Test Documentation

Release 2.0.0

Test

Jun 07, 2019

Contents

E-Cell System is a software platform for modeling, simulation and analysis of complex, heterogeneous and multi-scale systems like the cell.

E-Cell4 is a free and open-source software licensed under the GNU General Public License version 2. The source code is available on GitHub.

Please refer to https://github.com/ecell/ecell4 for information about **installation instructions**.

CHAPTER 1

Tutorials

1.1 1. Brief Tour of E-Cell4 Simulations

First of all, you have to load the E-Cell4 library:

[1]:
```
%matplotlib inline
from ecell4 import *
from ecell4_base.core import *
```

1.1.1 1.1. Quick Demo

There are three fundamental components consisting of E-Cell System version 4, which are `Model`, `World`, and `Simulator`. These components describe concepts in simulation.

- `Model` describes a problem to simulate as its name suggests.
- `World` describes a state, e.g. an initial state and a state at a time-point.
- `Simulator` describes a solver.

`Model` is independent from solvers. Every solver can share a single `Model` instance. Each solver alogrithm has a corresponding pair of `World` and `Simulator` (these pairs are capsulized into `Factory` class). `World` is not necessarily needed to be bound to `Model` and `Simulator`, but `Simulator` needs both `Model` and `World`.

Before running a simulation, you have to make a `Model`. E-Cell4 supports multiple ways to buld a `Model` (See **2. How to Build a Model** *local ipynb* readthedocs). Here, we explain the simplest way using the `with` statement with `reaction_rules`:

[2]:
```
with reaction_rules():
    A + B > C | 0.01  # equivalent to create_binding_reaction_rule
    C > A + B | 0.3   # equivalent to create_unbinding_reaction_rule

m1 = get_model()
print(m1)
```

```
<ecell4_base.core.NetworkModel object at 0x14fdde89bb90>
```

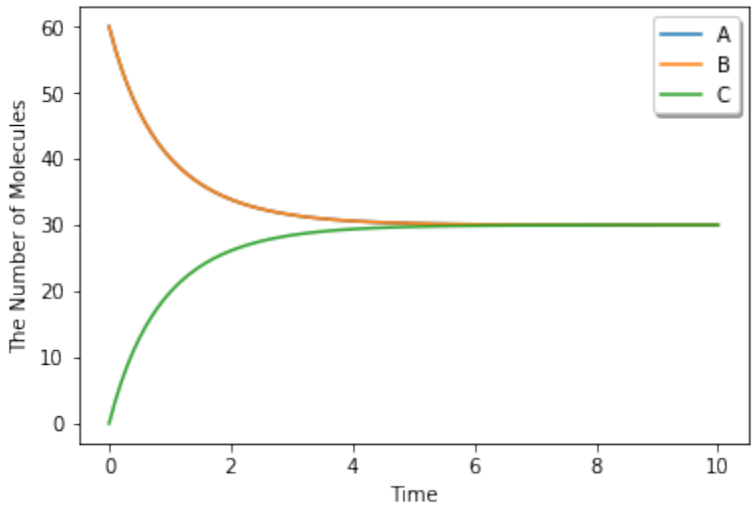
Please remember to write parentheses `()` after `reaction_rules`. Here, a `Model` with two `ReactionRules` named `m1` was built. Lines in the `with` block describe `ReactionRules`, a binding and unbinding reaction respectively. A kinetic rate for the mass action reaction is defined after a separator `|`, i.e. `0.01` or `0.3`. In the form of ordinary differential equations, this model can be described as:

$$[\mathrm{A}]' = [\mathrm{B}]' = -[\mathrm{C}] = -0.01[\mathrm{A}][\mathrm{B}] + 0.3[\mathrm{C}]$$

For more compact description, `A + B == C | (0.01, 0.3)` is also acceptable.

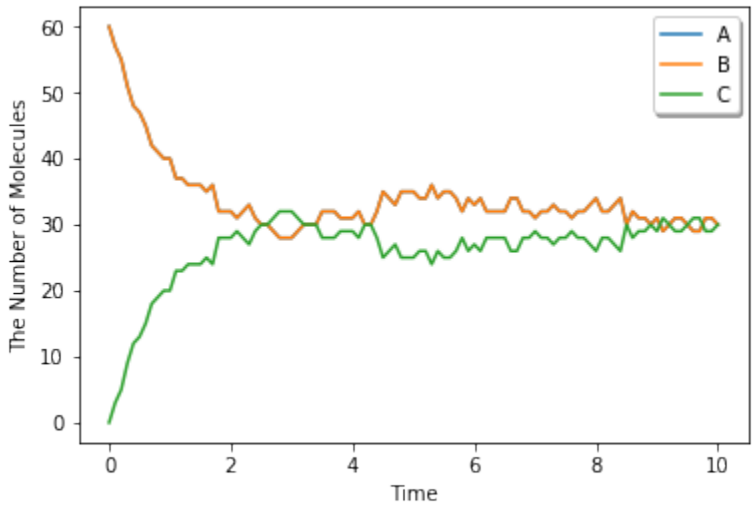
E-Cell4 has a simple interface for running simulation on a given model, called `run_simulation`. This enables for you to run simulations without instanciate `World` and `Simulator` by yourself. To solve this model, you have to give a volume, an initial value for each `Species` and duration of time:

[3]:
```
run_simulation(10.0, model=m1, y0={'A': 60, 'B': 60}, volume=1.0)
```



To switch simulation algorithm, you only need to give the type of solver (`ode` is used as a default) as follows:

[4]:
```
run_simulation(10.0, model=m1, y0={'A': 60, 'B': 60}, solver='gillespie')
```



1.1.2 1.2. Spatial Simulation and Visualization

E-Cell4 now supports multiple spatial simulation algorithms, `egfrd`, `spatiocyte` and `meso`. In addition to the model used in non-spatial solvers (`ode` and `gillespie`), these spatial solvers need extra information about each `Species`, i.e. a diffusion coefficient and radius.

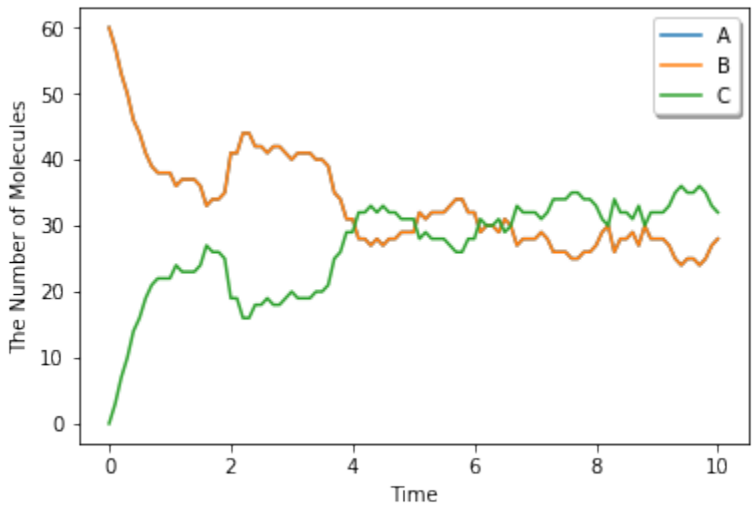
The `with` statement with `species_attributes` is available to describe these properties:

[5]:
```
with species_attributes():
    A | B | C | {'radius': 0.005, 'D': 1}  # 'D' is for the diffusion coefficient

with reaction_rules():
    A + B == C | (0.01, 0.3)

m2 = get_model()
```

Species attributes could be a string, boolean, integer or floating number.

Now you can run a spatial simulation in the same way as above (in the case of `egfrd`, the time it takes to finish the simulation will be longer):

[6]:
```
run_simulation(10.0, model=m2, y0={'A': 60, 'B': 60}, solver='meso')
```



Structure (e.g. membrane, cytoplasm and nucleus) is only supported by `spatiocyte` and `meso` for now. For the simulation, `location` and `dimension` that each species belongs to must be specified in its attribute.

[7]:
```
with species_attributes():
    A | {'D': 1, 'location': 'S', 'dimension': 3}  # 'S' is a name of the structure
    S | {'dimension': 3}

m3 = get_model()  # with no reactions
```

E-Cell4 supports primitive shapes as a structure like `Sphere`:

[8]:
```
sphere = Sphere(Real3(0.5, 0.5, 0.5), 0.48)  # a center position and radius
```

E-Cell4 provides various kinds of `Observers` which log the state during a simulation. In the following two observers are declared to record the position of the molecule. `FixedIntervalTrajectoryObserver` logs a trajectory of a molecule, and `FixedIntervalHDF5Observer` saves `World` to a HDF5 file at the given time interval:

[9]:
```
obs1 = FixedIntervalTrajectoryObserver(1e-3)
obs2 = FixedIntervalHDF5Observer(0.1, 'test%02d.h5')
```

`run_simulation` can accept structures and observers as arguments `structure` and `observers` (see also `help(run_simulation)`):

[10]:
```
run_simulation(1.0, model=m3, y0={'A': 60}, structures={'S': sphere},
               solver='spatiocyte', observers=(obs1, obs2), return_type=None)
```

E-Cell4 has a function to visualize the world which is also capable of interactive visualization named `viz.plot_world`. `viz.plot_world` plots positions of molecules in 3D. In addition, by using `load_world`, you can easily restore the state of `World` from a HDF5 file:

[11]:
```
# viz.plot_world(load_world('test00.h5'), species_list=['A'])
viz.plot_world(load_world('test00.h5'), species_list=['A'], interactive=True)
```

```
<IPython.core.display.HTML object>
```

Also, for `FixedIntervalTrajectoryObserver`,`viz.plot_trajectory` generates a plot of the trajectory. (Again, it is possible to generate interactive plots.):

[12]:
```
# viz.plot_trajectory(obs1)
viz.plot_trajectory(obs1, interactive=True)
```

```
<IPython.core.display.HTML object>
```

For more details, see **5. How to Log and Visualize Simulations** local ipynb readthedocs.

1.2 2. How to Build a Model

`Model` is composed of a set of `Species` and `ReactionRules`.

- `Species` describes a molecule entitie (e.g. a type or state of a protein) in the model. `Species` also has its attributes like the size.
- `ReactionRule` describes the interactions between `Species` (e.g. binding and unbinding).

[1]:
```
%matplotlib inline
from ecell4 import *
from ecell4_base.core import *
```

1.2.1 2.1. Species

`Species` can be generated by giving its name:

[2]:
```
sp1 = Species("A")
print(sp1.serial())
```

```
A
```

There are some naming conventions for the name of `Species`. This naming convention requires careful use of special symbols (e.g. parenthesis `()`, dot `.`, underbar `_`), numbers and blank.

`Species` has a set of APIs for handling its attributes:

[3]:
```
sp1.set_attribute("radius", 0.005)
sp1.set_attribute("D", 1)
sp1.set_attribute("location", "cytoplasm")
print(sp1.has_attribute("radius"))
print(sp1.get_attribute("radius").magnitude)
print(sp1.get_attribute("radius").units)
print(sp1.has_attribute("location"))
print(sp1.get_attribute("location"))
sp1.remove_attribute("radius")
print(sp1.has_attribute("radius"))
```

```
True
0.005

True
cytoplasm
False
```

The arguments in `set_attribute` is the name of attribute and its value. The name of an attribute is given as a string, and its value is a string, integer, float, or boolean. `get_attribute` returns the value set. For an integer or float attribute, `get_attribute` returns a quantity object, which is a pair of value (`magnitude`) and unit (`units`).

There is a shortcut to set the attributes above at once because `radius`, `D` (a diffusion coefficient) and `location` are frequently used.

[4]:
```
sp1 = Species("A", 0.005, 1, "cytoplasm")  # serial, radius, D, location
```

The equality between `Species` is just evaluated based on their `serial`:

[5]:
```
print(Species("A") == Species("B"), Species("A") == Species("A"))
```

```
False True
```

A Species consists of one or more UnitSpecies:

[6]:
```
sp1 = Species()
usp1 = UnitSpecies("C")
print(usp1.serial())
sp1.add_unit(usp1)
sp1.add_unit(UnitSpecies("A"))
sp1.add_unit(UnitSpecies("B"))
print(sp1.serial(), len(sp1.units()))
```

```
C
C.A.B 3
```

A `Species` can be reproduced from a serial. In a `serial`, all `UnitSpecies` are joined with the separator, dot `.`. The order of `UnitSpecies` affects the `Species` comparison.

[7]:
```
sp1 = Species("C.A.B")
print(sp1.serial())
print(Species("A.B.C") == Species("C.A.B"))
print(Species("A.B.C") == Species("A.B.C"))
```

```
C.A.B
False
True
```

`UnitSpecies` can have sites. Sites consists of a `name`, `state` and `bond`, and are sorted automatically in `UnitSpecies`. `name` must be unique in a `UnitSpecies`. All the value have to be string. Do not include

parenthesis, dot and blank, and not start from numbers except for `bond`.

[8]:
```
usp1 = UnitSpecies("A")
usp1.add_site("us", "u", "")
usp1.add_site("ps", "p", "_")
usp1.add_site("bs", "", "_")
print(usp1.serial())
```

```
A(bs^_,ps=p^_,us=u)
```

`UnitSpecies` can be also reproduced from its serial. Please be careful with the order of sites where a site with a state must be placed after sites with no state specification:

[9]:
```
usp1 = UnitSpecies()
usp1.deserialize("A(bs^_, us=u, ps=p^_)")
print(usp1.serial())
```

```
A(bs^_,ps=p^_,us=u)
```

Of course, a site of `UnitSpecies` is available even in `Species`' serial.

[10]:
```
sp1 = Species("A(bs^1, ps=u).A(bs, ps=p^1)")
print(sp1.serial())
print(len(sp1.units()))
```

```
A(bs^1, ps=u).A(bs, ps=p^1)
2
```

The information (`UnitSpecies` and its `site`) is used for rule-based modeling. The way of rule-based modeling in E-Cell4 will be explained in **7. Introduction of Rule-based Modeling** *local ipynb* readthedocs.

1.2.2 2.2. ReactionRule

`ReactionRule` consists of `reactants`, `products` and `k`. `reactants` and `products` are a list of `Species`, and `k` is a kinetic rate given as a floating number.

[11]:
```
rr1 = ReactionRule()
rr1.add_reactant(Species("A"))
rr1.add_reactant(Species("B"))
rr1.add_product(Species("C"))
rr1.set_k(1.0)
```

Here is a binding reaction from `A` and `B` to `C`. In this reaction definition, you don't need to set attributes to `Species`. The above series of operations can be written in one line using `create_binding_reaction_rule(Species("A"), Species("B"), Species("C"), 1.0)`.

You can use `as_string` function to check `ReactionRule`:

[12]:
```
rr1 = create_binding_reaction_rule(Species("A"), Species("B"), Species("C"), 1.0)
print(rr1.as_string())
```

```
A+B>C|1
```

You can also provide components to the constructor:

[13]:
```
rr1 = ReactionRule([Species("A"), Species("B")], [Species("C")], 1.0)
print(rr1.as_string())
```

```
A+B>C|1
```

Basically `ReactionRule` represents a mass action reaction with the rate `k`. `ode` solver also supports rate laws thought it's under development yet. `ode.ODERatelaw` is explained in **6. How to Solve ODEs with Rate Law Functions** *local ipynb* readthedocs.

1.2.3 2.3. NetworkModel

You have learned how to create some `Model` components. Next let's put the components in a `Model`.

[14]:
```
sp1 = Species("A", 0.005, 1)
sp2 = Species("B", 0.005, 1)
sp3 = Species("C", 0.01, 0.5)
```

[15]:
```
rr1 = create_binding_reaction_rule(Species("A"), Species("B"), Species("C"), 0.01)
rr2 = create_unbinding_reaction_rule(Species("C"), Species("A"), Species("B"), 0.3)
```

You can put the `Species` and `ReactionRule` with `add_species_attribute` and `add_reaction_rule`.

[16]:
```
m1 = NetworkModel()
m1.add_species_attribute(sp1)
m1.add_species_attribute(sp2)
m1.add_species_attribute(sp3)
m1.add_reaction_rule(rr1)
m1.add_reaction_rule(rr2)
```

Now we have a simple model with the binding and unbinding reactions. You can use `species_attributes` and `reaction_rules` to check the `Model`.

[17]:
```
print([sp.serial() for sp in m1.species_attributes()])
print([rr.as_string() for rr in m1.reaction_rules()])
```

```
['A', 'B', 'C']
['A+B>C|0.01', 'C>A+B|0.3']
```

The `Species` attributes are required for the spatial `Model`, but not required for the nonspatial `Model` (i.e. `gillespie` or `ode`). The attribute pushed first has higher priority than one pushed later. You can also attribute a `Species` based on the attributes in a `Model`.

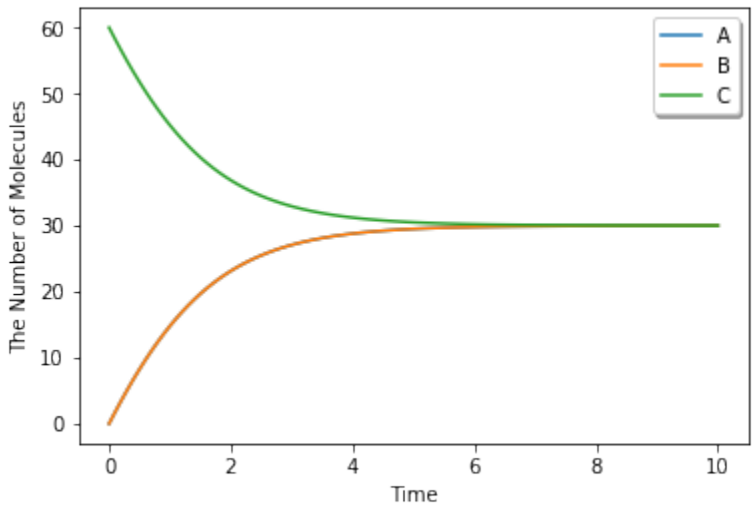
[18]:
```
sp1 = Species("A")
print(sp1.has_attribute("radius"))
sp2 = m1.apply_species_attributes(sp1)
print(sp2.has_attribute("radius"))
print(sp2.get_attribute("radius").magnitude)
```

```
False
True
0.005
```

For your information, all functions related to `Species`, `ReactionRule` and `NetworkModel` above are also available on C++ in the same way.

Finally, you can solve this model with `run_simulation` as explained in **1. Brief Tour of E-Cell4 Simulations** *local ipynb* readthedocs :

[19]:
```
run_simulation(10.0, model=m1, y0={'C': 60})
```



1.2.4 2.4. Python Utilities to Build a Model

As shown in **1. Brief Tour of E-Cell4 Simulations** *local ipynb* readthedocs, E-Cell4 also provides the easier way to build a model using `with` statement:

[20]:
```
with species_attributes():
    A | B | {'radius': 0.005, 'D': 1}
    C | {'radius': 0.01, 'D': 0.5}

with reaction_rules():
    A + B == C | (0.01, 0.3)

m1 = get_model()
```

For reversible reactions, <> is also available instead of == on Python 2, but deprecated on Python3. In the `with` statement, undeclared variables are automaticaly assumed to be a `Species`. Any Python variables, functions and statement are available even in the `with` block.

[21]:
```
from math import log

ka, kd, kf = 0.01, 0.3, 0.1
tau = 10.0

with reaction_rules():
    E0 + S == ES | (ka, kd)

    if tau > 0:
        ES > E1 + P | kf
        E1 > E0 | log(2) / tau
    else:
        ES > E0 + P | kf

m1 = get_model()
del ka, kd, kf, tau
```

Meanwhile, once some variable is declared even outside the block, you can not use its name as a `Species` as follows:

[22]:
```
A = 10

try:
    with reaction_rules():
        A + B == C | (0.01, 0.3)
except Exception as e:
    print(repr(e))

del A
```

```
TypeError("Argument 1 must be AnyCallable, ParseObj, InvExp or MulExp. 'int' was␣
↪given [10].",)
```

where `A + B == C` exactly means `10 + B == C`.

In the absence of left or right hand side of `ReactionRule` like synthesis or degradation, you may want to describe like:

```
with reaction_rules():
    A > | 1.0  # XXX: will raise SyntaxError
    > A | 1.0  # XXX: will raise SyntaxError
```

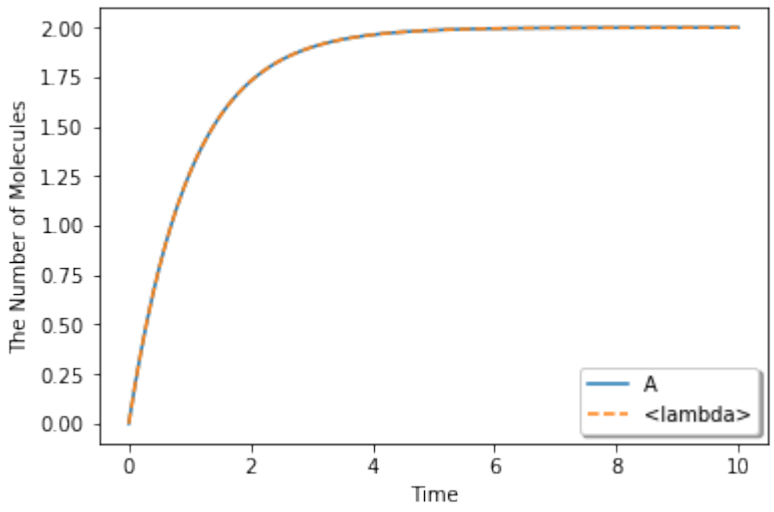
However, this is not accepted because of `SyntaxError` on Python. To describe this case, a special operator, tilde `~`, is available. `~` sets a stoichiometric coefficient of the following `Species` as zero, which means the `Species` is just ignored in the `ReactionRule`.

[23]:
```
with reaction_rules():
    ~A > A | 2.0  # equivalent to `create_synthesis_reaction_rule`
    A > ~A | 1.0  # equivalent to `create_degradation_reaction_rule`

m1 = get_model()
print([rr.as_string() for rr in m1.reaction_rules()])
```

```
['>A|2', 'A>|1']
```

The following `Species`' name is not necessarily needed to be the same as others. The model above describes $[A]' = 2 - [A]$:

[24]:
```
from math import exp
run_simulation(10.0, model=m1, opt_args=['-', lambda t: 2.0 * (1 - exp(-t)), '--'])
```



A chain of reactions can be described in one line. To split a line into two or more physical lines, wrap lines in a parenthesis:

[25]:
```
with reaction_rules():
    (E + S == ES | (0.5, 1.0)
         > E + P | 1.5)

m1 = get_model()
print([rr.as_string() for rr in m1.reaction_rules()])
```

```
['E+S>ES|0.5', 'ES>E+S|1', 'ES>E+P|1.5']
```

The method uses global variables in `ecell4.util.decorator` (e.g. `REACTION_RULES`) to cache objects created in the `with` statement:

[26]:
```
import ecell4.util.decorator

with reaction_rules():
    A + B == C | (0.01, 0.3)

print(ecell4.util.decorator.REACTION_RULES)  #XXX: Only for debugging
get_model()
print(ecell4.util.decorator.REACTION_RULES)  #XXX: Only for debugging
```

```
[<ecell4_base.core.ReactionRule object at 0x14e1ecfafaf8>, <ecell4_base.core.
↪ReactionRule object at 0x14e1ecfafa98>]
[]
```

Python decorator functions are also available. Decorator functions improve the modularity of the `Model`.

[27]:
```
@species_attributes
def attrgen1(radius, D):
    A | B | {'radius': radius, 'D': D}
    C | {'radius': radius * 2, 'D': D * 0.5}

@reaction_rules
def rrgen1(kon, koff):
    A + B == C | (kon, koff)

attrs1 = attrgen1(0.005, 1)
rrs1 = rrgen1(0.01, 0.3)
print(attrs1)
print(rrs1)
```

```
[<ecell4_base.core.Species object at 0x14e1ecfafaf8>, <ecell4_base.core.Species␣
↪object at 0x14e1ecfafb28>, <ecell4_base.core.Species object at 0x14e1ecfafa98>]
[<ecell4_base.core.ReactionRule object at 0x14e1ecfafb40>, <ecell4_base.core.
↪ReactionRule object at 0x14e1ecfafb58>]
```

In contrast to the `with` statement, do **not** add parentheses after the decorator here. The functions decorated by `reaction_rules` and `species_attributes` return a list of `ReactionRules` and `Species` respectively. The list can be registered to `Model` at once by using `add_reaction_rules` and `add_species_attributes`.

[28]:
```
m1 = NetworkModel()
m1.add_species_attributes(attrs1)
m1.add_reaction_rules(rrs1)
print(m1.num_reaction_rules())
```

```
2
```

This method is modular and reusable relative to the way using `with` statement.

1.3 3. How to Setup the Initial Condition

Here, we explain the basics of `World` classes. In E-Cell4, six types of World classes are supported now: `spatiocyte.SpatiocyteWorld`, `egfrd.EGFRDWorld`, `bd.BDWorld`, `meso.MesoscopicWorld`, `gillespie.GillespieWorld`, and `ode.ODEWorld`.

In the most of softwares, the initial condition is supposed to be a part of `Model`. But, in E-Cell4, the initial condition must be set up as `World` separately from `Model`. `World` stores an information about the state at a time point, such as a current time, the number of molecules, coordinate of molecules, structures, and random number generator. Meanwhile, `Model` contains the type of interactions between molecules and the common properties of molecules.

[1]:
```
from ecell4_base.core import *
```

1.3.1 3.1. Common APIs of World

Even though `World` describes the spatial representation specific to the corresponding algorithm, it has compatible APIs. In this section, we introduce the common interfaces of the six `World` classes.

[2]:
```
from ecell4_base import *
```

`World` classes accept different sets of arguments in the constructor, which determine the parameters specific to the algorithm. However, at least, all `World` classes can be instantiated only with their size, named `edge_lengths`. The type of `edge_lengths` is `Real3`, which represents a triplet of `Reals`. In E-Cell4, all 3-dimensional positions are treated as a `Real3`. See also 8. More about 1. Brief Tour of E-Cell4 Simulations.

[3]:
```
edge_lengths = Real3(1, 2, 3)
w1 = gillespie.World(edge_lengths)
w2 = ode.World(edge_lengths)
w3 = spatiocyte.World(edge_lengths)
w4 = bd.World(edge_lengths)
w5 = meso.World(edge_lengths)
w6 = egfrd.World(edge_lengths)
```

`World` has getter methods for the size and volume.

[4]:
```
print(tuple(w1.edge_lengths()), w1.volume())
print(tuple(w2.edge_lengths()), w2.volume())
print(tuple(w3.edge_lengths()), w3.volume())
print(tuple(w4.edge_lengths()), w4.volume())
print(tuple(w5.edge_lengths()), w5.volume())
print(tuple(w6.edge_lengths()), w6.volume())
```

```
(1.0, 2.0, 3.0) 6.0
(1.0, 2.0, 3.0) 6.0
(1.0124557603503803, 2.0091789367798976, 3.0) 6.102614364352381
(1.0, 2.0, 3.0) 6.0
(1.0, 2.0, 3.0) 6.0
(1.0, 2.0, 3.0) 6.0
```

`spatiocyte.World` (`w3`) would have a bit larger volume to fit regular hexagonal close-packed (HCP) lattice.

Next, let's add molecules into the World. Here, you must give `Species` attributed with **radius** and **D** to tell the shape of molecules. In the example below **0.0025** corresponds to **radius** and **1** to **D**. Positions of the molecules are randomly determined in the `World` if needed. **10** in **add_molecules** function represents the number of molecules to be added.

[5]:
```
sp1 = Species("A", 0.0025, 1)
w1.add_molecules(sp1, 10)
w2.add_molecules(sp1, 10)
w3.add_molecules(sp1, 10)
w4.add_molecules(sp1, 10)
w5.add_molecules(sp1, 10)
w6.add_molecules(sp1, 10)
```

After model is bound to world, you do not need to rewrite the **radius** and **D** once set in Species (unless you want to change it).

[6]:
```
m = NetworkModel()
m.add_species_attribute(Species("A", 0.0025, 1))
m.add_species_attribute(Species("B", 0.0025, 1))

w1.bind_to(m)
w2.bind_to(m)
w3.bind_to(m)
w4.bind_to(m)
w5.bind_to(m)
w6.bind_to(m)
w1.add_molecules(Species("B"), 20)
w2.add_molecules(Species("B"), 20)
w3.add_molecules(Species("B"), 20)
w4.add_molecules(Species("B"), 20)
w5.add_molecules(Species("B"), 20)
w6.add_molecules(Species("B"), 20)
```

Similarly, `remove_molecules` and `num_molecules_exact` are also available.

[7]:
```
w1.remove_molecules(Species("B"), 5)
w2.remove_molecules(Species("B"), 5)
w3.remove_molecules(Species("B"), 5)
w4.remove_molecules(Species("B"), 5)
w5.remove_molecules(Species("B"), 5)
w6.remove_molecules(Species("B"), 5)
```

[8]:
```
print(w1.num_molecules_exact(Species("A")), w2.num_molecules_exact(Species("A")), w3.
↪num_molecules_exact(Species("A")), w4.num_molecules_exact(Species("A")), w5.num_
↪molecules_exact(Species("A")), w6.num_molecules_exact(Species("A")))
print(w1.num_molecules_exact(Species("B")), w2.num_molecules_exact(Species("B")), w3.
↪num_molecules_exact(Species("B")), w4.num_molecules_exact(Species("B")), w5.num_
↪molecules_exact(Species("B")), w6.num_molecules_exact(Species("B")))
```

```
10 10 10 10 10 10
15 15 15 15 15 15
```

Unlike `num_molecules_exact`, `num_molecules` returns the numbers that match a given `Species` in rule-based fashion. When all `Species` in the `World` has no molecular interaction, `num_molecules` is same with `num_molecules_exact`.

[9]:
```
print(w1.num_molecules(Species("A")), w2.num_molecules(Species("A")), w3.num_
↪molecules(Species("A")), w4.num_molecules(Species("A")), w5.num_molecules(Species("A
↪")), w6.num_molecules(Species("A")))
```

(continues on next page)

(continued from previous page)

```
print(w1.num_molecules(Species("B")), w2.num_molecules(Species("B")), w3.num_
↪molecules(Species("B")), w4.num_molecules(Species("B")), w5.num_molecules(Species("B
↪")), w6.num_molecules(Species("B")))
```

```
10 10 10 10 10 10
15 15 15 15 15 15
```

`World` holds its simulation time.

[10]:
```
print(w1.t(), w2.t(), w3.t(), w4.t(), w5.t(), w6.t())
w1.set_t(1.0)
w2.set_t(1.0)
w3.set_t(1.0)
w4.set_t(1.0)
w5.set_t(1.0)
w6.set_t(1.0)
print(w1.t(), w2.t(), w3.t(), w4.t(), w5.t(), w6.t())
```

```
0.0 0.0 0.0 0.0 0.0 0.0
1.0 1.0 1.0 1.0 1.0 1.0
```

Finally, you can `save` and `load` the state of a `World` into/from a HDF5 file.

[11]:
```
w1.save("gillespie.h5")
w2.save("ode.h5")
w3.save("spatiocyte.h5")
w4.save("bd.h5")
w5.save("meso.h5")
w6.save("egfrd.h5")
del w1, w2, w3, w4, w5, w6
```

[12]:
```
w1 = gillespie.World()
w2 = ode.World()
w3 = spatiocyte.World()
w4 = bd.World()
w5 = meso.World()
w6 = egfrd.World()
print(w1.t(), tuple(w1.edge_lengths()), w1.volume(), w1.num_molecules(Species("A")),␣
↪w1.num_molecules(Species("B")))
print(w2.t(), tuple(w2.edge_lengths()), w2.volume(), w2.num_molecules(Species("A")),␣
↪w2.num_molecules(Species("B")))
print(w3.t(), tuple(w3.edge_lengths()), w3.volume(), w3.num_molecules(Species("A")),␣
↪w3.num_molecules(Species("B")))
print(w4.t(), tuple(w4.edge_lengths()), w4.volume(), w4.num_molecules(Species("A")),␣
↪w4.num_molecules(Species("B")))
print(w5.t(), tuple(w5.edge_lengths()), w5.volume(), w5.num_molecules(Species("A")),␣
↪w5.num_molecules(Species("B")))
print(w6.t(), tuple(w6.edge_lengths()), w6.volume(), w6.num_molecules(Species("A")),␣
↪w6.num_molecules(Species("B")))
```

```
0.0 (1.0, 1.0, 1.0) 1.0 0 0
0.0 (1.0, 1.0, 1.0) 1.0 0 0
0.0 (1.0124557603503803, 1.0045894683899488, 1.0) 1.0171023940587303 0 0
0.0 (1.0, 1.0, 1.0) 1.0 0 0
0.0 (1.0, 1.0, 1.0) 1.0 0 0
0.0 (1.0, 1.0, 1.0) 1.0 0 0
```

[13]:
```
w1.load("gillespie.h5")
w2.load("ode.h5")
w3.load("spatiocyte.h5")
w4.load("bd.h5")
w5.load("meso.h5")
w6.load("egfrd.h5")
print(w1.t(), tuple(w1.edge_lengths()), w1.volume(), w1.num_molecules(Species("A")),␣
↪w1.num_molecules(Species("B")))
print(w2.t(), tuple(w2.edge_lengths()), w2.volume(), w2.num_molecules(Species("A")),␣
↪w2.num_molecules(Species("B")))
print(w3.t(), tuple(w3.edge_lengths()), w3.volume(), w3.num_molecules(Species("A")),␣
↪w3.num_molecules(Species("B")))
print(w4.t(), tuple(w4.edge_lengths()), w4.volume(), w4.num_molecules(Species("A")),␣
↪w4.num_molecules(Species("B")))
print(w5.t(), tuple(w5.edge_lengths()), w5.volume(), w5.num_molecules(Species("A")),␣
↪w5.num_molecules(Species("B")))
print(w6.t(), tuple(w6.edge_lengths()), w6.volume(), w6.num_molecules(Species("A")),␣
↪w6.num_molecules(Species("B")))
del w1, w2, w3, w4, w5, w6
```

```
1.0 (1.0, 2.0, 3.0) 6.0 10 15
1.0 (1.0, 2.0, 3.0) 6.0 10 15
1.0 (1.0124557603503803, 2.0091789367798976, 3.0) 6.102614364352381 10 15
1.0 (1.0, 2.0, 3.0) 6.0 10 15
1.0 (1.0, 2.0, 3.0) 6.0 10 15
1.0 (1.0, 2.0, 3.0) 6.0 10 15
```

All the `World` classes also accept a HDF5 file path as an unique argument of the constructor.

