Computational Modeling and Analysis of Non-Small Cell Lung Cancer (NSCLC) Pathway using Static Analysis Approach to Identify Potential Biomarkers and Drug Targets

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Declaration

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This thesis is dedicated to *my beloved parents*

Acknowledgments

First of all, I am hugely beholden to Allah Almighty for His boundless blessings upon me in my life and qualifying me to accomplish this thesis auspiciously. I'm thankful for the audacity and inspiration He poured in my heart that guided me to this point where I am declaring this humble contribution before the world.

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Yawar Hayat

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Abstract

Latterly, a vital prototype shift has been manifested in the management of non-small cell lung Cancer (NSCLC). Owing to the fact that NSCLC could be sub-categorized on the basis of its physiological morphology along with concerned genetic alterations. Lung cancer regimen has been revolutionized with advancement of drugs that are to some extent effectual in targeting the prime driver mutations and immune control points. While, targeted therapy is anticipated to ameliorate patients results along with the standard of life. Computational simulation techniques have greatly contributed in the progression of molecular biology targeted based therapies by allowing the biological abstractions meticulous and demonstrable along with implementing reference map that confines together the discrete biological insights. The current research exercises one of the remarkable computational technique of software Pint under the parasol of Process Hitting. It enlightened us about an extensive catalogue of significant Biomarkers inclusive of presence of prolonged cell survival along with uninterrupted G1/S cell cycle progression and enhanced proliferation of the tumor cells marks down the footprints for an early and effective diagnosis of NSCLC. Application of cut set on AKT allowed us to regain homeostatic apoptotic process. It also contributed towards therapeutic strategies for NSCLC treatment by providing the important drug targets such as ALK, mTORC1, STK4, CCND1 and besides others. The current study tends to fulfil the scientific gap between wet lab studies and cost effective along with time saving computational strategies for an effectual treatment for deadly diseases like non-small cell lung cancer.

Keywords: *NSCLC, Biomarkers, Apoptotic process, Mutations*

Chapter 1

Introduction

1.1 Background

One of the root causes of cancer related deaths around globe is the lung cancer with most of individuals display histological sub type namely non small cell lung cancer that reportedly makes up to 80 to 85% of lung cancer cases and remaining 15% as by small cell lung cancers [2–4].

1.2 Morphology

The NSCLC is further branched into two categories as in the lung adenocarcinoma (LUAD) and lung squamous cell carcinoma [5]. Based on association of all key histological sub types of NSCLC with smoking of tobacco, in United states and other countries it makes up for 80% of cases that explained the typical causation of NSCLC [6, 7] in East Asia, environmental exposure of passive smoking with job-related carcinogens and genetic liability leads to lung cancer in nonsmokers especially among women [4, 6, 7].

1.3 Morbidity and Mortality Rate

At present, out of newly reported cases of cancer, almost 13% making it 1.8 million cases are ascribed to lung cancer with 1.6 million demises worldwide making 19.4% mortality rate annually [8]. The figure of new cases of lung cancer reckoned in 2014 in United States is 224,210 along with nearly 159,260 deaths. While, in Europe it makes 410,000 cases

in 2102 with 353,000 gauged deaths [9] and in Africa the decreased number of reported cases indicates the under-reporting of cases rather small incidence rate, where the figure of reported cases was 30,314 in 2012 having 27,083 mortalities (GLOBOCAN 2012). Over all in Asia, identified figure of cases is 1,045,000 with 936,051 deaths have been perceived. Developing countries with the passage of time tends to have low incidence of lung cancers but in under developed countries of the world inclusive of Africa, China, South America and Eastern Europe, the same rate is enhancing at a pace with incidence of 58% of approximated 1.8 million new cases across the world [8].

1.4 Diagnosis

Primarily the lung cancers are diagnosed at their later advanced stages because of lack of clinical manifestation along with no efficient screening techniques. Precise and reliable staging is decisive in terms of prognosis and therapy recourses [10, 11] Global combat against lung cancer needs a comprehensive approach with decimating the tobacco products usage. Along with that through socio-economic measures such as tax collection, media advertisements and other government measures including making nicotine usage lower in cigarettes to non-addictive scales in US food and drug administration (FDA) policy. Another concern is the e-cigarette usage with unspecified long-lasting consequential effects may allow new individuals to operate cigarette devices [12, 13].

1.5 Treatment

Platinum-based dual combination chemotherapy serves as the conventional first-line therapy that is given to patients that are in later stages of NSCLC. But, in this regard onset of major side effects and low progress with chemotherapy is one of the hurdles in this treatment. Henceforth, instead of ill-defined c hemotherapeutic s trategies and other chemical agents to control cancer, the drug development primarily concerning cancers treatment has switched to rationale designing of drugs that is molecularly target specific, to reduce the malignity and this has also revolutionized the clinical management. NSCLC has been reclassified molecularly into various further disease subsets since identification of diverse genetic modifications [2].

1.6 Onset of Mutations

The above paragon designates that the course of development of lung cancer is specifically regulated by the outcome of gene expression that epitomize the events significant during elementary generation of lung [14]. Mutations that drive the development of cancer foster nearly two-third of the individual cases that are therapeutically targeted [15].

1.7 On-Target and Off-Target Resistance

These therapeutic resistances exist in a biological continuance overlap manner. In NSCLC, stimulation of genetic alterations in epidermal growth factor receptor (EGFR or ERBB1) along with fused anaplastic lymphoma kinase and serine threonine kinase protein BRAF are designated for kinase-suppression therapy. In terms of resistance to the targeted therapy, when the predominant target of the drug undergoes alterations, impairing its capability to suppress its target is the on-target resistance while, the off-target resistance accounts for trigger of concomitant signaling cascades either in side-by-side or in downstream manner through directed cancer harbouring proteins which control cellular development along with its durability. Common unresponsiveness to the contemporary suppressors of EGFR tyrosine kinase handicaps the apoptotic reaction to therapy of EGFR tyrosine kinase inhibitors [16, 17].

1.8 Current Need

Integration of both preclinical models along with clinical samples have enabled interdisciplinary elucidation of resistance related mechanisms [18, 19]. Apprehension of the biology of molecularly heterogeneous ailment NSCLC is pivotal to compose effectual therapeutic treatments. Genetic modifications in Kirsten rat sarcoma (KRAS) and EGFR implicates their part in the commencement of cancers. This represents them as an agreeable target as well for therapeutic interposition. In most of the cases, both of these genetic alterations are found in an absolute manner otherwise, when both mutations occur in parallel then KRAS mediating mutations grant unresponsiveness to EGFR tyrosine kinase suppressors [20] Frequent incidence of genetic modifications in

tumor suppressor protein p53 have also been suggested in NSCLC [21]. Owing to the manifestation of cancer spread-out to other parts of body at the time of diagnosis of NSCLC is the root cause of enhanced mortality rate of lung cancer. Suggesting the need for efficient and systematic therapies for long-term survival [22].

1.9 Problem Statement

The analysis of the dynamics of Biological Regulatory Networks (BRNs) requires innovative methods to cope with the state-space explosion problem. Model reduction often results in loss of significant dynamics and may provide imprecise results. An efficient static analysis method is required to manage analysis of qualitative dynamics of BRNs. Process Hitting approach offers a promising perspective to the inference of gene regulatory networks even when a large amount of biological data must be processed, up till 10,000 components.

1.10 Ongoing Challenges

Non-small cell lung cancer is one of the fatal diseases owing to the fact that it does not display symptoms at an early stage and most of the diagnosis takes place at later final stages of cancer development. NSCLC is highly complex and an extensive pathway whose dynamics have not been completely studied due to limitations of any previous techniques. Continuous modeling strategy here seems hectic owing to the defining of all kinetic parameters of each entity [23]. It is overall difficult to deal with complete set of behaviors exhibited by the system owing to the limited size availability along with filtration of the noisy biological data to obtain and to prevent loss of important information.

1.11 Theme of the Study

After a thorough literature review delineating the molecular mechanism of NSCLC, the referenced pathway from KEGG pathway database has been fully curated with additional missing links. Various computational techniques implemented during the current study have been discussed. Computation modeling can be implicated to modulate the

pathway dynamics to compute diverse array of biological signaling pathway of NSCLC that selectively affects the cellular functions. Interlinking of holistic computational approaches in molecular biology enables the scientific investigation of intracellular dynamics. The extensive pathway created on Ginsim software was modeled in the Pint software working under the framework of Process Hitting which in this regard contributes by overcoming the issue of state space overflow by computing the required stable state through static analysis, for identification of disease Biomarkers [24]. Moreover, the final results obtained have been examined and reviewed in detail followed by the discussion.

Chapter 2

Literature Review

2.1 Molecular Mechanism of NSCLC

Near about 80% of lung mediated cancers are designated as non-small cell lung cancers with most as adenocarcinomas in nature [25]. Fundamental mechanisms that constitute the baseline of lung cancers evolve around the genetic modifications of KRAS, BRAF, EGFR along with EML4-ALK and repression of CDKN2A and RASSF1 tumor suppressor proteins [26]. Among these, around 4% of non-small cell lung cancers are attributed to mutations in BRAF gene [27].

2.2 Role of Proto-oncogenes

Proto-oncogenes (Normal genes) alteration can be termed as oncogenes. The regulation of different cell processes such as cell proliferation is monitored by the product of these proto-oncogenes. In most of the cases it turns out that this change of proto-oncogenes to oncogenes results in indecorous production of proteins. The presence of such condition allows the cell to divert from the normal cell growth and regulation towards the process of uncontrolled division of cells that is the uncontrolled proliferation [28]. A single cell contains different genes that encodes different proteins and these proteins are involved in the different functions such as activation of different signaling pathways and the main signaling pathways that anticipates in the therapy include: Growth inhibitory pathways (P14ARF(CDKN2), p53, Rb), Growth promoting pathways (Epidermal Growth Factor Receptor/ Phosphatidyl Inositol 3-Kinase/ Ras), preserved genes, repairing of DNA and

the apoptotic pathways (Bax/ BAD) . Oncogenes direct the regulatory signaling pathways, attributing cells with abnormal phenotypes and avoidance from normal cell death apoptosis. An addiction is caused to tumor cells by the mutated oncogenic proteins towards their abnormal functions, mentioned as oncogenic addiction. In contradistinction to normal cells, the survival of these addicted tumor cells depends on the overexpressed function of these oncogenes [29].

2.3 Mutations in Major Cellular Signaling Pathway

The major signaling pathways embracing the cells towards division, differentiation and survival through EGFR regulation are Ras-Mitogen activated protein kinase and PI3K-Akt pathways [30]. The deregulation of EGFR has been noticed in most of tumors types, primarily that includes non-small cell lung cancer (NSCLC) [31]. The over expression of EGFR i.e. 62% in squamous cell carcinoma and adeno carcinoma subtypes has been observed [32, 33]. The biological pathway of EGFR encompasses many sub pathways and interacting genes. One of the primary oncogenes that is often stimulated through mutations in cancers is KRAS downstream gene that encodes a small binding protein guanosine-5'-triphosphate. Nearly 20% of non-small cell lung cancer tends to have KRAS mutations, especially in smokers and in adenocarcinoma. Both of the genes, KRAS together with BRAF, whose kinase domain has structure identification to EGFR members, are the part of EGFR signaling cascade [34, 35]. Alterations in the oncogenes leads to cancer inclusive of BRAF [27], that stipulates to other standby pathways for cellular differentiation, proliferation and finally death [36]. Based on BRAF mutations which is found in 4% of non-small cell lung cancers [27] over expression of MEK-ERK signaling takes place through linkage of Ras to BRAF along with MEK proteins. While, ERK upon its trigger induces a negative feedback on its activators and thus, inhibits SOS, Ras and Raf among Ras-Raf-MEK-ERK signaling cascade [36, 37]. Primarily in non-small cell lung cancers, mutated replacement of thymine residue with adenine residue at 1799th nucleotide position takes place among 90% of BRAF mutations [38–42]. Oncogenic BRAF mediated over expression of Ras-Raf signaling is found in various malignancies [43–46]. Thus, imposes BRAF as one of the therapeutic targets [44, 47, 48].

2.3.1 Mutations in EGFR Signaling Pathway

Epidermal growth factor and transforming growth factor-alpha link to and phosphorylates the epidermal growth factor receptor or its family member ERBB2, to resultantly activate PKC [49] Followed up by receptor initialization, it forms a specific site of docking for adaptor protein Grb2 and PLC-gamma through its SH2 domain [50–54]. Hydrolyzation of PIP2 to integrate the essential messengers inclusive of 1,4,5-triphosphate (IP3) and diacylglycerol (DAG) takes place upon enrollment of PLC-gamma at endoplasmic reticulum where attachment of IP3 to its receptor impels the release of calcium. This calcium together with DAG derives the expression of protein kinase C (PKC) [51]. PKC interconnects with Raf protein through phosphatidic acid (PA), synthesized by hydrolyzation of phosphatidylcholine through phospholipase D (PLD) that is one of the notable substrates of PKC [55]. Thus, upregulates cellular proliferation [56]. Along with that EGFR stimulation also prompts SOS, which further activates Ras by exchanging its GDP to GTP [57] along with Raf and PI3K. Triggered Raf then directly phosphorylates MEK and its only substrate ERK1/2 successively [58–60] Resultantly, two signaling cascades gets initiated as in Ras-MAPK and PI3K-Akt [61–65] causing cellular proliferation along with quibbled angiogenesis. Moreover, cellular growth and multiplication is triggered upon binding of KRAS to BRAF in mutated forms. Small mutations arise in EGFR family member ERBB2 in NSCLC [66].

