INVITED PAPER

Centrality, Network Capacity, and Modularity as Parameters to Analyze the Core-Periphery Structure in Metabolic Networks

Methods and concepts have been developed to identify the overall structure of biological networks that operate to maintain life in human beings and other organisms.

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ABSTRACT | Genome-scale metabolic networks of organisms are normally very large and complex. Previous studies have shown that they are organized in a hierarchical and modular manner. In particular, a core-periphery modular organization structure has been proposed for metabolic networks. However, no methods or parameters are available in the literature to quantitatively evaluate or find the hierarchical and modular structure of metabolic networks. In this paper, we propose a parameter called "core coefficient" to quantitatively evaluate the core-periphery structure of a metabolic network. This parameter is defined based on the concept of closeness centrality of metabolites and a newly defined parameter: network capacity. To find or define the core and the periphery modules of a metabolic network, we further developed a method to decompose metabolic networks based on a quantitative parameter of modularity and a procedure of core extraction. The method has been developed with genome-scale metabolic networks of five representative organisms, which include *Aeropyrum pernix, Bacillus subtilis, Escherichia coli, Saccharomyces cerevisiae,* and *Homo sapiens.* The results were compared with two artificially generated network models.

KEYWORDS | Core-periphery structure; metabolic networks; network decomposition; systems biology

I. INTRODUCTION

The organization of individual molecules including DNA, proteins, and metabolites in living organisms follows a hierarchy. The understanding of how all these molecules interact to form a complex system is a challenging issue for systems biology. In recent years, different types of large-scale biological networks have been reconstructed to represent the various types of interactions among the cellular components. Among them, the metabolic network is of special interest because an organism-specific metabolic network can be directly reconstructed solely based on the genome annotation information. Structure analysis of genome-based metabolic networks (mainly based on graph theory) has provided important insights about the organization of the whole network. However, an in-depth functional analysis of the network often requires decomposing the whole network into small subsets termed as modules. Network decomposition is also important for metabolic pathway analysis using elementary flux modes [1] and/or extreme pathways [2], which have been shown to be useful in functional analysis of metabolic networks. Due to the problem of combinatorial

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Table 1 Networks Considered in This Work and Their Typical Structure Features

Network	# of nodes	# of edges	avg. Degree	Obs.
E. coli	473	574	2.42706	metabolic network
B. subtilis	421	498	2.36580	metabolic network
A. pernix	152	174	2.28947	metabolic network
S. cerevisiae	358	436	2.43575	metabolic network
H. sapiens	509	608	2.38900	metabolic network
Barabási-Albert	500	989	3.95600	artificial network
Newman-Watts-Strogatz	500	613	2.45200	artificial network

explosion, these methods cannot be directly applied to large-scale networks.

In biochemistry, it is well established that separate metabolic reactions are organized into pathways, which build discrete functional units of metabolism [3], [4]. These pathways are further nested to form modules and ultimately a complex metabolic network. Therefore, it is of great interest to develop efficient network decomposition methods to identify the functional modules from the structure of the whole network. Ravasz *et al.* [5] proposed a hierarchical modularity model for metabolic networks. According to this model, metabolic networks are organized as many small, but highly connected modules that combine in a hierarchical manner to larger, less cohesive units. Several other methods using concepts such as the reaction betweenness centrality and the dependency of metabolites have also been developed to identify hierarchical organization structure of metabolic networks [6], [7].

Another feature of metabolic networks is based on the fact that metabolic pathways can be distinguished between central pathways, including glycolysis and tricarboxylic acid cycle, and periphery pathways. Various carbon sources are converted to metabolites in the central pathways, and about 12 central metabolites are the common precursors for the synthesis of almost all the different products. Recently, a new network organization structure, which is termed as core-periphery organization, was found in many complex networks [8]. In such a structure, one subset of the network constitutes a densely connected core that is also central in terms of network distance, and the rest of the network

