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phraSED-ML: a Paraphrased, Human-Readable Adaptation of SED-ML

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Motivation: Model simulation exchange has been standardized with the Simulation Experiment Description Markup Language (SED-ML), but specialized software is needed to generate simulations in this format. Text-based languages allow researchers to create and modify experimental protocols quickly and easily, and export them to a common machine-readable format.

Results: phraSED-ML language allows modelers to use simple text commands to encode various elements of SED-ML (models, tasks, simulations, and results) in a format easy to read and modify. The library can translate this script to SED-ML for use in other softwares.

Availability: phraSED-ML language specification, `libphrasedml` library and source code are available under BSD license from <http://phrasedml.sourceforge.net/>

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1. Introduction

Reproducibility is a cornerstone of scientific research. In systems biology, the ability to losslessly encode and share computational models of biological systems is enabled with the development of Systems Biology Markup Language (SBML)⁹ and CellML¹². More recently, the Simulation Experiment Description Markup Language (SED-ML) was released¹⁶. This new markup language expanded the field of computer-exchangeable modeling from the models to the experiments performed on those models. The first version of SED-ML (Level 1 version 1) included the ability to encode uniform time course experiments only. Version 2 expanded SED-ML's capabilities to include 'repeated tasks', which allow more complicated experiments

such as parameter scans. SED-ML defines five basic classes: the Model references a particular XML-based model (usually in SBML or CellML), or a modified version of the same; the Simulation defines a particular algorithm; the Task relates an algorithm to a model; and an Output defines how the results of a Task are to be conveyed to the user, either as a plot or a report. The RepeatedTask introduced in Version 2 of the specification is a more specialized version of a Task that defines how to repeat another Task over a specified range. Elements inside referenced models are referred to through the use of XML Path Language (XPath) strings⁵, and algorithms and their parameters are referenced by their Kinetic Simulation Algorithm Ontology (KiSAO) ids⁶.

There are several programs that support SED-ML by importing and performing simulation described in a SED-ML file. Our own Tellurium (tellurium.analogmachine.org) translates SED-ML to Python code that utilizes Roadrunner's Python bindings¹⁵. Other simulators include the SBW Simulation Tool³ and the Systems Biology Simulation Core Library¹⁰. Apart from generic XML editors, some others let you edit or create SED-ML. SED-ML Script² defines a script-based language that is closely tied to SED-ML itself: each script function adds a particular SED-ML element to a document, with the arguments of that function setting all of the particular attributes and child elements of that root element. However, no particular attempt is made to hide the complexity or to error-check: all arguments to the script functions are passed as-is to the SED-ML creator, including XPath strings. While simpler than editing the XML directly, this approach leaves a burden on the user to comprehend the details of raw SED-ML.

On the other end of the complexity spectrum, Frank Bergmann created a SED-ML creator 'wizard' (<http://sysbioapps.dyndns.org/SED-ML/Web/Tools/>) which creates a 'standard' SED-ML file from an uploaded SBML file with few basic options. Another GUI-based SED-ML creator is SED-ED¹, which lets the user build up a SED-ML file element by element, with error-checking along the way, while providing a graphical overview of the relationships between the elements. It also provides automated methods for creating XPath strings and labeled fields for the necessary SED-ML attributes.

Another tool that allows the creation of SED-ML files is 'Copasi2SEDML', which allows conversion of a COPASI file⁸ with a time course simulation to the equivalent SED-ML. Similarly, CellDesigner⁷ allows both import and export of SED-ML.

Here, we provide phraSED-ML as a balance between these options, occupying a niche similar to that inhabited by Antimony¹⁴, which is a text-based language to define the models themselves. We distribute libraries for the language to integrate it with any other simulation software that can understand SED-ML, providing the users with a new option for SED-ML creation and exploration. Python bindings provide a unified scripting environment that can both execute and export their simulation experiment.

