NoPain – Meeting

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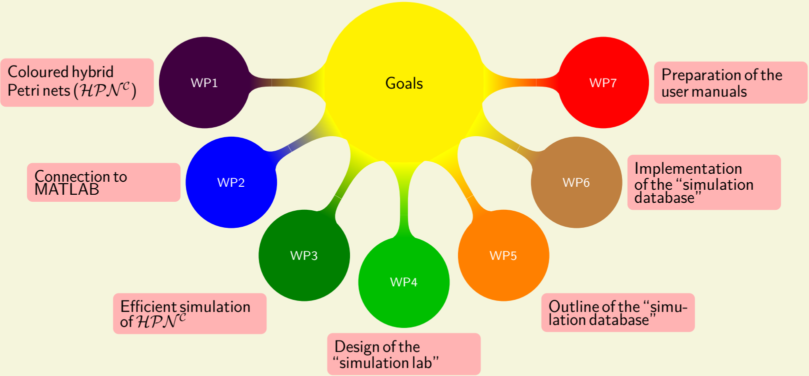
Work Packages



WP3

Efficient simulation of $\mathcal{HPN}^{\mathcal{C}}$

a. Predecessor WPs: BTU-WP1, OvGUM-WP1
b. Successor WPs: BTU-WP4

- Examination of the Petri net models with regard to parallelisation potential
- Investigation of optimisation possibilities and performance comparisons with alternative tools, i.e. StochKit2, Cain...

Parameter-free simulation

- Starting point: *The Signaling Petri Net-Based Simulator: A Non-Parametric Strategy for Characterizing the Dynamics of Cell-Specific Signaling Networks*
  D. Ruths, M. Muller, Jen-Te Tseng, L. Nakhleh, P. T. Ram
  Published: February 29, 2008; DOI: 10.1371/journal.pcbi.1000005
- „The key insight behind our approach is the assumption that, while all network parameters determine the actual signal propagation to some extent, the network connectivity is the most significant single determinant. While this is clearly a gross simplification, several researchers have observed that the connectivity of a biological network dictates, to a great extent, the network's dynamics."

Parameter-free simulation

- „Simulation of timed Petri nets with variable auto-concurrency".
- The least possible time step is 1 time unit.
- All enabled transitions that are not mutually exclusive, are forced to fire within a time-step, something like *maximum step*.
- When the net is filled up with tokens, every transition will fire.

Parameter-free simulation

Transition firing

- Generate a random sequence of all transitions $t \in \mathcal{PN}$.
- No extra conflict resolution needed, because of serial firing.
- *Maximum step* $\subseteq$ *random sequences*

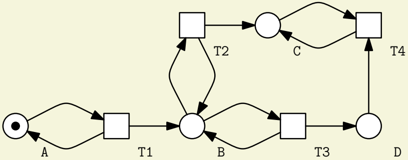
Example

Random sequences:

1. $(T_1, T_3, T_2, T_4) \rightarrow \{1, 1, 1, 0\}$
2. $(T_1, T_2, T_4, T_3) \rightarrow \{1, 1, 1, 1\}$
3. $(T_3, T_4, T_2, T_1) \rightarrow \{1, 1, 0, 0\}$

Maximum step:

1. $\{T_1\} \rightarrow \{1, 1, 0, 0\}$



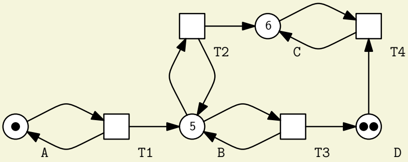
Parameter-free simulation

Transition firing

- A transition fires concurrently to itself, i.e. token flow increases.
- How often a transition concurrently fires depends on its enabledness degree and is randomly determined.
- $firing\ rate = random[0, enablness\ degree]$
- This approximates the stochastic behaviour of mass-action kinetics.

Example

- $(T_1, T_2, T_3, T_4) \rightarrow \{1, 5, 10, 0\}$
- $T_1 = 1 \rightarrow 0 \rightarrow \{1, 5, 6, 2\}$
- $T_2 = 5 \rightarrow 4 \rightarrow \{1, 5, 10, 2\}$
- $T_3 = 5 \rightarrow 2 \rightarrow \{1, 5, 10, 4\}$
- $T_4 = 4 \rightarrow 4 \rightarrow \{1, 5, 10, 0\}$



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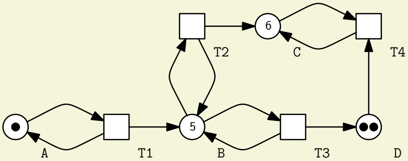

