

Logical Models Using Boolean Network to Study Breast Cancer Signalling Pathways

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Abstract— *The transformation of biological gene to a similar synthetic form is subjected to investigation of vulnerable components in a signaling pathway which contribute the development of drug therapy pointing out towards the aberrations in that pathway. Logic models were thus developed for analyzing the vulnerability of the components in multiple signaling pathways. The heterogeneities in signaling pathways among the patients address the different response of breast cancer from patients to patients. The targets accepted universally are those, whose vulnerabilities are invariably high among the others.*

Keywords— *Gene regulatory network, Boolean Network, Signaling pathways, Ligand, Activated Kinase A, Activated Kinase B, Activated Kinase C, Activated Protein D.*

I. INTRODUCTION

Worldwide breast cancer is the most common invasive cancer among females. Accounting for 16% of all female cancers and 22.9% of invasive cancers in women 18.2% of all cancer deaths worldwide, are from breast cancer, including both males and females. The rates of breast cancer is higher in developed nations as compared to the developing ones. There are several reasons for this, with possibly life-expectancy being one of the key factors-breast cancer is more common in elderly women; women in the richest countries live much longer than those in the poorest nations. The different lifestyles and eating habits of females in rich and poor countries are also contributory factors, experts believe.

The execution of biological functions are done through the interactions among genes, proteins and other intracellular molecules. The logic chains of interactions, i.e., pathways that mediate the signals inside cells, were actively under various researches to grab the knowledge of normal and abnormal processes. Cancer being a heterogeneous disease is not only of different types but it can also occur as single tumor. This intra-tumor heterogeneity might be a result of genetic changes, environmental factors, and/or variations in cell properties among the individuals, and could be a major obstacle in a cancer treatment due to a wide range of responding to any specific anticancer agent. Breast cancer, demonstrates significant heterogeneity from onset. Therefore, study of multiple intracellular pathways involved in cancer cells with enhanced survival and proliferation could provide variable information about the role of each components, in controlling the tumor growth.

Pathway biology aims to understand the cause-effect relationships among genes and such a system-level study is intended to integrate the information in published investigations to provide further understanding of pathways. To understand the behavior of animal cell, its abnormalities

and the experiment related to the cure of genetic diseases, like cancer, the recent view point has changed a little. Scientists are taking modern engineering approaches to deal with the problems. Lots of techniques were studied to bolster the debate of modeling cell behavior, inferring biological networks and controlling genetic diseases [10]. Gene regulatory networks (GRNs) is a set of genes, or parts of genes, that interact with each other to control a specific cell function. The GRNs are important in development, differentiation and responding to environmental cues. Various approaches have been proposed for the same among those Boolean networks (BNs) have been widely used to model the interaction among genes. This paper focuses on Boolean Network due to its relevant adaptation by the research community. BNs emerged as a very successful to better understand both structural and dynamical properties of GRNs. Boolean Networks proffers more realistic and rational analysis of high-level functional characteristics of GRN. It is the device for driving new logical experiments [9]. The activation and deactivation relationships are modeled by digital logic circuits where the active/deactive levels of gene nodes are indicated by ON/OFF states [1], this represents “true and false”. Genes are either “on” or “off”. When the gene is on, it is said to be activated and if not it is said to be deactivated. The state of gene is often known as expression level of gene [13].

Various studies have been carried out to estimate the vulnerability of a system. Over the past decades, advances in the estimation of gene regulatory networks have lead to an increased understanding of cellular regulation. The main focus is to understand how the cells executes the normal functioning and way if the cellular structure system fails to function, causing diseases [10]. To discover the knowledge of targeted gene perturbation experiments get involve in variety of diseases and is potentially able to design targeted interventions in broader sense. [14] Many network research struggles to detect complex multi-gene regulatory networks accurately. In a synthesis biological network, malfunction of a gene network in the pathway may result in the transition from a normal state to a defective one. Here in this paper, this function is carried on by activated protein D. The activated protein D is generally in a stagnant state unless and until it gets the signal from its neighboring protein. Only after getting the triggers its dormancy is affected and thus it become activated. One should keep this into consideration that if anything wrong happens in the activation of this protein it itself can turn into malignant. In this paper the dynamics of kinase A, Kinase B, kinase C and activated protein D pathway is captured using Boolean

network and the next state of target gene is obtained from simulation of logical model.

II. BOOLEAN NETWORK REPRESENTATION

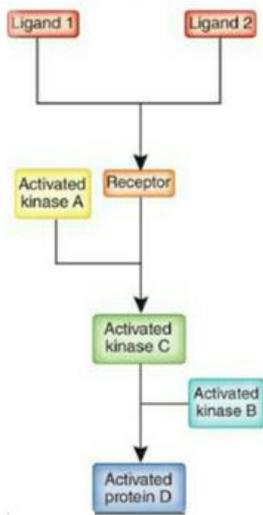


Fig. 1. Basic model of activated protein D pathway.

