

Supplement A

MCMC_CLIB – An advanced MCMC sampling package for ode models

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This Supplement provides some illustration for the chosen model. It shows, how a parameter sample is related to a model fit. This model has been chosen as an example for a hard problem: the model is large and cannot fit all of the observations simultaneously; the measurements are sparse, uncertain, and are provided in arbitrary units. Note: The reason for the mismatch will not be discussed. The data might have been obtained under erroneous assumptions which are consequently not reflected in the modeling setup or alternatively, the model is incorrect.

1 Notation of uncertainty

Throughout all documentation we use this notation for errors:

$$v = 1.71(12) := 1.71 \pm 0.12 \quad a = 42(3) \times 10^6 := (42 \pm 3) \times 10^6, \quad (1)$$

where we write only the significant digits of the error estimate. The magnitude of the error is communicated by rounding the reported number to the appropriate number of digits, example $a = \alpha \pm \delta$

$$\alpha = 3.14159265 \text{ kg}, \quad \delta = 0.00014672 \text{ kg}, \quad (2)$$

$$\text{will be reported as } a = 3.14159(15) \text{ kg}, \quad (3)$$

$$\text{as opposed to } a = (3.14159 \pm 0.00015) \text{ kg}. \quad (4)$$

This is shorter, better suited for tables and has advantages when reporting numbers with units of measurement.