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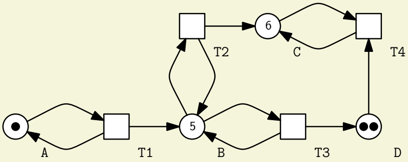

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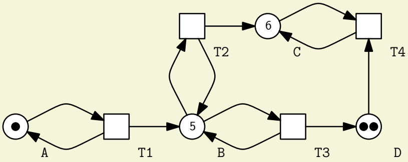

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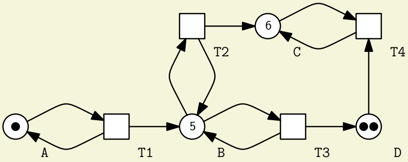


Parameter-free simulation

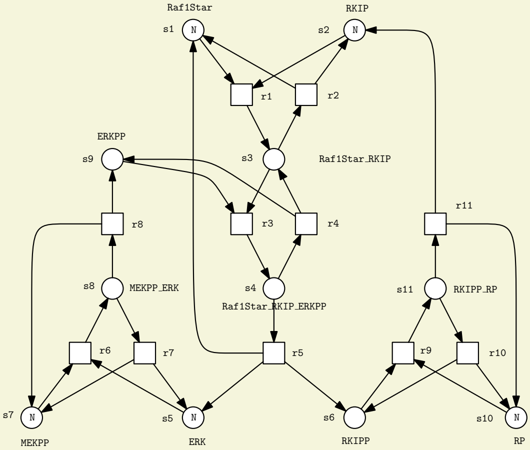
Algorithm 1 Parameter-free simulation algorithm

Require: $\mathcal{PN}$ with initial marking m_0, time interval $[\tau_0, \tau_{max}]$, runs r_{max}
Ensure: marking m at time point τ_{max}

for $r = 0;\ r < r_{max};\ r \leftarrow r + 1$ **do**
  $initRand(seed)$
  $time\ \tau \leftarrow \tau_0,\ marking\ m \leftarrow m_0,\ T_r \leftarrow T$
  while $\tau <= \tau_{max}$ **do**
    $T_r \leftarrow random\_shuffle(T_r)$
    for all transitions $t_j \in T_r$ **do**
      $e \leftarrow enablednessDegree(t_j, m)$
      $f \leftarrow random(0, e)$
      $m \leftarrow m + f * \Delta t_j$
    end for
    $generateResultPoint(\tau, m)$
    $\tau \leftarrow \tau + 1$
  end while
end for

RKIP inhibited ERK Pathway [Gilbert et al. 2006]

RKIP/MEK-ERK signalling pathway [wolkenhauer 2003], [Calder 2005]



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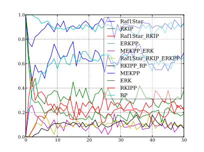
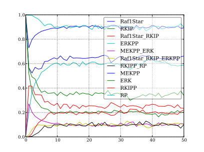
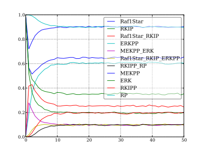


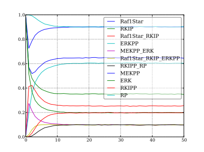
(a) SPN 100 runs (<1s)



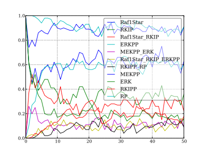
(b) SPN 1,000 runs (<1s)



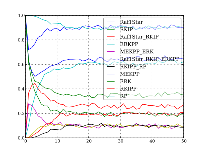
(c) SPN 10,000 runs (<1s)



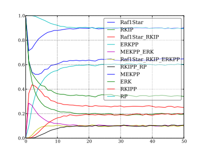
(d) SPN 100,000 runs (2s)



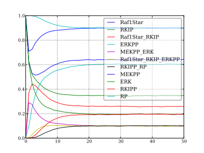
(e) QPN 100 runs (<1s)



(f) QPN 1,000 runs (<1s)



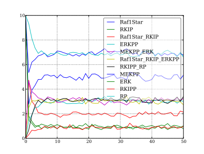
(g) QPN 10,000 runs (<1s)



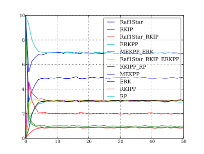
(h) QPN 100,000 runs (3s)

Figure: ERK, N=1

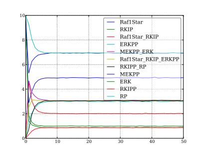
RKIP inhibited ERK Pathway



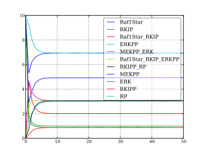
(a) SPN 100 runs (<1s)



