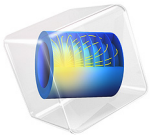

Model created in COMSOL Multiphysics 6.4

Oscillations in Metabolic Reaction Networks

Introduction

Oscillating chemical reactions were long thought to simply not exist in homogeneous solution, and even the poster child, the Belousov–Zhabotinsky reaction, met such an initial skepticism, that even though it was discovered in 1951, it took almost 20 years for it to gain widespread fame. Since this seminal discovery, many more oscillating reaction networks have been discovered, and this model studies the oscillatory behavior of a key part of glycolysis, the ubiquitous metabolic pathway common to a large part of the living organisms on earth.

Model Definition

It has been found that yeast cells, if first starved, and then subjected to small amounts of cyanide, and replenished with glucose, starts to consume the glucose at an oscillating rate. The fact that the variation in concentrations of metabolites can be measured macroscopically, means that the phase of the oscillations in individual yeast cells synchronize among billions of cells. This communication between cells occurs via molecular transport across cell membranes. The setup here models this intercellular transport via a fixed flux of glucose into the cell, acetaldehyde out of the cell, and an equilibrium of acetaldehyde across the cell membrane.

The minimal chemical reaction network presented in Ref. 1, which is formed by a subset of the glycolysis, is set up using 11 species in a Reaction Engineering interface. A 0D component, with a Reaction Engineering interface, is used to describe the reactions in the cytoplasm of the yeast cell. The individual reactions, and how they map to the reaction network is presented in Figure 1. A possible extension of this model could be to set up explicit cell membranes and solve the problem using a component in a higher dimension, resolving diffusion spatially.

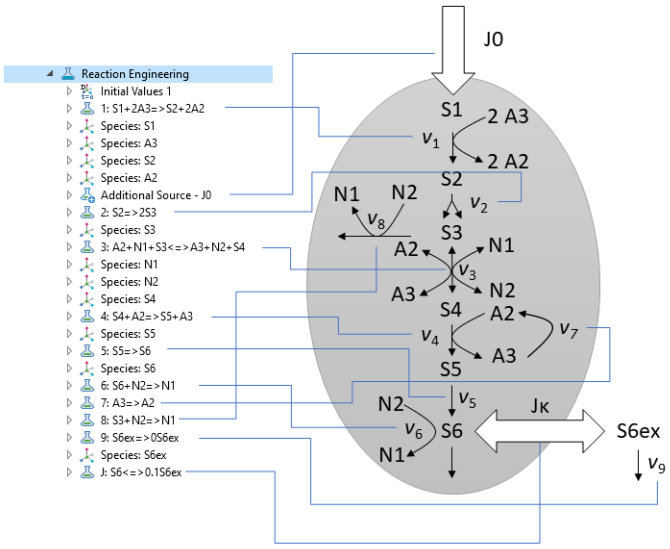

Figure 1: The relation between the reaction network and the features added to the Reaction Engineering interface.

Abbreviations for the metabolites are introduced for ease of input and brevity. The mappings of short names to their respective compound(s) are listed in Table 1.

TABLE 1: TABLE OF SPECIES NAMES.

SHORT NAME	CHEMICAL SPECIES
S1	Glucose
S2	Fructose-1,6-bisphosphate
S3	Triosephosphate, glyceraldehyde-3-phosphate, dihydroxyacetone phosphate
S4	3-phosphoglycerate
S5	Pyruvate
S6	Acetaldehyde
S6ex	Extracellular acetaldehyde
A2	ADP
A3	ATP
N1	NAD+
N2	NADH

Note how S3 represents a pool of metabolites, this is due to the model using lumped reactions to keep the number of variables low, while still reproducing the key features of the system.

KINETICS

Most reactions in the network are assigned mass action law expressions, the most prominent exception is that of the first reaction, where enzyme inhibition leads to a slightly more complicated expression, where a nonlinear factor enters the rate expression:

$$f(A_3) = \left[1 + \left(\frac{A_3}{K_i}\right)^n\right]^{-1} \tag{1}$$

The final rate expressions are shown in Table 2. The influx of glucose into the cell is accounted for using an additional source.

TABLE 2: RATE EXPRESSIONS.

