

# From SBTOOLBOX to •2

## + Experiments + SBPD

General

Models

Measurements

**Experiments**

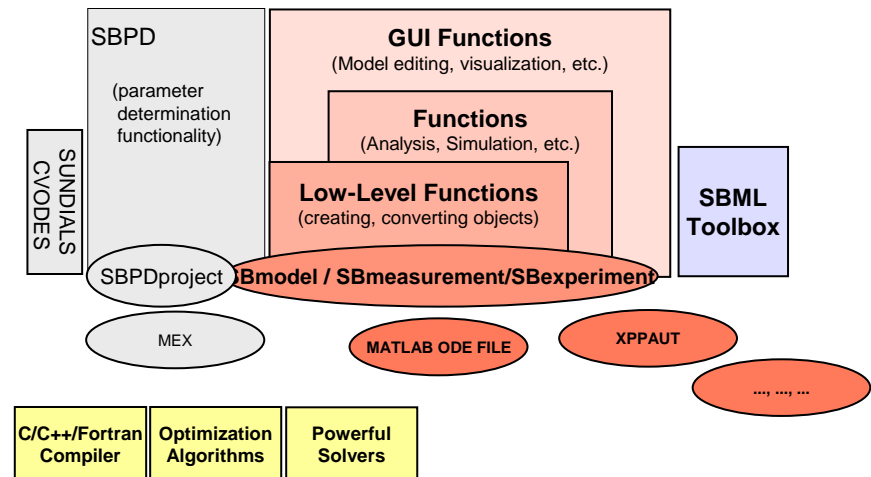
Projects

MEX simulation functions

## Modeling vs. Simulation of a single model

# General

- SBT2 is a platform, providing needed functionality
- Platform independent since based on MATLAB
- Allows users to publish new results in a directly useable form
- **Easily extensible (by the user!)**



# Functions Overview

- Installation of Toolbox
- **Model Creation and Handling**
- **Measurement Creation and Handling**
- **Experiment Creation and Handling**
- Simulation
- Plotting
- Simple Analysis
- Bifurcation Analysis
- Parameter Sensitivity Analysis
- Localization of Mechanisms leading to Complex Behaviors
- **Model Reduction**
- **Optimization**
- **Solvers**
- **Statistics**
- **Compilation of Fortran and C/C++ Code MEX Functions using MinGW**
- Other Functions

## Example ODE Model

```
***** MODEL STATES
d/dt(A) = -R
d/dt(B) = R
A(0) = 1
B(0) = 0
***** MODEL PARAMETERS
k1 = 0.5
***** MODEL REACTIONS
R = k1*f(A)
***** MODEL FUNCTIONS
f(x) = x^3
```

```
***** MODEL EVENTS
event = lt(A,0.3), A, 1, B, 0
```

# Example Reactions Model

```
***** MODEL STATE INFORMATION
B(0) = 1
***** MODEL PARAMETERS
k1 = 0.5
***** MODEL REACTIONS
A+B => 2*C : R1 % comment
      vf = k1*A*B
B <=> A+D : R2
      vf = 5.1*B
      vr = 3*A*D
2*A => A2 : R3
      vf = 2.7*A^2
```

## Import of SBML Models

- SBML Level 1 and 2 models can be imported
- The SBML Toolbox needs to be present

```
>> model = SBmodel('CellCycle.xml')
SBmodel
=====
Name: CellCycle
Number States:          13
Number Variables:      2
Number Parameters:     41
Number Reactions:      23
Number Functions:      1

>> SBsimulate(model,400)
```

# Export of SBML Models

- Additional information can be added in the text / textbc format

```
***** MODEL NAME
example

***** MODEL NOTES

***** MODEL STATES
d/dt(s1) = -re1 {isSpecie:cytosol:amount} % comment
d/dt(s2) = +re1 {isSpecie:cytosol:amount}
d/dt(s3) = -re2+re4 {isSpecie:cytosol:amount}
d/dt(s4) = +re2-re5 {isSpecie:cytosol:amount}
d/dt(s5) = (-re3)/nucleus {isSpecie:nucleus:concentration}
d/dt(s6) = +re3 {isSpecie:nucleus:amount}

s1(0) = 1

***** MODEL PARAMETERS
s7 = 1 {isParameter} % comment
s8 = 1 {isParameter}
cytosol = 1 {isCompartment:}
nucleus = 0.1 {isCompartment:cytosol}

***** MODEL VARIABLES

***** MODEL REACTIONS
re1 = 3 * s1 - 2 * s2 {reversible} % comment
re2 = s3
re3 = s4 * (s5 - s6) {reversible}
re4 = 1
re5 = s4
```

# Export of SBML Models

- To simplify the definition of the additional information a GUI can be used

```
>> model1 = SBmodel('novaktyson1.txt') % load an example model  
  
>> SBexportSBMLgui(model1)
```

