Biogranat: An Extensible Framework for the Visualization and Analysis of Gene Regulatory Networks

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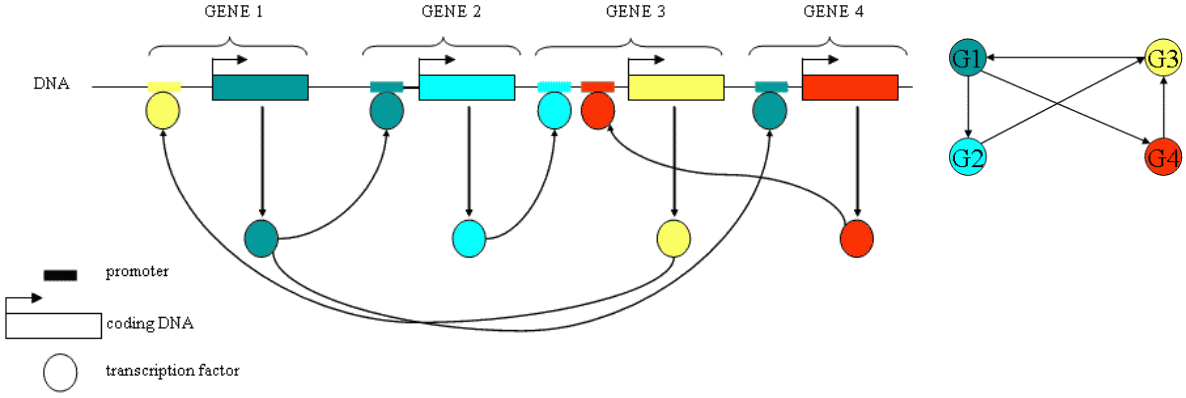
Gene Regulatory Networks

Gene regulatory networks (GRNs) are used in bioinformatics to model interaction between genes and transcription factors (proteins).



Weighted directed graph: Weights represent strength of gene activation or repression.

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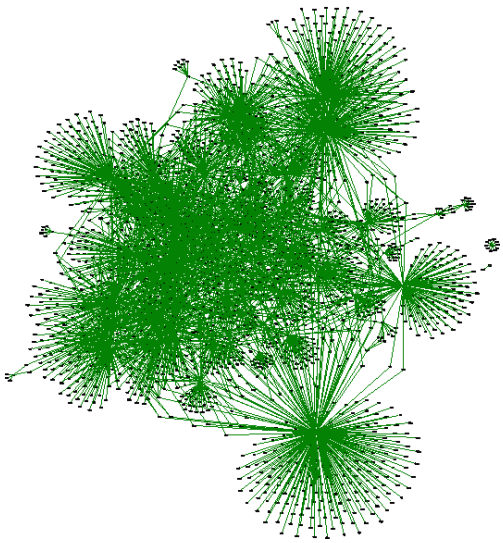
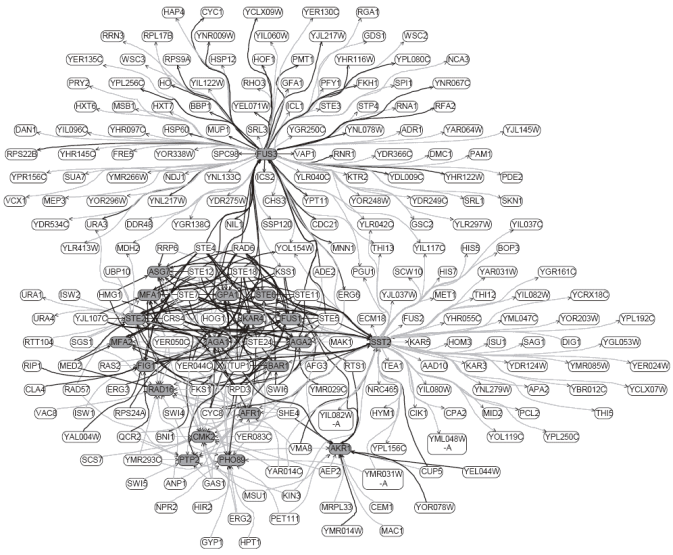
Gene Regulatory Networks

GRNs tend to be large, but have a specific structure: hub nodes with large number of outgoing edges.

