Modeling and Evaluating the Cdc2 and Cyclin Interactions in the Cell Division Cycle with a Time Dependent Petri Net (Case Study)

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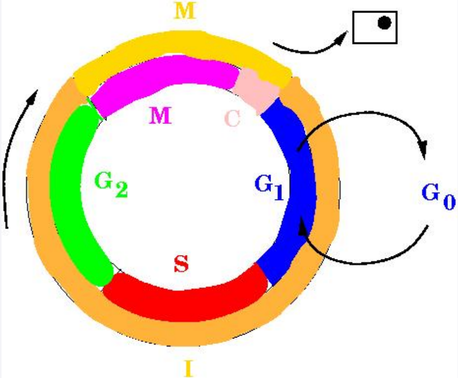
CS & P 2008, Groß Väter, Germany

Outline

Cell Division Cycle



Outer ring:
I = Interphase
M = M-phase
Inner ring:
G_1 = Growth phase 1
S = Synthesis
G_2 = Growth phase 2
M = Mitosis (Karyokinesis)
C = Cytokinesis

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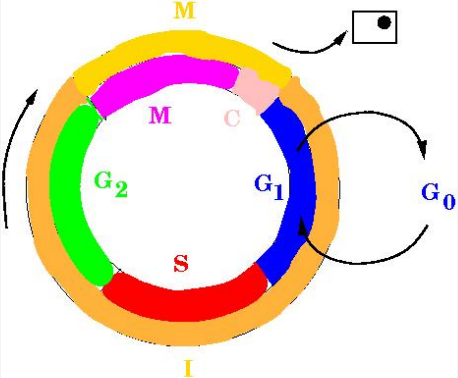

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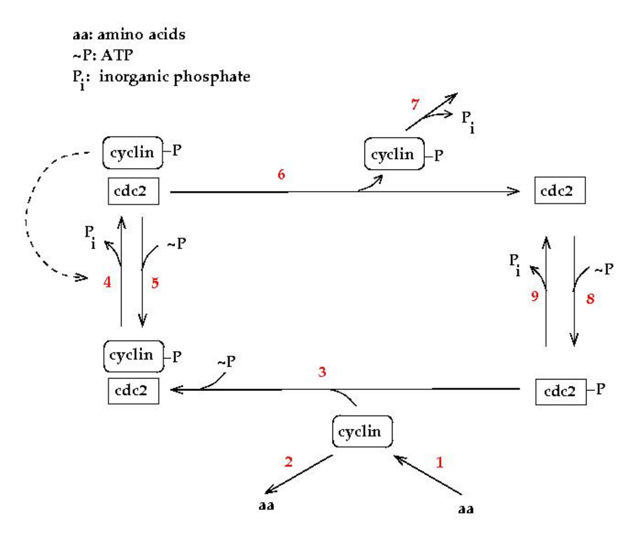
Leland H. Hartwell, R. Timothy Hunt, and Paul M. Nurse won the 2001 Nobel Prize in Physiology or Medicine for their complete description of cyclin and cyclin-dependent kinase mechanisms, central molecules in the regulation of the cell cycle.

The relationship between cyclin and cdc2 in the cell cycle



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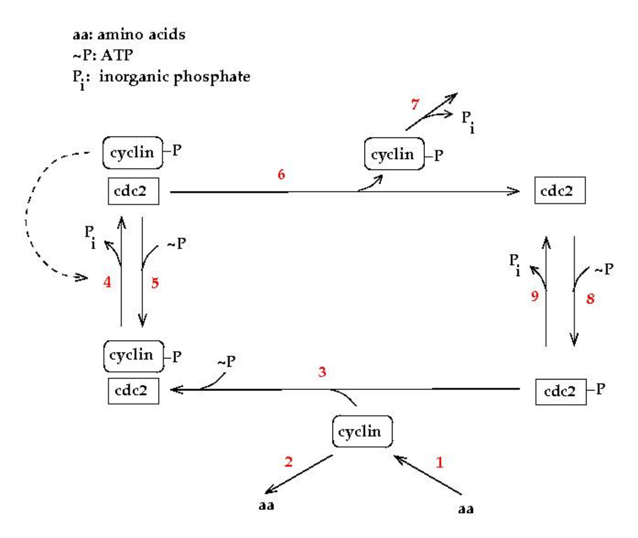