State Name	ODE RHS	Initial Condition	SBML Type	Unit Type	Compartment	Notes
<input type="checkbox"/> Cyclin	ODE RHS	0.0172	SBML Specie	Amount		Notes
<input type="checkbox"/> YT	ODE RHS	0.0116	SBML Specie	Amount		Notes
<input type="checkbox"/> PYT	ODE RHS	9.0E-4	SBML Specie	Amount		Notes
<input type="checkbox"/> PYTP	ODE RHS	0.0198	SBML Specie	Amount		Notes
<input type="checkbox"/> MPF	ODE RHS	0.073	SBML Specie	Amount		Notes
<input type="checkbox"/> Cdc25P	ODE RHS	0.9499	SBML Specie	Amount		Notes
<input type="checkbox"/> Wee1P	ODE RHS	0.9499	SBML Specie	Amount		Notes
<input type="checkbox"/> IEP	ODE RHS	0.242	SBML Specie	Amount		Notes
<input type="checkbox"/> APCstar	ODE RHS	0.3132	SBML Specie	Amount		Notes

**Amount**  
due to definition of ODEs

```
>> edit novaktyson1.txt
```

**Concentration**  
due to definition of ODEs

```
>> edit novaktyson2.txt
```

```
>> model2 = SBmodel('novaktyson2.txt') % load another example model - differences?  
  
>> SBexportSBMLgui(model2)
```

# Main Differences in the Two Models

## novaktyson1.txt

```
d/dt(Cyclin) = R1-R2-R3
d/dt(YT) = R4-R5-R6-R7+R8+R3
d/dt(PYT) = R5-R8-R9-R10+R11
d/dt(PYTP) = R12-R11-R13-R14+R9
d/dt(MPF) = R6-R4-R12-R15+R13
d/dt(Cdc25P) = R16
d/dt(Wee1P) = R17
d/dt(IEP) = R18
d/dt(APCstar) = R19
```

=> Amount units

## novaktyson2.txt

```
d/dt(Cyclin) = (R1-R2-R3)/compartment
d/dt(YT) = (R4-R5-R6-R7+R8+R3)/compartment
d/dt(PYT) = (R5-R8-R9-R10+R11)/compartment
d/dt(PYTP) = (R12-R11-R13-R14+R9)/compartment
d/dt(MPF) = (R6-R4-R12-R15+R13)/compartment
d/dt(Cdc25P) = (R16)/compartment
d/dt(Wee1P) = (R17)/compartment
d/dt(IEP) = (R18)/compartment
d/dt(APCstar) = (R19)/compartment
```

=> Concentration units

# Measurements

- The toolbox can handle 2 representation formats
  - Excel
  - Comma separated value (CSV)
- One Excel file can contain measurements of several experiments
- One CSV file can contain measurements of a single experiment

# Measurements – Excel format

	A	B	C	D	E	F	G	H
1	Name	Measurement Example 2						
2	Notes	Just some notes in a single line						
3	Component notes					Component B	Component C	
4	Components	time	A	A+	A-	B	C	
5	Values	0	0,0172	0,01892	0,01548	0,0116	0,0009	
6		49,0552	0,0171892	0,0189081	0,0154703	0,0115591	0,000865671	
7		98,9524	0,0170854	0,0187939	0,0153769	0,0114354	0,000835422	
8		128,814	0,0173518	0,0190087	0,0156166	0,0118688	0,000805422	
9		151,362	0,0169693	0,0186668	0,0152724	0,0109388	0,00104578	
10		160,548	0,0181534	0,0199687	0,0163381	0,0125635	0,00104271	
11		173,206	0,0170897	0,0187943	0,0153772	0,0119458	0,000671465	
12		189,85	0,0146315	0,0160957	0,0131692	0,00809325	0,0010277	
13		199,735	0,0150291	0,0165276	0,0135226	0,0080026	0,00138207	
14		207,51	0,0151929	0,0167152	0,0136725	0,00809325	0,00149481	
15		211,924	0,0173497	0,0190847	0,0156147	0,00929493	0,00295474	
16		217,317	0,0186011	0,0204612	0,0171111	0,0109388	0,00337649	
17		219,924	0,0190048	0,0209053	0,0171043	0,0109388	0,00270628	
18		217,317	0,0190811	0,0209892	0,017173	0,0109388	0,00120062	
19		226,538	0,0161404	0,0177545	0,0145264	0,0111411	0,000550005	
20		235,681	0,0135297	0,0148827	0,0121768	0,00717188	0,000783385	
21		241,166	0,0139325	0,0152258	0,0125393	0,00671213	0,00146087	
22		241,697	0,0140435	0,0154479	0,0126392	0,00672502	0,00178496	
23		242,971	0,0143499	0,0157849	0,0129149	0,00679063	0,00146087	
24		255,948	0,017554	0,0193094	0,0157986	0,00710143	0,00460672	

Measurement name

Notes about the measurement

Extra notes about the components

Names of the measured components. "time" appears here also in an arbitrary column

max (+) and min (-) values allowing the representation of error bounds

Measurement data  
Leave blank if unmeasured

Worksheets in an Excel book can contain any data. BUT if A1 is set to "Name" then the above format is expected.