2.3.2 EGFR Mediated Activation of PI3K-Akt Pathway

The propensity of Ras to be able to additionally stimulate signaling cascades like PI3K is among one of the reasons indicating Ras mediated mutations are among 30% of root cause of cancerous genetic modifications [67]. Through ligand mediated dimerization with family members of ERBB, consistent activation of EGFR is achieved by its transmutations [68, 69]. This leads to long-term cellular proliferation, causing downstream biological activities including cell growth, migration along with repression of apoptosis [59, 70–72], Transcription as well as translation attributed induction of CDK4/6-cyclin D1 complex by the cytoplasmic and nuclear targets of ERK1-ERK2 liaise the cellular proliferation. Downstream signaling cascade of PI3K could also be triggered by phosphorylated Ras [73–75]. Cyclin D1 upon its trigger enhances the expression of CDK4-6 which as a result phosphorylates RB. It is noteworthy that this complex of

CDK4/6-Cyclin D1 undergoes suppression by CDKN2A along with p21 genes. Followed by RB phosphorylation, it releases transcription factor of E2F that transcribes cyclin E and initiates progression of G1-S cell cycle to pass the restriction point (R) [76–78]. From above all besides EGFR, EGF upon its stimulation, sharply regulates PI3K pathway as well [79]. Activating mutations among members of EGFR, PI3K-Akt along with repressed tumor suppressor gene PTEN leads to overly activated PI3K-Akt-mTOR signaling pathway. PI3K possess a catalytic domain which enables phosphorylation of membrane bound phosphatidylinositol-4,5-bisphosphate (PIP2) that further evokes phosphatidylinositol-3,4,5-triphosphate (PIP3) [80–82]. PIP3 forwards the lipid kinase-based activity to recruit downstream Akt-PKB which gets triggered upon phosphorylation by PDK1. Akt performs its role of anti-apoptosis by prompting negatively phosphorylation of the proteins that may repress cyclin D1 expression. Thus, upon three proteins, Akt imposes negative phosphorylation inclusive of Bcl2-associated death (BAD) promoter, inhibition of Caspase-9 catalytic activity by phosphorylation and along with that suppresses FOXO1 activity through negative phosphorylation [83].

2.3.3 PI3K-Akt/m-TOR Pathway

Signaling of mammalian target of rapamycin m-TOR comprises key feature in Akt signaling cascade. Primarily through the Ras and PI3K mediated growth factors along with glucose and accessibility of oxygen, mTOR accrues the activating signals [84]. TSC1 and TSC2 are the cardinal suppressors of m-TOR, specifically m-TORC1 gets repressed by TSC2. Both inhibitors subdue Ras like GTPase RHEB that is essentially required for m-TORC1 regulation [85]. Through phosphorylation, Akt along with ERK1-ERK2 signaling cascade coincide to actuate mTORC1 by quelling TSC2, leading to cellular development and composition of proteins [86]. Oncogenesis based on genetic modifications in EGFR signaling cascade is often accompanied with long term proliferation caused by highly triggered levels of cyclin-D expression [87–92].

2.3.4 p53 Signaling Pathway and Its Down Regulation

The central gatekeeper that shields against genetic irregularity and malformation is the p53 gene. That responds to injury to DNA, induction of oncogenes and low oxygen concentration termed as hypoxia as the exhaust signals and derives cellular proliferation as an

aftereffect. It mediates downstream and upstream selected signaling genes upon recognizing strain signals encompassing normal cell death along with restoring of damaged DNA, G1-G2 arrest of cell cycle as downstream and CDKN2A or p14ARF as upstream functional genes [93]. Among many cancer-causing incentives namely DNA impairment, Ras and E2F1 cause CDKN2A upstream regulation, which subjugate MDM2 protein and thus, induces p53 expression, which further triggers gene expression including induction of its suppressor MDM2 protein along with CDKN1A that resultantly mitigates CDK4/6-Cyclin D1 complex. On other hand, downstream targeted proteins comprise of apoptotic proteins within mitochondria likewise, Bcl2 associated X antiapoptotic protein that gets triggered and its antagonist BAK that is proapoptotic protein, gets suppressed by p53 protein [94]. Consistent repression of these two proteins leads to mitochondrial along with death sensory receptors activated apoptosis. Escalated proliferation, metastasis and angiogenesis with antiapoptotic mechanisms have been manifested through PI3K-Akt signaling cascade which is liaised by its entities incorporating FOXO, BAD protein, glycogen synthase kinase 3 (GSK3) protein along with mammalian target of rapamycin 1 (mTORC1). The above pathway collaborates with guardian of genome and tumor repressor protein p53 by various mechanisms. Akt interposes phosphorylation of murine double minute (MDM2) and thereby, its activation ubiquitinates the p53 protein [95]. The resultant suppression of p53 has been embroiled as in the development and advancement of tumor in most of the cancers encompassing genetic modifications in PI3K-Akt pathway upstream proteins noteworthy Ras and EGFR [96, 97].

2.3.5 Down Regulation of RASSF1 Tumor Suppressor Protein

Ras effector namely Ras-associated domain family RASSF1A in a controlled manner blocks the cell cycle along with apoptosis by acting as tumor suppressor proteins. Communicating through NORE1A, RASSF1, mutated KRAS modulates apoptosis and cellular proliferation [98, 99]. Apoptotic attribute of Ras is interposed by its another effector NORE1A-MST1 complex. RASSF1A and its homologue NORE1A, which detects Ras conciliated apoptotic signals, affix with cyclin-D1 and proapoptotic kinase MST1 in a defined manner at C-terminal binding site of RASSF1 [100, 101]. While, Ras incited apoptosis gets terminated because of incapacity of MST1 to bind with is effector proteins [101, 102].

2.3.6 EML4-ALK Mediated Mutations

Nearly 7% of NSCLC cases are ascribed to periodic genetic integration of echinoderm microtubule associated protein like 4 (EML4) with fusion partners like anaplastic lymphoma kinase (ALK) [103, 104]. As an aftereffect, triggered ALK serves its role of inducing the Ras protein [16]. In this regard, EML4-ALK supports the histologic perspective of adenocarcinoma among never smokers through negative alliance with KRAS and EGFR genetic modifications. In NSCLS, EML4-ALK fusion oncogenic protein is marked as one of the significant genetic modifications [105]. A diverse range of downstream signaling cascades are triggered by tyrosine kinase EML4-ALK integration and EGFR mutations, notedly including Jak-Stat, MEK-ERK1/2-MAPK or PI3K-Akt through which it communicates the cellular mechanisms [106, 107], that as an end product it incites proliferation within the cells along with subdued apoptosis [108]. In lung adenocarcinoma models, Ras protein commands the MAPK signaling in effect of downstream EML4-ALK conciliated manner to procure tumor development and endurance [109].Proliferation, growth and vitality of the cells is retained by phosphorylation and instigation of STAT3 by Jak3 which is interposed by EML4-LK [110]. By means of its SH2 domain, PLC-gamma collaborates with ALK affixed with EML4. Now genetic modifications among these fused proteins further signifies the transmuted capabilities of ALK unit proteins [111].

2.4 Computational Modeling of EGFR Pathway Based on Brown Model Scheme

Now based on above experimental data Section :2.3.1, 2.3.2, a model for EGFR intervened ERK1-ERK2 signaling cascade was developed which encompassed cancer-based attributes as in RAS, BRAF and EGFR mutations along with upregulation.

The initial computational model, downloaded from Bio Models [112], of the above signaling cascade is based on [113] work that assigned figures and values to model parameters through experimental data. It enrolled 13 proteins with 16 biological reactions as in the SOS, Ras-Raf1 leading to ERK trigger along with SOS and Akt negative feedbacks upon this pathway[114].

2.4.1 New Computational Modeling of EGFR-ERK, PI3K/Akt Pathway

In the continuation of previous model, the new computation model encompassed 17 proteins required for 31 reactions[114].

2.4.2 Mathematical Modeling of Mitochondrial Signaling of Apoptosis Pathway

One dimensional linear pathway has been further continued by systems modeling approach using ordinary differential equations to highlight physiological stress induced signaling of apoptosis control. Phosphorylation of BAD protein mediates tumor instigating ability of stress. For qualitative analysis, various formal mathematical models of apoptosis mechanism have been proposed. At present, mitochondrial signaling of apoptosis has been enlightened under the light of mathematical modeling to develop therapeutic strategies [115]. Below represents formal modeling of strain induced anti-apoptotic pathway based on above experimental data.

2.4.3 Computational Modeling of p53 Regulatory Pathway

The complete p53 network has been simulated in computational mathematical modeling based on standard fourth order Runge-Kutta technique of numerical integration using 18 molecular entities with 35 reaction channels Section : 2.3.4. To understand the systems dynamics, the long established deterministic non-linear differential equation developed from above reactions was interpreted using numerical integration [116]. Figure 5 shows p53-MDM2 network's formal computational model.

2.5 Aim and Objectives

The key objectives of the present study are:

• Construction of Biological Automata Network of the abstracted pathway of non-small cell lung cancer in the Ginsim software.

• Modeling of the NSCLC pathway in PINT tool as Automata Network.

• Computation of the stable states of the complex pathway of NSCLC.

• Computation and analysis of the cut sets obtained from the dynamics of the NSCLC pathway.

• Analysis of the Reachability state graph.

• Identification of potential biomarkers from extensive pathway of NSCLC.

• Identification of Drug targets for therapeutic interventions.

• Reduction of the extensive model for further implementations.

Chapter 3

Methodology

3.1 Answer Set Programing

Answer set programing is an analytical high-level computational programing-based language that yields solution to the problems only based on designation of the computational rationale of the program without any specification of precise strategy to be followed. In this regard, the elaborated illustration of the problem, its related impediments along with other input data and optimization scheme is ciphered in the form of logical rules, referred to as answer set programing. The logical commands are then epitomized by ASP grounder such as grounder gringo and deciphered by an ASP solver as solver clasp. Both gringo as well as clasp are parts of Potsdam Answer Set Solving Collection, Potassco. Being proficient in deriving all optimal solutions to the problem, ASP adequately considers the complete search space. The methodology is having been completely executed and signifies its quantifiability and accuracy. The suitability of this approach with its standard results has already been enlightened through numerous case studies in contrast to other state of the art heuristic methods. With emerging role of synthetic biology for therapeutic practice of diagnostics and treatment, designing of gene circuits that selectively target the cells with so called circuits delivered in the body by either plasmids or viral vectors, serves to be reliable enough in identifying the cell's state within the body [117, 118]. In the work of Mohammadi and colleagues, ASP has been executed as classifier design in context of Boolean function that used micro-RNA profile as input having two distinct versions that as an output provides cellular state encoded with paired healthy or cancerous states. To make the classifier design as biolog-

ically applicable, they composed and satisfied the curtailments inclusive of the heuristic search space for exploration of optimal designs [119, 120]. While, over all search for the global optimal solutions is not undertaken by heuristic procedures implying that it is not ensured whether the ideal solutions are not surpassed. ASP has been exploited vigorously in solving constraints problems with accuracy in terms of classification of errors along with circuit simplicity in terms of number of inputs and gates used [121]. Secondly, Answer Set programing has been implemented to apprehend the effects of genetic alteration on signaling cascade of insulin model. At instances where signal transduction assays are laborious to execute, using qualitative logic-based theoretical perspective of the problem, the exploring potential of ASP could be effectuated to comprehend the complex signaling pathways along with their molecular perturbations. Thus, traversing the vent between the ground facts of biological signaling pathways, their genetic modifications with their resultant phenotypes to grasp a deep understanding of scientific mechanisms [122]. Similarly signaling pathway of Sulphur deprivation feedback in Arabidopsis thaliana [123] along with cellular cycle within yeast have been modeled through action language of ASP. Later, further extended their above ASP frameworks to Boolean networks and deduced that ASP provides pliability in terms of constituting the underlying assumptions and other knowledge along with that has adaptability of software while exhibiting exceptional cases within the ASP framework [124]. Lately ASP has been utilized in the establishment of one of the python libraries namely BioASP which is an assembled online program that enables quick fix for exploring and interpreting scientific biological models, powered by ASP tools of Potsdam Answer Set Solving Collection (Potassco) along with PyASP library that makes the easy availability and usage of this power of ASP. The general flowchart for application of ASP and its components for tackling complex combinatorial problems is shown in Figure 3.1.

BioASP allows compatibility of empirical data with their signaling pathways and may propose alternative pathway links that enhance the alliance between experimental data and the resultant pathway. BioASP gets applicable with the functionality of ASP, the Sign Consistency Model (SCM) that is enrolled by cytoscape plugged-in BioQuali [125].

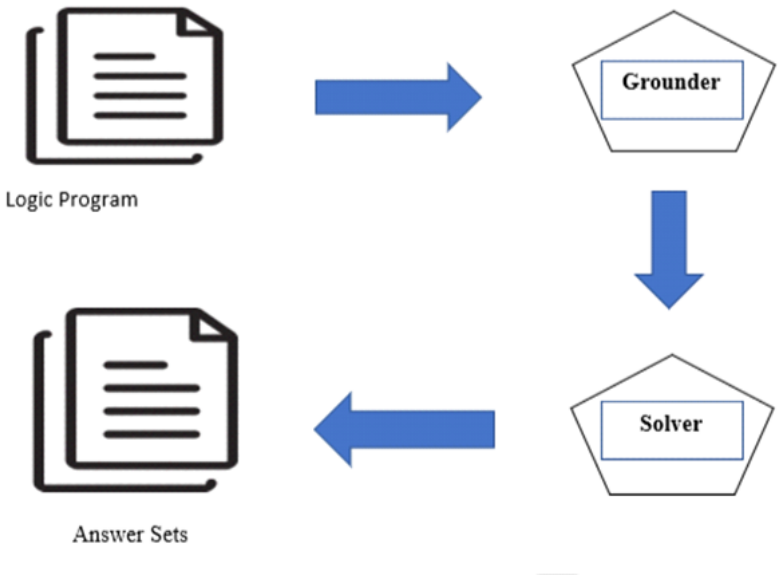

Figure 3.1: General Scheme for solving process [1]. Considering the specified logical program, the required commands are encoded within the ASP component grounder namely gringo. It is then subjected to the solver component that brings forth the solution in the form of Answer sets for the given combinatorial problem

3.2 Process Hitting

One of the conventional configurations for modeling the parallel regulatory systems constituting biological entities as RNA, proteins or genes etc. is Biological Regulatory Networks (BRNs) that usher constitutive analytical tools for complex irrational systems but appear with definite instinctive suppositions and other impediments. By traversing along the present models, we can utilize their primacy and broaden the horizon for analysis of immense and comprehensive systems of gene regulatory networks [126–128]. Here we fabricate just alike linkage amid Process Hitting [129] that is one of the latterly pioneered discrete configuration. It tackles the dilemma of scalability and masters the emanate of state-space overflow and intractability as faced by most of the present customary model- checking approaches for large interlinked regulatory systems [130], by exhibiting static analysis approach through abstract inference and definite restriction on the causality of actions in a finite-state system [131]. Process Hitting permits interpretation of BRNs with discrete values where at any one selected instance only one process is taken as a contemporary state of individual component inferred as a sort. Now a process gets altered by a sort just as is hit by at the most one further process [129]. Owing to its

capacity of being implemented to less definite complex systems and its assessment based on abstract analysis, the static analysis at the first place has been established within the framework of Process Hitting that is worthy upon the identification of disease states of Process Hitting dynamics [132]. While, this cannot be absolutely constituted by Rene Thomas' formalism by one illustration of Biological Regulatory Networks described with parameters. Henceforth, this framework can productively undertake the well-built complex Biological Regulatory Systems inclusive of evolution of G1-S phase of cell cycle switched by ERBB receptor activation having twenty entities [133]. On the other hand, the system comprising of forty entities in T-cell receptor model, produced from literature [134], have all been modeled under the parasol of Process Hitting framework. It is remarkable that the intricacy of the method is exponential in cardinal number of regulators of single entity and is rectilinear in the figure of components [135].

