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# Chapter 11

## Network modeling methods for precision medicine

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### Abstract:

We discuss in this chapter several network modeling methods and their applicability to precision medicine. We review several network centrality methods (degree centrality, closeness centrality, eccentricity centrality, betweenness centrality, and eigenvector-based prestige) and two systems controllability methods (minimum dominating sets and network structural controllability). We demonstrate their applicability to precision medicine on three multiple myeloma patient disease networks. Each network consists of protein-protein interactions built around a specific patient's mutated genes, around the targets of the drugs used in the standard of care in multiple myeloma, and around multiple myeloma-specific essential genes. For each

network we demonstrate how the network methods we discuss can be used to identify personalized, targeted drug combinations uniquely suited to that patient.

**Keywords:** Network medicine, computational modeling, precision medicine, drug repurposing, centrality measures, systems controllability, graph theory.

## 11.1. Introduction

Network medicine is a promising recent approach in which the goal is to analyze the dysregulation of a disease through its specific molecular interactions (Saqi et al. [2016], Tian et al. [2012]). The key analytic power of this approach is that knowledge about disease-drivers and specific pathway deregulations can be combined with mechanistic knowledge of drug mechanisms to identify optimal drug combinations, and do this dynamically throughout the evolution of the disease.

An exciting aspect of this approach is that it can, in principle, be applied in a personalized way, taking into account patient-specific aspects such as comorbidities, previous treatments, and the patient's own molecular data (such as her mutations, gene expression anomalies, corrupted signaling pathways). Therefore, a disease is seen as part of a patient's own molecular and clinical context, through the cumulative effect of various deregulations and anomalies. Also, drug therapies are seen as external interventions aiming to compensate for the effects of these anomalies in the patient-specific disease network. The focus is on identifying tailored drug combinations uniquely suited to that patient's disease network, in the current step of her disease progression.

This chapter introduces several network modeling methods and demon-

strates their potential applicability in personalized medicine. We survey several network centrality measures, aiming to identify parts of the network that are unusual in the context of its topology; we discuss their definitions and the intuition of their significance. We also discuss two systems controllability methods: network controllability and maximum dominating sets. The aim of these methods is to identify efficient interventions to change the network's configuration, and in principle to change from a setup associated with disease to one associated with a healthy state.

We demonstrate how these network modeling methods can be used in precision medicine for identifying targeted, personalized drug combinations. Our case study is multiple myeloma, an incurable cancer of the blood. We analyze a dataset consisting of the genetic mutations of three different patients. For each of them we construct their own personalized protein-protein directed interaction networks, and we analyze them with some of the methods in this chapter to extract personalized predictions of optimal drug combinations. We compare these results with the standard therapy lines in multiple myeloma.

We also include a brief discussion on the availability of software tools supporting this line of research.

The chapter is written in a tutorial style to facilitate the adoption of these methods.

## **11.2. Network modeling methods**

We discuss in this section a number of network analysis methods: network centrality measures (including degree centralities, proximity centralities, path centralities and spectral centralities) and two systems controllability methods

(network controllability and minimum dominating sets). We apply several of these methods to a medical case-study in Section 11.3.

## 11.2.1. Network centrality methods

Real-world networks often include a large number of nodes and connections, but the importance of the nodes is generally not the same. The simplest way to measure the importance of a given node is to compute its degree: the number of incident edges. However, in many cases, more sophisticated approaches are required to produce meaningful measures of importance. In the most general sense, a centrality measure can be defined in the following way.

**Definition 11.1 (*Centrality*):** Let  $G = (V, E)$  be a network. A *centrality measure* is any function  $f : V \rightarrow \mathbb{R}$ .

This definition imposes no constraints on  $f$ , but most centrality measures take into account the structural properties of the network  $G$  — node connectivity, edge weights, etc. Based on which structural properties they take into account, centrality measures can be grouped into the following categories:

- *degree centralities*: measures based on the degree of a node;
- *proximity centralities*: measures based on how close a node is to the other nodes in the network;
- *path centralities*: measures based on the role the node plays in paths that traverse it;
- *spectral centralities*: measures related to the algebraic properties of the adjacency matrix of the network (in particular its eigenvectors and eigenvalues).

While the majority of centralities focus on individual nodes, one can define

measures focused on other structures: edges, subsets of nodes, etc. Most of these measures are straightforward derivations from node-based centralities (e.g., edge and group betweenness in [Brandes, 2008]), and we will not discuss them here. Furthermore, we only consider unweighted networks, and we focus on structural measures which do not take into account any possible dynamical states.

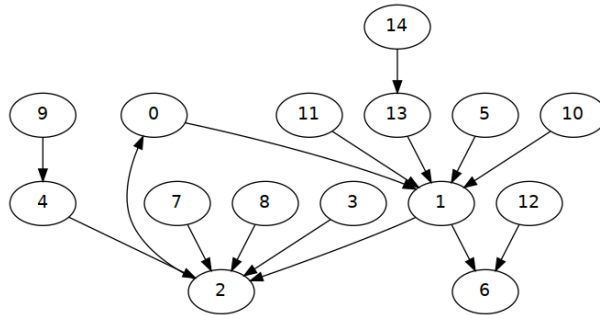
In the rest of this subsection, we discuss some well-known and often used centrality measures in detail. In particular, we give the intuitive motivations, the formal definitions, and the highlighted properties of the network. Furthermore, we give references to algorithms for computing the centrality measures and briefly discuss their time complexities. Finally, we describe *network centrality indices* — network-wide scores measuring the centralization of a network as a whole, and allowing for comparisons between networks.

While we aim at a comprehensive overview of the state of the art, we do not always provide a fully detailed discussion of all subjects. For in-depth treatment, we refer the reader to [Koschützki, 2007, Brandes and Erlebach, 2005, Newman, 2010].

In the following sections we will frequently refer to undirected and directed star-topology networks. The  $k$ -node undirected star-topology network is  $U_k^* = (V, E)$  (also known as the full bipartite graph  $K_{1,k}$ ), where  $V = \{1, \dots, k\}$  and  $E = \{\{i, 1\} \mid 2 \leq i \leq k\}$ . The  $k$ -node directed star-topology network is  $G_k^* = (V, E')$ , where  $V$  is the same as in  $U_k^*$  and  $E' = \{(i, 1) \mid 2 \leq i \leq k\}$ . Note that  $E$  consist of unordered pairs of vertices, while  $E'$  consist of ordered pairs. We will also write  $U^*$  and  $G^*$  to refer to the general notion of undirected and directed star-topology networks respectively.

### 11.2.1.1. Running example

We will use the directed network in Figure 11.1 to illustrate the centrality measures and the related concepts. This is a scale-free random network generated using the Python library *NetworkX* [Hagberg et al., 2008, 2021c] with the following line of code: `networkx.scale_free_graph(10, alpha=.7, beta=.2, gamma=.1, seed=3)`.



**Figure 11.1:** The network serving as a running example to illustrate centralities and the related concepts.

### 11.2.1.2. Degree centralities

Degree centrality was first introduced in [Shaw, 1954] to study the structure and behavior of groups of individuals in a society. It measures the importance of a node by directly counting the adjacent edges.

**Definition 11.2 (Degree centrality):** Let  $G = (V, E)$  be a network.

- If  $G$  is undirected, then the *degree centrality* is the function  $\mathcal{C}_D : V \rightarrow \mathbb{R}$  assigning to every node its degree:  $\mathcal{C}_D(v) = \text{deg}(v)$ .
- If  $G$  is directed, then the *in-degree centrality* is the function  $\mathcal{C}_D^- : V \rightarrow \mathbb{R}$ , assigning to every node its in-degree:  $\mathcal{C}_D^-(v) = \text{deg}^-(v)$ . The *out-degree*

centrality  $\mathcal{C}_D^+ : V \rightarrow \mathbb{R}$  assigns to every node its out-degree  $\mathcal{C}_D^+(v) = \text{deg}^+(v)$ .

The (full) degree centrality is the function  $\mathcal{C}_D(v) = \mathcal{C}_D^+(v) + \mathcal{C}_D^-(v)$ .

It follows from these definitions that  $\mathcal{C}_D(v)$  (or  $\mathcal{C}_D^+(v)$  and  $\mathcal{C}_D^-(v)$ ) is large when the node  $v$  is adjacent to a high number of nodes. The extreme cases are  $\mathcal{C}_D(v) = k - 1$ , in which  $v$  is connected to all other nodes in a  $k$ -node network and  $\mathcal{C}_D(v) = 0$ , when  $v$  is isolated in the network.

The degree centrality is strongly related to the number of nodes in a network. As a trivial example, consider the degree centrality of the central node in the star-topology network  $U_k^*$ :  $\mathcal{C}_D^+(1) = k - 1$ . The centrality of node 1 is larger in larger networks with this topology, even though the intuitive idea of the importance of this node is essentially the same: it is connected to all other nodes of the network in both cases. Normalized degree centrality may be used to better capture the independence of the notion of centrality on the size of the network.

**Definition 11.3 (Normalized degree centrality):** Let  $G = (V, E)$  be a (either directed, or undirected) network. The *normalized degree centrality* is the function  $\tilde{\mathcal{C}}_D : V \rightarrow \mathbb{R}$  defined as follows:

$$\tilde{\mathcal{C}}_D(v) = \frac{\mathcal{C}_D(v)}{|V| - 1}.$$

Normalized degree centrality  $\tilde{\mathcal{C}}_D(v)$  therefore gives the ratio of the nodes adjacent to  $v$ , and it follows from the definition that  $0 \leq \tilde{\mathcal{C}}_D(v) \leq 1$ .  $\tilde{\mathcal{C}}_D(v)$  can be thought of as the probability of  $v$  to be connected to another node  $w$  picked at random, an intuition that can be useful when generating random networks with a fixed degree distribution.



**Example 11.1:** *The following table gives the degree, in-degree, and out-degree centralities respectively for the example network in Figure 11.1.*

$v$	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
$\mathcal{C}_D(v)$	2	7	6	1	2	1	2	1	1	1	1	1	1	2	1
$\mathcal{C}_D^-(v)$	1	5	5	0	1	0	2	0	0	0	0	0	0	1	0
$\mathcal{C}_D^+(v)$	1	2	1	1	1	1	0	1	1	1	1	1	1	1	1

The complexity of computing the degree centrality of every individual node of a network depends linearly on the number of nodes and edges:  $O(|V| + |E|)$  (e.g., [Das et al., 2018]). Computing the centrality of any given node may be of the complexity  $O(|V|)$  or  $O(|E|)$ , depending on the data structure used to represent the connections.

The degree centrality is a useful tool for identifying “targets” in a given network, but also for deciding which nodes may be discarded without impacting the quality of the model. This is common in network biology, see [Hahn and Kern, 2004], [Koschützki and Schreiber, 2008]. However, degree centrality is a strongly local measure, mostly focusing on individual nodes and their immediate neighborhoods. In practice, this means that many nodes may often have close degree centralities, requiring finer measures to discern relevant features (e.g. [Kang et al., 2011]).

### 11.2.1.3. Proximity centralities

In this section we discuss closeness, harmonic, and eccentricity centralities.

The degree centrality measure is a very straightforward approach to evaluate the importance of a node in a network. However, the nodes which are connected by a small number of edges to many others in a network are also important: their “influence” can reach many other nodes quickly. Counting the

neighbors of a node clearly does not suffice to assess this kind of closeness to other nodes. The important aspect is rather having a small average distance to the other nodes in the network. This leads to the following definition of the closeness centrality measure as the reciprocal of farness [Bavelas, 1950, Leavitt, 1949, Sabidussi, 1966].

**Definition 11.4 (Closeness centrality):** Let  $G = (V, E)$  be an undirected network. The *closeness centrality* is the function  $\mathcal{C}_C : V \rightarrow \mathbb{R}$  defined as follows:

$$\mathcal{C}_C(v) = \frac{1}{\sum_{u \in V} d(u, v)}.$$

As in the case of degree centralities, the size of the network has an impact on the closeness centrality of its nodes: the larger the network, the more paths it contains, and the lower closeness centralities tend to become. To make closeness centralities more uniform, [Beauchamp, 1965] proposed the normalized version of this measure.

**Definition 11.5 (Normalized closeness centrality):** Let  $G = (V, E)$  be a connected undirected network. The *normalized closeness centrality* is the function  $\tilde{\mathcal{C}}_C : V \rightarrow \mathbb{R}$  is defined as follows:

$$\tilde{\mathcal{C}}_C(v) = \frac{|V| - 1}{\sum_{u \in V} d(u, v)}.$$

Normalized closeness centrality can be thought of as the inverse of the mean of the distances to  $v$  from all other nodes. The bounds on the values of the normalized closeness centrality  $\tilde{\mathcal{C}}_C$  are the same as the bounds on the values of  $\mathcal{C}_C$ :  $0 < \tilde{\mathcal{C}}_C(v) \leq 1$ , but  $\tilde{\mathcal{C}}_C(v)$  reaches its maximal value 1 for any node  $v$

adjacent to all the other nodes of a given network.

A major drawback of closeness centrality is that it does not yield meaningful values on disconnected networks. Indeed, if no path connects nodes  $u$  and  $v$ , by definition  $d(u, v) = \infty$ , and therefore a single isolated node would make the sums of distances in the definition of closeness infinite, and the closeness centralities themselves will all become 0. There are several different ways in which this can be addressed:

- Restrict the notion of closeness centrality to strongly connected graphs (or strongly connected components of arbitrary graphs). This avoids the problem of having pairs of nodes  $(u, v)$  whose distance is infinite, on the grounds of  $v$  being unreachable from  $u$ .
- Restrict the sum of distances in the definition of closeness centrality to pairs of reachable nodes, addressing the same issue of infinite distances.
- Replace any infinite distances with a large enough constant, as proposed in [Rochat, 2009] and [Csárdi and Nepusz, 2006].

Closeness centrality can also be defined for directed networks. To do this, we can consider in the definition either the distances  $d(u, v)$  from all ancestors of  $v$  to  $v$ , or distances  $d(v, u)$  from  $v$  to all its descendants. This is important when using the closeness centrality measure as a proxy for the notion of either a node that is reachable (and modifiable) from many directions, or that of a node that is influential in being able to reach many other nodes. One example of such a definition is the *Lin index* [Lin, 1976]. The software package *NetworkX* computes the distances from the nodes which reach  $v$  [Hagberg et al., 2021a], and normalizes with respect to the number of these nodes. The difficulties with infinite distances for pairs of unreachable nodes persist also in the directed case, with possible solutions similar to those for the undirected case.

