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.

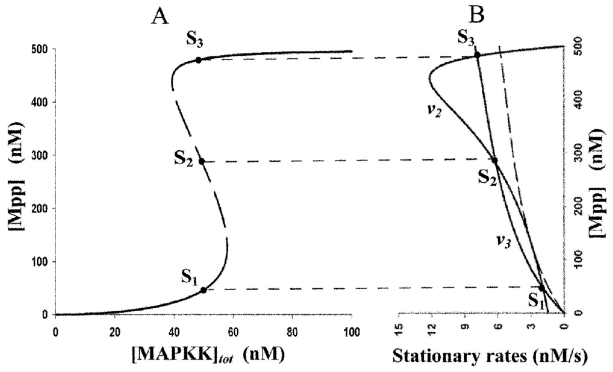


Figure 1: Figure 3 from [6].

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.

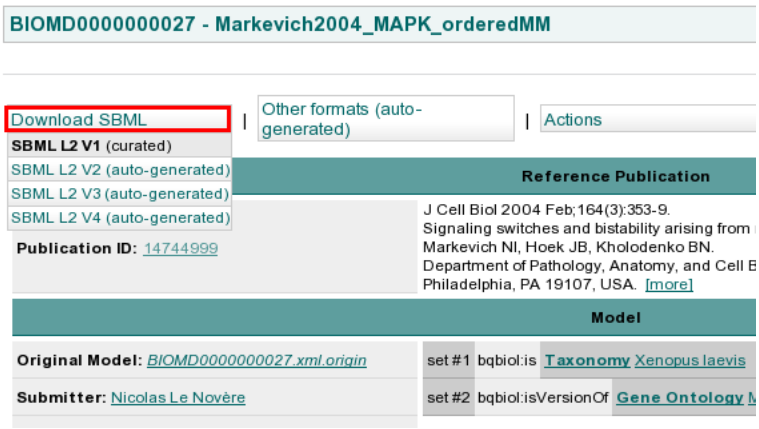
The second option, using the installer, is the best option. Get the correct installer from the download location of libSBML and install it. During installation, make sure that you additionally select the MATLAB interface. Next, from the download location of the SBML Toolbox, get the setup program and 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* BIOMD0000000027, this can be checked in the relevant notes. Choose to download the curated SBML-file. The file `BIOMD0000000027.xml` will be stored on your computer.



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→System→import SBML', see Figure 2.

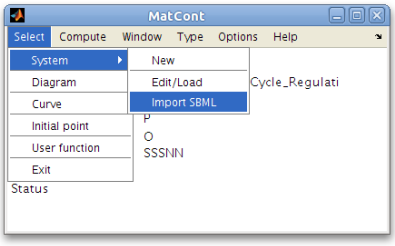


Figure 2: Main MatCont window with selection to import an SBML-file.

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 `BIOMD0000000027.xml` was downloaded and click open as in Figure 3.

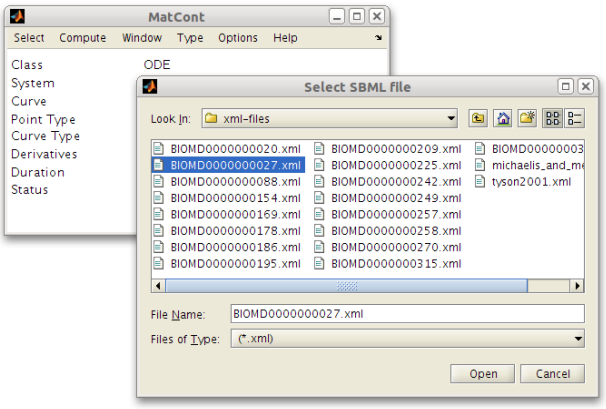


Figure 3: Select SBML-file in filechooser.

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

$$\begin{aligned} M' &= v_4 \cdot Mp - v_1 \cdot M \\ Mp' &= v_1 \cdot M - v_2 \cdot Mp + v_3 \cdot Mpp - v_4 \cdot Mp \\ Mpp' &= v_2 \cdot Mp - v_3 \cdot Mpp \end{aligned}$$