The diagrammatic representation of protein kinase A protein kinase B, protein kinase C is introduced to implement the Boolean network [2] in figure 1.

To control Gene Expression Level genetic regulation is required which includes the interaction between DNA-protein and Protein-Protein in an organism. The modeling of different process of gene expression and genetic regulatory system are thus investigated to differentiate between normal and abnormal (diseased) gene[3].

Genes can be viewed as the nodes in the gene regulatory network, proteins or ligands as input and gene expression is as output. For any particular job when the gene is expressed, the gene expression is in 'ON' state i.e. 1 and when it is not expressed, it is in 'OFF' state i.e. 0. So, it has two states similar to the Boolean Network [8].

It is proposed in this paper an equivalent Boolean model for a particular pathway of activated protein kinase to show a state transition process between the given protein kinases .

This paper introduces certain new elements ,they are:

LIGAND-The ligand is usually a molecule which produces signal by binding to a site on a target protein. Ligand is for serving biological purpose.

RECEPTOR-A receptor is a protein molecule that receives chemical signals from outside a cell .When such chemical signals bind to a receptor ,they cause some form of cellular/tissue response.

ACTIVATED KINASE A- The protein Kinase A enzyme is also known as (cyclic amp) cAmp-dependent enzyme because it is activated only when cAmp is present .Hormones such as glucagon and epinephrine begin the activation cascade(that triggers protein Kinase A)by binding to a G protein-coupled receptor(GPCR) on the target cell. When a GPCR is activated by its extra cellular Ligand, a conformational change is induced in the receptor that is transmitted to an attached intracellular heterotrimeric G protein complex by protein

domain dynamics [4]. Activated Kinase A is a metabolic regulator and it regulates the metabolic changes of cancer cells.

ACTIVATED KINASE B- Proteins kinase B Is A Serine/Threonine-Specific protein kinase that plays a key role in multiple cellular processes such as glucose metabolism, apoptosis, cell proliferation, transcription and cell migration. The activation occurs by certain diverse stimuli such as hormones, growth factors and other trigger mechanisms. It plays a great role in cellular signaling pathways. Activated protein kinase B promotes many of the processes critical to the malignant phenotype. Thus, it is an attractive therapeutic target for cancer [5].

ACTIVATED KINASE C-It Is responsible for regulating numerous cellular responses including gene expressions, protein secretions, cell proliferations and the inflammatory response [6]. Kinase C contains an auto-inhibitory pseudo-substrate domain that binds a catalytic domain sequence to inhibit kinase activity. It plays an important role in signal transduction pathways, involved in hormone release, Mito-Genesis and tumor promotion. Acting as an anti-oncogene, in breast cancer, where an increase in its activity correlates with increased resistance and metastatic potential.

ACTIVATED PROTIEN D- Protein kinase D or protein kinase D1 (PKD1) is a serine-threonine kinase that regulates various functions within the cell, including cell proliferation, apoptosis, adhesion, and cell motility [7]. It plays a role in both diseased and normal cells. In normal cells, this protein plays key roles in multiple signaling pathways by relaying information from the extracellular environment and/or upstream kinases and converting them into a regulated intracellular response. PKD1 resides primarily as an inactive kinase in the cytoplasm under resting conditions, but when it gets the trigger from other proteins it is activated. This protein is capable of diversing the signaling pathways, thus regulates multiple biological functions that are crucial for the normal cell functioning. The dysfunctional of this protein may cause adverse effect on cells causing certain reverse actions.

III. NETWORK IMPLEMENTATION

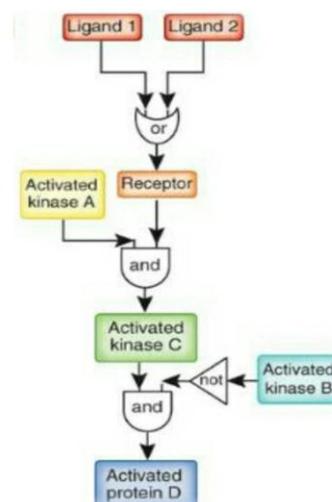


Fig. 2. Logic based model of given pathway.

This model represents the logic diagram. Here it is seen the different types of logic gates representing the equations. The given diagram is implemented in the truth table represented as Table. 1.

$RECEPTOR = LIGAND\ 1\ OR\ LIGAND\ 2$

$ACTIVATED\ KINASE\ C = RECEPTOR\ AND\ ACTIVATED\ KINASE\ A$

$ACTIVATED\ PROTIEN\ D = ACTIVATED\ KINASE\ C\ AND\ NOT\ ACTIVATED\ KINASE\ B$

Where AND represents multiplication and OR represents addition.

L1 is Ligand 1,

L2 is Ligand 2,

R is receptor,

KA is activated kinase A,

KB(A) is activated kinase B,

KB(NA) is not activated kinase B,

KC is activated kinase C,

PD is activated protein D.

TABLE 1. Truth table for GRN (Gene regulatory network).