**Example 11.2:** *The following table gives the closeness centralities and the normalized closeness centralities, rounded to two digits after the decimal point, for the nodes of the example network in Figure 11.1. The lines  $C_C^u(v)$  and  $\tilde{C}_C^u(v)$  take this network to be undirected, meaning that the directed edges appearing in the figure can be traversed both ways. The calculations for directed networks were done with NetworkX, using the approach explained above.*

$v$	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
$C_C(v)$	0.03	0.04	0.05	0.00	1.00	0.00	0.03	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00
$\tilde{C}_C(v)$	0.40	0.48	0.60	0.00	1.00	0.00	0.36	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00
$C_C^u(v)$	0.03	0.05	0.04	0.03	0.03	0.03	0.03	0.03	0.03	0.02	0.03	0.03	0.02	0.03	0.02
$\tilde{C}_C^u(v)$	0.48	0.64	0.58	0.38	0.40	0.40	0.42	0.38	0.38	0.29	0.40	0.40	0.30	0.42	0.30

Computing the closeness centrality of a node  $v$  requires finding the shortest paths to  $v$  from all other nodes of the network. Since constructing all shortest path to one particular node  $v$  is of complexity  $O(|E|)$ , using e.g. a breadth-first search, computing the closeness centrality for all the nodes within a network is of complexity  $O(|V| \cdot |E|)$ . This means that computing the exact value of closeness centrality is impractical for many biological networks, which often contain thousands of nodes and tens of thousands of connections. It turns out that, in practice, one often only needs the first  $k$  nodes with the highest closeness centrality, without requiring the actual centrality values. Such rankings can be computed in reasonable time even for very large networks, see, e.g., [Bergamini et al., 2019].

Due to its non-locality, closeness centrality is a finer tool for structural network analysis than degree centrality. For example, closeness fares better in identifying influential groups of nodes which may not individually have high degree centrality. Closeness centrality has been show to perform particularly

well in biological network analysis. For example, [Ma and Zeng, 2003] shows that a slightly modified closeness measure allows for associating 8 of the top 10 metabolites of the metabolic network of *E. coli* with the glycolysis and citric acid cycle pathways.

A modification of closeness centrality, addressing the difficulty of infinite distances, consists in swapping the summation out of the denominator, effectively transforming what is an inverse arithmetic mean in normalized closeness centrality into inverse *harmonic* mean. This new centrality measure was first discussed in [Marchiori and Latora, 2000], then independently introduced in [Dekker, 2005] under the name “valued centrality”, and finally gained its current name of harmonic centrality in [Rochat, 2009].

**Definition 11.6 (Harmonic centrality):** Let  $G = (V, E)$  be a (either directed, or undirected) network. The *harmonic centrality* is the function  $\mathcal{C}_H : V \rightarrow \mathbb{R}$  defined as follows:

$$\mathcal{C}_H(v) = \sum_{u \in V \setminus \{v\}} \frac{1}{d(u, v)}.$$

Note that all nodes  $u$  which are not connected to  $v$  do not contribute to  $\mathcal{C}_H(v)$ , because  $d(u, v) = \infty$ , meaning that  $1/d(u, v) = 0$ .

As with closeness centrality, the same definition of harmonic centrality can be used for directed networks, in which case the order of nodes in the denominator  $d(u, v)$  becomes important. If  $v$  has in-degree 0,  $\mathcal{C}_H(v) = 0$  by direct computation of the formula in the definition.

To avoid an increase in harmonic centrality only due to the increase in the size of the network, one defines the normalized version.

**Definition 11.7 (Normalized harmonic centrality):** Let  $G = (V, E)$  be a (either directed, or undirected) network. The *normalized harmonic centrality* is the function  $\tilde{\mathcal{C}}_H : V \rightarrow \mathbb{R}$  defined as follows:

$$\tilde{\mathcal{C}}_H(v) = \frac{1}{|V| - 1} \sum_{u \in V \setminus \{v\}} \frac{1}{d(u, v)}.$$

It follows that  $0 \leq \tilde{\mathcal{C}}_H(v) \leq 1$  (and  $0 \leq \mathcal{C}_H(v) \leq |V| - 1$ ) both in directed and undirected networks.  $\tilde{\mathcal{C}}_H(v) = 0$  for isolated vertices, while  $\tilde{\mathcal{C}}_H(v) = 1$  ( $\mathcal{C}_H(v) = |V| - 1$ ) for the center of a star network, in both directed and undirected cases, because both in  $U_k^*$  and  $G_k^*$  every node is connected to the central node 1.

Note that central nodes in large connected components will have greater values of harmonic centrality than central nodes in small connected components. Furthermore, nodes in disconnected networks will tend to have lower harmonic centralities than nodes in connected networks.

**Example 11.3:** *The following table gives the harmonic centralities and the normalized harmonic centralities, rounded to two digits after the decimal point, for the nodes of the example network in Figure 11.1. The lines  $\mathcal{C}_H^u(v)$  and  $\tilde{\mathcal{C}}_H^u(v)$  take this network to be undirected, meaning that the directed edges appearing in the figure can be traversed both ways.*

$v$	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
$\mathcal{C}_H(v)$	5.42	7.58	8.33	0.00	1.00	0.00	6.37	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00
$\tilde{\mathcal{C}}_H(v)$	0.39	0.54	0.60	0.00	0.07	0.00	0.45	0.00	0.00	0.00	0.00	0.00	0.00	0.07	0.00
$\mathcal{C}_H^u(v)$	7.50	10.33	9.67	6.00	6.67	6.25	6.92	6.00	6.00	4.82	6.25	6.25	4.95	6.92	4.95
$\tilde{\mathcal{C}}_H^u(v)$	0.54	0.74	0.69	0.43	0.48	0.45	0.49	0.43	0.43	0.34	0.45	0.45	0.35	0.49	0.35

The computational complexities related to the harmonic centrality are the

same as those of the closeness centrality, because of the similarities in the definitions of the two measures. Since finding the shortest path is of complexity  $O(|E|)$ , computing the harmonic centrality in a given directed or undirected network  $G = (V, E)$  is of complexity  $O(|V| \cdot |E|)$ . For very large networks, approximate calculation strategies can be used, or alternatively the direct computation of centrality can be replaced by finding the top  $k$  nodes with the highest centrality value, similarly to [Bergamini et al., 2019].

Like closeness centrality, harmonic centrality has great potential for analysis of biological networks, because it captures the intuition of the influence of a node decaying with the distance, while also naturally handling disconnected networks. Online resources for systems biology offer tools to compute harmonic centrality (e.g., [Zhang et al., 2016]), and this centrality measure is used in analysing simulations of growth of biological networks [Paul and Kollmannsberger, 2020]. We remark however that several papers use the term “harmonic centrality” to refer to a rather different centrality measure, e.g. [Ren et al., 2015, Mao et al., 2020].

Another modification to closeness centrality we will briefly consider in this subsection was introduced in [Dangalchev, 2006]. This work goes beyond harmonic centrality and adds an exponential to the denominator:

$$\mathcal{D}(v) = \sum_{u \in V \setminus \{v\}} \frac{1}{2^{d(u,v)}}.$$

Like harmonic centrality,  $\mathcal{D}$  treats disconnected networks naturally. In addition,  $\mathcal{D}$  interacts conveniently with various operations on graphs, in particular with different kinds of graph union [Dangalchev, 2006, Section 2]. Finally, this

centrality measure can be generalized to the following form [Dangalchev, 2011]:

$$\mathcal{D}'(v) = \sum_{u \in V \setminus \{v\}} \alpha^{d(u,v)},$$

where  $\alpha \in (0, 1)$ . Clearly, for  $\alpha = \frac{1}{2}$ ,  $\mathcal{D}'(v) = D_C(v)$ , and as  $\alpha$  increases between 0 and 1,  $\mathcal{D}'$  moves from local (mostly immediate neighbours count) to global (even long-distance connections count).

Even though the centrality measures we surveyed so far in this subsection are all based on the notion of closeness, one should underline that they are not true extensions of the closeness centrality. Indeed, the paper [Yang and Zhuhadar, 2011] shows that, even on a 7-node tree, these centrality measures yield close, but different values.

The last centrality measure based on the length of paths to a given node that we discuss is the eccentricity centrality. It formalizes the intuition that important nodes are those from which any other node is quickly reachable. It was originally introduced in [Hage and Harary, 1995], but we give here the mathematical definition from [Koschützki, 2007].

**Definition 11.8 (Eccentricity centrality):** Let  $G = (V, E)$  be a strongly connected (either directed, or undirected) network. The *eccentricity centrality* is the function  $\mathcal{C}_e : V \rightarrow \mathbb{R}$  defined as follows:

$$\mathcal{C}_e(v) = \frac{1}{\max_{u \in V} d(v, u)}.$$

The value in the denominator of  $\mathcal{C}_e$  is the longest *shortest path* in  $G$  starting at  $v$  and is usually referred to as the *eccentricity* of  $v$ .

The same definition of eccentricity centrality can be used for undirected



and directed networks. In the latter case, the order of  $v$  and  $u$  in  $d$  becomes important, and the directed network is often required to be strongly connected [Koschützki, 2007]. In networks which are not strongly connected, the shortest is computed only to nodes reachable from  $v$ . Moreover, if the out-degree of  $v$  is 0, then by definition  $\mathcal{C}_e(v) = 0$ .

The bounds on eccentricity centrality are the same as for normalized closeness centrality:  $0 \leq \mathcal{C}_e(v) \leq 1$ .  $\mathcal{C}_e$  reaches its maximal value for every node which is directly connected to other nodes, as is the case of the center of a star-topology network or any node of a complete network.

Unlike closeness or harmonic centralities, eccentricity centrality does not directly depend on the size of the network, which is why normalization is not generally considered for this measure.

**Example 11.4:** *The following table gives the eccentricity centralities for the nodes of the example network in Figure 11.1. Since the example network is not strongly connected, the centralities  $\mathcal{C}_e(v)$  are computed as inverses of the lengths of the longest shortest paths to reachable nodes. The line labeled with  $\mathcal{C}_e^u(v)$  takes this network to be undirected, meaning that the directed edges appearing in the figure can be traversed both ways.*

$v$	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
$\mathcal{C}_e(v)$	$\frac{1}{2}$	$\frac{1}{2}$	$\frac{1}{3}$	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{3}$	0	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{5}$	$\frac{1}{3}$	$\frac{1}{3}$	$\frac{1}{1}$	$\frac{1}{3}$	$\frac{1}{4}$
$\mathcal{C}_e^u(v)$	$\frac{1}{3}$	$\frac{1}{3}$	$\frac{1}{3}$	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{5}$	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{5}$	$\frac{1}{4}$	$\frac{1}{5}$

Similarly to closeness centrality, computing the eccentricity centrality of a node  $v$  requires finding the shortest paths to all other nodes in the network, meaning that computing  $\mathcal{C}_e(v)$  is of time complexity  $O(|V| \cdot |E|)$ .

Like closeness centrality, eccentricity centrality is able to capture well the notion of importance of a node as a function of its connections to the other

nodes. For example, [Wuchty and Stadler, 2003] uses several centrality measures to analyse the networks of *E. coli* and *S. cerevisiae*, and shows that both closeness and eccentricity centralities produce very similar rankings of the top metabolites. On the other hand, eccentricity centrality was not able to distinguish essential from non-essential proteins in the PPI network of *S. cerevisiae*.

#### 11.2.1.4. Path centrality: betweenness

Betweenness centrality measures the importance of a node by counting in how many connections between other nodes it is implicated. For example, the central node 1 of  $U_k^*$  is involved in all shortest paths between all other nodes. The idea of betweenness, i.e. being situated between other nodes, was introduced in the discussion of point centrality in [Bavelas, 1948], and the first formal definition was given in [Freeman, 1977].

Given a (either directed, or undirected) network, we denote the set of all shortest paths (also referred to as *geodesics*) between nodes  $u$  and  $w$  by  $\rho_{uw}$ , and by  $\rho_{uw}(v)$  the set of those shortest paths from  $\rho_{uw}$  which pass through  $v$ . We further denote  $g_{uw} = |\rho_{uw}|$  and  $g_{uw}(v) = |\rho_{uw}(v)|$ . Finally, we use the following notation:

$$p_{uw}(v) = \begin{cases} \frac{g_{uw}(v)}{g_{uw}}, & \rho_{uw} \neq \emptyset, \\ 0, & \text{otherwise.} \end{cases}$$

$p_{uw}(v)$  can be seen as the probability of finding  $v$  in a shortest path between  $u$  and  $w$  chosen at random from  $g_{uw}$ , in the case in which  $w$  is reachable from  $u$  [Freeman, 1977, 1978].

**Definition 11.9 (Betweenness centrality):** Let  $G = (V, E)$  be a (either

directed, or undirected) network. The *betweenness centrality* is the function  $\mathcal{C}_B : V \rightarrow \mathbb{R}$  defined as follows:

$$\mathcal{C}_B(v) = \sum_{\substack{u, w \in V \setminus \{v\} \\ u \neq w}} p_{uw}(v).$$

Note that in this case too, there are subtle distinctions between directed and undirected networks. Thus, while in the case of undirected networks  $\rho_{uw}$  (as well as  $\rho_{uw}(v)$ ) is conceptually the same as  $\rho_{wu}$  ( $\rho_{wu}(v)$ , resp.), and consequently the pair is not considered separately, this is not the case of directed networks. Hence, while the betweenness centrality function involves a  $(k-1)(k-2)/2$  summation for undirected networks, i.e., the number of unordered pairs of nodes distinct from  $v$ , in the case of directed networks it consists of a  $(k-1)(k-2)$  summation.

