ADMIT

Tutorial – Examples

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Examples

A **Michaelis-Menten kinetics** [Rumschinski et al., 2011, BMC Syst. Biol.]

- step-by-step workflow illustration and explanation
- **parameter estimation**
    - outerbounding
    - bisectioning

B **Carnitine Transport mechanism** [Rumschinski et al., 2011, BMC Syst. Biol.]

- data import from table, data uncertainty description
- **state estimation**
- **uncertainty analysis**

C **Bio-Reactor system** [Savchenko et al., 2011, IFAC World Congress]

- binary variables
- **detection of discrete state changes (fault detection and diagnosis)**
- **reachability analysis**
- **Monte-Carlo**

D **Adaptation process** [Rumschinski et al. 2012, in press]

- combination of quantative data and qualitative information
- **combined parameter and state estimation**
- **invalidation of model hypotheses**

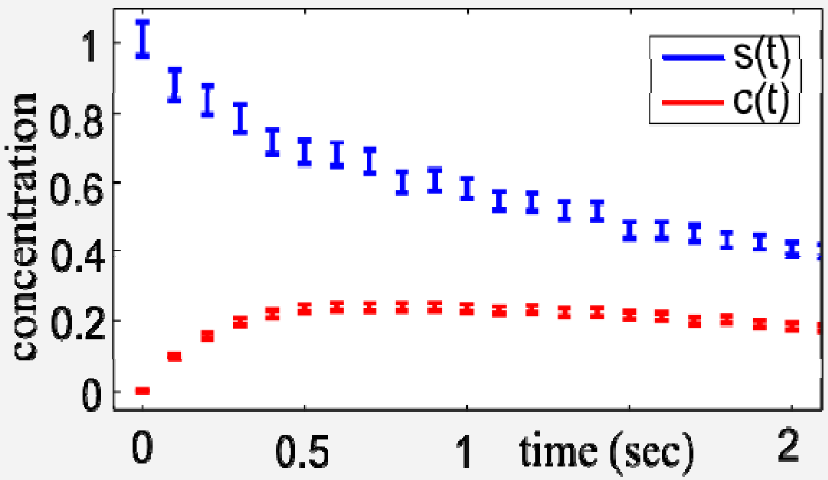
➡ **Refer ADMIT/examples/**

Example A: Michaelis-Menten (Overview)

Task: parameter estimation for Michaelis-Menten kinetics

Measurements

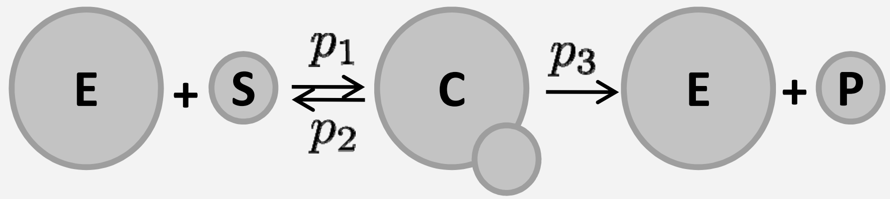
- 20 measurements (sustrate + complex)
- uncertain (ca 5% relative error)



A priori knowledge (parameters)

$0.1 \leq p_i \leq 10, \;\; i \in [1:3]$

Dynamical model



- mass action kinetics
- **three unknown parameters**

Continuous-time:

$$\dot{s}(t) = p_1(c(t) - 1)s(t) + p_2 c(t))$$
$$\dot{c}(t) = p_1(1 - c(t))s(t) - (p_2 + p_3)c(t)$$

➡ **ADMIT/examples/MichaelisMenten/analyzeModel.m**

Workflow and Example Highlights

Step	Function	Highlight
Initialize project	`ADMITproject()`	read project from 'opt'-file
Set options	`ADMITsetOptions()`	choose estimation method
Compose feasibility problem	`ADMITcompose()`	
Estimate	`ADMITestimate()`	
Visualize	`ADMITplotResults()` `ADMITplotBisectioning()`	plot outerbounding/ bisectioning results

Michaelis-Menten: Structure and syntax of the 'opt' file

Variable section

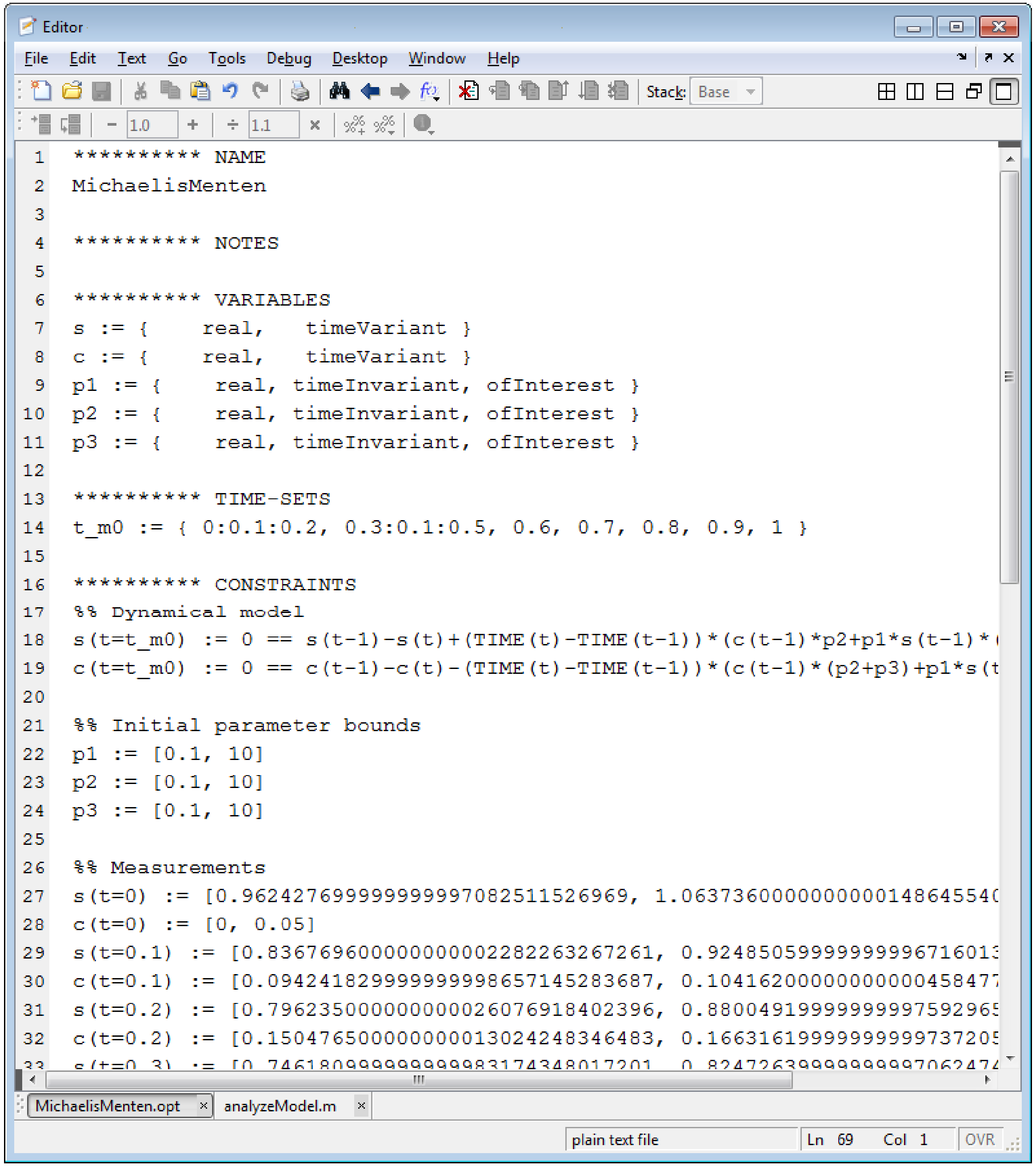
- states: real, time-variant
- **parameters:** real, time-invariant, **of interest**

Time-set section

- time-points from sampling

Constraints section

- **model dynamics,** discrete-time version
- **a priori data** e.g. parameter bounds
- **measurements**