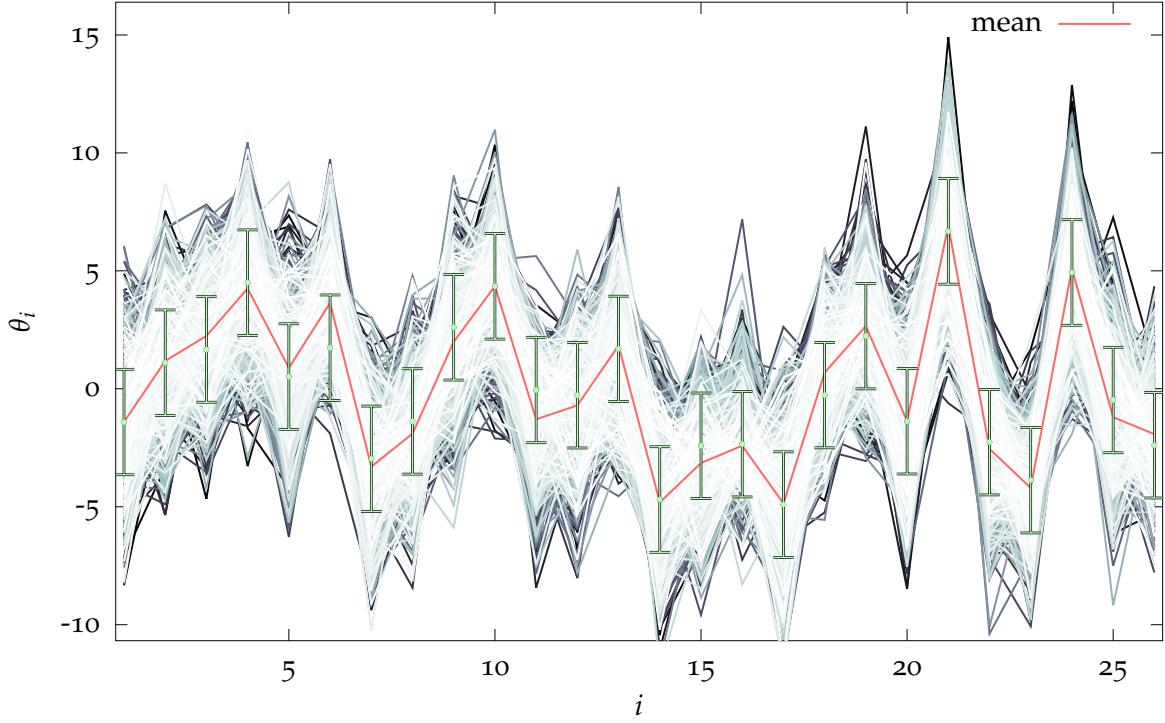


Figure 1: The Posterior Sample of size $N = 1 \times 10^6$, as obtained from the MCMC_CLIB; thinned out using the integrated autocorrelation length $\tau_{\text{int},l} = 340(30)$ (estimated using the log-posterior l as observable). The red line indicates the maximum posterior estimate, while the green errorbars indicate the used prior distribution (Gaussian). The colorpalette reflects the value of the log-posterior for each sampled point. Here, we have incorporated our prior knowledge about the parameter values in the prior parameter density. Yet, we have chosen to let the prior span several orders of magnitude.

tuning duration	1000 points
target acceptance a_0	0.500
observed acceptance a	0.498
auto-correlation length $\tau_{\text{int},l}$	340(30)
failed Likelihood evaluations [CVODES]	16

Table 1: Sample Properties.

2 Two different ways to sample the provided model

The sample was obtained in $t_s = 267385$ s (about 74 h). Considering the auto-correlation $\tau_{\text{int},l} = 340(30)$, the effective sampling speed is:

$$v = \frac{N}{2\tau_{\text{int},l} t_s} = 5.50(49) \times 10^{-3} \text{ s}^{-1}. \quad (5)$$

The properties recorded during sampling are summarised in Table 1. The sample is plotted in Figure 1 using parallel coordinates (each sampled parameter vector is shown component wise, as a line). Figure 2 shows the output trajectories obtained from forward simulations using the sampled parameters. There is partial agreement between model and data (black errorbars).

2.1 Alternative sampling approach

As in the given example, it is often the case that observations $y_i(t_j, \theta, u_k)$ are reported in arbitrary units. However, we do not fit the unknown data scaling constant. We expect this scaling to be different when the experiment is repeated. In biological experiments this unknown scaling will reflect conditions like dilution of bacteria samples, exposure time for western blotting and similar, which does change with repetition. Therefore, we are not interested in the values of these scaling constants¹. To deal with this issue, we take the ratios between the observations and some reference experiment results, which are often called «control» by biologists. This reference measurement is performed under identical observation conditions and has the same scaling; thus, the scaling cancels in the ratios. But, since the *simulation* of this reference value using the model depends on the parameters $\rho = \exp(\theta)$, we have a parameter dependant scaling:

$$\tilde{y}_{ijk} = \frac{y_i(t_j, \theta, u_k)}{y_i(t_j, \theta, u_0)}, \quad (6)$$

where u_0 characterises the reference conditions. This results in dramatically different fits. This method effectively eliminates all observation parameters and results in a smaller MCMC problem than trying to estimate the observational scaling.

