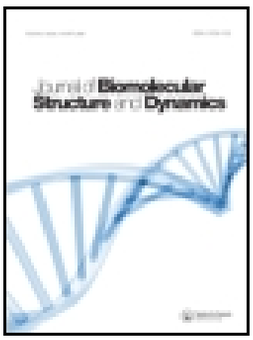

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ABSTRACT

Atrazine is the most commonly used herbicide worldwide in the agricultural system. The increased environmental concentration of the atrazine showed the toxic effects on the non-target living species. Biodegradation of the atrazine is possible with the bacterial systems. The present study investigated biodegradation potential of atrazine degrading bacteria and the impact of atrazine on environmental systems. Model of atrazine fate in ecological systems constructed using the cell designer. The used model further analyzed and simulated to know the biochemistry and physiology of the atrazine in different cellular networks. Topological analysis of the atrazine degradation confirmed the 289 nodes and 300 edges. Our results showed that the overall biomagnification of the atrazine in the different environmental systems. Atrazine is showing toxic effects on humans and plants, whereas degraded by the bacterial systems. To date, no one has analyzed the complete degradation and poisonous effects of the atrazine in the environment. Therefore, this study is useful for overall system biology based modeling and simulation analysis of atrazine in living systems.

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KEYWORDS
Atrazine; system biology; modeling; environment; biodegradation

1. Introduction

Pesticides are commonly used throughout the world to feed the large scale populations and other basic household requirements (Huang et al., 2019). Pesticides are used in the form of insecticides, herbicides, rodenticides, and others (Bhatt et al., 2020a, 2020b, 2020c). One of the widely used herbicide is atrazine belongs to the triazine class of chemicals (Szewczyk et al., 2020; Wang et al., 2020; Bhatt et al., 2020d, 2020e). Throughout the world consumption of the atrazine is 70,000 to 90,000 tons (Hansen et al., 2019). This herbicide is mainly used to control the grassy and broadleaf weed in the crops maize, wheat, sugarcane, conifers, canola, sorghum, and nuts (Singh et al., 2018). Atrazine is recalcitrant in the environment and persists up to a long time in an environment that can contaminate the groundwater. The residues of atrazine were found up to 21 years in unsaturated soil of Germany (Vonberg et al., 2014). It is included in the category of toxic chemicals which disrupt the endocrine receptors (Hansen et al., 2019). Atrazine is toxic to living systems. The main characteristics caused by it are genotoxicity, mutagenicity, defective cell division, hormonal imbalance, etc. (Abdulelah et al., 2020). Due to the severe toxicity caused by atrazine is it banned in the European Union since 2004 (Szewczyk et al., 2020). At present, it is widely used in the USA, Australia, and other parts of the world. To remove the atrazine from the environment biodegradation is an important aspect. Physicochemical methods of the atrazine degradation are costly and not safer than bioremediation approaches (Wang et al., 2020).

Microbial techniques are eco-friendly and cost-effective approaches for the degradation of pesticides (Mishra et al., 2020; Zhan et al., 2020; Bhatt et al., 2020f). To reduce the residues of the atrazine from the environment, indigenous microbial strains and their consortium can be applied at contaminated sites. To date, various researchers have confirmed the atrazine degrading microbial strains from the contaminated sites. These strains are able to use the atrazine as the sole source of carbon and nitrogen and efficiently transformed it into the non toxic environments (Zhang et al., 2019). Microbial degradation of atrazine is a complex process mediated by several sets of enzymes. The degradation of the atrazine formed the hydroxy, dealkylated, and dechlorinated byproducts such as hydroxyatrazine, deisopropylatrazine which can be microbially transformed into other intermediate compounds (Singh et al., 2018). Complete mineralization of atrazine converts it into the non toxic and environmentally accepted metabolites. The bacterial strains belongs to

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Arthrobacter aurescens TC1, *Rhodococcus* sp. NI86/21, *Pseudomonas, Actinobacteria, Klebsiella variicola* strain FH-1 (Zhang et al., 2019), *Citricoccus* sp. strain TT3 (Yang et al., 2018), *Arthrobacter* sp., DNS10 (Jiang et al., 2019), *Bacillus velezensis* MHNK1 (Jakinala et al., 2019) are able to degrade the atrazine efficiently under the various environmental conditions (Fernandes et al., 2020; Lihl et al., 2020). Whereas the fungi *Metarhizum*, *Pleurotus,* and *Phanerochaete* are able to degrade the atrazine through their metabolic pathways (Khromonygina et al., 2004; Mougin et al., 1994; Szewczyk et al., 2020). In addition to microbial degradation, cells can be used as a biosensor to check the contaminant at the natural environmental sites (Silverman et al., 2020). The microbial metabolic pathways of atrazine confirmed in the laboratory by various techniques such as HPLC, GC, and compound-specific chlorine isotope fractionation methods (Lihl et al., 2020). For the catabolism of the atrazine in bacteria, six genes are required, which is encoded by the *atzABC* and *atzDEF* genes. The proteins encoded by the atzA, atzB, and atzC play important role in removal of chlorine atoms and production of cyanuric acid as intermediate metabolite (García-González et al., 2003). Furthermore, cyanuric acid converted into ammonia and carbon dioxide via the action of the genes *atzDEF* (Porrúa et al., 2010). Some of the gram-positive bacteria produced the amidohydrolase act as regulatory enzyme for atrazine degradation (Fernandes et al., 2020; Mulbry et al., 2002).

