A Hybrid Petri Net Model of the Eukaryotic Cell Cycle

A Case Study of $GHPN_{bio}$

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Agenda

- Introduction
- Generalized Hybrid Petri Nets
- The Eukaryotic Cell Cycle Model
- Simulation Results
- Live Demo using Snoopy
- Conclusions and Outlook

Introduction

- Some biological models require to be represented in hybrid way (Cells/Molecular interactions in one model).
- Continuous deterministic simulation does not consider the fluctuation of molecules, specially when there is a low number of them.
- Stochastic Simulation is computational expensive (fast reactions, large number of molecules).

CPN and XSPN

- Continuous Petri Nets:
  - Continuous places
  - Continuous transitions
- Extended Stochastic Petri Nets [1]
  - Discrete places
  - Stochastic transitions
  - Immediate transitions
  - Deterministic transitions
  - Scheduled transitions

[1] Marwan et al., Book Chapter 2012

Features of $GHPN_{bio}$

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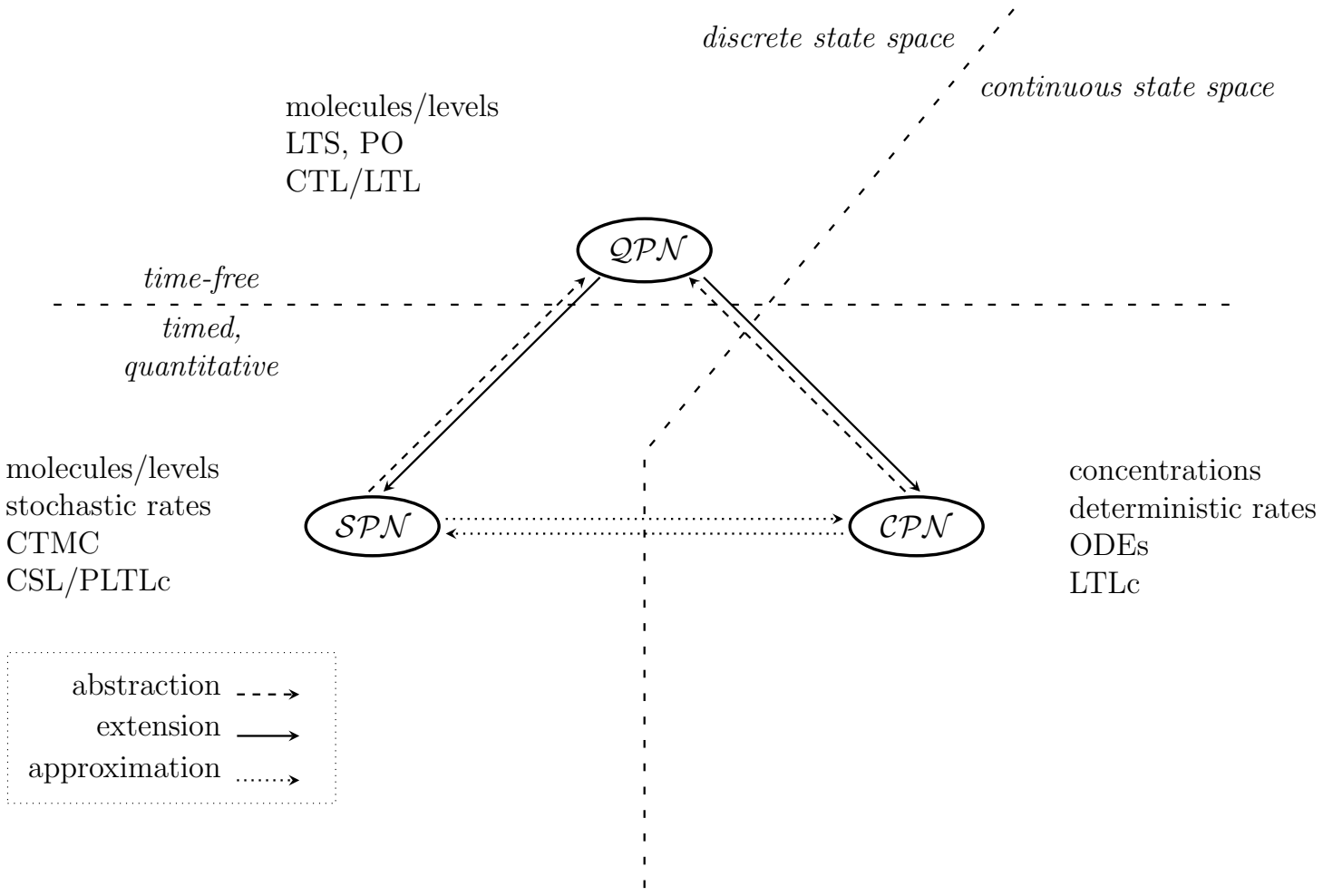
$GHPN_{bio}$: the Big Picture



