Krishna Kanhaiya | Vladimir Rogojin | Keivan Kazemi | Eugen Czeizler | Ion Petre

NetControl4BioMed: A pipeline for biomedical data acquisition and analysis of network controllability

Turku Centre *for* Computer Science

TUCS Technical Report
No 1163, June 2016

NetControl4BioMed: A pipeline for biomedical data acquisition and analysis of network controllability

Krishna Kanhaiya
Computational Biomodeling Laboratory
Turku Centre for Computer Science
Åbo Akademi University, 20500 Turku, Finland
kkanhaiy@abo.fi

Vladimir Rogojin
Computational Biomodeling Laboratory
Turku Centre for Computer Science
Åbo Akademi University, 20500 Turku, Finland
vrogojin@abo.fi

Keivan Kazemi
Computational Biomodeling Laboratory
Turku Centre for Computer Science
Åbo Akademi University, 20500 Turku, Finland
keivan.kazemi@abo.fi

Eugen Czeizler
Computational Biomodeling Laboratory
Turku Centre for Computer Science
Åbo Akademi University, 20500 Turku, Finland
eczeizle@abo.fi

Ion Petre
Computational Biomodeling Laboratory
Turku Centre for Computer Science
Åbo Akademi University, 20500 Turku, Finland
ipetre@abo.fi

TUCS Technical Report

No 1163, June 2016

Abstract

Network controllability studies focus on discovering combinations of external interventions that can drive a biological system to a desired configuration. In practice, this approach translates into finding a combined multi-drug therapy in order to achieve a desired response from a cell; this can lead to developments of novel therapeutic approaches for systemic diseases like cancer. We develop a novel bioinformatics data analysis pipeline (called *NetControl4BioMed*) based on structural control of linear networks. Our pipeline generates a cellular molecular interaction network by combining pathway data from various public databases according to the user's query. The pipeline identifies a minimal set of driven proteins needed to control a given, user-defined set of *target proteins* in the network. We provide here both the source code of the pipeline as well as an online web-service based on this pipeline. The pipeline can be used by researchers for controlling and better understanding of molecular interaction networks through combinatorial multi-drug therapies, for better disease diagnostic, efficient therapeutic approaches and personalized medicine.

Introduction

Over the last decade, high-throughput experimental technologies like gene sequencing, proteomics, etc. became the core of biomedical research and have generated a large set of biomedical data [Bolouri *et al.*, 2014]. The recent advances in experimental data acquisitions allow researchers to study functions and properties of proteins, RNAs and genes, as well as to explore a network of interactions between them. The network of protein-protein interactions (*PPIs*) is the backbone of signaling pathways [Pawson *et al.*, 2000], metabolic pathways [Durek *et al.*, 2008], and various essential cell processes for normal cell function [Kolch *et al.*, 2015, Yamada *et al.*, 2009]. In recent years, analysis of PPI networks has been central for the current biological research, providing novel insights into modern molecular biology from the network perspective [Barabasi *et al.*, 2011]. In order to study the structure, function and dynamics of PPI networks, multiple computational system biology approaches have been employed to reveal important links in various biological networks [Cho *et al.*, 2012]. This includes, among others, finding physical interactions (e.g., between proteins in PPI networks) and functional interactions (e.g., between genes with similar or related functions, direct or indirect regulatory relationships between genes), identifying network modules (clusters of intensively interacting molecules) [Cho *et al.*, 2012], interaction patterns and topological properties of disease networks (such as cancers, HIV infections, diabetes mellitus, Parkinson, Alzheimer, etc.) [Zhou *et al.*, 2014].

