MATCONT SBML Tutorial 1: Using MATCONT for researching biological models in SBML

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1 Introduction

This tutorial will go through the steps needed to work with a biological model in a SBML-file by using MATCONT, a graphical MATLAB software package for the interactive numerical study of dynamical systems [1, 2]. An example paper from *The Journal of Cell Biology* is taken, *Signaling switches and bistability arising from multisite phosphorylation in protein kinase cascades* [6]. The corresponding SBML-file is located and part of Figure 3 from the article is recreated, see Figure 1. On one of the locations where MATCONT detects a bifurcation, a further study is done.



Figure 1: Figure 3 from [6].

2 Installation

• MatCont

Download location: http://sourceforge.net/projects/matcont/files/

• libSBML

Download location: http://sourceforge.net/projects/sbml/files/libsbml/ Installation instructions: http://sbml.org/Software/libSBML/docs/cpp-api/libsbml-installation.html

• SBML Toolbox

Download location: http://sourceforge.net/projects/sbml/files/SBMLToolbox/

Installation instructions: http://sbml.org/Software/SBMLToolbox/docs/ManualV3.pdf

Get the latest version of MATCONT, the file to download is called matcont<version>.zip. Extract it in a folder matcont<version>, no further installation is needed. MATCONT can be started by changing the path in MATLAB to the folder matcont<version> and typing matcont at the MATLAB command line.

The libraries *libSBML* and *SBML Toolbox* need to be installed. There are three options, depending on your situation and platform. (1) Compile and install from source, (2) use an installer corresponding to your platform or (3) unzip a folder with prebuild libraries in matcont<version>/SBML.

The first option, compiling and installing from source, can be used when this is the only way to install the software on your system. See the relevant documentation for your platform in the installation instructions.

The second option, using the installer, is the best option. Get the correct installer from the download location of libSBML and install it. During installation, make sure that you additionally select the MATLAB interface. Next, from the download location of the SBML Toolbox, get the setup program and install it. On some systems the setup program has to be run from the MATLAB command window, this has to be done with a command like cd('c:\Program Files\SBML\SBMLToolbox<version>\toolbox\'); install.

The third option might be the only option when using a system where you don't have administrator rights. It will only work on 32-bits Windows systems. From the MATCONT download location, get the zip-file SBML_libs_win32.zip, this zip-file contains a folder called win32. Place it in matcont<version>/SBML/. Now you should have a folder matcont<version>/SBML/win32.

3 Paper and SBML-file

Download the pdf of the paper at http://www.jcb.org/cgi/doi/10.1083/jcb.200308060.

Many published biological models are maintained in the BioModels Database at http://www.ebi.ac.uk/ biomodels-main/. Go to that website and enter the name of the main author, Markevich, in the search box. A selection of all models with the author's name in it will be shown. Several models are available, the needed model is *BioModels ID* BIOMD000000027, this can be checked in the relevant notes. Choose to download the curated SBML-file. The file BIOMD000000027.xml will be stored on your computer.

BIOMD000000027 - Ma	rkevich2004_MAP	K_ord	leredMI	M	
Download SBML SBML L2 V1 (curated)	Other formats (auto generated)	-	I	Actions	
SBML L2 V2 (auto-generated)			Re	eference	Publication
SBML L2 V3 (auto-generated) SBML L2 V4 (auto-generated)		J Cell E Signali	Biol 2004 na switch	Feb;164(3):353-9. stability arising from (
Publication ID: <u>14744999</u>		Markev Depart Philade	vich NI, H ment of P elphia, PA	oek JB, Kh athology, J 19107, U	nolodenko BN. Anatomy, and Cell E SA. <u>[more]</u>
				Mo	del
Original Model: <u>BIOMD00000</u>	00027.xml.origin	set#1	bqbiol:is	Taxonor	ny <u>Xenopus laevis</u>
Submitter: <u>Nicolas Le Novère</u>		set #2	bqbiol:is	VersionOf	Gene Ontology N

4 Working with the SBML-file

4.1 Importing into MATCONT

After starting MATCONT with the command matcont in MATLAB, the main MATCONT window appears. Select the menu 'Select \rightarrow System \rightarrow import SBML', see Figure 2.

			MatC	ont				
Select	Compute	W	/indow T	Vpe	Option	ns	Help	¥
Syst	em	Þ	New					
Dia	gram		Edit/L	oad		Су	cle_Regul	ati
Cur	ve		Impor	t SBM	L			
Initi	al point		P					
Use	r function		SSSNN					
Exit								
Status			-					

Figure 2: Main MATCONT window with selection to import an SBML-file.