[1] Heiner et al. Petri nets 2012

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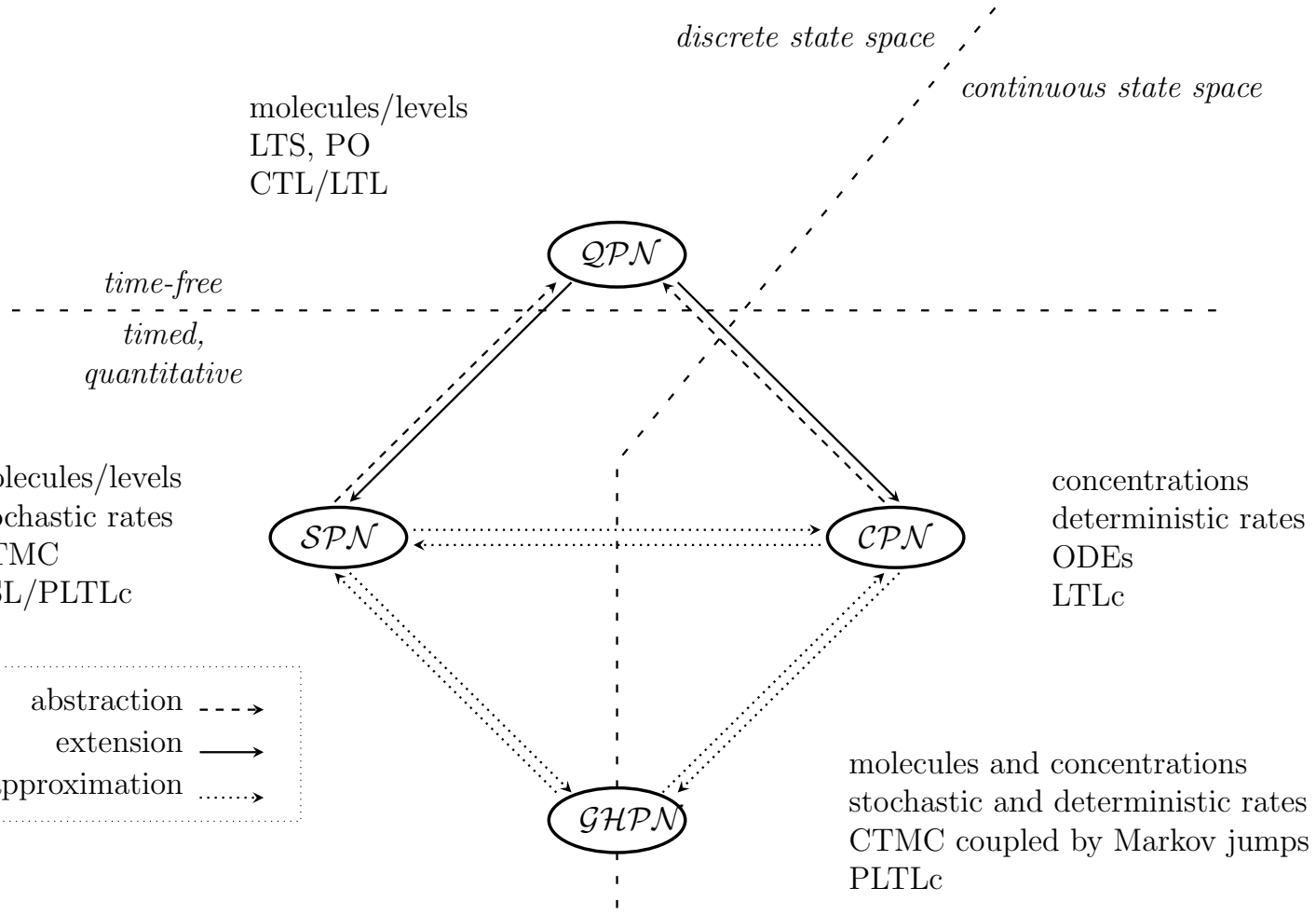

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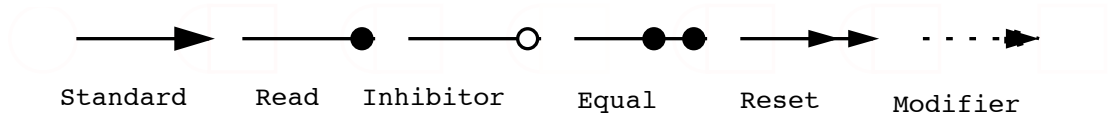
Elements

Places

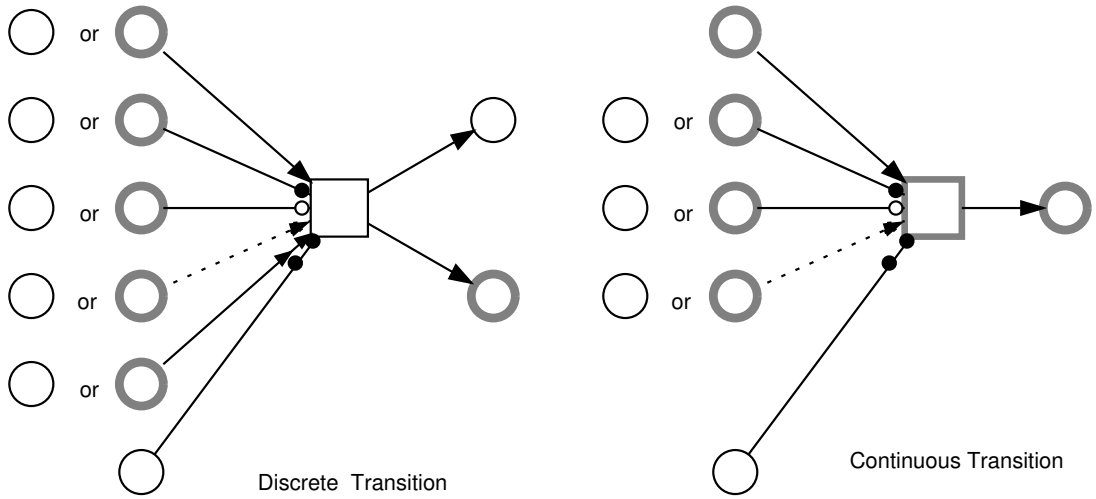
Transitions

Edges

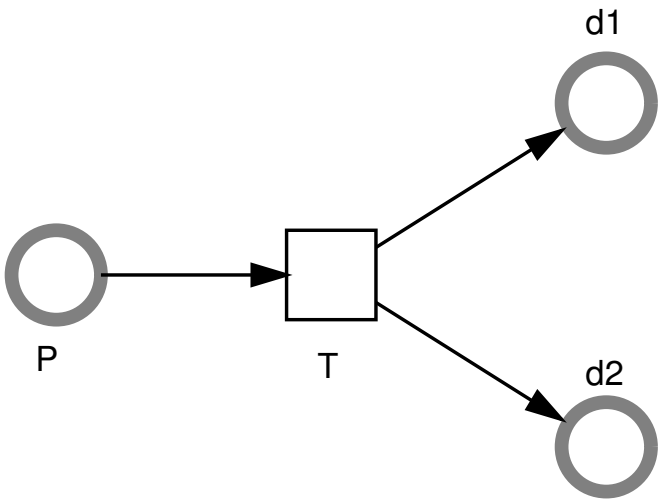


[1] M. Herajy and M. Heiner, NAHS (2012)

Connectivity



Self-modifying Weights and Cell Division



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[2] Valk, CALP (1978)

