Coloured Hybrid Petri Nets for Systems Biology

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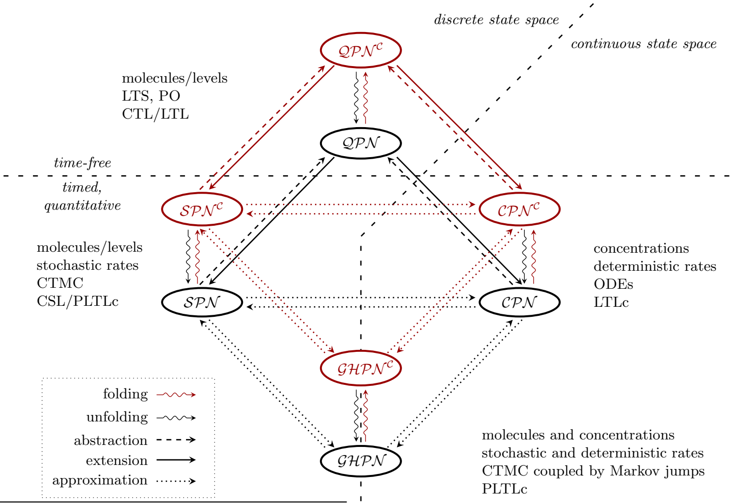
Agenda

Petri Nets in Snoopy [1]



[1] Heiner et al. 2012

Motivations for $\mathcal{GHPN}^{\mathcal{C}}$

- The rabid change of the size of biological models
- Certain biological phenomena necessitates the existence of discrete and continuous variables as well as continuous and stochastic processes in one and the same model
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- Combines both CPN and GSPN into one class
- Different transition types→ different reaction types can be modelled using GHPN
- Stiff biochemical networks can be easily modelled and simulated using GHPN
- The final model can be simulated using either static or dynamic partitioning
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Elements

Places

Transitions

Arcs

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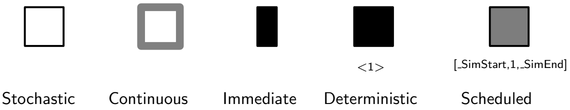

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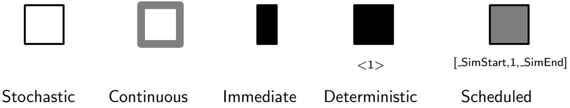

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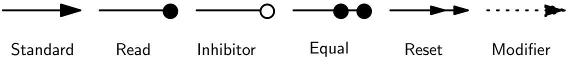
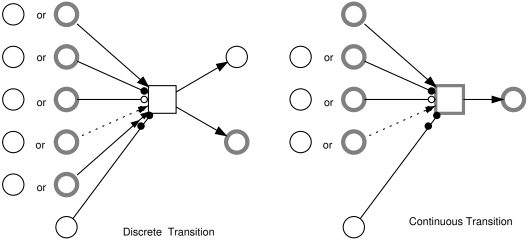


M. Herajy and M. Heiner, NAHS (2012)

Connectivity



The restrictions are:

- discrete places cannot be connected with continuous transitions using standard arcs,
- continuous places cannot be tested with equal arcs,
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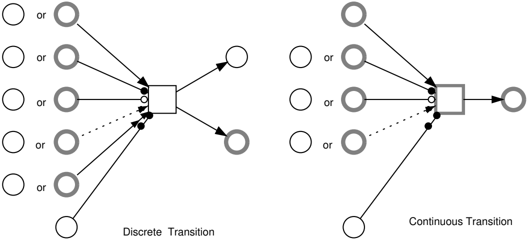

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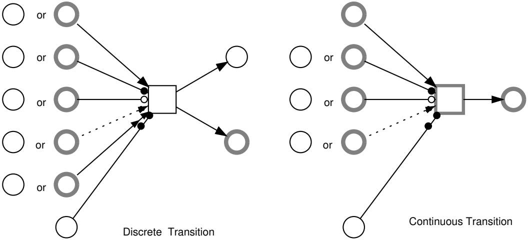

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Simulation of $\mathcal{GHPN}^{\mathcal{C}}$

Unfolding

- Coloured hybrid Petri nets can be unfolded into uncoloured ones where many analysis and simulation techniques can be applied.
- The conversion between uncoloured and coloured Petri nets changes the style of representation, but does not change the actual net structure of the underlying biological reaction network.

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- If the colour set of each variable in a transition guard has a finite integer domain, a constraint satisfaction approach is used to obtain all valid transition instances.
- Otherwise, a general unfolding algorithm is adopted, in which some optimization techniques like partial binding partial test and pattern matching are used

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Two key issues are very important in simulating $\mathcal{GHPN}^{\mathcal{C}}$:

- The partitioning of the net transitions into stochastic and continuous ones.
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Synchronization Mechanism

One option is to use (1) [2]:

$$g(\mathbf{x}) = \int_{t}^{t+\tau} a_0^s(\mathbf{x})dt - \xi = 0\,, \qquad (1)$$

where ξ is a random number exponentially distributed with a unit mean, and $a_0^s(\mathbf{x})$ is the cumulative rate of all the stochastic transitions.