Betweenness centrality reaches its minimal value 0 for isolated nodes and its maximal value for nodes  $v$  situated on *all* shortest paths between all other nodes of the network. For a  $k$ -node network with  $k \geq 2$ , this maximal value equals the number of pairs of nodes different from  $v$ :  $\mathcal{C}_B(v) = (k-1)(k-2)/2$  for undirected networks, and  $\mathcal{C}_B(v) = (k-1)(k-2)$  for the directed ones. In the case of undirected networks, this value will be reached for the central node of a  $k$ -node star-topology network  $U_k^*$ . In the case of directed networks, this maximal value will be reached for the central node of the  $k$ -node star topology network, in which there are two symmetric edges between the central node and the non-central nodes:  $\tilde{G}_k^* = (V, E)$ , with  $V = \{1, \dots, k\}$  and  $E = \{(1, i), (i, 1) \mid 2 \leq i \leq k\}$ .

In fact, not only  $\mathcal{C}_B$  reaches its maximal value for the central node of a star-topology network, but the existence of a node for which  $\mathcal{C}_B$  reaches its

maximal value is sufficient to guarantee that the network is a star.

**Lemma 11.1:** *Let  $k \geq 2$  and let  $U = (V, E)$  be a  $k$ -node undirected network ( $|V| = k$ ) having a node  $v \in V$  for which  $C_B(v) = (k-1)(k-2)/2$ . Then  $U$  is isomorphic to  $U_k^*$ .*

*Proof.* The fact that  $C_B(v) = (k-1)(k-2)/2$  means that  $v$  appears in *all* shortest paths between all other nodes. This implies on the one hand that  $v$  is connected to all other nodes, and on the other hand that there are no other edges in  $U$ . Indeed, if  $v$  were not connected to some of the other nodes, then there would exist a pair of nodes  $u, w \in V$  with the property  $g_{uw}(v) = 0$ , meaning that  $C_B(v) < (k-1)(k-2)/2$ . On the other hand, if there existed an edge between two vertices  $u, w \in V$ , then the only shortest path from  $u$  to  $w$  would not traverse  $v$ , which again would mean that  $g_{uw}(v) = 0$  and  $C_B(v) < (k-1)(k-2)/2$ .  $\square$

A similar result for directed networks imposes that any directed network  $G$  having a node with maximal betweenness centrality should be isomorphic to  $\bar{G}_k^*$ .

**Lemma 11.2:** *Let  $k \geq 2$  and let  $G = (V, E)$  be a  $k$ -node directed network ( $|V| = k$ ) having a node  $v \in V$  for which  $C_B(v) = (k-1)(k-2)$ . Then  $G$  is isomorphic to  $\bar{G}_k^*$ .*

Note that in the case of the star-topology directed network  $G_k^*$  in which there are arcs going from all non-central nodes to the central node 1 and no arcs going out of 1, the betweenness centrality of all nodes will be 0, because all paths in this network have length 1.

To avoid the increase in betweenness centrality due only to the increase

in the size of the network, one typically defines its normalized version. Unlike normalized closeness and harmonic centralities, in the case of betweenness one needs to normalize with respect to the number of pairs of nodes, rather than the number of nodes.

**Definition 11.10 (Normalized betweenness centrality):** Let  $G = (V, E)$  be a (either directed, or undirected) network. The *normalized betweenness centrality* is the function  $\tilde{C}_B : V \rightarrow \mathbb{R}$  defined as follows:

$$\begin{aligned} \text{a) } \tilde{C}_B(v) &= \frac{2}{(|V| - 1)(|V| - 2)} \sum_{\substack{u, w \in V \setminus \{v\} \\ u \neq w}} p_{uw}(v), & \text{ for undirected networks,} \\ \text{b) } \tilde{C}_B(v) &= \frac{1}{(|V| - 1)(|V| - 2)} \sum_{\substack{u, w \in V \setminus \{v\} \\ u \neq w}} p_{uw}(v), & \text{ for directed networks.} \end{aligned}$$

Normalized betweenness centrality ranges between 0 for isolated vertices and 1 for central nodes of star-topology networks.

**Example 11.5:** *The following table gives the betweenness centralities and the normalized betweenness centralities, rounded to two digits after the decimal point, for the nodes of the example network in Figure 11.1. The lines  $C_B^u(v)$  and  $\tilde{C}_B^u(v)$  take this network to be undirected, meaning that the directed edges appearing in the figure can be traversed both ways.*

$v$	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
$C_B(v)$	12.00	23.00	21.00	0.00	4.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	4.00	0.00
$\tilde{C}_B(v)$	0.07	0.13	0.12	0.00	0.02	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.00
$C_B^u(v)$	0.00	68.00	54.00	0.00	13.00	0.00	13.00	0.00	0.00	0.00	0.00	0.00	0.00	13.00	0.00
$\tilde{C}_B^u(v)$	0.00	0.75	0.59	0.00	0.14	0.00	0.14	0.00	0.00	0.00	0.00	0.00	0.00	0.14	0.00

Enumerating all shortest paths between all pairs of nodes different from a given node  $v$  is rather expensive. The seminal work [Freeman, 1977] suggests computing powers of the adjacency matrix of the network to count the shortest paths, according to the methods detailed in [Harary et al., 1965]. However, [Brandes, 2001] proposes a less expensive algorithm running in time  $O(|V| \cdot |E|)$ , and avoiding extra non-optimal paths which matrix multiplication would reveal. A more recent work [Nasre et al., 2014] proposes an even faster incremental algorithm, which updates the betweenness centralities of all nodes when a new edge is added. This algorithm runs in time  $O(m|V|)$ , where  $m$  is the maximal length of the shortest path in the network. Finally, the paper [Borassi and Natale, 2019] proposes a random approximation algorithm which computes betweenness centralities in time  $|E|^{1/2+o(1)}$  with high probability, much faster than exact algorithms.

Betweenness centrality has been successfully applied in biological network analysis to identify significant nodes. For example, the work [Sahoo et al., 2016] used betweenness centrality to identify proteins significant in the context of cancer growth. In [Yu et al., 2007], the authors rely on betweenness centrality to identify bottlenecks in PPI networks. Moreover, the authors show that these nodes have a high tendency of representing essential proteins. The work [Joy et al., 2005] shows that nodes with high betweenness centrality in yeast PPI networks are more likely to be essential and that the evolutionary age of proteins is positively correlated with their betweenness centrality.

We conclude this subsection by mentioning a well-known extension of the betweenness centrality: *percolation centrality*. This measure was introduced in [Piraveenan et al., 2013] with the goal of taking into account the dynamical states of the nodes of the network. Intuitively, percolation centrality extends

the definition of betweenness centrality by multiplying  $p_{uv}(v)$  by *percolation*: a factor derived from the degree to which the nodes in the paths from  $u$  to  $w$  are involved in the spread of some value (information, infection, etc.) through the network. Since percolation centrality considers network states, we do not discuss it in this section.

### 11.2.1.5. Spectral centralities

In this section we discuss eigenvector-based centralities: the eigenvector centrality, Katz centrality, and PageRank centrality.

The idea of using eigenvectors for assessing the importance of nodes in networks was first introduced in [Bonacich, 1987] and further discussed in several fundamental works, e.g. [Ruhnau, 2000, Newman, 2008] with the goal of taking into account the fact that not all connections in a network are equal — being connected to a highly central node has more impact than being connected to a more peripheral node. Before defining eigenvector centrality, we introduce some additional notations.

Given a (either directed, or undirected) network  $G = (V, E)$ , we denote its adjacency matrix by  $\mathbf{A}$ , in which  $A_{uv} = 1$  if and only if  $G$  contains an edge from node  $u$  to node  $v$ . For a centrality measure  $\mathcal{C} : V \rightarrow \mathbb{R}$ , we will denote by  $\mathbf{c}$  the vector obtained by computing  $\mathcal{C}$  for every node of  $G$ , i.e.  $\mathbf{c}_v = \mathcal{C}(v)$ .

For a fixed node  $v$ , the idea that the contributions of its neighbors are proportional to their own centralities can be expressed as follows:

$$\mathcal{C}(v) = \frac{1}{\lambda} \sum_{u \in V} A_{uv} \mathcal{C}(u),$$

where  $\lambda > 0$  is a real constant. This relation can be rewritten in the matrix

form:

$$\lambda \mathbf{c} = \mathbf{A} \mathbf{c}, \tag{11.1}$$

which effectively defines  $\mathbf{c}$  as an eigenvector, and  $\lambda$  as an eigenvalue of the adjacency matrix  $\mathbf{A}$  of the network  $G$ . Since  $\mathbf{A}$  is a real square matrix (its elements are 0 and 1 in the case of unweighted networks), according to the Perron-Frobenius theorem of linear algebra,  $\mathbf{A}$  has a unique largest real eigenvalue  $\lambda$  and one can choose the corresponding eigenvector  $\mathbf{c}$  to be strictly positive, which allows defining a meaningful centrality measure [Newman, 2008].

**Definition 11.11 (*Eigenvector centrality*):** Let  $G = (V, E)$  be a (either directed, or undirected) network and  $\mathbf{A}$  its adjacency matrix. Let  $\lambda$  be the largest real eigenvalue of  $\mathbf{A}$  and  $\mathbf{c}$  a corresponding eigenvector with strictly positive components. An *eigenvector centrality* is a function  $\mathcal{C}_E : V \rightarrow \mathbb{R}$  defined as follows:  $\mathcal{C}_E(v) = \mathbf{c}_v$ .

Eigenvalue centrality is sometimes referred to as eigencentality or eigenvector prestige. The same definition can be used for directed networks, in which case the adjacency matrix  $\mathbf{A}$  may not be diagonally symmetric.

We will refer to eigenvectors  $\mathbf{c}$  satisfying the constraints of the previous definition as *principal* eigenvectors of  $\mathbf{A}$  and of the network  $G$ . In fact, it follows from (11.1) that any other vector  $\alpha \mathbf{c}$ ,  $\alpha > 0$ , is also a principal eigenvector of  $\mathbf{A}$ . This means that the components of  $\mathbf{c}$  (and therefore the values of  $\mathcal{C}_E$ ) indicate relative centralities of the nodes of  $G$  with respect to one another, rather than some absolute centrality score.

A standard way of fixing a preferred principal eigenvector  $\mathbf{c}$  to avoid ambiguity is by normalizing  $\mathbf{c}$ . Several ways to normalize eigenvectors for centrality exist; we focus here on three norms studied in [Ruhnau, 2000] and we discuss



implications of these normalizations for the eigenvector centrality index — a network-wide measure of centralization. The results from [Ruhnau, 2000] also rely on the work of [Papendieck and Recht, 2000] which studies maximal entries in the principal eigenvector of a graph.

Normalizing an  $n$ -vector  $\mathbf{a}$  typically consists in dividing its components by a  $p$ -norm, which is commonly defined as follows:

$$\|\mathbf{a}\|_p = \begin{cases} \left( \sum_{i=1}^n a_i^p \right)^{\frac{1}{p}}, & 1 \leq p < \infty, \\ \max_{1 \leq i \leq n} |a_i|, & p = \infty. \end{cases}$$

One of the ways of normalizing the vector  $\mathbf{c}$  from Definition 11.11 is by dividing all of its components by the  $\infty$ -norm, also known as the maximum norm.

**Definition 11.12 ( $\infty$ -norm eigenvector centrality):** Let  $G = (V, E)$  be a (either directed, or undirected) network and  $\mathbf{c}$  be the principal eigenvector of  $G$ . The  $\infty$ -norm eigenvector centrality is the function  $\mathcal{C}_E^{(\infty)} : V \rightarrow \mathbb{R}$  defined as follows:

$$\mathcal{C}_E^{(\infty)}(v) = \frac{\mathbf{c}_v}{\|\mathbf{c}\|_\infty} = \frac{\mathbf{c}_v}{\max_{u \in |V|} \mathbf{c}_u}.$$

It follows directly from this definition that  $0 \leq \mathcal{C}_E^{(\infty)}(v) \leq 1$ , and that every connected network  $G$  has a node  $v^*$  for which  $\mathcal{C}_E^{(\infty)}(v^*) = 1$ .

Another way of normalizing the eigenvector centrality is by using the 1-norm, also known as the sum norm.

**Definition 11.13 (1-norm eigenvector centrality):** Let  $G = (V, E)$  be a (either directed, or undirected) network and  $\mathbf{c}$  be the principal eigenvector of

$G$ . The *1-norm eigenvector centrality* is the function  $\mathcal{C}_E^{(1)} : V \rightarrow \mathbb{R}$  defined as follows:

$$\mathcal{C}_E^{(1)}(v) = \frac{\mathbf{c}_v}{\|\mathbf{c}\|_1} = \frac{\mathbf{c}_v}{\sum_{u \in V} \mathbf{c}_u}.$$

$\mathcal{C}_E^{(1)}(v)$  can be seen as the proportion of centrality that  $v$  reaches in  $G$ . The bounds on the values of the 1-norm eigenvector centrality are as follows [Ruhnanu, 2000]:

$$0 \leq \mathcal{C}_E^{(1)}(v) \leq \frac{1}{1 + (2 \cos \frac{\pi}{n+1})^{-1}}.$$

This centrality measure cannot ever reach 1 for any network with 2 or more connected nodes. The upper bound is only reached for the nodes of a network which only contains one edge [Papendieck and Recht, 2000]. In the case of networks with more than 2 connected nodes, it is not known what is the actual maximal value  $\mathcal{C}_E^{(1)}$  can achieve, nor in which kind of network topologies this value can be achieved. For example, the central node of a star-topology network *does not* reach the maximal value.

One last way of normalizing the eigenvector centrality which we consider in this section is by using the 2-norm, also known as the Euclidean norm.

**Definition 11.14 (2-norm eigenvector centrality):** Let  $G = (V, E)$  be a (either directed, or undirected) network and  $\mathbf{c}$  be the principal eigenvector of  $G$ . The *2-norm eigenvector centrality* is the function  $\mathcal{C}_E^{(2)} : V \rightarrow \mathbb{R}$  defined as follows:

$$\mathcal{C}_E^{(2)}(v) = \frac{\mathbf{c}_v}{\|\mathbf{c}\|_2} = \frac{\mathbf{c}_v}{\sqrt{\sum_{u \in V} \mathbf{c}_u^2}}.$$

The bounds on the 2-norm eigenvector centrality are  $0 \leq \mathcal{C}_E^{(2)}(v) \leq \frac{1}{\sqrt{2}}$ . The maximal value  $\frac{1}{\sqrt{2}}$  is only reached by the center of the star topology

network [Ruhnau, 2000]. One may define a derived measure ranging from 0 to 1 by multiplying  $\mathcal{C}_E^{(2)}$  by  $\sqrt{2}$ .

