# yaml2sbml

***Release 0.2.4***

**Jakob Vanhoefer, Marta R. A. Matos, Dilan Pathirana, Yannik Schä**

**May 28, 2021**

# MAIN

**Release** 0.2.4

**Source code** https://github.com/yaml2sbml-dev/yaml2sbml


**yaml2sbml** allows the user to convert a system of ODEs specified in a YAML file to SBML. In addition, if experimental data is provided in the YAML file, it can also be converted to PEtab.

CHAPTER

ONE

# INSTALLATION

This package requires Python 3.6 or later. Miniconda provides a small installation.

## 1.1 Install from PyPI

Install yaml2sbml from PyPI via:

```
pip install yaml2sbml
```

## 1.2 Install from GitHub

To work with the latest development version, install yaml2sbml from GitHub via:

```
pip install https://github.com/yaml2sbml-dev/yaml2sbml/archive/develop.zip
```

or clone the repository and install from local via:

```
git clone https://github.com/yaml2sbml-dev/yaml2sbml
cd yaml2sbml
git checkout develop
pip install -e .
```

where `-e` is short for `--editable` and links the installed package to the current location, such that changes there take immediate effect.

## 1.3 Additional dependencies for running the examples

The notebooks come with additional dependencies. Information on the installation of the ODE simulator AMICI is given in its installation guide. Further dependencies can be installed via:

```
pip install yaml2sbml[examples]
```

CHAPTER

TWO

# INPUT FORMAT FOR YAML2SBML

## 2.1 General scope

- *yaml2sbml*: translate ODEs (initial value problems) of the form *x' = f(t, x, p)* with time *t*, states *x* and (potentially) unknown parameters *p* into an SBML file for simulation purpose.
- *yaml2PEtab*: define a fitting problem of the form *y(t_i) = h(x(t_i), p) + eps_i* with independent normal- or Laplace-distributed error terms *eps*. *h* denotes the mapping from system states to observables. PEtab allows one to formulate MLE and MAP based fitting problems.

## 2.2 General remarks

- All identifiers of states, parameters etc. need to be valid SBML identifiers. Therefore, identifiers must consist of only upper and lower case letters, digits and underscores, and must not start with a digit.
- Mathematical equations are parsed by *libsbml`s `parseL3Formula*. Hence for correct syntax see its documentation and the corresponding section of the format specification.
- Equations starting with a minus must be surrounded by brackets or quotation marks, since a leading minus also has a syntactic meaning in YAML and the YAML file will not be valid otherwise.

## 2.3 time [optional]

```yaml
time:
  variable: t
```

Define the **time variable**, in case the right hand side of the ODE is time-dependent.

## 2.4 parameters [optional]

```yaml
parameters:
  - parameterId: p_1
    nominalValue: 1

  - parameterId: p_2
    ...
```

Define **parameters**. *nominalValue* is optional for SBML/PEtab generation, but will be needed for model simulation. Further optional entries are *parameterName, parameterScale, lowerBound, upperBound, estimate* and entries regarding priors. These entries will be written in the corresponding column of the _parameter **table_** by *yaml2PEtab*.

For a detailed description see the documentation of the PEtab parameter table "PEtab parameter table documentation").

Further entries are possible and will be written to the _parameter **table_** as well but are currently not part of the PEtab standard.

## 2.5 odes

```
odes:
    - stateId: x_1
      rightHandSide: p_1 * x_1
      initialValue: 1

    - stateId: x_2
      ...
```

Define **ODEs** (and states). An ODE consists of a *stateId* (string), a *rightHandSide* (string, encoding a mathematical expression), and an *initial value*. Initial values can be either numerical values or parameter Ids.

For a more detailed description of the parsing of mathematical expressions ( for *rightHandSide*) we refer to the corresponding section of this documentation.

## 2.6 assignments [optional]

```
assignments:
    - assignmentId: sum_of_states
      formula: x_1 + x_2

    - assignmentId: ...
      ...
```

**Assign** the mathematical expression *formula* to the term *assignmentId*. The value is dynamically updated and can depend on parameters, states and time. In SBML, assignments are represented via parameter assignment rules.

For a more detailed description of the parsing of mathematical expressions (e.g. for *formula*) we refer to the [corresponding section](#parsing-of-mathematical-equations) of this documentation.

## 2.7 functions [optional]

```
functions:
    - functionId: g_1
      arguments: x_1, s
      formula: s * x_1 + 1

    - functionId: g_2
      ...
```

Define **functions**, which can be called in other parts of the ODE definitions, e.g. in the example above via *g_1(x_1, s)*.

**Please note** that all unknowns appearing in the formula (e.g. also parameters or the time variable) also have to be arguments of the function.

For a more detailed description of the parsing of mathematical expressions (e.g. for *formula*) we refer to the [corresponding section](#parsing-of-mathematical-equations) of this documentation.

## 2.8 observables [optional]

```
observables:

    - observableId: Obs_1
      observableFormula: x_1 + x_2

      noiseFormula: noiseParameter1
      noiseDistribution: normal

    - observableId: Obs_2
      ...
```

Define **observables**. Observables are not part of the SBML standard. If the SBML is generated via the *yaml2sbml.yaml2sbml* command and the *observables_as_assignments* flag is set to *True*, observables are represented as assignments to parameters of the form observable_<observable_id>. If the SBML is created via *yaml2sbml.yaml2petab*, observables are represented in the PEtab observables table. The entries are written to the corresponding columns of the PEtab observable table. According to the PEtab standard, an observable table can take the following entries: *observableId, observableName, observableFormula, observableTransformation, noiseFormula, noiseDistribution*.

For a detailed discussion see the corresponding part of the PEtab documentation <https://github.com/PEtab-dev/PEtab/blob/master/doc/documentation_data_format.rst#observables-table>`_.

## 2.9 conditions [optional]

```
conditions:

    - conditionId: condition1
      p_1: 1
      x_1: 2
      ...
```

Conditions allow one to set parameters or initial conditions of states to a numeric value/unknown parameter. This allows for the specification of different experimental setups in the data generation (e.g. different initial conditions for different runs of an experiment).

The "trivial condition table" (if only one setup exists) is generated by:

```
conditions:
      - conditionId: condition1
```

For a detailed discussion see the corresponding part of the PEtab documentation.

## 2.10 Parsing of mathematical equations

Throughout *yaml2sbml* formulas are parsed by *libsbml's parseL3Formula* function. Further information on the syntax are given by:

- the working with math - section of the *libsbml* documentation.
- the documentation of *libsbml.parseL3Formula*.

This gives access to e.g.:

- +, -, *, /, and `power;
- trigonometric/hyperbolic functions;
- exponential/logarithmic functions;
- piecewise defined functions (via *piecewise*); and
- boolean expressions like "<".

CHAPTER

THREE

# EXAMPLES

We provide the following Jupyter notebooks with examples:

- Three notebooks use the Lotka Volterra equations as a running example for the Python tool, CLI and the Model Editor.
- A notebook demonstrating format features with minimal examples.
- A notebook showing the Sorensen model as a real world application.
- A notebook implementing the Finite State Projection.

These examples can also be found on Github here.

