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Rich Club in Metabolic Pathways: *Switches*

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Abstract: The study of metabolic pathways has been the key areas of interest for researchers in bioinformatics. The data in the form of pathways provides an organizational and simple form of representing data. Such representation is easy to understand and implement. One of the most basic elements of these pathways is switches. Switches may used to connect two complex pathways or may be used in one big pathway itself to regulate some part of a complex pathway. Many cellular components are found to be performing as switches regulating various activities of the cell. It is of foremost importance to identify such switches in a network to study its effect on the regulation and the function of the cell.

Keywords: metabolic pathways, bioinformatics, switches, cell components.

1 INTRODUCTION

Owing to the advances in bioinformatics and information technology we are provided with vast amounts of relevant data. The source of this data is the completion of various genome projects of different organisms. Most of the metabolic processes in the sequenced organisms has been known but a universal method of representation of all of this data is still one of the major concern in this field.

The representation of the data in the form of metabolic pathways has been the most influential approach till date. The genome sequences of many organisms are available and the organism specific metabolic networks can be faithfully reconstructed from genome information **[1-4]**. The metabolites are graphically represented in a metabolic network. A graph consists of nodes, which are metabolites in the case of a metabolic network, and the interconnections amongst the nodes in the form of edges, which are reactions or enzymes in a metabolic network.

A switch in a metabolic pathway is more or less like an electronic switch that can be turned on or off as and when required. Several metabolic switches have been identified till date and have been suitably exploited to study its effect on regulation. In case of a cell the switches found in them have a system with multiple stable states are of particular biological interest because they can retain a "memory" of past inputs and cellular decisions **[5-8]**. Bistability is a particularly interesting case of multi-stability, as it leads to switch-like behavior. Chemical stimuli can trigger a state change from one stable state to another. The current state of the chemical system is therefore a "memory" of this earlier stimulus.

2 SWITCHING GRAPHS

A switch graph is an undirected graph in which the edges incident to each vertex are partitioned into two subsets. Each vertex of the switch graph corresponds to two vertices of the skew-symmetric graph (a directed graph that is isomorphic to its own transpose graph, the graph formed by reversing all of its edges). Each edge of the switch graph corresponds to two edges of the skew-symmetric graph. The vertices of a switch graph can be visualized as points where multiple tracks of a train track come together: if a train enters a switch via a track that comes in from one direction, it must exit via a track in the other direction. The problem of finding non-self-intersecting smooth curves between given points in a train track comes up in testing whether certain kinds of graph drawings are valid and are modeled as the search for a regular path in a skew-symmetric graph **[9-11]**.

Switching graphs are graphs containing switches. By using boolean functions called switch settings, these switches can be put in a fixed direction to obtain an ordinary graph. For many problems, switching graphs are a remarkable straightforward and natural model, but they have hardly been studied **[12, 13]**.

3 CURRENT STRATEGIES FOR SWITCH DETECTION

3.1 Determination of clusters:

Switches are hypothesized to be extremely rare in the complex system. However many cellular components have been found to be acting as switches when triggered by a stimulus. The approach applied for switch detection within a huge complex network is applying the clustering coefficient and breaking the complex network into smaller clusters. This is a value based approach in which the nodes with similar values are kept in one specific cluster **[14-17]**.

As the amount of data available with us is enormous the clustering is a crucial graph-theoretic problem in data and, more specifically, network analysis. It has been studied for decades and applied in many settings such as data mining, biochemistry and social studies **[18-20]**. The applications of clustering involve studying the intrinsic properties of the clusters like the nature and type of connections of the clusters. The application of these techniques have been justified both theoretically as well as experimentally, although, their application in real world is not so simple **[21-25]**.

In an undirected graph, the clustering coefficient of node v measures the extent of its neighbors to form a clique. The mathematical definition is as follows:

$$CC(v) = \frac{2|N(v)|}{d(v)(d(v)-1)}$$

Where,
|N(v)| denotes the number of links between neighbors of node v and d(v) is the degree of the node v.

The clustering coefficient of a particular dataset lies between 0 to 1 depending upon the connections of the neighbors with each other

[26-28]. Clusters of the datasets are acquired and the most clustered and the least clustered are then studied and the properties are then determined. After the clustering is completed the data is validated and the suitable clusters are determined based upon the values of the clusters **[29, 30]**.

4 APPLICATION IN METABOLIC ENGINEERING

4.1 Cellular RNA as switches

Cellular RNA are known to perform a variety of functions. Functions include forming essential components of the transcription/translation machinery to natural or in vitro selected ribozymes or aptamers and different classes of gene expression regulators **[31]**. Due to the rearrangement and modification of the base pairs of the RNA, they can exhibit optical activity and also form secondary rearrangements. Yet, because of their limited four-letter alphabet and strong base pair stacking energies, RNAs are also prone to adopt long-lived misfolded structures **[32]**.

It has long been proposed that, during transcription, the progressive folding of nascent RNAs limits the number of folding pathways, presumably facilitating their rapid folding into proper native structures. However, it is not clear whether native domains fold sequentially and independently from one another or whether co-transcriptional folding paths result from more intricate interactions between domains and individual helices. Transcriptional RNA switches provide interesting examples of co-transcriptional folding paths with local competition between newly formed and alternative helices. Such natural RNA switches are typically found in virus or plasmid genomes **[33]** and in bacterial mRNA UTRs where they regulate gene expression at the level of transcription elongation (e.g. through termination/anti-termination mechanism) or at the level of translation initiation (e.g. through sequestration of Shine–Dalgarno motifs) **[34]**. The structural changes controlling their regulatory function may correspond to a switch in equilibrium structure or in co-transcriptional folding path caused by binding an effector (e.g. a protein, a small metabolite or an antisense sequence). Alternatively, RNA switches may operate through spontaneous or assisted relaxation of an initially metastable co-transcriptional fold **[35]**. Hence, RNA switches can have stringent needs to control their folding between alternative structural folds, which makes them ideal candidates to dissect RNA co-transcriptional folding mechanisms and estimate the minimal sequence constraints to encode them.

Hence by knowing the exact symmetry and the orientation of the RNA in concern it is possible to design pairs of synthetic RNA switches that can be used in variety of applications and studying regulatory factors. Switches also exhibit an on and off mechanism. So if it is possible to detect such switches in a huge metabolic pathway we can regenerate the pathway and the switches and then effectively turn the switch "on" and check its influence on the pathway or can "off" the switch to get results **[36]**.

A metabolic pathway is a pool of metabolites which are highly interconnected and reactive. The entire pathway can only be carried out by the participation of all the metabolites. However there are certain core metabolites of the system and the rest may potentially be helper or co-metabolites. If we can find the switches in the network we can hypothesize upon the core elements in the network and can conclude that if these elements are blocked in a network then that would influence the entire network.

5 CONCLUSION

It can be concluded that detection and construction of synthetic switches proves to be important milestones in pathway engineering studies. Studies have already proved the mutations can cause switching behavior in cellular components such as RNA or proteins. The studies done in this aspect of metabolic engineering however is not substantional and the concept has to be dealt with in a deeper manner to facilitate greater understanding of the metabolic pathways.

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