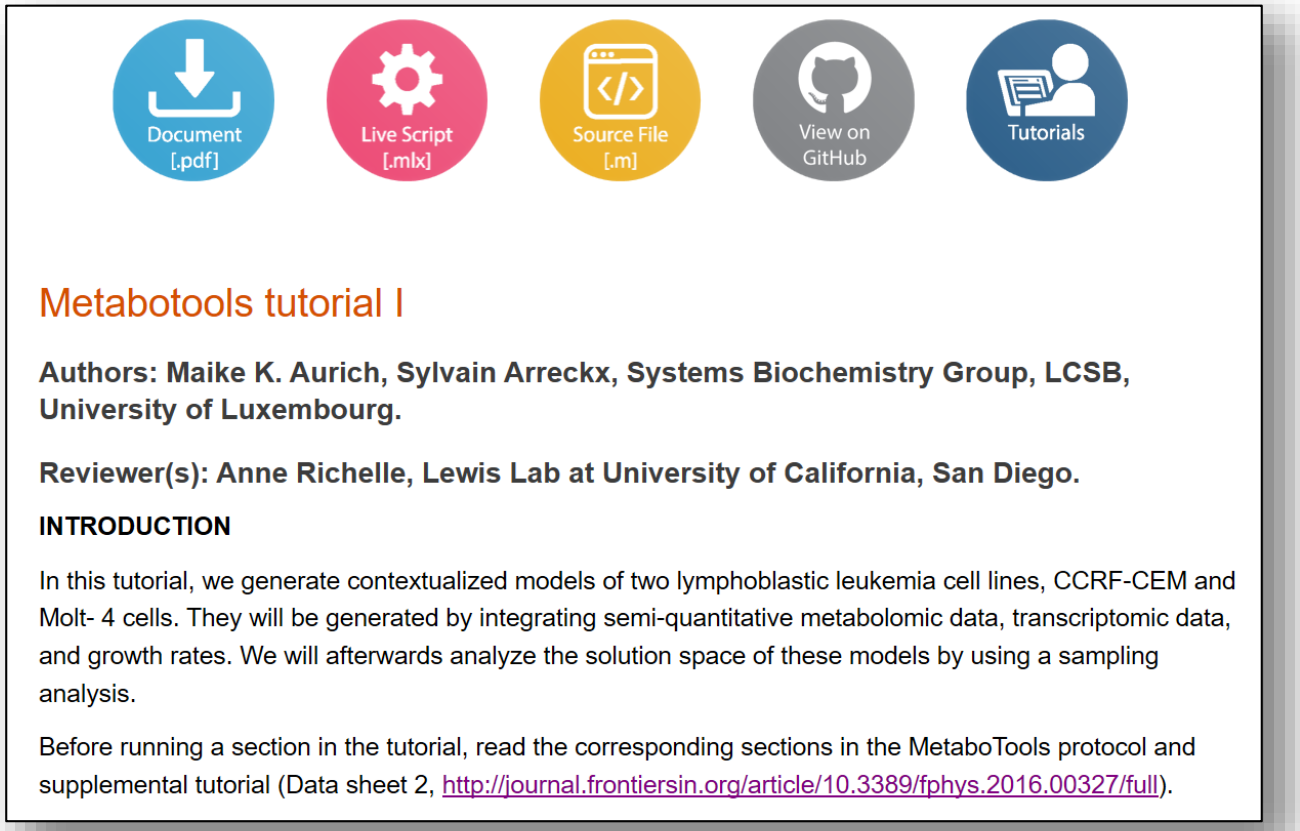
Semi-quantitative Condition-Specific Model Creation

