Комплексный подход для формального описания, графического представления и моделирования широкого круга биологических и других сложных систем

Biosoft.Ru

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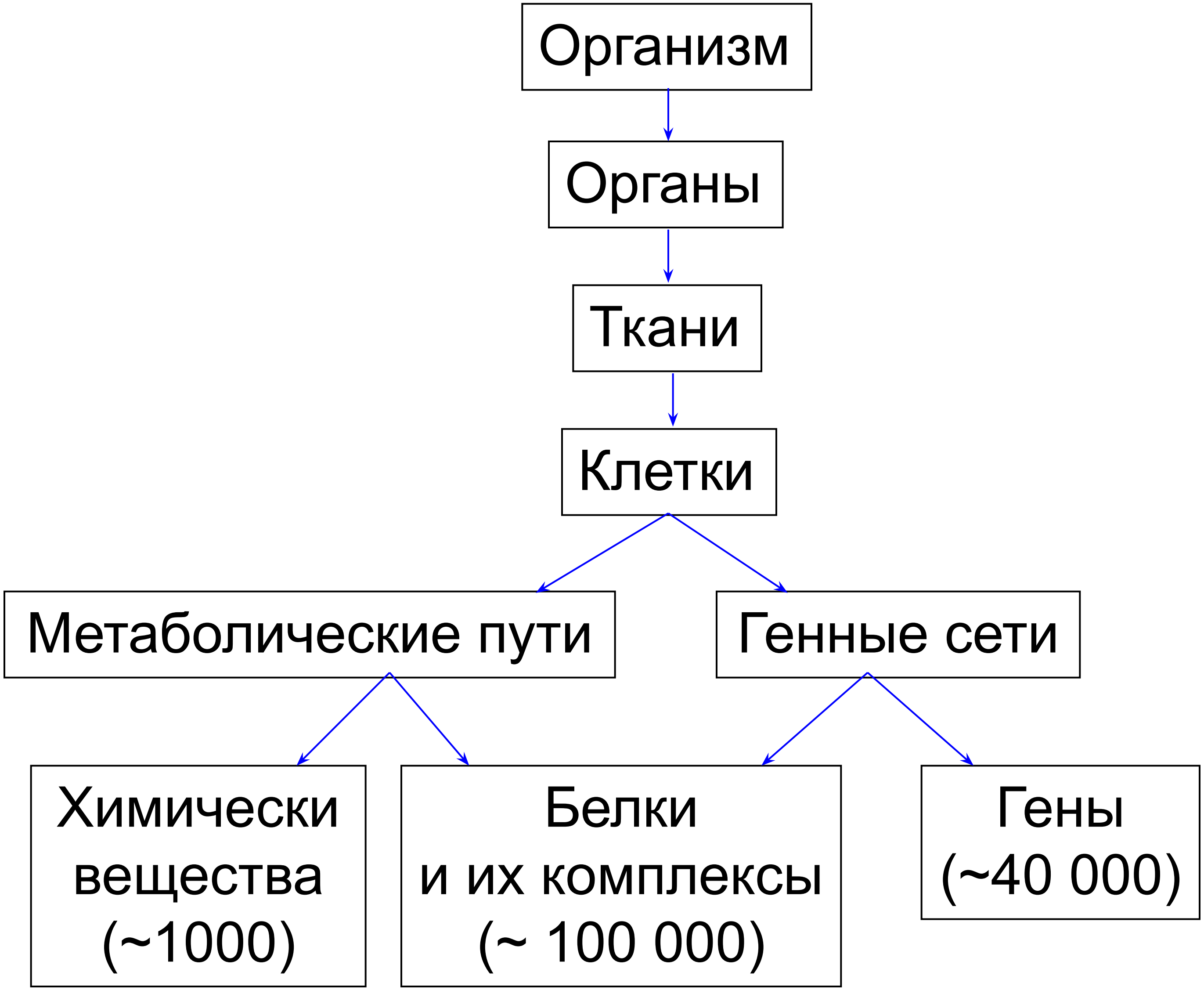
Лабораработория Биоинформатики КТИ ВТ СО РАН

http://www.biouml.org



Организм

Органы

Ткани

Клетки

Метаболические пути

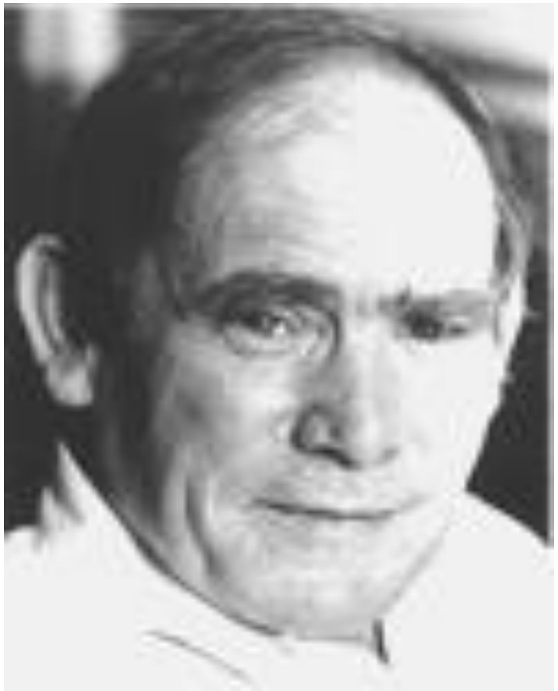
Генные сети

Химически
вещества
(~1000)

Белки
и их комплексы
(~ 100 000)

Гены
(~40 000)

Базы данных
(более 500 баз данных, общий объем сотни гигабайт)



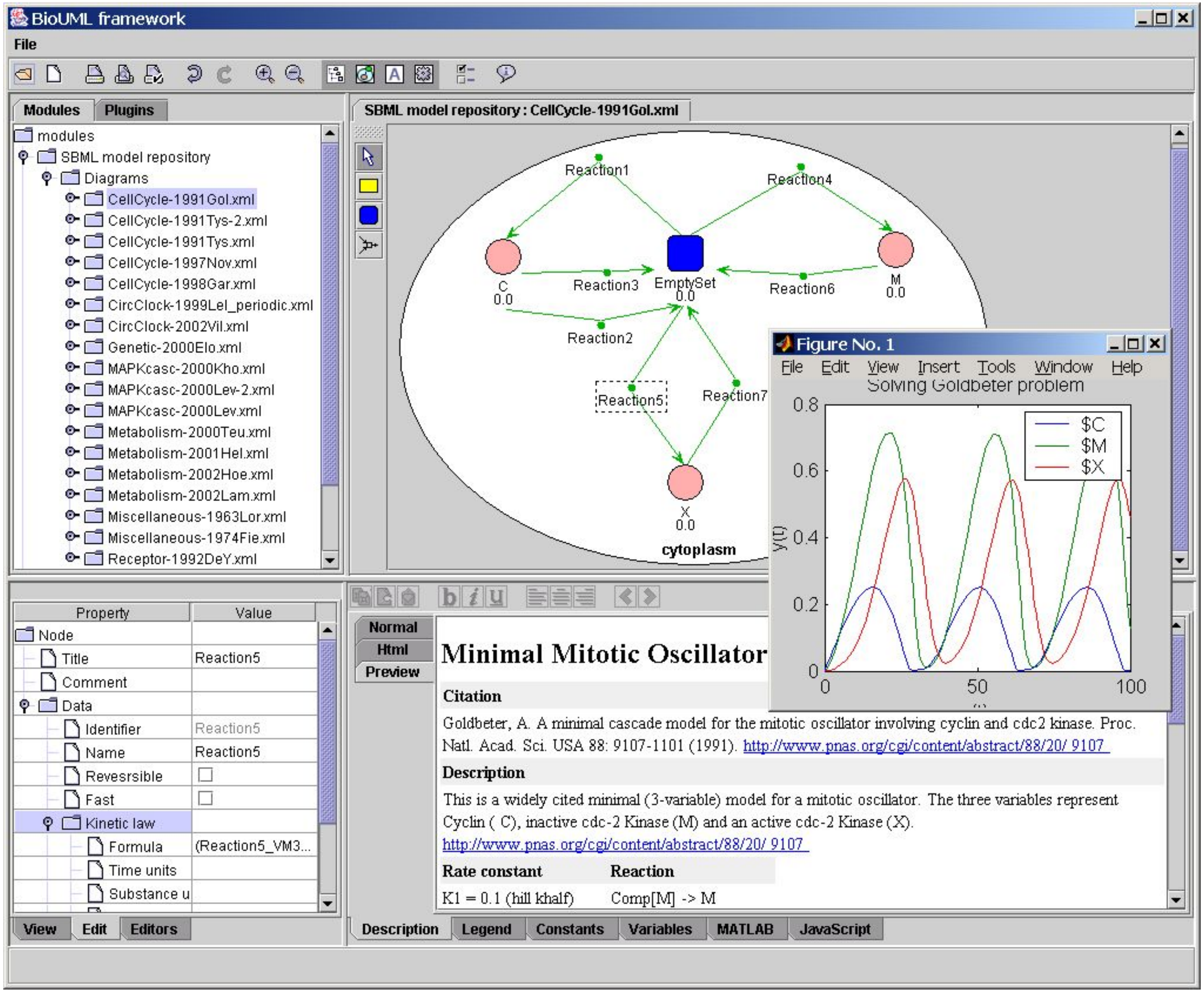
Сидней Бреннер, лауреат Нобелевской премии 2002 года в области медицины

