Applying XP (eXtreme Programming) methodology for model development. Apoptosis model as an example.

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The modular model of apoptosis

- 13 modules
- 279 species
- 372 reactions
- 459 parameters

Kutumova E.O. et al., Advances in Experimental Medicine and Biology, 2012, 736(2):235-245
Extreme programming (XP) methodology

- **Planning**
  - User stories
  - Make frequent small releases
  - The project is divided into iterations

- **Coding**
  - Code must be written to agreed standards
  - Unit test first
  - Integrate often
  - Collective ownership

- **Testing**
  - Unit/acceptance tests
XP adaptation to modeling

• Planning
  ◦ **User stories**: requirements for the model based on the experimental data
  ◦ **Make frequent small releases**
  ◦ **Iterations**: after each iteration a new set of experimental data should be reproduced

• Coding
  ◦ **Standards**: SBGN, SBML, modular extension
  ◦ **Unit test first**
  ◦ **Integrate often**: model is saved into public database
  ◦ **Collective ownership**: collaborative editing and chat

• Testing
  ◦ **Unit/acceptance tests**: BioUML provides the facilities for testing the models.
Types of the acceptance tests

- Steady-state
- Time course
- Control of the variable values
Implementation of tests in BioUML
Execution phase of apoptosis
User stories: requirements for the model

- No external signals $\rightarrow$ concentration of the cleaved PARP is zero.
- CD95L signaling $\rightarrow$ dynamics of pro-8 and casp-8 according to Bentele et. al.
- TNF-a signaling $\rightarrow$ dynamics of pro-8 and casp-8 according to Janes et. al.
User stories: requirements for the model

- No external signals $\rightarrow$ concentration of the cleaved PARP is zero.
- CD95L signaling $\rightarrow$ dynamics of pro-8 and casp-8 according to Bentele et. al.
- TNF-a signaling $\rightarrow$ dynamics of pro-8 and casp-8 according to Janes et. al.
# Iterations and acceptance tests

## Iteration 1

1. Steady-state case
   - Steady state: cleaved PARP
   - Time limit: 10.0

## Iteration 2

2. CD95L signaling
   - Info: Experiment: Bentele et. al., procaspase-8
   - Time limit: 20.0

## Iteration 3

3. CD95L signaling
   - Info: Experiment: Bentele et. al., caspase-8
   - Time limit: 30.0

4. TNFα signaling
   - Info: Experiment: Janes et. al., procaspase-8
   - Time limit: 10.0

5. TNFα signaling
   - Info: Experiment: Janes et. al., caspase-8
   - Time limit: 30.0
Iteration 1: execution phase

Steady-state acceptance test

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<tr>
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<td>Steady-state</td>
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Concentration

Time

- cPARP
Iteration 2: CD95-signaling
Iteration 2: CD95-signaling

Experiment time courses for pro-8 and casp-8 according to the data by Bentele, et. al., 2004
Iteration 3: TNF-a-signaling

Rangamani et.al., 2006
Iteration 3: TNF-a-signaling

The deviation between the table data and the simulation result is greater than the maximum allowable value.
Iteration 1: Stable state

![Diagram showing TNF-a module and CD95L module with 'X' marks indicating inactivity.]

**Unit Test**

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Iteration 2: CD95-signaling

- **TNF-a module**
  - pro8
  - casp8

- **CD95L module**
  - Signaling
  - pro8
  - casp8

**Execution phase**

**Unit test**

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Iteration 3: TNF-a-signaling

**TNF-a module**
- Pro8
- Casp8

**CD95L module**
- Pro8
- Casp8

**Execution phase**
- Pro8
- Casp8

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The next iterations

**TNF-α module**
- IKK
- pro8
- casp8

**CD95L module**
- pro8
- casp8

**TRAIL module**
- pro8
- casp8

**NF-κB module**
- IKK

**Execution phase**
- pro8
- casp8

**Apoptotic Activity**
- 442.82
- 0.0
Thank you for your attention!
CD95L module
The model of M. Bentele et. al., 2004
The model decomposed into modules

- **CD95L module**
  - pro8
  - casp8

- **Apoptotic Activity**
  - Apoptotic Activity

- **Module of the direct effector caspases activation**
  - pro8
  - casp8
  - Apoptotic Activity
  - casp6
  - casp7
  - pro3
  - pro7

- **Mitochondrial module**
  - casp8
  - Apoptotic Activity
  - casp3
  - Cyt C
  - Smac

- **Cytocrome C module**
  - pro7
  - pro3
  - Cyt C
  - IAP

- **PARP module**
  - casp7
  - casp3
  - Apoptotic Activity

- **Smac module**
  - IAP
  - Smac

- **Apoptotic Activity**
  - Apoptotic Activity
  - 0.0
Execution phase of apoptosis

CD95L module
- pro8
- casp8

Module of the direct effector caspases activation
- pro8
- casp8
- casp6
- casp7
- pro3
- pro7

Mitochondrial module
- casp8
- Apoptotic Activity
- casp3
- Cyt C
- Smac

Cytocrome C module
- pro7
- pro3
- Cyt C
- casp7
- casp3
- Apoptotic Activity

PARP module
- casp7
- casp3
- Apoptotic Activity
- casp6

Execution phase
- Apoptotic Activity 0.0
- Smac
- LAP
- Casp 0.0
- Casp 0.0
- Casp 0.0
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- Casp 0.0

The modules modifications

The same collection of tests:

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