A number of computational pipelines and softwares have been developed [Doncheva *et al.*, 2012] to perform various analysis of the interaction partners,

topological properties, and visualization of PPI networks. The majority of these approaches are focusing on finding structurally important disease-associated protein interactions in a network [Yildirim *et al*., 2007, Jiang *et al*., 2015]. However, so far there are no known software solutions analysing biochemical interaction networks and providing information on how to control them. Recently, several algorithms have been developed to perform network structural analysis and suggesting optimal sets of so-called *driven* nodes through which one can control a network [Liu *et al*., 2011, Kanhaiya *et al*., 2016, Czeizler *et al*., 2016]. We say that a system is *controllable* through a set of driven nodes if there exists a time-dependent sequence of input signals delivered through these nodes in such a way that the system can be driven from any initial state to any desired final state within finite time [Liu *et al*., 2011, Lin *et al*., 1974]. Recently, the use of structural controllability of biological networks has been suggested on *undirected PPI networks* through minimum dominating sets (MDSet) proteins approach [Wuchty *et al*., 2014]. An efficient method to select a minimal set of driven nodes in a *directed PPI network* in order to reach its full controllability was recently presented in ([Liu *et al*., 2011]). However, it was shown through a number of computer-based experimental tests in [Liu *et al*., 2011] that in biological networks one may have to control as much as 80% of the nodes of a gene-regulatory network in order to reach the full controllability. This makes the full network controllability approach for biological and medical purposes. In many cases, it is more practical to control only a certain properly selected subset of the network's nodes (for instance, a disease-specific set of essential genes) in order to reach a desired overall behavior of the system [Kanhaiya *et al*., 2016, Czeizler *et al*., 2016]. This approach may lead, for instance, to an effective combined multi-drug therapy for a particular disease.

We develop a bioinformatics data analysis pipeline (called *NetControl4BioMed*) and its web-based front-end in order to provide a web-based service for automatic generation of combined multi-drug therapy suggestions through the analysis of user-given directed biochemical interaction networks. The core of the pipeline consists of the implementation of the algorithm proposed in [Czeizler *et al*., 2016] that for a given directed network and a set of target nodes, it calculates a minimal set of driven nodes through which one can control the target nodes. Based on the user's query, the pipeline generates automatically intracellular molecular interaction networks by combining the interactions between genes, proteins and other intracellular components from various public pathway repositories. Then, the resulting networks are subjected to the structural controllability analysis in order to identify the minimal set of driven genes [Czeizler *et al*., 2016]. The data from public drug repositories is used to maximize the use of drug-targetable genes and proteins as driven nodes, to increase the practical applicability of the approach. The results of this analysis are returned to the user in form of reports in *CSV* tables, *PDF* documents and *GRAPHML* files.

1 Methods

We build here a data analysis pipeline and its web-based front-end in order to provide a web-based service for automatic generation of combined multi-drug therapies suggestions. The core of the pipeline consists of the implementation of the algorithm (proposed in [Czeizler *et al*., 2016] and briefly discussed in Section 1.1) that for a given set of target nodes calculates a minimal set of driven nodes through which one can control the target nodes. Based on the user's query, the pipeline generates automatically intracellular chemical interaction networks by combining the interactions between genes, proteins, and other intracellular components from various public pathway repositories. Then, the resulting networks are subjected to the structural controllability analysis in order to identify the minimal set of driven genes [Czeizler *et al*., 2016]. The data from public drug repositories is used to maximize the use of drug-targetable genes and proteins as driven nodes, to increase the practical applicability of the approach. The results of this analysis are returned to the user in form of reports in *PDF* documents, *XML* files and files readable by *Cytoscape*.

1.1 Structural network control

Here we present theoretical aspects of the algorithm that we have proposed in [Czeizler *et al*., 2016]. This algorithm is aimed to minimize the size of the set of driven nodes that can be used to control a given set of target nodes. The algorithm uses several heuristic strategies for a more efficient exploration of the search space, which leads to faster and better (smaller sets of driven nodes) results in comparison to [Gao *et al*., 2014]. The Python implementation of the algorithm is available in (*http://combio.abo.fi/research/network-controlability-project/*).