Semi-quantitative Model Creation

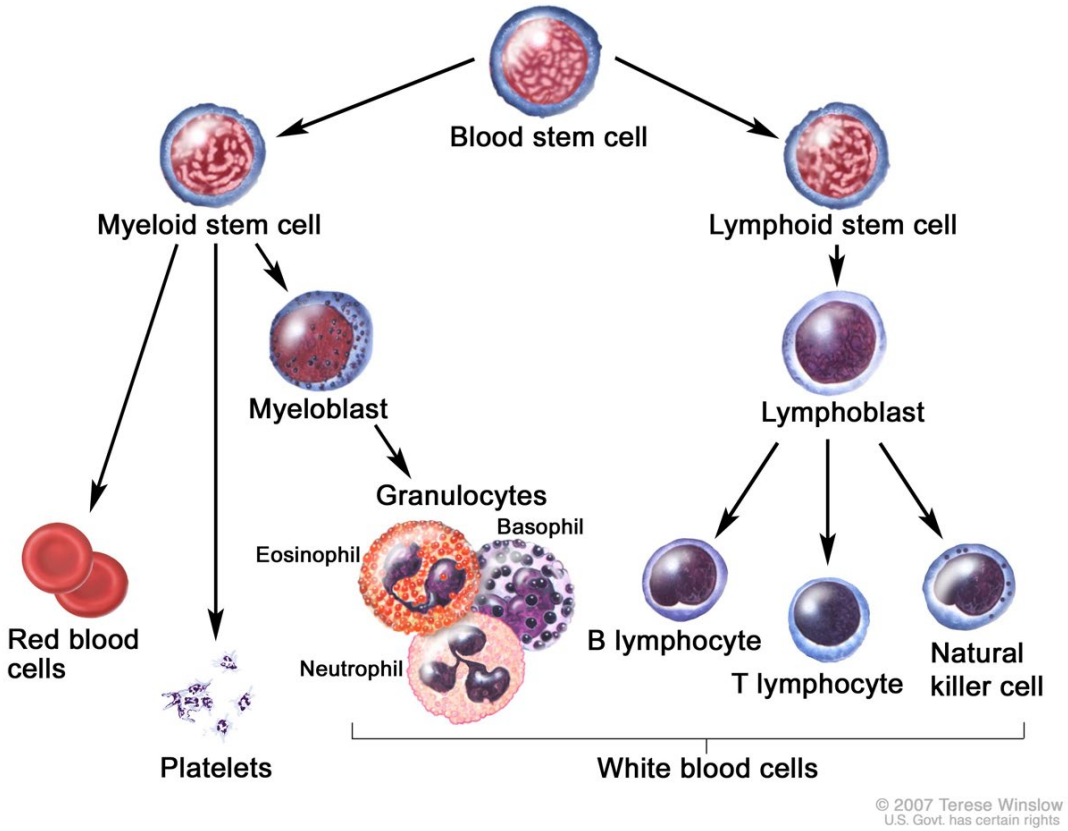
- Based on Matlab Metabotools tutorials
  - *Aurich, Maike K., Ronan MT Fleming, and Ines Thiele. "MetaboTools: a comprehensive toolbox for analysis of genome-scale metabolic models." Frontiers in physiology (2016): 327.*
- Generate context-sensitive models for two different leukemia cell lines from semi-quantitative metabolomic data, transcriptomic data and growth rates.
  - *Aurich, Maike K., et al. "Prediction of intracellular metabolic states from extracellular metabolomic data." Metabolomics 11.3 (2015): 603-619.*
- Analyze the solution space of these models using sampling analysis



https://opencobra.github.io/cobratoolbox/stable/tutorials/tutorialMetabotoolsI.html

Childhood Acute Lymphoblastic Leukemia (ALL)