Finding eigenvectors and eigenvalues of a given square matrix is closely related to finding the roots of polynomials. It follows from the Abel-Ruffini theorem that there exists no algorithm computing exactly the eigenvectors and eigenvalues for square matrices of size greater than 4 (e.g., [Golub and van der Vorst, 2000]). Therefore, iterative algorithms are usually used, one of the most popular being the power iteration method (used e.g., in *NetworkX* [Hagberg et al., 2008]). The complexity of such iterative methods is generally between  $O(|V|^2)$  and  $O(|V|^3)$ , while the convergence rate ranges from linear to cubic [Demmel, 1997].

Eigenvalue centrality measures are a fine instrument for measuring the importance of nodes in a network, because they acknowledge the difference in impact between a connection to a high-centrality neighbor and a connection to a low-centrality one. With eigenvalue centrality, a node with a smaller number of “high-quality” connections may outrank a node with a larger number of “low-quality” connections [Newman, 2008]. The work [Estrada, 2006] applies closeness, betweenness, and eigenvector centralities to identifying essential proteins in PPI networks, and concludes that spectral centralities show the best performance. The paper [Negre et al., 2018] uses eigenvector centrality to pinpoint key amino acids in terms of their relevance in the allosteric regulation. The study [Melak and Gakkhar, 2015] uses different centrality measures to identify potential drug targets of *Mycobacterium tuberculosis*, the etiological agent of tuberculosis (TB), and show that eigenvalue centrality fares best.

Another centrality measure based on the algebraic properties of the adjacency matrix is *Katz centrality* (also referred to as *Katz prestige* or *Katz status*

*index*). This method was proposed in [Katz, 1953] and it gives a centrality score by taking into consideration all the nodes of a given network. According to a reasoning similar to the one made for closeness centrality and its variants (Subsection 11.2.1.3), a node is of high importance if it is connected to many other nodes, but nodes situated farther away count less toward the total centrality score.

**Definition 11.15 (Katz centrality):** Let  $G = (V, E)$  be a (either directed, or undirected) loop-free network. Let  $\mathbf{A}$  be its adjacency matrix and  $\lambda$  be its largest positive eigenvalue. The *Katz centrality* is the function  $\mathcal{C}_K : V \rightarrow \mathbb{R}$  defined as follows:

$$\mathcal{C}_K(v) = \sum_{i=1}^{\infty} \sum_{u \in V} \alpha^i (\mathbf{A}^i)_{uv},$$

where  $\alpha$  is a constant,  $0 \leq \alpha \leq 1/\lambda$ , and  $(\mathbf{A}^i)_{uv}$  is the element in row  $u$  and column  $v$  of the  $i$ -th power of  $\mathbf{A}$ .

Since  $(\mathbf{A}^i)_{uv}$  is non-zero if and only if there exists a path of length exactly  $i$  between  $u$  and  $v$ , Katz centrality can be interpreted as a generalization of degree centrality [Koschützki, 2007]. Indeed, the role of the factor  $\alpha^i$  is to scale down the contributions of longer paths, and without it  $\mathcal{C}_K(v)$  essentially becomes the *reachability index*: the number of nodes from which  $v$  can be reached. If  $\alpha$  is close to 0, the contributions of longer paths are essentially discarded, and  $\mathcal{C}_K$  approaches a form of degree centrality. On the other hand, as  $\alpha$  approaches  $1/\lambda$ ,  $\mathcal{C}_K$  approaches eigenvector centrality [Newman, 2010].

Let  $\mathbf{c}_K$  be the vector collecting Katz centralities of a node in a given network:  $(\mathbf{c}_K)_v = \mathcal{C}_K(v)$ . Then  $\mathbf{c}_K$  can be expressed in a more compact matrix

multiplication form in the following way [Koschützki, 2007]:

$$\mathbf{c}_K = ((\mathbf{I} - \alpha \mathbf{A}^T)^{-1} - \mathbf{I})\mathbf{1},$$

where  $\mathbf{I}$  is the identity matrix of the same size as  $\mathbf{A}$ ,  $\mathbf{A}^T$  is the transpose of  $\mathbf{A}$ ,  $(\cdot)^{-1}$  denotes matrix inversion, and  $\mathbf{1}$  is a  $|V|$ -vector whose components are all 1.

Due to similarities with eigenvector centrality, exact Katz centrality can be computed by similar algorithms with similar running time complexities. In particular, the power iteration method can be applied (e.g., [Hagberg et al., 2021b]). Faster approximate algorithms exist, in particular [Foster et al., 2001] presents an iterative algorithm with time complexity  $O(|V| + |E|)$ , given a constant desired precision.

Typical applications of Katz centrality concern directed networks, in particular directed acyclic networks, in which eigenvector centrality appears less useful [Newman, 2010]. Katz centrality has found promising applications in neuroscience. The work [Fletcher and Wennekers, 2018] shows that Katz centrality is the best predictor of firing rate given the network structure, with almost perfect correlation in all cases studied. The paper [Mantzaris et al., 2013] uses Katz centrality to analyse fMRI data of human brain activity during learning, and shows how key brain regions contributing to the process can be discovered.

A third eigenvalue and eigenvector-related centrality measure we briefly discuss in this section is PageRank, one of the algorithms used by Google to measure the importance of web pages [Google, 2011]. Multiple variants of PageRank have been proposed. We start with the definition from [Langville and Meyer, 2005].

**Definition 11.16 (PageRank):** Let  $G = (V, E)$  be a directed network and  $\mathbf{A}$  its adjacency matrix. The *PageRank* centrality is the function  $\mathcal{C}_P : V \rightarrow \mathbb{R}$  satisfying the following equation:

$$\mathcal{C}_P(v) = \sum_{u \in V} A_{uv} \frac{\mathcal{C}_P(u)}{\text{deg}^+(u)},$$

where  $\text{deg}^+(u)$  is the out-degree of the node  $u$ .

According to this definition, the centrality  $\mathcal{C}_P(v)$  depends on the centralities of the nodes  $u$  from which there is an edge going to  $v$  ( $A_{uv} \neq 0$ ). The contribution of each of these nodes  $u$  to  $\mathcal{C}_P(v)$  is inversely proportional to the number of edges going out of  $u$ . Thus, nodes connected to many other nodes contribute less to each of their neighbors than nodes which are connected to fewer nodes.

The complete definition of PageRank centrality (which was used in the first versions of the Google search engine) includes two additional parameters:

$$\mathcal{C}_P^{(0)}(v) = \alpha \sum_{u \in V} A_{uv} \frac{\mathcal{C}_P(u)}{\text{deg}^+(u)} + \beta,$$

where  $\alpha$  can be seen as a decay factor, and  $\beta$  as a vector of initial centralities (source ranks), scaled by  $\alpha$ . We take this definition from [Franceschet, 2021], which gives a slightly simplified and generalized version of the original definition from [Page et al., 1999].

The PageRank centrality is related to eigenvector centrality in the way the adjacency matrix of the network is exploited to define relative centrality scores. Since the formulae for computing PageRank are more complex, using iterative algorithms is often preferred, especially for large networks [Langville

and Meyer, 2005, Page et al., 1999]. Several specific and faster algorithms have been proposed for computing PageRank. In particular, the paper [Corso et al., 2005] proposes an algorithm consisting in reducing PageRank computation to computing solutions of linear systems, while the article [Bahmani et al., 2010] proposes Monte Carlo methods for incremental computation of PageRank.

PageRank is a relatively recent centrality measure, but it has already shown some promising performance in analysis of biological networks. In the work [Iván and Grolmusz, 2010], the authors computed PageRank centralities for the metabolic network of the Mycobacterium tuberculosis and the PPI networks of melanoma patients, and in both cases important proteins received a high centrality score.

**Example 11.6:** *The following table gives eigenvector ( $\mathcal{C}_E^X$ ), Katz ( $\mathcal{C}_K^X$ ), and PageRank ( $\mathcal{C}_P^X$ ) centralities for the nodes of the example network in Figure 11.1, as computed with NetworkX [Hagberg et al., 2021c] and rounded to two digits after the decimal point.*

$v$	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
$\mathcal{C}_E^X$	0.50	0.50	0.50	0.00	0.00	0.00	0.50	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$\mathcal{C}_K^X$	0.26	0.35	0.36	0.23	0.25	0.23	0.29	0.23	0.23	0.23	0.23	0.23	0.23	0.25	0.23
$\mathcal{C}_P^X$	0.19	0.25	0.20	0.02	0.03	0.02	0.14	0.02	0.02	0.02	0.02	0.02	0.02	0.03	0.02

## 11.2.2. System controllability methods

One of the important aspects when dealing with a biomedical network is to be able to influence part of, or even the totality of its nodes. This objective is not restricted to biomedical networks, but is one of the earliest and most studied network theory problems, generally known as the (target) network controllability problem. This is intrinsically an optimization problem, as any

network can be controlled from a sufficiently large controlling set, e.g., the entire set of nodes. However, one is interested in finding the minimal set of nodes needed in order to achieve such control. Early works in the field come from the 60's, however it was in early 2010's that one of the key results from the field has been provided in [Liu et al., 2011], namely the possibility of efficiently determining the minimum set of nodes needed to control an entire network. This result sparked a new interest in the field, with a strong emphasis on possible applications in the biomedical field.

The prospect of enforcing control over a biomedical network has been investigated within two main methodological approaches: that of (structural) network controllability, see, e.g., [Liu et al., 2011, Czeizler et al., 2018, Guo et al., 2018, Kanhaiya et al., 2017] and that of dominating sets [Wuchty, 2014, Nacher and Akutsu, 2016, Zhang et al., 2015]. In the current section we review both approaches, detailing the theoretical, algorithmic and biomedical applicability aspects of these methods.

### **11.2.2.1. Network Controlability**

In general terms, we say that a directed network, or generally any dynamical system, is controllable from a set of input nodes if, with a suitable selection of input values for these nodes, the entire network can be driven from any initial state to any desired final state within a finite time. The state of a node is given by its numerical value; in the context of biomedical networks this could be for example the expression level of a gene/protein. From one time point to another this value/state evolves depending (linearly) on the values/states of its neighbors; this is why such systems are also known as linear time invariant dynamical systems (LTIS), as their evolution can be described by the system



of linear differential equations:

$$\frac{dx(t)}{dt} = Ax(t), \quad (11.2)$$

where  $x(t) = (x_1(t), \dots, x_n(t))^T$  is the  $n$ -dimensional vector describing the system's state at time  $t$ , and  $A \in \mathbb{R}^{n \times n}$  is the time-invariant *state transition matrix*, describing how each of these states are influencing the dynamics of the system. Namely, for any nodes  $i, j$ ,  $1 \leq i, j \leq n$  within the network, the entry  $a_{i,j}$  of matrix  $A$  either documents the weight of the influence of node  $j$  over the node  $i$ , if there exists a (directed) edge  $(i, j)$ , or is equal to 0 otherwise. By convention, from now on during this section, all vectors are considered to be column vectors so that the matrix-vector multiplications are well defined.

Assume we allow the system to be influenced through an  $m$ -dimensional input controller, i.e. an input vector  $u$  of real functions,  $u : \mathbb{R} \rightarrow \mathbb{R}^m$  acting upon some  $m$  nodes of the network. Consider the subset of input nodes  $I \subseteq \{1, 2, \dots, n\}$ ,  $I = \{i_1, \dots, i_m\}$ ,  $1 \leq m \leq n$ , as the nodes of the network on which the external input is applied to; such nodes are also known as *driver/driven* nodes. The system (11.2) becomes:

$$\frac{dx(t)}{dt} = Ax(t) + B_I u(t), \quad (11.3)$$

where  $B_I \in \mathbb{R}^{n \times m}$  is the characteristic matrix associated to the subset  $I$ ,  $B_I(r, s) = 1$  if  $r = i_s$  and  $B_I(r, s) = 0$  otherwise, for all  $1 \leq r \leq n$  and  $1 \leq s \leq m$ .

It is often the case, particularly in the bio-medical field, that it is enough to enforce control only over a subset of the network nodes to get the desired change in the network dynamics. The associated optimization problem is known

as the *target controllability problem*, or more generally as the *output controllability problem*. Thus, consider a subset of target nodes  $T \subseteq \{1, 2, \dots, n\}$ ,  $T = \{t_1, \dots, t_l\}$ ,  $m \leq l \leq n$ , thought of as a subset of the nodes of the linear dynamical system, whose dynamics we aim to control (as defined below) through a suitable choice of input nodes and of an input vector. The subset of target nodes can also be defined through its characteristic matrix  $C_T \in \mathbb{R}^{l \times n}$ , defined as  $C_T(r, s) = 1$  if  $t_r = s$  and  $C_T(r, s) = 0$  otherwise, for all  $1 \leq r \leq l$  and  $1 \leq s \leq n$ . We will denote by the triplet  $(A, I, T)$  the targeted linear (time-invariant) dynamical system defined by matrix  $A$ , with input set  $I$ , and target set  $T$ . In case  $T$  is the entire network, we can omit it from the notation.

**Definition 11.17 (Target controllability of linear networks):** Given a target linear dynamical system  $(A, I, T)$  (or similarly a linear network), we say that this system is *target controllable* (or simply controllable if the target is the entire network) if for any  $x(0) \in \mathbb{R}^n$  and any  $\alpha \in \mathbb{R}^l$ , there is an input vector  $u : \mathbb{R} \rightarrow \mathbb{R}^m$  such that the solution  $\tilde{x}$  of (11.3) eventually coincides with  $\alpha$  on its  $T$ -components, i.e.,  $C_T \tilde{x}(\tau) = \alpha$ , for some  $\tau \geq 0$ .

Note that, the general case of *output controllability* is defined similarly, with the only difference that instead of a 0–1 characteristic matrix  $C_T$  we have an arbitrary matrix  $C \in \mathbb{R}^{n \times m}$ , with  $m \leq n$ , defining the output  $y \in \mathbb{R}^m$  of the LTIS as a linear combination of the solution  $x(t)$  of equation (11.3).

