Computational Systems Biology
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Lecture - 39
Lab: Example Biological Model

In this lab, we will focus on a nice biological example, which talks about sustained oscillations and glycolysis, and we will see how we can use MATLAB and the models already available online at bio-models to build and simulate such systems.

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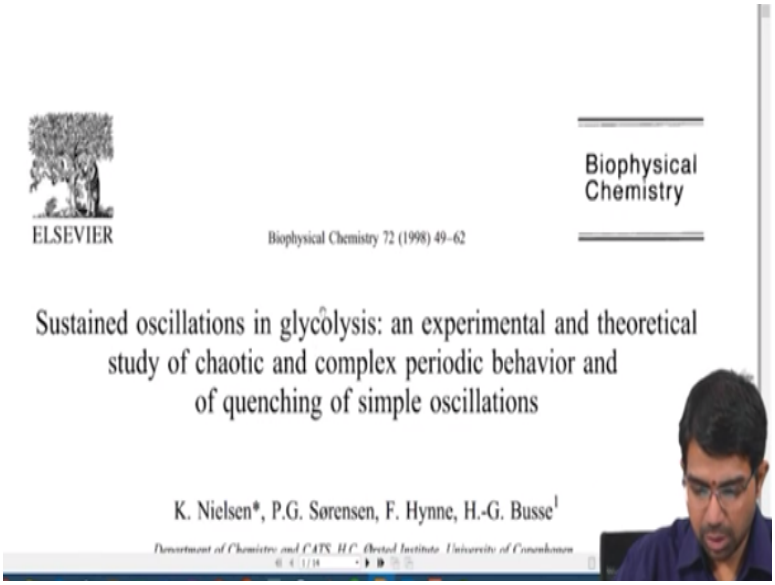

So this is the paper that talks about sustained oscillations in glycolysis, and you find some interesting outputs like this. These are some experimental values. Let us look at. This is perturbations with some UTP and for different species and so on. So let us look at this.

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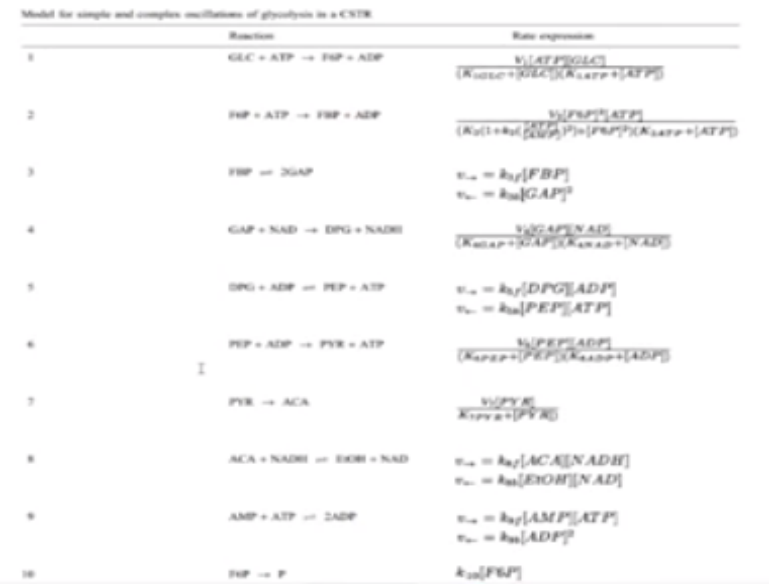

Model for simple and complex oscillations of glycolysis in a CSTR

	Reaction	Rate expression
1	GLC + ATP → FBP + ADP	$\frac{V_1[ATP][GLC]}{(K_{1GLC}+[GLC])(K_{1ATP}+[ATP])}$
2	FBP + ATP → FBP + ADP	$\frac{V_2[FBP]^4[ATP]}{(K_2(1+k_{2l}\frac{[ATP]}{[ADP]})^4+[FBP]^4)(K_{2ATP}+[ATP])}$
3	FBP ⇌ 2GAP	$v_{3+} = k_{3f}[FBP]$ $v_{3-} = k_{3b}[GAP]^2$
4	GAP + NAD → DPG + NADH	$\frac{V_4[GAP][NAD]}{(K_{4GAP}+[GAP])(K_{4NAD}+[NAD])}$
5	DPG + ADP ⇌ PEP + ATP	$v_{5+} = k_{5f}[DPG][ADP]$ $v_{5-} = k_{5b}[PEP][ATP]$
6	PEP + ADP → PYR + ATP	$\frac{V_6[PEP][ADP]}{(K_{6PEP}+[PEP])(K_{6ADP}+[ADP])}$
7	PYR → ACA	$\frac{V_7[PYR]}{K_{7PYR}+[PYR]}$
8	ACA + NADH ⇌ EtOH + NAD	$v_{8+} = k_{8f}[ACA][NADH]$ $v_{8-} = k_{8b}[EtOH][NAD]$
9	AMP + ATP ⇌ 2ADP	$v_{9+} = k_{9f}[AMP][ATP]$ $v_{9-} = k_{9b}[ADP]^2$
10	FBP → F	$k_{10}[FBP]$

