SELANSI: a toolbox for simulation of stochastic gene regulatory networks

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Abstract

Motivation: Gene regulation is inherently stochastic. In many applications concerning Systems and Synthetic Biology such as the reverse engineering and the de novo design of genetic circuits, stochastic effects (yet potentially crucial) are often neglected due to the high computational cost of stochastic simulations. With advances in these fields there is an increasing need of tools providing accurate approximations of the stochastic dynamics of gene regulatory networks (GRNs) with reduced computational effort.

Results: This work presents SELANSI (SEmi-LAgrangian SImulation of GRNs), a software toolbox for the simulation of stochastic multidimensional gene regulatory networks. SELANSI exploits intrinsic structural properties of gene regulatory networks to accurately approximate the corresponding Chemical Master Equation with a partial integral differential equation that is solved by a semi-lagrangian method with high efficiency. Networks under consideration might involve multiple genes with self and cross regulations, in which genes can be regulated by different transcription factors. Moreover, the validity of the method is not restricted to a particular type of kinetics. The tool offers total flexibility regarding network topology, kinetics and parameterization, as well as simulation options.

Availability and implementation: SELANSI runs under the MATLAB environment, and is available under GPLv3 license at https://sites.google.com/view/selansi.

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1 Introduction

Understanding the dynamics of Gene Regulatory Networks (GRNs) requires appropriate modeling and simulation tools to efficiently represent their underlying stochastic nature. At this level, the states of the system are random variables whose evolution can only be predicted probability-wise via the Chemical Master Equation (CME). Unfortunately, such description, which consists of a large dimensional set of coupled ODEs, does not admit a closed form solution in most cases of practical interest (Keyven et al., 2015). Apart from the now classical Stochastic Simulation Algorithm (SSA) (Gillespie, 2007), numerical solutions of the CME range from discrete to continuous approximations. SSA methods including their software implementations (e.g. Hoops et al., 2006; Maarleveld et al., 2013; Ramsey et al., 2003; Sanft et al., 2011) make use of Monte Carlo type simulations to reconstruct the probability function from a large number of realizations of the stochastic GRN (Gillespie, 2007). Although such methods are generally applicable, they may become prohibitive due to the computational burden.

Discrete approximations such as the finite state projection (FSP) or moment based (MB) methods, reduce the number of state variables by either restricting the states to those most probable, or by computing the most relevant moments of the underlying distribution. Related software tools include StochDynTools by Hespanha et al. (2008), CmePy by Hegland et al. (2010) (available at https://
github.com/begland/cmepy), MOCA by Schnoerr et al. (2015) and SHAVE by Lapin et al. (2011). Despite truncation, accuracy typically demands the number of remaining variables in FSP methods to be substantially large, what makes problems computationally involved.

MB methods would be preferable in those situations where one is interested in computing some particularly relevant moments of the distribution rather than its precise form (see Engblom, 2006). However, reconstructing the probability density function (pdf) from the moments is in general, not straight-forward, since this requires assumptions on the form of the pdf (and relates to the accuracy of the moment closure). This might be simple in some cases (e.g. if near Gaussian, two parameters/moments are enough) but not in others, as for instance under nonlinear kinetics or in characterizing multi-modal distributions (Hasenauer et al., 2014; Pajaro et al., 2017).

Finally, Fokker-Plank (FP) based methods are a class of continuous approximations developed on systems size expansions (Hespanha et al., 2008; Thomas et al., 2013), which inherit similar limitations as the MB methods when the resulting distribution diverges from a Gaussian. A collection of software tools that includes FSP and MB methods can be found in the recently developed toolbox CERENA by Kazeroonian et al. (2016).

In between discrete and FP approximations, first Friedman et al. (2006) for uni-dimensional GRN and most recently Pajaro et al. (2017) for multi-dimensional GRN, proposed a partial integral differential equation (PIDE) approximation based on a time-scale separation property, denoted in what follows as protein bursting condition. The protein bursting condition, which is shared by most GRNs in prokaryotic and eukaryotic organisms (e.g. Dar et al., 2012). The software tool SELANSI (SEmi-LAgrangian Simulation of gene regulatory networks) approximates the CME by the PIDE model in Pajaro et al. (2017) and computes its numerical solution by an efficient and scalable semilagrangian method, providing the temporal evolution of the protein probability density function (together with its stationary state).