Michaelis-Menten: General Workflow

Read 'opt' file

Set options

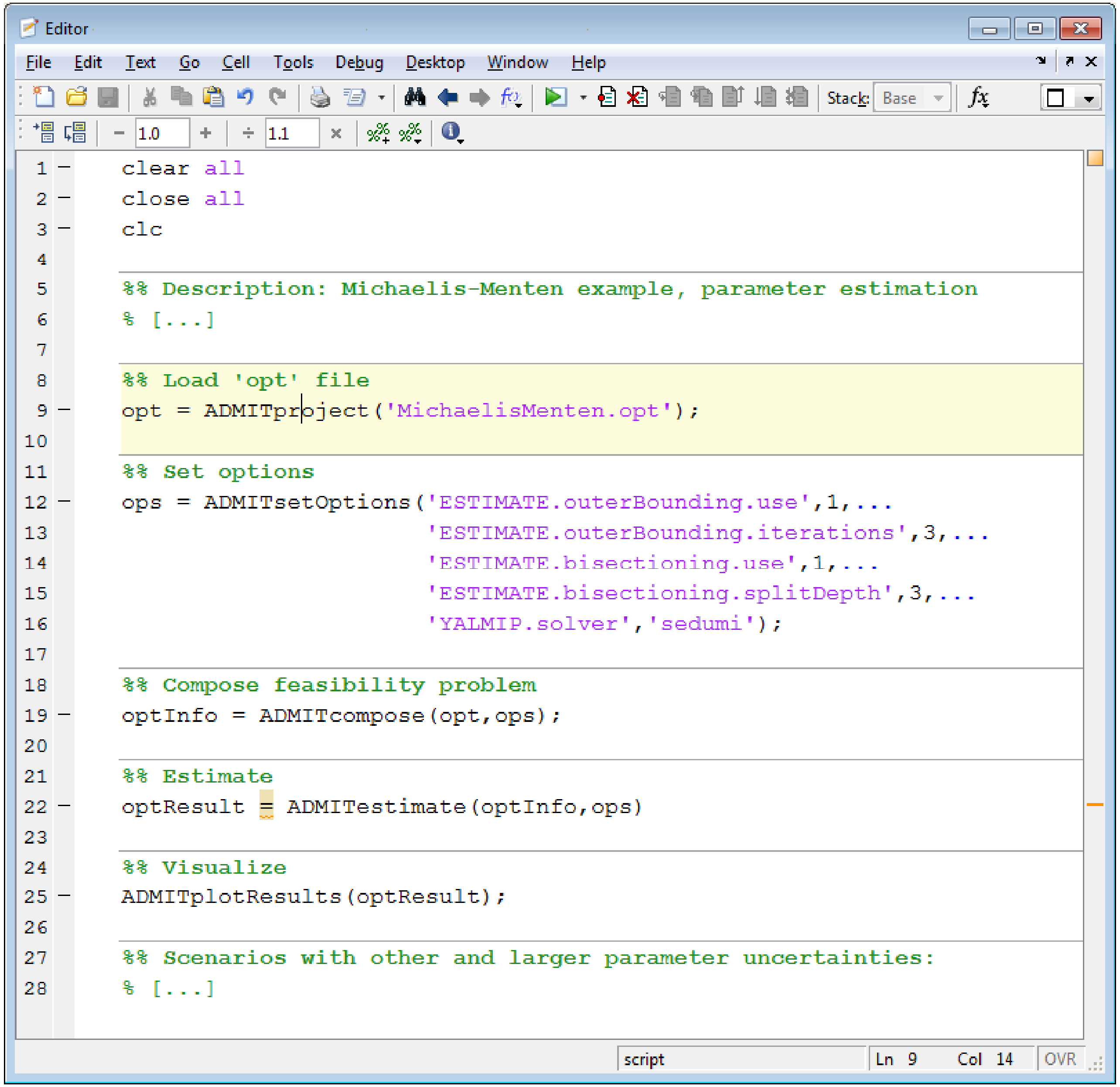
- **outer bounding**
  - **5 iterations**
- bisectioning
  - 3 recursions
- solver
  - **SDP: SeDuMi**
  - LP: cplex, gurobi

Compose problem

Estimate

Visualize

Further scenarios



Summary and Results: Outer-bounding

Outer-bounding of the parameters p1, p2, p3

```
opt = ADMITproject('MichaelisMenten.opt')
```

Variables

```
p1 := {real,timeInvariant,ofInterest}
p2 := {real,timeInvariant,ofInterest}
p3 := {real,timeInvariant,ofInterest}
```

Set options

```
ops =ADMITsetOptions(...
  'ESTIMATE.outerBounding.use',1,...
  'ESTIMATE.outerBounding.iterations',3)
```

Compose

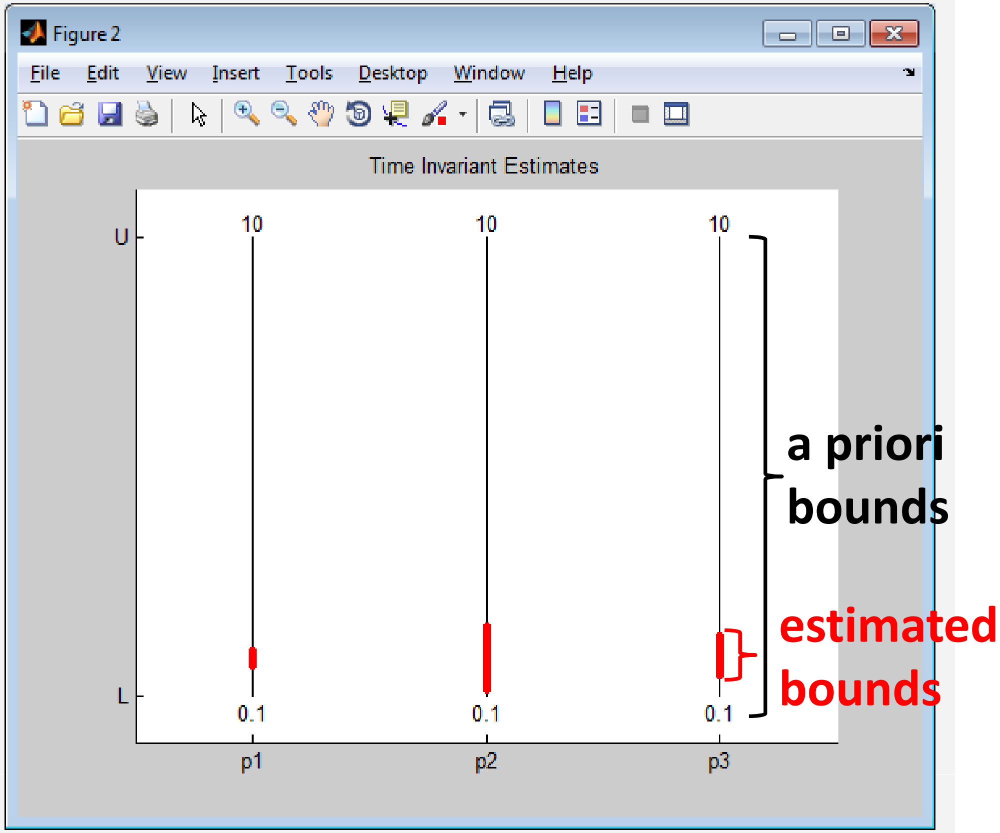
```
optInfo = ADMITcompose(opt,ops)
```

Estimate

```
optResult = ADMITestimate(optInfo,ops)
```

Visualize results

```
ADMITplotResults(optResult,ops)
```



Summary and Results: Bisectioning

Bisection for the parameters p1, p2, p3

```
opt = ADMITproject('MichaelisMenten.opt')
```

Variables

```
p1  := {real,timeInvariant,ofInterest}
p2  := {real,timeInvariant,ofInterest}
p3  := {real,timeInvariant,ofInterest}
```

Set options

```
ops = ADMITsetOptions(...
    'ESTIMATE.bisectioning.use',1,...
    'ESTIMATE.bisectioning.splitDepth',3)
```

Compose

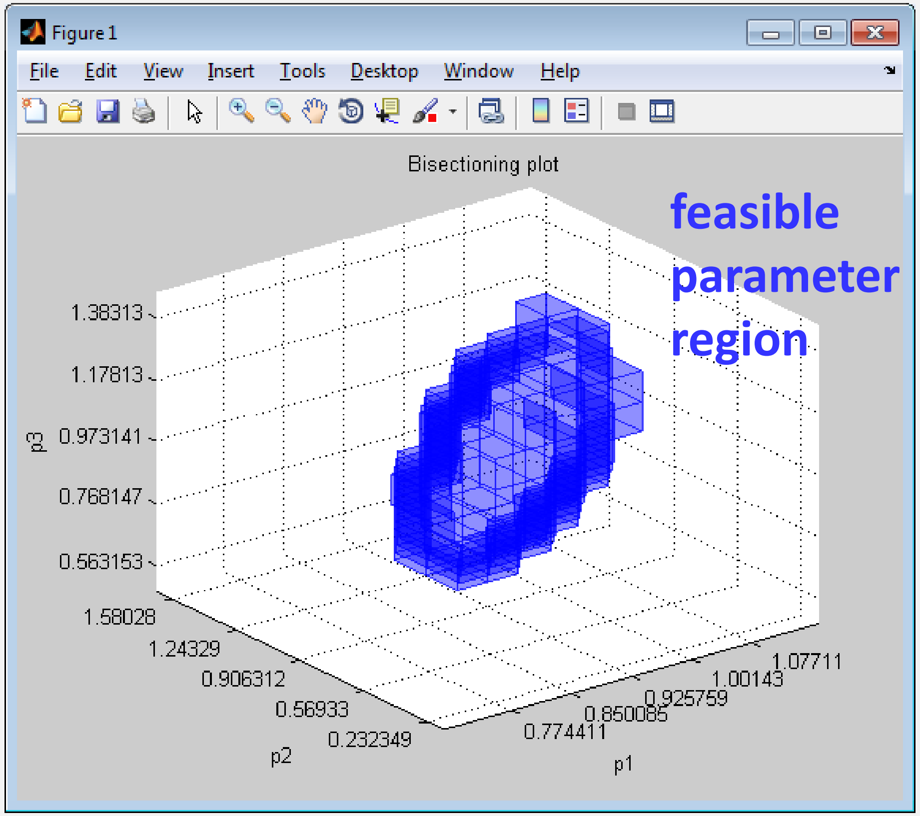
```
optInfo = ADMITcompose(opt,ops)
```

Estimate

```
optResult = ADMITestimate(optInfo,ops)
```

Visualize results

```
ADMITplotBisectioning(optResult,ops)
```



Example B: Carnitine-Transport (Overview)

