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.

Gene Regulatoy 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.

Example: Finding functionally related genes.

Genes predicted to be functionally related, because they share many targets.
Analysis of Gene Regulatory Networks

Other things of interest for GRN analysis:

- **Connectivity**: strongly or weakly 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 $U(r)$ of node positions $\{r\}$, 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 $F(r) = -\nabla U(r)$ acting on nodes.
- Minimize energy using simulated annealing.

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

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

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

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.
Example: Accessing Services

```java
// 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

```java
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.


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.
Literature I


Literature II


