

# The Bio-PEPA Tool Suite

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# Introduction

Bio-PEPA is a timed process algebra designed specifically for the description of biological phenomena and their analysis through quantitative methods such as stochastic simulation and probabilistic model-checking.

# Context

The context of application we consider is that of biochemical networks.

- ▶ A biochemical network is composed of  $N$  species which interact through  $M$  reactions;
- ▶ the dynamics of reaction  $j$  is described by a kinetic law.
- ▶ The quantitative behaviour of a biochemical network depends on the initial values of the involved species and on the kinetic parameters.

# The Bio-PEPA language

## Sequential component (species component)

$$S ::= (\alpha, \kappa) \text{ op } S \mid S + S \mid C \quad \text{where op} = \downarrow \mid \uparrow \mid \oplus \mid \ominus \mid \odot$$

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$$P ::= P \underset{\mathcal{L}}{\boxtimes} P \mid S(I)$$

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The parameter  $I$  is abstract, recording quantitative information about the species.

Depending on the interpretation, this quantity may be:

- ▶ number of molecules (SSA),
- ▶ concentration (ODE) or
- ▶ a level within a semi-quantitative model (CTMC).

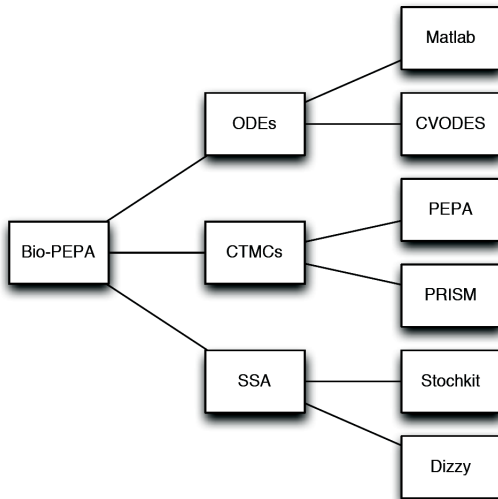
# Software Tools

Two software tools are available for modelling with Bio-PEPA,

- ▶ the Bio-PEPA Workbench, and
- ▶ the Bio-PEPA Eclipse Plugin.

Both modelling tools allow the user to analyse their model both in the discrete stochastic regime and in the deterministic continuous regime while maintaining only a single source in the Bio-PEPA language.

# The Bio-PEPA Workbench



# Stochastic simulation

With respect to stochastic simulation, the Bio-PEPA Workbench generates the kinetic laws and propensity function descriptions which are needed to perform an analysis of the model via stochastic simulation using Gillespie's Stochastic Simulation Algorithm (SSA) and other stochastic simulation algorithms such as Gibson-Bruck.



## Model-checking

As an alternative to simulation, the Bio-PEPA Workbench can also generate a CTMC model in the format accepted by the PRISM model-checker together with a reward structure and typical formulae of CSL logic which can be checked against the PRISM model.

Each species component gives rise to one PRISM module.

Custom rate expressions are generated to ensure that the generated PRISM model correctly reflects the dynamic behaviour of the input Bio-PEPA model.

## Continuous simulation

For continuous simulation, the Bio-PEPA Workbench generates the reaction rate equations in the form of a system of coupled ODEs.

The system variables of the ODEs allow us to determine the quantity of each chemical species in the reaction at any point up to a finite time horizon, and in the long run.

# The Bio-PEPA Eclipse Plug-in

The Bio-PEPA Eclipse Plug-in is a rich modelling environment for Bio-PEPA which aims to provide strong support for investigating the average case dynamic behaviour of systems.

Users can compare stochastic ensembles of independent simulation runs with the mean trajectory obtained by generating the differential equation model and numerically integrating this.

# The Bio-PEPA Eclipse Plugin

PEPA - Bio-PEPA modelling/mass-action.biopepa - Eclipse SDK

File Edit Navigate Search Project Bio-PEPA Run Window Help

Time Series Analysis

PEPA Java

mass-action.biopepa

```

species X: H=100, N=2, MO = 20, M=20;
species Y: H=100, N=2, MO=10, M=10;
species Z: N=3, H=10, M=30, MO=0 ; // notice, order swapped

//constants
tau = 0.0001 + 0.0001;
sigma = 0.003;

//kinetic laws
//the predefined function function fMA is considered
//the form of the function is r*(X^2)^Y
//the reactants (X and Y) of the reaction are extracted from the s:

kineticLawOf alpha : fMA(tau);
kineticLawOf gamma : fMA(sigma);

//Sequential components
X = (alpha, 2) >> X + (gamma, 2) << X;

```

Species (3)

- X Initial Concentration = 20.0
- Y Initial Concentration = 10.0
- Z Initial Concentration = 0.0

Reactions (2)

- alpha, 2 -> 2X + Y
- gamma, 2X + Y -> Z

Problems AST View State Space View Graph View Console

Figure 11 Figure 12 Figure 13 Figure 14 Figure 15

mass-action.biopepa

Number of Molecules

Time

X  
Y  
Z

Writable Insert 20 : 11

# The Bio-PEPA Eclipse Plugin

The screenshot displays the Eclipse IDE with the Bio-PEPA plugin. The main editor shows the following code for a mass-action model:

```

species X: H=100, N=2, MO = 20, M=20;
species Y: H=100, N=2, MO=10, M=10;
species Z: N=3, H=10, M=30, MO=0; // notice, order swapped

//constants
c = 0.0001 + 0.0001;
s = 0.003;

//kinetic laws
//the predefined function function fNA is considered
//the form of the function is r*(X^2)*Y

//Sequential components
X = (alpha, 2) >> X + (gamma, 2) << X;
  
