Precision Targeting of Non-Small Cell Lung Cancer: Identifying Optimal Drug Targets and FDA-Approved Combinations for Enhanced Therapeutic Efficacy

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Abstract— **This study proposes a Boolean network model to identify optimal drug targets and select the most effective FDA-approved drug combinations for Non-Small Cell Lung Cancer (NSCLC). The Boolean network models the signaling pathways in NSCLC to capture the intricate molecular interactions driving tumor progression. We evaluate the model by employing the size difference (SD) score, which reflects the degree of cell dysregulation due to gene mutations and allows us to identify optimal drug targets in NSCLC cells to address this dysregulation. Specifically, leveraging the FDA-approved drug database, we identified the robust drug or drug combination for 1, 2, and 3 mutations that maximize tumor cell death and minimize cell proliferation for NSCLC-associated gene mutations. Our findings provide a strong foundation for personalized therapeutic strategies and hold promise for advancing precision oncology to effectively combat NSCLC.**

Keywords—boolean network, combination drug therapy, computational model, non-small cell lung cancer, signaling pathway, targeted therapy.

I. Introduction

Lung cancer remains one of the leading causes of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) accounting for approximately 85% of all diagnosed cases [1],[2]. Despite significant advances in therapeutic strategies, the management of NSCLC remains a formidable challenge due to its complex and multifaceted nature. The five-year survival rates for completely removed stage I NSCLC can vary from 50% to 70%, whereas for stage IIIA NSCLC, the survival rates typically fall within the range of 10% to 30% [3]. Developing a deeper understanding of the underlying cellular mechanisms driving NSCLC progression is crucial for identifying effective drug intervention targets and improving patient outcomes.

In recent years, computational modeling has emerged as a powerful tool in cancer research, enabling researchers to study intricate cellular processes and pathways systematically and comprehensively. By integrating experimental data with mathematical and computational techniques [4]-[8], these models can simulate and predict the behavior of biological systems, providing valuable insights that are often difficult to obtain through traditional experimental approaches alone.

In this study, we present a computational model of the NSCLC pathway based on basic logic gates, aiming to unravel the intricate network of molecular interactions that govern the progression and survival of NSCLC cells. By integrating specific proteins, and their interconnections in the context of NSCLC, our computational model captures the behavior of its gene regulatory network [9],[10] and cellular processes that govern the development, maintenance, and regulation of tissues associated with NSCLC development and progression.

Several molecularly targeted therapies are designed to address various receptor tyrosine kinases (RTKs) that play a pivotal role in cellular growth and survival. In non-small cell lung cancer (NSCLC), RTKs are frequently subject to mutations, resulting in the amplification of RTK signaling and the activation of downstream and alternative signaling pathways. These pathways often converge on common downstream signaling effectors that contribute to tumorigenesis [11]. When these growth factor receptors are mutated, they can lead to the upregulation and amplification of various downstream signaling pathways, including the MAP kinase, PI3K/AKT, and mTOR pathways. These pathways are responsible for promoting cell survival, proliferation, migration, and angiogenesis in cancerous cells [12].

The primary objective of this research is to leverage our computational model to identify optimal drug intervention points within the NSCLC pathway for targeted therapy of this disease. By simulating this model and analyzing the resulting changes in normal (healthy or non-cancerous) cellular processes, we can prioritize potential drug targets and predict the efficacy of various interventions[7]. This approach has the potential to significantly enhance our understanding of NSCLC pathogenesis and facilitate the design of personalized therapeutic strategies tailored to individual patients.

The current standard of care for Non-Small Cell Lung Cancer (NSCLC) typically involves a multimodal approach, which may include surgery, radiation therapy, chemotherapy, and immunotherapy, depending on the stage and molecular characteristics of the tumor. The advent of targeted therapies has revolutionized the management of NSCLC and has demonstrated impressive results in specific subsets of patients.

