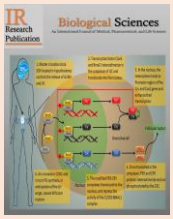
RESEARCH ARTICLE

Biological Sciences
(An International Journal of Medical, Pharmaceutical, and Life Sciences)

Journal home: https://irrespub.com/biolsciences/index.php/1/index



Static Analysis of Dengue Biological Regulatory Network's

Abdullah Khan[1]*, Shmmon Ahmad[2], Bibi Tahira[3], Amina Khalid[4]

[1]*Department of Computer & Software Technology, University of Swat, Pakistan*
[2]*Glocal University Pharmacy College, Glocal University Saharanpur, India*
[3]*Department of Computer Science, Govt. Degree College Kabal Affiliated with University of Swat, Pakistan*
[4]*Department of Software Engineering, University of Lahore, Pakistan*

ARTICLE HISTORY

Received: 12-04-2023
Revised: 05-05-2023
Accepted: 05-05-2023
Online: 13-05-2023

KEYWORDS

Automata Networks Model
DENGUE Model Analysis
Computational Biology
Logical Modeling Analysis
Clearance DENV Model
Identification Fix-Point Cut-Sets
Bifurcation Reachable State Graph

ABSTRACT

Dengue is an acute viral illness caused by the RNA virus of the family Flaviviridae and spread by Aedes mosquitoes. Intense dengue is a spreading cause of serious disease and death in some 'Asian and South American' countries. Pathogenesis is associated with the amended functioning of our innate immune system during infection. Toll Like Receptor is influential for the involucre of innate immunity able to cause dengue infection disease like pattern receptor recognition. Toll-like receptors induced by injury of a certain severity arbitrate activation of interferons and Fc receptors arbitrate the involucre of cytokines. Clearance of dengue virus is associated with interferon protein; however regulatory mechanisms have been adopted against this modified effect. The clearance is considered to be a steady state known to be characterized by a low threshold level of DENV. The pathogenic state is characterized by a high threshold level of SOCS. SOCS protein is also induced due to interferon and cytokine-amended signaling, which can subsequently play its part in the regulation of interferon and cytokine production. Our hypothesis in this research the innate immunity system is associated between the pathogenesis of the dengue virus and the SOCS-amended inhibition. We used the static formalism model of the biological regulatory network of Toll-like receptors induced by the pathogenesis of dengue amended signaling pathway. A model verification method used in GINsim was used to deduce the logical parameters for the qualitative modelling. Therefore, a multidisciplinary and translational study we constructed a formal model constraint the approach with a static and integrative computational analysis, which may identify new immunopathological mechanisms and biomarkers for differential diagnosis, opening the way for the development of specific therapies that will reduce mortality and induce morbidity by dengue virus.

*Address for correspondence
Department of Computer & Software Technology, University of Swat, Pakistan
Email: abdukhan553@gmail.com
DOI: https://doi.org/10.55006/biolsciences.2023.3203
Published by IRResearchPublication;

Introduction

Dengue Virus infectious and have spread rapidly disease in the last few decade [1]. Now day there are almost 4 billion people, the world population is about the DENV transmission is in those areas where there is a current "(WHO)" report on

homology. Almost 400 million Dengue virus infections show results per year, including 100 million cases of dengue hemorrhagic fever (DHF), and 40,000 cases of death around the world (Dengue 2021). DENV interaction between the genus Flavivirus and the family Flaviviridae. It has the following 4 types DENV1, DENV2, DENV3, and DENV4, the center of their infection is caused by the female Aedes aegypti mosquito; the blood of an infected person by the female Aedes aegypti acquires this disease [2, 3]. The virus affects mosquitoes and transfers during a period of 8 to 12 days which then is delegated to living things on the next bite. The dengue virus infection shows symptoms or results in dengue fever (DF), headache, joint pain, fever, and skin rash [4]. Dengue fever is the most common infection transmitted to humans through bites of infected mosquitoes. The virus to blame for causing dengue is known as dengue virus [5]. Intense dengue, some people are dying as a result of a rapidly spreading disease or virus. "Asian and South American" countries. There is no individual treatment for dengue disease. Sooner as the virus detection of disease progression (WHO) Report). When combined with dengue fever, it having access to appropriate medical care reduces the number of severe deaths. Dengue fever, less than 1% of dengue viruses are located in most tropical areas of the world, dengue is found in cities and towns and rural areas (Treatment Dengue Fever). The presence comprising a normal state (DENV = 0, TLR = 0, DENV = 1, SOCS = 1) will now be used. To represent the stable state, the SOCS (Cytokine) entity considers the inhibited threshold level synthesis of IFNAB and TLR while it's IFNAB's production and positively regulating network change [1, 6].

Dengue model vectors function of a gene

- Dengue virus is a serious disease spread by mosquitoes. Considering the character of 'headache, fever, pains, joints, and skin rash.
- Toll-like receptor, a class of pattern recognition receptors known as toll-like receptors, triggers the innate immune response by detecting conserved disease patterns that accede to early pathogen detection.
- Interferons are proteins produced by the cells membranes in response to disease infection that delegates the growth of the disease. Interferon further spreads inside human activation.
- Cytokines are proteins produced by cells that carry signals to neighboring cells. Cytokines include interferon. Cytokine proteins form part of a functional deactivated response system that regulates cytokine signal transition.