We consider discrete time-invariant linear dynamical systems as models of biological entities (genes, proteins) influencing each other. Such a system can be modeled by

$$x_{t+1} = Ax_t + Bu_t, \qquad y_t = Cx_t,$$

where A, B, C are matrices of size $n \times n$, $n \times m$, and $l \times n$, respectively, $x_t \in \mathbf{R}^n$, $u_t \in \mathbf{R}^m$ and $y_t \in \mathbf{R}^l$ are the state vectors, input vectors and output vectors, for all $t \in \mathbf{N}$. Matrix A describes the interactions *within* the system under scrutiny, B describes the influence of the m *driver nodes* over the internal nodes of the system, while C describes the l *output nodes* as a function of the internal nodes of the system. We call *driven node* any $j \in \{1, \ldots, n\}$ such that $B_{ij} \neq 0$, for some $i \in \{1, \ldots, m\}$; in other words a driven nodes is any internal node linked to an external driver node through matrix B. We say that an output vector $y \in \mathbf{R}^l$ is *reachable* from an initial state $x_0 \in \mathbf{R}^n$ if there exists a finite sequence of inputs $u_0, u_1, \ldots, u_t \in \mathbf{R}^m$ such that $y_t = y$.

In this paper we focus on target controllability, i.e., on the case when the focus is on controlling a well-defined subset of the internal nodes of the system. To

capture this case, we consider matrices C with $l \leq n$ and such that on each row of matrix C there is at most one non-zero value; this effectively selects the internal nodes of interest as outputs of the dynamical system. We say that such a system is *target controllable* if any output vector is reachable from any input state. It is known that a system is target controllable if and only if

$$rank[CB, CAB, CA^2B, \ldots, CA^{n-1}B] = l,$$

see [Czeizler *et al.*, 2016] and references therein. A related notion is that of *structural target controllability*, that refers to a system that becomes target controllable by changing the non-zero values of A and B with some well-chosen non-zero values (we call such matrices *equivalent*); moreover, it is well known that a system is structurally target controllable if and only if it is target controllable for almost all (in a mathematically well-defined sense) equivalent matrices A and B. This allows the problem to be redefined as a graph-theoretical problem since the target controllability depends on the *structure* of the system and not on its numerical setup. Due to space restrictions we skip all these details here and refer to [Czeizler *et al.*, 2016] and references therein. We only mention that the problem may be reduced to the following problem on directed graphs: given a directed graph $G = (V, E)$ with n nodes and a subset $T \subseteq V$ with l nodes, decide if there exists a set of l directed paths in G such that each node in T is an end point of one such path and no two paths intersect at the same distance from their end points, see [Lin *et al.*, 1974]. In an additional refinement of the problem, one may also be given a subset $D \subseteq V$ of driven nodes and require that the directed paths preferably start from nodes in D.

1.2 NetControl4BioMed

Here we discuss software tools used to build our pipeline as well as the data used in it.

1.2.1 Workflow engine: Anduril

The pipeline is developed for the *Anduril* workflow framework [Ovaska *et al.*, 2010]. Anduril is an open source component-based pipeline engine for scientific data analysis. Anduril defines an API that allows to integrate rapidly a vast range of existing software analysis and simulation tools and algorithms into a single data analysis pipeline. An Anduril pipeline represents a set of interconnected executable programs (called components) through well-defined I/O ports. Upon the termination of the execution of an Anduril component, its output results are delivered as inputs to the other (downstream) components by means of connecting the output port of the component to the input ports of its downstream components. When an Anduril pipeline is being executed, a component can be executed as soon as all the necessary input data at the input ports (from the upstream components) become available.

1.2.2 Biological data and network generation

Our pipeline uses the *Moksiskaan* platform [Laakso *et al.*, 2010] to generate molecular interaction networks based on the user's query. Moksiskaan integrates pathways, protein-protein interactions, genome and literature mining data into comprehensive networks for a given list of proteins (so-called "seed nodes"). It combines the relations between genes and proteins from different known pathways in order to address the fact that pathways crosstalk and influence each other. In our pipeline, Moksiskaan constructs a comprehensive network for the list of seed nodes by using and combining all imported pathways in the following manner: it connects all seed nodes by all known paths of length not exceeding the "gap" value (a parameter of our pipeline). The intermediate proteins from the paths need not necessarily belong to the given set of seed nodes.