¹see the mathematical documentation for details on this topic

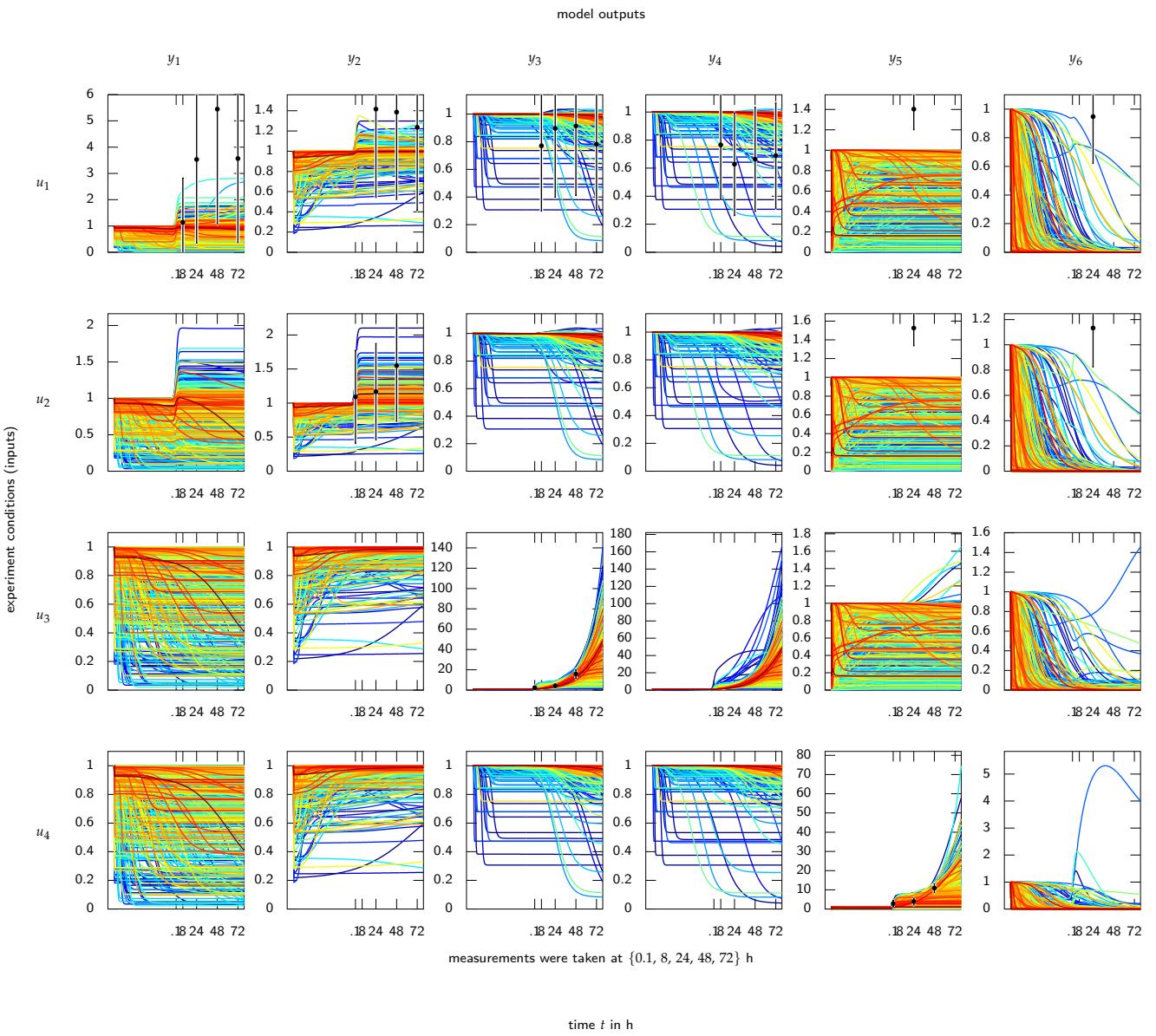


Figure 2: output trajectories per parameter sample member; to reduce the number of lines these trajectory lines are once again plotted for every 3534^{th} ($2(\tau_{\text{int},l} + \delta_\tau)$) parameter in the parameter sample. The green, vertical errorbars represent the data and its measurement error estimation. The data is sparse (not all outputs were observed at all measurement instances. The model does not fit all data points.)