Computational modeling in biological systems

For biologists and clinical doctors, it is still challenging to comprehend the basic mechanisms and molecular processes behind the development of cancer disease. High-throughput technological advances recently encourage systems biology to produce more accurate models for complicated disorders. We are gradually using computational and mathematical models to better understand the omics data generated by high-throughput research methods [7]. We may investigate the pathophysiology of complicated diseases, deepen our comprehension of hidden biological pathways, and advance the development of new drugs by using computer models in biological sciences[8]. For the analysis of different logic pathways, there are some strategies. With the handoff, the Computational regulatory network approach and used for the analysis of different based instruction fix points, cut sets, reachability, state graphs, mutations, bifurcation, and some others.

Complication statements

Dengue fever is a type of severe illness that manifests symptoms before the adaptive immune response is activated. Dengue fever cases have been growing year by year. There are no specific drugs for treating dengue fever and no commercially available dengue vaccine for Dengue Fever Problem (Problem Statement of Dengue Fever, 2022) [4, 9]. By blocking the IFNA/B mediated signaling pathway, this infection also recently viral particles to many organs/molecular proteins such as "Liver, Spleen, Lymph Nodes, Brain, and Spinal Cord". TLR signaling and subsequent actions must be therefore to maintain and preserve immunological balance. SOCS roots, which play a critical role in stabling and maintaining homeostasis both in pathogen titter and cytokine-mediated hyper-inflammation, have been identified as TLR signaling suppressors. Our BRN findings further show that timely activation and deactivation of SOCS protein is critical for DENV infection pathogen clearance [1, 10].

Aims and objectives

However, there are no effective vaccines yet for all the dengue viruses we plan to investigate (Dengue, [transmitted by Aedes aegypti]; Yellow Fever, [transmitted mainly by Haemagogus leucocealenus]). To identify common therapeutic targets and new biomarkers, we will perform a static and integrative analysis of the vaccine immune response transcriptome model induced by dengue disease. These strategies are both time and cost-efficient. In addition, we will identify the co-expression networks of genes essential to the immune response against the virus through a static and integrative model approach.

Logical modeling & analysis workflow

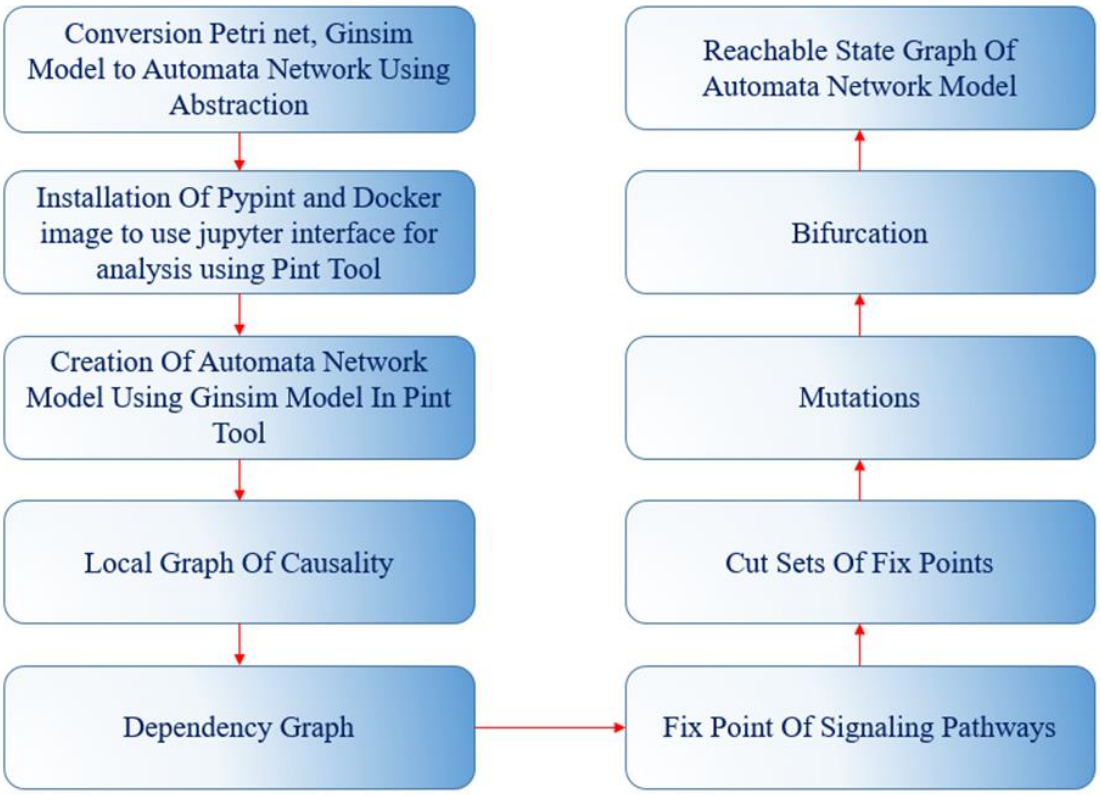


Fig 1. Logical modeling & analysis workflow.