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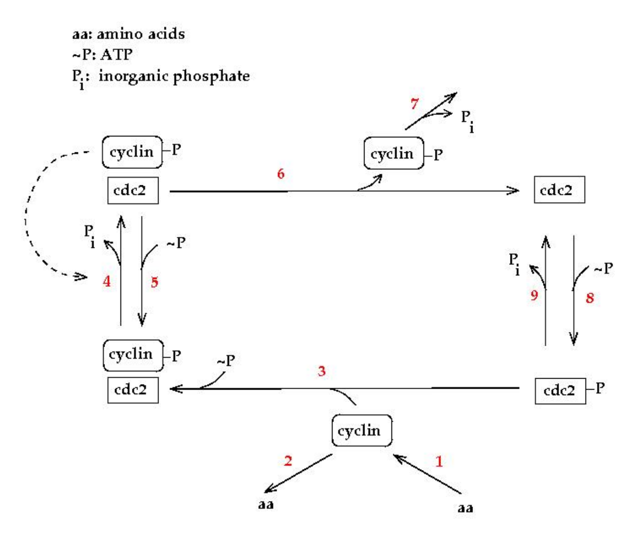

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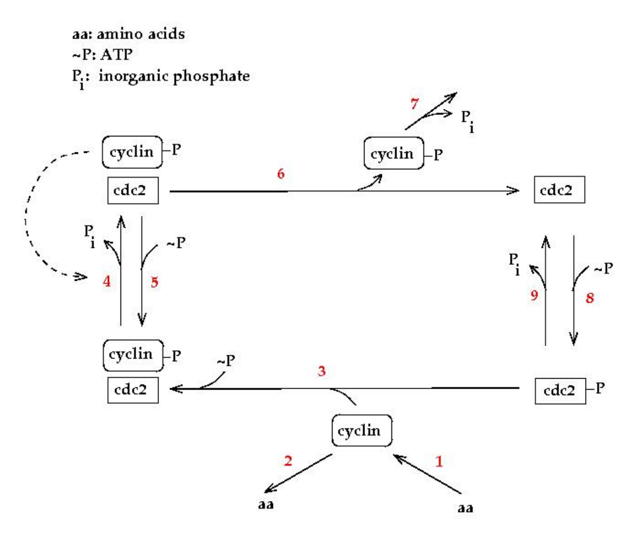

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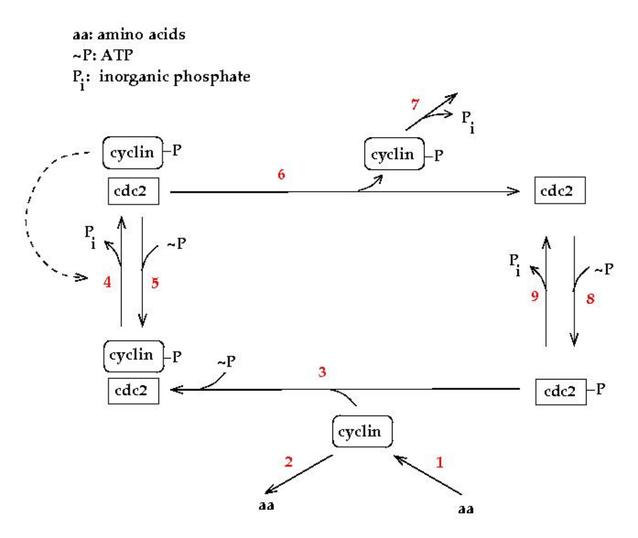

