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Applications Note

Systems biology

Compartor: a toolbox for the automatic generation of moment equations for dynamic compartment populations

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Abstract

Summary: Many biochemical processes in living organisms take place inside compartments that can interact with each other and remodel over time. In a recent work, we have shown how the stochastic dynamics of a compartmentalized biochemical system can be effectively studied using moment equations. With this technique, the time evolution of a compartment population is summarized using a finite number of ordinary differential equations, which can be analyzed very efficiently. However, the derivation of moment equations by hand can become time-consuming for systems comprising multiple reactants and interactions. Here we present Compartor, a toolbox that automatically generates the moment equations associated with a user-defined compartmentalized system. Through the moment equation method, Compartor renders the analysis of stochastic population models accessible to a broader scientific community.

Availability and implementation: Compartor is provided as a Python package and is available at https://pypi.org/project/compartor/. Source code and usage tutorials for Compartor are available at https://github.com/zechnerlab/Compartor.

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1 Introduction

Moment-based approaches provide an effective means to study the dynamics of noisy biochemical networks (Ruess and Lygeros, 2015; Schnoerr et al., 2017; Singh and Hespanha, 2006). These approaches are based on systems of ordinary differential equations (ODEs), which capture the statistical properties of the reaction network such as average concentrations and their variability. However, the derivation of moment equations by hand can become exceedingly tedious, especially for systems comprising multiple chemical species and reactions. To address this problem, toolboxes have been developed to generate moment equations directly from the stoichiometric specification of a network, which greatly boosts the applicability of these approaches (Fan *et al.*, 2016; Hespanha, 2007; Kazeroonian *et al.*, 2016).

Existing moment generators apply to well-mixed reaction environments or compartmentalized systems with fixed spatial arrangement. However, many biological processes are organized within compartments that can remodel and interact dynamically. Examples include cell growth and division dynamics in cell communities or the fusion and fission events of sub-cellular transport vesicles. In our recent theoretical work (Duso and Zechner, 2020), we have shown how the method of moments can be extended to such situations. In this framework, we consider a population of reaction compartments where both the molecular contents and the compartments themselves can stochastically interact and change over time. Manually deriving moment equations for such models is even more tedious than for standard reaction systems, because additional higher-order statistics arise.

In this work we present Compartor, an automatic moment equation generator for stochastic compartment populations. Compartor starts from a set of provided interaction rules and derives the associated moment equations. In its current version, equations can be exported as LaTeX, Python or Julia code. In the following, we explain Compartor and illustrate it for an examplary model (see Fig. 1). A short tutorial on the usage of Compartor is provided in dedicated Jupyter notebooks at https://github.com/zechnerlab/Compartor.

2 Materials and methods

Compartor is based on the formalism introduced by Duso and Zechner (2020). A compartment population consists of a time-varying number $N(t)$ of compartments, each associated with a D-dimensional molecular content $\mathbf{x} \in \mathbb{X} \subseteq \mathbb{N}_0^D$. The state of the

A Definition of the model

```
Intake      = TransitionClass( {} -to> [(y[0],0)], 'k_I', pi=pi_I, name='I' )
Fusion      = TransitionClass( [x] + [y] -to> [x+y], 'k_F', name='F' )
Conversion  = TransitionClass( [x] -to> [x + (-1,1)], 'k_c', x[0], name='c' )
Degradation = TransitionClass( [x] -to> [x + (0,-1)], 'k_d', x[1], name='d' )

transitions = [ Intake, Fusion, Conversion, Degradation ]
display_transition_classes(transitions)
```

$$\emptyset \xrightarrow{h_I} [(y_0, 0)] \qquad h_I = k_I \pi_I(y_0; \lambda)$$

$$[x] + [y] \xrightarrow{h_F} [x + y] \qquad h_F = k_F \frac{(n(y) - \delta_{xy})\, n(x)}{\delta_{xy} + 1}$$

$$[x] \xrightarrow{h_c} [(-1,\ 1) + x] \qquad h_c = k_c n(x) x_0$$

$$[x] \xrightarrow{h_d} [(0,\ -1) + x] \qquad h_d = k_d n(x) x_1$$

C Automated derivation of moment equations

```
desired_moments = [Moment(0,0), Moment(0,1), Moment(0,1)**2]
equations = automated_moment_equations(2,transitions,desired_moments)
```

Computed moment equations for desired moments $\langle N \rangle$, $\langle M^{(0,1)} \rangle$ and $\left\langle \left(M^{(0,1)} \right)^2 \right\rangle$.