Intuitively, the system being target controllable means that for any input state  $x_0$  and any desired final state  $\alpha$  of the target nodes, there is a suitable input vector  $u$  driving the target nodes to  $\alpha$ . Obviously, the input vector  $u$  depends on  $x_0$  and  $\alpha$ .

It is known from Kalman [1963] that the system  $(A, I)$  is controllable from

some input controller  $u(t)$  if and only if the rank of the matrix  $(B_I | AB_I | A^2B_I | \dots | A^{n-1}B_I)$ , known as the *controllability matrix*, is equal to  $n$ , the number of nodes in the network. The operator  $|$  denotes here the simple matrix concatenation operation. This criterion is known as the *Kalman's criterion for full controllability* [Kalman, 1963], and it is easily extendable to the case of target (or generally, output) controllability:

**Theorem 11.1:** *A targeted linear dynamical system with inputs  $(A, I, T)$  is controllable if and only if the rank of its controllability matrix  $(C_T B_I | C_T A B_I | C_T A^2 B_I | \dots | C_T A^{n-1} B_I')$  is equal with  $|T|$  [Kalman, 1963].*

Intuitively, the controllability matrix describes all weighted paths from the input nodes to the target nodes in the directed graph associated to the linear dynamical system. This leads to the notion of *control path* from an input node to a target node and an input node *controlling* a target node. This line of thought can be further developed into a structural formulation of the targeted controllability. Thus, although the Kalman controllability criterion seems to suggest that the (target) controllability problem is strictly related to a particular valuation of the state transition matrix  $A$ , it turns out that this is actually a network property. To explain this, we define two matrices  $C, D$  of the same size to be *equivalent* if they have the same set of non-zero entries. The key concept here is that of *structural controllability*:

**Definition 11.18 (Structural target controllability of linear networks):**

We say that a given targeted linear dynamical system  $(A, I, T)$  (or similarly a linear network) is *structural target controllable* if there exists a matrix  $A'$  equivalent with  $A$  such that the system  $(A', I, T)$  is target controllable. That is,  $(A, I, T)$  becomes controllable by replacing  $A$  with any suitable equivalent

matrix  $A'$ , or similarly, by replacing the weights of the network's edges with any other non-zero values.

The key result, proved in [Lin, 1974, Shields and Pearson, 1976], is that if a system  $(A, I)$  is structurally controllable, then it is controllable for all, except a *thin* set, of equivalent matrices  $A'$ . We recall that a thin subset of the  $n$ -dimensional complex space is nowhere dense and has Lebesgue measure 0. This indicates that the controllability problem can indeed be reduced to its structural version, known as the *structural (target) controllability problem*, which is ultimately a property of the network's connectivity rather than of the effective edge weights. This problem can be defined both as a decision problem (is the linear time-invariant dynamical system  $(A, I, T)$  structurally target controllable?) as well as an optimization problem (given matrix  $A$  of size  $n \times n$  and a subset of target nodes  $T \subseteq \{1, 2, \dots, n\}$ , find the minimal  $m$ ,  $m \leq n$ , and a suitable choice for the size- $m$  set of input nodes  $I$  such that  $(A, I, T)$  is structurally target controllable). We are most interested in the latter formulation of the problem.

From an algorithmic standpoint, the Kalman criterion for controllability from Theorem 11.1 can lead to an efficient/polynomial time algorithm for verifying whether a given network can be (target) controlled from a given input controller, acting upon some of the network nodes. However, it does not lead to an efficient way of computing the composition of such a minimal controller, or even its (minimal) size. As it turns out, the (target) control optimization problem has been open for more than 20 years, before it was shown in [Liu et al., 2011] that there exists a low polynomial time algorithm (i.e., cubic in the size of the network) that can provide both the size and the composition of the minimum input controller needed to control an entire network. It was thus

surprising that the corresponding result for the target control optimization problem was proved by [Czeizler et al., 2018] to be NP-hard, meaning that any exact optimization algorithm would have to run in exponential time. Several approximation algorithms have been developed for this latter problem, with good results when applied to both real-word networks, e.g. bio-medical, social, electrical etc., as well as artificial networks [Kanhaiya et al., 2017, Czeizler et al., 2018, Gao et al., 2014].

Another generalization coming from the practical application of network controllability in pharmacology and biomedicine considers the case when the input controller should, or it is desired to, be selected mostly from a subset  $P \subseteq \{1, 2, \dots, n\}$  of the network nodes. For example, in network pharmacology studies, it is more advantageous to consider controllers consisting of those genes/proteins for which there already exist approved drugs known to target that particular element. This leads to the so-called *input-constrained targeted structural controllability* problem:

**Definition 11.19 (*Input-constrained, structural target controllability*):**

Given a linear dynamical system defined by a matrix  $A \in \mathbb{R}^{n \times n}$ , a set of target nodes  $T$  and a set of preferred nodes  $P$ , the *input-constrained structural targeted controllability* problem asks to find a smallest-sized input set  $I$  whose intersection with  $P$  is maximal, such that the targeted linear dynamical system with inputs  $(A, I, T)$  is controllable, i.e., such that the rank of the matrix  $(C_T B_I \mid C_T A B_I \mid C_T A^2 B_I \mid \dots \mid C_T A^{n-1} B_I)$  is equal with  $|T|$ .

While this optimization problem is also NP-hard (as a generalization of the previous case), several efficient approximation algorithms have been introduced in [Kanhaiya et al., 2017] and [Popescu et al., 2020] and analyzed particularly

with respect to bio-medical networks.

### 11.2.2.2. Minimum dominating sets

The second frequently used controllability technique, applied especially in the case of undirected networks, relies on the notion of domination.

**Definition 11.20**(*Dominating set*): Given a size  $n$  network, we say that a subset  $D \subseteq \{1, 2, \dots, n\}$  of its nodes is *dominating* the network if any node within the network is either in  $D$  or it is adjacent to a node in  $D$ .

**Definition 11.21**(*The Minimum Dominating Set Problem*): Given a (undirected) network, the *Minimum Dominating Set Problem (MDSP)* asks to find a dominating set of minimum cardinality. Such MDS can thus be considered as an efficient first-hand controlling set for the respective network.

From an algorithmic point of view MDSP is a classical NP-hard problem [Garey and Johnson, 1990]. However, as before, there are many efficient approximation algorithms providing efficient solutions even in the case of large networks [Hedar and Ismail, 2012, Alon, 1990, Nacher and Akutsu, 2014].

The MDS approach has been applied in connection to various fields such as the controllability of biological networks [Wuchty, 2014, Nacher and Akutsu, 2016, Zhang et al., 2015], design and analysis of wireless computer networks [Yu et al., 2013, Wu et al., 2006], the study of social networks [Daliri Khomami et al., 2018, Wang et al., 2011], etc. Several generalizations of MDSP have also been considered:

**Definition 11.22**(*The Minimum  $k$ -Dominating Set Problem*): Given a (undirected) network, a set  $D$  of its nodes is  *$k$ -path dominating* if any node

from the network is either in  $D$  or it is connected to a node in  $D$  through a path of length at most  $k$ . The *minimum  $k$ -dominating set problem* (MkDP), also known as the  *$d$ -hop dominating problem*, asks to find a  $k$ -path dominating set of minimal cardinality.

**Definition 11.23** (*The Red–Blue ( $k$ -)Dominating Problem*): Given a network and two subsets of its nodes, Red and Blue, the *Red–Blue ( $k$ -)domination problem*, asks to find a minimum subset of the Blue nodes ( $k$ -path) dominating all the Red nodes.

Such generalizations were considered in [Penso and Barbosa, 2004, Nguyen et al., 2020, Santos Coelho et al., 2017] and in [Abu-Khzam et al., 2011], respectively. All these generalizations, while preserving the algorithmic complexity of the original MDSP, provide sometimes a closer connection to practical applications.

Compared to the structural network controllability formalism, the dominating set methodology enforces a reachability type of control. Indeed, in the latter case, the dominating nodes are controlling the network either by direct interactions, in case of MDSP, or by paths of length at most  $k$ , for MkDSP. This is different than within the structural network controllability formalism, where each controller node is asked to enforce an independent control over its dominating nodes. This requirement imposes that each controlled node, i.e. *target* node, is positioned at the end of a different lengthed path starting from the controller, i.e., the *driver* node.

### 11.2.3. Software

In this section we briefly present several applications and libraries which can be used for generating, visualizing or analyzing graphs and networks. All of the mentioned software is open-source, free to use and still supported as of the time of writing (namely, it was updated in the past two years and it runs on the latest versions of the most common operating systems or using the most recent versions of the corresponding programming languages).

#### 11.2.3.1. NetworkX

*NetworkX* ([Hagberg et al., 2008]) is a Python package for the creation, manipulation, and study of the structure, dynamics, and functions of complex networks ([Hagberg et al., 2021c]). As all of the networks described in this chapter (except the simple demonstrative network from Figure 11.1) represent personalized protein-protein interaction networks and have been generated externally, we have focused the usage of the *NetworkX* package solely on analyzing them. The package provides out-of-the-box implemented algorithms and functions for identifying all of the centrality measures presented in this chapter. It is worth noting that *NetworkX* also provides several algorithms for different layout routines, and basic interconnections with dedicated graph visualization packages, such as *Matplotlib* ([Matplotlib, 2021]) and *Graphviz* ([Ellson et al., 2021]). However, graph visualization does not represent the main goal of *NetworkX*, and its creators recommend using a dedicated and fully-featured tool instead.

An alternative to *NetworkX* is the *igraph* collection ([igraph core team, 2021]), which provides network analysis libraries and packages for R, Mathematica and C/C++ in addition to Python.



**Table 11.1:** The *NetworkX* functions used for computing the centrality methods.

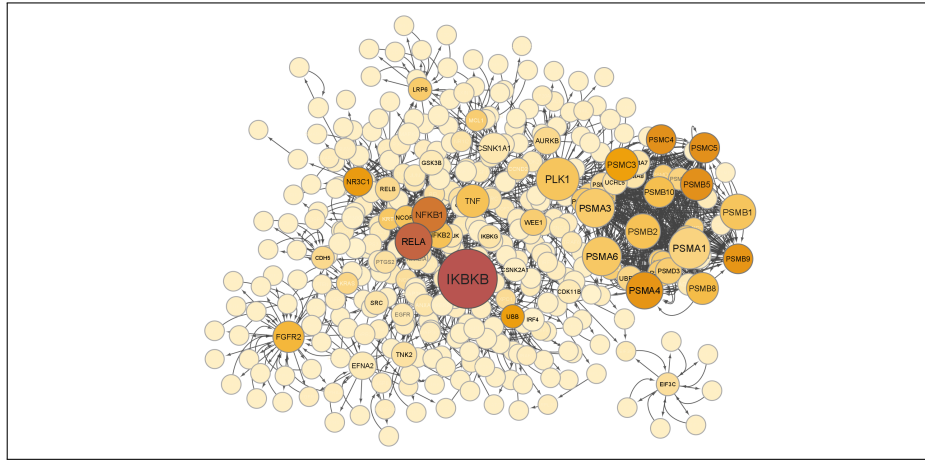
Method	Function	Parameters
Degree centrality	<i>in_degree_centrality</i>	-
Closeness centrality	<i>closeness_centrality</i>	default
Harmonic centrality	<i>harmonic_centrality</i>	default
Eccentricity centrality	<i>eccentricity</i>	default
Betweenness centrality	<i>betweenness_centrality</i>	default
Eigenvector-based prestige	<i>eigenvector_centrality</i>	default

We used the *NetworkX* package to compute the centrality measures corresponding to the nodes in all of the networks presented in this chapter. Specifically, the functions used for ranking the nodes according to the corresponding centrality method described in Section 11.2.1 are presented in Table 11.1.

Additionally, we used the *dominating\_set* function with the default parameters to run the MDS analysis described in Section 11.2.2 for each network. While the package does not provide a direct equivalent for the MkDS algorithm, it allows for the initial network manipulation (i.e. parsing the network and adding specific edges) required to transform the default MDS analysis into an MkDS one. The methodology and results are presented in detail in Section 11.3.3.

### 11.2.3.2. Cytoscape

*Cytoscape* ([Shannon et al., 2003]) is a standalone software platform implemented in Java for visualizing complex networks, together with attribute data integration ([Shannon et al., 2021]). *Cytoscape* was initially developed for biological research and biological networks visualization and analysis. In addition to the basic functionality, *Cytoscape* provides extended functionality through

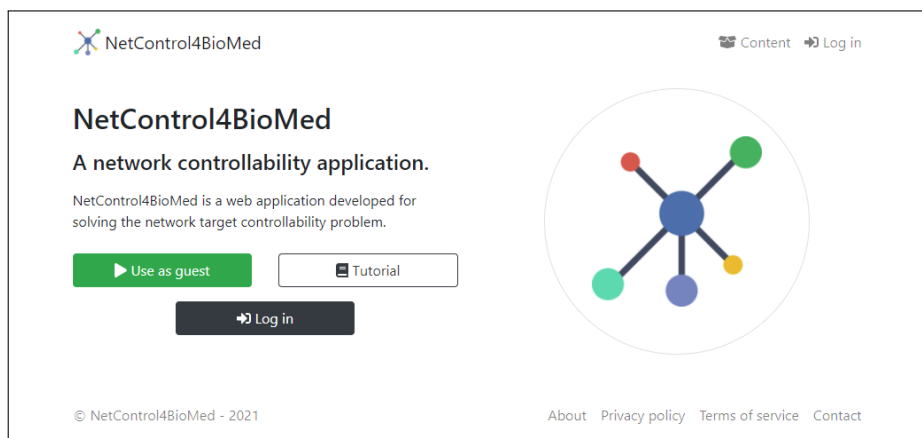


**Figure 11.2:** Example of network visualization with *Cytoscape*. The color of a node is proportional to its indegree (darker nodes have higher indegree), while the size of a node is proportional to its outdegree (larger nodes have higher outdegree).

the use of so-called apps, which can be community-developed and add support for additional analysis methods, layouts, or database connections, among others.

Another well-established desktop network visualization software is *Gephi* ([Bastian et al., 2021]), a Java application with the same capabilities, including the usage of plugins for extended functionality.

We have used the *Cytoscape* application to render all of the network visualizations presented throughout this chapter. The layout of the nodes was automatically calculated and applied using the default preferred layout algorithm, while the general design of the networks (e.g. labels, colors, or sizes) is based on the default style. A screenshot with the visualization of a network, can be seen in Figure 11.2.