You have all the equations here, can you now implement this, a dx/dt dot m, a function that will compute your dx/dt is f(x), except that here x is a vector, vector of several concentrations and so on. So this just takes a step aside

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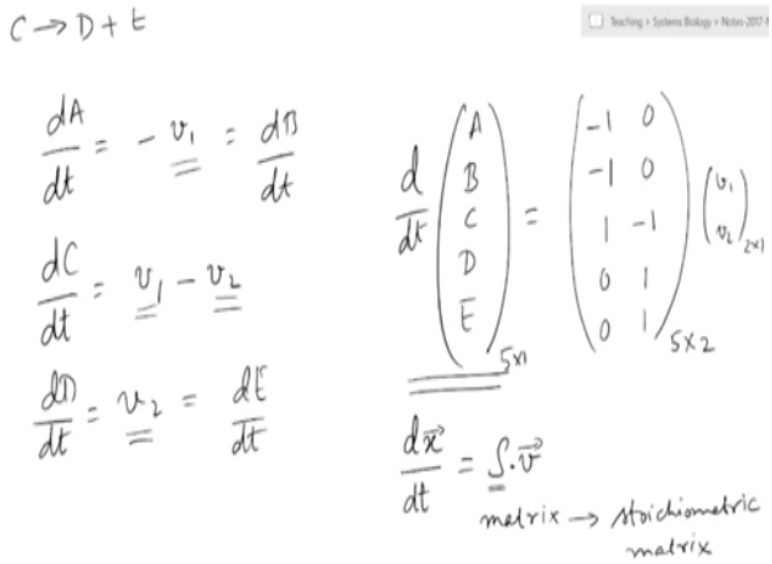

What is dA/dt, dA/dt will be just -v1 = dB/dt, dC/dt = v1-v2, dD/dt = v2, is that fine very simple. So there is a way to represent this you can just say d/dt = this is 5X1, 2X1 you need a 5X2 matrix that connects to, and here I would basically just put -1, -1, 1, 0, 0, 0, 0, 0, -1, 1, 1, straight forward, just matrices, or I would say dx/dt = S*v. This is a matrix actually known as the stochiometric matrix.

This is central to the next module of the course when we talk about flux balance analysis and constraint methods for studying metabolic networks. But this is very important to know right here, why because these are differential equations. If you are able to write expressions for all

the v's, you can simulate it. Let us go back, here are the expressions for all the v's, so your reactions are GLC+ATP giving F6P+ADP, F6P+ATP giving FBP+ADP.

So you have to carefully identify the coefficients for each of these. If you look at this a little more closely, what are these coefficients in this matrix? The stochiometric coefficient negative for reactant, positive for products, that is it. So you do not have to actually worry about writing these equations out. You really do not have to worry about writing out all these equations.

So you can basically the moment I give you a list of reactions, you can directly write out the stochiometric matrix, which is what you can do in this example potentially, you will have to hand code everything. So thankfully somebody has already done this, so if you look at i.

