A multi-objective mathematical model for the optimization of the transittability of complex biomolecular networks

Ali Ayadi, Cecilia Zanni-Merk, François de Bertrand de Beuvron, Saoussen Krichen

▶ **To cite this version:**

Ali Ayadi, Cecilia Zanni-Merk, François de Bertrand de Beuvron, Saoussen Krichen. A multi-objective mathematical model for the optimization of the transittability of complex biomolecular networks. KES 2018, Sep 2018, Belgrade, Serbia. pp.498–506, ⟨10.1016/j.procs.2018.07.284⟩. ⟨hal-02047106⟩

HAL Id: hal-02047106

https://hal.science/hal-02047106v1

Submitted on 5 Jun 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Distributed under a Creative Commons CC BY-NC-ND 4.0 - Attribution - Non-commercial use - No Derivative Works - International License

Available online at www.sciencedirect.com

ScienceDirect

Procedia Computer Science 126 (2018) 498–506

Procedia Computer Science

www.elsevier.com/locate/procedia

22th International Conference on Knowledge Based and Intelligent Information and Engineering Systems

A multi-objective mathematical model for the optimization of the transittability of complex biomolecular networks

Ali Ayadi[a,c,*], Cecilia Zanni-Merk[b], François de Bertrand de Beuvron[a], Saoussen Krichen[c]

[a]*ICUBE Team (UMR CNRS 7357)-Pole API BP 10413, Illkirch 67412, France*
[b]*Normandie Université, INSA Rouen, LITIS, 76000 Rouen, France*
[c]*LARODEC Laboratory, Institut Supérieur de Gestion de Tunis, University of Tunis, Rue de la liberté, 2000 Bardo, Tunisia*

Abstract

The fundamental goal of systems biology is to understand the dynamic aspects of cells and their behaviour. This organism is represented by a network so-called complex biomolecular network in which the nodes represent the different cellular components and the edges represent the interactions occurring among them. Through this network, it is easy to study the transition states and the dynamic behaviour of cells. Indeed, perturbing some nodes of the biomolecular network induce the transition of all the network. This process, known as the "transittability", expresses the idea of steering the complex biomolecular network from an unexpected state to a desired state.

In this context, we are thus interested in how to use the transittability of biomolecular networks to increase the efficiency of translational medicine for improving human health and disease, including genetic and environmental factors of of patient's well-being. This is a great opportunity to understand diseases, and find new diagnoses and treatments.

Due to its complexity, the transittability of complex biomolecular networks can be considered as an optimization problem. Up to a recent date only few studies have been carried out in this problem. Most of them focused only on the minimization of the required nodes to steer the entire network, and others considered the minimization of the number of stimuli to be applied on the network. However, this assumption is not always realistic, because steering complex biomolecular networks is in general a multi-objective optimization problem. It requires finding appropriate trade-offs among various objectives, for example between the appropriate nodes to be stimulated and the number of external stimuli to be used and their cost, and the impact on patient's well-being.

In this paper, the optimization of the transittability of complex biomolecular networks is investigated from the multi-objective perspective. In the mathematical model four criteria are considered simultaneously: the minimization of the number of external stimuli, the minimization of their total cost, the minimization of the number of target nodes, and the minimization of the patient discomfort. All these objectives are described theoretically and mathematically in detail.

© 2018 The Authors. Published by Elsevier Ltd.
This is an open access article under the CC BY-NC-ND license (https://creativecommons.org/licenses/by-nc-nd/4.0/)
Selection and peer-review under responsibility of KES International.

Keywords: Complex biomolecular network, transittability, multi-objective optimization algorithm , optimization, systems biology.

