# Practical Exercise: Metabolic Networks

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COBRApy is a python implementation of COnstraint-Based Reconstruction and Analysis (COBRA, originally written for MATLAB ) methods, a set of tools that allows us manipulate metabolic models. Class Model of COBRApy is presented in Figure 1.

## 2.1 Testing COBRApy installation

To test you COBRApy installation, execute the following:

```
from cobra.test import test_all
```

**Object**
id: str
notes: dict
annotation: dict

**Model**
compartments: dict
description: str
genes: DictList
metabolites: DictList
reactions: DictList
solution: Solution
add_reactions()
optimize()
remove_reactions()
to_array_based_model()

**Reaction**
gene_reaction_rule: str
lower_bound: float
name: str
objective_coefficient: float
reaction: str
upper_bound: float
add_metabolites()
check_mass_balance()
get_coefficients()
get_gene()
get_model()
get_products()
get_reactants()
remove_from_model()
subtract_metabolites()

**Metabolite**
charge: float
compartment: str
formula: Formula
name: str
get_model()
get_reaction()
remove_from_model()

**Solution**
f: float
status: str
solver: str
x: numpy.array
x_dict: dict
y: numpy.array
y_dict: dict

**Formula**
elements: dict
formula: str
weight: float

**Gene**
functional: bool
locus_end: int
locus_start: int
strand: str

**DictList(list)**
get_by_id()
query()

**ArrayBasedModel**
S: scipy.sparse
b: numpy.array
constraint_sense: list
lower_bounds: numpy.array
objective_coefficients: numpy.array
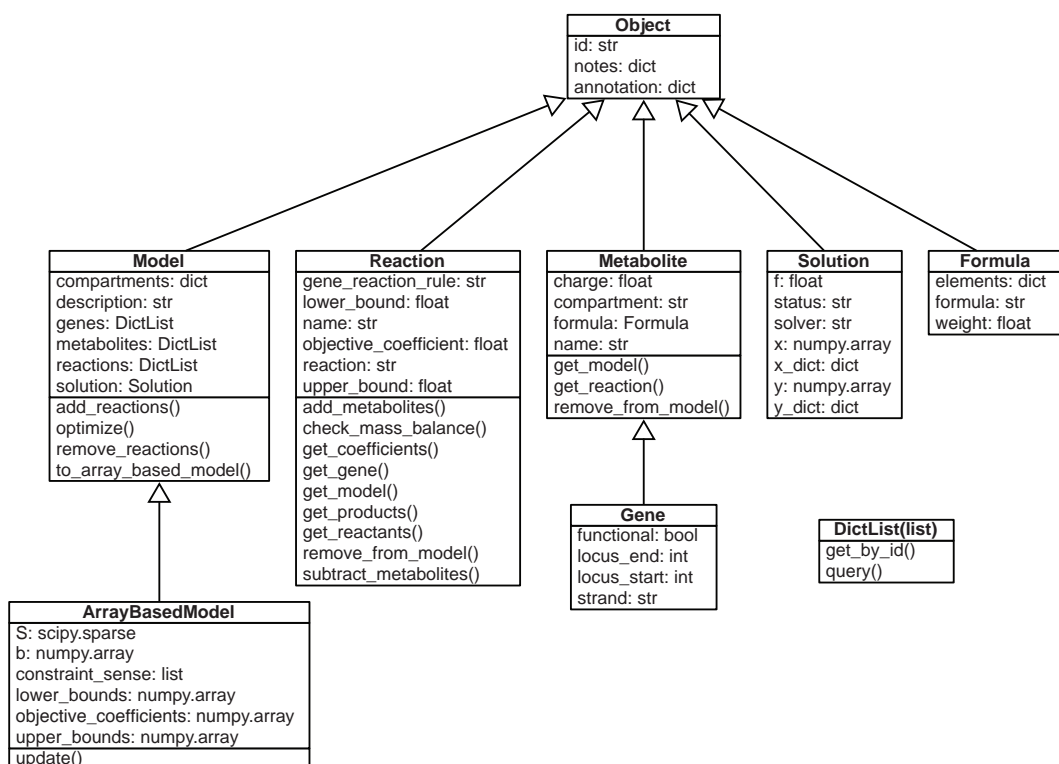upper_bounds: numpy.array
update()

Figure 1: Core clases in COBRApy with their attributes and methods list. Additional attributes and methods are described in the docummentation. From [1]

```
test_all()
```

## 2.2  Generating a Metabolic Model Step by Step

# 3  Case Study: Core *Escherichia coli* Network

In this section, we will use the core *Escherichia coli* metabolism as network, figure 2.

To begin, we will load the model from the smbl file:

```
model = cobra.io.read_sbml_model("ecoli_core_TP.xml")
```

How many reactions and metabolites compose the model? Which is the objective function of the model? Use information of Figure 1 to investigate the model.