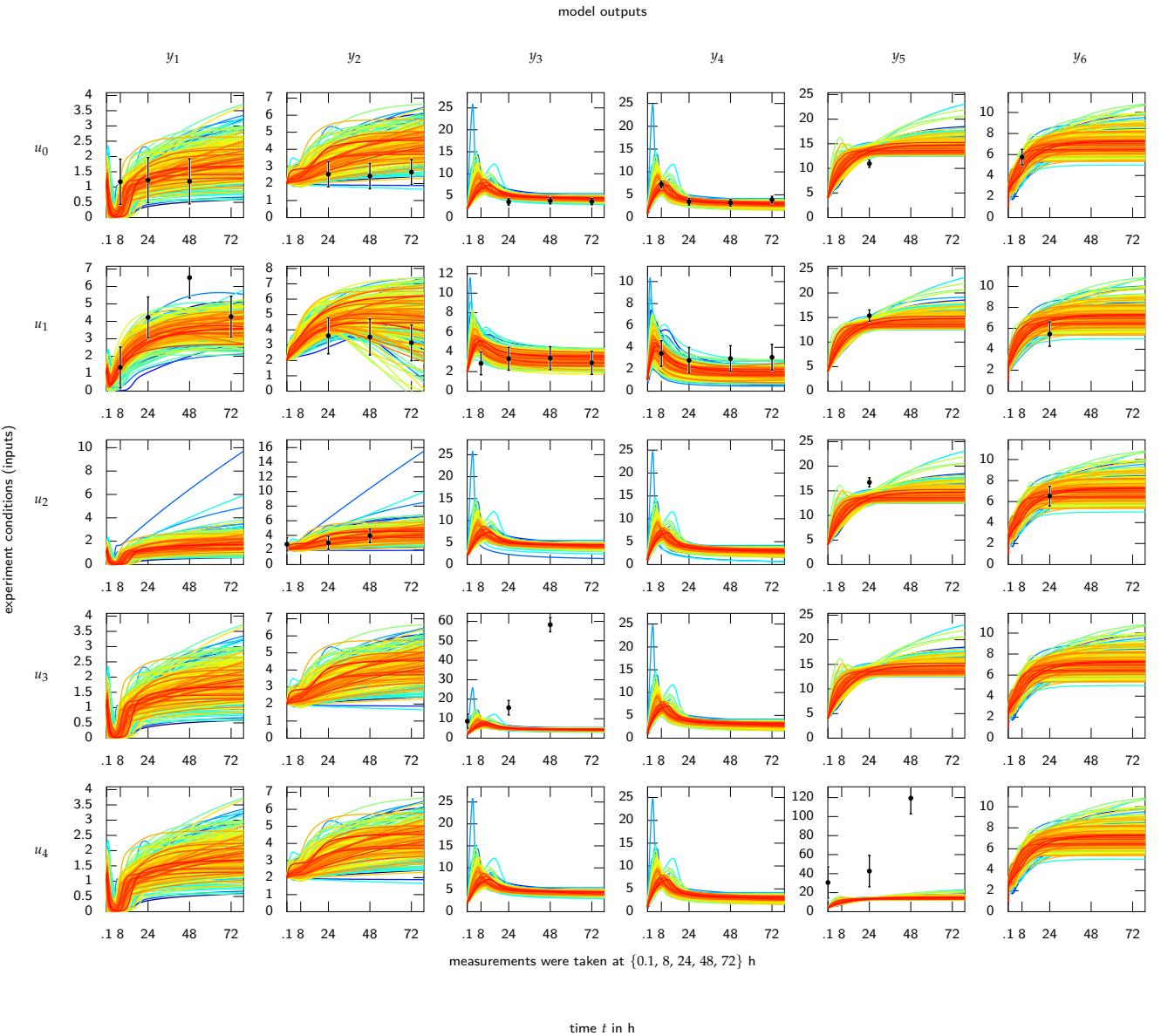


Figure 3: Treating the data as absolute, the fit changes (u_0 is the setup for the reference experiment). Some data points get an improved fit, some system behaviour cannot be reproduced. Note that this treatment of the data is incorrect and is done for illustration purposes; we show the difference between fitting absolute and relative data. To obtain these Trajectories, we have used a different, uninformative, iid, Gaussian prior during sampling. The resulting parameter sample is shown in Figure 4