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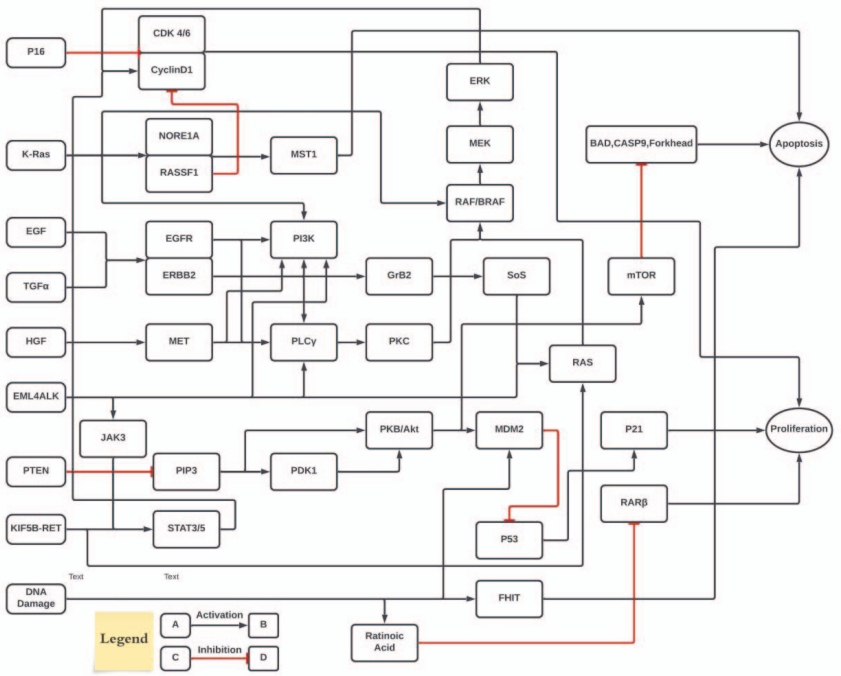

Fig. 1. NSCLC signaling pathway. Legend: The black arrow from A to B shows activation, and the red arrow from C to D shows inhibition.

In some cases, targeted therapies have shown superiority over conventional chemotherapy, leading to improved response rates and prolonged survival [13]. Furthermore, targeted therapies may be associated with fewer adverse effects compared to traditional treatments, resulting in improved patient tolerability and compliance [13]. With ongoing research and advancements in molecular profiling, the role of targeted therapies is expected to grow further, possibly supplementing conventional treatments in specific patient populations. However, it is important to note that targeted therapies are not a one-size-fits-all solution, as not all patients have actionable genetic mutations or molecular alterations. Therefore, a combination of targeted therapies with traditional treatments and immunotherapies may provide a comprehensive approach to effectively manage NSCLC [13].

II. Understanding the NSCLC Pathway

Non-small cell lung cancer (NSCLC) is characterized by a complex interplay of genetic and molecular alterations that drive cancer cells' initiation, progression, and metastasis within the lung tissue [14],[15]. A comprehensive understanding of the NSCLC pathway is paramount to developing effective therapeutic interventions. This section provides an overview of the key molecular processes and signaling pathways implicated in NSCLC development, highlighting the crucial factors driving disease progression.

A. Genetic Mutations:

NSCLC is characterized by a multitude of genetic alterations/mutations that contribute to the malignant transformation of lung epithelial cells. The most frequently observed mutations involve oncogenes such as epidermal growth factor receptor (EGFR) [16], Erb-B2 Receptor Tyrosine Kinase 2 (ERBB2)/ human epidermal growth factor receptor 2 (HER2) [17], Mesenchymal Epithelial Transition factor (MET) [18], Kirsten rat sarcoma viral oncogene homolog (KRAS) [19], and anaplastic lymphoma kinase fusion gene (EML4ALK) [20]-[22]. These mutations lead to dysregulated signaling cascades, promoting cell survival, proliferation, angiogenesis, and evasion of apoptosis. Furthermore, tumor suppressor genes, including FHIT [23], P53, and p16/INK4 [24] are often inactivated, further exacerbating the malignant phenotype. In precancerous non-small cell lung cancer (NSCLC) cells, the p16/INK4a protein plays a crucial role by inhibiting the formation of CDK-cyclin-D complexes through competitive binding with CDK4 and CDK6 [25]. However, it is often observed that NSCLC exhibits a loss of p16INK4a expression, which contributes to the uncontrolled cell cycle progression in cancer cells [26]. Another important factor in NSCLC is the Retinoic Acid Receptor-beta (RAR-beta) [27],[28], which functions as a nuclear receptor with vitamin-A-dependent transcriptional activity. Additionally, the RASSF1A [29] protein has the ability to form heterodimers with Nore-1, an effector of the RAS pathway. Consequently, the loss of RASSF1A might disrupt the balance of RAS activity, leading to a growth-promoting effect in NSCLC cells. This alteration in RAS signaling may further contribute to the development and progression of NSCLC.