* Corresponding author. Tel.: +33 6 56 76 34 46.
E-mail address: ali.ayadi@unistra.fr

1877-0509 © 2018 The Authors. Published by Elsevier Ltd.
This is an open access article under the CC BY-NC-ND license (https://creativecommons.org/licenses/by-nc-nd/4.0/)
Selection and peer-review under responsibility of KES International.
10.1016/j.procs.2018.07.284

1. Introduction

The cell is a complex system consisting of thousands of diverse molecular entities (genes, proteins and metabolites) which interact with each other physically, functionally and logically creating a biomolecular network [1,2]. Recently, some authors have started to address the dynamic aspects of these complex networks, and have introduced concepts such as the 'controllability' [3] of a network, where the ability to steer a complex network from any initial state toward any other desired state is measured by the minimum number of required driver nodes (nodes with the ability to steer the entire network). It has been shown that in order to achieve complete controllability, the minimum number of driver nodes is 80% of the nodes in a regulatory biomolecular network. Indeed, rather than control and stimulate the network as a whole, it is preferable to control only some nodes. According to the literature, a network cannot be guaranteed to transit from one specific state to any other state by acting on all its nodes, but on acting on some specific nodes called driver nodes. Furthermore, this result led other groups to develop a theoretic framework for studying transitions between specific states of complex networks, a concept they call 'transittability' [1]. In general, this concept expresses the idea of steering the complex biomolecular network from an unexpected state to a desired state by acting only on the minimum numbers of steering nodes. Moreover, these authors proved that the minimum number of steering nodes required for transittability are much less than those for complete controllability.

This is where the present study is situated. Indeed, the most recent biological studies prove that the transittability of biomolecular networks can be useful to translational biomedical medicine research for improving human health and disease, including genetic and environmental factors of of patient's well-being. This is a great opportunity to understand diseases, and find new diagnoses and treatments [1,3,4,5]. Thus, we in our research we are working on how to exploit the transittability of biomolecular networks, by integrating information about molecular entities (DNA, RNA, proteins, and metabolites) with information about clinical entities (patients, diseases, symptoms, and drugs), to improve patient care and our understanding of systems biology. This work is a continuation of our previous research [18,19,20] in which we propose a detailed logic-based modelling and a semantic architecture for the optimization of the transittability of complex biomolecular networks.

In the recent literature, several problems in biology can be considered and formulated as optimization problems, such as the optimization of the design of optimal dynamic experiments, biological network alignment, biochemical reaction networks, etc. However, only few studies have focused on the optimization of the transittability of complex biomolecular networks. Most of them are mono-objective, since they only focus on the minimization of the number of required driver nodes for steering the network and/or on the minimization of the number of external stimuli to be applied on the network. However, even these two criteria are necessary conditions, but they are not sufficient for completely steering complex biomolecular networks.

To this end, we propose a multi-objective mathematical formulation for optimizing the transittability of complex biomolecular networks in which we take into account more criteria such as the minimization of the number of input signals, the minimization of the cost of these signals, the minimization of the number of target nodes, the minimization of the patient discomfort. Applications of the proposed approach can be the design of treatments such as chemotherapy, the identification of potential drug targets in a signalling network of human cancer, or to study the phenotype transitions (for example, to direct a biomolecular network from its abnormal or disease phenotype to a healthy phenotype).

The reminder of this paper is organized as follows. In Section 2, we summarize the related studies advocated for optimizing the problem of steering complex biomolecular networks. Section 3 presents a description of the problem tackled in this study. Furthermore, we propose the theoretical and mathematical modelling of the addressed problem by introducing its parameters, decision variables, objective functions and constraints in Section 4. Finally, Section 5 concludes this paper and discusses some possible future directions.

2. Literature review

Several problems in systems biology can be considered and formulated as optimization problems [6,7,8,9,10]. In this section we focus only on those that were interested only in the task of steering complex biomolecular networks also called the *control theory* [3,11]. Indeed, few studies have been focused on this problem. Among them we cite the works of Wen-Xu Wang et al. [12] who propose a general approach to optimize the controllability of complex networks by

minimizing the structural perturbations. This approach consists to drive the biological network using a minimum signals of perturbation. Therefore, they aim to minimize the number of signals to be applied into the biological network rather than using a signal for each node. As well as, they propose to use only one control signal to achieve the optimal controllability of networks by adding a minimum number of links. To do this, they formulate their approach into an optimization problem using the concept of *matching path* which is based on the maximum matching algorithm. In the same topic, Kim et al.[13] propose an optimization algorithm for searching the minimum steering node set. This algorithm is used only with Boolean networks. They use a realistic T-cell cancer network to demonstrate the practicality of their approach. Even if this approach promotes to study the transittability, it needs to know the exact expression of nonlinear functions and parameters in the Boolean model of complex systems, which is generally unavailable in practice[1].

