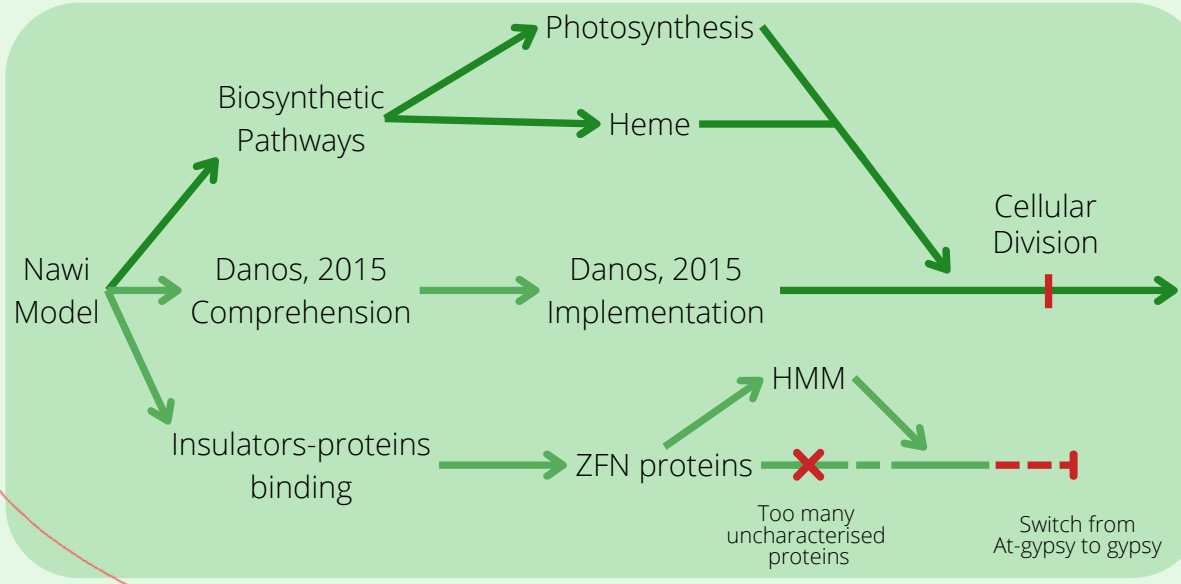
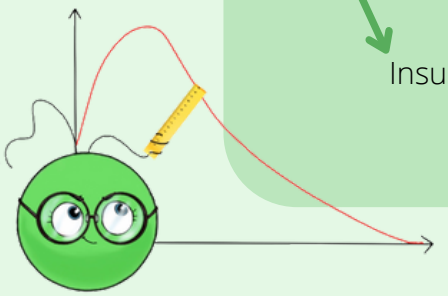
Modelling

Model Summary

We built a model to simulate cell function in order to predict our heme production and also to optimize growth and verify that we do not lose some nutrient values by removing photosynthesis. Our model is based on Danos's 2015 paper “Mechanistic links between cellular trade-offs, gene expression, and growth” this model approximates cell functioning by the protein machinery. We thus have a dynamic system composed of differential equations representing the kinetics of nutrient uptake from the extracellular medium to enzymatic production and protein production.

Here is a small timeline of the work roughly done : initially, the work was divided into three parts, one part for bibliographic research related to biosynthetic pathways, one part for understanding the model of the article and the last one for bioinformatics research on nucleic sequences related to insulators. There were several twists and turns for the latter and it was abandoned.





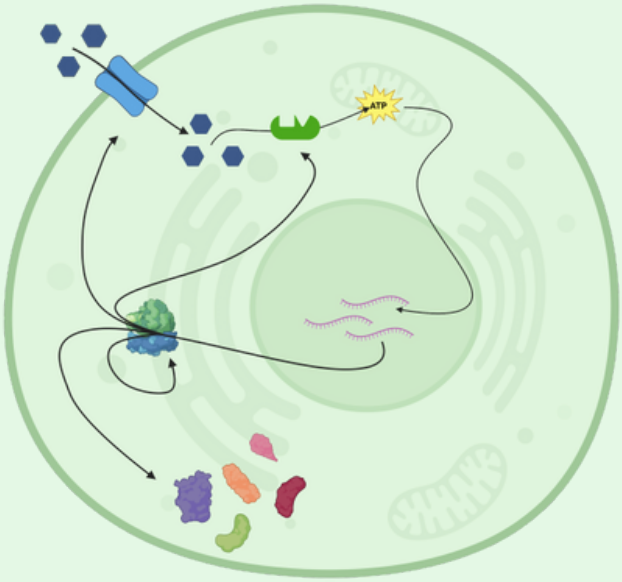
Modelling

Explanation

Now we'll take a look at the model itself. We will show you the different parts of it and explain them step by step.