Due to the large scale use of atrazine in the agricultural sectors, the residual concentration is increasing into the environment. The high concentration of atrazine not degraded in the environment easily so that it can affect every living system via biomagnification process. The application of atrazine is only used for the control of pests while not monitored for the other harmful effects on the living systems. Due to the its residual concentration atrazine found in every trophic level of the ecosystem. It can affect humans, plants, and living soil system. Advancement in the next generation highthroughput sequencing techniques explores the huge amount of data for the atrazine degradation and hazardous effect in the living system (Rawat & Rangarajan, 2019). System biology is a popular tool for the analysis of the complete degradation of pesticides and their effect on the living systems (Bhatt et al., 2019a, 2019b, 2019c; Bhatt & Barh, 2018). Modeling and simulation make the study easy to understand the biochemistry and physiology of the pesticides (Pathak et al., 2017).

To date, various researchers have tried to isolate and characterize atrazine degrading microbial strains. On the biomagnification aspect, no one has given a clear concept about the residual atrazine in the environment. This research work could be helpful to understand the detailed microbial system biology associated with atrazine degradation and associated impact in living systems. The simulation and modeling of atrazine have been explored in this study for depth molecular understanding and bioremediation at complex environments.

2. Materials and methods

2.1. Establishment of the model

Previous literature was thoroughly explored to investigate the link between atrazine, bacteria, weed, soil, atmosphere and human systems. To develop a model at biochemical level, it is necessary to estimate the reactions in individual systems. System Biology Graphical Notation (SBGN) was used for contriving the biological network to illustrate data in a precise and simple manner (Kitano, 2003) (Figure 1). Atrazine biodegradation pathway in bacteria, insects, and humans were produced in cell designer 4.4. Pathways have stored Systems Biology Mark-up Language (SBML), which is a machine-readable expression for delineating biological network (Bornstein et al., 2008; Funahashi et al., 1998, 2003, 2008; Kitano et al., 2005). Cell designer bench work provides all the required tools to design living cells. The system is a graphical user interface that contains all the components including DNA, RNA, Protein, Catalysis, stimulation, inhibition, phosphorylation, degradation, activation, transcription, translation to make new cellular pathways. Pathways simulation can be performed by using SBML ODE solver and Copsai tools of cell designer. It is useful for quantitative analysis, simulation, and leading parameters (Gupta & Misra, 2013; Pathak et al., 2017).

2.2. Kinetic rate equations

SBML squeezer 2.1 version of cell designer was used to predict kinetic rate reactions for the established model (Dräger et al., 2015). Kinetic rate equations via cell designer make the cellular system simple and errorless as compared to the complicated manual assignment of rate equations. Cell designer plugin utilizes SBGN representation data from all the components of the atrazine network (Bacteria, insects, and Humans), and SBML squeezer determines Systems Biology Ontology (SBO) annotations to fetch the essential data (Dräger et al., 2008; Gupta & Misra, 2013). Different rate laws consist of various types of enzyme kinetics and mass action. Equations for atrazine degradation are generated by SMBL squeezer. The enzymatic reaction follows Michaelis–Menten kinetics and hill equation for single substrate reactions, irreversible non-modulated non-interacting reactant and enzymes, di-uni enzyme reactions, di–di enzyme reactions, thermodynamics and kinetic modular rate laws (Dräger et al., 2015; Liebermeister et al., 2010).

2.3. Dynamics and simulation of the model

SBML ODE solver library (SOSlib) of the cell designer has been used for the dynamic nature of the predicted atrazine model (Funahashi et al., 2003; Machné et al., 2006). This tool allows for establishing normal differential equations (ODE) based simulations. These simulations are common operational procedures for the quantitative investigation of pesticide biodegradation networks (Pathak et al., 2017). SOSlib programming library is widely applied in the symbolic and numerical analysis of biochemical reaction network models encoded in the SBML. Cell designer acts as a workbench to allow the use of third party modeling and simulation tools such as SOSlib, COPASI, and core simulation library (Hoops et al., 2006; Keller et al., 2013; Machné et al., 2006). The deterministic algorithm was used to construct the atrazine model in bacteria, insects, and humans. To deal with the pesticide bioremediation networks, important