## 3.1 Example: "Lotka-Volterra" Equations

### 3.1.1 Scope

This notebook introduces the **input format** of yaml2sbml and showcases the **Python interface** of the tool. Furthermore, this notebook demonstrates the **simulation** of an SBML model using AMICI and **parameter estimation** from PEtab using pyPESTO.

### 3.1.2 Equations

The "Lotka-Volterra" Equations are given by

$$\frac{d}{dt}x_1 = \alpha x_1 - \beta x_1 x_2,$$
$$\frac{d}{dt}x_2 = \delta x_1 x_2 - \gamma x_2.$$

Here $x_1$ denotes the number of a prey and $x_2$ the number of a predator species and $\alpha, \beta, \gamma, \delta$ are positive parameters describing the birth/death and interactions of the two species.

### 3.1.3 YAML file for model simulation in SBML:

The **states** $x_1$ and $x_2$, as well as their initial values and dynamics are defined in the `odes:` section:

```
odes:
    - stateId: x_1
      rightHandSide: alpha * x_1 - beta * x_1 * x_2
      initialValue: 2

    - stateId: x_2
      rightHandSide: delta * x_1 * x_2 - gamma * x_2
      initialValue: 2
```

Furthermore, the **parameters** together with their values are defined in the `parameters:` section:

```
parameters:
    - parameterId: alpha
      nominalValue: 2

    - parameterId: beta
      nominalValue: 4

   ...
```

The full file is given in `Lotka_Volterra_basic.yml`.

### 3.1.4 Format validation of the YAML model:

The YAML model can be validated by the `yaml2sbml` package via:

[1]:
```
import yaml2sbml

yaml_file_basic = 'Lotka_Volterra_basic.yml'
yaml2sbml.validate_yaml(yaml_dir=yaml_file_basic)
```

```
YAML file is valid
```

### 3.1.5 Conversion to SBML for model simulation:

We now want to convert the YAML file into a SBML file. Within Python this is possible via:

[2]:
```
import yaml2sbml

sbml_output_file = 'Lotka_Volterra_basic.xml'
yaml2sbml.yaml2sbml(yaml_file_basic, sbml_output_file)
```

We will now use the SBML simulator AMICI to simulate the ODEs. First `AMICI` generates the models' C++ code.

[3]:
```
%%capture

import amici
```

(continues on next page)

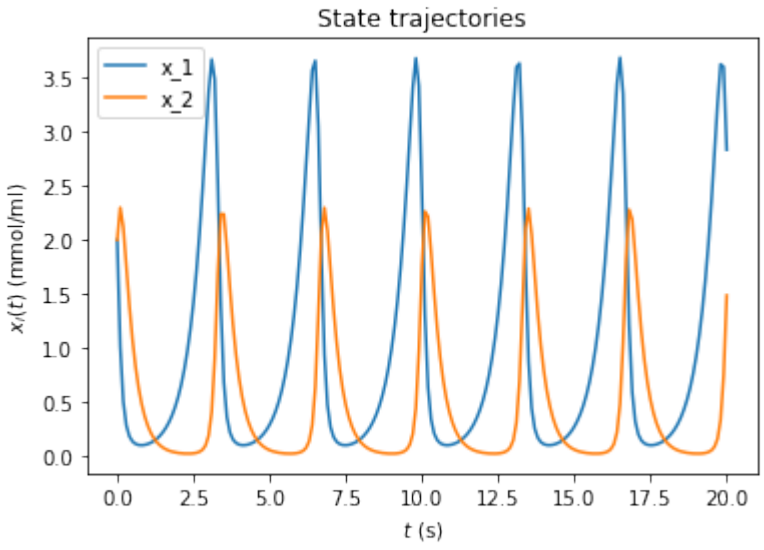
(continued from previous page)

```
import amici.plotting

model_name = 'Lotka_Volterra'
model_output_dir = 'Lotka_Volterra_AMICI'

sbml_importer = amici.SbmlImporter(sbml_output_file)
sbml_importer.sbml2amici(model_name,
                         model_output_dir)
```

Then we can reload and simulate the compiled model.

[4]:
```
%%capture

import os
import sys
import importlib
import numpy as np

# import model
sys.path.insert(0, os.path.abspath(model_output_dir))
model_module = importlib.import_module(model_name)

# create model + solver instance
model = model_module.getModel()
solver = model.getSolver()

# Define time points and run simulation using default model parameters/solver␣
↪options
model.setTimepoints(np.linspace(0, 20, 201))
rdata = amici.runAmiciSimulation(model, solver)
```

[5]:
```
# plot trajectories
amici.plotting.plotStateTrajectories(rdata, model=model)
```



### 3.1.6 Conversion to PEtab for parameter fitting:

In order to obtain valid PEtab tables, we need to extend the `.yml` file. The extended `.yml` file is given as `Lotka_Volterra_PEtab.yml`.

#### Parameters:

The `parameters:` section can be extended to store parameter bounds, transformations, … This information is written to the PEtab *parameter table*.

```
parameters:
    - parameterId: alpha
      nominalValue: 2
      parameterScale: log10
      lowerBound: 0.01
      upperBound: 100
      estimate: 1

   ...
```

(**Note:** PEtab measurement tables are outside of the scope of `yaml2sbml`. Hence a predefined measurement table for this example is given under `./Lotka_Volterra_PEtab/measurement_table.tsv`.)

#### Observables:

The `observables:` section allows to specify the mapping of system state to measurement and the measurement noise. This information is written in the PEtab *observable table*.

```
observables:
    - observableId: prey_measured
      observableFormula: log10(x_1)
      observableTransformation: lin
      noiseFormula: 1
      noiseDistribution: normal
```

#### Conditions:

The `conditions:` section allows to specify different experimental setups. This information is written in the PEtab *condition table*. This example only defines the trivial condition table, consisting of only one experimental setup.

```
conditions:
    - conditionId: condition1
```

### yaml2petab:

We want to create the corresponding PEtab tables for the model in `Lotka_Volterra_PEtab.yml`. Since the definition of PEtab measurement tables is outside of the scope of `yaml2sbml`, a predefined measurement table is given under `./Lotka_Volterra_PEtab/measurement_table.tsv`.

[6]:
```
yaml_file_petab = 'Lotka_Volterra_PEtab.yml'
PEtab_dir = './Lotka_Volterra_PEtab/'
PEtab_yaml_name = 'problem.yml'
measurement_table_name = 'measurement_table.tsv'
model_name = 'Lotka_Volterra_with_observables'

yaml2sbml.yaml2petab(yaml_file_petab,
                     PEtab_dir,
                     model_name,
                     PEtab_yaml_name,
                     measurement_table_name)
```

`yaml2petab` created the PEtab files. In the following we show how to import and fit a PEtab problem in pyPESTO.