RATE VARIABLE	RATE EXPRESSION
v1	k1[S1][A1]f([A3])
v2	k2[S2]
v3	k3fwd[A2][N1][S3] - k3rev[A3][N2][S4]
k3fwd	kGAPDHp*kPGKp/v3_denom
k3rev	kGAPDHm*kPGKm/v3_denom
v3_denom	kGAPDHm[N2]+kPGKp(A-[A3])
v4	k4[S4](A-[A3])
v5	k5[S5]
v6	k6[S6][N2]
v7	k7[A3]
v8	k8[S3][N2]
v9	k9[S6ex]

The stoichiometric coefficients associated with each rate expression are given in Figure 1.

PARAMETERS

The parameter values associated with the kinetic model are presented in Table 3.

TABLE 3: PARAMETER VALUES.

PARAMETER NAME	VALUE
J0	50.0[mM/min]
k1	550.0[1/mM/min]
Ki	1.0[mM]

TABLE 3: PARAMETER VALUES.

PARAMETER NAME	VALUE
k2	9.8/min
kGAPDHp	323.8[1/mM/min]
kPGKp	323.8[1/mM/min]
kPGKm	76411.1[1/mM/min]
k4	80[1/mM/min]
k5	9.7[1/min]
k6	2000[1/mM/min]
k7	28[1/min]
k8	85.7[1/mM/min]
kappa	375[1/min]
phi	0.1
A	4.0[mM]
N	1.0[mM]
n	4

The model is solved for a duration of 5 minutes using the time-dependent solver.

Results and Discussion

The result of the time integration is shown in Figure 2. Note how large the oscillations are in relative terms for glucose (S1).

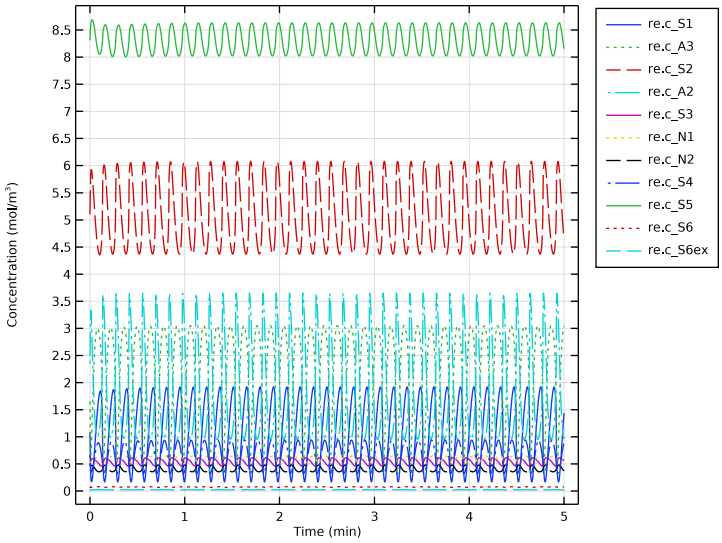

Figure 2: Time evolution of concentrations.

Figure 3 highlights the covariation between ATP and NADH.

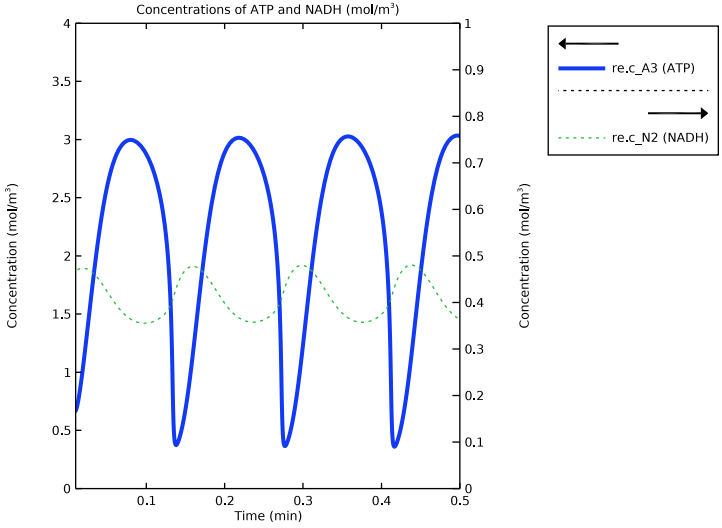

Figure 3: Time evolution of ATP and NAHD.

