Generic GA-PPI-Net: Generic Evolutionary Algorithm to Detect Semantic and Topological Biological Communities

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Abstract: Community detection aims to identify topological structures and discover patterns in complex networks. It presents an important problem of great significance in many fields. In this paper, we are interested in the detection of communities in biological networks. These networks represent protein-protein or gene-gene interactions which corresponds to a set of proteins or genes that collaborate at the same cellular function. The goal is to identify such semantic and/or topological communities from gene annotation sources such as Gene Ontology. We propose a Genetic Algorithm (GA) based technique as a clustering approach to detect communities from biological networks. For this purpose, we introduce four specific components to the GA: a fitness function based on a similarity measure and the interaction value between proteins or genes, a solution for representing a community with dynamic size, an heuristic crossover to strengthen links in the communities and a specific mutation operator. Experimental results show the ability of our Genetic Algorithm to detect communities of genes that are semantically similar or/and interacting.

1 INTRODUCTION

Community detection in networks is one of the most popular topics of modern network science (Fortunato and Hric, 2016). It deals with an interesting computational technique for the analysis of networks. It can yield useful insights into the structural organization of a network and can serve as a basis for understanding the correspondence between structure and function (specific to the domain of the network).

In this paper, we are interested in detecting communities in biological networks. These networks have received much attention in the last few years since they model the complex interactions occurring among different components in the cell (Pizzuti and Rombo, 2014). We mainly focus on Protein-protein or Gene-gene interaction networks[1] known as PPI networks. Their nodes correspond to proteins or genes and the edges correspond to pairwise interactions between genes or proteins. These communities give us an idea about the perception of the network's structure. The ultimate goal in biology is to determine how genes or proteins encode function in the cell. This work is multidisciplinary as it brings the field of biology and computer science in the broad sense.

Thus, the goal is to find communities of genes having a biological sense (that participate in the same biological processes or that perform together specific biological functions) from gene annotation sources. To make this task, we have combined three levels of information:

1. Semantic level: information contained in biological ontologies such as Gene Ontology (GO) (Ashburner et al., 2000) and information obtained by the use of a similarity measure such as GO-based similarity of gene sets (GS2) (Ruths et al., 2009). It assesses the semantic similarity between proteins or genes.
2. Functional level: information contained in public databases describing the interactions of proteins or genes such as Search Tool for Recur-

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[1] Protein-protein or Gene-gene interaction networks are mathematical representations of the physical contacts between proteins or genes in the cell.

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ring Instances of Neighbouring Gene (STRING) database (Mering et al., 2003).

3. Networks level: information contained in pathway databases that present community of proteins or genes such as Kyoto Encyclopedia of Genes and Genomes (KEGG) database (Kanehisa and Goto, 2000).

A lot of research effort has been put into community detection in different academic fields such as physics, mathematics and computer science. Meanwhile, various algorithms based on Genetic Algorithms (GA) have been proposed. These algorithms are used to overcome some drawbacks such as scaling up of network size. Indeed, some of the community detection algorithms are unsuitable for very large networks and require a priori knowledge about the community structure, as the number and the size of communities which is not easy or impossible to obtain in real-world networks (Tasgin et al., 2007). The algorithms based on GA are very effective for community detection especially in very large complex networks (Jiao et al., 2012). However, the vast majority of optimization methods proposed to detect community in PPI networks use graph topology and do not use similarity measures between proteins or genes (Pizzuti and Rombo, 2014).

This paper presents a new generic community detection algorithm in PPI networks based on GA. The proposed GA is parameterized according to the importance affected to each measure criterion (semantic measure and interaction measure). The aim is to detect communities according to either both criteria, or only one criterion. The obtained communities could then be analyzed and compared for a better comprehension of the topological and similarity measures and the relation between them. This work is a generalization of a previous method (named as GA-PPI-Net) (Ben M'barek et al., 2019). Thus, we propose a GA based approach that allows to find communities having different sizes using the interaction and/or similarity criterion. Alike the previous proposed algorithms, the new proposed method uses the similarity measures as well as the interaction measure between proteins or genes and tries to find the best proteins/genes' community by maximizing the concept of community measure. The main novelties of the approach can be summarized as follows. We adopt a lighter representation of a community with dynamic size than the one adopted in GA-PPI-Net, and we propose a new fitness function that generalizes the previous one. It is still based on the concept of community measure but it allows to combine the semantic and the interaction criterion by choosing their respective contribution to the fitness function according to thresholds. This concept provides a generic solution of a partitioning communities that are semantically similar or/and interacting. Moreover, a new genetic operation that is a specific heuristic crossover operator adapted to our problem is introduced. This heuristic crossover help the GA to build communities with high values of similarities or/and interaction between genes. The algorithm outputs the final community by selectively exploring the search space. Experiments on real datasets show the ability of the proposed approach to correctly detect communities having different sizes which are similar and/or interact.

The contents of this paper are organized in six main sections. The next section presents an overview of the existing community detection algorithms. Section 3 provides the problem definition. Section 4 depicts our main proposed algorithm for community detection. In section 5, experimental results on real data sets are presented and analyzed. Finally, section 6 reports the conclusion.

2 COMMUNITY DETECTION RELATED METHODS

Network community detection has an important role in the networked data mining field. Community detection helps to discover latent patterns in networked data and it affects the ultimate knowledge presentation (Cai et al., 2016).