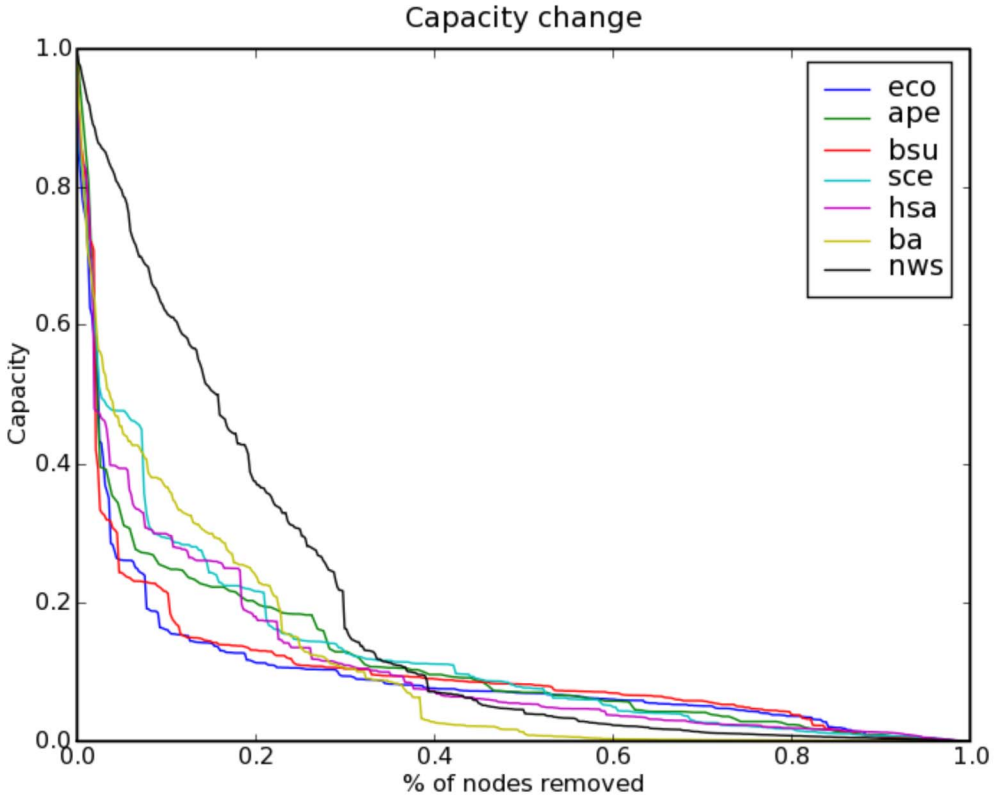

Fig. 1. ***Change in capacity for the networks by removal of the most central nodes successively.***

forms a periphery. In this paper, we present a new quantitative measure to determine if a network has a core-periphery structure, based on which we further develop a new metabolic network decomposition method that distinguishes the central pathways from the periphery pathways.

II. NETWORKS USED IN THIS PAPER

For this paper, the genome-scale metabolic networks of *Aeropyrum pernix*, *Bacillus subtilis*, *Escherichia coli*, *Saccharomyces cerevisiae*, and *Homo sapiens* were used as representatives of different genus or families of organisms. These networks were reconstructed from the updated genome annotation information using the methods described by Ma and Zeng [9]. In the study reported in this paper, we considered only the largest weakly connected part [10] and ignored the direction of the reactions. The number of nodes and links and some typical structure features of these networks are shown in Table 1.

Artificial networks were generated for comparison purposes to show the properties of networks not presenting a core-periphery structure. Two methods were used to generate the artificial networks. One was from Barabási–Albert [11], [12] and the other one from Newman *et al.* [13]. Artificial networks based on these methods were generated with 500 nodes (chosen based on the average of the real networks for a better comparison). The average number of neighbors of each node in each network is similar to the value in the metabolic networks studied to make the comparison of the artificial networks and the metabolic networks more meaningful.

III. TERMS AND PARAMETERS USED FOR NETWORK ANALYSIS

To understand better the methods proposed in this paper, some key concepts and parameters used in the methods are briefly described below.