# Measurements – CSV format

## [Name]

Measurement Example CSV

## [Notes]

Notes about the measurement / experiment

## [Components]

time,A,A+,A-,B,C

## [Componentnotes]

A: Component A

B: Component B

## [Values]

0, 0.0172, 0.01892, 0.01548, 0.0116, 0.0009  
49.0552, 0.0171892, 0.0189081, , 0.0115591, 0.000865671  
98.9524, 0.0170854, 0.0187939, NaN, 0.0114354, 0.000858473  
128.814, 0.0173518, 0.019087, 0.0156166, 0.0118688, 0.000825422  
151.362, 0.0169693, 0.0186663, 0.0152724, 0.0109388, 0.00104578  
160.548, 0.0181534, 0.0199687, 0.0163381, 0.0125635, 0.00104271

### Good practice

Give a useful name and document the measurement data with telling notes

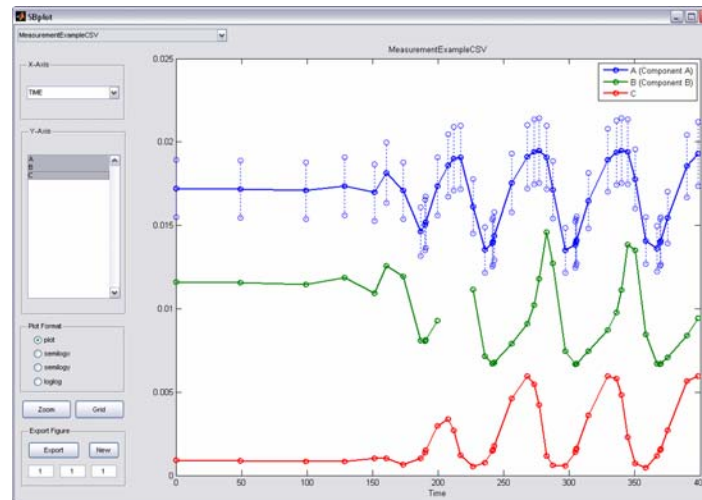
Measurement data  
Leave empty or set to NaN if unmeasured

**Important:**  
The measurements should be given in units that are to be used for the models components!

# Handle Measurement Data

- Visualizing the data

```
>> SBvisualizedata(data)
```

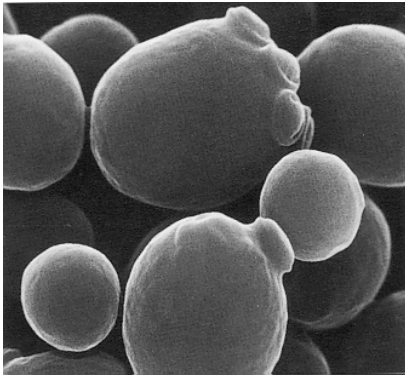


- Extract information

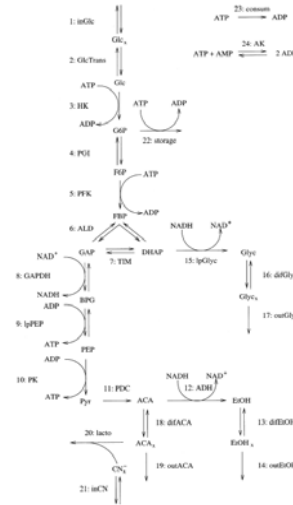
```
>> [time, componentNames, values, minvalues, maxvalues] = SBmeasurementdata(data)
```