[7]:
```
%%capture
import pypesto
import pypesto.petab
import pypesto.optimize as optimize
import pypesto.visualize as visualize

# import PEtab problem
importer = pypesto.petab.PetabImporter.from_yaml(os.path.join(PEtab_dir, PEtab_
↪yaml_name),
                                                 model_name=model_name)
problem = importer.create_problem()
```

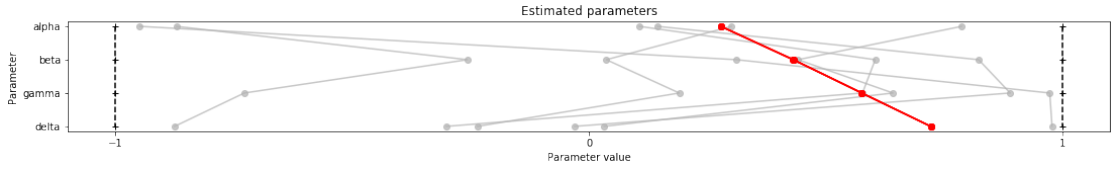
Perfomr the fitting:

[8]:
```
%%capture
# perform optimization
optimizer = optimize.ScipyOptimizer()
result = optimize.minimize(problem,
                           optimizer=optimizer,
                           n_starts=10)
```

Next we want to visualize the results using parallel coordinate plots.

[9]:
```
visualize.parameters(result)
```

[9]:
```
<matplotlib.axes._subplots.AxesSubplot at 0x7ff95ff93d30>
```



## 3.2 Command Line Interface

This notebook shows the **command line interface** of `yaml2sbml`, using the "Lotka Volterra" example. For details on * the definition of the `.yaml` file * simulation of the SBML model using AMICI (Python) * fitting the PEtab problem using pyPESTO (Python),

see the *corresponding notebook*

### 3.2.1 YAML validation:

`yaml2sbml` allows to validate the input `YAML` via

```
yaml2sbml_validate <yaml_inout_file>
```

[1]:
```
!yaml2sbml_validate ../Lotka_Volterra_python/Lotka_Volterra_basic.yml
```

```
Path to yaml file: ../Lotka_Volterra_python/Lotka_Volterra_basic.yml
Validating...
YAML file is valid
```

### 3.2.2 SBML generation

`yaml2sbml` generates an **SBML** via

```
yaml2sbml <yaml_input_file> <sbml_output_file>
```

[2]:
```
!yaml2sbml ../Lotka_Volterra_python/Lotka_Volterra_basic.yml Lotka_Volterra_
↪basic.xml
```

```
Path to yaml file: ../Lotka_Volterra_python/Lotka_Volterra_basic.yml
Path to sbml file: Lotka_Volterra_basic.xml
Converting...
```

### 3.2.3 PEtab generation:

The basic way of generating **PEtab** tables is given by

```
yaml2petab <yaml_input_file> <petab_output_directory> <model_name>
```

[3]:
```
# create target directory, if it doesn't exist yet
!mkdir -p ./Lotka_Volterra_PEtab/
# needed .yml /measurement files in current directory.
!cp ../Lotka_Volterra_python/Lotka_Volterra_PEtab/measurement_table.tsv ./
↪Lotka_Volterra_PEtab/
!cp ../Lotka_Volterra_python/Lotka_Volterra_PEtab.yml .
```

[4]:
```
# This is the actual command
!yaml2petab Lotka_Volterra_PEtab.yml ./Lotka_Volterra_PEtab Lotka_Volterra
```

```
Path to yaml file: Lotka_Volterra_PEtab.yml
Output directory: ./Lotka_Volterra_PEtab
Path to sbml/petab files: Lotka_Volterra
Converting...
```

#### Further Options:

Two further optional arguments to the `yaml2petab` command allow to create a *PEtab yaml* file and a measurement table. A PEtab yaml allows for a easier input of a PEtab problem to some toolboxes: * In the directory , given by `--petab_yaml`, a yaml file, that groups the PEtab problem, will be created. * `--measurement_table` allows to specify the measurement table. This option is only possible in combination with `--petab_yaml`.

[5]:
```
# now generate the PEtab table:
!yaml2petab Lotka_Volterra_PEtab.yml ./Lotka_Volterra_PEtab Lotka_Volterra --
↪petab_yaml petab_problem.yml --measurement_table measurement_table.tsv
```

```
Path to yaml file: Lotka_Volterra_PEtab.yml
Output directory: ./Lotka_Volterra_PEtab
Path to sbml/petab files: Lotka_Volterra
Converting...
```

### 3.2.4 Checking the PEtab files

Finally, PEtab offers a PEtab-linter (no output = no error found). (This is a feature of the PEtab python library, not of yaml2sbml.)

[6]:
```
!petablint -vy Lotka_Volterra_PEtab/petab_problem.yml
```

```
Checking SBML model...
Checking measurement table...
Checking condition table...
Checking observable table...
Checking parameter table...
OK
```

## 3.3 Model Editor

This notebook demonstrates functionality of the `yaml2sbml` model editor using the Lotka Volterra equations as an example. The "Lotka-Volterra" equations are given by

$$\frac{d}{dt}x_1 = \alpha x_1 - \beta x_1 x_2,$$
$$\frac{d}{dt}x_2 = \delta x_1 x_2 - \gamma x_2.$$

### 3.3.1 ODE model

We first generate a basic model, that only contains all necessary information for generating an SBML file for model simulation.

[1]:
```
from yaml2sbml import YamlModel

# generate model
model = YamlModel()

# add ODEs
model.add_ode(state_id='x_1',
              right_hand_side='alpha*x_1 - beta*x_1*x_2',
              initial_value=2)
model.add_ode(state_id='x_2',
              right_hand_side='delta*x_1*x_2 - gamma*x_2',
              initial_value=2)

# add parameters
model.add_parameter(parameter_id='alpha', nominal_value=2)
model.add_parameter(parameter_id='beta', nominal_value=4)
model.add_parameter(parameter_id='gamma', nominal_value=3)
model.add_parameter(parameter_id='delta', nominal_value=3)
```

`yaml2sbml` can export the `model` object either to YAML or to SBML directly, via

[2]:
```
# write to YAML
model.write_to_yaml('Lotka_Volterra_basic.yaml', overwrite=True)

# write to SBML
model.write_to_sbml('Lotka_Volterra_basic.xml', overwrite=True)
```

There are further functions to: * get all `parameter_ids` via `model.get_parameter_ids()` * get a parameter by its id (`model.get_parameter_by_id('alpha')`) * delete a parameter by its id (`model.delete_parameter('alpha')`)

Similar functions also exist for the other model components.

### 3.3.2 Parameter Estimation Problem

Now we want to extend the current `model` to include all the necessary information for parameter estimation in PEtab. Therefore we load the model from the `.yaml` file and modify the parameters, such that it also contains all information that is going to be written into the PEtab parameter table.