A. Centrality in Metabolic Networks

Centrality is a concept for identifying key nodes in a network. Different definitions of centrality [14] have been proposed in the literature. Degree centrality is, for example, a measure to show the nodes with the highest number of connections in the network. This helps to identify the "hubs" in the network. In a metabolic network, these represent nodes that can be directly converted into more metabolites. Betweenness centrality is another measure for the importance of nodes in a network. The node with the highest betweenness centrality is the one with the highest number of shortest pathways passing through it. For a metabolic network, nodes with a

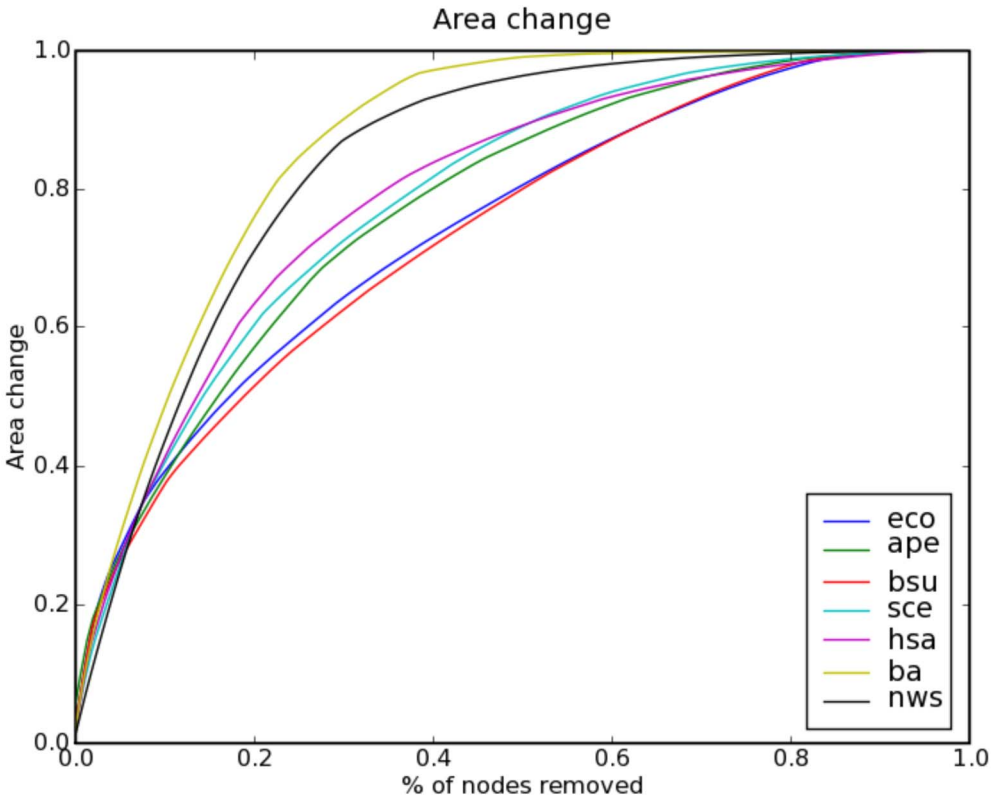

Fig. 2. ***Accumulated capacity for the networks by removal of the most central nodes.***

high betweenness centrality may participate in many metabolic conversions and are often the key points for metabolic flux control. With the term closeness centrality, one can identify nodes that are more central in the network and nodes in the periphery part. Nodes in the central part of the network have a shorter distance to other nodes in the network (they are closer to other nodes, therefore the name "closeness"). In a metabolic network, they represent metabolites that can be converted into other metabolites in the smallest number of steps.

IV. MODULARITY OF NETWORK

Modularity is a parameter defined by Newman [15] for detecting the presence of communities in a network. It is defined as [15], [16]

$$M = \sum_{s=1}^{N_M} \left[\frac{l_s}{L} - \left(\frac{d_s}{2L} \right)^2 \right] \tag{1}$$

where N_M is the number of modules, L is the number of links in the network, l_s is the number of links between nodes in module s, and d_s is the sum of the degrees of the nodes in module s.

V. CORE-PERIPHERY STRUCTURE OF NETWORK

A possible large-scale network design principle is that one part of the network constitutes a densely connected core that also is central in terms of network distance, and the rest of the network forms a periphery [8].

In a network with core-periphery structure, not only are the nodes organized into communities but also these communities have different roles and organization. The core module (or community) has the function of communicating with the periphery modules. Hence its components have relation with many modules. In other words, the core should be composed of central nodes that have connections to different modules. Many of the biologic networks, including metabolic networks studied in this paper, have a core-periphery structure [8].