[14]:
```
print(gillespie.World("gillespie.h5").t())
print(ode.World("ode.h5").t())
print(spatiocyte.World("spatiocyte.h5").t())
print(bd.World("bd.h5").t())
print(meso.World("meso.h5").t())
print(egfrd.World("egfrd.h5").t())
```

```
1.0
1.0
1.0
1.0
1.0
1.0
```

1.3.2 3.2. How to Get Positions of Molecules

`World` also has the common functions to access the coordinates of the molecules.

[15]:
```
w1 = gillespie.World()
w2 = ode.World()
w3 = spatiocyte.World()
w4 = bd.World()
w5 = meso.World()
w6 = egfrd.World()
```

First, you can place a molecule at the certain position with `new_particle`.

[16]:
```
sp1 = Species("A", 0.0025, 1)
pos = Real3(0.5, 0.5, 0.5)
(pid1, p1), suc1 = w1.new_particle(sp1, pos)
(pid2, p2), suc2 = w2.new_particle(sp1, pos)
pid3 = w3.new_particle(sp1, pos)
(pid4, p4), suc4 = w4.new_particle(sp1, pos)
(pid5, p5), suc5 = w5.new_particle(sp1, pos)
(pid6, p6), suc6 = w6.new_particle(sp1, pos)
```

`new_particle` returns a particle created and whether it's succeeded or not. The resolution in representation of molecules differs. For example, `GillespieWorld` has almost no information about the coordinate of molecules. Thus, it simply ignores the given position, and just counts up the number of molecules here.

`ParticleID` is a pair of `Integers` named `lot` and `serial`.

[17]:
```
print(pid6.lot(), pid6.serial())
print(pid6 == ParticleID((0, 1)))
```

```
0 1
True
```

Particle simulators, i.e. `spatiocyte`, `bd` and `egfrd`, provide an interface to access a particle by its id. `has_particle` returns if a particles exists or not for the given `ParticleID`.

[18]:
```
# print(w1.has_particle(pid1))
# print(w2.has_particle(pid2))
print(w3.has_particle(pid3))  # => True
print(w4.has_particle(pid4))  # => True
# print(w5.has_particle(pid5))
print(w6.has_particle(pid6))  # => True
```

```
True
True
True
```

After checking the existency, you can get the partcle by `get_particle` as follows.

[19]:
```
# pid1, p1 = w1.get_particle(pid1)
# pid2, p2 = w2.get_particle(pid2)
pid3, p3 = w3.get_particle(pid3)
pid4, p4 = w4.get_particle(pid4)
# pid5, p5 = w5.get_particle(pid5)
pid6, p6 = w6.get_particle(pid6)
```

`Particle` consists of `species`, `position`, `radius` and `D`.

[20]:
```
# print(p1.species().serial(), tuple(p1.position()), p1.radius(), p1.D())
# print(p2.species().serial(), tuple(p2.position()), p2.radius(), p2.D())
print(p3.species().serial(), tuple(p3.position()), p3.radius(), p3.D())
print(p4.species().serial(), tuple(p4.position()), p4.radius(), p4.D())
# print(p5.species().serial(), tuple(p5.position()), p5.radius(), p5.D())
print(p6.species().serial(), tuple(p6.position()), p6.radius(), p6.D())
```

```
A (0.5062278801751902, 0.5080682368868706, 0.5) 0.0025 1.0
A (0.5, 0.5, 0.5) 0.0025 1.0
A (0.5, 0.5, 0.5) 0.0025 1.0
```

In the case of `spatiocyte`, a particle position is automatically round to the center of the voxel nearest to the given position.

You can even move the position of the particle. `update_particle` replace the particle specified with the given `ParticleID` with the given `Particle` and return `False`. If no corresponding particle is found, create new particle and return `True`. If you give a `Particle` with the different type of `Species`, the `Species` of the `Particle` will be also changed.

[21]:
```
newp = Particle(sp1, Real3(0.3, 0.3, 0.3), 0.0025, 1)
# print(w1.update_particle(pid1, newp))
# print(w2.update_particle(pid2, newp))
print(w3.update_particle(pid3, newp))
print(w4.update_particle(pid4, newp))
# print(w5.update_particle(pid5, newp))
print(w6.update_particle(pid6, newp))
```

```
False
False
False
```

`list_particles` and `list_particles_exact` return a list of pairs of `ParticleID` and `Particle` in the `World`. `World` automatically makes up for the gap with random numbers. For example, `GillespieWorld` returns a list of positions randomly distributed in the `World` size.

[22]:
```
print(w1.list_particles_exact(sp1))
# print(w2.list_particles_exact(sp1))  # ODEWorld has no member named list_particles
print(w3.list_particles_exact(sp1))
print(w4.list_particles_exact(sp1))
print(w5.list_particles_exact(sp1))
print(w6.list_particles_exact(sp1))
```

```
[(<ecell4_base.core.ParticleID object at 0x150e376a79a8>, <ecell4_base.core.Particle␣
↪object at 0x150e376a79f0>)]
[(<ecell4_base.core.ParticleID object at 0x150e376a79a8>, <ecell4_base.core.Particle␣
↪object at 0x150e376a79c0>)]
[(<ecell4_base.core.ParticleID object at 0x150e376a79a8>, <ecell4_base.core.Particle␣
↪object at 0x150e376a7930>)]
[(<ecell4_base.core.ParticleID object at 0x150e376a79a8>, <ecell4_base.core.Particle␣
↪object at 0x150e376a79f0>)]
[(<ecell4_base.core.ParticleID object at 0x150e376a79a8>, <ecell4_base.core.Particle␣
↪object at 0x150e376a79c0>)]
```

You can remove a specific particle with `remove_particle`.

[23]:
```
# w1.remove_particle(pid1)
# w2.remove_particle(pid2)
w3.remove_particle(pid3)
w4.remove_particle(pid4)
# w5.remove_particle(pid5)
w6.remove_particle(pid6)
# print(w1.has_particle(pid1))
# print(w2.has_particle(pid2))
print(w3.has_particle(pid3))  # => False
print(w4.has_particle(pid4))  # => False
# print(w5.has_particle(pid5))
print(w6.has_particle(pid6))  # => False
```

```
False
False
False
```

1.3.3 3.3. Lattice-based Coordinate

In addition to the common interface, each `World` can have their own interfaces. As an example, we explain methods to handle lattice-based coordinate here. `SpatiocyteWorld` is based on a space discretized to hexiagonal close packing lattices, `LatticeSpace`.

[24]:
```
w = spatiocyte.World(Real3(1, 2, 3), voxel_radius=0.01)
w.bind_to(m)
```

The size of a single lattice, called `Voxel`, can be obtained by `voxel_radius()`. `SpatiocyteWorld` has methods to get the numbers of rows, columns, and layers. These sizes are automatically calculated based on the given `edge_lengths` at the construction.

[25]:
```
print(w.voxel_radius())  # => 0.01
print(tuple(w.shape()))  # => (64, 152, 118)
# print(w.col_size(), w.row_size(), w.layer_size())  # => (64, 152, 118)
print(w.size())  # => 1147904 = 64 * 152 * 118
```

```
0.01
(64, 152, 118)
1147904
```

A position in the lattice-based space is treated as an `Integer3`, column, row and layer, called a global coordinate. Thus, `SpatiocyteWorld` provides the function to convert the `Real3` into a lattice-based coordinate.

[26]:
```
# p1 = Real3(0.5, 0.5, 0.5)
# g1 = w.position2global(p1)
# p2 = w.global2position(g1)
# print(tuple(g1))  # => (31, 25, 29)
# print(tuple(p2))  # => (0.5062278801751902, 0.5080682368868706, 0.5)
```

In `SpatiocyteWorld`, the global coordinate is translated to a single integer. It is just called a coordinate. You can also treat the coordinate as in the same way with a global coordinate.

[27]:
```
# p1 = Real3(0.5, 0.5, 0.5)
# c1 = w.position2coordinate(p1)
# p2 = w.coordinate2position(c1)
# g1 = w.coord2global(c1)
# print(c1)  # => 278033
# print(tuple(p2))  # => (0.5062278801751902, 0.5080682368868706, 0.5)
# print(tuple(g1))  # => (31, 25, 29)
```

With these coordinates, you can handle a `Voxel`, which represents a `Particle` object. Instead of `new_particle`, `new_voxel` provides the way to create a new `Voxel` with a coordinate.

[28]:
```
# c1 = w.position2coordinate(Real3(0.5, 0.5, 0.5))
# ((pid, v), is_succeeded) = w.new_voxel(Species("A"), c1)
# print(pid, v, is_succeeded)
```

A `Voxel` consists of `species`, `coordinate`, `radius` and `D`.

[29]:
```
# print(v.species().serial(), v.coordinate(), v.radius(), v.D())  # => (u'A', 278033,␣
↪0.0025, 1.0)
```

Of course, you can get a voxel and list voxels with `get_voxel` and `list_voxels_exact` similar to `get_particle` and `list_particles_exact`.

[30]:
```
# print(w.num_voxels_exact(Species("A")))
# print(w.list_voxels_exact(Species("A")))
# print(w.get_voxel(pid))
```

You can move and update the voxel with `update_voxel` corresponding to `update_particle`.

[31]:
```
# c2 = w.position2coordinate(Real3(0.5, 0.5, 1.0))
# w.update_voxel(pid, Voxel(v.species(), c2, v.radius(), v.D()))
# pid, newv = w.get_voxel(pid)
# print(c2)  # => 278058
# print(newv.species().serial(), newv.coordinate(), newv.radius(), newv.D())  # => (u
↪'A', 278058, 0.0025, 1.0)
# print(w.num_voxels_exact(Species("A")))  # => 1
```

Finally, `remove_voxel` remove a voxel as `remove_particle` does.

[32]:
```
# print(w.has_voxel(pid))  # => True
# w.remove_voxel(pid)
# print(w.has_voxel(pid))  # => False
```

1.3.4 3.4 Structure

[33]:
```
w1 = gillespie.World()
w2 = ode.World()
w3 = spatiocyte.World()
w4 = bd.World()
w5 = meso.World()
w6 = egfrd.World()
```

By using a `Shape` object, you can confine initial positions of molecules to a part of `World`. In the case below, 60 molecules are positioned inside the given `Sphere`. Diffusion of the molecules placed here is **NOT** restricted in the `Shape`. This `Shape` is only for the initialization.

[34]:
```
sp1 = Species("A", 0.0025, 1)
sphere = Sphere(Real3(0.5, 0.5, 0.5), 0.3)
w1.add_molecules(sp1, 60, sphere)
w2.add_molecules(sp1, 60, sphere)
w3.add_molecules(sp1, 60, sphere)
w4.add_molecules(sp1, 60, sphere)
w5.add_molecules(sp1, 60, sphere)
w6.add_molecules(sp1, 60, sphere)
```

A property of `Species`, `'location'`, is available to restrict diffusion of molecules. `'location'` is not fully supported yet, but only supported in `spatiocyte` and `meso`. `add_structure` defines a new structure given as a pair of `Species` and `Shape`.

[35]:
```
membrane = SphericalSurface(Real3(0.5, 0.5, 0.5), 0.4)  # This is equivalent to call␣
↪`Sphere(Real3(0.5, 0.5, 0.5), 0.4).surface()`
w3.add_structure(Species("M"), membrane)
w5.add_structure(Species("M"), membrane)
```

After defining a structure, you can bind molecules to the structure as follows:

[36]:
```
sp2 = Species("B", 0.0025, 0.1, "M")  # `'location'` is the fourth argument
w3.add_molecules(sp2, 60)
w5.add_molecules(sp2, 60)
```

The molecules bound to a `Species` named `B` diffuse on a structure named `M`, which has a shape of `SphericalSurface` (a hollow sphere). In `spatiocyte`, a structure is represented as a set of particles with `Species` `M` occupying a voxel. It means that molecules not belonging to the structure is not able to overlap the voxel and it causes a collision. On the other hand, in `meso`, a structure means a list of subvolumes. Thus, a structure doesn't avoid an incursion of other particles.

1.3.5 3.5. Random Number Generator

A random number generator is also a part of `World`. All `World` except `ODEWorld` store a random number generator, and updates it when the simulation needs a random value. On E-Cell4, only one class `GSLRandomNumberGenerator` is implemented as a random number generator.

[37]:
```
rng1 = GSLRandomNumberGenerator()
print([rng1.uniform_int(1, 6) for _ in range(20)])
```

```
[6, 1, 2, 6, 2, 3, 6, 5, 4, 5, 5, 4, 2, 5, 4, 2, 3, 3, 2, 2]
```

With no argument, the random number generator is always initialized with a seed, `0`.

[38]:
```
rng2 = GSLRandomNumberGenerator()
print([rng2.uniform_int(1, 6) for _ in range(20)])  # => same as above
```

```
[6, 1, 2, 6, 2, 3, 6, 5, 4, 5, 5, 4, 2, 5, 4, 2, 3, 3, 2, 2]
```

You can initialize the seed with an integer as follows:

[39]:
```
rng2 = GSLRandomNumberGenerator()
rng2.seed(15)
print([rng2.uniform_int(1, 6) for _ in range(20)])
```

```
[6, 5, 2, 4, 1, 1, 3, 5, 2, 6, 4, 1, 2, 5, 2, 5, 1, 2, 2, 6]
```

When you call the `seed` function with no input, the seed is drawn from the current time.

[40]:
```
rng2 = GSLRandomNumberGenerator()
rng2.seed()
print([rng2.uniform_int(1, 6) for _ in range(20)])
```

```
[5, 3, 1, 4, 3, 2, 4, 3, 1, 5, 2, 2, 2, 5, 3, 4, 3, 5, 2, 1]
```

`GSLRandomNumberGenerator` provides several ways to get a random number.

[41]:
```
print(rng1.uniform(0.0, 1.0))
print(rng1.uniform_int(0, 100))
print(rng1.gaussian(1.0))
```

```
0.03033520421013236
33
0.8935555455208181
```

`World` accepts a random number generator at the construction. As a default, `GSLRandomNumberGenerator()` is used. Thus, when you don't give a generator, behavior of the simulation is always same (determinisitc).

[42]:
```
rng = GSLRandomNumberGenerator()
rng.seed()
w1 = gillespie.World(Real3(1, 1, 1), rng=rng)
```

You can access the `GSLRandomNumberGenerator` in a `World` through `rng` function.

[43]:
```
print(w1.rng().uniform(0.0, 1.0))
```

```
0.6781027028337121
```

`rng()` returns a shared pointer to the `GSLRandomNumberGenerator`. Thus, in the example above, `rng` and `w1.rng()` point exactly the same thing.

1.4 4. How to Run a Simulation

In sections 2 and 3, we explained the way to build a model and to setup the intial state. Now, it is the time to run a simulation. Corresponding to `World` classes, six `Simulator` classes are there: `spatiocyte.SpatiocyteSimulator`, `egfrd.EGFRDSimulator`, `bd.BDSimulator`, `meso.MesoscopicSimulator`, `gillespie.GillespieSimulator`, and `ode.ODESimulator`. Each `Simulator` class only accepts the corresponding type of `World`, but all of them allow the same `Model`.

[1]:
```
from ecell4_base.core import *
```

1.4.1 4.1. How to Setup a Simulator

Except for the initialization (so-called constructor function) with arguments specific to the algorithm, all `Simulators` have the same APIs.

[2]:
```
from ecell4_base import *
```

Before constructing a `Simulator`, parepare a `Model` and a `World` corresponding to the type of `Simulator`.

[3]:
```
from ecell4 import species_attributes, reaction_rules, get_model

with species_attributes():
    A | B | C | {'D': 1, 'radius': 0.005}

with reaction_rules():
    A + B == C | (0.01, 0.3)

m = get_model()
```

[4]:
```
w1 = gillespie.World()
w2 = ode.World()
w3 = spatiocyte.World()
w4 = bd.World()
w5 = meso.World()
w6 = egfrd.World()
```

`Simulator` requires both `Model` and `World` in this order at the construction.

[5]:
```
sim1 = gillespie.Simulator(w1, m)
sim2 = ode.Simulator(w2, m)
sim3 = spatiocyte.Simulator(w3, m)
sim4 = bd.Simulator(w4, m)
sim5 = meso.Simulator(w5, m)
sim6 = egfrd.Simulator(w6, m)
```

If you bind the `Model` to the `World`, you need only the `World` to create a `Simulator`.

[6]:
```
w1.bind_to(m)
w2.bind_to(m)
w3.bind_to(m)
w4.bind_to(m)
w5.bind_to(m)
w6.bind_to(m)
```

[7]:
```
sim1 = gillespie.Simulator(w1)
sim2 = ode.Simulator(w2)
sim3 = spatiocyte.Simulator(w3)
sim4 = bd.Simulator(w4)
sim5 = meso.Simulator(w5)
sim6 = egfrd.Simulator(w6)
```

Of course, the `Model` and `World` bound to a `Simulator` can be drawn from `Simulator` in the way below:

[8]:
```
print(sim1.model(), sim1.world())
print(sim2.model(), sim2.world())
print(sim3.model(), sim3.world())
print(sim4.model(), sim4.world())
print(sim5.model(), sim5.world())
print(sim6.model(), sim6.world())
```

```
<ecell4_base.core.Model object at 0x145cf5fee7b0> <ecell4_base.gillespie.
↪GillespieWorld object at 0x145cf5ff1720>
<ecell4_base.core.Model object at 0x145cf5feeab0> <ecell4_base.ode.ODEWorld object at␣
↪0x145cf5ff16f0>
<ecell4_base.core.Model object at 0x145cf5feeab0> <ecell4_base.spatiocyte.
↪SpatiocyteWorld object at 0x145cf5ff1720>
<ecell4_base.core.Model object at 0x145cf5feea30> <ecell4_base.bd.BDWorld object at␣
↪0x145cf5ff16f0>
<ecell4_base.core.Model object at 0x145cf5feeab0> <ecell4_base.meso.MesoscopicWorld␣
↪object at 0x145cf5ff1738>
<ecell4_base.core.Model object at 0x145cf5feea30> <ecell4_base.egfrd.EGFRDWorld␣
↪object at 0x145cf5ff16f0>
```

After updating the `World` by yourself, you must initialize the internal state of a `Simulator` before running simulation.

[9]:
```
w1.add_molecules(Species('C'), 60)
w2.add_molecules(Species('C'), 60)
w3.add_molecules(Species('C'), 60)
w4.add_molecules(Species('C'), 60)
w5.add_molecules(Species('C'), 60)
w6.add_molecules(Species('C'), 60)
```

[10]:
```
sim1.initialize()
sim2.initialize()
```

(continues on next page)

(continued from previous page)

```
sim3.initialize()
sim4.initialize()
sim5.initialize()
sim6.initialize()
```

For algorithms with a fixed step interval, the `Simulator` also requires `dt`.

[11]:
```
sim2.set_dt(1e-6)  # ode.Simulator. This is optional
sim4.set_dt(1e-6)  # bd.Simulator
```

1.4.2 4.2. Running Simulation

For running simulation, `Simulator` provides two APIs, `step` and `run`.

`step()` advances a simulation for the time that the `Simulator` expects, `next_time()`.

[12]:
```
print(sim1.t(), sim1.next_time(), sim1.dt())
print(sim2.t(), sim2.next_time(), sim2.dt())  # => (0.0, 1e-6, 1e-6)
print(sim3.t(), sim3.next_time(), sim3.dt())
print(sim4.t(), sim4.next_time(), sim4.dt())  # => (0.0, 1e-6, 1e-6)
print(sim5.t(), sim5.next_time(), sim5.dt())
print(sim6.t(), sim6.next_time(), sim6.dt())  # => (0.0, 0.0, 0.0)
```

```
0.0 0.06981637440659177 0.06981637440659177
0.0 1e-06 1e-06
0.0 6.666666666666667e-05 6.666666666666667e-05
0.0 1e-06 1e-06
0.0 0.0024540697478422522 0.0024540697478422522
0.0 0.0 0.0
```

[13]:
```
sim1.step()
sim2.step()
sim3.step()
sim4.step()
sim5.step()
sim6.step()
```

[14]:
```
print(sim1.t())
print(sim2.t())  # => 1e-6
print(sim3.t())
print(sim4.t())  # => 1e-6
print(sim5.t())
print(sim6.t())  # => 0.0
```

```
0.06981637440659177
1e-06
6.666666666666667e-05
1e-06
0.0024540697478422522
0.0
```

`last_reactions()` returns a list of pairs of `ReactionRule` and `ReactionInfo` which occurs at the last step. Each algorithm have its own implementation of `ReactionInfo`. See `help(module.ReactionInfo)` for details.

[15]:
```
print(sim1.last_reactions())
# print(sim2.last_reactions())
print(sim3.last_reactions())
print(sim4.last_reactions())
print(sim5.last_reactions())
print(sim6.last_reactions())
```

```
[(<ecell4_base.core.ReactionRule object at 0x145cf5ff1780>, <ecell4_base.gillespie.
↪ReactionInfo object at 0x145cf5ff1798>)]
[]
[]
[]
[]
```

`step(upto)` advances a simulation for `next_time` if `next_time` is less than `upto`, or for `upto` otherwise. `step(upto)` returns whether the time does **NOT** reach the limit, `upto`.

[16]:
```
print(sim1.step(1.0), sim1.t())
print(sim2.step(1.0), sim2.t())
print(sim3.step(1.0), sim3.t())
print(sim4.step(1.0), sim4.t())
print(sim5.step(1.0), sim5.t())
print(sim6.step(1.0), sim6.t())
```

```
True 0.2285050559395263
True 2e-06
True 0.00013333333333333334
True 2e-06
True 0.004146250248941816
True 0.0
```

To run a simulation just until the time, `upto`, call `step(upto)` while it returns `True`.

[17]:
```
while sim1.step(1.0): pass
while sim2.step(0.001): pass
while sim3.step(0.001): pass
while sim4.step(0.001): pass
while sim5.step(1.0): pass
while sim6.step(0.001): pass
```

[18]:
```
print(sim1.t())  # => 1.0
print(sim2.t())  # => 0.001
print(sim3.t())  # => 0.001
print(sim4.t())  # => 0.001
print(sim5.t())  # => 1.0
print(sim6.t())  # => 0.001
```

```
1.0
0.001
0.001
0.001
1.0
0.001
```

This is just what `run` does. `run(tau)` advances a simulation upto `t()+tau`.

[19]:
```
sim1.run(1.0)
sim2.run(0.001)
```

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```
sim3.run(0.001)
sim4.run(0.001)
sim5.run(1.0)
sim6.run(0.001)
```

[20]:
```
print(sim1.t())  # => 2.0
print(sim2.t())  # => 0.002
print(sim3.t())  # => 0.002
print(sim4.t())  # => 0.002
print(sim5.t())  # => 2.0
print(sim6.t())  # => 0.02
```

```
2.0
0.002
0.002
0.002
2.0
0.002
```

`num_steps` returns the number of steps during the simulation.

[21]:
```
print(sim1.num_steps())
print(sim2.num_steps())
print(sim3.num_steps())
print(sim4.num_steps())
print(sim5.num_steps())
print(sim6.num_steps())
```

```
29
2001
28
2001
921
599
```

1.4.3 4.3. Capsulizing Algorithm into a Factory Class

Owing to the portability of a `Model` and consistent APIs of `Worlds` and `Simulators`, it is very easy to write a script common in algorithms. However, when switching the algorithm, still we have to rewrite the name of classes in the code, one by one.

To avoid the trouble, E-Cell4 also provides a `Factory` class for each algorithm. `Factory` encapsulates `World` and `Simulator` with their arguments needed for the construction. By using `Factory` class, your script could be portable and robust agaist changes in the algorithm.

`Factory` just provides two functions, `world` and `simulator`.

[22]:
```
def singlerun(f, m):
    w = f.world(Real3(1, 1, 1))
    w.bind_to(m)
    w.add_molecules(Species('C'), 60)

    sim = f.simulator(w)
    sim.run(0.01)
    print(sim.t(), w.num_molecules(Species('C')))
```

`singlerun` above is free from the algorithm. Thus, by just switching `Factory`, you can easily compare the results.

[23]:
```
singlerun(gillespie.Factory(), m)
singlerun(ode.Factory(), m)
singlerun(spatiocyte.Factory(), m)
singlerun(bd.Factory(bd_dt_factor=1), m)
singlerun(meso.Factory(), m)
singlerun(egfrd.Factory(), m)
```

```
0.01 60
0.01 59
0.01 60
0.01 60
0.01 59
0.01 60
```

When you need to provide several parameters to initialize `World` or `Simulator`, `run_simulation` also accepts `Factory` instead of `solver`.

[24]:
```
from ecell4.util import run_simulation
print(run_simulation(0.01, model=m, y0={'C': 60}, return_type='array',␣
↪solver=gillespie.Factory())[-1])
print(run_simulation(0.01, model=m, y0={'C': 60}, return_type='array', solver=ode.
↪Factory())[-1])
print(run_simulation(0.01, model=m, y0={'C': 60}, return_type='array',␣
↪solver=spatiocyte.Factory())[-1])
print(run_simulation(0.01, model=m, y0={'C': 60}, return_type='array', solver=bd.
↪Factory(bd_dt_factor=1))[-1])
print(run_simulation(0.01, model=m, y0={'C': 60}, return_type='array', solver=meso.
↪Factory())[-1])
print(run_simulation(0.01, model=m, y0={'C': 60}, return_type='array', solver=egfrd.
↪Factory())[-1])
```

```
[0.01, 0.0, 0.0, 60.0]
[0.01, 0.17972919304002502, 0.17972919304002502, 59.820270806960046]
[0.01, 1.0, 1.0, 59.0]
[0.01, 0.0, 0.0, 60.0]
[0.01, 1.0, 1.0, 59.0]
[0.01, 0.0, 0.0, 60.0]
```

1.5 5. How to Log and Visualize Simulations

Here we explain how to take a log of simulation results and how to visualize it.

[1]:
```
%matplotlib inline
import math
from ecell4 import *
from ecell4_base import *
from ecell4_base.core import *
```

1.5.1 5.1. Logging Simulations with Observers

E-Cell4 provides special classes for logging, named `Observer`. `Observer` class is given when you call the `run` function of `Simulator`.

[2]:
```
def create_simulator(f=gillespie.Factory()):
    m = NetworkModel()
    A, B, C = Species('A', 0.005, 1), Species('B', 0.005, 1), Species('C', 0.005, 1)
    m.add_species_attribute(A)
    m.add_species_attribute(B)
    m.add_species_attribute(C)
    m.add_reaction_rule(create_binding_reaction_rule(A, B, C, 0.01))
    m.add_reaction_rule(create_unbinding_reaction_rule(C, A, B, 0.3))
    w = f.world()
    w.bind_to(m)
    w.add_molecules(C, 60)
    sim = f.simulator(w)
    sim.initialize()
    return sim
```

One of most popular `Observer` is `FixedIntervalNumberObserver`, which logs the number of molecules with the given time interval. `FixedIntervalNumberObserver` requires an interval and a list of serials of `Species` for logging.

[3]:
```
obs1 = FixedIntervalNumberObserver(0.1, ['A', 'B', 'C'])
sim = create_simulator()
sim.run(1.0, obs1)
```

`data` function of `FixedIntervalNumberObserver` returns the data logged.

[4]:
```
print(obs1.data())
```

```
[[0.0, 0.0, 0.0, 60.0], [0.1, 4.0, 4.0, 56.0], [0.2, 4.0, 4.0, 56.0], [0.
↪30000000000000004, 4.0, 4.0, 56.0], [0.4, 5.0, 5.0, 55.0], [0.5, 6.0, 6.0, 54.0],␣
↪[0.6000000000000001, 8.0, 8.0, 52.0], [0.7000000000000001, 9.0, 9.0, 51.0], [0.8,␣
↪10.0, 10.0, 50.0], [0.9, 10.0, 10.0, 50.0], [1.0, 13.0, 13.0, 47.0]]
```

`targets()` returns a list of `Species`, which you specified as an argument of the constructor.

[5]:
```
print([sp.serial() for sp in obs1.targets()])
```

```
['A', 'B', 'C']
```

`NumberObserver` logs the number of molecules after every steps when a reaction occurs. This observer is useful to log all reactions, but not available for `ode`.

[6]:
```
obs1 = NumberObserver(['A', 'B', 'C'])
sim = create_simulator()
sim.run(1.0, obs1)
print(obs1.data())
```

```
[[0.0, 0.0, 0.0, 60.0], [0.02260889225454991, 1.0, 1.0, 59.0], [0.02969136490582789,␣
↪2.0, 2.0, 58.0], [0.03733168118750063, 3.0, 3.0, 57.0], [0.07073952925465954, 4.0,␣
↪4.0, 56.0], [0.130436288313097, 5.0, 5.0, 55.0], [0.24790263332591864, 6.0, 6.0, 54.
↪0], [0.3617656247136509, 7.0, 7.0, 53.0], [0.3766811515853057, 8.0, 8.0, 52.0], [0.
↪49416987912466614, 9.0, 9.0, 51.0], [0.5432711094028326, 10.0, 10.0, 50.0], [0.
↪71741755480935, 11.0, 11.0, 49.0], [0.7488858466586021, 12.0, 12.0, 48.0], [0.
↪7793994960089041, 11.0, 11.0, 49.0], [0.8704209616639759, 12.0, 12.0, 48.0], [0.
↪9744942945378776, 13.0, 13.0, 47.0], [0.9795754005617485, 14.0, 14.0, 46.0], [1.0,␣
↪14.0, 14.0, 46.0]]
```

`TimingNumberObserver` allows you to give the times for logging as an argument of its constructor.

[7]:
```
obs1 = TimingNumberObserver([0.0, 0.1, 0.2, 0.5, 1.0], ['A', 'B', 'C'])
sim = create_simulator()
sim.run(1.0, obs1)
print(obs1.data())
```

```
[[0.0, 0.0, 0.0, 60.0], [0.1, 4.0, 4.0, 56.0], [0.2, 4.0, 4.0, 56.0], [0.5, 8.0, 8.0,␣
↪52.0], [1.0, 14.0, 14.0, 46.0]]
```

`run` function accepts multile `Observers` at once.

[8]:
```
obs1 = NumberObserver(['C'])
obs2 = FixedIntervalNumberObserver(0.1, ['A', 'B'])
sim = create_simulator()
sim.run(1.0, [obs1, obs2])
print(obs1.data())
print(obs2.data())
```

```
[[0.0, 60.0], [0.02260889225454991, 59.0], [0.02969136490582789, 58.0], [0.
↪03733168118750063, 57.0], [0.07073952925465954, 56.0], [0.3144142385275013, 55.0],␣
↪[0.44722512356903055, 54.0], [0.5302331233889856, 53.0], [0.5597228247745124, 52.0],
↪ [0.6798940199866744, 51.0], [0.7165839475888072, 50.0], [0.9254471286586852, 49.0],
↪ [0.9492284464115648, 48.0], [0.9602086431679366, 47.0], [1.0, 47.0]]
[[0.0, 0.0, 0.0], [0.1, 4.0, 4.0], [0.2, 4.0, 4.0], [0.30000000000000004, 4.0, 4.0],␣
↪[0.4, 5.0, 5.0], [0.5, 6.0, 6.0], [0.6000000000000001, 8.0, 8.0], [0.
↪7000000000000001, 9.0, 9.0], [0.8, 10.0, 10.0], [0.9, 10.0, 10.0], [1.0, 13.0, 13.
↪0]]
```

`FixedIntervalHDF5Observedr` logs the whole data in a `World` to an output file with the fixed interval. Its second argument is a prefix for output filenames. `filename()` returns the name of a file scheduled to be saved next. At most one format string like `%02d` is allowed to use a step count in the file name. When you do not use the format string, it overwrites the latest data to the file.

[9]:
```
obs1 = FixedIntervalHDF5Observer(0.2, 'test%02d.h5')
print(obs1.filename())
sim = create_simulator()
sim.run(1.0, obs1) # Now you have steped 5 (1.0/0.2) times
print(obs1.filename())
```