Task: Parameter estimation and uncertainty analysis for Carnitine shuttle

Reference parameter

Sym	Value	Unit
p_1^*	5.00e-4	$\mu M s^{-1}$
p_2^*	1.03e-1	$\mu(M s)^{-1}$
p_3^*	2.36e-2	s^{-1}
p_4^*	1.85e-2	$\mu(M s)^{-1}$
p_5^*	2.50e-2	s^{-1}
C_0	0.33	μM
C_0^m	1.00	μM

Measurements

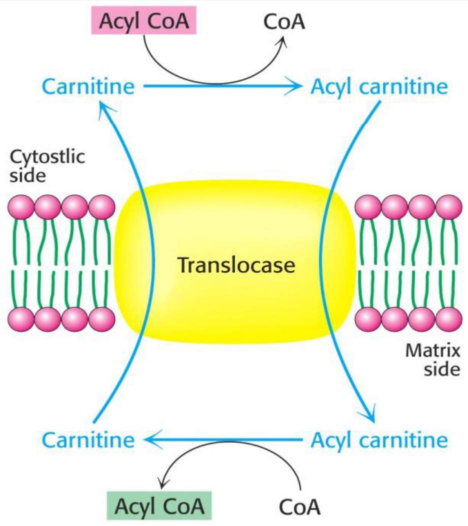
- 25 measurements,
- uncertain (2-4% rel. error)

A priori knowledge

$$0.33 p_i^* \leq p_i \leq 3 p_i^*, \quad i \in [1:5]$$

Dynamical model

- mass action kinetics
- **five unknown parameters**



$$\dot{x}_1 = p_1 u - p_2 x_1 x_2 + p_3 (C_0 - x_2))$$
$$\dot{x}_2 = -p_2 x_1 x_2 + p_3 (C_0 - x_2) + p_4 (C_0 - x_2) x_4)$$
$$\dot{x}_3 = -p_2 x_3 x_4 + p_3 (C_0^m - x_4) - p_5 x_3)$$
$$\dot{x}_4 = -p_4 (C_0 - x_2) x_4 - p_2 x_3 x_4 + p_3 (C_0^m - x_4))$$

➡ **ADMIT/examples/Carnitineshuttle/analyzeModel_parameterEstimation.m**

General Workflow and Example Highlights

Initialize project	`ADMITproject()`

Import data, preprocess data	`ADMITimportData()`
	`ADMITprocessData()`
	`ADMITaddData()`

Set options	`ADMITsetOptions()`
Compose	`ADMITcompose()`
Estimate	`ADMITestimate()`
Visualize	`ADMITplotResults()` `ADMITplotBisectioning()`

- **read measurements from a table**
- **add uncertainty decription**

Carnitine-Transport: Structure and syntax of the 'opt' file

Variables

- states: x1-x4
- **parameters: p1-p5, of interest**
- constants: C0, C0m, u

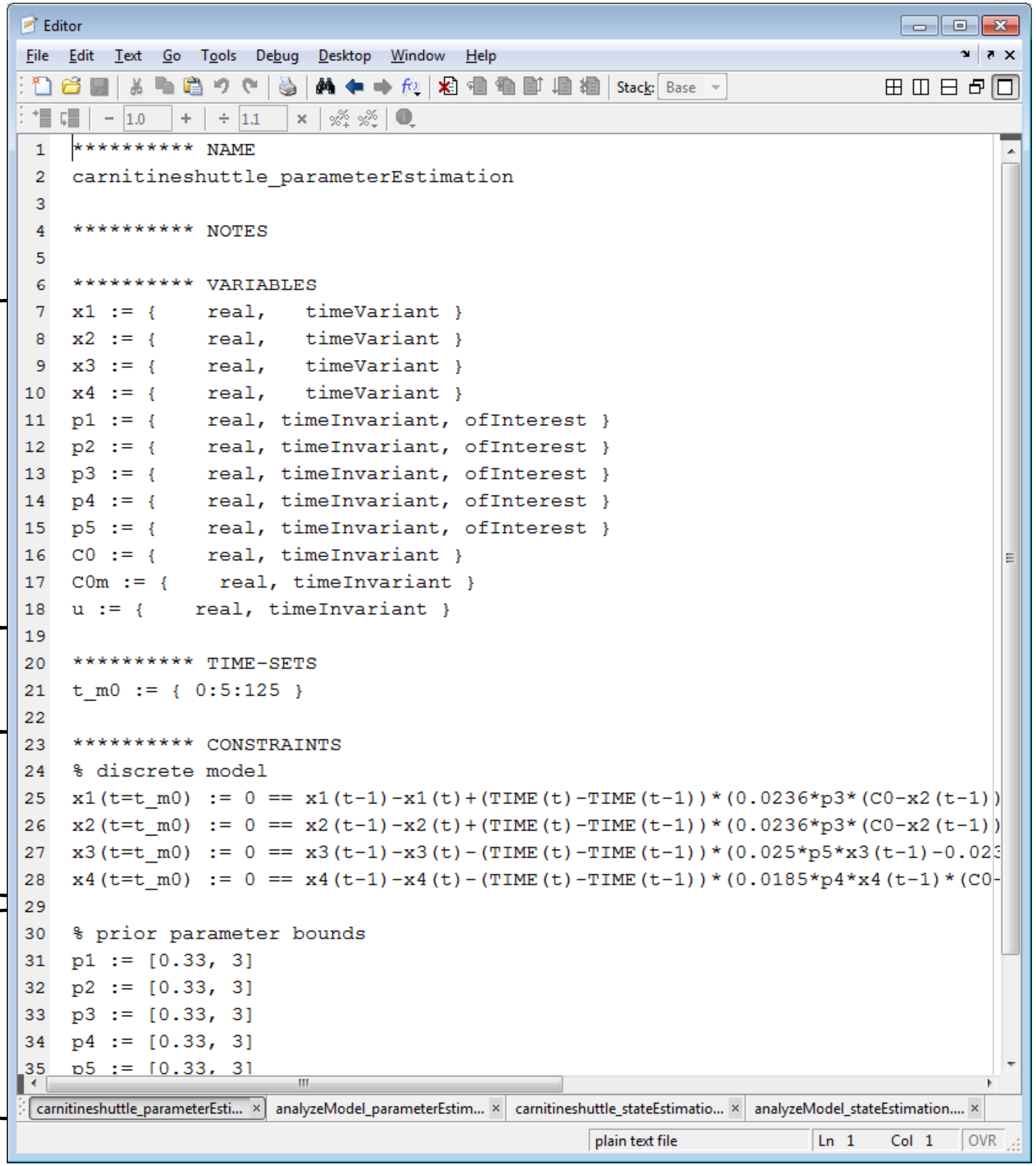
Time-vector

Model dynamics

- discrete-time model

A priori data

- a priori bounds on parameters and constants



```
********** NAME
carnitineshuttle_parameterEstimation

********** NOTES

********** VARIABLES
x1  := {     real,    timeVariant }
x2  := {     real,    timeVariant }
x3  := {     real,    timeVariant }
x4  := {     real,    timeVariant }
p1  := {     real, timeInvariant, ofInterest }
p2  := {     real, timeInvariant, ofInterest }
p3  := {     real, timeInvariant, ofInterest }
p4  := {     real, timeInvariant, ofInterest }
p5  := {     real, timeInvariant, ofInterest }
C0  := {     real, timeInvariant }
C0m  := {     real, timeInvariant }
u := {     real, timeInvariant }

********** TIME-SETS
t_m0 := { 0:5:125 }

********** CONSTRAINTS
% discrete model
x1(t=t_m0)  := 0 == x1(t-1)-x1(t)+(TIME(t)-TIME(t-1))*(0.0236*p3*(C0-x2(t-1))
x2(t=t_m0)  := 0 == x2(t-1)-x2(t)+(TIME(t)-TIME(t-1))*(0.0236*p3*(C0-x2(t-1))
x3(t=t_m0)  := 0 == x3(t-1)-x3(t)-(TIME(t)-TIME(t-1))*(0.025*p5*x3(t-1)-0.02
x4(t=t_m0)  := 0 == x4(t-1)-x4(t)-(TIME(t)-TIME(t-1))*(0.0185*p4*x4(t-1)*(C0-

% prior parameter bounds
p1  := [0.33,  3]
p2  := [0.33,  3]
p3  := [0.33,  3]
p4  := [0.33,  3]
p5  := [0.33,  3]
```

Carnitine-Transport: Measurements

Measurement data import

- measurements can be included from a table (csv, xls,...)
- here: **import from table** (csv), carnitine.dat

```
optData = ADMITimportData('carnitinedata.dat')
```

Measurement uncertainties

- **add uncertainty description** if available, here:
  additive **relative error of 4%** of all measurements

```
optData = ADMITprocessData(optData,{'x1','x2','x3','x4'},[0:5:125],0.04,0.0)
```

species → {'x1','x2','x3','x4'}
time-points → [0:5:125]
relative uncertainty [%] → 0.04
absolute uncertainty → 0.0

- data can be plotted and then added to the ADMITproject

```
ADMITplotData(optData,{'x1','x2','x3','x4'})
opt = ADMITaddData(opt,optData)
```