Equations were iteratively added for $\langle N^2 \rangle$, $\langle M^{(1,0)} \rangle$, $\langle M^{(1,0)} M^{(0,1)} \rangle$ and $\left\langle \left(M^{(1,0)} \right)^2 \right\rangle$.

Gamma closures were substituted for $\langle N^3 \rangle$.

```
display_moment_equations(equations)
```

$$\frac{d}{dt}\langle N \rangle = \frac{k_F \langle N \rangle}{2} - \frac{k_F \langle N^2 \rangle}{2} + k_I$$

$$\frac{d}{dt}\langle N^2 \rangle = -k_F \left(-\langle N \rangle \langle N^2 \rangle + \frac{2\langle N^2 \rangle^2}{\langle N \rangle} \right) - \frac{k_F \langle N \rangle}{2} + \frac{3k_F \langle N^2 \rangle}{2} + 2k_I \langle N \rangle + k_I$$

$$\frac{d}{dt}\left\langle M^{(1,0)} \right\rangle = \lambda k_I - k_c \left\langle M^{(1,0)} \right\rangle$$

$$\frac{d}{dt}\left\langle \left(M^{(1,0)} \right)^2 \right\rangle = \lambda^2 k_I + 2\lambda k_I \left\langle M^{(1,0)} \right\rangle + \lambda k_I + k_c \left\langle M^{(1,0)} \right\rangle - 2k_c \left\langle \left(M^{(1,0)} \right)^2 \right\rangle$$

$$\frac{d}{dt}\left\langle M^{(0,1)} \right\rangle = k_c \left\langle M^{(1,0)} \right\rangle - k_d \left\langle M^{(0,1)} \right\rangle$$

$$\frac{d}{dt}\left\langle \left(M^{(0,1)} \right)^2 \right\rangle = 2k_c \left\langle M^{(0,1)} M^{(1,0)} \right\rangle + k_c \left\langle M^{(1,0)} \right\rangle + k_d \left\langle M^{(0,1)} \right\rangle - 2k_d \left\langle \left(M^{(0,1)} \right)^2 \right\rangle$$

$$\frac{d}{dt}\left\langle M^{(0,1)} M^{(1,0)} \right\rangle = \lambda k_I \left\langle M^{(0,1)} \right\rangle - k_c \left\langle M^{(0,1)} M^{(1,0)} \right\rangle - k_c \left\langle M^{(1,0)} \right\rangle + k_c \left\langle \left(M^{(1,0)} \right)^2 \right\rangle - k_d \left\langle M^{(0,1)} M^{(1,0)} \right\rangle$$

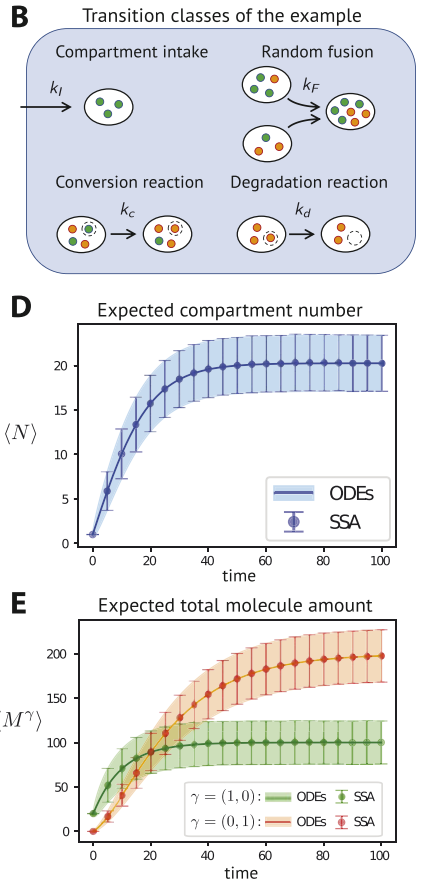

Fig. 1. Usage example of Compartor. (**A**) Definition of the transition classes for the considered exemplary model. (**B**) Illustration of the transition classes for the considered model. The white-filled ovals represent compartments, while the green and orange circles denote two different molecular species. The intake process generates new compartments containing a Poisson-distributed amount of green molecules with mean parameter λ. (**C**) One-step derivation of a closed system of moment equations for a set of desired moments. Here, Compartor recognized automatically the need of including additional moment dynamics and applied a third-order Gamma closure. (**D,E**) Plot of the expected number of compartments $\langle N \rangle$, and the total molecular amounts $\langle M^{(1,0)} \rangle$ and $\langle M^{(0,1)} \rangle$, surrounded above and below by one standard deviation. Full lines and shaded areas show the result of moment equations (ODEs), while dots and error bars correspond to the average of 10^4 stochastic simulations (SSA) (Gillespie, 2007). The standard deviation for $\langle N \rangle$ is obtained from the moment equations as $\sqrt{\langle N^2 \rangle - \langle N \rangle^2}$, and analogously for the other moments. The rate constants were set to $(k_I, k_F, k_c, k_d, \lambda) = (1, 5 \cdot 10^{-3}, 0.1, 0.05, 10)$. The initial condition is given by one compartment with 20 green molecules and zero orange molecules