```
test00.h5
test06.h5
```

[10]:
```
w = load_world('test05.h5')
print(w.t(), w.num_molecules(Species('C')))
```

```
1.0 47
```

The usage of `FixedIntervalCSVObserver` is almost same with that of `FixedIntervalHDF5Observer`. It saves positions (x, y, z) of particles with the radius (r) and serial number of `Species` (sid) to a CSV file.

[11]:
```
obs1 = FixedIntervalCSVObserver(0.2, "test%02d.csv")
print(obs1.filename())
sim = create_simulator()
sim.run(1.0, obs1)
print(obs1.filename())
```

```
test00.csv
test06.csv
```

Here is the first 10 lines in the output CSV file.

[12]:
```
print(''.join(open("test05.csv").readlines()[: 10]))
```

```
x,y,z,r,sid
0.605209,0.35387,0.426092,0,0
0.7105,0.699568,0.662126,0,0
0.362397,0.863948,0.0881481,0,0
0.663826,0.79369,0.763512,0,0
0.669228,0.605234,0.23582,0,0
0.597962,0.472582,0.458323,0,0
0.153892,0.781189,0.738202,0,0
0.972426,0.643748,0.545462,0,0
0.793828,0.519622,0.299548,0,0
```

For particle simulations, E-Cell4 also provides `Observer` to trace a trajectory of a molecule, named `FixedIntervalTrajectoryObserver`. When no `ParticleID` is specified, it logs all the trajectories. Once some `ParticleID` is lost for the reaction during a simulation, it just stop to trace the particle any more.

[13]:
```
sim = create_simulator(spatiocyte.Factory(0.005))
obs1 = FixedIntervalTrajectoryObserver(0.01)
sim.run(0.1, obs1)
```

[14]:
```
print([tuple(pos) for pos in obs1.data()[0]])
```

```
[(0.8573214099741124, 0.964174949546675, 0.19), (0.8001666493091716, 0.
↪8140638795573724, 0.24), (0.5470527092215764, 0.8169506309033205, 0.525), (0.
↪6450322989329036, 0.626425042070744, 0.385), (0.7021870595978444, 0.
↪35507041555161983, 0.5650000000000001), (0.68585712797929, 0.4763139720814413, 0.
↪765), (0.8001666493091716, 0.6235382907247958, 0.65), (0.6205374015050719, 0.
↪48497422611928565, 0.5700000000000001), (0.5470527092215764, 0.5658032638058333, 0.
↪31), (0.28577380332470415, 0.7736493607140986, 0.27), (0.27760883751542687, 0.
↪9266471820493494, 0.225)]
```

Generally, `World` assumes a periodic boundary for each plane. To avoid the big jump of a particle at the edge due to the boundary condition, `FixedIntervalTrajectoryObserver` tries to keep the shift of positions. Thus, the positions stored in the `Observer` are not necessarily limited in the cuboid given for the `World`. To track the diffusion over the boundary condition accurately, the step interval for logging must be small enough. Of course, you can disable this option. See `help(FixedIntervalTrajectoryObserver)`.

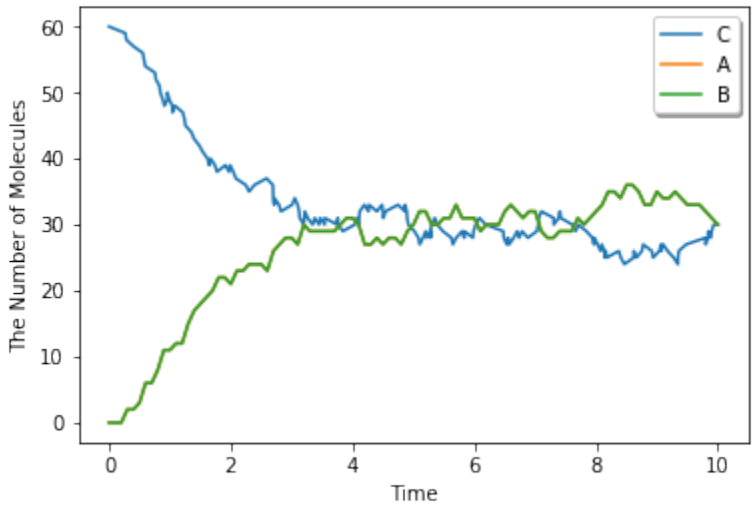
1.5.2 5.2. Visualization of Data Logged

In this section, we explain the visualization tools for data logged by `Observer`.

Firstly, for time course data, `viz.plot_number_observer` plots the data provided by `NumberObserver`, `FixedIntervalNumberObserver` and `TimingNumberObserver`. For the detailed usage of `viz.plot_number_observer`, see `help(viz.plot_number_observer)`.

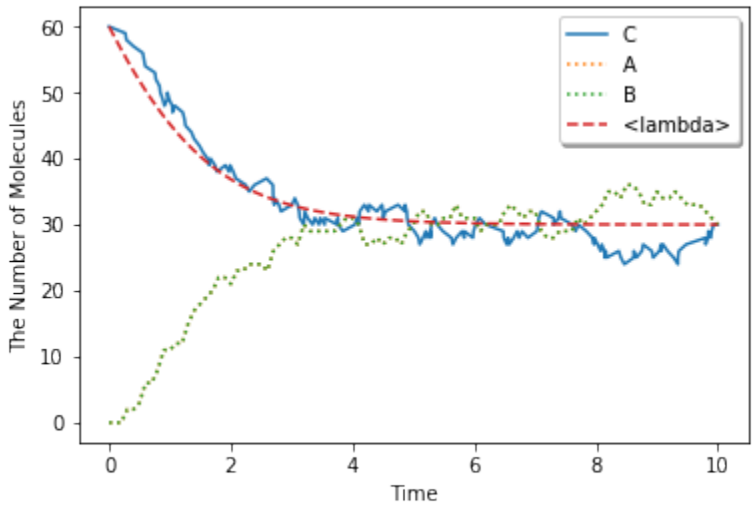
[15]:
```
obs1 = NumberObserver(['C'])
obs2 = FixedIntervalNumberObserver(0.1, ['A', 'B'])
sim = create_simulator()
sim.run(10.0, [obs1, obs2])
```

[16]:
```
viz.plot_number_observer(obs1, obs2)
```



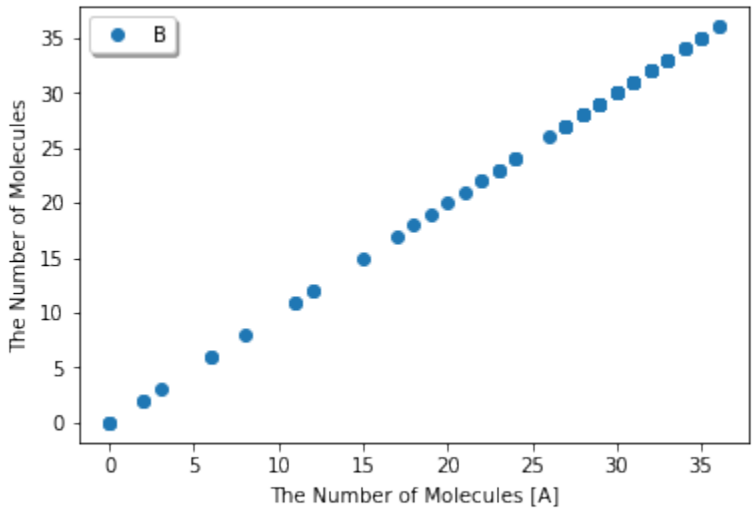
You can set the style for plotting, and even add an arbitrary function to plot.

[17]:
```
viz.plot_number_observer(obs1, '-', obs2, ':', lambda t: 60 * (1 + 2 * math.exp(-0.9
↪* t)) / (2 + math.exp(-0.9 * t)), '--')
```



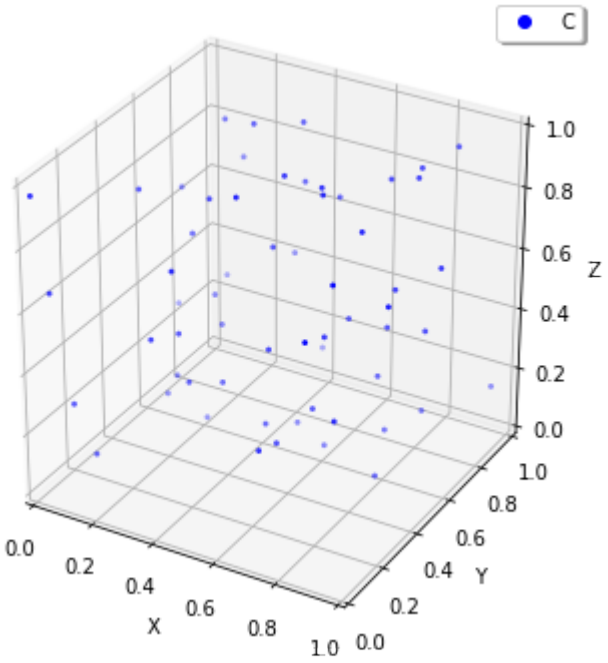
Plotting in the phase plane is also available by specifing the x-axis and y-axis.

[18]:
```
viz.plot_number_observer(obs2, 'o', x='A', y='B')
```



For spatial simulations, to visualize the state of `World`, `viz.plot_world` is available. This function plots the points of particles in three-dimensional volume in the interactive way. You can save the image by clicking a right button on the drawing region.

[19]:
```
sim = create_simulator(spatiocyte.Factory(0.005))
# viz.plot_world(sim.world())
viz.plot_world(sim.world(), interactive=False)
```



You can also make a movie from a series of HDF5 files, given as a `FixedIntervalHDF5Observer`. NOTE: `viz.plot_movie` requires an extra library, `ffmpeg`, when `interactive=False`.

[20]:
```
sim = create_simulator(spatiocyte.Factory(0.005))
obs1 = FixedIntervalHDF5Observer(0.02, 'test%02d.h5')
sim.run(1.0, obs1)
```

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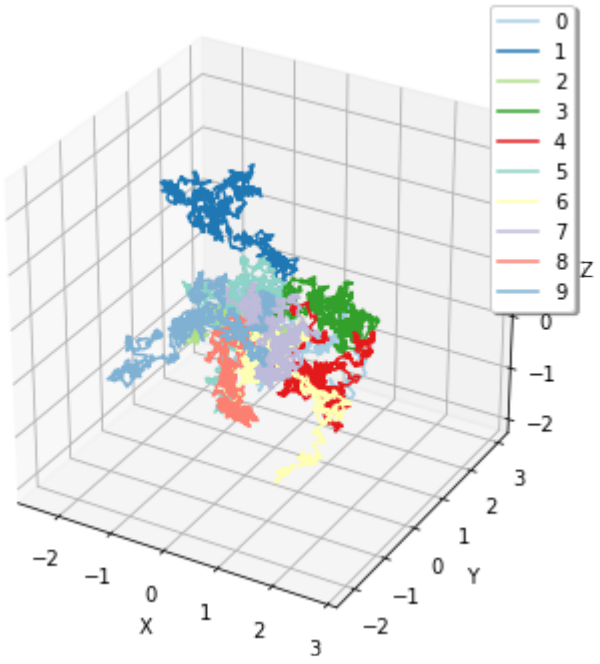
```
viz.plot_movie(obs1)
```

```
<IPython.core.display.HTML object>
```

Finally, corresponding to `FixedIntervalTrajectoryObserver`, `viz.plot_trajectory` provides a visualization of particle trajectories.

[21]:
```
sim = create_simulator(spatiocyte.Factory(0.005))
obs1 = FixedIntervalTrajectoryObserver(1e-3)
sim.run(1, obs1)
# viz.plot_trajectory(obs1)
viz.plot_trajectory(obs1, interactive=False)
```



1.6 6. How to Solve ODEs with Rate Law Functions

In general, `ReactionRule` describes a mass action kinetics with no more than two reactants. In case of a reaction with a complecated rate law, `ReactionRule` could be extensible with `ReactionRuleDescriptor`. Here, we explan the use of `ReactionRuleDescriptor` especially for `ode`.

[1]:
```
%matplotlib inline
from ecell4 import *
from ecell4_base import *
from ecell4_base.core import *
```

1.6.1 6.1. ReactionRuleDescriptor

`ReactionRule` defines reactants, products, and a kinetic rate.

[2]:
```
rr1 = ReactionRule()
rr1.add_reactant(Species("A"))
rr1.add_reactant(Species("B"))
rr1.add_product(Species("C"))
rr1.set_k(1.0)
print(len(rr1.reactants()))  # => 2
print(len(rr1.products()))  # => 1
print(rr1.k())  # => 1.0
print(rr1.as_string())  # => A+B>C|1
print(rr1.has_descriptor())  # => False
```

```
2
1
1.0
A+B>C|1
False
```

In addition to that, `ReactionRule` could be extensible with `ReactionRuleDescriptor`.

[3]:
```
desc1 = ReactionRuleDescriptorMassAction(1.0)
print(desc1.k())
rr1.set_descriptor(desc1)
```

```
1.0
```

`ReactionRuleDescriptor` is accessible from `ReactionRule`.

[4]:
```
print(rr1.has_descriptor())
print(rr1.get_descriptor())
print(rr1.get_descriptor().k())
```

```
True
<ecell4_base.core.ReactionRuleDescriptorMassAction object at 0x154e09b03190>
1.0
```

`ReactionRuleDescriptor` can store stoichiometric coefficients for each reactants:

[5]:
```
desc1.set_reactant_coefficient(0, 2)  # Set a coefficient of the first reactant
desc1.set_reactant_coefficient(1, 3)  # Set a coefficient of the second reactant
desc1.set_product_coefficient(0, 4)  # Set a coefficient of the first product
print(rr1.as_string())
```

```
2*A+3*B>4*C|1
```

You can get the list of coefficients in the following way:

[6]:
```
print(desc1.reactant_coefficients())  # => [2.0, 3.0]
print(desc1.product_coefficients())  # => [4.0]
```

```
[2.0, 3.0]
[4.0]
```

Please be careful that `ReactionRuleDescriptor` works properly only with `ode`.

1.6.2 6.2. ReactionRuleDescriptorPyFunc

`ReactionRuleDescriptor` provides a function to calculate a derivative (flux or velocity) based on the given values of `Species`. In this section, we will explain the way to define your own kinetic law.

[7]:
```
rr1 = ReactionRule()
rr1.add_reactant(Species("A"))
rr1.add_reactant(Species("B"))
rr1.add_product(Species("C"))
print(rr1.as_string())
```

```
A+B>C|0
```

First, define a rate law function as a Python function. The function must accept six arguments and return a floating number. The first and second lists contain a value for each reactants and products respectively. The third and fourth represent volume and time. The coefficients of reactants and products are given in the last two arguments.

[8]:
```
def ratelaw(r, p, v, t, rc, pc):
    return 1.0 * r[0] * r[1] - 2.0 * p[0]
```

`ReactionRuleDescriptorPyFunc` accepts the function.

[9]:
```
desc1 = ReactionRuleDescriptorPyfunc(ratelaw, 'test')
desc1.set_reactant_coefficients([1, 1])
desc1.set_product_coefficients([1])
rr1.set_descriptor(desc1)
print(desc1.as_string())
print(rr1.as_string())
```

```
test
1*A+1*B>1*C|0
```

A `lambda` function is available too.

[10]:
```
desc2 = ReactionRuleDescriptorPyfunc(lambda r, p, v, t, rc, pc:  1.0 * r[0] * r[1] -␣
↪2.0 * p[0], 'test')
desc2.set_reactant_coefficients([1, 1])
desc2.set_product_coefficients([1])
rr1.set_descriptor(desc2)
print(desc1.as_string())
print(rr1.as_string())
```

```
test
1*A+1*B>1*C|0
```

To test if the function works properly, evaluate the value with `ode.World`.

[11]:
```
w = ode.World()
w.set_value(Species("A"), 10)
w.set_value(Species("B"), 20)
w.set_value(Species("C"), 30)

print(w.evaluate(rr1))  # => 140 = 1 * 10 * 20 - 2 * 30
```

```
140.0
```

1.6.3 6.3. NetworkModel

`NetworkModel` accepts `ReactionRules` with and without `ReactionRuleDescriptor`.

[12]:
```
m1 = NetworkModel()
rr1 = create_unbinding_reaction_rule(Species("C"), Species("A"), Species("B"), 3.0)
```

(continues on next page)

(continued from previous page)

```
m1.add_reaction_rule(rr1)
rr2 = create_binding_reaction_rule(Species("A"), Species("B"), Species("C"), 0.0)
desc1 = ReactionRuleDescriptorPyfunc(lambda r, p, v, t, rc, pc: 0.1 * r[0] * r[1],
↪"test")
desc1.set_reactant_coefficients([1, 1])
desc1.set_product_coefficients([1])
rr2.set_descriptor(desc1)
m1.add_reaction_rule(rr2)
```

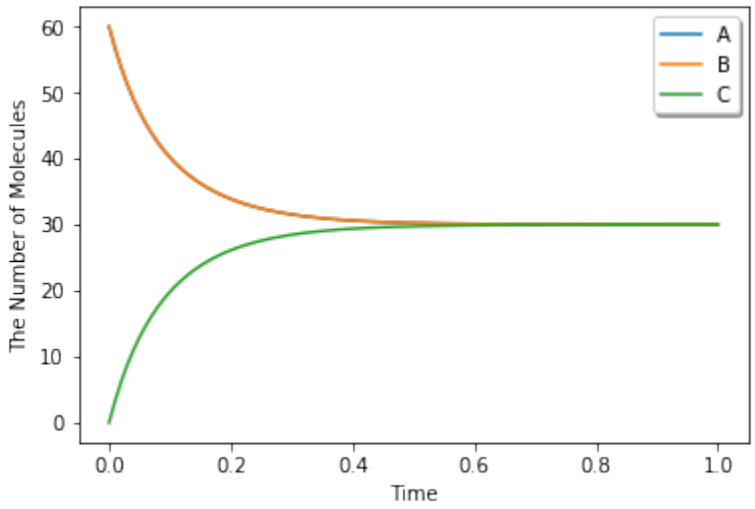
You can access to the list of `ReactionRules` in `NetworkModel` via its member `reaction_rules()`.

[13]:
```
print([rr.as_string() for rr in m1.reaction_rules()])
```

```
['C>A+B|3', '1*A+1*B>1*C|0']
```

Finally, you can run simulations in the same way with other solvers as follows:

[14]:
```
run_simulation(1.0, model=m1, y0={'A': 60, 'B': 60})
```



Modeling with Python decorators is also available by specifying a function instead of a rate (floating number). When a floating number is set, it is assumed to be a kinetic rate of a mass action reaction, but not a constant velocity.

[15]:
```
from functools import reduce
from operator import mul

with reaction_rules():
    A + B == C | (lambda r, *args: 0.1 * reduce(mul, r), 3.0)

m1 = get_model()
```

For the simplicity, you can directory defining the equation with `Species` names as follows:

[16]:
```
with reaction_rules():
    A + B == C | (0.1 * A * B, 3.0)

m1 = get_model()
```

When you call a `Species` (in the rate law) which is not listed as a reactant or product, it is automatically added to the list as an enzyme.

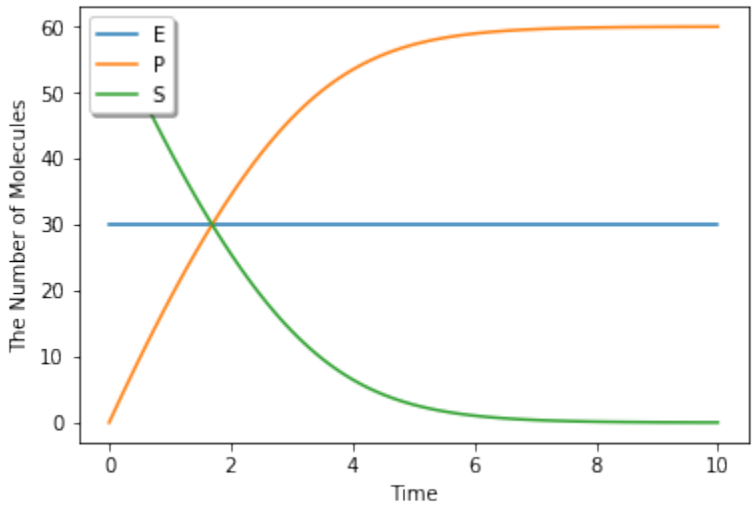
[17]:
```
with reaction_rules():
    S > P | 1.0 * E * S / (30.0 + S)

m1 = get_model()
print(m1.reaction_rules()[0].as_string())
print(m1.reaction_rules()[0].get_descriptor().as_string())
```

```
1*S+1*E>1*P+1*E|0
((1.0*E*S)/(30.0+S))
```

where `E` in the equation is appended to both reacant and product lists.

[18]:
```
run_simulation(10.0, model=m1, y0={'S': 60, 'E': 30})
```



Please be careful about typo in `Species`' name. When you make a typo, it is unintentionally recognized as a new enzyme:

[19]:
```
with reaction_rules():
    A13P2G > A23P2G | 1500 * A13B2G  # typo: A13P2G -> A13B2G

m1 = get_model()
print(m1.reaction_rules()[0].as_string())
```

```
1*A13P2G+1*A13B2G>1*A23P2G+1*A13B2G|0
```

When you want to disable the automatic declaration of enzymes, inactivate `util.decorator.ENABLE_IMPLICIT_DECLARATION`. If its value is `False`, the above case will raise an error:

[20]:
```
util.decorator.ENABLE_IMPLICIT_DECLARATION = False

try:
    with reaction_rules():
        A13P2G > A23P2G | 1500 * A13B2G
except RuntimeError as e:
    print(repr(e))

util.decorator.ENABLE_IMPLICIT_DECLARATION = True
```

```
RuntimeError('[A13B2G] is unknown [(1500*{0})].',)
```

Although E-Cell4 is specialized for a simulation of biochemical reaction network, by using a synthetic reaction rule, ordinary differential equations can be translated intuitively. For example, the Lotka-Volterra equations:

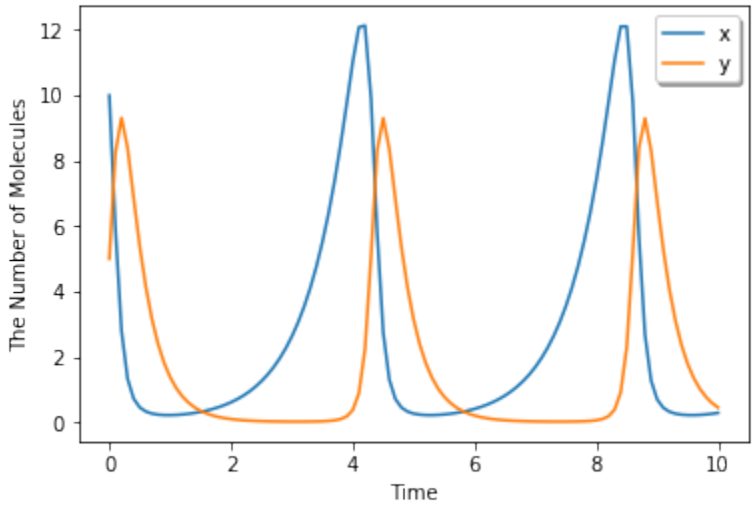
$$\frac{dx}{dt} = Ax - Bxy$$
$$\frac{dy}{dt} = -Cx + Dxy$$

where $A = 1.5, B = 1, C = 3, D = 1, x(0) = 10, y(0) = 5$, are solved as follows:

[21]:
```
with reaction_rules():
    A, B, C, D = 1.5, 1, 3, 1

    ~x > x | A * x - B * x * y
    ~y > y | -C * y + D * x * y

run_simulation(10, model=get_model(), y0={'x': 10, 'y': 5})
```



1.6.4 6.4. References in a Rate Law

Here, we exlain the details in the rate law definition.

First, when you use simpler definitions of a rate law with `Species`, only a limited number of mathematical functions (e.g. `exp`, `log`, `sin`, `cos`, `tan`, `asin`, `acos`, `atan`, and `pi`) are available there even if you declare the function outside the block.

[22]:
```
try:
    from math import erf

    with reaction_rules():
        S > P | erf(S / 30.0)
except TypeError as e:
    print(repr(e))
```

```
TypeError('must be real number, not DivExp',)
```

This error happens because `erf` is tried to be evaluated agaist `S / 30.0`, which is not a floating number. In contrast, the following case is acceptable:

[23]:
```
from math import erf

with reaction_rules():
    S > P | erf(2.0) * S

m1 = get_model()
print(m1.reaction_rules()[0].get_descriptor().as_string())
```

```
(0.9953222650189527*S)
```

where only the result of `erf(2.0)`, `0.995322265019`, is passed to the rate law. Thus, the rate law above has no reference to the `erf` function. Similarly, a value of variables declared outside is acceptable, but not as a reference.

[24]:
```
kcat, Km = 1.0, 30.0

with reaction_rules():
    S > P | kcat * E * S / (Km + S)

m1 = get_model()
print(m1.reaction_rules()[0].get_descriptor().as_string())
kcat = 2.0  # This doesn't affect the model
print(m1.reaction_rules()[0].get_descriptor().as_string())
```

```
((1.0*E*S)/(30.0+S))
((1.0*E*S)/(30.0+S))
```

Even if you change the value of a variable, it does **not** affect the rate law.

On the other hand, when you use your own function to define a rate law, it can hold a reference to variables outside.

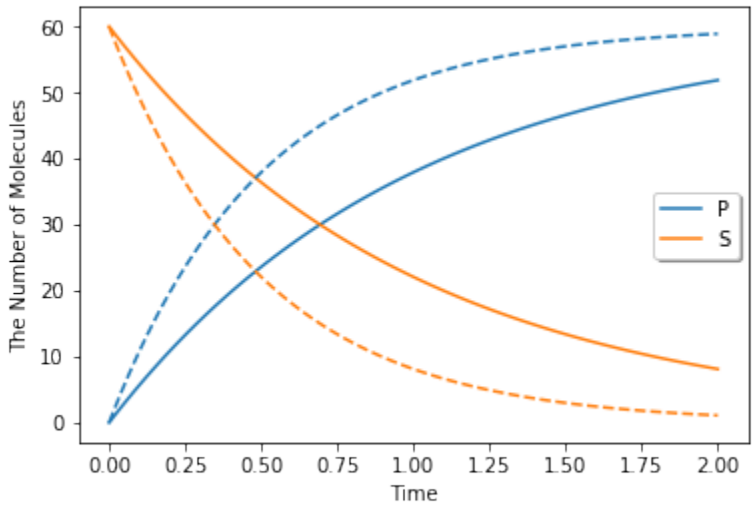
[25]:
```
k1 = 1.0

with reaction_rules():
    S > P | (lambda r, *args: k1 * r[0])  # referring k1

m1 = get_model()

obs1 = run_simulation(2, model=m1, y0={"S": 60}, return_type='observer')
k1 = 2.0  # This could change the result
obs2 = run_simulation(2, model=m1, y0={"S": 60}, return_type='observer')

viz.plot_number_observer(obs1, '-', obs2, '--')
```

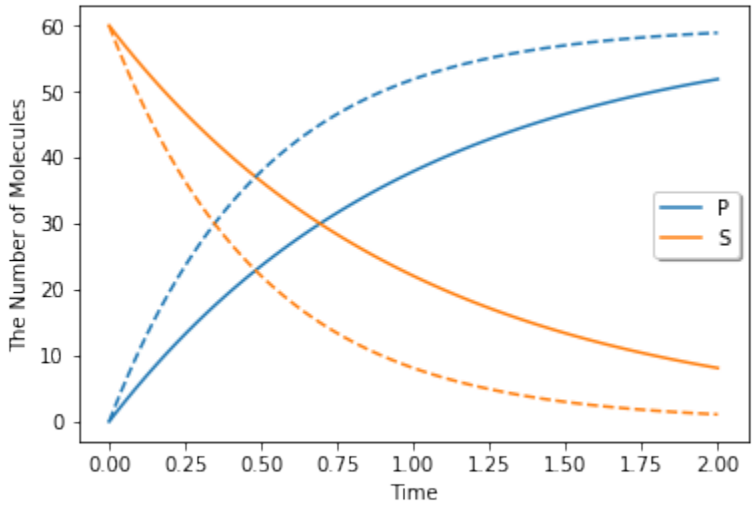


However, in this case, it is better to make a new model for each set of parameters.

[26]:
```
def create_model(k):
    with reaction_rules():
        S > P | k

    return get_model()

obs1 = run_simulation(2, model=create_model(k=1.0), y0={"S": 60}, return_type=
↪'observer')
obs2 = run_simulation(2, model=create_model(k=2.0), y0={"S": 60}, return_type=
↪'observer')
viz.plot_number_observer(obs1, '-', obs2, '--')
```



1.6.5 6.5. More about ode

In `ode.World`, a value for each `Species` is a floating number. However, for the compatibility, the common member `num_molecules` and `add_molecules` regard the value as an integer.

[27]:
```
w = ode.World()
w.add_molecules(Species("A"), 2.5)
print(w.num_molecules(Species("A")))
```

```
2
```

To set/get a real number, use `set_value` and `get_value`:

[28]:
```
w.set_value(Species("B"), 2.5)
print(w.get_value(Species("A")))
print(w.get_value(Species("B")))
```

```
2.0
2.5
```

As a default, `ode.Simulator` employs the Rosenblock method, called `ROSENBROCK4_CONTROLLER`, to solve ODEs. In addition to that, two solvers, `EULER` and `RUNGE_KUTTA_CASH_KARP54`, are available. `ROSENBROCK4_CONTROLLER` and `RUNGE_KUTTA_CASH_KARP54` adaptively change the step size during time evolution due to error controll, but `EULER` does not.

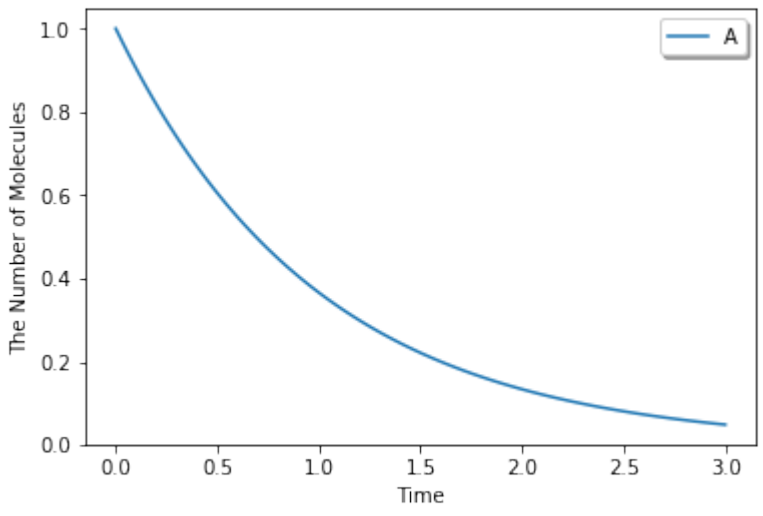
[29]:
```
with reaction_rules():
    A > ~A | 1.0

m1 = get_model()

w1 = ode.World()
w1.set_value(Species("A"), 1.0)
sim1 = ode.Simulator(w1, m1, ode.EULER)
sim1.set_dt(0.01) # This is only effective for EULER
sim1.run(3.0, obs1)
```

`ode.Factory` also accepts a solver type and a default step interval.

[30]:
```
run_simulation(3.0, model=m1, y0={"A": 1.0}, solver=('ode', ode.EULER, 0.01))
```



See also examples listed below:

- Glycolysis of Human Erythrocytes
- *Drosophila Circadian Clock*

- *Attractors*

1.7 7. Introduction of Rule-based Modeling

E-Cell4 provides the rule-based modeling environment.

[1]:
```
%matplotlib inline
from ecell4 import *
from ecell4_base import *
from ecell4_base.core import *
```

1.7.1 7.1. count_species_matches

First, `count_species_matches` counts the number of matches between `Species`.

[4]:
```
sp1 = Species("A(b^1).B(b^1)")
sp2 = Species("A(b^1).A(b^1)")
pttrn1 = Species("A")
print(count_species_matches(pttrn1, sp1))  # => 1
print(count_species_matches(pttrn1, sp2))  # => 2
```

```
1
2
```

In the above case, `Species.count` just returns the number of `UnitSpecies` named `A` in `Species` regardless of its sites. To specify the occupancy of a bond:

[5]:
```
pttrn1 = Species("A(b)")
pttrn2 = Species("A(b^_)")
print(count_species_matches(pttrn1, sp1))  # => 0
print(count_species_matches(pttrn2, sp1))  # => 1
```