According to, Gao et al.[4], it is not necessary to control the whole network but it would be preferable to explore the target control which is a preselected subset of nodes. To do this, they minimize the number of driver nodes needed for target control. Their optimization approach is based on the 'k-walk' theory for directed networks, and on a greedy algorithm for treating general networks.

Wu et al.[5,14,15,16] address the problem of drug target identification by formulating it as a problem of finding the steering kernel in the network. To accomplish this goal, they propose a graph-theoretic algorithm to find a minimum set of steering nodes in biomolecular networks which can be a potential set of drug targets.

However, Wang Le-Zhi et al.[17] consider that the optimization methods cited previously (which control the network using the minimum set of driver nodes) can cause the development of unexpected phenomenon. As well as, they have seen that a network cannot be controlled with a small number of drivers, but it is necessary to balance the number of driver nodes and control signals. To overcome this difficulty, they propose a physical controllability framework based on the probability of achieving the real control by increasing the set of input signals on properly chosen nodes.

A summary of these works is given in the comparison Table 1. Based on this comparison, we note that only few works focus on the driving of complex biomolecular networks. As well as, most of them are mono-objective or bi-objective, and neglect other criteria for steering biomolecular networks. Indeed, applying a minimum of external stimuli on a minimum of steering nodes is a necessary condition, but not a sufficient condition, for completely driving complex biomolecular networks. Therefore, we conclude that to understand how these networks steer we have to take into account more criteria such as the minimization of the number of input signals, the minimization of the cost of these signals, the minimization of the number of target nodes, the minimization of the patient discomfort.

Table 1: Comparison table of the main approaches applied to the steering of biological networks according to their characteristics.

		References							
		Cornelius S. et al.[13]	Gao J. et al.[4]	Wu L. et al.[14]	Wu L. et al.[15]	Wu L. et al.[16]	Wu L. et al.[5]	Wang L. Z. et al.[17]	Our approach
Type of optimization problem	*mono-objective*	✓	✓	✓	✓	✓	✓	-	-
	bi-objective	-	-	-	-	-	-	✓	-
	multi-objective	-	-	-	-	-	-	-	✓
Objective functions	*minimize the number of driver nodes*	✓	✓	✓	✓	✓	✓	✓	✓
	minimize the number of input signals	-	-	-	-	-	-	✓	✓
	minimize the cost of input signals	-	-	-	-	-	-	✓	✓
	minimize the patient discomfort	-	-	-	-	-	-	-	✓

3. Problem statement

According to the transittability notion, a complex biomolecular network can be steered from a state to another one through appropriate stimuli. These stimuli can be internal, such as the changes of the physical and chemical properties of the cell, or external such as environment effects and drugs. Therefore, we can define a stimulus as an action or condition that interferes with a node, which can in turn affect other nodes and consequently causes the transition of the entire network. The transition of the biomolecular network starts when one (or more) stimuli triggers one (or more) nodes. Indeed, when the stimulus triggers a node, the state or the concentration of this molecular component will change to reach a specific node threshold. This threshold defines the type of the interaction that will be occur and the condition that activates it. The state change of a node provokes the change of the overall network state (changing a node automatically modifies other network nodes) creating the stimulus-response behaviour of the biomolecular network. Thus, the state of the biomolecular network at an instant t is a set represented by the set of the states of all components in the network at time t.

Formally, the biomolecular network is defined as an undirected graph denoted by $BN = (M, I)$. Where a node $m_i \in M$ corresponds to a molecular component which can be a gene, protein or metabolite. And an edge $i = (m_i, m_j) \in I$; $m_i, m_j \in M$ expresses the different types of interactions among the molecular components. The partition of the graph nodes induces a partition of the different types of interactions into intraomic interactions (interactions among molecular components of the same type) and interomic interactions (interactions among molecular components of different types). We have three intraomic interactions: between genes I_{GG}, proteins I_{PP}, and metabolites I_{MM}. Six interomic interactions: four interactions are considered among the genes and proteins (I_{GP}, I_{PG}), and among proteins and metabolites (I_{PM}, I_{MP}). Two interactions among the genes and metabolites (I_{GM}, I_{MG}) are not taken into account because there is no direct interaction between the genes and metabolites and vice versa. For each molecular component m_i, we associate a concentration c_i^t which represents the value of its concentration at time t. The concentration level c_i^t should be inside the interval $[c_i^{min}, c_i^{max}]$, where c_i^{min} and c_i^{max} represent the minimum and maximum concentration value of the molecular component m_i, respectively.