Carnitine-Transport: Workflow

Initialize

Import data

- import from table
- 4% relative error

Set options

- **outerbounding**
  - **5 iterations**
- LP: cplex

Compose

Estimate

Visualize

Further scenarios

```
clear all
close all
clc

%% Description : Carnitine-transport, parameter estimation
% [...]

%% Load 'opt' file
opt = ADMITproject('carnitineshuttle_parameterEstimation.opt');

%% Import and modify data
% import from Table
optData = ADMITimportData('carnitinedata.dat');
% uncertainty description, 4% relative error
optData = ADMITprocessData(optData,{'x1','x2','x3','x4'},[0:5:125],0.04);
% add data to ADMITproject
opt = ADMITaddData(opt,optData);

%% Set options (outer-bounding, 5 iterations)
% [...]
ops =  ADMITsetOptions('ESTIMATE.bisectioning.use',0,...
                       'ESTIMATE.outerBounding.iterations',5,...
                       'YALMIP.solver','cplex');

%% Compose feasibility problem
optInfo = ADMITcompose(opt,ops);

%% Estimate
optResult = ADMITestimate(optInfo,ops)

%% Visualize
ADMITplotResults(optResult,ops);

%% Scenarios with other and larger parameter uncertainties:
% [...]
```

Carnitine-Transport: Results (outer-bounding)

Outer bounding, 4% relative measurement uncertainty

```
opt=ADMITproject('carnitineshuttle_param...
```

Variables

```
p1 := {real,timeInvariant,ofInterest}
p2 := {real,timeInvariant,ofInterest}
p3 := {real,timeInvariant,ofInterest}
p4 := {real,timeInvariant,ofInterest}
p5 := {real,timeInvariant,ofInterest}
```

A priori data

- $0.33p_i^* \leq p_i \leq 3p_i^*,\ i \in [1:5]$

Measurements

- 4% relative error on x1-x4

Set options

```
ops = ADMITsetOptions(...
  'ESTIMATION.outerBounding.use',1,...
  'ESTIMATION.outerBounding.iterations',5)
```

Compose

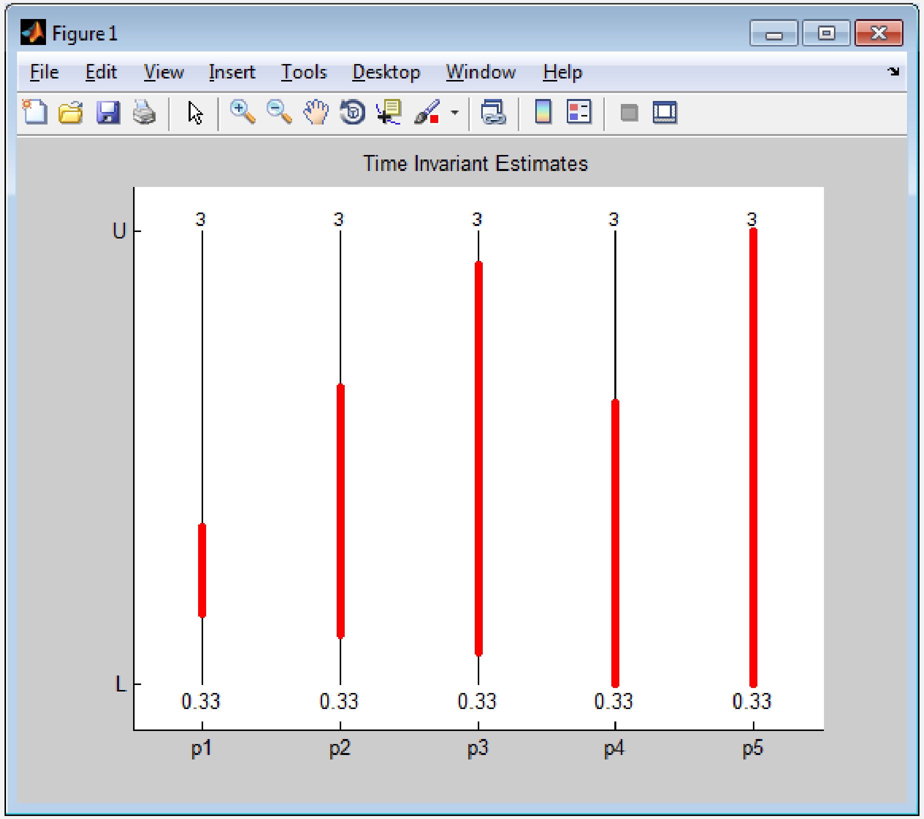
```
optInfo = ADMITcompose(opt,ops)
```

Estimate

```
optResult = ADMITestimate(optInfo,ops)
```

Visualize results

```
ADMITplotResults(optResult,ops)
```



Carnitine-Transport: Results (state estimation,outer-bounding)

2% relative uncertainty, uncertain parameters

```
opt = ADMITproject('carnitineshuttle_state...
```

Variables

```
x1 := {real,timeVariant,ofInterest}
```

A priori data

- $0 \leq x_1(t) \leq 1,\ t \geq 0$
- $0.95p_i^* \leq p_i \leq 1.05p_i^*,\ i \in [1:5]$

Measurements

- 2% relative error on x1-x4

Set options

```
ops = ADMITsetOptions(...
      'ESTIMATE.outerBounding.use',1,...
      'ESTIMATE.outerBounding.iterations',3,...
      'YALMIP.solver,'cplex')
```

Compose

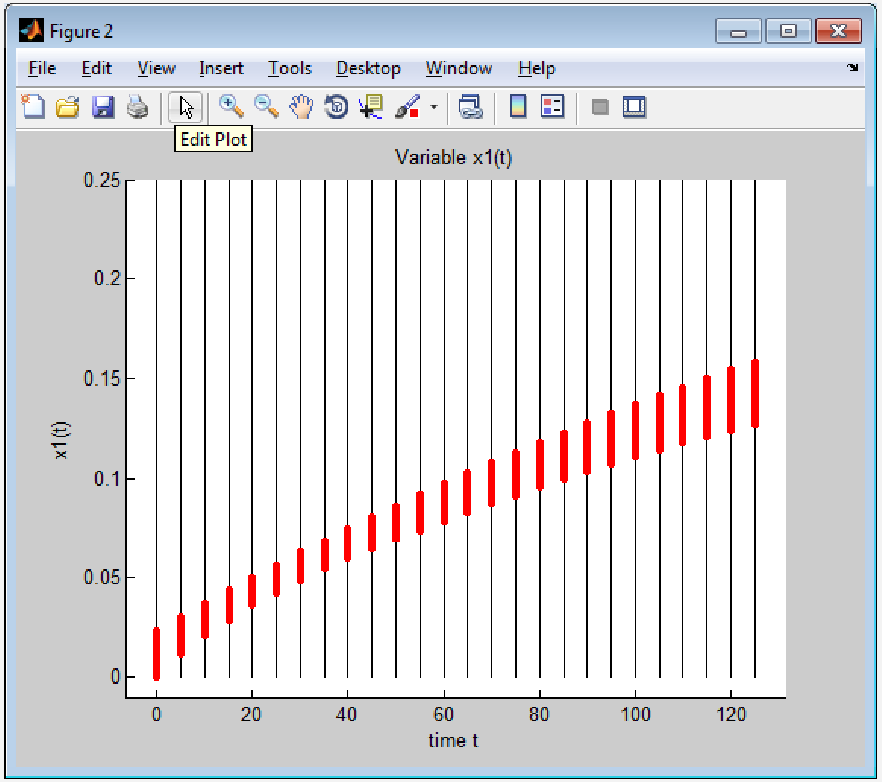
```
optInfo = ADMITcompose(opt,ops)
```

Estimate

```
optResult = ADMITestimate(optInfo,ops);
```

Visualize results

```
ADMITplotResults(optResult,ops)
```



Carnitine-Transport: Results (state estimation,outer-bounding)

2% relative uncertainty, exact parameters

```
opt = ADMITproject('carnitineshuttle_state...
```

Variables

```
x1 := {real,timeVariant,ofInterest}
```

A priori data

- $0 \leq x_1(t) \leq 1,\ t \geq 0$
- $p_i = p_i^*,\ i \in [1:5]$ (exact!)