```
0
1
```

where `A(b)` suggests that bond `b` is empty, and `A(b^_)` does that bond `b` is occupied. Underscore _ means wildcard here. Similarly, you can also specify the state of sites.

[7]:
```
sp1 = Species("A(b=u)")
pttrn1 = Species("A(b)")
pttrn2 = Species("A(b=u)")
print(count_species_matches(pttrn1, sp1))  # => 1
print(count_species_matches(pttrn2, sp1))  # => 1
```

```
1
1
```

`A(b)` says nothing about the state, but `A(b=u)` specifies both state and bond. `A(b=u)` means that `UnitSpecies` named `A` has a site named `b` which state is `u` and the bond is empty. Wildcard _ is acceptable even in a state and name.

[8]:
```
sp1 = Species("A(b=u^1).B(b=p^1)")
pttrn1 = Species("A(b=_^_)")  # This is equivalent to `A(b^_)` here
pttrn2 = Species("_(b^_)")
print(count_species_matches(pttrn1, sp1))  # => 1
print(count_species_matches(pttrn2, sp1))  # => 2
```

```
1
2
```

Wildcard _ matches anything, and the pattern matched is not consistent between wildcards even in the `Species`. On the other hand, named wildcards, `_1`, `_2` and so on, confer the consistency within the match.

[9]:
```
sp1 = Species("A(b^1).B(b^1)")
pttrn1 = Species("_._")
pttrn2 = Species("_1._1")
print(count_species_matches(pttrn1, sp1))  # => 2
print(count_species_matches(pttrn2, sp1))  # => 0
```

```
2
0
```

where the first pattern matches in two ways (`A.B` and `B.A`), but the second matches nothing. `count_species_matches` always distinguishes the order of `UnitSpecies` even in the symmetric case. Thus, `_1._1` does **not** mean the number of dimers.

[10]:
```
sp1 = Species("A(b^1).A(b^1)")
pttrn1 = Species("_1._1")
print(count_species_matches(pttrn1, sp1))  # => 2
```

```
2
```

1.7.2 7.2. ReactionRule.count and generate

`ReactionRule` also has a function to count matches agaist the given list of reactants.

[11]:
```
rr1 = create_unimolecular_reaction_rule(Species("A(p=u)"), Species("A(p=p)"), 1.0)
sp1 = Species("A(b^1,p=u).B(b^1)")
print(rr1.count([sp1]))  # => 1
```

```
1
```

`ReactionRule.generate` returns a list of `ReactionRules` generated based on the matches.

[12]:
```
print([rr.as_string() for rr in rr1.generate([sp1])])
```

```
['A(b^1,p=u).B(b^1)>A(b^1,p=p).B(b^1)|1']
```

`ReactionRule.generate` matters the order of `Species` in the given list:

[13]:
```
rr1 = create_binding_reaction_rule(Species("A(b)"), Species("B(b)"), Species("A(b^1).
↪B(b^1)"), 1.0)
sp1 = Species("A(b)")
sp2 = Species("B(b)")
print([rr.as_string() for rr in rr1.generate([sp1, sp2])])
print([rr.as_string() for rr in rr1.generate([sp2, sp1])])
```

```
['A(b)+B(b)>A(b^1).B(b^1)|1']
[]
```

On the current implementation, `ReactionRule.generate` does **not** always return a list of unique `ReactionRules`.

[14]:
```
sp1 = Species("A(b,c^1).A(b,c^1)")
sp2 = Species("B(b,c^1).B(b,c^1)")
print(rr1.count([sp1, sp2]))  # => 4
print([rr.as_string() for rr in rr1.generate([sp1, sp2])])
```

```
4
['A(b,c^1).A(b,c^1)+B(b,c^1).B(b,c^1)>A(b^1,c^2).A(b,c^2).B(b^1,c^3).B(b,c^3)|1',␣
↪'A(b,c^1).A(b,c^1)+B(b,c^1).B(b,c^1)>A(b^1,c^2).A(b,c^2).B(b,c^3).B(b^1,c^3)|1',␣
↪'A(b,c^1).A(b,c^1)+B(b,c^1).B(b,c^1)>A(b,c^1).A(b^2,c^1).B(b^2,c^3).B(b,c^3)|1',␣
↪'A(b,c^1).A(b,c^1)+B(b,c^1).B(b,c^1)>A(b,c^1).A(b^2,c^1).B(b,c^3).B(b^2,c^3)|1']
```

`ReactionRules` listed above look different, but all the products suggest the same.

[17]:
```
print(set([format_species(rr.products()[0]).serial() for rr in rr1.generate([sp1,␣
↪sp2])]))
```

```
{'A(b,c^1).A(b^2,c^1).B(b^2,c^3).B(b,c^3)'}
```

This is because these `ReactionRules` are generated based on the diffent matches though they produces the same `Species`. For details, See the section below.

Wildcard is also available in `ReactionRule`.

[18]:
```
rr1 = create_unimolecular_reaction_rule(Species("A(p=u^_)"), Species("A(p=p^_)"), 1.0)
print([rr.as_string() for rr in rr1.generate([Species("A(p=u^1).B(p^1)")])])
```

```
['A(p=u^1).B(p^1)>A(p=p^1).B(p^1)|1']
```

Of course, a wildcard can work as a name of `UnitSpecies`.

[20]:
```
rr1 = create_unimolecular_reaction_rule(Species("_(p=u)"), Species("_(p=p)"), 1.0)
print([rr.as_string() for rr in rr1.generate([Species("A(p=u)")])])
print([rr.as_string() for rr in rr1.generate([Species("B(b^1,p=u).C(b^1,p=u)")])])
```

```
['A(p=u)>A(p=p)|1']
['B(b^1,p=u).C(b^1,p=u)>B(b^1,p=p).C(b^1,p=u)|1', 'B(b^1,p=u).C(b^1,p=u)>B(b^1,p=u).
↪C(b^1,p=p)|1']
```

Named wildcards in a state is useful to specify the correspondence between sites.

[21]:
```
rr1 = create_unbinding_reaction_rule(Species("AB(a=_1, b=_2)"), Species("B(b=_2)"),␣
↪Species("A(a=_1)"), 1.0)
print([rr.as_string() for rr in rr1.generate([Species("AB(a=x, b=y)")])])
print([rr.as_string() for rr in rr1.generate([Species("AB(a=y, b=x)")])])
```

```
['AB(a=x, b=y)>B(b=y)+A(a=x)|1']
['AB(a=y, b=x)>B(b=x)+A(a=y)|1']
```

Nameless wildcard _ does not care about equality between matches. Products are generated in order.

[22]:
```
rr1 = create_binding_reaction_rule(Species("_(b)"), Species("_(b)"), Species("_(b^1)._
↪(b^1)"), 1.0)
print(rr1.as_string())
print([rr.as_string() for rr in rr1.generate([Species("A(b)"), Species("A(b)")])])
print([rr.as_string() for rr in rr1.generate([Species("A(b)"), Species("B(b)")])])
```

```
_(b)+_(b)>_(b^1)._(b^1)|1
['A(b)+A(b)>A(b^1).A(b^1)|1']
['A(b)+B(b)>A(b^1).B(b^1)|1']
```

For its symmetry, the former case above is sometimes preffered to have a half of the original kinetic rate. This is because the number of combinations of molecules in the former is $n(n-1)/2$ even though that in the later is n^2, where both numbers of A and B molecules are n. This is true for `gillespie` and `ode`. However, in `egfrd` and `spatiocyte`, a kinetic rate is intrinsic one, and not affected by the number of combinations. Thus, in E-Cell4, no modification in the rate is done even for the case. See Homodimerization and Annihilation for the difference between algorithms.

In constrast to nameless wildcard, named wildcard keeps its consistency, and always suggests the same value in the `ReactionRule`.

[23]:
```
rr1 = create_binding_reaction_rule(Species("_1(b)"), Species("_1(b)"), Species("_1(b^
↪1)._1(b^1)"), 1.0)
print(rr1.as_string())
print([rr.as_string() for rr in rr1.generate([Species("A(b)"), Species("A(b)")])])
print([rr.as_string() for rr in rr1.generate([Species("A(b)"), Species("B(b)")])])  #␣
↪=> []
```

```
_1(b)+_1(b)>_1(b^1)._1(b^1)|1
['A(b)+A(b)>A(b^1).A(b^1)|1']
[]
```

Named wildcard is consistent even between `UnitSpecies`' and `site`'s names, technically.

[24]:
```
rr1 = create_binding_reaction_rule(Species("A(b=_1)"), Species("_1(b)"), Species(
↪"A(b=_1^1)._1(b^1)"), 1.0)
print(rr1.as_string())
print([rr.as_string() for rr in rr1.generate([Species("A(b=B)"), Species("A(b)")])])
↪# => []
print([rr.as_string() for rr in rr1.generate([Species("A(b=B)"), Species("B(b)")])])
```

```
A(b=_1)+_1(b)>A(b=_1^1)._1(b^1)|1
[]
['A(b=B)+B(b)>A(b=B^1).B(b^1)|1']
```

1.7.3 7.3. NetfreeModel

`NetfreeModel` is a `Model` class for the rule-based modeling. The interface of `NetfreeModel` is almost same with `NetworkModel`, but takes into account rules and matches.

[25]:
```
rr1 = create_binding_reaction_rule(Species("A(r)"), Species("A(l)"), Species("A(r^1).
↪A(l^1)"), 1.0)

m1 = NetfreeModel()
m1.add_reaction_rule(rr1)
print(m1.num_reaction_rules())

m2 = NetworkModel()
m2.add_reaction_rule(rr1)
print(m2.num_reaction_rules())
```

```
1
1
```

Python notation explained in *2. How to Build a Model* is available too. To get a model as `NetfreeModel`, set `is_netfree` `True` in `get_model`:

[26]:
```
with reaction_rules():
    A(r) + A(l) > A(r^1).A(l^1) | 1.0

m1 = get_model(is_netfree=True)
print(repr(m1))
```

```
<ecell4_base.core.NetfreeModel object at 0x1487588aa6d0>
```

`Model.query_reaction_rules` returns a list of `ReactionRules` agaist the given reactants. `NetworkModel` just returns `ReactionRules` based on the equality of `Species`.

[27]:
```
print(len(m2.query_reaction_rules(Species("A(r)"), Species("A(l)"))))  # => 1
print(len(m2.query_reaction_rules(Species("A(l,r)"), Species("A(l,r)"))))  # => 0
```

```
1
0
```

On the other hand, `NetfreeModel` genarates the list by applying the stored `ReactionRules` in the rule-based way.

[28]:
```
print(len(m1.query_reaction_rules(Species("A(r)"), Species("A(l)"))))  # => 1
print(len(m1.query_reaction_rules(Species("A(l,r)"), Species("A(l,r)"))))  # => 1
```

```
1
1
```

`NetfreeModel` does not cache generated objects. Thus, `NetfreeModel.query_reaction_rules` is slow, but needs less memory.

[29]:
```
print(m1.query_reaction_rules(Species("A(l,r)"), Species("A(l,r)"))[0].as_string())
print(m1.query_reaction_rules(Species("A(l,r^1).A(l^1,r)"), Species("A(l,r)"))[0].as_
↪string())
print(m1.query_reaction_rules(Species("A(l,r^1).A(l^1,r)"), Species("A(l,r^1).A(l^1,r)
↪"))[0].as_string())
```

```
A(l,r)+A(l,r)>A(l,r^1).A(l^1,r)|2
A(l,r^1).A(l^1,r)+A(l,r)>A(l,r^1).A(l^1,r^2).A(l^2,r)|1
A(l,r^1).A(l^1,r)+A(l,r^1).A(l^1,r)>A(l,r^1).A(l^1,r^2).A(l^2,r^3).A(l^3,r)|2
```

`NetfreeModel.expand` expands `NetfreeModel` to `NetworkModel` by iteratively applying `ReactionRules` agaist the given set of `Species` (called seed).

[30]:
```
with reaction_rules():
    _(b) + _(b) == _(b^1)._(b^1) | (1.0, 1.0)

m3 = get_model(True)
print(m3.num_reaction_rules())

m4 = m3.expand([Species("A(b)"), Species("B(b)")])
print(m4.num_reaction_rules())
print([rr.as_string() for rr in m4.reaction_rules()])
```

```
2
6
['A(b)+A(b)>A(b^1).A(b^1)|1', 'A(b)+B(b)>A(b^1).B(b^1)|1', 'B(b)+B(b)>B(b^1).
↪B(b^1)|1', 'A(b^1).A(b^1)>A(b)+A(b)|1', 'A(b^1).B(b^1)>A(b)+B(b)|1', 'B(b^1).
↪B(b^1)>B(b)+B(b)|1']
```

To avoid the infinite iteration for expansion, you can limit the maximum number of iterations and of `UnitSpecies` in a `Species`.

[31]:
```
m2 = m1.expand([Species("A(l, r)")], 100, {Species("A"): 4})
print(m2.num_reaction_rules())  # => 4
print([rr.as_string() for rr in m2.reaction_rules()])
```

```
4
['A(l,r)+A(l,r)>A(l,r^1).A(l^1,r)|2', 'A(l,r^1).A(l^1,r)+A(l,r^1).A(l^1,r)>A(l,r^1).
↪A(l^1,r^2).A(l^2,r^3).A(l^3,r)|2', 'A(l,r)+A(l,r^1).A(l^1,r)>A(l,r^1).A(l^1,r^2).
↪A(l^2,r)|2', 'A(l,r)+A(l,r^1).A(l^1,r^2).A(l^2,r)>A(l,r^1).A(l^1,r^2).A(l^2,r^3).
↪A(l^3,r)|2']
```

1.7.4 7.4. Differences between Species, ReactionRule and NetfreeModel

The functions explained above is similar, but there are some differences in the criteria.

[32]:
```
sp1 = Species("A(b^1).A(b^1)")
sp2 = Species("A(b)")
rr1 = create_unbinding_reaction_rule(sp1, sp2, sp2, 1.0)
print(count_species_matches(sp1, sp1))
print([rr.as_string() for rr in rr1.generate([sp1])])
```

```
2
['A(b^1).A(b^1)>A(b)+A(b)|1']
```

Though `count_species_matches` suggests two different ways for matching (left-right and right-left), `ReactionRule.generate` returns only one `ReactionRule` because the order doesn't affect the product.

[34]:
```
sp1 = Species("A(b^1).B(b^1)")
rr1 = create_unbinding_reaction_rule(
    sp1, Species("A(b)"), Species("B(b)"), 1.0)
sp2 = Species("A(b^1,c^2).A(b^3,c^2).B(b^1).B(b^3)")
print(count_species_matches(sp1, sp2))
print([rr.as_string() for rr in rr1.generate([sp2])])
```

```
2
['A(b^1,c^2).A(b^3,c^2).B(b^1).B(b^3)>A(b,c^1).A(b^2,c^1).B(b^2)+B(b)|1', 'A(b^1,c^2).
↪A(b^3,c^2).B(b^1).B(b^3)>A(b^1,c^2).A(b,c^2).B(b^1)+B(b)|1']
```

In this case, `ReactionRule.generate` works similarly with `count_species_matches`. However, `NetfreeModel.query_reaction_rules` returns only one `ReationRule` with higher kinetic rate:

[35]:
```
m1 = NetfreeModel()
m1.add_reaction_rule(rr1)
print([rr.as_string() for rr in m1.query_reaction_rules(sp2)])
```

```
['A(b^1,c^2).B(b^1).A(b^3,c^2).B(b^3)>A(b,c^1).A(b^2,c^1).B(b^2)+B(b)|2']
```

`NetfreeModel.query_reaction_rules` checks if each `ReactionRule` generated is the same with others, and summalizes it if possible.

As explaned above, `ReactionRule.generate` matters the order of `Species`, but `Netfree.query_reaction_rules` does not.

[36]:
```
sp1 = Species("A(b)")
sp2 = Species("B(b)")
rr1 = create_binding_reaction_rule(sp1, sp2, Species("A(b^1).B(b^1)"), 1.0)
m1 = NetfreeModel()
m1.add_reaction_rule(rr1)
```

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```
print([rr.as_string() for rr in rr1.generate([sp1, sp2])])
print([rr.as_string() for rr in m1.query_reaction_rules(sp1, sp2)])
print([rr.as_string() for rr in rr1.generate([sp2, sp1])])  # => []
print([rr.as_string() for rr in m1.query_reaction_rules(sp2, sp1)])
```

```
['A(b)+B(b)>A(b^1).B(b^1)|1']
['A(b)+B(b)>A(b^1).B(b^1)|1']
[]
['A(b)+B(b)>A(b^1).B(b^1)|1']
```

Named wildcards must be consistent in the context while nameless wildcards are not necessarily consistent.

[37]:
```
sp1 = Species("_(b)")
sp2 = Species("_1(b)")
sp3 = Species("A(b)")
sp4 = Species("B(b)")
rr1 = create_binding_reaction_rule(sp1, sp1, Species("_(b^1)._(b^1)"), 1)
rr2 = create_binding_reaction_rule(sp2, sp2, Species("_1(b^1)._1(b^1)"), 1)
print(count_species_matches(sp1, sp2))  # => 1
print(count_species_matches(sp1, sp3))  # => 1
print(count_species_matches(sp2, sp2))  # => 1
print(count_species_matches(sp2, sp3))  # => 1
print([rr.as_string() for rr in rr1.generate([sp3, sp3])])
print([rr.as_string() for rr in rr1.generate([sp3, sp4])])
print([rr.as_string() for rr in rr2.generate([sp3, sp3])])
print([rr.as_string() for rr in rr2.generate([sp3, sp4])])  # => []
```

```
1
1
1
1
['A(b)+A(b)>A(b^1).A(b^1)|1']
['A(b)+B(b)>A(b^1).B(b^1)|1']
['A(b)+A(b)>A(b^1).A(b^1)|1']
[]
```

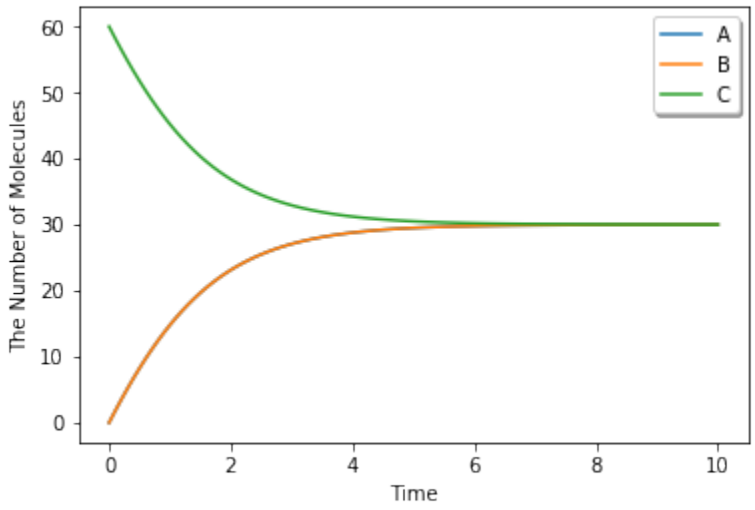
1.8 8. More about 1. Brief Tour of E-Cell4 Simulations

Once you read through *1. Brief Tour of E-Cell4 Simulations*, it is NOT difficult to use `World` and `Simulator`. `volume` and `{'C': 60}` is equivalent of the `World` and solver is the `Simulator` below.

[1]:
```
%matplotlib inline
from ecell4 import *

with reaction_rules():
    A + B == C | (0.01, 0.3)

run_simulation(10.0, {'C': 60}, volume=1.0)
```



Here we give you a breakdown for `run_simulation`. `run_simulation` use ODE simulator by default, so we create `ode.World` step by step.

1.8.1 8.1. Creating ODEWorld

You can create `World` like this.

[2]:
```
from ecell4_base.core import *
from ecell4_base import *
```

[3]:
```
w = ode.World(Real3(1, 1, 1))
```

`Real3` is a coordinate vector. In this example, the first argument for `ode.World` constructor is a cube. Note that you can NOT use volume for `ode.World` argument, like `run_simulation` argument.

Now you created a cube box for simulation, next let's throw molecules into the cube.

[4]:
```
w = ode.World(Real3(1, 1, 1))
w.add_molecules(Species('C'), 60)
print(w.t(), w.num_molecules(Species('C')))  # must return (0.0, 60)
```

```
0.0 60
```

Use `add_molecules` to add molecules, `remove_molecules` to remove molecules, `num_molecules` to know the number of molecules. First argument for each method is the `Species` you want to know. You can get current time by `t` method. However the number of molecules in ODE solver is real number, in these `_molecules` functions work only for integer number. When you handle real numbers in ODE, use `set_value` and `get_value`.

1.8.2 8.2. How to Use Real3

Before the detail of `Simulator`, we explaing more about `Real3`.

[5]:
```
pos = Real3(1, 2, 3)
print(pos)  # must print like <ecell4.core.Real3 object at 0x7f44e118b9c0>
print(tuple(pos))  # must print (1.0, 2.0, 3.0)
```

```
<ecell4_base.core.Real3 object at 0x1487e8ec41e0>
(1.0, 2.0, 3.0)
```

You can not print the contents in `Real3` object directly. You need to convert `Real3` to Python tuple or list once.

[6]:
```
pos1 = Real3(1, 1, 1)
x, y, z = pos[0], pos[1], pos[2]
pos2 = pos1 + pos1
pos3 = pos1 * 3
pos4 = pos1 / 5
print(length(pos1))  # must print 1.73205080757
print(dot_product(pos1, pos3))  # must print 9.0
```

```
1.7320508075688772
9.0
```

You can use basic function like `dot_product`. Of course, you can convert `Real3` to numpy array too.

[7]:
```
import numpy
a = numpy.asarray(tuple(Real3(1, 2, 3)))
print(a)  # must print [ 1.  2.  3.]
```

```
[1. 2. 3.]
```

`Integer3` represents a triplet of integers.

[8]:
```
g = Integer3(1, 2, 3)
print(tuple(g))
```

```
(1, 2, 3)
```

Of course, you can also apply simple arithmetics to `Integer3`.

[9]:
```
print(tuple(Integer3(1, 2, 3) + Integer3(4, 5, 6)))  # => (5, 7, 9)
print(tuple(Integer3(4, 5, 6) - Integer3(1, 2, 3)))  # => (3, 3, 3)
print(tuple(Integer3(1, 2, 3) * 2))  # => (2, 4, 6)
print(dot_product(Integer3(1, 2, 3), Integer3(4, 5, 6)))  # => 32
print(length(Integer3(1, 2, 3)))  # => 3.74165738677
```

```
(5, 7, 9)
(3, 3, 3)
(2, 4, 6)
32
3.7416573867739413
```

1.8.3 8.3. Creating and Running ODE Simulator

You can create a `Simulator` with `Model` and `World` like

[10]:
```
with reaction_rules():
    A + B > C | 0.01  # equivalent to create_binding_reaction_rule
    C > A + B | 0.3   # equivalent to create_unbinding_reaction_rule

m = get_model()

sim = ode.Simulator(w, m)
sim.run(10.0)
```

then call `run` method, the simulation will run. In this example the simulation runs for 10 seconds.

You can check the state of the `World` like this.

[11]:
```
print(w.t(), w.num_molecules(Species('C')))  # must return (10.0, 30)
```

```
10.0 30
```

You can see that the number of the `Species C` decreases from 60 to 30.

`World` describes the state at a timepoint, so you can NOT tack the transition during the simulation with the `World`. To obtain the time-series result, use `Observer`.

[12]:
```
w = ode.World(Real3(1, 1, 1))
w.add_molecules(Species('C'), 60)
sim = ode.Simulator(w, m)

obs = FixedIntervalNumberObserver(0.1, ('A', 'C'))
sim.run(10.0, obs)
print(obs.data())  # must return [[0.0, 0.0, 60.0], ..., [10.0, 29.994446899691276,␣
↪30.0055531003087521]
```

```
[[0.0, 0.0, 60.0], [0.1, 1.7722206143224584, 58.22777938567754], [0.2, 3.
↪4860124975248006, 56.51398750247521], [0.30000000000000004, 5.137633294323578, 54.
↪862366705676436], [0.4, 6.7240908315276045, 53.27590916847241], [0.5, 8.
↪2431297778128, 51.75687022218721], [0.6000000000000001, 9.693203786964157, 50.
↪30679621303585], [0.7000000000000001, 11.073435610343822, 48.926564389656185], [0.8,
↪ 12.383567710238625, 47.61643228976138], [0.9, 13.623905934263576, 46.
↪37609406573643], [1.0, 14.795258697983998, 45.204741302016004], [1.1, 15.
↪898873915953542, 44.101126084046456], [1.2000000000000002, 16.936375649258018, 43.
↪06362435074198], [1.3, 17.909702127696086, 42.090297872303914], [1.4000000000000001,
↪ 18.821046480898254, 41.17895351910174], [1.5, 19.672801194656238, 40.
↪32719880534375], [1.6, 20.467507011344757, 39.532492988655235], [1.7000000000000002,
↪ 21.207806726765288, 38.7921932732347], [1.8, 21.896404106006866, 38.
↪10359589399312], [1.9000000000000001, 22.53602795042438, 37.4639720495756], [2.0,␣
↪23.129401196247105, 36.87059880375288], [2.1, 23.679214810305954, 36.
↪320785189694035], [2.2, 24.188106166226664, 35.811893833773333], [2.3000000000000003,
↪ 24.6586415307847, 35.341358469215294], [2.4000000000000004, 25.093302260285835, 34.
↪906697739714154], [2.5, 25.494474296223075, 34.505525703776904], [2.6, 25.
↪864440553798364, 34.13555944620162], [2.7, 26.205375812342282, 33.7946241876577],␣
↪[2.8000000000000003, 26.519343739941075, 33.480656260058915], [2.9000000000000004,␣
↪26.808295712922448, 33.19170428707754], [3.0, 27.074071122047478, 32.
↪925928877952515], [3.1, 27.318398889554317, 32.68160111044567], [3.2, 27.
↪54289995329749, 32.45710004670249], [3.3000000000000003, 27.749090505157007, 32.
↪250909494842965], [3.4000000000000004, 27.93838580001201, 32.061614199987797], [3.5,␣
↪28.11210437846467, 31.887895621535307], [3.6, 28.27147257094361, 31.
↪728527429056367], [3.7, 28.41762917272733, 31.582370827272648], [3.8000000000000003,
↪ 28.551630198838193, 31.448369801161785], [3.9000000000000004, 28.674453644762753,␣
↪31.325546355237226], [4.0, 28.78700419370472, 31.212995806295257], [4.
↪1000000000000005, 28.890117823751574, 31.109882176248405], [4.2, 28.98456627912797,␣
↪31.015433720872007], [4.3, 29.071061378816175, 30.928938621183804], [4.4, 29.
↪150259143439115, 30.849740856560864], [4.5, 29.222763727609138, 30.77723627239084],␣
↪[4.6000000000000005, 29.289131150117587, 30.710868849882393], [4.7, 29.
↪349872818534465, 30.650127181465514], [4.800000000000001, 29.40545884814348, 30.
↪5945411518565], [4.9, 29.456321177785775, 30.543678822214204], [5.0, 29.
↪502856487234418, 30.497143512765556], [5.1000000000000005, 29.545428922270702, 30.
↪454571077729277], [5.2, 29.584372634768023, 30.415627365231956], [5.300000000000001,
↪ 29.619994145881115, 30.380005854118863], [5.4, 29.652574540951854, 30.
↪347425459048125], [5.5, 29.68237150503112, 30.317628494968858], [5.6000000000000005,
↪ 29.709621208023663, 30.290378791976316], [5.7, 29.73454004842796, 30.
↪26545995157202], [5.800000000000001, 29.757326264497603, 30.242673735502358], [5.9,␣
↪29.77816142142091, 30.22183857857907], [6.0, 29.797211782822988, 30.
↪2027882171769951, [6.100000000000000, 29.814629574557085, 30.185370425442898], [6.
↪2, 29.830391146361813, 30.169608853638177], [6.300000000000001, 29.84511305275851,␣
↪30.154886947241472], [6.4, 29.858423017523837, 30.141576982476145], [6.5, 29.
↪870590858963563, 30.129409141036442], [6.6000000000000005, 29.88171431121031, 30.
↪118285688789673], [6.7, 29.891882789671147, 30.108117210328835], [6.800000000000001,
```

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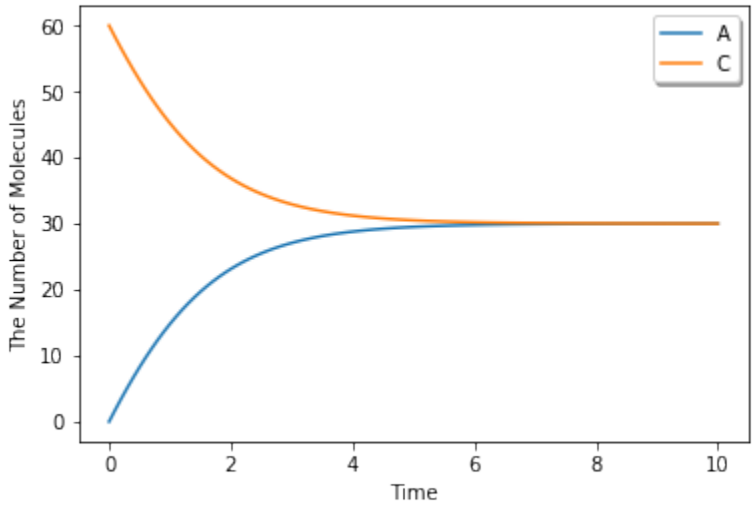
There are several types of `Observers` for E-Cell4. `FixedIntervalNumberObserver` is the simplest `Observer` to obtain the time-series result. As its name suggests, this `Observer` records the number of molecules for each time-step. The 1st argument is the time-step, the 2nd argument is the molecule types. You can check the result with `data` method, but there is a shortcut for this.

[13]:
```
show(obs)
```



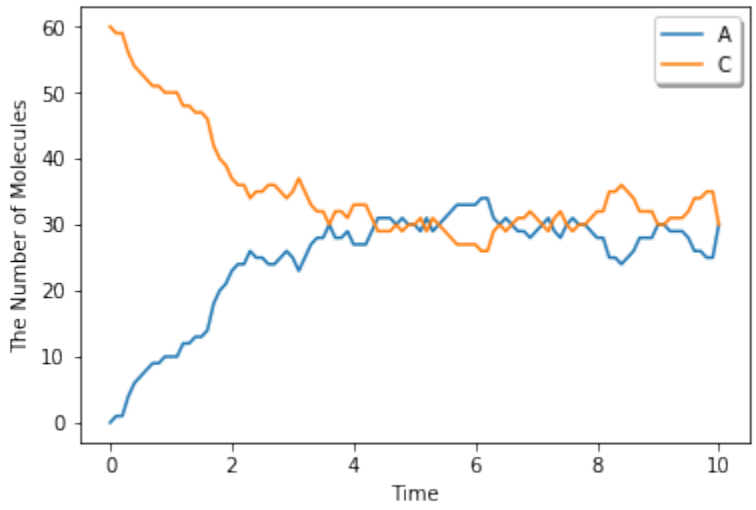
This plots the time-series result easily.

We explained the internal of `run_simulation` function. When you change the `World` after creating the `Simulator`, you need to indicate it to `Simulator`. So do NOT forget to call `sim.initialize()` after that.

1.8.4 8.4. Switching the Solver

It is NOT difficult to switch the solver to stochastic method, as we showed `run_simulation`.

[14]:
```
from ecell4 import *

with reaction_rules():
    A + B == C | (0.01, 0.3)

m = get_model()

# ode.World -> gillespie.World
w = gillespie.World(Real3(1, 1, 1))
w.add_molecules(Species('C'), 60)

# ode.Simulator -> gillespie.Simulator
sim = gillespie.Simulator(w, m)
obs = FixedIntervalNumberObserver(0.1, ('A', 'C'))
sim.run(10.0, obs)

show(obs)
```



`World` and `Simulator` never change the `Model` itself, so you can switch several `Simulators` for one `Model`.

1.9 9. Spatial Gillespie Method

1.9.1 9.1. Spaces in E-Cell4

What the space in E-Cell4 looks like?

[1]:
```
from ecell4 import *
from ecell4_base import *
from ecell4_base.core import *

w1 = ode.World(ones())
w2 = gillespie.World(ones())
```

We created a cube size, `1`, on a side for `ode.World` and `gillespie.World`. In this case the volume only matters, that is

[2]:
```
w3 = ode.World(Real3(2, 0.5, 1))  # is almost equivalent to 'w1'
w4 = gillespie.World(Real3(2, 2, 0.25))  # is almost equivalent to 'w2'
```

This returns the same results. Because the volume is same as `1`.