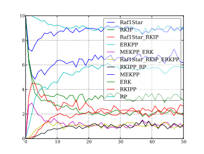
(b) SPN 1,000 runs (<1s)



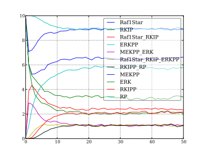
(c) SPN 10,000 runs (8s)



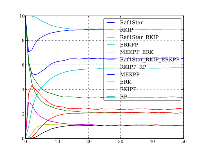
(d) SPN 100,000 runs (1m19s)



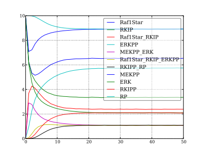
(e) QPN 100 runs (<1s)



(f) QPN 1,000 runs (<1s)



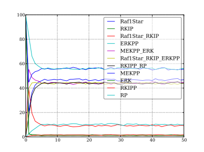
(g) QPN 10,000 runs (<1s)



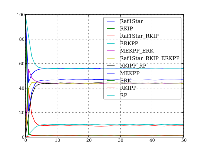
(h) QPN 100,000 runs (4s)

Figure: ERK, N=10

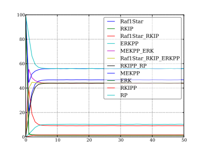
RKIP inhibited ERK Pathway



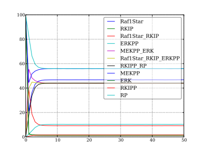
(a) SPN 100 runs (1s)



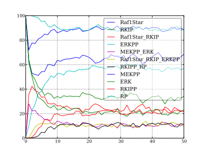
(b) SPN 1,000 runs (9s)



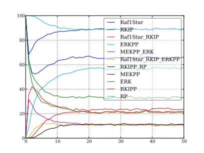
(c) SPN 10,000 runs (1m41s)



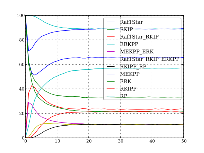
(d) SPN 100,000 runs (17m4s)



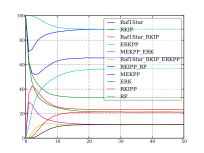
(e) QPN 100 runs (<1s)



(f) QPN 1,000 runs (<1s)



(g) QPN 10,000 runs (<1s)

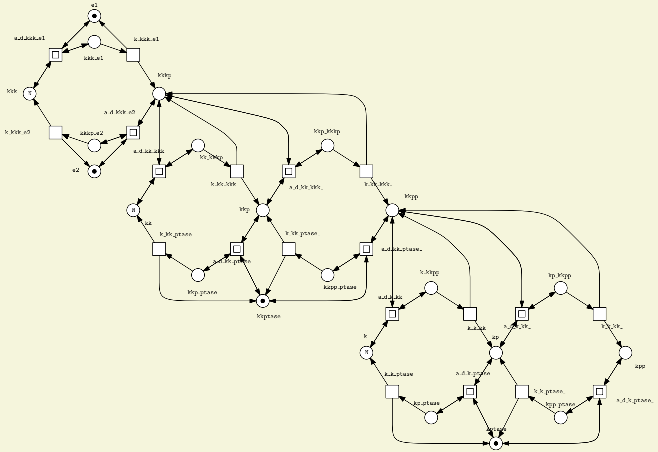


(h) QPN 100,000 runs (4s)

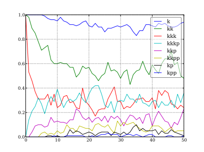
Figure: ERK, N=100

Example

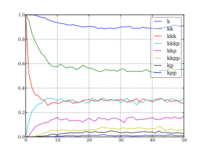
Mitogen-activated Protein Kinase [Huang et al. 1996], [Gilbert et al. 2007]



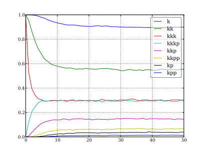
Mitogen-activated Protein Kinase



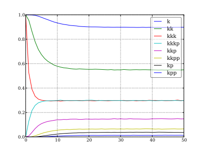
(a) SPN 100 runs (4s)



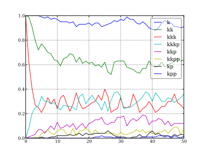
(b) SPN 1,000 runs (4s)



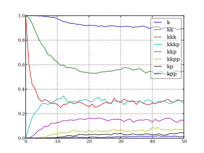
(c) SPN 10,000 runs (4s)