The Moksiskaan platform defines a generic database schema to store the pathways from a number of different pathway databases and can be scaled to include the pathway data from new sources (such as new databases and user's own data). Currently, Moksiskaan has built-in support for the integration of the pathway data from, among others, KEGG pathway database [Kanehisa *et al.*, 1996], Pathway Commons [Cerami *et al.*, 2011], and WikiPathways [Kutmon *et al.*, 2015, Kelder *et al.*, 2011]. In order to import the data from a new source, the user has to implement an import mechanism fetching and translating the data from the new source into the format defined by the Moksiskaan database schema. After the Moksiskaan database is populated, it can be used by the Moksiskaan Anduril components to import the pathways data into Anduril pipelines.

We use in our pipeline drug-target protein data from the open source DrugBank database [Law *et al.*, 2014]. The DrugBank database combines detailed drug (i.e. chemical, pharmacological and pharmaceutical) data with comprehensive drug target (i.e. sequence, structure, and pathway) information from bioinformatics and cheminformatics resources. For drug-target identifiers we have selected in total 1507 FDA-approved drugs with known mechanisms.

In our pipeline, we provide the user with a number of predefined sets of target proteins associated to some specific cancer cell lines. These target proteins are cancer-specific essential proteins. We have included in the pipeline data for three types of cancer from the COLT-Cancer database [Koh *et al.*, 2012]. In particular, we considered 29, 23 and 15 cell lines respectively for breast, pancreatic and ovarian cancer. The collected data follows the GARP and GARP-P value of corresponding proteins mentioned in the database. Previous studies [Marcotte *et al.*, 2012] showed that proteins with lower GARP score are more essential and directly associated with oncogenesis. Therefore, we have selected only those essential proteins whose GARP value is in the negative range, and moreover, whose GARP-P value is less than 0.05. Following the above criteria, we identified proteins for breast, pancreatic and ovarian cancer respectively.

1.2.3 Pipeline structure

Here we describe the pipeline structure as well as its input and output.

INPUT

Our pipeline currently accepts the following inputs from the user:

1. **Seed proteins**: List of proteins that will be used as seed nodes by Moksiskaan to generate the network. This input can be any protein ID of Homo sapiens.

2. **User-defined network**: The user has an option to use a custom network in the pipeline instead of the Moksiskaan network.

3. **Cancer Cell Lines**: A cancer cell line whose set of essential proteins will be used as target nodes for the network controllability algorithm. These nodes can act also as seed nodes if the user decides so. The user has also the option not to include any of the cell lines. However, in this case the next field should not be empty.

4. **Additional target proteins**: A set of target nodes defined in addition to those in the "Cancer Cell Lines". This input can be left empty if the previous field is set to a cancer cell line. These nodes can act also as seed nodes if the user decides so.

5. **Gap**: The gap parameter used by Moksiskaan to generate the network.

6. **Include drug information**: Should the pipeline include also the drug target information for the driven nodes. If so, then the driven nodes for which there exist FDA approved drugs will be specifically highlighted in the output of the pipeline.

OUTPUT

The pipeline generates as the result of the computation a *zip*-archive with the following files. Table *driven.csv* contains the drug-targetable driven nodes and the number of targets (e.g., cancer essential proteins) controlled by them. If *driven.csv* is empty, it means that our algorithm didn't find any cancer essential protein (or generally any target) inside the generated PPI network which can be controlled by the drug-target driven protein. Table *extra.csv* contains the non-drug targetable driven nodes (no FDA-approved drug target proteins are known to be targeting the node) and and the number of targets (e.g., cancer essential proteins) controlled by them. Similarly as *driven.csv*, if *extra.csv* is empty then it follows that our algorithm didn't find any cancer essential protein (or generally any target) inside the generated PPI network which needs to be controlled from a non-drug-targetable driven protein. In *details.txt* the first line indicates the heuristics which was used for obtaining the result in the file. A blank line follows, then the names of the driven nodes, each on a separate line. After another blank line, the control path

for each target is provided. File *graph.xml* contains the generated network and can be visualized in *Cytoscape* and further downloaded as a *node.csv* from *Cytoscape*. The archive also contains a visualization of the controlled graph (as a PDF file) generated with GraphML, see Figure 2.