3.3 Pint

The software Pint affable at http://loicpauleve.name/ pint, is steadfast to the evaluation of trajectories within very extensive Boolean, asynchronous and multiplex biological systems. One of the most suitable frameworks for bioinformatics tools is the Jupyter notebook that has the aptitude of being applicable to perplexed computational biological networks [133, 135, 136]. Pint appears with Python module pypint that elicit an impeccable integration with Jupyter notebook that is a menu-driven web interface which enables to effortlessly reclaim, procreate and contribute workings of model perusal and other manipulation of biological systems to assuage the model's management and summons to Pint [137]. Its central attribute is its validation upon the presence of a trajectory extending out to the concerned state along with discerning of recurrent points among all those trajectories cardinal to that significant state specified as the cut sets and the legitimate prognosis of mutations impeding the outstretch of any path of states to that significant state [138]. Based on abstract elucidation and causality of trajectories, Pint enables static explication of the traces within the biological systems. In either case, the yielded findings have the capacity of fulfilling the requisites for adequate and necessary constraints [139].

3.3.1 Directed Graph

According to graph theory, directed graph is a tuple of two elements comprising of D (V, E) where V labels a set of elements termed as vertices or nodes and the term E allots organized pairs of vertices designated as directed arcs or directed edges. Directed graph is also delineated as digraph where an edge is certainly directed from one node to the other node with D - (x) and D+ (x) is taken as antecedent and descendent nodes concerning a particular node [140].

3.3.2 Automata Networks

"An automata network is defined by a tuple (Îč, S,L, T) where;
Îč is the finite set of automata identifiers.
S is the finite set of global states.
L is the finite set of transition labels.
T is the mapping from automata to their finite set of local transitions[141]."
Automata network is a discrete definable-state model of collaborating components that are extensively administered for qualitative modeling of discrete, Boolean systems [142–145] implying further synchronous or allochronic transitions guided by the state of other automata within biological signaling systems. At any instance, the individual automaton exists in merely one local state thus, forming global state of the system by congregating the local states of formulated automata [141]. In this regard here, the automata network of three entities is taken into account whereby each entity is referred to as single automata that is interconnected with others through transitions within the complex system.

3.3.3 Graph of Local Causality

The graph of local causality enables elucidation of distinct complex regulatory models by abstracting the dynamical restraints and thus casts the underlying basis of static analysis that is one of the major attributes of Process Hitting framework. It averts high-priced classification of the prospective candidates and seeks tractability on substantially complex systems [141]. There are well assorted structures of Graph of Local Causality that primarily build upon the semantics of the definite system. It characterizes the

local states whose initial incidence is imperative to the reachability of notable local state within an automata network that is traced by causality links between objectives to resolve that reachability [137], as shown below in Figure 3.2

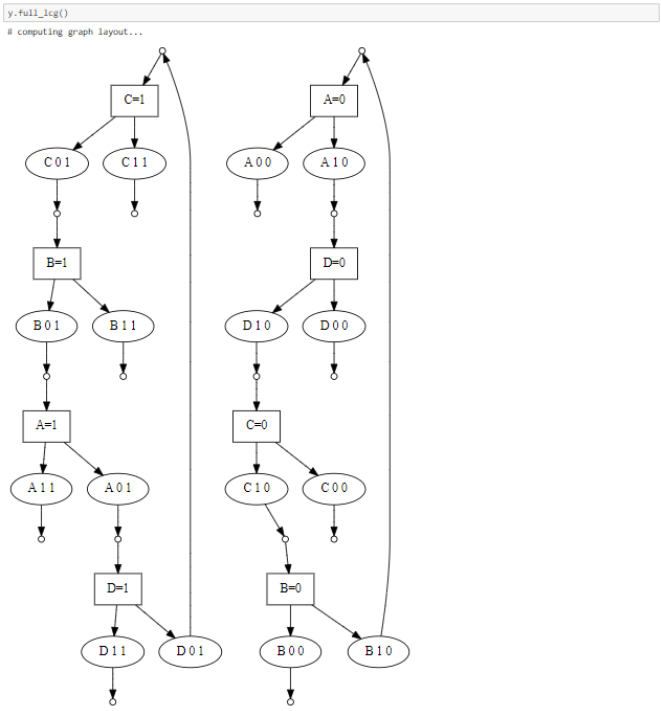

Figure 3.2: Local Causality Graph represents the definite sets of interactions of the states required in the level prior to the occurrence of the concerned state. Based on the understanding of the local causality, the reachability towards the state of interest requires the occurrence of interactions of the other states within the biological automata network

3.3.4 Dependency Graph

Dependency Graph renders a directed graph that is obtained by the aggregation of all the local states and their trajectories within a biological system that can undergo further amendments along with can be manifested on the Jupyter notebook. In this regard, activation of all the arcs within a dependency graph is a prerequisite to permit a node to process, whose dependencies are perhaps Boolean function of other vertices in the automata network [129]. Here the trajectory from entity A to B designates that any single path of B is resultant from the state of entity A as depicted below in Figure 3.3

```
y.dependency_graph()
# computing graph layout...
```

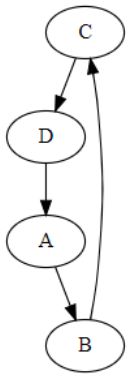

Figure 3.3: Dependency graph of 4 Automata enlightens the leaning of each vertex in terms of its interaction on to other vertices. It indicates how the state C depends on the trajectories of other states B, A and D within the automata network of these entities.

3.3.5 Fix Points

Within the confines o f P rocess H itting s ubstructure, s tatic a nalysis s o f ar h as been performed primarily for procuring the complete checklist of stable states of Process Hitting dynamics, assigning value to each vertex of the network [129]. Owing to the applicability of Process Hitting to non-specific B oolean d ynamical b iological systems, by exercising more elucidated interaction graph and its evaluation allows the provision of the disease states [146] that are locked in all viable dynamics and have no further outreach trajectories passing through them. The derivation of **fix points** for the automata network encompassing 4 entities A, B, C and D after implementation of static analysis through Pint software has been enlightened in the Figure 3.4.

```
fps = y.fixpoints()
import pandas as pd # for pretty display of fixpoints
pd.DataFrame(fps)
```

	A	B	C	D
0	0	0	0	0
1	1	1	1	1

Figure 3.4: Fixpoint Analysis refers to the list of all those entities that have been upregulated in a constant manner thus, causing the occurrence of the disease. The upregulation of the expression levels of A,B,C and D entities within their automata network represents their deviation from the homeostatic balance resulting in the abnormal condition.

3.3.6 Mutations

Formal substantiation and effectual static analysis enforced by the software Pint indicates exhaustive evaluation over conjugated biological automata networks that allows strict reasoning for temporal attributes namely reachability towards definite state along with abstraction of sets of variations that fortify evasion of the fixpoint. By intercepting the occurrence of goal, the provided catalogue of mutations obstructs any transient trigger of the vertex and thus, limits the passage of any trajectory towards disease state or stable state [146]. Inference of list of entities that undergo alteration in their expression levels in the form of mutations and whose as it is implementation impedes the reachability towards the stable state is represented in the Figure 3.5.

```
y.oneshot_mutations_for_cut("B=1")
```

This computation is an *under-approximation*: returned mutations are all valid, but they may be non-minimal, and some solutions may be missed.

Limiting solutions to mutations of at most 5 automata. Use `maxsize` argument to change.

```
[{'A': 0}, {'D': 0}]
```

Figure 3.5: Mutations Analysis represents the alteration of the expression level of the specified entities that steer towards the fix point occurrence. Declining the expression levels of entity, A and D to 0 directly hinders the reachability towards the disease state

3.3.7 Bifurcations

Pint employs static enlightenment of those trajectories within Boolean multiplex networks following which the goal defined as stable state is no further obtainable. Bifurcation transitions are distinctly pertinent to comprehend which states and their concerned routes are exhibiting major contribution towards the diseased state [147]. Generation of bifurcation in the expropriate entity undoubtedly obstructs the reachability of the concerned state [139]. The Figure 3.6 refers to the derivation of alternative trajectories in the form of bifurcations for the states that are involved in the path leading towards stable state.

3.3.8 Cut sets

The current technique involving Pint usage allows formal consideration over huge scale networks encompassing colossal number of entities with two local states either 0 or 1 being Boolean in nature. After static reachability speculation, Pint comes up with the

```
y.bifurcations("B=1")
```

This computation is an *under-approximation*: returned transitions are all bifurcation transitions, but some may have been missed. Use `method="exact"` for complete identification.

```
["D" 1 -> 0" when "C"=0", "A" 1 -> 0" when "D"=0"]
```

Figure 3.6: Bifurcations refers to opting the path of states other than those that leads to the disease state occurrence. Digressing the pathway from D and A by making expression level of C as 0 and D as 0 respectively, provides another path that leads away from the diseased states path.

listing of cut sets applied on the transitions that are generally interpreted upon the interacting graph as set of nodes whose projection is significant in order to reach the concerned state as stable state or disease state from some initial global state in a finite biological automata network. Now, impeding all the local states from that list within the model and then execute model analysis whether concerned reachability is still correct. In case if not, then the definite cut set gets verified in terms of its function of hindering the reachability towards goal [139]. Computation of list of entities in the cut sets function for the automata network of 4 entities as in A, B, C and D, whose knockdown obstructs the reachability towards fix point, has been shown in the Figure 3.7.

```
y.cutsets("B=1",maxsize=45)
```

This computation is an *under-approximation*: returned cut-sets are all valid, but they may be non-minimal, and some cut-sets may be missed.

Limiting results to cut-sets with at most 45 elements. Use `maxsize` argument to change.

```
[{'A': 1}, {'D': 1}]
```

Figure 3.7: Cut sets Analysis marks down all those states whose prior occurrence with upregulated expression levels leads towards the diseased condition. Direct knock down or removal of the paths encompassing the enlisted entities as A and D with expression levels 1 will resultantly impede the path towards the stable state.

3.3.9 Reachable State Graph

The software Pint through its execution of static evaluation enables a distinct reachable state graph assessment from a definite set of initial states in the model. It must be understood that such sort of perspective is bounded in terms of extensibility. Hence, from an initial state, it indicates the reachability towards all possible states in the given complex model of NSCLC. The state graph for the automata network of A, B, C and D entities representing the reachability based on the causality of states has been shown in the Figure 3.8

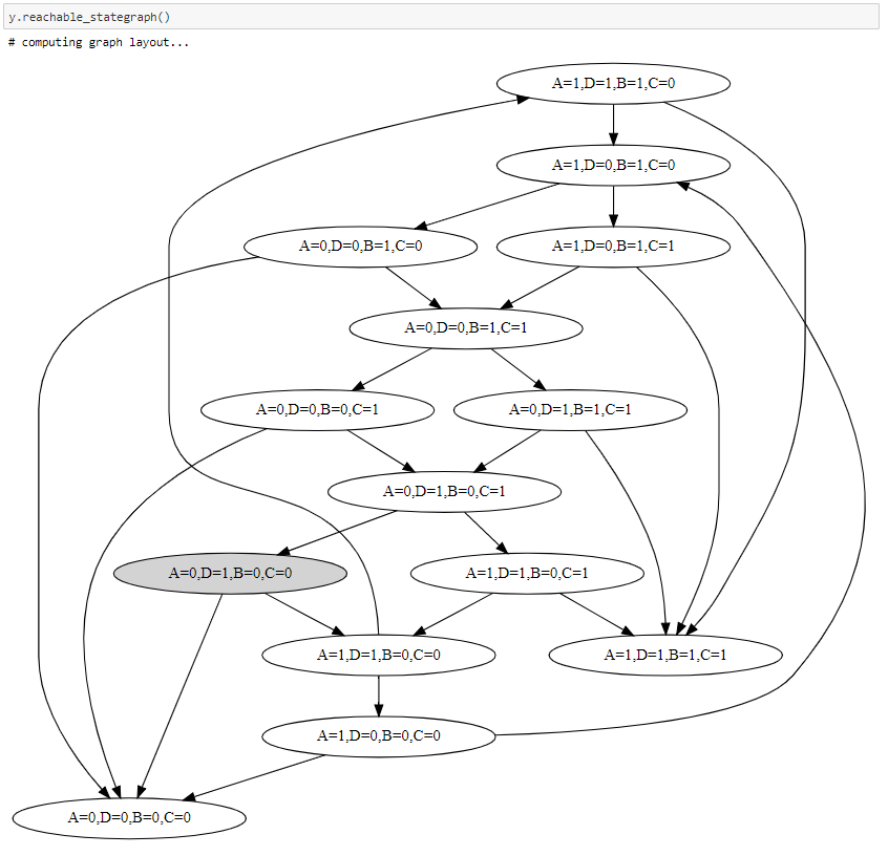

Figure 3.8: Reachability state graph analysis revolves around the Biological Regulatory Network here encompassing the entities A,B,C and D. The nodes indicate the entities or the states with edges mention the change of one state to the other through their transitions in between. The particular state having the upregulated expression level of all entities of BRN as A=1,B=1,C=1,D=1 enlightens the incident of diseased state.