The state transition of the biomolecular network occurs by changing at least the concentration of one of its nodes. These changes in the concentration of the molecules can occur either by an *internal stimulus* (for example, due to reactions that are internal to the cell) already seen with the aggregate function presented in our previous works [18]) or by an *external stimulus* generated outside the cell (for example, because of a medicine taken by the patient). Let S be the external stimuli set. Each stimulus interferes with a node at time of introduction $\Delta_{c,k,i}^t$, changing its concentration with a certain concentration $S_{k,i}^t$ leading to an increase (or a decrease) of its actual concentration. Moreover, for each stimulus, we associate a cost $CostStim_k$. In addition, the patient discomfort is measured during all the transittability process and should not reach its maximum value denoted by $Discomfort_P^{max}$.

Our goal is to optimize simultaneously the different criteria involved in the transittability of biomolecular networks, in particular the number of external stimuli, their cost, the number of target nodes and the patient discomfort. Especially by finding the best compromise among these criteria to optimize the steering of the biomolecular network from an unexpected state to a desired state.

4. Proposed multi-objective mathematical model

In this section, we propose a multi-objective mathematical model for optimizing the transittability of complex biomolecular networks considering diverse criteria, such as: the minimization of the number of external stimuli, the minimization of their total cost, the minimization of the number of target nodes, and the minimization of the patient discomfort. The notation, parameters, decision variables and constraints of the model are presented in the following sections.

4.1. Parameters

Table 2 enumerates the parameters of the proposed multi-objective mathematical model.

Table 2: Nomenclature used in the proposed mathematical model.

Symbol	***Description***
P	a patient
$BN = (M, I)$	the complex biomolecular network of nodes M and edges I
$M = \{1, \ldots, m\}$	the set of all the molecular components of the network
$I = \{1, \ldots, n\}$	the set of all the interaction among the molecular components of the network
$S = \{1, \ldots, k\}$	the set of external stimuli
$t = \{1, \ldots, T\}$	the time period
$StartTransi_{BN}$	the starting time of the biomolecular network's transition
$FinishTransi_{BN}$	the finishing time of the biomolecular network's transition
$S^t_{k,i}$	the time of introduction of the stimulus k to the node i
$e_{k,i}$	the execution time of the stimulus k on the node i
c^t_i	the level of concentration of the node i at time t
c^{min}_i	the minimum level of concentration of the node i
c^{max}_i	the maximum level of concentration of the node i
$\Delta^t_{c,k,i}$	the change in concentration caused by the stimulus k on the node i at time t
$Discomfort^{max}_P$	the maximum amount of discomfort that a patient P can feel during the transittability process

4.2. Decisions variables

- $x^t_{k,i}$: Binary variable equal to 1 if and only if the stimuli k affect the molecular component i at time t, 0 otherwise.
- $y^t_{k,i}$: Binary variable equal to 1 if and only if the molecular component i is stimulated by the stimuli k at time t, 0 otherwise.
- $CostStim_k$: Real variable corresponding to the cost of the stimuli k which affect the molecular component i at time t.
- $Discomfort^t_P$: Nominal variable denotes the level of the discomfort of patient P at time t. As described in Section 4.3.4, this variable is categorized as $Discomfort_P = 1 : No\ discomfort$; $Discomfort_P = 2 : Light\ discomfort$; $Discomfort_P = 3 : Medium\ discomfort$; $Discomfort_P = 4 : Strong\ discomfort$; $Discomfort_P = 5 : Extreme\ discomfort$.

4.3. Objective functions

In this section, we detail each one of the different criteria considered to optimize the transittability of complex biomolecular networks.

4.3.1. Minimizing the number of the external stimuli

As discussed in the previous sections, external stimuli called also *input signals* or *structural perturbations* are necessary for steering biomolecular networks from their actual state to a desired state. Indeed, external stimuli are the key element since they are responsible for steering biomolecular networks.