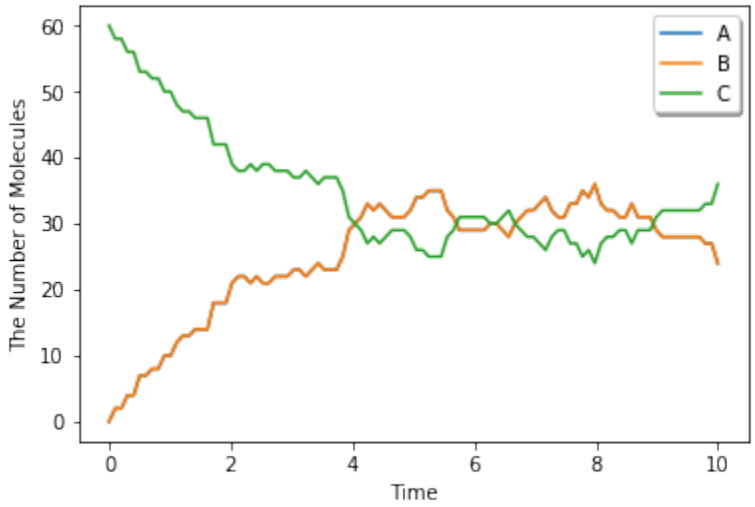
This seems reasonable in homogeneous system, but the cell is NOT homogeneous. So we need to consider a space for molecular localization.

You can use several types of space and simulation methods in E-Cell4. We show an example with spatial Gillespie method here.

1.9.2 9.2. Spatial Gillespie Method

In E-Cell4, the Spatial Gillespie method is included in `meso` module. Let's start with `run_simulation` like `ode`.

[3]:
```
%matplotlib inline
import numpy
from ecell4 import *

with reaction_rules():
    A + B == C | (0.01, 0.3)

run_simulation(numpy.linspace(0, 10, 100), {'C': 60}, solver='meso')
```



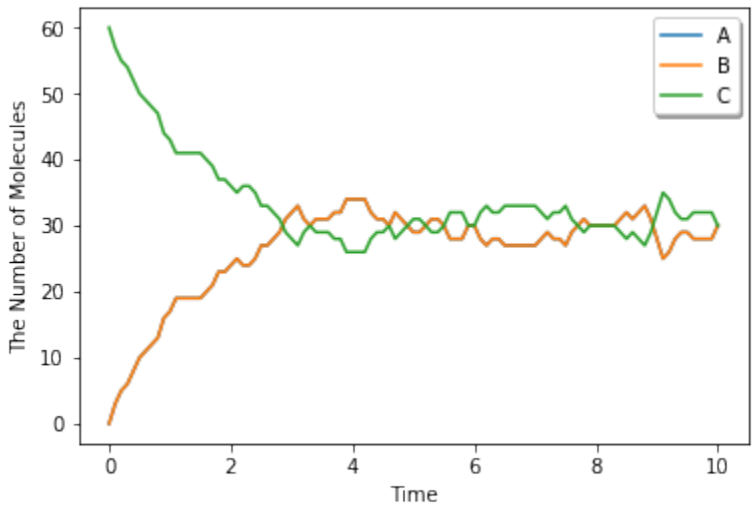
At the steady state, the number of `C` is given as follows:

$$\frac{d\mathrm{C}}{dt} = 0.01 \cdot \frac{\mathrm{A}}{V} \cdot \frac{\mathrm{B}}{V} - 0.3 \cdot \frac{\mathrm{C}}{V} = 0$$
$$0.01\,(60 - \mathrm{C})^2 = 0.3\mathrm{C} \times V$$
$$\mathrm{C} = 30.$$

You will obtain almost the same result with `ode` or `gillespie` (may take longer time than `ode` or `gillespie`). This is not surprising because `meso` module is almost same with Gillespie unless you give additional spatial parameter.

Next we will decompose `run_simulation`.

[4]:
```
from ecell4 import *
from ecell4_base import *
from ecell4_base.core import *

with reaction_rules():
    A + B == C | (0.01, 0.3)

m = get_model()

w = meso.World(ones(), Integer3(1, 1, 1))  # XXX: Point2
w.bind_to(m)  # XXX: Point1
w.add_molecules(Species('C'), 60)

sim = meso.Simulator(w)  # XXX: Point1
obs = FixedIntervalNumberObserver(0.1, ('A', 'B', 'C'))
sim.run(10, obs)

show(obs)
```

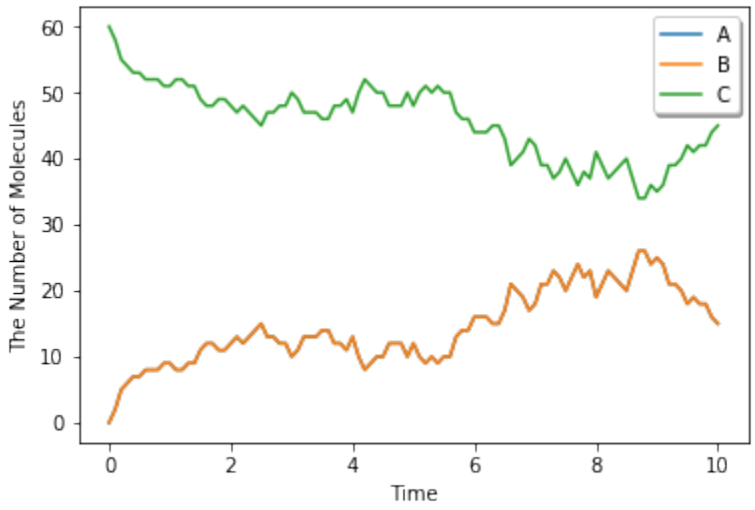


This is nothing out of the ordinary one except for `meso.World` and `meso.Simulator`, but you can see some new elements.

First in `w.bind_to(m)` we asscociated a `Model` to the `World`. In the basic exercises before, we did NOT do this. In spatial methods, `Species` attributes are necessary. Do not forget to call this. After that, only the `World` is required to create a `meso.Simulator`.

Next, the important difference is the second argument for `meso.World`, i.e. `Integer3(1, 1, 1).ode.World` and `gillespie.World` do NOT have this second argument. Before we explain this, let's change this argument and run the simulation again.

[5]:
```
from ecell4 import *
from ecell4_base import *
from ecell4_base.core import *

with reaction_rules():
    A + B == C | (0.01, 0.3)

m = get_model()

w = meso.World(ones(), Integer3(4, 4, 4))  # XXX: Point2
w.bind_to(m)  # XXX: Point1
w.add_molecules(Species('C'), 60)

sim = meso.Simulator(w)  # XXX: Point1
obs = FixedIntervalNumberObserver(0.1, ('A', 'B', 'C'))
sim.run(10, obs)

show(obs)
```



You must have the different plot. If you increase value in the `Integer3`, you will have more different one.

Actually this second argument means the number of spatical partitions. `meso` is almost same with `gillespie`, but `meso` divides the space into cuboids (we call these cuboids subvolumes) and each subvolume has different molecular concentration by contrast `gillespie` has only one uniform closed space. So in the preceding example, we divided `1` cube with sides `1` into `64` (4x4x4) cubes with sides `0.25`. We threw 60 `C` molecules into the `World`. Thus, each `subvolume` has 1 species at most.

1.9.3 9.3. Defining Molecular Diffusion Coefficient

Where the difference is coming from? This is because we do NOT consider molecular diffusion coefficient, although we got a space with `meso`. To setup diffusion coefficient, use `Species` attribute `'D'` in the way described before (*2. How to Build a Model*). As shown in *1. Brief Tour of E-Cell4 Simulations*, we use E-Cell4 special notation here.

[6]:
```
with species_attributes():
    A | {'D': 1}
    B | {'D': 1}
    C | {'D': 1}

    # A | B | C | {'D': 1}  # means the same as above

get_model()
```

[6]:
```
<ecell4_base.core.NetworkModel at 0x15475e7e98d0>
```

You can setup diffusion coefficient with `with species_attributes():` statement. Here we set all the diffusion coefficient as `1`. Let's simulate this model again. Now you must have the almost same result with `gillespie` even with large `Integer3` value (the simulation will takes much longer than `gillespie`).

How did the molecular diffusion work for the problem? Think about free diffusion (the diffusion coefficient of a Species is D) in 3D space. The unit of diffusion coefficient is the square of length divided by time like $\mu\mathrm{m}^2/s$ or $\mathrm{nm}^2/\mu s$.

It is known that the average of the square of point distance from time 0 to t is equal to $6Dt$. Conversely the average of the time scale in a space with length scale l is about $l^2/6D$.

In the above case, the size of each subvolume is 0.25 and the diffusion coefficient is 1. Thus the time scale is about 0.01 sec. If the molecules of the `Species` `A` and `B` are in the same subvolume, it takes about 1.5 sec to react, so in most cases the diffusion is faster than the reaction and the molecules move to other subvolume even dissociated in the same subvolume. The smaller l, the smaller subvolume's volume l^3, so the reaction rate after dissociation is faster, and the time of the diffusion and the transition between the subvolume gets smaller too.

1.9.4 9.4. Molecular localization

We have used `add_molecules` function to add molecules to `World` in the same manner as `ode` or `gillespie`. Meanwhile in `meso.World`, you can put in molecules according to the spatial presentation.

[7]:
```
from ecell4 import *
from ecell4_base import *
from ecell4_base.core import *

w = meso.World(ones(), Integer3(3, 3, 3))
w.add_molecules(Species('A'), 120)
w.add_molecules(Species('B'), 120, Integer3(1, 1, 1))
```

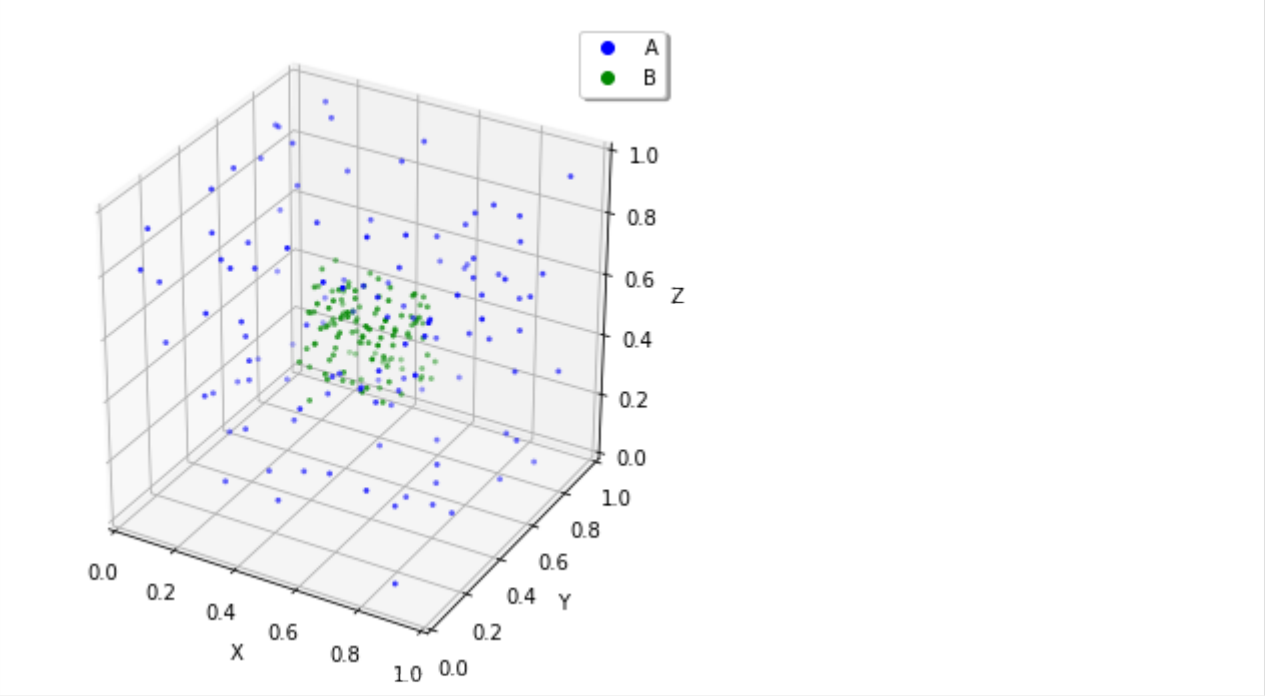
In `meso.World`, you can set the subvolume and the molecule locations by giving the third argument `Integer3` to `add_molecules`. In the above example, the molecule type `A` spreads all over the space, but the molecule type `B` only locates in a subvolume at the center of the volume. To check this, use `num_molecules` function with a coordinate.

[8]:
```
print(w.num_molecules(Species('B')))  # must print 120
print(w.num_molecules(Species('B'), Integer3(0, 0, 0)))  # must print 0
print(w.num_molecules(Species('B'), Integer3(1, 1, 1)))  # must print 120
```

```
120
0
120
```

Furthermore, if you have Jupyter Notebook environment, you can visualize the molecular localization with `ecell4.viz` module, `viz.plot_world` or simply `show`.

[9]:
```
# viz.plot_world(w, radius=0.01)
viz.plot_world(w, interactive=False)
```



`viz.plot_world` function visualize the location of the molecules in Jupyter Notebook cell by giving the `World`. You can set the molecule size with `radius`. Now you can set the molecular localization to the `World`, next let's simulate this. In the above example, we set the diffusion coefficient 1 and the World side 1, so 10 seconds is enough to stir this. After the simulation, check the result with calling `viz.plot_world` again.

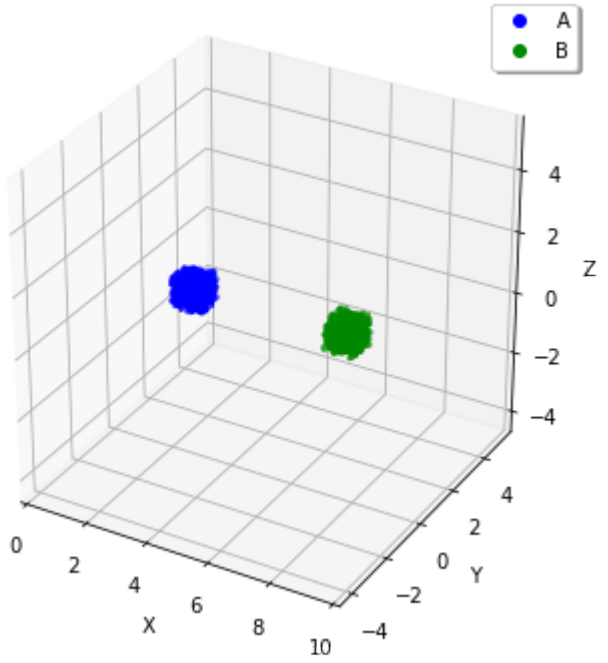
1.9.5 9.5. Molecular initial location and the reaction

This is an extreme example to check how the molecular localization affects the reaction.

[10]:
```
%matplotlib inline
from ecell4 import *
from ecell4_base import *
from ecell4_base.core import *

with species_attributes():
    A | B | C | {'D': '1'}

with reaction_rules():
    A + B > C | 0.01

m = get_model()
w = meso.World(Real3(10, 1, 1), Integer3(10, 1, 1))
w.bind_to(m)
```

This model consists only of a simple binding reaction. The `World` is a long x axis cuboid, and molecules are located off-center.

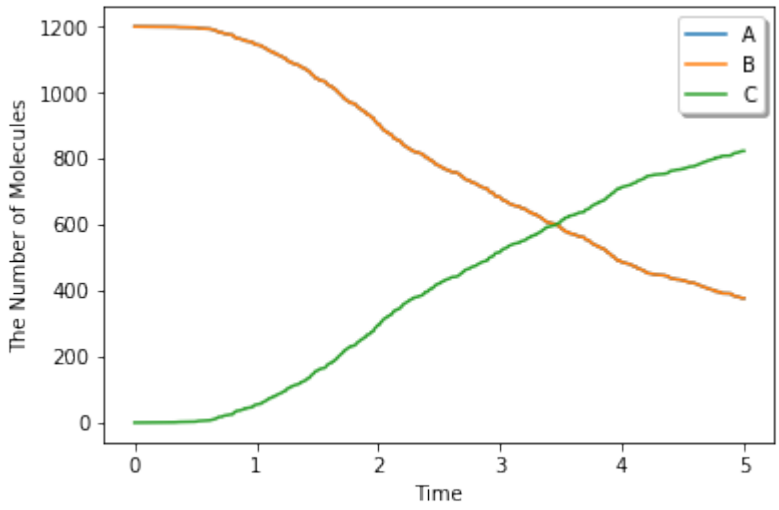
[11]:
```
w.add_molecules(Species('A'), 1200, Integer3(2, 0, 0))
w.add_molecules(Species('B'), 1200, Integer3(7, 0, 0))
# viz.plot_world(w, radius=0.025)
viz.plot_world(w, interactive=False)
```



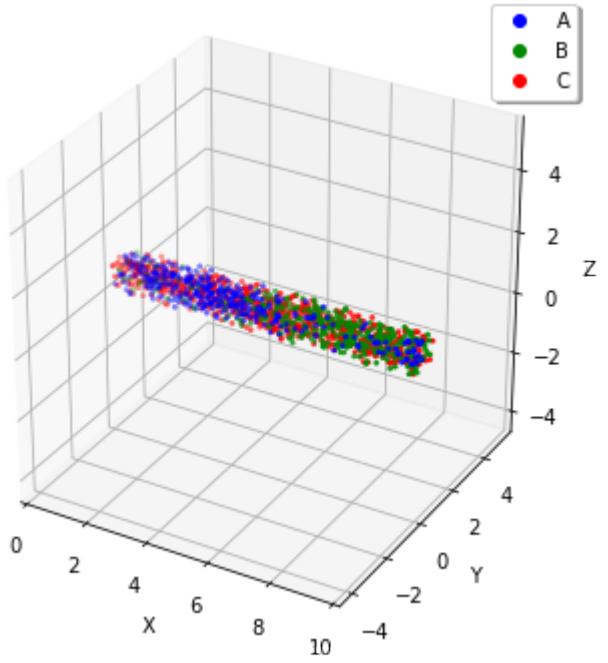
On a different note, there is a reason not to set `Integer3(0, 0, 0)` or `Integer3(9, 0, 0)`. In E-Cell4, basically we adopt periodic boundary condition for everything. So the forementioned two subvolumes are actually adjoining.

After realizing the location expected, simulate it with `meso.Simulator`.

[12]:
```
sim = meso.Simulator(w)
obs1 = NumberObserver(('A', 'B', 'C'))  # XXX: saves the numbers after every steps
sim.run(5, obs1)
show(obs1)
```

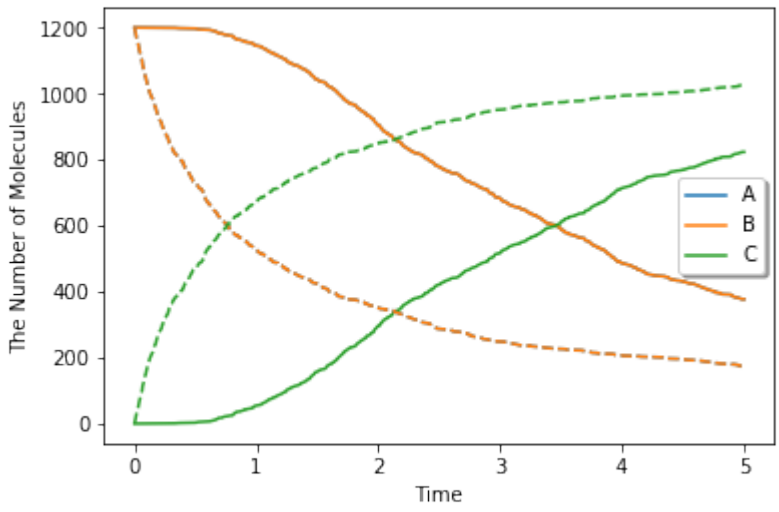


[13]:
```
# viz.plot_world(w, radius=0.025)
viz.plot_world(w, interactive=False)
```



To check the effect of initial coordinates, we recommend that you locate the molecules homogeneously with `meso` or simulate with `gillespie`.

[14]:
```
w = meso.World(Real3(10, 1, 1), Integer3(10, 1, 1))
w.bind_to(m)
w.add_molecules(Species('A'), 1200)
w.add_molecules(Species('B'), 1200)

sim = meso.Simulator(w)
obs2 = NumberObserver(('A', 'B', 'C'))  # XXX: saves the numbers after every steps
sim.run(5, obs2)

show(obs1, "-", obs2, "--")
```



The solid line is biased case, and the dash line is non-biased. The biased reaction is obviously slow. And you may notice that the shape of time-series is also different between the solid and dash lines. This is because it takes some time for the molecule A and B to collide due to the initial separation. Actually it takes $4^2/2(D_{\mathrm{A}} + D_{\mathrm{B}}) = 4$ seconds to move the initial distance between A and B (about 4).

1.10 10. Spatiocyte Simulations at Single-Molecule Resolution

We showed an example of E-Cell4 spatial representation.
Next let's simulate the models with more detailed spatial representation called "single molecule resolution".

[1]:
```
%matplotlib inline
from ecell4 import *
from ecell4_base import *
from ecell4_base.core import *
```

1.10.1 10.1. Spatiocyte Lattice-based Method

In spatical Gillespie method, we divided the Space into smaller Space, then we diffuse the molecules in the subvolumes. However, we treated the molecules in each subvolume just as the number of the molecules, and the location of the molecules are NOT determinated.

In other words, the spatical resolution of spatical Gillespie method is equal to the side of a subvolume l. To improve this resolution, we need to make the size of l small. But in this method the l must be larger than the (at least) 10 times the diameter of molecule R.

How can we improve the spatical resolution to the size of the molecule? The answer is the simulation with single-molecule resolution. This method simulate the molecule not with the number of the molecules, but with the spatical reaction diffusion of each molecule.

E-Cell4 has multiple single-molecule resolution method, here we explain about Spatiocyte lattice-based method. Spatiocyte treats each molecule as hard spheres, and diffuses the molecules on hexagonal close-packed lattice.

Spatiocyte has an ID for each molecule and the position of the molecule with single-molecule resolution. For the higher spatial resolution, Spatiocyte has 100 times smaller time-step than spatical Gillespie, because the time scale of diffusion increases with the square of the distance.

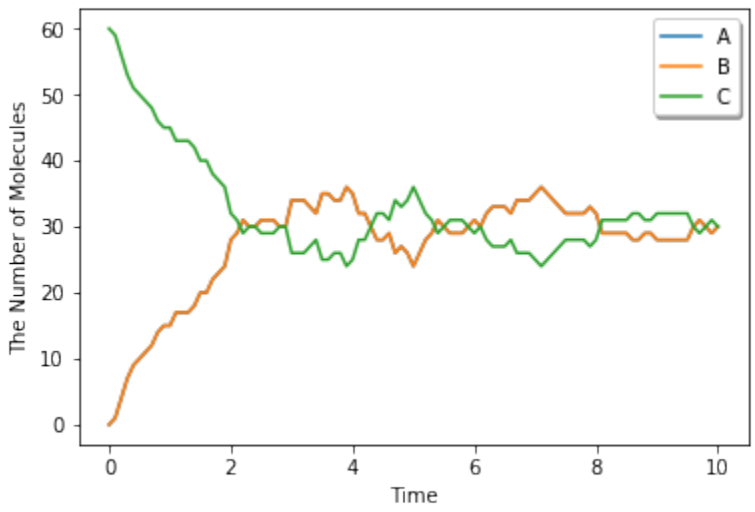
Next, let's try the Spatiocyte method.

[2]:
```
with species_attributes():
    A | B | C | {'D': 1}

with reaction_rules():
    A + B == C | (0.01, 0.3)

m = get_model()

w = spatiocyte.World(ones(), 0.005)  # The second argument is 'voxel_radius'.
w.bind_to(m)
w.add_molecules(Species('C'), 60)

sim = spatiocyte.Simulator(w)
obs = FixedIntervalNumberObserver(0.1, ('A', 'B', 'C'))
sim.run(10, obs)
```

There is a distinct difference in the second argument for `spatiocyte.World`. This is called `voxel radius`. Spatiocyte defines the locations of the molecules with dividing the space with molecule size, and call the minimum unit for this space as `Voxel`.

In most cases the size of the molecule would be good for `voxel radius`. In this example, we set 5 nm as the radius of the molecule in the space with the side 1 μm . It takes more time to simulate, but the result is same with ODE or Gillespie.

[3]:
```
show(obs)
```



1.10.2 10.2. The Diffusion Movement of Single Molecule

Next let's simulate single molecule diffusion to check the resolution.

[4]:
```
with species_attributes():
    A | {'D': 1}

m = get_model()

w = spatiocyte.World(ones(), 0.005)
w.bind_to(m)

pid = w.new_particle(Species('A'), 0.5 * ones())
```

`new_particle` method tries to place a particle to a coordinate in `spatiocyte.World`. It returns the particle's `ParticleID` (`pid`). If `new_particle` fails to place the particle, it returns `None` instead of a `ParticleID`. If a particle is already placed in the coordinate, you can NOT place a particle over it.

`Particle` contains the particle position, species type, radius, and diffusion coefficient. You can inspect the `Particle` with the particle's ID, `pid`.

Let's check `Particle` first.

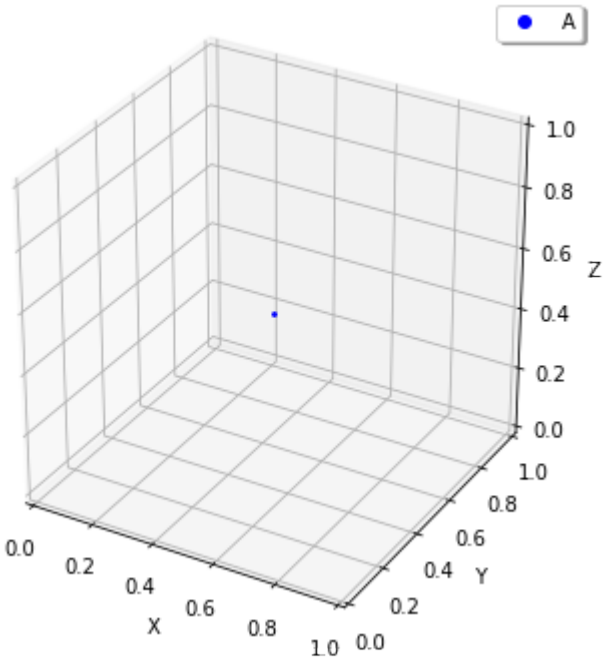
[5]:
```
pid, p = w.get_particle(pid)
print(p.species().serial())  # must print: A
print(p.radius(), p.D())  # must print: (0.005, 1.0)
print(tuple(p.position()))  # must print: (0.49806291436591293, 0.49652123150307814,␣
↪0.5)
```

```
A
0.005 1.0
(0.49806291436591293, 0.49652123150307814, 0.5)
```

`get_particle` method receives a particle ID and returns the ID and particle (of cource the ID are same with the given one). You can inspect the coordinate of the particle as `Real3` with `position()` method. It is hard to directly read the coordinate, here we printed it after converting to tuple. As you can see the tuple coodinate is slightly different from the original position given as a `Real3`. This is because Spatiocyte can place the molecule only on the lattice. `SpatiocyteWorld` places the molecule a center position of the nearest lattice for the argument `Real3`.

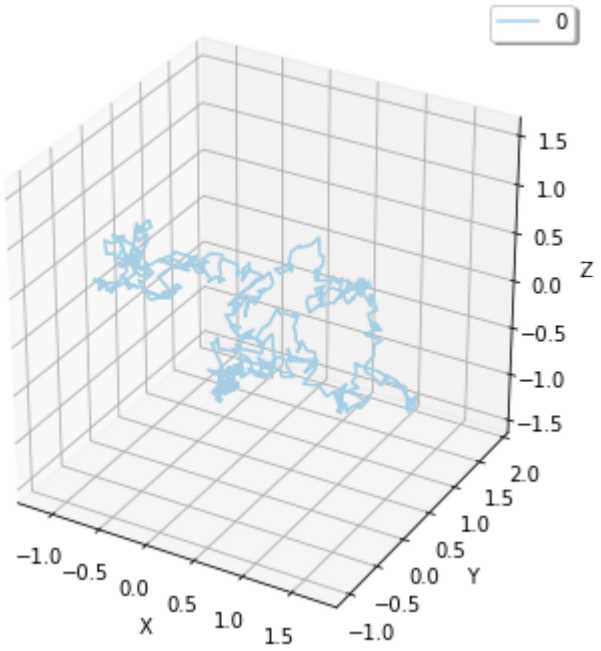
You can visualize the coordinate of the molecule with `viz.plot_world` method, and check the molecule in the center of the World.

[6]:
```
viz.plot_world(w, interactive=False)
# viz.plot_world(w)
```



And you can use `FixedIntervalTrajectoryObserver` to track the trajectory of molecular diffusion process.

[7]:
```
sim = spatiocyte.Simulator(w)
obs = FixedIntervalTrajectoryObserver(0.002, [pid])
sim.run(1, obs)
viz.plot_trajectory(obs, interactive=False)
# viz.plot_trajectory(obs)
```



Here we visualized the trajectory with `viz.plot_trajectory` method, you can also obtain it as `Real3` list with `data()` method.

[8]:
```
print(len(obs.data()))  # => 1
print(len(obs.data()[0]))  # => 501
```

```
1
501
```

`data()` method returns nested list. First index means the index of the particle. Second index means the index of the `Real3`. In this case we threw just one particle, so the first result is `1`, and next `501` means time-series coordinate of the only one particle (initial coordinate and the coordinates in 1/0.002 = 500 time points).

Also you can obtain the particles in bulk with `list_particles_exact` method and a `Species`.

[9]:
```
w.add_molecules(Species('A'), 5)

particles = w.list_particles_exact(Species('A'))
for pid, p in particles:
    print(p.species().serial(), tuple(p.position()))
```

```
A (0.7756717518813399, 0.5051814855409226, 0.435)
A (0.7430118886442307, 0.5051814855409226, 0.145)
A (0.08981462390204988, 0.8862326632060756, 0.085)
A (0.040824829046386304, 0.028867513459481287, 0.28)
A (0.11430952132988166, 0.09526279441628825, 0.745)
A (0.16329931618554522, 0.8660254037844386, 0.68)
```

Please remember `list_particles_exact` method, this method can be used for other World as well as `add_molecules` method.

1.10.3 10.3 The Diffusion Coefficient and the Second-order Reaction

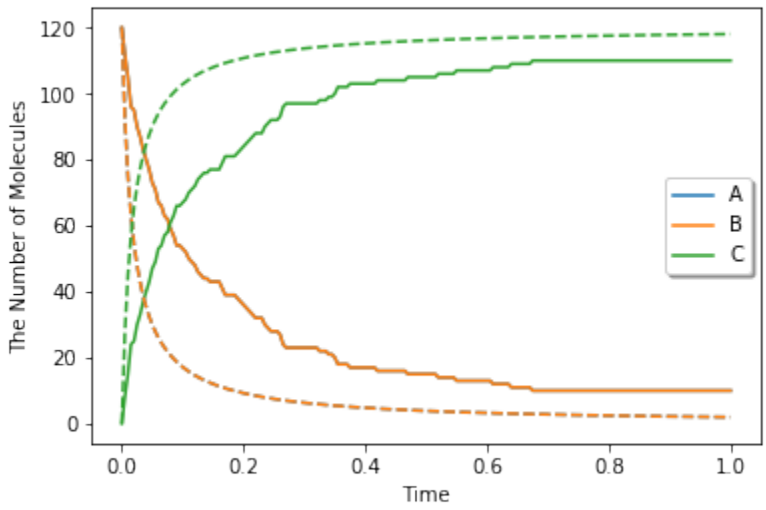
The models we have addressed contains a second-order reaction. Let's look at the relationship between this second-order reaction and the diffusion coefficient in Spatiocyte.

[10]:
```
with species_attributes():
    A | B | C | {'D': 1}

with reaction_rules():
    A + B > C | 1.0

m = get_model()
```

[11]:
```
w = spatiocyte.World(Real3(2, 1, 1), 0.005)
w.bind_to(m)
w.add_molecules(Species('A'), 120)
w.add_molecules(Species('B'), 120)

obs = FixedIntervalNumberObserver(0.005, ('A', 'B', 'C'))
sim = spatiocyte.Simulator(w)
sim.run(1.0, obs)
```

[12]:
```
odew = ode.World(Real3(2, 1, 1))
# odew.bind_to(m)
odew.add_molecules(Species('A'), 120)
odew.add_molecules(Species('B'), 120)

odeobs = FixedIntervalNumberObserver(0.005, ('A', 'B', 'C'))
odesim = ode.Simulator(odew, m)
odesim.run(1.0, odeobs)
```

[13]:
```
show(obs, "-", odeobs, "--")
```



Although we used faster kinetic constant than before, the result is same. But by contrast with ODE simulation, you can find the difference between them (solid line is `spatiocyte`, dash line is `ode`). Is this fault of Spatiocyte? (No) Actually Spatiocyte reaction rate couldn't be faster, while ODE reaction rate can be faster infinitely.

This is caused by the difference between the definition of reaction rate constant in ODE solver and single molecule

simulation method. The former is called "macroscopic" or "effective" reaction rate constant, the latter is called "microscopic" or "intrinsic" reaction rate constant.