[3]:
```
model = YamlModel.load_from_yaml('Lotka_Volterra_basic.yaml')

# extend parameters
model.add_parameter(parameter_id='alpha',
                    nominal_value=2,
                    parameter_scale='log10',
                    lower_bound=0.1,
                    upper_bound=10,
                    estimate=1,
```

(continues on next page)

(continued from previous page)

```
                      overwrite=True)

model.add_parameter(parameter_id='beta',
                      nominal_value=4,
                      parameter_scale='log10',
                      lower_bound=0.1,
                      upper_bound=10,
                      estimate=1,
                      overwrite=True)

model.add_parameter(parameter_id='gamma',
                      nominal_value=3,
                      parameter_scale='log10',
                      lower_bound=0.1,
                      upper_bound=10,
                      estimate=1,
                      overwrite=True)

model.add_parameter(parameter_id='delta',
                      nominal_value=3,
                      parameter_scale='log10',
                      lower_bound=0.1,
                      upper_bound=10,
                      estimate=1,
                      overwrite=True)
```

A parameter fitting problem in PEtab allows for the specification of observables and experimental conditions:

[4]:
```
# specify an observable:
model.add_observable(observable_id='prey_measured',
                     observable_formula='log10(x_1)',
                     noise_formula='noiseParameter1_prey_measured',
                     noise_distribution='normal',
                     observable_transformation='lin')

# specify trivial condition
model.add_condition(condition_id='condition1',
                      condition_dict={})
```

The modified model can either be exported to YAML or PEtab via

[5]:
```
# write to YAML
model.write_to_yaml('Lotka_Volterra_PEtab.yaml', overwrite=True)

# write to PEtab
model.write_to_petab(output_dir='./Lotka_Volterra_PEtab',
                     model_name='Lotka_Volterra',
                     petab_yaml_name='Lotka_Volterra_problem',
                     measurement_table_name='measurement.tsv')
```

## 3.4 Toy Examples of Format Features

This notebook demonstrates minimal examples of the following format features:

- Time-dependent right hand sides
- Step functions in the right hand side
- Function definitions

### 3.4.1 Time-dependent right hand side:

`time_dependent_rhs.yml` implements the ODE

$$\dot{x} = -\frac{x}{t+1} \tag{3.1}$$

$$x(0) = 1 \tag{3.2}$$

via

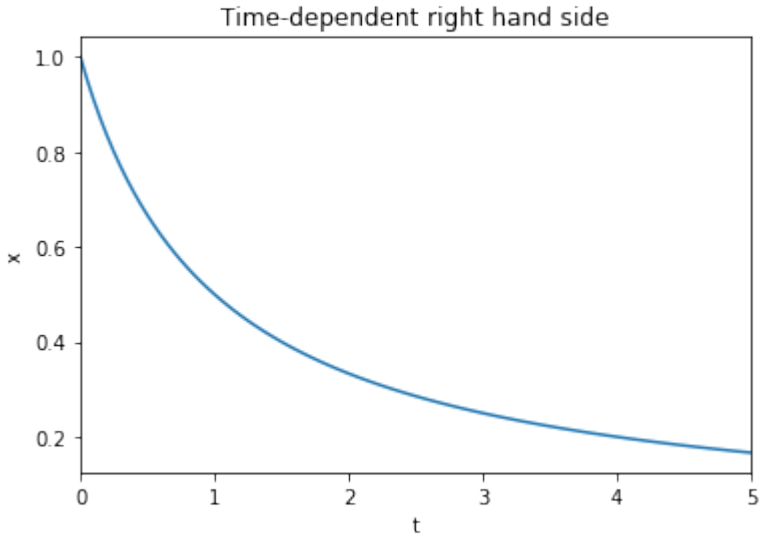
```yaml
time:
    variable: t

odes:
    - stateId: x
      rightHandSide: -x/(t+1)
      initialValue: 1
```

The time variable `t` needs to be defined.

[1]:
```
import yaml2sbml

yaml_file_basic = 'time_dependent_rhs.yml'
sbml_output_file = 'time_dependent_rhs.xml'

yaml2sbml.yaml2sbml(yaml_file_basic, sbml_output_file)
```

For the sake of brevity, simulation and plotting is done in a separate function. Details on these steps can be found in other notebooks.

[2]:
```
%matplotlib inline

from simulation_and_plotting import simulate_AMICI, plot_AMICI
import amici.plotting

#simulate
amici_model, rdata = simulate_AMICI(sbml_output_file)
#plot
plot_AMICI(amici_model, rdata, 'Time-dependent right hand side')
```




### 3.4.2 Step functions in the right hand side

`step_function.yml` implements the ODE

$$\dot{x} = \begin{cases} x, & t < 1 \\ -x, & \text{otherwise} \end{cases}$$

via

```yaml
time:
    variable: t

odes:
    - stateId: x
      rightHandSide: piecewise(x, t < 1, -x)
      initialValue: 1
```

More details on `piecewise` functions can be found in the libsbml documentation.

[3]:
```
import yaml2sbml

yaml_file_basic = 'step_function.yml'
sbml_output_file = 'step_function.xml'

# translate yaml file to sbml
yaml2sbml.yaml2sbml(yaml_file_basic, sbml_output_file)
```

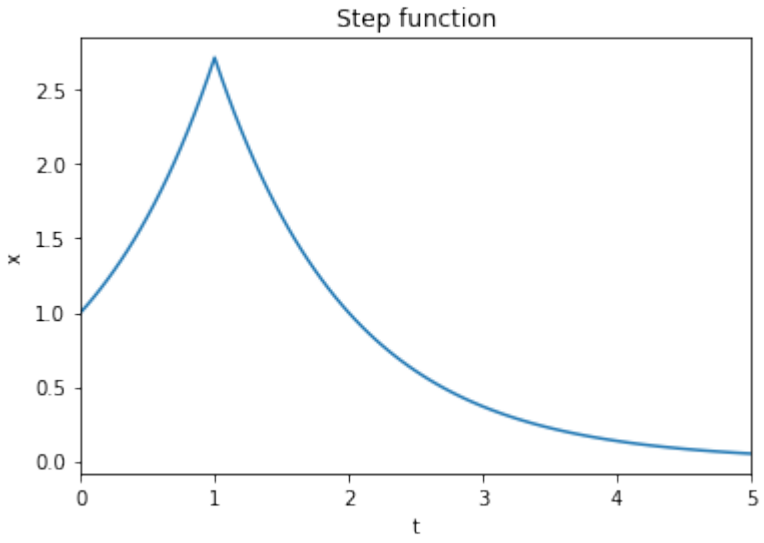
As discussed above, we plot via:

[4]:
```
%matplotlib inline

#simulate
amici_model, rdata = simulate_AMICI(sbml_output_file)
```

(continues on next page)

(continued from previous page)

```
#plot
plot_AMICI(amici_model, rdata, 'Step function')
```