3.3.10 Model Reduction

The software Pint enables detection of part of trajectories that no longer serves role in the minimal paths towards reaching the stable state. Depending on the static analysis, the entities of the identified cut sets are eliminated from the biological automata network through Pint's attribute of model reduction. This results in exterminating their transitions along with all those traces as well which do not contribute to the minimal path of stable state. The reduced biological system is dynamically contracted enhancing its tractability and further applicability [148]. Figure 3.9 refers to the derivation of reduced model after removal of states enlisted in the cut sets function along with elimination of all those entities and their transitions that either no longer play role in reaching towards

disease state.

```
y = y.having(A=1).reduce_for_goal("A=1,B=1,C=1,D=1")
#y.save_as("newfil6.an")
```

gen/colomotoa3k4b0jp.an

Figure 3.9: Model Reduction encompasses the removal of the particular states and their transitions that no longer contribute towards the reachability to the disease state. The list of cut sets provided entities are also removed in order to impede the reachability towards the fix point. The reduced model can further be implemented for the biological applications.

Chapter 4

Results and Discussion

4.1 Results

Non-small cell lung cancer well known as NSCLC is one of the catastrophic diseases with indigent prognosis. Oncogenic alterations of the genes have led to the onset of resistance to the available treatment of lung cancer. But, advancements in the molecular targeted therapy depends on thorough understanding and learning of basic mechanism of the lung cancer. Recently, various computational techniques have been employed to decode the complex biological system in less time and cost-effective manner.

4.1.1 Construction of BRN of NSCLC

Primarily, the complete Biological Regulatory Network of non-small cell lung cancer is constructed on the software Ginsim. Besides individual interactions, complete cartesian products of all sets of interactions among all the states within the NSCLC pathway was defined, Below represents the constructed Biological Automata Network for NSCLC pathway on the software Ginsim with defined inhibitory and upregulated interactions as shown in the Figure 4.1.

4.1.2 Inference of Interaction Parameters

In order to construct a qualitative model of NSCLC, logical interaction parameters in the form of AND/OR rule were defined on the basis of in-depth literature regarding NSCLC pathway. the parameters are given in Table 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9,

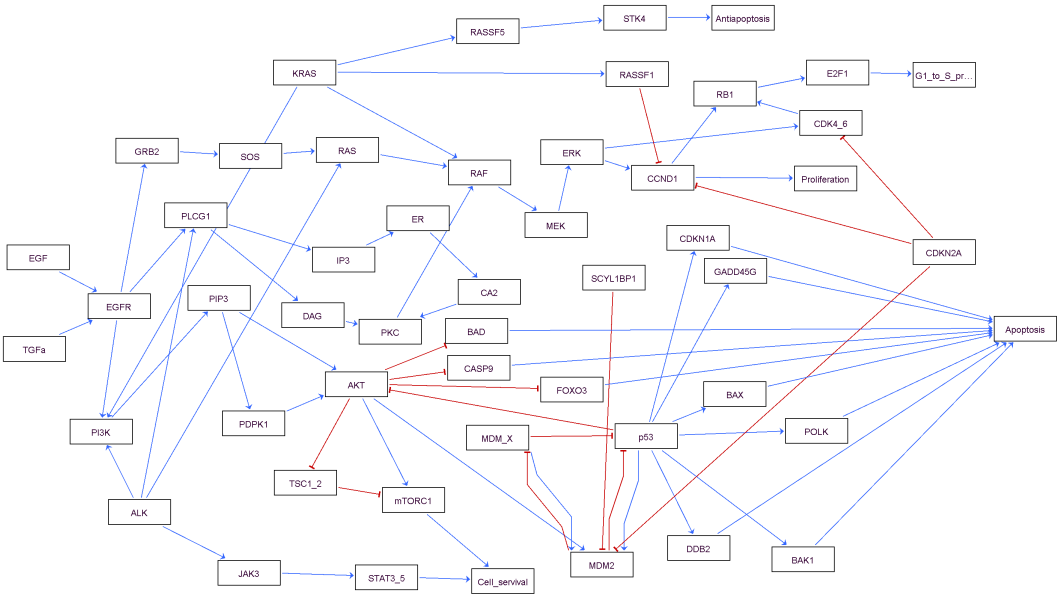

Figure 4.1: Biological Automata Network of NSCLC Pathway fabricated on Ginsim software. The pathway revolves around 49 nodes that have the entities of the complex pathway. These 49 nodes tend to have trajectories interconnecting one node to other through vertex. In depth literature review enabled the evaluation of parameters that defines the interactions over all within the biological network of NSCLC.

4.10, 4.11, 4.12, 4.13, 4.14, 4.15, 4.16, 4.17, 4.18, 4.19, 4.20.

4.1.3 Stable State (Fix point Analysis) for Mutated NSCLC pathway

The software Pint under the parasol of Process Hitting framework exercises an effectual abstract-based analysis and can undertake NSCLC such complex integrated systems. In the prevailing research, various novel Biomarkers have been unearthed based on the identified stable state or disease state followed by the tractability of Pint over complex automata networks. The intellectual Biomarkers are displayed in Figure 4.2, 4.3.

A crystal-clear differentiation has been observed in the functional attributes of a normal biological system of NSCLC to the genetically altered disease pathway of NSCLC. This could be viewed from the stable state below generated in case of non-mutated NSCLC pathway where normal functional attributes have been elucidated.

Stable state in case of Mutated NSCLC Pathway:	
Upregulated	AKT, CA2, CCND1, CDK4_6, TGFa, DAG, E2F1, EGF, EGFR, ER, ERK, G1_to_S_progression, GRB2, IP3, JAK3, KRAS, MDM_X, Proliferation, ALK, MEK, PDk1, PI3K, PIP3, PKC, PLCG1, Antiapoptosis, RAS, RAF, RASSF5, RB1, SCYL1BP1, SOS, STAT3_5, STK4, Cell_survival, mTORC1,
Downregulated	BAD, BAK1, BAX, CASP9, CDKN1A, CDKN2A, DDB2, FOXO3, GADD45G, MDM2, POLK, RASSF1, TSC1_2, p53, Apoptosis

Figure 4.2: Represents the stable state generated d in cased of the Mutated NSCLC pathway, resulted by the static analysis extensively carried out over the complete pathway of NSCLC by the Pint software within the Process Hitting framework. Pathways encompassing states that are disease triggering entities are upregulated and overly expressed on the basis of mutations that over all derive the NSCLC pathway

Stable state in case of non- mutated Pathway:	
Upregulated	BAD, BAK1, BAX, CASP9, CCND1 CDKN1A, DDB2, EGF, EGFR, ERK, FOXO3, GADD45G, GRB2, MDM_X, MEK, PKC, PLCG1, POLK, RAS, RAF, RASSF5, SCYL1BP1, SOS, STK4, p53, Apoptosis
Downregulated	AKT, CA2, CDK4_6, CDKN2A, TGFa, DAG, E2F1, ER, G1_to_S_progression, IP3, JAK3, KRAS, MDM2, Proliferation, ALK, PDk1, PI3K, PIP3, Antiapoptosis, RASSF1, RB1, STAT3_5, Cell_survival, TSC1_2 mTORC1,

Figure 4.3: Enlightens the impact of absence of mutations on NSCLC pathway. The preconditioned mutations in the entities as in EGFR, KRAS, EML4-ALK, p53 genes leads towards the diseased state. Their normal regulations steer the pathway towards less fatal state.

4.1.4 Mutations and Bifurcations Evaluation

Supplication of mutations functions enabled the modified expression level of mutated entities during disease that could as it is impede the reachability towards fixpoint. Mutations had been applied on the following entities; cell survival, Antiapoptosis, G1 to S progression attributes as shown in Figure 4.4, 4.5, 4.6, 4.7. In addition to that no defi-

nite bifurcation transitions appearing with those trajectories that have the potential to alter the path from disease state to normal homeostatic functioning could be elucidated. Since at different cellular levels, the mutations halt the normal function towards disease state.

```
y.oneshot_mutations_for_cut("Cell_servival = 1")
```

This computation is an *under-approximation*: returned mutations are all valid, but they may be non-minimal, and some solutions may be missed.

Limiting solutions to mutations of at most 5 automata. Use `maxsize` argument to change.

```
[{'PI3K': 0, 'STAT3_5': 0},
 {'ALK': 0, 'PI3K': 0},
 {'JAK3': 0, 'PI3K': 0},
 {'AKT': 0, 'STAT3_5': 0},
 {'PIP3': 0, 'STAT3_5': 0},
 {'STAT3_5': 0, 'mTORC1': 0},
 {'STAT3_5': 0, 'TSC1_2': 1},
 {'AKT': 0, 'ALK': 0},
 {'ALK': 0, 'PIP3': 0},
 {'ALK': 0, 'mTORC1': 0},
 {'ALK': 0, 'TSC1_2': 1},
 {'AKT': 0, 'JAK3': 0},
 {'JAK3': 0, 'PIP3': 0},
 {'JAK3': 0, 'mTORC1': 0},
 {'JAK3': 0, 'TSC1_2': 1},
 {'ALK': 0, 'EGFR': 0, 'KRAS': 0},
 {'ALK': 0, 'EFG': 0, 'KRAS': 0, 'TGFa': 0}]
```

Figure 4.4: Cell survival

```
y.oneshot_mutations_for_cut("Antiapoptosis = 1")
```

This computation is an *under-approximation*: returned mutations are all valid, but they may be non-minimal, and some solutions may be missed.

Limiting solutions to mutations of at most 5 automata. Use `maxsize` argument to change.

```
[{'RASSF5': 0}, {'STK4': 0}, {'KRAS': 0}]
```

Figure 4.5: Antiapoptosis

```
y.oneshot_mutations_for_cut("Proliferation = 1")
```

This computation is an *under-approximation*: returned mutations are all valid, but they may be non-minimal, and some solutions may be missed.

Limiting solutions to mutations of at most 5 automata. Use `maxsize` argument to change.

```
[{'CCND1': 0},
 {'RAF': 0},
 {'MEK': 0},
 {'ERK': 0},
 {'CDKN2A': 1},
 {'RASSF1': 1},
 {'KRAS': 0, 'PLCG1': 0, 'RAS': 0},
 {'KRAS': 0, 'PKC': 0, 'RAS': 0},
 {'IP3': 0, 'KRAS': 0, 'RAS': 0},
 {'DAG': 0, 'KRAS': 0, 'RAS': 0},
 {'ER': 0, 'KRAS': 0, 'RAS': 0},
 {'CA2': 0, 'KRAS': 0, 'RAS': 0},
 {'ALK': 0, 'EGFR': 0, 'KRAS': 0},
 {'ALK': 0, 'GRB2': 0, 'KRAS': 0, 'PLCG1': 0},
 {'ALK': 0, 'GRB2': 0, 'KRAS': 0, 'PKC': 0},
 {'ALK': 0, 'GRB2': 0, 'IP3': 0, 'KRAS': 0},
 {'ALK': 0, 'DAG': 0, 'GRB2': 0, 'KRAS': 0},
 {'ALK': 0, 'ER': 0, 'GRB2': 0, 'KRAS': 0},
 {'ALK': 0, 'CA2': 0, 'GRB2': 0, 'KRAS': 0},
 {'ALK': 0, 'KRAS': 0, 'PLCG1': 0, 'SOS': 0},
 {'ALK': 0, 'KRAS': 0, 'PKC': 0, 'SOS': 0},
 {'ALK': 0, 'IP3': 0, 'KRAS': 0, 'SOS': 0},
 {'ALK': 0, 'DAG': 0, 'KRAS': 0, 'SOS': 0},
 {'ALK': 0, 'ER': 0, 'KRAS': 0, 'SOS': 0},
 {'ALK': 0, 'CA2': 0, 'KRAS': 0, 'SOS': 0},
 {'ALK': 0, 'EFG': 0, 'KRAS': 0, 'TGFa': 0}]
```

Figure 4.6: Proliferation

```
y.oneshot_mutations_for_cut("G1_to_S_progression = 1")
```

This computation is an *under-approximation*: returned mutations are all valid, but they may be non-minimal, and some solutions may be missed.

Limiting solutions to mutations of at most 5 automata. Use `maxsize` argument to change.

```
[{'CCND1': 0},
 {'RAF': 0},
 {'MEK': 0},
 {'ERK': 0},
 {'E2F1': 0},
 {'RB1': 0},
 {'CDK4_6': 0},
 {'CDKN2A': 1},
 {'RASSF1': 1},
 {'KRAS': 0, 'PLCG1': 0, 'RAS': 0},
 {'KRAS': 0, 'PKC': 0, 'RAS': 0},
 {'IP3': 0, 'KRAS': 0, 'RAS': 0},
 {'DAG': 0, 'KRAS': 0, 'RAS': 0},
 {'ER': 0, 'KRAS': 0, 'RAS': 0},
 {'CA2': 0, 'KRAS': 0, 'RAS': 0},
 {'ALK': 0, 'EGFR': 0, 'KRAS': 0},
 {'ALK': 0, 'GRB2': 0, 'KRAS': 0, 'PLCG1': 0},
 {'ALK': 0, 'GRB2': 0, 'KRAS': 0, 'PKC': 0},
 {'ALK': 0, 'GRB2': 0, 'IP3': 0, 'KRAS': 0},
 {'ALK': 0, 'DAG': 0, 'GRB2': 0, 'KRAS': 0},
 {'ALK': 0, 'ER': 0, 'GRB2': 0, 'KRAS': 0},
 {'ALK': 0, 'CA2': 0, 'GRB2': 0, 'KRAS': 0},
 {'ALK': 0, 'KRAS': 0, 'PLCG1': 0, 'SOS': 0},
 {'ALK': 0, 'KRAS': 0, 'PKC': 0, 'SOS': 0},
 {'ALK': 0, 'IP3': 0, 'KRAS': 0, 'SOS': 0},
 {'ALK': 0, 'DAG': 0, 'KRAS': 0, 'SOS': 0},
 {'ALK': 0, 'ER': 0, 'KRAS': 0, 'SOS': 0},
 {'ALK': 0, 'CA2': 0, 'KRAS': 0, 'SOS': 0},
 {'ALK': 0, 'EFG': 0, 'KRAS': 0, 'TGFa': 0}]
```

Figure 4.7: G1 to S progression

4.1.5 Identification of Drug Targets

The remarkable software also enabled us with listing of potential drug targets that is the basis of therapeutic therapies. The phenomenal list of Drug targets is inclusive of 4.8, 4.9, 4.10, 4.11.

```
y.cutsets("Cell_servival = 1",maxsize=45)
```

This computation is an *under-approximation*: returned cut-sets are all valid, but they may be non-minimal, and some cut-sets may be missed.