The task for network community detection is to divide the whole network into small parts or groups which are also called communities. There is no uniform definition for community in the literature, but in academic domain, a community (also called a cluster or a module) is a group of nodes that are connected densely inside the group but connected sparely with the rest of the network. Radicchi et al. (Radicchi et al., 2004) propose two definitions of community. These definitions are based on the degree of a node (or valency)[2]. In the first definition, a community is a subgraph in a strong sense: each node has more connections within the community than the rest of the graph. In the second definition, a community is a subgraph in a weak sense: the sum of all incident edges in a node is greater than the sum of the out edges.

The problem of community detection has been receiving a lot of attention, in recent years, and many different approaches have been proposed. The literature survey is divided into two categories: community detection based on analytical approaches and those

[2] The degree of a node is the number of edges incident to the node.

based on evolutionary approaches (Pizzuti, 2018).

Analytical methods firstly split networks into subgroups according to their topological characteristics, then the modularity assessment is carried out. The modularity is defined as the fraction of edges inside communities minus the expected value of the fraction of edges, if edges fall at random without regard to the community structure. Values of modularity approaching 1 indicate strong community structure. A well known algorithm in this category is the one presented by Girvan and Newman (Girvan and Newman, 2002; Newman and Girvan, 2004). It is a divisive hierarchical clustering method based on an iterative removal of edges from the network. The edge removal splits the network in communities. The removed edges are chosen by using betweenness measures (that represents the number of shortest paths between all vertex pairs that run along the edge). The idea underlying the edge betweenness comes from the observation that if two communities are joined by a few inter-community edges, then all the paths from vertices in one community to vertices in the must pass through these edges. Paths determine the betweenness score to compute for the edges. By counting all the paths passing through each edge, and removing the edge scoring the maximum value, the connections inside the network are broken. This process is repeated, thus dividing the network into smaller components until a stop criterion is reached. The criterion adopted to stop the division is the modularity. In (Newman, 2004), the author presents an agglomerative hierarchical algorithm that optimizes the concept of modularity. Thus the algorithm computes the modularity of all the clusters obtained by applying the hierarchical approach, and returns as result the clusters having the highest value of modularity.

Analytical algorithms do not reach the expected successful results in community detection from complex networks. Therefore, various evolutionary based algorithms (EAs) have been proposed to provide different approaches to solve the community detection problem (Atay et al., 2017). Many community evaluation criteria have been proposed and quantities of methods that combine either single objective or multiobjective EAs with community detection have emerged. Most if not all of these methods share the common feature that they model the community detection problem as an optimization problem (Cai et al., 2016). The single objective methods optimize a single property, while the multiobjective approaches simultaneously optimize competing objectives. The most popular single evaluation criterion is the modularity proposed by Newman and Girvan (Newman and Girvan, 2004). Since 2002, several methods that divide networks into clusters according to the modularity criterion have been developed (Atay et al., 2017). In (Tasgin and Bingol, 2006) and (Liu et al., 2007), the authors presented an approach based on a GA to optimize the network modularity introduced by Newman and Girvan (Girvan and Newman, 2002). However, some studies have indicated that the optimization of modularity has several drawbacks (Cai et al., 2016). First, it has the resolution limitation, i.e., maximising the modularity can fail in finding communities smaller than a fixed scale, even if these communities are well defined. The scale depends on the total size of the network and the interconnection degree of the communities (Fortunato and Barthélemy, 2007). Second, maximizing the modularity is proved to be NP-hard (Cai et al., 2016). These drawbacks can constitute a weakness for all those methods whose objective is to optimize the modularity. To avoid the resolution limitation of modularity, many multi-resolution models have been developped (Cai et al., 2016). Pizzuti (Pizzuti, 2008) has proposed an algorithm named GA-Net and has used a special assessment function called community score that uses only graph topology. This community score takes one parameter r which is hard to tune because higher values of r help to detect communities and low values of this paramter return no communities. A modification of the modularity has been proposed in (Li et al., 2008) with the concept of modularity density. The authors prove that modularity density has a number of advantages with respect to modularity, such as detecting communities of different sizes.

Single objective optimization identifies a single best solution that gives insights on the graph organization. However, this solution could be biased toward a particular structure inherent inside the criterion to optimize (Cai et al., 2016). These methods have obtained very good results on both artificial and real-world networks (Pizzuti, 2018). The intuitive notion of community that the number of edges inside a community should be much higher than the number of edges connecting to the remaining nodes of the graph, has two different objectives: 1) maximizing the internal connection links and 2) minimizing the external connection links (Pizzuti, 2018). Thus, on the basis of these objectives, many multi-objective community models have been established. The first proposal framework to uncover community structure has been presented by Pizzuti (Pizzuti, 2011; Pizzuti, 2009). In particular, the method introduces two objectives: maximizing the community score proposed by (Pizzuti, 2008) and minimizing the community fitness put forward by (Lancichinetti et al., 2009). Then, the fast elitist non-dominated sorting genetic algorithm

(NSGA-II) proposed in (Deb et al., 2002) has been applied. A variation of this method has been proposed by Agrawal (Agrawal, 2011). The objectives to minimize are the modularity proposed by Newman and Girvan (Girvan and Newman, 2002) and the community score proposed by Pizzuti (Pizzuti, 2008). Surveys on the selection of objective functions in multi-objective community detection can be found in Shi et al. (Shi et al., 2011; Shi et al., 2014).

Multi-objective evolutionary approaches, like the single objective ones, are able to discover community structures of quality comparable with, or even better than, those obtained by analytical methods. Optimizing multiple objectives allows a simultaneous evaluation of community structure from different perspectives, then it is the user's responsibility to choose a solution (Cai et al., 2016). The choice of the objectives to optimize should take into account the suggestions given by Shi et al.(Shi et al., 2010), where a comparison of several objective functions in a multi-objective framework has been performed (Pizzuti, 2018).