Note how the phases between ATP and NADH are offset by almost 180°. In this case, we can confirm the validity of our results by confirming that we reproduce the results of the referenced journal article. But more often than not, such a reference is not available, and hence it is never a bad idea to check how well the numerical solution respects invariants. Figure 4 shows how accurately mass conservation is fulfilled for ATP/ADP and NADH/NAD+. Note that the error is minuscule and on the order of machine precision.

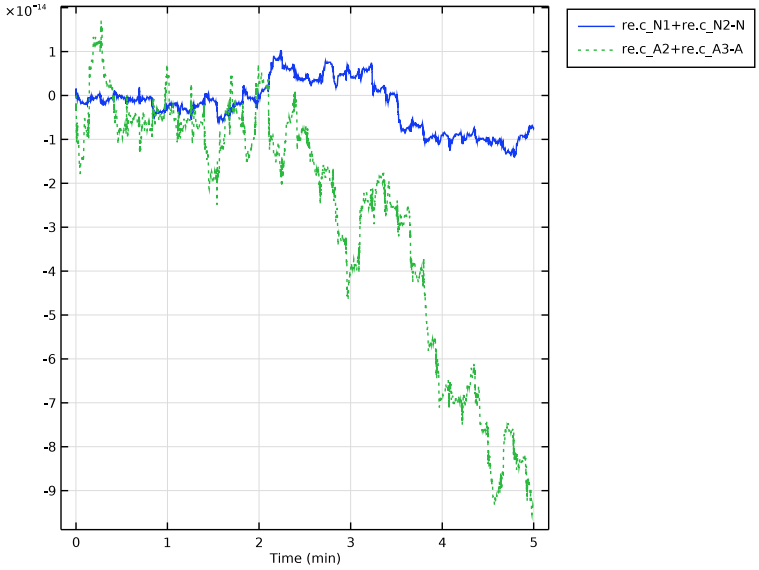

Figure 4: Mass conservation of ATP/ADP and NADH/NAD+ over time.

Reference

1. J. Wolf and others, "Transduction of Intracellular and Intercellular Dynamics in Yeast Glycolytic Oscillations," *Biophysical Journal*, vol. 78, pp. 1145–1153, 2000.

Application Library path: `Chemical_Reaction_Engineering_Module/Ideal_Tank_Reactors/glycolytic_oscillations`

Modeling Instructions

From the **File** menu, choose **New**.

NEW

In the **New** window, click **Model Wizard**.

MODEL WIZARD

1 In the **Model Wizard** window, click **0D**.

2 In the **Select Physics** tree, select **Chemical Species Transport** > **Reaction Engineering (re)**.

3 Right-click and choose **Add Physics**.

4 Click **Study**.

5 In the **Select Study** tree, select **General Studies** > **Time Dependent**.

6 Click **Done**.

REACTION ENGINEERING (RE)

1 In the **Model Builder** window, under **Component 1 (comp1)** click **Reaction Engineering (re)**.

2 In the **Settings** window for **Reaction Engineering**, locate the **Mixture Properties** section.

3 From the **Phase** list, choose **Liquid**.

GLOBAL DEFINITIONS

Parameters 1

Read in a set of parameters to be used in the model (naming matches terminology in referenced paper).

1 In the **Model Builder** window, under **Global Definitions** click **Parameters 1**.

2 In the **Settings** window for **Parameters**, locate the **Parameters** section.

3 Click **Load from File**.

4 Browse to the model's Application Libraries folder and double-click the file `glycolytic_oscillations_parameters.txt`.

DEFINITIONS

Variables 1

1 In the **Model Builder** window, under **Component 1 (comp1)** right-click **Definitions** and choose **Variables**.

2 In the **Settings** window for **Variables**, locate the **Variables** section.

3 Click **Load from File**.

4 Browse to the model's Application Libraries folder and double-click the file `glycolytic_oscillations_variables.txt`.

REACTION ENGINEERING (RE)

Reaction 1

1 In the **Reaction Engineering** toolbar, click **Reaction**.

2 In the **Settings** window for **Reaction**, locate the **Reaction Formula** section.

3 In the **Formula** text field, type `S1+2A3=>S2+2A2`.

4 Locate the **Reaction Rate** section. From the list, choose **User defined**.

5 In the r_j text field, type `k1*re.c_S1*re.c_A3*f_A3`.

6 Locate the **Reaction Orders** section. Find the **Volumetric overall reaction order** subsection. In the **Forward** text field, type `2`.