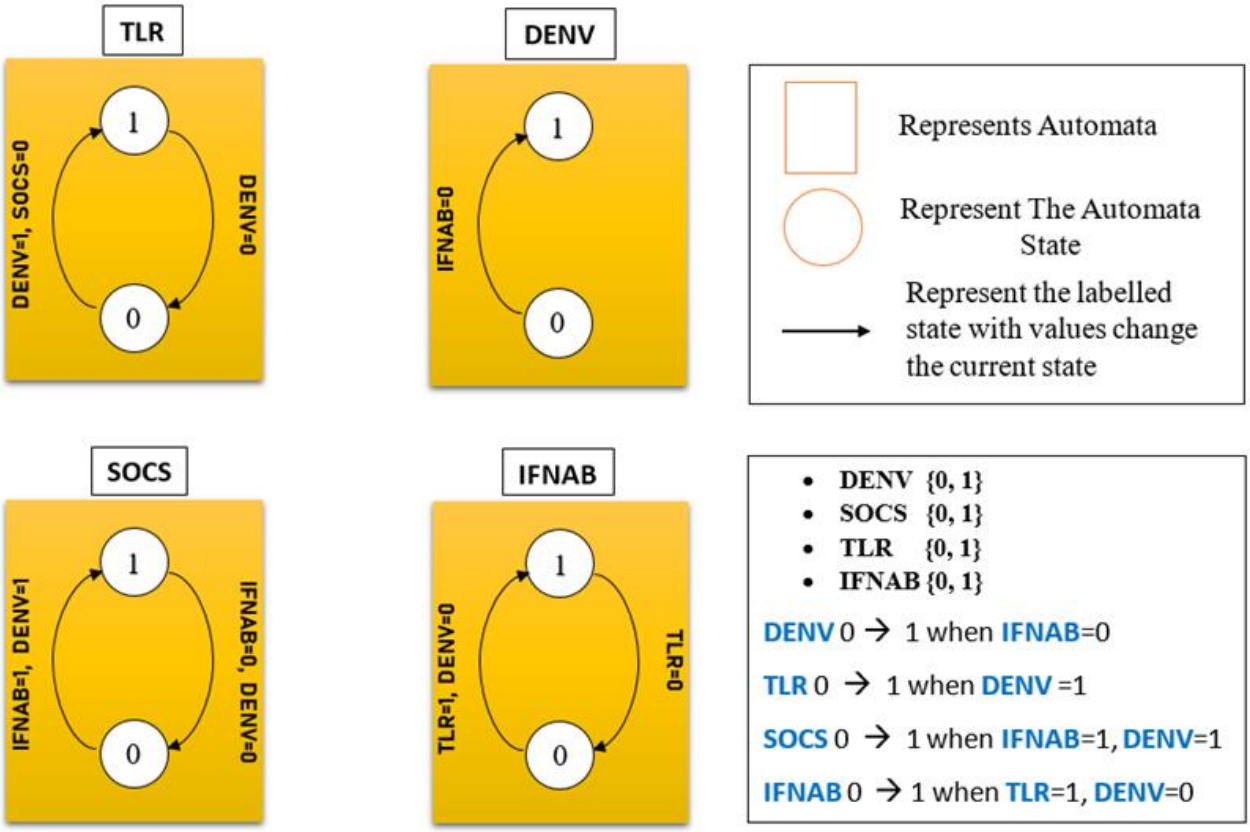


Fig 2. Represent the transition graph and schematic of automata networks, Automata are shown by labelled boxes, and circle show the local states where are the automata have ticks as their identifier for example, SOCS-0 local state is a circle having tick 0 in the box SOCS. In the same automaton two local states having a directed edge is transition which can be marked with set of other automaton's local states.

