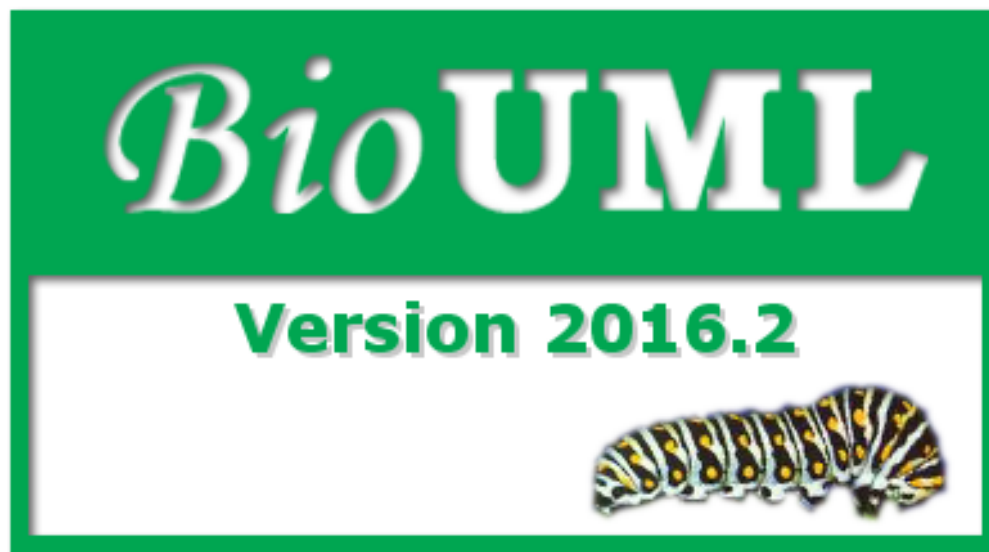


Платформа для моделирования биологических систем BioUML



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ИНСТИТУТ
ВЫЧИСЛИТЕЛЬНЫХ
ТЕХНОЛОГИЙ СО РАН



КТИ ВТ

BioUML

- Написана на языках Java и java-script
- Бесплатная, с открытым исходным кодом.
- Математическое визуальное моделирование
- Модульное моделирование
- Поддерживает языки R, java-script, MATLAB
- Доступ к базам данных (Kegg, BioModels, Transpath, etc.)
- Анализ данных
- Модульная (plugin-based) структура

Больше информации: wiki.biouml.org , bio-store.org

BioUML

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BioUML

BioUML workbench

File Database Data Help

Use journal name Research: Apoptosis

Databases Data Analyses Users

data

- Collaboration
- Examples
 - Antimony
 - AntimonyComposite
 - Bionetgen
 - DAE models
 - Optimization
 - Population Models
 - SBGN
 - Diagrams
 - Glycolysis
 - IGF signaling
 - IRF 1 gene induction
 - MAPK_cascade
 - Neuro-muscular junction
 - Repressinator
 - SedML
 - Public
 - galaxy_test

SBGN : Neuro-muscular junction

The diagram illustrates the Neuro-muscular junction (NMJ) process across four compartments: synaptic button, synaptic vesicle, synaptic cleft, and muscle cytosol. In the synaptic button, choline is synthesized from acetyl CoA and CHT1, then packaged into synaptic vesicles by vAChT. In the synaptic vesicle, ACh is synthesized from choline and acetyl CoA. Upon release into the synaptic cleft, ACh binds to nAChR on the muscle cytosol, causing it to open and release Ca²⁺ from the ER. AChE in the cleft breaks down ACh into acetate and choline. ATP is used for vesicle cycling and nAChR closure.

muscle cytosol

	name	Initial v...	Initial ty...	Type	Output ...	Units	Bound...	Const...	Show i...	Plot lin...	Comm...
0	muscle cytosol	0.0	amount	concentrat...	amount	litre	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Al	
1	muscle cytosol.ADP	0.0	amount	concentrat...	amount		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Al	
2	muscle cytosol.ATP	0.0	amount	concentrat...	amount		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Al	
3	muscle cytosol.Ca2+	0.0	amount	concentrat...	amount		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Al	
4	muscle cytosol.ER	0.0	amount	concentrat...	amount	litre	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Al	
5	muscle cytosol.ER.Ca2+	0.0	amount	concentrat...	amount		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Al	
6	muscle cytosol.Pi	0.0	amount	concentrat...	amount		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Al	

Clipboard Layout Units FBC table Antimony Parameters Variables Simulation Script Search linked Tasks SQL editor

Description States References Application Log Search results

Property Value

Compartment

- Title AChE
- Show title
- Shape Size 70.0 40.0
- Comment
- Role

View Edit Editors

BioUML

BioUML workbench

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 - Public
 - galaxy_test

SBGN : Neuro-muscular junction

Панель инструментов

Модель

Репозиторий

Свойства элемента

Property	Value
Compartment	
Title	ACHE
Show title	<input checked="" type="checkbox"/>
Shape Size	70.0 40.0
Comment	
Role	

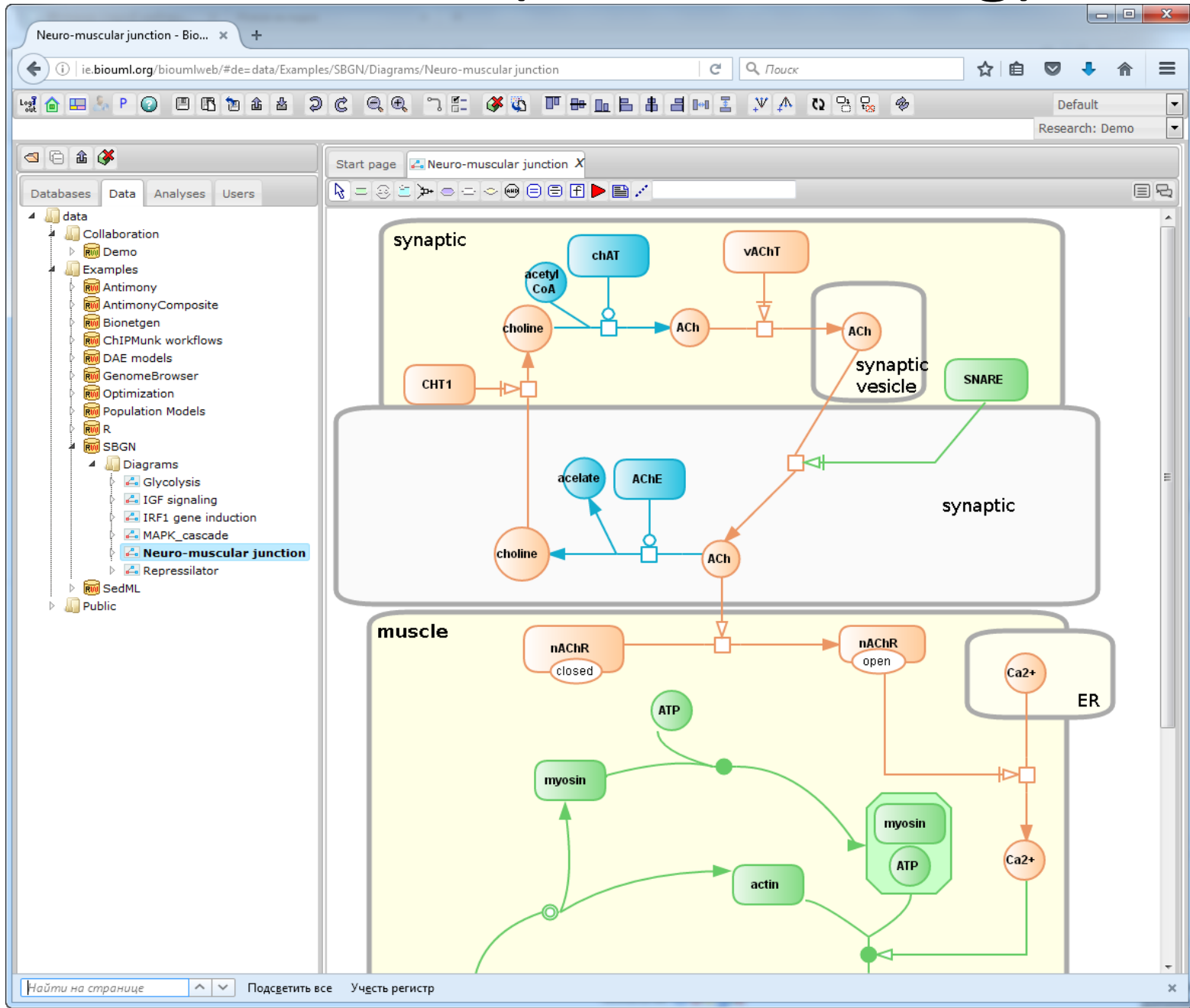
	name	Initial v...	Initial ty...	Type	Output ...	Units	Bound...	Const...	Show i...	Plot lin...	Comm...
0	muscle cytosol	0.0	amount	concentrat...	amount	litre	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Al	
1	muscle cytosol.ADP	0.0	amount	concentrat...	amount		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Al	
2	muscle cytosol.ATP	0.0	amount	concentrat...	amount		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Al	
3	muscle cytosol.Ca2+	0.0	amount	concentrat...	amount		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Al	
4	muscle cytosol.ER	0.0	amount	concentrat...	amount	litre	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Al	
5	muscle cytosol.ER.Ca2+	0.0	amount	concentrat...	amount		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Al	
6	muscle cytosol.Pi	0.0	amount	concentrat...	amount		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Al	

Clipboard Layout Units FBC table Antimony Simulation Script Search linked Tasks SQL editor

Description States Application Log Search results

Вкладки

BioUML (ie.biouml.org)



Стандарты описания моделей

Математическое описание

- SBML (Systems Biology Markup Language, sbml.org)

Визуальное описание

- SBGN (Systems Biology Markup Language, sbgn.org)
- BioUML-нотация

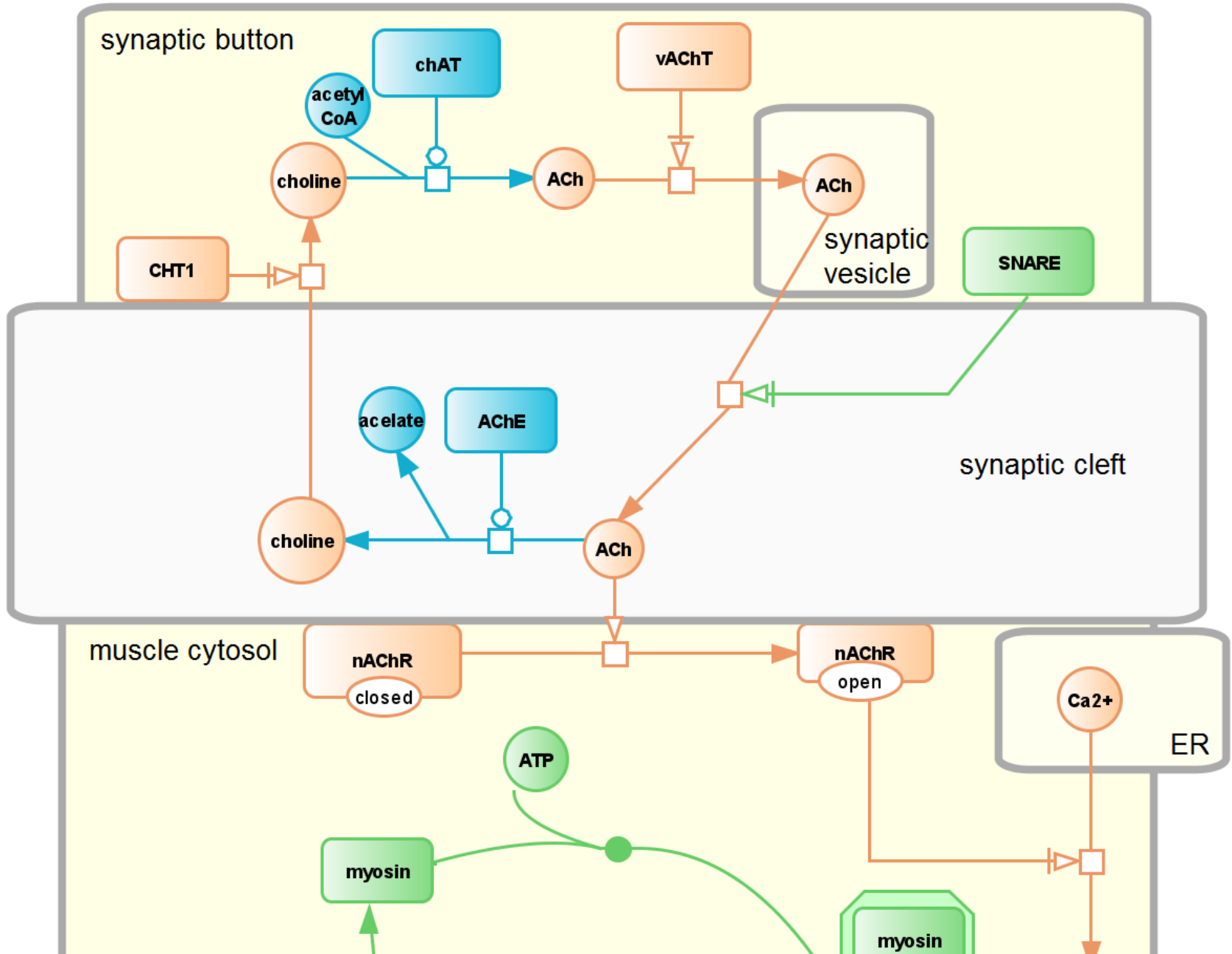
Описание численных экспериментов

- Sed-ML (Simulation Experiment Description Markup Language, sed-ml.org)

SBML

```
<sbml xmlns="http://www.sbml.org/sbml/level3/version1/core" level="3" version="1.0">
  <model id="Neuro_muscular_junction" name="Neuronal_Muscle_signalling">
    <listOfCompartments>
      <compartment constant="false" id="muscle_cytosol" name="" size="0.0" spatialDimension="3" />
      <compartment constant="false" id="ER" name="" size="0.0" spatialDimension="3" />
      <compartment constant="false" id="synaptic_button" name="" size="0.0" spatialDimension="3" />
      <compartment constant="false" id="synaptic_vesicle" name="" size="0.0" spatialDimension="3" />
      <compartment constant="false" id="synaptic_cleft" name="" size="0.0" spatialDimension="3" />
    </listOfCompartments>
    <listOfSpecies>
      <species boundaryCondition="false" compartment="muscle_cytosol" constant="false" />
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      <species boundaryCondition="false" compartment="ER" constant="false" />
      <species boundaryCondition="false" compartment="muscle_cytosol" constant="false" />
      <species boundaryCondition="false" compartment="muscle_cytosol" constant="false" />
      <species boundaryCondition="false" compartment="muscle_cytosol" constant="false" />
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      <species boundaryCondition="false" compartment="muscle_cytosol" constant="false" />
      <species boundaryCondition="false" compartment="muscle_cytosol" constant="false" />
      <species boundaryCondition="false" compartment="muscle_cytosol" constant="false" />
      <species boundaryCondition="false" compartment="synaptic_button" constant="false" />
    </listOfSpecies>
  </model>
</sbml>
```

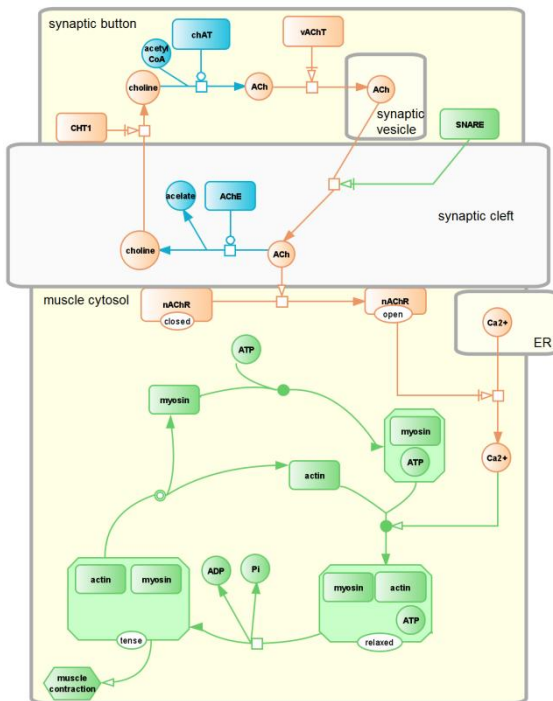

SBGN



Нотация BioUML

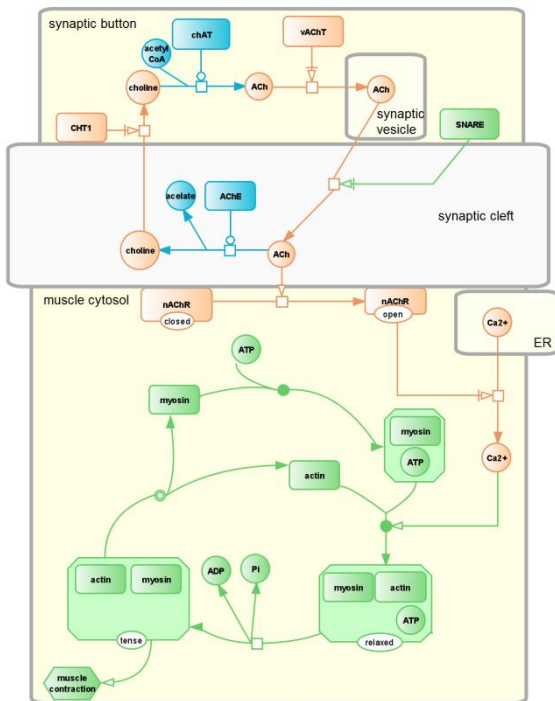
Визуальное моделирование

- Графическая нотация (например SBGN)