# Experiment Descriptions

- The System



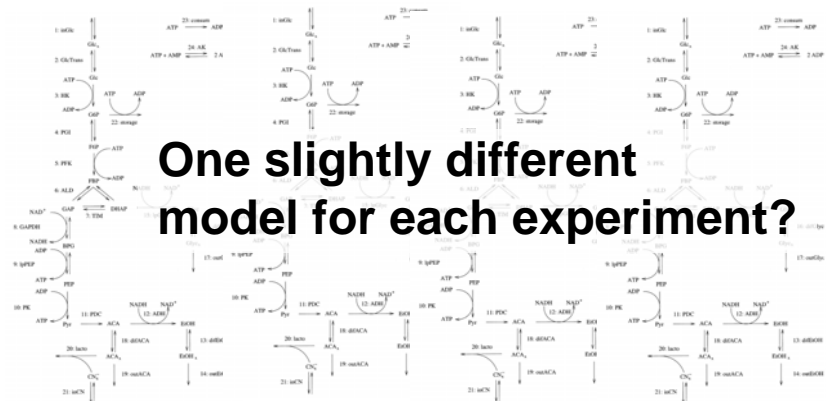
## The Model



- The Experiments

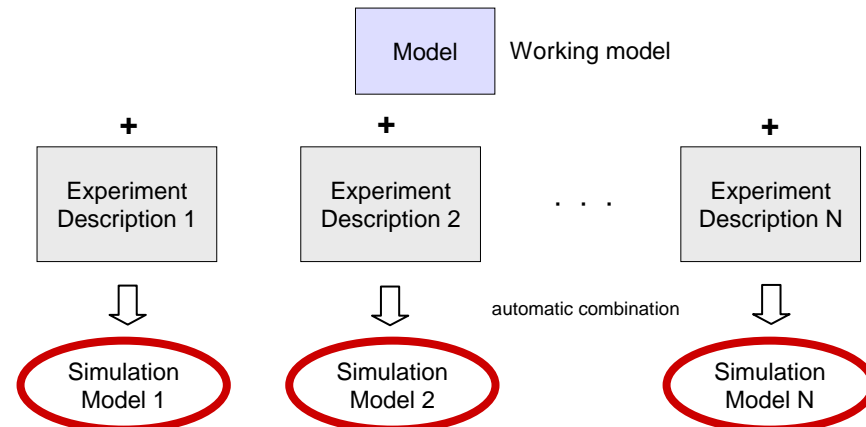
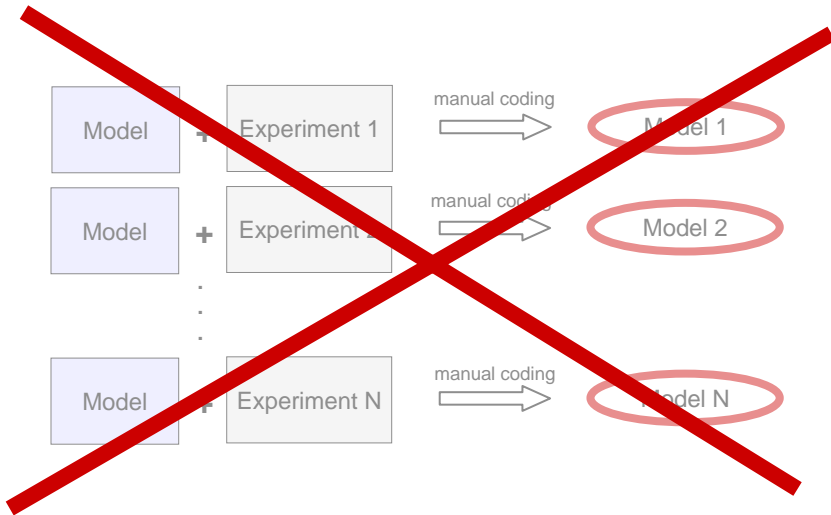
- Knockout
- Overexpression
- Change of concentration 1
- Change of concentration 2
- etc.

**One slightly different model for each experiment?**



# Experiment Descriptions – Why?

- Typically many different biological experiments
- Coding each experimental setting in the model leads to
  - very complicated models or
  - a large number of models to keep track of



# Experiment Descriptions

- Experiment descriptions allow to define experimental settings insilico
- Experiment descriptions in the SBTOOLBOX2 allow to
  - change initial conditions
  - change parameter values
  - change parameter values over time
  - change parameter values as a function of other *variables*
  - change state variables at given time instants
- more is planned

# Experiment Descriptions – How does it work?

```
***** MODEL NAME
Simple model
***** MODEL STATES
d/dt(A) = -R
d/dt(B) = R
A(0) = 1
B(0) = 0
***** MODEL PARAMETERS
k1 = 0.5
***** MODEL REACTIONS
R = k1*A
```

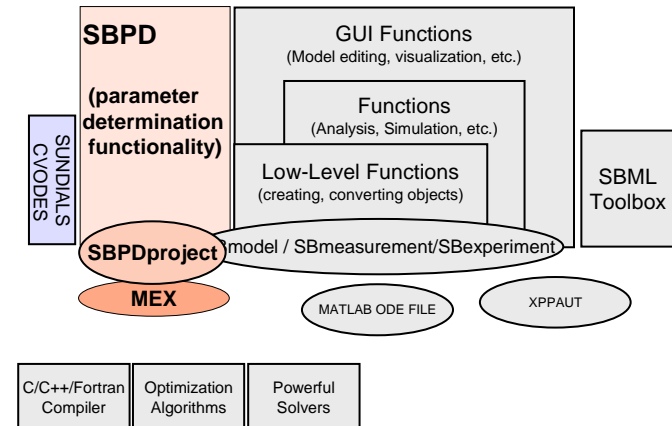
```
***** EXPERIMENT NAME
Simple Experiment for simple model
***** EXPERIMENT INITIAL PARAMETER AND STATE SETTINGS
k1 = 2
***** EXPERIMENT PARAMETER CHANGES
***** EXPERIMENT STATE CHANGES
time=10, A=1
```

```
***** MODEL NAME
Simple model
***** MODEL STATES
d/dt(A) = -R
d/dt(B) = R
A(0) = 1
B(0) = 0
***** MODEL PARAMETERS
k1 = 2
***** MODEL REACTIONS
R = k1*A
***** MODEL EVENTS
StateChange_1 = ge(time,10),A,1
```

The result is a new model where the experimental settings have been added

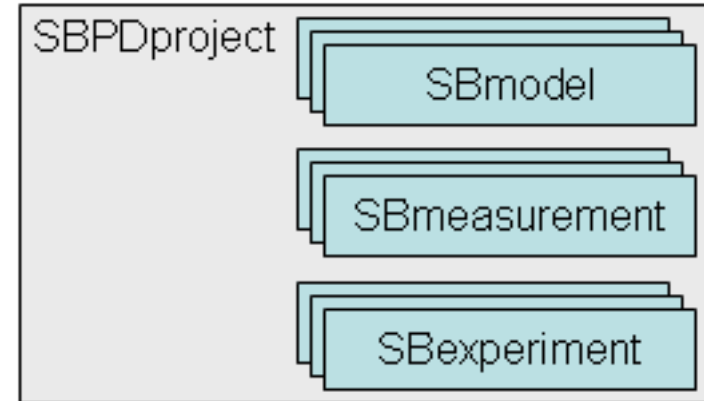
# SBPD - General

- SBPD is an addon package for the SBTOOLBOX2
- Providing functionality crucial for parameter determination
  - Parameter estimation
  - Manual parameter tuning
  - Fit analysis
  - Model reduction
  - Identifiability analysis
- Improved modeling features (kinetic rate laws)
- High speed computation via SUNDIALS CVODE