PIPELINE

Our pipeline consists of the following three parts, see Figure 1:

1. **DATA IMPORT**: Integrate the user's defined input into the pipeline. Either generate the network with Moksiskan, basing on the user's defined input or get the user-defined network in GRAPHML format.

2. **NETWORK CONTROLLABILITY**: Compute the minimal set of driven nodes for the given target genes in the network generated at the previous step.

3. **POSTPROCESSING AND OUTPUT**: Highlight those driven nodes that can be targeted by FDA approved drugs. Generate the network file (*GRAPHML*, *Cytoscape* and *PDF*) from the original network and by adding additional annotations to the nodes representing selected driven genes/proteins, drug-targetable driven genes/proteins, if any, and target genes. Generate CSV tables with the information about the driven genes/proteins, and the list of target genes and their control paths from the driven nodes.

2 Discussion

The structural network controllability approach allows to get a better insight into a system modeled as a directed graph: for a set of target nodes it is possible to identify a set of driven nodes through which one can control the target nodes by an external intervention through using the internal "wiring" of the network. We use here a recently developed algorithm [Czeizler *et al.*, 2016] for structural targeted network controllability that identifies a minimal set of driven nodes for a user-given set of target nodes. We implemented this algorithm through a pipeline (that can be downloaded and installed as a stand-alone software) and through a related online service (a publicly available web interface for an instance of the pipeline installed on our servers). The pipeline performs an automatic generation of intracellular molecular interaction networks (by combining publicly available pathway data) and identification of driven nodes (that also can be targeted by FDA approved drugs) for a set of target genes/proteins defined by the user.

In this paper we also address the interesting problem of using the controllability approach for a combination of data on FDA-approved drug targets and data on cancer essential genes for different types of cancers. Users can also apply this pipeline if they have other disease target (essential) genes. We anticipate that further developments on our pipeline have the potential in suggesting novel therapeutic strategies by using currently known drugs.

Acknowledgments

This work was supported by the Academy of Finland through grant 272451, and by the Finnish Funding Agency for Innovation through grant 1758/31/2016.

References

[Bolouri *et al.*, 2014] Bolouri,H. *et al.* (2014) Modeling genomic regulatory networks with big data, *Trends in Genetics*, **30(5)**, 182-91.

[Pawson *et al.*, 2000] Pawson,T. and Nash,P. (2000) Protein - protein interactions define specificity in signal transduction, *Genes & Dev*, **14**, 1027-47.

[Kolch *et al.*, 2015] Kolch,W. *et al.* (2015) The dynamic control of signal transduction networks in cancer cells, *BMC Nature Reviews*, **15**, 515-27.

[Yamada *et al.*, 2009] Yamada,T. and Bork,P. (2009) Evolution of biomolecular networks - lessons from metabolic and protein interactions, *Nature Reviews Molecular Cell Biology*, **10**, 791-803.

[Barabasi *et al.*, 2011] Barabasi,A.L. *et al.* (2011) Network medicine: a network-based approach to human disease, *Nature Reviews Genetics*, **12**, 56-58.

[Doncheva *et al.*, 2012] Doncheva,T.N. *et al.* (2012) Topological analysis and interactive visualization of biological networks and protein structures, *Nature Protocols*, **7**, 670-85.

[Yildirim *et al.*, 2007] Yildirim,M.A. *et al.* (2007) Drug-target network, *Nature Biotechnology*, **25(10)**, 1119-26.

[Jiang *et al.*, 2015] Jiang,P. *et al.* (2015) Network analysis of gene essentiality in functional genomics experiments, *Genome Biology*, **16:239**.

[Liu *et al.*, 2011] Liu,Y.Y. *et al.* (2011) Controllability of complex networks, *Nature*, **473**, 167-173.

[Kanhaiya *et al.*, 2016] Kanhaiya,K. *et al.* (2016) Controlling Directed Protein Interaction Networks in Cancer. *TUCS Technical Reports*, **1155**.