Additional Source - J0

1 In the **Reaction Engineering** toolbar, click **Additional Source**.

2 In the **Settings** window for **Additional Source**, type `Additional Source - J0` in the **Label** text field.

3 Locate the **Additional Rate Expression** section. In the **Volumetric species** table, enter the following settings:

Species	Additional rate expression (mol/(m^3*s))
S1	J0

Reaction 2

1 In the **Reaction Engineering** toolbar, click **Reaction**.

2 In the **Settings** window for **Reaction**, locate the **Reaction Formula** section.

3 In the **Formula** text field, type `S2=>2S3`.

4 Locate the **Rate Constants** section. In the k^{f} text field, type `k2`.

Reaction 3

1 In the **Reaction Engineering** toolbar, click **Reaction**.

2 In the **Settings** window for **Reaction**, locate the **Reaction Formula** section.

3 In the **Formula** text field, type `A2+N1+S3<=>A3+N2+S4`.

4 Locate the **Rate Constants** section. In the k^{f} text field, type `k3fwd`.

5 In the k^{r} text field, type `k3rev`.

Reaction 4

1 In the **Reaction Engineering** toolbar, click  **Reaction**.

2 In the **Settings** window for **Reaction**, locate the **Reaction Formula** section.

3 In the **Formula** text field, type `S4+A2=>S5+A3`.

4 Locate the **Rate Constants** section. In the k^{f} text field, type `k4`.

Reaction 5

1 In the **Reaction Engineering** toolbar, click  **Reaction**.

2 In the **Settings** window for **Reaction**, locate the **Reaction Formula** section.

3 In the **Formula** text field, type `S5=>S6`.

4 Locate the **Rate Constants** section. In the k^{f} text field, type `k5`.

Reaction 6

1 In the **Reaction Engineering** toolbar, click  **Reaction**.

2 In the **Settings** window for **Reaction**, locate the **Reaction Formula** section.

3 In the **Formula** text field, type `S6+N2=>N1`.

4 Locate the **Rate Constants** section. In the k^{f} text field, type `k6`.

Reaction 7

1 In the **Reaction Engineering** toolbar, click  **Reaction**.

2 In the **Settings** window for **Reaction**, locate the **Reaction Formula** section.

3 In the **Formula** text field, type `A3=>A2`.

4 Locate the **Rate Constants** section. In the k^{f} text field, type `k7`.

Reaction 8

1 In the **Reaction Engineering** toolbar, click  **Reaction**.

2 In the **Settings** window for **Reaction**, locate the **Reaction Formula** section.

3 In the **Formula** text field, type `S3+N2=>N1`.

4 Locate the **Rate Constants** section. In the k^{f} text field, type `k8`.

Reaction 9

1 In the **Reaction Engineering** toolbar, click  **Reaction**.

2 In the **Settings** window for **Reaction**, locate the **Reaction Formula** section.

3 In the **Formula** text field, type `S6ex=>OS6ex`.

4 Locate the **Rate Constants** section. In the k^{f} text field, type `k9`.

J: S6<=>0.1S6ex

1 In the **Reaction Engineering** toolbar, click **Reaction**.

2 In the **Settings** window for **Reaction**, locate the **Reaction Formula** section.

3 In the **Formula** text field, type `S6<=>0.1S6ex`.

4 In the **Label** text field, type `J: S6<=>0.1S6ex`.

5 Locate the **Reaction Rate** section. In the r_j text field, type `kappa*(re.c_S6-re.c_S6ex)`.

6 Locate the **Reaction Orders** section. Find the **Volumetric overall reaction order** subsection. In the **Forward** text field, type `1`.