Therefore, the goal of this objective function is to identify the minimum number of stimuli that are most likely to steer the global biomolecular network from the initial state to the desired state. In other words, this criteria aims to give priority to the quality of the external stimuli over their quantity. Figure 1 explains this notion through an example of biomolecular network which can be steered to the desired state through three possibilities. These possibilities are explained from the point of view of the number of indispensable external stimuli for steering the network from a state to another one. We can reach the desired state via three different stimulation strategies (a, b and c). In the strategy a, each node receives an external stimulus. In the strategy b, we use three external stimuli. And in the strategy c, we only use two external stimuli. As a result, we note that the strategy c is the best one because we use the minimum external stimuli for steering the network.

To do this, we define the objective function $Z_1(x)$ which aims to minimize the number of external stimuli for achieving the transittability of complex biomolecular networks using Eq. (1).

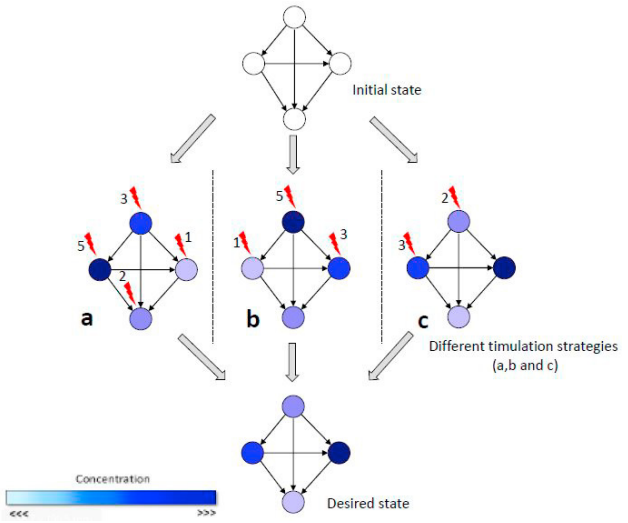

Fig. 1: A simple illustration of the transittability of complex biomolecular networks from the number and cost of external stimuli perspective.

$$Minimize\ Z_1(X) = \sum_{k=1}^{S} \sum_{i=1}^{M} \sum_{t=1}^{T} x_{k,i}^{t} \tag{1}$$

4.3.2. Minimizing the cost of the external stimuli

This criteria is related to the first objective function (Section 4.3.1). In fact, the cost of external stimuli can be proportional to the number of external stimuli. So, if we have a number of external stimuli equal to the number of nodes and all the external stimuli have the same cost, the transittability process of the complex biomolecular network will be very expensive. For these reasons, this criteria aims to find the best compromise between the quality of the external stimuli and their cost. We clarify this objective in the same example used in the first Section 4.3.1 (Figure 1). Here we focus only on the cost of the stimuli. In the strategy a, the total cost of external stimuli is 11 $(5+3+1+2)$. In the strategy b, the cost of external stimuli is 9 $(5+1+3)$. And in the strategy c, the total cost of external stimuli is 5 $(2+3)$. Consequently, the strategy c offers the best cost of external stimuli for steering the network.

Thus, we define the objective function $Z_2(x)$ which aims to minimize the cost of the external stimuli considering their quality for achieving the transittability of complex biomolecular networks using Eq. (2).

$$Minimize\ Z_2(X) = \sum_{k=1}^{S} \sum_{i=1}^{M} \sum_{t=1}^{T} x_{k,i}^{t} \times CostStim_k \tag{2}$$

4.3.3. Minimizing the number of target nodes

Several research studies have revealed that among all the nodes composing the biomolecular network, there are some specific nodes that have the ability to steer the network from its actual state to another specific state. Moreover, the stimulation of all the nodes of the network, may place the patient at risk of developing additional adverse effects caused by the external stimuli such as ultraviolet irradiation [14,15,16]. Thus, instead of stimulating all the nodes randomly, it is better to have a stimulation strategy which targets a set of specific nodes. This will allow to stimulate only a minimum number of nodes thus allowing the transition of the network to the desired state, so-called the *minimum steering nodes*.