The "macroscopic" rate represents the reaction rate in mixed molecular state, meanwhile "microscopic" rate represents the reactivity in molecule collision. So in "microscopic" perspective, the first thing molecules need to react is collision. In Spatiocyte, however, you make this "microscopic" rate faster, you can NOT make the actual reaction rate faster than collision rate. This is called "diffusion-limited" condition. This is similar to what the molecules coordinated disproportionately need time to react.

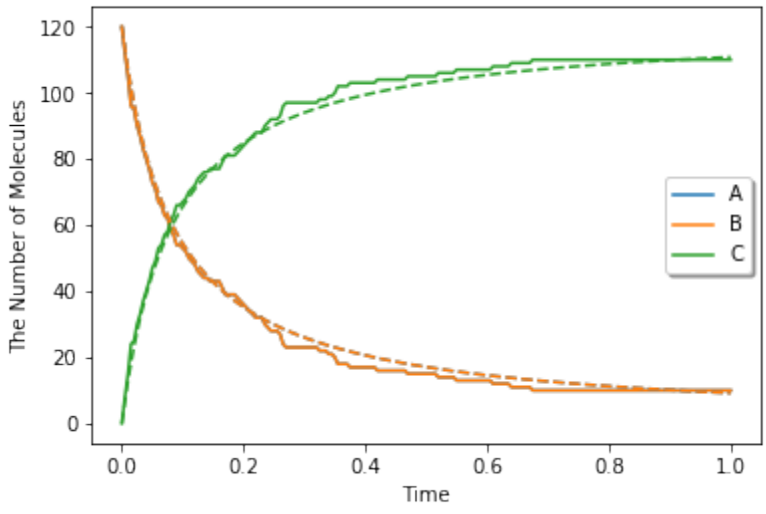
It is known that there is a relationship between this macroscopic rate constant k_{on} and microscopic rate constant k_a in 3D space.

$\frac{1}{k_{\mathrm{on}}} = \frac{1}{k_a} + \frac{1}{4\pi R D_{\mathrm{tot}}}$,

where R is the sum of two molecule's radius in collision, D_{tot} is the sum of diffusion coefficients.

In the case of the above Jupyter Notebook cell, $k_D = 4\pi R D_{\mathrm{tot}}$ is almost 0.25 and "microscopic" rate constant is 1.0. So the "macroscopic" rate constant is almost 0.2. (However unless you specify the configuration for Spatiocyte, the second order reaction rate must be slower than $3\sqrt{2}RD$, and the dissociation constant k_D is also $3\sqrt{2}RD$.) The single molecule simulation method can separate molecular "diffusion" and "reaction" in accurate manner contrary to ODE or Gillespie method supposed well mixed system (that is diffusion coefficient is infinite). However if the microscopic rate constant k_D is small enough, the macroscopic rate constant is almost equal to microscopic one (reaction rate-limited).

[14]:
```
import numpy

kD = 4 * numpy.pi * (0.005 * 2) * (1 * 2)
ka = 1.0
kf = ka * kD / (ka + kD)

with reaction_rules():
    A + B > C | kf

odeobs = run_simulation(1, y0={'A': 120, 'B': 120}, volume=2, return_type='observer')

show(obs, "-", odeobs, "--")
```



1.10.4 10.4. The Structure in the Spatiocyte Method

Next we explain a way to create a structure like cell membrane. Although The structure feature in E-Cell4 is still in development, Spatiocyte supports the structure on some level. Let's look a sphere structure as an example.

To restrict the molecular diffusion inside of the sphere, first we create it.

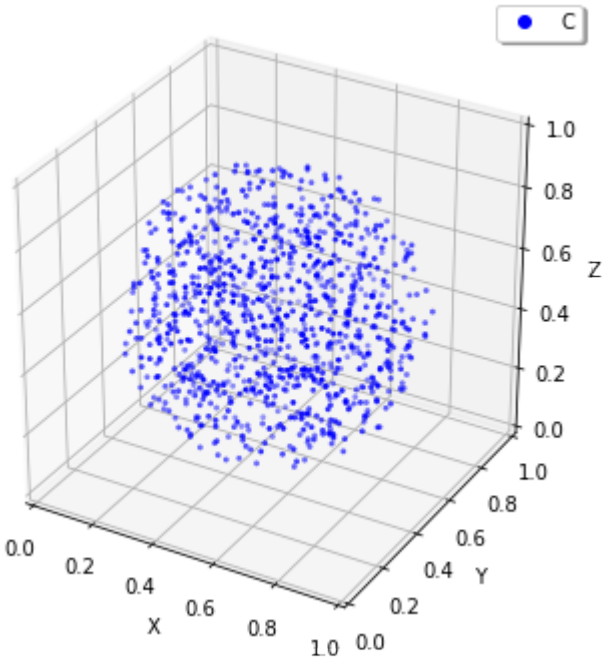
[15]:
```
with species_attributes():
    A | {'D': 1, 'location': 'C', 'dimension': 3}
    C | {'dimension': 3}

m = get_model()
```

[16]:
```
w = spatiocyte.SpatiocyteWorld(ones(), 0.005)
w.bind_to(m)
sph = Sphere(0.5 * ones(), 0.45)
print(w.add_structure(Species('C'), sph))  # will print 539805
```

```
539805
```

Visualize the state of the `World`.

[17]:
```
viz.plot_world(w, interactive=False)
# viz.plot_world(w)
```



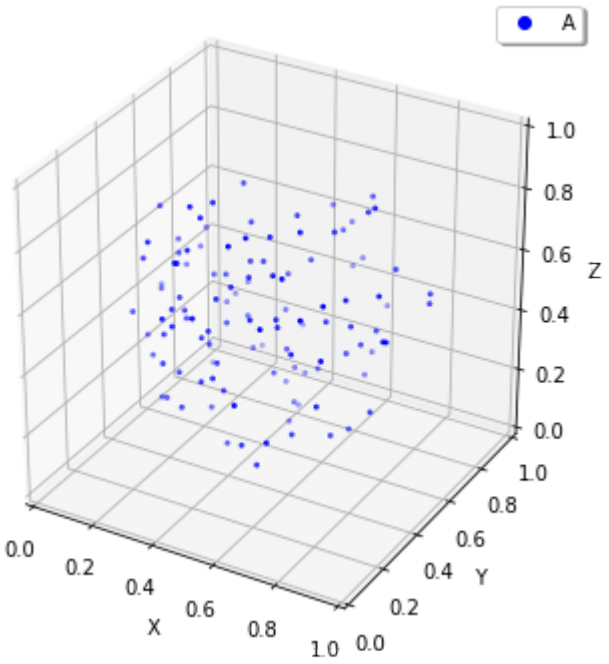
The `Sphere` class first argument is the center of the sphere, and second argument is the radius. Then we created a `Species` named `C` and added it inside the `Sphere`. The structure in the Spatiocyte method is described by filling the space with the `Voxel`. In the example above, the `Voxels` in the sphere are occupied with `Species` named `C`.

You can see those distribution with `viz.plot_world` as above. (However, the number of the species is too large to visualize all. So we plot only a part of it, but actually the sphere is fully occupied with the `Species`.)

Next we create Species moving inside this sphere. To that end we give `location` attribute to the `Species`. After that, you just throw-in molecules to the `World` with `add_molecules` function.

[18]:
```
w.add_molecules(Species('A'), 120)
```

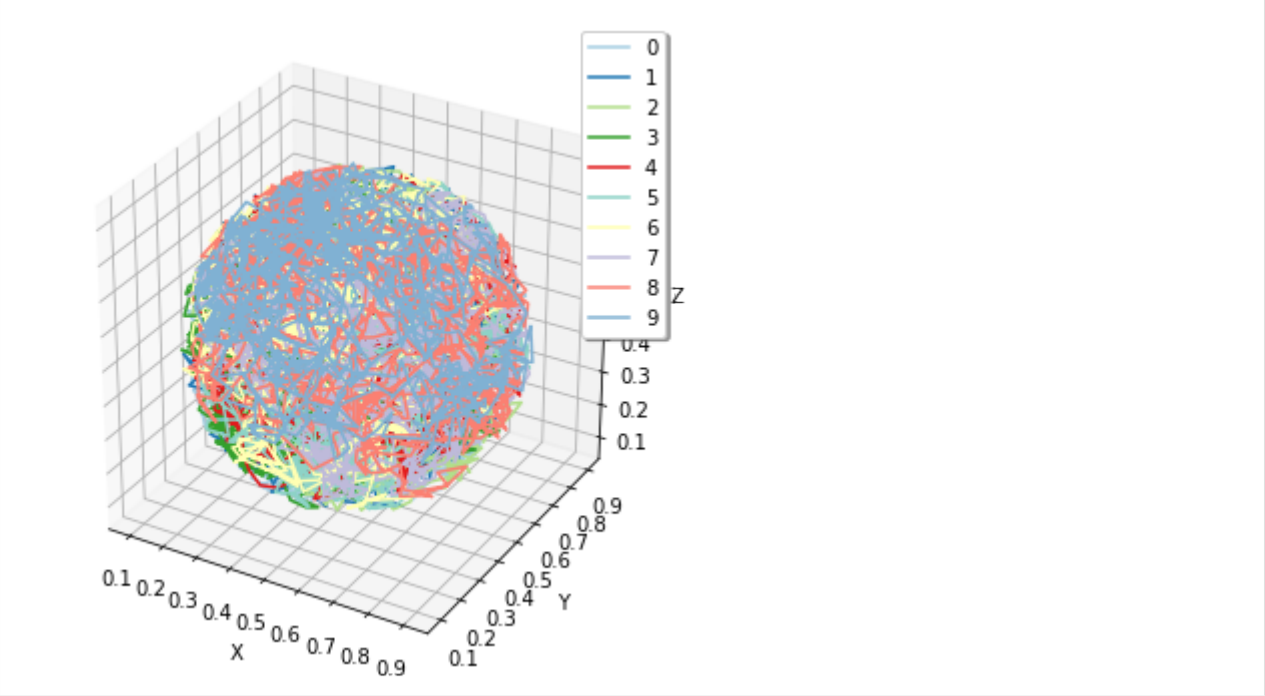
[19]:
```
viz.plot_world(w, species_list=('A',), interactive=False)  # visualize A-molecules
↪only
# viz.plot_world(w, species_list=('A',))  # visualize A-molecules only
```



Now we restricted the trajectories of `Species A` on the structure of Species `C`, and `add_molecules` works like that. As a note, you need to create the structure before `add_molecule`.

We can use `FixedIntervalTrajectoryObserver` to check the restriction of the diffusion area.

[20]:
```
pid_list = [pid for pid, p in w.list_particles(Species('A'))[: 10]]
obs = FixedIntervalTrajectoryObserver(1e-3, pid_list)
sim = spatiocyte.Simulator(w)
sim.run(1, obs)
viz.plot_trajectory(obs, interactive=False)
# viz.plot_trajectory(obs)
```



`pid_list` is a list of the first 10 `ParticleID`s of `A` molecules. The trajectories are colored by this 10 species. Certainly the trajectories are restricted in the sphere.

1.10.5 10.5 The structure and the reaction

At the end, we explain about molecular translocation among the structures.

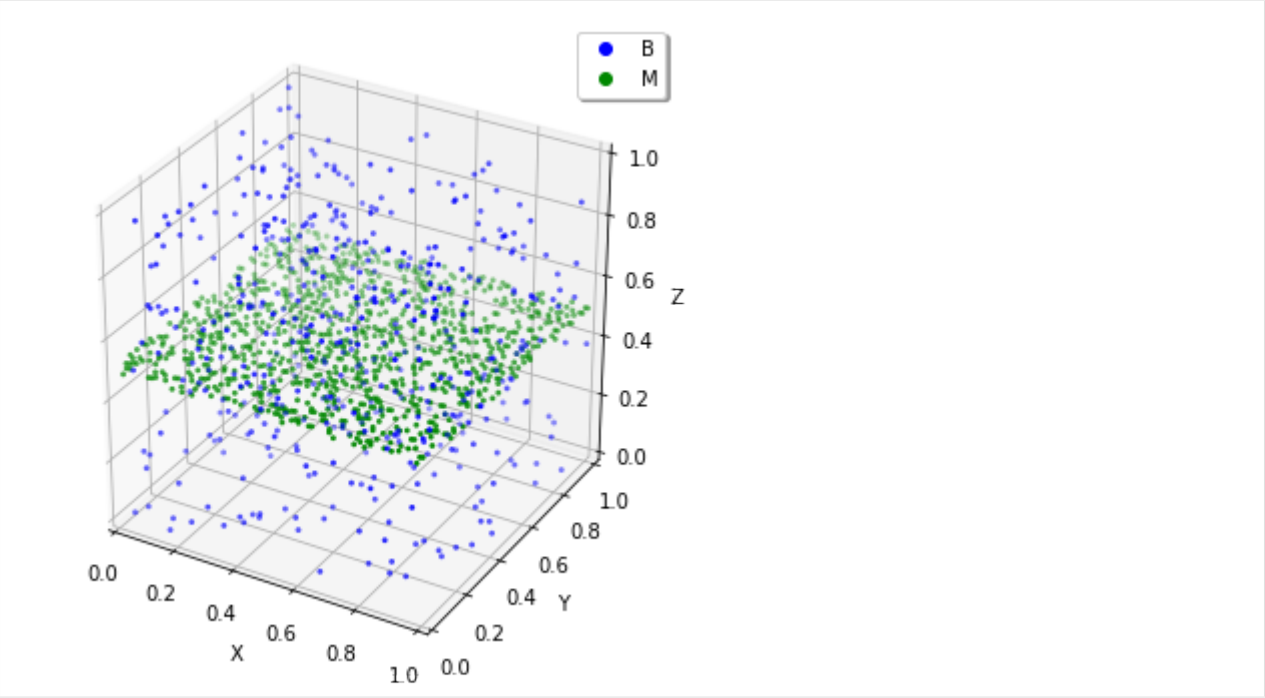
A `Species` without `location` attribute is not an member of any structures. In the example above, if you do NOT write `location` attribute with Species `A`, `A` is placed outside of the sphere.

Next let's create a planar surface structure. To create a surface, we need to use three Real3, those are original point (`origin`) and two axis vector (`unit0`, `unit1`): `ps = PlanarSurface(origin, unit0, unit1)`.

Suppose Species `A` on the surface, `ps`, and a normal Species `B`.

[21]:
```
with species_attributes():
    A | {'D': 0.1, 'location': 'M', 'dimension': 2}
    B | {'D': 1}
    M | {'dimension': 2}

m  = get_model()

w = spatiocyte.World(ones())
w.bind_to(m)

origin = Real3(0, 0, 0.5)
w.add_structure(
    Species('M'), PlanarSurface(origin, unitx(), unity()))  # Create a structure first

w.add_molecules(Species('B'), 480)  # Throw-in B-molecules
```

[22]:
```
viz.plot_world(w, species_list=('B', 'M'), interactive=False)
# viz.plot_world(w, species_list=('B', 'M'))
```



It might be hard to see them, but actually the `Species B` are placed only not on a surface. Then how can we make absorbed this `Species B` to a surface `M` and synthesize a `Species A`?

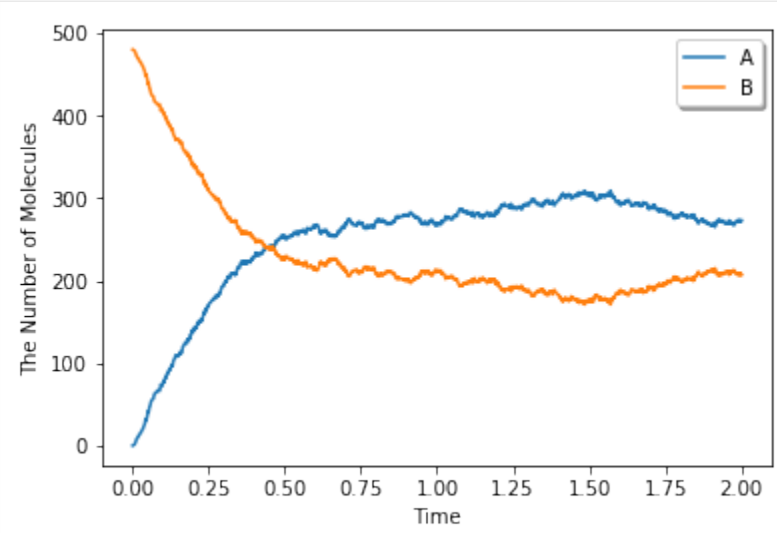
[23]:
```
with species_attributes():
    A | {'D': 0.1, 'location': 'M', 'dimension': 2}
    B | {'D': 1}
    M | {'dimension': 2}

with reaction_rules():
    B + M == A | (1.0, 1.5)

m = get_model()
```

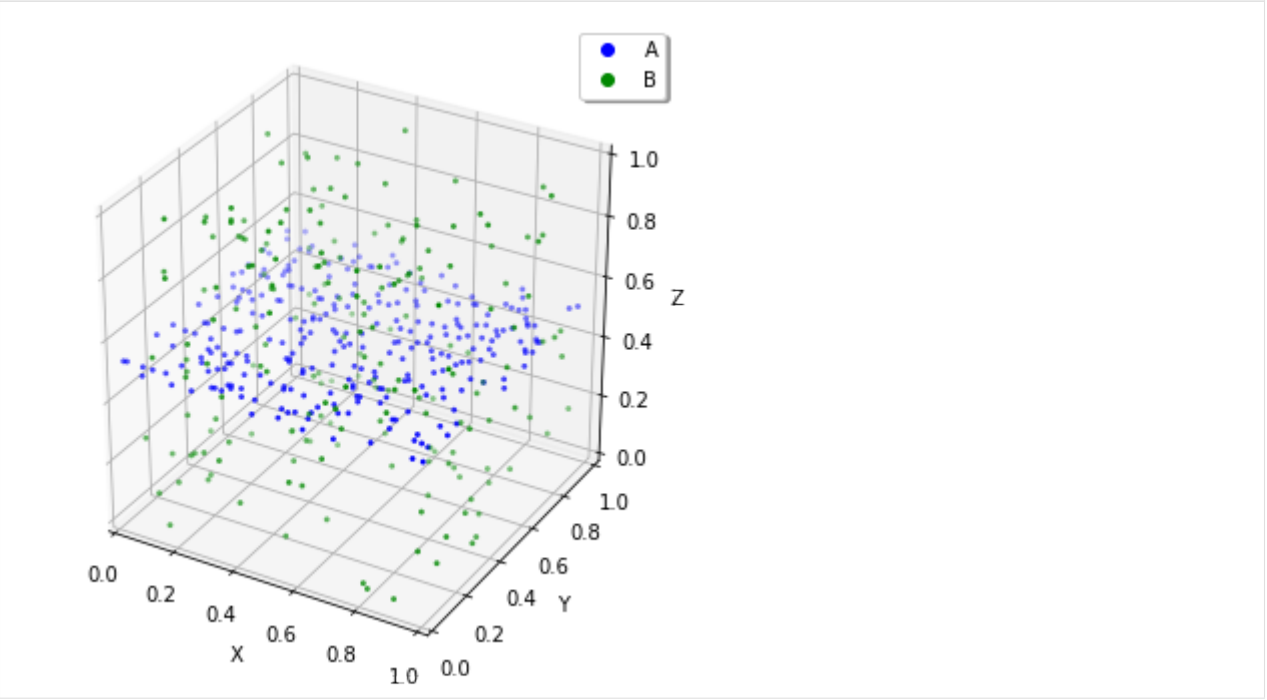
This means that a `Species B` becomes `A` when `B` collides with a structure `M`. On the other hand, a species `A` dissociates from the structure, and becomes `M` and `B` on as the reverse reaction direction.

Now you can simulate this model with a structure.

[24]:
```
w.bind_to(m)

sim = spatiocyte.Simulator(w)
obs = NumberObserver(('A', 'B'))
sim.run(2, obs)
```

[25]:
```
viz.plot_number_observer(obs)
viz.plot_world(w, species_list=('A', 'B'), interactive=False)
# viz.plot_world(w, species_list=('A', 'B'))
```





In the dissociation from a structure, you can skip to write the structure. Thus, `A > B` just means the same as `A > B + M` in the above. But in the binding, you can **NOT**. Because it is impossible to create `A` from `B` with no `M` around there. By contrast the species `A` wherever on the sphere `M` can create the species `B`. The first order reaction occurs in either presence or absence of the structure. But, in the case of the binding, the second order reaction turns into the first order reaction and the meaning of rate constant also changes if you ignore `M` in the left-hand side.

CHAPTER 2

Examples

2.1 Attractors

[1]:
```
%matplotlib inline
import numpy
from ecell4 import *
util.decorator.ENABLE_RATELAW = True
```

2.1.1 Rössler attractor

[2]:
```
a, b, c = 0.2, 0.2, 5.7

with reaction_rules():
    ~x > x | (-y - z)
    ~y > y | (x + a * y)
    ~z > z | (b + z * (x - c))
```

[3]:
```
run_simulation(numpy.linspace(0, 200, 4001), y0={'x': 1.0}, return_type='nyaplot',
               opt_args={'x': 'x', 'y': ('y', 'z'), 'to_png': True})
```

```
<IPython.core.display.HTML object>
```

2.1.2 Modified Chua chaotic attractor

[4]:
```
alpha, beta = 10.82, 14.286
a, b, d = 1.3, 0.1, 0.2

with reaction_rules():
    h = -b * sin(numpy.pi * x / (2 * a) + d)
    ~x > x | (alpha * (y - h))
```

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```
    ~y > y | (x - y + z)
    ~z > z | (-beta * y)
```

[5]:
```
run_simulation(numpy.linspace(0, 250, 5001),
               y0={'x': 0, 'y': 0.49899, 'z': 0.2}, return_type='nyaplot',
               opt_args={'x': 'x', 'y': 'y', 'to_png': True})
```

```
<IPython.core.display.HTML object>
```

2.1.3 Lorenz system

[6]:
```
p, r, b = 10, 28, 8.0 / 3

with reaction_rules():
    ~x > x | (-p * x + p * y)
    ~y > y | (-x * z + r * x - y)
    ~z > z | (x * y - b * z)
```

[7]:
```
run_simulation(numpy.linspace(0, 25, 2501),
               y0={'x': 10, 'y': 1, 'z': 1}, return_type='nyaplot',
               opt_args={'x': 'x', 'y': ('y', 'z'), 'to_png': True})
```

```
<IPython.core.display.HTML object>
```

2.1.4 Tamari attractor

[8]:
```
a = 1.013
b = -0.021
c = 0.019
d = 0.96
e = 0
f = 0.01
g = 1
u = 0.05
i = 0.05

with reaction_rules():
    ~x > x | ((x - a * y) * cos(z) - b * y * sin(z))
    ~y > y | ((x + c * y) * sin(z) + d * y * cos(z))
    ~z > z | (e + f * z + g * a * atan((1 - u) / (1 - i) * x * y))
```

[9]:
```
run_simulation(numpy.linspace(0, 800, 8001),
               y0={'x': 0.9, 'y': 1, 'z': 1}, return_type='nyaplot',
               opt_args={'x': 'x', 'y': ('y', 'z'), 'to_png': True})
```

```
<IPython.core.display.HTML object>
```

2.1.5 Moore-Spiegel attractor

[10]:
```
T, R = 6, 20
with reaction_rules():
    ~x > x | y
    ~y > y | z
    ~z > z | (-z - (T - R + R * x * x) * y - T * x)
```

[11]:
```
run_simulation(numpy.linspace(0, 100, 5001),
               y0={'x': 1, 'y': 0, 'z': 0}, return_type='nyaplot',
               opt_args={'x': 'x', 'y': 'y', 'to_png': True})
```

```
<IPython.core.display.HTML object>
```

2.2 Drosophila Circadian Clock

This is a model of the oscillating Drosophila period protein(PER). This model is based on the model introduced in the following publication.

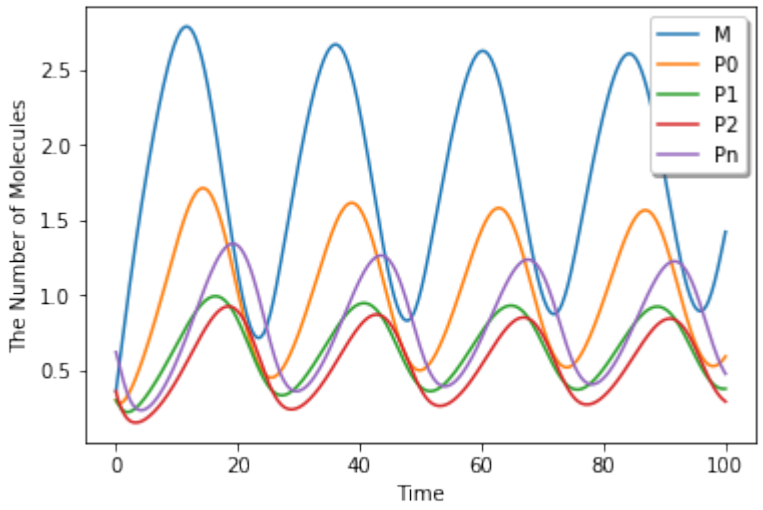
- A. Goldbeter, "A model for circadian oscillations in the Drosophila period protein(PER)", Proc R Soc Lond B Biol Sci, Vol.261:319-324, Sep 1995.

[1]:
```
%matplotlib inline
import numpy
from ecell4 import *
```

[2]:
```
with reaction_rules():
    ~M > M | 0.76 / (1 + Pn ** 3)
    M > ~M | 0.65 * M / (0.5 + M)
    ~P0 > P0 | 0.38 * M
    P0 == P1 | (3.2 * P0 / (2 + P0), 1.58 * P1 / (2 + P1))
    P1 == P2 | (5 * P1 / (2 + P1), 2.5 * P2 / (2 + P2))
    P2 == Pn | (1.9, 1.3)
    P2 > ~P2 | 0.95 * P2 / (0.2 + P2)
```

[3]:
```
y0 = {"M": 3.61328202e-01, "Pn": 6.21367e-01, "P0": 3.01106835e-01, "P1": 3.01106835e-
↪01, "P2": 3.61328202e-01}
obs = run_simulation(numpy.linspace(0, 100, 400), y0, return_type='observer')
```

[4]:
```
show(obs)
```



[5]:
```
viz.plot_number_observer_with_nya(obs, x="Pn", y=("M", "P0", "P1", "P2"), to_png=True)
```

```
<IPython.core.display.HTML object>
```

2.3 Dual Phosphorylation Cycle

[1]:
```
from ecell4_base.core import *
from ecell4.util import species_attributes, reaction_rules, show
```

[2]:
```
@species_attributes
def attrgen(radius, D):
    K | Kp | Kpp | KK | PP | K_KK | Kp_KK | Kpp_PP | Kp_PP | {"radius": radius, "D":␣
↪D}

@reaction_rules
def rulegen(kon1, koff1, kcat1, kon2, koff2, kcat2):
    (K + KK == K_KK | (kon1, koff1)
        > Kp + KK | kcat1
        == Kp_KK | (kon2, koff2)
        > Kpp + KK | kcat2)

    (Kpp + PP == Kpp_PP | (kon1, koff1)
        > Kp + PP | kcat1
        == Kp_PP | (kon2, koff2)
        > K + PP | kcat2)
```

[3]:
```
m = NetworkModel()
```

[4]:
```
for i, sp in enumerate(attrgen(0.0025, 1.0)):
    print(i, sp.serial(), sp.get_attribute("radius").magnitude, sp.get_attribute("D").
↪magnitude)
    m.add_species_attribute(sp)
```

```
0 K 0.0025 1.0
1 Kp 0.0025 1.0
```

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```
2 Kpp 0.0025 1.0
3 KK 0.0025 1.0
4 PP 0.0025 1.0
5 K_KK 0.0025 1.0
6 Kp_KK 0.0025 1.0
7 Kpp_PP 0.0025 1.0
8 Kp_PP 0.0025 1.0
```

[5]:
```
ka1, kd1, kcat1 = 0.04483455086786913, 1.35, 1.5
ka2, kd2, kcat2 = 0.09299017957780264, 1.73, 15.0

for i, rr in enumerate(rulegen(ka1, kd2, kcat1, ka2, kd2, kcat2)):
    reactants, products, k = rr.reactants(), rr.products(), rr.k()
    print(i, rr.as_string())
    m.add_reaction_rule(rr)
```

```
0 K+KK>K_KK|0.0448346
1 K_KK>K+KK|1.73
2 K_KK>Kp+KK|1.5
3 Kp+KK>Kp_KK|0.0929902
4 Kp_KK>Kp+KK|1.73
5 Kp_KK>Kpp+KK|15
6 Kpp+PP>Kpp_PP|0.0448346
7 Kpp_PP>Kpp+PP|1.73
8 Kpp_PP>Kp+PP|1.5
9 Kp+PP>Kp_PP|0.0929902
10 Kp_PP>Kp+PP|1.73
11 Kp_PP>K+PP|15
```

[6]:
```
show(m)
```

```
K|{'radius': <ecell4_base.core.Quantity object at 0x150173e96748>, 'D': <ecell4_base.
↪core.Quantity object at 0x150173e96588>}
Kp|{'D': <ecell4_base.core.Quantity object at 0x150173e96588>, 'radius': <ecell4_base.
↪core.Quantity object at 0x150173e96e80>}
Kpp|{'radius': <ecell4_base.core.Quantity object at 0x150173e96748>, 'D':␣
↪<ecell4_base.core.Quantity object at 0x150173e96588>}
KK|{'radius': <ecell4_base.core.Quantity object at 0x150173e96748>, 'D': <ecell4_base.
↪core.Quantity object at 0x150173e96e80>}
PP|{'D': <ecell4_base.core.Quantity object at 0x150173e96e80>, 'radius': <ecell4_base.
↪core.Quantity object at 0x150173e96588>}
K_KK|{'D': <ecell4_base.core.Quantity object at 0x150173e96588>, 'radius':␣
↪<ecell4_base.core.Quantity object at 0x150173e96e80>}
Kp_KK|{'D': <ecell4_base.core.Quantity object at 0x150173e96e80>, 'radius':␣
↪<ecell4_base.core.Quantity object at 0x150173e96588>}
Kpp_PP|{'D': <ecell4_base.core.Quantity object at 0x150173e96588>, 'radius':␣
↪<ecell4_base.core.Quantity object at 0x150173e96e80>}
Kp_PP|{'radius': <ecell4_base.core.Quantity object at 0x150173e96748>, 'D':␣
↪<ecell4_base.core.Quantity object at 0x150173e96588>}
K+KK>K_KK|0.0448346
K_KK>K+KK|1.73
K_KK>Kp+KK|1.5
Kp+KK>Kp_KK|0.0929902
Kp_KK>Kp+KK|1.73
Kp_KK>Kpp+KK|15
Kpp+PP>Kpp_PP|0.0448346
Kpp_PP>Kpp+PP|1.73
```

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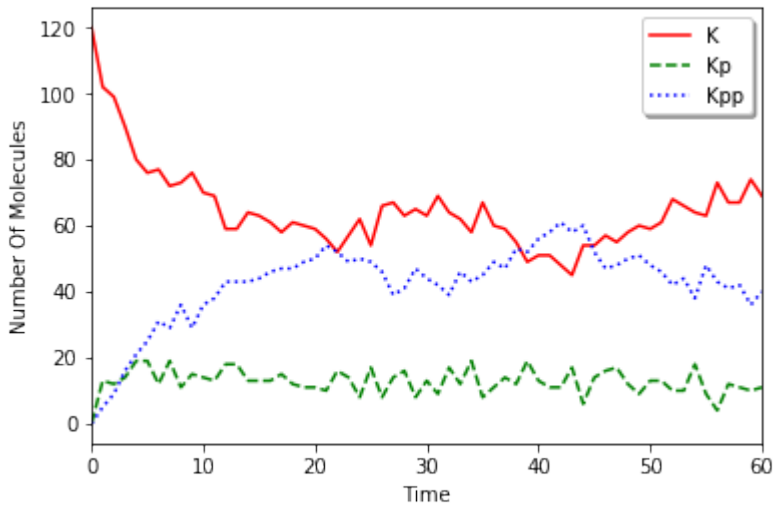
```
Kpp_PP>Kp+PP|1.5
Kp+PP>Kp_PP|0.0929902
Kp_PP>Kp+PP|1.73
Kp_PP>K+PP|15
```

[7]:
```
from ecell4_base import gillespie, ode

f = gillespie.Factory()
# f = ode.Factory()

w = f.world(ones())
# w.bind_to(m)
w.add_molecules(Species("K"), 120)
w.add_molecules(Species("KK"), 30)
w.add_molecules(Species("PP"), 30)

sim = f.simulator(w, m)
```

[8]:
```
obs = FixedIntervalNumberObserver(1.0, ["K", "K_KK", "Kp", "Kp_KK", "Kp_PP", "Kpp",
↪"Kpp_PP"])
sim.run(60, [obs])
```

[9]:
```
%matplotlib inline
import matplotlib.pylab as plt
from numpy import array

data = array(obs.data()).T
plt.plot(data[0], data[1] + data[2], "r-", label="K")
plt.plot(data[0], data[3] + data[4] + data[5], "g--", label="Kp")
plt.plot(data[0], data[6] + data[7], "b:", label="Kpp")
plt.xlabel("Time")
plt.ylabel("Number Of Molecules")
plt.xlim(data[0][0], data[0][-1])
plt.legend(loc="best", shadow=True)
plt.show()
```



2.4 Simple EGFR model

- http://bionetgen.org/index.php/Simple_EGFR_model
- M.L. Blinov, J.R. Faeder, B. Goldstein, W.S. Hlavacek, "A network model of early events in epidermal growth factor receptor signaling that accounts for combinatorial complexity.", Biosystems, 83(2-3), 136-151, 2006.