VI. METHOD DEVELOPMENT AND RESULTS

Not all networks present a core-periphery structure. For networks presenting such a structure, there should be a module, usually a central one, which works as a link to different parts of the network. In this paper, a method to evaluate the extent of such a structure is first proposed that uses the concept of network capacity. In the second part, a method based on network modularity is proposed to decompose metabolic networks into several modules and distinguish the core module for identifying the core-periphery structure. First, we introduce the concept of network capacity, which we later use for the identification of a core-periphery structure in a network.

Table 2 Core Coefficient Based on Network Capacity for Various Networks

network	core coefficient
E. coli	0.64693
B. subtilis	0.64608
A. pernix	0.55921
S. cerevisiae	0.51676
H. sapiens	0.51866
Barabási-Albert	0.30000
Newman-Watts-Strogatz	0.34000

VII. NETWORK CAPACITY

We introduce the parameter network capacity as a property of a network to measure the connectivity of a network. It is defined as

$$C = \sum_{i=1}^{n} \frac{1}{PL_i} \tag{2}$$

where n is the total number of connected pairs in the network and PL_i is the shortest path between each pair. A network with more paths should have a higher capacity. In the same way, if the paths in the network are shorter, the capacity will be higher.

VIII. CORE COEFFICIENT AS A MEASURE OF CORE-PERIPHERY STRUCTURE IN METABOLIC NETWORK

As mentioned above, capacity is a parameter to measure the connectivity of a network. On the other side, the core in a core-periphery network should have the most connectivity to other parts of the network. Therefore, the removal of the nodes in the core should decrease the capacity of the network more significantly than the removal of nodes in the periphery part. To test this conjecture, we removed nodes from the test networks based on the order of node closeness centrality and calculated the capacity of the networks after the removal of each node. The results are shown in Fig. 1. The model from Barabási–Albert [11] is represented as *ba* in the graph and the model from Newman *et al.* [13] as *nws*.

In the examples of Fig. 1, the nodes were removed in decreasing order of closeness centrality.

In networks that have the core-periphery structure, the removal of the core nodes will decrease the capacity faster than in networks not presenting this structure because

Table 3 Core Coefficient Based on the Variation of the Biggest Connected Part of a Network by Removal of the Most Central Nodes

network	core coefficient
E. coli	0.75949
B. subtilis	0.75118
A. pernix	0.69281
S. cerevisiae	0.63231
H. sapiens	0.77059
Barabási-Albert	0.37924
Newman-Watts-Strogatz	0.41118

many periphery nodes will be disconnected from the network without the links from the core. The removal of the core will "break" the network.

To get a numerical parameter to detect the core-periphery structure, the term *accumulated capacity* is introduced here. It is generated from the integration of the capacity change (e.g., Fig. 1), resulting in the smoother curves shown in Fig. 2.

From the analysis of the curves in Fig. 2, we found that the variation of capacity accumulates faster in networks not presenting a core-periphery structure. It can be seen from the graph that in networks presenting a core-periphery structure, the graph reaches 0.9 only after more than 50% of the nodes are removed, while in artificial networks not presenting such a structure, this happens before half of the nodes are removed. This behavior can be explained by the fact that in networks with a core-periphery structure, the network will break into many parts (periphery modules) after removal of the core nodes, leading to an abrupt decrease of the network capacity. In networks not presenting a core-periphery structure, the removal of the nodes will not affect capacity so quickly because the modules are more interconnected.

Based on the above observations, we further define a parameter called *core coefficient* (cc) as

$$cc = \frac{n}{N} \tag{3}$$

where N is the total number of nodes in the network and n should satisfy the equation