B. Dysregulated Signaling Pathways:

Several signaling pathways play critical roles in NSCLC pathogenesis, orchestrating cellular processes and contributing to tumor growth and metastasis [30]. The mitogen-activated protein kinase (MAPK) pathway, phosphoinositide 3-kinase (PI3K)/AKT/mTOR pathway, ErbB pathway, Ras pathway (Rat Sarcoma), and cell cycle (like, p53, p16) pathway [31] are frequently dysregulated in NSCLC [32],[33]. The NSCLC signaling pathway with all its elements [31]-[33] is shown in Fig. 1. Aberrant activation of these pathways can lead to uncontrolled cell growth,

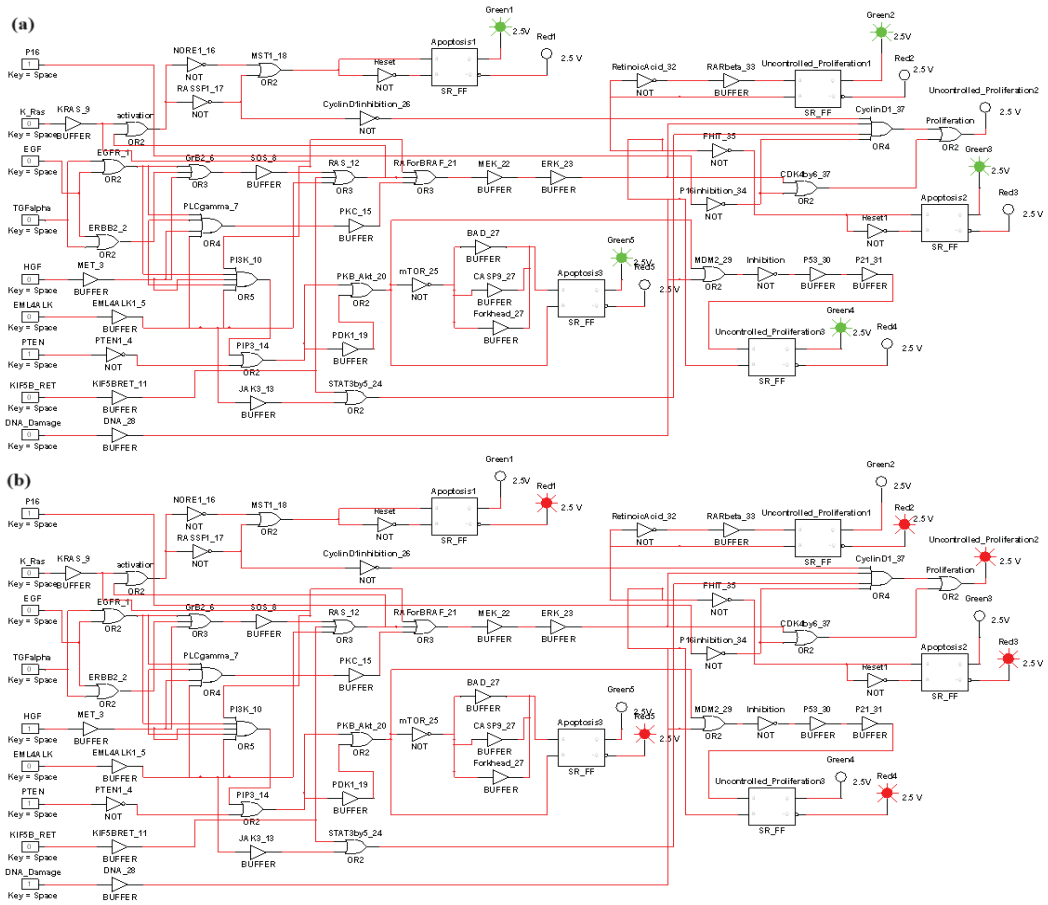

Fig. 2. Boolean Network model for NSCLC pathway (a) without any fault where all necessary apoptosis is turned on and all proliferation is under control, (b) with faults where some necessary apoptosis is turned off and some cell proliferation is constitutively activated.