The use of evolutionary methods for community detection presents a number of advantages (Pizzuti, 2018):

- During the search process, the communities' number is generated automatically;
- Domain-specific knowledge can be incorporated inside the method, such as biased initialization, or specific variation operators instead of random, allowing a more effective exploration of the state space of possible solutions;
- The efficient implementations of population-based models can be realized to deal with large size networks.

Most evolutionary approaches to detect communities have been applied in social networks and have used only graphical topology and no semantic similarity between nodes (Pizzuti and Rombo, 2014). In this paper we propose a generic evolutionary algorithm to detect semantic or/and topological communities in biological networks. This new algorithm tries to find the best community by maximizing the concept of community measure. This measure is based on both the graph topology (interaction) and the semantic similarity between nodes. It is different to the community score introduced by Pizzuti since it is not related to the density introduced in (Pizzuti, 2008) and not related to the modularity of the sub-networks.

3 PROBLEM DEFINITION

The network of interactions between proteins is generally represented as an interaction graph $G = (V,E)$ where V is a set of objects, called nodes or vertices, representing proteins and E is a set of links, called edges, representing pairwise interactions. A community (or cluster) in a network is a group of vertices having a high density of edges within them, and a lower density of edges between groups. In this work, we design a community C as a group of genes or proteins that are semantically similar and interact with each other. A set of genes $C = \{G_1, G_2, ..., G_n\}$ is a community if it respects the following property:

$$\forall\, G_i, G_j \in C,\ S(G_i,G_j) \geq \nabla_S \ or\ I(G_i,G_j) \geq \nabla_I \quad (1)$$

Where:

- $S(G_i,G_j)$: the similarity value between two genes G_i and G_j. To calculate the similarity between two genes, we need to use a measure allowing to compare sets of terms that annotate these genes thus we can quantify the similarity between these sets. In this work, we use the semantic similarity measure GS2 (GO-based similarity of gene sets) (Ruths et al., 2009). This measure averages the similarity contributed by each gene in C. Each gene is compared with the remaining set of genes by calculating how closely that gene follows the functionality distribution of the remaining genes. The functionality distribution is represented by the distribution of ancestor GO terms for each gene (Ruths et al., 2009).
- $I(G_i,G_j)$: the score of interaction between two genes extracted from STRING Database (Mering et al., 2003). This score explains the protein-protein or the gene-gene associations known and predicted according to different criteria in a bibliographic reference.
- ∇_S and ∇_I are two thresholds. They are defined for both the semantic and the interaction criterion respectively. Their values are fixed according to the recommendations of our biological expert.
- Each gene G can be annotated with a set of GO (Gene Ontology) terms (Camon et al., 2003). We use TP to denote the set of GO terms that annotate a gene, this set is denoted by A(G). A(G).It consists of an association between a gene and a GO term. For example, the MEIKIN gene is identified by ID: 728637 and annotated by the following sets: ”GO: 0007060”, ”GO: 0010789”, ”GO: 0016321”, ”GO: 0045143”, ”GO: 0051754”. More formally,

$$A(G) = \{TP\ that\ annotate\ G\ /TP \in GO\} \quad (2)$$

4 PROPOSED APPROACH

GAs have proved to be competitive alternative methods to traditional optimization and search techniques and they have been applied to many problems in diverse research and application areas such neural nets evolution, planning and scheduling, machine learning and pattern recognition (Goldberg, 1989; Petrowski and Ben-Hamida, 2017). Thus, it would be also suitable for solving the community detectionSIM group problem.

We describe, in this section, the GA proposed in this work as well as the genetic representation and the variation operators that we propose.

The population is composed of individuals that are the solutions of the problem. In our approach, an individual is a set of proteins or genes that form a community. A community may have different sizes. To evaluate a solution, we propose a fitness function based on a community measure. The latter uses the similarity value and the interaction score of every pair of genes making up the solution. Moreover, we modify the steps of GA to satisfy the needs of our algorithm. Thus, we propose a new heuristic crossover operator, a new mutation operator and insert some additional steps during the population initialization. The algorithm works as follows:

Algorithm 1: General Algorithm of the Generic GA-PPI-Net approach.

```
Require: algorithm parameters, problem instance
Ensure: best solution to the optimization problem
Begin
Initialize population
Evaluate the initial population
for $i = 1$ to max_iteration do
    Select parents for mating
    for each pair of candidates in the set of parents do
        Generate an offspring through genetic operator - crossover and mutation - with respectively a probability $p_c$ and $p_m$
        Evaluate the fitness of the offspring
        Replace the worst existing individual in the population by the obtained offspring
    end for
end for
End
```

The various steps of the GA are described in the following subsections.

4.1 Genetic Representation

A solution to our problem is a community of proteins or genes. We represent it by a vector T. In this representation, each individual stores: the size *n* of the corresponding community (= the number of proteins or genes in the community) and the list of the *n* components. Each component (gene or protein) is designed by its name. A solution corresponds to an individual in GA terms. Figure 1 illustrates the representation of an individual adopted in our algorithm.

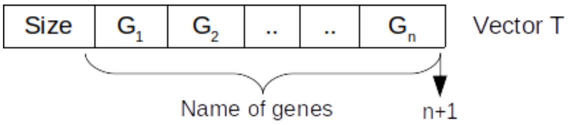
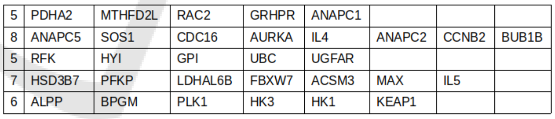


Figure 1: Example of individual representation designing a community.