# Projects

- A project is a container for
  - Models
  - Measurement data
  - Experiment descriptions
  - Modeling information

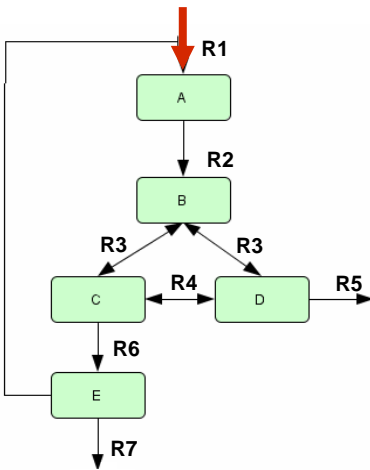


- Parameter estimation, etc., can directly be run on projects

# Projects – An Example

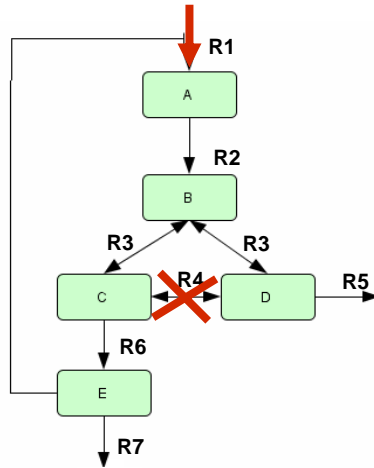
- Experiments and corresponding measurements

Vin\_increased



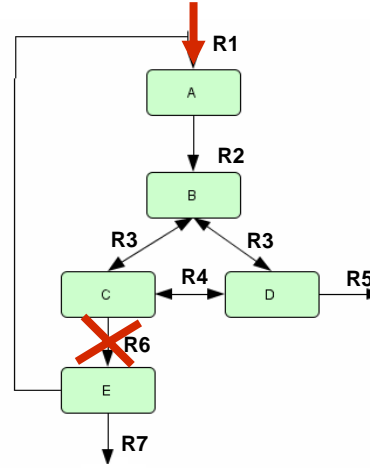
```
***** ...
Vin = 0.5
```

Vin\_increased\_R4delta



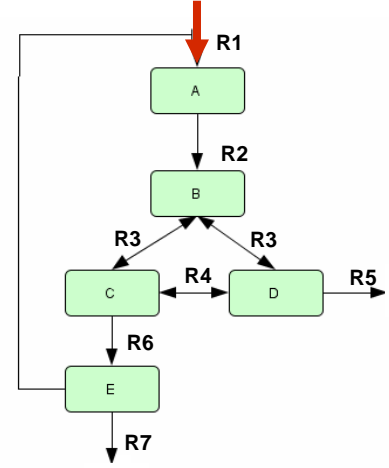
```
***** ...
Vin = 0.5
K4f = 0
K4r = 0
```

Vin\_increased\_R6delta



```
***** ...
Vin = 0.5
V6 = 0
```

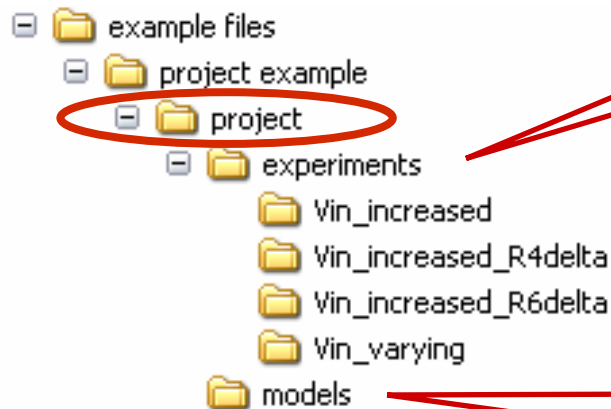
Vin\_varying



```
***** ...
Vin = interp0SB(
[0 10 20 30 40 50],
[0.2 0.5 0.1 0.3 0.6 0.1],
time)
```

# Projects – Representation

- Representation of the project
  - Folder structure, containing
    - Models
    - Experiments
    - Measurements