As discussed in Section 2, a number of researches focused on the minimum steering sets and prove that identify the minimum set of nodes to be affected by external stimuli is a primordial condition to study biomolecular network's transitions. According to Butcher et al. [21] and Yang et al. [22] there are some biomolecular networks for which the perturbation of a minimum number of nodes can contribute to their transition from a state to a specific state, such as the promyelocytic leukemia network [22]. However, this is not the case for all biomolecular networks. That is why, we have to select only indispensable nodes (driver nodes) among neutral nodes (not profitable nodes). We explain this point by reference to the example presented in Figure 1 and from the point of view of the number of indispensable nodes for steering the network from its initial state to the desired state. We can reach the desired state via three

different stimulation strategies (a, b and c). In the strategy a, we interfere all the network nodes. In the strategy b, we interfere three nodes among four. And in the strategy c, we only interfere two nodes. Therefore, we note that the strategy c is the best one because there is only two indispensable nodes for steering the network.

So, we define the objective function $Z_3(x)$ which aims to identify the minimum number of nodes that are indispensable for steering the network from a state to another using Eq. (3).

$$Minimize\ Z_3(X) = \sum_{i=1}^{M} \sum_{k=1}^{S} \sum_{t=1}^{T} y_{i,k}^{t} \tag{3}$$

4.3.4. Minimizing the patient discomfort

The transittability of a biomolecular network can potentially be uncomfortable. By way of example, let's take the chemotherapy which is an anti-cancer treatment that consists of acting on cancer cells through toxic drugs (either by injection, or sometimes in the form of infusion) until they die and disappear. This treatment corresponds to the transittability of a biomolecular network which generally causes acute pain, vomiting, dizziness, fatigue and stress. As well as, it has been proved that the patient discomfort negatively impacts emotional and mental health of patients, the quality of their life and increases the use of health care resources[23,24]. For all these reason, we must consider this important criterion in the transittability process.

Therefore, our objective here is to reduce the patient discomfort during a certain treatment (while finding the best compromise with the other objective functions cited previously). In our context, the patient discomfort encompasses different aspects such as patient pain, stress, vomiting, dizziness, anxiety, fatigue, etc.

Based on the IPREA questionnaire proposed by Kalfon et al.[25] which focuses on the assessment of discomfort perceived by patients related to their intensive care, we define the uncomfortable level felt by a patient as an integer between 0 and 4. The patient is asked to mark his uncomfortable level on the line between the two extremities. These levels are defined as follows:

- Level 0 corresponds to *no discomfort*,
- Level 1 corresponds to *light discomfort*,
- Level 2 corresponds to *medium discomfort*,
- Level 3 corresponds to *strong discomfort*,
- Level 4 corresponds to *extreme discomfort*.

Therefore, patient discomfort is one of the major aims to be achieved during the optimization of the transittability of biomolecular network. This goal is represented by the objective function $Z_4(x)$ aims to minimize the patient discomfort using Eq. (4).

$$Minimize\ Z_4(X) = \sum_{t=1}^{T} Discomfort_P^t \tag{4}$$

4.4. Constraints

In this section, all constraints required to steer the complex biomolecular network from a state to another are presented.

- Constraint (5) ensures that the time of introduction of the stimulus k on a node i is greater than (after) the starting time of the transittability process of the biomolecular network BN.

$$S_{k,i}^{t} > StartTransi_{BN} \quad \forall k \in S, t \in T \tag{5}$$

- Constraint (6) ensures that the time of introduction of the stimulus k on a node i is smaller than the finishing time of the transittability process of the biomolecular network BN.

$$S_{k,i}^{t} < FinishTransi_{BN} \quad \forall k \in S, t \in T \tag{6}$$

- Constraint (7) ensures that the stimuli are introduced by order of time: stimulus $k+1$ begins after the stimulus k finished its perturbation.

$$S^t_{k,i} + e_{k,i} \leq S^t_{k+1,i} \quad \forall i \in M, k \in S, t \in T \tag{7}$$

- Constraint (8) ensures that both stimuli and nodes are acting simultaneously.

$$if \ \sum_{k=1}^{S} x^t_{k,i} = 1 \ then \ \sum_{i=1}^{M} y^t_{i,k} = 1 \quad \forall i \in M, k \in S, t \in T \tag{8}$$

- Constraint (9) ensures that the sum of the costs of the selected external stimuli does not exceed the total cost of all stimuli.

