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*This form is a summary description of the model entitled "GPPP – Glycolysis and Pentose Phosphate Pathway" proposed for the Model Checking Contest @ Petri Nets. Models can be given in several instances parameterized by scaling parameters. Colored nets can be accompanied by one or many equivalent, unfolded P/T nets. Models are given together with property files (possibly, one per model instance) giving a set of properties to be checked on the model.*

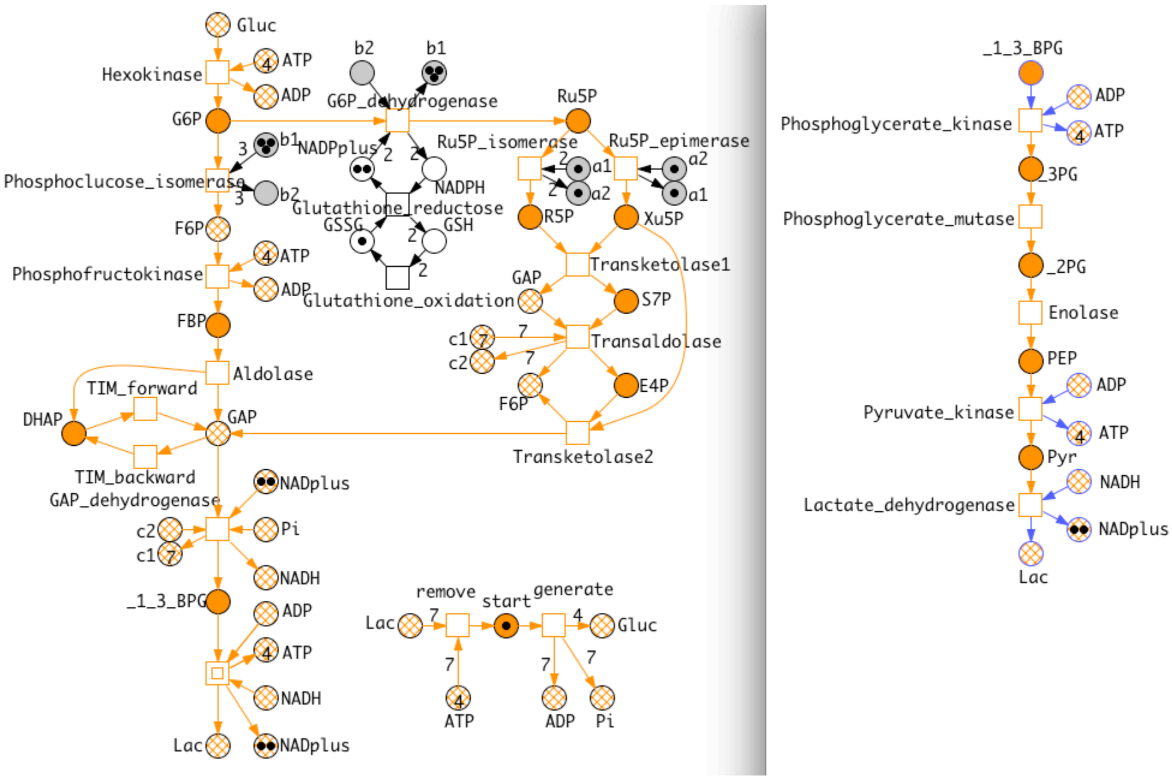
## Description

The interplay of the Glycolytic and Pentose Phosphate Pathways (G-PPP) belongs to the core metabolism of living organisms and is a popular textbook example. It is sufficiently complex to illustrate unexpected effects, even in this simplified version introduced in [RLM96] and elaborated in more detail in [H98], [HK04], and [KH08]. The glycolysis pathway (GP) converts glucose into lactate releasing small amounts of ATP (Adenosine triphosphate), often called the 'molecular unit of currency'. The pentose phosphate pathway (PPP) starts with glucose as well, but produces NADPH, before later rejoining GP.

Metabolic networks are typically open nets and, thus, unbounded. This bounded version has been derived from the open network by determining its total equation and adding its reverse as environment behaviour (the place *start* and its pre/post-transitions), plus controlling critical dynamic conflicts by adding control loops ($a1$–$a2$, $b1$–$b2$, $c1$–$c2$) according to the steady-state ratio of the involved transitions. These control places come in pairs, forming P-invariants. We obtain a self-contained (closed) Petri net; see [KH08] for details.

The net has been constructed with SNOOPY, structural analyses were done with CHARLIE, and model checking (state space generation, checking for empty bad siphons) with MARCIE.