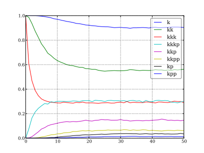
(d) SPN 100,000 runs (4s)



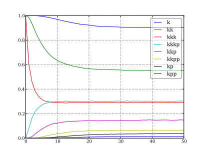
(e) QPN 100 runs (4s)



(f) QPN 1,000 runs (4s)



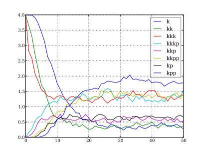
(g) QPN 10,000 runs (4s)



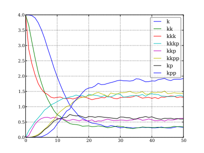
(h) QPN 100,000 runs (4s)

Figure: MAPK, N=1

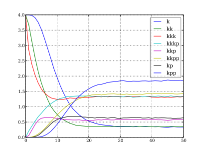
Mitogen-activated Protein Kinase



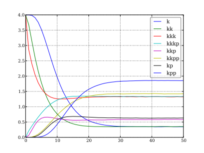
(a) SPN 100 runs (<1s)



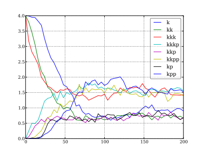
(b) SPN 1,000 runs (<1s)



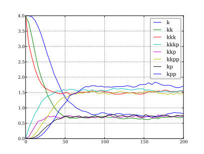
(c) SPN 10,000 runs (2s)



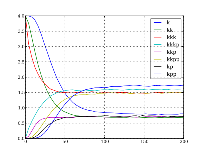
(d) SPN 100,000 runs (25s)



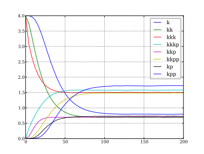
(e) QPN 100 runs (<1s)



(f) QPN 1,000 runs (<1s)



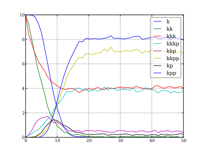
(g) QPN 10,000 runs (3s)



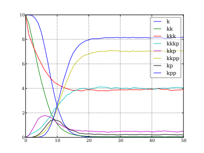
(h) QPN 100,000 runs (33s)

Figure: MAPK, N=4

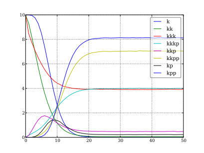
Mitogen-activated Protein Kinase



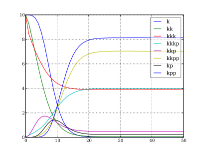
(a) SPN 100 runs (<1s)



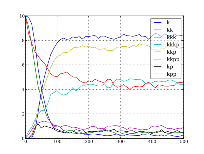
(b) SPN 1,000 runs (<1s)



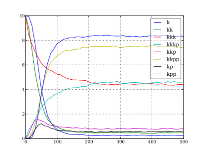
(c) SPN 10,000 runs (3s)



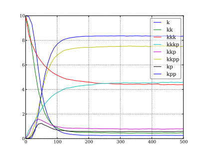
(d) SPN 100,000 runs (39s)



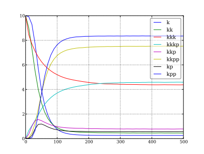
(e) QPN 100 runs (<1s)



(f) QPN 1,000 runs (<1s)



(g) QPN 10,000 runs (8s)

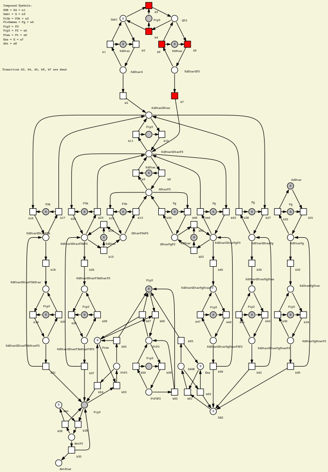


(h) QPN 100,000 runs (1m20s)

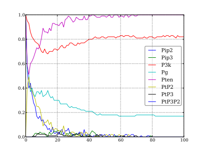
Figure: MAPK, N=10

Example

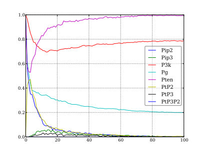
Angiogenesis [Napione et al. 2009]



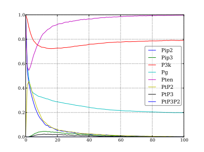
Angiogenesis



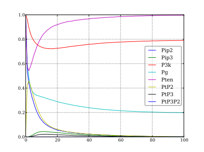
(a) SPN 100 runs (<1s)