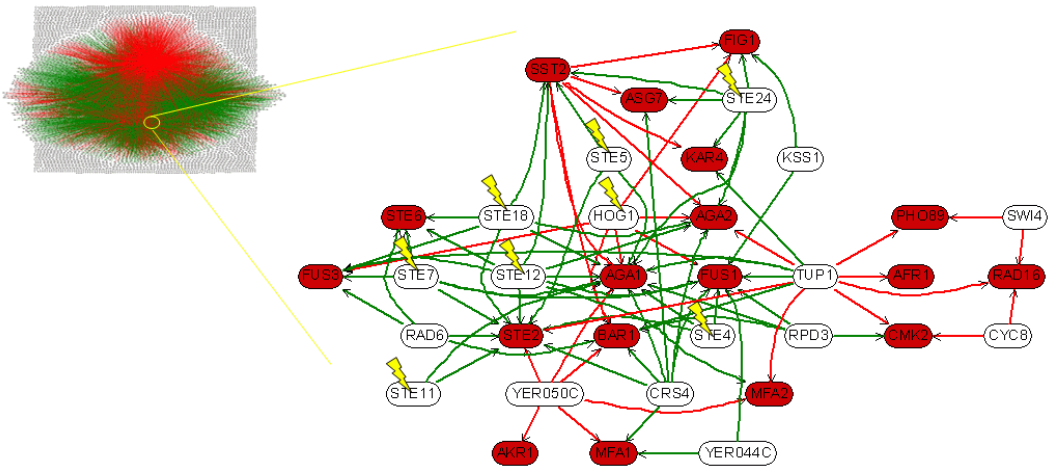




Analysis of Gene Regulatory Networks

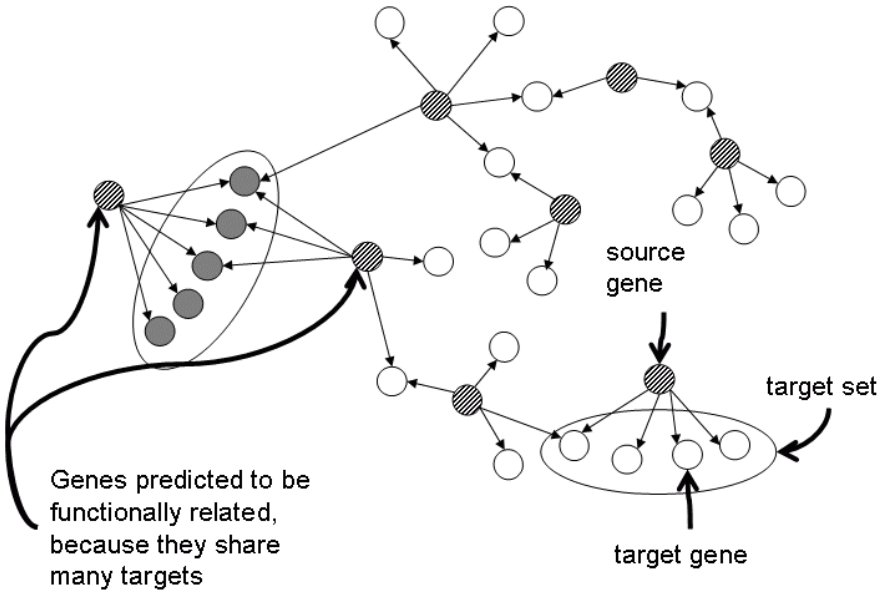
Main aim of GRN analysis:
Finding “important” genes and understanding their function.

Subnetworks are of interest, e. g., red core set and next neighbors.



Analysis of Gene Regulatory Networks

Example: Finding functionally related genes.



Analysis of Gene Regulatory Networks

Other things of interest for GRN analysis:

- Connectivity: strongly or weekly connected components.
- Clustering of nodes and edges.
- Statistics, e. g., distribution of node degrees (number of incoming and outgoing edges).
- Mutant networks: change of graph properties after removing "important" nodes or edges.
- Randomization: change of graph properties after randomly changing nodes or edges.