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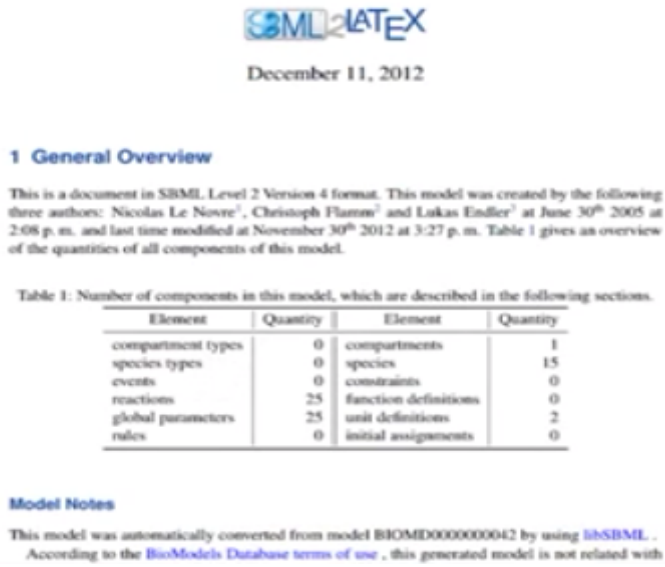

SBML2LATEX

December 11, 2012

1 General Overview

This is a document in SBML Level 2 Version 4 format. This model was created by the following three authors: Nicolas Le Novre[1], Christoph Flamm[2] and Lukas Endler[3] at June 30th 2005 at 2:08 p. m. and last time modified at November 30th 2012 at 3:27 p. m. Table 1 gives an overview of the quantities of all components of this model.

Table 1: Number of components in this model, which are described in the following sections.

Element	Quantity	Element	Quantity
compartment types	0	compartments	1
species types	0	species	15
events	0	constraints	0
reactions	25	function definitions	0
global parameters	25	unit definitions	2
rules	0	initial assignments	0

Model Notes

This model was automatically converted from model BIOMD0000000042 by using libSBML . According to the BioModels Database terms of use , this generated model is not related with

So this kind of file is available from bio-models.net, and in fact this is a very interesting file. So bio-models also allows you to get an SBML report a PDF report of any SBML file. It has curetted several SBML file so it calls this file Nielsen1998_Glycolysis, and this has a lot of details. This is essentially from the SBML, if you remember SBML from a few classes ago, so the compartment well as just cut to the chase.

These are your species, so you want to do a dAt/dt, dADP/dt, dAMP/dt all of these.

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5 Parameters

This model contains 25 global parameters.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
V1			0.500		☑
K1GLC			0.100		☑
K1ATP			0.063		☑
V2			1.500		☑
K2			0.002		☑
k2			0.017		☑
K2ATP			0.010		☑
k3f			1.000		☑
k3b			50.000		☑
V4			10.000		☑
K4G&P			1.000		☑
K4NAD			1.000		☑
k5f			1.000		☑
k5b			0.500		☑
V6			10.000		☑
K6PEP			0.200		☑
K6ADP			0.300		☑
V7			2.000		☑
K7PYR			0.300		☑
k8f			1.000		☑
k8b			$1.43 \cdot 10^{-4}$		☑
k9f			10.000		☑
k9b			10.000		☑
k10			0.050		☑
flow			0.011		☑

These are all your parameters, they are in the manuscript, which I was just showing you and these are all your reactions, these are ATP input source and sync reaction, but these are your main reactions. It has about 10 reactions and the good part is it already gives you v1=volume of compartment you can keep that as 1 if you want, is 3.5-ATP*flow, it is your ATP flow. Let us look at the other reactions, this is essentially your stochiometric matrix derived from the stochiometric matrix.

So v16 is this, reaction 2 is this, which is this, you need to write those out dATP/dt is v1, that is also hyperlink by the way can just click and go to v1.

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7.5 Species F6P

MIRIAM Annotation This biological entity is:

- urn:miriam:obo.chebi:CHEBI%3A20935.
- urn:miriam:kegg.compound:C05345.

Initial amount 0.65939 mmol

This species takes part in four reactions (as a reactant in F6Pflow, reaction_2, reaction_10 and as a product in reaction_1).

$$\frac{d}{dt}\text{F6P} = v_{16} - v_6 - v_{17} - v_{25} \quad (55)$$

7.6 Species FBP

MIRIAM Annotation This biological entity is:

- urn:miriam:obo.chebi:CHEBI%3A16905.
- urn:miriam:kegg.compound:C05378.

Initial amount 0.00770135 mmol

So dNA/dt is v4+v23-v19, dF6P/dt is v16-v6-v17-v25, and so on and all these have been defined previously, what is v25, it is here. So bio-model actually gives you files for octave

not for MATLAB, you can just make a few small tweaks and use it with MATLAB. There are also other tools that you can use it with. So how does this look. I would recommend this architecture for any ODE solving problem.