in which

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

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

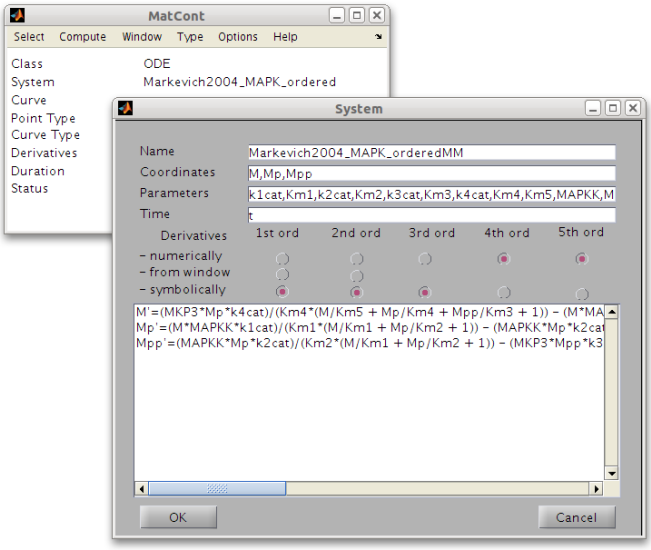


Figure 4: System window with imported system.

4.2 Numerical integration until equilibrium

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

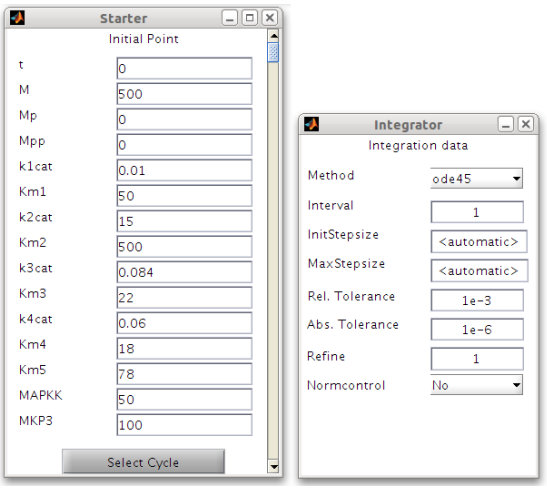


Figure 5: Starter and integrator window with initial values.

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 $2D$-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→Forward'), $[Mpp]$ will reach its steady state, close to 50. Selecting 'Compute→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.

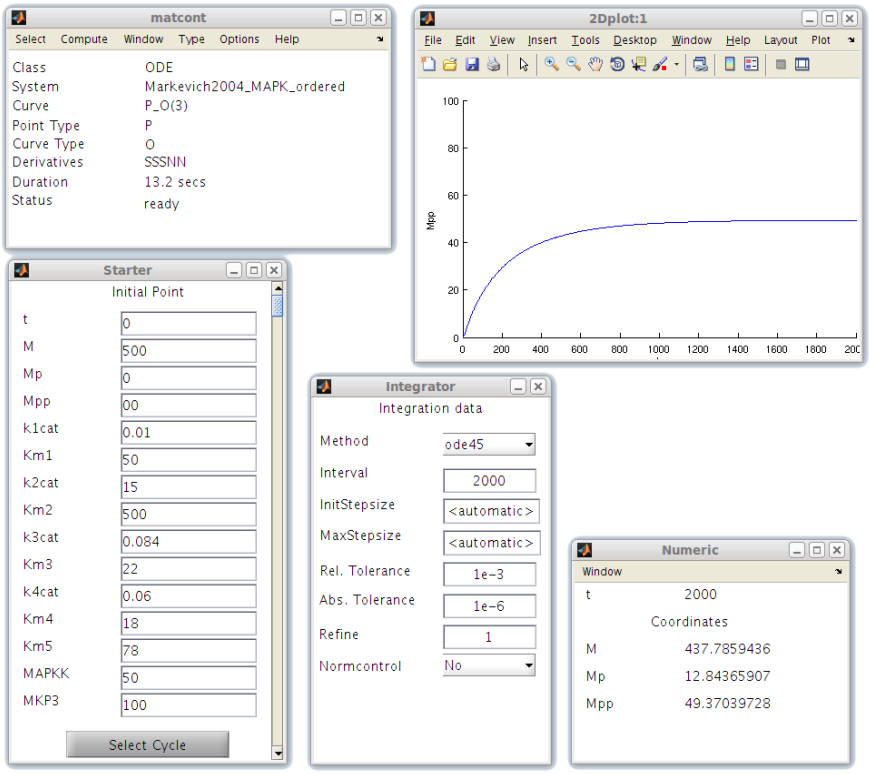


Figure 6: Setup and result of numerical integration to first equilibrium.

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],

$$[Mp] = M_{tot} - [M] - [Mpp], \tag{1}$$

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→ 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
Mpp	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→Initial Point→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.