### 3.4.3 Function definition

yaml2sbml allows to define functions, that can then be called in other parts of the model. functions_in_rhs.yaml implements the ODE

$$\dot{x}_1 = f(x_2, 1, 2)$$
$$\dot{x}_2 = f(x_1, -1, 0),$$

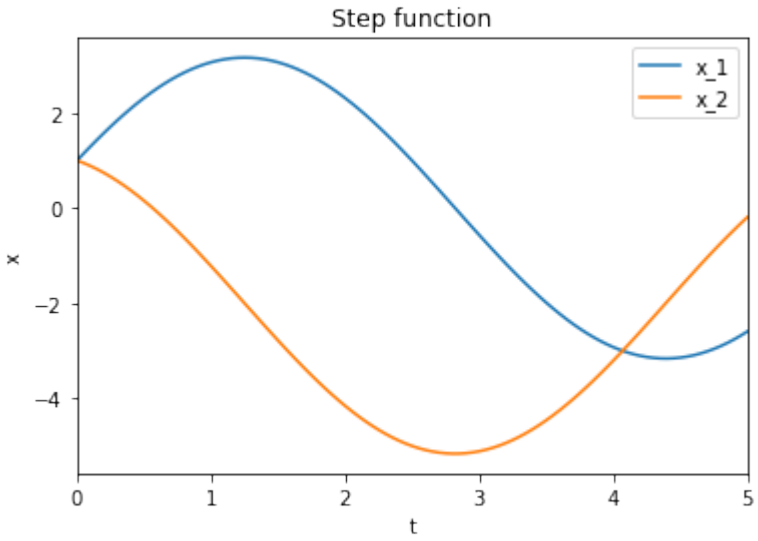
where $f(x, a, b) = a \cdot x + b$ via

```
odes:
    - stateId: x_1
      rightHandSide: f(x_2, 1, 2)
      initialValue: 1

    - stateId: x_2
      rightHandSide: f(x_1, -1, 0)
      initialValue: 1

functions:
    - functionId: f
      arguments: x, a, b
      formula: a * x + b
```

[6]:
```
import yaml2sbml

yaml_file_basic = 'functions_in_rhs.yml'
sbml_output_file = 'functions_in_rhs.xml'

# translate yaml file to sbml
yaml2sbml.yaml2sbml(yaml_file_basic, sbml_output_file)
```

We now follow the usual work flow for simulation and plotting.

[7]:
```
%matplotlib inline

#simulate
amici_model, rdata = simulate_AMICI(sbml_output_file)

#plot
plot_AMICI(amici_model, rdata, 'Step function')
```




## 3.5 Glucose Insulin Metabolism Model by Sorensen (1985).

In this notebook, the model of glucose and insulin metabolism, from the thesis of Thomas J. Sorensen, 1985 *[1]*, is used as an example of how the `yaml2sbml.YamlModel` class can be used to easily extend a pre-existing `yaml2sbml` model.

Specifically, the model is edited to reproduce a figure from the original thesis (Fig 71) *[1]*. The implementation that is loaded here is based on the implementation provided by Panunzi et al., 2020 *[2]*.

In the end, the model is exported to SBML and simulated via AMICI.

### 3.5.1 Extend the current YAML model

The Sorensen model has already been encoded in the YAML format. Within this notebook, the model is loaded, extended in order to model an intravenous infusion administration of glucose, using the `yaml2sbml` Model editor. The extended model is then plotted, to reproduce a figure from Sorensens PhD thesis.

#### Load the model

[1]:
```
import yaml2sbml
from yaml2sbml import YamlModel

yaml_model = YamlModel.load_from_yaml('Sorensen1985.yaml')
```

#### Define the glucose infusion term

An intravenous infusion administration of glucose is added to the model. After 17 minutes of initialization, glucose is infused at a rate of 64.81 mM/min for a three-minute period.

In the YAML model, this is represented by a novel term `IVG` ("intravenous glucose"), that is set by a step function in an assignment rule.

[2]:
```
# describe the intravenous glucose infusion
yaml_model.add_assignment('IVG', formula='piecewise(64.81, 17 <= t && t < 20,␣
↪0)')
```

#### Add the glucose infustion term to the model

`IVG` is now added to the ODE of the glucose concentration of heart and lung space `GlucH`. Therefore, the current ODE is overwritten.

[3]:
```
# Get the current ODE.
gluch_ode_old = yaml_model.get_ode_by_id('GlucH')
gluch_rhs_old = gluch_ode_old['rightHandSide']

# Modify the ODE. `IVG` is divided by the volume term `VolGH` to
# model concentration.
gluch_rhs_new = gluch_rhs_old + ' + (IVG / VolGH)'

# Set the new ODE.
yaml_model.add_ode(state_id='GlucH',
                   right_hand_side=gluch_rhs_new,
                   initial_value=gluch_ode_old['initialValue'],
                   overwrite=True)
```

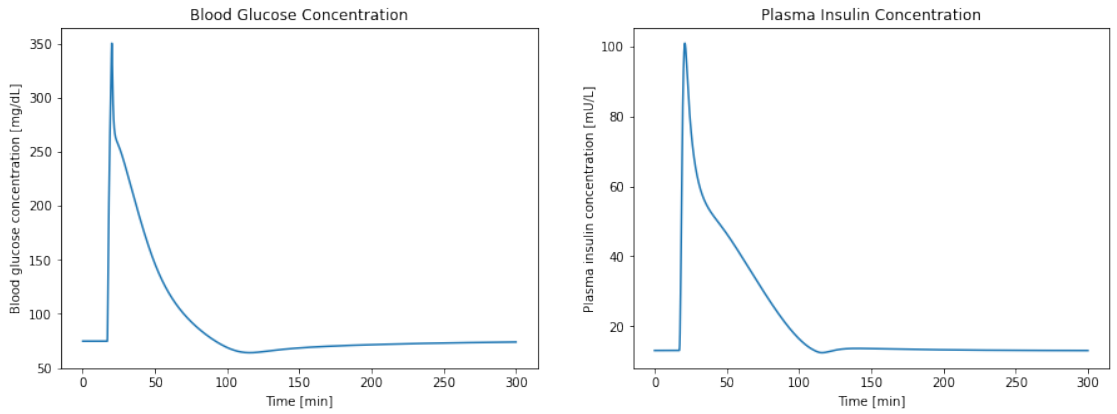
#### Export to SBML

[4]:
```
# Write to SBML
yaml_model.write_to_sbml('Fig71_Sorensen1985.xml', overwrite=True)
```

### 3.5.2 Simulation in AMICI

The model is now setup to reproduce to the figure. The utility function `simulate_and_plot_sorensen` simulates and plots the Sorensen model in AMICI.

[5]:
```
%matplotlib inline
from utils import simulate_and_plot_sorensen

simulate_and_plot_sorensen('Fig71_Sorensen1985.xml')
```




Trajectories are plotted, which closely match the original thesis figures.

Note that this figure has a shift in the x-axis, as the simulation here started at `time == 0`, but in the thesis started at approximately `time == -20`. As there are no explicit time dependencies in the model, the figure is otherwise similar.

## 3.6 References

[1] Sorensen, J. T. (1985). "A physiologic model of glucose metabolism in man and its use to design and assess improved insulin therapies for diabetes." https://dspace.mit.edu/handle/1721.1/15234

[2] Panunzi, S., Pompa, M., Borri, A., Piemonte, V., & De Gaetano, A. (2020). A revised Sorensen model: Simulating glycemic and insulinemic response to oral and intra-venous glucose load. Plos one, 15(8), e0237215. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0237215

## 3.7 Finite State Projection of a Gene Transmission Model

### 3.7.1 Model

In this application example, we consider the two-stage model of gene transmission, discussed e.g. in. *[1]*. The two-stage model describes the stochastic transcription and translation of a gene by the reactions

$$
\begin{aligned}
R_1 &: \emptyset \rightarrow mRNA \\
R_2 &: mRNA \rightarrow \emptyset \\
R_3 &: mRNA \rightarrow mRNA + P \\
R_4 &: P \rightarrow \emptyset.
\end{aligned}
$$

The solution to the Chemical Master Equation (CME) *[2]* gives the probabilities of the states at a given time point as the solution of an infinite dimensional ODE

$$
\begin{aligned}
\frac{d}{dt} x_{r,p} = &- \big(k_1 + (k_2 + k_3) \cdot r + k_4 \cdot p\big) \cdot x_{r,p} \\
&+ k_1 \cdot x_{r-1,p} \\
&+ k_2 \cdot (r+1) \cdot x_{r+1,p} \\
&+ k_3 \cdot r \cdot x_{r,p-1} \\
&+ k_4 \cdot (p+1) \cdot x_{r,p+1}
\end{aligned}
$$

We assume the initial probabilites to be independent Poisson distributions for mRNA and Protein abundances.