Визуальное моделирование

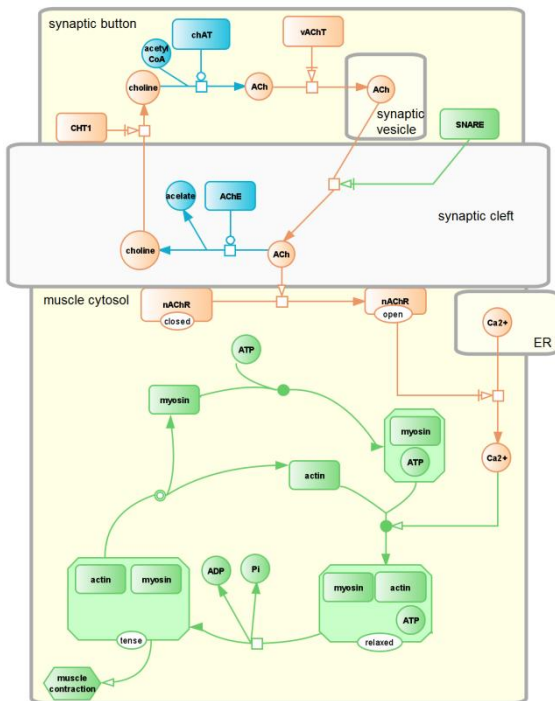
- Графическая нотация (например SBGN)
- Численная модель (Java код)



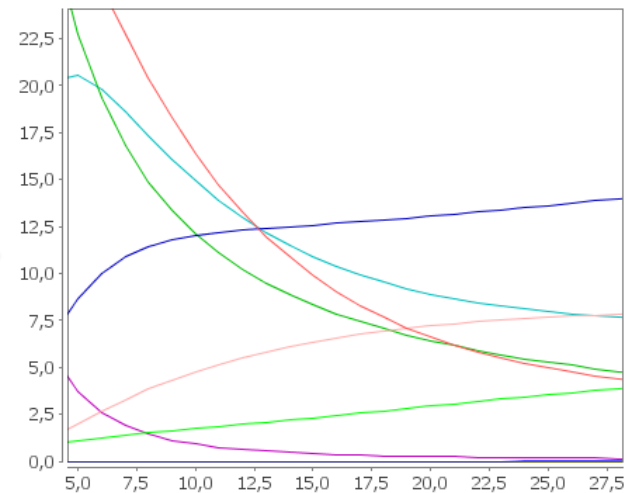
```
public double[] dy_dt(double time, double[]  
{  
    this.time = time;  
    this.x_values = x_values;  
    final double[] dydt = new double[19];  
    calculateReactionRates();  
    dydt[0] = +rate_RCT006027-rate_RCT006028;  
    dydt[1] = +rate_RCT006029-rate_RCT006030;  
    dydt[2] = -rate_RCT006044+rate_RCT006045;  
    dydt[3] = +rate_RCT006046-rate_RCT006047;  
    dydt[4] = -rate_RCT006037+rate_RCT006038;  
    dydt[5] = +rate_RCT006044-rate_RCT006045;  
    dydt[6] = -rate_RCT006029+rate_RCT006030;  
    dydt[7] = +rate_RCT006033-rate_RCT006034;  
    dydt[8] = +rate_RCT006048-rate_RCT006049;  
    dydt[9] = +rate_RCT006025-rate_RCT006026;  
    dydt[10] = -rate_RCT006025+rate_RCT006026;  
    dydt[11] = +rate_RCT006031-rate_RCT006032;  
    dydt[12] = -rate_RCT006025+rate_RCT006026;  
    dydt[13] = +rate_RCT006036+rate_RCT006037;  
    dydt[14] = -rate_RCT006034+rate_RCT006035;  
    dydt[15] = +rate_RCT006050-rate_RCT006051;  
    dydt[16] = -rate_RCT006037+rate_RCT006038;  
    dydt[17] = +rate_RCT006041-rate_RCT006042;  
}
```

Визуальное моделирование

- Графическая нотация (например SBGN)
- Численная модель (Java код)
- Результат вычислений



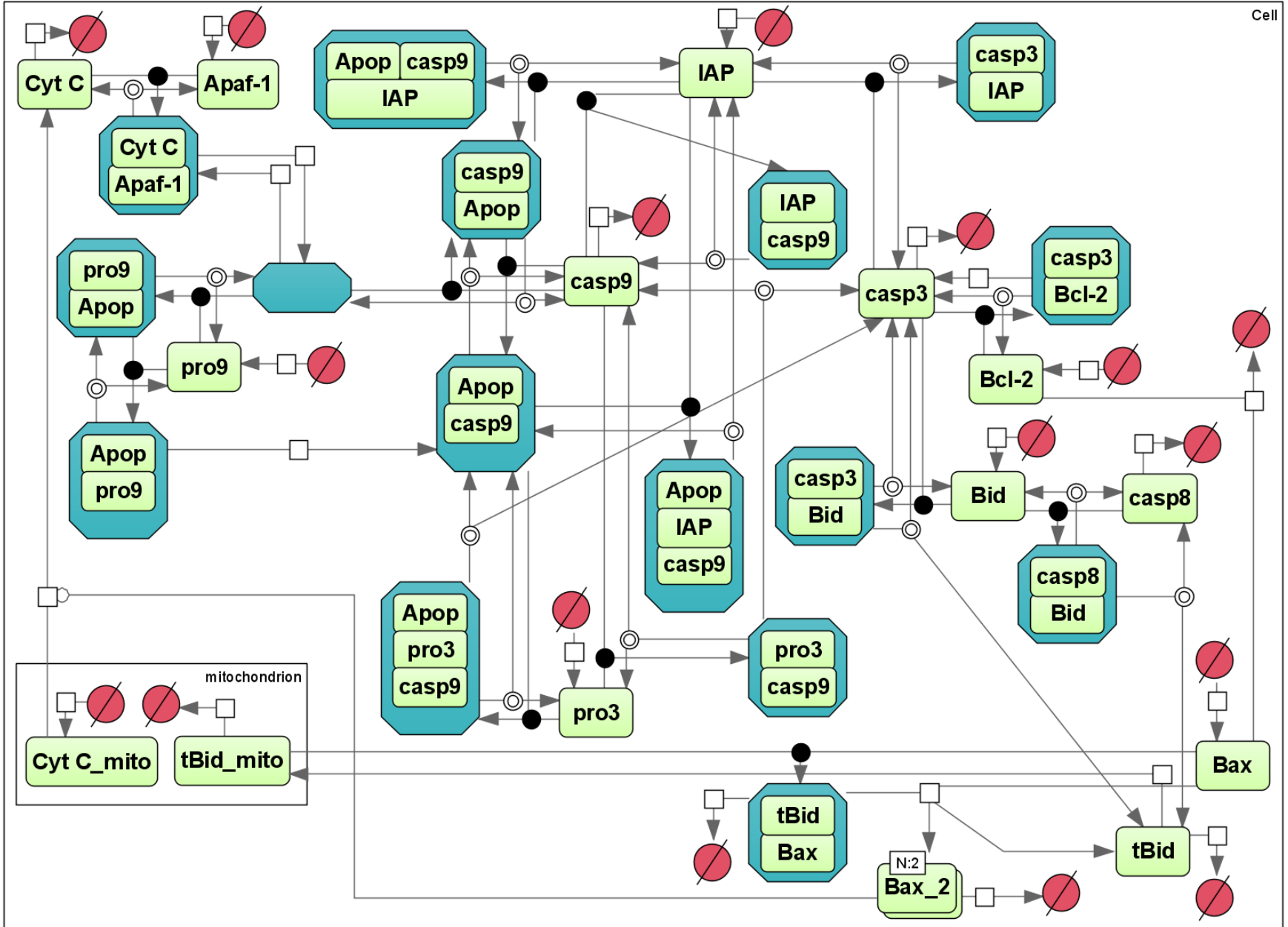
```
public double[] dy_dt(double time, double[]  
{  
    this.time = time;  
    this.x_values = x_values;  
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    calculateReactionRates();  
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    dydt[1] = +rate_RCT006029-rate_RCT006030;  
    dydt[2] = -rate_RCT006044+rate_RCT006045;  
    dydt[3] = +rate_RCT006046-rate_RCT006047;  
    dydt[4] = -rate_RCT006037+rate_RCT006038;  
    dydt[5] = +rate_RCT006044-rate_RCT006045;  
    dydt[6] = -rate_RCT006029+rate_RCT006030;  
    dydt[7] = +rate_RCT006033-rate_RCT006034;  
    dydt[8] = +rate_RCT006048-rate_RCT006049;  
    dydt[9] = +rate_RCT006025-rate_RCT006026;  
    dydt[10] = -rate_RCT006025+rate_RCT006026;  
    dydt[11] = +rate_RCT006031-rate_RCT006032;  
    dydt[12] = -rate_RCT006025+rate_RCT006026;  
    dydt[13] = +rate_RCT006036+rate_RCT006037;  
    dydt[14] = -rate_RCT006034+rate_RCT006035;  
    dydt[15] = +rate_RCT006050-rate_RCT006051;  
    dydt[16] = -rate_RCT006037+rate_RCT006038;  
    dydt[17] = +rate_RCT006041-rate_RCT006042;  
}
```



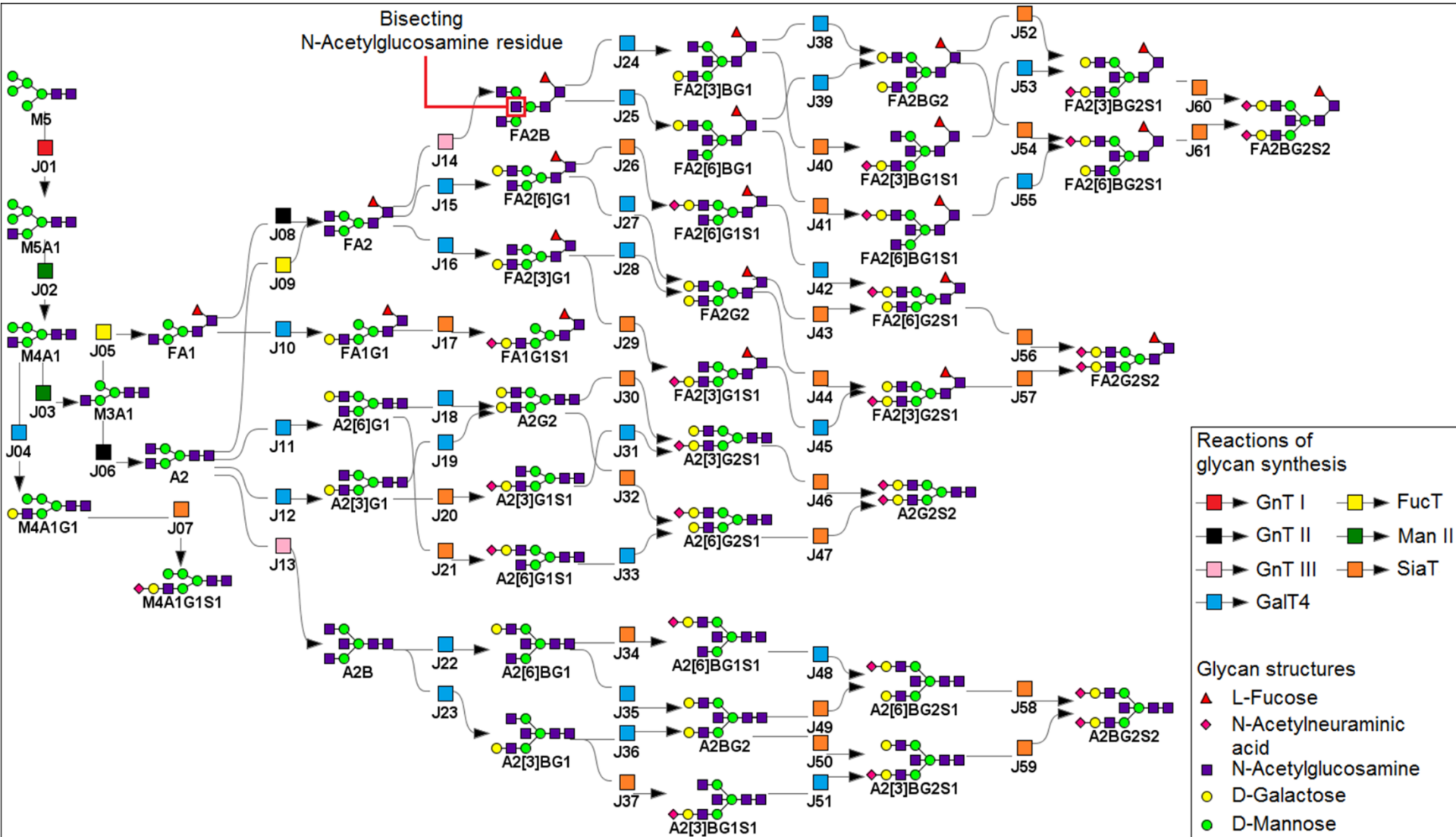
Типы моделей

- Сеть биохимических реакций
- ОДУ
- Алгебраические уравнения
- учП
- Мгновенные события
- Модульные модели
- Популяционные модели

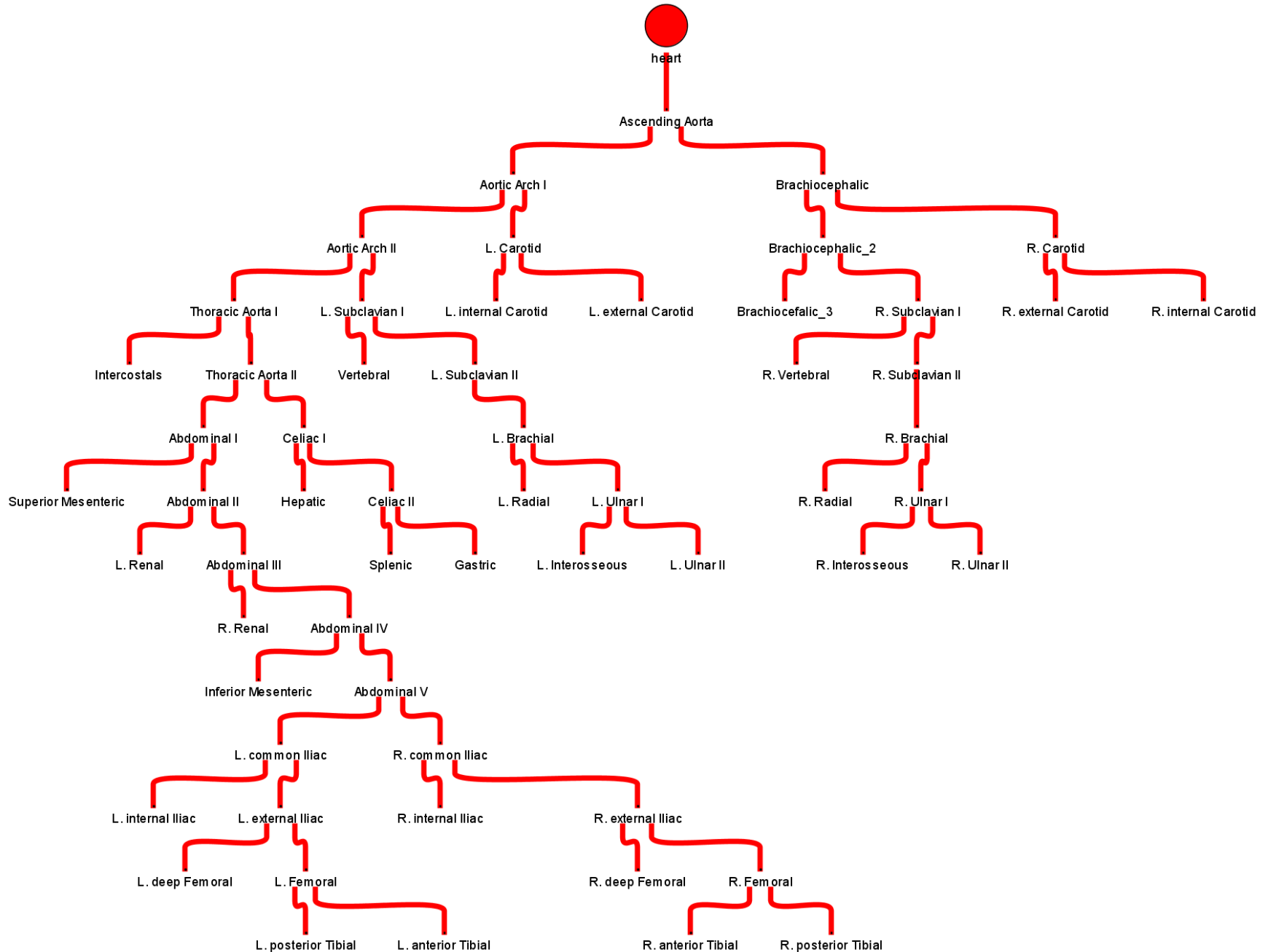
Модель апоптоза



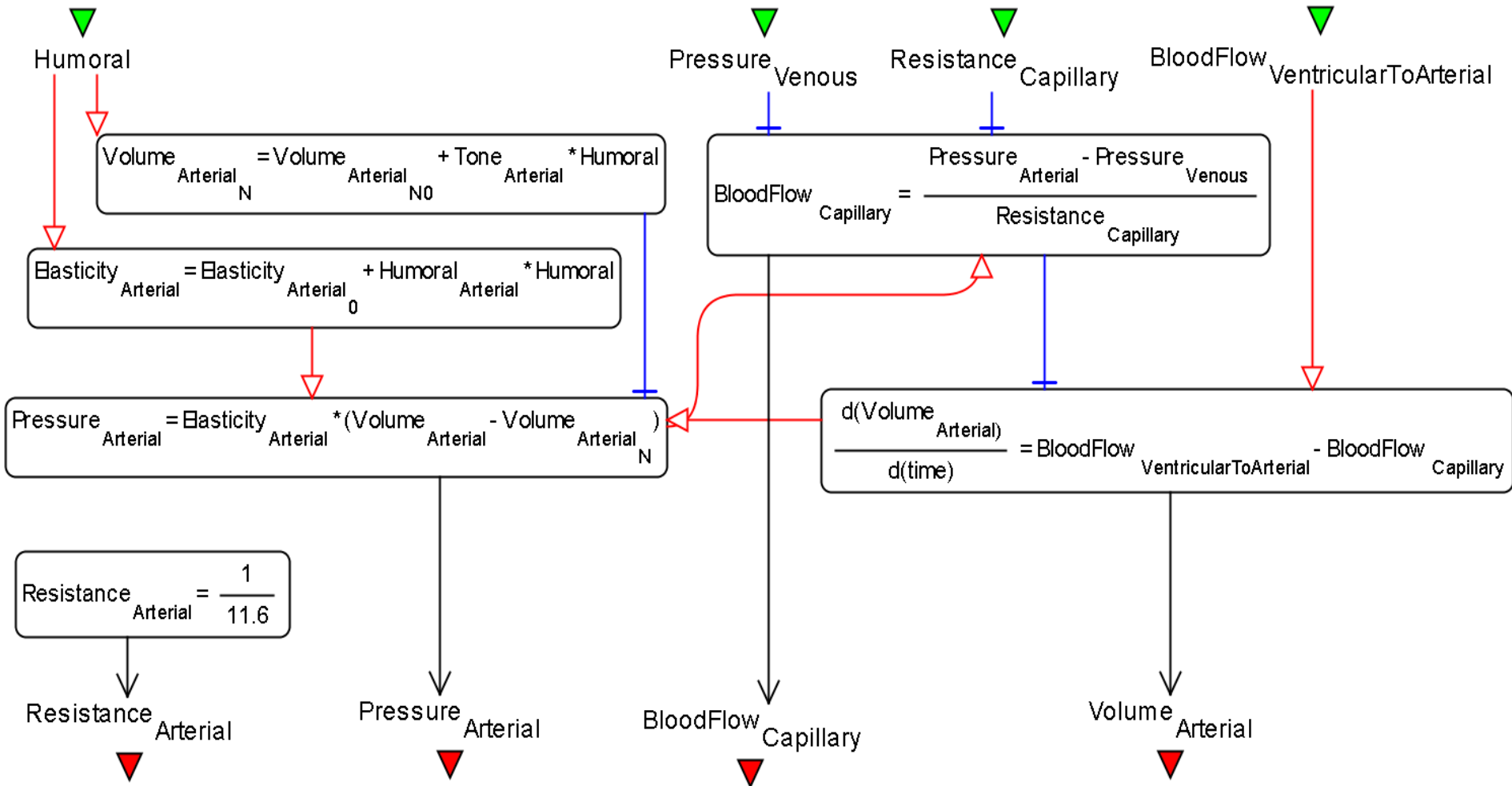
Модель гликозилирования



Модель артериального дерева



Модель сердечно-сосудистой системы



Численная модель

$$\begin{cases} \frac{dx}{dt} = f(x, y, z, t), \\ g(x, y, z, t) = \bar{0}, \\ z(t) = h(x, y, z, t). \end{cases}$$

ЕСЛИ $trigger_i(X, t)$ ТО $X = A_i(X, t)$, $i = 1, \dots, m$.