4.2 Population Initialization

In this work, the population is defined as a two-dimensional array of individuals. It represents some potential solutions of the problem. In order to initialize this population, we first randomly recover communities from the KEGG pathway database (Kanehisa and Goto, 2000). Then, we randomly create the population with the recovered genes. The population is composed by individuals having different sizes (Ben M'barek et al., 2019). Figure 2 presents an example of an initial population with five individuals having different sizes.



5	PDHA2	MTHFD2L	RAC2	GRHPR	ANAPC1			
8	ANAPC5	SOS1	CDC16	AURKA	IL4	ANAPC2	CCNB2	BUB1B
5	RFK	HYI	GPI	UBC	UGFAR			
7	HSD3B7	PFKP	LDHAL6B	FBXW7	ACSM3	MAX	IL5	
6	ALPP	BPGM	PLK1	HK3	HK1	KEAP1		

Figure 2: Example of an initial population.

4.3 Fitness Function

The fitness function relates to the ability of the candidate to survive and reproduce. It takes as input a candidate solution to the problem and produces as output a performance measure of the solution with respect to the considered problem. The choice of the fitness function is a critical step for obtaining good solutions. In the context of community detection, the most popular function is the modularity, originally introduced by Girvan and Newman (Girvan and Newman, 2002). In our work, we do not directly take into account the modularity. Nevertheless, the topological propriety of a community is taken into account through the interaction score between proteins or genes. Moreover, the fitness function is enriched with semantic information. Indeed, we define a fitness function based on the computation of similarity value and the interaction score of each pair of genes in a community C. Thus, as a first step for the fitness computation, a similarity matrix is computed using the GS2 measure (section 3). Likewise, an interaction matrix is computed designing the interaction score between each pair of genes. The proposed fitness function F is then defined as follows:

$$F = \sum_{i \neq j, i=1, j=1}^{n} M_{ij}(G_i, G_j) \tag{3}$$

$$M_{ij}(G_i, G_j) = \begin{cases} 0 \text{ if } S(G_i, G_j) \leq \nabla_S \text{ or } I(G_i, G_j) \leq \nabla_I. \\ S(G_i, G_j) + I(G_i, G_j) \quad \text{otherwise.} \end{cases} \tag{4}$$

Where:

- $S(G_i, G_j)$ and $I(G_i, G_j)$ are, respectively, the similarity and the interaction values of each pair of genes (G_i,G_j) introduced in section 3;
- ∇_S and ∇_I are two thresholds defining respectively the topology and the semantic levels. Their values are fixed in the beginning of the evolution.

This fitness function generalizes the previous method that we proposed in (Ben M'barek et al., 2019). The used fitness function in GA-PPI-Net was based on the computation of the average similarity value and the average interaction score of each two genes existing in the community C. It is defined as follows (Ben M'barek et al., 2018; Ben M'barek et al., 2019):

$$F1(C) = W_1\, AVGS(C) + W_2\, AVGI(C) \tag{5}$$

With:

- AVGS and AVGI being the average similarity value and the average interaction value of genes in C respectively.
- W_1 and W_2 : weights $\in [0, 1]$.

F1 corresponds to a particular case of F when choosing specific values of the thresholds ($\nabla_S = \nabla_I = 0$).

4.4 Selection

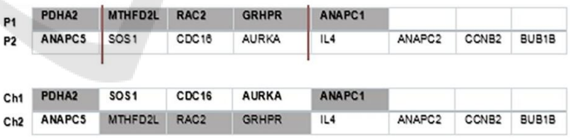
In this stage of a GA loop, individuals are selected from the population to be parents which mate and recombine to create offspring for the next generation. Selection is very crucial to the convergence rate of the GA as good parents drive individuals to fitter solutions. The problem is how to select these individuals. In literature, there are many methods to select the best individuals such as roulette wheel selection, tournament selection, rank selection, elitism... (Goldberg and Deb, 1991). For our problem we use the popular tournament selection because it is highly efficient and easy to implement (Goldberg and Deb, 1991).

4.5 Genetic Operators

After the generation of an initial population, a GA carries out the genetic operators to generate offspring. Once a new population is created, the genetic process is performed iteratively until an optimal result is found or a maximum number of generations is met.

Crossover and mutation are two basic operators of GA. The algorithm performance depends tightly on the choice of these operators. Indeed, crossover and mutation operators guide the convergence of the algorithm towards a solution for the problem. Their goal is to both exploit the best solutions and explore the search space.

For this work, we propose the use of two types of crossover. The first one is the classic two-point crossover. It is a generalization of the one-point crossover. To apply this operator, two cross-points are chosen randomly respecting the condition that their positions do not exceed the longest parent size. Then, the contents bracketed by these sites are exchanged between two mated parents to get two new offspring. A clean up phase is used in order to delete the redundant gene in the created offspring. To better understand this kind of crossover, a graphical illustration is given in Figure 3. In this example, two sites are chosen at random in position 1 and 4. Then two offspring (Ch1,Ch2) are generated by exchanging the values of the selected parents (P1,P2).



P1	PDHA2	MTHFD2L	RAC2	GRHPR	ANAPC1			
P2	ANAPC5	SOS1	CDC16	AURKA	IL4	ANAPC2	CCNB2	BUB1B

Ch1	PDHA2	SOS1	CDC16	AURKA	ANAPC1			
Ch2	ANAPC5	MTHFD2L	RAC2	GRHPR	IL4	ANAPC2	CCNB2	BUB1B

Figure 3: Example of a two points crossover operator.

The second crossover operator is a new heuristic crossover. It is specific to our problem. The main purpose of this operator is to create an offspring with higher value of similarity or interaction or both similarity and interaction. It is applied according to the Algorithm 2.