Measurements

- 2% relative error on x2-x4

Set options

```
ops = ADMITsetOptions(...
   'ESTIMATE.outerBounding.use',1,...
   'ESTIMATE.outerBounding.iterations',3,...
   'YALMIP.solver,'cplex')
```

Compose feasibility problem

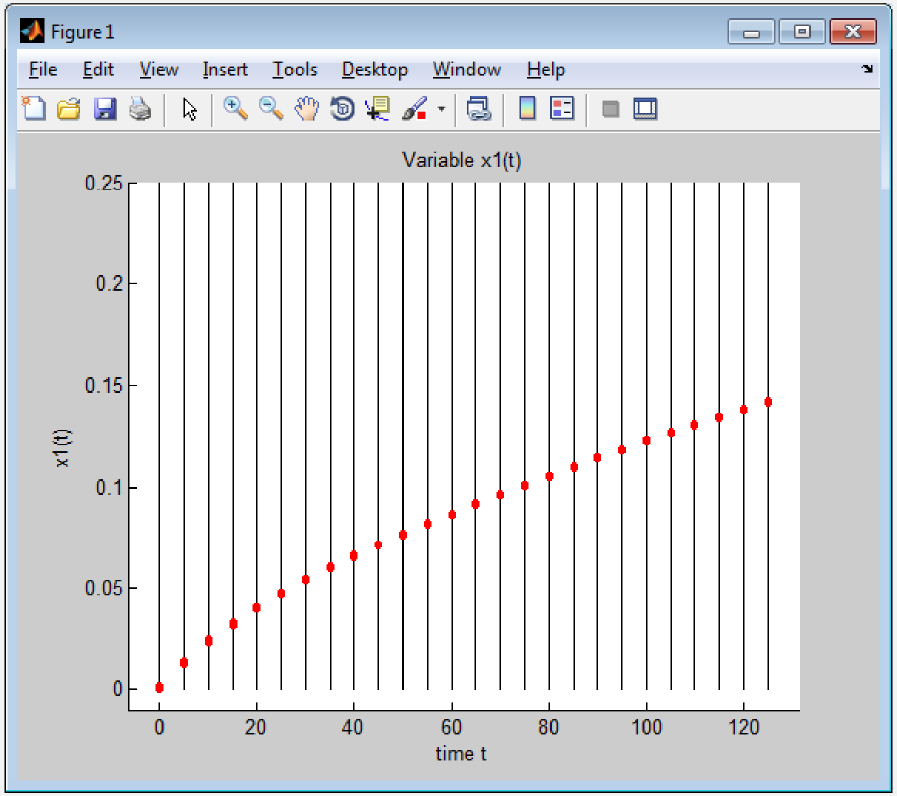
```
optInfo = ADMITcompose(opt,ops)
```

Estimate

```
optResult = ADMITestimate(optInfo,ops)
```

Visualize results

```
ADMITplotResults(optResult,ops)
```



Example C: Two Tank Bioreactor (Overview Fault Diagnosis)

Task: Fault Diagnosis for two tank bioreactor

Reference parameter

Sym	Value	Unit
c_{12}	6.00e-4	$m^{5/2}s^{-1}$
c_2	2.00e-4	$m^{5/2}s^{-1}$
c_L	2.60e-4	$m^{5/2}s^{-1}$
$\bar{q}_p$	4.50e-4	$m^{5/2}s^{-1}$

Measurements (artifical)

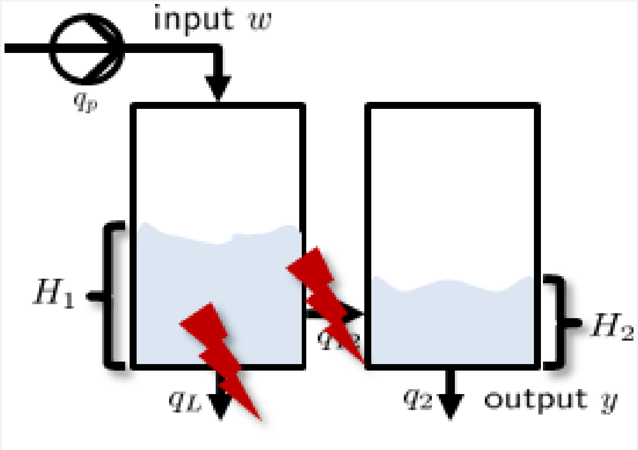
- uncertain (5% rel. error)

A priori parameter knowledge

- uncertain (±2.5e-5 abs. error)

Dynamical model

- four uncertain parameters
- two fault scenarios



$$\dot{H}_1 = \frac{1}{A}(q_p(t) - q_L(t) - q_{12}(t))$$

$$\dot{H}_2 = \frac{1}{A}(q_{12}(t) - q_2(t))$$

$$\begin{aligned} q_p(t) &= \bar{q}_p d_p(t)(1 - \sqrt{H_1(t)/h_{\max}}) \\ q_L(t) &= c_L d_L(t) s_2 \sqrt{H_1(t)} \\ q_{12}(t) &= c_{12} s_1 \sqrt{H_1(t) - H_2(t)} \\ q_2(t) &= c_2 d_2(t) \sqrt{H_2(t)} \end{aligned}$$

⇒ ADMIT/examples/TwoTanks/analyzeModel_faultDiagnosis.m

Two Tank System: Workflow (Fault Diagnosis)

Variables

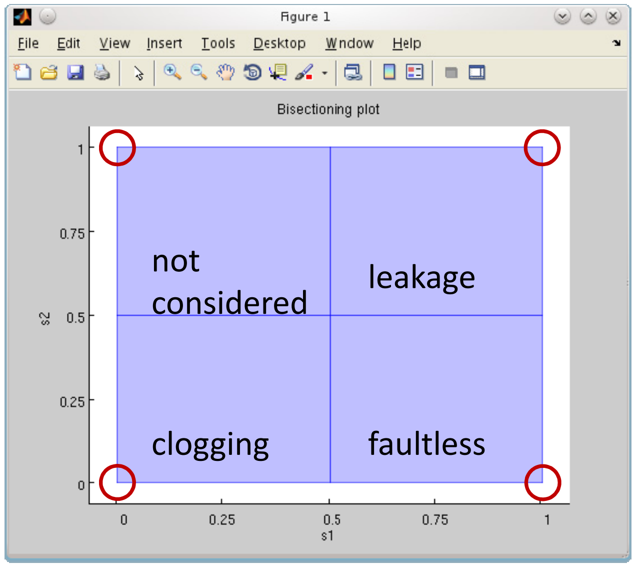
- measurements created for 300s with possible occurence of the fault at 150s
- we consider only one fault at a time
- fault scenarios are modelled using **binary** variables s1, s2:

```
s1 := {binary,timeInvariant,ofInterest}
s2 := {binary,timeInvariant,ofInterest}
```

- **s1**: 0 – when valve between tanks is clogged, 1 – when valve functions normally
- **s2**: 0 – when tank 1 is sealed, 1 – when tank 1 is leaking

Estimate

- estimate values of s1, s2 that are consistent with (simulated) measurements data
- fault is **detected** if (s1,s2)=(1,0) is **not consistent** with the data
- fault is **uniquely diagnosed** if only **one** of the pairs { (1,0), (0,0), (1,1) } is **consistent** with the data



Notes

- here we estimate values of s1, s2 via **bisectioning**

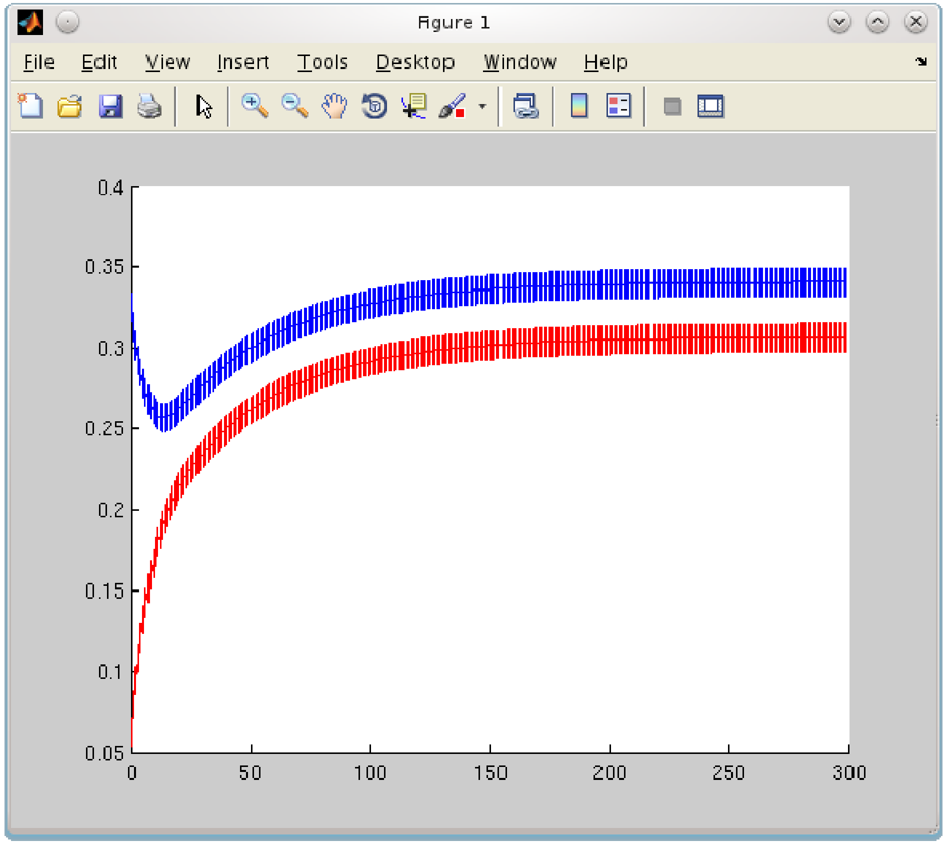
Two Tank System: Result I (Fault Diagnosis)