$X = (x_1, \dots, x_N)^T$ – вектор всех переменных модели;

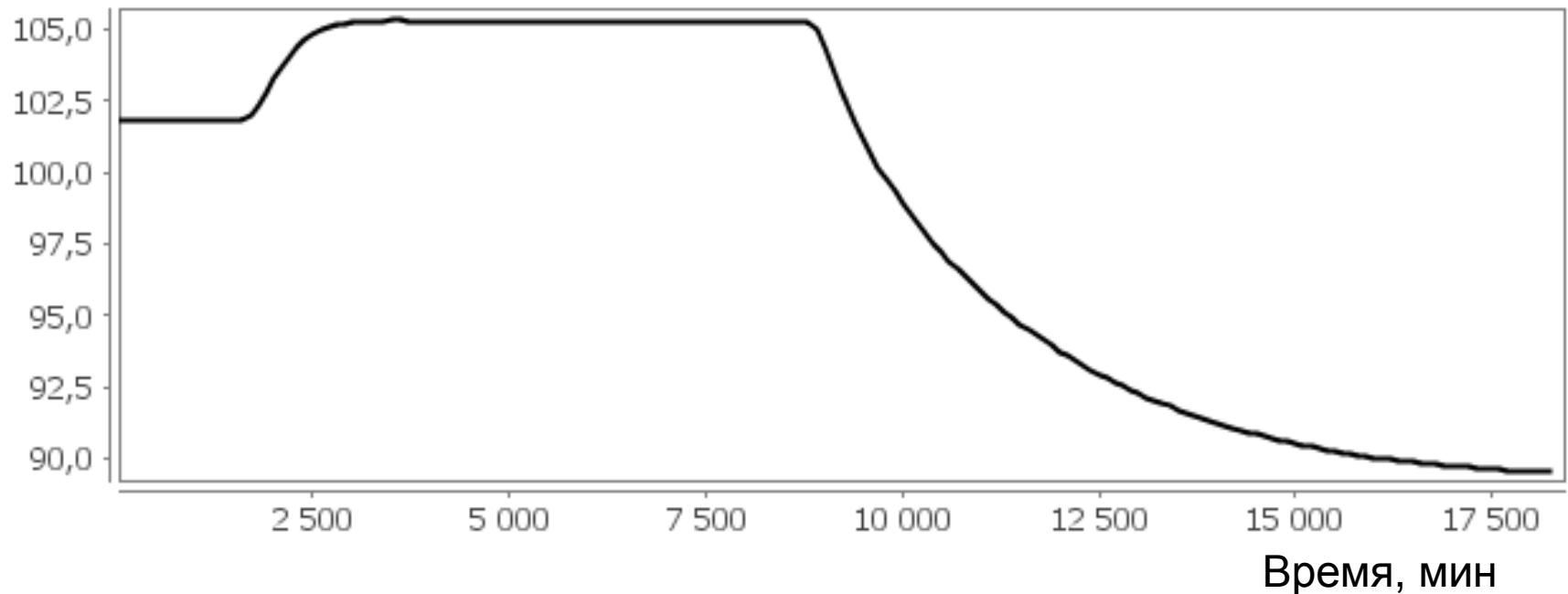
$x = (x_1, \dots, x_d)^T$ – переменные модели, для которых есть дифференциальные уравнения;

$y = (y_1, \dots, y_a)^T$ – неизвестные алгебраической системы;

$z = (z_1, \dots, z_s)^T$ – переменные модели, для которых есть правила присваивания;

Эксперимент с потреблением соли

Среднее артериальное давление, мм рт. ст.

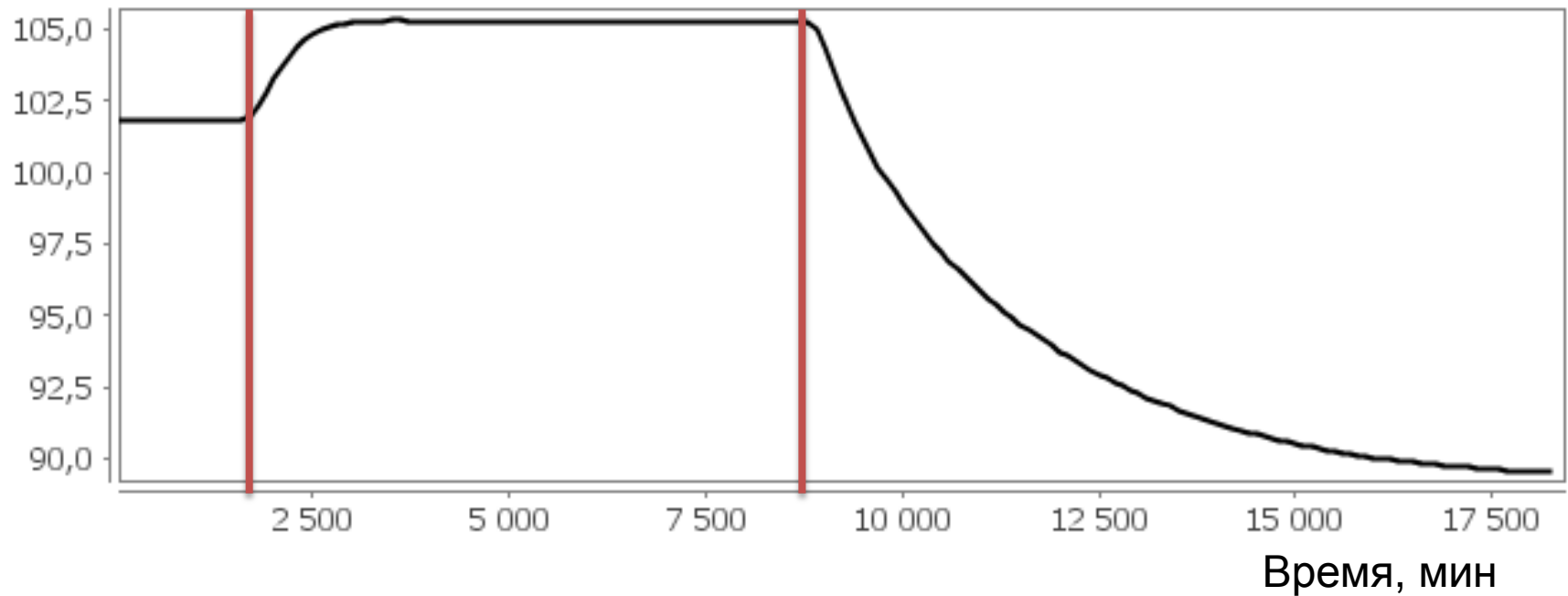


Общее время эксперимента – 14 дней.

Потребление соли увеличено с 0.126 до 0.26 мЭкв/л через 1 день и уменьшено до 0.02 мЭкв/л через 6 дней.

Эксперимент с потреблением соли

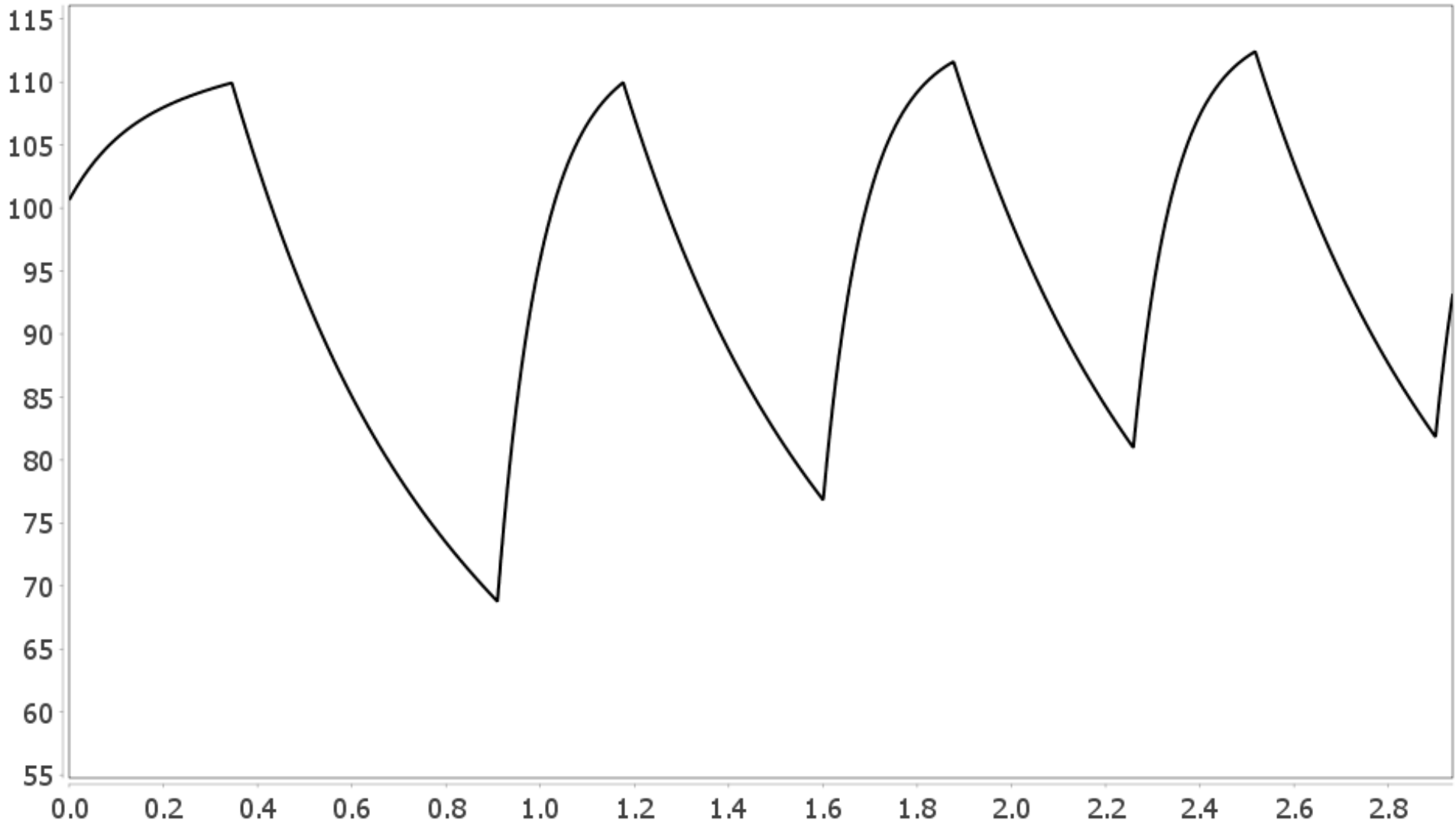
Среднее артериальное давление, мм рт. ст.



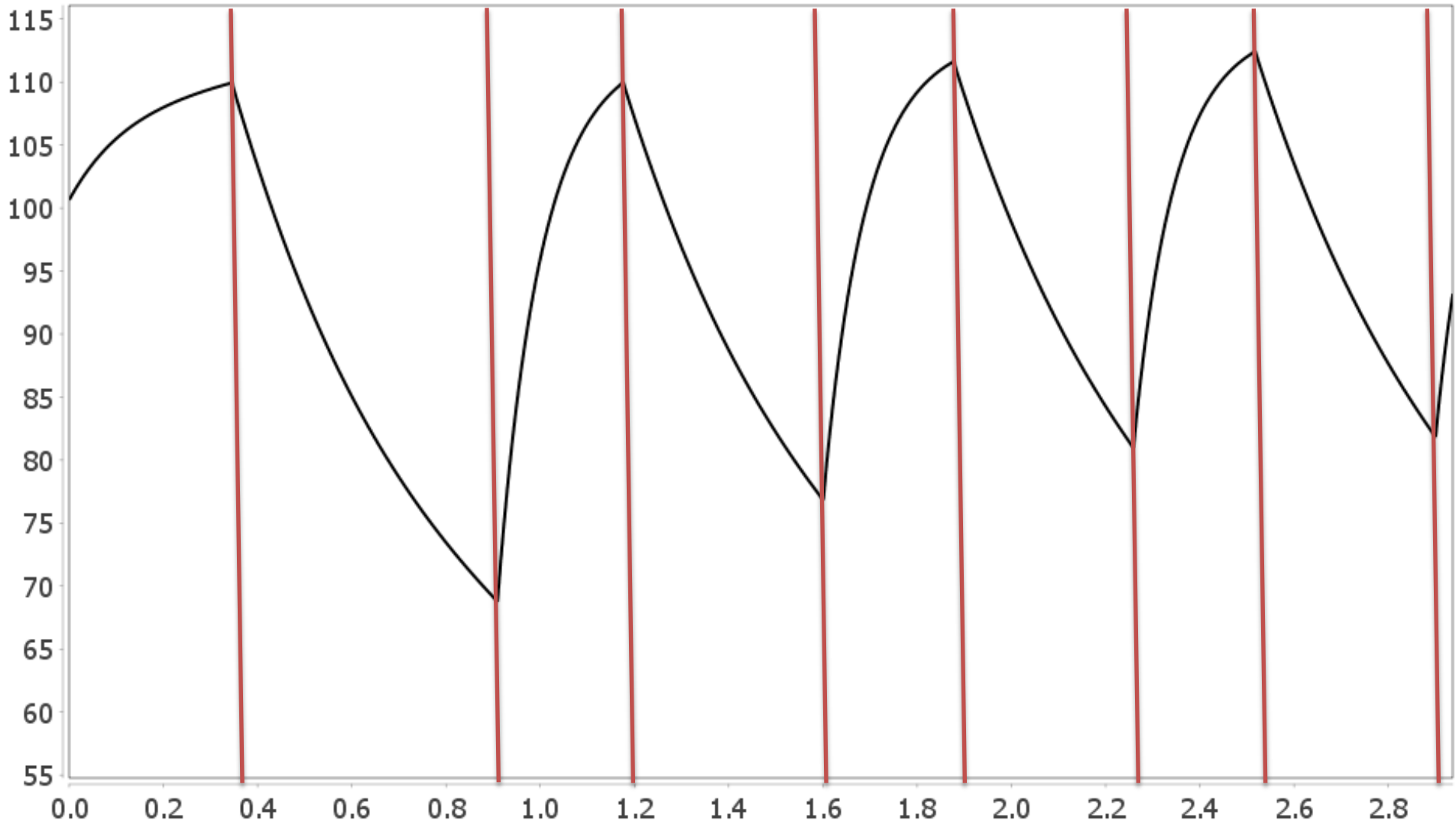
Общее время эксперимента – 14 дней.

Потребление соли увеличено с 0.126 до 0.26 мЭкв/л через 1 день и уменьшено до 0.02 мЭкв/л через 6 дней.