```

The Outline view on the right shows the model structure:

- Species (3)
  - X Initial Concentration = 20.0
  - Y Initial Concentration = 10.0
  - Z Initial Concentration = 0.0
- Reactions (2)
  - alpha, 2 -> 2.X + Y
  - gamma, 2.X + Y -> Z

The graph at the bottom, titled "mass-action.biopepa", plots the "Number of Molecules" (Y-axis, 0 to 25) against "Time" (X-axis, 0.0 to 2.1). Three lines represent the species: X (red), Y (blue), and Z (green). Species X starts at 20 and decreases to approximately 6. Species Y starts at 10 and decreases to approximately 3. Species Z starts at 0 and increases to approximately 6. The lines show step-like changes corresponding to reaction events.

# The Bio-PEPA Eclipse Plugin

The screenshot displays the Bio-PEPA Eclipse Plugin interface. The main window is titled "PEPA - Bio-PEPA modelling/mass-action.biopepa - Eclipse SDK". The interface includes a Navigator on the left, a Code Editor in the center, and a Graph View at the bottom.

**Code Editor Content:**

```

species X: H=100, N=2, M0 = 20, M=20;
species Y: H=100, N=2, M0=10, M=10;
species Z: N=3, H=10, M=30, M0=0; // notice, order swapped

//constants
tau = 0.0001 + 0.0001;
sigma = 0.003;

//kinetic laws
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**Graph View:**

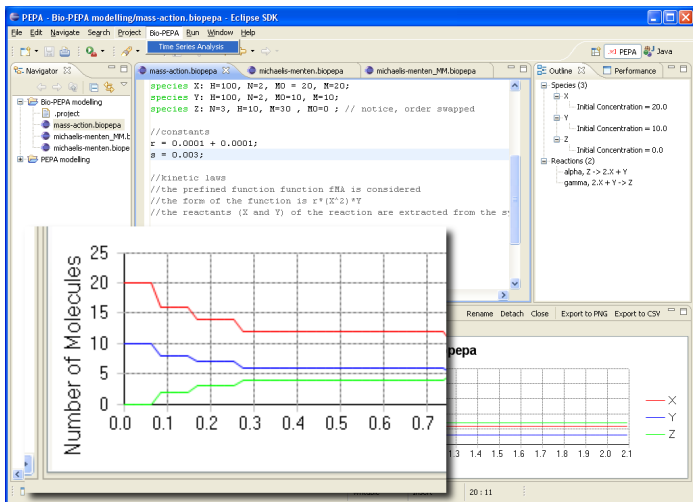
The graph view, titled "mass-action.biopepa", shows the "Number of Molecules" on the y-axis (ranging from 0 to 25) and "Time" on the x-axis (ranging from 0.0 to 2.1). Three data series are plotted: X (red line), Y (blue line), and Z (green line). The initial concentration of X is 20, Y is 10, and Z is 0. The graph shows X decreasing from 20 to approximately 6, Y decreasing from 10 to approximately 3, and Z increasing from 0 to approximately 6 over time.

**Reactions (2):**

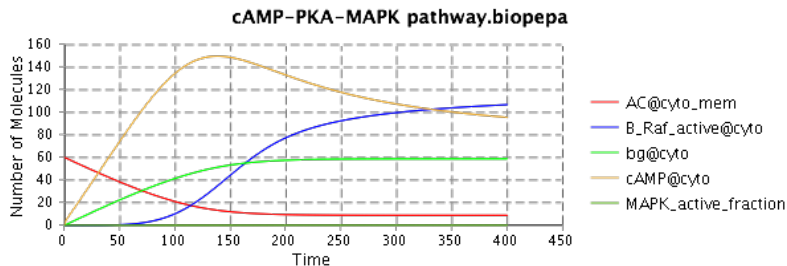
- alpha,  $Z \rightarrow 2.X + Y$
- gamma,  $2.X + Y \rightarrow Z$

**Initial Concentration = U**

# The Bio-PEPA Eclipse Plugin



## Example results





## Advantages of process calculus

Being able to compare simulation results and ODE solutions has allowed us to discover errors in published modelling studies in computational biology. This illustrates the strength of a high-level modelling language such as a process calculus.



Stronger computational modelling of signalling pathways using both continuous and discrete-state methods.

M. Calder, A. Duguid, S. Gilmore, and J. Hillston.

Computational Methods in Systems Biology, Trento, Italy, 2006.

Additionally we are working on developing appropriate notions of equivalence and abstraction for biological models.

# Availability

The Bio-PEPA software is available for free download from <http://www.biopepa.org>.

# Acknowledgements

Work on Bio-PEPA is supported by the Engineering and Physical Sciences Research Council (EPSRC) and the Biology and Biological Sciences Research Council (BBSRC) through the following grants:

- ▶ EP/C543696/1 “Process Algebra Approaches to Collective Dynamics” .
- ▶ EP/E031439/1 “Stochastic Process Algebra for Biochemical Signalling Pathway Analysis” .