The application of this heuristic crossover helps the GA to build communities with high values of similarities and interaction between genes than the imposed thresholds. Figure 4 presents a graphical illustration to understand the proposed heuristic crossover. Two individuals (P1,P2) are chosen randomly from the parent population. This operator is usually applied with

Algorithm 2: Heuristic Crossover Algorithm.

```
Choose randomly two parents (P1,P2) from the the parent population;
Merge the values of two parents (P1,P2) by removing the redundant content (genes) to obtain one individual P;
for each two genes $G_i$ and $G_j \in P$ do
    if $i \neq j$ then
        Compute the similarity Sim($G_i$,$G_j$);
        Compute the interaction Interaction($G_i$,$G_j$);
    end if
end for
for each two genes $G_i$ and $G_j \in P$ do
    if Sim($G_i$,$G_j$) $\geq \nabla_S$ then
        Add the genes to the first offspring Ch1;
    end if
    if Interaction $(G_i, G_j) \geq \nabla_I$ then
        Add the genes to the second offspring Ch2;
    end if
end for
Remove the redundant content (genes) to the obtained offspring Ch1 and Ch2;
```

a high probability (p_c) (Pizzuti, 2018). Then, the values of two parents (P1,P2) are merged by removing the redundant content (genes) to obtain one individual P. After that two offspring (Ch1,Ch2) are created according to the following conditions:

1. $\forall i \neq j : G_i, G_j \in P$, if $\mathrm{Sim}(G_i, G_j) \geq \nabla_S$ then add the gene G_i to the first offspring Ch1;
2. $\forall i \neq j : G_i, G_j \in P$, if Interaction $(G_i, G_j) \geq \nabla_I$ then else add the gene G_i to the second offspring Ch2;

The mutation is an operator that acts in a rarer fashion and in an unpredicted form to modify the genes of the individual, promoting the diversification of the population. However, the mutation must not be too destructive and a speed bump for the process of finding an optimal solution (Pizzuti, 2018). For these purpose, we propose for the present problem a new specific mutation operator called *Optimized Community Mutation (OCM)*. Mutation may be defined as a small random tweak in the individual, to get a new solution. It is used to maintain and introduce diversity in the population and is usually applied with a low probability (p_m). If the probability is very high, the GA gets reduced to a random search (Pizzuti, 2018). We present now the used mutation operator already defined in our previous work (Ben M'barek et al., 2018). Its goal is to maximize the chance of creating a better solution than the original one. This operator can integrate a new gene in order to replace a gene having a poor quality or to enlarge the size of the community. To mutate a solution C, the mutation operator alters only one gene at a time and uses a score function, denoted GS, applied to each gene in C. This score helps us to detect the gene having the best score in a community as well as the gene having the worst score. It is equal to the sum of the average similarity and the average interaction score of a gene in a community (Ben M'barek et al., 2018). It is defined as follows:

$$AVGSim(G) = \sum_{i=1}^{n} S(G, Gi)/n \qquad (6)$$

$$AVGInteraction(G) = \sum_{i=1}^{n} I(G, G_i)/n \qquad (7)$$

$$GS(G) = AVGSim(G) + AVGInteraction(G) \qquad (8)$$

Where:

- S(G, G_i): The similarity value between a gene G and the gene G_i in the community C;
- I(G, G_i): The interaction score of a gene G compared to the gene G_i in the community C.
- n: size of an individual (community).

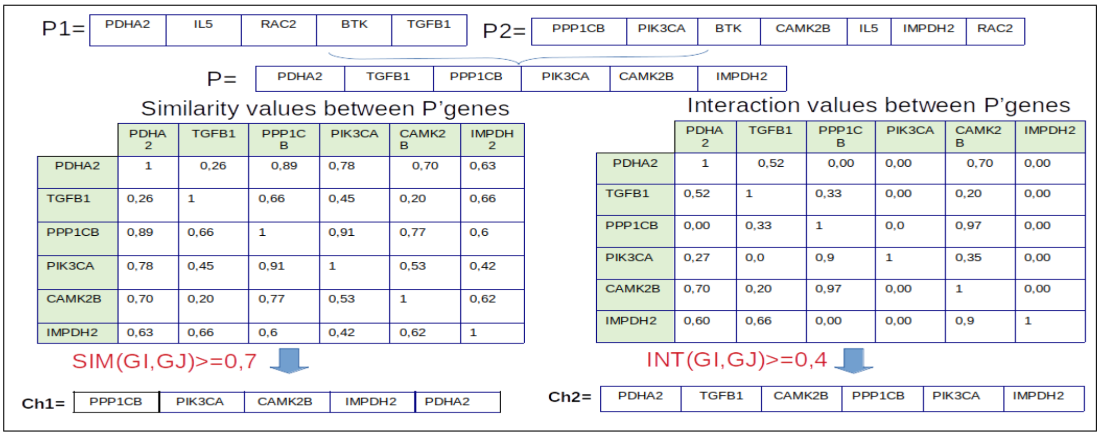
The *OCM* mutation operator is applied according to the following steps (Ben M'barek et al., 2019) presented in algorithm 3.

Algorithm 3: OCM algorithm.

```
1: Select in a solution $C$ a gene having the highest score $GS$ that will be called "bestGene";
2: Randomly search a gene $G'$ from the "interaction" table with which the "bestGene" interacts and $G' \notin C$;
3: Get the gene having the lowest score GS in C, it will be called "worstGene";
4: Fix a threshold $\theta$ (i.e $\theta = 0.5$);
5: if $GS(\text{"}worstGene\text{"}) \leq \theta$ then
6:     replace the "worstGene" by the gene G' selected in the second step;
7: else
8:     Insert into the end position of the solution the gene G' selected in the second step and update the size.
9: end if
```

5 EXPERIMENTAL RESULTS

In this section, we study the effectiveness of our approach on real data sets (Pathways selected from KEGG Pathway database). A set of preliminary tests have been carried out to tune the GA parameters: population size, crossover and mutation rate and maximum number of generations. The retained values are summarized in Table 1.