population at time t is fully characterized by knowing the number $n(\mathbf{x}, t)$ of compartments for each possible content $\mathbf{x} \in \mathbb{X}$. A population moment is generally defined as the sum $M^{\gamma}(t) = \sum_{\mathbf{x} \in \mathbb{X}} \mathbf{x}^{\gamma} n(\mathbf{x}, t)$, where $\mathbf{x}^{\gamma} = \prod_{d=0}^{D-1} x_d^{\gamma_d}$ and γ is a vector of non-negative integer exponents. In particular, $M^{\mathbf{0}}(t) = \sum_{\mathbf{x} \in \mathbb{X}} n(\mathbf{x}, t) = N(t)$ corresponds to the number of compartments at time t. Note that any population moment is an integer random variable that evolves stochastically. We denote the expectation of a moment $M^{\gamma}(t)$ by $\langle M^{\gamma}(t) \rangle$. Our goal is to derive equations that describe the expected evolution of a certain set of moments or functions thereof. Compartor allows the user to specify the dynamical rules—which we refer to as *transition classes*—that govern the compartment population and generates the corresponding system of moment equations.

2.1 Defining the model

In Compartor, the user defines a transition class through a stoichiometric-like equation where the reactant compartments on the left-hand side are converted into the product compartments on the right-hand side (see Fig. 1A). The tool supports transition classes up to order two, meaning that at most two compartments can react with one another during an event. Similarly, biochemical reactions inside a single compartment are restricted to at most two reactant molecules.

The definition of a transition class requires a propensity function that determines the transition rate in dependency of the involved compartment contents. Note that propensity functions must be polynomials in $\mathbf{x}$ for the moment method to be applicable. The specification of the transition propensities occurs together with the definition of the associated transition classes, as shown in the script of Figure 1A. An illustration of the four transition classes defining this example is provided in Figure 1B. For further information about the definition of transition classes, the reader may refer to Duso and Zechner (2020).

2.2 Moment equation generation

For the specified population model, the user provides Compartor with a set of moments for which equations should be derived. Compartor then carries out the necessary symbolic computations and returns the corresponding moment equations. Note that the derived system of moment equations is often not closed, meaning that it may involve other moments for which equations have not yet been generated. In these cases, the tool detects the presence of additional moments for which the governing equations are missing. The user can then opt to generate further equations for these moments or, alternatively, ask Compartor to apply a moment closure to approximate them by functions of the available ones. Currently, Compartor supports mean-field and third-order Gamma closures (Lakatos *et al.*, 2015).

As shown in Figure 1C, the tool offers a one-step feature to automatically handle the process of moment identification, equation generation and moment closure. This is accomplished by iteratively expanding the system of equations until it closes by itself, or until the highest-order moments reach order three, at which point the proposed Gamma and/or mean-field closures are applied. When the user does not specify any initial set of desired moments, Compartor returns the minimal system of moment equations sufficient to describe the expected dynamics of compartment number and total mass for each chemical species. In Figure 1D and E, we show the solution of the system of moment equations for the given example. The obtained moment trajectories are in agreement with the Monte Carlo averages obtained by exact stochastic simulations.

2.3 Code export

At any time, the user can decide to export the equations generated by Compartor as LaTeX source, or as Python or Julia code compatible with standard ODE solvers in the respective language.

3 Discussion

Compartor is a code generator that enables efficient analysis of stochastic compartment population models through the moment equation method. The tool can be applied to arbitrary models comprising compartment interactions and biochemistry up to second order. Additionally, the propensity functions must satisfy a polynomial form for the moment equation method to be applicable. Compartor is equipped with mean-field and third-order multivariate Gamma closures to approximate systems whose moment dynamics is not closed. We emphasize that the accuracy of any moment closure is model dependent (Schnoerr *et al.*, 2014) and, consequently, the obtained system of equations needs to be validated case by case. Future releases may extend Compartor to account for additional closure schemes and kinetic laws.

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