$$\int_{i=0}^{n} C_i = 0.9 \int_{j=0}^{N} C_j \tag{4}$$

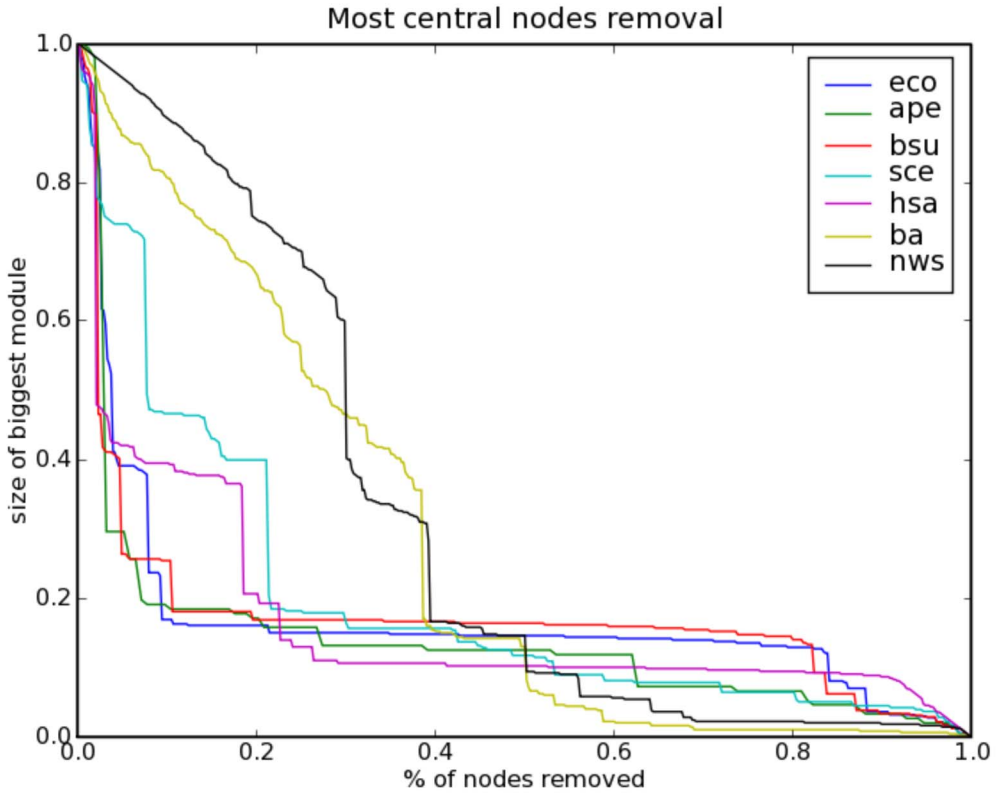

Fig. 3. ***Variation in the size of the biggest connected part of the networks by removal of the most central nodes.***

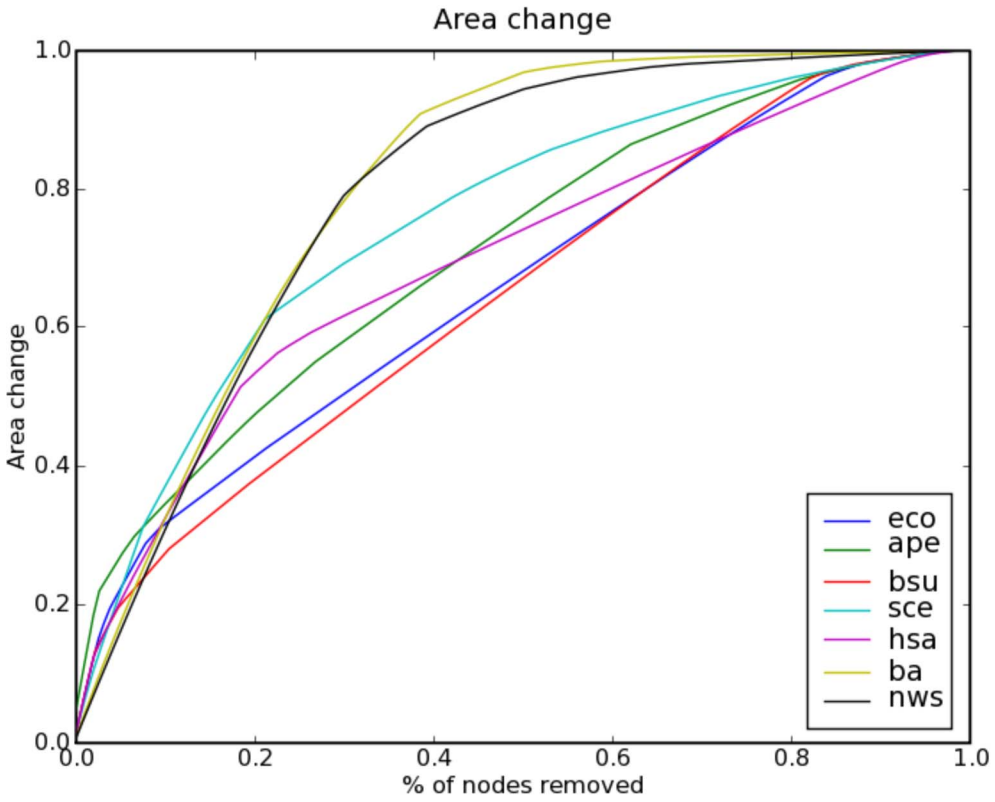

Fig. 4. ***Variation in the size of the biggest connected part of the networks by removal of the most central nodes after integration.***

or, considering that the data are discrete

$$\sum_{i=0}^{n} C_i = 0.9 \sum_{j=0}^{N} C_j \tag{5}$$

where C_i is the capacity of the network after removal of i nodes.