**Figure 11.3:** Screenshot with the home page of *NetControl4BioMed*.

### 11.2.3.3. NetControl4BioMed

*NetControl4BioMed* ([Kanhaiya et al., 2018], updated version in [Popescu et al., 2021]) is a C# (.NET Core) web application for the generation and structural target controllability analysis of protein-protein interaction networks, freely available at <https://netcontrol.combio.org/>. To this end, the application integrates and combines multiple protein and protein-protein interaction databases which, based on the user input, are used in the process.

We have used the *NetControl4BioMed* platform to generate the personalized protein-protein interaction networks presented in this chapter. The details of the network generation method (e.g. used interaction databases, or algorithm parameters) are presented in Section 11.3.1. A screenshot with the home page of the application can be seen in Figure 11.3.

Additionally, we used the network analysis section of the application, with the default parameters, to run the structural target controllability analysis described in Section 11.2.2 for each network. The methodology and results are presented in detail in Section 11.3.3.

## **11.3. Applications of network modeling in personalized medicine**

We demonstrate our approach to personalized medicine on three multiple myeloma patients, through the analysis of customized networks built around the mutated genes of each patient, the disease-specific survivability-essential genes, and the genes targeted by drugs in the standard therapy for multiple myeloma.

### **11.3.1. Constructing personalized disease networks**

We used the patient data documented in [Lohr et al., 2014], which includes information about the evolution of the mutation, the mutated genes, and the stage of treatment, as well as details about the patient characteristics, such as age, race, and gender, among others. In this study we focus on the mutated genetic information for tumor samples 28, 38 and 191.

We used a list of 70 multiple myeloma-specific essential genes presented in [Matthews et al., 2017, Tiedemann et al., 2012, Krönke et al., 2014] and shown in Table 11.2.

We used the multiple myeloma standard treatment drugs described in [Foundation, 2019, Engelhardt et al., 2019, Mateos et al., 2018] and their corresponding drug-targets from DrugBank [Wishart et al., 2017]. The list thus obtained is presented in Table 11.3 while the associated drugs and the standard drug therapies are documented in Tables 11.4 and 11.5, respectively.

**Table 11.2:** The disease-specific survivability-essential genes for multiple myeloma ([Matthews et al., 2017, Tiedemann et al., 2012, Krönke et al., 2014]).

AGTRAP	EIF3C	KIFC2	PLK1	RGAG1	TRIM68
AURKB	EIF4A3	LEPROT	PRPF8	RPL27	TUBGCP6
CARS	GNRH2	MAF	PSMA1	RPL38	UBB
CCND2	GPR77	MCL1	PSMA3	RRM1	UBQLNL
CDK11	HIP1	MED14	PSMA4	RSF1	ULK3
CDK11A	IK	MED15	PSMA6	SF3A1	USP36
CDK11B	IKBKB	NDC80	PSMC3	SLC25A23	USP8
CKAP5	IKZF1	NFKB1	PSMC4	SNRPA1	WBSCR22
COPB2	IKZF3	NFKB2	PSMC5	SNW1	WEE1
CSNK1A1	IRF4	NUF2	RAB11A	TNK2	XPO1
CUL9	KIF11	PCDH18	RELA	TPMT	
EFNA2	KIF18A	PIM2	RELB	TRIM21	

**Table 11.3:** The targets of the drugs used in standard therapy lines for multiple myeloma.

ANXA1	GSR	NR0B1	PSMB2	SLAMF7	TUBB
CD38	HSD11B1	NR1I2	PSMB5	TNF	XPO1
CDH5	NFKB1	NR3C1	PSMB8	TNFSF11	
CRBN	NOLC1	PSMB1	PSMB9	TOP2A	
FGFR2	NOS2	PSMB10	PTGS2	TUBA4A	

We used the *NetControl4BioMed* application, briefly presented in Section 11.2.3.3, to build a personalized protein-protein interaction network for each multiple myeloma patient around the seed genes defined by the patient-specific mutated genes, the disease-specific survivability-essential genes, and the drug-target genes corresponding to the standard treatment drugs. We used the interaction data from the *KEGG*, *OmniPath*, *InnateDB* and *SIGNOR* databases. The networks include all paths of length at most three between the seed proteins that could be formed with these interactions. We added to the network all intermediary nodes that were not part of the set of seed nodes. An

**Table 11.4:** The main drugs for treating multiple myeloma.

Bortezomib	PSMB1;PSMB5
Carfilzomib	PSMB1;PSMB10;PSMB2;PSMB5;PSMB8;PSMB9
Carmustine	GSR
Cisplatin	A2M;ATOX1;MPG;TF
Cyclophosphamide	NR1I2
Dacetuzumab	CD40
Daratumumab	CD38
Dexamethasone	ANXA1;NOS2;NR0B1;NR1I2;NR3C1
Doxorubicin	NOLC1;TOP2A
Elotuzumab	SLAMF7
Etoposide	TOP2A;TOP2B
Ixazomib	PSMB5
Lenalidomide	CDH5;CRBN;PTGS2;TNFSF11
Liposomal doxorubicin	TOP2A;TOP2B
Oprozomib	LMP7;PSMB5
Panobinostat	HDAC1;HDAC2;HDAC3;HDAC6;HDAC7;HIF1A;VEGF
Plerixafor	CXCR4
Pomalidomide	CRBN;PTGS2;TNF
Prednisone	HSD11B1;NR3C1
Selinexor	XPO1
Thalidomide	CRBN;FGFR2;NFKB1;PTGS2;TNF
Vincristine	TUBA4A;TUBB

overview of the generated networks is presented in Table 11.6.

We used the *NetworkX* package, briefly presented in Section 11.2.3.1, to rank the genes in each of the generated networks based on the centrality measures described in Section 11.2.1. Tables 11.7, 11.8, 11.9, 11.10, 11.11, and 11.12 present, for each network, the essential genes that have the corresponding centrality measure higher than the median among all other genes in the network.

**Table 11.5:** Lines of therapy for treating multiple myeloma.

<b>First line of therapy</b>
Lenalidomide;Bortezomib;Dexamethasone (RVD)
Bortezomib;Cyclophosphamide;Dexamethasone (VKD)
Bortezomib;Thalidomide;Dexamethasone (VTD)
Bortezomib;Melphalan;Prednisone
Vincristine;Doxorubicin;Dexamethasone (VAD)
Melphalan;Dexamethasone
Daratumumab;Bortezomib;Thalidomide;Dexamethasone
Carfilzomib;Thalidomide;Dexamethasone (KTD)
<b>Second line of therapy</b>
Carfilzomib;Lenalidomide;Dexamethasone (KRD)
Ixazomib;Lenalidomide;Dexamethasone
Elotumuzab;Lenalidomide;Dexamethasone
Bendamustine;Lenalidomide;Dexamethasone
<b>Third line of therapy</b>
Pomalidomide;Dexamethasone
Panobinostat;Bortezomib;Dexamethasone
Daratumumab

## 11.3.2. Analysis methods

In this section, we describe the methodology applied for the analysis of the data presented in Section 11.3.1, and using the centrality measures presented in Section 11.2.1 and the controllability methods presented in Section 11.2.2.

All analyses follow a similar flow, aiming to identify, through the different controllability methods, a subset of “important” drug-target genes in the network, ranked according to the number of essential genes that they control. Once a set has been identified, the corresponding drugs are ranked based on a very similar criterion, taking into account the number of essential genes that their drug-targets control. The three top ranked drugs are then reported

**Table 11.6:** The summary of the generated personalized protein-protein interaction networks.

<b>Network</b>	<b>G</b>	<b>N</b>	<b>E</b>	<b>CC</b>	<b>D</b>	<b>AD</b>
Tumor sample 28	36	360	1486	4	12	6.02
Tumor sample 38	117	446	1732	5	12	5.77
Tumor sample 191	218	515	1955	3	12	5.74

**G:** number of mutated genes in the sample; **N:** number of nodes in the network; **E:** number of edges; **CC:** number of connected components; **D:** the network diameter; **AD:** the network average degree.

as a personalized drug combination therapy customized to the patient, and compared with the standard lines of therapy.

Firstly, we ran each type of analysis on the complete networks and data sets, considering as targets the essential genes presented in Table 11.2 and as preferred inputs the drug-target genes in Table 11.3. Then, to reduce the noise in the data, for each network and each centrality measure we focused on the subgraphs formed by the top ranked essential genes and the drug-targets that can reach them through a path of length of 3 or less, and all the interactions between them. For each such subgraph, all analyses consider as targets the corresponding essential genes, and as preferred inputs the corresponding drug-target genes.

We used the *NetControl4BioMed* application, briefly presented in Section 11.2.3.3, to run the structural target controllability analyses with the previously described setup. We used the default parameters, with a set maximum path length of 3. The analysis outputs a set of genes that can control the entire target set, from which only the controlling drug-targets are selected and further considered.

Similarly, we used the *NetworkX* package, presented in Section 11.2.3.1,



**Table 11.7:** The top ranked genes based on their in-degree centrality, for each network.

Tumor sample 28		Tumor sample 38		Tumor sample 191	
IKBKB	AURKB	IKBKB	CCND2	RELA	CCND2
RELA	XPO1	RELA	XPO1	IKBKB	XPO1
NFKB1	EIF3C	NFKB1	EIF3C	NFKB1	EIF3C
PSMC4	TNK2	PSMC4	TNK2	PSMC4	TNK2
PSMC5	CSNK1A1	PSMC5	CSNK1A1	PSMC5	RPL38
PSMA4	KIF11	PSMA4	KIF11	UBB	CSNK1A1
UBB	EFNA2	UBB	CDK11B	PSMA4	SNW1
PSMC3	CDK11B	PSMC3	SNW1	PSMC3	CDK11B
NFKB2	SNW1	NFKB2	EFNA2	NFKB2	KIF11
PLK1	USP8	PLK1	IKZF3	PLK1	IKZF3
PSMA6	IKZF3	MCL1	MED14	MCL1	IKZF1
PSMA3	RSF1	PSMA6	USP8	PSMA6	EFNA2
MCL1	IKZF1	WEE1	RSF1	WEE1	RRM1
WEE1	RPL38	PSMA3	IKZF1	PSMA3	USP8
PSMA1	TRIM21	RELB	RPL38	RELB	TRIM21
CCND2	MAF	PSMA1	TRIM21	PSMA1	RSF1
RELB		AURKB		AURKB	RPL27

**Table 11.8:** The top ranked genes based on their closeness centrality, for each network.

Tumor sample 28		Tumor sample 38		Tumor sample 191	
UBB	CSNK1A1	IKBKB	PSMA4	RELA	PSMA4
IKBKB	PSMA4	UBB	XPO1	UBB	CSNK1A1
RELA	XPO1	RELA	CSNK1A1	IKBKB	PSMC3
NFKB1	PLK1	NFKB1	PSMC3	NFKB1	XPO1
NFKB2	SNW1	NFKB2	SNW1	NFKB2	SNW1
RELB	PSMC3	RELB	TRIM21	RELB	PSMC4
WEE1	PSMC4	PSMA3	PIM2	WEE1	AURKB
PSMA3	PSMC5	MCL1	PSMC4	PSMA3	PSMC5
MCL1	TRIM21	WEE1	PSMC5	MCL1	PIM2
RSF1	KIF11	RSF1	PSMA1	RSF1	PSMA1
CCND2	PSMA1	CCND2	KIF11	CCND2	TRIM21
PSMA6	PIM2	PLK1	TNK2	PSMA6	KIF11
		PSMA6	AURKB	PLK1	TNK2

**Table 11.9:** The top ranked genes based on their harmonic centrality, for each network.

Tumor sample 28		Tumor sample 38		Tumor sample 191	
IKBKB	PSMC3	IKBKB	PSMC5	RELA	PSMC3
RELA	PSMA6	RELA	PLK1	IKBKB	PLK1
NFKB1	MCL1	NFKB1	CCND2	NFKB1	PSMA6
UBB	CCND2	UBB	RSF1	UBB	RSF1
NFKB2	RSF1	NFKB2	XPO1	NFKB2	CCND2
PSMA4	PLK1	RELB	PSMA1	RELB	PSMA1
RELB	XPO1	PSMA4	CSNK1A1	PSMA4	AURKB
PSMA3	PSMA1	PSMA3	SNW1	WEE1	CSNK1A1
WEE1	CSNK1A1	WEE1	TRIM21	PSMA3	XPO1
PSMC4	SNW1	MCL1	PIM2	PSMC4	SNW1
PSMC5		PSMC3	AURKB	MCL1	PIM2
		PSMA6	TNK2	PSMC5	TRIM21
		PSMC4	KIF11		

**Table 11.10:** The top ranked genes based on their eccentricity, for each network.

Tumor sample 28		Tumor sample 38		Tumor sample 191	
IKBKB	RELB	IKBKB	EFNA2	IKBKB	EFNA2
RELA	MCL1	RELA	RELB	RELA	MCL1
NFKB1	EFNA2	NFKB1	MCL1	NFKB1	TNK2
PSMA4	TNK2	PLK1	TNK2	PLK1	CCND2
PLK1	CCND2	PSMA4	CCND2	PSMA4	EIF3C
PSMC3	EIF3C	PSMC3	EIF3C	PSMC5	CDK11B
PSMC5	CDK11B	PSMC5	CDK11B	PSMC4	XPO1
PSMC4	XPO1	PSMC4	XPO1	PSMC3	SNW1
PSMA6	IRF4	PSMA6	IRF4	PSMA6	RPL38
PSMA1	SNW1	PSMA1	SNW1	PSMA1	IRF4
PSMA3	USP8	PSMA3	PIM2	PSMA3	PIM2
UBB	PIM2	UBB	MED14	UBB	USP8
NFKB2	HIP1	NFKB2	USP8	NFKB2	IKZF1
WEE1	KIF11	WEE1	RSF1	CSNK1A1	HIP1
CSNK1A1	RSF1	AURKB	HIP1	WEE1	KIF11
AURKB		CSNK1A1	KIF11	AURKB	IKZF3
				RELB	RAB11A