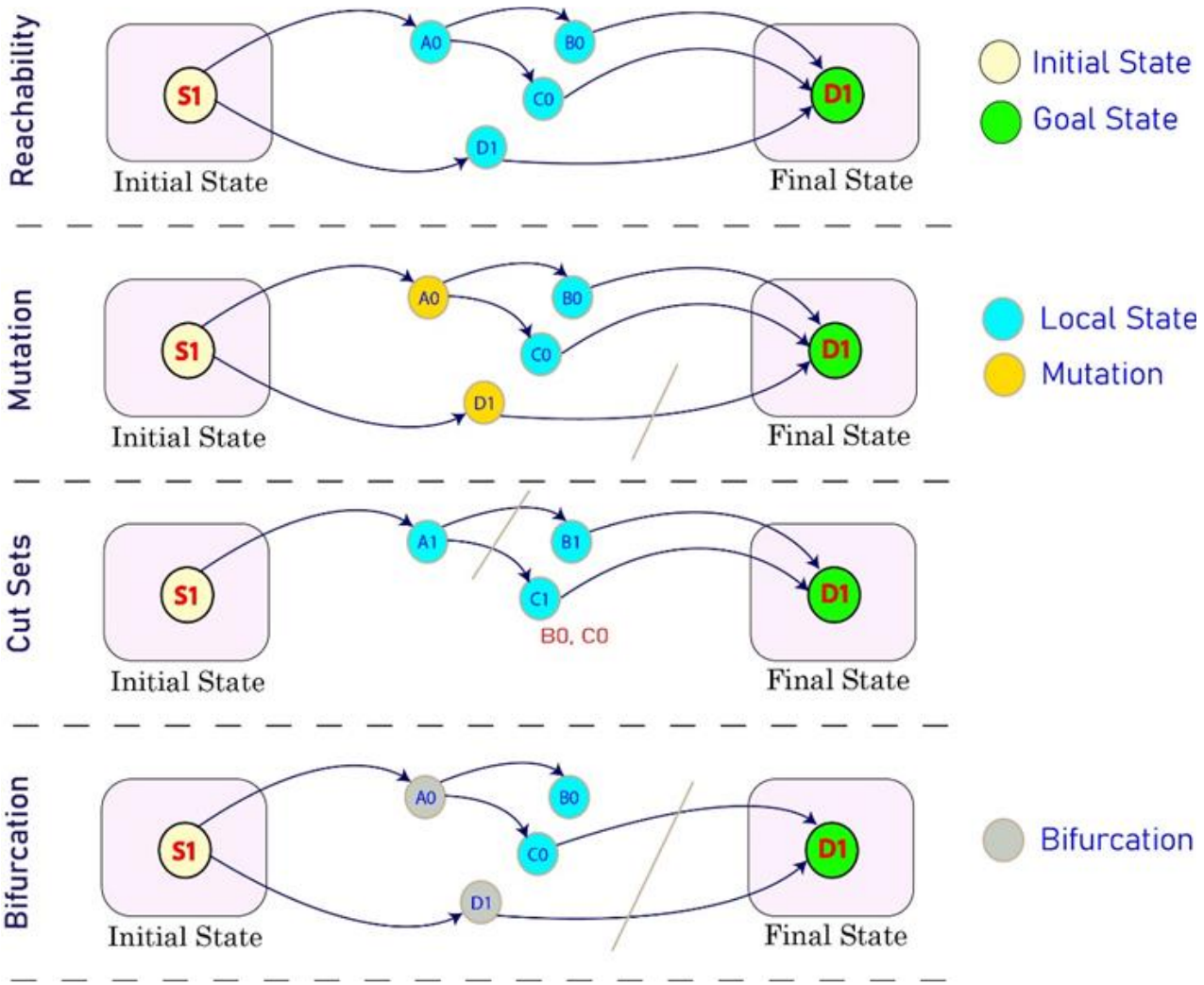


Fig 3. The illustration of important feature of Pint associated to the transient reachability from set of initial states to the set of goal states and the arrows show the transition. The Arc in red color crossing the transitions show the cut set.

- Develop a model of dengue biological regulatory networks with a directed graph.
- Static analysis of Dengue pathway of BRN's.
- Static analysis and modeling of BRN of the Dengue pathway of longevity to observe the Fix-Point, Cut-Sets, Mutation, and Bifurcation.
- The qualitative model and analysis of the dengue pathway of BRN reachable state graph.
- Static analysis and modeling of BRN of the dengue pathway of longevity to perceive homeostasis and stable state [11].

Materials and methods

The Dengue modeling methodology was thoroughly considered in search of the method and procedure cross framework implementation for the static analysis of the dengue model BRN signaling pathways, static analysis of the dengue model pathway is represented in the logical instruction/parameters striving in the study to showing the analysis of different frameworks and explained in the following ways [11].

Directed graph

- A directed graph of G = (V, E) is an order pair of two elements.
- Where V is a finite non-empty set of vertices.
- E is a set of order pairs of distinct edges.
- Each edge of the BRN order pair of expression level threshold interaction by [11, 12].
- Positive Interaction (+), Negative Interaction (-)

Pint tool

For formal predictions for trajectory control, pint tool software is used for the implementation and evaluation of trajectories within the Boolean system. The jupyter notebook (Jupyter Notebook, 2022) used this framework for performing formal modeling analysis. The Pint tool is used for analysis, Python-3 library [13]. Pypint makes for easy integration into the jupyter notebook framework and provides an analysis of the model. The Colomoto-Docker images provide a usable pint of documentation for all usual OS (Mac OS, Linux,

Windows), and especially the jupyter notebook browser interface. The Pint imports a model with a Python command or 'Pypint. load()' python function and Pint can be automatically converted from model expression to Boolean operation network signaling pathways. For online, the quick tutorial is available at

https://nbviewer.org/github/pauleve/pint/blob/master/notebook/quick-tutorial.ipynb.

Automata network

A-Network is a collection of these elements SIGMA, STATES, LABELS, TRANSITIONS, and FUNCTIONS. Automata means "Something that works automatically". An Automata Network is a collection of the following here [11, 14].

- SIGMA: Finite set of input letters, in which input strings are identifiers and formed.
- STATE: Finite set of input letters from 8 Global States.
- LABEL: Finite set of transition labels (Some basic words are specified in the label).
- TRANSITION: Finite set of transitions (How to move from one state to another).
- FUNCTION: Finite set of functions that denote the semigroup generated by the composition of an element.