Bisectioning of the fault switches s1, s2

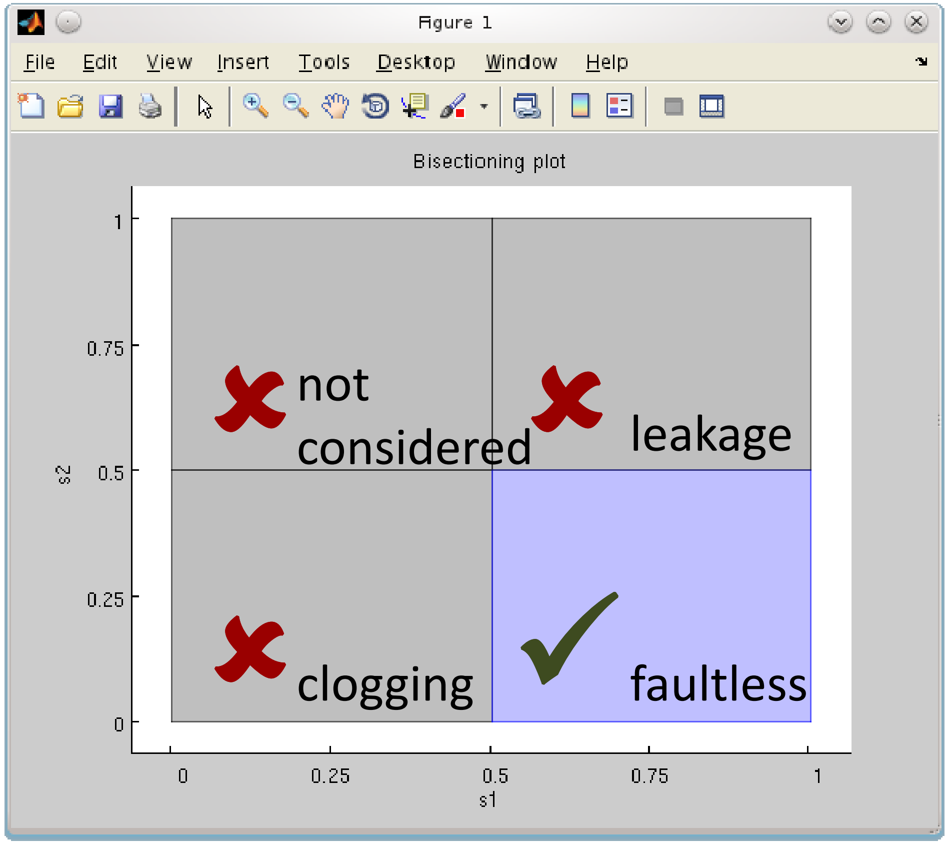
Fault Diagnosis

- measurement data (uncertain) provided from the real plant (here **simulated**)
- **goal**: discard fault scenarios, that cannot represent this measurement data

Faultless system (simulated data)



Results I:

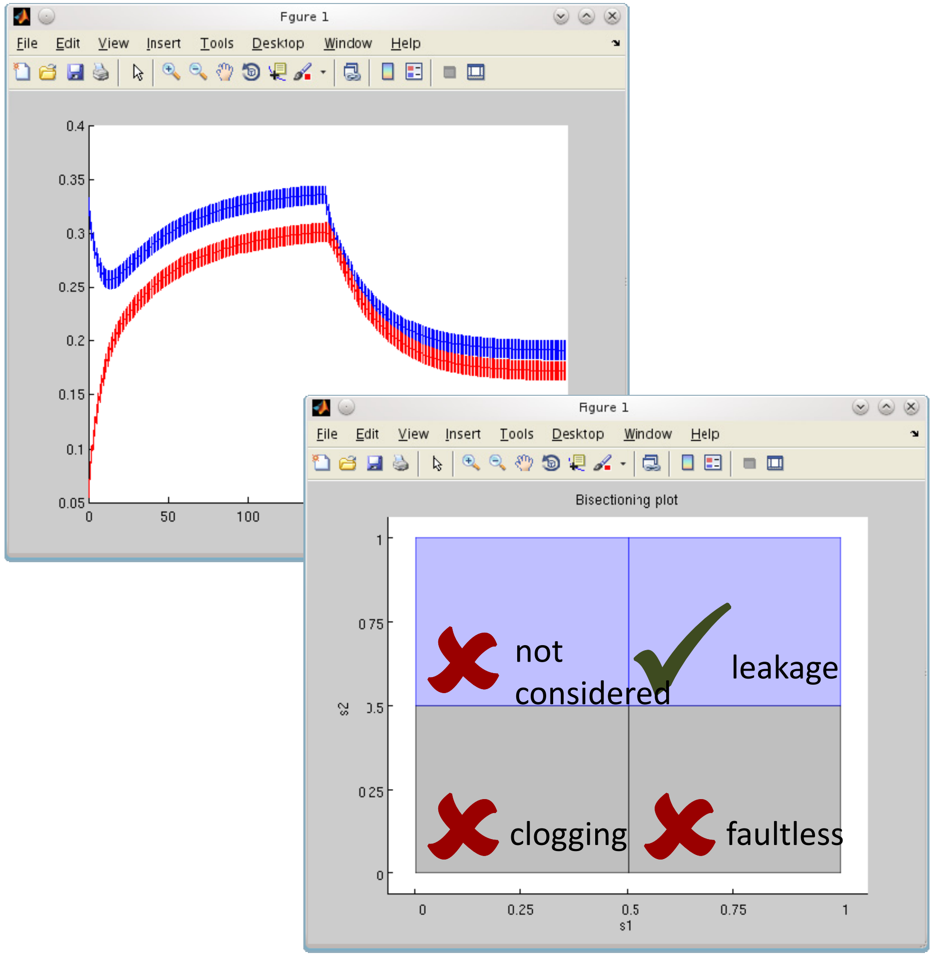


Two Tank System: Result II (Fault Diagnosis)

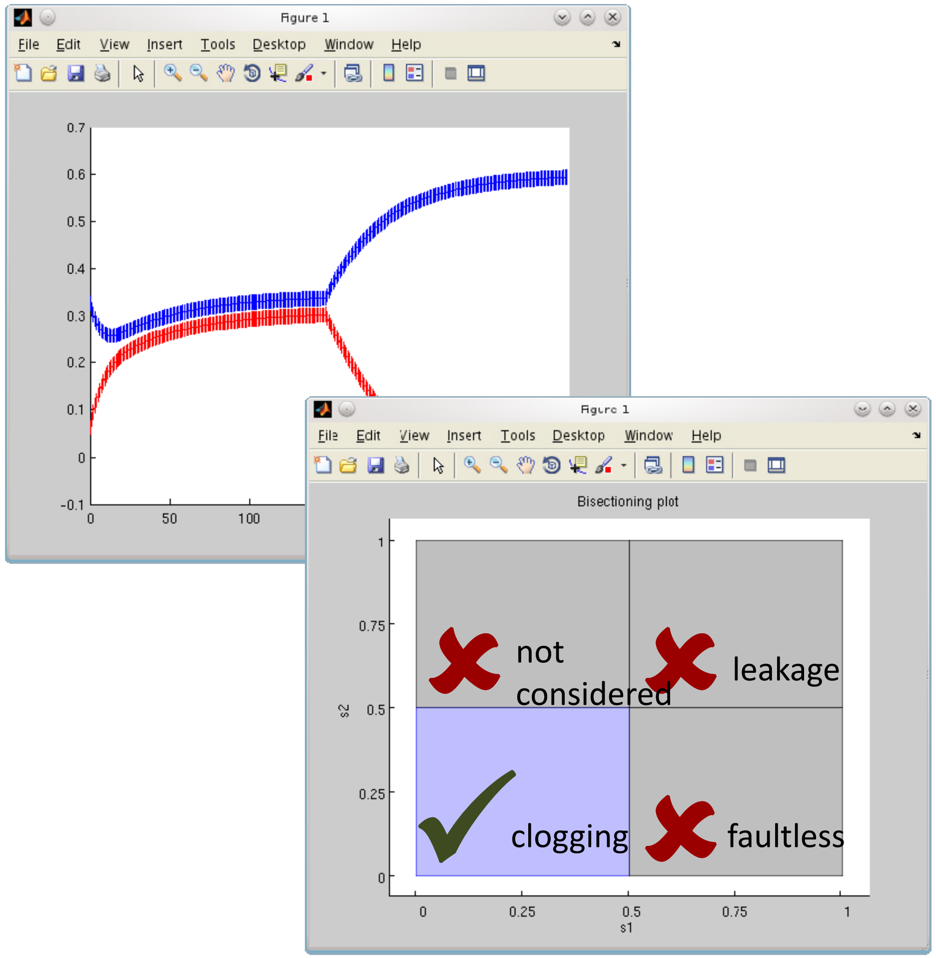
Bisectioning of the fault switches s1, s2

- simulated appearance of the faults (**leakage** in the tank 1 or **clogging** of the valve)
- **unique fault diagnosis**: only one considered faulty model is consistent with the data

Leakage at 150s (simulated data)



Clogging at 150s (simulated data)



Two Tank System: Overview (Reachability Analysis)

Task: Reachabilty Analysis for two tank example

Reference parameter

Sym	Value	Unit
c_{12}	6.00e-4	$m^{5/2}s^{-1}$
c_2	2.00e-4	$m^{5/2}s^{-1}$
c_L	2.60e-4	$m^{5/2}s^{-1}$
$\bar{q}_p$	4.50e-4	$m^{5/2}s^{-1}$

Measurements

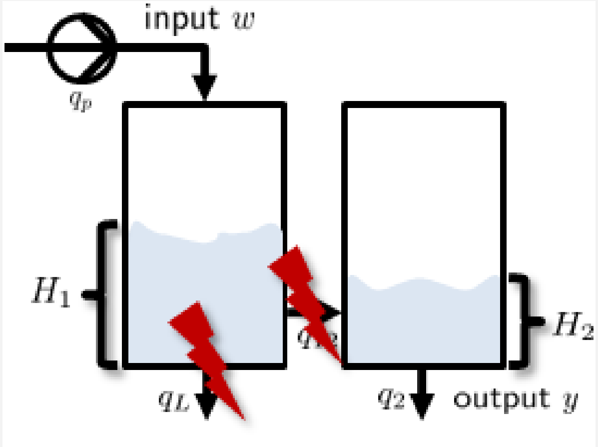
- only (uncertain) initial data (first time step)