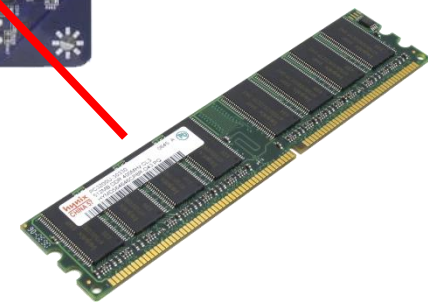
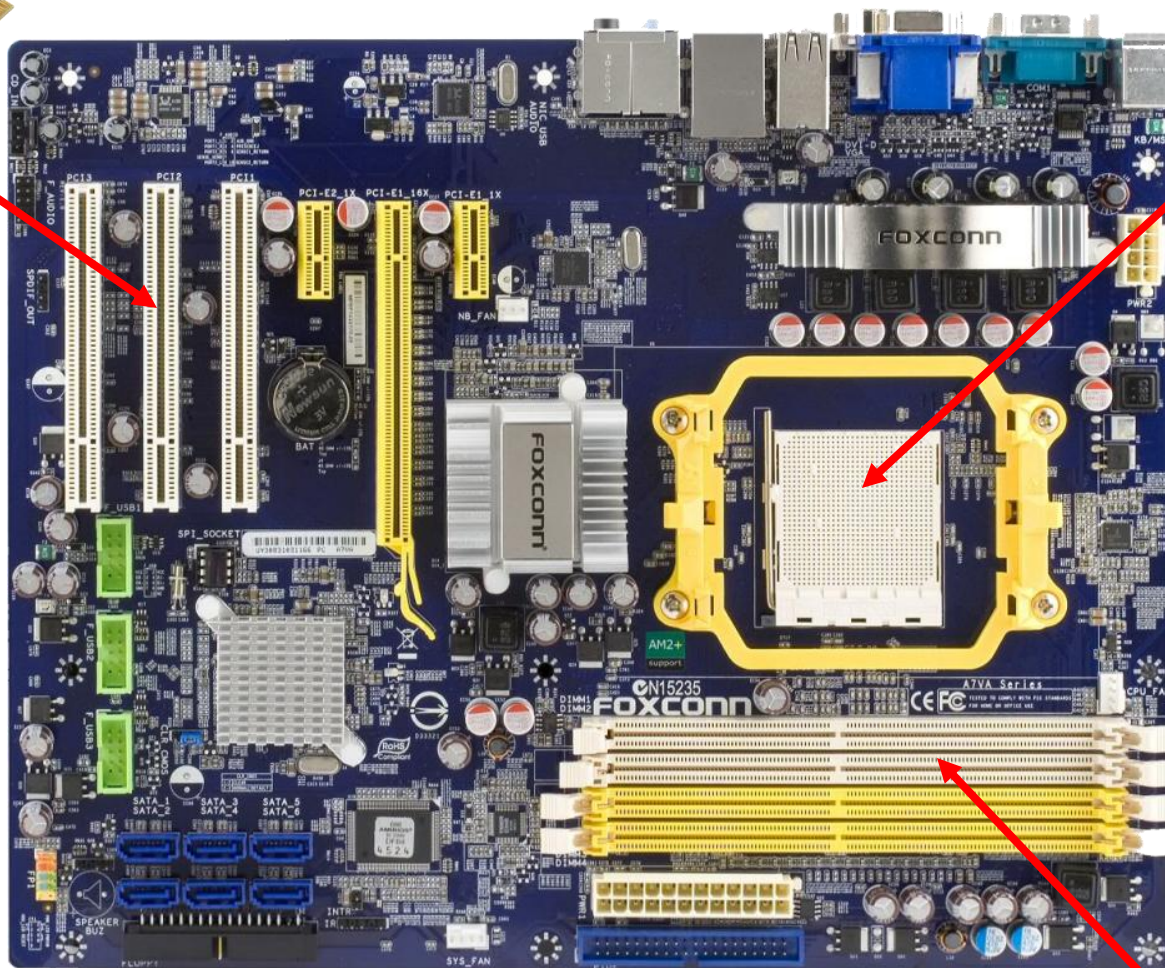
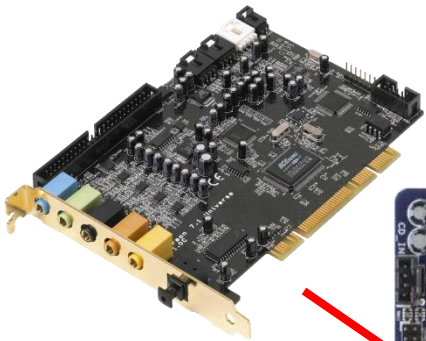
Биение сердца



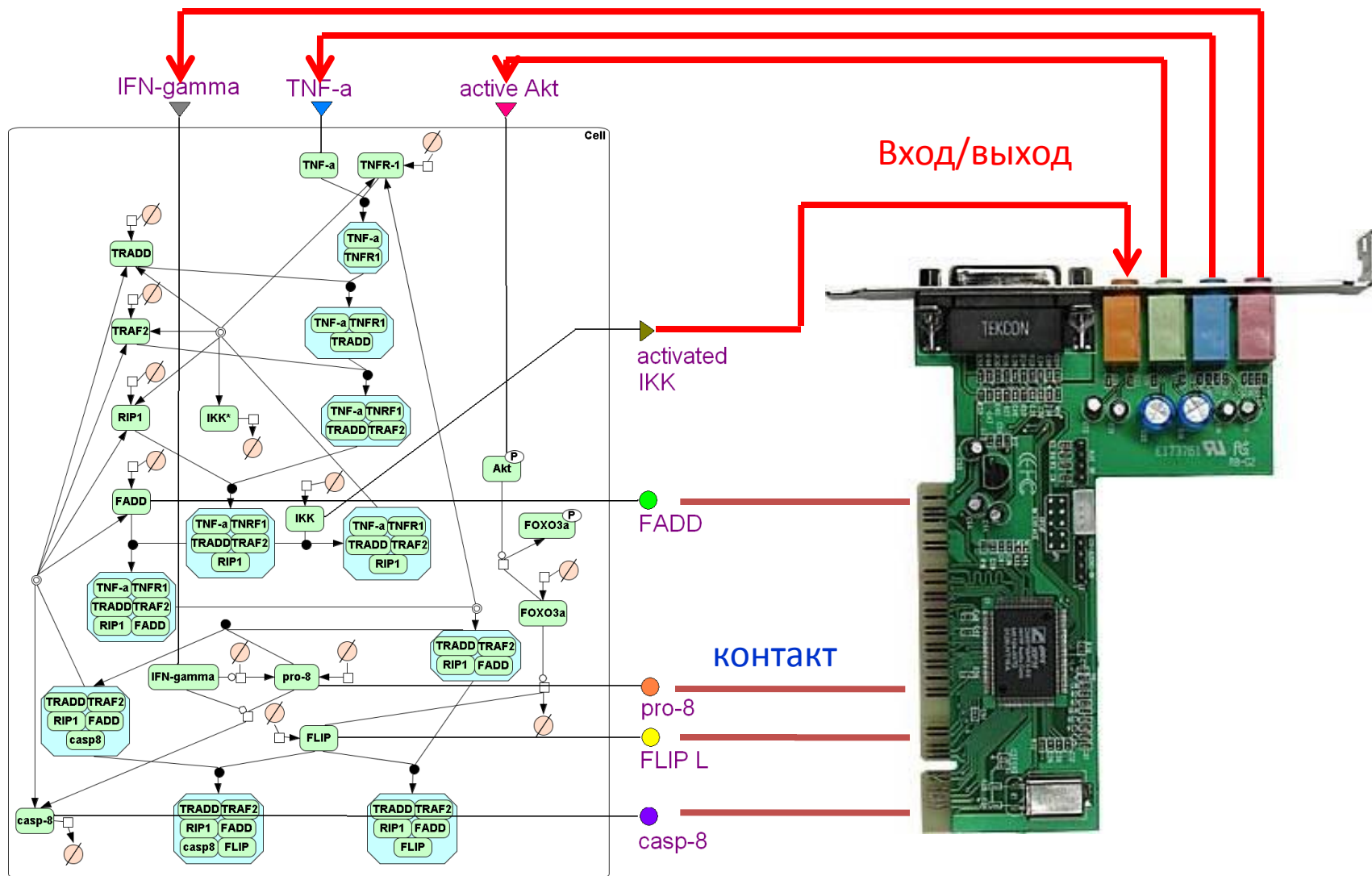
Биение сердца



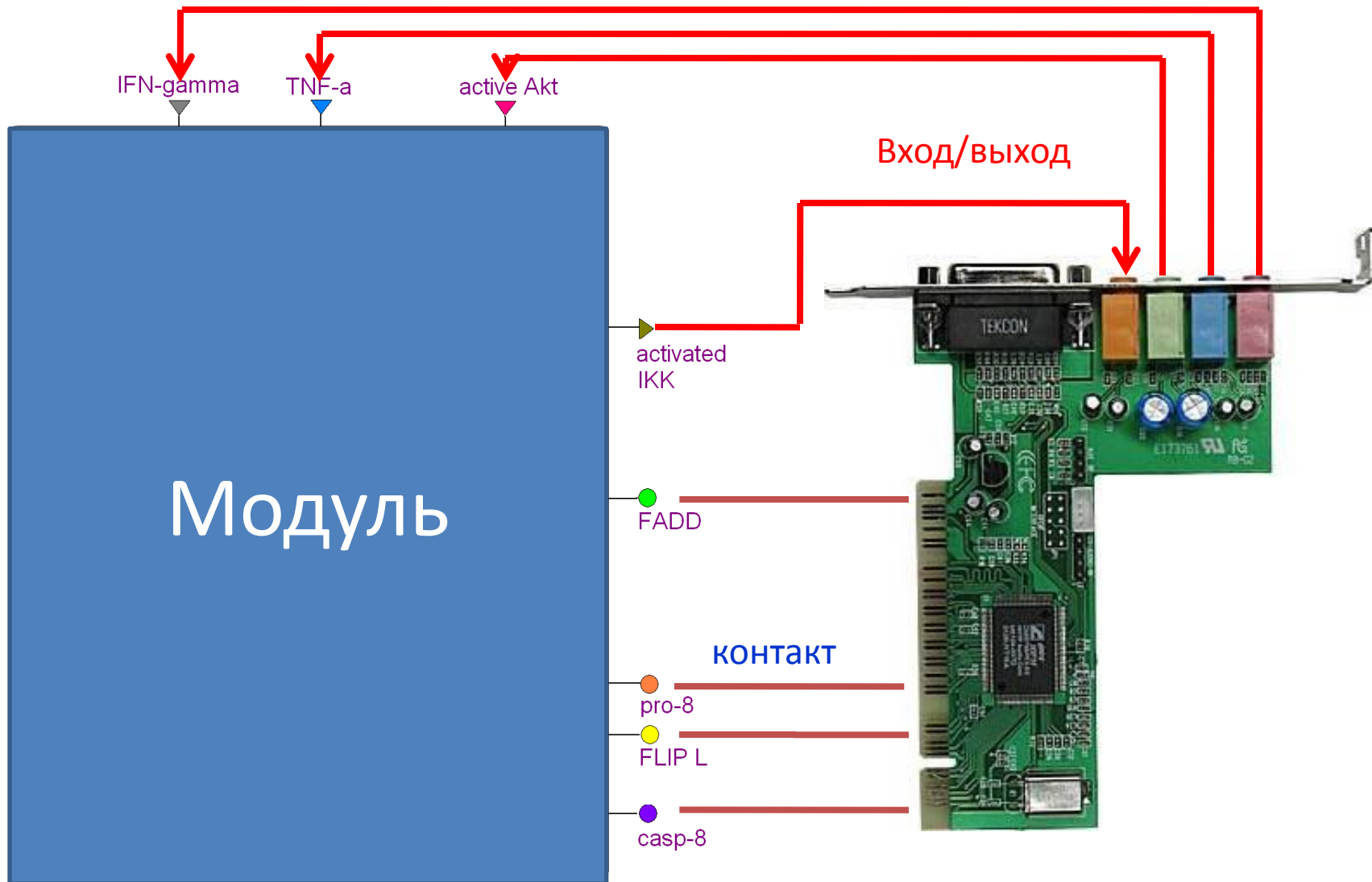
Модульный подход



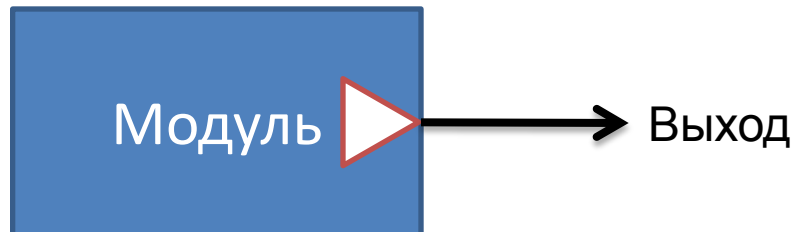
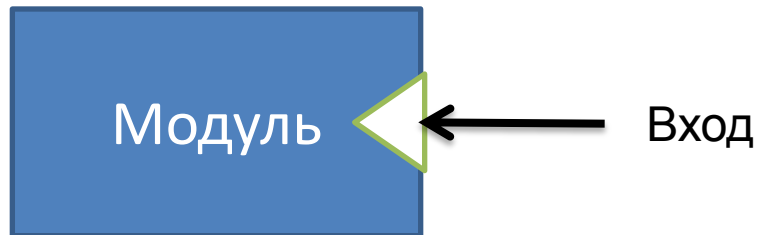
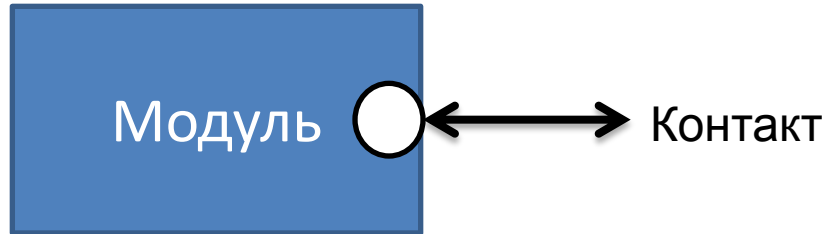
Явное определение интерфейсов



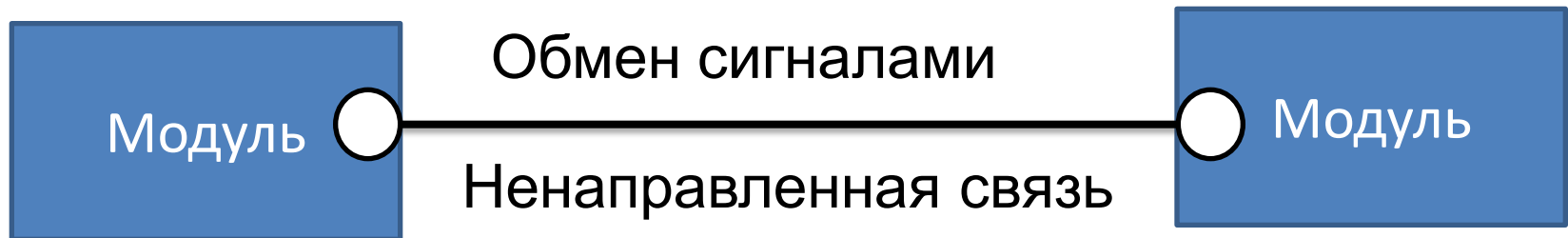
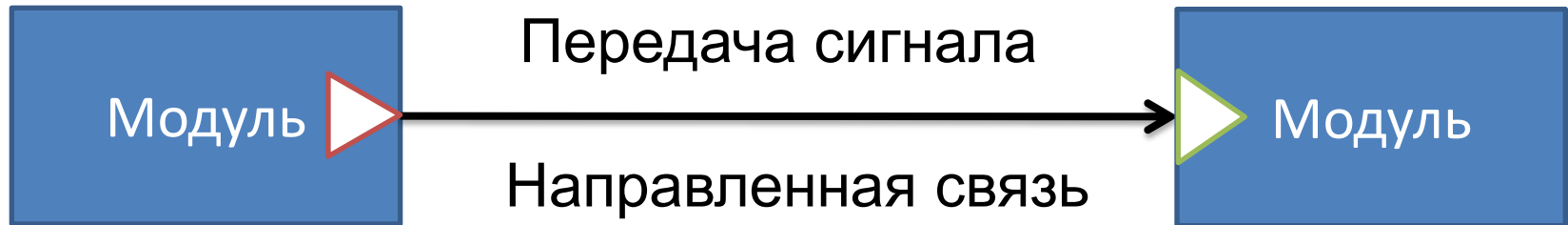
Явное определение интерфейсов



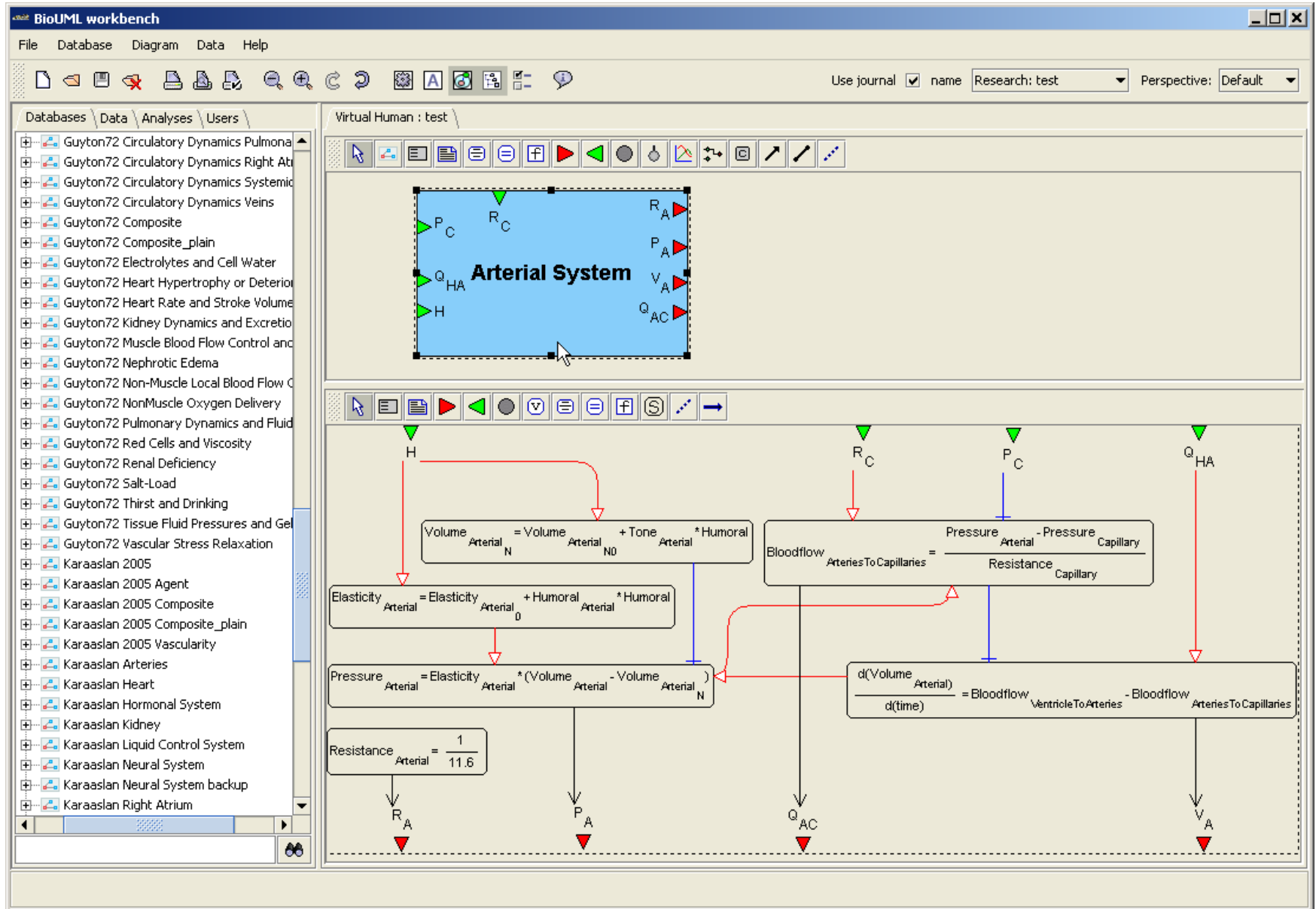
Модули и СВЯЗИ



Модули и связи



Модульное моделирование в BioUML



Модульное моделирование в BioUML

The screenshot displays the BioUML workbench interface. The top menu bar includes File, Database, Diagram, Data, and Help. The toolbar contains various icons for navigation and editing. The left-hand pane shows a list of databases and models, including Guyton72 and Karaaslan 2005 models. The main workspace is titled "Virtual Human : test" and contains two high-level diagrams: "Arterial System" and "Heart".