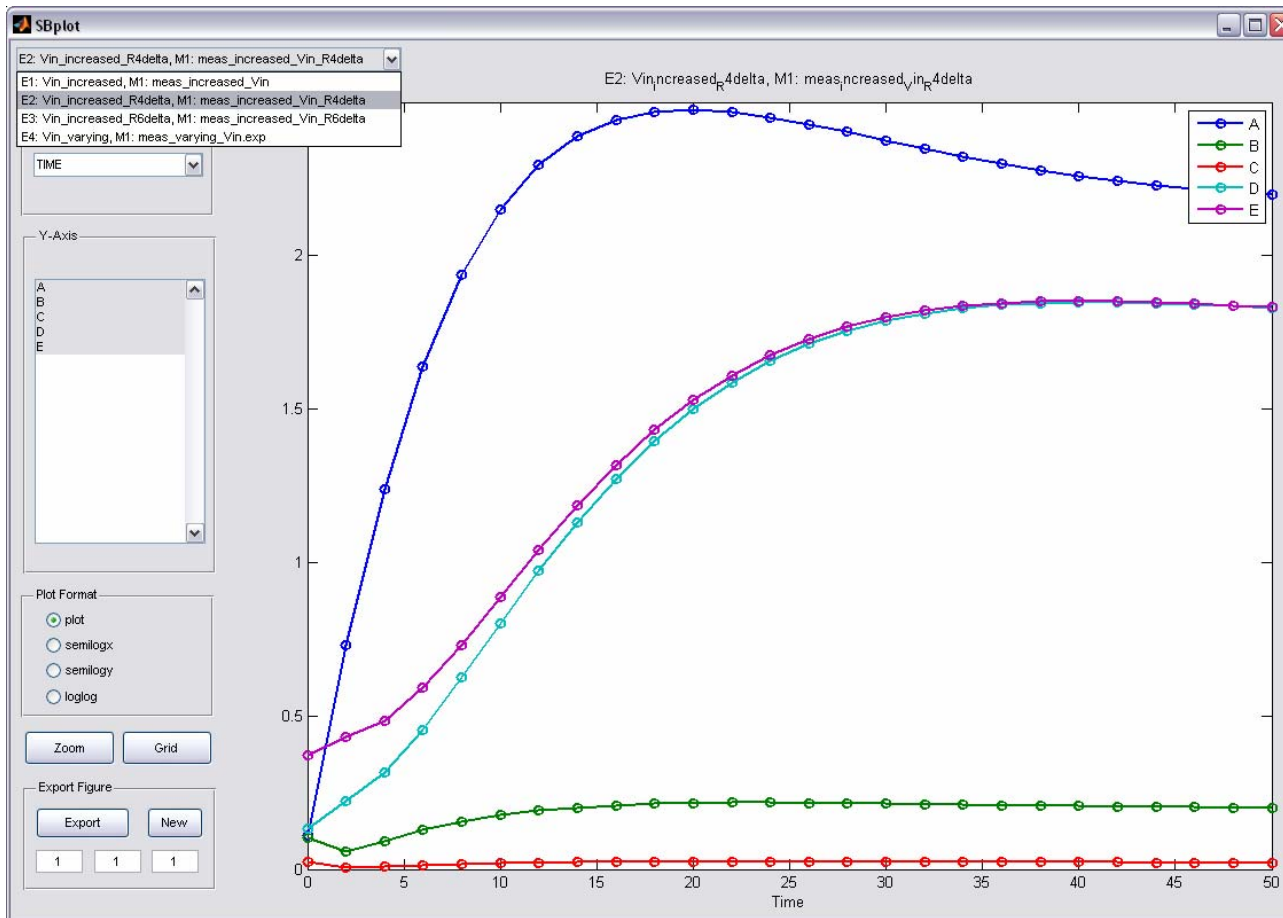
Experiment folders containing experiment description file and corresponding measurement data

Folder containing model TEXT (ODE and/or BC) and/or SBML models

# Projects – Visualize Measurement Data

- Measurement data can be plotted by

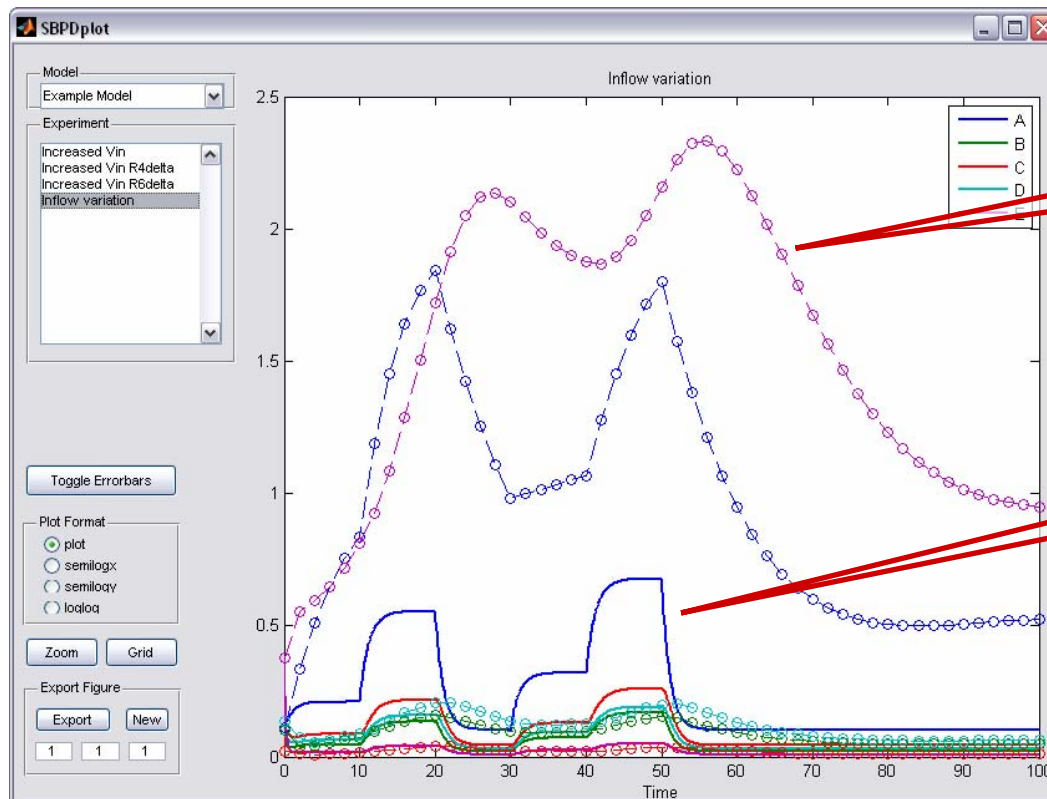
```
>> SBPDplotmeasurements(sbp)
```



# Projects – Simple Simulation

- Simulation of the experiments in the project
- Comparison with the measurement data

```
>> SBPDcomparemeasurements(sbp)
```