Graph Drawing

Aesthetic criteria of graph drawing may contradict each other:

- Crossing minimization.
- Bend minimization.
- Area minimization.
- Angle maximization.
- Length minimization.
- Symmetry preservation.
- Clustering.

Graph Drawing

Classic approach: force-directed layout.

- Define energy function $U(\boldsymbol{r})$ of node positions $\{\boldsymbol{r}\}$, e. g., based on a spring model with optimal node distance d_0.
- Start with a random layout (or better, a sophisticated guess).
- Compute forces $\boldsymbol{F}(\boldsymbol{r}) = -\nabla U(\boldsymbol{r})$ acting on nodes.
- Minimize energy using simulated annealing.

Fruchterman-Reingold model (with nodes/vertices V, edges E),

$$U = \sum_{\{u,v\}\in E} \frac{1}{3\,d_0} \left\|\boldsymbol{r}(u) - \boldsymbol{r}(v)\right\|^3 - \sum_{\{u,v\}\in V^2} d_0^2 \ln \left\|\boldsymbol{r}(u) - \boldsymbol{r}(v)\right\| .$$

- Attractive forces: $\left\|\boldsymbol{F}_{\text{att}}\right\| \propto \frac{\|\boldsymbol{r}(u)-\boldsymbol{r}(v)\|^2}{d_0}$.
- Repulsive forces: $\left\|\boldsymbol{F}_{\text{rep}}\right\| \propto \frac{d_0^2}{\|\boldsymbol{r}(u)-\boldsymbol{r}(v)\|}$.

Requirements

Requirements for a GRN analysis tool:

- Network visualization, using graph drawing methods, generating “nice” and usable graph layouts.
- Network analysis, using fundamental graph algorithms (e. g., connected components, shortest paths).
- Extensibility by new algorithms implemented as plugins, preferably in Java.
- Possibility to use existing plugins within new plugins.
- Platform-independent open-source software.
- Command logging/scripting functionality, batch execution.

Existing Solutions

Existing software tools and libraries (selection):

- Tools: Cytoscape, Pajek, BioLayout Express 3D.
- Matlab toolboxes: Bioinformatics, SimBiology.
- Graph libraries: LEDA, Graphviz/Grappa, JUNG, yFiles.

Miscellaneous drawbacks:

- Exclusive focus on graph drawing, missing extensibility.
- Proprietary software.
- Non-open-source and/or platform-specific software.
- “Strange” programming languages like Python or C++.

System Architecture: OSGi

OSGi (formerly *Open Services Gateway initiative*) provides the core plugin architecture of Biogranat.

- Open standard, developed since 1999 by *OSGi Alliance*.
- Implementations: Apache Felix, Eclipse Equinox, many others.
- Dynamic, component-based service platform for Java.
- Service-oriented architecture on local machine.
- OSGi framework manages lifecycle of bundles (components).
  - Bundles can be installed, updated, and uninstalled at runtime.
  - Bundle dependencies are resolved.

System Architecture and Data Model

System architecture

- Every system component is implemented as an OSGi bundle, including GUI, OpenGL renderer, and graph model.
- Every bundle provides one or more services, e. g., graph, node, and edge services, connected component service.
- User interface and implementation of a bundle are separated.

Data model

- Graph model: nodes, edges, selections, meta information (e. g., analysis results).
- Graph layout model: node and edge positions, colors, etc.