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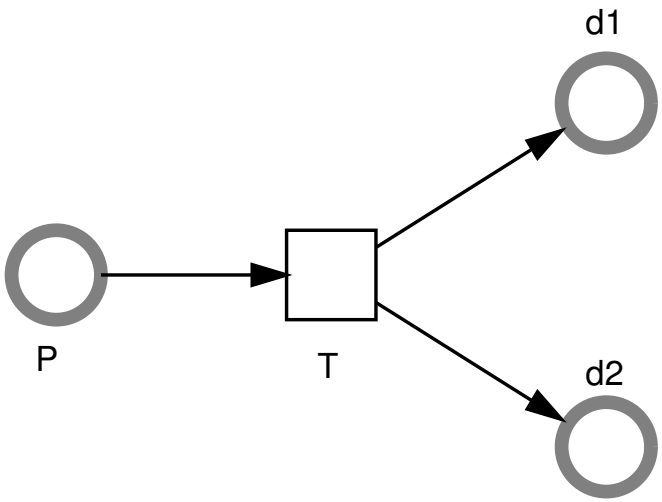
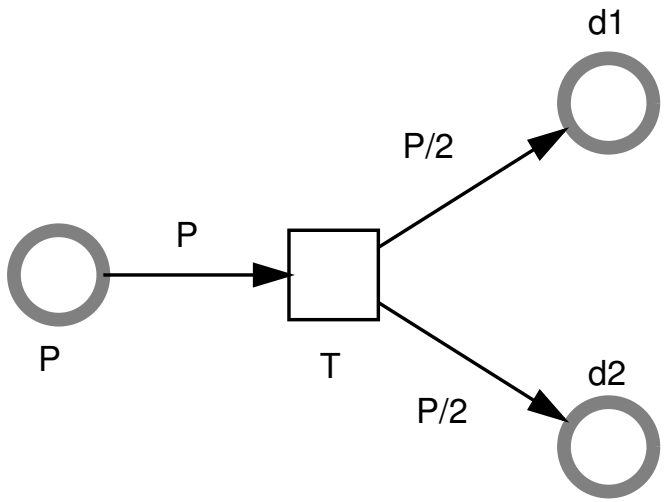


cell division cannot be modelled



cell division can intuitively be modelled

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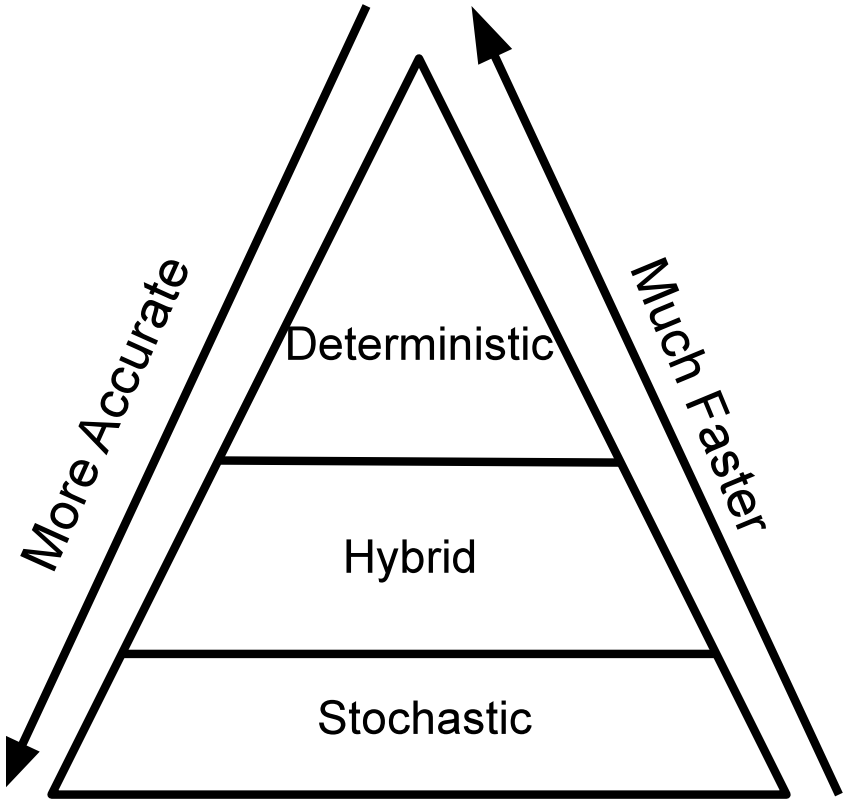
Simulation Methods



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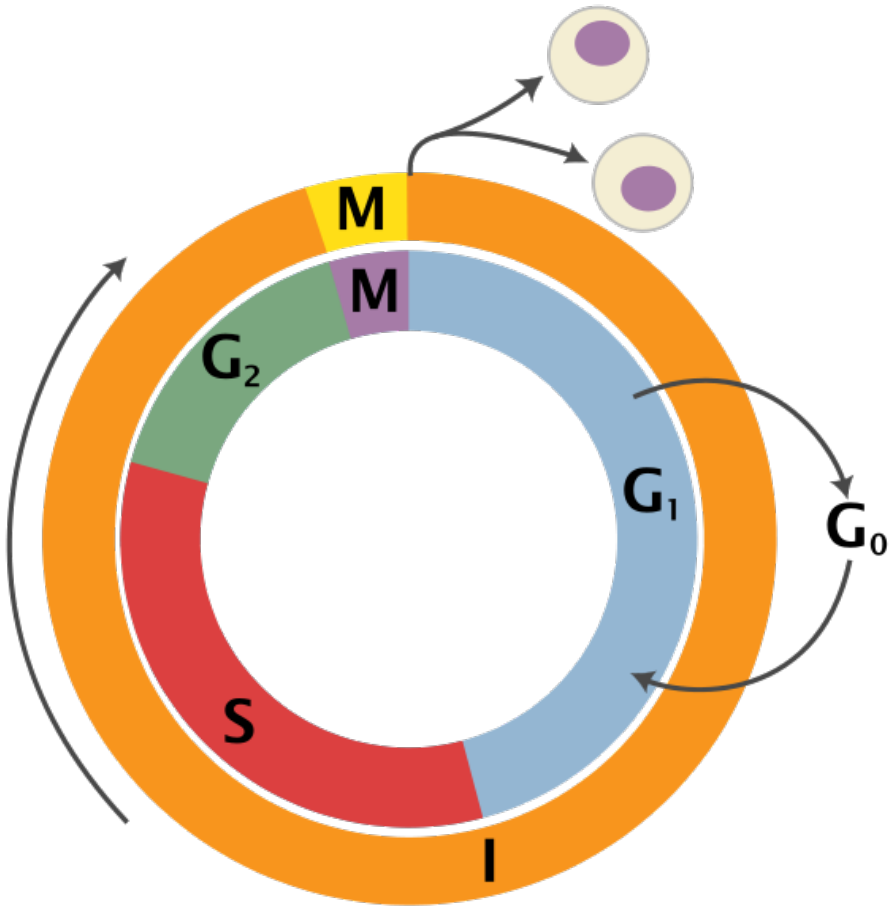
Simulation of GHPN