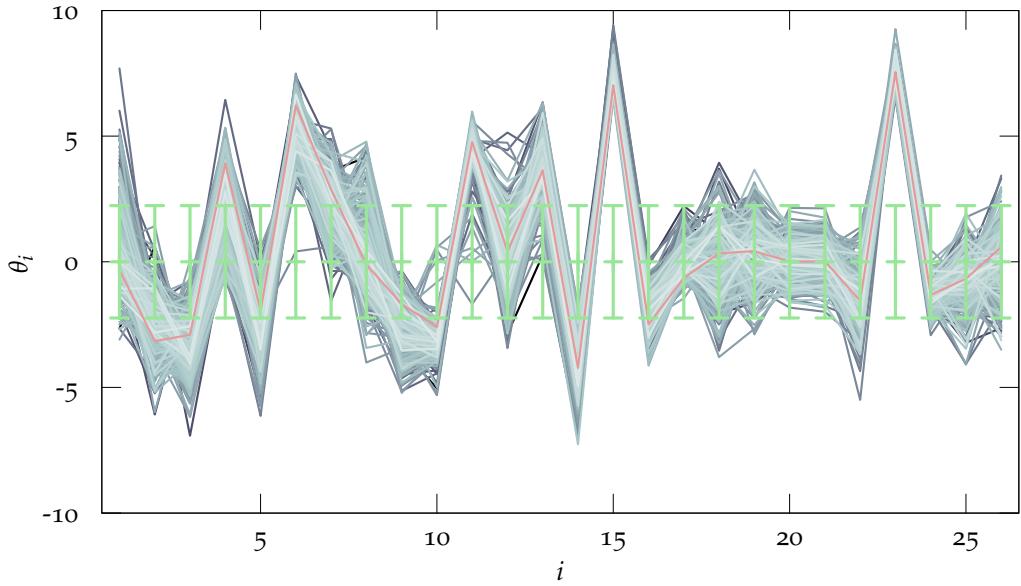


Figure 4: The parameters obtained from the assumption that provided data is absolute (molecule numbers or mols). Here, an uninformative prior was used.

Just for demonstration purposes, we ignore the source of the data and pretend, that the measurements are absolute (gauged). The reference experiment has been included as input line u_0 . Although this is wrong, the problem size is the same and the model can still fit some of the data, but note that different data entries are fitted well compared to the relative data fit. Figure 3 shows this alternative fit. Specifically the model cannot fit the dynamic behaviour in experiment (u_3, y_4) and (u_4, y_5) which it could before, see Figure 2. Most problematic is the fact that the parameter fit cannot be reproduced by repeating the data acquisition experiment; the scaling will be different.

2.2 Model Setup

Listing 1: Model

```

1  <?xml version="1.0" ?>
2  <VectorField Name="ODEmodel11S26P4U" Description="A model for testing purposes">
3  <Parameter Name="theta_1" DefaultValue="1.0"/>
4  <Parameter Name="theta_2" DefaultValue="1.0"/>
5  <Parameter Name="theta_3" DefaultValue="1.0"/>
6  <Parameter Name="theta_4" DefaultValue="1.0"/>
7  <Parameter Name="theta_5" DefaultValue="1.0"/>
8  <Parameter Name="theta_6" DefaultValue="1.0"/>
9  <Parameter Name="theta_7" DefaultValue="1.0"/>
10 <Parameter Name="theta_8" DefaultValue="1.0"/>
11 <Parameter Name="theta_9" DefaultValue="1.0"/>
```