An automata network is a network of genes each holding a local update function that changes a node according to the genes of neighboring genes. Different kinds of networks have been used for different kinds of networks, i.e., computational, mathematical, statistical, and other ones. Biological networks, social networks, gene networks, neural networks, network coding, etc. [15]. They can also represent a computational network model. (AN) is a set model of elaborate activities for qualitative modeling of discrete Boolean systems. (AN) has a set of state and dependency graphs interconnected with each other through states and different logical transitions and systems [16].

Fix-point

Within the confines of a process, a framework to perform the fixed-point analysis, the fix-point states considered in the graph model can be activated and inhibited, to control all the graph model fix-point nodes [11, 17]. This method is crucial in determining the characteristics of a cell state. To control the problem of fixed points, it provides two methods for designing and analyzing fixed points. First, a root that enables and changes an expression level to positive activation is proposed and used in the model. Second, the root method is disabled, changing the expression level to negative inhibition, and using the model, a stable graph is proposed [18]. Finally, we consider both method problems using only one graph, analyzing the given signaling pathways and showing some results.

Mutation

The mutation method is performing changes in some parameters on different entities, also known as mutation. Individuals who consider these changes are known as mutants [19]. State mutations that cause changes in the base sequence of a state are known as state mutations or point mutations. E.g., TLR=1 should be activated during the time, which comes with a sequential change to different connected states.

Cut sets

To start constructing the graph with an initial state and a final state of analysis interest, the Pint framework gives a few methods to control the transition reachability of the final state. The most scalable approach identifies the cut sets of all paths of transitions leading to the final state. A cut set includes one or a few local states of the graph which are mandatory for the final reachability: if one inhibits the transitions consisting of these local states, the final state is disconnected from the initial state [20]. OR consider a linked graph, G = (V, E). If removing every edge from G causes G to disconnect, then the subset 'E' of E is referred to as a cut set of G. A graph is said to be disconnected if a certain number of its edges are removed; in this case, the removed edges are referred to as the cut set of the graph. Jump to the site [11].

Bifurcation

Bifurcation is a way that is not leading to a particular goal in a pathway. It's an abnormal route from a normal pathway. As a parameter of a dynamical system, different qualitative changes in the phase portrait may occur at special values of the parameter. This change is called "bifurcation." Bifurcation has become a common two-parameter neighboring system and has been extensively researched. These parameters change the type of stability in the dynamic system. The implementation analysis result shows a condition [21, 22]. One of the genes is one of the solution's parameters. E.g., TLR=1 will be checked for the abnormal route pathway condition, SOCS 0 to 1. When the change becomes a state, then DENV = 1.

Reachable state graph

A graph containing a node for each reachable state. Reachable entity graph creation/construction by starting a set of source nodes and calculating all directly reachable states and other pathways. Reachability considers the result of a Boolean operation as true or false from the source to the destination during the transition. This static analysis was discovered using the Pint tool software[21][23]. E.g., If there is a sequence of firings V = E0, E,1 E2 that transforms E0 to En, the marking E can be reached from marking E0. More examples are explained in the following table of implementation analysis files 1 & 2.

Dependency graph

This local state representation of various genes within a biological regulatory network is similar to that of a directed graph. The flow of the parse tree is represented by the dependency graph. The source-to-destination node process involves Boolean operations to resolve the reachability [17]. The following figure of implementation analysis files 1 and 2 show all results.

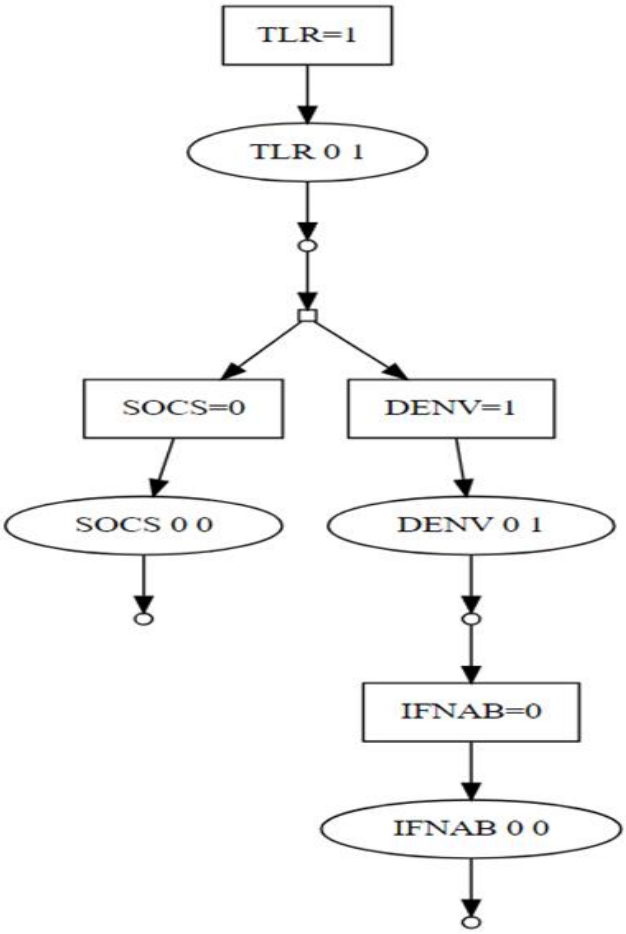


Fig 4. Biological Regulatory Network (BRNs) of DENGUE Model signals. The signal/pathway is made of 4 genes, which present the parse tree of complex signals. These genes have different entities, activation, and inhibition interconnection to each other by 0 and 1 [11].