- Static partitioning: partitioning is done off-line before the simulation starts.
- Dynamic partitioning: partitioning is done on-line during the simulation.

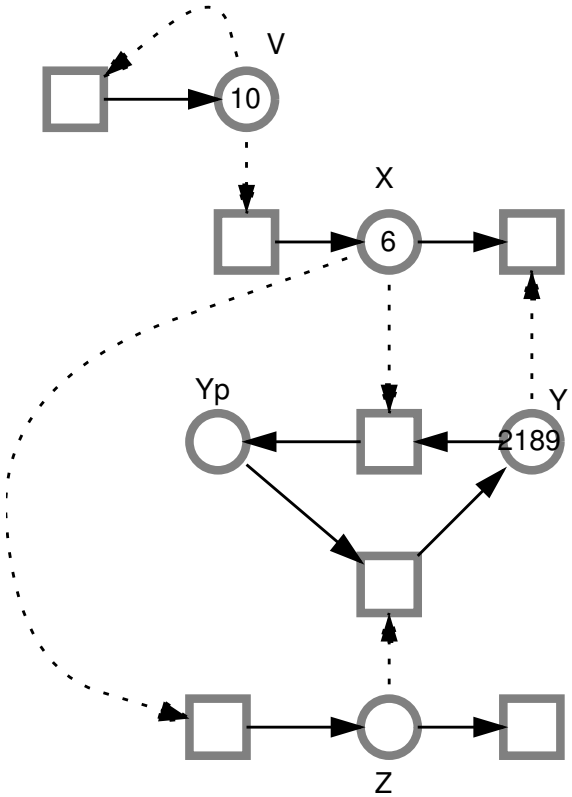
The Eukaryotic Cell Cycle Model

Cell Cycle Regulation

- S phase (synthesis)
- G2 gap
- M phase (mitosis)
- G1 gap



Basic Model



- V: cellular Volume
- X: CycB-Cdk1
- Y: free Cdh1-APC
- Y_p: phosphorylated Cdh1-APC
- Z: effects of Cdc20 and Cdc14

[1] Tyson-Novak Model, Theoretical Biology (2001)