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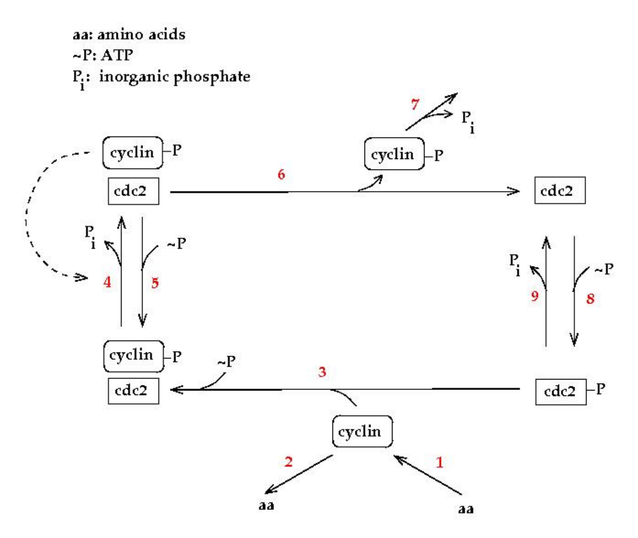

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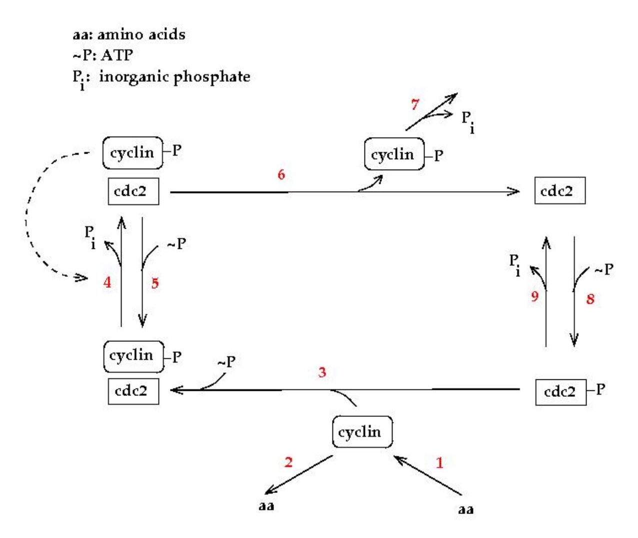

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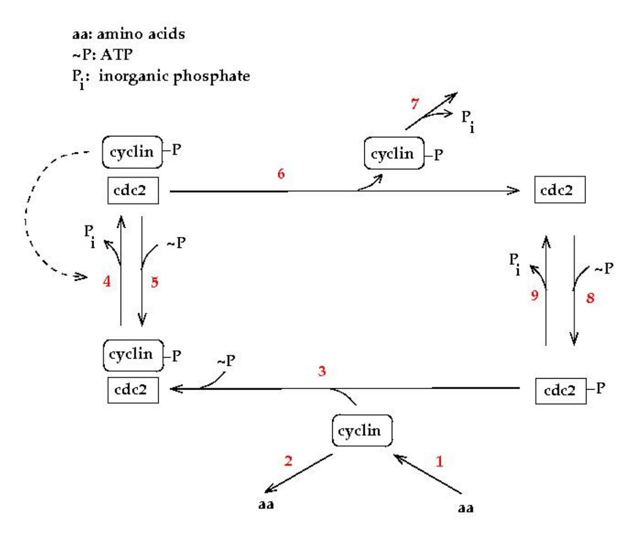

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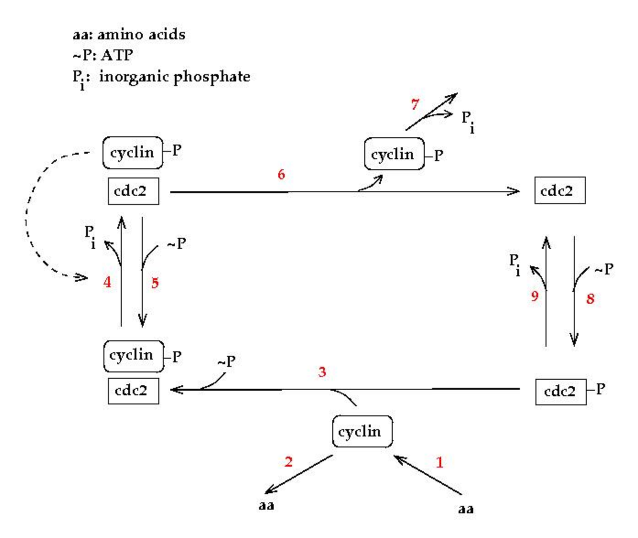

Nuclear division is triggered when a sufficient quantity of MPF has been activated, but concurrently active MPF is destroyed by (step 6). Breakdown of the MPF complex releases phosphorylated cyclin, which is subject to rapid proteolysis (step 7). Finally, the cdc2 subunit is phosphorylated (step 8), possibly reversed by step 9, and the cycle repeats itself.