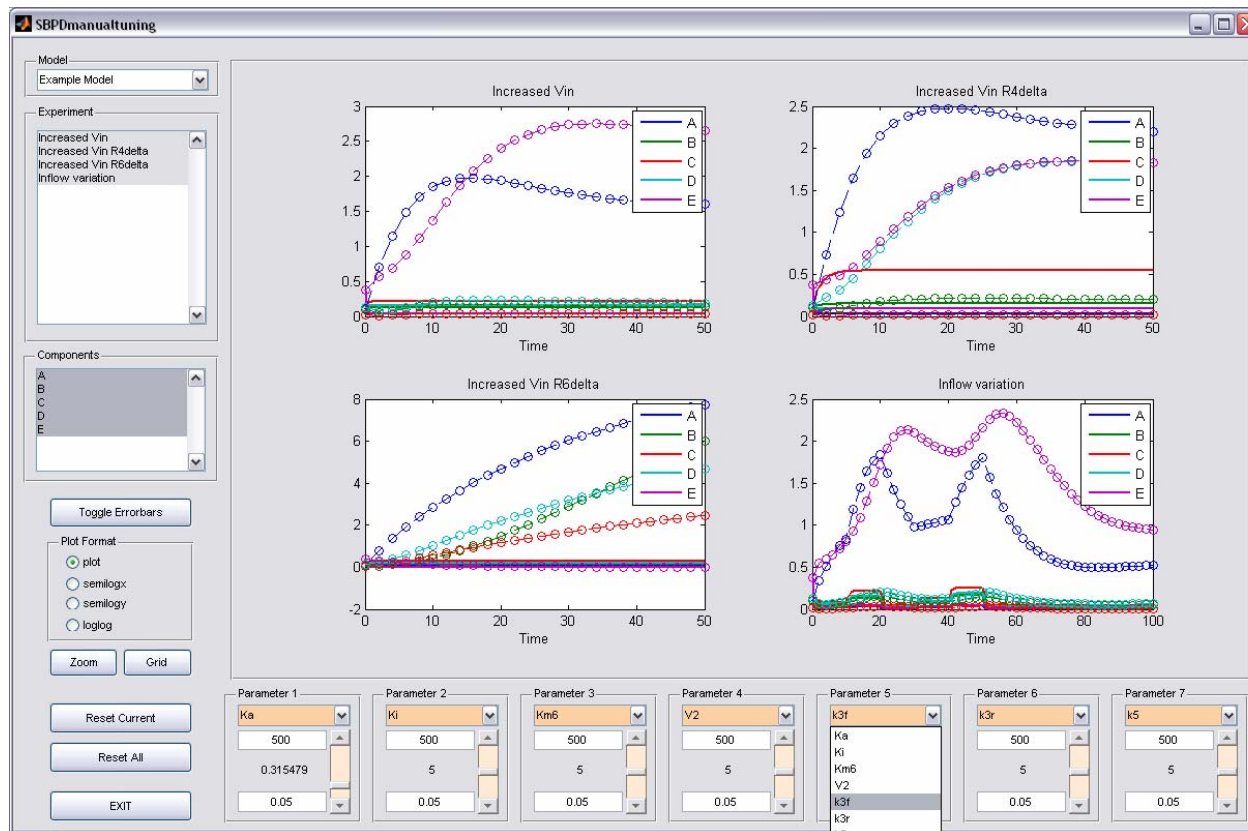
Measurements (-o-)

Simulations (-)

