

**Worksheet: STANDARDS, SOFTWARE, DATABASES and  
STRUCTURAL ANALYSIS (29. May 2012)  
Lecture "Computational Systems Biology", Dr. Jürgen Pahle**

1) Navigate to the Biomodels database at <http://www.ebi.ac.uk/biomodels-main> and download the model that is described in the article Leloup JC, Goldbeter A (1999) Chaos and birhythmicity in a model for circadian oscillations of the PER and TIM proteins in drosophila. *J Theor Biol* **198**(3):445-59.

- a) Investigate the SBML code. Which databases do the MIRIAM annotations link the different entities to? What is "RDF"? Does the SBML model contain a "list of rules". What for?
- b) Import the model in COPASI, define an appropriate plot and simulate it over 100 s. What does the asymptotic dynamics look like? Does the model also have a steady state with this parameter set? If yes, what is its stability?

2) A canonical view of the upper part of glycolysis starts with glucose and comprises the following reactions (in brackets: possible abbreviations): The enzyme hexokinase (HK, E1) phosphorylates glucose (Gluc, S1) to glucose-6-phosphate (G6P, S2) under consumption of ATP (S5) and production of ADP (S6). The enzyme phosphoglucosomerase (PGI, E2) converts glucose-6-phosphate to fructose-6-phosphate (F6P, S3). The enzyme phosphofructokinase (PFK, E3) phosphorylates F6P a second time to yield fructose-1,6-bisphosphate (F16BP, S4). The enzyme fructosebisphosphatase (E4) catalyzes the reverse reaction.

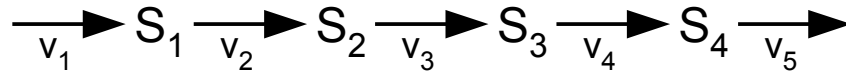
- a) Sketch the reaction network and formulate a set of differential equations (without specifying the kinetics of the individual reactions).
- b) Formulate the stoichiometric matrix  $N$ . What is the rank of  $N$ ?
- c) Calculate steady state-fluxes (matrix  $K$ ) and conservation relations (matrix  $G$ ).

3) Given the following networks:

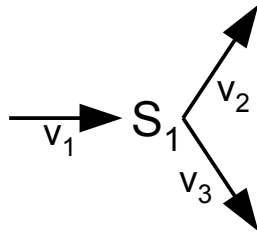
N1:

$$S_1 + S_2 + S_3 \xleftrightarrow{v_1} S_4 + 2 S_5$$

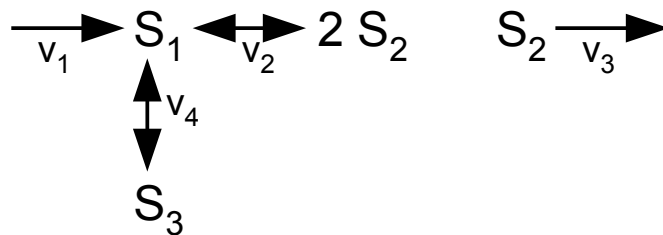
N2:



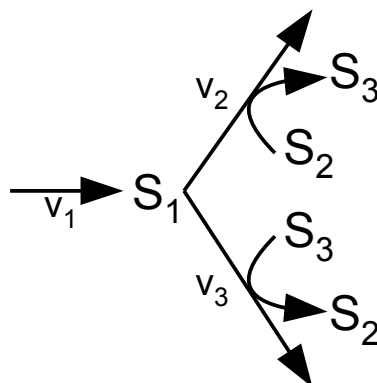
N3:



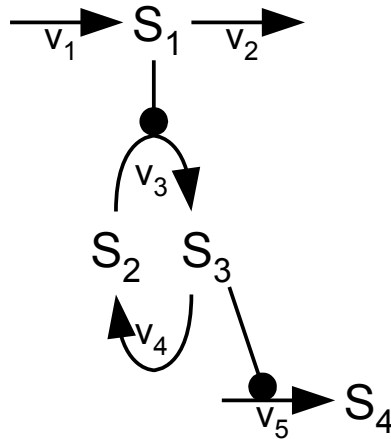
N4:



N5:



N6:



(arrows with filled circles at the end denote activation)

- Write down the sets of differential equations for the networks N1 - N6 given above without specifying their kinetics.
- Determine the rank of the stoichiometric matrices, independent steady state-fluxes, and conservation relations.

Do all systems have a (nontrivial) steady state?

4) Inspect networks N3 and N4 given in 3). Can you find elementary flux modes? Use an available tool (COPASI, Metatool, etc.) to check this.