, \(r_i\) and \(G_i\) for each reaction \(i\); \(G_i\) is computed using trapezoidal approximation when \(\tau\)-leaping and exactly when performing SSA. Lastly, the implicit \(\tau\)-leaping algorithm requires the inverse Jacobian of the reaction propensities. For small systems this can be computed symbolically in Matlab and supplied to matLeap for additional speedup; otherwise it is estimated numerically.

2 Implementation

matLeap implements the adaptive explicit-implicit \(\tau\)-leaping algorithm \[4\], switching to implicit \(\tau\)-leaping if the computed leap size is much greater when excluding reaction pairs in equilibrium. Non-negativity of species is ensured using critical reactions. We slightly modified the algorithm to switch to SSA if the waiting to the next critical reaction is
comparable to the waiting time to the next reaction preventing critical, very fast reactions from forcing the system to perform $\tau$-leaping over very small intervals.

matLeap is implemented in C/C++ using the Eigen [9] and Boost (http://boost.org) libraries. It generates a mex-file that can be called with variable initial conditions and model parameters; control parameters determine the accuracy of the $\tau$-leaping approximation, and behavior with respect to critical species (see Supplemental Information). Models are specified using SBML and loaded using libSBML [2]. The Matlab symbolic computing and compiler toolboxes are required.

The mex file can be called with a matrix of initial conditions for all species, and/or a matrix of parameter values to be used which is especially useful for parameter inference settings. We note that this is in contrast to StochKit and SimBiology which require the user to create new configuration files or structures, respectively, before rerunning.

3 Results

We compared matLeap against two frameworks, StochKit 2.0 [11] and the Matlab SimBiology toolbox, for three models: the prokaryotic auto-regulatory gene network model [13] (Figure 1), the Ras/cAMP/PKA pathway in *S. cerevisiae* [1] (Figure 2), and a stiff decaying-dimerizing reaction set [10] (Figure 3).

Figure 1: Comparison of SSA, $\tau$-leaping using StochKit, and $\tau$-leaping using matLeap for the prokaryotic auto-regulatory gene network model [13].
Figure 2: Comparison of SSA, \( \tau \)-leaping using StochKit, and \( \tau \)-leaping using matLeap for the Ras/cAMP/PKA pathway [1]
Figure 3: Comparison of SSA, $\tau$-leaping using StochKit, and $\tau$-leaping using matLeap for the stiff decaying-dimerizing reaction set [10]
| Method         | Auto-regulation KL-div. | Run time | Ras/cAMP/PKA KL-div. | Run time | Stiff dimerizing/decaying KL-div. | Run time |
|----------------|-------------------------|----------|----------------------|----------|----------------------------------|----------|
| StochKit SSA   | 0.0034±0.0013           | 0.0110   | 0.0021±0.0014        | 0.1464   | 0.0023±0.0017                    | 0.2605   |
| StochKit τ-leap| 0.0036±0.0012           | 0.1803   | 0.0051±0.0172        | 0.1891   | 0.0023±0.0018                    | 0.4018   |
| matLeap        | 0.0037±0.0012           | 0.0046   | 0.0057±0.0187        | 0.1472   | 0.0408±0.1213                    | 0.0042   |
| matLeap (symbolic) | 0.0038±0.0013       | 0.0046   | n.a.                 | n.a.     | 0.0414±0.1220                    | 0.0037   |
| SimBiology     | n.a.                   | 0.0419   | n.a.                 | 0.8574   | n.a.                             | 1.4818   |

Table 1: Average (std.) Kullback-Leibler divergence and run-time comparison of matLeap and StochKit evaluated for $\epsilon = 0.03$ ($10^4$ simulations for StochKit and matLeap, 20 for SimBiology). Run times reported as average per simulation (all standard deviations < 4%, n=5).

In each case we compute the accuracy, given by the Kullback-Leibler divergence, averaged over all time points and species, with respect to exact SSA (Table 1). We used $10^4$ stochastic simulations and 5 replicates, see Supplemental Information for comparison of simulated trajectories. For the τ-leaping methods, we set the control parameter $\epsilon$ to 0.03. StochKit τ-leaping determines automatically at run-time the appropriate (explicit or implicit) algorithm.

matLeap is as accurate as StochKit τ-leaping except for the dimerization model, where it underestimates the variance of two fast species (c.f. Figure 3). This is a known limitation of the implicit τ-leaping algorithm [10]. However, matLeap can be run in fully explicit τ-leaping or SSA-mode if higher accuracy for the variances of fast species is needed. In each case matLeap runs at least as fast as the faster of StochKit SSA or τ-leaping; in some cases it runs nearly 100 times as fast. For the dimerization model using the symbolic Jacobian provides an additional \approx 14% speedup. Furthermore, matLeap runs between approximately 6 and 350 times faster than Matlab SimBiology. Due to the excessive run time, we did not evaluate the accuracy of Matlab SimBiology. We note that StochKit necessarily writes all results to disk (as plain text) which contributes to its run time. Also, SimBiology saves the complete reaction path of all species, which significantly slows its performance and greatly increases memory consumption.

4 Discussion

Stochastic simulation is a mature field with many exact and approximate solvers available. However, few of the existing methods are available for
direct use with Matlab. Comprehensive packages such as Matlab Sim-
Biology can prove difficult to configure, prohibitively slow, and do not
adaptively switch to accommodate varying problem stiffness. We take an
alternative approach providing a simple and very fast adaptive τ-leaping
solver aimed at practitioners. matLeap is at least as fast as current widely
used implementations, while also uniquely providing the summary statistics \( r_i \) and \( G_i \), introduced above, which are very valuable for Bayesian
inference in chemical reaction networks. An example of multicore parallel-
ization is included in the Supplementary Information.

5 Declarations

Availability of data and material
The datasets generated during and/or analysed during the current study
are available at https://github.com/claassengroup/matLeap, as is the
matLeap package.

Competing interests
The authors declare that they have no competing interests.

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Authors’ contributions
JF conceived of and implemented the numerical method. SG performed
testing and implemented the Matlab package. JF wrote the manuscript.
MC provided support and supervision.

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