Limiting results to cut-sets with at most 45 elements. Use `maxsize` argument to change.

```
[{'PI3K': 1, 'STAT3_5': 1},
 {'ALK': 1, 'PI3K': 1},
 {'JAK3': 1, 'PI3K': 1},
 {'STAT3_5': [0, 1]},
 {'ALK': 1, 'STAT3_5': 0},
 {'JAK3': 1, 'STAT3_5': 0},
 {'AKT': 1, 'STAT3_5': 1},
 {'PIP3': 1, 'STAT3_5': 1},
 {'STAT3_5': 1, 'mTORC1': 1},
 {'STAT3_5': 1, 'TSC1_2': 0},
 {'AKT': 1, 'ALK': 1},
 {'ALK': 1, 'PIP3': 1},
 {'ALK': 1, 'mTORC1': 1},
 {'ALK': 1, 'TSC1_2': 0},
 {'AKT': 1, 'JAK3': 1},
 {'JAK3': 1, 'PIP3': 1},
 {'JAK3': 1, 'mTORC1': 1},
 {'JAK3': 1, 'TSC1_2': 0},
 {'EGFR': [0, 1], 'STAT3_5': 1},
 {'ALK': 1, 'EGFR': [0, 1]},
 {'EGFR': [0, 1], 'JAK3': 1},
 {'ALK': [0, 1], 'EGFR': 1},
 {'ALK': 1, 'EGFR': 1, 'KRAS': 1},
 {'PDPk1': [0, 1], 'STAT3_5': 1},
 {'ALK': 1, 'PDPk1': [0, 1]},
 {'JAK3': 1, 'PDPk1': [0, 1]},
 {'EFG': [0, 1], 'EGFR': 0, 'STAT3_5': 1},
 {'ALK': 1, 'EFG': [0, 1], 'EGFR': 0},
 {'EFG': [0, 1], 'EGFR': 0, 'JAK3': 1},
 {'ALK': [0, 1], 'EFG': [0, 1]},
 {'ALK': 1, 'EFG': [0, 1], 'KRAS': 1},
 {'EFG': 1, 'EGFR': 0, 'STAT3_5': 1, 'TGFa': 1},
 {'ALK': 1, 'EFG': 1, 'EGFR': 0, 'TGFa': 1},
 {'EFG': 1, 'EGFR': 0, 'JAK3': 1, 'TGFa': 1},
 {'ALK': [0, 1], 'EFG': 1, 'TGFa': 1},
 {'ALK': 1, 'EFG': 1, 'KRAS': 1, 'TGFa': 1}]
```

Figure 4.8: Cell survival

```
y.cutsets("Antiapoptosis = 1")
```

This computation is an *under-approximation*: returned cut-sets are all valid, but they may be non-minimal, and some cut-sets may be missed.

Limiting results to cut-sets with at most 45 elements. Use `maxsize` argument to change.

```
[{'RASSF5': 1}, {'STK4': 1}, {'KRAS': 1}]
```

Figure 4.9: Antiapoptosis

```
y.cutsets("Proliferation = 1",maxsize=45)
```

This computation is an *under-approximation*: returned cut-sets are all valid, but they may be non-minimal, and some cut-sets may be missed.

Limiting results to cut-sets with at most 45 elements. Use `maxsize` argument to change.

```
[{'CCND1': 1},
 {'RAF': 1},
 {'MEK': 1},
 {'ERK': 1},
 {'CDKN2A': 0},
 {'RASSF1': 0},
 {'RAS': [0, 1]},
 {'GRB2': 1, 'RAS': 0, 'SOS': 0},
 {'ALK': 1, 'GRB2': 1, 'RAS': 0},
 {'RAS': 0, 'SOS': [0, 1]},
 {'EGFR': 1, 'RAS': 0, 'SOS': 0},
 {'ALK': 1, 'RAS': 0, 'SOS': 1},
 {'ALK': 1, 'EGFR': 1, 'RAS': 0},
 {'PKC': 0, 'PLCG1': 1, 'RAS': 1},
 {'KRAS': 1, 'PLCG1': 1, 'RAS': 1},
 {'PKC': [0, 1], 'RAS': 1},
 {'IP3': 1, 'PKC': 0, 'RAS': 1},
 {'DAG': 1, 'PKC': 0, 'RAS': 1},
 {'ER': 1, 'PKC': 0, 'RAS': 1},
 {'CA2': 1, 'PKC': 0, 'RAS': 1},
 {'KRAS': 1, 'PKC': 1, 'RAS': 1},
 {'IP3': 1, 'KRAS': 1, 'RAS': 1},
 {'DAG': 1, 'KRAS': 1, 'RAS': 1},
 {'ER': 1, 'KRAS': 1, 'RAS': 1},
 {'CA2': 1, 'KRAS': 1, 'RAS': 1},
 {'ALK': 1, 'EGFR': 1, 'PKC': 0},
 {'ALK': 1, 'EGFR': 1, 'KRAS': 1},
 {'GRB2': 1, 'PKC': 0, 'PLCG1': 1, 'SOS': 0},
 {'GRB2': 1, 'KRAS': 1, 'PLCG1': 1, 'SOS': 0},
 {'GRB2': 1, 'PKC': [0, 1], 'SOS': 0},
 {'GRB2': 1, 'IP3': 1, 'PKC': 0, 'SOS': 0},
 {'DAG': 1, 'GRB2': 1, 'PKC': 0, 'SOS': 0},
 {'ER': 1, 'GRB2': 1, 'PKC': 0, 'SOS': 0},
 {'CA2': 1, 'GRB2': 1, 'PKC': 0, 'SOS': 0},
 {'GRB2': 1, 'KRAS': 1, 'PKC': 1, 'SOS': 0},
 {'GRB2': 1, 'IP3': 1, 'KRAS': 1, 'SOS': 0},
 {'DAG': 1, 'GRB2': 1, 'KRAS': 1, 'SOS': 0},
 {'ER': 1, 'GRB2': 1, 'KRAS': 1, 'SOS': 0},
 {'CA2': 1, 'GRB2': 1, 'KRAS': 1, 'SOS': 0},
 {'ALK': 1, 'GRB2': 1, 'PKC': 0, 'PLCG1': 1},
```

Figure 4.10: Proliferation

```
y.cutsets("G1_to_S_progression = 1",maxsize=45)
```

This computation is an *under-approximation*: returned cut-sets are all valid, but they may be non-minimal, and some cut-sets may be missed.

Limiting results to cut-sets with at most 45 elements. Use `maxsize` argument to change.

```
[{'CCND1': 1},
 {'RAF': 1},
 {'MEK': 1},
 {'ERK': 1},
 {'E2F1': 1},
 {'RB1': 1},
 {'CDK4_6': 1},
 {'CDKN2A': 0},
 {'RASSF1': 0},
 {'RAS': [0, 1]},
 {'GRB2': 1, 'RAS': 0, 'SOS': 0},
 {'ALK': 1, 'GRB2': 1, 'RAS': 0},
 {'RAS': 0, 'SOS': [0, 1]},
 {'EGFR': 1, 'RAS': 0, 'SOS': 0},
 {'ALK': 1, 'RAS': 0, 'SOS': 1},
 {'ALK': 1, 'EGFR': 1, 'RAS': 0},
 {'PKC': 0, 'PLCG1': 1, 'RAS': 1},
 {'KRAS': 1, 'PLCG1': 1, 'RAS': 1},
 {'PKC': [0, 1], 'RAS': 1},
 {'IP3': 1, 'PKC': 0, 'RAS': 1},
 {'DAG': 1, 'PKC': 0, 'RAS': 1},
 {'ER': 1, 'PKC': 0, 'RAS': 1},
 {'CA2': 1, 'PKC': 0, 'RAS': 1},
 {'KRAS': 1, 'PKC': 1, 'RAS': 1},
 {'IP3': 1, 'KRAS': 1, 'RAS': 1},
 {'DAG': 1, 'KRAS': 1, 'RAS': 1},
 {'ER': 1, 'KRAS': 1, 'RAS': 1},
 {'CA2': 1, 'KRAS': 1, 'RAS': 1},
 {'ALK': 1, 'EGFR': 1, 'PKC': 0},
 {'ALK': 1, 'EGFR': 1, 'KRAS': 1},
 {'GRB2': 1, 'PKC': 0, 'PLCG1': 1, 'SOS': 0},
 {'GRB2': 1, 'KRAS': 1, 'PLCG1': 1, 'SOS': 0},
 {'GRB2': 1, 'PKC': [0, 1], 'SOS': 0},
 {'GRB2': 1, 'IP3': 1, 'PKC': 0, 'SOS': 0},
 {'DAG': 1, 'GRB2': 1, 'PKC': 0, 'SOS': 0},
 {'ER': 1, 'GRB2': 1, 'PKC': 0, 'SOS': 0},
 {'CA2': 1, 'GRB2': 1, 'PKC': 0, 'SOS': 0},
 {'GRB2': 1, 'KRAS': 1, 'PKC': 1, 'SOS': 0},
 {'GRB2': 1, 'IP3': 1, 'KRAS': 1, 'SOS': 0},
 {'DAG': 1, 'GRB2': 1, 'KRAS': 1, 'SOS': 0},
```

Figure 4.11: G1 to S progression

Chosen cutsets are given in Table 4.1

S•No	Drug Targets
1	ALK = 1
2	mTORC1 = 1
3	STK4 = 1
4	CCND1 = 1
5	E2F1 = 1

Table 4.1: Drug Targets

According to this catalogue of cut sets, the complex model of NSCLC was reduced with the removal of cut set provided entities transitions. The final reduced model tends to have limited dynamics thus enhancing its appositeness along with its tractability in terms of computational systems biology.

4.2 Discussion

Lethal diseases like non-small cell lung cancer is often marked with onset of sudden mutations and thus, has poor prognostication. The detection of disease in the early stages is crucial for effective treatment courses as well as its better ramification. The enlightened Biomarkers along with the drug targets could be further processed to the wet lab experimental validation. But, the present up to the mark software Pint allows us to visualize how cut down of the specified entities effectually hinders the passage towards disease state or the stable state. Not only the results of this software are cost effective and time saving, it aims being tractable to further complex biological systems that are too difficult to visualize and understand through wet lab experiments.

4.3 Conclusion

NSCLC is considered to be one of the lethal diseases that has growing number of cases due to ill practices of smoke, cigarette and other pollution causing agents. Due to the impediments of foregoing computational techniques, the complete dynamics of this extensive pathway could not be studied well previously. The remarkable Process Hitting

framework with software Pint contributes in this regard by providing a vast range of list of Biomarkers to mark down the presence of disease. Besides that, the novel drug targets designated by the results of the Pint software accords with a sound therapeutic strategy to combat the disease.

Automata Network File in Pint Format
"Apoptosis" 1 -> 0" when "POLK"=0 and "CASP9"=1 and "CDKN1A"=0 and "DDB2"=1 and "BAD"=1 and "GADD45G"=0"
"Apoptosis" 0 -> 1" when "DDB2"=1 and "POLK"=1 and "BAX"=0 and "BAK1"=0 and "FOXO3"=0 and "CASP9"=0 and "BAD"=1 and "GADD45G"=0"
"RB1" 1 -> 0" when "CDK4_6"=0 and "CCND1"=1"
"Apoptosis" 1 -> 0" when "CDKN1A"=0 and "DDB2"=1 and "POLK"=0 and "BAX"=1 and "BAK1"=1 and "FOXO3"=0 and "CASP9"=0 and "BAD"=0 and "GADD45G"=1"
"RAF" 0 -> 1" when "KRAS"=1 and "RAS"=0 and "PKC"=0"
"Apoptosis" 1 -> 0" when "CDKN1A"=0 and "DDB2"=1 and "POLK"=1 and "BAX"=1 and "BAK1"=1 and "FOXO3"=0 and "CASP9"=0 and "BAD"=0 and "GADD45G"=0"
"Apoptosis" 0 -> 1" when "CDKN1A"=0 and "POLK"=1 and "BAX"=0 and "BAK1"=0 and "FOXO3"=1 and "CASP9"=0 and "BAD"=0 and "GADD45G"=1"
"RAS" 0 -> 1" when "ALK"=1 and "SOS"=0"
"Apoptosis" 1 -> 0" when "GADD45G"=0 and "FOXO3"=1 and "CASP9"=1 and "CDKN1A"=0 and "POLK"=1"
"PLCG1" 0 -> 1" when "EGFR"=1"
"Apoptosis" 0 -> 1" when "CDKN1A"=0 and "DDB2"=1 and "POLK"=0 and "BAX"=0 and "BAK1"=0 and "FOXO3"=1 and "CASP9"=0 and "BAD"=0 and "GADD45G"=1"

Table 4.2: Automata Network File in Pint Format (Parameters 1)