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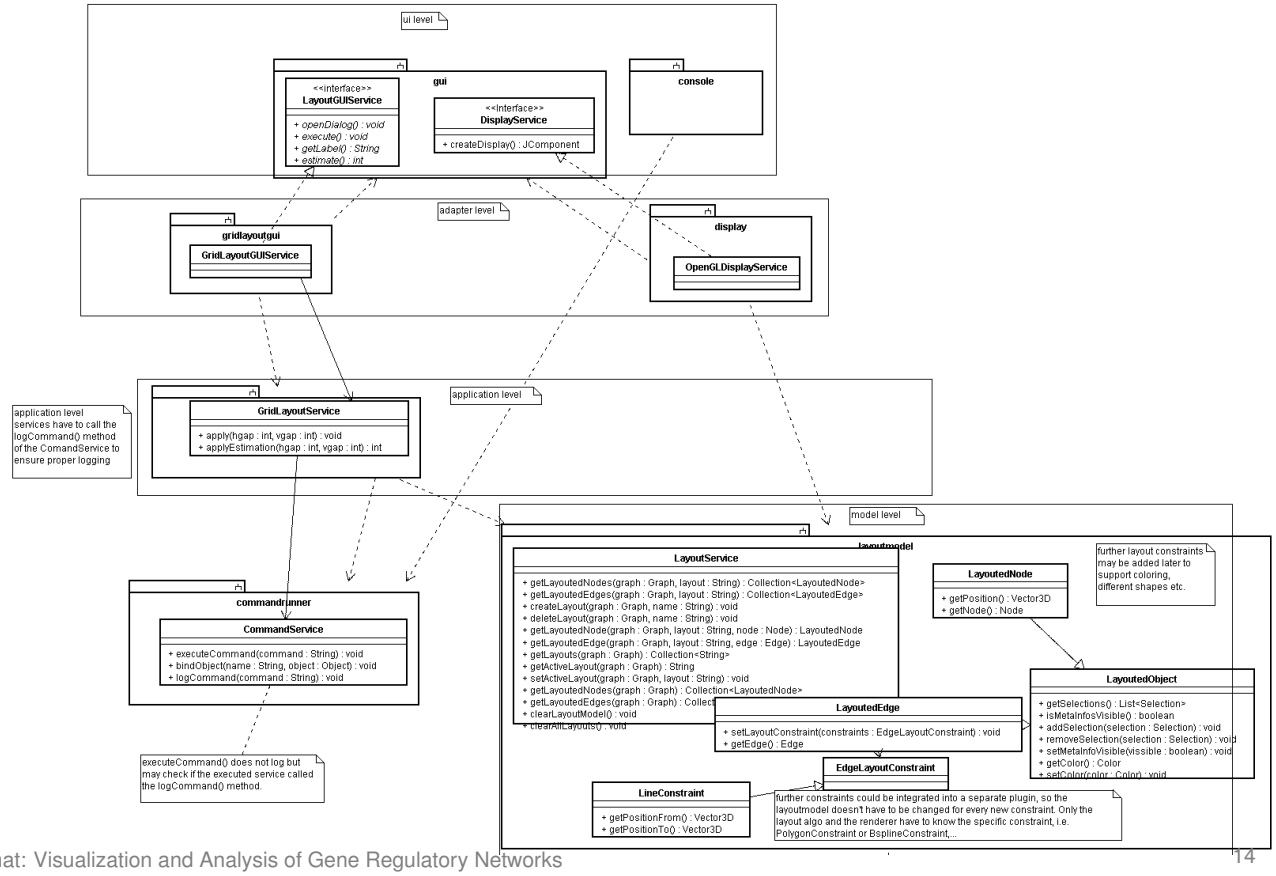
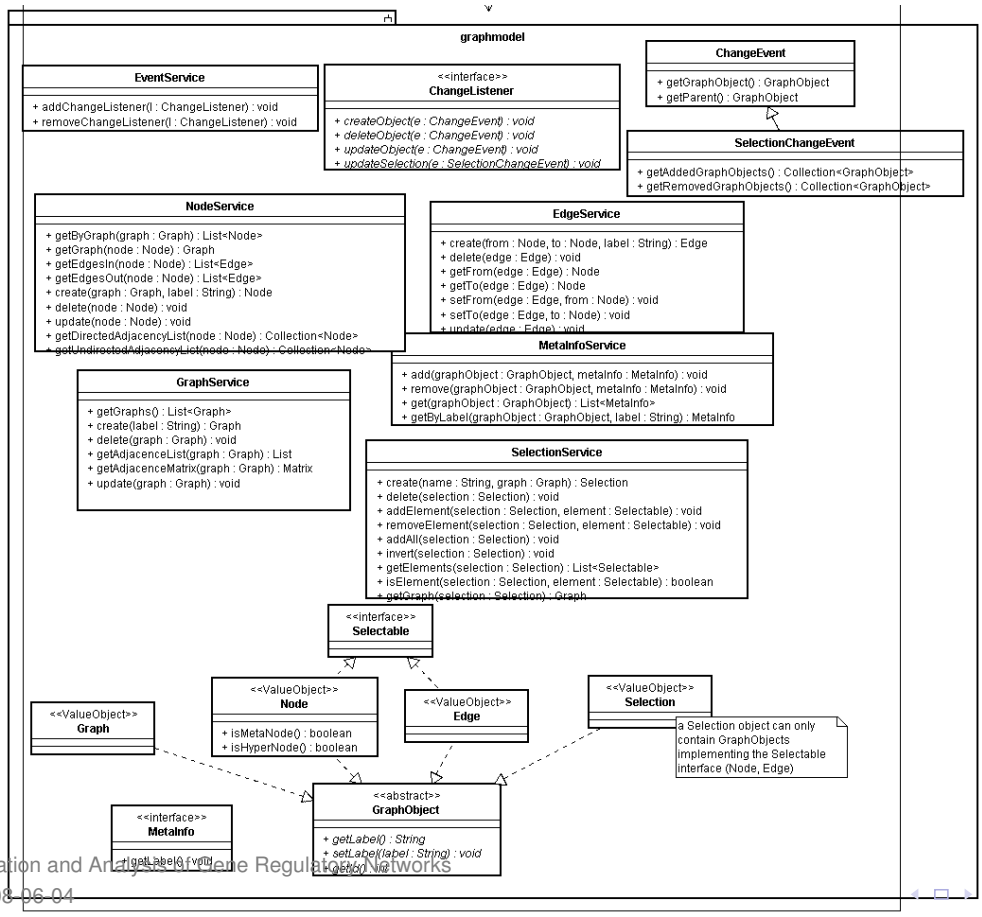