[Czeizler *et al.*, 2016] Czeizler,E. *et al.* (2016)Target controllability of linear networks. *TUCS Technocal Report.* **1157**.

[Gao *et al.*, 2014] Gao,M. *et al.* (2014) Target control of complex networks, *Nature Communications*, **5:5415**.

[Wuchty *et al.*, 2014] Wuchty,S. *et al.* (2014) Controllability in protein interaction networks, *Proc Natl Acad Sci U S A*, **111(19)**, 7156-60.

[COMBIO, 2016] COMBIO. (2016) Network Controlability Project, Url = http://combio.abo.fi/research/
network-controlability-project/

[Ovaska *et al*., 2010] Ovaska,K. and Laakaso,M. (2010) Large-scale data integration framework provides a comprehensive view on glioblastoma multiforme, *Genome Medicine*, **2:65**.

[Laakso *et al*., 2010] Laakso,M. and Hautaniemi,S. (2010) Integrative platform to translate gene sets to networks.*Bioinformatics*, **26**, 1802 - 1803.

[Kanehisa *et al*., 1996] Kanehisa,M.*et al*. (1996) Toward pathway engineering: a new database of genetic and molecular pathways. *Science & Technology Japan*, **59**, 34-38.

[Cerami *et al*., 2011] Cerami,E.G. *et al*. (2011) Pathway Commons, a web resource for biological pathway data. *Nucleic Acids Res.*, **39**, D685-90.

[Kutmon *et al*., 2015] Kutmon,M. *et al*. (2015) WikiPathways: capturing the full diversity of pathway knowledge. *Nucleic Acids Research*, **44**, D488- 494.

[Kelder *et al*., 2011] Kelder,T. *et al*. (2015) WikiPathways: building research communities on biological pathways. *Nucleic Acids Research*, **40**, D1301-1307.

[Law *et al*., 2014] Law,V. *et al* DrugBank 4.0: shedding new light on drug metabolism. *Nucl. Acids Res*. **1-7**.

[Koh *et al*., 2012] Koh,Y.L.J. *et al*. (2014) COLT-Cancer: functional genetic screening resource for essential genes in human cancer cell lines. *Nucl. Acids Res.*, **40**, D957- 963.

[Marcotte *et al*., 2012] Marcotte,R. *et al*. (2012) Essential Gene Profiles in Breast, Pancreatic, and Ovarian Cancer Cells. *Cancer Discovery*. **2(2)**, 172-89.

[Lin *et al*., 1974] Lin,C.T. *et al*. (1974) Structural controllability.*IEEE Transactions on Automatic Control*, **19(3)**, 201- 208.

[Durek *et al*., 2008] Durek,H. and Walther,D. (2008) The integrated analysis of metabolic and protein interaction networks reveals novel molecular organizing principles, *BMC Systems Biology*, **2(100)**.

[Cho *et al*., 2012] Cho,D-Y. *et al*. (2012) Chapter 5: Network Biology Approach to Complex Diseases, *PLoS Comput Biol*, **8(12): e1002820**.

[Zhou *et al*., 2014] Zhou,X.Z. *et al*. (2014) Human symptoms-disease network, *Nat Commun*, **5**, 4212.