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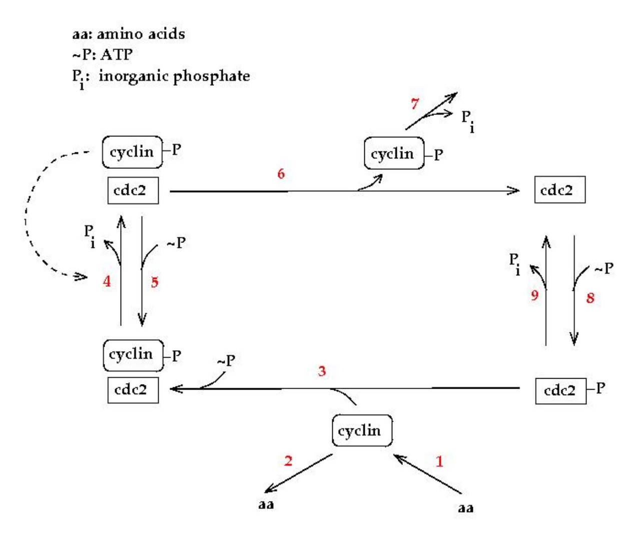

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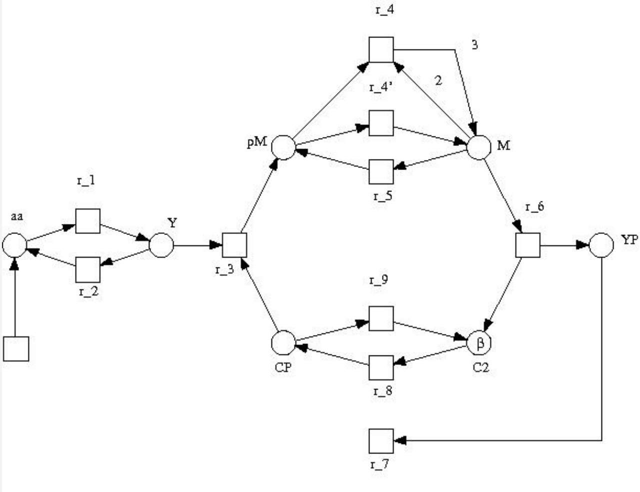
Tyson,J., *"Modeling the cell division cycle: cdc2 and cyclin interactions"*, Prod.Nat.Acad.Sci. USA,Vol. 88, 1991)

The relationship between cyclin and cdc2 in the cell cycle as a PN

A PN model of the continuous system:



Minimum Conditions a Model has to fulfilled

A PN model of the system (a biochemical network) should be

- **bounded** and
- **live**

in the time.

Time Context for the Model

Computing a min/max duration from a min/max rate using the mass-action equation:

- Each reversible reaction $A + B \leftrightharpoons A' + B'$ is described by a mass-action equation. It combines the *rate equations* of the both reactions in the equilibrium.
  - For the reaction $A + B \rightarrow A' + B'$ the *simple rate equation* is of the form:
    $$\text{affinity} = k[A]^a[B]^b.$$
    Writing the dissociated active mass at some point in time as x, the rate of reaction is given as
    $$\frac{dx}{dt} = k([A] - x)^a([B] - x)^b$$
  - *Complicated rate equations* are not of the form above.
- At equilibrium the two rates of reaction and reverse reaction must be equal.