SBML files have the extension .xml. The file selection dialog that opens will filter on files with that extension. Now go to the location where the file BIOMD000000027.xml was downloaded and click open as in Figure 3.

		M	atCont					×							
Select	Compute	Windov	/ Туре	Opt	ions	Help		3	•						
Class		OE	Ε												
System	ı						Sel	ect SBM	L fil	e					โ
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			BIOMD	0000	00016	59 xml	Ē	BIOMDOG	000	00257	cml				
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_			вюмр	0000	00018	36.xml		BIOMDOO	000	00270.)	ml				
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								10000						Þ	
		F	le <u>N</u> ame:	1	BIOMD	00000	000	27.xml							
		Fi	les of <u>Ty</u>	pe: [(*.xm	0								-	
											0	pen		Cancel	

Figure 3: Select SBML-file in filechooser.

The biological model in the SBML-file is now read. The species, parameters and reactions from the biological model are converted to coordinates, parameters and differential equations for use by MATCONT. The *System window*, Figure 4, will open.

Most importantly, the importer will generate the system of differential equations

$$M' = v_4 \cdot Mp - v_1 \cdot M$$
$$Mp' = v_1 \cdot M - v_2 \cdot Mp + v_3 \cdot Mpp - v_4 \cdot Mp$$
$$Mpp' = v_2 \cdot Mp - v_3 \cdot Mpp$$

in which

$$\begin{split} v_1 &= \frac{MAPKK * k1cat}{Km1 * (M/Km1 + Mp/Km2 + 1)} \\ v_2 &= \frac{MAPKK * k2cat}{Km2 * (M/Km1 + Mp/Km2 + 1)} \\ v_3 &= \frac{MKP3 * k3cat}{Km3 * (M/Km5 + Mp/Km4 + Mpp/Km3 + 1)} \\ v_4 &= \frac{MKP3 * k4cat}{Km4 * (M/Km5 + Mp/Km4 + Mpp/Km3 + 1)}. \end{split}$$

If desirable, modifications can be done. For now, just press 'OK'.

-	MatCont		_ 🗆 X			
Select Compute	Window Type Opt	ions Help	''			
Class System	ODE Markevich2004	_MAPK_orde	red			
Curve Point Type			System			×
Curve Type						
Derivatives	Name	Markevich2	004_MAPK_	orderedMM		
Duration	Coordinates	М,Мр,Мрр				
Status	Parameters	k1cat,Km1	k2cat,Km2,k	3cat,Km3,k4	cat,Km4,Km	5,MAPKK,M
	Time	t				
	Derivatives	1st ord	2nd ord	3rd ord	4th ord	5th ord
	- numerically	Q	0	0	۲	۲
	- symbolically	() ()	0	۲		
	M'=(MKP3*Mp*k Mp'=(M*MAPKK* Mpp'=(MAPKK*M	4cat)/(Km4* k1cat)/(Km1 lp*k2cat)/(Ki	(M/Km5 + Mj *(M/Km1 + N n2*(M/Km1	»/Кт4 + Мр Ир/Кт2 + 1 + Мр/Кт2 -	p/Km3 + 1))) – (MAPKK ⊦ 1)) – (MKP3) - (M*MA ^ Mp*k2cat 3*Mpp*k3

Figure 4: System window with imported system.

4.2 Numerical integration until equilibrium

Now choose the menu 'Type \rightarrow Initial Point \rightarrow Point' so that the *Starter* and *Integrator window* will open as in Figure 5.

*	Starter	- x		
	Initial Point			
t	0			
М	500			
Mp	0			ator – X
Мрр	0		Integra	tion data
k1cat	0.01		Method	odo4E -
Km1	50		Internet	00245
k2cat	15		interval	1
Km2	500		InitStepsize	<automatic></automatic>
k3cat	0.084		MaxStepsize	<automatic></automatic>
Km3	22		Rel. Tolerance	1e-3
k4cat	0.06		Abs. Tolerance	1e-6
Km4	18		Pafina	160
Km5	78		Kenne	1
МАРКК	50		Normcontrol	No •
МКРЗ	100			
	Select Cycle			

Figure 5: Starter and integrator window with initial values.

The initial values are already filled in as retrieved from the model during the import. From Figure 1 it is clear that for $[MAPKK]_{tot} = 50$ there are three steady states. Starting from [M] = 500 and [Mp] = [Mpp] = 0 we find the first one by a forward integration.