## 3.1  Performing a FBA

Performing a FBA is easy using COBRApy:

```
sol = model.optimize()
```

We can explore effects of certain variables in the model. For example, reaction EX_glc_e_ has a lower bound of -10, representing glucose intake rate. How different glucose intake rates affect the maximal growth?

Create an array of maximal growth rates, using a loop to change lower bounds.

### 3.1.1  Using matplotlib for graphical representation

**matplotlib** (http://matplotlib.org/) is a 2D plotting library for python. We will use this library to make graphical representation of our results.

The following code is used to produce a simple plot, where x and y are numerical vectors:

```
import matplotlib.pyplot as plt
import numpy as np
```

```
 x = np.arange(-100,100)
 y = x*x

lines, = plt.plot(x,y)
```

Modify the code above to show the variation of the maximal growth rate with respect to glucose intake.

## 3.2   Flux Variability Analysis

Flux Variability Analysis is a technique which allows us study the possible variation of fluxes in a model. In general, we maximize and minimize each flux, imposing an additional constraint over the biomass flux (e.g, 90% of their maximal value).

COBRApy already incorporate this tool:

```
fva=cobra.flux_analysis.flux_variability_analysis(model,
fraction_of_optimum=0.9)
```

Using **matplotlib**, try to get a graphical representation of the fluxes.

## 3.3   Gene knock out

As mentionned, genes code for enzymes that may catabolyze one or several reactions. Performing a gene knock out thus corresponds to force the flux value of these reactions to zero (by playing with the upper and lower bounds). This has obviously some effects on the optimal growth rate.

`cobra.flux_analysis.single_deletion` computes the growth rates after having knocking out every genes one by one.

# References

[1] Ebrahim, A., Lerman, J. A., Palsson, B. O. & Hyduke, D. R. **COBRApy: COnstraints-Based Reconstruction and Analysis for Python**. BMC Syst Biol 7, 1-1 (2013).

[2] Orth, J, Fleming, R, Palsson, B. **Reconstruction and Use of Microbial Metabolic Networks: the Core Escherichia coli Metabolic Model as an Educational Guide**. EcoSal Plus (2010); doi:10.1128/ecosalplus.10.2.1
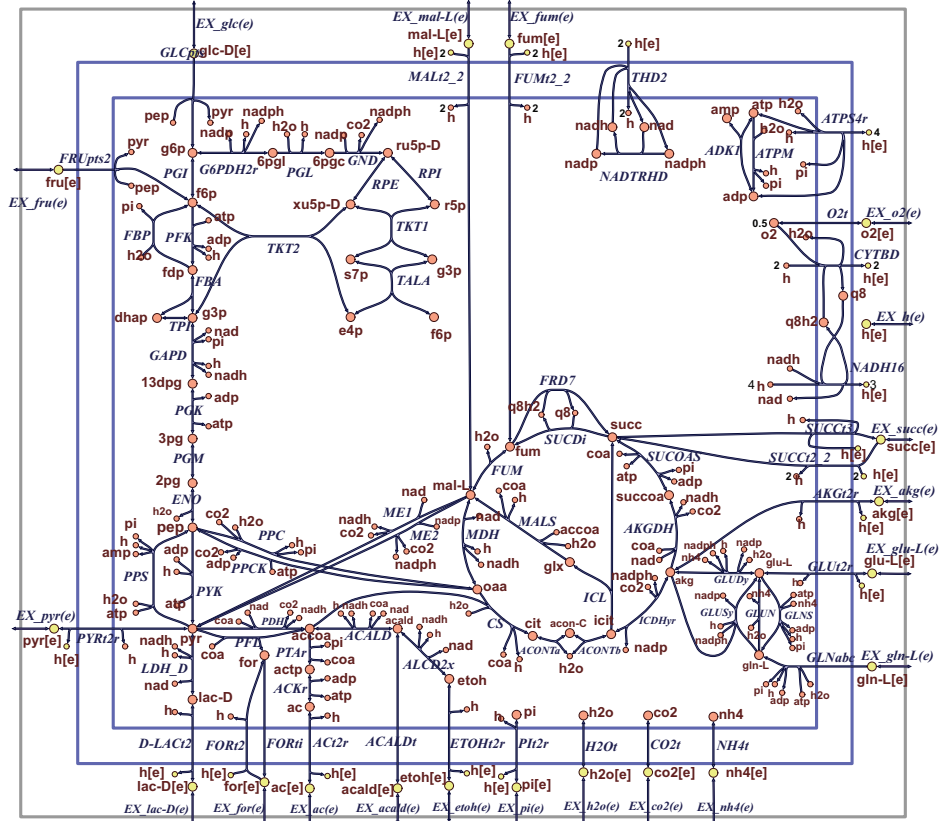
Figure 2: An overview of core *E. coli metabolism*. Grey box represent the boundary between the model and the environmental source of substrates and sink for waste metabolites. The outer and inner blue boxes represents the outer and inner surface of the cytoplasmic membrane. The periplasmic space is outside the scope of the model. Cytosolic metabolites are represented by orange circles and extracellular metabolites are represented by yellow circles. From [2].