**Table 11.11:** The top ranked genes based on their betweenness centrality, for each network.

Tumor sample 28		Tumor sample 38		Tumor sample 191	
IKBKB	PSMA6	IKBKB	RELB	IKBKB	RELB
NFKB1	EIF3C	RELA	CCND2	RELA	UBB
RELA	RELB	NFKB1	EIF3C	NFKB1	PSMA6
PLK1	PSMA1	PLK1	PSMA1	PLK1	PSMA1
CSNK1A1	PSMA4	PSMC3	PSMA4	NFKB2	PSMC5
NFKB2	PSMC5	NFKB2	PSMC5	WEE1	PSMA4
PSMA3	EFNA2	WEE1	EFNA2	CSNK1A1	EFNA2
WEE1	USP8	PSMA3	MED14	CDK11B	PSMC4
PSMC3	PIM2	CDK11B	USP8	PSMA3	RAB11A
CDK11B	PSMC4	CSNK1A1	PIM2	MCL1	USP8
MCL1	MED14	TNK2	PSMC4	AURKB	MED14
TNK2	RPL38	AURKB	RSF1	EIF3C	MAF
AURKB	MAF	MCL1	SNW1	PSMC3	PIM2
XPO1	RSF1	XPO1	RPL38	TNK2	SNW1
CCND2	SNW1	PSMA6	MAF	XPO1	RPL38
UBB		UBB		CCND2	RSF1

**Table 11.12:** The top ranked genes based on their eigenvector-based prestige, for each network.

Tumor sample 28		Tumor sample 38		Tumor sample 191	
PSMC4	NFKB1	PSMC4	NFKB2	PSMC4	CCND2
PSMC5	CCND2	PSMC5	CCND2	PSMC5	WEE1
PSMA4	NFKB2	PSMA4	WEE1	PSMA4	MCL1
PSMC3	WEE1	PSMC3	MCL1	PSMC3	RELB
PSMA6	MCL1	PSMA6	RELB	PSMA6	RSF1
PSMA3	RELB	PSMA3	PLK1	PSMA3	AURKB
PSMA1	RSF1	PSMA1	RSF1	PSMA1	PLK1
UBB	SNW1	UBB	SNW1	UBB	SNW1
IKBKB	XPO1	IKBKB	XPO1	IKBKB	XPO1
RELA	PLK1	RELA	AURKB	RELA	KIF11
		NFKB1		NFKB1	RPL27
				NFKB2	PIM2

**Table 11.13:** The drug-target genes in the controlling set obtained by the structural target controllability analysis.

Tumor sample 28		Tumor sample 38		Tumor sample 191	
ANXA1	NOLC1	ANXA1	PSMB1	ANXA1	PSMB2
NFKB1		NOLC1	TNF		

to run the minimum dominating set analyses with the previously described setup. An additional step was required in order to enable the default function to perform the required minimum  $k$ -dominating set analysis. To this end, we transformed the analyzed networks by adding a direct edge between each pair of nodes indirectly connected by a path of length of  $k$  or less. We set  $k = 3$ , and used the default parameters. The analysis outputs a set of genes that can dominate the entire target set, from which only the dominating drug-targets are selected and further considered.

### 11.3.3. Results

In this section, we present and discuss the results of the analyses described in Section 11.3.2, with the aim of suggesting personalized treatments.

#### 11.3.3.1. Structural controllability analysis

We applied the input-constrained structural target controllability method on the complete networks and sets of essential and drug-target genes. The drug-target genes in the obtained controlling sets are presented in Table 11.13.

Next, we applied the method once more on the subgraphs described in Section 11.3.2 and corresponding to each centrality measure. The drug-target genes in the controlling sets obtained for each measure are presented in Ta-

**Table 11.14:** The drug-target genes in the controlling set obtained by the structural target controllability analysis corresponding to the top ranked essential genes based on their in-degree centrality.

Tumor sample 28		Tumor sample 38		Tumor sample 191	
ANXA1	NOLC1	ANXA1	TNF	ANXA1	NOLC1
NFKB1	TNF	NFKB1		NFKB1	TNF

**Table 11.15:** The drug-target genes in the controlling set obtained by the structural target controllability analysis corresponding to the top ranked essential genes based on their closeness centrality.

Tumor sample 28		Tumor sample 38		Tumor sample 191	
ANXA1	PSMB8	FGFR2	PSMB5	ANXA1	PSMB1
NFKB1	TNF	NFKB1	TNF	NFKB1	TNF
		NR3C1		NR3C1	XPO1

bles 11.14, 11.15, 11.16, 11.17, 11.18 and 11.19.

Next, we studied the results in the context of drug therapy. For each network and centrality measure, the drug-target genes were matched with all the multiple myeloma standard treatment drug targeting them, while the latter was sorted according to the number of top ranked essential genes controlled through one or more of their drug-target genes. Then, we selected the three top drugs as our proposed drug combination for that patient's treatment. Informally, this approach aims for a reinforced influential effect over as many essential genes as possible through a minimal combination of at most 3 drugs. The chosen drugs are documented in Tables 11.20, 11.22, 11.24, 11.26, 11.28

**Table 11.16:** The drug-target genes in the controlling set obtained by the structural target controllability analysis corresponding to the top ranked essential genes based on their harmonic centrality.

Tumor sample 28		Tumor sample 38		Tumor sample 191	
ANXA1	PTGS2	ANXA1	TNF	ANXA1	PSMB1
NFKB1	TNF	NFKB1	XPO1	NFKB1	TNF
PSMB1	XPO1	PSMB10			

**Table 11.17:** The drug-target genes in the controlling set obtained by the structural target controllability analysis corresponding to the top ranked essential genes based on their eccentricity.

Tumor sample 28	Tumor sample 38	Tumor sample 191
ANXA1 PSMB1 NFKB1 TNF	ANXA1 NR3C1 NFKB1	ANXA1 NFKB1

**Table 11.18:** The drug-target genes in the controlling set obtained by the structural target controllability analysis corresponding to the top ranked essential genes based on their betweenness centrality.

Tumor sample 28	Tumor sample 38	Tumor sample 191
ANXA1 TNF NFKB1	ANXA1 PTGS2 NFKB1 TNF PSMB10	ANXA1 PTGS2 NFKB1 TNF

**Table 11.19:** The drug-target genes in the controlling set obtained by the structural target controllability analysis corresponding to the top ranked essential genes based on their eigenvector-based prestige.

Tumor sample 28	Tumor sample 38	Tumor sample 191
NFKB1 XPO1 PSMB1	ANXA1 PSMB5 NFKB1 TNF PSMB2	ANXA1 TNF NFKB1

**Table 11.20:** The proposed drug therapy and the number of essential genes it controls, for the structural target controllability analysis corresponding to the top ranked essential genes based on their in-degree.

<b>Tumor Sample</b>	<b>Proposed therapy</b>	<b>Controlled EG</b>
MM-0028-Tumor	Dexamethasone;Thalidomide;Doxorubicin	29
MM-0038-Tumor	Dexamethasone;Thalidomide;Pomalidomide	24
MM-0191-Tumor	Dexamethasone;Thalidomide;Pomalidomide	28

**Table 11.21:** The most effective standard drug therapy and the number of essential genes it controls, for the structural target controllability analysis corresponding to the top ranked essential genes based on their in-degree.

<b>Tumor Sample</b>	<b>Standard therapy</b>	<b>Controlled EG</b>
MM-0028-Tumor	Bortezomib;Thalidomide;Dexamethasone	27
MM-0038-Tumor	Bortezomib;Thalidomide;Dexamethasone	24
MM-0191-Tumor	Bortezomib;Thalidomide;Dexamethasone	28

and 11.30. Following an identical procedure, we also suggest a personalized drug combination in Table 11.32 based on the conclusions reached by the controllability analysis on the whole tumor network. The associated most effective standard drug therapy for each tumor sample and centrality measure are given in Tables 11.21, 11.23, 11.25, 11.27, 11.29, 11.31 and 11.33.

It is immediate to see that Thalidomide and Dexamethasone are predicted to be extremely suitable for treating the unique disease circumstances afflicting all the patients. These two drugs are commonly preferred as a first choice

**Table 11.22:** The proposed drug therapy and the number of essential genes it controls, for structural target controllability analysis corresponding to the top ranked essential genes based on their closeness.

<b>Tumor Sample</b>	<b>Proposed therapy</b>	<b>Controlled EG</b>
MM-0028-Tumor	Thalidomide;Dexamethasone;Pomalidomide	21
MM-0038-Tumor	Thalidomide;Pomalidomide;Dexamethasone	23
MM-0191-Tumor	Thalidomide;Dexamethasone;Selinexor	24

**Table 11.23:** The most effective standard drug therapy and the number of essential genes it controls, for the structural target controllability analysis corresponding to the top ranked essential genes based on their closeness.

Tumor Sample	Standard therapy	Controlled EG
MM-0028-Tumor	Bortezomib;Thalidomide;Dexamethasone	21
MM-0038-Tumor	Bortezomib;Thalidomide;Dexamethasone	24
MM-0191-Tumor	Bortezomib;Thalidomide;Dexamethasone	24

**Table 11.24:** The proposed drug therapy and the number of essential genes it controls, for the structural target controllability analysis corresponding to the top ranked essential genes based on their harmonic centrality.

Tumor Sample	Proposed therapy	Controlled EG
MM-0028-Tumor	Thalidomide;Dexamethasone;Selinexor	21
MM-0038-Tumor	Dexamethasone;Thalidomide;Pomalidomide	22
MM-0191-Tumor	Dexamethasone;Thalidomide;Bortezomib	22

**Table 11.25:** The most effective standard drug therapy and the number of essential genes it controls, for the structural target controllability analysis corresponding to the top ranked essential genes based on their harmonic centrality.

Tumor Sample	Standard therapy	Controlled EG
MM-0028-Tumor	Bortezomib;Thalidomide;Dexamethasone	20
MM-0038-Tumor	Bortezomib;Thalidomide;Dexamethasone	22
MM-0191-Tumor	Bortezomib;Thalidomide;Dexamethasone	22

**Table 11.26:** The proposed drug therapy and the number of essential genes it controls, for the structural target controllability analysis corresponding to the top ranked essential genes based on their eccentricity.

Tumor Sample	Proposed therapy	Controlled EG
MM-0028-Tumor	Thalidomide;Pomalidomide;Bortezomib	25
MM-0038-Tumor	Dexamethasone;Prednisone;Thalidomide	3
MM-0191-Tumor	Thalidomide;Dexamethasone	26

**Table 11.27:** The most effective standard drug therapy and the number of essential genes it controls, for the structural target controllability analysis corresponding to the top ranked essential genes based on their eccentricity.

Tumor Sample	Standard therapy	Controlled EG
MM-0028-Tumor	Bortezomib;Thalidomide;Dexamethasone	26
MM-0038-Tumor	Bortezomib;Thalidomide;Dexamethasone	3
MM-0191-Tumor	Bortezomib;Thalidomide;Dexamethasone	26



**Table 11.28:** The proposed drug therapy and the number of essential genes it controls, for the structural target controllability analysis corresponding to the top ranked essential genes based on their betweenness.

Tumor Sample	Proposed therapy	Controlled EG
MM-0028-Tumor	Thalidomide;Pomalidomide;Dexamethasone	26
MM-0038-Tumor	Thalidomide;Pomalidomide;Dexamethasone	26
MM-0191-Tumor	Dexamethasone;Thalidomide;Pomalidomide	27

**Table 11.29:** The most effective standard drug therapy and the number of essential genes it controls, for the structural target controllability analysis corresponding to the top ranked essential genes based on their betweenness.

Tumor Sample	Standard therapy	Controlled EG
MM-0028-Tumor	Bortezomib;Thalidomide;Dexamethasone	26
MM-0038-Tumor	Bortezomib;Thalidomide;Dexamethasone	26
MM-0191-Tumor	Bortezomib;Thalidomide;Dexamethasone	27

**Table 11.30:** The proposed drug therapy and the number of essential genes it controls, for the structural target controllability analysis corresponding to the top ranked essential genes based on their eigenvector centrality.

Tumor Sample	Proposed therapy	Controlled EG
MM-0028-Tumor	Thalidomide;Selinexor;Bortezomib	3
MM-0038-Tumor	Dexamethasone;Thalidomide;Pomalidomide	19
MM-0191-Tumor	Thalidomide;Dexamethasone;Pomalidomide	21

**Table 11.31:** The most effective standard drug therapy and the number of essential genes it controls, for the structural target controllability analysis corresponding to the top ranked essential genes based on their eigenvector centrality.

Tumor Sample	Standard therapy	Controlled EG
MM-0028-Tumor	Bortezomib;Thalidomide;Dexamethasone	2
MM-0038-Tumor	Bortezomib;Thalidomide;Dexamethasone	19
MM-0191-Tumor	Bortezomib;Thalidomide;Dexamethasone	21

**Table 11.32:** The proposed drug therapy and the number of essential genes it controls, for the structural target controllability analysis corresponding to the essential genes in the patient network.

Tumor Sample	Proposed therapy	Controlled EG
MM-0028-Tumor	Thalidomide;Doxorubicin;Dexamethasone	31
MM-0038-Tumor	Thalidomide;Pomalidomide;Doxorubicin	28
MM-0191-Tumor	Dexamethasone;Carfilzomib	25

**Table 11.33:** The most effective standard drug therapy and the number of essential genes it controls, for the structural target controllability analysis corresponding to the essential genes in the patient network.

<b>Tumor Sample</b>	<b>Standard therapy</b>	<b>Controlled EG</b>
MM-0028-Tumor	Bortezomib;Thalidomide;Dexamethasone	29
MM-0038-Tumor	Bortezomib;Thalidomide;Dexamethasone	29
MM-0191-Tumor	Lenalidomide;Bortezomib;Dexamethasone	24

when approaching multiple myeloma cases and are part of two therapies in combination with either Bortezomib or Carfilzomib frequently use in latest medical practice, namely VTD and KTD respectively. These two combinations are supported by successful outcomes in different studies, such as [Roussel et al., 2020, Wester R, 2019].