Model History

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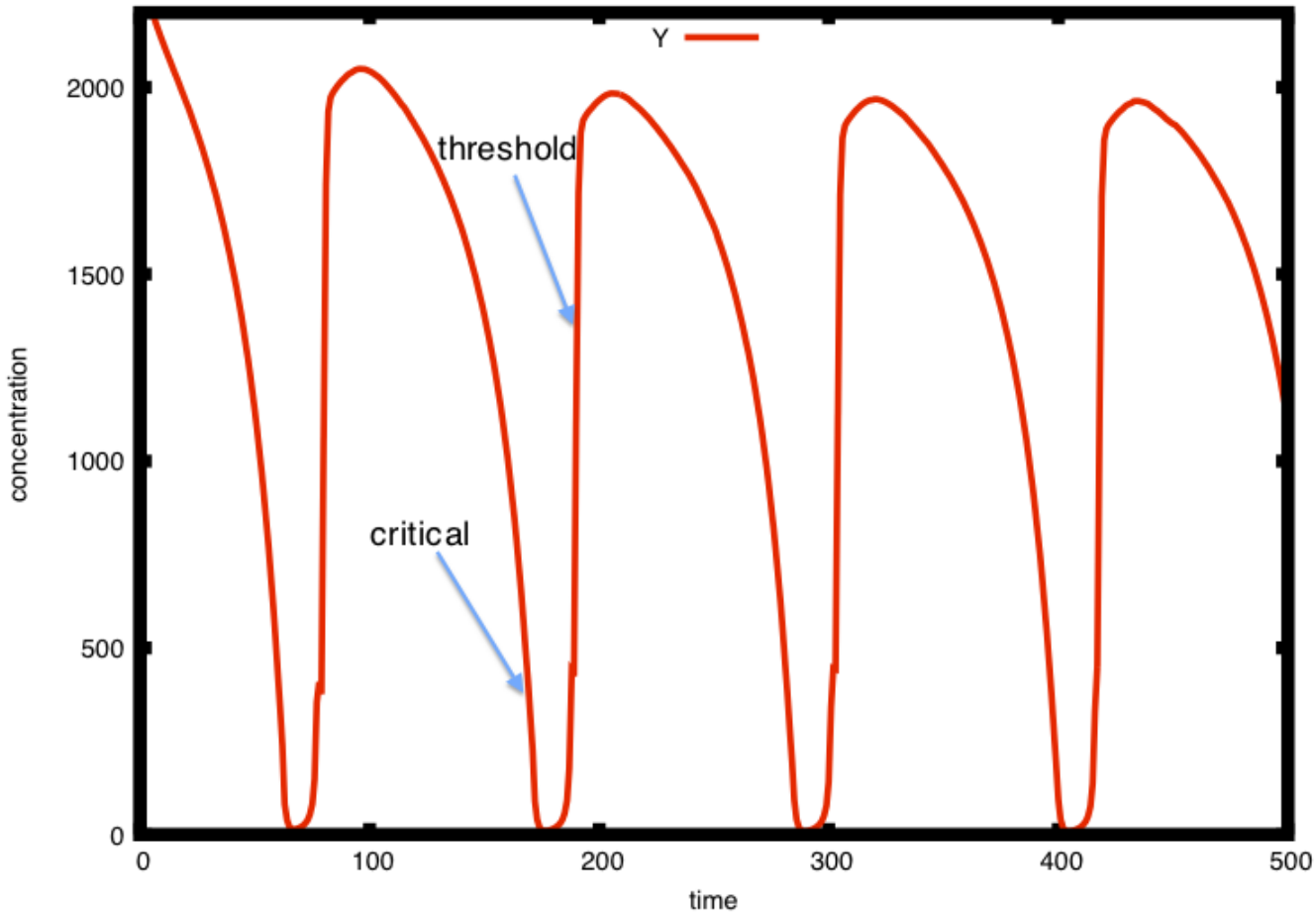
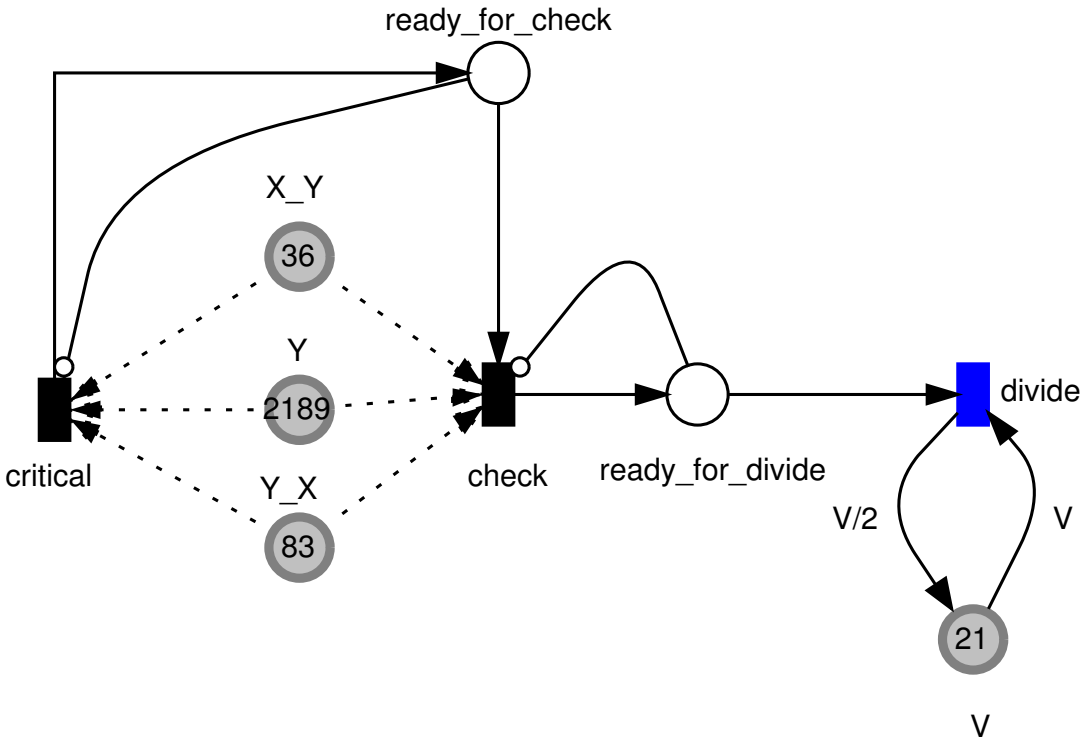
- Kar et al. (2009): a stochastic model using mass-action kinetics

Deciding the Division



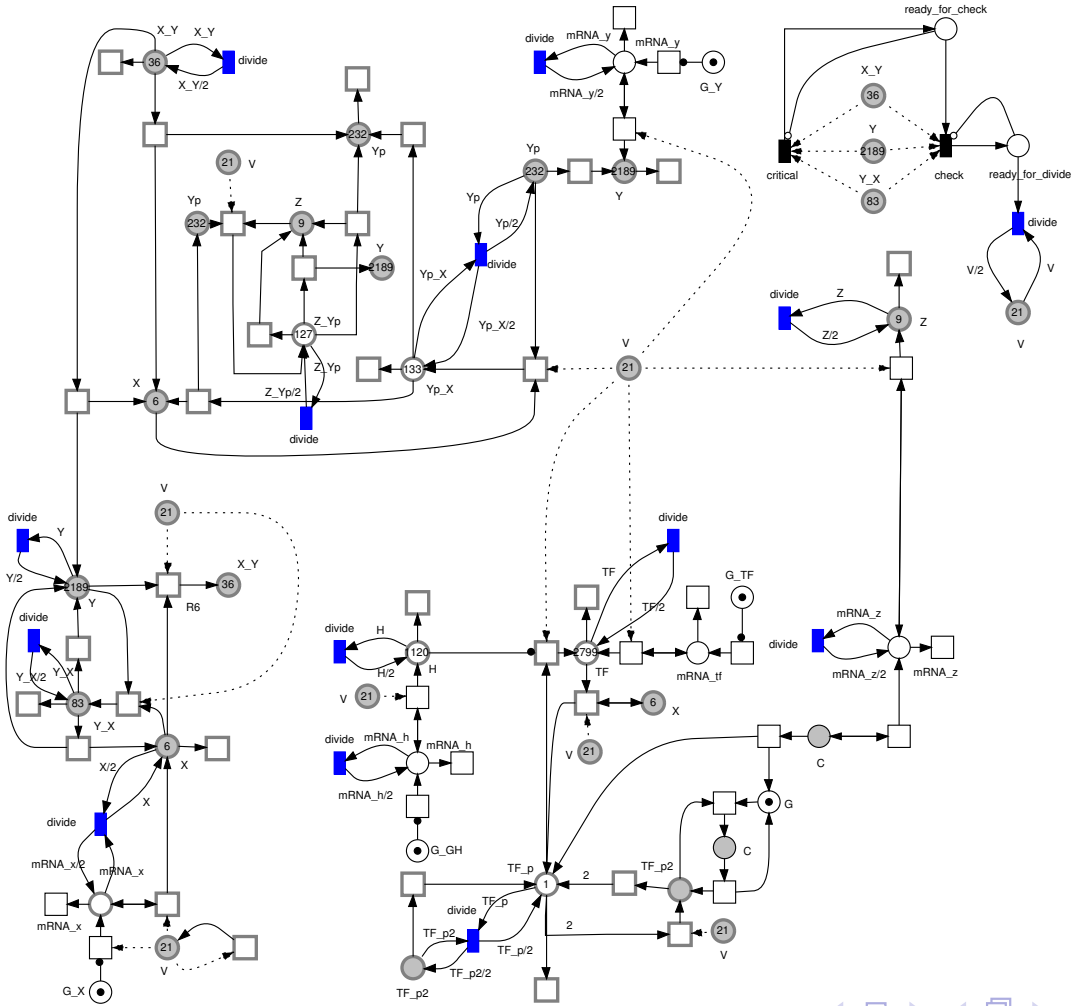
Deciding the Division (cont.)