Dummy BRN interaction four gene

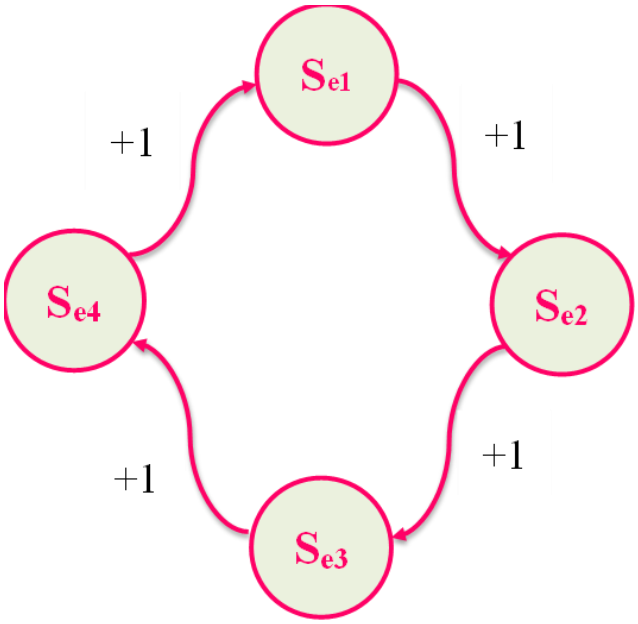


Fig 5. Dummy BRN. An example of BRN is in which the interaction between genes Se1, Se2, Se3 and Se4 are labeled with + sign representing activation and an integer "1" representing the threshold levels [1].

Results and discussions

This section discusses the practical implementation analysis of the DENGUE model done using the Pypint package to Automata Network models of signaling pathways. BRNs can be effectively treated at the molecular level with logical/instruction techniques. However, progress in molecular targeted therapy depends on a detailed knowledge of the fundamental workings and terminology of the DENGUE signaling networks. Recently, a variety of logical and instruction techniques have been used to quickly and affordably decode complicated biological systems [24, 25].

Abstract of BRN's DENV signaling pathways

The GINsim tool [26] constructs the abstracted BRN of the DENGUE pathway as depicted in Figure 1 from the detailed DENGUE pathway. It is important to note that the biological Regulatory Network of DENGUE pathways is a unique contribution in and of itself[27]. We developed it following a thorough literature search of the relevant molecular entities and interactions, and then we methodically abstracted them as we have done in previous work [12].

Automata network's of dengue pathways

As seen in **Figure 3**, the GINsim tool of the DENGUE model pathway is used to generate the automata network. The Automata Network of the DENGUE

Table 1. Table of States, Resources and Logical Parameters.

S_{e1}	S_{e2}	S_{e3}	S_{e4}	Qs_{e1}	Qs_{e2}	Qs_{e3}	Qs_{e4}	$K_{e1\ (Se1)}$	$K_{e2\ (Se2)}$	$K_{e3\ (Se3)}$	$K_{e4\ (Se4)}$
0	0	0	0	()	()	()	()	0	0	0	0
0	0	0	1	(e4)	()	()	()	1	0	0	0
0	0	1	0	()	()	()	(e3)	0	0	0	1
0	0	1	1	(e4)	()	()	(e3)	1	0	0	1
0	1	0	0	()	()	(e2)	()	0	0	1	0
0	1	0	1	(e4)	()	(e2)	()	1	0	1	0
0	1	1	0	()	()	(e2)	(e3)	0	0	1	1
0	1	1	1	(e4)	()	(e2)	(e3)	1	0	1	1
1	0	0	0	()	(e1)	()	()	0	1	0	0
1	0	0	1	(e4)	(e1)	()	()	1	1	0	0
1	0	1	0	()	(e1)	()	(e3)	0	1	0	1
1	0	1	1	(e4)	(e1)	()	(e3)	1	1	0	1
1	1	0	0	()	(e1)	(e2)	()	0	1	1	0
1	1	0	1	(e4)	(e1)	(e2)	()	1	1	1	0
1	1	1	0	()	(e1)	(e2)	(e3)	0	1	1	1
1	1	1	1	(e4)	(e1)	(e2)	(e3)	1	1	1	1
All the states (S_e)				Set of resources (Qs_e)				Logical Parameters K_e (S_e)			

Table 2. DENGUE Model's Gene Interconnection.