Automata Network File in Pint Format
"PLCG1" 0 -> 1" when "ALK"=1 and "EGFR"=0"
"Apoptosis" 1 -> 0" when "CDKN1A"=0 and "DDB2"=1 and "POLK"=0 and "BAX"=1 and "FOXO3"=0 and "CASP9"=0 and "BAD"=1 and "GADD45G"=1"
"MEK" 1 -> 0" when "RAF"=0"
"PKC" 1 -> 0" when "DAG"=0"
"Apoptosis" 0 -> 1" when "CDKN1A"=0 and "DDB2"=1 and "POLK"=0 and "BAX"=0 and "FOXO3"=0 and "CASP9"=0 and "BAD"=1 and "GADD45G"=0"
"Apoptosis" 1 -> 0" when "CDKN1A"=0 and "DDB2"=1 and "POLK"=0 and "BAX"=1 and "BAK1"=1 and "FOXO3"=0 and "CASP9"=0 and "BAD"=1 and "GADD45G"=0"
"Cell_servival" 0 -> 1" when "STAT3_5"=0 and "mTORC1"=1"
"CDK4_6" 1 -> 0" when "ERK"=0"
"PIP3" 1 -> 0" when "PI3K"=0"
"Apoptosis" 0 -> 1" when "DDB2"=0 and "POLK"=1 and "BAX"=1 and "BAK1"=0 and "FOXO3"=0 and "CASP9"=1 and "BAD"=0 and "GADD45G"=0"
"Apoptosis" 0 -> 1" when "CDKN1A"=1 and "DDB2"=1 and "POLK"=1 and "BAX"=1 and "BAK1"=1 and "FOXO3"=1 and "CASP9"=1 and "BAD"=1 and "GADD45G"=1"
"Apoptosis" 0 -> 1" when "FOXO3"=0 and "CASP9"=0 and "CDKN1A"=0 and "DDB2"=1 and "POLK"=0 and "BAD"=0 and "GADD45G"=0"
"Apoptosis" 0 -> 1" when "CDKN1A"=0 and "POLK"=1 and "BAX"=0 and "BAK1"=0 and "FOXO3"=0 and "CASP9"=1 and "BAD"=0 and "GADD45G"=1"
"Apoptosis" 0 -> 1" when "CDKN1A"=0 and "DDB2"=1 and "POLK"=1 and "BAX"=0 and "FOXO3"=0 and "CASP9"=0 and "BAD"=0 and "GADD45G"=0"

Table 4.3: Automata Network File in Pint Format (Parameters 2)

Automata Network File in Pint Format
"Apoptosis" 1 -> 0" when "FOXO3"=0 and "CASP9"=1 and "BAD"=1 and "CDKN1A"=1"
"Apoptosis" 1 -> 0" when "CDKN1A"=1 and "DDB2"=0 and "POLK"=0 and "BAK1"=1 and "FOXO3"=0 and "CASP9"=1 and "BAD"=0 and "GADD45G"=0"
"Apoptosis" 0 -> 1" when "DDB2"=1 and "POLK"=1 and "BAX"=0 and "BAK1"=0 and "FOXO3"=1 and "CASP9"=0 and "BAD"=0 and "GADD45G"=0"
"ER" 1 -> 0" when "IP3"=0"
"Apoptosis" 1 -> 0" when "FOXO3"=1 and "CDKN1A"=0 and "DDB2"=1 and "POLK"=0 and "BAD"=1 and "GADD45G"=0"
"RAF" 1 -> 0" when "KRAS"=0 and "RAS"=0 and "PKC"=0"
"EFG" 0 -> 1""
"G1_to_S_progression" 0 -> 1" when "E2F1"=1"
"Apoptosis" 1 -> 0" when "CDKN1A"=0 and "DDB2"=0 and "POLK"=0 and "BAX"=1 and "FOXO3"=1 and "CASP9"=1 and "BAD"=0 and "GADD45G"=0"
"Apoptosis" 0 -> 1" when "CDKN1A"=1 and "DDB2"=1 and "BAX"=0 and "BAK1"=0 and "FOXO3"=0 and "CASP9"=1 and "BAD"=0 and "GADD45G"=0"
"Apoptosis" 1 -> 0" when "CDKN1A"=0 and "DDB2"=1 and "POLK"=0 and "BAX"=0 and "BAK1"=0 and "FOXO3"=1 and "CASP9"=1 and "BAD"=1 and "GADD45G"=1"
"mTORC1" 1 -> 0" when "AKT"=0"
"Cell_servival" 0 -> 1" when "STAT3_5"=1"
"Apoptosis" 0 -> 1" when "FOXO3"=0 and "CASP9"=0 and "CDKN1A"=0 and "DDB2"=0 and "POLK"=0 and "BAD"=1 and "GADD45G"=0"
"Apoptosis" 1 -> 0" when "CDKN1A"=0 and "DDB2"=0 and "POLK"=0 and "BAX"=1 and "FOXO3"=0 and "CASP9"=1 and "BAD"=1 and "GADD45G"=0"

Table 4.4: Automata Network File in Pint Format (Parameters 3)

Automata Network File in Pint Format
"Apoptosis" 1 -> 0" when "CDKN1A"=1 and "DDB2"=1 and "POLK"=1 and "BAX"=0 and "BAK1"=1 and "FOXO3"=0 and "BAD"=0 and "GADD45G"=0"
"BAD" 1 -> 0" when "AKT"=1"
"EGFR" 0 -> 1" when "EFG"=1"
"RAF" 0 -> 1" when "RAS"=0 and "PKC"=1"
"BAK1" 1 -> 0" when "p53"=0"
"BAK1" 0 -> 1" when "p53"=1"
"Apoptosis" 1 -> 0" when "CDKN1A"=1 and "DDB2"=1 and "POLK"=0 and "BAX"=1 and "FOXO3"=0 and "CASP9"=0 and "BAD"=0 and "GADD45G"=1"
"Apoptosis" 1 -> 0" when "CDKN1A"=1 and "DDB2"=1 and "POLK"=1 and "BAX"=0 and "FOXO3"=1 and "CASP9"=1 and "BAD"=1 and "GADD45G"=1"
"Apoptosis" 1 -> 0" when "FOXO3"=0 and "CASP9"=1 and "CDKN1A"=1 and "DDB2"=1 and "BAD"=0 and "GADD45G"=0 and "BAX"=1"
"AKT" 1 -> 0" when "PDPk1"=0 and "PIP3"=0"
"Apoptosis" 1 -> 0" when "FOXO3"=1 and "CASP9"=0 and "CDKN1A"=1 and "DDB2"=1 and "BAD"=0 and "GADD45G"=1"
"PI3K" 0 -> 1" when "ALK"=0 and "KRAS"=1 and "EGFR"=0"
"Apoptosis" 0 -> 1" when "CDKN1A"=0 and "DDB2"=1 and "POLK"=0 and "BAX"=0 and "BAK1"=0 and "FOXO3"=0 and "CASP9"=0 and "BAD"=1 and "GADD45G"=1"
"Apoptosis" 0 -> 1" when "CDKN1A"=1 and "DDB2"=0 and "POLK"=0 and "BAK1"=0 and "FOXO3"=1 and "CASP9"=0 and "BAD"=0 and "GADD45G"=0"
"Apoptosis" 1 -> 0" when "CDKN1A"=1 and "DDB2"=1 and "POLK"=1 and "BAX"=1 and "BAK1"=0 and "FOXO3"=0 and "CASP9"=0 and "BAD"=0 and "GADD45G"=0"

Table 4.5: Automata Network File in Pint Format (Parameters 4)

Automata Network File in Pint Format
"Apoptosis" 0 -> 1" when "CDKN1A"=0 and "DDB2"=1 and "POLK"=0 and "BAX"=1 and "BAK1"=0 and "FOXO3"=1 and "CASP9"=0 and "BAD"=0 and "GADD45G"=0"
"Apoptosis" 0 -> 1" when "FOXO3"=0 and "CASP9"=0 and "DDB2"=0 and "POLK"=1mand "BAD"=0 and "GADD45G"=0"
"Apoptosis" 1 -> 0" when "FOXO3"=1 and "CASP9"=1 and "CDKN1A"=0 and "DDB2"=1 and "POLK"=0 and "GADD45G"=0"
"Apoptosis" 1 -> 0" when "CDKN1A"=0 and "POLK"=1 and "BAX"=0 and "BAK1"=1 and "FOXO3"=0 and "CASP9"=0 and "BAD"=1 and "GADD45G"=1"
"STK4" 0 -> 1" when "RASSF5"=1"
"MDM_X" 0 -> 1" when "MDM2"=0"
"Apoptosis" 1 -> 0" when "CDKN1A"=1 and "DDB2"=0 and "POLK"=1 and "BAX"=0 and "BAK1"=0 and "FOXO3"=1 and "CASP9"=1 and "BAD"=1 and "GADD45G"=1"
"Apoptosis" 0 -> 1" when "CDKN1A"=1 and "DDB2"=0 and "BAX"=0 and "BAK1"=0 and "FOXO3"=0 and "CASP9"=0 and "BAD"=1 and "GADD45G"=1"
"Apoptosis" 1 -> 0" when "FOXO3"=1 and "CASP9"=1 and "CDKN1A"=1 and "POLK"=0 and "BAD"=1 and "GADD45G"=1"
"Apoptosis" 1 -> 0" when "CDKN1A"=1 and "DDB2"=0 and "POLK"=1 and "BAX"=1 and "FOXO3"=1 and "CASP9"=1 and "BAD"=1 and "GADD45G"=1"
"Apoptosis" 0 -> 1" when "FOXO3"=0 and "CASP9"=0 and "CDKN1A"=1 and "POLK"=0 and "BAD"=0 and "GADD45G"=0"
"Apoptosis" 1 -> 0" when "FOXO3"=0 and "CASP9"=0 and "CDKN1A"=1 and "DDB2"=1 and "BAD"=1 and "GADD45G"=1"
"CCND1" 1 -> 0" when "ERK"=0"
"Proliferation" 0 -> 1" when "CCND1"=1"
"PDPk1" 0 -> 1" when "PIP3"=1"

Table 4.6: Automata Network File in Pint Format (Parameters 5)

Automata Network File in Pint Format
"Apoptosis" 1 -> 0" when "CDKN1A"=1 and "DDB2"=1 and "BAX"=0 and "BAK1"=1 and "FOXO3"=0 and "CASP9"=0 and "BAD"=1 and "GADD45G"=0"
"Apoptosis" 1 -> 0" when "CDKN1A"=1 and "DDB2"=0 and "POLK"=1 and "BAX"=1 and "FOXO3"=0 and "CASP9"=0 and "BAD"=0 and "GADD45G"=1"
"PDPk1" 1 -> 0" when "PIP3"=0"
"Apoptosis" 0 -> 1" when "FOXO3"=0 and "CASP9"=0 and "DDB2"=0 and "POLK"=1 and "BAD"=0 and "GADD45G"=1 and "BAX"=0"
"Apoptosis" 0 -> 1" when "CDKN1A"=1 and "DDB2"=1 and "BAX"=0 and "BAK1"=0 and "FOXO3"=1 and "CASP9"=0 and "BAD"=0 and "GADD45G"=0"
"Apoptosis" 1 -> 0" when "FOXO3"=0 and "CASP9"=1 and "CDKN1A"=1 and "DDB2"=0 and "BAD"=0 and "GADD45G"=1 and "BAX"=1"
"Apoptosis" 0 -> 1" when "CDKN1A"=0 and "DDB2"=1 and "POLK"=0 and "BAX"=0 and "BAK1"=0 and "FOXO3"=0 and "CASP9"=1 and "BAD"=0 and "GADD45G"=1"
"CDK4_6" 1 -> 0" when "CDKN2A"=1 and "ERK"=1"
"CA2" 1 -> 0" when "ER"=0"
"CCND1" 1 -> 0" when "CDKN2A"=1 and "ERK"=1"
"Apoptosis" 1 -> 0" when "FOXO3"=1 and "CASP9"=0 and "BAD"=1 and "CDKN1A"=0 and "GADD45G"=1"
"Apoptosis" 1 -> 0" when "FOXO3"=0 and "CASP9"=1 and "CDKN1A"=1 and "DDB2"=1 and "BAD"=0 and "GADD45G"=1"
"Apoptosis" 0 -> 1" when "CDKN1A"=1 and "DDB2"=0 and "BAX"=0 and "BAK1"=0 and "FOXO3"=0 and "CASP9"=1 and "BAD"=0 and "GADD45G"=1"
"TSC1_2" 1 -> 0" when "AKT"=1"

Table 4.7: Automata Network File in Pint Format (Parameters 6)

Automata Network File in Pint Format
"Apoptosis" 0 -> 1" when "FOXO3"=1 and "CASP9"=0 and "CDKN1A"=0 and "DDB2"=0 and "POLK"=0 and "BAD"=0 and "GADD45G"=0"
"Apoptosis" 1 -> 0" when "CDKN1A"=0 and "DDB2"=0 and "POLK"=0 and "BAX"=1 and "BAK1"=1 and "FOXO3"=1 and "CASP9"=0 and "BAD"=0 and "GADD45G"=1"
"Apoptosis" 0 -> 1" when "CDKN1A"=1 and "DDB2"=1 and "POLK"=1 and "BAX"=0 and "BAK1"=0 and "FOXO3"=0 and "BAD"=0 and "GADD45G"=0"
"E2F1" 0 -> 1" when "RB1"=1"
"Apoptosis" 0 -> 1" when "DDB2"=0 and "POLK"=1 and "BAX"=1 and "BAK1"=0 and "FOXO3"=0 and "CASP9"=0 and "BAD"=1 and "GADD45G"=0"
"Apoptosis" 0 -> 1" when "CDKN1A"=0 and "DDB2"=0 and "POLK"=0 and "BAX"=0 and "FOXO3"=1 and "CASP9"=0 and "BAD"=1 and "GADD45G"=0"
"Apoptosis" 1 -> 0" when "CDKN1A"=0 and "DDB2"=0 and "POLK"=0 and "BAX"=1 and "BAK1"=1 and "FOXO3"=0 and "CASP9"=0 and "BAD"=1 and "GADD45G"=1"
"Apoptosis" 1 -> 0" when "FOXO3"=1 and "CASP9"=1 and "BAD"=0 and "CDKN1A"=0 and "GADD45G"=1"
"Apoptosis" 1 -> 0" when "CDKN1A"=0 and "DDB2"=1 and "POLK"=0 and "BAX"=1 and "FOXO3"=0 and "CASP9"=1 and "BAD"=0 and "GADD45G"=1"
"Apoptosis" 0 -> 1" when "FOXO3"=0 and "CASP9"=1 and "DDB2"=0 and "POLK"=1 and "BAD"=0 and "GADD45G"=0 and "BAX"=0"
"Apoptosis" 1 -> 0" when "CDKN1A"=1 and "DDB2"=0 and "BAX"=0 and "BAK1"=1 and "FOXO3"=1 and "CASP9"=0 and "BAD"=0 and "GADD45G"=1"

Table 4.8: Automata Network File in Pint Format (Parameters 7)