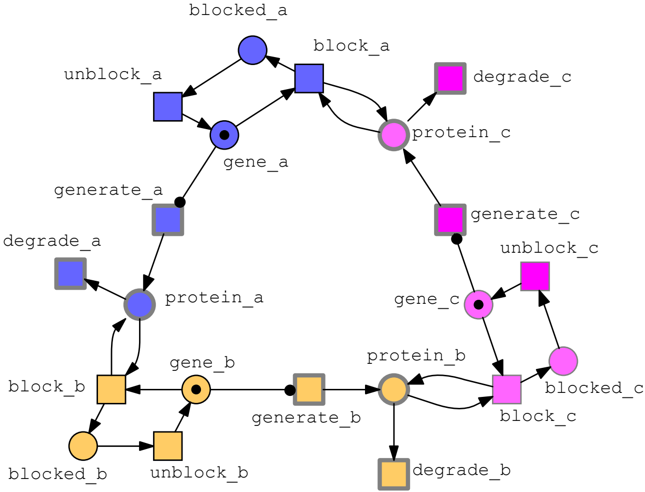
[2] Gillespie 91, Markov Processes

Case Study

Repressilator

- It is an example of a synthetic circuit.
- The repressilator system is a regulatory cycle of three genes (gene a, gene b and gene c).
- Each gene represses its successor, namely, gene a inhibits gene b, gene b inhibits gene c, and gene c inhibits gene a.
- This negative regulation is realized by the repressors, protein a, protein b and protein c.

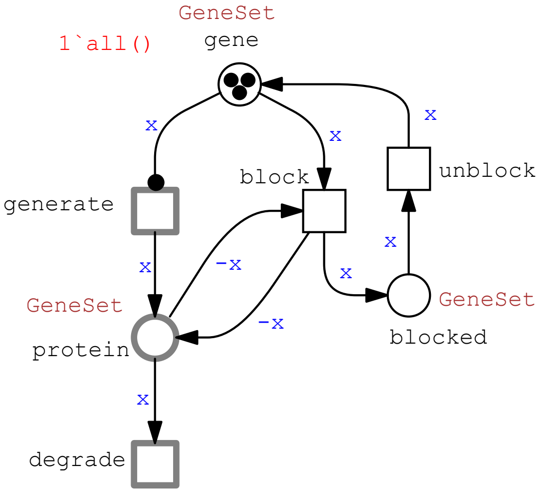
$\mathcal{GHPN}$ Representation



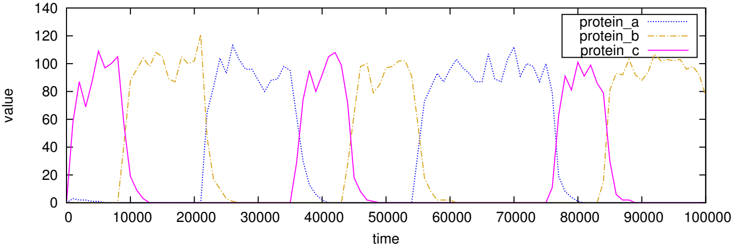
$\mathcal{GHPN}^{\mathcal{C}}$ Net Partitioning

- The 1-bounded places as determined by P-invariant analysis and the related transitions as determined by T-invariant analysis are kept discrete.
- The unbounded places and related transitions are approximated by continuous places and transitions, respectively.

$\mathcal{GHPN}^{\mathcal{C}}$ Representation



$\mathcal{GHPN}^{\mathcal{C}}$ Simulation Result



Implementation

All the features of $\mathcal{GHPN}^{\mathcal{C}}$ are implemented in:

- Snoopy – a unifying Petri net editing tool.
- S^4 – Snoopy Steering and Simulation Server

Conclusion

- In this paper we have introduced a class of coloured Petri nets called Coloured Generalised Hybrid Petri Nets ($\mathcal{GHPN}^{\mathcal{C}}$).
- $\mathcal{GHPN}^{\mathcal{C}}$ are particularly tailored to systems biologists needs to model and analyse multiscales models.
- $\mathcal{GHPN}^{\mathcal{C}}$ provide the interplay between stochastic and continuous regimes on the coloured level

Future work

- Adding marking-dependent arc weights.
- Simulation of $\mathcal{GHPN}^{\mathcal{C}}$ on the coloured level
- Implementing more complex case studies.

Acknowledgement

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Thank You