Сейчас у нас есть беспрецендентная возможность собирать и накапливать данные о природе, тем не менее в современной биологии развивается кризис, который состоит в том что полностью неструктрированные данные не улучшают нашего понимания. Нам нужна система (framework) в которую мы могли бы поместить все эти знания и данные – это то и становится проблемой в биологии.

Мы достигли уровня когда мы больше не можем разговаривать друг с другом – мы стали слишком специализированы. Нам нужна система, используя которую люди могли бы сказать: "Да, я понял.". Создание такой системы является действительно большим вызовом.

Sydney Brenner, 2003

BioUML - Biological Unified Modeling Language



Property	Value
Node	
Title	Reaction5
Comment	
Data	
Identifier	Reaction5
Name	Reaction5
Revesrsible	☐
Fast	☐
Kinetic law	
Formula	(Reaction5_VM3...
Time units	
Substance u	

Minimal Mitotic Oscillator

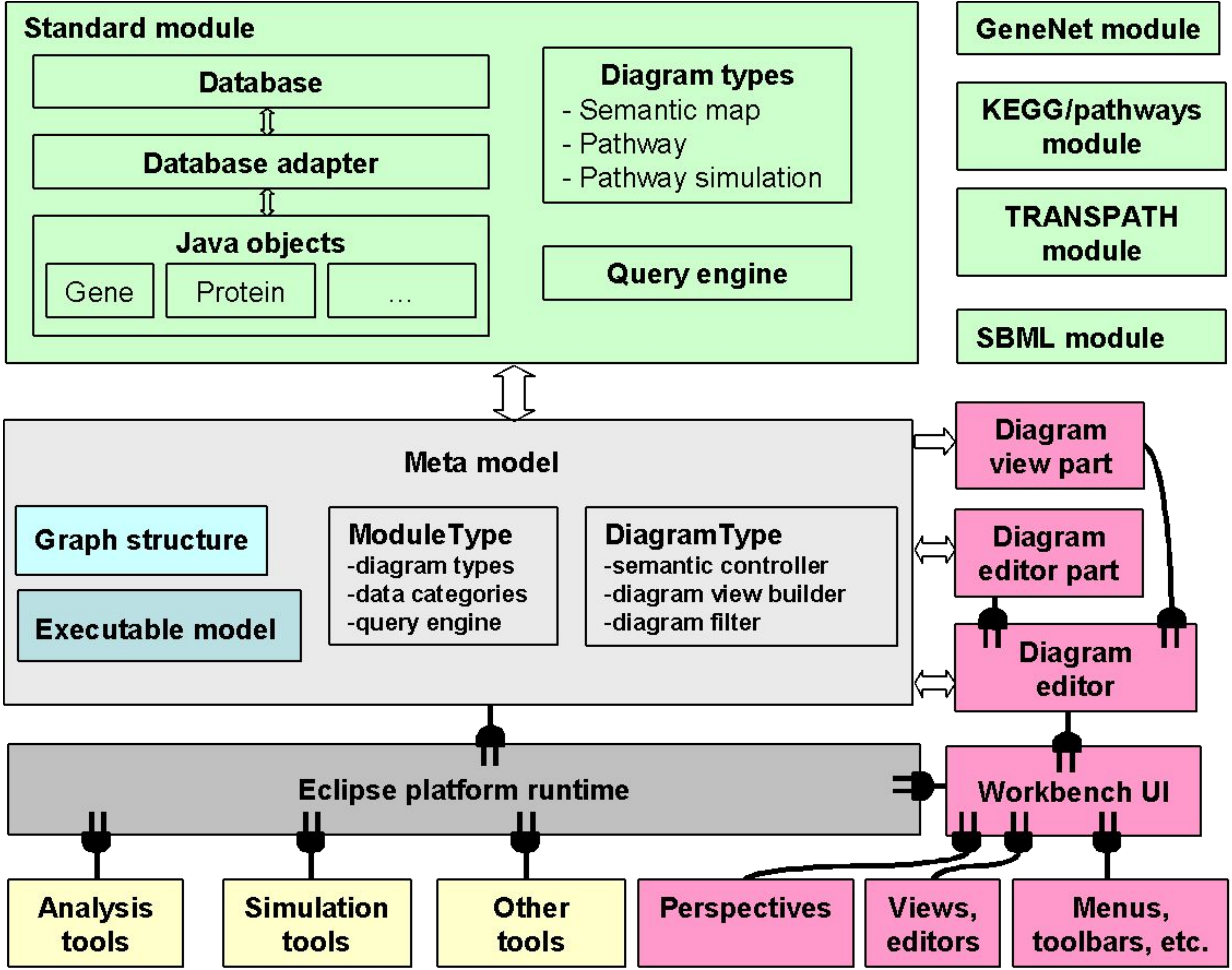
Citation

Goldbeter, A. A minimal cascade model for the mitotic oscillator involving cyclin and cdc2 kinase. Proc. Natl. Acad. Sci. USA 88: 9107-1101 (1991). http://www.pnas.org/cgi/content/abstract/88/20/ 9107

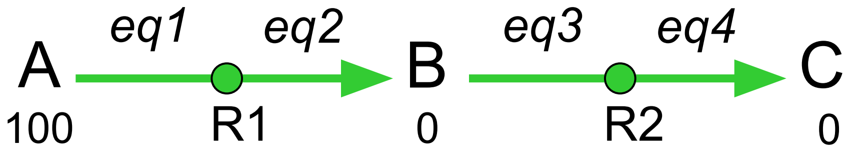
Description

This is a widely cited minimal (3-variable) model for a mitotic oscillator. The three variables represent Cyclin (C), inactive cdc-2 Kinase (M) and an active cdc-2 Kinase (X). http://www.pnas.org/cgi/content/abstract/88/20/ 9107

Rate constant	Reaction
K1 = 0.1 (hill khalf)	Comp[M] -> M


Standard module
Database
Database adapter
Java objects
Gene
Protein
...
Diagram types
- Semantic map
- Pathway
- Pathway simulation
Query engine
GeneNet module
KEGG/pathways module
TRANSPATH module
SBML module
Meta model
Graph structure
Executable model
ModuleType
-diagram types
-data categories
-query engine
DiagramType
-semantic controller
-diagram view builder
-diagram filter
Diagram view part
Diagram editor part
Diagram editor
Eclipse platform runtime
Workbench UI
Analysis tools
Simulation tools
Other tools
Perspectives
Views, editors
Menus, toolbars, etc.