A priori parameter knowledge

- uncertain (±2.5e-5 abs. error)

Dynamical model

- four uncertain parameters
- two fault scenarios
- H1, H2 unknown



$$\dot{H}_1 = \frac{1}{A}(q_p(t) - q_L(t) - q_{12}(t))$$

$$\dot{H}_2 = \frac{1}{A}(q_{12}(t) - q_2(t))$$

$$\begin{aligned} q_p(t) &= \bar{q}_p d_p(t)(1 - \sqrt{H_1(t)/h_{\max}}) \\ q_L(t) &= c_L d_L(t) s_2 \sqrt{H_1(t)} \\ q_{12}(t) &= c_{12} s_1 \sqrt{H_1(t) - H_2(t)} \\ q_2(t) &= c_2 d_2(t) \sqrt{H_2(t)} \end{aligned}$$

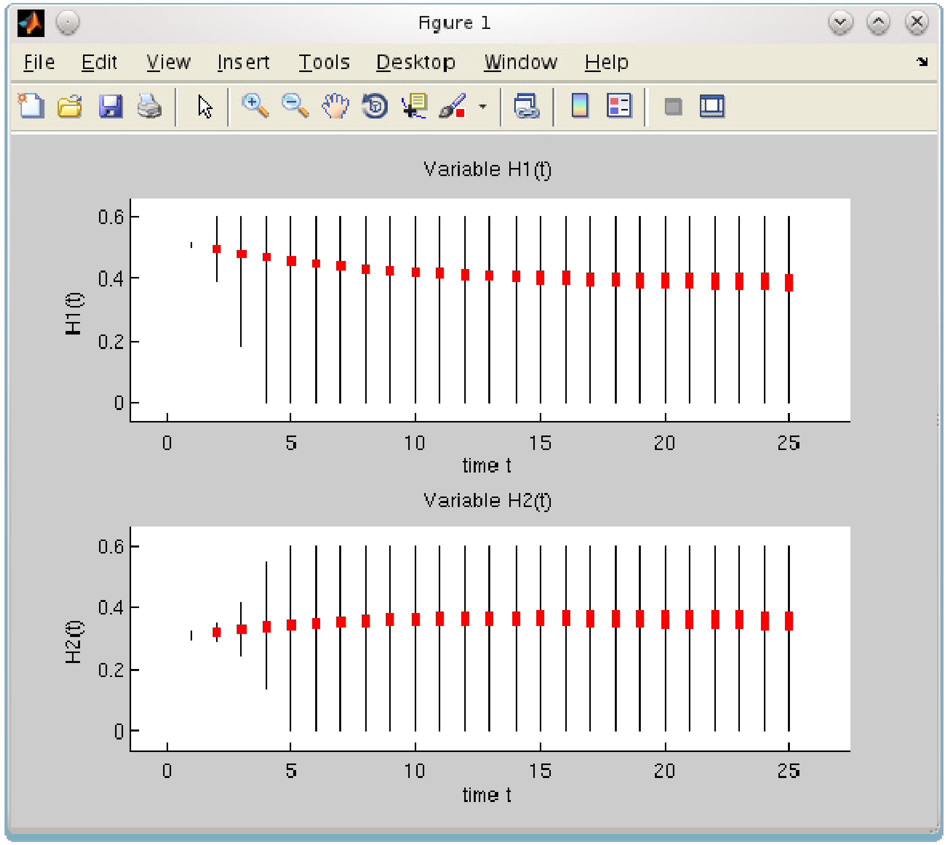
➡ **ADMIT/examples/TwoTanks/analyzeModel_reachability.m**

Two Tank System: Result (Reachability Analysis)

Outer bounding of the states for a given time horizon.

Reachability Analysis

- initial states (uncertain) provided
- global bounds assumed unmeasured states
- goal: **state estimation** under parametric uncertainty



Notes

- user can estimate bounds on the states at **specific time instances** (here at every time instance but the first one)
- user can **fix the values** of faulty switches s1, s2 or leave them uncertain
- initial global bounds **improved** by toolbox via interval arithmetic (thin bars)

Two Tank System: Overview (Monte Carlo)

Task: Monte Carlo sampling for two tank example

Reference parameter

Sym	Value	Unit
c_{12}	6.00e-4	$m^{5/2}s^{-1}$
c_2	2.00e-4	$m^{5/2}s^{-1}$
c_L	2.60e-4	$m^{5/2}s^{-1}$
$\bar{q}_p$	4.50e-4	$m^{5/2}s^{-1}$

Measurements

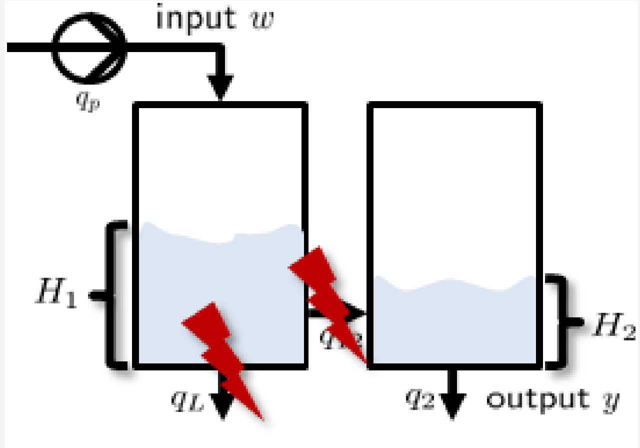
- time-course data
- uncertain (5% rel. error)

A priori parameter knowledge

- $\mathbf{c_L}$ uncertain (±2.5e-4 abs.)
- $\mathbf{c_2}$, $\mathbf{c_{12}}$, $\mathbf{\bar{q}_p}$ uncertain (±2.5e-5 abs.)

Dynamical model

- four uncertain parameters
- two fault scenarios



$$\dot{H}_1 = \frac{1}{A}(q_p(t) - q_L(t) - q_{12}(t))$$

$$\dot{H}_2 = \frac{1}{A}(q_{12}(t) - q_2(t))$$

$$q_p(t) = \bar{q}_p d_p(t)(1 - \sqrt{H_1(t)/h_{\max}})$$

$$q_L(t) = c_L d_L(t) s_2 \sqrt{H_1(t)}$$

$$q_{12}(t) = c_{12} s_1 \sqrt{H_1(t) - H_2(t)}$$

$$q_2(t) = c_2 d_2(t) \sqrt{H_2(t)}$$

⇨ **ADMIT/examples/TwoTanks/analyzeModel_MonteCarlo.m**

Two Tank System: Result (Monte Carlo Sampling)

Monte Carlo sampling

Estimation

- user can create Monte Carlo samples after the problem is formulated in QP format (**optInfo**):

```
[fS,iS] = ADMITMonteCarlo(optInfo,100,ops)
```

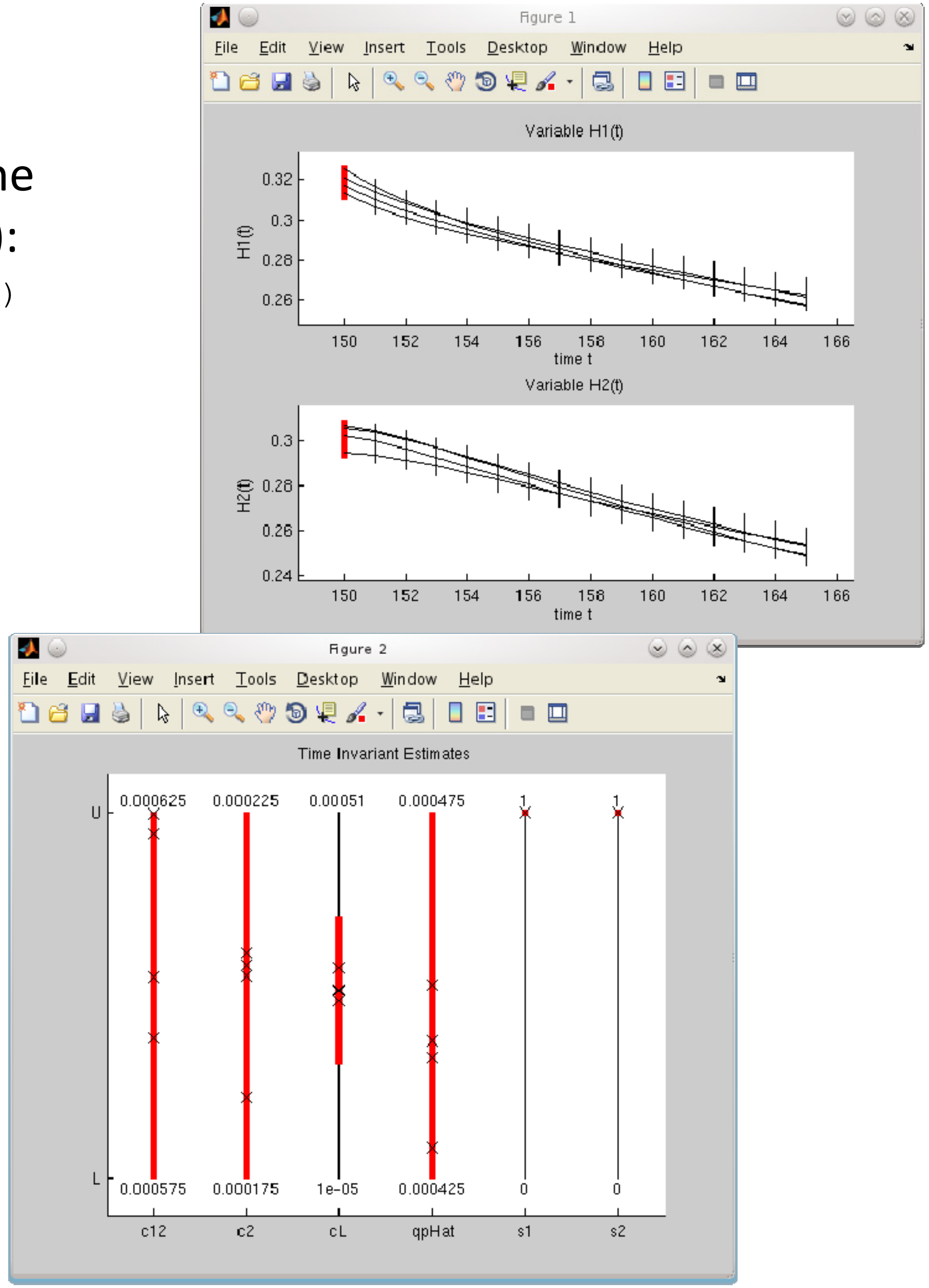
- function produces 100 samples and evaluates in(feasibility)