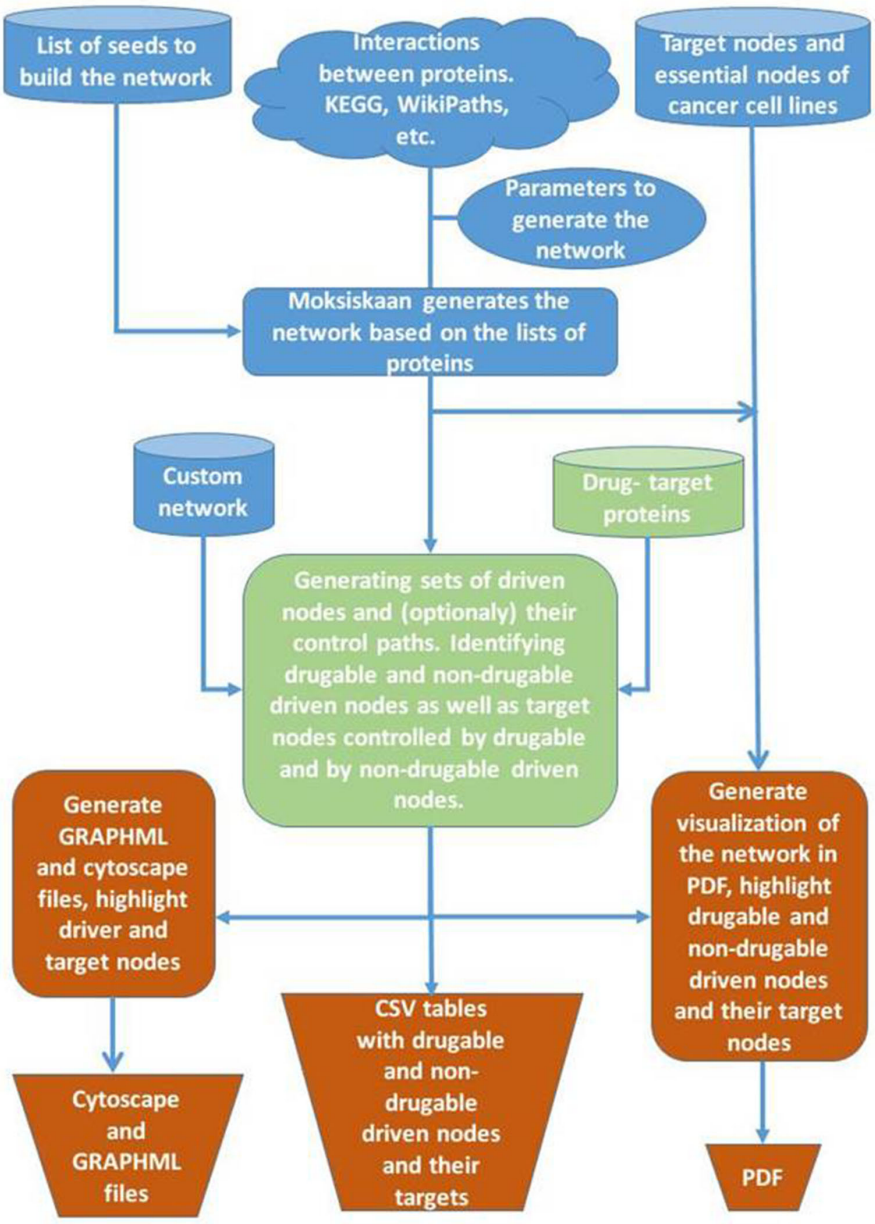

Figure 1: **The general scheme of the** *NetControl4BioMed* **pipeline.** The pipeline consists of three parts. In the first part we perform data input and preprocessing: we get from the user the list of seed nodes, the predefined list of essential proteins for a selected cancer essential cell line, and the list of additional target nodes, if provided by the user. Moksiskaan generates the network based on the seed proteins provided by the user; the seed can also include the predefined list of cancer essential cell lines and the optional list of user-defined target nodes. The user also can provide for the analysis a custom network instead of that generated by Moksiskaan. The second part of the pipeline deals with the network structural controllability analysis, where a minimal set of driven nodes is computed for the given set of target nodes (user-defined target nodes and cancer cell line-associated essential proteins). In the third part of the pipeline the post-processing is performed and the output is generated. In the output, the user gets the network generated by Moksiskaan and the information about driven nodes, target nodes and drug-targetable driven nodes.