The G-PPP model is parameterized by two quantities $C$ and $N$, which can be chosen individually in any combination. $C$ is the scaling factor for the control part, causing dead states for $C > 1$. $C = 1$ prevents the bad siphons of running empty, keeping the net live and reversible. $N$ is the scaling factor for the ubiquitous substances ATP, $NAD^+$, $NADP^+$, and GSSH.





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- The Petri net layout takes advantage of two SNOOPY features: (1) hierarchy helps to hide a purely linear path of five reactions in a macro transition (drawn as two centric squares, bottom left); its contents is shown on the right; (2) logical nodes (grey or hashed tangerine places) connect net parts while avoiding arc crossing.
- There are 21 minimal bad siphons, their union is given in tangerine or hashed tangerine. Thus, there is no marking fulfilling the Siphon-Trap Property (STP), and the net is not monotonously live [HMS10].
- The shown marking is the minimal 'good' one to get the model bounded+live+reversible, scalable by $N$ while preserving these properties. But there are also initial markings covering the good one and yielding dead states (scaling by $C$), proving the non-monotone liveness of this example.

## References

[H98] M. Heiner: *Application of Petri Nets to Metabolic Networks* (in German); Talk, Humboldt University Berlin, August (1998), slides available at http://www-dssz.informatik.tu-cottbus.de.

[HK04] M. Heiner, I. Koch: *Petri Net Based Model Validation in Systems Biology*; Proc. ICATPN, Springer, LNCS 3099, pp. 216–237, Springer (2004).

[HMS10] M. Heiner, C. Mahulea and M. Silva: *On the Importance of the Deadlock Trap Property for Monotonic Liveness*; Int. Workshop on Biological Processes & Petri Nets (BioPPN), satellite event of Petri Nets 2010, Braga, Portugal, pp. 39–54 (2010).

[KH08] I. Koch and M. Heiner: *Petri Nets*. In Biological Network Analysis, (BH Junker and F Schreiber, Eds.), John Wiley & Sons, pp. 139–179 (2008).

[RLM96] VN. Reddy, ML. Liebman, ML. Mavrovouniotis: *Qualitative Analysis of Biochemical Reaction Systems*. Comput. Biol. Med. 26(1), pp. 9–24 (1996).

## Scaling parameter

| Parameter name | Parameter description | Chosen parameter values |
|---|---|---|
| $C$–$N$ | $C$: scaling factor for the control part, $N$: scaling factor for the ubiquitous substances | 1–1, 1–10, 1–100, 1–1 000, 1–10 000, 1–100 000, 10–10, 10–100, 10–1 000 000 000, 100–10, 100–100, 100–1 000, 100–10 000, 100–100 000, 1 000–10, 1 000–100, 1 000–1 000 (17 in total). |

## Size of the model

Although the model is parameterized, its size does not depend on parameter values.

| | |
|---|---|
| number of places: | 33 |
| number of transitions: | 22 |
| number of arcs: | 83 |

## Structural properties

**ordinary** — *all arcs have multiplicity one* ✗
**simple free choice** — *all transitions sharing a common input place have no other input place* ✗ (a)
**extended free choice** — *all transitions sharing a common input place have the same input places* ✗ (b)
**state machine** — *every transition has exactly one input place and exactly one output place* ✗ (c)
**marked graph** — *every place has exactly one input transition and exactly one output transition* ✗ (d)

(a) the net is not ordinary.
(b) the net is not ordinary.
(c) the net is not ordinary.
(d) the net is not ordinary.

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**connected** — *there is an undirected path between every two nodes (places or transitions)* ✔ [e]
**strongly connected** — *there is a directed path between every two nodes (places or transitions)* ✔ [f]
**source place(s)** — *one or more places have no input transitions* ✗ [g]
**sink place(s)** — *one or more places have no output transitions* ✗ [h]
**source transition(s)** — *one or more transitions have no input places* ✗ [i]
**sink transitions(s)** — *one or more transitions have no output places* ✗ [j]
**loop-free** — *no transition has an input place that is also an output place* ✔ [k]
**conservative** — *for each transition, the number of input arcs equals the number of output arcs* ✗ [l]
**subconservative** — *for each transition, the number of input arcs equals or exceeds the number of output arcs* ✗ [m]
**nested units** — *places are structured into hierarchically nested sequential units* [n] ✗