$$\sum_{k=1}^{S} \sum_{i=1}^{M} x^t_{k,i} \times CostStim_k \leq \sum_{k=1}^{S} CostStim_k \tag{9}$$

- Constraint (10) ensures the minimum number of indispensable nodes required for the transittability process.

$$\sum_{i=1}^{M} \sum_{k=1}^{S} y_{i,k} \geq 1 \quad \forall i \in M, k \in S \tag{10}$$

- Constraint (11) ensures the minimum number of external stimuli required for the transittability process.

$$\sum_{k=1}^{S} \sum_{i=1}^{M} x_{k,i} \geq 1 \quad \forall k \in S, i \in M \tag{11}$$

- Constraint (12) ensures the non-negativity constraints.

$$\begin{aligned} & c^t_i \geq 0 \\ & \Delta^t_{c,k,i} \geq 0 \\ & Discomfort^t_P \geq 0 \\ & CostStim_k \geq 0 \end{aligned} \tag{12}$$

- Constraint (13) represents the binary constraints.

$$\begin{aligned} & x^t_{k,i} \in \{0,1\} \quad \forall k \in S, i \in M, t \in T \\ & y^t_{i,k} \in \{0,1\} \quad \forall i \in M, k \in S, t \in T \end{aligned} \tag{13}$$

- Constraint (14) ensures that the patient discomfort felt during the transittability process should not exceed the limit (maximum) of discomfort.

$$\sum_{t=StartTransi_{BN}}^{FinishTransi_{BN}} Discomfort^t_P \leq Discomfort^{max}_P \quad \forall t \in T \tag{14}$$

- Constraint (15) ensures that each stimulus affect only one node and each node is stimulated by only one stimulus at a time t.

$$\begin{aligned} & \sum_{k=1}^{S} x^t_{k,i} = 1 \quad \forall k \in S, i \in M, t \in T \\ & \sum_{i=1}^{M} y^t_{i,k} = 1 \quad \forall i \in M, k \in S, t \in T \end{aligned} \tag{15}$$

- Constraint (16) ensures that the change in concentration applied by the stimulus k on the node i does not exceed both limits minimum and maximum of concentration of the node i.

$$\begin{aligned} & \Delta^t_{c,k,i} + c^t_i \geq c^{min}_i \\ & \Delta^t_{c,k,i} + c^t_i \leq c^{max}_i \end{aligned} \tag{16}$$

5. Conclusion and future works

In this paper, an important problem in systems biology, the ”transittability” of complex biomolecular networks has been formulated as a multi-objective mathematical programming problem. Indeed, the transittability of complex biomolecular networks is a multi-criteria problem by nature since there are several potentially conflicting criteria to consider while steering the network from a state to a desired state. In this paper, four essential criteria, which need to be minimizing simultaneously to steer complex biomolecular networks from their actual state to a desired state, are presented and described in detail. There are: the minimization of the number of input signals, the minimization of the cost of these external stimuli, the minimization of the number of target nodes and the minimization of the patient discomfort. Applying a minimum number of external stimuli on a minimum number of steering nodes has been already considered in existing mathematical models in literature, however these criteria are not sufficient for completely steering complex biomolecular networks. That is why other criteria have been considered in this model.

Future works will focus on the implementation of this proposed model using a multi-objective genetic algorithm-based method and its application in real complex biomolecular networks.