The "Arterial System" diagram shows inputs P_C , R_C , Q_{HA} , and H , and outputs R_A , P_A , V_A , and Q_{AC} . The "Heart" diagram shows inputs H , P_V , R_V , R_A , and P_A , and outputs V_{out} , Q_{HA} , and Q_{VH} .

Below these diagrams is a detailed compartmental model of the ventricle. It consists of three main boxes:

- Flow to Arteries:**
$$\text{Bloodflow}_{\text{VentricleToArteries}} = \text{Stage}_{\text{Sistole}} \cdot \frac{\text{Pressure}_{\text{Sistole}} - \text{Pressure}_{\text{Arterial}}}{\text{Resistance}_{\text{Arterial}}}$$
- Flow from Veins:**
$$\text{Bloodflow}_{\text{VeinsToVentricle}} = (1 - \text{Stage}_{\text{Sistole}}) \cdot \frac{\text{Pressure}_{\text{Venous}} - \text{Pressure}_{\text{Diastole}}}{\text{Resistance}_{\text{Venous}}} - 1$$
- Ventricular Volume Change:**
$$\frac{d(\text{Volume}_{\text{Ventricular}})}{d(\text{time})} = \text{Bloodflow}_{\text{VeinsToVentricle}} - \text{Bloodflow}_{\text{VentricleToArteries}}$$

The diastolic pressure is calculated as:

$$\text{Pressure}_{\text{Diastole}} = A_{29} \cdot (\text{Volume}_{\text{Ventricular}} - \text{Volume}_{\text{Ventricular}_N}) + (A_{24} \cdot (\text{Volume}_{\text{Ventricular}} - \text{Volume}_{\text{Ventricular}_N}) + \text{Elasticity}_{\text{Myocard}})$$

Модульное моделирование в BioUML

The screenshot displays the BioUML workbench interface. The top window shows a high-level diagram of a cardiovascular model with two main components: 'Arterial System' and 'Heart'. The 'Arterial System' has inputs P_C , R_C , Q_{HA} , and H , and outputs R_A , P_A , V_A , and Q_{AC} . The 'Heart' has inputs H , P_V , R_V , R_A , and P_A , and outputs V_{out} , Q_{HA} , and Q_{VH} .

The bottom window shows a detailed compartmental model with the following equations:

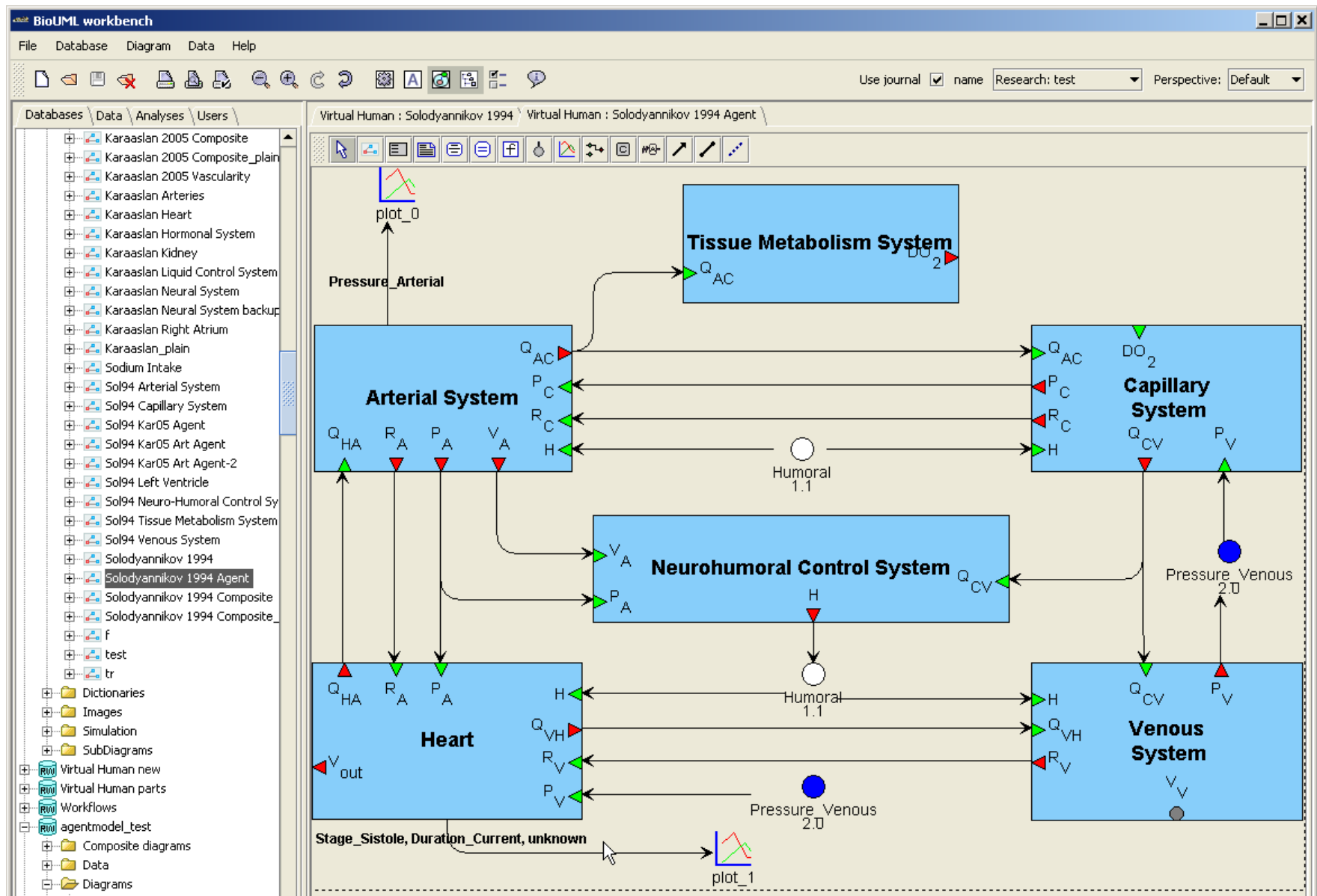
Bloodflow $VentriclesToArteries = Stage_{Sistole} * \frac{Pressure_{Sistole} - Pressure_{Arterial}}{Resistance_{Arterial}}$

Bloodflow $VeinsToVentricle = (1 - Stage_{Sistole}) * \frac{Pressure_{Venous} - Pressure_{Diastole}}{Resistance_{Venous}} - 1$

$\frac{d(Volume_{Ventricular})}{d(time)} = Bloodflow_{VeinsToVentricle} - Bloodflow_{VentricleToArteries}$

$Pressure_{Diastole} = A_{29} * (Volume_{Ventricular} - Volume_{Ventricular_N}) * (A_{24} * (Volume_{Ventricular} - Volume_{Ventricular_N}) + Elasticity_{Myocard})$

Модульное моделирование в BioUML

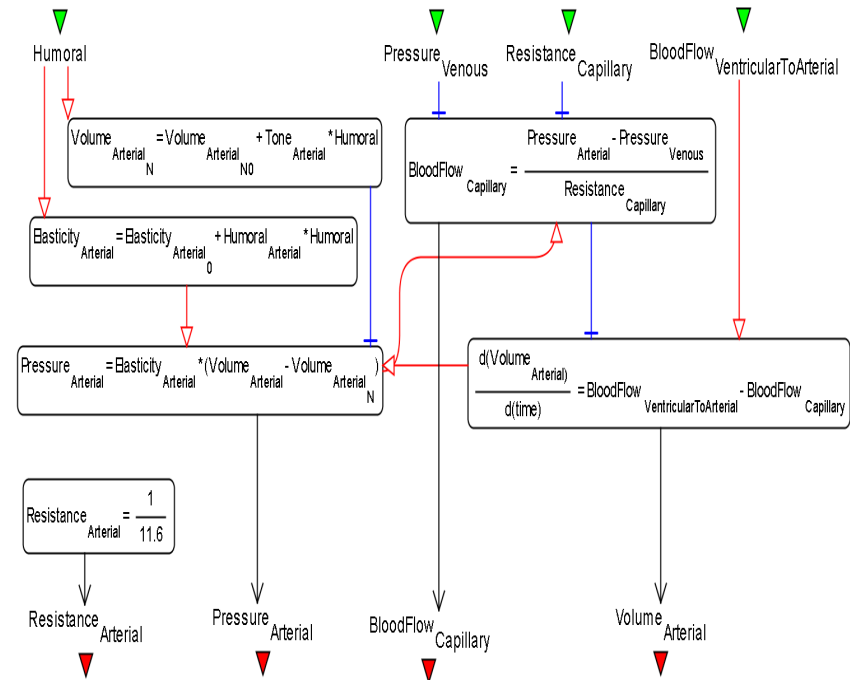
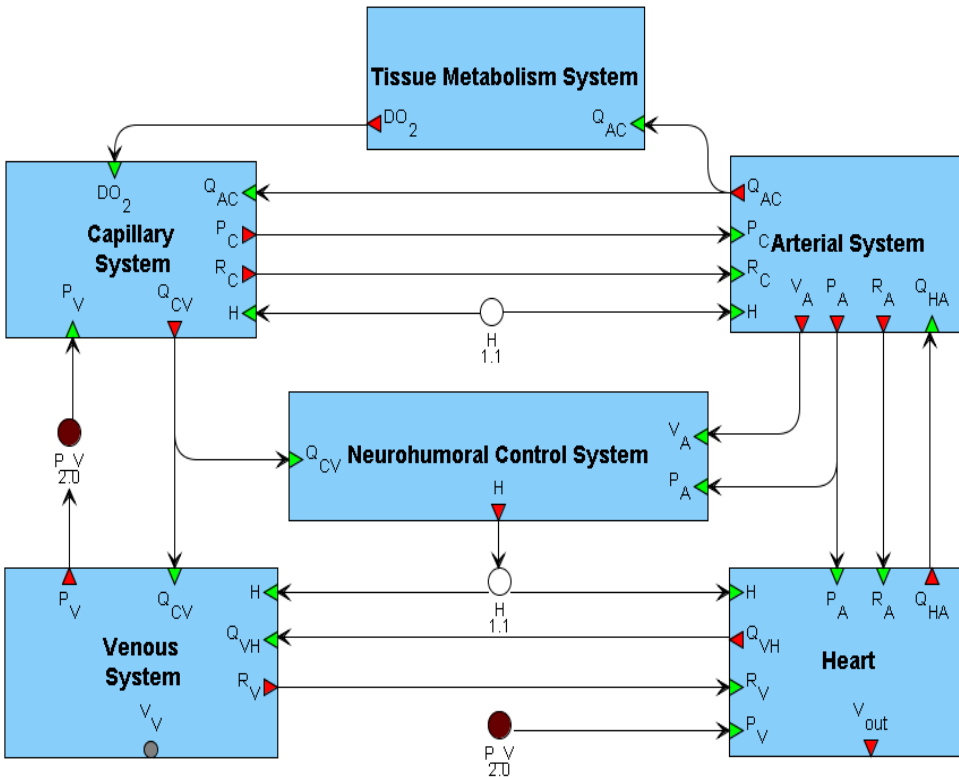


Сочетание подходов снизу-вверх и сверху-вниз

ВНИЗ

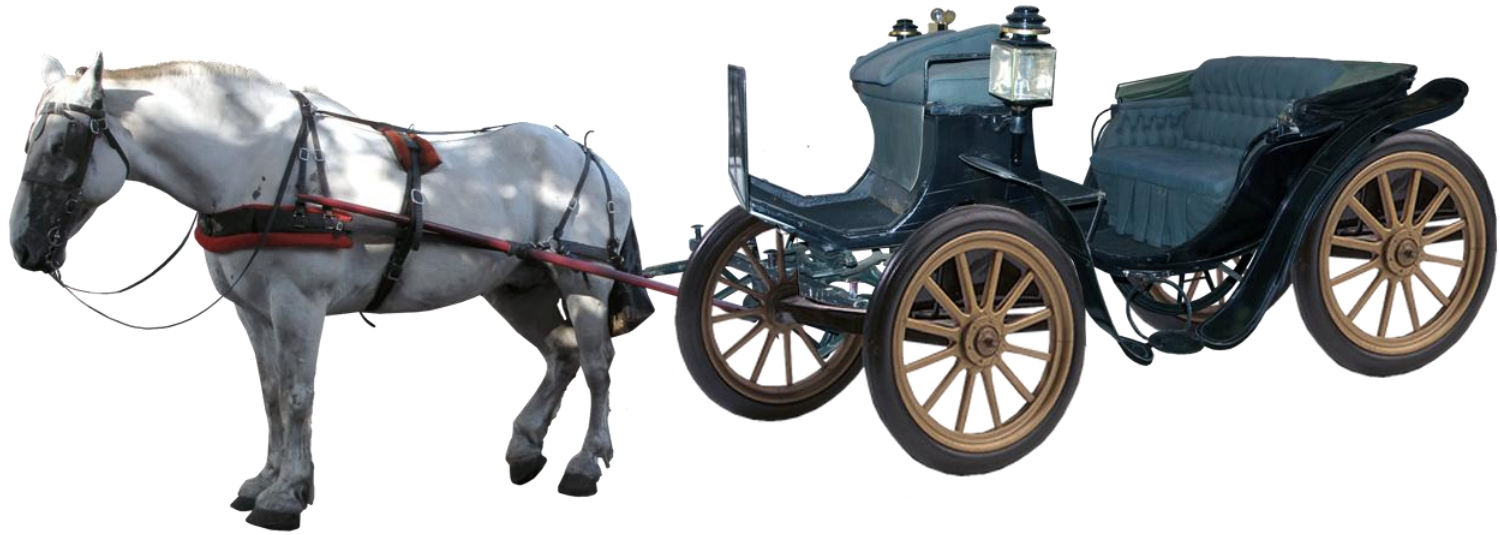
top-down

bottom-up







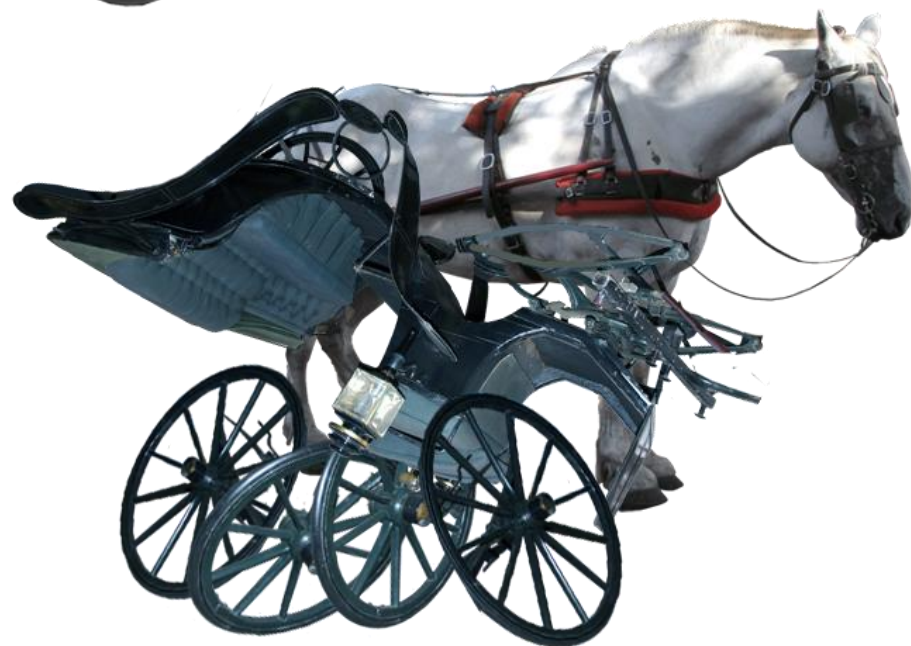


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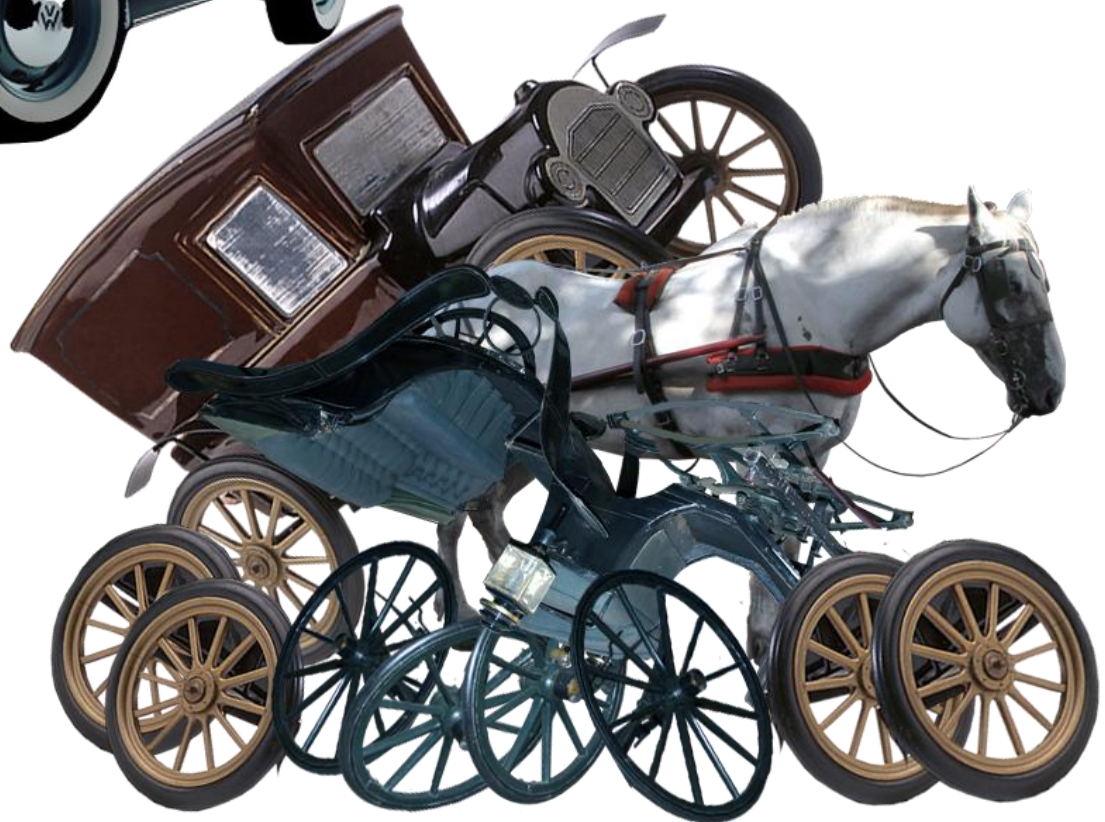
Trash