Пример двух последовательных химических реакций



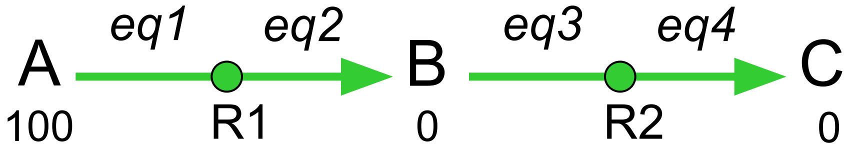
Соответствующая ему математическая модель

$$\frac{dA}{dt} = eq1$$

$$\frac{dB}{dt} = eq2 + eq3$$

$$\frac{dC}{dt} = eq4$$

BioUML мета-модель позволяет описать сложную систему на 3 уровнях



```
ID   A
CC  ..
...
//
```

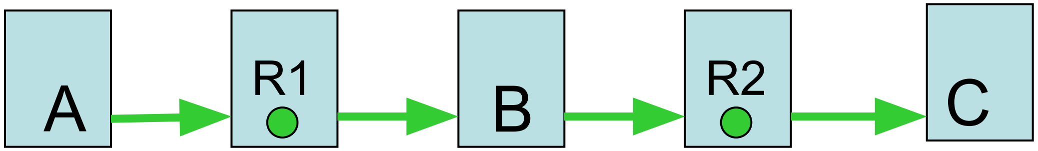
```
ID   R1
   A->B
...
//
```

```
ID   B
CC  ..
...
//
```

```
ID   R2
   B->C
...
//
```

```
ID   C
CC  ..
...
//
```

Описание компонентов системы в базе данных

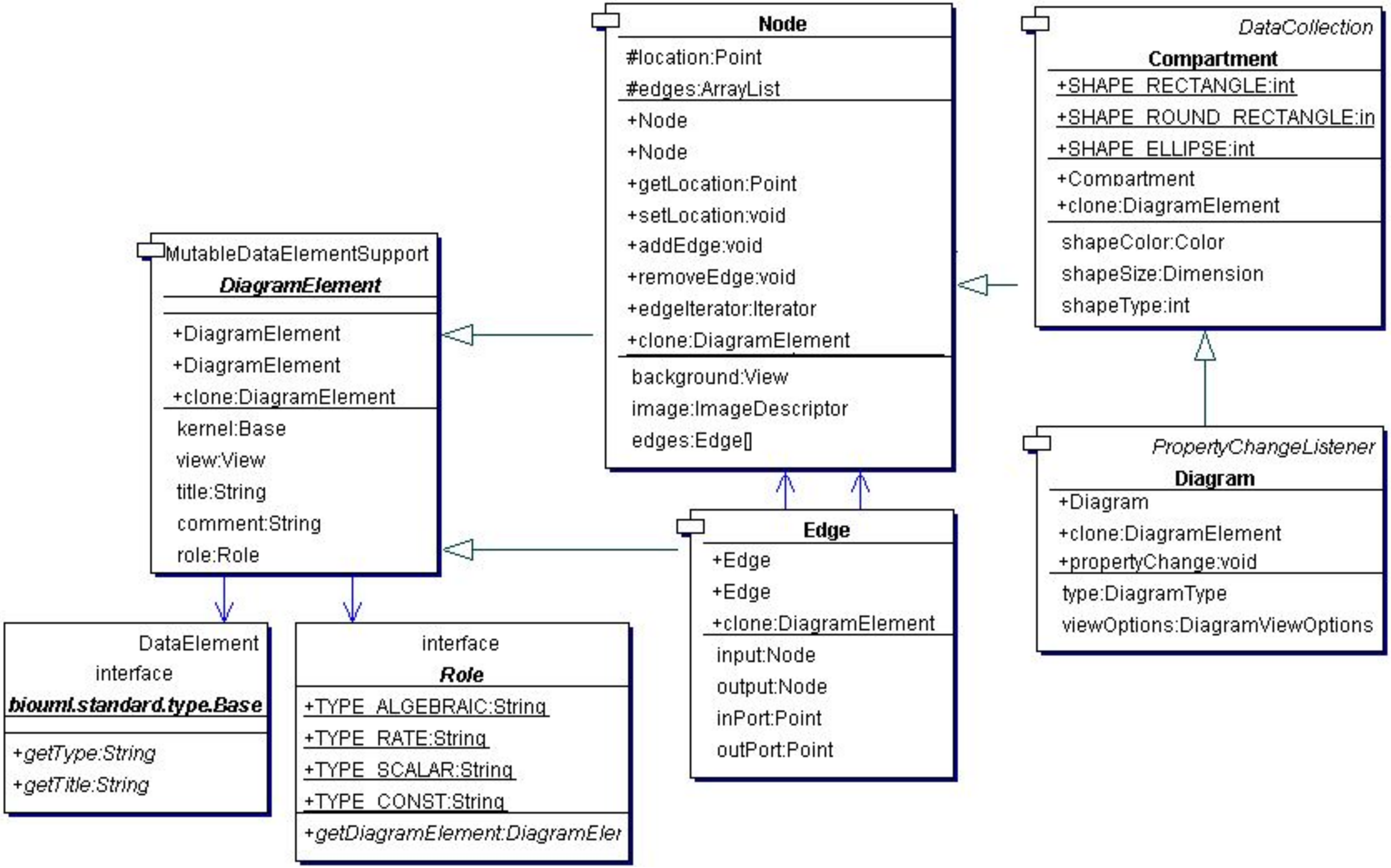


Описание структуры системы в виде графа

100 *eq1* *eq2* 0 *eq3* *eq4* 0

Математическая модель системы

Основные классы BioUML мета-модели для описания структуры графа



MutableDataElementSupport
DiagramElement
+DiagramElement
+DiagramElement
+clone:DiagramElement
kernel:Base
view:View
title:String
comment:String
role:Role

Node
#location:Point
#edges:ArrayList
+Node
+Node
+getLocation:Point
+setLocation:void
+addEdge:void
+removeEdge:void
+edgeIterator:Iterator
+clone:DiagramElement
background:View
image:ImageDescriptor
edges:Edge[]

DataCollection
Compartment
+SHAPE_RECTANGLE:int
+SHAPE_ROUND_RECTANGLE:in
+SHAPE_ELLIPSE:int
+Compartment
+clone:DiagramElement
shapeColor:Color
shapeSize:Dimension
shapeType:int

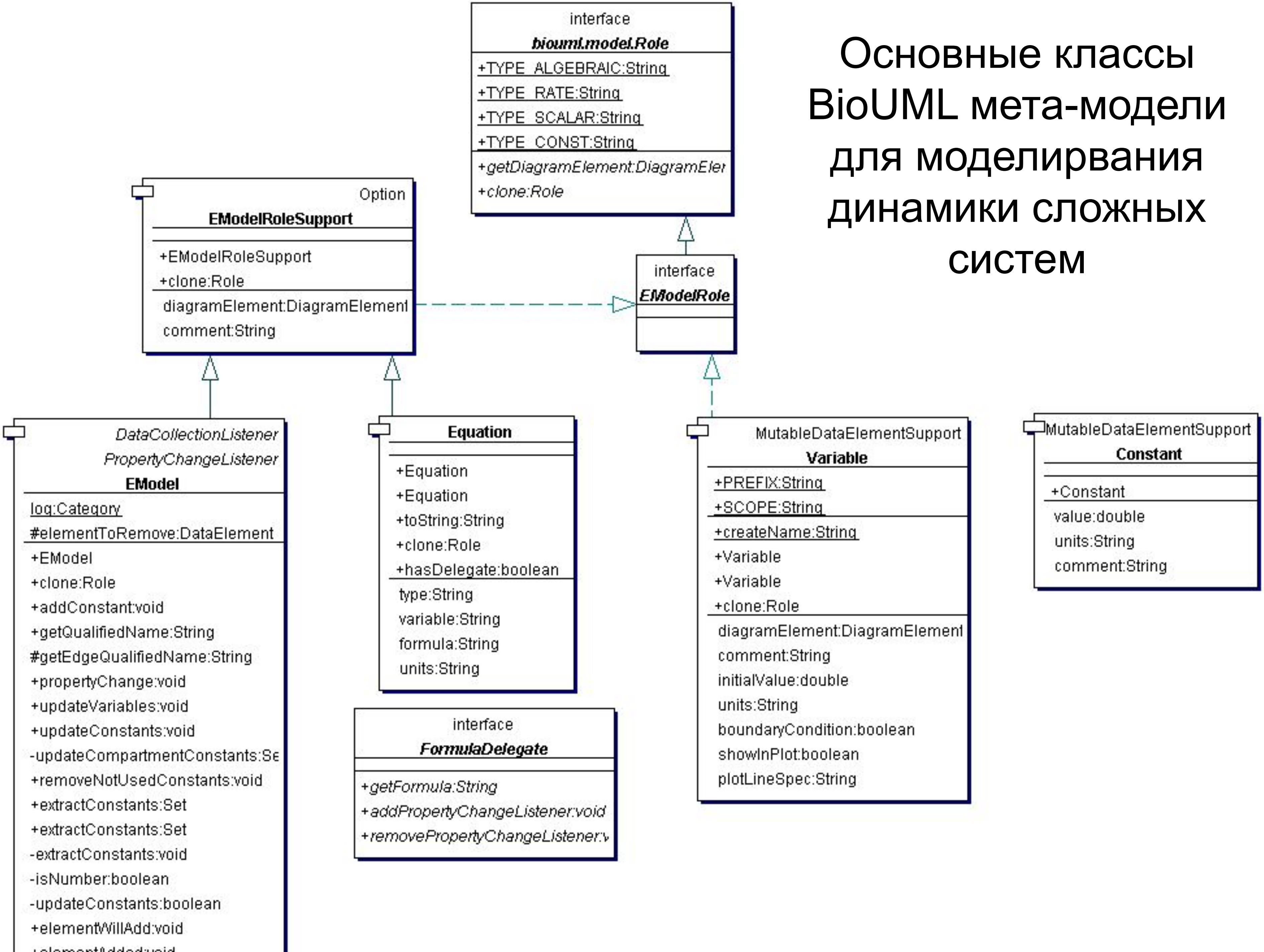
PropertyChangeListener
Diagram
+Diagram
+clone:DiagramElement
+propertyChange:void
type:DiagramType
viewOptions:DiagramViewOptions