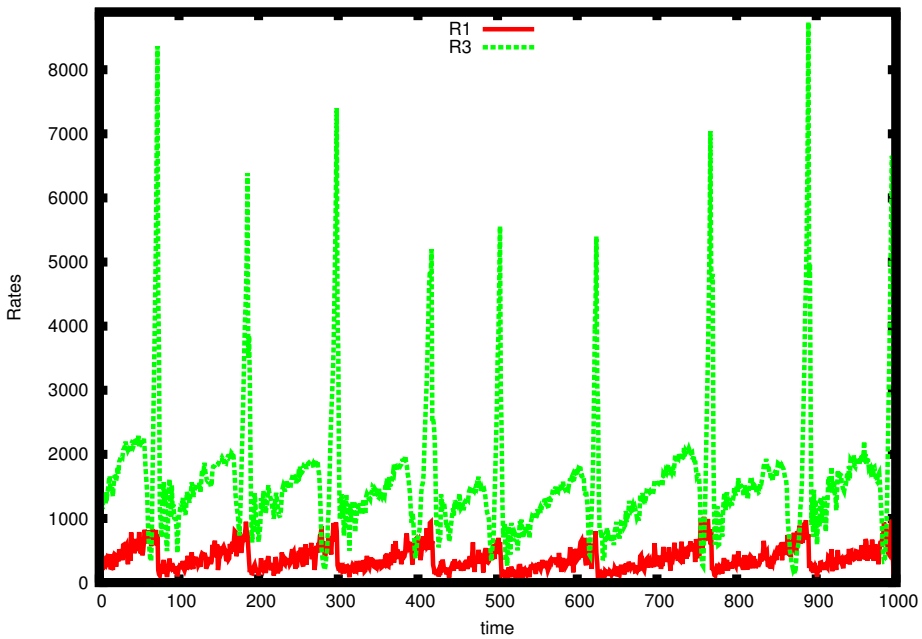
critical: $Y + X\_Y + Y\_X < CriticalValue$

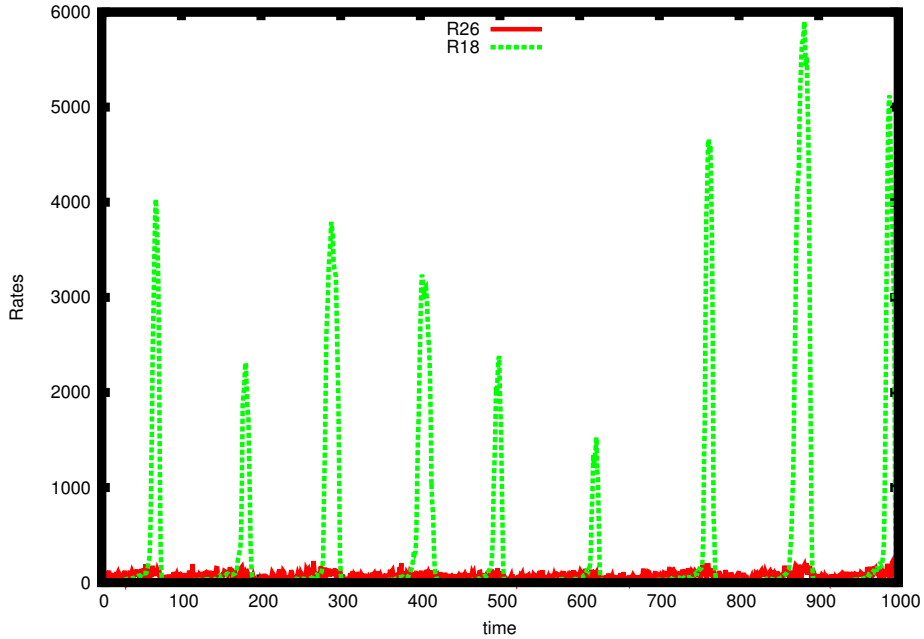
check: $Y + X\_Y + Y\_X > ThresholdValue$

The Model


X_Y
X_Y
36
divide
X_Y/2
232
Yp
21
V
Yp
232
Z
9
Y
2189
Z_Yp
127
Z_Yp
133
Yp_X
Z_Yp/2
divide
X
6
divide
mRNA_y
mRNA_y
G_Y
mRNA_y/2
Yp
232
2189
Y
Yp
Yp/2
divide
Yp_X
Yp_X/2
V
21
ready_for_check
X_Y
36
Y
2189
Y_X
83
critical
check
ready_for_divide
divide
V/2
V
21
V
divide
Z
9
Z
Z/2
V
21
divide
Y
Y/2
2189
Y
X_Y
36
R6
divide
Y_X/2
Y_X
83
Y_X
6
X
X/2
X
divide
mRNA_x/2
mRNA_x
mRNA_x
21
V
G_X
divide
H
120
H
H/2
V
21
divide
mRNA_h
mRNA_h
mRNA_h/2
G_GH
divide
TF
2799
TF
TF/2
G_TF
mRNA_tf
6
X
V
21
divide
mRNA_z
mRNA_z/2
mRNA_z
C
G
C
TF_p
1
2
TF_p2
TF_p
divide
TF_p2
TF_p/2
TF_p2/2
TF_p2
2
21
V