invasion, and resistance to apoptosis [34]. Additionally, DNA damage regulates cell fate determination, and proliferation is often implicated in NSCLC development [35], as shown in Fig. 1.

III. Design Methodology

The signaling pathways discussed earlier play a crucial role in regulating various cellular processes, including proliferation, survival, and apoptosis. In normal cellular conditions, these pathways are tightly controlled to maintain cellular homeostasis. However, genetic mutations disrupting these pathways can result in the loss of cell cycle control, leading to diseases such as cancer. Hence, investigating these pathways can provide valuable insights into their behavior and aid in the identification of potential drug targets. Computational modeling has been widely employed in the study of biological signaling pathways [7], [36]. Different computational methods, including linear models, differential equations, Boolean networks, and Bayesian networks, have been successfully utilized for studying the holistic behavior of signaling pathways [4], [6]-[8]. The complex interactions occurring within signaling pathways establish a cause-effect relationship between upstream and downstream molecules. To model such interactions in this paper, we employed Boolean Networks (BN)(Figs. 2, 3). BNs integrate pathway information derived from the biological literature, enabling the study of the effects of mutations and drug interventions within the pathways [7]. The details about BN modeling for the problem of interest are discussed in the subsections to follow. This is crucial for identifying optimal drug targets within the pathway. Additionally, since publicly available large-scale gene expression data specifically of NSCLC are limited, exclusively data-driven models cannot be reliably employed for analyzing gene interactions in NSCLC [37]. BN models based on pathway literature do not require data for model building or training, therefore they provide a solution to this challenge and offer an appropriate modeling technique for studying the NSCLC pathway.

In this study, the primary goal is to investigate the functioning of the NSCLC pathway under normal (healthy) conditions and in the presence of genetic alterations. We aim to elucidate the fundamental concepts involved in creating a Boolean Network (BN) model and demonstrate its utility in studying the NSCLC pathway. Specifically, we want to understand how various genetic mutations affect the pathway and how they relate to the two desired outcomes: increased apoptosis (programmed cell death) and suppressed cell proliferation. Additionally, we extend the BN model to evaluate the effects of small molecule inhibitor drugs on these genetic mutations. The objective of analyzing the drug effects

TABLE I. DRUGS USED IN THIS DESIGN AND CORRESPONDING TARGETS

Drugs	Targets	Drug Type
Osimertinib [42]	EGFR	Inhibitor
Trastuzumab deruxtecan [43]	ERBB2	Inhibitor
Capmatinib [44]	EM4ALK	Inhibitor
Selpercatinib [45]	KIF5BRET	Inhibitor
Dabrafenib+Trametinib [46]	RAF/BRAF	Inhibitor
Copanlisib [47]	PTEN	Inhibitor
Alpelisib [48]	PI3K	Inhibitor
Enzastaurin [49]	PKC	Inhibitor
Lumakras [50]	RAS/KRAS	Inhibitor
RG7388 [51]	MDM2	Inhibitor
Ribociclib+Fulvestrant [52]	CDK4/6	Inhibitor
Everolimus [53]	mTOR	Inhibitor
Curcumin [54, 55]	STAT 3/5	Activator

is to identify potential therapeutic agents that can target specific genetic alterations and modulate the NSCLC pathway towards increased apoptosis and suppressed cell proliferation. Therefore, the drugs' aim is to act as inhibitors or modifiers of the pathway components affected by genetic mutations, with the ultimate goal of promoting cancer cell death and hindering tumor growth.