To obtain this, we leave the default method of integration, ode45, in the *Integrator window*, but change the interval of integration to 2000. To see visually what is happening, we open the numerics window with the menu 'Window→Numerics' and we open a 2*D*-plot with the menu 'Window→Graphics→2Dplot'. Since we are doing a time integration, it is natural to change the abscissa from 'Coordinates' to 'Time'. We are interested in the behavior of the coordinate Mpp, so change the ordinate to coordinate Mpp. Now on the 2Dplot window, choose the menu 'Layout→Plotting region' and make sure that the abscissa runs from 0 to 2000 and the ordinate from 0 to 100.

Using forward integration (menu 'Compute \rightarrow Forward'), [Mpp] will reach its steady state, close to 50. Selecting 'Compute \rightarrow Extend' a couple of times, the value of [Mpp] will get stuck in its equilibrium. The setup and result should be as in Figure 6.



Figure 6: Setup and result of numerical integration to first equilibrium.

This should also be done for other values of [Mpp] close by. Let's change the initial point Mpp to [Mpp] = 80. Because of Formula 1 in [6],

$$[Mp] = M_{tot} - [M] - [Mpp],$$
(1)

either [M] or either [Mp] needs to be changed. Set [M] = 420. A forward computation gives Figure 7.

4.3 Continuation of the system

From the equilibrium we can start a continuation. First the initial point has to be selected. To do this choose the menu 'Select \rightarrow Initial Point' and select the last point of the orbit in the window. The *Starter window* is automatically updated with the values of the selected point and contains the values of Table 1.

time	0	2000	4000	0	2000	4000
M	500	437.785	437.730	420	437.692	437.729
Mp	0	12.843	12.851	0	12.853	12.852
Мрр	0	49.370	49.418	80	49.453	49.417

Table 1: Numeric values after time integration.

Since we have an equilibrium of the system, select 'Type \rightarrow Initial Point \rightarrow Equilibrium'. The *Continuer window* will open, and in the *Starter window* the parameter of continuation can be chosen by clicking the corresponding button, take MAPKK. The setup should be as in Figure 8.



Figure 7: The numeric integration of the system.

*	Starter						
	Initial Point						
М	437.69258		Continue	r _ 🗆 🔍			
Mp	12.853441		Continuation	Data			
Мрр	49.453983		InitStepsize	0.01			
⊖k1cat	0.01		MinStepsize	1e-5			
⊖Km1	50		MaxStepsize	01			
⊖k2 cat	15		Corrector E	Data			
⊖Km2	500		MaxNewtonIters	3			
⊖k3cat	0.084		MaxCorriters	10			
⊖Km3	22		MaxTestIters	10		Numeric	_ D X
⊖k4cat	0.06		VarTolerance	1e-6	Window		-
⊖Km4	18		FunTolerance	1e-6		Coordinates	
⊖Km5	78		TestTolerance	1e-5	M		
MAPKK	50		Adapt	3	Mp		
ОМКРЗ	100		Stop Dat	a	Мрр		
	Jacobian Data		MaxNumPoints	300		Parameters	
increment	1e-05		ClosedCurve	50	k1cat		
	Monitor Singularit	ies 🔳			Km1		

Figure 8: Updated starter window.

When selecting 'Compute \rightarrow Forward' to start the continuation, we get the following error: 'No convergence at x0'. The problem is that the system is linearly dependent. By (1) the sum of the concentrations remains constant.

Therefore the system has to be edited to make the equations lineary independent, choose 'Select \rightarrow System \rightarrow Edit/Load'. In the Systems selection window, choose the current system, Markevich2004_MAPK_orderedMM.m and select 'Edit'. In the System window, change the equations by replacing the equation for Mp' by Mp = 500 - M - Mpp and remove Mp from the 'Coordinates'. The System window should now look like Figure 9.

.	MatCont		- • ×			
Select Compute	Window Type Option	is Help	2			
Class System Curve	ODE Markevich2004_N	1APK_order	ed			
Point Type	<u>.</u>		System			
Curve Type						
Duration	Name	Markevich	2004_MAPK_	orderedMM		
Status	Coordinates	M,Mpp				
	Parameters	k1cat,Km1	,k2cat,Km2,k	3cat,Km3,k4	lcat,Km4,Km	5,МАРКК,М
	Time	t				_
	Derivatives	1st ord	2nd ord	3rd ord	4th ord	5th ord
	– numerically – from window	0	0	0	۲	۲
	- symbolically	ē	ĕ	۲		0
	Mp=500-M-Mpp M=(MK9*Mp*4 Mpp'=(MAPKK*Mp	cat)/(Km4* o*k2cat)/(K	(M/Km5 + Mp m2*(M/Km1 -	o/Km4 + Mp + Mp/Km2 +	.p/Km3 + 1)) ⊢ 1)) - (MKP3) - (M*MA * Mpp*k3
	OK				_	Cancel

Figure 9: Edited system to make it linear independent.