- Childhood acute lymphoblastic leukemia (ALL) is a type of cancer in which the bone marrow makes too many immature lymphocytes (a type of white blood cell).
- In a healthy child, the bone marrow makes blood stem cells (immature cells) that become mature blood cells over time. A blood stem cell may become a myeloid stem cell or a lymphoid stem cell.
- A myeloid stem cell becomes one of three types of mature blood cells:
  - Red blood cells that carry oxygen and other substances to all tissues of the body.
  - Platelets that form blood clots to stop bleeding.
  - White blood cells that fight infection and disease.
- A lymphoid stem cell becomes a lymphoblast cell and then one of three types of lymphocytes (white blood cells):
  - B lymphocytes that make antibodies to help fight infection.
  - T lymphocytes that help B lymphocytes make the antibodies that help fight infection.
  - Natural killer cells that attack cancer cells and viruses.
- In a child with ALL, too many stem cells become lymphoblasts, B lymphocytes, or T lymphocytes. The cells do not work like normal lymphocytes and are not able to fight infection very well. These cells are cancer (leukemia) cells. Also, as the number of leukemia cells increases in the blood and bone marrow, there is less room for healthy white blood cells, red blood cells, and platelets. This may lead to infection, anemia, and easy bleeding.



"Childhood Acute Lymphoblastic Leukemia Treatment". *National Cancer Institute*. 8 December 2017. Retrieved 20 December 2017.

Lymphoblastic Leukemia Cell Lines

MOLT-4 Cell Line (CRL-1582)	
Organism	*Homo sapiens, human*
Cell Type	T lymphoblast
Product Format	frozen
Morphology	lymphoblast
Culture Properties	suspension
Disease	acute lymphoblastic leukemia
Age	19 years
Gender	male
Applications	This cell line is a suitable transfection host.
Storage Conditions	liquid nitrogen vapor phase

https://www.atcc.org/products/all/CRL-1582.aspx

CCRF-CEM Cell Line (CCL-119)	
Organism	*Homo sapiens, human*
Cell Type	T lymphoblast, peripheral blood
Product Format	frozen
Morphology	lymphoblast
Culture Properties	suspension
Disease	acute lymphoblastic leukemia
Age	4 years juvenile
Gender	female, Caucasian
Applications	This cell line is a suitable transfection host.
Storage Conditions	liquid nitrogen vapor phase

https://www.atcc.org/products/all/CCL-119.aspx

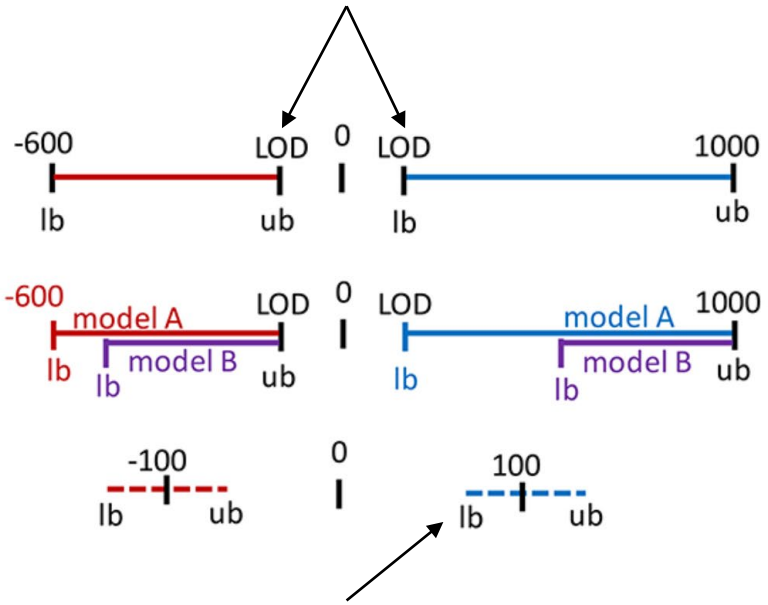
Comparing the Performance of Two Condition-Specific Cell Line Models

Select the exchange reactions to be used by the models based on the media (RPMI 1640), the metabolomics data, and other special constraints

Using the metabolomics data to determine if an exchange reaction uptakes and which secretes

Using the slope ratio of the metabolomics data to determine the relative difference in the lower bounds of the two cell line's exchange reactions