### 3.7.2 Finite State Projection

The Finite State Projection *[3]* approximates this CME by restricting the states to a finite domain and approximating the probability of the left out states by zero. In our case, we ill restrict the states to $x_{r,p}$ for $(r, p) \in [0, r_{max} - 1] \times [[0, p_{max} - 1]]$.

### 3.7.3 Model Construction:

The model is constructed using the `yaml2sbml` Model Editor and exported to SBML. This takes only a few lines of code:

[1]:
```
from yaml2sbml import YamlModel
from itertools import product
from scipy.stats import poisson

model = YamlModel()

r_max = 20
p_max = 50

lambda_r = 5
lambda_p = 5

# add parameters
```

(continues on next page)

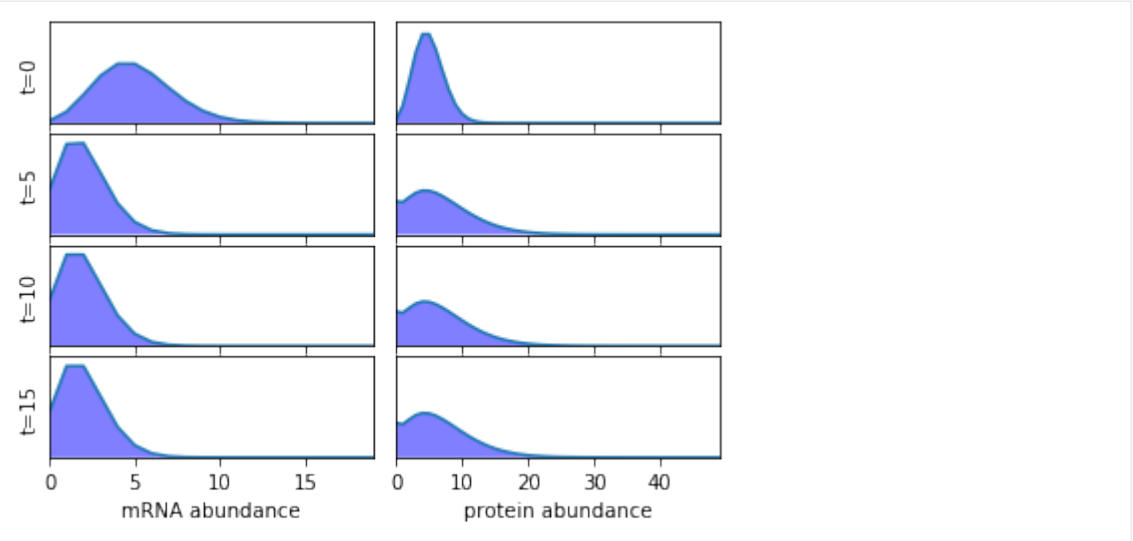
(continued from previous page)

```
model.add_parameter(parameter_id='k_1', nominal_value=2)
model.add_parameter(parameter_id='k_2', nominal_value=1)
model.add_parameter(parameter_id='k_3', nominal_value=10)
model.add_parameter(parameter_id='k_4', nominal_value=3)

# add ODEs & construct the rhs
for r, p in product(range(r_max), range(p_max)):

    rhs = f'-(k_1 + (k_2 + k_3)*{r} + k_4*{p}) * x_{r}_{p} '

    if r>0:
        rhs += f'+ k_1 * x_{r-1}_{p}'
    if r+1 < r_max:
        rhs += f'+ k_2 * {r+1} * x_{r+1}_{p}'
    if  p>0:
        rhs += f'+ k_3 * {r} * x_{r}_{p-1}'
    if p+1 < p_max:
        rhs += f'+ k_4 * {p+1} * x_{r}_{p+1}'

    model.add_ode(state_id = f"x_{r}_{p}",
                  right_hand_side=rhs,
                  #convert from np.float to float
                  initial_value=float(poisson.pmf(r, lambda_r)*poisson.pmf(p,␣
↪lambda_p))
                 )

model.write_to_sbml('gene_expression.xml', overwrite=True)
```

### 3.7.4 Model Simulation

We now use AMICI to simulate the generated model and plot the marginal distributions of the mRNA and protein abundance.

[2]:
```
%matplotlib inline

import numpy as np
from utils import plot_AMICI

# sim, model = compile_and_simulate('gene_expression.xml', 0.1 * np.arange(10),␣
↪r_max, p_max)

plot_AMICI('gene_expression.xml', [0, 5, 10, 15], r_max, p_max)
```




## 3.8 References

[1] Shahrezaei, V., and Swain, P.S. (2008). "Analytical distributions for stochastic gene expression" PNAS 17256–17261 https://www.pnas.org/content/105/45/17256

[2] Gillespie, D. T. (1992). "A rigorous derivation of the chemical master equation" Physica A: Statistical Mechanics and its Applications https://www.sciencedirect.com/science/article/abs/pii/037843719290283V

[3] Munsky, B. and Khammash, M. (2006) "The finite state projection algorithm for the solution of the chemical master equation" The Journal of chemical physics https://aip.scitation.org/doi/full/10.1063/1.2145882

CHAPTER

# FOUR

# API DOCUMENTATION

## 4.1 Convert YAML to SBML

Translate ODEs in the YAML format into SBML.

yaml2sbml.yaml2sbml.**main**()
Command-Line Interface.

yaml2sbml.yaml2sbml.**yaml2sbml**(*yaml_dir*, *sbml_dir*, *observables_as_assignments=False*)
Parse a YAML file with the specification of ODEs and write it to SBML.

SBML is written within this function. If *observables_as_assignments=True*, observables will be translated into parameter assignments of the form *observable_<observable_id>*.

**Parameters**

- **yaml_dir** (str) – directory to the YAML file with the ODEs specification
- **sbml_dir** (str) – directory to the SBML file to be written out
- **observables_as_assignments** (bool) – indicates whether there should be parameter assignments of the form *observable_<observable_id>*.

## 4.2 Validate YAML file

yaml2sbml.**validate_yaml**(*yaml_dir*)
Validate the syntax of the YAML file.

**Parameters** **yaml_dir** (str) – path to YAML file to be validated

**Returns** jsonschema.validate

## 4.3 Convert YAML to PEtab

yaml2sbml.**yaml2petab**(*yaml_dir*, *output_dir*, *sbml_name*, *petab_yaml_name=None*, *measurement_table_name=None*)
Translate a YAML model into a PEtab model.