Initial Values 1

1 In the **Model Builder** window, click **Initial Values 1**.

2 In the **Settings** window for **Initial Values**, locate the **Volumetric Species Initial Values** section.

3 In the table, enter the following settings:

Species	Concentration (mol/m^3)
A2	A-A30
A3	A30
N1	N-N20
N2	N20
S1	1.09
S2	5.1
S3	0.55
S4	0.66
S5	8.31
S6	0.08
S6ex	0.02

STUDY 1

Step 1: Time Dependent

1 In the **Model Builder** window, under **Study 1** click **Step 1: Time Dependent**.

2 In the **Settings** window for **Time Dependent**, locate the **Study Settings** section.

3 In the **Output times** text field, type `range(0,0.01,5)`.

4 From the **Time unit** list, choose **min**.

5 In the **Study** toolbar, click = **Compute**.

6 Click = **Compute**.

RESULTS

Concentration (re)

1 In the **Settings** window for **1D Plot Group**, click to expand the **Title** section.

2 From the **Title type** list, choose **None**.

3 Locate the **Legend** section. From the **Layout** list, choose **Outside graph axis area**.

Global 1

1 In the **Model Builder** window, expand the **Concentration (re)** node, then click **Global 1**.

2 In the **Settings** window for **Global**, click to expand the **Coloring and Style** section.

3 Find the **Line style** subsection. From the **Line** list, choose **Cycle**.

This is Figure 2.

Concentration (re) ATP and NADH vs. Time

1 In the **Model Builder** window, right-click **Concentration (re)** and choose **Duplicate**.

2 In the **Settings** window for **1D Plot Group**, type `Concentration (re) ATP and NADH vs. Time` in the **Label** text field.

3 Locate the **Title** section. From the **Title type** list, choose **Manual**.

4 In the **Title** text area, type `Concentrations of ATP and NADH (mol/m<sup>3</sup>)`.

5 Locate the **Plot Settings** section. Select the **Two y-axes** checkbox.

6 Locate the **Axis** section. Select the **Manual axis limits** checkbox.

7 In the **x minimum** text field, type `0.01`.

8 In the **x maximum** text field, type `0.5`.

9 In the **y minimum** text field, type `0`.

10 In the **y maximum** text field, type `4`.

11 In the **Secondary y minimum** text field, type `0`.

12 Locate the **Grid** section. Clear the **Show grid** checkbox.

13 Locate the **Legend** section. From the **Layout** list, choose **Outside graph axis area**.

Global 1

1 In the **Model Builder** window, expand the **Concentration (re) ATP and NADH vs. Time** node, then click **Global 1**.

2 In the **Settings** window for **Global**, locate the **y-Axis Data** section.

3 Click **Clear Table**.

4 In the table, enter the following settings:

Expression	Unit	Description
re.c_A3	mol/m^3	Concentration

Global 2

1 Right-click **Results** > **Concentration (re) ATP and NADH vs. Time** > **Global 1** and choose **Duplicate**.

2 In the **Settings** window for **Global**, locate the **y-Axis** section.

3 Select the **Plot on secondary y-axis** checkbox.

4 Locate the **y-Axis Data** section. In the table, enter the following settings:

Expression	Unit	Description
re.c_N2	mol/m^3	Concentration

5 Click to expand the **Legends** section. From the **Legends** list, choose **Manual**.

6 In the table, enter the following settings:

Legends
re.c_N2 (NADH)

Global 1

1 In the **Model Builder** window, click **Global 1**.

2 In the **Settings** window for **Global**, locate the **Coloring and Style** section.

3 From the **Width** list, choose **3**.

4 Locate the **Legends** section. From the **Legends** list, choose **Manual**.

5 In the table, enter the following settings:

Legends
re.c_A3 (ATP)

6 In the **Concentration (re) ATP and NADH vs. Time** toolbar, click **Plot**.

This is Figure 3.

Mass Conservation A and N

1 In the **Model Builder** window, right-click **Concentration (re)** and choose **Duplicate**.

2 In the **Settings** window for **1D Plot Group**, type `Mass Conservation A and N` in the **Label** text field.

3 Locate the **Title** section. From the **Title type** list, choose **None**.

4 Locate the **Legend** section. From the **Layout** list, choose **Outside graph axis area**.

Global 1

1 In the **Model Builder** window, expand the **Mass Conservation A and N** node, then click **Global 1**.

2 In the **Settings** window for **Global**, locate the **y-Axis Data** section.

3 Click **Clear Table**.

4 In the table, enter the following settings:

Expression	Unit	Description
`re.c_N1+re.c_N2-N`	`mol/m^3`	
`re.c_A2+re.c_A3-A`	`mol/m^3`	

5 In the **Mass Conservation A and N** toolbar, click **Plot**.

This is Figure 4.