You first set up a file just like we had in the previous example, ODE.M or rather analyse the ODE and your dx/dt, which is basically something like the ODE of the model, model ODE.M. So I have something like that here, so I have ODE model_42.M and analyse model_42.M, 42 happens to be the bio-models id for this particular Nielsen_Glycolysis model.

Then you code all these parameters. All these parameters are available in the manuscript, if you look at it carefully.

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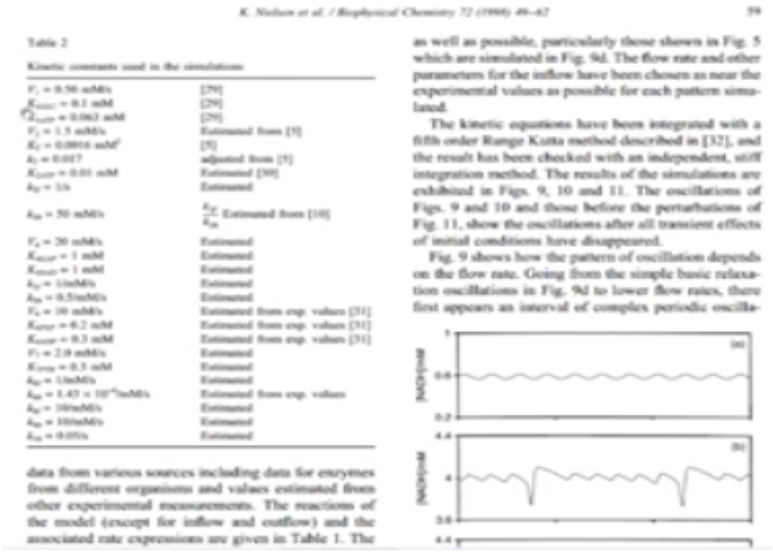

So v1 is .5, K1GLC is .1 mili-molor, K10 is 0.05 per second and so on and so forth. We have all these values that are listed here and so it goes, we have all the equations listed here, X.1 is this, X.2 is this, X.15 is this. Now you can actually solve this, in your analyse model 42.M solve it, what you need to do here. First is set up the initial conditions, then create a vector where you want to simulate it.

Then basically the same old thing, t, y is ODE 15S of ODE model 42 t, y0, y or x, you will probably have it as x here. Let us just run this.

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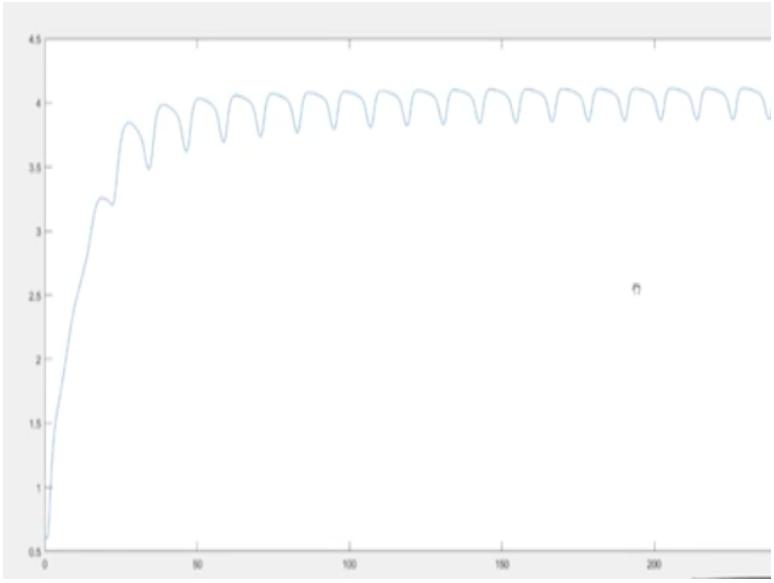

You see much like the same oscillation that is there in the paper, something of this sort. The equations can we look at the MAT equations. So basically call them as X. is f(t, x), this is essentially you get from the stochiometric matrix. So this is a vector having x1., x2., x3. All your species, not 5, here there are many more metabolites, there are 15 metabolites, Q have 15 initial conditions if you look up.