A. Construction of the NSCLC Pathway Network

The construction of the NSCLC pathway model involved a systematic process of model development and pathway compilation. Our approach relied on a thorough exploration of various sources, including publicly available databases [31], scientific literature, and experimental findings [36]-[39]. Through this genetic network curation process, we gathered pertinent information on NSCLC-related genes, signaling pathways, protein-protein interactions, and gene regulatory relationships. This curated data formed the foundation for the construction of the pathway model, enabling us to investigate the functioning of the NSCLC pathway under normal and genetically altered conditions, as well as to assess the effects of small molecule inhibitor drugs on these genetic mutations.

B. Boolean Modeling and Logical Rules

The network was designed using a Boolean network modeling approach, a computational framework suitable for capturing the qualitative behavior of biological systems. Nodes in the network represented genes or proteins, and edges represented the regulatory relationships between them; like activation, inhibition, association, dimerization, etc. The network topology was defined based on known interactions and literature evidence [31], [37], [38]. Each node in the NSCLC pathway network was assigned a Boolean variable, representing its activation state (ON or OFF). The logical rules governing the activation or inhibition of each node were defined based on experimental evidence, and a literature survey [36], [38], [39]. These logical rules capture the qualitative behavior of the biological system such as

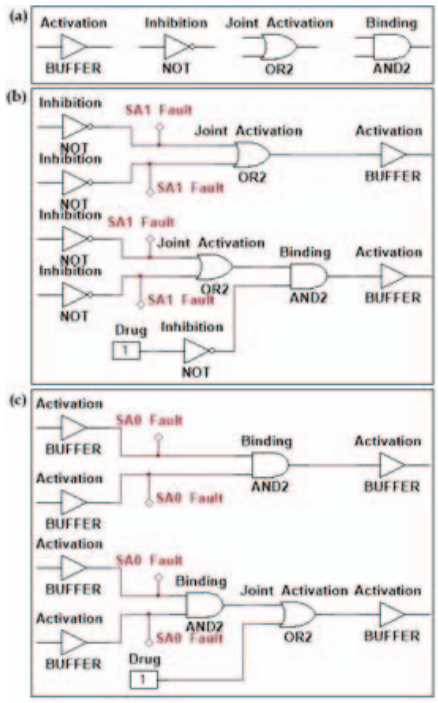

Fig. 3. (a) Basic Boolean logic functions used for NSCLC signaling pathway (BN) circuit design, (b) drug intervention model(inhibitor) for SA1 fault, (c) drug intervention model(activator) for SA0 fault. All fault models have an input value of '1' (on state) in their input node.

activation and inhibition. In Fig. 2 the complete BN circuit is shown for the NSCLC pathway (Fig. 1) both with fault and without faults. In Fig.1 RAS protein is activating MST1 downstream which is known as a pro-apoptotic gene [40], [41]. In cancer, RAS becomes upregulated(K-RAS) or overexpressed (always turned on), but the loss of MST1 is a cause for NSCLC. In Fig.3(a) all logic behind the main design is shown, here mainly four basic Boolean logic gates (buffer, not, or, and) are used for NSCLC pathway design as well as drug delivery (Figs. 3 (b), (c)) in the faulty locations. More details regarding these are presented in the two subsections below.

C. Defining Genetical Mutation Using Fault Model

Cancer comprises a group of diseases characterized by abnormal cell growth (uncontrolled cell proliferation), decreased cell death (apoptosis), and the potential spread of cancer cells to other parts of the body (metastasis). This abnormality can arise from disruptions in normal signaling pathways, resulting in the loss of control over cell cycle regulation leading to uncontrolled cell growth and tumor formation. One well-known cause of such disruptions is gene mutations, leading to either excessive or reduced expression of the gene. In a Boolean network (BN) model, this type of aberration can be represented as a "stuck-at"(SA) fault, where the gene's value becomes fixed at either 0 or 1(SA0 or SA1 fault), making it independent of the activity status of other genes. To understand the faults with and without drugs in Figs. 3 (b), (c) we consider all the inputs are at '1' then the next state is supposed to be '0' for Fig 3(b) and '1' for Fig 3(c) but at the next state the desired value changes and is stuck to a faulty value, SA1 in Fig 3(b) and SA0 in Fig 3(c) irrespective of the input values whose states remained fixed.