The third drug combination spot is usually taken by Pomalidomide. While this drug is mostly considered in later stages of the treatment in the context of traditional care, the analysis predicts this drug to have a strong reinforcement impact on the activity of Thalidomide for these specific cases, as it shares the same controlled essential genes with the latter. Our approach also identifies several outliers to the predominant 3-drug combination, namely Selinexor, Doxorubicin, Prednisone, Bortezomib, and Carfilzomib. The first two drugs are not considered until the last stages of the treatment in standard therapy lines. Although the conclusions collected by this study for these three patients align with this traditional approach, they still provide grounds to consider them over other late stage drugs if the treatment progresses to an evolved phase. On the other hand, the remaining three are relevant in starting medical diagnosis, with Bortezomib being specially remarkable. Following a more traditional approach, these three drugs may be given preference over Pomalidomide for the first prescriptions.

**Table 11.34:** The drug-target genes in the dominating set obtained by the minimum dominating set analysis.

Tumor sample 28		Tumor sample 38		Tumor sample 191	
ANXA1	PSMB5	ANXA1	PSMB5	ANXA1	PSMB5
NFKB1	PSMB9	NFKB1	PSMB8	NFKB1	PTGS2
NOLC1	PTGS2	NOLC1	PSMB9	NOLC1	TNF
NR3C1	TNF	NR3C1	PTGS2	NR3C1	TNFSF11
PSMB1	TNFSF11	PSMB1	TNF		
PSMB2	TOP2A	PSMB10	TNFSF11		
		PSMB2	TOP2A		

The suggested drug therapies are predicted to control most of the considered essential genes in the whole network and each of the centrality subnetworks. Consequently, it is expected for them to have a significant favorable impact on the condition of our targeted patients. Furthermore, the prescribed sequence of drugs are very close to the known therapies frequently used in the current state of the art treatment. All of these events provide a strong foundation for the feasibility of this method in personalized medicine.

### 11.3.3.2. Minimum dominating set analysis

We applied the input-constrained minimum 3-dominating set method on the complete networks and sets of essential and drug-target genes. The drug-target genes in the obtained dominating sets are shown in Table 11.34.

Next, we applied the method once more on the subgraphs described in Section 11.3.2 and corresponding to each centrality measure. The drug-target genes in the dominating set obtained for each measure are presented in Tables 11.35, 11.36, 11.37, 11.38, 11.39 and 11.40.

The examination of these results follows an analogous procedure to the one introduced for target controllability. For each network and centrality measure,

**Table 11.35:** The drug-target genes in the dominating set obtained by the minimum dominating set analysis corresponding to the top ranked essential genes based on their in-degree centrality.

<b>Tumor sample 28</b>	<b>Tumor sample 38</b>	<b>Tumor sample 191</b>
ANXA1 PSMB5	ANXA1 NR3C1	ANXA1 NR3C1
NFKB1 PSMB9	NFKB1 TNF	NFKB1 TNF
NOLC1 PTGS2	NOLC1 TNFSF11	NOLC1 TNFSF11
NR3C1 TNF		
PSMB1 TNFSF11		
PSMB2 TOP2A		

**Table 11.36:** The drug-target genes in the dominating set obtained by the minimum dominating set analysis corresponding to the top ranked essential genes based on their closeness centrality.

<b>Tumor sample 28</b>	<b>Tumor sample 38</b>	<b>Tumor sample 191</b>
ANXA1 TNF	ANXA1 TNF	ANXA1 TNF
NFKB1 TNFSF11	NFKB1 TNFSF11	NFKB1 TNFSF11
NR3C1	NR3C1	NR3C1

**Table 11.37:** The drug-target genes in the dominating set obtained by the minimum dominating set analysis corresponding to the top ranked essential genes based on their harmonic centrality.

<b>Tumor sample 28</b>	<b>Tumor sample 38</b>	<b>Tumor sample 191</b>
ANXA1 TNF	ANXA1 TNF	ANXA1 TNF
NFKB1	NFKB1 TNFSF11	NFKB1 TNFSF11
	NR3C1	NR3C1

**Table 11.38:** The drug-target genes in the dominating set obtained by the minimum dominating set analysis corresponding to the top ranked essential genes based on their eccentricity.

<b>Tumor sample 28</b>	<b>Tumor sample 38</b>	<b>Tumor sample 191</b>
ANXA1 TNF	ANXA1 TNF	ANXA1 NR3C1
NFKB1 TNFSF11	NFKB1 TNFSF11	NFKB1 TNF
NR3C1	NR3C1	NOLC1 TNFSF11

**Table 11.39:** The drug-target genes in the dominating set obtained by the minimum dominating set analysis corresponding to the top ranked essential genes based on their betweenness centrality.

Tumor sample 28		Tumor sample 38		Tumor sample 191	
ANXA1	PSMB5	ANXA1	PTGS2	ANXA1	PTGS2
NFKB1	PSMB9	NFKB1	TNF	NFKB1	TNF
NOLC1	PTGS2	NR3C1	TNFSF11	NR3C1	TNFSF11
NR3C1	TNF				
PSMB1	TNFSF11				
PSMB2	TOP2A				

**Table 11.40:** The drug-target genes in the dominating set obtained by the minimum dominating set analysis corresponding to the top ranked essential genes based on their eigenvector-based prestige.

Tumor sample 28		Tumor sample 38		Tumor sample 191	
ANXA1	TNF	ANXA1	TNF	ANXA1	TNF
NFKB1		NFKB1		NFKB1	

as well as the network associated to the whole minimum dominating set, we ascertain a drug therapy including the top ranked drugs on terms of reached essential genes. The chosen drugs are documented in Tables 11.41, 11.43, 11.45, 11.47, 11.49 and 11.51. Furthermore, the drugs corresponding to the dominating set associated to all the essential genes in the original patient network are shown in Table 11.53. The associated most effective standard drug therapy for each tumor sample and centrality measure are given in Tables 11.42, 11.44, 11.46, 11.48, 11.50, 11.52 and 11.54.

From the point of view of centrality analysis, the results are consistent over all the networks and centrality measures with the prescription of the 3-drug combination of Thalidomide, Pomalidomide and Dexamethasone. The parallel outcomes yielded by this approach and the one focused on target controllability support our hypothesis of an interrelationship between the network topological properties and the genes influencing the disease. On these grounds, we propose

**Table 11.41:** The proposed drug therapy and the number of essential genes it dominates, for the minimum dominating set corresponding to the top ranked essential genes based on their in-degree.

Tumor Sample	Proposed therapy	Dominated EG
MM-0028-Tumor	Thalidomide;Pomalidomide;Dexamethasone	28
MM-0038-Tumor	Thalidomide;Pomalidomide;Dexamethasone	27
MM-0191-Tumor	Thalidomide;Pomalidomide;Dexamethasone	29

**Table 11.42:** The most effective standard drug therapy and the number of essential genes it dominates, for the minimum dominating set corresponding to the top ranked essential genes based on their in-degree.

Tumor Sample	Standard therapy	Dominated EG
MM-0028-Tumor	Bortezomib;Thalidomide;Dexamethasone	28
MM-0038-Tumor	Bortezomib;Thalidomide;Dexamethasone	27
MM-0191-Tumor	Bortezomib;Thalidomide;Dexamethasone	29

**Table 11.43:** The proposed drug therapy and the number of essential genes it dominates, for the minimum dominating set corresponding to the top ranked essential genes based on their closeness.

Tumor Sample	Proposed therapy	Dominated EG
MM-0028-Tumor	Thalidomide;Pomalidomide;Dexamethasone	24
MM-0038-Tumor	Thalidomide;Pomalidomide;Dexamethasone	26
MM-0191-Tumor	Thalidomide;Pomalidomide;Dexamethasone	26

**Table 11.44:** The most effective standard drug therapy and the number of essential genes it dominates, for the minimum dominating set corresponding to the top ranked essential genes based on their closeness.

Tumor Sample	Standard therapy	Dominated EG
MM-0028-Tumor	Bortezomib;Thalidomide;Dexamethasone	24
MM-0038-Tumor	Bortezomib;Thalidomide;Dexamethasone	26
MM-0191-Tumor	Bortezomib;Thalidomide;Dexamethasone	26

**Table 11.45:** The proposed drug therapy and the number of essential genes it dominates, for the minimum dominating set corresponding to the top ranked essential genes based on their harmonic centrality.

Tumor Sample	Proposed therapy	Dominated EG
MM-0028-Tumor	Thalidomide;Pomalidomide;Dexamethasone	21
MM-0038-Tumor	Thalidomide;Pomalidomide;Dexamethasone	26
MM-0191-Tumor	Thalidomide;Pomalidomide;Dexamethasone	24

**Table 11.46:** The most effective standard drug therapy and the number of essential genes it dominates, for the minimum dominating set corresponding to the top ranked essential genes based on their harmonic centrality.

Tumor Sample	Standard therapy	Dominated EG
MM-0028-Tumor	Bortezomib;Thalidomide;Dexamethasone	21
MM-0038-Tumor	Bortezomib;Thalidomide;Dexamethasone	26
MM-0191-Tumor	Bortezomib;Thalidomide;Dexamethasone	24

**Table 11.47:** The proposed drug therapy and the number of essential genes it dominates, for the minimum dominating set corresponding to the top ranked essential genes based on their eccentricity.

Tumor Sample	Proposed therapy	Dominated EG
MM-0028-Tumor	Thalidomide;Pomalidomide;Dexamethasone	26
MM-0038-Tumor	Thalidomide;Pomalidomide;Dexamethasone	26
MM-0191-Tumor	Thalidomide;Pomalidomide;Dexamethasone	26

**Table 11.48:** The most effective standard drug therapy and the number of essential genes it dominates, for the minimum dominating set corresponding to the top ranked essential genes based on their eccentricity.

Tumor Sample	Standard therapy	Dominated EG
MM-0028-Tumor	Bortezomib;Thalidomide;Dexamethasone	26
MM-0038-Tumor	Bortezomib;Thalidomide;Dexamethasone	26
MM-0191-Tumor	Bortezomib;Thalidomide;Dexamethasone	26

**Table 11.49:** The proposed drug therapy and the number of essential genes it dominates, for the minimum dominating set corresponding to the top ranked essential genes based on their betweenness.

Tumor Sample	Proposed therapy	Dominated EG
MM-0028-Tumor	Thalidomide;Pomalidomide;Dexamethasone	27
MM-0038-Tumor	Thalidomide;Pomalidomide;Dexamethasone	27
MM-0191-Tumor	Thalidomide;Pomalidomide;Dexamethasone	27

**Table 11.50:** The most effective standard drug therapy and the number of essential genes it dominates, for the minimum dominating set corresponding to the top ranked essential genes based on their betweenness.

Tumor Sample	Standard therapy	Dominated EG
MM-0028-Tumor	Bortezomib;Thalidomide;Dexamethasone	27
MM-0038-Tumor	Bortezomib;Thalidomide;Dexamethasone	27
MM-0191-Tumor	Bortezomib;Thalidomide;Dexamethasone	27

**Table 11.51:** The proposed drug therapy and the number of essential genes it dominates, for the minimum dominating set corresponding to the top ranked essential genes based on their eigenvector centrality.

Tumor Sample	Proposed therapy	Dominated EG
MM-0028-Tumor	Thalidomide;Pomalidomide;Dexamethasone	20
MM-0038-Tumor	Thalidomide;Pomalidomide;Dexamethasone	21
MM-0191-Tumor	Thalidomide;Pomalidomide;Dexamethasone	24

**Table 11.52:** The most effective standard drug therapy and the number of essential genes it dominates, for the minimum dominating set corresponding to the top ranked essential genes based on their eigenvector centrality.

Tumor Sample	Standard therapy	Dominated EG
MM-0028-Tumor	Bortezomib;Thalidomide;Dexamethasone	20
MM-0038-Tumor	Bortezomib;Thalidomide;Dexamethasone	21
MM-0191-Tumor	Bortezomib;Thalidomide;Dexamethasone	24

**Table 11.53:** The proposed drug therapy and the number of essential genes it dominates, for the minimum dominating set corresponding to the essential genes in the patient network.

Tumor Sample	Proposed therapy	Dominated EG
MM-0028-Tumor	Thalidomide;Pomalidomide;Dexamethasone	31
MM-0038-Tumor	Thalidomide;Pomalidomide;Dexamethasone	31
MM-0191-Tumor	Thalidomide;Pomalidomide;Dexamethasone	31

**Table 11.54:** The most effective standard drug therapy and the number of essential genes it dominates, for the minimum dominating set corresponding to the essential genes in the patient network.

Tumor Sample	Standard therapy	Dominated EG
MM-0028-Tumor	Bortezomib;Thalidomide;Dexamethasone	31
MM-0038-Tumor	Bortezomib;Thalidomide;Dexamethasone	31
MM-0191-Tumor	Bortezomib;Thalidomide;Dexamethasone	31



hub genes ascertained by the centrality analysis of a disease network to be considered as basis for the discovery of new essential genes and drug targets.

## 11.4. Conclusion

Network medicine is an exciting and promising field of research, with a high potential for personalized approaches. It brings together approaches in graph theory, network science, systems biology, bioinformatics and medicine, opening the door to detailed patient- and disease-specific insights. We discussed in this chapter several basic methods of network modeling and their potential applicability in personalized medicine. We also demonstrated their potential on three multiple myeloma patient datasets. We showed how various methods (topological analysis, systems controllability) can be combined to predict optimal and personalized drug combinations therapies. In some cases, they differ from the initial standard therapy lines routinely offered to multiple myeloma patients, and resemble in part the options becoming available later in the disease progression. More studies (especially longitudinal studies) are needed to explore the full potential of these methods and convincingly demonstrate their applicability in the clinical practice.

The results we obtained on the three datasets differ slightly from method to method. This is not surprising, as each method identifies different nodes and paths in the graphs that are of interest from various computational points of view. Which ones work best in practice should be explored with other research instruments, and it is likely the results may differ from case to case.

The results in network medicine are critically dependent on the quality of the patient networks being applied to. The patient data that can be included in

such networks can be quite diverse, including genetic mutations, copy number variations, differential gene expression, co-morbidities, and concurrent treatments. All these data sources contribute to the set of nodes in the network. The interactions included in the network typically come from various interaction databases (some of which we discussed in this chapter). The data going into these databases is very diverse: some of it is experimental (but not always on human samples), some is inferred from other experiments, while others are deduced through various machine learning methods. The importance of curating these datasets or at least choosing carefully which to include in the analyses cannot be underestimated.

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