[1]:
```
%matplotlib inline
from ecell4 import *
from ecell4_base.core import *
```

[2]:
```
NA = 6.02e23  # Avogadro's number (molecules/mol)
f = 1  # Fraction of the cell to simulate
Vo = f * 1.0e-10  # Extracellular volume=1/cell_density (L)
V = f * 3.0e-12  # Cytoplasmic volume (L)

EGF_init = 20 * 1e-9 * NA * Vo  # Initial amount of ligand (20 nM) converted to␣
↪copies per cell

# Initial amounts of cellular components (copies per cell)
EGFR_init = f * 1.8e5
Grb2_init = f * 1.5e5
Sos1_init = f * 6.2e4

# Rate constants
# Divide by NA*V to convert bimolecular rate constants
# from /M/sec to /(molecule/cell)/sec
kp1 = 9.0e7 / (NA * Vo)  # ligand-monomer binding
km1 = 0.06  # ligand-monomer dissociation
kp2 = 1.0e7 / (NA * V)  # aggregation of bound monomers
km2 = 0.1  # dissociation of bound monomers
kp3 = 0.5  # dimer transphosphorylation
km3 = 4.505  # dimer dephosphorylation
kp4 = 1.5e6 / (NA * V)  # binding of Grb2 to receptor
km4 = 0.05  # dissociation of Grb2 from receptor
kp5 = 1.0e7 / (NA * V)  # binding of Grb2 to Sos1
km5 = 0.06  # dissociation of Grb2 from Sos1
deg = 0.01  # degradation of receptor dimers
```

[3]:
```
with reaction_rules():
  # R1: Ligand-receptor binding
  EGFR(L, CR1) + EGF(R) == EGFR(L^1, CR1).EGF(R^1) | (kp1, km1)

  # R2: Receptor-aggregation
  EGFR(L^_, CR1) + EGFR(L^_, CR1) == EGFR(L^_,CR1^1).EGFR(L^_,CR1^1) | (kp2, km2)

  # R3: Transphosphorylation of EGFR by RTK
  EGFR(CR1^_, Y1068=U) > EGFR(CR1^_, Y1068=P) | kp3

  # R4: Dephosphorylation
  EGFR(Y1068=P) > EGFR(Y1068=U) | km3

  # R5: Grb2 binding to pY1068
  EGFR(Y1068=P) + Grb2(SH2) == EGFR(Y1068=P^1).Grb2(SH2^1) | (kp4, km4)

  # R6: Grb2 binding to Sos1
  Grb2(SH3) + Sos1(PxxP) == Grb2(SH3^1).Sos1(PxxP^1) | (kp5, km5)
```

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```
  # R7: Receptor dimer internalization/degradation
  (EGF(R^1).EGF(R^2).EGFR(L^1,CR1^3).EGFR(L^2,CR1^3) > ~EmptySet | deg
       | ReactionRule.STRICT | ReactionRule.DESTROY)

m = get_model(is_netfree=True, effective=True)
```

[4]:
```
y0 = {"EGF(R)": EGF_init, "EGFR(L,CR1,Y1068=U)": EGFR_init, "Grb2(SH2,SH3)": Grb2_
↪init, "Sos1(PxxP)": Sos1_init}

#XXX
tmp = {}
for key, value in y0.items():
    tmp[format_species(Species(key)).serial()] = value
y0 = tmp
```

[5]:
```
newm = m.expand([Species(serial) for serial in y0.keys()])
```

[6]:
```
print("{} species and {} reactions were generated.".format(len(newm.list_species()),␣
↪len(newm.reaction_rules())))

for i, sp in enumerate(newm.list_species()):
    print("{}: {}".format(i + 1, sp.serial()))

for i, rr in enumerate(newm.reaction_rules()):
    print("{}: {}".format(i + 1, rr.as_string()))
```

```
22 species and 86 reactions were generated.
1: EGF(R)
2: EGF(R^1).EGFR(CR1,L^1,Y1068=P)
3: EGF(R^1).EGFR(CR1,L^1,Y1068=P^2).Grb2(SH2^2,SH3)
4: EGF(R^1).EGFR(CR1,L^1,Y1068=P^2).Grb2(SH2^2,SH3^3).Sos1(PxxP^3)
5: EGF(R^1).EGFR(CR1,L^1,Y1068=U)
6: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=P).EGF(R^3)
7: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=P^4).EGF(R^3).Grb2(SH2^4,SH3)
8: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=P^4).EGF(R^3).Grb2(SH2^4,
↪SH3^5).Sos1(PxxP^5)
9: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=U).EGF(R^3)
10: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=P^5).EGF(R^4).Grb2(SH2^5,
↪SH3).Grb2(SH2^3,SH3)
11: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=P^5).EGF(R^4).Grb2(SH2^5,
↪SH3).Grb2(SH2^3,SH3^6).Sos1(PxxP^6)
12: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=P^5).EGF(R^4).Grb2(SH2^5,
↪SH3^6).Sos1(PxxP^6).Grb2(SH2^3,SH3^7).Sos1(PxxP^7)
13: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=U).EGF(R^4).Grb2(SH2^3,
↪SH3)
14: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=U).EGF(R^4).Grb2(SH2^3,
↪SH3^5).Sos1(PxxP^5)
15: EGF(R^1).EGFR(CR1^2,L^1,Y1068=U).EGFR(CR1^2,L^3,Y1068=U).EGF(R^3)
16: EGFR(CR1,L,Y1068=P)
17: EGFR(CR1,L,Y1068=P^1).Grb2(SH2^1,SH3)
18: EGFR(CR1,L,Y1068=P^1).Grb2(SH2^1,SH3^2).Sos1(PxxP^2)
19: EGFR(CR1,L,Y1068=U)
20: Grb2(SH2,SH3)
21: Grb2(SH2,SH3^1).Sos1(PxxP^1)
22: Sos1(PxxP)
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1: EGF(R)+EGFR(CR1,L,Y1068=U)>EGF(R^1).EGFR(CR1,L^1,Y1068=U)|1.49502e-06
2: Grb2(SH2,SH3)+Sos1(PxxP)>Grb2(SH2,SH3^1).Sos1(PxxP^1)|5.5371e-06
3: EGF(R^1).EGFR(CR1,L^1,Y1068=U)>EGF(R)+EGFR(CR1,L,Y1068=U)|0.06
4: EGF(R^1).EGFR(CR1,L^1,Y1068=U)+EGF(R^1).EGFR(CR1,L^1,Y1068=U)>EGF(R^1).EGFR(CR1^2,
 ↪L^1,Y1068=U).EGFR(CR1^2,L^3,Y1068=U).EGF(R^3)|2.76855e-06
5: Grb2(SH2,SH3^1).Sos1(PxxP^1)>Grb2(SH2,SH3)+Sos1(PxxP)|0.06
6: EGF(R^1).EGFR(CR1^2,L^1,Y1068=U).EGFR(CR1^2,L^3,Y1068=U).EGF(R^3)>EGF(R^1).
 ↪EGFR(CR1,L^1,Y1068=U)+EGF(R^1).EGFR(CR1,L^1,Y1068=U)|0.1
7: EGF(R^1).EGFR(CR1^2,L^1,Y1068=U).EGFR(CR1^2,L^3,Y1068=U).EGF(R^3)>EGF(R^1).
 ↪EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=U).EGF(R^3)|1
8: EGF(R^1).EGFR(CR1^2,L^1,Y1068=U).EGFR(CR1^2,L^3,Y1068=U).EGF(R^3)>|0.01
9: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=U).EGF(R^3)>EGF(R^1).
 ↪EGFR(CR1,L^1,Y1068=P)+EGF(R^1).EGFR(CR1,L^1,Y1068=U)|0.1
10: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=U).EGF(R^3)>EGF(R^1).
 ↪EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=P).EGF(R^3)|0.5
11: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=U).EGF(R^3)>EGF(R^1).
 ↪EGFR(CR1^2,L^1,Y1068=U).EGFR(CR1^2,L^3,Y1068=U).EGF(R^3)|4.505
12: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=U).EGF(R^3)+Grb2(SH2,SH3^1).
 ↪Sos1(PxxP^1)>EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=U).EGF(R^4).
 ↪Grb2(SH2^3,SH3^5).Sos1(PxxP^5)|8.30565e-07
13: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=U).EGF(R^3)+Grb2(SH2,
 ↪SH3)>EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=U).EGF(R^4).Grb2(SH2^3,
 ↪SH3)|8.30565e-07
14: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=U).EGF(R^3)>|0.01
15: EGF(R^1).EGFR(CR1,L^1,Y1068=P)>EGF(R)+EGFR(CR1,L,Y1068=P)|0.06
16: EGF(R^1).EGFR(CR1,L^1,Y1068=P)+EGF(R^1).EGFR(CR1,L^1,Y1068=P)>EGF(R^1).EGFR(CR1^2,
 ↪L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=P).EGF(R^3)|2.76855e-06
17: EGF(R^1).EGFR(CR1,L^1,Y1068=P)+EGF(R^1).EGFR(CR1,L^1,Y1068=U)>EGF(R^1).EGFR(CR1^2,
 ↪L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=U).EGF(R^3)|5.5371e-06
18: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=P).EGF(R^3)>EGF(R^1).
 ↪EGFR(CR1,L^1,Y1068=P)+EGF(R^1).EGFR(CR1,L^1,Y1068=P)|0.1
19: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=U).EGF(R^4).Grb2(SH2^3,
 ↪SH3^5).Sos1(PxxP^5)>EGF(R^1).EGFR(CR1,L^1,Y1068=P^2).Grb2(SH2^2,SH3^3).
 ↪Sos1(PxxP^3)+EGF(R^1).EGFR(CR1,L^1,Y1068=U)|0.1
20: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=U).EGF(R^4).Grb2(SH2^3,
 ↪SH3)>EGF(R^1).EGFR(CR1,L^1,Y1068=P^2).Grb2(SH2^2,SH3)+EGF(R^1).EGFR(CR1,L^1,
 ↪Y1068=U)|0.1
21: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=U).EGF(R^4).Grb2(SH2^3,
 ↪SH3^5).Sos1(PxxP^5)>EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=P^4).
 ↪EGF(R^3).Grb2(SH2^4,SH3^5).Sos1(PxxP^5)|0.5
22: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=U).EGF(R^4).Grb2(SH2^3,
 ↪SH3)>EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=P^4).EGF(R^3).Grb2(SH2^4,
 ↪SH3)|0.5
23: EGF(R^1).EGFR(CR1,L^1,Y1068=P)>EGF(R^1).EGFR(CR1,L^1,Y1068=U)|4.505
24: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=P).EGF(R^3)>EGF(R^1).
 ↪EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=U).EGF(R^3)|9.01
25: EGF(R^1).EGFR(CR1,L^1,Y1068=P)+Grb2(SH2,SH3^1).Sos1(PxxP^1)>EGF(R^1).EGFR(CR1,L^1,
 ↪Y1068=P^2).Grb2(SH2^2,SH3^3).Sos1(PxxP^3)|8.30565e-07
26: EGF(R^1).EGFR(CR1,L^1,Y1068=P)+Grb2(SH2,SH3)>EGF(R^1).EGFR(CR1,L^1,Y1068=P^2).
 ↪Grb2(SH2^2,SH3)|8.30565e-07
27: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=P).EGF(R^3)+Grb2(SH2,SH3^1).
 ↪Sos1(PxxP^1)>EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=P^4).EGF(R^3).
 ↪Grb2(SH2^4,SH3^5).Sos1(PxxP^5)|1.66113e-06
28: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=P).EGF(R^3)+Grb2(SH2,
 ↪SH3)>EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=P^4).EGF(R^3).Grb2(SH2^4,
 ↪SH3)|1.66113e-06
29: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=U).EGF(R^4).Grb2(SH2^3,
 ↪SH3^5).Sos1(PxxP^5)>EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=U).
 ↪EGF(R^3)+Grb2(SH2,SH3^1).Sos1(PxxP^1)|0.05
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30: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=U).EGF(R^4).Grb2(SH2^3,
↪SH3)>EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=U).EGF(R^3)+Grb2(SH2,
↪SH3)|0.05
31: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=U).EGF(R^4).Grb2(SH2^3,
↪SH3)+Sos1(PxxP)>EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=U).EGF(R^4).
↪Grb2(SH2^3,SH3^5).Sos1(PxxP^5)|5.5371e-06
32: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=U).EGF(R^4).Grb2(SH2^3,
↪SH3^5).Sos1(PxxP^5)>EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=U).
↪EGF(R^4).Grb2(SH2^3,SH3)+Sos1(PxxP)|0.06
33: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=P).EGF(R^3)>|0.01
34: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=U).EGF(R^4).Grb2(SH2^3,
↪SH3^5).Sos1(PxxP^5)>|0.01
35: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=U).EGF(R^4).Grb2(SH2^3,
↪SH3)>|0.01
36: EGF(R)+EGFR(CR1,L,Y1068=P)>EGF(R^1).EGFR(CR1,L^1,Y1068=P)|1.49502e-06
37: EGF(R^1).EGFR(CR1,L^1,Y1068=P^2).Grb2(SH2^2,SH3^3).Sos1(PxxP^3)>EGF(R)+EGFR(CR1,L,
↪Y1068=P^1).Grb2(SH2^1,SH3^2).Sos1(PxxP^2)|0.06
38: EGF(R^1).EGFR(CR1,L^1,Y1068=P^2).Grb2(SH2^2,SH3)>EGF(R)+EGFR(CR1,L,Y1068=P^1).
↪Grb2(SH2^1,SH3)|0.06
39: EGF(R^1).EGFR(CR1,L^1,Y1068=P^2).Grb2(SH2^2,SH3^3).Sos1(PxxP^3)+EGF(R^1).EGFR(CR1,
↪L^1,Y1068=P^2).Grb2(SH2^2,SH3^3).Sos1(PxxP^3)>EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).
↪EGFR(CR1^2,L^4,Y1068=P^5).EGF(R^4).Grb2(SH2^5,SH3^6).Sos1(PxxP^6).Grb2(SH2^3,SH3^7).
↪Sos1(PxxP^7)|2.76855e-06
40: EGF(R^1).EGFR(CR1,L^1,Y1068=P^2).Grb2(SH2^2,SH3)+EGF(R^1).EGFR(CR1,L^1,Y1068=P^2).
↪Grb2(SH2^2,SH3^3).Sos1(PxxP^3)>EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,
↪Y1068=P^5).EGF(R^4).Grb2(SH2^5,SH3).Grb2(SH2^3,SH3^6).Sos1(PxxP^6)|5.5371e-06
41: EGF(R^1).EGFR(CR1,L^1,Y1068=P)+EGF(R^1).EGFR(CR1,L^1,Y1068=P^2).Grb2(SH2^2,SH3^3).
↪Sos1(PxxP^3)>EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=P^4).EGF(R^3).
↪Grb2(SH2^4,SH3^5).Sos1(PxxP^5)|5.5371e-06
42: EGF(R^1).EGFR(CR1,L^1,Y1068=P^2).Grb2(SH2^2,SH3^3).Sos1(PxxP^3)+EGF(R^1).EGFR(CR1,
↪L^1,Y1068=U)>EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=U).EGF(R^4).
↪Grb2(SH2^3,SH3^5).Sos1(PxxP^5)|5.5371e-06
43: EGF(R^1).EGFR(CR1,L^1,Y1068=P^2).Grb2(SH2^2,SH3)+EGF(R^1).EGFR(CR1,L^1,Y1068=P^2).
↪Grb2(SH2^2,SH3)>EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=P^5).
↪EGF(R^4).Grb2(SH2^5,SH3).Grb2(SH2^3,SH3)|2.76855e-06
44: EGF(R^1).EGFR(CR1,L^1,Y1068=P)+EGF(R^1).EGFR(CR1,L^1,Y1068=P^2).Grb2(SH2^2,
↪SH3)>EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=P^4).EGF(R^3).Grb2(SH2^4,
↪SH3)|5.5371e-06
45: EGF(R^1).EGFR(CR1,L^1,Y1068=P^2).Grb2(SH2^2,SH3)+EGF(R^1).EGFR(CR1,L^1,
↪Y1068=U)>EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=U).EGF(R^4).
↪Grb2(SH2^3,SH3)|5.5371e-06
46: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=P^4).EGF(R^3).Grb2(SH2^4,
↪SH3^5).Sos1(PxxP^5)>EGF(R^1).EGFR(CR1,L^1,Y1068=P)+EGF(R^1).EGFR(CR1,L^1,Y1068=P^2).
↪Grb2(SH2^2,SH3^3).Sos1(PxxP^3)|0.1
47: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=P^4).EGF(R^3).Grb2(SH2^4,
↪SH3)>EGF(R^1).EGFR(CR1,L^1,Y1068=P)+EGF(R^1).EGFR(CR1,L^1,Y1068=P^2).Grb2(SH2^2,
↪SH3)|0.1
48: EGFR(CR1,L,Y1068=P)>EGFR(CR1,L,Y1068=U)|4.505
49: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=P^4).EGF(R^3).Grb2(SH2^4,
↪SH3^5).Sos1(PxxP^5)>EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=U).
↪EGF(R^4).Grb2(SH2^3,SH3^5).Sos1(PxxP^5)|4.505
50: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=P^4).EGF(R^3).Grb2(SH2^4,
↪SH3)>EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=U).EGF(R^4).Grb2(SH2^3,
↪SH3)|4.505
51: EGFR(CR1,L,Y1068=P)+Grb2(SH2,SH3^1).Sos1(PxxP^1)>EGFR(CR1,L,Y1068=P^1).Grb2(SH2^1,
↪SH3^2).Sos1(PxxP^2)|8.30565e-07
52: EGFR(CR1,L,Y1068=P)+Grb2(SH2,SH3)>EGFR(CR1,L,Y1068=P^1).Grb2(SH2^1,SH3)|8.
↪30565e-07
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53: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=P^4).EGF(R^3).Grb2(SH2^4,
↪SH3^5).Sos1(PxxP^5)+Grb2(SH2,SH3^1).Sos1(PxxP^1)>EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).
↪EGFR(CR1^2,L^4,Y1068=P^5).EGF(R^4).Grb2(SH2^5,SH3^6).Sos1(PxxP^6).Grb2(SH2^3,SH3^7).
↪Sos1(PxxP^7)|8.30565e-07
54: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=P^4).EGF(R^3).Grb2(SH2^4,
↪SH3^5).Sos1(PxxP^5)+Grb2(SH2,SH3)>EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,
↪Y1068=P^5).EGF(R^4).Grb2(SH2^5,SH3).Grb2(SH2^3,SH3^6).Sos1(PxxP^6)|8.30565e-07
55: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=P^4).EGF(R^3).Grb2(SH2^4,
↪SH3)+Grb2(SH2,SH3^1).Sos1(PxxP^1)>EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,
↪Y1068=P^5).EGF(R^4).Grb2(SH2^5,SH3).Grb2(SH2^3,SH3^6).Sos1(PxxP^6)|8.30565e-07
56: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=P^4).EGF(R^3).Grb2(SH2^4,
↪SH3)+Grb2(SH2,SH3)>EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=P^5).
↪EGF(R^4).Grb2(SH2^5,SH3).Grb2(SH2^3,SH3)|8.30565e-07
57: EGF(R^1).EGFR(CR1,L^1,Y1068=P^2).Grb2(SH2^2,SH3^3).Sos1(PxxP^3)>EGF(R^1).EGFR(CR1,
↪L^1,Y1068=P)+Grb2(SH2,SH3^1).Sos1(PxxP^1)|0.05
58: EGF(R^1).EGFR(CR1,L^1,Y1068=P^2).Grb2(SH2^2,SH3)>EGF(R^1).EGFR(CR1,L^1,
↪Y1068=P)+Grb2(SH2,SH3)|0.05
59: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=P^4).EGF(R^3).Grb2(SH2^4,
↪SH3^5).Sos1(PxxP^5)>EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=P).
↪EGF(R^3)+Grb2(SH2,SH3^1).Sos1(PxxP^1)|0.05
60: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=P^4).EGF(R^3).Grb2(SH2^4,
↪SH3)>EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=P).EGF(R^3)+Grb2(SH2,
↪SH3)|0.05
61: EGF(R^1).EGFR(CR1,L^1,Y1068=P^2).Grb2(SH2^2,SH3)+Sos1(PxxP)>EGF(R^1).EGFR(CR1,L^1,
↪Y1068=P^2).Grb2(SH2^2,SH3^3).Sos1(PxxP^3)|5.5371e-06
62: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=P^4).EGF(R^3).Grb2(SH2^4,
↪SH3)+Sos1(PxxP)>EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=P^4).EGF(R^3).
↪Grb2(SH2^4,SH3^5).Sos1(PxxP^5)|5.5371e-06
63: EGF(R^1).EGFR(CR1,L^1,Y1068=P^2).Grb2(SH2^2,SH3^3).Sos1(PxxP^3)>EGF(R^1).EGFR(CR1,
↪L^1,Y1068=P^2).Grb2(SH2^2,SH3)+Sos1(PxxP)|0.06
64: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=P^4).EGF(R^3).Grb2(SH2^4,
↪SH3^5).Sos1(PxxP^5)>EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=P^4).
↪EGF(R^3).Grb2(SH2^4,SH3)+Sos1(PxxP)|0.06
65: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=P^4).EGF(R^3).Grb2(SH2^4,
↪SH3^5).Sos1(PxxP^5)>|0.01
66: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=P^4).EGF(R^3).Grb2(SH2^4,
↪SH3)>|0.01
67: EGF(R)+EGFR(CR1,L,Y1068=P^1).Grb2(SH2^1,SH3^2).Sos1(PxxP^2)>EGF(R^1).EGFR(CR1,L^1,
↪Y1068=P^2).Grb2(SH2^2,SH3^3).Sos1(PxxP^3)|1.49502e-06
68: EGF(R)+EGFR(CR1,L,Y1068=P^1).Grb2(SH2^1,SH3)>EGF(R^1).EGFR(CR1,L^1,Y1068=P^2).
↪Grb2(SH2^2,SH3)|1.49502e-06
69: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=P^5).EGF(R^4).Grb2(SH2^5,
↪SH3^6).Sos1(PxxP^6).Grb2(SH2^3,SH3^7).Sos1(PxxP^7)>EGF(R^1).EGFR(CR1,L^1,Y1068=P^2).
↪Grb2(SH2^2,SH3^3).Sos1(PxxP^3)+EGF(R^1).EGFR(CR1,L^1,Y1068=P^2).Grb2(SH2^2,SH3^3).
↪Sos1(PxxP^3)|0.1
70: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=P^5).EGF(R^4).Grb2(SH2^5,
↪SH3).Grb2(SH2^3,SH3^6).Sos1(PxxP^6)>EGF(R^1).EGFR(CR1,L^1,Y1068=P^2).Grb2(SH2^2,
↪SH3)+EGF(R^1).EGFR(CR1,L^1,Y1068=P^2).Grb2(SH2^2,SH3^3).Sos1(PxxP^3)|0.1
71: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=P^5).EGF(R^4).Grb2(SH2^5,
↪SH3).Grb2(SH2^3,SH3)>EGF(R^1).EGFR(CR1,L^1,Y1068=P^2).Grb2(SH2^2,SH3)+EGF(R^1).
↪EGFR(CR1,L^1,Y1068=P^2).Grb2(SH2^2,SH3)|0.1
72: EGFR(CR1,L,Y1068=P^1).Grb2(SH2^1,SH3^2).Sos1(PxxP^2)>EGFR(CR1,L,Y1068=P)+Grb2(SH2,
↪SH3^1).Sos1(PxxP^1)|0.05
73: EGFR(CR1,L,Y1068=P^1).Grb2(SH2^1,SH3)>EGFR(CR1,L,Y1068=P)+Grb2(SH2,SH3)|0.05
74: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=P^5).EGF(R^4).Grb2(SH2^5,
↪SH3^6).Sos1(PxxP^6).Grb2(SH2^3,SH3^7).Sos1(PxxP^7)>EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).
↪EGFR(CR1^2,L^3,Y1068=P^4).EGF(R^3).Grb2(SH2^4,SH3^5).Sos1(PxxP^5)+Grb2(SH2,SH3^1).
↪Sos1(PxxP^1)|0.1
```

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```
75: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=P^5).EGF(R^4).Grb2(SH2^5,
↪SH3).Grb2(SH2^3,SH3^6).Sos1(PxxP^6)>EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,
↪Y1068=P^4).EGF(R^3).Grb2(SH2^4,SH3)+Grb2(SH2,SH3^1).Sos1(PxxP^1)|0.05
76: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=P^5).EGF(R^4).Grb2(SH2^5,
↪SH3).Grb2(SH2^3,SH3^6).Sos1(PxxP^6)>EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,
↪Y1068=P^4).EGF(R^3).Grb2(SH2^4,SH3^5).Sos1(PxxP^5)+Grb2(SH2,SH3)|0.05
77: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=P^5).EGF(R^4).Grb2(SH2^5,
↪SH3).Grb2(SH2^3,SH3)>EGF(R^1).EGFR(CR1^2,L^1,Y1068=P).EGFR(CR1^2,L^3,Y1068=P^4).
↪EGF(R^3).Grb2(SH2^4,SH3)+Grb2(SH2,SH3)|0.1
78: EGFR(CR1,L,Y1068=P^1).Grb2(SH2^1,SH3)+Sos1(PxxP)>EGFR(CR1,L,Y1068=P^1).Grb2(SH2^1,
↪SH3^2).Sos1(PxxP^2)|5.5371e-06
79: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=P^5).EGF(R^4).Grb2(SH2^5,
↪SH3).Grb2(SH2^3,SH3^6).Sos1(PxxP^6)+Sos1(PxxP)>EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).
↪EGFR(CR1^2,L^4,Y1068=P^5).EGF(R^4).Grb2(SH2^5,SH3^6).Sos1(PxxP^6).Grb2(SH2^3,SH3^7).
↪Sos1(PxxP^7)|5.5371e-06
80: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=P^5).EGF(R^4).Grb2(SH2^5,
↪SH3).Grb2(SH2^3,SH3)+Sos1(PxxP)>EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,
↪Y1068=P^5).EGF(R^4).Grb2(SH2^5,SH3).Grb2(SH2^3,SH3^6).Sos1(PxxP^6)|1.10742e-05
81: EGFR(CR1,L,Y1068=P^1).Grb2(SH2^1,SH3^2).Sos1(PxxP^2)>EGFR(CR1,L,Y1068=P^1).
↪Grb2(SH2^1,SH3)+Sos1(PxxP)|0.06
82: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=P^5).EGF(R^4).Grb2(SH2^5,
↪SH3^6).Sos1(PxxP^6).Grb2(SH2^3,SH3^7).Sos1(PxxP^7)>EGF(R^1).EGFR(CR1^2,L^1,
↪Y1068=P^3).EGFR(CR1^2,L^4,Y1068=P^5).EGF(R^4).Grb2(SH2^5,SH3).Grb2(SH2^3,SH3^6).
↪Sos1(PxxP^6)+Sos1(PxxP)|0.12
83: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=P^5).EGF(R^4).Grb2(SH2^5,
↪SH3).Grb2(SH2^3,SH3^6).Sos1(PxxP^6)>EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,
↪L^4,Y1068=P^5).EGF(R^4).Grb2(SH2^5,SH3).Grb2(SH2^3,SH3)+Sos1(PxxP)|0.06
84: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=P^5).EGF(R^4).Grb2(SH2^5,
↪SH3^6).Sos1(PxxP^6).Grb2(SH2^3,SH3^7).Sos1(PxxP^7)>|0.01
85: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=P^5).EGF(R^4).Grb2(SH2^5,
↪SH3).Grb2(SH2^3,SH3^6).Sos1(PxxP^6)>|0.01
86: EGF(R^1).EGFR(CR1^2,L^1,Y1068=P^3).EGFR(CR1^2,L^4,Y1068=P^5).EGF(R^4).Grb2(SH2^5,
↪SH3).Grb2(SH2^3,SH3)>|0.01
```

[7]:
```
species_list = ["EGFR",
                "EGF(R)",
                "EGFR(CR1^_)",
                "EGFR(Y1068=P^_0)",
                "Grb2(SH2, SH3^1).Sos1(PxxP^1)",
                "EGFR(Y1068^1).Grb2(SH2^1, SH3^2).Sos1(PxxP^2)"]
run_simulation(120, model=newm, y0=y0, species_list=species_list,
               opt_kwargs={'interactive': True, 'to_png': True})
```

```
<IPython.core.display.HTML object>
```

2.5 A Simple Model of the Glycolysis of Human Erythrocytes

This is a model for the glycolysis of human erythrocytes which takes into account ATP-synthesis and -consumption. This model is based on the model introduced in the following publication.

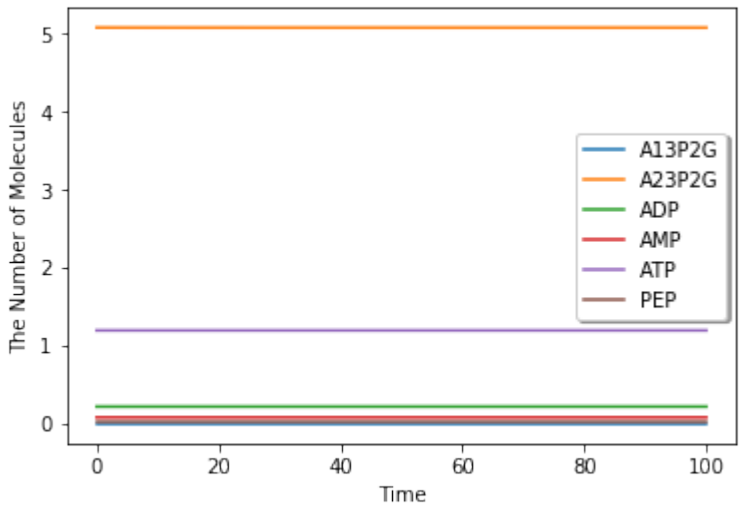
- Rapoport, T.A. and Heinrich, R. (1975) "Mathematical analysis of multienzyme systems. I. Modelling of the glycolysis of human erythrocytes.", Biosystems., 7, 1, 120-129.
- Heinrich, R. and Rapoport, T.A. (1975) "Mathematical analysis of multienzyme systems. II. Steady state and transient control.", Biosystems., 7, 1, 130-136.

[1]:
```
%matplotlib inline
from ecell4 import *
```

[2]:
```
with reaction_rules():
    2 * ATP > 2 * A13P2G + 2 * ADP | (3.2 * ATP / (1.0 + (ATP / 1.0) ** 4.0))
    A13P2G > A23P2G | 1500
    A23P2G > PEP | 0.15
    A13P2G + ADP > PEP + ATP | 1.57e+4
    PEP + ADP > ATP | 559
    AMP + ATP > 2 * ADP | (1.0 * (AMP * ATP - 2.0 * ADP * ADP))
    ATP > ADP | 1.46
```

[3]:
```
y0 = {"A13P2G": 0.0005082, "A23P2G": 5.0834, "PEP": 0.020502,
      "AMP": 0.080139, "ADP": 0.2190, "ATP": 1.196867}
```

[4]:
```
run_simulation(100, y0=y0)
```



2.6 Hodgkin-Huxley Model

- A.L. Hodgkin, A.F. Huxley, "A quantitative description of membrane current and its application to conduction and excitation in nerve", J. Physiol., 117, 500-544, 1952.