The numeric integration has to be redone. Make sure that the starting coordinates are [M] = 500 and [Mpp] = 0. Select 'Type→Initial point→Point'. Now do a forward computation with 'Compute→Forward'. Again select as initial point the last point ('Select→Initial point'). The initial point should be [M] = 437.78813 and [Mpp] = 49.382181. Select 'Type→Initial Point→Equilibrium' and in the *Starter window* choose MAPKK as the free parameter. The *Starter window* should now look as Figure 10.

	(0)						
	Starter						
м	427 20012		Continu)		
L	437.78813		_				
Мрр	49.382181		Continuatio	on Data			
Ok1cat	0.01		InitStepsize	0.01			
⊖Km1	50		MinStepsize	10-5			
⊖k2cat	15		MaxStepsize	0.1			
OKm2	500		Corrector	Data			
01.2	0.084			5444			
OKSCAL	0.084		MaxNewtonIters	3			
⊖Km3	22		MaxCorriters	10			
Ok4cat	0.06		MaxTestIters	10			
OKm4	18		VarTolerance	10		Numeric	_ – ×
OKm5	78		E . T. I	16-0	Window		3
			Funitolerance	1e-6		Coordinates	
MAPKK	50		TestTolerance	1e-5		Coordinates	8
ОМКРЗ	100		Adapt	3	м		
	Jacobian Data		Stop D	-	Mpp		
increment	4		Stop D	ata		Parameters	
	11e-05		MaxNumPoints	300	k1 sat		
	Monitor Singularit	ies	ClosedCurve	50	KICat		
Branching					Km1		

Figure 10: Updated starter window of linear independent system.

Open a 2D plot with 'Window \rightarrow Graphic \rightarrow 2Dplot' and set the abscissa to the parameter $MAPKK \in [30, 70]$ and the ordinate to the state variable (coordinate) $Mpp \in [0, 500]$. Use the menus 'Layout \rightarrow Variables on axes' and 'Layout \rightarrow Plotting region' on the 2DPlot window. Choosing 'Compute \rightarrow Forward' or 'Compute \rightarrow Backward' and 'Compute \rightarrow Extend' one or more times, will continue the equilibrium. When MATCONT detects a bifurcation, it will pause at that position. To resume the continuation, press 'Resume' as in Figure 11.

Figure 12 shows the complete continuation.

Drawing the curve can be sped up by changing 'Options-Output'. By default this value is 1. This can be



Figure 11: Setup and output of an equilibrium continuation.



Figure 12: Continuation of equilibrium.

set to a higher value, in Figure 13 this is set to 100. While the calculations will be as precise as before, the drawing will now only be done after 100 steps are calculated.

Outp	out 💷 🔍
Plot	after
100	points
ОК	Cancel

Figure 13: Changing the interval between redraws.

By default, the continuer will continue 300 points. In this case more than 5000 will have to be continued. After the first 300 points, we can extend the curve with 'Compute \rightarrow Extend'. If it is known that the curve needs to be extended many times, *MaxNumPoints* in *Continuer window* can be set to a larger value.

4.4 Continuation in 2 free parameters

Continuation in 2 parameters is possible. Then the bifurcation boundaries corresponding to the limit point bifurcations are curves in the parameter plane. For instance, select the second limit point with 'Select—Initial point'. MATCONT will now do a LP-LP continuation. The starter loads automatically the values in and will look as in Figure 14. We select km1 and MAPKK as free parameters.



Figure 14: Starter window for LP-LP continuation.

It is best to look at the parameter plane. Select a 2DPlot with on the axes the relevant parameters, MAPPK and Km1. A good plotting region for MAPKK is from 35 to 60 and for Km1 from 30 to 270. A forward continuation ('Compute \rightarrow Forward') gives Figure 15. At M = 249.921974, Mpp = 240.426057, km1 = 246.269558, MAPKK = 41.157105 a cusp bifurcation is detected.



Figure 15: LP-LP continuation.

References

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