The implementation of this parameter in software is straightforward and the computation very fast once the values for the capacity are calculated.

As shown in Table 2, networks with a core-periphery structure have a generally higher core coefficient (CC) than the artificial networks without a core-periphery structure. A CC value of 0.5 seems to be a reasonable cutoff to distinguish core-periphery networks from artificial none core-periphery networks.

An alternative to the method based on the variation in network capacity to measure the core-periphery structure is to use the variation in the size of the biggest connected part in the network by the removal of the most central nodes. The advantage of this method is that it is faster to measure the size of the biggest connected part than to calculate the capacity after the removal of each node of the network.

If the network has a core, the removal of the nodes belonging to the core will "break" the network into smaller parts (the periphery modules) that will be disconnected between each other because of the absence of the "connecting" nodes from the core.

The calculation of capacity takes into account the size of the pathways in the network. If the largest connected part of the network changes little, the value of capacity will also not change much. But if the network is "broken" in the middle, both the size of the biggest connected part and the capacity will decrease significantly.

Because of this relation between the size of the remaining biggest connected part in the network and the capacity, both methods present similar results as shown Table 3 and Figs. 3 and 4. The main difference between the two methods is that the one based on capacity is more mathematically grounded, as it uses the capacity parameter as defined in this paper, which can evaluate the robustness of the network. The disadvantage with this method is that the computation of the network capacity is time-consuming, as it should be calculated after the removal of each node. The other method, which is based on the size of the biggest connected part, is much faster in terms of computation. Both methods are presented for comparison purposes.