Automata Network File in Pint Format
"MDM2" 0 -> 1" when "CDKN2A"=0 and "p53"=1 and
"AKT"=0 and "SCYL1BP1"=0"
"ALK" 0 -> 1"
"PKC" 1 -> 0" when "DAG"=1 and "CA2"=0"
"Apoptosis" 1 -> 0" when "CDKN1A"=0 and "POLK"=1 and
"BAX"=0 and "BAK1"=1 and "FOXO3"=1 and "CASP9"=0 and
"BAD"=0 and "GADD45G"=1"
"Apoptosis" 1 -> 0" when "CDKN1A"=0 and "DDB2"=1 and
"POLK"=1 and "BAX"=1 and "FOXO3"=0 and "CASP9"=0 and
"BAD"=0 and "GADD45G"=1"
"BAD" 0 -> 1" when "AKT"=0"
"SOS" 0 -> 1" when "GRB2"=1"
"Apoptosis" 1 -> 0" when "FOXO3"=1 and "CASP9"=0 and
"CDKN1A"=1 and "DDB2"=0 and "BAD"=0 and "GADD45G"=1
and "BAX"=1"
"CASP9" 1 -> 0" when "AKT"=1"
"Apoptosis" 0 -> 1" when "FOXO3"=0 and "CASP9"=0 and
"DDB2"=0 and "POLK"=1 and "BAD"=1 and "GADD45G"=0 and
"BAX"=0"
"Apoptosis" 0 -> 1" when "CDKN1A"=0 and "DDB2"=0 and
"POLK"=0 and "BAX"=1 and "BAK1"=0 and "FOXO3"=0 and
"CASP9"=1 and "BAD"=0 and "GADD45G"=1"
"IP3" 0 -> 1" when "PLCG1"=1"
"Apoptosis" 1 -> 0" when "FOXO3"=1 and "CASP9"=0 and
"BAD"=1 and "CDKN1A"=1"
"p53" 1 -> 0""
"Apoptosis" 1 -> 0" when "DDB2"=1 and "POLK"=1 and
"BAX"=0 and "BAK1"=1 and "FOXO3"=1 and "CASP9"=0 and
"BAD"=0 and "GADD45G"=0"
"POLK" 0 -> 1" when "p53"=1"
"ER" 0 -> 1" when "IP3"=1"
"Apoptosis" 0 -> 1" when "CDKN1A"=0 and "POLK"=1 and
"BAX"=0 and "BAK1"=0 and "FOXO3"=0 and "CASP9"=0 and
"BAD"=1 and "GADD45G"=1"

Table 4.9: Automata Network File in Pint Format (Parameters 8)

Automata Network File in Pint Format
"Apoptosis" 1 -> 0" when "FOXO3"=0 and "CASP9"=0 and "DDB2"=1 and "POLK"=1and "BAD"=1 and "GADD45G"=0 and "BAX"=1"
"Apoptosis" 1 -> 0" when "CDKN1A"=0 and "DDB2"=0 and "POLK"=0 and "BAX"=1 and "BAK1"=0 and "FOXO3"=1 and "CASP9"=1 and "BAD"=1 and "GADD45G"=0"
"CDKN1A" 1 -> 0" when "p53"=0"
"Apoptosis" 1 -> 0" when "CDKN1A"=1 and "DDB2"=1 and "POLK"=1 and "BAX"=1 and "BAK1"=0 and "FOXO3"=1 and "CASP9"=1 and "BAD"=1 and "GADD45G"=1"
"CCND1" 1 -> 0" when "RASSF1"=1 and "CDKN2A"=0 and "ERK"=1"
"Apoptosis" 1 -> 0" when "CDKN1A"=0 and "DDB2"=1 and "POLK"=0 and "BAX"=1 and "BAK1"=1 and "FOXO3"=0 and "CASP9"=1 and "BAD"=0 and "GADD45G"=0"
"Apoptosis" 0 -> 1" when "CDKN1A"=1 and "DDB2"=0 and "POLK"=1 and "BAX"=0 and "BAK1"=1 and "FOXO3"=1 and "CASP9"=1 and "BAD"=1 and "GADD45G"=1"
"Apoptosis" 0 -> 1" when "CDKN1A"=0 and "DDB2"=0 and "POLK"=0 and "BAX"=0 and "BAK1"=1 and "FOXO3"=0 and "CASP9"=0 and "BAD"=0 and "GADD45G"=0"
"GADD45G" 1 -> 0" when "p53"=0"
"Apoptosis" 0 -> 1" when "CDKN1A"=1 and "DDB2"=1 and "BAX"=0 and "BAK1"=0 and "FOXO3"=0 and "CASP9"=0 and "BAD"=1 and "GADD45G"=0"
"MDM2" 0 -> 1" when "CDKN2A"=0 and "MDM_X"=1 and "p53"=0 and "AKT"=0 and "SCYL1BP1"=0"
"Apoptosis" 0 -> 1" when "CDKN1A"=0 and "DDB2"=1 and "POLK"=0 and "BAX"=1 and "BAK1"=0 and "FOXO3"=0 and "CASP9"=0 and "BAD"=1 and "GADD45G"=0"

Table 4.10: Automata Network File in Pint Format (Parameters 9)

Automata Network File in Pint Format
"Apoptosis" 1 -> 0" when "FOXO3"=0 and "CASP9"=0 and "CDKN1A"=1 and "DDB2"=1 and "POLK"=1 and "BAD"=0 and "GADD45G"=1"
"POLK" 1 -> 0" when "p53"=0"
"MDM2" 1 -> 0" when "MDM_X"=0 and "p53"=0 and "AKT"=0 and "SCYL1BP1"=0"
"Apoptosis" 0 -> 1" when "FOXO3"=0 and "CASP9"=1 and "CDKN1A"=0 and "DDB2"=0 and "POLK"=0 and "BAD"=0 and "GADD45G"=0"
"Cell_servival" 1 -> 0" when "STAT3_5"=0 and "mTORC1"=0"
"FOXO3" 1 -> 0" when "AKT"=1"
"Apoptosis" 0 -> 1" when "CDKN1A"=0 and "DDB2"=1 and "POLK"=1 and "BAX"=0 and "BAK1"=0 and "FOXO3"=0 and "CASP9"=0 and "BAD"=0 and "GADD45G"=1"
"Apoptosis" 1 -> 0" when "CDKN1A"=0 and "POLK"=1 and "BAX"=0 and "BAK1"=1and "FOXO3"=0 and "CASP9"=1 and "BAD"=0 and "GADD45G"=1"
"PI3K" 1 -> 0" when "ALK"=0 and "KRAS"=0 and "EGFR"=0"
"PI3K" 0 -> 1" when "EGFR"=1"
"Apoptosis" 0 -> 1" when "CDKN1A"=1 and "DDB2"=0 and "BAX"=0 and "BAK1"=0 and "FOXO3"=1 and "CASP9"=0 and "BAD"=0 and "GADD45G"=1"
"Apoptosis" 1 -> 0" when "CDKN1A"=1 and "DDB2"=1 and "BAX"=0 and "BAK1"=1 and "FOXO3"=1 and "CASP9"=0 and "BAD"=0 and "GADD45G"=0"
"RAF" 0 -> 1" when "RAS"=1"
"Apoptosis" 0 -> 1" when "CDKN1A"=0 and "DDB2"=0 and "POLK"=0 and "BAX"=1 and "FOXO3"=0 and "CASP9"=0 and "BAD"=0 and "GADD45G"=0"
"RAS" 1 -> 0" when "ALK"=0 and "SOS"=0"

Table 4.11: Automata Network File in Pint Format (Parameters 10)

Automata Network File in Pint Format
"MDM2" 1 -> 0" when "CDKN2A"=1 and "AKT"=1 and "SCYL1BP1"=0"
"Apoptosis" 1 -> 0" when "CDKN1A"=1 and "DDB2"=0 and "BAX"=0 and "BAK1"=1 and "FOXO3"=0 and "CASP9"=0 and "BAD"=1 and "GADD45G"=1"
"Apoptosis" 1 -> 0" when "DDB2"=1 and "POLK"=1 and "BAX"=0 and "BAK1"=1 and "FOXO3"=0 and "CASP9"=0 and "BAD"=1 and "GADD45G"=0"
"DDB2" 0 -> 1" when "p53"=1"
"Apoptosis" 1 -> 0" when "FOXO3"=1 and "CASP9"=0 and "DDB2"=1 and "POLK"=1 and "BAD"=0 and "GADD45G"=0 and "BAX"=1",
"KRAS" 0 -> 1"",
"RB1" 1 -> 0" when "CCND1"=0",
"Apoptosis" 1 -> 0" when "FOXO3"=0 and "CASP9"=0 and "CDKN1A"=0 and "POLK"=1 and "BAD"=1 and "GADD45G"=1 and "BAX"=1"
"Apoptosis" 0 -> 1" when "CDKN1A"=0 and "DDB2"=1 and "POLK"=0 and "BAX"=1 and "BAK1"=0 and "FOXO3"=0 and "CASP9"=1 and "BAD"=0 and "GADD45G"=0"
"E2F1" 1 -> 0" when "RB1"=0"
"Apoptosis" 0 -> 1" when "FOXO3"=0 and "CASP9"=0 and "DDB2"=1 and "POLK"=0 and "BAD"=0 and "GADD45G"=1 and "BAX"=0"
"TSC1_2" 0 -> 1" when "AKT"=0"
"Apoptosis" 0 -> 1" when "CDKN1A"=0 and "DDB2"=0 and "POLK"=1 and "BAX"=1 and "BAK1"=0 and "FOXO3"=0 and "CASP9"=0 and "BAD"=0 and "GADD45G"=1"

Table 4.12: Automata Network File in Pint Format (Parameters 11)

Automata Network File in Pint Format
"Apoptosis" 0 -> 1" when "CDKN1A"=0 and "DDB2"=1 and
"POLK"=1 and "BAX"=1 and "BAK1"=0 and "FOXO3"=0 and
"CASP9"=0 and "BAD"=0 and "GADD45G"=0"
"AKT" 0 -> 1" when "PDPk1"=0 and "PIP3"=1"
"Apoptosis" 1 -> 0" when "CDKN1A"=0 and "DDB2"=1 and
"POLK"=0 and "BAX"=0 and "BAK1"=1 and "FOXO3"=1 and
"CASP9"=0 and "BAD"=0 and "GADD45G"=1"
"CA2" 0 -> 1" when "ER"=1"
"CDKN1A" 0 -> 1" when "p53"=1"
"Apoptosis" 1 -> 0" when "CDKN1A"=0 and "DDB2"=0 and
"POLK"=0 and "BAX"=0 and "BAK1"=0 and "FOXO3"=0 and
"CASP9"=0 and "BAD"=0 and "GADD45G"=0"
"MEK" 0 -> 1" when "RAF"=1"
"MDM2" 0 -> 1" when "CDKN2A"=0 and "AKT"=1 and
"SCYL1BP1"=0"
"Apoptosis" 1 -> 0" when "FOXO3"=0 and "CASP9"=1 and
"BAD"=1 and "CDKN1A"=0 and "GADD45G"=1"
"Apoptosis" 1 -> 0" when "FOXO3"=1 and "CASP9"=0 and
"CDKN1A"=0 and "POLK"=1 and "BAD"=0 and "GADD45G"=1 and
"BAX"=1"
"Apoptosis" 1 -> 0" when "CDKN1A"=0 and "DDB2"=1 and
"POLK"=0 and "BAX"=0 and "BAK1"=1 and "FOXO3"=0 and
"CASP9"=0 and "BAD"=1 and "GADD45G"=1"
"GRB2" 1 -> 0" when "EGFR"=0"
"SCYL1BP1" 0 -> 1""
"CASP9" 0 -> 1" when "AKT"=0"
"MDM2" 1 -> 0" when "CDKN2A"=1 and "MDM_X"=1 and "p53"=0
and "AKT"=0 and "SCYL1BP1"=0"
"Apoptosis" 0 -> 1" when "CDKN1A"=0 and "DDB2"=0 and
"POLK"=0 and "BAX"=1 and "BAK1"=0 and "FOXO3"=1 and
"CASP9"=0 and "BAD"=0 and "GADD45G"=1"

Table 4.13: Automata Network File in Pint Format (Parameters 12)

Automata Network File in Pint Format
"Apoptosis" 0 -> 1" when "CDKN1A"=0 and "DDB2"=1 and "POLK"=0 and "BAX"=1 and "BAK1"=0 and "FOXO3"=1 and "CASP9"=0 and "BAD"=0 and "GADD45G"=0"
"Apoptosis" 0 -> 1" when "FOXO3"=0 and "CASP9"=0 and "DDB2"=0 and "POLK"=1mand "BAD"=0 and "GADD45G"=0"
"Apoptosis" 1 -> 0" when "FOXO3"=1 and "CASP9"=1 and "CDKN1A"=0 and "DDB2"=1 and "POLK"=0 and "GADD45G"=0"
"Apoptosis" 1 -> 0" when "CDKN1A"=0 and "POLK"=1 and "BAX"=0 and "BAK1"=1 and "FOXO3"=0 and "CASP9"=0 and "BAD"=1 and "GADD45G"=1"
"STK4" 0 -> 1" when "RASSF5"=1"
"MDM_X" 0 -> 1" when "MDM2"=0"
"Apoptosis" 1 -> 0" when "CDKN1A"=1 and "DDB2"=0 and "POLK"=1 and "BAX"=0 and "BAK1"=0 and "FOXO3"=1 and "CASP9"=1 and "BAD"=1 and "GADD45G"=1"
"Apoptosis" 0 -> 1" when "CDKN1A"=1 and "DDB2"=0 and "BAX"=0 and "BAK1"=0 and "FOXO3"=0 and "CASP9"=0 and "BAD"=1 and "GADD45G"=1"
"Apoptosis" 1 -> 0" when "FOXO3"=1 and "CASP9"=1 and "CDKN1A"=1 and "POLK"=0 and "BAD"=1 and "GADD45G"=1"
"Apoptosis" 1 -> 0" when "CDKN1A"=1 and "DDB2"=0 and "POLK"=1 and "BAX"=1 and "FOXO3"=1 and "CASP9"=1 and "BAD"=1 and "GADD45G"=1"
"Apoptosis" 0 -> 1" when "FOXO3"=0 and "CASP9"=0 and "CDKN1A"=1 and "POLK"=0 and "BAD"=0 and "GADD45G"=0"
"Apoptosis" 1 -> 0" when "FOXO3"=0 and "CASP9"=0 and "CDKN1A"=1 and "DDB2"=1 and "BAD"=1 and "GADD45G"=1"
"CCND1" 1 -> 0" when "ERK"=0"
"Proliferation" 0 -> 1" when "CCND1"=1"
"PDPk1" 0 -> 1" when "PIP3"=1"