Trash

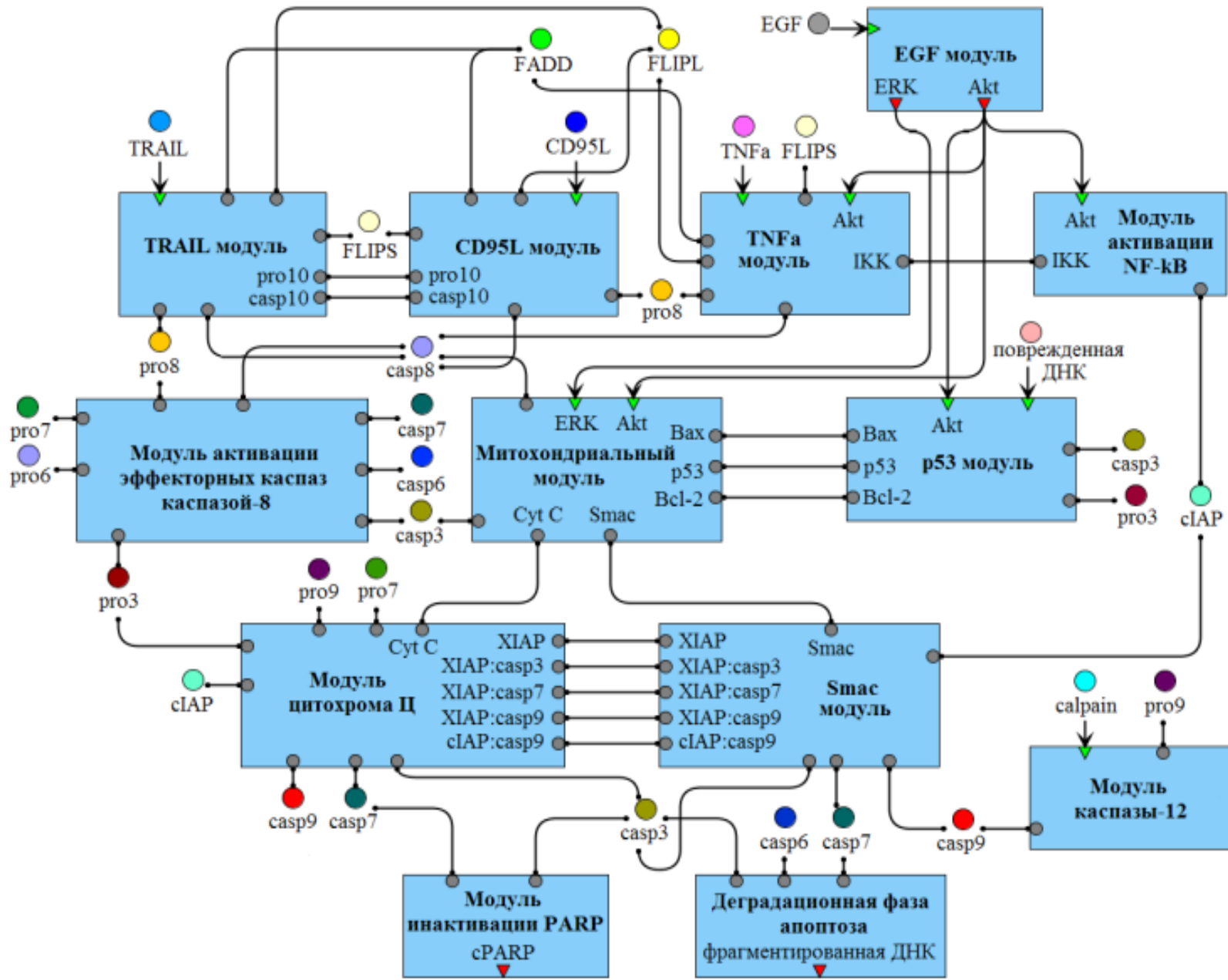


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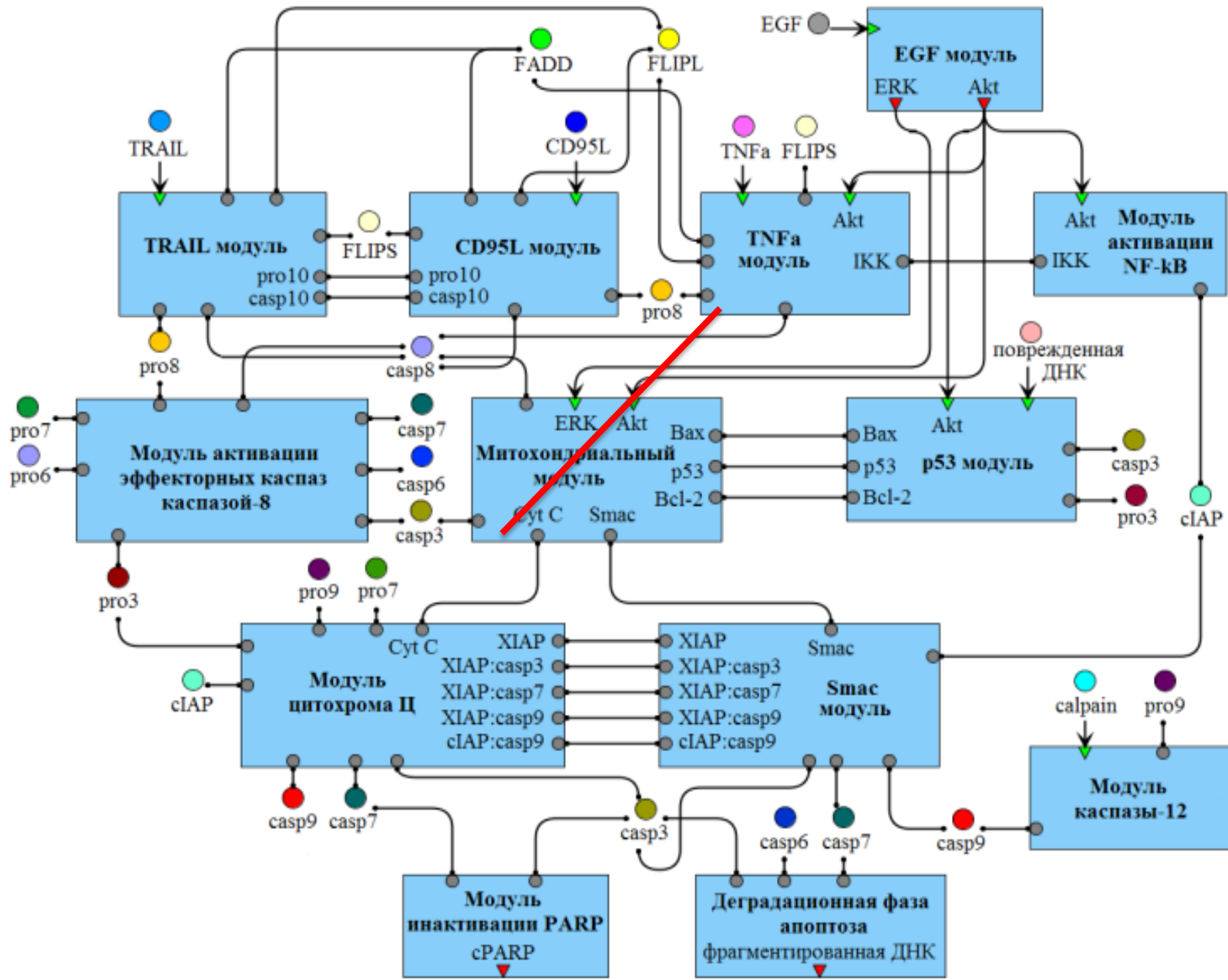


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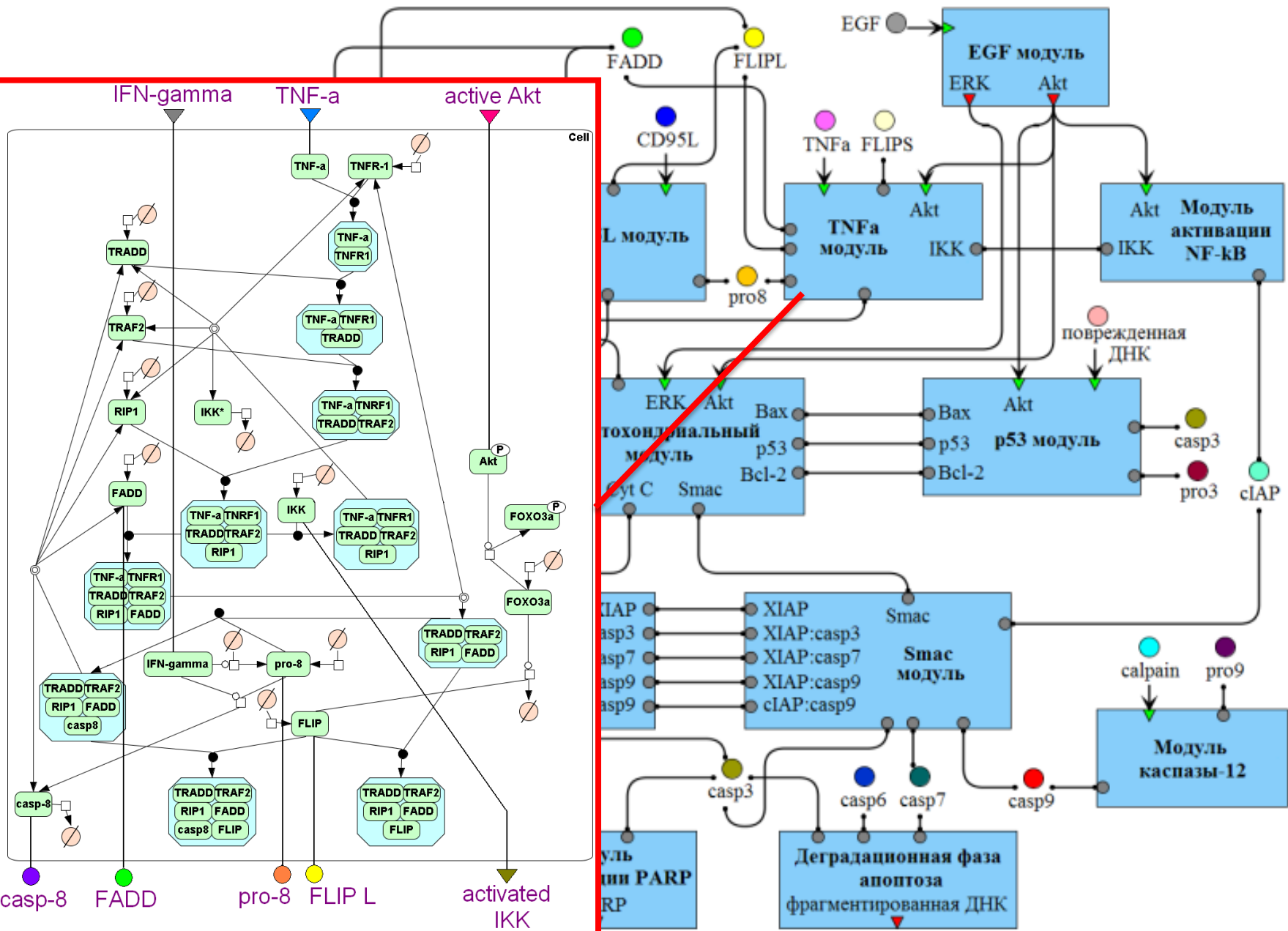
Модульная модель апоптоза



