The exam contains 3 essay questions, 4 problem solving questions and 10 short questions. Essay and problem solving questions give 5 points each. Short questions give 1 point each.

- The **questions 1, 2, 4 and 5** are connected to Systems biology and –omics lectures. **Choose three out of the four questions.**
- The **questions 3, 6 and 7** are connected to Metabolic modeling lectures. **Choose two out of three questions.**

Answering more than the required number of questions does not give additional points!

Essay questions:

1. Essay Question (5 points)

A main feature of the concept of Systems Biology is the importance attributed to interactions between cellular components. A) Reflect on the validity of this concept. B) What type of interactions exist within the cellular context and how can they be experimentally addressed?

2. Essay Question (5 points)

Mass spectrometry is routinely used for proteomics studies. Describe the complete workflow from sample preparation until obtaining the results (also discuss the type of instruments used, data handling)). What additional information can be obtained by using chemical or metabolic labeling strategies?

3. Essay Question (5 points)

Metabolic flux analysis (in relation to individual pathway rates in the network)

Problem solving questions:

4. Problem-solving (5 points)

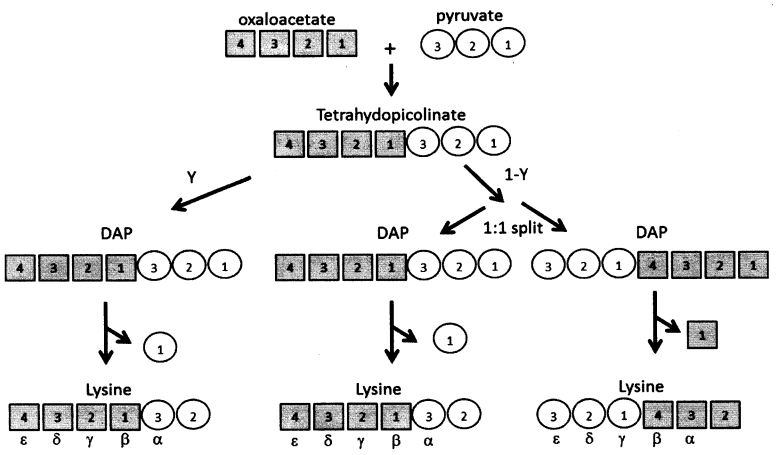
You are working as a consultant in a Life Science Company specializing in the development of tests for personalized medicines. Your task is to prepare a proposal for the management in which of the –omics techniques (genomics, transcriptomics, proteomics, metabolomics) to invest and why, in case:

a) the disease is caused by point mutations in the promoter regions of several genes leading to increased expression levels of the encoded glycolytic enzymes.
b) the disease is caused by the proteolytic processing of the target proteins. The disease is believed to be caused by exposure to an environmental toxin.

5. Problem-solving (5 points)

In bacteria lysine is derived from the precursor metabolites oxaloacetate and pyruvate, which in a series of reactions are converted into tetrahydrodipicolinate (H4D). H4D is converted to meso-α,ε-diaminopimelate (DAP), and this conversion may proceed via two different routes. In the last step meso-DAP is decarboxylated to lysine. The four-step pathway involves a symmetric intermediate, and the epimerase catalyzing the last step in the pathway may therefore lead to formation of DAP with two different carbon compositions (both configurations contribute 50% to the lysine produced). From the analysis of the labeling pattern you know that 70% of the lysine is labeled at ß-carbon, 30% of the lysine is labeled at the γ-carbon atom.

a) Calculate the flux ratios for the 3 different reactions
b) Which position of the precursor molecules (pyruvate and oxaloacetate) have been labeled?



6. Problem-solving (5 points)

Assume that you have carried out an anaerobic S*accharomyces cerevisiae* fermentation. Substrates were glucose (s) and ammonia (n). Metabolic products included carbon dioxide (c), water (w), ethanol (e) and glycerol (g). The composition of biomass was $CH_{1.61}O_{0.52}N_{0.15}$ and stoichiometry can be described following:

$$-CH_2O - Y_{sn}NH_3 + Y_{sx}CH_{1.61}O_{0.52}N_{0.15} + Y_{sc}CO_2 + Y_{se}CH_3O_{0.5} + Y_{sg}CH_{8/3}O + Y_{sw}H_2O = 0$$

The fermentation was modeled using a black-box model with volumetric yield and consumption rates q_s, q_x and q_g as measured variables and the rest of the fluxes, i.e. q_c, q_n, q_w and q_e as calculated variables as functions of the measured variables, and solved as follows:

$$\begin{pmatrix} q_c \\ q_n \\ q_w \\ q_e \end{pmatrix} := \begin{pmatrix} -0.333 & -0.313 & -0.222 \\ 0 & -0.15 & 0 \\ 0 & 0.45 & -0.167 \\ -0.667 & -0.687 & -0.778 \end{pmatrix} \cdot \begin{pmatrix} q_s \\ q_x \\ q_g \end{pmatrix}$$

Calculate the yield coefficients Y_{sn}, Y_{sc}, Y_{se} and Y_{sw} and q_c, q_n, q_w and q_e for the reaction when biomass yield from substrate Y_{sx}=0,128, glycerol yield from biomass Y_{xg}=0,67, specific growth rate was 0,1 h^{-1} and the biomass concentration was 14 g/L. Finally, calculate carbon balance and the reduction balances with the yield coefficients.

a) Suppose that the enzyme pathway follows Michaelis-Menten kinetics and v_{max} = 50 and K_M= 0,08 mM:

$$v = \frac{S \cdot v_{max}}{S + K_M}$$

What is the elasticity of the enzyme to the substrate, when the substrate concentration is 1) 0,03 mM and 2) 0,25 mM?

b) Citrulline is synthesized in mitochondria with reactions:

1) $NH_4^+ + HCO_3^- + 2ATP \rightarrow carbamoylP + 2ADP + P_i$

2) $carbamoylP + ornithine \rightarrow citrulline + P_i$

The reaction *1)* is catalyzed by a carbamoyl phosphate synthase (CPS), and the reaction *2)* by ornithine transcarbamoylase (OTC). If the elasticity of these two enzymes in relation to carbamoyl phosphate (cp) are $\varepsilon_{cp}^{CPS} = -0{,}05$ and $\varepsilon_{cp}^{OTC} = 0{,}85$, what are the values of their relative flux control coefficients C_{CPS}^{J} and C_{OTC}^{J} and which enzyme has the main flux control?

Short questions:

Define/describe shortly (1 point per question). All questions must be answered.

A. What is the significance of gene ontologies?
B. next generation sequencing
C. hierarchical clustering
D. selected reaction monitoring
E. microarray
F. what is a module or network motif
G. How to regenerate the NAD+ lost in glycolysis?
H. What is the main focus of genome-scale modeling?
I. What does the connectivity theorem state?
J. What are overdetermined systems?