[1]:
```
%matplotlib inline
import numpy as np
from ecell4 import *
```

[2]:
```
Q10 = 3.0
GNa = 120.0 # mS/cm^2
GK = 36.0 # mS/cm^2
gL = 0.3 # mS/cm^2
EL = -64.387 # mV
ENa = 40.0 # mV
EK = -87.0 # mV
Cm = 1.0 # uF/cm^2
```

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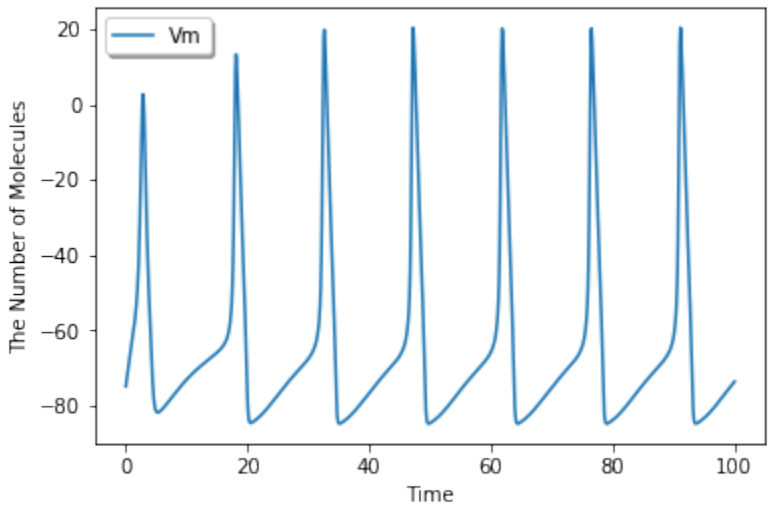
```
T = 6.3 # degrees C
Iext = 10.0 # nA

with reaction_rules():
    Q = Q10 ** ((T - 6.3) / 10)

    alpha_m = -0.1 * (Vm + 50) / (exp(-(Vm + 50) / 10) - 1)
    beta_m = 4 * exp(-(Vm + 75) / 18)
    ~m > m | Q * (alpha_m * (1 - m) - beta_m * m)

    alpha_h = 0.07 * exp(-(Vm + 75) / 20)
    beta_h = 1.0 / (exp(-(Vm + 45) / 10) + 1)
    ~h > h | Q * (alpha_h * (1 - h) - beta_h * h)

    alpha_n = -0.01 * (Vm + 65) / (exp(-(Vm + 65) / 10) - 1)
    beta_n = 0.125 * exp(-(Vm + 75) / 80)
    ~n > n | Q * (alpha_n * (1 - n) - beta_n * n)

    gNa = (m ** 3) * h * GNa
    INa = gNa * (Vm - ENa)
    gK = (n ** 4) * GK
    IK = gK * (Vm - EK)
    IL = gL * (Vm - EL)
    ~Vm > Vm | (Iext - (IL + INa + IK)) / Cm

hhm = get_model()
```

[3]:
```
for rr in hhm.reaction_rules():
    print(rr.as_string())
```

```
1*Vm>1*m+1*Vm|0
1*Vm>1*h+1*Vm|0
1*Vm>1*n+1*Vm|0
1*m+1*h+1*n>1*Vm+1*m+1*h+1*n|0
```

[4]:
```
run_simulation(np.linspace(0, 100, 1001), model=hhm, y0={'Vm': -75}, species_list=['Vm
↪'])
```



2.7 FitzHugh–Nagumo Model

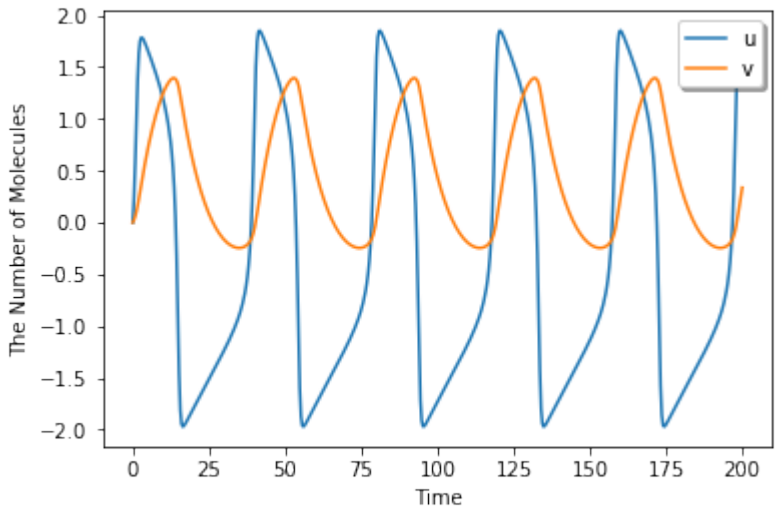
- R. FitzHugh, "Mathematical models of threshold phenomena in the nerve membrane.", Bull. Math. Biophysics, 17:257—278, 1955.

[5]:
```
a = 0.7
b = 0.8
c = 12.5
Iext = 0.5

with reaction_rules():
    ~u > u | -v + u - (u ** 3) / 3 + Iext
    ~v > v | (u - b * v + a) / c

fnm = get_model()
```

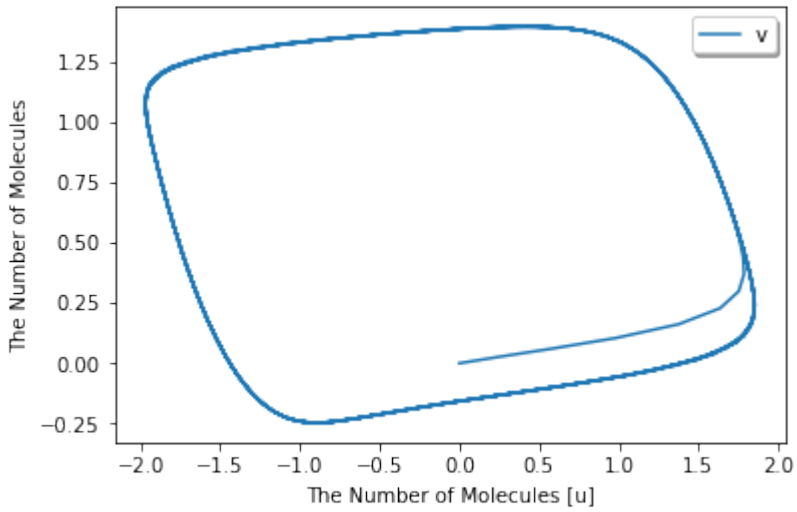
[6]:
```
for rr in fnm.reaction_rules():
    print(rr.as_string())
```

```
1*v>1*u+1*v|0
1*u>1*v+1*u|0
```

[7]:
```
run_simulation(np.linspace(0, 200, 501), model=fnm)
```



[8]:
```
run_simulation(np.linspace(0, 200, 501), model=fnm, # return_type='nyaplot',
               opt_kwargs={'x': 'u', 'y': ['v']})
```



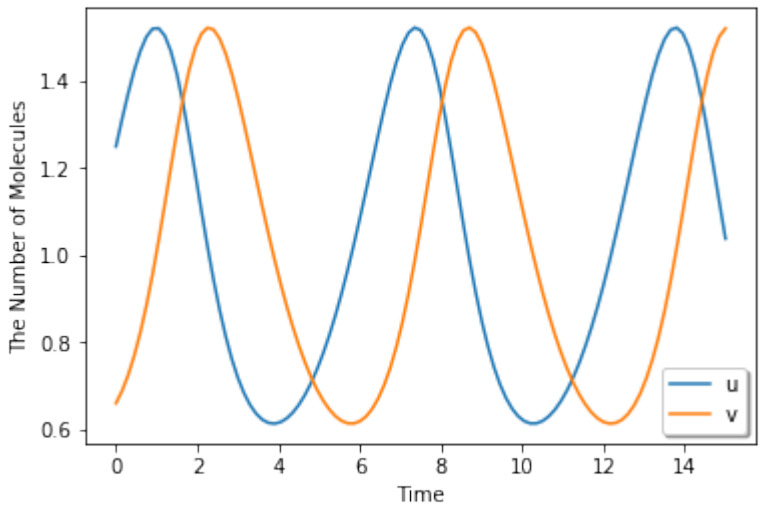
2.8 Lotka-Volterra 2D

2.8.1 The Original Model in Ordinary Differential Equations

[1]:
```
%matplotlib inline
from ecell4 import *
```

[2]:
```
alpha = 1

with reaction_rules():
    ~u > u | u * (1 - v)
    ~v > v | alpha * v * (u - 1)

m = get_model()
```

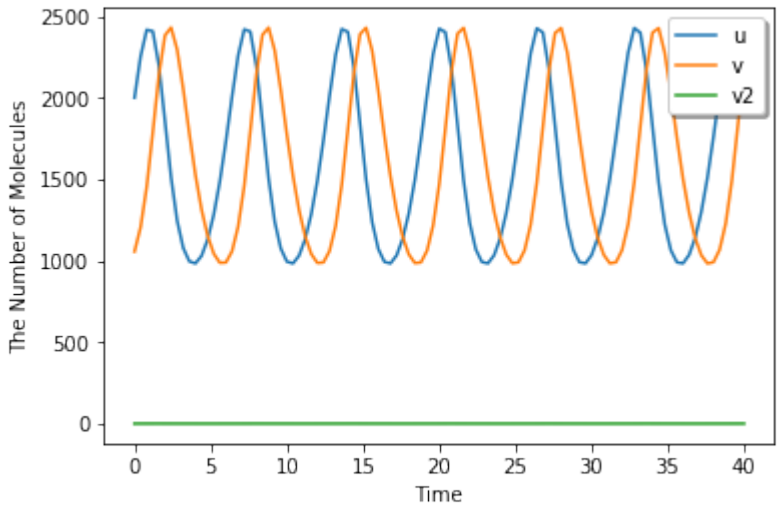
[3]:
```
run_simulation(15, {'u': 1.25, 'v': 0.66}, model=m)
```



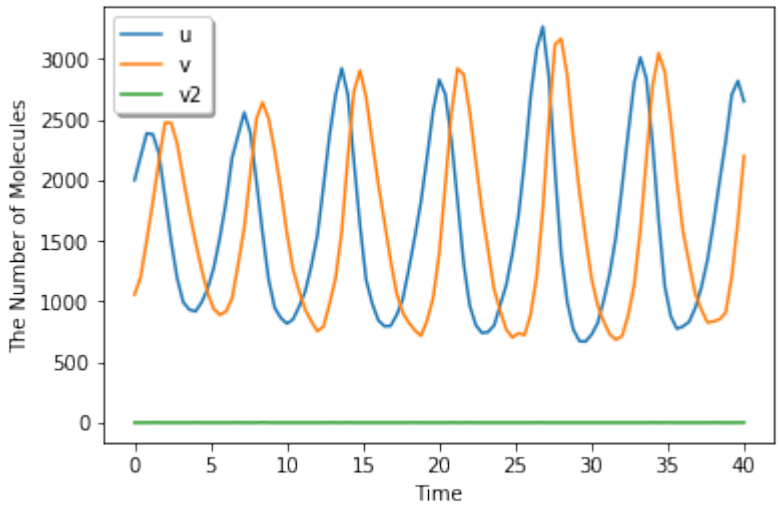
2.8.2 The Modified Model Decomposed into Elementary Reactions

[4]:
```
alpha = 1

with species_attributes():
    u | {'D': 0.1}
    v | {'D': 0.1}

with reaction_rules():
    u > u + u | 1.0
    u + v > v | 1.0

    u + v > u + v2 | alpha
    v2 > v + v | alpha * 10000.0
    v > ~v | alpha

m = get_model()
```

[5]:
```
run_simulation(40, {'u': 1.25 * 1600, 'v': 0.66 * 1600}, volume=1600, model=m)
```

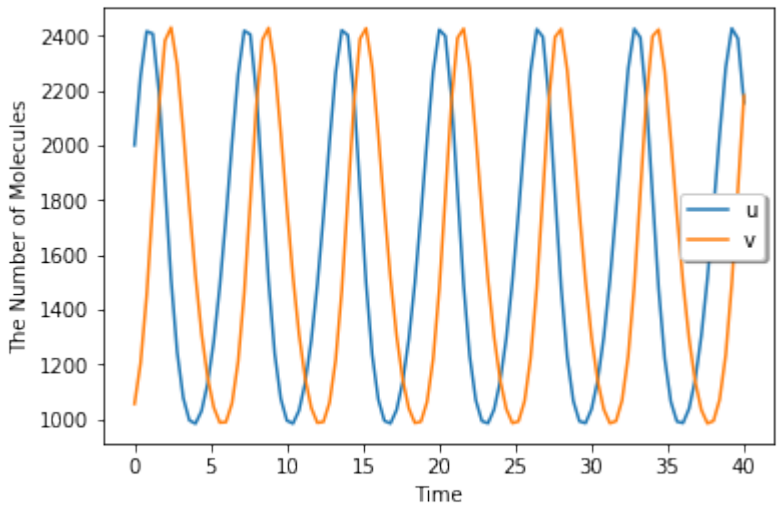


[6]:
```
run_simulation(40, {'u': 1.25 * 1600, 'v': 0.66 * 1600}, volume=1600, model=m, solver=
↪'gillespie')
```

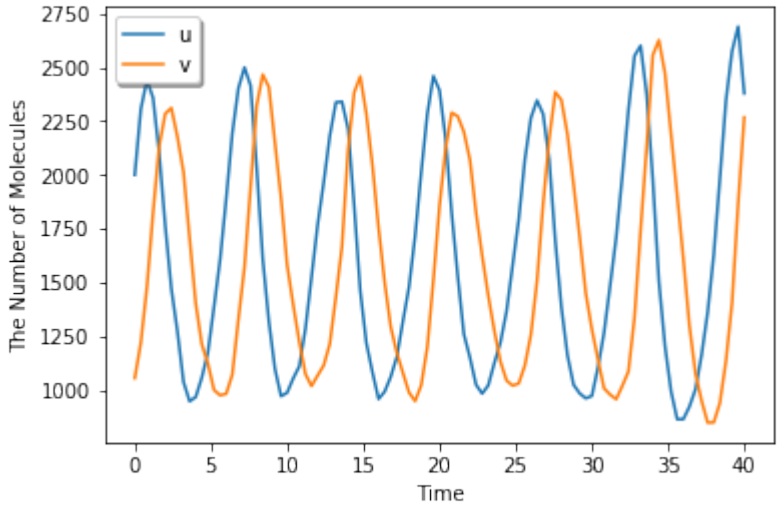


[7]:
```
alpha = 1

with species_attributes():
    u | v | {'D': 0.1}

with reaction_rules():
    u > u + u | 1.0
    u + v > v | 1.0
    u + v > u + v + v | alpha
    v > ~v | alpha

m = get_model()
```

[8]:
```
run_simulation(40, {'u': 1.25 * 1600, 'v': 0.66 * 1600}, volume=1600, model=m)
```



[9]:
```
run_simulation(40, {'u': 1.25 * 1600, 'v': 0.66 * 1600}, volume=1600, model=m, solver=
↪'gillespie')
```



2.8.3 A Lotka-Volterra-like Model in 2D

[10]:
```
from ecell4_base.core import *
from ecell4_base import meso
```

[11]:
```
rng = GSLRandomNumberGenerator()
rng.seed(0)
```

[12]:
```
w = meso.World(Real3(40, 40, 1), Integer3(160, 160, 1), rng)
w.bind_to(m)
```

[13]:
```
V = w.volume()
print(V)
```

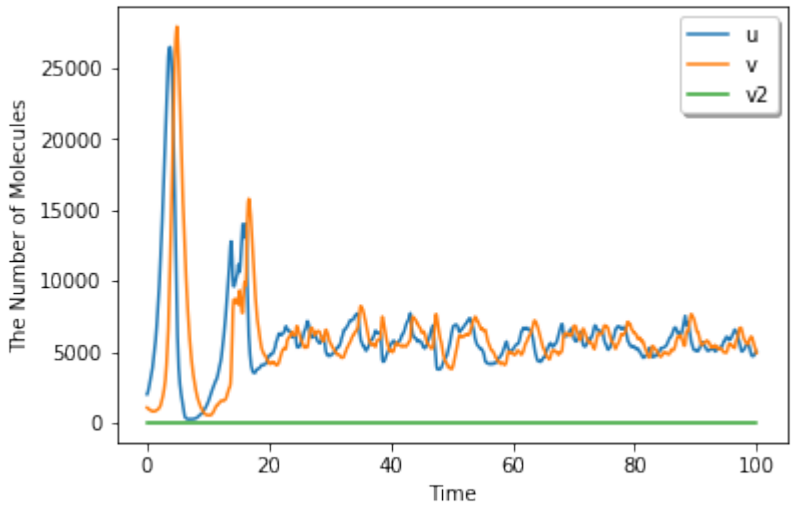
```
1600.0
```

[14]:
```
w.add_molecules(Species("u"), int(1.25 * V))
w.add_molecules(Species("v"), int(0.66 * V))
```

[15]:
```
sim = meso.Simulator(w)
obs1 = FixedIntervalNumberObserver(0.1, ('u', 'v', 'v2'))
obs2 = FixedIntervalHDF5Observer(2, "test%03d.h5")
```

[16]:
```
sim.run(100, (obs1, obs2))
```

[17]:
```
viz.plot_number_observer(obs1)
```



[18]:
```
viz.plot_world(w, radius=0.2)
```

```
<IPython.core.display.HTML object>
```

[19]:
```
viz.plot_movie_with_attractive_mpl(
    obs2, linewidth=0, noaxis=True, figsize=6, whratio=1.4,
    angle=(-90, 90, 6), bitrate='10M')
```

```
<IPython.core.display.HTML object>
```

[20]:
```
# from zipfile import ZipFile
# with ZipFile('test.zip', 'w') as myzip:
#     for i in range(obs2.num_steps()):
#         myzip.write('test{:03d}.h5'.format(i))
```

2.9 MinDE System with Mesoscopic Simulator

Fange D, Elf J (2006) Noise-Induced Min Phenotypes in E. coli. PLoS Comput Biol 2(6): e80. doi:10.1371/journal.pcbi.0020080

[1]:
```
%matplotlib inline
from ecell4 import *
from ecell4_base.core import *
from ecell4_base import meso
```

Declaring `Species` and `ReactionRules`:

[2]:
```
with species_attributes():
    D | DE | {"D": 0.01, "location": "M"}
    D_ADP | D_ATP | E | {"D": 2.5, "location": "C"}

with reaction_rules():
    D_ATP + M > D | 0.0125
    D_ATP + D > D + D | 9e+6 * (1e+15 / N_A)
    D + E > DE | 5.58e+7 * (1e+15 / N_A)
```

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```
    DE > D_ADP + E | 0.7
    D_ADP > D_ATP | 0.5

m = get_model()
```

Make a `World`. The second argument, `0.05`, means its subvolume length:

[3]:
```
w = meso.World(Real3(4.6, 1.1, 1.1), 0.05)
w.bind_to(m)
```

Make a structures. `Species` `C` is for cytoplasm, and `M` is for membrane:

[4]:
```
rod = Rod(3.5, 0.55, w.edge_lengths() * 0.5)
w.add_structure(Species("C"), rod)
w.add_structure(Species("M"), rod.surface())
```

Throw-in molecules:

[5]:
```
w.add_molecules(Species("D_ATP"), 2001)
w.add_molecules(Species("D_ADP"), 2001)
w.add_molecules(Species("E"), 1040)
```

Run a simulation for 120 seconds. Two `Observers` below are for logging. `obs1` logs only the number of molecules, and `obs2` does a whole state of the `World`.

[6]:
```
sim = meso.Simulator(w)
obs1 = FixedIntervalNumberObserver(0.1, [sp.serial() for sp in m.list_species()])
obs2 = FixedIntervalHDF5Observer(1.0, 'minde%03d.h5')
```

[7]:
```
from ecell4.util.progressbar import progressbar_notebook
```

[8]:
```
duration = 120
progressbar_notebook(sim).run(duration, (obs1, obs2))
```

```
HBox(children=(FloatProgress(value=0.0), HTML(value='')))
```

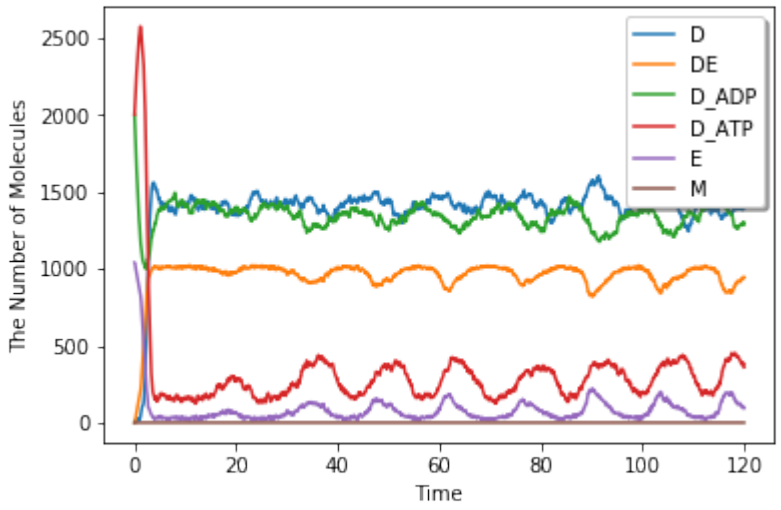
Visualize the final state of the `World`:

[9]:
```
viz.plot_world(w, radius=0.01, species_list=('D', 'DE'))
```

```
<IPython.core.display.HTML object>
```

Plot a time course of the number of molecules:

[10]:
```
show(obs1)
```



[11]:
```
viz.plot_movie_with_matplotlib(obs2, species_list=('D', 'DE'))
```

```
<IPython.core.display.HTML object>
```

2.10 MinDE System with Spatiocyte Simulator

[1]:
```
%matplotlib inline
from ecell4 import *
from ecell4_base.core import *
from ecell4_base import spatiocyte
```

Declaring Species and ReactionRules:

[2]:
```
with species_attributes():
    cytoplasm | {'radius': 1e-8, 'D': 0, 'dimension': 3}
    MinDatp | MinDadp | {'radius': 1e-8, 'D': 16e-12, 'location': 'cytoplasm',
↪'dimension': 3}
    MinEE_C | {'radius': 1e-8, 'D': 10e-12, 'location': 'cytoplasm', 'dimension': 3}
    membrane | {'radius': 1e-8, 'D': 0, 'location': 'cytoplasm', 'dimension': 2}
    MinD | MinEE_M | MinDEE | MinDEED | {'radius': 1e-8, 'D': 0.02e-12, 'location':
↪'membrane', 'dimension': 2}

with reaction_rules():
    membrane + MinDatp > MinD | 2.2e-8
    MinD + MinDatp > MinD + MinD | 3e-20
    MinD + MinEE_C > MinDEE | 5e-19
    MinDEE > MinEE_M + MinDadp | 1
    MinDadp > MinDatp | 5
    MinDEE + MinD > MinDEED | 5e-15
    MinDEED > MinDEE + MinDadp | 1
    MinEE_M > MinEE_C | 0.83

m = get_model()
```

Make a World.

[3]:
```
f = spatiocyte.Factory(1e-8)
w = f.world(Real3(4.6e-6, 1.1e-6, 1.1e-6))
w.bind_to(m)
```

Make a Structures.

[4]:
```
rod = Rod(3.5e-6, 0.51e-6, w.edge_lengths() * 0.5)
w.add_structure(Species('cytoplasm'), rod)
w.add_structure(Species('membrane'), rod.surface())
```

[4]:
```
47496
```

Throw-in molecules.

[5]:
```
w.add_molecules(Species('MinDadp'), 1300)
w.add_molecules(Species('MinDEE'), 700)
```

Run a simulation for 240 seconds.

[6]:
```
sim = f.simulator(w, m)
```

[7]:
```
# from functools import reduce
# alpha = reduce(lambda x, y: min(x, sim.calculate_alpha(y)), m.reaction_rules())
# sim.set_alpha(alpha)
```

[8]:
```
from ecell4.util.progressbar import progressbar_notebook
```

[9]:
```
obs1 = FixedIntervalNumberObserver(0.1, ('MinDatp', 'MinDadp', 'MinEE_C', 'MinD',
↪'MinEE_M', 'MinDEE', 'MinDEED'))
```

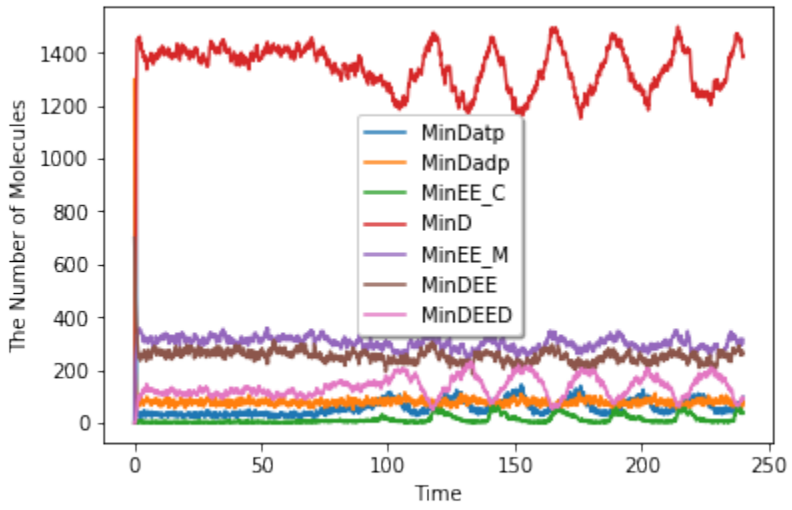
[10]:
```
obs2 = FixedIntervalHDF5Observer(1.0, "minde%03d.h5")
```

[11]:
```
duration = 240
```

[12]:
```
progressbar_notebook(sim).run(duration, (obs1, obs2))
```

```
HBox(children=(FloatProgress(value=0.0), HTML(value='')))
```

[13]:
```
show(obs1)
```



[14]:
```
viz.plot_movie_with_matplotlib([spatiocyte.SpatiocyteWorld("minde%03d.h5" % i) for i␣
↪in range(obs2.num_steps())], species_list=('MinD', 'MinEE_M', 'MinDEE', 'MinDEED'))
```

```
<IPython.core.display.HTML object>
```

[15]:
```
viz.plot_world(spatiocyte.SpatiocyteWorld("minde240.h5"), species_list=('MinD',
↪'MinEE_M', 'MinDEE', 'MinDEED'))
```

```
<IPython.core.display.HTML object>
```

2.11 Simple Equilibrium

This is a simple equilibrium model as an example. Here, we explain how to model and run a simulation without using decorators (`species_attributes` and `reaction_rules`) and `run_simulation` method.

[1]:
```
%matplotlib inline
from ecell4 import *
from ecell4_base.core import *
from ecell4_base import *
```

Choose one module from a list of methods supported on E-Cell4.

[2]:
```
# f = gillespie.Factory
# f = ode.Factory()
# f = spatiocyte.Factory()
# f = bd.Factory()
# f = meso.Factory()
f = egfrd.Factory()
```

Set up parameters:

[3]:
```
L, N, kd, U, D, radius = 1.0, 60, 0.1, 0.5, 1.0, 0.01
volume = L * L * L
ka = kd * volume * (1 - U) / (U * U * N)
```

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```
sp1, sp2, sp3 = Species("A", radius, D), Species("B", radius, D), Species("A_B",␣
↪radius, D)
rr1, rr2 = create_binding_reaction_rule(sp1, sp2, sp3, ka), create_unbinding_reaction_
↪rule(sp3, sp1, sp2, kd)
```

Create a model:

[4]:
```
m = NetworkModel()
m.add_species_attribute(sp1)
m.add_species_attribute(sp2)
m.add_species_attribute(sp3)
m.add_reaction_rule(rr1)
m.add_reaction_rule(rr2)
```

Create a world and simulator:

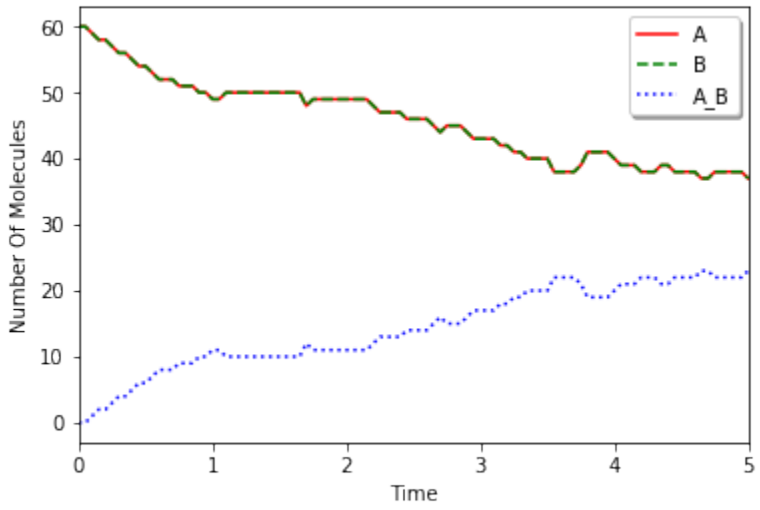
[5]:
```
w = f.world(Real3(L, L, L))
w.bind_to(m)
w.add_molecules(Species("A"), N)
w.add_molecules(Species("B"), N)

sim = f.simulator(w)
sim.set_dt(1e-3) #XXX: This is too large to get the accurate result with BDSimulator.
```

Run a simulation:

[6]:
```
next_time, dt = 0.0, 0.05
data = [(w.t(), w.num_molecules(sp1), w.num_molecules(sp2), w.num_molecules(sp3))]
for i in range(100):
    next_time += dt
    while (sim.step(next_time)): pass
    data.append((w.t(), w.num_molecules(sp1), w.num_molecules(sp2), w.num_
↪molecules(sp3)))
```

Plot with Matplotlib:

[7]:
```
import matplotlib.pylab as plt
from numpy import array

data = array(data)
plt.plot(data.T[0], data.T[1], "r-", label=sp1.serial())
plt.plot(data.T[0], data.T[2], "g--", label=sp2.serial())
plt.plot(data.T[0], data.T[3], "b:", label=sp3.serial())
plt.xlabel("Time")
plt.ylabel("Number Of Molecules")
plt.xlim(data.T[0][0], data.T[0][-1])
plt.legend(loc="best", shadow=True)
plt.show()
```



See also Reversible and Reversible (Diffusion-limited) in the Tests section for more detailed comparisons between methods.

2.12 Tyson1991

This model is described in the article:

- J.J. Tyson, "Modeling the cell division cycle: cdc2 and cyclin interactions.", Proc. Natl. Acad. Sci. U.S.A., 88(16), 7328-32, 1991.

Abstract: The proteins cdc2 and cyclin form a heterodimer (maturation promoting factor) that controls the major events of the cell cycle. A mathematical model for the interactions of cdc2 and cyclin is constructed. Simulation and analysis of the model show that the control system can operate in three modes: as a steady state with high maturation promoting factor activity, as a spontaneous oscillator, or as an excitable switch. We associate the steady state with metaphase arrest in unfertilized eggs, the spontaneous oscillations with rapid division cycles in early embryos, and the excitable switch with growth-controlled division cycles typical of nonembryonic cells.

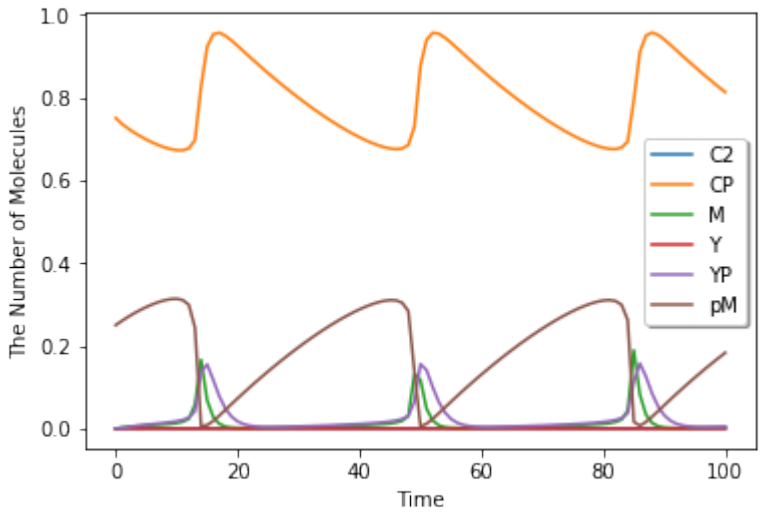
[1]:
```
%matplotlib inline
from ecell4 import *
```

[2]:
```
with reaction_rules():
    YT = Y + YP + M + pM
    CT = C2 + CP + M + pM

    ~Y > Y | 0.015 / CT
    Y > ~Y | 0.0 * Y
    CP + Y > pM | 200.0 * CP * Y / CT
    pM > M | pM * (0.018 + 180 * ((M / CT) ** 2))
    M > pM | 0.0 * M
    M > C2 + YP | 1.0 * M
    YP > ~YP | 0.6 * YP
    C2 > CP | 1000000.0 * C2
    CP > C2 | 1000.0 * CP

m = get_model()
```

[3]:
```
for rr in m.reaction_rules():
    print(rr.as_string(), rr.get_descriptor().as_string())
```

```
1*C2+1*CP+1*M+1*pM>1*Y+1*C2+1*CP+1*M+1*pM|0 (0.015/(C2+CP+M+pM))
1*Y>|0 (0.0*Y)
1*CP+1*Y+1*C2+1*M>1*pM+1*C2+1*M|0 ((200.0*CP*Y)/(C2+CP+M+pM))
1*pM+1*C2+1*CP>1*M+1*C2+1*CP|0 (pM*(0.018+(180*pow((M/(C2+CP+M+pM)),2))))
1*M>1*pM|0 (0.0*M)
1*M>1*C2+1*YP|0 (1.0*M)
1*YP>|0 (0.6*YP)
1*C2>1*CP|0 (1000000.0*C2)
1*CP>1*C2|0 (1000.0*CP)
```

[4]:
```
run_simulation(100.0, model=m, y0={'CP': 0.75, 'pM': 0.25})
```



CHAPTER 3

API