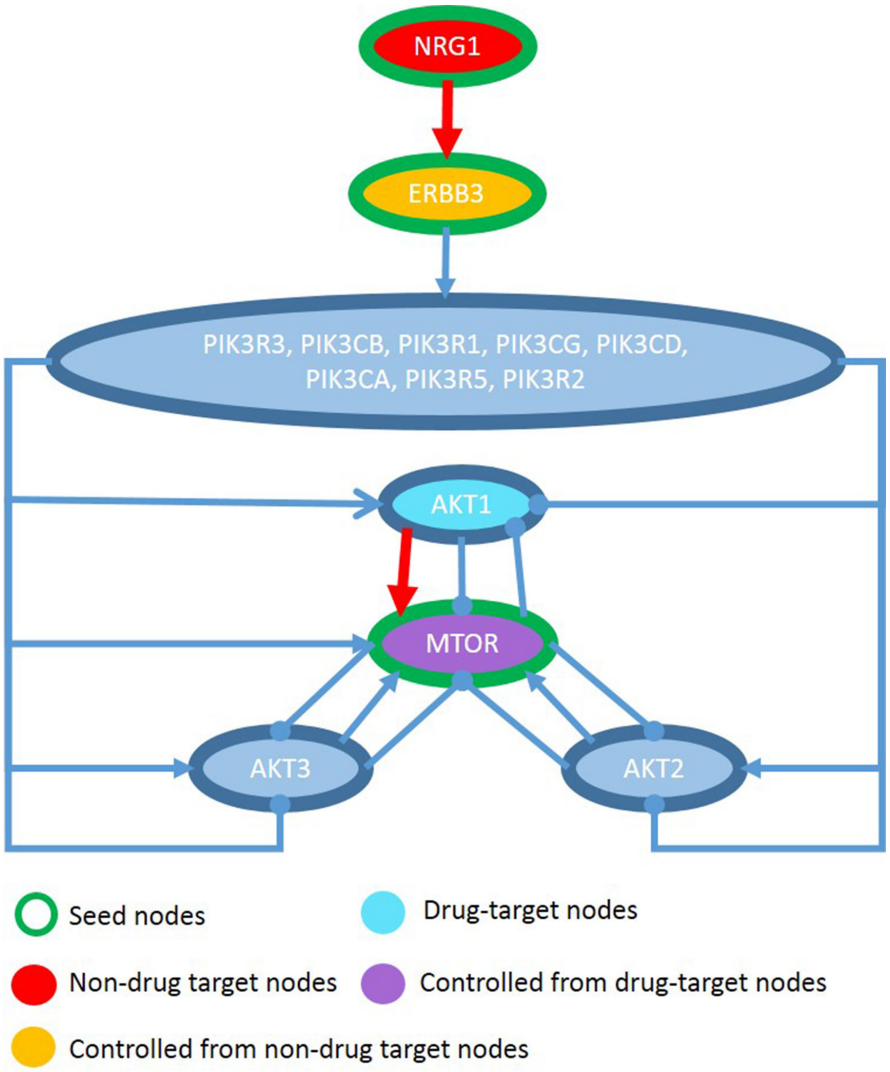

Figure 2: **A visualization of the generated network from the pipeline.** Proteins PIK3R3, PIK3CB, PIK3R1, PIK3CG, PIK3CD, PIK3CA, PIK3R5 and PIK3R2 are promoted/activated by ERBB3. They promote/activate AKT1, AKT2, AKT3 and MTOR and inhibit AKT1, AKT2 and AKT3. Proteins PIK3R3, PIK3CB, PIK3R1, PIK3CG, PIK3CD, PIK3CA, PIK3R5 and PIK3R2 have no interactions between each other. NRG1 controls ERBB3 and AKT1 controls MTOR. The colors have the following meaning: *"seed nodes"* are shown in green circle (NRG1, ERBB3, MTOR), *"driven drug-target nodes"* are represented as aqua color (AKT1), *"controlled from drug-target nodes"* are shown in purple color (MTOR), *"driven non-drug- target nodes"* are shown in red color (NRG1) and *"controlled from non-drug-target nodes"* are shown in orange yellow (ERBB3).

Turku
Centre *for*
Computer
Science

Joukahaisenkatu 3-5 A, 20520 TURKU, Finland | www.tucs.fi

University of Turku
Faculty of Mathematics and Natural Sciences
- Department of Information Technology
- Department of Mathematics and Statistics

Turku School of Economics
- Institute of Information Systems Sciences

Åbo Akademi University
- Computer Science
- Computer Engineering

ISBN 978-952-12-3426-2
ISSN 1239-1891