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- using a simple mass-action equation:
  for all transitions except r_4.
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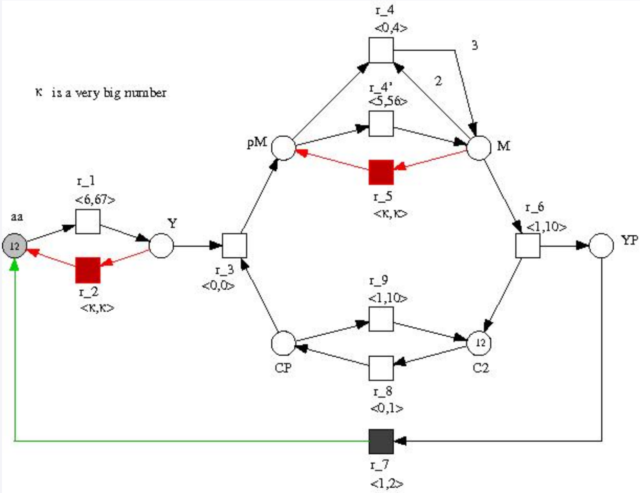
- The time dependent model of the system is a **DIPN (Duration Interval Petri Net)**

Min/max durations values for the Tyson-PN:

t_i	k_i	min_rate	max_rate	min_dur.	max_dur.	$[\lceil$min_dur.$\rceil, \lceil$max_dur.$\rceil]$
r_1	0.015	0.015	0.18	$\frac{100}{18}$	$\frac{200}{3}$	$[6, 67]$
r_3	200	200	28800	$\frac{1}{28800}$	$\frac{1}{200}$	$[0, 0]^1$
r_4	10	$\frac{5}{18}$	$\frac{2560}{144}$	$\frac{144}{2560}$	$\frac{18}{5}$	$[0, 4]$
r_4'	0.018	$\frac{9}{500}$	$\frac{27}{125}$	$\frac{125}{27}$	$\frac{500}{9}$	$[5, 56]$
r_6	0.1	0.1	1.2	$\frac{5}{6}$	10	$[1, 10]$
r_7	0.6	0.6	7.2	$\frac{5}{36}$	$\frac{5}{3}$	$[1, 2]$
r_8	10	10	1200	$\frac{1}{120}$	$\frac{1}{10}$	$[0^1, 1]$
r_9	0.1	0.1	1.2	$\frac{5}{6}$	10	$[1, 10]$

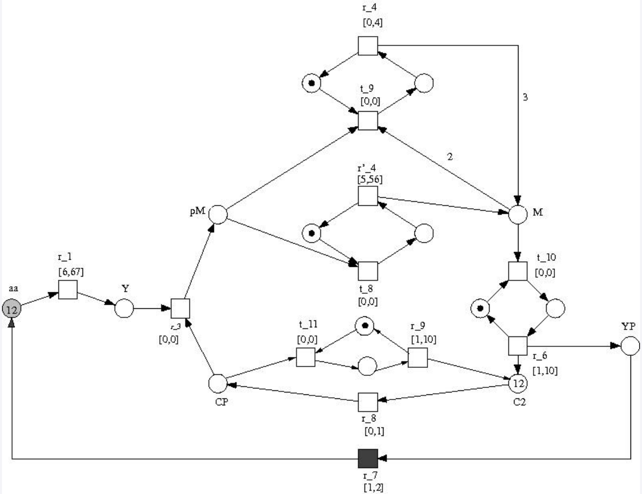
The relationship between cyclin and cdc2 in the cell cycle as a DIPN

A DIPN model :



The relationship between cyclin and cdc2 in the cell cycle as a TPN

Translation of the DIPN model into a TPN model:



Basic Properties

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The DIPN model is **bounded** and **live?**, because:

- The skeleton is bounded. Its state space contains 101,840 markings. Proved with INA and proved with tina.
- The construction of the reachability graph for the TPN failed with "memory exhausted", after computation of 384 millions states in about 41 hours. Proved with tina.

Quantitative Properties

- The minimal time distance between the initial state and an arbitrary state in which k_4 is ready to fire is 24 min; Proved with tina.