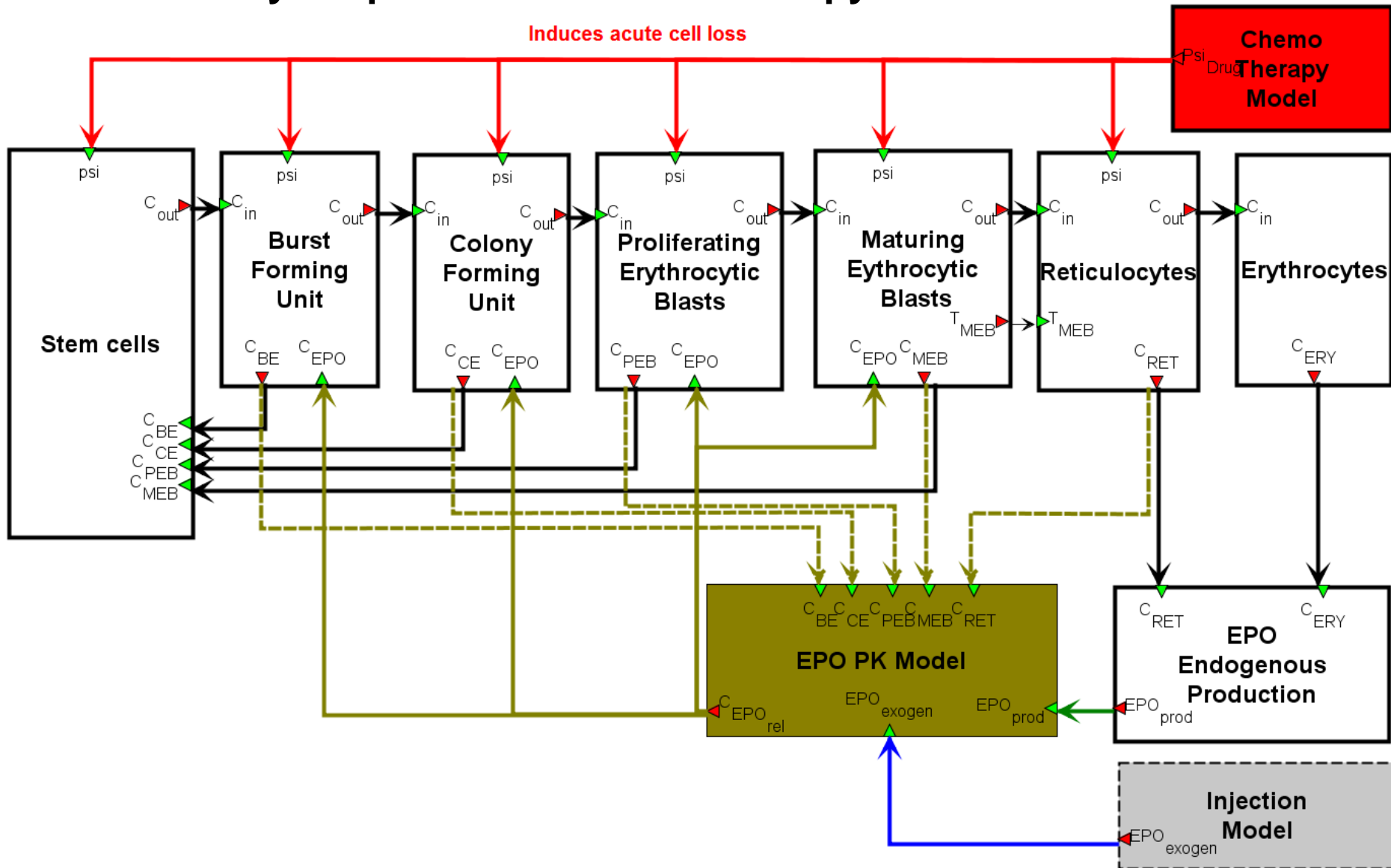
Модульная модель апоптоза



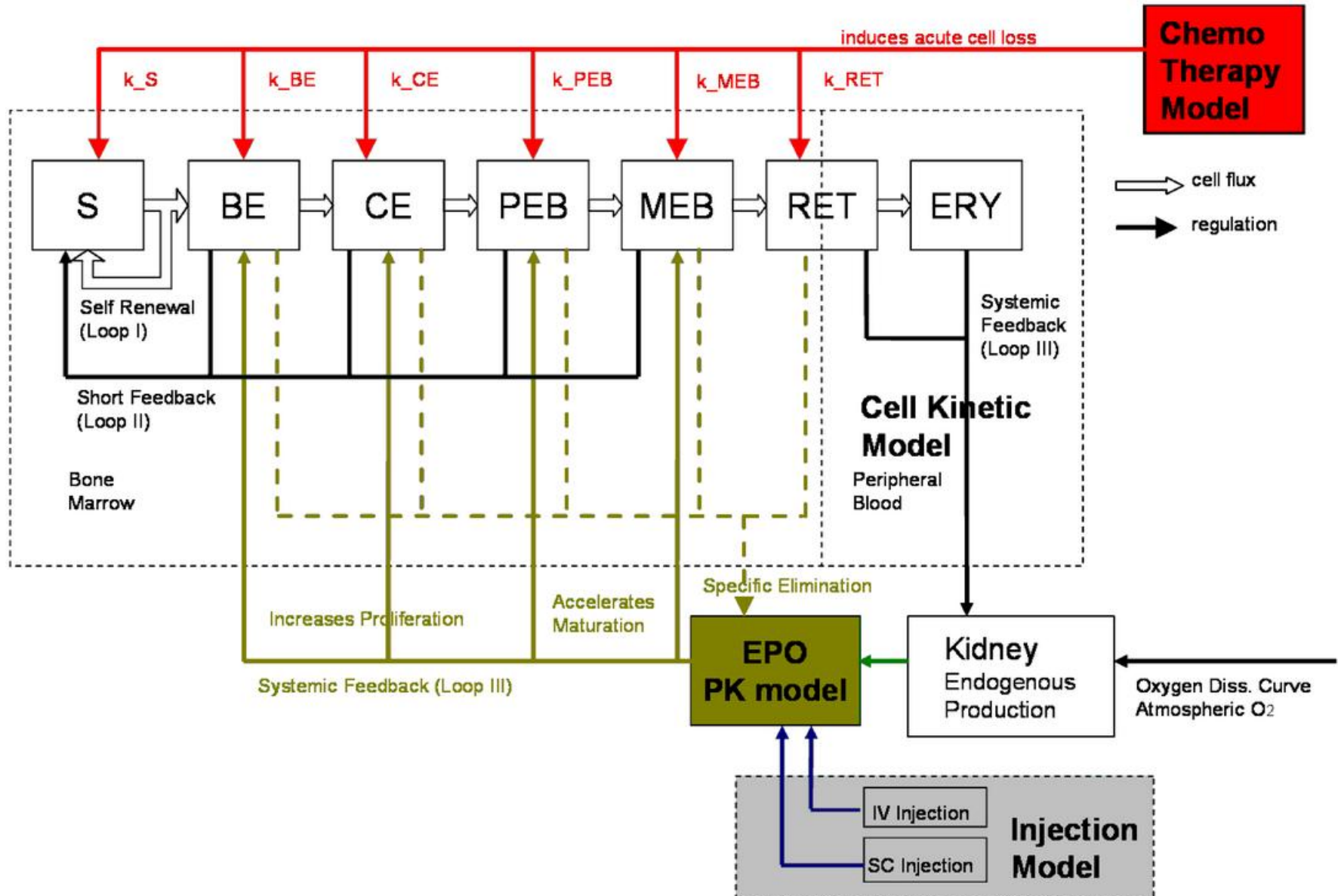
Модульная модель апоптоза

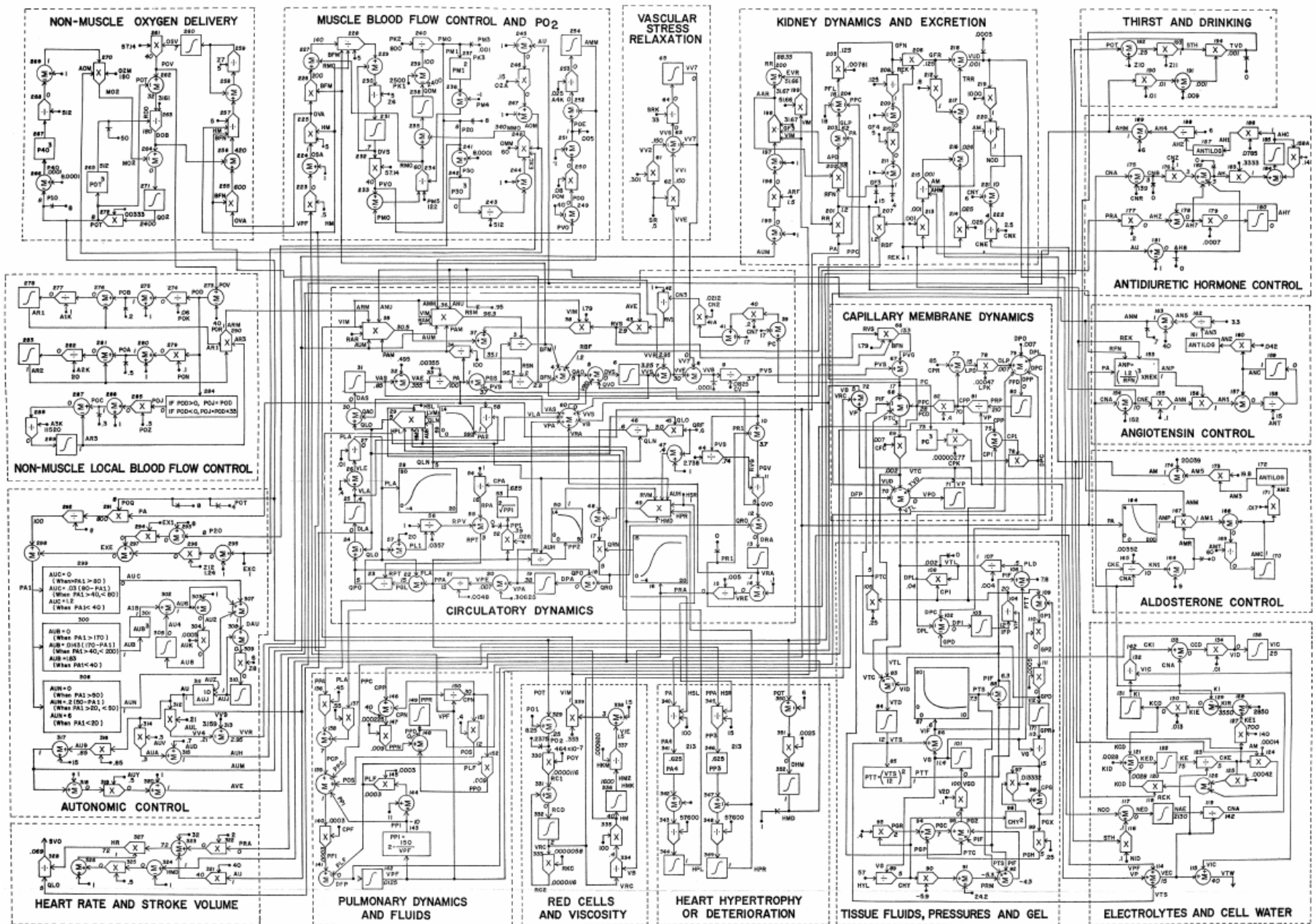


A Biomathematical Model of Human Erythropoiesis under Erythropoietin and Chemotherapy Administration



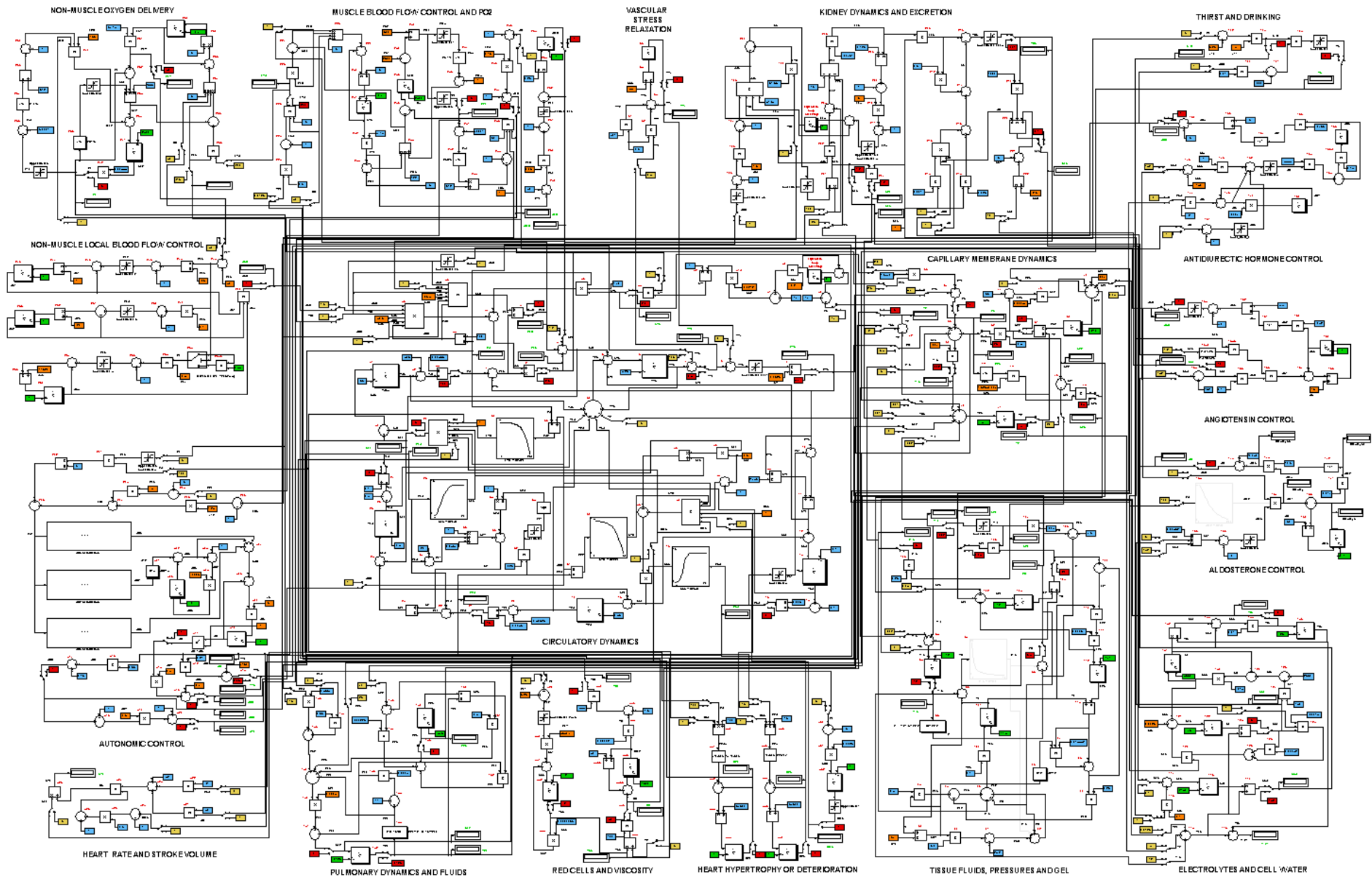
A Biomathematical Model of Human Erythropoiesis under Erythropoietin and Chemotherapy Administration





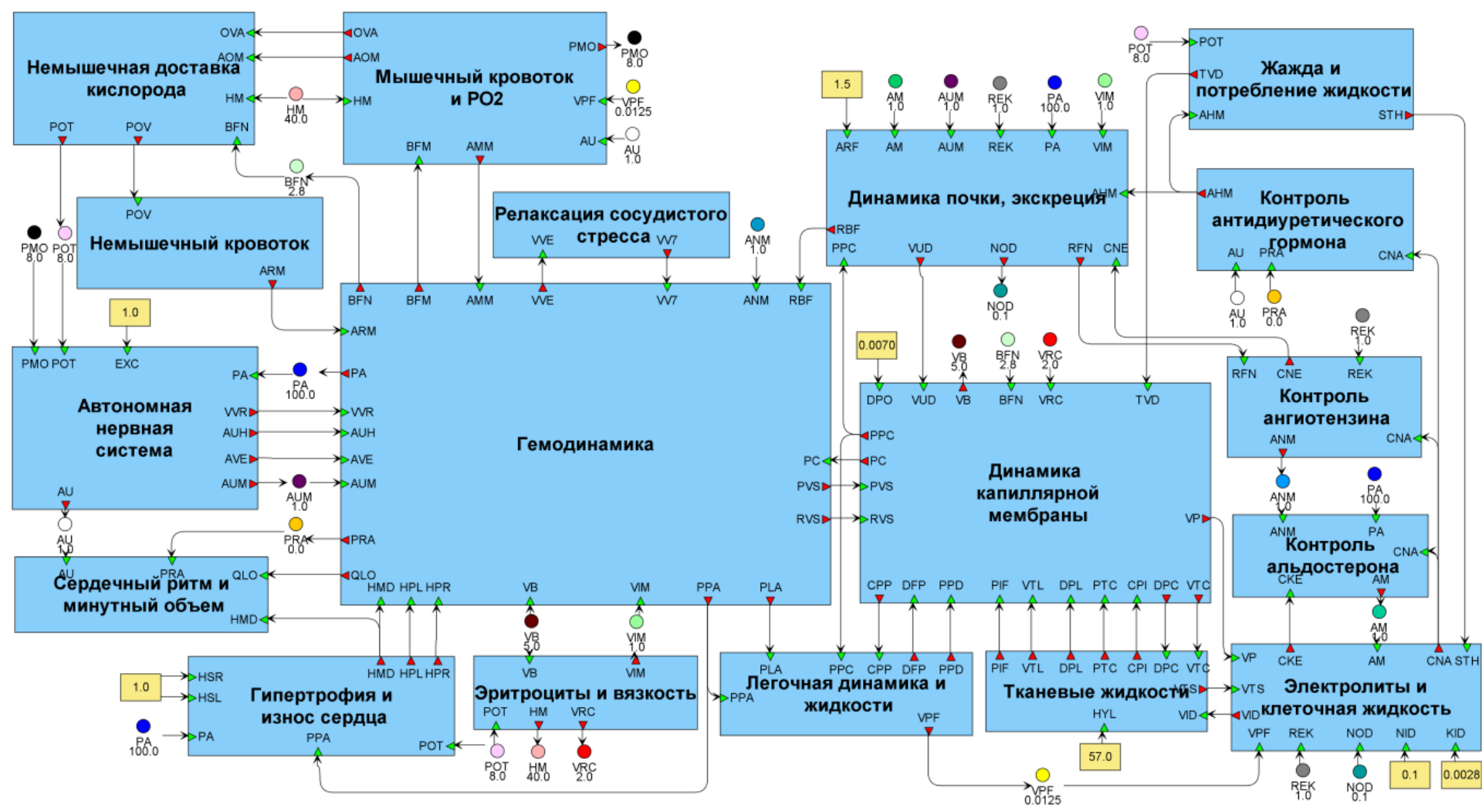
Guyton A.C., Coleman T.G., Grander H.J. Circulation: Overall Regulation.

Ann Rev Physiol. 1972. 41:13-41



J. Kofránek, J. Rusz. Restoration of Guyton Diagram for Regulation of the Circulation as a Basis for Quantitative Physiological Model Development. *Physiol Res.* 2010 Jun 9.

Модель в BioUML



Guyton A.C., Coleman T.G., Grander H.J. Circulation: Overall Regulation.

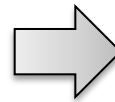
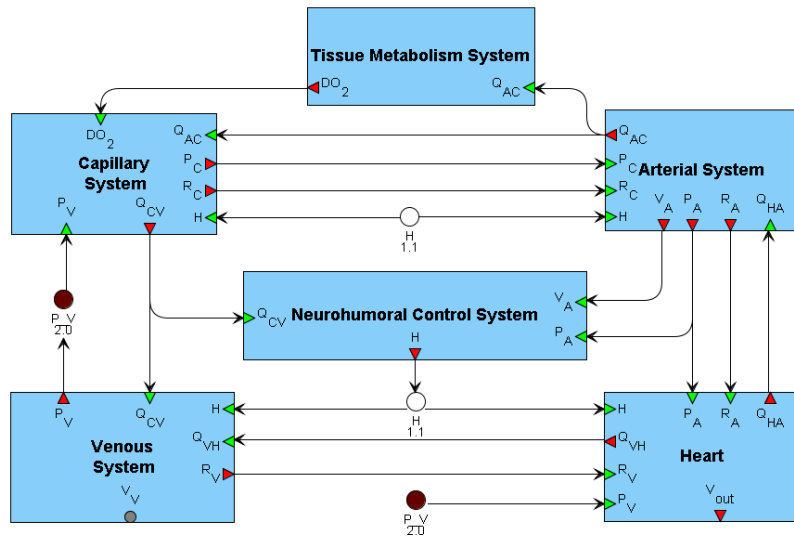
Ann Rev Physiol. 1972. 41:13-41

Генерация плоской модели

Все модули имеют единый формализм:
ОДУ с мгновенными событиями

Модульная модель

“Плоская” модель



Systemic Veins

$$\text{Venous Conductivity} = \text{Venous Conductivity}_{p0} + A_6 \cdot \text{Venous Pressure} + A_7 \cdot \text{Oxygen Need}$$

$$\text{Venous Conductivity}_{p0} = A_{10} - A_{10} \cdot \frac{P}{P_0}$$

$$\text{Venous Pressure} = \text{Venous Elasticity} \cdot (\text{Venous Volume} - \text{Venous Volume}_N)$$

$$\text{Venous Basticity} = \text{Venous Basticity}_{p0} + \text{Venous Tone} \cdot \text{Humoral}$$

$$\text{Venous Volume} = \text{Full Volume} - \text{Chamber Volume} - \text{Arterial Volume}$$

Systemic Arteries

$$\text{Arterial Pressure} = \text{Arterial Elasticity} \cdot (\text{Arterial Volume} - \text{Arterial Volume}_N)$$

$$\text{Arterial Elasticity} = \text{Arterial Elasticity}_{p0} + \text{Arterial Humoral}$$

$$d(\text{Arterial Volume}) = \text{BloodFlow}_{\text{ChamberToArteria}} - \text{Capillary BloodFlow}$$

$$\text{Arterial Volume}_N = \text{Arterial Volume}_N + \text{Arterial Tone} \cdot \text{Humoral}$$

Tissue Metabolism

$$\text{Oxygen Delivery} = \text{Capillary BloodFlow} \cdot (\text{Arterial Oxygen} - \text{Venous Oxygen})$$

$$d(\text{time Oxygen}) = \text{Venous Oxygen} \cdot \text{Sensitivity} \cdot (\text{Oxygen Delivery} - \text{Oxygen Need})$$

$$d(\text{Oxygen Debt}) = -\text{Oxygen UtilizationSpeed} \cdot (\text{Oxygen Delivery} - \text{Oxygen Need})$$

Sistole -> Diastole

where: $\text{Chamber Volume} = \text{Chamber Volume}_{\text{Diastole}} \cdot (1 - k_1) + k_1$ && $\text{SistoleStage} = 1$

$$\text{SistoleStage} = 0$$

$$\text{SistoleDuration} = \text{CurrentStageDuration}$$

$$\text{CurrentStageDuration} = 0$$

$$\text{Cardiac Output} = \frac{(\text{Chamber Volume}_{\text{Diastole}} - \text{Chamber Volume}_{\text{Diastole}}) \cdot \text{Humoral} \cdot \text{Diastole}}{1000}$$