D. Drug Selection and Modelling Drug Intervention

Typically, drugs exert their effects by interacting with receptors present on cell surfaces or enzymes within cells. Depending on their mechanisms of action, drugs can act as inhibitors (Fig.3(b)), blocking the function of a specific protein, or as enhancers, promoting its effect, by binding to the respective target receptor sites (Fig.3(c)). In the context of a Boolean network (BN), the drug-gene interaction can be represented by forcibly suppressing or enhancing the value of the gene at the relevant position in the network.

All the target-specific drugs used for this experiment are FDA-approved [42]-[55] and listed in TABLE I, except 'Curcumin' because there are still no FDA-approved drugs for inhibiting STAT 3/5 mutation [54], [55]. Drugs or drug combinations were demonstrated to inhibit uncontrolled cell proliferation and increase apoptosis in the NSCLC pathway.

E. Simulation and Analysis

Using the established Boolean model outlined above, we are now equipped to contrast various combinations of drugs and assess their effectiveness. The aim is to identify the most optimal therapeutic combination for mitigating the adverse effects of each mutation or fault. Referring to the Boolean model depicted in Fig. 2, we have a total of nine inputs and six corresponding outputs. For mathematical analysis, we can express these inputs and outputs as row vectors. Within this representation, a value of zero signifies an inactive gene at the corresponding position, while a value of one signifies an active gene. Consequently, the binary input and output vectors can be expressed as follows:

Input = [P16, KRAS, EGF, TGFα, HGF, EML4ALK, PTEN, KIF5BRET, DNA Damage] and

Output = [Proliferation1, Proliferation2, Proliferation3, Apoptosis1, Apoptosis2, Apoptosis3]

The ideal values for those are,

Input = [1, 0, 0, 0, 0, 0, 1, 0, 0] and

Output = [0, 0, 0, 1, 1, 1]

In the ideal scenario of input [100000100], the tumor suppressors are active, and the growth factors are inactive. This input indicates a lack of cell proliferation and no reduction in apoptosis. In the fault-free Boolean network, this input leads to the output [000111], which also signifies an absence of cell proliferation and no inhibition of apoptosis. However, in the presence of network faults, the same input will result in a different output vector than that for the fault-free case. Our objective is to steer this faulty output vector closer to the ideal output by employing medication. From a biological perspective, this is analogous to directing a mutated pathway towards non-proliferation and unhampered apoptosis through therapeutic intervention. To evaluate the efficacy of potential drug interventions, the designed NSCLC pathway model was simulated under both untreated and treated conditions. Those FDA-approved drugs (TABLE I) selected for simulation were based on their known mechanisms of action targeting specific nodes or interactions within the pathway [56]. The simulation outputs were analyzed using quantitative metrics to assess the impact of drug interventions on the NSCLC pathway. We used Python programming to design all fault models and to simulate that model using different choices of drugs or drug combinations. GitHub link: https://github.com/PranabeshTAMU/NSCLC

As previously mentioned, our focus lies in guiding the output vector of a network that contains faults toward the direction of a favorable output vector. To assess the degree of mismatch between two output vectors, we used a metric named Size Difference (SD) that quantifies the potential efficacy of therapy. It measures the dissimilarity between the two vectors. The following mathematical description defines the Size Difference (SD) between two n-dimensional binary-valued vectors a = $(a_1,...a_n)$ and b = $(b_1,...b_n)$. We use a confusion matrix M which consists of four values: A, B, C, and D, which represent counts of matches and mismatches between the vectors:

$$M = \begin{matrix} b_i = 1 \\ b_i = 0 \end{matrix} \begin{matrix} a_i = 1 & a_i = 0 \end{matrix} \begin{pmatrix} A & B \\ C & D \end{pmatrix} \quad (1)$$