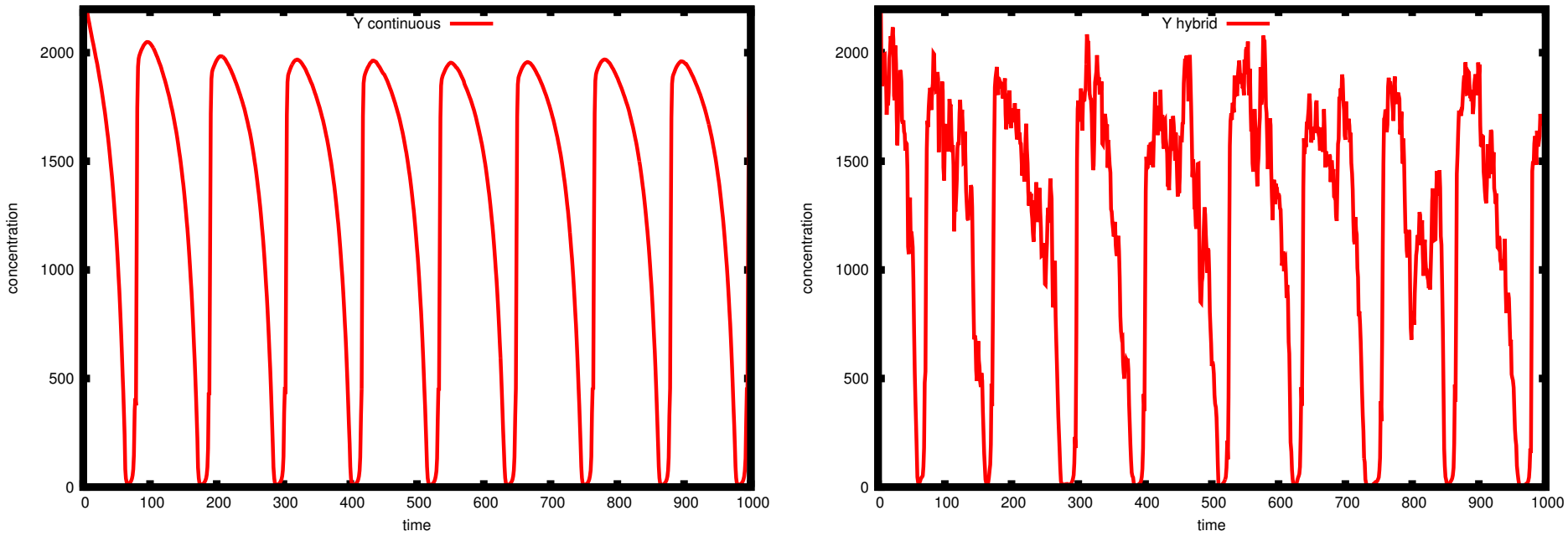
Transition Partitioning





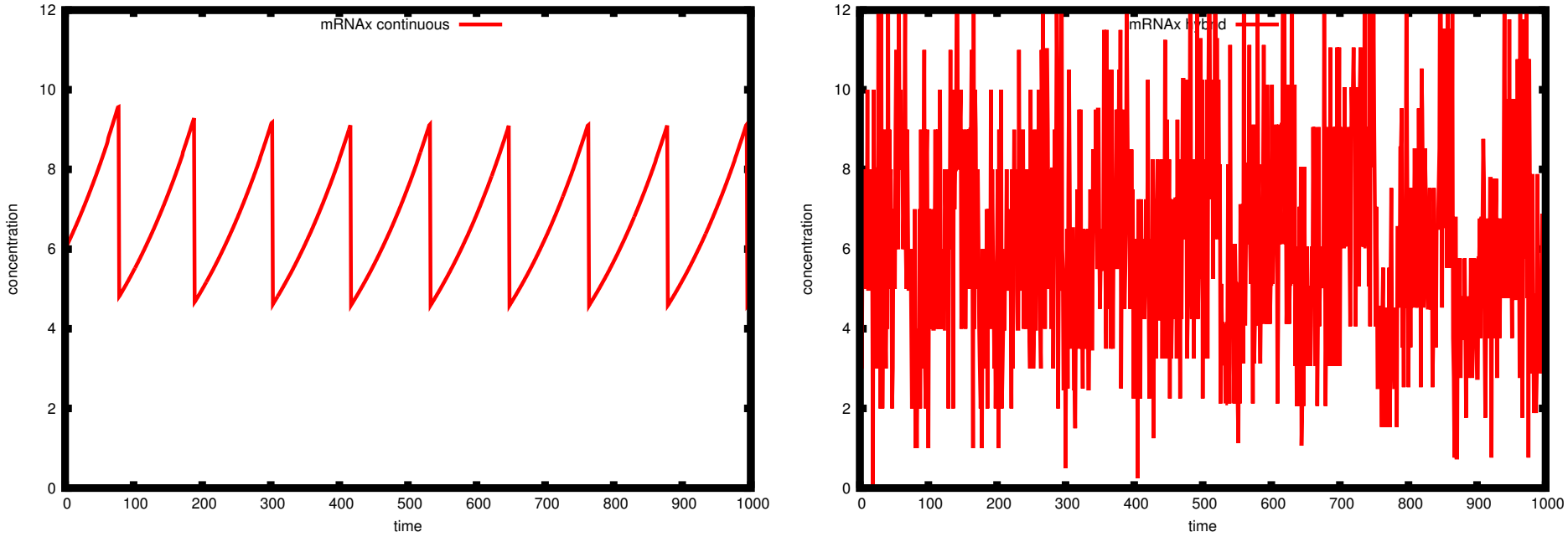
transitions with different rates

Simulation Results



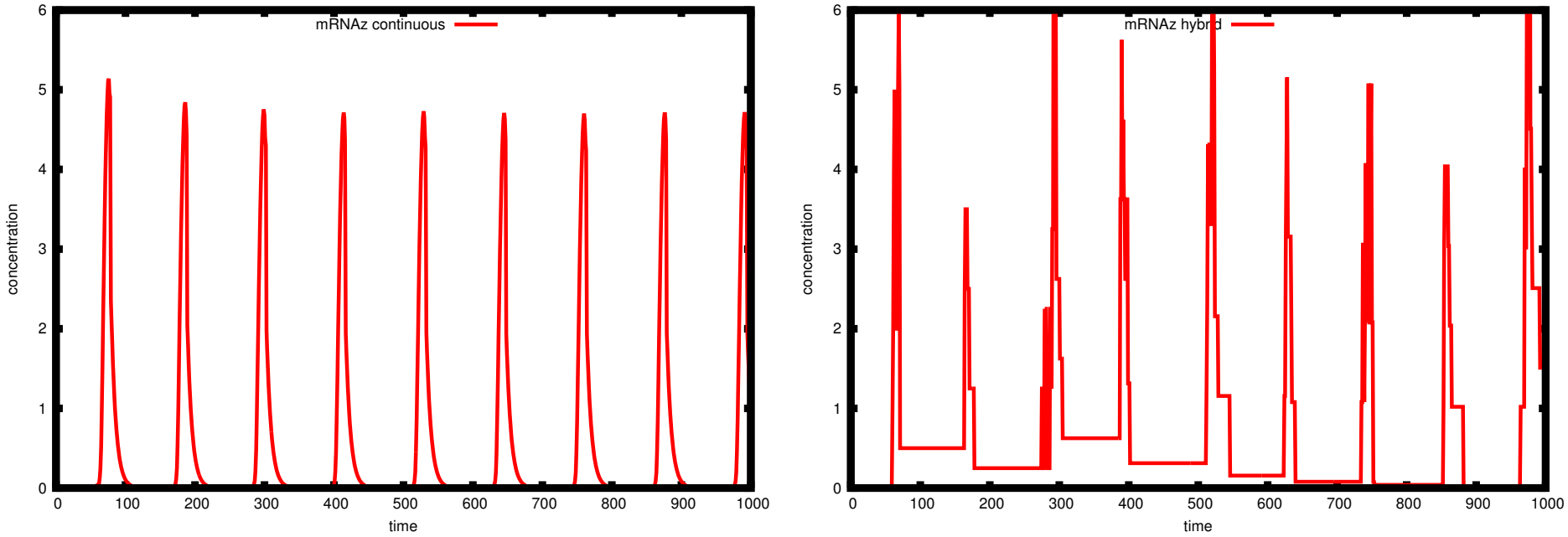
time course simulation results of Y: continuous (left) and hybrid (right)

Simulation Results (cont.)



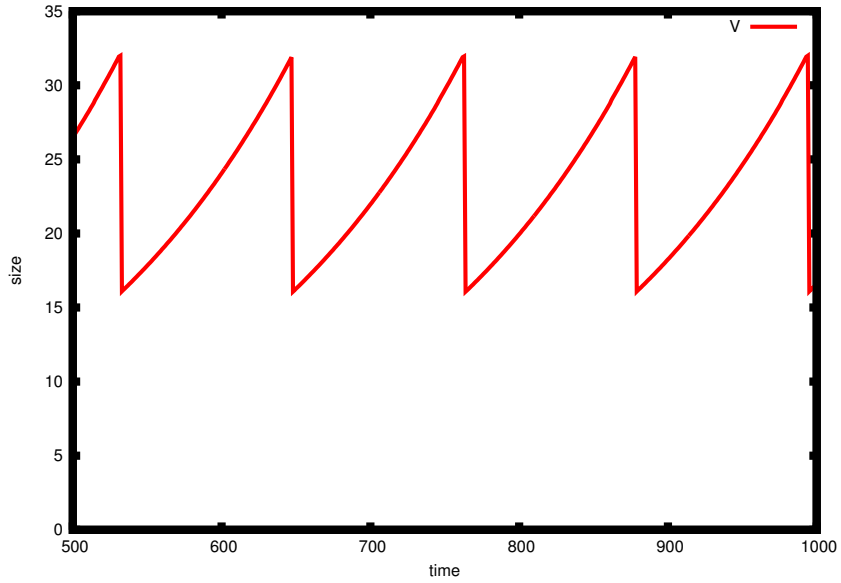
time course simulation results of Mx: continuous (left) and hybrid (right)

Simulation Results (cont.)