References

1. Wu, F. X., Wu, L., Wang, J., Liu, J. and Chen, L.: Transittability of complex networks and its applications to regulatory biomolecular networks. *Scientific reports*. 2014; **4**.
2. Karp, Gerald.: Biologie cellulaire et moléculaire: Concepts and experiments. *De Boeck Supérieur*. 2010.
3. Liu, Y. Y., Slotine, J. J., & Barabási, A. L.: Controllability of complex networks. *Nature*. 2011; **473(7346)**, 167.
4. Gao, J., Liu, Y. Y., D'souza, R. M., & Barabási, A. L.: Target control of complex networks. *Nature communications*. 2014; **5**, 5415.
5. Wu, L., Tang, L., Li, M., Wang, J., & Wu, F. X.: Biomolecular network controllability with drug binding information. *IEEE transactions on nanobioscience*. 2017; **16(5)**, 326-332.
6. Greenberg, H. J., Hart, W. E., & Lancia, G.: Opportunities for combinatorial optimization in computational biology. *INFORMS Journal on Computing*. 2004; **16(3)**, 211-231.
7. Larranaga, P., Calvo, B., Santana, R., Bielza, C., Galdiano, J., Inza, I., ... & Robles, V.: Machine learning in bioinformatics. Briefings in bioinformatics. 2006; 86-112.
8. Looger, L. L., & Hellinga, H. W.: Generalized dead-end elimination algorithms make large-scale protein side-chain structure prediction tractable: implications for protein design and structural genomics1. *Journal of molecular biology*. 2001; **307(1)**, 429-445.
9. Wang, Y., Zhang, X. S., & Chen, L.: Optimization meets systems biology. 2010.
10. Festa, P.: Optimization problems in molecular biology: A survey and critical review. *In Int. Math. Forum*. 2008; **3(6)**, 269-289.
11. Lombardi, A., & Hörnquist, M.: Controllability analysis of networks. *Physical Review E*. 2007; **75(5)**, 056110.
12. Wang, W. X., Ni, X., Lai, Y. C., & Grebogi, C.: Optimizing controllability of complex networks by minimum structural perturbations. *Physical Review E*. 2012; **85(2)**, 026115.
13. Cornelius, S. P., Kath, W. L., & Motter, A. E.: Realistic control of network dynamics. *Nature communications*. 2013; **4**, 1942.
14. Wu, L., Shen, Y., Li, M., & Wu, F. X.: Drug target identification based on structural output controllability of complex networks. *In International Symposium on Bioinformatics Research and Applications*. 2014; Springer, Cham. 188-199.
15. Wu, L., Shen, Y., Li, M., & Wu, F. X.: Network output controllability-based method for drug target identification. *IEEE transactions on nanobioscience*. 2015; **14(2)**, 184-191.
16. Wu, L., Li, M., Wang, J., & Wu, F. X.: Minimum steering node set of complex networks and its applications to biomolecular networks. *IET systems biology*. 2016; **10(3)**, 116-123.
17. Wang, L. Z., Chen, Y. Z., Wang, W. X., & Lai, Y. C.: Physical controllability of complex networks. *Scientific reports*. 2017; **7**, 40198.
18. Ayadi, A., Zanni-Merk, C., & de Beuvron, F. D. B.: Understanding the Behaviour of Complex Biomolecular Networks by Combining Logical and Semantic Modeling. *In SWAT4LS*. 2016.
19. Ayadi, A., Zanni-Merk, C., de Beuvron, F. D. B., & Krichen, S.: BNO: An ontology for describing the behaviour of complex biomolecular networks. *Procedia Computer Science*. 2017; **112**, 524-533.
20. Ayadi, A., Zanni-Merk, C., de Bertrand de Beuvron, F. and Krichen, S.: Logical and Semantic Modeling of Complex Biomolecular Networks. *Procedia Computer Science*. 2016; Volume **396**:475-484.
21. Butcher, E. C., Berg, E. L., & Kunkel, E. J.: Systems biology in drug discovery. *Nature biotechnology*. 2008; **22(10)**. 1253.
22. Yang, K., Bai, H., Ouyang, Q., Lai, L., & Tang, C.: Finding multiple target optimal intervention in disease-related molecular network. *Molecular systems biology*. 2008; **4(1)**. 228.
23. Gallagher, R. M., & Rosenthal, L. J.: Chronic pain and opiates: balancing pain control and risks in long-term opioid treatment. *Archives of physical medicine and rehabilitation*. 2008; **89(3)**. S77-S82.
24. Trescot, A. M., Helm, S., Hansen, H., Benyamin, R., Glaser, S. E., Adlaka, R., ... & Manchikanti, L.: Opioids in the management of chronic non-cancer pain: an update of American Society of the Interventional Pain Physicians'(ASIPP) Guidelines. *Pain physician*. 2008; **11(2)**. S5-S62.
25. Kalfon, P., Mimoz, O., Auquier, P., Loundou, A., Gauzit, R., Lepape, A., ... & Mallédant, Y.: Development and validation of a questionnaire for quantitative assessment of perceived discomforts in critically ill patients. *Intensive care medicine*. 2010; **36(10)**. 1751-1758.