Patent Claims

1. A method for determining if process data acquired during the cultivation of a mammalian or bacterial cell is affected by a problem comprising the following steps:

- fitting the process data acquired during the cultivation of the mammalian or bacterial cell expressing a recombinant, heterologous polypeptide using a metabolic model generated for the same mammalian or bacterial cell expressing the same recombinant, heterologous polypeptide,

- determining that the cultivation is affected by a problem if
(i) the modeled fit shows an offset with respect to the raw data of more than 10 %,
or
(ii) the modeled fit has a chi^2 value determined by a Pearson's chi-squared test of more than 5.

2. A method for selecting a cell expressing a heterologous polypeptide, wherein the method comprises the following steps:

a) separately cultivating a multitude of mammalian or bacterial cell clones that produce the same heterologous polypeptide, whereby during the cultivating temporal process data is recorded,

b) fitting the process data acquired in step a) of each clone individually using the same metabolic model, which had been generated for the same mammalian or bacterial cell,

c) determining that a cultivation of step a) is affected by a problem if the fit obtained in step b) for the process data of said cultivation obtained in step a) in said metabolic model (i) shows an offset with respect to the raw data of more than 10 %, or (ii) the chi^2 value determined by a Pearson's chi-squared test for the fit is 5 or more,

d) repeating steps a) to c) with the clones that had a problem in the cultivation as determined in step c)
or
if no clone had a problem in the cultivation as determined in step c)

selecting the clone from the multitude of clones as cell expressing a heterologous polypeptide that has (i) the highest titer, and/or (ii) the highest level of intended product quality attribute(s), and/or (iii) the preferred metabolic phenotype/highest rang in metabolic performance indicators.

3. The method according to any one of claims 1 to 2, wherein the chi^2 value determined by a Pearson's chi-squared test for the fit is 1 or more.

4. The method according to any one of claims 1 to 3, wherein the cell is (i) a mammalian cell is a CHO cell, and/or (ii) a bacterial cell is E. coli.

5. The method according to any one of claims 1 to 4, wherein the heterologous polypeptide is an antibody.

6. The method according to any one of claims 1 to 5, wherein the process data comprises the temporal values of at least 15 process parameters.

7. The method according to any one of claims 1 to 6, wherein the process data comprises the temporal values of at least 12 on-line process parameters and at least 28 off-line process parameters.

8. The method according to any one of claims 1 to 7, wherein the process data comprises at least 6 temporal values for each process parameter.

9. The method according to any one of claims 1 to 8, wherein
   - the metabolic model is a genome-based metabolic model, and/or
   - the metabolic model comprises the five compartments cytosol, mitochondria, endoplasmatic reticulum, Golgi apparatus and bioreactor, and/or
   - the metabolic model comprises the central metabolic pathways of glycolysis, citric acid cycle, pentose phosphate pathway, and respiratory chain, the biosynthesis of the major biomass constituents' protein, lipid, RNA, DNA, and carbohydrates, C1-metabolism, and amino acid degradation pathways.

10. The method according to any one of claims 1 to 9, wherein the metabolic model includes at least 600 reactions, 500 metabolites and 250 genes.

11. The method according to any one of claims 1 to 10, wherein the problem is resulting from bacterial or fungal contamination of the cultivation, or associated with a hardware used for performing or monitoring the cultivation.