Example: Accessing Services

```
// get bundle context from bundle activator
BundleContext context = Activator.getContext();

// create dynamic graph service tracker
ServiceTracker activeGraphServiceTracker =
    new ServiceTracker(context,
        ActiveGraphService.class.getName(), null);
activeGraphServiceTracker.open();

// access graph service
ActiveGraphService activeGraphService =
    (ActiveGraphService)
        activeGraphServiceTracker.getService();
```

Example: Obtaining Graph Information

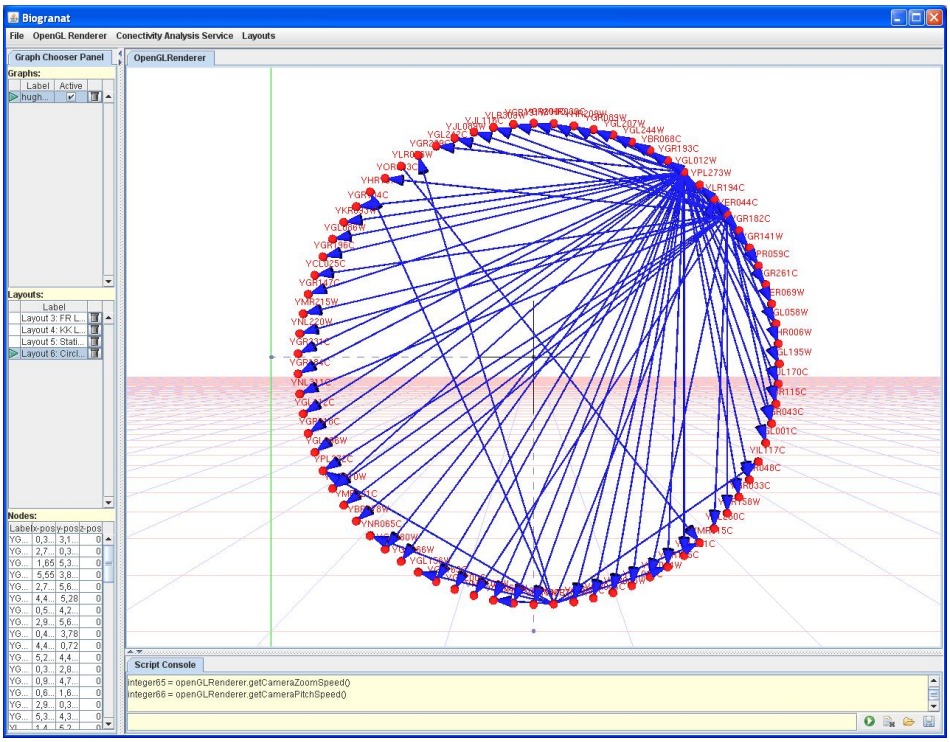
```
ArrayList<Graph> graphs = (ArrayList<Graph>)
    activeGraphService.getAll();
String message = "Graphs: " + graphs.size() + "\n";
for (Graph graph : graphs) {
  ArrayList<Node> nodes = (ArrayList<Node>)
      nodeService.getByGraph(graph);
  ArrayList<Edge> edges = (ArrayList<Edge>)
      edgeService.getByGraph(graph);
  message += "- Graph " + graph.getId() + " -\n"
      + "Nodes: " + nodes.size() + "\n"
      + "Edges: " + edges.size() + "\n";
}
JOptionPane.showMessageDialog(null, message);
```