Table 4.14: Automata Network File in Pint Format (Parameters 13)

Automata Network File in Pint Format
"Apoptosis" 0 -> 1" when "DDB2"=1 and "POLK"=1 and
"BAX"=0 and "BAK1"=0 and "FOXO3"=0 and "CASP9"=1 and
"BAD"=0 and "GADD45G"=0"
"CDKN2A" 1 -> 0""
"Apoptosis" 0 -> 1" when "FOXO3"=1 and "CASP9"=0 and
"DDB2"=0 and "POLK"=1 and "BAD"=0 and "GADD45G"=0 and
"BAX"=0"
"Apoptosis" 1 -> 0" when "CDKN1A"=1 and "DDB2"=0 and
"BAX"=0 and "BAK1"=1 and "FOXO3"=0 and "CASP9"=1 and
"BAD"=0 and "STK4" 1 -> 0" when "RASSF5"=0"
"Apoptosis" 0 -> 1" when "CDKN1A"=0 and "DDB2"=0 and
"POLK"=0 and "BAX"=0
"Apoptosis" 1 -> 0" when "DDB2"=0 and "POLK"=1 and
"BAX"=1 and "BAK1"=1 and "FOXO3"=0 and "CASP9"=1 and
"BAD"=0 and "GADD45G"=0"
"Apoptosis" 1 -> 0" when "CDKN1A"=0 and "DDB2"=1 and
"POLK"=1 and "BAX"=0 and "BAK1"=1 and "FOXO3"=0 and
"CASP9"=0 and "BAD"=0 and "GADD45G"=1"
"JAK3" 1 -> 0" when "ALK"=0"
"mTORC1" 1 -> 0" when "TSC1_2"=1 and "AKT"=1"
"Apoptosis" 0 -> 1" when "CDKN1A"=0 and "DDB2"=1 and
"POLK"=0 and "BAX"=1 and "BAK1"=0 and "FOXO3"=0 and
"CASP9"=0 and "BAD"=0 and "GADD45G"=1"
"RAS" 0 -> 1" when "SOS"=1"
"MDM2" 1 -> 0" when "AKT"=0 and "SCYL1BP1"=1"
"RASSF5" 0 -> 1" when "KRAS"=1"
"Apoptosis" 1 -> 0" when "FOXO3"=0 and "CASP9"=1 and
"CDKN1A"=0 and "POLK"=1 and "BAD"=0 and "GADD45G"=1 and
"BAX"=1"

Table 4.15: Automata Network File in Pint Format (Parameters 14)

Automata Network File in Pint Format
"Apoptosis" 1 -> 0" when "FOXO3"=0 and "CASP9"=0 and "CDKN1A"=1 and "DDB2"=1 and "BAD"=1 and "GADD45G"=0 and "BAX"=1"
"Apoptosis" 0 -> 1" when "FOXO3"=0 and "CASP9"=0 and "DDB2"=0 and "POLK"=0 and "BAD"=0 and "GADD45G"=1"
"TSC1_2"=0 and "AKT"=1"
"IP3" 1 -> 0" when "PLCG1"=0"
"MDM2" 1 -> 0" when "CDKN2A"=1 and "p53"=1 and "AKT"=0 and "SCYL1BP1"=0"
"Apoptosis" 0 -> 1" when "CDKN1A"=0 and "DDB2"=1 and "POLK"=0 and "BAX"=0 and "FOXO3"=1 and "CASP9"=0 and "BAD"=0 and "GADD45G"=0"
"MDM_X" 1 -> 0" when "MDM2"=1"
"Apoptosis" 0 -> 1" when "CDKN1A"=0 and "DDB2"=1 and "POLK"=0 and "BAX"=0 and "FOXO3"=0 and "CASP9"=1 and "BAD"=0 and "GADD45G"=0"
"Apoptosis" 0 -> 1" when "DDB2"=0 and "POLK"=1 and "BAX"=1 and "BAK1"=0 and "FOXO3"=1 and "CASP9"=0 and "BAD"=0 and "GADD45G"=0"
"RASSF1" 1 -> 0""
"Apoptosis" 0 -> 1" when "CDKN1A"=0 and "DDB2"=0 and "POLK"=0 and "BAX"=1 and "BAK1"=1 and "FOXO3"=1 and "CASP9"=1 and "BAD"=1 and "GADD45G"=0"
"PI3K" 0 -> 1" when "ALK"=1 and "EGFR"=0"
"Apoptosis" 1 -> 0" when "CDKN1A"=0 and "DDB2"=0 and "POLK"=1 and "BAX"=1 and "BAK1"=1 and "FOXO3"=0 and "CASP9"=0 and "BAD"=0 and "GADD45G"=1"
"Apoptosis" 0 -> 1" when "CDKN1A"=0 and "DDB2"=1 and "POLK"=0 and "BAX"=0 and "BAK1"=1 and "FOXO3"=1 and "CASP9"=1 and "BAD"=1 and "GADD45G"=1"

Table 4.16: Automata Network File in Pint Format (Parameters 15)

Automata Network File in Pint Format
"AKT" 0 -> 1" when "PDPk1"=1"
"Apoptosis" 0 -> 1" when "CDKN1A"=0 and "DDB2"=0 and "POLK"=0 and "BAX"=0 and "FOXO3"=0 and "CASP9"=1 and "BAD"=0 and "GADD45G"=1"
"Apoptosis" 1 -> 0" when "CDKN1A"=0 and "DDB2"=1 and "POLK"=0 and "BAX"=1 and "FOXO3"=1 and "CASP9"=1 and "BAD"=1 and "GADD45G"=1"
"EGFR" 0 -> 1" when "TGFa"=1 and "EFG"=0"
"GADD45G" 0 -> 1" when "p53"=1"
"Apoptosis" 1 -> 0" when "CDKN1A"=0 and "DDB2"=1 and "POLK"=0 and "BAX"=0 and "BAK1"=1 and "FOXO3"=0 and "CASP9"=1 and "BAD"=0 and "GADD45G"=1"
"Apoptosis" 1 -> 0" when "FOXO3"=0 and "CASP9"=0 and "CDKN1A"=1 and "DDB2"=0 and "BAD"=1 and "GADD45G"=1 and "BAX"=1"
"Apoptosis" 1 -> 0" when "CDKN1A"=1 and "DDB2"=1 and "BAX"=0 and "BAK1"=1 and "FOXO3"=0 and "CASP9"=1 and "BAD"=0 and "GADD45G"=0"
"Apoptosis" 1 -> 0" when "FOXO3"=1 and "CASP9"=0 and "CDKN1A"=1 and "DDB2"=1 and "BAD"=0 and "GADD45G"=0 and "BAX"=1"
"PLCG1" 1 -> 0" when "ALK"=0 and "EGFR"=0"
"JAK3" 0 -> 1" when "ALK"=1"
"Apoptosis" 0 -> 1" when "CDKN1A"=1 and "DDB2"=1 and "POLK"=1 and "BAX"=1 and "BAK1"=1 and "FOXO3"=0 and "CASP9"=0 and "BAD"=0 and "GADD45G"=0"
"Apoptosis" 1 -> 0" when "FOXO3"=1 and "CASP9"=1 and "CDKN1A"=0 and "DDB2"=0 and "POLK"=0 and "BAD"=1 and "GADD45G"=1"
"EGFR" 1 -> 0" when "TGFa"=0 and "EFG"=0"

Table 4.17: Automata Network File in Pint Format (Parameters 16)

Automata Network File in Pint Format
"Apoptosis" 1 -> 0" when "GADD45G"=0 and "FOXO3"=1 and "BAD"=1 and "CDKN1A"=0 and "POLK"=1"
"Antiapoptosis" 1 -> 0" when "STK4"=0"
"CCND1" 0 -> 1" when "RASSF1"=0 and "CDKN2A"=0 and "ERK"=1"
"BAX" 1 -> 0" when "p53"=0"
"RB1" 0 -> 1" when "CDK4_6"=1 and "CCND1"=1"
"Apoptosis" 0 -> 1" when "CDKN1A"=1 and "DDB2"=0 and "POLK"=0 and "BAK1"=0 and "FOXO3"=0 and "CASP9"=1 and "BAD"=0 and "GADD45G"=0"
"STAT3_5" 0 -> 1" when "JAK3"=1"
"ERK" 0 -> 1" when "MEK"=1"
"Apoptosis" 1 -> 0" when "DDB2"=1 and "POLK"=1 and "BAX"=0 and "BAK1"=1 and "FOXO3"=0 and "CASP9"=1 and "BAD"=0 and "GADD45G"=0"
"Apoptosis" 1 -> 0" when "DDB2"=0 and "POLK"=1 and "BAX"=1 and "BAK1"=1 and "FOXO3"=0 and "CASP9"=0 and "BAD"=1 and "GADD45G"=0"
"CDK4_6" 0 -> 1" when "CDKN2A"=0 and "ERK"=1"
"Apoptosis" 0 -> 1" when "CDKN1A"=0 and "DDB2"=0 and "POLK"=0 and "BAX"=0 and "BAK1"=0 and "FOXO3"=1 and "CASP9"=1 and "GADD45G"=0"
"Antiapoptosis" 0 -> 1" when "STK4"=1"
"MDM2" 1 -> 0" when "AKT"=1 and "SCYL1BP1"=1"
"Apoptosis" 0 -> 1" when "CDKN1A"=0 and "DDB2"=0 and "POLK"=0 and "BAX"=0 and "FOXO3"=0 and "CASP9"=0 and "BAD"=1 and "GADD45G"=1"
"Apoptosis" 1 -> 0" when "FOXO3"=0 and "CASP9"=1 and "DDB2"=1 and "POLK"=1 and "BAD"=0 and "GADD45G"=0 and "BAX"=1"

Table 4.18: Automata Network File in Pint Format (Parameters 17)

Automata Network File in Pint Format
"PKC" 0 -> 1" when "DAG"=1 and "CA2"=1"
"Proliferation" 1 -> 0" when "CCND1"=0"
"Apoptosis" 1 -> 0" when "CDKN1A"=1 and "DDB2"=0 and
"POLK"=0 and "BAK1"=1and "FOXO3"=0 and "CASP9"=0 and
"BAD"=1 and "GADD45G"=0"
"DDB2" 1 -> 0" when "p53"=0"
"PIP3" 0 -> 1" when "PI3K"=1"
"Apoptosis" 1 -> 0" when "FOXO3"=1 and "CASP9"=1 and
"BAD"=1 and "CDKN1A"=0 and "POLK"=1"
"Apoptosis" 0 -> 1" when "CDKN1A"=1 and "DDB2"=0 and
"POLK"=0 and "BAK1"=0 and "FOXO3"=0 and "CASP9"=0 and
"BAD"=1 and "GADD45G"=0"
"Apoptosis" 1 -> 0" when "DDB2"=0 and "POLK"=1 and
"BAX"=1 and "BAK1"=1 and "FOXO3"=1 and "CASP9"=0 and
"BAD"=0 and "GADD45G"=0"
"Apoptosis" 1 -> 0" when "CDKN1A"=0 and "DDB2"=0 and
"POLK"=0 and "BAX"=0 and "BAK1"=1 and "FOXO3"=1 and
"CASP9"=1 and "GADD45G"=0"
"FOXO3" 0 -> 1" when "AKT"=0"
"Apoptosis" 1 -> 0" when "FOXO3"=1 and "CASP9"=1 and
"BAD"=0 and "CDKN1A"=1
"Apoptosis" 0 -> 1" when "CDKN1A"=0 and "DDB2"=0 and
"POLK"=0 and "BAX"=0 and "FOXO3"=1 and "CASP9"=0 and
"BAD"=0 and "GADD45G"=1"
"TGFa" 0 -> 1""
"DAG" 0 -> 1" when "PLCG1"=1"
"SOS" 1 -> 0" when "GRB2"=0"
"Apoptosis" 1 -> 0" when "CDKN1A"=1 and "DDB2"=0 and
"POLK"=0 and "BAK1"=1 and "FOXO3"=1 and "CASP9"=0 and
"BAD"=0 and "GADD45G"=0"

Table 4.19: Automata Network File in Pint Format (Parameters 18)

Automata Network File in Pint Format
"Apoptosis" 1 -> 0" when "CDKN1A"=0 and "DDB2"=1 and "POLK"=0 and "BAX"=1 and "BAK1"=1 and "FOXO3"=1 and "CASP9"=0 and "BAD"=0 and "GADD45G"=0"
"Apoptosis" 1 -> 0" when "CDKN1A"=0 and "DDB2"=0 and "POLK"=0 and "BAX"=1 and "BAK1"=1 and "FOXO3"=0 and "CASP9"=1 and "BAD"=0 and "GADD45G"=1"
"Apoptosis" 1 -> 0" when "CDKN1A"=0 and "DDB2"=1 and "POLK"=0 and "BAX"=1 and "FOXO3"=1 and "CASP9"=0 and "BAD"=0 and "GADD45G"=1"
"Apoptosis" 1 -> 0" when "FOXO3"=1 and "CASP9"=1 and "BAD"=1 and "CDKN1A"=1 and "GADD45G"=0"
"Apoptosis" 0 -> 1" when "CDKN1A"=0 and "DDB2"=0 and "POLK"=0 and "BAX"=1 and "BAK1"=0 and "FOXO3"=0 and "CASP9"=0 and "BAD"=1 and "GADD45G"=1"
"DAG" 1 -> 0" when "PLCG1"=0"
"STAT3_5" 1 -> 0" when "JAK3"=0"
"Apoptosis" 1 -> 0" when "CDKN1A"=0 and "DDB2"=0 and "POLK"=0 and "BAX"=1 and "FOXO3"=1 and "CASP9"=0 and "BAD"=1 and "GADD45G"=0"
"Apoptosis" 1 -> 0" when "POLK"=1 and "CASP9"=1 and "BAD"=1 and "CDKN1A"=0 and "GADD45G"=0"
"G1_to_S_progression" 1 -> 0" when "E2F1"=0"

Table 4.20: Automata Network File in Pint Format (Parameters 19)

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