Edge
+Edge
+Edge
+clone:DiagramElement
input:Node
output:Node
inPort:Point
outPort:Point

DataElement
interface
biouml.standard.type.Base
+getType:String
+getTitle:String

interface
Role
+TYPE_ALGEBRAIC:String
+TYPE_RATE:String
+TYPE_SCALAR:String
+TYPE_CONST:String
+getDiagramElement:DiagramEler

Основные классы BioUML мета-модели для моделирвания динамики сложных систем



interface
biouml.model.Role
+TYPE_ALGEBRAIC:String
+TYPE_RATE:String
+TYPE_SCALAR:String
+TYPE_CONST:String
+getDiagramElement:DiagramEler
+clone:Role

Option
EModelRoleSupport
+EModelRoleSupport
+clone:Role
diagramElement:DiagramElement
comment:String

interface
EModelRole

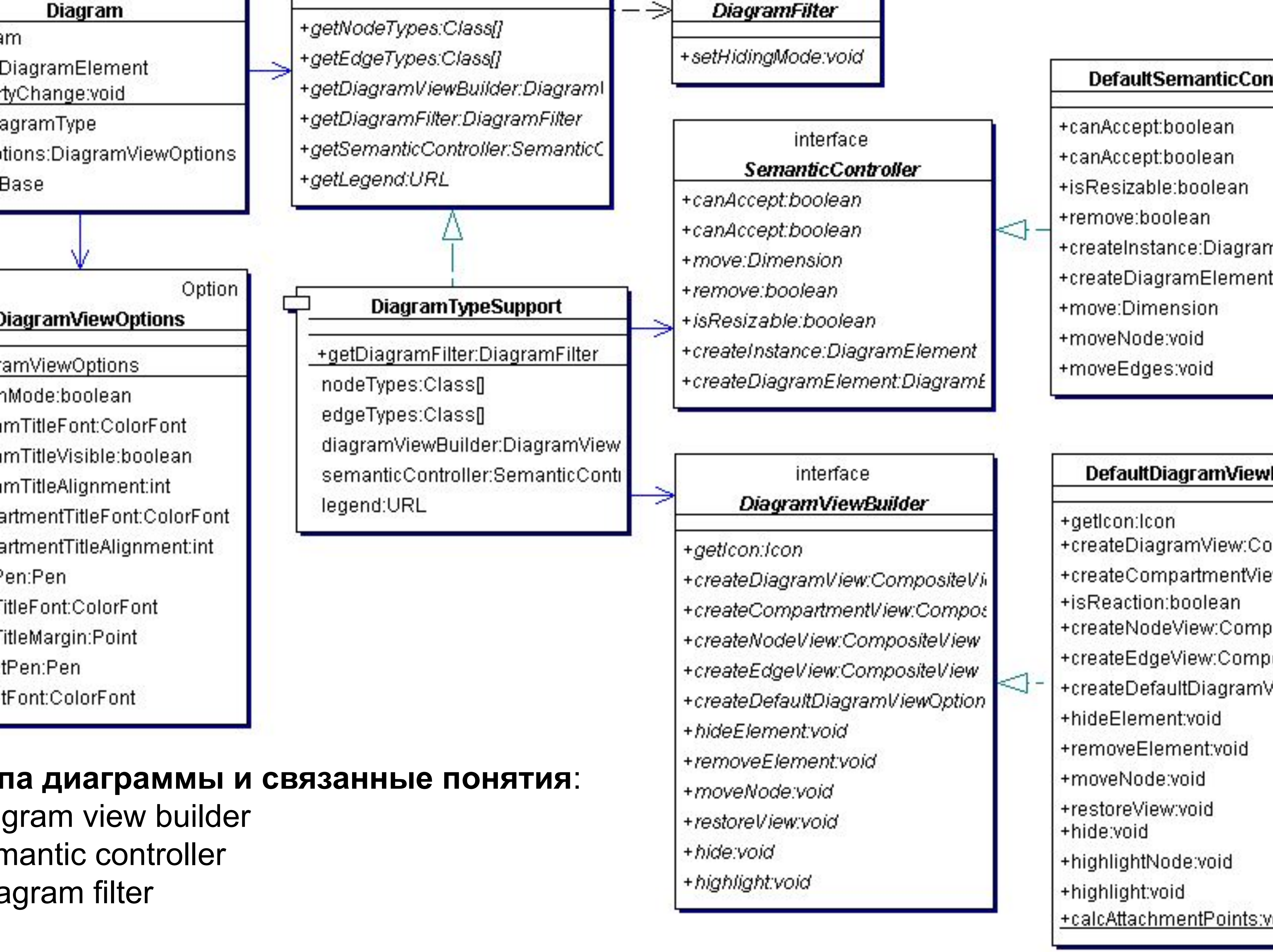
DataCollectionListener
PropertyChangeListener
EModel
log:Category
#elementToRemove:DataElement
+EModel
+clone:Role
+addConstant:void
+getQualifiedName:String
#getEdgeQualifiedName:String
+propertyChange:void
+updateVariables:void
+updateConstants:void
-updateCompartmentConstants:Se
+removeNotUsedConstants:void
+extractConstants:Set
+extractConstants:Set
-extractConstants:void
-isNumber:boolean
-updateConstants:boolean
+elementWillAdd:void
+elementAdded:void

Equation
+Equation
+Equation
+toString:String
+clone:Role
+hasDelegate:boolean
type:String
variable:String
formula:String
units:String

interface
FormulaDelegate
+getFormula:String
+addPropertyChangeListener:void
+removePropertyChangeListener:v