2. Features

2.1. *Simple Abstractions*

The phraSED-ML language is designed to be easily readable and writable without the need to reference the documentation at each turn. The format of each line is declarative, and because the subject of SED-ML is the act of simulation, all keywords are verbs. Model objects are declared with the keyword ‘model’, simulations with the keyword ‘simulate’, tasks with the keyword ‘run’, repeated tasks with the keyword ‘repeat’, and output with the keyword ‘plot’ and ‘report’. The DataGenerator object is abstracted away entirely - objects are created as needed according to user directives parsed in the requested outputs. The following illustrates a typical phraSED-ML code.

```
mod1 = model "sbml_model.xml"
sim1 = simulate uniform(0,10,100)
task1 = run sim1 on mod1
plot time vs S1
```

XPath expressions are avoided on the user end by allowing model elements to be referenced by ID alone (e.g. ‘S1’), which the `libphrasedml` library translates to an appropriate XPath string. Element attribute values are similarly translated behind the scenes, made possible by the use of `libsbml` library to parse the referenced model to determine which element attribute must be used. This restricts the scope of phraSED-ML somewhat from the broader abilities of SED-ML, which can perform arbitrary XML transformations. However, this restriction was not deemed too onerous, particularly in light of the simplification it offered.

2.2. *Allowed Complexity*

Some of the more advanced features of SED-ML may still be accessed with phraSED-ML. KiSAO terms are not necessary, but if the user wishes to use backward differentiation formula for solving ordinary differential equation (ODE), for example, they may use the ‘bdf’ keyword:

```
sim1.algorithm = bdf
```

which will be translated to SED-ML as KiSAO id 288. The KiSAO id may also be used directly:

```
sim1.algorithm = kisao.288
```

which is useful for algorithms for which there are no built-in keywords. Similarly, algorithm parameters may be defined either by keyword or KiSAO id. Here, the relative tolerance (KiSAO id 209) is set:

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```
sim1.algorithm.relative_tolerance = 0.001
sim1.algorithm.209 = 0.001
```

SED-ML ‘repeated tasks’ also have phraSED-ML equivalents:

```
task2 = repeat task1 for S1 in [1, 10, 15]
task3 = repeat task1 for S2 in uniform(0,10,100)
```

which set up tasks looping S1 through a vector of values, and S2 through a ‘uniformRange’ of evenly-spaced values.

3. Implementation and Distribution

The cross-platform library is written in Bison (<https://www.gnu.org/software/bison>) and C++, with a simple C API, along with Python bindings. It uses libSEDML (<https://github.com/fbergmann/libSEDML>) to parse and create SED-ML files, and libSBML⁴ to parse the SBML files to which the SED-ML documents refer. It also uses the check library (<http://libcheck.github.io/check/>) for unit tests. A standalone command-line tool (phrasedml-convert) is provided for easy conversion between phraSED-ML and SED-ML. Source code, executables, libraries, and documentation are available at <http://phrasedml.sf.net>.

4. Integration into Tellurium

Additionally, Python bindings for `libphrasedml` have been incorporated into Tellurium, a Python-based environment for systems and synthetic biology modeling. Tellurium users can define a simulation experiment in phraSED-ML, and have it executed directly via `libRoadRunner`¹⁵. Tellurium provides wrapper functions for handling of phraSED-ML code through the `experiment` module. The `experiment` module takes lists of models in Antimony and simulation setups in phraSED-ML string, which can be simulated through the `execute` function. Conversion between phraSED-ML and SED-ML code is straightforward as the library provides a function that accepts both phraSED-ML and SED-ML and translates to the other. Because Tellurium can translate SED-ML to Python scripts, users can define simulation setups in phraSED-ML and execute them directly.

5. Examples

Several examples of application involving phraSED-ML are demonstrated below. We use the Mitogen-Activated Protein (MAP) kinase cascade model¹¹ as the model of interest for most of the examples.

5.1. Simple Time Course Simulation

The simplest example illustrating the use of phraSED-ML is a simple time course simulation. The code below performs a time course simulation on the model from 0 to 4000 with 1000 time points, and plots time versus MAP kinase, phosphorylated MAP kinase, and double phosphorylated MAP kinase as the output.