In the matrix M, A represents the number of occurrences where the i^{th} element of vectors 'a' and 'b' are both 1. B represents the count of cases where the i^{th} element of vector 'a' is '0' while that of 'b' is '1'. Similarly, C represents the count of cases where the i^{th} element of vector 'a' is '1' while that of 'b' is '0'. Lastly, D represents the number of occurrences where both the i^{th} elements of vectors 'a' and 'b' are '0'. Therefore, A and D correspond to the number of matches between the vector components, whereas B and C indicate the number of mismatches between the vector components. Consequently, using the confusion matrix M, the formula for the Size Difference (SD) in terms of the components of the matrix M can be as follows:

$$SD(a,b) = \left(\frac{B+C}{A+B+C+D}\right)^2 \quad (2)$$

From Eqs.1,2 it is clear that the SD varies between '0' and '1', where a score of '0' indicates that the vectors are identical, and a score of '1' represents that none of the entries in the two vectors match. Therefore, as the SD value increases, the difference between the vectors becomes larger. In this study, the healthy output state of the fault-free BN requires all output genes to be in the state mentioned in the output vector above. However, when faults or mutations are introduced into the network, the output genes deviate from this healthy state. Consequently, our objective is to identify a drug or combination of drugs that can drive the output genes toward a state close to the healthy output state, even in the presence of faults. In the process of identifying the most potent drug for a specific fault, our approach involves selecting the drug associated with the smallest Size Difference (SD). For ascertaining the most potent drug across all possible faults, our approach involves computing the normalized mean size difference spanning these faults. This entails normalizing the mean SD by comparing it to the mean SD observed in the untreated scenario, and the results are documented in the "normalized mean SD" (Eq. 3) format in TABLE II corresponding to the number of mutations. Due to the space limitations only the best drug combinations are shown here in TABLE II. The calculation of the normalized mean SD (NMSD) for a specific drug/combination (Drug_i) is carried out using the following equation:

$$NMSD(Drug_i) = \frac{Mean(SD(Drug_i))}{Mean(SD(Untreated))} \quad (3)$$

A higher SD value suggests that the drug is unable to effectively suppress the cancerous genes in the network.

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TABLE II. DRUG / DRUG COMBINATIONS WITH THEIR CORRESPONDING SD SCORE FOR SINGLE, DOUBLE, AND TRIPLE MUTATIONS

Drug combinations	Single Mutation	Two Mutations	Three Mutations
Untreated	1	1	1
Alpelisib	0.555556	0.664062	0.726732
Lumakras + RG7388	0.305556	0.354403	0.394645
Lumakras + RG7388 + Everolimus	0.180556	0.202414	0.226986
Dabrafenib & Trametinib + Lumakras + RG7388 + Everolimus	0.138889	0.157670	0.184191

Conversely, an SD value closer to '0' indicates that the drug is more successful in suppressing the cancerous output genes. To evaluate the efficacy of drugs, we consider the possibility of simultaneous faults occurring in the network. This means that the NSCLC pathway can have multiple mutations at the same time. However, due to computational complexity, our study limits the analysis to a maximum of three faults (mutations) at a time.

IV. RESULTS & DISCUSSION

We computed the normalized NMSD (Eq.3) for each drug combination in the Boolean Network (BN) model, considering one, two, and three faults (mutations) at a time. Since there are 37 distinct fault locations in the network, we considered a total of $37C_1 + 37C_2 + 37C_3 = 8473$. Since there are 13 drugs and we analyzed combinations of up to four drugs, this resulted in a total of $13C_1 + 13C_2 + 13C_3 + 13C_4 = 1093$ drug combinations. With 8,473 combinations of faults, the resulting NMSD (Eq.3) matrix has dimensions of 1093 (drugs) by 8,473 (faults). Due to the impracticality of presenting and comprehending such a large matrix, we included the NMSD scores for each drug combination under one, two, and three fault networks in supplemental files. Additionally, within each supplemental table, the results have been reported with the selected 13 most effective drug combinations for each fault combination, ranging from single-drug interventions to three-drug combinations in the subsequent subsections. The whole list of drug combinations with their corresponding NMSD score is given in the supplementary file.

A. Drug Efficacy for Single Mutation

The BN design was first simulated for one fault, which means only one mutation is present at a time, for each drug combination scenario**.** For this experiment, 37 fault locations were activated one at a time. In Fig. 4 some of the drug combinations are shown to have the lowest SD scores. From TABLE II, for single mutations, the most effective single drug, in terms of the lowest NMSD score, is "Alpelisib". Lower scores were achieved using multiple drug cocktails such as "Dabrafenib & Trametinib + Lumakras + RG7388 + Everolimus" followed by "Lumakras + RG7388 + Everolimus".