Takes a YAML file with the ODE specification, parses it, converts it into SBML format, and writes the SBML file. Further it translates the given information into PEtab tables.

If a *petab_yaml_name* is given, a YAML file is created, that organizes the PEtab problem. If additionally a *measurement_table_file_name* is specified, this file name is written into the created YAML file.

**Parameters**

- **yaml_dir** (str) – path to the YAML file with the ODEs specification
- **output_dir** (str) – path the output file(s) are be written out
- **sbml_name** (str) – name of SBML model
- **petab_yaml_name** (Optional[str]) – name of YAML organizing the PEtab problem.
- **measurement_table_name** (Optional[str]) – Name of measurement table

## 4.4 Validate PEtab tables

yaml2sbml.**validate_petab_tables**(*sbml_dir*, *output_dir*)

Validate the PEtab tables via *petab.lint*.

Throws an error if the PEtab tables do not follow the PEtab format standard.

**Parameters**

- **sbml_dir** (str) – directory of the sbml
- **output_dir** (str) – output directory for petab files

**Raises** **Errors are raised by lint, if PEtab files are invalid...** –

## 4.5 Model editor

**class** yaml2sbml.**YamlModel**

Functionality to set up, edit, load and write yaml models.

**add_assignment**(*assignment_id*, *formula*, *overwrite=False*)

Add assignment.

Overwrite an existing assignment with the same id, if *overwrite==True*.

**Parameters**

- **assignment_id** (str) – str, function id
- **formula** (str) – str, right hand side of assignment definition.
- **overwrite** (bool) – bool, indicates if an existing assignment should be overwritten

**add_condition**(*condition_id*, *condition_dict*, *overwrite=False*, *condition_name=None*)

Add condition *condition_id*.

Conditions are not represented inside an SBML and only play a role when generating a PEtab problem (see PEtabs condition table).

Overwrite an existing condition with the same id, if *overwrite==True*.

**Parameters**

- **condition_id** (str) – str, condition id
- **condition_dict** (dict) – dict, of the form {<parameter or state id>: <value>}. Corresponds to entries in the PEtab condition table. See details there.
- **overwrite** (bool) – bool, indicates if an existing condition should be overwritten

- **condition_name** (Optional[str]) – Condition name. Optional.

**add_function**(*function_id*, *arguments*, *formula*, *overwrite=False*)
Add function.

Overwrite an existing function with the same id, if *overwrite==True*.

**Parameters**

- **function_id** (str) – str, function id
- **arguments** (str) – str, arguments, separated by a comma
- **formula** (str) – str, right hand side of the function definition
- **overwrite** (bool) – bool, indicates if an existing function should be overwritten

**add_observable**(*observable_id*, *observable_formula*, *noise_formula*, *overwrite=False*, *observable_name=None*, *observable_transformation=None*, *noise_distribution=None*)
Add observable.

Observables are not represented inside an SBML and only play a role when generating a PEtab problem see PEtabs observable table).

Overwrite an existing observable with the same id, if *overwrite==True*.

**Parameters**

- **observable_id** (str) – str, observable id
- **observable_formula** (str) – str, formula of the observable function
- **noise_formula** (str) – str, formula of the noise
- **overwrite** (bool) – bool, indicates if an existing observable should be overwritten
- **observable_name** (Optional[str]) – Observable name. Optional.
- **observable_transformation** (Optional[str]) – Observable transformation ('lin'/'log'/'log10'). Optional

**add_ode**(*state_id*, *right_hand_side*, *initial_value*, *overwrite=False*)
Add state/ODE.

Overwrite an existing state/ODE with the same id, if *overwrite==True*.

**Parameters**

- **state_id** (str) – str, state id
- **right_hand_side** (Union[float, str]) – str or float, right hand side of the ODE.
- **initial_value** (Union[float, str]) – str or float, initial value of the ODE at t=0
- **overwrite** (bool) – bool, indicates if an existing state/ODE should be overwritten

**add_parameter**(*parameter_id*, *overwrite=False*, *nominal_value=None*, *parameter_name=None*, *parameter_scale=None*, *lower_bound=None*, *upper_bound=None*, *estimate=None*)
Add a parameter.

Overwrite an existing parameter with the same id, if *overwrite==True*.

**Parameters**

- **parameter_id** (str) – str, parameter id
- **overwrite** (bool) – bool, indicates if an existing state/ODE should be overwritten
- **nominal_value** (Optional[float]) – float, nominal value of the parameter.

- **parameter_name** (Optional[str]) – str, name of parameter in PEtab parameter table, optional.
- **parameter_scale** (Optional[str]) – str. scale of parameter in PEtab parameter table, optional.
- **lower_bound** (Optional[float]) – float, lower bound of parameter in PEtab parameter table, optional.
- **upper_bound** (Optional[float]) – float, upper bound of parameter in PEtab parameter table, optional.
- **estimate** (Optional[int]) – int, estimate flag of parameter in PEtab parameter table, optional.

**delete_assignment**(*assignment_id*)
Delete an assignment.

Raise a ValueError, if assignment does not exist.

**delete_condition**(*condition_id*)
Delete a condition.

Raise a ValueError, if condition does not exist.

**delete_function**(*function_id*)
Delete a function.

Raise a ValueError, if function does not exist.

**delete_observable**(*observable_id*)
Delete an observable.

Raise a ValueError, if observable does not exist.

**delete_ode**(*state_id*)
Delete a state + ODE.

Raise a ValueError, if state does not exist.

**delete_parameter**(*parameter_id*)
Delete a parameter.

Raise a ValueError, if parameter does not exist.

**delete_time**()
Delete time variable.

**get_assignment_by_id**(*assignment_id*)
Return dict for corresponding assignment.

Raise a *ValueError*, if the assignment does not exist.

**get_assignment_ids**()
Return a list with all assignment ids.

**get_condition_by_id**(*condition_id*)
Return dict for corresponding condition.

Raise a *ValueError*, if the condition does not exist.

**get_condition_ids**()
Return a list with all conditions ids.

**get_function_by_id**(*function_id*)
Return dict for corresponding function.

Raise a *ValueError*, if the function does not exist.

**get_function_ids**()
Return a list with all function ids.

**get_observable_by_id**(*observable_id*)
Return dict for corresponding observable.

Raise a *ValueError*, if the observable does not exist.

**get_observable_ids**()
Return a list with all observable ids.

**get_ode_by_id**(*state_id*)
Return dict for corresponding ODE/state.

Raise a *ValueError*, if the ODE/state does not exist.

**get_ode_ids**()
Return a list with all state ids.

**get_parameter_by_id**(*parameter_id*)
Return dict for corresponding parameter.

Raise a `ValueError, if the parameter does not exist.

**get_parameter_ids**()
Return a list with all parameter ids.

**get_time**()
Get time variable.

**is_set_time**()
Check whether there is a time variable.

**static load_from_yaml**(*yaml_dir*)
Create a model instance from a YAML file.

**Parameters** **yaml_dir** (str) – directory to the YAML file, that should be imported

**Returns** new model

**Return type** cls

**set_time**(*time_variable*)
Set time variable.

**validate_model**()
Validate the YAML model.

**Raises** **ValidationError** –

**write_to_petab**(*output_dir*, *model_name*, *petab_yaml_name=None*, *measurement_table_name=None*)
Write the YamlModel as a PEtab problem.