Sl No	L1	L2	K A	K B (A)	K B (NA)	R	K C	PD
1.	0	0	0	1	0	0	0	0
2.	0	0	1	0	1	0	0	0
3.	0	0	1	1	0	0	0	0
4.	0	1	0	0	1	1	0	0
5.	0	1	0	1	0	1	0	0
6.	0	1	1	0	1	1	1	1
7.	0	1	1	1	0	1	1	0
8.	1	0	0	0	1	1	0	0
9.	1	0	0	1	0	1	0	0
10.	1	0	1	0	1	1	1	1
11.	1	0	1	1	0	1	1	0
12.	1	1	0	0	1	1	0	0
13.	1	1	0	1	0	1	0	0
14.	1	1	1	0	1	1	1	1
15.	1	1	1	1	0	1	1	0

IV. RESULT AND DISCUSSION

The truth table is constructed manually and it has been simulated by the Logicy software.

$RECEPTOR = LIGAND\ 1\ OR\ LIGAND\ 2$

If either of the Ligand is present then receptor will become activated. If both the Ligands are in 0 state then receptor is also in 0. So when Ligand1 and Ligand 2 are 0 and 0 respectively Receptor is OFF.

$ACTIVATED\ KINASE\ C = RECEPTOR\ AND\ ACTIVATED\ KINASE\ A$

Presence of both receptor and activated kinase A will activate kinase c or else the activation is null. Thus Activated Kinase A=1 and Receptor=1 then Activated Kinase C=1

$ACTIVATED\ PROTIEN\ D = ACTIVATED\ KINASE\ C\ AND\ NOT\ ACTIVATED\ KINASE\ B$

When activated kinase B is ON state NOT Activated Kinase B is OFF state and vice versa.

So to Activate Protein D, Activated Kinase B has to be in OFF state to let NOT activated kinase B in ON state which further in combined with ON state Activated Kinase C produce the above protein. Like when Activated kinase B is 1 / 0 NOT Activated Kinase B is 0/1 respectively and Activated

Kinase C is also changing for Activated protein D which is activated only when NOT Activated Kinase B and Activated Kinase C is 1.

V. SIMULATION

Here the four cases have been presented to show the activation and the deactivation of protein D in the following figures.

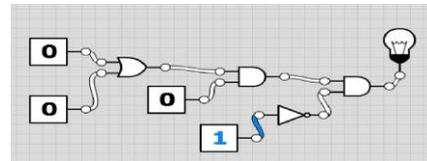


Figure 3. Row 1 of the truth table is verified in this figure. This is the first case where Protein D is not activated. Here the proper inputs have been taken a bulb is fitted as the output which is not glowing, means Activated protein D is inactive.

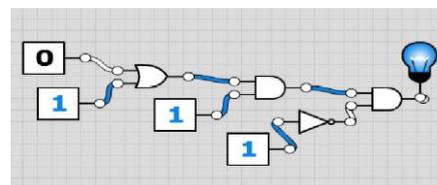


Figure 4. Verification of row 6 of truth table is shown in this figure. This is the first activated case for protein D. All the inputs are taken properly and at the end the bulb is glowing, showing the activation of protein D.

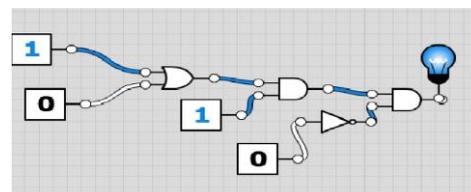


Figure 5. Row 10 of the truth table is verified in this figure. This is the second case of activation of protein D. This is also glowing.

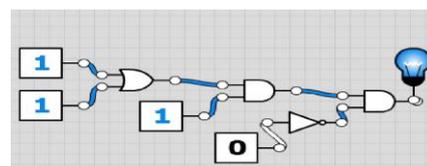


Figure 6. Verification of row 14 is shown in this figure. This is last case for the activation of protein D. This is also successfully shown.

Thus by changing the inputs as given in the truth table and fitting a bulb to get the outcome, the desired results are produced.

VI. CONCLUSION

Since the networks are high dimensional, structure objects the assessments are very crucial and complicated [11]. GRNs represents many types of physical biochemical interactions between gene structures. Currently, the number of GRNs is difficult to estimate but based on the fundamental results it is said there are more than 200 different GRNs for human alone. Thus establishing the relationship is quite complex. However, diseased cells manifesting tumors have their own characteristic networks implying that there are probably thousands of different gene networks in Human [12]. The pathway of Ligand 1, Ligand 2, Activated Kinase A, Activated Kinase B, Activated Kinase C and Activated Protein D, have been selected, to study the dynamics of gene regulatory network. Random Boolean network model is realized to study the characteristic of target gene and its regulators. To analyze the fact, simulation is being done manually, which is further verified by Logically software, and got the desired result. This work may further be extended for other complex gene regulatory network.

ACKNOWLEDGEMENT

The author thanks her teacher Dr. Sanghamitra Chatterjee for guiding her in the right direction. She also thanks Camellia Institute of Technology, for providing research facilities.

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