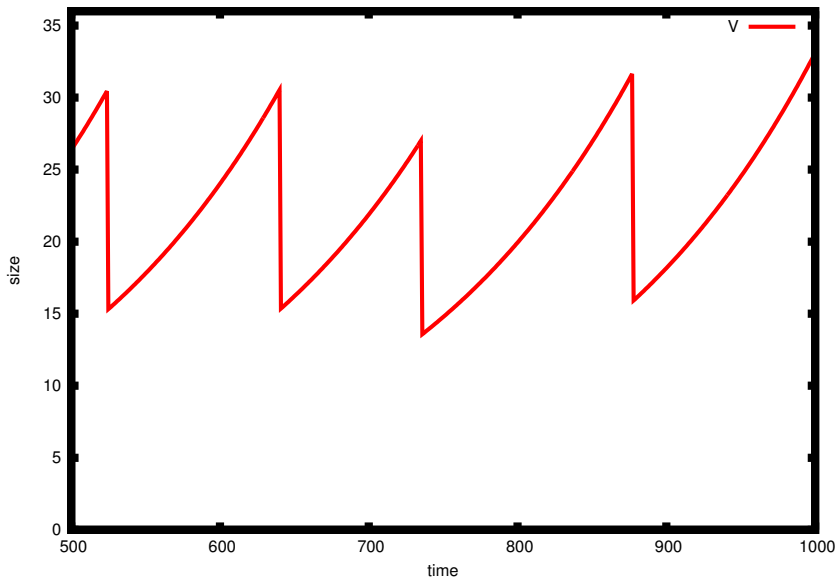


time course simulation results of Mz: continuous (left) and hybrid (right)

Cellular Volume



Deterministic



Hybrid

Live Demo using Snoopy

Conclusions

- $GHPN_{bio}$ Can intuitively represent and execute the eukaryotic cell cycle
- The model can be executed using either continuous, or hybrid simulators

Future Work

- Better justification of the partitioning
- Modelling extrinsic noises
- Use this network as a subnet in bigger models

Thank You