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- The minimal time distance between the initial state and an arbitrary state in which *k_4* is ready to fire is 24 min; Proved with tina.
- The feasible run which realizes the distance 24 min is
  $0,\ t6,\ 0,\ t11,\ 0,\ t6,\ 0,\ t6,\ 0,\ t6,\ 6,\ t0,\ 0,\ t1,\ 0,\ t7,\ 0,\ t11,\ 0,\ t6,$
  $0,\ t8,\ 6,\ t0,\ 0,\ t1,\ 2,\ t2,\ 0,\ t10,\ 0,\ t7,\ 0,\ t11,\ 0,\ t6,\ 0,\ t8,\ 4,\ t0,$
  $0,\ t1,\ 1,\ t2,\ 0,\ t7,\ 0,\ t6,\ 0,\ t11,\ 0,\ t8,\ 5,\ t0,\ 0,\ t2,\ 0,\ t4,\ 0,\ t6,$
  $0,\ t1,\ 0,\ t7,\ 0,\ t6,\ 0,\ t11,\ 0,\ t9$
  and it consists of 35 transitions.

Quantitative Properties

- The maximal time distance between the initial state and an arbitrary state in which k_4 is ready to fire (ignoring loops) cannot be computed at present because of the size of the state space.

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- A lower bound for such a maximal time distance is 107 min.
- The feasible run which realizes the distance 107 min consists of 61 transitions.

A Short Part of the Bibliography

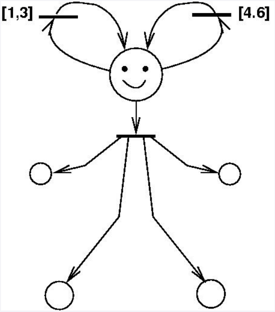
Popova-Zeugmann, L.
Time and Petri Nets (in German).
Habilitation Thesis, Humboldt University at Berlin, Berlin, 2007.

Popova-Zeugmann, L. .
Quantitative Evaluation of Time Dependent Petri Nets and Applications to Biochemical Networks.
(to appear), 2008.

Tyson, J.J.
Modeling the cell division cycle: cdc2 and cyclin interactions.
In *Proceedings of the National Academy of Sciences of the United States of America*, volume 88(16), pages 73328–7332, 1991.

For more see:
http://http://www2.informatik.hu-berlin.de/∼starke/ina.html
http://www.laas.fr/tina/

Thank you!



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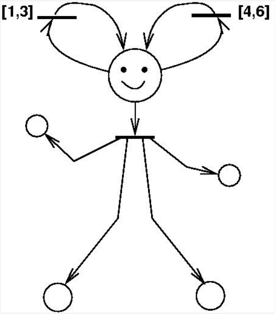

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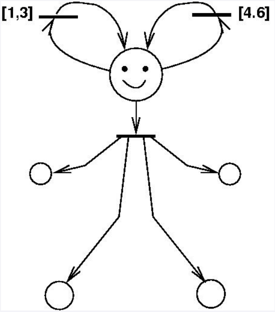
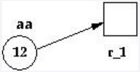


Computation the minimal and maximal durations for the transition *r_1*:

$$r_1 = k_1 \cdot [aa] \Longrightarrow$$
$$r_{1-min} = 0.015 \cdot 1 = 0.015 \Longrightarrow max\_dur(r\_1) = \frac{200}{3}$$
$$r_{1-max} = 0.015 \cdot 12 = 0.18 \Longrightarrow min\_dur(r\_1) = \frac{50}{9}$$



Computation the minimal and maximal durations for the transition *r_3*:

$$r_3 = k_3 \cdot [Y] \cdot [CP] \Longrightarrow$$
$$r_{3-min} = 200 \cdot 1 \cdot 1 = 200 \Longrightarrow max\_dur(r\_3) = \frac{1}{200}$$
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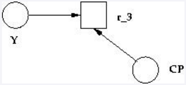

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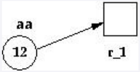

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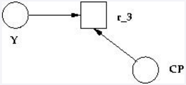

Computation the minimal and maximal durations for the transition *r_4*:

$$r_4 = k_4 \cdot [pM] \cdot (\tfrac{[M]}{[CT]})^2, \text{ and } [CT] = [pM] + [M] + [C2] + [CP] \Longrightarrow$$
$$r_{4-min} = 10 \cdot 1 \cdot (\tfrac{2}{12})^2 = \frac{10}{36} \Longrightarrow max\_dur(r\_4) = \frac{18}{5}$$
$$r_{4-max} = 10 \cdot 4 \cdot (\tfrac{8}{12})^2 = \frac{160}{9} \Longrightarrow min\_dur(r\_4) = \frac{9}{160}$$