Set constraint bounds based on experimental limit of detection (LOD)

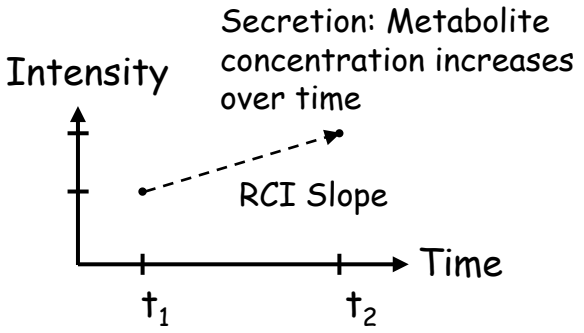


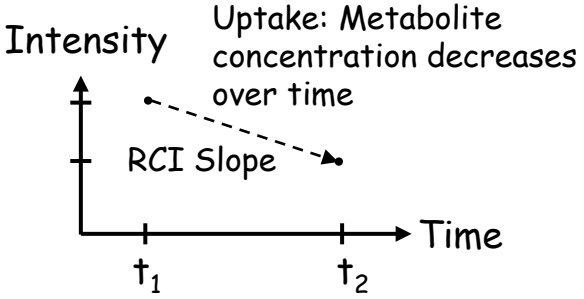
The Biomass function value will be adjusted to have +/- tolerance

Qualitative constraints based on detection limits, possible secretion, possible uptake.

Semi-Quantitative constraints based on relative differences, secretion (modelA, model B), uptake (modelA, model B).

Quantitative constraints based on absolute differences (± error), possible secretion, possible uptake.





$$Slope\ Ratio = \frac{RCI\ SlopeModel_A}{RCI\ SlopeModelB}$$

RCI = Relative Change in Intensity

Semi-quantitative Model Creation Process

Step 0: Load the starting model

Step 1: Define the model's external environment

Step 2: Calculate the limit of detection (LODs) for each measured metabolite

Step 3: Define the uptake and secretion profiles (Metabolomics Data)

Step 4: Calculate the slopes (relative change of intensity) and the slope ratios

Step 5: Enforce uptake and secretion rates using qualitative constraints

Step 6: Setting the semi-quantitative constraints

Step 7: Adjust growth constraints

Step 8: Delete absent genes (Transcriptomics Data)

Step 9: Extract and analyze condition-specific models

Create condition-specific models of Molt-4 and CCRF-CEM cancer cells

This tutorial describes step-by-step the generation of two condition-specific, lymphoblastic leukemia cell line models based on semi-quantitative metabolomic data as in [1]. The condition-specific models will be the Molt-4 (CRL-1582) and CCRF-CEM (CCL-119) T lymphoblast cancer cell lines [1,2].

In [1]:
```
import cobra
from cobrapy_bigg_client import client

import pandas as pd
pd.set_option('display.max_rows', 1000)
pd.set_option('display.max_columns', 100)
pd.set_option('display.width',100)
pd.set_option('display.max_colwidth',None)
```

Functions

boundsTable is a function that lists the upper and lower bounds for all exchange reactions.

In [2]:
```
def boundsTable(model_test):
    reaction_ids = [r.id for r in model_test.exchanges]
    reaction_lb = []
    reaction_ub = []

    for r in reaction_ids:
        reaction_lb.append(model_test.reactions.get_by_id(r).lower_bound)
        reaction_ub.append(model_test.reactions.get_by_id(r).upper_bound)

    df_1 = pd.DataFrame(reaction_ids)
    df_2 = pd.DataFrame(reaction_lb).round(6)
    df_3 = pd.DataFrame(reaction_ub).round(6)

    df_4 = pd.concat([df_1,df_2,df_3], ignore_index=True, axis=1)
    df_4.columns = ['Exchange Reactions', 'Lower Bounds', 'Upper Bounds']

    return(df_4)
```

Semi-quantitative_Metabolomics.ipynb