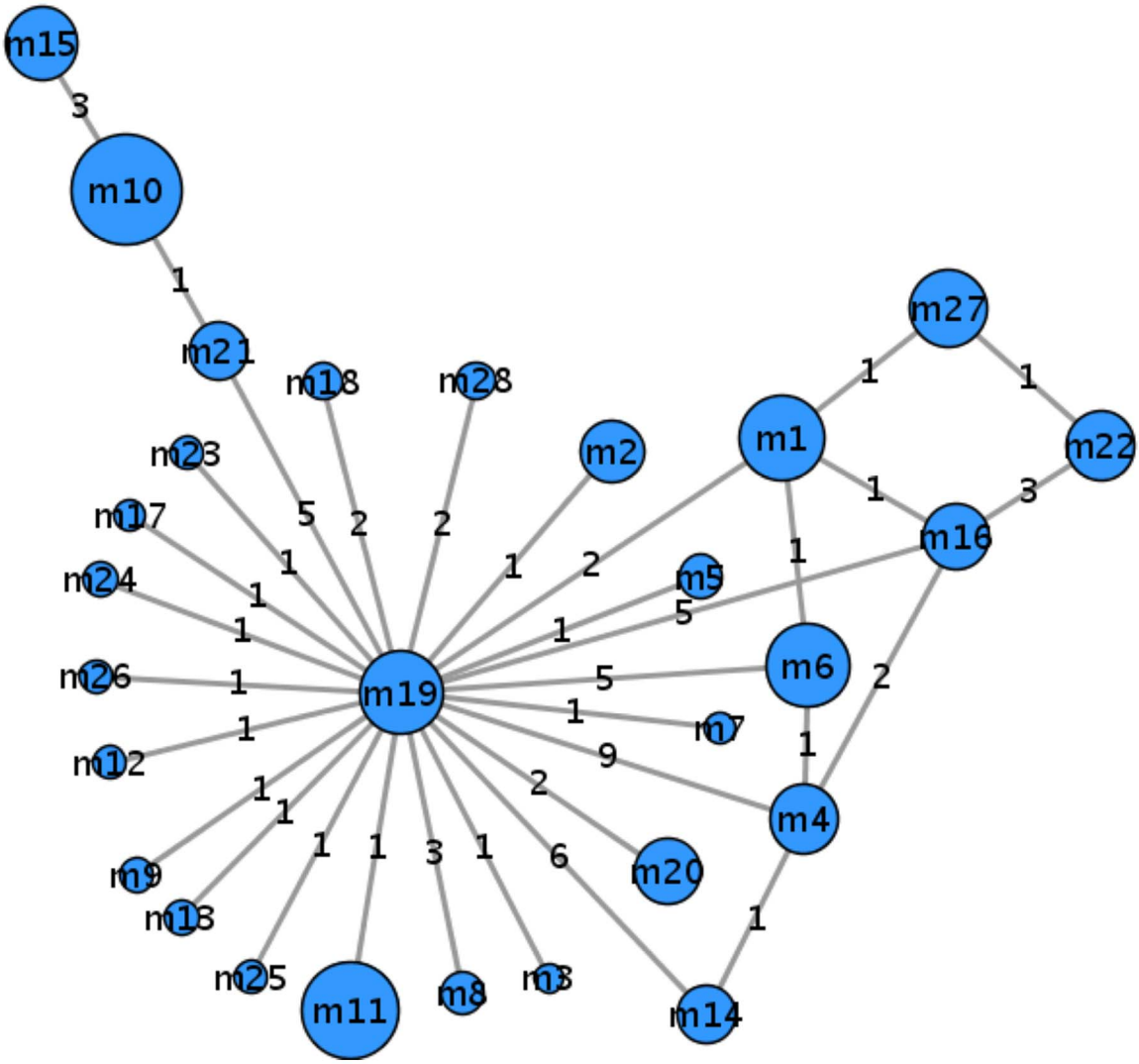

Fig. 5. ***Core extraction using closeness centrality.***

For the calculation of the core coefficient using the biggest connected part of the network, a variation of (3)–(5) is applied, changing capacity (C_i) by the size of the biggest connected part of the network after the removal of the nodes (BM_i). The results are shown in Table 3.

IX. FINDING THE CORE-PERIPHERY STRUCTURE BY NETWORK DECOMPOSITION BASED ON MODULARITY

Newman proposed [15] to use the parameter modularity not only as a measure of the structure of a network but also for network clustering. The objective of his method is to optimize the modularity over all possible divisions to find the best one. However, algorithms considering all the possible ways to cluster a network normally take a very long calculation time and are infeasible even for networks with nodes only slightly higher than 30 [15]. As an alternative, a "greedy" optimization algorithm could be used where nodes are clustered in successive steps [15]. In this kind of algorithm, the network is considered as each node is a module itself. At the beginning, the number of modules is the same as the number of nodes. Then, the modules are joined in pairs, forming new modules, choosing at each step the join that results in the greatest increase (or smallest decrease) in modularity.

We tried to use the modularity proposed by Newman to determine the core-periphery structure of metabolic networks and found that the core module was broken at the end of the decomposition in most cases. The reason for this is that the modularity-based algorithm alone is not well suited for dealing with networks having a core-periphery

structure. The algorithm tries to create modules to have, as much as possible, connections inside themselves and as few as possible connections between modules. The core is a highly connected module having many connections to other modules as it interconnects the periphery modules. Because of this, the algorithm according to Newman tends to split the core in many modules to better separate the nodes according to its rules.

To avoid this problem and to decompose metabolic networks into a core-periphery structure using the method based on modularity, we proposed a variation algorithm in this paper that first extracts the core to avoid the breakage during the decomposition. In the first step of the algorithm, an initial module including the most central nodes is created as the core. It should be central and with most of the other nodes connecting to it. To achieve this, we tested three different types of centralities: closeness, betweenness, and degree centrality [14]. These different centralities were tested in known networks to see which one would be more successful on the identification of the core module. After the extraction of the initial core module, the algorithm then runs as the normal decomposition algorithm until all the nodes are clustered and the module decomposition with the highest modularity is chosen.