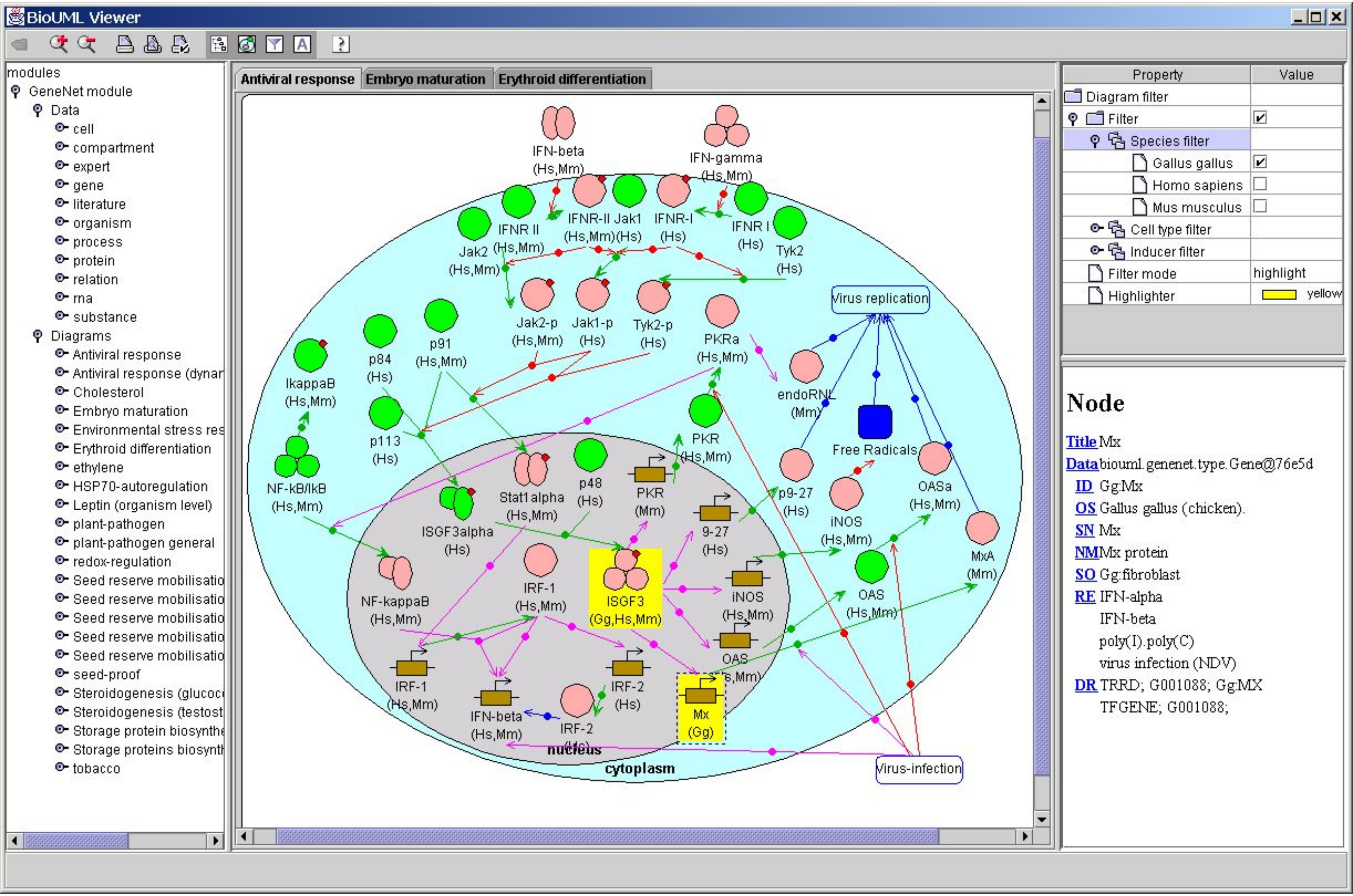
MutableDataElementSupport
Variable
+PREFIX:String
+SCOPE:String
+createName:String
+Variable
+Variable
+clone:Role
diagramElement:DiagramElement
comment:String
initialValue:double
units:String
boundaryCondition:boolean
showInPlot:boolean
plotLineSpec:String

MutableDataElementSupport
Constant
+Constant
value:double
units:String
comment:String



па диаграммы и связанные понятия:

- gram view builder
- mantic controller
- agram filter



Property	Value
Diagram filter	
Filter	☑
Species filter	
Gallus gallus	☑
Homo sapiens	☐
Mus musculus	☐
Cell type filter	
Inducer filter	
Filter mode	highlight
Highlighter	yellow

Node

Title Mx
Data biouml.genenet.type.Gene@76e5d
ID Gg:Mx
OS Gallus gallus (chicken).
SN Mx
NM Mx protein
SO Gg:fibroblast
RE IFN-alpha
IFN-beta
poly(I).poly(C)
virus infection (NDV)
DR TRRD; G001088; Gg:MX
TFGENE; G001088;

```
<!-- BioUML diagrams markup language (DML) v. 0.9.2 -->

<!ELEMENT dml (diagramInfo?, diagram, executableModel?)>
<!ATTLIST dml
   version CDATA "0.9.2"
   appVersion CDATA "0.7.0" >

<!ELEMENT diagramInfo>
<!ATTLIST diagramInfo value CDATA >

<!ELEMENT diagram (compartmentInfo, nodes, edges)>
<!- "diagramType" attribute contains name of Java class ->
<!ATTLIST diagram
    diagramType CDATA #REQUIRED
>

<!ELEMENT nodes (compartment|equivalentNodeGroup|node)*>

<!ELEMENT edges (edge)*>
```

```
<!ELEMENT compartment (compartmentInfo, nodes, edges)>
<!ATTLIST compartment>

<!ELEMENT compartmentInfo (image?)>
<!-
   "kernel" attribute contains complete path for data
      element used as kernel; currently path is relative
      module/Data
  "shape" attribute possible values are:
      0-rectangle; 1-round_rectangle; 2-oval
-->
<!ATTLIST compartmentInfo
   kernel   CDATA  #REQUIRED
   x        CDATA  #REQUIRED
   y        CDATA  #REQUIRED
   width    CDATA  #REQUIRED
   height   CDATA  #REQUIRED
   title    CDATA
   comment  CDATA
   shape    CDATA  "0"
   color    CDATA  "255, 255, 255"
>
```

```
<!ELEMENT node (image?)>
<!ATTLIST node
  kernel   CDATA #REQUIRED
  title    CDATA
  comment  CDATA
  x        CDATA
  y        CDATA
>

<!ELEMENT edge>
<!ATTLIST edge
  kernel   CDATA #REQUIRED
  in       CDATA #REQUIRED
  out      CDATA #REQUIRED
  title    CDATA
  comment  CDATA
  inPort   CDATA
  outPort  CDATA
>
```

```
<!--===================================================== -->
<!-- Executable model                                     -->
<!--===================================================== -->
<!ELEMENT executableModel (constant*, variable*, equation*)>
<!ATTLIST executableModel
   class          CDATA #REQUIRED
   initialTime    CDATA #REQUIRED
   completionTime CDATA #REQUIRED
   comment        CDATA
>

<!ELEMENT constant>
<!ATTLIST constant
   name    CDATA #REQUIRED
   value   CDATA #REQUIRED
   units   CDATA
   comment CDATA
>
```

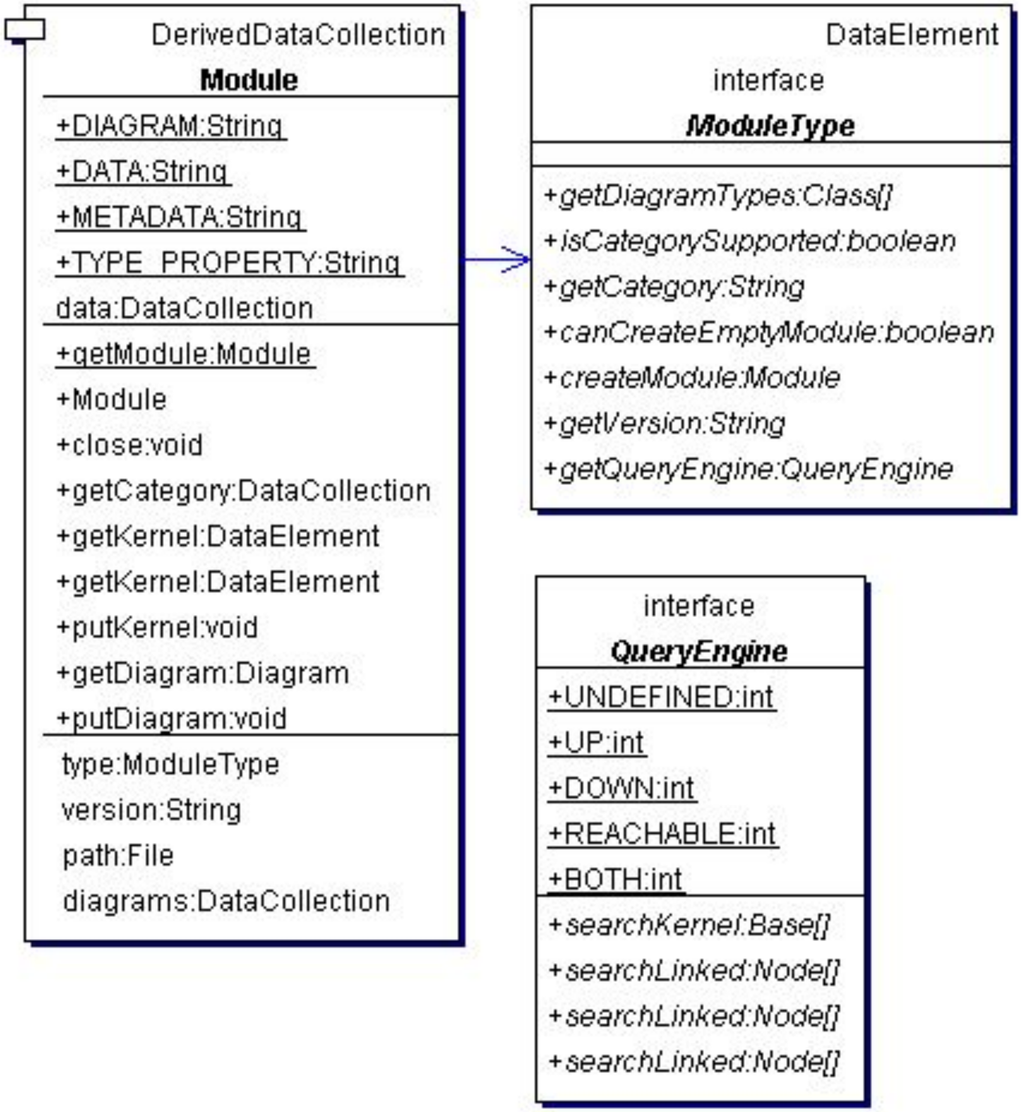
```
<!ELEMENT variable>
<!-- "diagramElement" attribute - diagram element name -->
<!ATTLIST variable
   diagramElement        CDATA  #REQUIRED
   initialValue          CDATA  "0.0"
   boundaryCondition     CDATA  "false"
   showInPlot            CDATA  "true"
   plotLineSpec          CDATA  "-"
   units                 CDATA
   comment               CDATA
>

<!ELEMENT equation>
<!–
 "diagramElement" attribute - diagram element name
 "type" attribute - equation type.
  Possible values are:   algebraic, rate or scalar. -->
<!ATTLIST equation
   diagramElement      CDATA  #REQUIRED
   variable            CDATA  #REQUIRED
   formula             CDATA  #REQUIRED
   type                CDATA  "rate"
   units               CDATA
   comment             CDATA
>
```