NODES	**INTERCONNECTION**
DENV [0,1]	DENV 0 → 1 When IFNAB = 0 DENV 1 → 0 When IFNAB = 1 and DENV 1 → 0 When TLR = 1
TLR [0,1]	TLR 0 → 1 When SOCS = 0 TLR 1 → 0 When DENV = 0 and TLR 1 → 0 When SOCS = 1
SOCS [0,1]	SOCS 0 → 1 When IFNAB = 1 and SOCS 0 → 1 When DENV = 1 SOCS 1 → 0 When IFNAB = 0 and SOCS 1 → 0 When DENV = 0
IFNAB [0,1]	IFNAB 0 → 1 When TLR=1 and IFNAB 0 → 1 When DENV = 0 IFNAB 1 → 0 When TLR = 0

Table 3. Fix-Point Analysis of DENGUE Model.

	TLR	**IFNAB**	**SOCS**	**DENV**
Diseased States (0)	**0**	**0**	**1**	**1**
Homeostatic States (1)	**1**	**1**	**0**	**0**

Table 4. Cut Sets Analysis of DDENGUE Model

S.No	**Biomarker-Gene**	**Cut Sets**
1	IFNAB = 1	TLR: 1, SOCS: 0, DENV: 0, (SOCS: 1, DENV: 0)
2	DENV = 1	IFNAB: 0
3	TLR = 1	DENV: 1, SOCS: 0
4	SOCS = 1	IFNAB: 0, DENV: 1

Table 5. Expression Level Up and Down of DENV Model.

Up Regulated	**TLR**	**IFNAB**	**SOCS**	**DENV**
Down Regulated	**SOCS**	**DENV**	**TLR**	**IFNAB**

route in **Table 2** previously mentioned displays the set of all potential local genes of automata (DENV,

SOCS, TRL, and IFNAB) dependent on the circumstances of another automaton in the network's local gene

Fix-point analysis of dengue model pathways

Dengue routes are effectively analyzed on an abstract basis, and it is also capable of handling these backend difficult systems. As shown in **Table 3**, Automata Network was used in a recent study to identify a large number of novel biomarkers based on diseased or stable states [28].

The Automata Network of DENGUE signal transition is used to find the fixed points or normal root of the model pathway. The model results are shown in **Table 3** below. **Table 3** contains the entities DENV,

Table 6. Cut Sets Effect On Reachability.

IFNAB	DENV = 0 → False **DENV = 1 → True** SOCS = 0 → False **SOCS = 1 → True** TLR = 0 → True **TLR = 1 → False**
DENV	IFNAB = 0 → False **IFNAB = 1 → True**
TLR	DENV = 0 → True **DENV = 1 → False** SOCS = 0 → False **SOCS = 1 → True**

Table 7. Mutation Effect on Reachability.

DEVN = 1	IFNAB: 1
TLR = 1	IFNAB: 1, SOCS: 1, DENV: 0
SOCS = 1	IFNAB: 1, DENV: 0
IFNAB = 1	TLR: 0, SOCS: 1, DENV: 0 (SOCS: 0, DEVN: 1)

Table 8. Bifurcation's Effect on Reachability.

GOAL	**BIFURCATION**
TLR = 1	SOCS 0 → 1 When DENV = 1
IFNAB = 1	TLR 1 → 0 When SOCS = 1
SOCS = 0	TLR 1 → 0 When SOCS = 1
DENV = 0	TLR 1 → 0 When SOCS = 1

SOCS, TLR, and INFA and depicts two stable states; the first row shows the diseased state, and the second row depicts the healthy state. Although DENV and SOCS are overexpressed in a sick condition, their downregulation maintains a healthy state of the system.

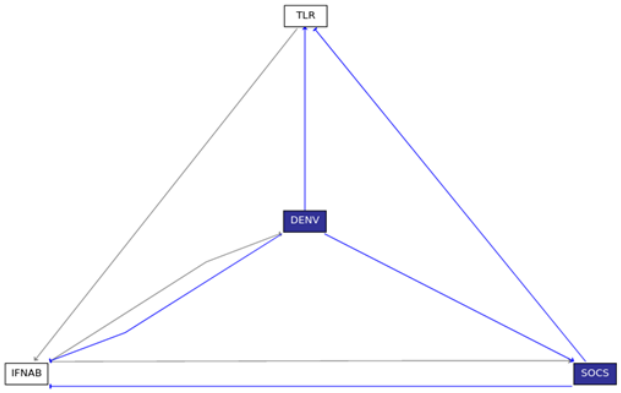


Fig 6. Biological regulatory networks of Dengue pathway. The interaction consists of 4 roots that depict the biological states of the complex signals. These four roots have trajectory interconnection with each other in vertices [1, 26].

DENV and SOCS are therefore identified as ARVC indicators and are hence potential therapeutic targets. The homeostatic root of the states in Column 2 emphasizes the impact of the lack of mutations, while Column 3 in Table 3 displays the current analysis of mutations on the DENGUE signal transition. Preconditioned mutations in the entities TLR and INFA cause the sick state [29]. Resulted by The nodes in **Table 4** show the unstable root produced in the impacted node. "Mutable" represents the normal root produced in the condition of mutated DENGUE signal transition, produced as a result of the Boolean static analysis showing output over the entire DENGUE pathway by the Pint software in **Table 4**. The node-within routes that virus-causing substances are highly produced and up-down regulated as a result of mutations that collectively result in the DENGUE pathway.