Monte Carlo

- measurement data (uncertain) provided
- **goal**: find Monte Carlo samples, that fit this measurement data

Notes

- outer bounding was performed for the same problem to compare the results
- **guaranteed:** feasible Monte Carlo samples **within** the estimated bounds



Example D: Adaptation (Overview)

Task: combined parameter and state estimation for adaptation process, using (uncertain) quantitative measurements and qualitative information

Measurements

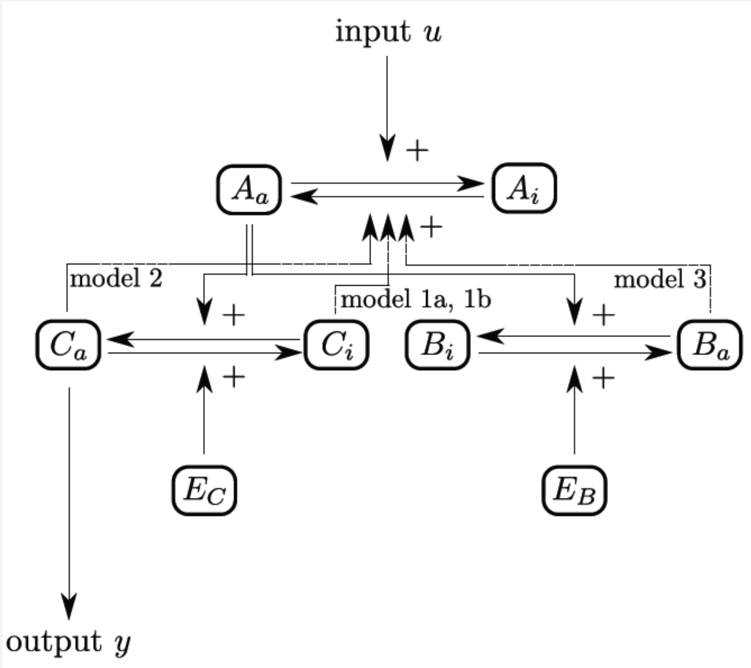
- time-course data (Aa + Ba)
- uncertain (2% relative error)

Qualitative Information (for Ca)

A priori data

- parameters

Dynamical model

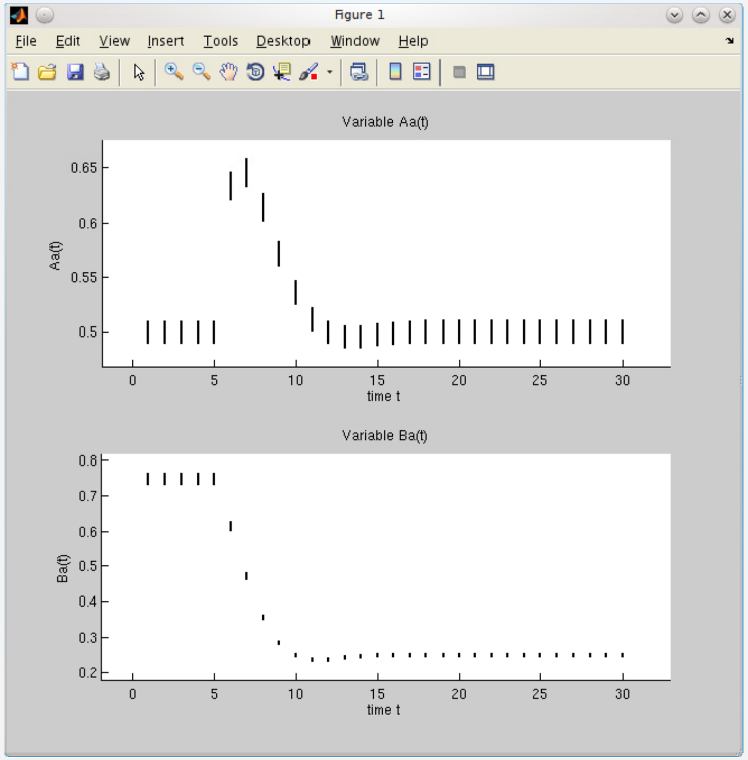


- Michaelis-Menten kinetics
- **five unknown parameters**

➡ **ADMIT/examples/Adaptation/analyzeModel.m**

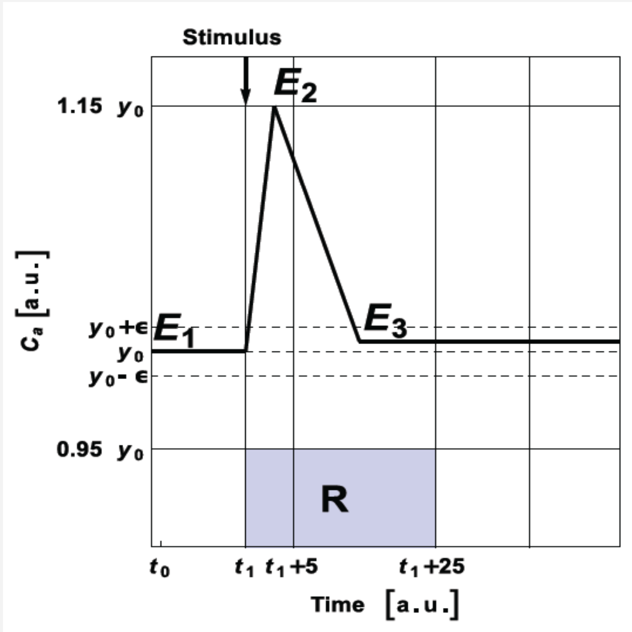
Adaptation (Data)

Measurements



- time-course data (Aa + Ba)
- uncertain (2% relative error)

Qualitative Information (Ca)



1. after stimulus withdrawal, system adapts to prestimulus level within 30s (adaptation)
2. Ca never drops below 95% of its initial condition
3. Ca reaches maximum within 5 s after stimulus is withdrawn

Adaptation (Results)

Task: combined parameter and state estimation for adaptation process

Variables

```
p  := {binary,timeVariant,ofInterest}
p1 := {binary,timeVariant,ofInterest}
p2 := {binary,timeVariant,ofInterest}
```

Add qualitative information

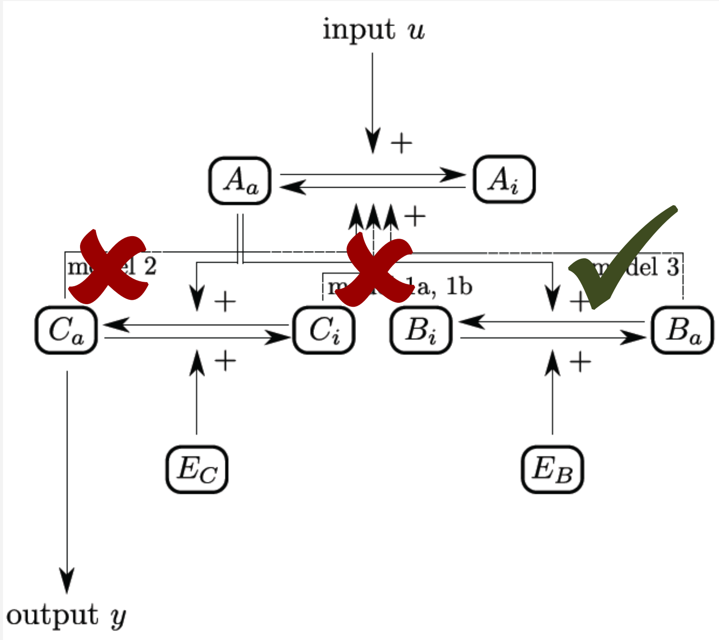
AND linked propositions:

```
ADMITconstraint('p <==> &{p1,p2}')
```

OR linked propositions:

```
ADMITconstraint('p <==> |{p1,p2} ')
```

Results (Illustration)



- models which does not admit the required qualitative behavior (adaptation) are invalidated

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