

Generating WESTPA templates of BioNetGen language models

Abstract

WEBNG is a tool to simplify WESTPA simulations of BNGL models.

Introduction

Models of biochemical systems can get complicated, resulting in a large number of chemical species. Frequently these models result in combinatorial complexity when species have multiple states that they can be in. A rule-based modelling approach was developed to avoid manually enumerating every possible species and reactions. Rule-based models define rules which specify how species can interact and all possible reactions and species are generated off of these rules. BioNetGen (BNG) is an open-source rule-based modelling software package that allows for model construction in BioNetGen language (BNGL) and simulation of BNGL models.

Rare events in modelling are events that take a long time to occur compared to the time scale of the fastest process in the model. For some models, rare events are unavoidable because the fastest process in the system must be modelled for accuracy. This is frequently the case for biological models and while some modelling methods allow for simplification of the fastest process, it's generally ideal to model everything if possible. Models with rare events are also frequently hard to simulate because it takes many events to get a statistically robust estimate of any aspect of a biological process which means the simulations need to run for a long time to get enough rare events to occur.

Tackling this problem has been a focus of the computational modelling field for a while and many rare event sampling methods have been developed. One of these methods is called weighted ensemble method. Weighted ensemble path sampling works by organizing multiple parallel trajectories, resampling them at a fixed time interval. Each trajectory is assigned a statistical weight that are tracked during WE resampling. This allows WE resampling scheme to keep model kinetics statistically rigorous while replicating trajectories making progress towards the rare event of interest and terminating trajectories that aren't.

WESTPA is an open-source, scalable and interoperable software package that applies the WE strategy. WESTPA has been successfully used to study multiple challenging biological processes and is being actively maintained. WESTPA is interoperable and is designed to interface with any stochastic simulator, which makes it ideal to use with BNG stochastic simulation methods.

In bioinformatics modelling, researchers frequently ignore rare events because it is easier to coarse grain the fastest processes and keep the timescale separation in a model relatively small, reducing computational cost. However, this does come at the cost of accuracy and not being able to understand how the kinetics of the fast processes in a model affect the slow ones. Rare event sampling methods can alleviate this issue, allowing researchers to tackle more detailed, challenging models that contain rare events.

To this end we have developed a templating tool named WEBNG that makes it easier to setup WESTPA simulations of a BNGL model. The user needs to supply WESTPA parameters along with a BNGL model and the tool creates a WESTPA simulation folder which can then be ran like any other WESTPA simulation. The tool also comes with some analyses built-in and is designed to tackle high dimensional WE simulations that are better suited for BNG models. WEBNG tries to lower the entry barrier for bioinformatics researchers to use weighted ensemble rare event sampling method and explore more models where rare events occur without having to worry about the computational cost.

How to use WEBNG

Validation and efficiency

Conclusion and future directions