## Behavioural properties

**safe** — *in every reachable marking, there is no more than one token on a place* ✗ [o]
**deadlock** — *there exists a reachable marking from which no transition can be fired* ? [p]
**reversible** — *from every reachable marking, there is a transition path going back to the initial marking* ? [q]
**quasi-live** — *for every transition $t$, there exists a reachable marking in which $t$ can fire* ✔ [r]
**live** — *for every transition $t$, from every reachable marking, one can reach a marking in which $t$ can fire* ? [s]

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(e) confirmed by CÆSAR.BDD version 2.7 on all 17 instances (see all aforementioned scaling parameter values).
(f) confirmed by CÆSAR.BDD version 2.7 on all 17 instances (see all aforementioned scaling parameter values).
(g) confirmed by CÆSAR.BDD version 2.7 on all 17 instances (see all aforementioned scaling parameter values).
(h) confirmed by CÆSAR.BDD version 2.7 on all 17 instances (see all aforementioned scaling parameter values).
(i) confirmed by CÆSAR.BDD version 2.7 on all 17 instances (see all aforementioned scaling parameter values).
(j) confirmed by CÆSAR.BDD version 2.7 on all 17 instances (see all aforementioned scaling parameter values).
(k) confirmed by CÆSAR.BDD version 2.7 on all 17 instances (see all aforementioned scaling parameter values).
(l) confirmed by PNML2NUPN 1.5.3 on all 17 instances (see all aforementioned scaling parameter values).
(m) confirmed by PNML2NUPN 1.5.3 on all 17 instances (see all aforementioned scaling parameter values).
(n) the definition of Nested-Unit Petri Nets (NUPN) is available from `http://mcc.lip6.fr/nupn.php`
(o) confirmed by CÆSAR.BDD version 2.7 on all 17 instances (see all aforementioned scaling parameter values).
(p) if $C = 1$ then ✗ else ✔.
(q) if $C = 1$ then ✔ else ✗.
(r) if $C = 1$ then implied by liveness else implied by language (firing sequences) inclusion for monotonously increased initial markings.
(s) if $C = 1$ then ✔ else ✗.

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## Size of the marking graphs

| Parameter | Number of reachable markings | Number of transition firings | Max. number of tokens per place | Max. number of tokens per marking |
|---|---|---|---|---|
| 1–1 | 10 380 | 42 408 | 11 | 41 |
| 1–10 | 1 655 346 | 9 555 726 | 47 | 133 |
| 1–100 | 145 476 966 | 869 739 366 | 407 | 1 033 |
| 1–1 000 | 14 353 505 166 | 86 140 343 766 | 4007 | 10 033 |
| 1–10 000 | 1 433 414 987 166 | 8 605 723 187 766 | 40 007 | 100 033 |
| 1–100 000 | ? | ? | ? | $\geq$ 900013 (t) |
| 10–10 | 23 537 012 497 | 210 473 063 264 | 110 | 404 |
| 10–100 | 176 894 515 156 | 1 642 095 510 873 | 407 | 1 280 |
| 10–1 000 000 000 | 176 894 515 156 | 1 642 095 510 873 | 4 000 000 007 | 9 000 000 380 |
| 100–10 | 14 184 612 091 | 119 827 378 533 | 740 | 3 103 |
| 100–100 | 2 454 033 179 726 092 | 23 483 505 980 070 599 | 1 100 | 4 004 |
| 100–1 000 | 20 292 531 036 711 574 | 198 318 550 841 337 903 | 4 007 | 12 800 |
| 100–10 000 | 20 292 531 036 711 574 | 198 318 550 841 337 903 | 40 007 | 93 800 |
| 100–100 000 | ? | ? | ? | $\geq$ 90 1201 (u) |
| 1 000–10 | 14 184 612 091 | 119 827 378 533 | 7 040 | 30 103 |
| 1 000–100 | 1 140 616 996 412 371 | 10 253 231 949 128 928 | 7 400 | 31 003 |
| 1 000–1 000 | ? | ? | ? | $\geq$ 21 001 (v) |

## Other properties

The Petri net is Extended Simple (ES) and covered by P- and T-invariants (CPI, CTI). The Siphon-Trap Property (STP) does never hold (for any marking), because there are 21 bad siphons (siphons not containing a trap).

CTL model checking could be used to check if a minimal bad siphon runs out of tokens, i.e.,

$$EF\,[\,\bigwedge_{i=1}^{k}(p_i = 0)\,],$$

for all $k$ places $p_i$ of a minimal bad siphon. This property will never be true if $C = 1$, but may be a reason for dead states if $C > 1$.

(t) lower bound given by the number of initial tokens.
(u) lower bound given by the number of initial tokens.
(v) lower bound given by the number of initial tokens.