Features

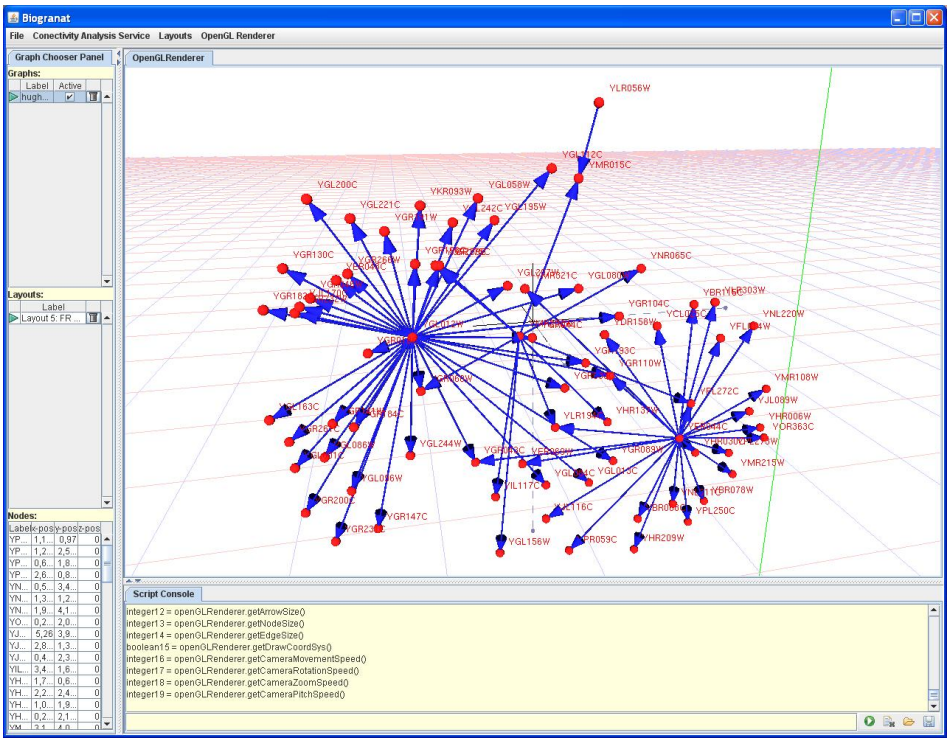
Overview of user features of Biogranat:

- Different graph layouts using JUNG library (*Java Universal Network/Graph Framework*), including circle, Fruchterman-Reingold (FR), and Kamada-Kawai (KK) layouts.
- Command logging using Java Scripting Framework (Java 6 `javax.script`).
- Configurable 3D OpenGL renderer JOGL (*Java OpenGL Bindings*).
- Import and export of graphs in ASCII and XML-based GraphML formats.
- Fundamental graph algorithms, e. g., connected components, reverse topological sort.