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xdot(1) = ATPflow - v_1 - v_2 + v_5 + v_6 - v_9;
xdot(2) = ADPflow + v_1 + v_2 - v_5 - v_6 +  2.0 * v_9;
xdot(3) = -AMPflow - v_9;
xdot(4) = GLCflow - v_1;
xdot(5) = -F6Pflow + v_1 - v_2 - v_10;
xdot(6) = -FBPflow + v_2 - v_3;
xdot(7) = -GAPflow +  2.0 * v_3 - v_4;
xdot(8) = NADflow - v_4 + v_8;
xdot(9) = NADHflow + v_4 - v_8;
xdot(10) = -DPGflow + v_4 - v_5;
xdot(11) = -PEPflow + v_5 - v_6;
xdot(12) = -PYRflow + v_6 - v_7;
xdot(13) = -ACAflow + v_7 - v_8;
xdot(14) = -EtOHflow + v_8;
xdot(15) = -Pflow + v_10;
```

The initial conditions will be set up here, x1 is ATP, x2 is ADP, x3 is AMP, GLC, F6P, FBP, so on DTOH. So all your glycolysis parameters and phosphate whatever. All the metabolites involved in glycolysis, bisphosphoglycerate, phosphoenolpyruvate, pyruvate acetate, ethanol, glyceraldehyde phosphate. From extra deviation, we can see that ATP is present in B1 reaction1, reaction 2, reaction 5 and reaction 6 and reaction 9.

Whatever velocity it is having that is present, of course. Then what is ATP flow is. That is like input sort of to the whole system. If you need a steady state of glycolysis, you need a steady supply of ATP, ATP and all of these actually in steady state. So this model is described in great detail in this paper and also all the mathematical details are basic. In fact, this is very interesting. All these information is encoded inside your SBML file.

So this is just literally an SBML to PDF kind of routine that was run to extract all this information out. So it is actually done by SBML delay tech. x dot should contain variable in terms of that x only right, x.1 should be in terms of x1, not necessarily. It is multidimensional right, so no problem.

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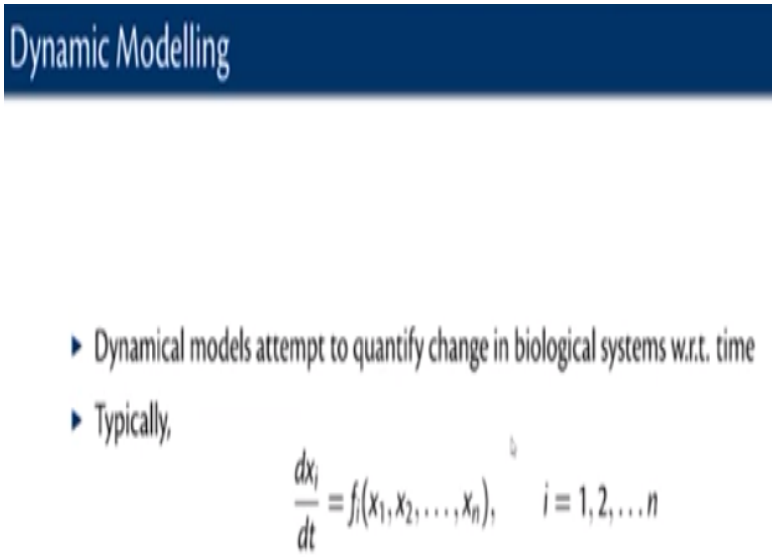

If you remember the very first slide for today, dxi/dt is fi(x1, 2) and does not matter, so you will have to figure this out. You have try out a few examples. It is not difficult, but it involves rigor. You have to be very careful. You cannot make like some -1, +2 mistakes kind of thing. You have to rigorously set up the equations, then you can simulate them nicely. I will share these files with you, it will become clearer.

You need to take a look at this file again. This analyse model, ODE model all of these files, I will share with you. Any questions. **"Professor - student conversation starts"** Actually the ODE package in all of these models are working in the octave only, can we do this without this ODE. Yeah, the file is same, so you can obviously just download the M file from bio-models and run it on octave even.

You told these are written octave, we have to make some tweaks to get in. Yeah, I made some tweaks already very minor tweaks, but in this you will have a bunch of find and replaces kind of thing, you will be able to run it in MATLAB. **"Professor - student conversation ends"** So I hope you had a good overview of one uses MATLAB to work with models on bio-models.net to run simulations and plot graphs and so on.

In the next video, we will start looking at parameter optimization or parameter estimation, which is an optimization problem essentially and we will also have a brief overview of biochemical systems theory just before we get started with parameter estimation.