Left Ventricle

$$\text{BloodFlow}_{\text{ChamberToArteria}} = \text{SistoleStage} \cdot \text{Arterial Conductivity} \cdot (\text{Chamber SistolePressure} - \text{Arterial Pressure})$$

$$\text{BloodFlow}_{\text{VeinsToChamber}} = (1 - \text{SistoleStage}) \cdot \text{Venous Conductivity} \cdot (\text{Venous Pressure} - \text{Chamber DiastolePressure})$$

$$\text{Chamber DiastolePressure} = A_{20} \cdot (\text{Chamber Volume} - \text{Chamber Volume}_N) + (A_{24} \cdot (\text{Chamber Volume} - \text{Chamber Volume}_N)) \cdot \text{Myocardial Elasticity}$$

$$d(\text{Chamber Volume}) = \text{BloodFlow}_{\text{VeinsToChamber}} - \text{BloodFlow}_{\text{ChamberToArteria}}$$

Neuro-humoral control

$$d(\text{Humoral}) = \text{HeartCenter Reactivity} \cdot \left(\frac{\text{HeartCenter BR} \cdot \text{Capillary BloodFlow}}{\text{Arterial Volume}} - \text{HeartCenter Stress} \cdot (\text{Arterial Pressure} - P_0) - \text{Humoral} \right)$$

Capillary

$$\text{Capillary Conductivity} = \text{Capillary Conductivity}_{p0} + \text{Capillary Debt} \cdot \text{Oxygen Debt} + \text{Capillary Humoral} \cdot \text{Humoral}$$

$$\text{Capillary BloodFlow} = \text{Capillary Conductivity} \cdot (\text{Arterial Pressure} - \text{Venous Pressure})$$

$$d(\text{CurrentStageDuration}) = 1 - \text{Local time}$$

Diastole -> Sistole

when: $\text{CurrentStageDuration} + \text{SistoleDuration} - \frac{1.0}{\text{Humoral Diastole}} > 0$ && $\text{SistoleStage} = 0$

$$\text{SistoleStage} = 1$$

$$\text{Chamber SistolePressure} = \text{Chamber SistolePressure} + S_1 \cdot (\text{SistoleDuration} - \frac{S_2}{\text{Humoral Diastole}} - S_3 \cdot (1 - k_1))$$

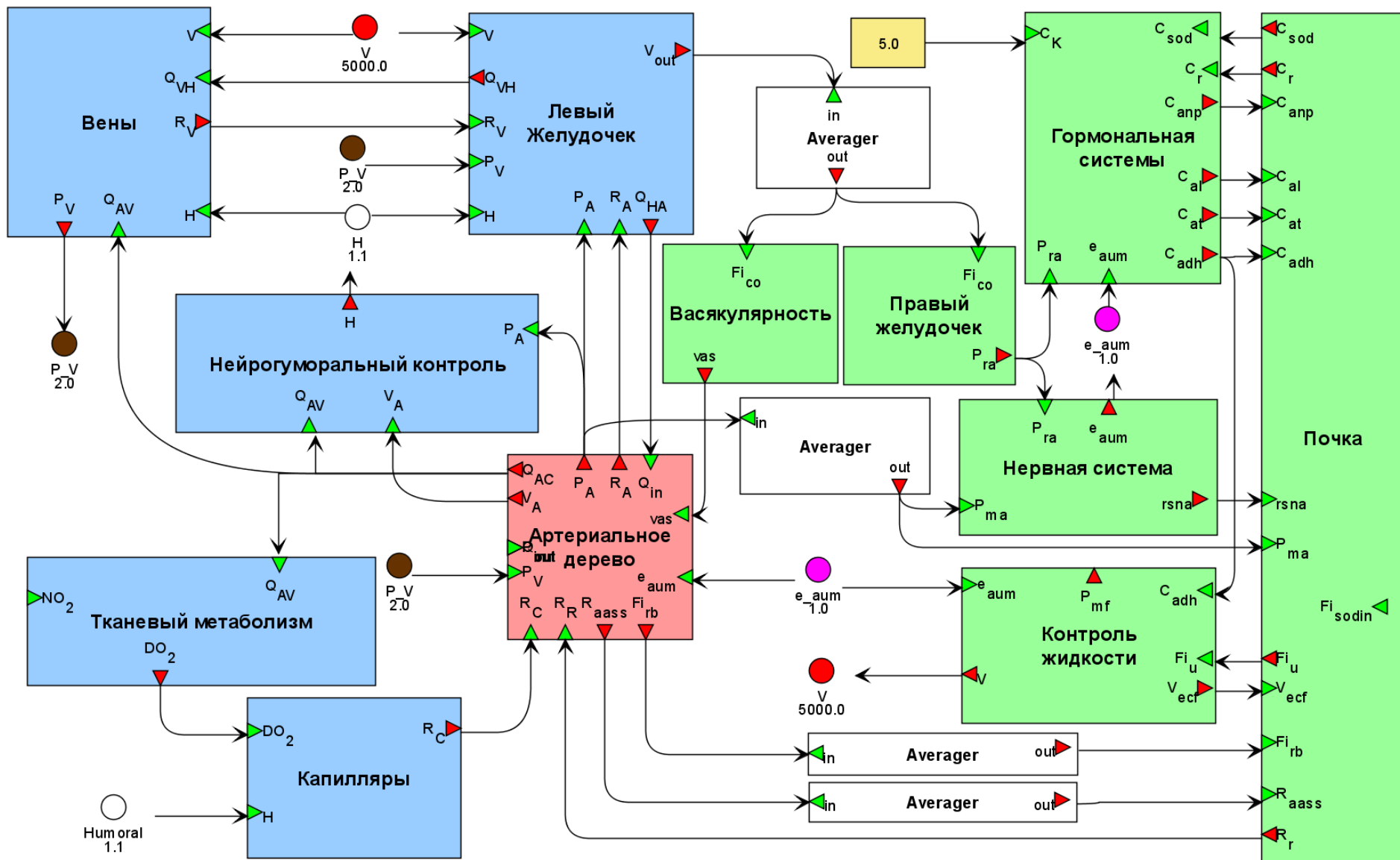
$$\text{Humoral Diastole} = \text{Humoral}$$

$$\text{Chamber Volume}_{\text{Diastole}} = \text{Chamber Volume}_{\text{Diastole}}$$

$$\text{SistoleDuration} = 0$$

$$\text{CurrentStageDuration} = 0$$

Комплексная модель кровообращения



Агентное моделирование

Агент

Входной сигнал



Выходной сигнал



Агентное моделирование

Агент

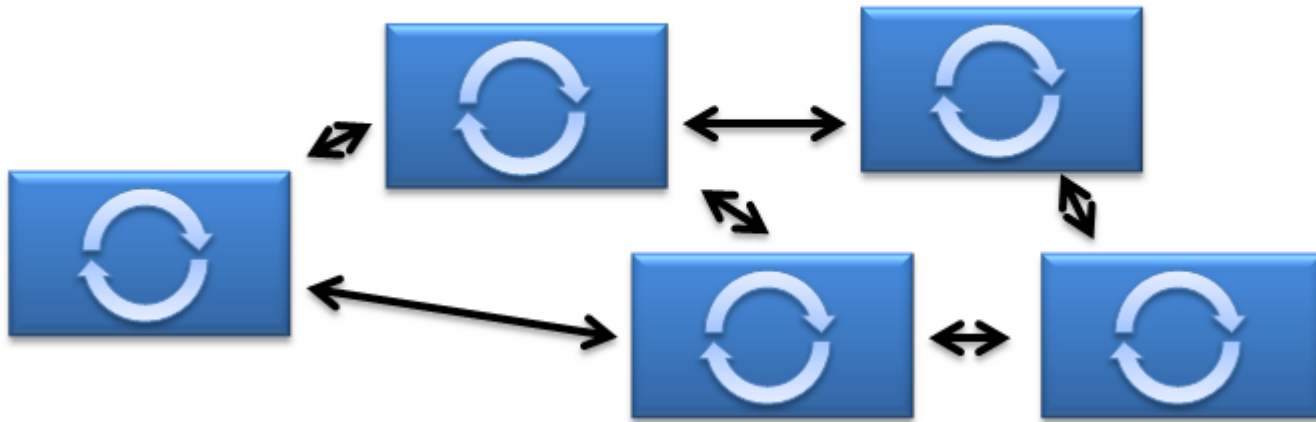
Входной сигнал



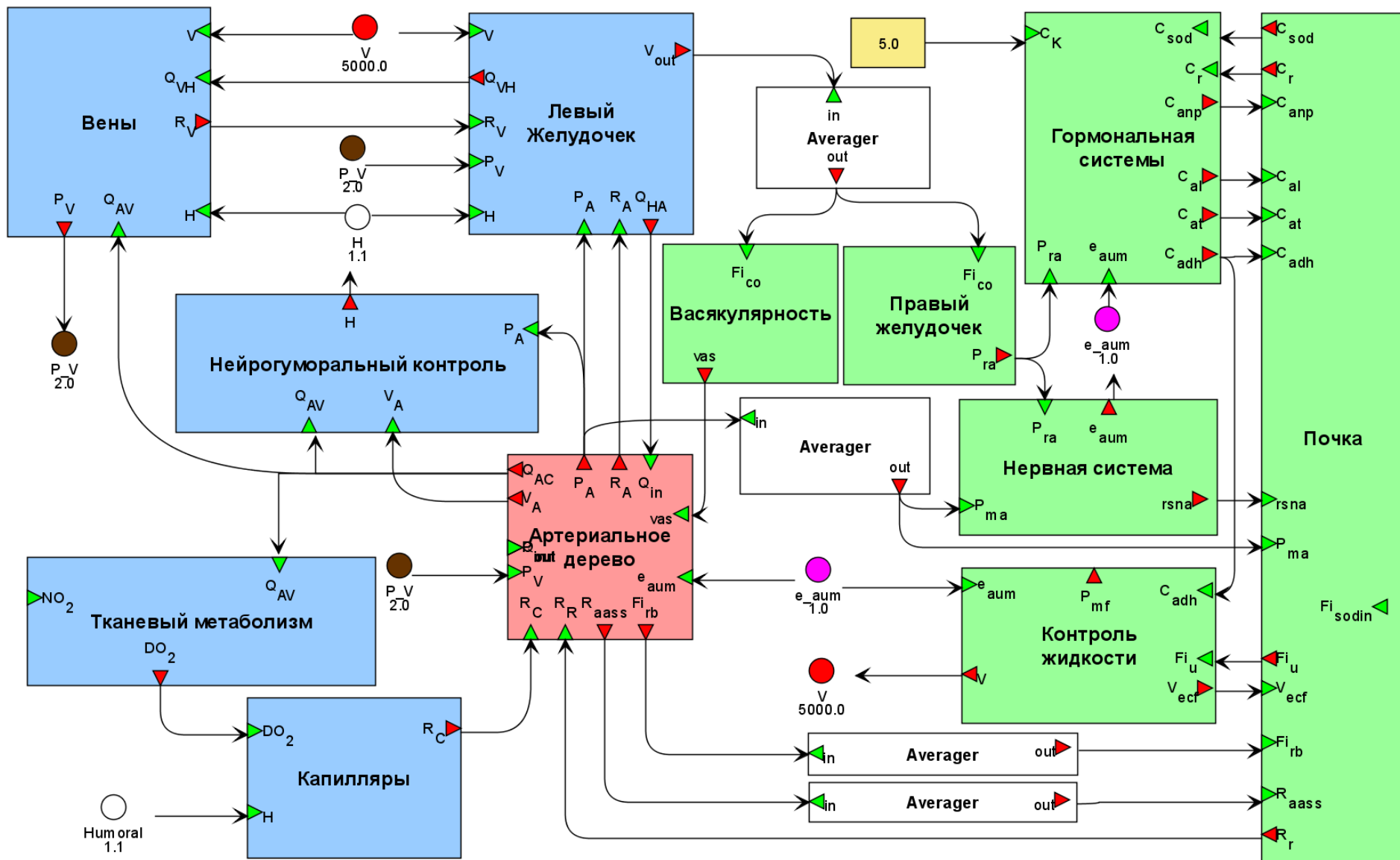
Выходной сигнал



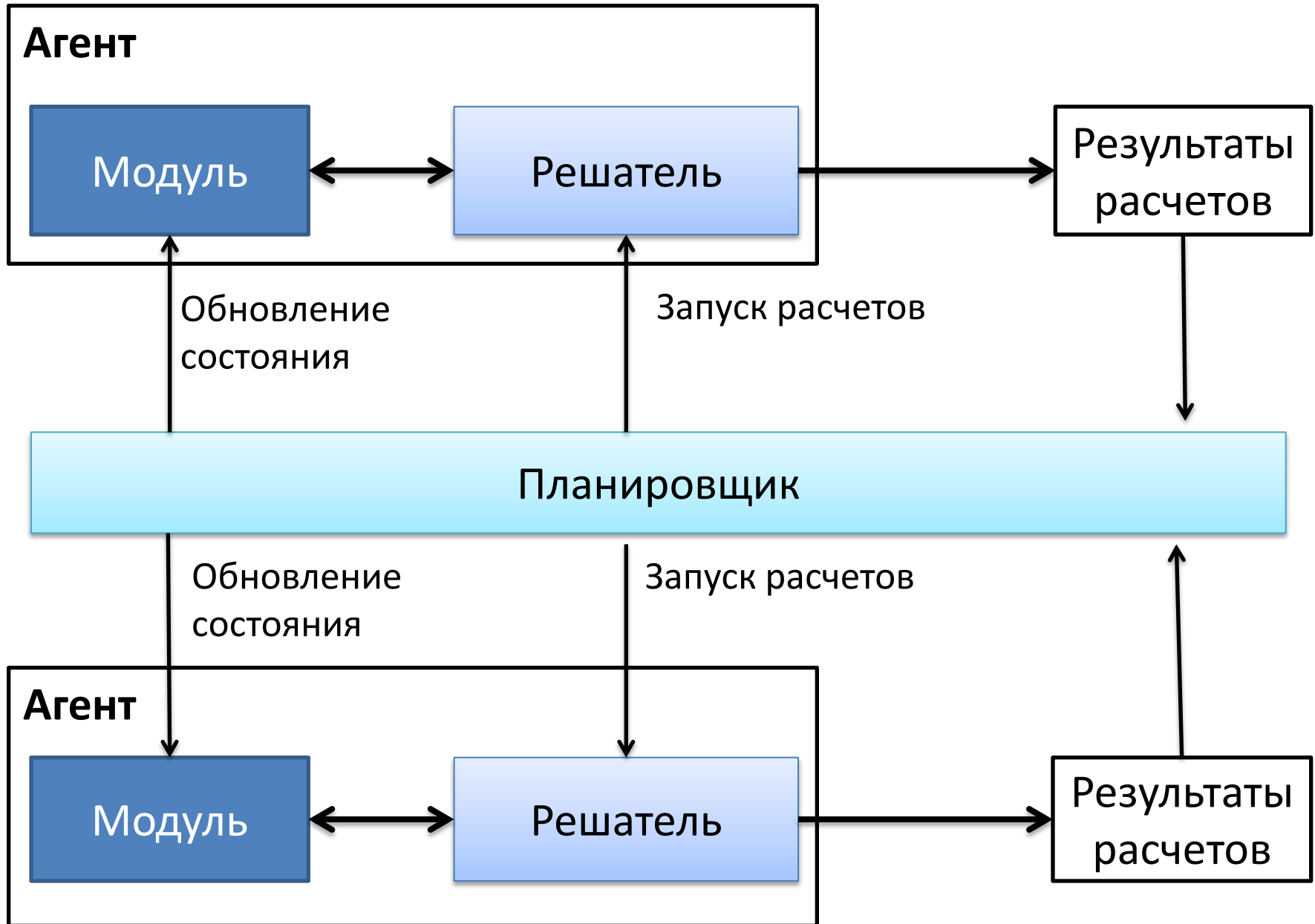
Внешняя Среда



Комплексная модель кровообращения

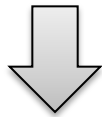
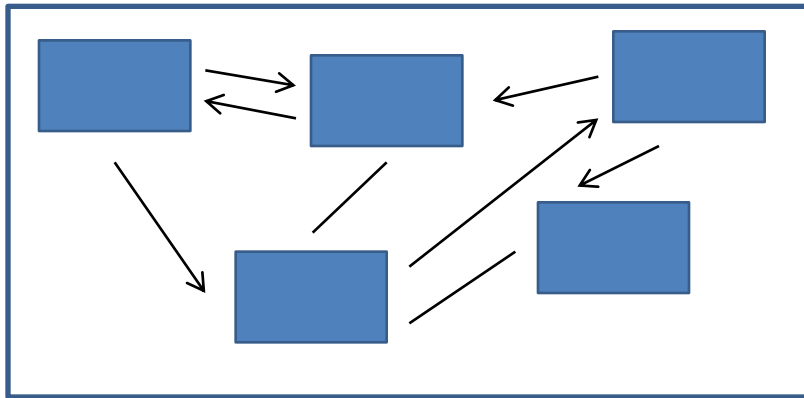


Агентное моделирование



Сравнение подходов

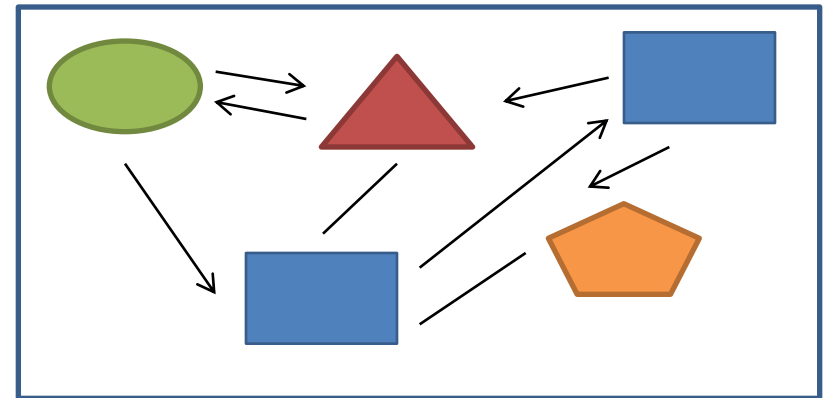
Одинаковые формализмы



Генерация плоской модели

- ✦ Строгое математическое обоснование
- ✖ Ограничение на тип модулей

Различные формализмы



Агентная симуляция

- ✦ Нет ограничения на формализм модуля (ОДУ, УЧП, стохастика, и т.д.)
- ✖ Недостаток математического обоснования

Спасибо за внимание

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