B. Drug Efficacy for Two Mutations

After simulating for one mutation, the BN design was simulated for two mutations, which means two mutations are present at a time, for each drug combination scenario**.** This experiment had 37 fault locations activating two at a time. A few of the best results are shown in Fig.4. From TABLE II we can observe that the result is along the same lines as that for a single mutation; however, with more mutations, the ability for a single drug to return the regulatory pathways back to a normal state is diminished.

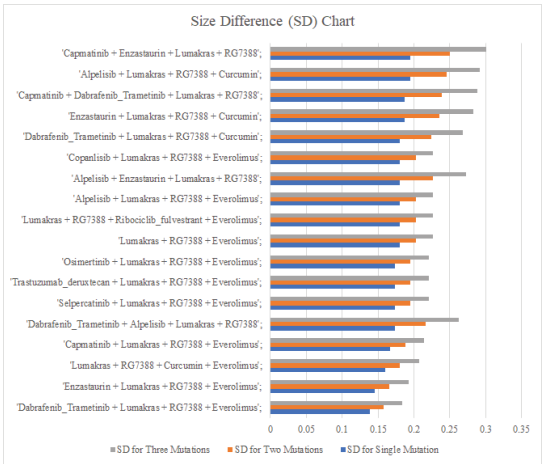

Fig. 4. Bar graph showing most effective drug combinations and respective size differences for single mutation, two mutations, and three mutations.

C. Drug Efficacy for Three Mutations

In Fig. 4 drug efficacies for three mutations are shown, in this case, three faults are present at a time for each drug combination scenario. The "supplementary file 1" contains all SD values, but this table contains the best results only along with the untreated ones. As in the previous two subsections, here "Alpelisib" is the best single drug for targeted treatment, and the lowest overall score is achieved by the drug cocktail "Dabrafenib & Trametinib + Lumakras + RG7388 + Everolimus".

V. CONCLUSION

Non-small cell lung cancer (NSCLC) is a highly aggressive form of lung cancer. Based on the results presented in the last section, it is evident that the combination of "Dabrafenib & Trametinib + Lumakras + RG7388 + Everolimus" stands out as the most effective drug combination, as determined by our NSCLC signaling pathway model. These drugs target key molecules such as BRAF, KRAS, MDM2, and mTOR, aligning with the FDA-approved targeted drug list and our experimental computational model. Current research has solidified the crucial role of BRAF in NSCLC progression [57], with KRAS being central players in governing a wide array of cellular processes, including but not limited to proliferation, cell cycle progression, angiogenesis, metastasis, apoptosis,

and the development of drug resistance; in NSCLC KRAS mutations occur in up to 30% of all cases [58]. MDM2 has long been recognized as a potential therapeutic target for NSCLC [59], [60], as has mTOR [61], [62], due to their involvement in cellular apoptosis which is very important in controlling tumor growth. These targets hold promise for combatting NSCLC [63]. In TABLE II, it is observed that increasing the number of drugs leads to lower size difference (SD) values, this also likely increases off-target toxicity. Therefore, a balance between on-target effectiveness and off-target toxicity needs to be considered. These tools provide insight into the potential therapeutic benefits of increasing the number of drugs used. Our model is built upon a robust theoretical foundation supported by existing literature in the field of NSCLC and targeted therapy. The model considers pathways involved in NSCLC and the results are consistent with observations in existing biological literature.

VI. Limitations & Future Work

The results presented here are completely computational; no clinical trials or in-vivo/vitro models have been used to verify them. A positive aspect of our study is that all the drugs used here are FDA-approved ones, and so their toxicities and doses are known. The conclusion we have obtained is constrained by certain assumptions that align with prior evidence, but no practical experiment has been done. Our model predicted some potential therapeutic targets and drug combinations for NSCLC treatment. These predictions can serve as valuable starting points for future experimental studies to treat NSCLC. A potential avenue for future expansion of this study could involve integrating the impacts of immunotherapy into the existing model, potentially yielding even more favorable outcomes than those achieved.

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