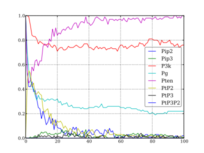
(b) SPN 1,000 runs (<1s)



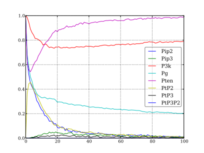
(c) SPN 10,000 runs (<1s)



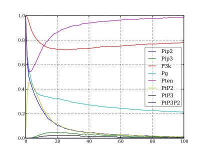
(d) SPN 100,000 runs (7s)



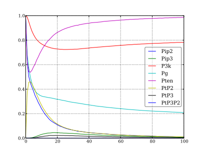
(e) QPN 100 runs (<1s)



(f) QPN 1,000 runs (<1s)



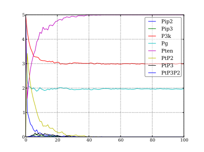
(g) QPN 10,000 runs (2s)



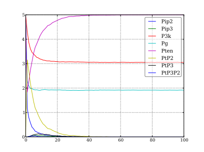
(h) QPN 100,000 runs (21s)

Figure: ANG, N=1

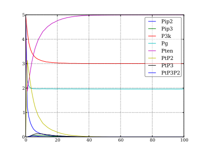
Angiogenesis



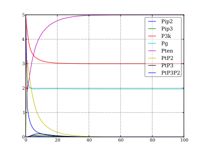
(a) SPN 100 runs (<1s)



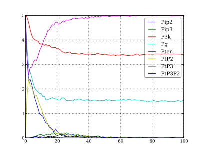
(b) SPN 1,000 runs (<1s)



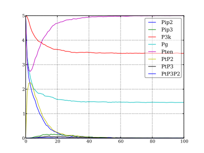
(c) SPN 10,000 runs (1s)



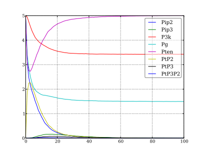
(d) SPN 100,000 runs (13s)



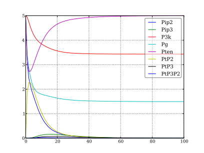
(e) QPN 100 runs (<1s)



(f) QPN 1,000 runs (<1s)



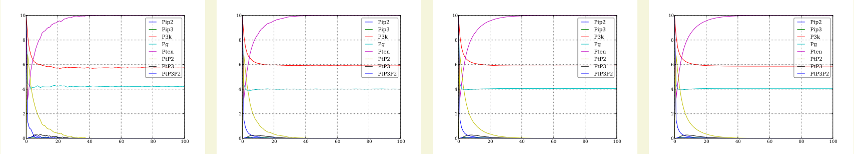
(g) QPN 10,000 runs (2s)



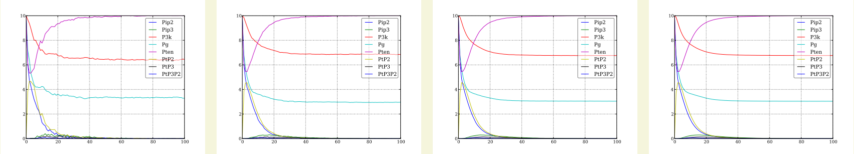
(h) QPN 100,000 runs (22s)

Figure: ANG, N=5

Angiogenesis



(a) SPN 100 runs (<1s) (b) SPN 1,000 runs (<1s) (c) SPN 10,000 runs (2s) (d) SPN 100,000 runs (23s)



(e) QPN 100 runs (<1s) (f) QPN 1,000 runs (<1s) (g) QPN 10,000 runs (2s) (h) QPN 100,000 runs (23s)

Figure: ANG, N=10

Parameter-free simulation

Conclusions

- Mixed results:
  1. performance comparable to stochastic simulation, some times better, some time worse
  2. correct results for $N = 1$, contradictory for $N > 1$
- Potential solutions:
  1. weighted shuffle of transitions
  2. mass-action kinetics: $c_t \cdot \prod_{p \in \bullet t} \binom{m(p)}{f(p,t)}$

     enabledness degree: $min_{p \in \bullet t} \left(\left\lfloor \frac{m(p)}{f(p,t)} \right\rfloor \right)$

Milestones

	2013				2014				2015			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
WP1		M1										
WP2				M2								
WP3						M3						
WP4								M4				
WP5								M4				
WP6												M5
WP7												M6

Next steps...

- Model compilation for simulation, i.e. a Petri net model and the simulation algorithm will be compiled into an executable file.
- Performance comparisons with alternative simulation tools, i.e. Stochkit2, Cain, Copasi, StochPy...

Thank you for your attention!