P1=	PDHA2	IL5	RAC2	BTK	TGFB1		
P2=	PPP1CB	PIK3CA	BTK	CAMK2B	IL5	IMPDH2	RAC2
P=	PDHA2	TGFB1	PPP1CB	PIK3CA	CAMK2B	IMPDH2	

Similarity values between P'genes

	PDHA2	TGFB1	PPP1CB	PIK3CA	CAMK2B	IMPDH2
PDHA2	1	0,26	0,89	0,78	0,70	0,63
TGFB1	0,26	1	0,66	0,45	0,20	0,66
PPP1CB	0,89	0,66	1	0,91	0,77	0,6
PIK3CA	0,78	0,45	0,91	1	0,53	0,42
CAMK2B	0,70	0,20	0,77	0,53	1	0,62
IMPDH2	0,63	0,66	0,6	0,42	0,62	1

SIM(GI,GJ)>=0,7

Ch1=	PPP1CB	PIK3CA	CAMK2B	IMPDH2	PDHA2

Interaction values between P'genes

	PDHA2	TGFB1	PPP1CB	PIK3CA	CAMK2B	IMPDH2
PDHA2	1	0,52	0,00	0,00	0,70	0,00
TGFB1	0,52	1	0,33	0,00	0,20	0,00
PPP1CB	0,00	0,33	1	0,0	0,97	0,00
PIK3CA	0,27	0,0	0,9	1	0,35	0,00
CAMK2B	0,70	0,20	0,97	0,00	1	0,00
IMPDH2	0,60	0,66	0,00	0,00	0,9	1

INT(GI,GJ)>=0,4

Ch2=	PDHA2	TGFB1	CAMK2B	PPP1CB	PIK3CA	IMPDH2

Figure 4: Example of an heuristic crossover operator ($\nabla_S = 0.7$ and $\nabla_I = 0.4$).

Table 1: GA parameters.

Parameters	Values
Population size	30
Generation number	100
Crossover rate	0.8
Mutation rate	0.01
Individual'size in the initial population	[5,40]
∇_S	≥ 0.5 [3]
∇_I	≥ 0.4 [3]

Table 2: The used datasets.

Datasets	Genes'Number
Apoptosis[4]	88
B cell receptor signalling [5]	75
Purine metabolism[6]	159
Rna degradation[7]	159
Oocyte meiosis[8]	114
Total	595

A community of genes is accepted if the value of the thresholds ∇_S and ∇_I are sufficient. The role of these two thresholds is to vary the weight of the quality of a community. The ∇_S allows to quantify the similarity value. It is is set according to the GO annotations among a set of genes by averaging the contribution of each gene's GO terms and their ancestor terms with respect to the GO vocabulary graph (Ben M'barek et al., 2018). If it is greater than or equal to 0.5 then these two genes are similar, else they are not (Ben M'barek et al., 2018). The ∇_I refers to the interaction value which defines the number of citation of this interaction in the literature. If this value is greater than or equal to 0.4 then these two genes have a strong interaction. The values of ∇_S and ∇_I are proposed by the biological expert and modified as needed.

To check the capability of our approach to successfully detect the communities of a network, we pick a set of proteins or genes randomly from the reference database KEGG pathway. More precisely, our approach has been tested with five datasets proposed by our biological expert. Their names and their corresponding genes' numbers are described in Table 2. These datasets correspond to existing communities presented in KEGG pathway database.

The first evaluation consists to verify how the proposed method is likely to find gene communities having high similarity or/and high interaction.

The obtained communities are analyzed and compared for a better comprehension of the topological (interaction between genes) or/and the semantic similarity measures. We performed tests with different values of the proposed thresholds ∇_S and ∇_I of the fitness function to determine communities of genes. These values were proposed by the biological expert. Actually, the tests showed that it was possible to detect three types of existing communities of genes or proteins having high interaction and/or high similarity between their genes:

1. $\nabla_S \geq 0.5$ and $\nabla_I = 0$: detect similarity based group of genes.
2. $\nabla_S \geq 0.5$ and $\nabla_I \geq 0.4$: detect similarity and in-

[3] values proposed by the biological expert and modified as needed

[4] https://www.genome.jp/dbget-bin/www_bget?pathway:hsa04210

[5] https://www.genome.jp/dbget-bin/www_bget?pathway:hsa04662

[6] https://www.genome.jp/dbget-bin/www_bget?pathway:hsa00230

[7] https://www.genome.jp/dbget-bin/www_bget?pathway:hsa03018

[8] https://www.genome.jp/dbget-bin/www_bget?pathway:hsa04114

teraction based genes communities.

3. $\nabla_S < 0.5$ and $\nabla_I \geq 0.4$: detect interaction based group of genes.

To determine these three types of communities, we realized different experiments. We apply our approach with proteins or genes chosen randomly from the five proposed datasets (see Table 2). We vary the values of the thresholds ∇_S and ∇_I in the range $[0..1]$ and we retained each time the best community. For the first runs, we set the threshold values such that $\nabla_S \geq 0.5$ and $\nabla_I \geq 0.4$. We use $\nabla_S = 0.6$ and $\nabla_I = 0.4$. The preliminary results showed clearly that our proposed GA is able to detect similarity and interaction based genes communities. For instance, Figure 5 clearly shows a solution in these category of experiments to detect communities of genes that are semantically similar or/and interact (where the edge value $I \geq 0.4$ and $S \geq 0.5$).