```
model1 = model "MAPKcascade"
sim1 = simulate uniform(0,4000,1000)
task1 = run sim1 on model1
plot task1.time vs task1.MAPK, task1.MAPK_P, task1.MAPK_PP
```

Listing 1. Simple Time Course, see Figure 1

The output of the phraSED-ML string is shown in Figure 1. The Python translation which is used internally by Tellurium to execute the setup is also provided in the Supplementary Material as a reference.

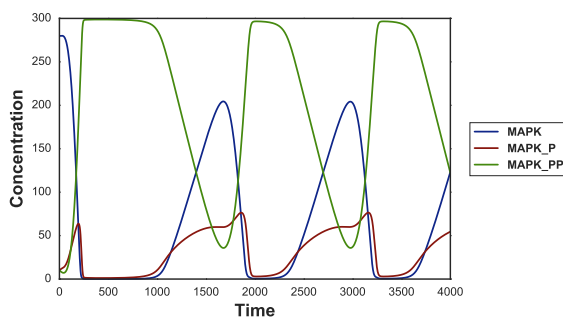


Fig. 1. Output of a simple time course simulation. Blue line represents MAP kinase, red line represents phosphorylated MAP kinase, and green line represents double phosphorylated MAP kinase.

5.2. Phase Portrait

The following example shows how it is possible to specify a simple phase portrait. In this case we run a simulation of the Lorenz attractor¹³ which under certain parameter values exhibits chaotic behavior. In Figure 2 we plot the variable z versus x .

```
model1 = model "lorenz"
sim1 = simulate uniform(0, 15, 2000)
task1 = run sim1 on model1
plot task1.z vs task1.x
```

Listing 2. Lorenz Attractor Phase Plot, see Figure 2

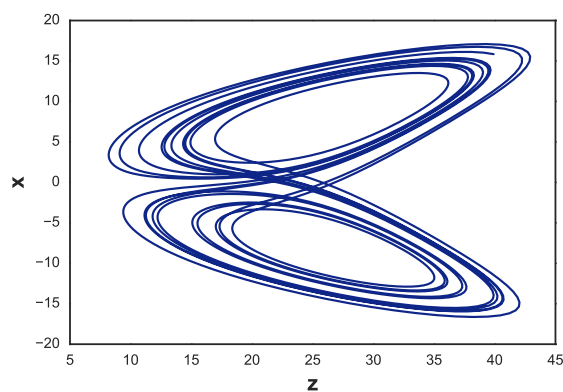


Fig. 2. Phase plot of Lorenz attractor resulted from running the phraSED-ML code in listing 2

5.3. 1-Dimensional Parameter Scan

Running parameter scan is simple and intuitive using phraSED-ML by using ‘repeat’. The example below runs a 1-Dimensional parameter scan on parameter ‘J1_KK2’ with values 1, 10, and 100, while resetting the model back to initial condition every time. The output is shown in Figure 3.

```

modell1 = model "MAPKcascade"
sim1 = simulate uniform(0,4000,1000)
task1 = run sim1 on modell1
repeat1 = repeat task1 for J1_KK2 in [1, 10, 100], reset=true
plot repeat1.time vs repeat1.MKK, repeat1.MKK_P

```

Listing 3. 1-Dimensional Parameter Scan, see Figure 3

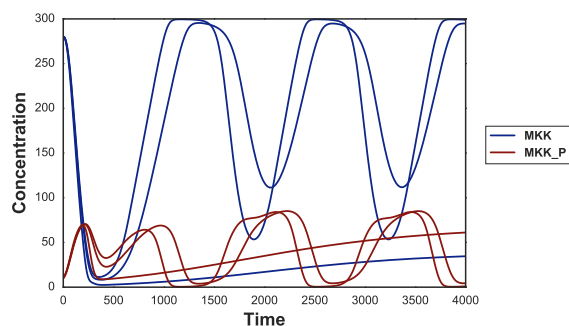


Fig. 3. Typical output of phraSED-ML string running 1-dimensional parameter scan. The blue lines represent MAP kinase kinase and red lines represent phosphorylated MAP kinase kinase.

5.4. Multi-Dimensional Parameter Scan

Expanding from 1-Dimensional parameter scan, parameter scan on two different parameters can be achieved through repeats of ‘repeat’. The code below illustrates 2-Dimensional parameter scan where parameter ‘J1_KK1’ is varied as before while parameter ‘J4_KK5’ is changed from 0 to 100 in 10 uniform steps. The output is plotted on Figure 4.