Концепция модуля

- Чтобы обеспечить интеграцию различных баз данных в среду BioUML, мы вводим концепцию модуля.

- Как правило, модуль создается для отдельной базы данных и определяет способ представления информации из этой базы данных в виде объектов языка Java. Модуль также может содержать специфичные для этой базы данных типы диаграмм и способы их графического отображения.

Концепция модуля



DerivedDataCollection

Module

+DIAGRAM:String
+DATA:String
+METADATA:String
+TYPE_PROPERTY:String
data:DataCollection

+getModule:Module
+Module
+close:void
+getCategory:DataCollection
+getKernel:DataElement
+getKernel:DataElement
+putKernel:void
+getDiagram:Diagram
+putDiagram:void

type:ModuleType
version:String
path:File
diagrams:DataCollection

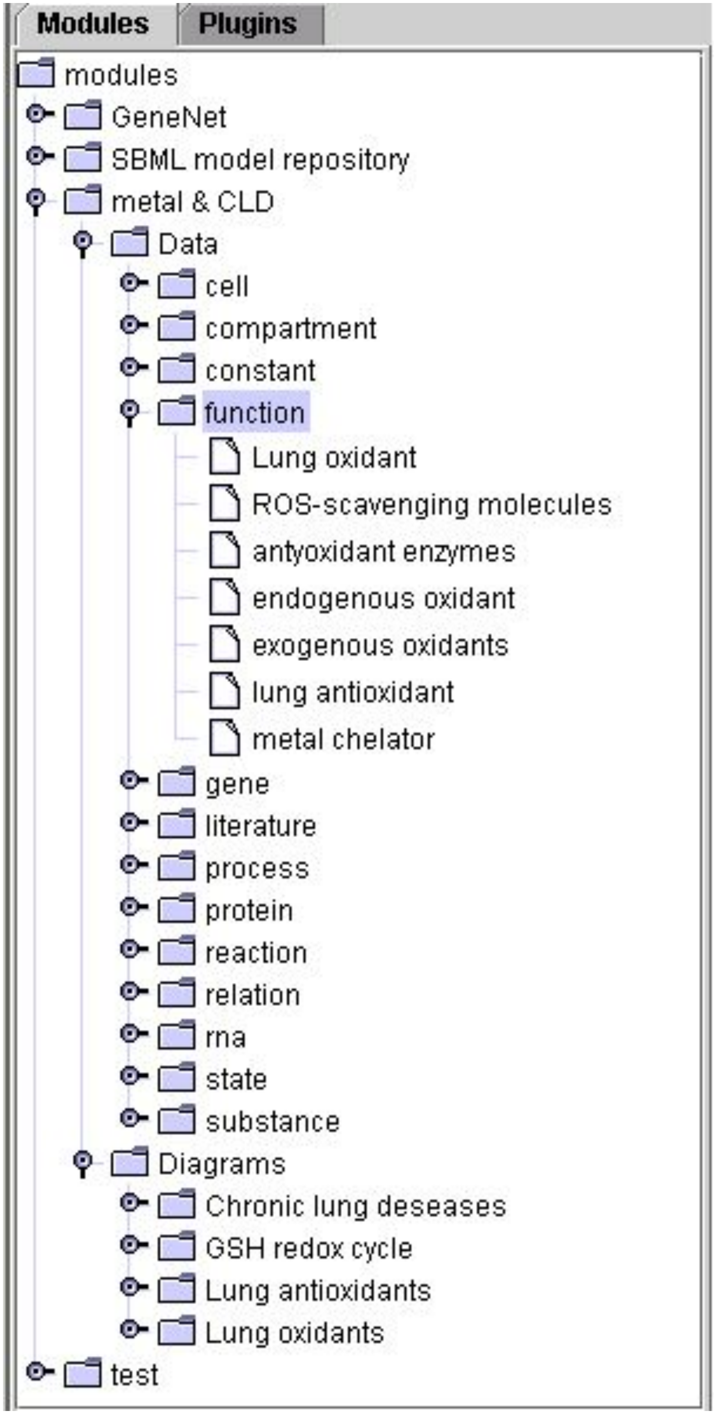
DataElement
interface
ModuleType

+getDiagramTypes:Class[]
+isCategorySupported:boolean
+getCategory:String
+canCreateEmptyModule:boolean
+createModule:Module
+getVersion:String
+getQueryEngine:QueryEngine

interface
QueryEngine

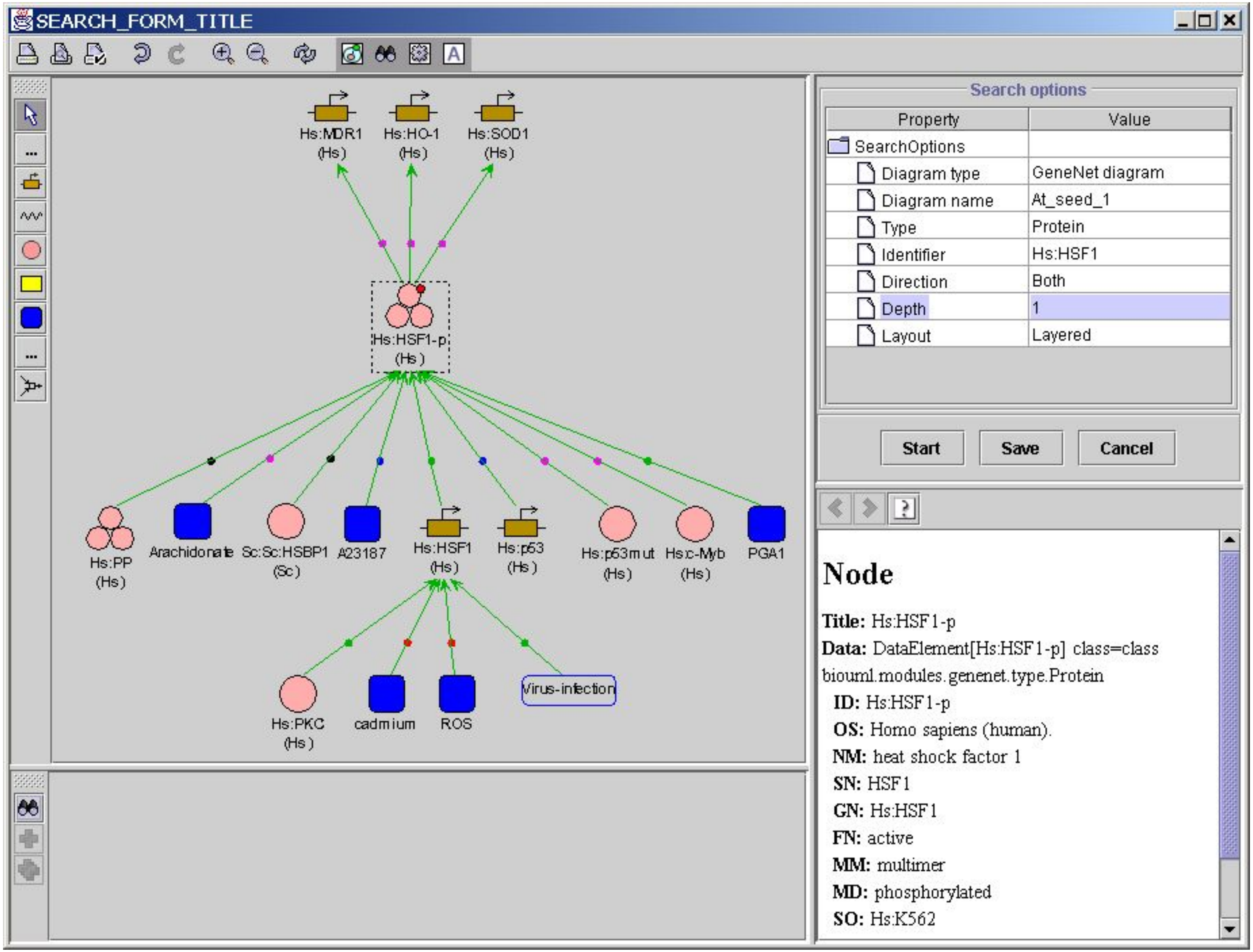
+UNDEFINED:int
+UP:int
+DOWN:int
+REACHABLE:int
+BOTH:int