2 Multidimensional PIDE model

SELANSI uses a generalized description of GRNs in which each protein can interact with its corresponding gene to regulate its own expression (self-regulation) and/or with any other gene(s) in the network (cross-regulation). For $n$ genes, which are expressed into $n$ different protein types, the number of molecules of each protein is encoded in a vector $x = (x_1, \ldots, x_n)$. The PIDE model implemented in SELANSI exploits the protein bursting assumption (i.e. proteins being produced in episodic bursts), which is valid whenever messenger RNA degrades much faster than proteins. As it has been discussed in Pajaro et al. (2017) the PIDE model provides good approximations already for degradation rate ratios in the order of 3–5. Under this assumption, the governing equation of the GRN dynamics (Pajaro et al., 2017) reads:

$$
\frac{\partial p(t,x)}{\partial t} = \sum_{i=1}^{n} \left( \frac{\partial}{\partial x_i} \left[ \frac{c_i(x)p(t,x)}{x_i} \right] - k_{im}^c c_i(x)p(t,x) \right)
+ k_{im}^b \int_0^\infty o_0(x_i - y_i)c_i(y_i)p(t,y)\,dy_i
$$

(1)

where $p(t,x)$ denotes the probability distribution function associated to the $n$ proteins expressed in the network. Functions $o_0(x_i - y_i)$ describe the conditional probability for proteins jumping from a state $y_i$ to $x_i$. Under the bursting condition, these functions follow an exponential-type distribution of the form

$$
o_0(x_i - y_i) = \frac{1}{b_i} \exp \left( -\frac{x_i - y_i}{b_i} \right)
$$

(2)

where $b_i = \frac{k_{im}^b}{\gamma_i}$ denotes translation frequency and relates to burst size.

Network regulation topology as well as the activation/inactivation gene state dynamics are encoded through functions $c_i(x)$. When the promoter switching rates between on and off states are much faster than transcription-translation, the corresponding expressions $c_i$ are defined in terms of Hill-type functions. SELANSI incorporates pre-defined Hill functions but can accommodate other kinetics (for different ratios of switching rates versus transcription-translation) through appropriate $c_i$ expressions.

Equation (1) is defined in a domain $\Omega = \prod_{i=1}^{n} (0, L_i) \subset \mathbb{R}^n$, with $L_i > 0$, and a time interval $[0,T]$. SELANSI approximates the domain $\Omega$ by a uniform (protein) mesh and computes the solution on a uniform time grid by a semilagrangian method (Pajaro et al., 2017). The computational burden depends directly on the size of the mesh and indirectly on the number of genes involved (since higher order networks will require more mesh points for equal accuracy). Guidelines about levels of discretization, computational efficiency and accuracy are provided in the user’s manual. By way of indication, SELANSI provides affordable computation times for reasonably smooth solutions up to 5 coupled genes.

3 Main features of SELANSI

SELANSI is a toolbox for simulation of stochastic multidimensional gene regulatory networks implemented in Matlab, working on Windows, Linux and MacOs. The SELANSI toolbox offers:

- **High Flexibility**: Gene networks under consideration might involve multiple genes with self and cross regulations, in which genes can be regulated by different transcription factors. The user can specify the size and topology of the network, as well as the kinetics, parameter values, time horizon and discretization levels for simulation.

- **Generality**: The validity of the method is not restricted to a particular type of kinetics (mass action, Hill, etc.). Although input functions of the Hill type are predefined in SELANSI, the user can easily define his/her own input functions by modifying the available templates.

- **High computational efficiency**: The semilagrangian method implemented in SELANSI is proven efficient and scalable. For networks involving 4 to 5 coupled genes, speed-up factors in computation times are typically of two orders of magnitude with respect to SSAs (Pajaro et al., 2017).

The available tasks in the SELANSI toolbox are listed and briefly summarized below.

- **Definition of the problem**: The routine SELANSI_Gnetmod allows the user to easily define a new model (i.e. number of genes, interactions, type of kinetics and parameters), the simulation specifications (i.e. initial condition, time horizon for simulation and discretization including time and protein meshes), as well as the time steps for which the solution is saved.

- **Modification of an existing problem**: SELANSI_Gnetmod and SELANSI_Meshmod allow the user to modify, respectively, the parameters and simulation specifications of an existing problem. Specifically, SELANSI_Gnetmod modifies the
default network parameters and feedback mechanism, while SELANSI_Meshmod modifies the default mesh for the semi-Lagrangian method and the initial condition.

iii. Stochastic simulation: SELANSI_Solve computes the (approximated) numerical solution of the CME obtaining the temporal evolution of the species’ probability density function. It saves also the solution according to the user’s specifications.

iv. Results and Visualization: SELANSI_Plot depicts marginal and joint probability densities (in multidimensional case) for the time steps selected by the user.

As an illustrative example (this and other examples with different number of genes, connectivities and kinetics are provided with the toolbox) we consider a two dimensional gene regulatory network in which the two genes mutually repress each other. Figure 1 shows a scheme of the inputs provided by the user and the results of the simulation computed by SELANSI (for space reasons, we include only a few snapshots). For the selected values of the parameters the network behaves as a transcriptional switch with a bimodal stationary distribution.

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Fig. 1. Simulation with SELANSI of a two dimensional stochastic gene network with mutual repression and Hill kinetics. User inputs include (A) number of genes and kinetics, (B) kinetic constants, Hill coefficients and (C) protein and time meshes. (D) Samples of joint probability snapshots provided by SELANSI