# Projects – Advanced Simulation / Manual Tuning

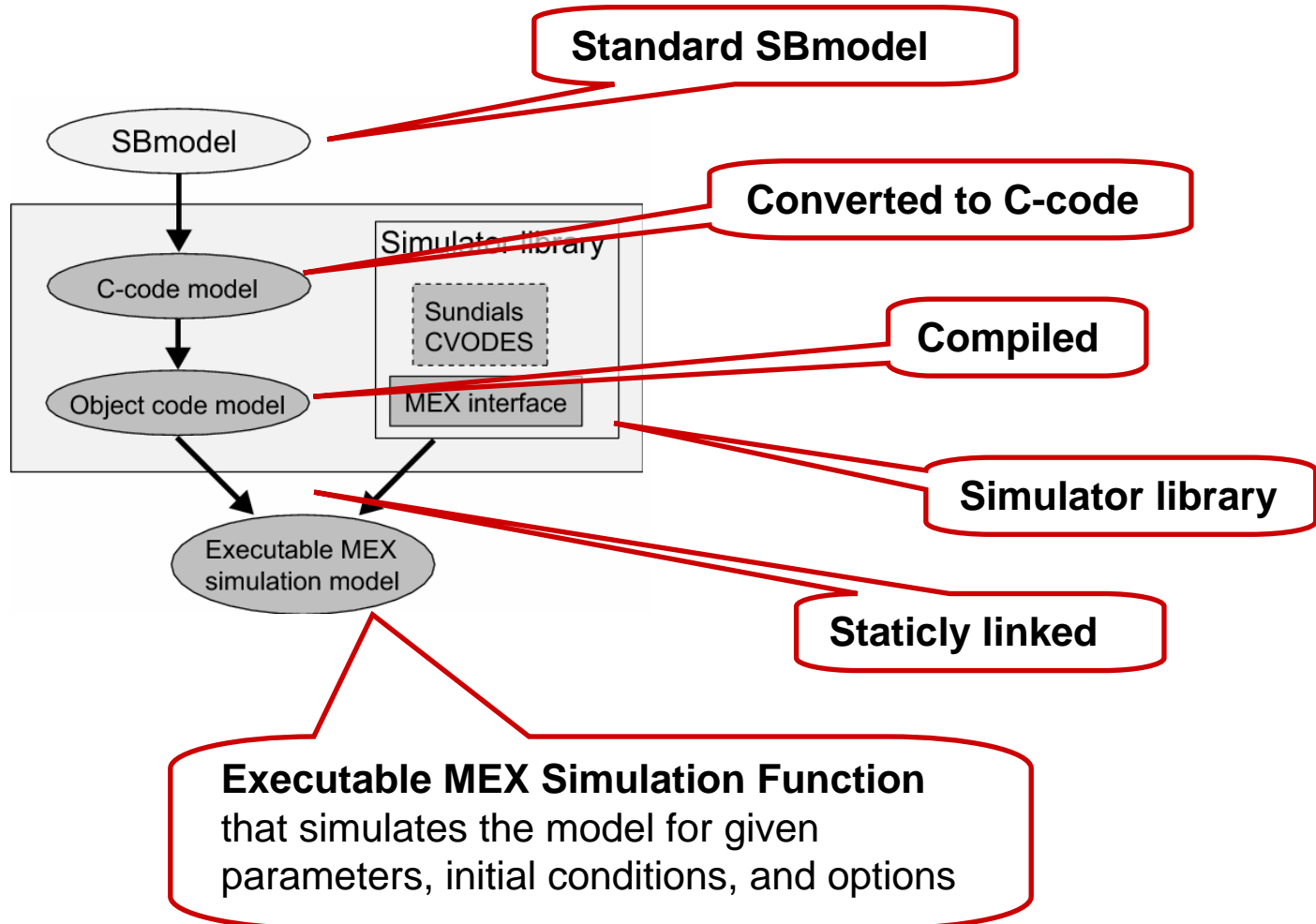
- Manual tuning of parameters

```
>> SBPDmanualtuning(sbp)
>> SBPDmanualtuning(sbp,1)
```



# MEX Simulation Functions

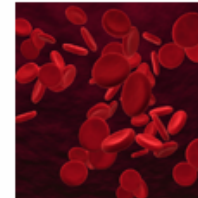
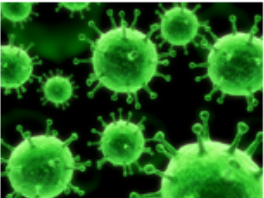
- What are MEX Simulation Functions?



# MEX Simulation Functions – Why?

- Parameter estimation requires **many repeated simulations**
- => Simulation speed matters a lot
- Benchmark (SBPD (MinGW) vs. ODE15s)

	Model 1	Model 2	Model 3
<b>Model description</b>	Novak Tyson cell-cycle model	Full-scale model of glycolysis in yeast	Model 14 from the Biomodels.net database
<b>End time (TEND)</b>	1000	50	300
<b>Number simulation points (NRPOINTS)</b>	1000	200	300
<b>Average time ODE15S [ms]</b>	3442	3448	743
<b>Average time SBPD [ms]</b>	24	68	24
<b>Speedup by SBPD</b>	<b>144x</b>	51x	<b>30x</b>



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  - PLmaddon

## User's Reference (SBTOOLBOX2)

### Model Representation - Overview

**Model Representation** Models are represented in 2 different ways in the toolbox, leaving the user considerable freedom and ensuring easy reuse of already available MATLAB models.

### Experiment Representation - Overview

**Experiment Representation** The toolbox allows the representation of experiments and the merging with models.

### Measurement Representation - Overview

**Measurement Representation** The toolbox allows handling and use of measurement data.

### Functions - Overview

#### Installation of Toolbox

<b><a href="#">installSB</a></b>	Installation script for the toolbox.
<b><a href="#">convert2SB</a></b>	Help function to convert SBTOOLBOX TEXT and TEXTC models to the SBTOOLBOX2 format.

#### Model Creation and Handling

<b><a href="#">SBmodel</a></b>	Creating a new SBmodel.
<b><a href="#">SBcreateTEXTmodel</a></b>	Creates new SBmodel TEXT file and opens it in editor.
<b><a href="#">SBcreateTEXTBCmodel</a></b>	Creates new SBmodel TEXTBC file and opens it in editor.
<b><a href="#">SBstruct</a></b>	Returns the internal data structure of an SBmodel as a MATLAB structure.
<b><a href="#">SBedit</a></b>	Graphical user interface, allowing to edit and simulate SBmodels.