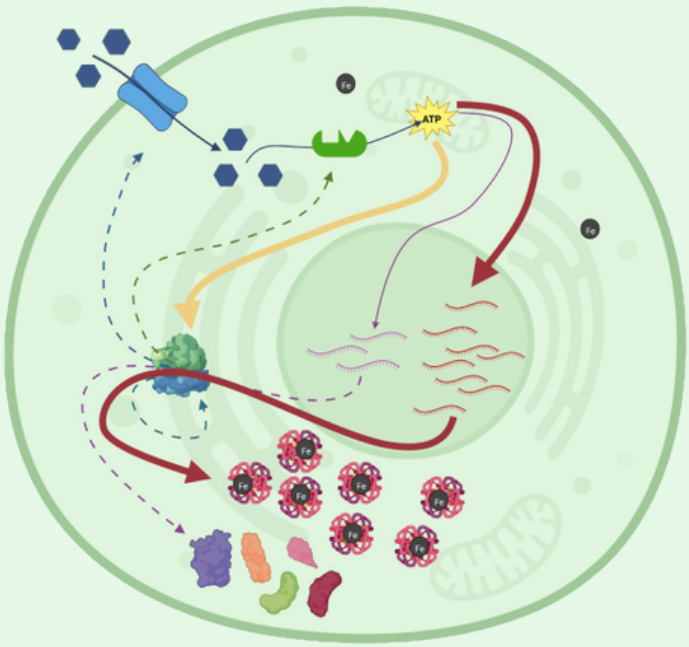
First of all we have nutrients present in the extracellular medium.

These enter the microalgae thanks to transporters. This step is modeled using Michaelis-Menten equations which describe the kinetics of an enzymatic reaction.



$$\nu_i = \nu_{max} \frac{[S]_0}{K_M + [S]_0}$$

This system of equations is an assembly of kinetic equations, evolution equations and equilibrium equations between the different substrates. These equations describe the different steps leading to the production of proteins: the transport of nutrients from the extracellular medium to the intracellular medium, their transformation into ATP, the production of mRNA and their translation by ribosomes into protein. While describing the maintenance of cellular life by monitoring the life of ribosomes and housekeeping proteins.



This model allows us to do three things:

First, to model different metabolic pathways in order to verify that the overexpression of our gene of interest does not have a negative impact on cell development as well as to verify that other pathways using iron as a nutrient are not destabilized.

Then it allows us to anticipate the metabolic changes induced by the deletion of [gene_name], which is part of photosynthesis.

And finally, it allows us to predict the production of our target protein: heme

$$
\begin{cases}
\dot{s}_i = \nu_{imp}(e_t, s) - \nu_{cat}(e_m, s_i) - \lambda s_i \\
\dot{a} = n_s.\nu_{cat}(e_m, s_i) - \sum_{x\in\{r,t,m,q,p\}}(n_x\nu_x(c_x, a) - k_b r m_x + k_u c_x), \\
\dot{r} = \nu_r(c_r, a) - \lambda_r + \sum_{x\in\{r,t,m,q,p\}}(\nu_x(c_x, a) - k_b r m_x + k_u c_x), \\
\dot{e}_t = \nu_t(c_t, a) - \lambda e_t, \\
\dot{e}_m = \nu_m(c_m, a) - \lambda e_m, \\
\dot{q} = \nu_q(c_q, a) - \lambda q, \\
\\
\dot{m}_x = \omega_x(a) - (\lambda + d_m)m_x + \nu_x(c_x, a) - k_b r m_x + k_u c_x, & x \in \{r, t, m, q, p\} \\
\dot{c}_x = -\lambda c_x + k_b r m_x - k_u c_x - \nu_x(c_x, a), & x \in \{r, t, m, q, p\}
\end{cases}
$$

We succeeded in implementing the model in python and using the parameters in Danos et al., we were able to obtain growth curves for the control cells (normal thb1 expression) and mutant cells (overexpression of thb1). We're are currently working on a more complicated model version of the model where we would be able to simulate cell multiplication by considering that cells divide after reaching a certain size. We are also working on implementing a stochastic version of the model with parameters distributed around a mean value. There are no curves because we are currently trying to calibrate the model to the recent control datas from our lab and from the IGEM-UESTC team's lab. After calibration we should be able to predict the production, deduce the best production environment and thus give a better estimation of the final product cost.