+searchKernel:Base[]
+searchLinked:Node[]
+searchLinked:Node[]
+searchLinked:Node[]



- modules
  - GeneNet
  - SBML model repository
  - metal & CLD
    - Data
      - cell
      - compartment
      - constant
      - function
        - Lung oxidant
        - ROS-scavenging molecules
        - antyoxidant enzymes
        - endogenous oxidant
        - exogenous oxidants
        - lung antioxidant
        - metal chelator
      - gene
      - literature
      - process
      - protein
      - reaction
      - relation
      - rna
      - state
      - substance
    - Diagrams
      - Chronic lung deseases
      - GSH redox cycle
      - Lung antioxidants
      - Lung oxidants
  - test

Система поиска взаимодействующих друг с другом компонентов биологических систем



Property	Value
SearchOptions	
Diagram type	GeneNet diagram
Diagram name	At_seed_1
Type	Protein
Identifier	Hs:HSF1
Direction	Both
Depth	1
Layout	Layered

Node

Title: Hs:HSF1-p

Data: DataElement[Hs:HSF1-p] class=class biouml.modules.genenet.type.Protein

ID: Hs:HSF1-p

OS: Homo sapiens (human).

NM: heat shock factor 1

SN: HSF1

GN: Hs:HSF1

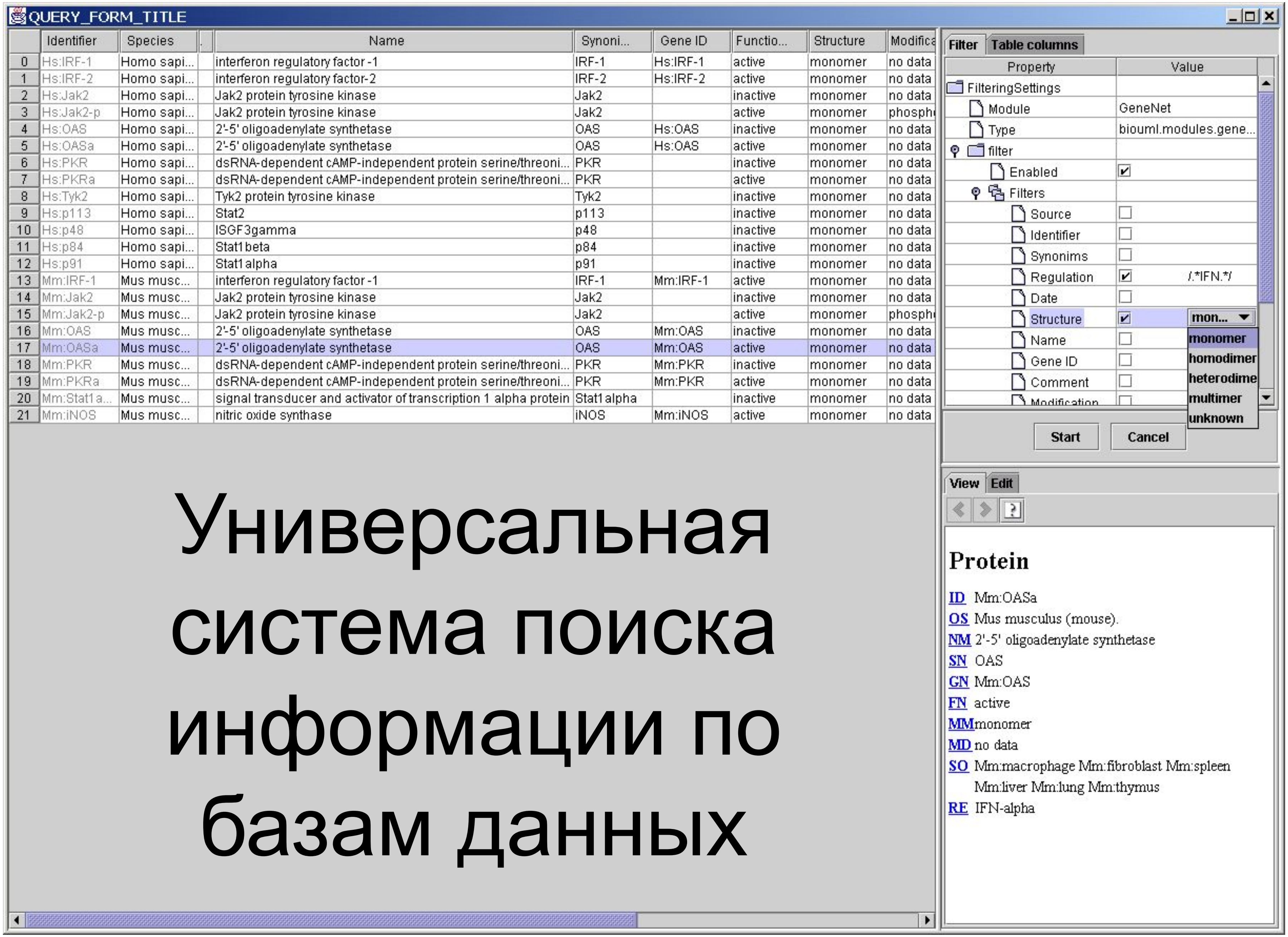
FN: active

MM: multimer

MD: phosphorylated

SO: Hs:K562

Универсальная система поиска информации по базам данных



	Identifier	Species	.	Name	Synoni...	Gene ID	Functio...	Structure	Modifica
0	Hs:IRF-1	Homo sapi...		interferon regulatory factor -1	IRF-1	Hs:IRF-1	active	monomer	no data
1	Hs:IRF-2	Homo sapi...		interferon regulatory factor-2	IRF-2	Hs:IRF-2	active	monomer	no data
2	Hs:Jak2	Homo sapi...		Jak2 protein tyrosine kinase	Jak2		inactive	monomer	no data
3	Hs:Jak2-p	Homo sapi...		Jak2 protein tyrosine kinase	Jak2		active	monomer	phosphi
4	Hs:OAS	Homo sapi...		2'-5' oligoadenylate synthetase	OAS	Hs:OAS	inactive	monomer	no data
5	Hs:OASa	Homo sapi...		2'-5' oligoadenylate synthetase	OAS	Hs:OAS	active	monomer	no data
6	Hs:PKR	Homo sapi...		dsRNA-dependent cAMP-independent protein serine/threoni...	PKR		inactive	monomer	no data
7	Hs:PKRa	Homo sapi...		dsRNA-dependent cAMP-independent protein serine/threoni...	PKR		active	monomer	no data
8	Hs:Tyk2	Homo sapi...		Tyk2 protein tyrosine kinase	Tyk2		inactive	monomer	no data
9	Hs:p113	Homo sapi...		Stat2	p113		inactive	monomer	no data
10	Hs:p48	Homo sapi...		ISGF3gamma	p48		inactive	monomer	no data
11	Hs:p84	Homo sapi...		Stat1beta	p84		inactive	monomer	no data
12	Hs:p91	Homo sapi...		Stat1alpha	p91		inactive	monomer	no data
13	Mm:IRF-1	Mus musc...		interferon regulatory factor -1	IRF-1	Mm:IRF-1	active	monomer	no data
14	Mm:Jak2	Mus musc...		Jak2 protein tyrosine kinase	Jak2		inactive	monomer	no data
15	Mm:Jak2-p	Mus musc...		Jak2 protein tyrosine kinase	Jak2		active	monomer	phosphi
16	Mm:OAS	Mus musc...		2'-5' oligoadenylate synthetase	OAS	Mm:OAS	inactive	monomer	no data
17	Mm:OASa	Mus musc...		2'-5' oligoadenylate synthetase	OAS	Mm:OAS	active	monomer	no data
18	Mm:PKR	Mus musc...		dsRNA-dependent cAMP-independent protein serine/threoni...	PKR	Mm:PKR	inactive	monomer	no data
19	Mm:PKRa	Mus musc...		dsRNA-dependent cAMP-independent protein serine/threoni...	PKR	Mm:PKR	active	monomer	no data
20	Mm:Stat1a...	Mus musc...		signal transducer and activator of transcription 1 alpha protein	Stat1alpha		inactive	monomer	no data
21	Mm:iNOS	Mus musc...		nitric oxide synthase	iNOS	Mm:iNOS	active	monomer	no data