Equivalent to calling `yaml2petab on the file produced by the YAML output.

If a `petab_yaml_name is given, a YAML file is created, that organizes the petab problem. If additionally a `measurement_table_file_name is specified, this file name is written into the created YAML file.

**Parameters**

- **output_dir** (str) – path the output file(s) are be written out

- **model_name** (str) – name of SBML model
- **petab_yaml_name** (Optional[str]) – name of the YAML organizing the PEtab problem.
- **measurement_table_name** (Optional[str]) – Name of measurement table

**write_to_sbml**(*sbml_dir*, *overwrite=False*)
Write the model as an SBML file to the directory given in *sbml_dir*.

**Parameters**

- **sbml_dir** (str) – path/file, where the sbml should be written
- **overwrite** (bool) – Indicates, whether an existing yaml should be overwritten

**Raises**

- **ValueError** –
- **FileExistsError** –

**write_to_yaml**(*yaml_dir*, *overwrite=False*)
Write the model to a YAML file given as *yaml_dir*.

**Parameters**

- **yaml_dir** (str) – path/file, where the YAML should be written
- **overwrite** (bool) – Indicates, whether an existing YAML should be overwritten

**Raises**

- **ValueError** –
- **FileExistsError** –

CHAPTER

FIVE

# RELEASE NOTES

## 5.1 0.2 series

### 5.1.1 0.2.4 (2021-05-28)

- JOSS badge in the README (#133)
- Citation section in the README (#133)

### 5.1.2 0.2.3 (2021-05-25)

- Add additional names to the license (#128).
- Add information about the installation of dependencies for the example notebooks (#128).

### 5.1.3 0.2.2 (2021-03-19)

- Add checks in SBML conversion, e.g. to catch invalid identifiers and equations (# 118, #123).
- Add tests for MacOS and Windows (#115).
- Fix pydocstyle and swig (#120).
- Add a logo license. (#116)
- Smaller fixes in notebooks (#113, #117).

### 5.1.4 0.2.1 (2021-02-22)

- New option to write observables as assignments in *yaml2sbml* (#105).
- Set SBML file name as model id in the SBML (#105).
- Clarify docs and warnings, e.g. if formula starts with a minus (#109).
- Add issue template (#96).
- Restructure README (#55, #103, #104).
- Testing via tox (#88, #94, #95).
- Replace *requirements.txt* and *setup.py* by *setup.cfg* (#87).

### 5.1.5 0.2.0 (2021-02-03)

- Initial release on *pypi*.

CHAPTER

SIX

# LICENSE

This package is licensed under an MIT license.

CHAPTER

SEVEN

# LOGO


yaml2sbml's logo can be found in multiple variants in the doc/logo folder, in svg and png format. It is made available under a Creative Commons CC0 1.0 Universal (CC0 1.0) license, with the terms given in doc/logo/LICENSE.md. We encourage to use it e.g. in presentations and posters.

We thank Elba Raimúndez for her contributions to the logo design.

CHAPTER

# EIGHT

# CONTACT

Feel free to submit an issue or send us an e-mail.

CHAPTER

NINE

# CONTRIBUTE

## 9.1 Documentation

To make yaml2sbml easily usable, we try to provide good documentation, including code annotation and usage examples. The documentation is hosted on yaml2sbml.readthedocs.io and updated automatically every time the `main` branch is updated. To create the documentation locally, first install the requirements via:

```
pip install .[doc]
```

and then compile the documentation via:

```
cd doc
make html
```

## 9.2 Test environment

We use the virtual testing tool tox for all unit tests, format and quality checks and notebooks. Its configuration is specified in `tox.ini`. To run it locally, first install:

```
pip install tox
```

and then simply execute:

```
tox
```

To run only selected tests (see `tox.ini` for what is tested), use e.g.:

```
tox -e pyroma,flake8
```

For continuous integration testing we use GitHub Actions. All tests are run there on pull requests and required to pass. The configuration is specified in *.github/workflows/ci.yml*.

## 9.3 Unit tests

Unit tests are located in the `tests` folder. All files starting with `test_` contain tests and are automatically run on GitHub Actions. Run them locally via:

```
tox -e unittests
```

which boils mostly down to:

```
python3 -m pytest tests
```

You can also run only specific tests.

Unit tests can be written with pytest or unittest.

## 9.4 PEP8

We try to respect the PEP8 coding standards. We run flake8 as part of the tests. The flake8 plugins used are specified in `tox.ini` and the flake8 configuration given in `.flake8`. You can run it locally via:

```
tox -e flake8
```

## 9.5 Workflow

If you start working on a new feature or a fix, please create an issue on GitHub shortly describing the issue and assign yourself.

To get your code merged, please:

1. create a pull request to develop
2. if not already done in a commit message, use the pull request description to reference and automatically close the respective issue (see https://help.github.com/articles/closing-issues-using-keywords/)
3. check that all tests pass
4. check that the documentation is up-to-date
5. request a code review

CHAPTER

# TEN

# DEPLOY

New production releases should be created every time the `main` branch is updated.

## 10.1 Versions

On every merge to `main`, the version number in `yaml2sbml/version.py` should be incremented. We use version numbers `A.B.C`, where roughly

- `C` is increased for bug fixes,
- `B` is increased for new features and minor API breaking changes,
- `A` is increased for major API breaking changes.

as suggested by the Python packaging guide.

## 10.2 Create a new release

After new commits have been added via pull requests to the `develop` branch, changes can be merged to `main` and a new version of yaml2sbml can be released.

### 10.2.1 Merge into main

1. create a pull request from `develop` to `main`,
2. check that all tests pass,
3. check that the documentation is up-to-date,
4. update the version number in `yaml2sbml/version.py` (see above),
5. update the release notes in `doc/release_notes.rst`,
6. request a code review.

To be able to actually perform the merge, sufficient rights may be required. Also, at least one review is required.

### 10.2.2 Create a release on GitHub

After merging into `main`, create a new release on GitHub. This can be done either directly on the project GitHub website, or via the CLI as described in Git Basics - Tagging. In the release form,

- specify a tag with the new version as specified in `yaml2sbml/version.py`,
- include the latest additions to `doc/release_notes.rst` in the release description.

## 10.3 Upload to PyPI

The upload to the Python package index PyPI has been automated via GitHub Actions, specified in `.github/workflows/deploy.yml`, and is triggered whenever a new release tag is created.

To manually upload a new version to PyPI, proceed as follows: First, create a so-called "wheel" via:

```
python setup.py sdist bdist_wheel
```

A wheel is essentially a ZIP archive which contains the source code and the binaries (if any).

Then upload the archive:

```
twine upload dist/yaml2sbml-x.y.z-py3-non-any.wheel
```

replacing x.y.z by the respective version number.

See also the section on distributing packages of the Python packaging guide.

# PYTHON MODULE INDEX

# INDEX