```
model1 = model "MAPKcascade"
sim1 = simulate uniform(0,4000,1000)
task1 = run sim1 on model1
repeat1 = repeat task1 for J1_KK2 in [1, 10, 100], reset=true
repeat2 = repeat repeat1 for J4_KK5 in uniform(1, 100, 10), reset=true
plot repeat2.time vs repeat2.MKK, repeat2.MKK_P
```

Listing 4. Multi-Dimensional Parameter Scan, see Figure 4

5.5. Repeated Stochastic Simulations

Another application of phraSED-ML shows how to run a repeated stochastic simulations on models. The following phraSED-ML string demonstrates the differences between stochastic simulations with and without a given seed. Typical output of the simulation setup is shown in Figure 5.

```
model1 = model "MAPKcascade"
timecourse1 = simulate uniform_stochastic(0, 4000, 1000)
timecourse1.algorithm.seed = 1003
timecourse1.algorithm.variable_step_size = false
timecourse2 = simulate uniform_stochastic(0, 4000, 1000)
timecourse2.algorithm.variable_step_size = false
task1 = run timecourse1 on model1
task2 = run timecourse2 on model1
repeat1 = repeat task1 for local.x in uniform(0, 5, 5), reset=true
repeat2 = repeat task2 for local.x in uniform(0, 5, 5), reset=true
plot "Repeats with SEED" repeat1.time vs repeat1.MKK, repeat1.MKK_P
plot "Repeats without SEED" repeat2.time vs repeat2.MKK, repeat2.MKK_P
```

Listing 5. Repeated Stochastic Simulations, see Figure 5

6. Future Developments

SED-ML continues to be developed by the community (<http://sed-ml.org/>) and changes to phraSED-ML will follow this development. Of particular interest are planned changes to SED-ML that will allow a richer set of symbols to be specified when generating output, i.e. eigenvalues or sensitivity coefficients. These new symbols will be added to phraSED-ML once the new SED-ML specification has been approved.

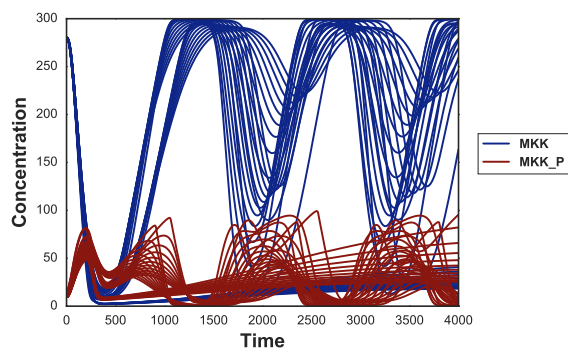


Fig. 4. Typical output of phraSED-ML string running 2-dimensional parameter scan. The blue lines represent MAP kinase kinase and red lines represent phosphorylated MAP kinase kinase.

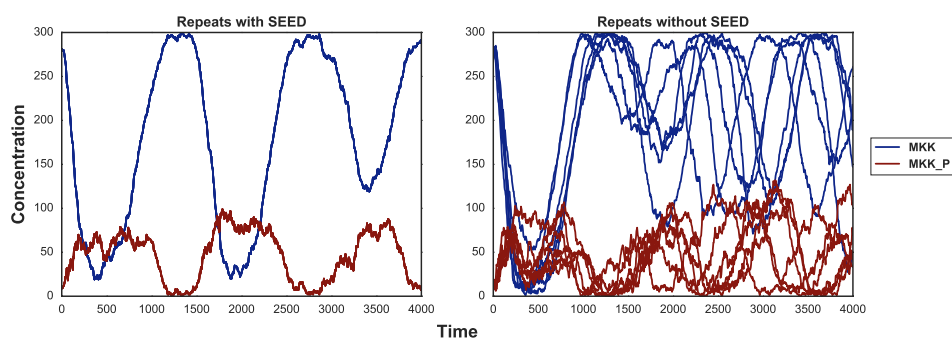


Fig. 5. The same plot as Figure 3 but using the stochastic Gillespie algorithm. The blue lines represent MAP kinase kinase and red lines represent phosphorylated MAP kinase kinase. The left panel shows stochastic simulations with a single seed. The right panel shows stochastic simulations with varying seeds.

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