Property	Value
FilteringSettings	
Module	GeneNet
Type	biouml.modules.gene...
filter	
Enabled	☑
Filters	
Source	☐
Identifier	☐
Synonims	☐
Regulation	☑ /.*IFN.*/
Date	☐
Structure	☑ mon...
Name	☐
Gene ID	☐
Comment	☐
Modification	☐

Protein

ID Mm:OASa
OS Mus musculus (mouse).
NM 2'-5' oligoadenylate synthetase
SN OAS
GN Mm:OAS
FN active
MM monomer
MD no data
SO Mm:macrophage Mm:fibroblast Mm:spleen Mm:liver Mm:lung Mm:thymus
RE IFN-alpha

Модули

BioUML standard – стандартный модуль для описания и моделирования биологических систем (преимущественно на молекулярно-клеточном уровне)

SBML – Systems Biology Markup Language, level 1
http:// www.sbml.org

GeneNet - база данных по генным сетям
ИЦиГ, Новосибирск, http://wwwmgs.bionet.nsc.ru

KEGG/Ligand - Kyoto Encyclopedia of Genes and Genomes, база данных метаболических путей
Kyoto University, Japan, http://www.kegg.com

TRANSPATH - база данных по путям передачи сигнала в клетке
Biobase GmbH, Germany.

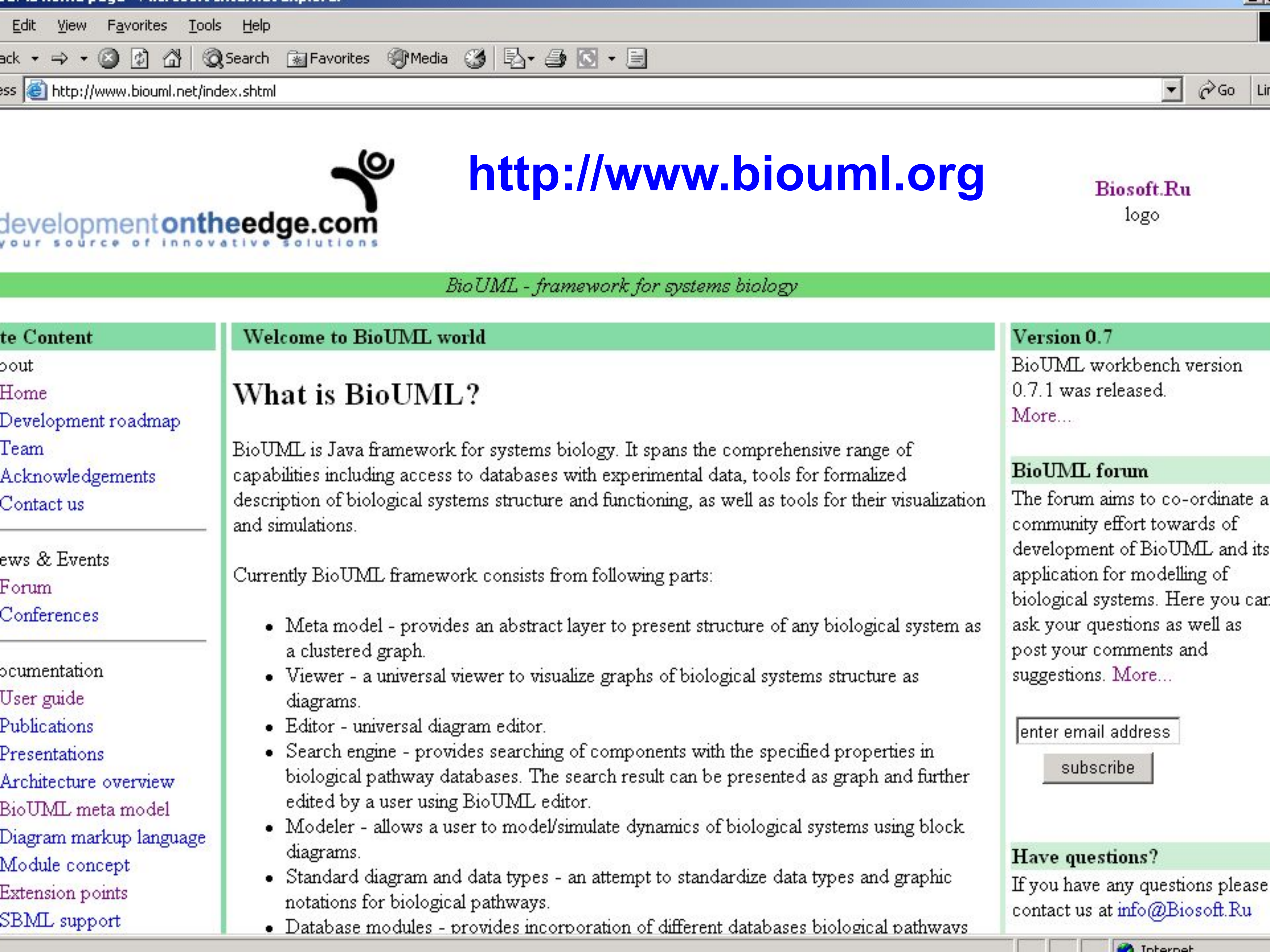
SBML – Systems Biology Markup Language, level 2
http:// www.sbml.org

CellML – Cell Markup Language
http://www.cellml.org

GO – Gene Ontology
http://wwwmgs.bionet.nsc.ru

UMLS – Unified Medical Language System
http://www.nlm.nih.gov/research/umls/

BioPax – Biological Pathways Exchange
http://www.biopax.org



http://www.biouml.org

BioUML - framework for systems biology

te Content

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- Home
- Development roadmap
- Team
- Acknowledgements
- Contact us

ews & Events
- Forum
- Conferences

ocumentation
- User guide
- Publications
- Presentations
- Architecture overview
- BioUML meta model
- Diagram markup language
- Module concept
- Extension points
- SBML support

Welcome to BioUML world

What is BioUML?

BioUML is Java framework for systems biology. It spans the comprehensive range of capabilities including access to databases with experimental data, tools for formalized description of biological systems structure and functioning, as well as tools for their visualization and simulations.

Currently BioUML framework consists from following parts:

- Meta model - provides an abstract layer to present structure of any biological system as a clustered graph.
- Viewer - a universal viewer to visualize graphs of biological systems structure as diagrams.
- Editor - universal diagram editor.
- Search engine - provides searching of components with the specified properties in biological pathway databases. The search result can be presented as graph and further edited by a user using BioUML editor.
- Modeler - allows a user to model/simulate dynamics of biological systems using block diagrams.
- Standard diagram and data types - an attempt to standardize data types and graphic notations for biological pathways.
- Database modules - provides incorporation of different databases biological pathways

Version 0.7

BioUML workbench version 0.7.1 was released. More...

BioUML forum

The forum aims to co-ordinate a community effort towards of development of BioUML and its application for modelling of biological systems. Here you can ask your questions as well as post your comments and suggestions. More...

Have questions?

If you have any questions please contact us at info@Biosoft.Ru