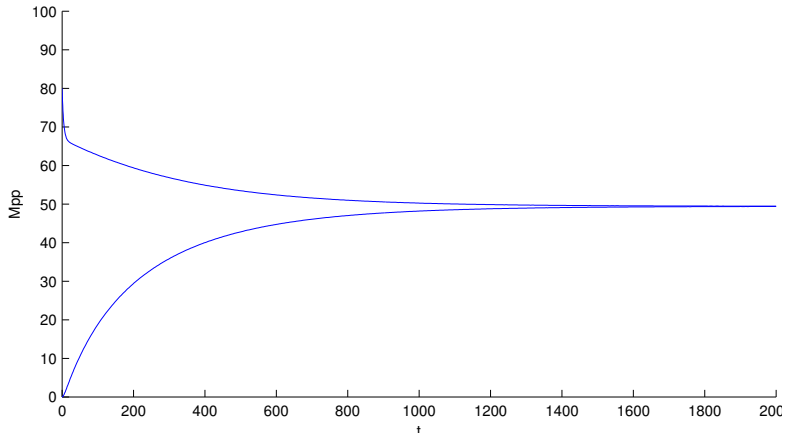


Figure 7: The numeric integration of the system.

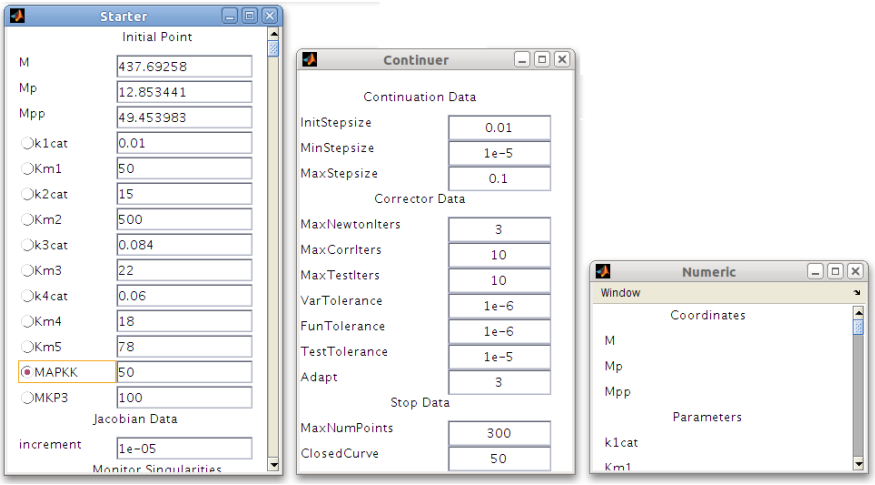


Figure 8: Updated starter window.

When selecting 'Compute→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→System→ 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.

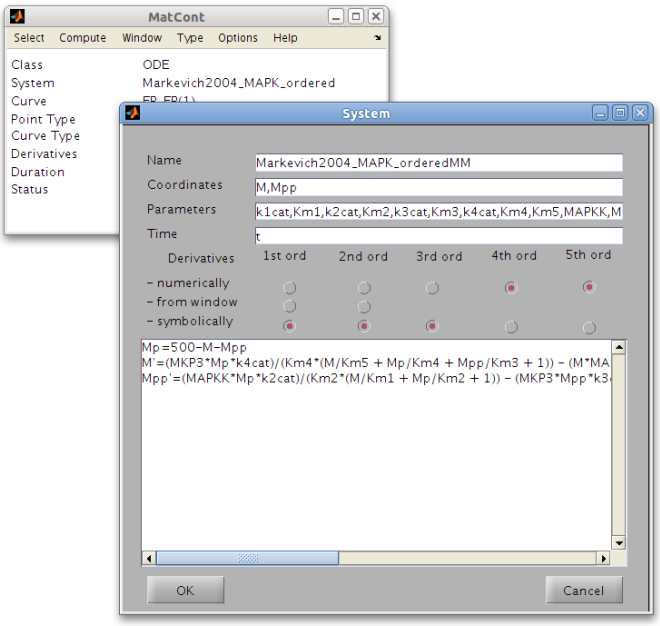


Figure 9: Edited system to make it linear independent.

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.