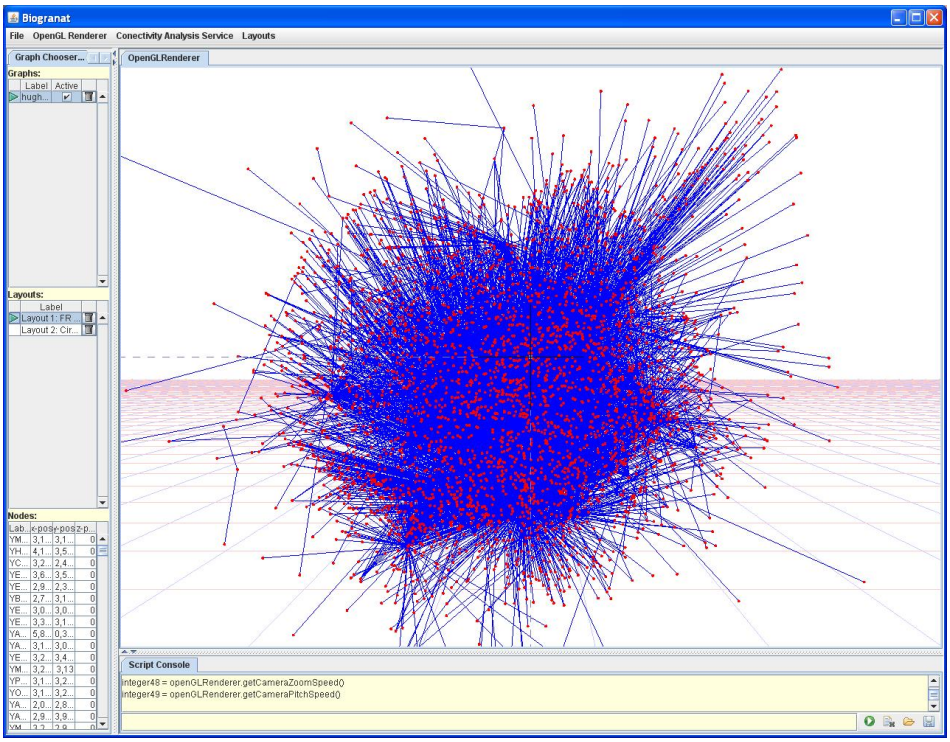
Demonstration: Circle Layout



Demonstration: Fruchterman-Reingold (FR) Layout



Demonstration: Large Graph (3197 nodes)



Project Organization

Bilateral meetings take place at Hannover and London.

- DAAD/British Council travel grant for 2007–2009 (PPP/ARC, *Programm des projektbezogenen Personenaustauschs/Academic Research Collaboration*).

Most work has been done within student projects.

- Bachelor thesis in summer semester 2007.
- Master project in winter semester 2007/08, OSGi architecture.

Drawbacks of student projects:

- Limited documentation and long-term support.
- Missing continuity.

Ongoing Work

Master and PhD theses at London

- Analysis algorithms for bioinformatics research, e. g., studying effects of network randomization.

Bachelor and Master theses at Hannover

- Vector graphic (SVG) export for 2D projections of 3D layouts.
- Specialized graph and tree layouts for gene regulatory networks.
- Wrappers for further graph libraries, e. g., *Graphviz*.
- Computing 3D graph layouts on the graphics processing unit (GPGPU approach).

Conclusion

Key features of Biogranat graph analysis tool:

- Extensible plugin architecture based on Java 6 and OSGi.
- 2D and 3D graph layouts using JUNG library and OpenGL renderer.
- Command logging using Java Scripting Framework.

Next tasks:

- Stabilizing the graph model kernel.
- Implementing algorithms for analyzing gene regulatory networks.
- Adding wrappers for further graph libraries.
- Adding interfaces to bioinformatics tools.

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