Then, we test our GA with $\nabla_S \geq 0.5$ and $\nabla_I = 0$. We turn our algorithm with values: $\nabla_S = 0.6$ and $\nabla_I = 0$. And, we obtain as result a group of genes that are semantically similar and do not interact with each other. One solution in these category of experiments is shown in Figure 6 which represents a group of genes having size 9.

For the last set of experiments, we set the thresholds such as $\nabla_S < 0.5$ and $\nabla_I \geq 0.4$. We use $\nabla_S = 0.3$ and $\nabla_I = 0.4$. The obtained results show the capability of the proposed GA to build an interaction based group. Figure 7 illustrates an example of a detected group of genes.

To conclude, the main goal by introducing thresholds in the fitness function is to allow the GA to detect three types of genes or proteins' communities:

- a group of genes with high similarity (if $\nabla_S \geq 0.5$).
- a group of genes with high interaction (if $\nabla_I \geq 0.4$).
- a community of genes with high interaction and high similarity (if $\nabla_S \geq 0.5$ and $\nabla_I \geq 0.4$).

To interpret biologically the obtained communities, our biological expert proposed to evaluate them by checking if they exist in KEGG or other biological pathway databases. Each new community found by our generic GA-PPI-Net is presented to the DAVID tools (Database for Annotation Visualization and Integrated Discovery) (Sherman et al., 2007), which compares the founded community, denoted by Rnew, with others in different databases and gives the percentage of Rnew genes that belong to the existing communities in those databases. DAVID bioinformatics resources consist of an integrated biological knowledge-base and analytic tools that aim at systematically extracting biological meaning from large gene/protein lists. It is the most popular functional annotation programs used by biologists (Sherman et al., 2007). It takes a list of genes as input and exploits the functional annotations available on these genes in a public database such as, KEGG Pathways in order to find common functions that are sufficiently specific to these genes.

For each types of genes or proteins' communities, we run our approach 20 times with proteins or genes chosen randomly from the five proposed datasets in Table 2. And, we retained each time the best community. Thus, we have 20 best communities for each type. We evaluate these obtained communities by checking if they exist in biological pathway databases. The biological databases used to evaluate our results are KEGG, Biocarta, Reactome, BBID and EC Number. The results of this evaluation are shown in Table 3 column Ben M'barek et al. 2020.

Our new approach is parameterized according to the importance affected to each measure criterion (semantic similarity measure and interaction measure). This parameters allows us to detect communities according to either both criteria, or only one criterion. The results presented in Table 3 column Ben M'barek et al. 2020 show that the new communities obtained by our algorithm correspond to some "parts" of real networks existing in other biological pathway databases, and in some cases to a complete network (percentage 100%). The Generic GA-PPI-Net achieves the highest percentage 80%, 90% and 100% when the fitness function is based on both similarity and interaction values. And it achieves the percentage 90% and 100% when the fitness function is based on semantic similarity criterion or interaction criterion respectively.

These results are considered very satisfactory by the biology expert. They constitute an initial validation of our algorithm and show the relevance of the used fitness function. These tests should be supplemented on a larger scale with other datasets and different communities.

Moreover, we compare the results obtained by our new algorithm with the one proposed in (Ben M'barek et al., 2019). We design these approaches as Ben M'barek et al. 2019 and Ben M'barek et al. 2020 respectively. A thorough comparison is not easy because the obtained communities for both propositions haven't the same sizes and the same constitution. Hence, the same datasets proposed by the biological expert in Table 2 and the same GA parameters were used for both approaches. The two algorithms were executed 20 times. We also used the DAVID tools

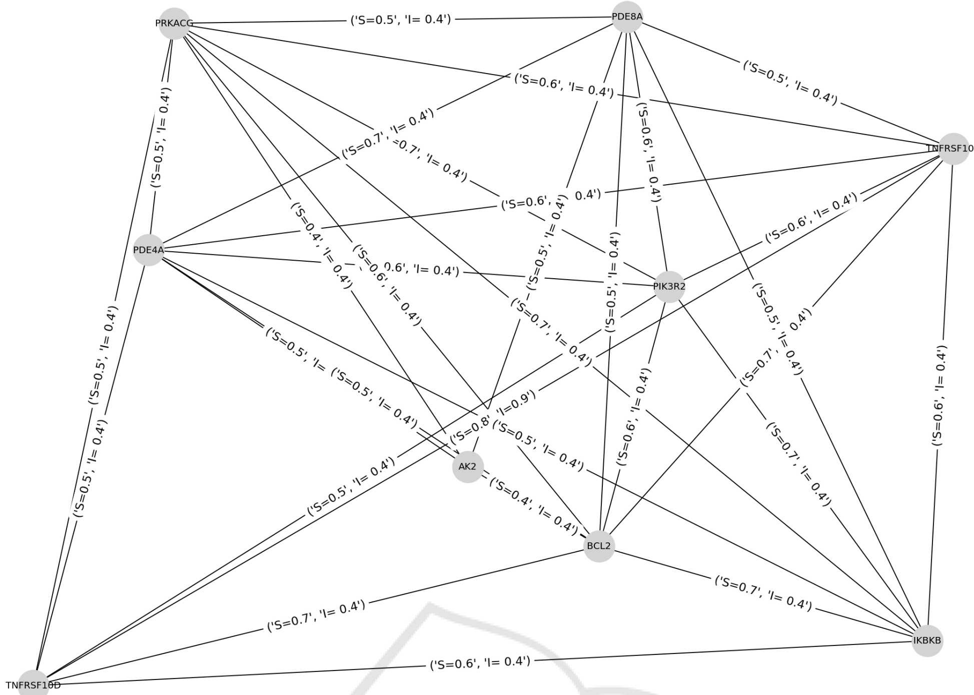


Figure 5: Example of a detected community of genes having high similarity and interaction scores ($\nabla_S \geq 0.5$ and $\nabla_I \geq 0.4$).