The best results were achieved using the parameter closeness centrality [17]. For the degree centrality, many nodes interconnecting nodes inside a peripheral module were identified as part of the core. Betweenness centrality also failed in the identification because the most active pathways are not necessarily the shortest ones in a metabolic network. Sometimes some longer pathways will attend more reactions and, because of this, will be more active. For *E. coli*, the decomposition results using closeness centrality are depicted in Fig. 5. The edge labels represent the number of edges connecting two modules. Node size represents the amount of nodes inside the module (bigger nodes means a higher number of nodes in the module). The core-periphery structure is present (according to the core coefficient—Table 3—also possible to see it by the graph) but some modules are not connected directly to the core, like modules 10, 15, 22, and 27. This behavior appeared only in the *E. coli* network. Other networks had much better core-periphery decomposition.

Table 4 Pathways for Module Decomposition Using Closeness Centrality

Module ID	Pathways
13	Valine, leucine and isoleucine degradation Valine, leucine and isoleucine biosynthesis
12	Aminosugars metabolism
11	Galactose metabolism Nucleotide sugars metabolism
10	Purine metabolism
17	Pentose phosphate pathway
16	Histidine metabolism Citrate cycle (TCA cycle) Glutamate metabolism Butanoate metabolism
15	Folate biosynthesis Riboflavin metabolism One carbon pool by folate
14	Glycerophospholipid metabolism Glycerolipid metabolism
19	Pyruvate metabolism Glycolysis / Gluconeogenesis
18	Propanoate metabolism Valine, leucine and isoleucine degradation
9	Pentose and glucuronate interconversions Glyoxylate and dicarboxylate metabolism
8	Fructose and mannose metabolism
7	D-Alanine metabolism
6	Glycine, serine and threonine metabolism Methionine metabolism Glutathione metabolism
10	Pentose and glucuronate interconversions
4	Glyoxylate and dicarboxylate metabolism Glycine, serine and threonine metabolism
3	Glycine, serine and threonine metabolism
1	Lysine biosynthesis Peptidoglycan biosynthesis Aminosugars metabolism beta-Alanine metabolism Alanine and aspartate metabolism
26	Benzoate degradation via CoA ligation
27	Pyrimidine metabolism
25	Fructose and mannose metabolism
22	Urea cycle and metabolism of amino groups Arginine and proline metabolism
23	Arginine and proline metabolism
21	Pantothenate and CoA biosynthesis Valine, leucine and isoleucine biosynthesis Valine, leucine and isoleucine degradation Pentose and glucuronate interconversions Pentose phosphate pathway Carbon fixation
28	Fatty acid biosynthesis

This suggests that in the *E. coli* network, there are some kind of "subcores" that interconnect parts of the network not directly related.

For the analysis of the decomposition from a biological point of view, Table 4 shows the main metabolic functions of the metabolites in each module. The highlighted module is the core module. From this table, we can see that the core was well identified (module 19) having most of its nodes in glycolysis and pyruvate metabolism. Another central pathway, TCA cycle, appears in module 16. From Fig. 5, we can see that module 16 acts as a "subcore" linking some other modules to the core. Although it is better to have only one core, by the use of modularity as criterion for decomposition, it is hard to keep one core and keep this core small. If we join modules 19 and 16 into one single core, the results of final modularity would be not optimal as the core will became too big. For other modules, the results are also biologically justified.

X. CONCLUSION

The core coefficients defined based on the capacity change or the change of size of the biggest connected part of the network after sequential removal of the most central nodes can be used to detect the presence of a core-periphery structure in a large network and were successfully used to distinguish the metabolic networks from the artificially generated networks without a core-periphery structure. The new network decomposition method based on the initial extraction of the core was proved to be efficient in identifying the core and periphery modules in all the metabolic networks studied. It is worth mentioning that a consideration of existing biochemical knowledge can further help decomposition of complex metabolic networks, especially in making a decision on which nodes belong to the initial core module and how to divide other metabolites into different modules during the decomposition process.

To detect the presence of a core-periphery structure in metabolic networks, two methods were presented: one based on a new parameter called network capacity and another based on the size of the biggest connected part of the network after removal of some most central nodes. Both methods proved to be adequate in the detection of a core-periphery structure. In particular, the latter one is more straightforward and much faster in terms of computation.

The new methods and parameters can be used to decompose metabolic networks. It is worth mentioning that a consideration of existing biochemical knowledge can further help decomposition of complex metabolic networks, especially in making a decision on which nodes belong to which part of the core module and how to divide other metabolites into different modules during the decomposition process. ■

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