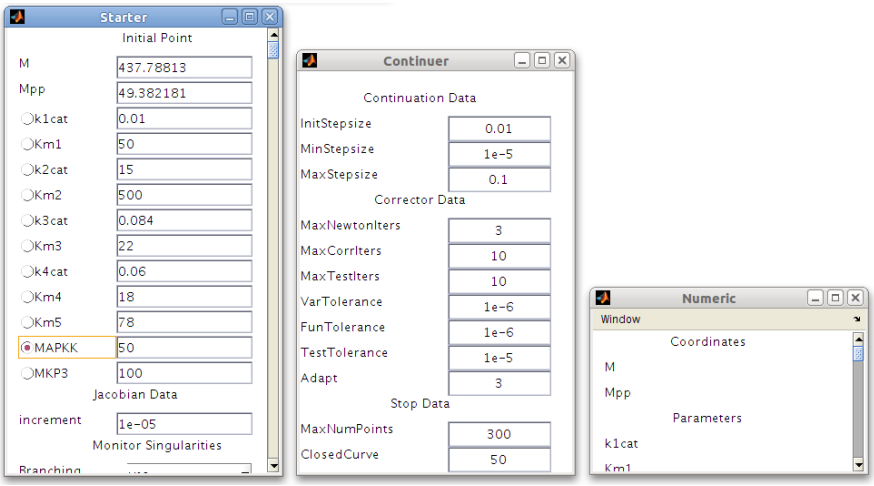


Figure 10: Updated starter window of linear independent system.

Open a 2D plot with 'Window→Graphic→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→Variables on axes' and 'Layout→Plotting region' on the *2DPlot window*. Choosing 'Compute→Forward' or 'Compute→Backward' and 'Compute→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

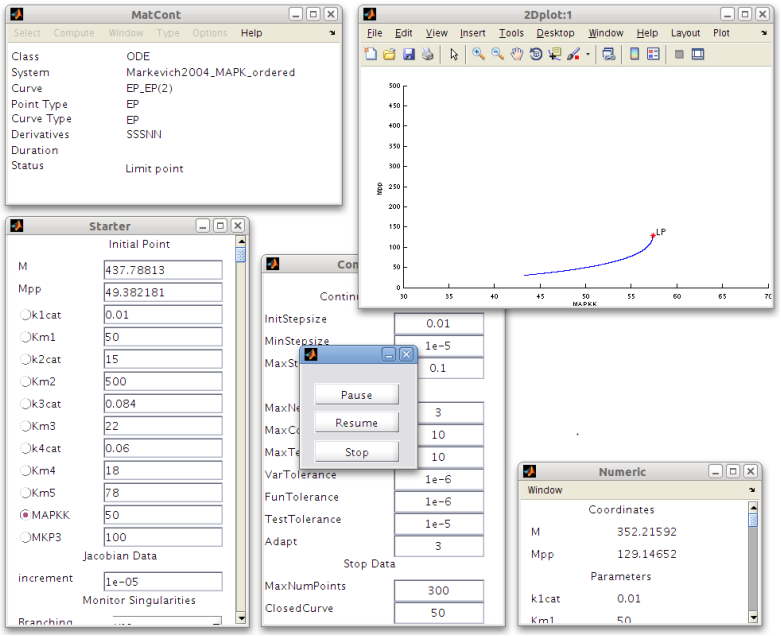


Figure 11: Setup and output of an equilibrium continuation.

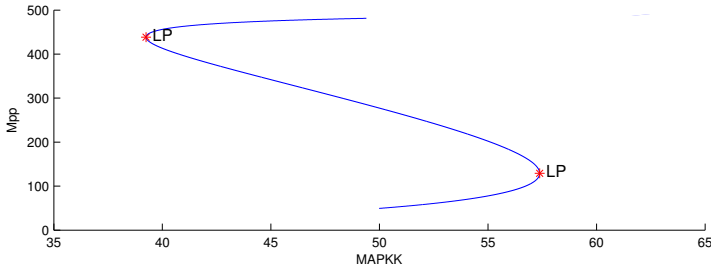


Figure 12: Continuation of equilibrium.

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.

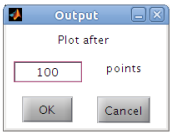


Figure 13: Changing the interval between redraws.

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→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.