Cut sets analysis of dengue pathways

Pint proposes a list of cut sets in the correlation graph as a collection of genes whose transition is important to lead to a distention entity, based on static reachability speculation of Boolean values with 0 and 1 [30]. If the destination is hampered, it means the specific cut sets are interfering with the goal's reachability. The Automata Network's list of roots was computed using the cut set function. They are four entities: IFNAB, TLR, DENV, and SOCS (**Table 4**) [31].

The reduction of pathways leading to DENV and SOCS activation, as well as TLR inactivation, can save the system and help it return to health. **Table 6**

shows how their knockdown makes it difficult to achieve fixed spots. Another option is to disable IFNAB, which will aid DENV. As stated in **Table 4**, the analysis of 'Cut Sets' has shown three states (IFNAB, DENV, and TLR) that are promising enough to be used as possible biomarkers. As shown in **Table 6**, the cut sets IFNAB, TLR, and DENV have Boolean values that indicate the states do not lead to reachability (diseased state) [32]. The reachability of the distention of the unstable condition is true or false by disabling in a specific Cut Set with root 0 or 1 of marking set IFNAB, DENV, and TLR, as mentioned in **Table 5**.

The Pint tool assists us in identifying the most effective entities that can be altered to improve the system's performance. The induction of mutation has the potential to save the organism from death. TLR, DENV, and SOCS are the three hypothesized mutant genes. If DENV and SOCS are deactivated, TLR will be activated, and the goal of keeping IFNAB active will be met. The IFNAB value of '1' promotes DENV degradation, which leads to apoptosis. The DENV is encouraged to degrade by the IFNAB value "1," which triggers entities. They are the constructive expression of biological networks [33].

Mutation goal reachability of identification

The Pint tool assists us in identifying the most effective entities that can be altered to improve the system's performance. The induction of mutation has the potential to save the organism from death. TLR, DENV, and SOCS are the three hypothesized mutant genes. If DENV and SOCS are deactivated, TLR will be activated, and the goal of keeping IFNAB active will be met. The IFNAB value of '1' promotes DENV degradation, which leads to apoptosis. The DENV is encouraged to degrade by the IFNAB value "1," which triggers entities. They are the constructive expression of biological networks [19, 34]. The optimal circumstance **Table 7** shows the pathological state of the route that mutation roots with values (TLR = 1, DENV = 0, SOCS = 1) will avoid, and vice versa, showing the appropriate result of Jupyter Notebook using for Analysis Pint Tool [20, 35].

Bifurcation analysis of dengue paths

When used, bifurcations are secret remedies in pathways that can rescue the system from a state of impasse. We discovered two paths that deviate from the pathological state and lead to the ideal situation. **Table 8** demonstrates that by maintaining DENV and SOCS expression levels at 0 and 1, respectively, we may be able to delay the pathway through TLR and INFAB. It can help to promote health by getting out of a diseased state. When TLR is -1, activate IFNAB. There are two main goals: One bifurcation in the DENGUE route, one pathogenic (IFNAB = 1), and one homeostatic (TLR = 1), which prevents them from reaching their desired states [21, 22]. While SOCS = 1 denotes a sick state, DENV = 1 denotes a healthy state.

There are two objectives. The DENGUE pathway has one bifurcation, one of which is homeostatic (TLR = 1) and the other is pathogenic (IFNAB = 1), which prevents them from they've arrived at their desired states. DENV = 1 indicates a healthy state, but SOCS = 1 indicates a pathological state.

Conclusion

The primary computational evidence for the many pathogenic effects caused by the imbalanced cytokine profile in DENV signaling is presented in this paper. Computational static analysis modeling can result in a variety of effects if the entities involved in the TLR-mediated IFN/B production signaling pathway lose a precise pattern of initiation and inactivation. Static analysis results provide us to evaluate the logical parameters of BRN based on static formalism. Our analysis shows the potential system behavior toward DENV propagation and clearance. Investigation of the static model reveals how the SOCS protein affects DENV propagation, and the findings support the idea that an imbalance in cytokine levels during the late stages of DENV infection causes the system to transition from homeostasis to illness. To investigate the primary focuses of static analysis and dengue virus infection, which can be a flowing infection to protective and therapeutic in human targets that can be towards treatment and disease.

Contribution of authors

A. Khan & A. Khalid designed the research. A. Khan & B.T wrote the manuscript. S.A and A. Khalid modified and copyedited the manuscript as per journal guidelines and are involved in the submission of the work. S.A and B.T did the overall modification. All authors reviewed and approved the final manuscript.

Acknowledgments

All authors are highly obliged to their respective College/Universities for providing the necessary facilities to carry out these works.

Conflict of interest

The authors proclaim no competing interests.

Funding

This study did not receive any funding in any form.

Data availability & supplementary file

A reporting summary for this article is available as a Supplementary Information file. All data generated in this study are provided in the Supplementary Data/Source Data files. The source data underlying the Main and Supplementary Figures are provided as a Source Data file. Source data are provided in this paper. All Python packages used in this manuscript are described in the Reporting Summary and are available at the following link https://github.com/abdukhan555/

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