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<Parameter Name="theta_10" DefaultValue="1.0"/>
<Parameter Name="theta_11" DefaultValue="1.0"/>
<Parameter Name="theta_12" DefaultValue="1.0"/>
<Parameter Name="theta_13" DefaultValue="1.0"/>
16 <Parameter Name="theta_14" DefaultValue="1.0"/>
<Parameter Name="theta_15" DefaultValue="1.0"/>
<Parameter Name="theta_16" DefaultValue="1.0"/>
<Parameter Name="theta_17" DefaultValue="1.0"/>
<Parameter Name="theta_18" DefaultValue="1.0"/>
21 <Parameter Name="theta_19" DefaultValue="1.0"/>
<Parameter Name="theta_20" DefaultValue="1.0"/>
<Parameter Name="theta_21" DefaultValue="1.0"/>
<Parameter Name="theta_22" DefaultValue="1.0"/>
<Parameter Name="theta_23" DefaultValue="1.0"/>
26 <Parameter Name="theta_24" DefaultValue="1.0"/>
<Parameter Name="theta_25" DefaultValue="1.0"/>
<Parameter Name="theta_26" DefaultValue="1.0"/>
<Parameter Name="u1" DefaultValue="0.0"/>
<Parameter Name="u2" DefaultValue="0.0"/>
31 <Parameter Name="u3" DefaultValue="0.0"/>
<Parameter Name="u4" DefaultValue="0.0"/>
<Expression Name="logistic" Formula="1.0/(1+exp(-t))"/>
<Expression Name="U1t" Formula="u1*logistic"/>
<Expression Name="U2t" Formula="u2*logistic"/>
36 <Expression Name="U3t" Formula="u3*logistic"/>
<Expression Name="U4t" Formula="u4*logistic"/>
<Expression Name="S1" Formula="X4+X5"/>
<Expression Name="S2" Formula="(theta_22)*X9*X7"/>
<Expression Name="A1" Formula="(theta_1)*X2"/>
41 <Expression Name="A2" Formula="(theta_2)*X1"/>
<Expression Name="A3" Formula="(theta_3)*X3*X2"/>
<Expression Name="A4" Formula="(theta_4)*X4"/>
<Expression Name="A5" Formula="(theta_10)*X4"/>
<Expression Name="A51" Formula="(theta_10)*X5"/>
46 <Expression Name="A6" Formula="(theta_13)*X7"/>
<Expression Name="A7" Formula="(theta_14)*S1*X6"/>
<Expression Name="A8" Formula="(theta_19)*X10*S1"/>
<Expression Name="A9" Formula="(theta_20)*X8"/>
<Expression Name="A10" Formula="(theta_22)*X11*X7"/>
51 <Expression Name="A11" Formula="(theta_21)*X9"/>
<StateVariable Name="X1"
               DefaultInitialCondition="1000.0"
               Formula="A1-A2+(theta_5)*(0.1+S2)-(theta_7)*X1" />
<StateVariable Name="X2"
               DefaultInitialCondition="1000.0"
               Formula="-A1+A2-(theta_8)*X2" />
56 <StateVariable Name="X3"
               DefaultInitialCondition="1000.0"
               Formula="-A3+A4+(theta_6)+(theta_12)*U2t-(theta_9)*X3" />

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61 <StateVariable Name="X4"
                  DefaultInitialCondition="1000.0"
                  Formula="A3-A4-A5" />
<StateVariable Name="X5"
                  DefaultInitialCondition="0.0"
66          Formula="+(theta_11)*Uit-A51" />
<StateVariable Name="X6"
                  DefaultInitialCondition="1000.0"
                  Formula="A6-A7+(theta_15)+(theta_18)*U3t-(theta_16)*X6" />
<StateVariable Name="X7"
                  DefaultInitialCondition="1000.0"
                  Formula="-A6+A7-(theta_17)*X7" />
<StateVariable Name="X8"
                  DefaultInitialCondition="1000.0"
                  Formula="+A8-A9-(theta_24)*X8" />
76 <StateVariable Name="X9"
                  DefaultInitialCondition="1000.0"
                  Formula="+A9-A11" />
<StateVariable Name="X10"
                  DefaultInitialCondition="1000.0"
51          Formula="-A8+A10" />
<StateVariable Name="X11"
                  DefaultInitialCondition="1000.0"
                  Formula="-A10+A11+(theta_23)+(theta_26)*U4t-(theta_25)*X11" />
<Function Name="Y1" Formula="(X4+X5)"/>
86 <Function Name="Y2" Formula="(X3+X5)"/>
<Function Name="Y3" Formula="(X7+X6)"/>
<Function Name="Y4" Formula="(X6)"/>
<Function Name="Y5" Formula="(X10+X9+X11+X8)"/>
<Function Name="Y6" Formula="X8"/>
91 </VectorField>

```