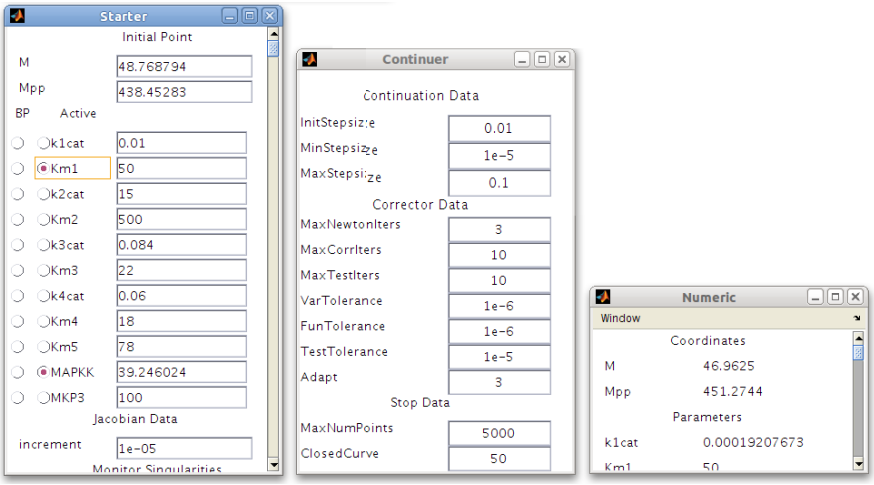


Figure 14: Starter window for LP-LP continuation.

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→Forward') gives Figure 15. At $M = 249.921974$, $Mpp = 240.426057$, $km1 = 246.269558$, $MAPKK = 41.157105$ a cusp bifurcation is detected.

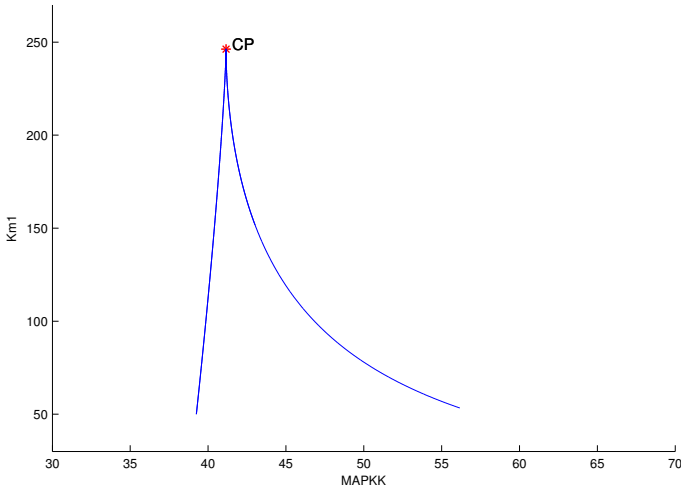


Figure 15: LP-LP continuation.

References

[1] A. Dhooge, W. Govaerts, and Yu.A. Kuznetsov. MATCONT: a MATLAB package for numerical bifurcation analysis of ODEs. *ACM Transactions on Mathematical Software (TOMS)*, 29(2):141–164, 2003.

[2] A. Dhooge, W. Govaerts, Yu.A. Kuznetsov, W. Mestrom, A.M. Riet, and B. Sautois. MATCONT and CL_MATCONT: Continuation toolboxes in Matlab. `http://sourceforge.net/projects/matcont/`, 2004.

[3] W. Govaerts, Yu.A. Kuznetsov, and B. Sautois. MATCONT. *Scholarpedia*, 1(9):1375, 2006.

[4] M. Hucka, A. Finney, H.M. Sauro, H. Bolouri, J.C. Doyle, H. Kitano, A.P. Arkin, B.J. Bornstein, D. Bray, A. Cornish-Bowden, A.A. Cuellar, S. Dronov, E.D. Gilles, M. Ginkel, V. Gor, I.I. Goryanin, W.J. Hedley, T.C. Hodgman, J.H. Hofmeyr, P.J. Hunter, N.S. Juty, J.L. Kasberger, A. Kremling, U. Kummer, N. Le Novère, L.M. Loew, D. Lucio, P. Mendes, E. Minch, E.D. Mjolsness, Y. Nakayama, M.R. Nelson, P.F. Nielsen, T. Sakurada, J.C. Schaff, B.E. Shapiro, Shimizu T.S., H.D. Spence, J. Stelling, K. Takahashi, M. Tomita, J. Wagner, and J. Wang. The systems biology markup language (SBML): a medium for representation and exchange of biochemical network models. *Bioinformatics*, 19(4):524–531, 2003.

[5] C. Li, M. Donizelli, N. Rodriguez, H. Dharuri, L. Endler, V. Chelliah, L. Li, E. He, A. Henry, M.I. Stefan, et al. Biomodels database: An enhanced, curated and annotated resource for published quantitative kinetic models. *BMC systems biology*, 4(1):92, 2010.

[6] N.I. Markevich, J.B. Hoek, and B.N. Kholodenko. Signaling switches and bistability arising from multisite phosphorylation in protein kinase cascades. *The Journal of cell biology*, 164(3):353, 2004.