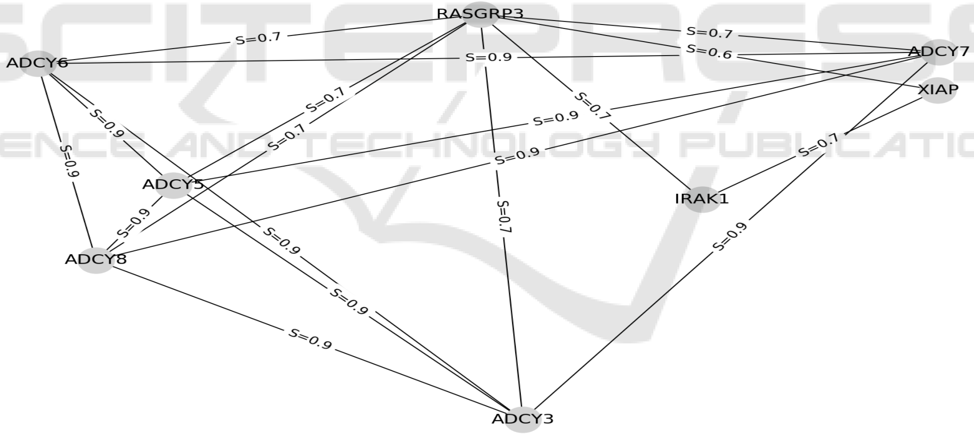


Figure 6: Example of a detected similarity based groups of genes ($\nabla_S \geq 0.5$ and $\nabla_I = 0$).

to estimate the recovery rate of the found communities with existing communities in different biological databases. Table 3 column Ben M'barek et al. 2019 illustrates the results of the approach presented in (Ben M'barek et al., 2019).

Table 3 shows how the present approach (Ben M'barek et al. 2020) has additional abilities, according to the use of thresholds in the fitness function, to detect communities of genes based only on semantic similarity or interaction criterion. Otherwise, according to the results in the last two columns in Table 3, the ability to detect communities based on both crite-

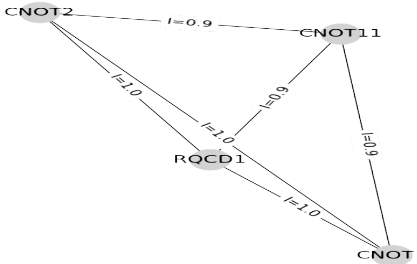


Figure 7: Example of a detected interaction based groups of genes ($\nabla_S < 0.5$ and $\nabla_I \geq 0.4$).

Table 3: Evaluation of the obtained communities. Comparison with Ben M'barek et al. 2019 approach.

Pathway DBs	Ben M'barek et al. 2020						Ben M'barek et al. 2019	
	SIM groups		INT groups		SIM & INT communities			
	%Min	%Max	%Min	%Max	%Min	%Max	%Min	%Max
BBIB	20%	45%	15%	50%	20%	90%	25%	50%
Biocarta	10%	70%	20 %	50%	20%	100%	20%	66%
EC Number	10%	90%	10%	60%	30%	100%	10%	100%
KEGG	9%	78%	10%	62%	11%	100%	15%	100%
Reactome	20%	75%	15%	100%	10%	80%	14%	100%

ria of the new GA is similar or better than the one of Ben M'barek 2019 GA. Indeed, our new GA achieves a higher percentage than Ben M'barek et al.2019 approach in 4 pathway databases: Kegg, Biocarta, BBIB and Ec Number when the fitness function is based on both similarity and interaction values. In other respects, the Ben M'barek et al. 2019 approach has a higher result than the Ben M'barek et al. 2020 approach in the Reactome pathway. Nevertheless, the new GA keeps satisfactory percentage for the three types of detected communities (75% for SIM groups column, 100% for INT groups column and 80% for SIM & INT communities column). The obtained percentage values corresponds to a complete communities or to some "parts" of the real communities.

To conclude, the obtained results show the ability of the GA proposed in this paper to effectively deal with community detection in networks. Moreover, the new GA allows to detect communities of genes or proteins having different size according to the use of thresholds in the fitness function. This thresholds allows us to detect communities according to either both criteria, or only one criterion. Thus, we obtain three types of genes or proteins' communities, which improve that this approach is a generic approach of Ben M'barek et al. 2019 approach. Further extensions experiments will be carried out to detect communities with larger size and identify new communities not yet known in the public biological databases.

6 CONCLUSIONS

In this paper, we have proposed a generic approach based on GA to detect communities of interacting genes or proteins. This approach is a generalization of a previous work. It introduces the concept of community measure and searches for an optimal partitioning of the network by maximizing this measure. Our contribution in this paper is threefold. First, we apply GA to community detection in PPI networks. Second, we modify the previous proposed fitness function to allow our GA to detect communities of genes that are semantically similar and/or interacting. Third, we define a specific heuristic crossover operator adapted to the considered biological problem. Dense communities existing in the network are obtained at the end of the evolution by selectively exploring the search space, without the need to know in advance the community size. The experimental results showed the ability of the GA approach to correctly detect communities having different sizes which are semantically similar and/or interacting. Future research will aim at extending the proposed fitness function by adding the modularity value and applying a multi-objective optimization to improve the quality of the results.

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