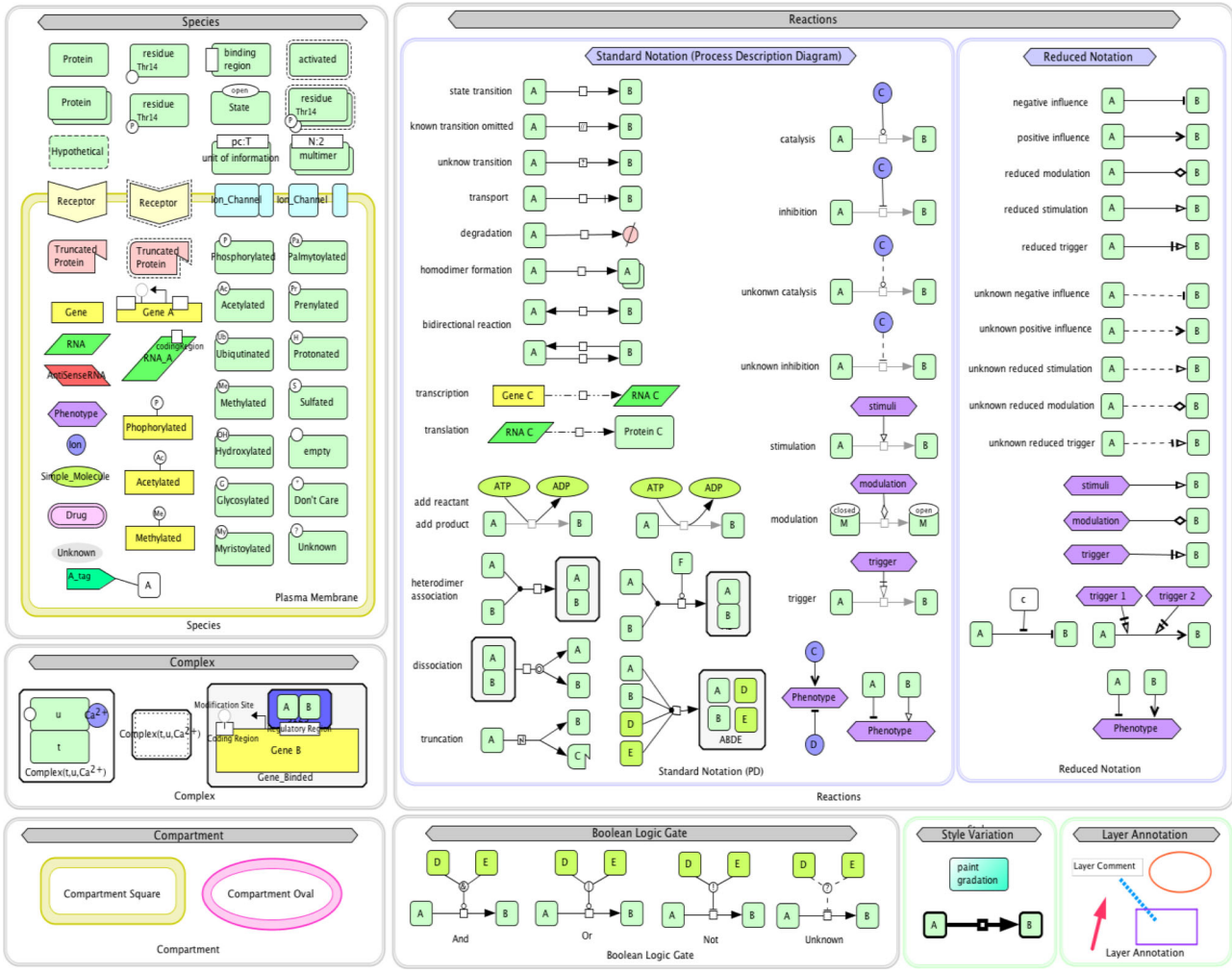


Figure 1. System biology graphical notations used in cell designer.

parameters were analyzed to achieve their complete environmental fate. The native library uses a simulation engine, and results are shown in JAVA based Windows Graphical User Interface (GUI) (Dräger & Palsson, 2014; Funahashi et al., 2008; Pathak et al., 2017).

2.4. Network analysis

Atrazine bioremediation and biomagnification model was constructed in cell designer 4.4 and exported to SBML format (Shannon et al., 2003) that was used in cytoscape version 2.8.3 through Biological network manager (BiNoM) (Zinovyev et al., 2008). BiNoM acts as Cytoscape plugin to support the operation of system biology network (SBML, SBGN, BioPAX) format and deals with complex biological reaction network (Bonnet et al., 2013). Different types of plugins are available to decode the complexity of biological networks (Assenov et al., 2008; Smoot et al., 2011). During this study, we used the network analyzer plugin to assess atrazine bioremediation and biomagnifications effects. Detailed analysis of each component was performed in bacteria, insects, and human systems (Autiero et al., 2009; Pathak et al., 2017).

3. Results

3.1. Description of constructed model

To date, the atrazine signaling model using system biology graphical notation (SBGN) has not been constructed. The goal of the study is to know the bio-remediation of hazardous herbicide (atrazine) for understanding the quantitative and qualitative analysis of herbicide effective pathways in the environment. To date number of scientific reports available on biodegradation of atrazine group of herbicide using the bacterial system, but no one has given complete biomagnification pattern. In this study, we are first hypothesizing complete biodegradation as well as the possible residual amount in different environmental systems. The molecular mechanisms were modeled based on the system biology approach to determine the duration of atrazine pathway responses as well as try to identify key components involved in the regulation of pathway for achieving the effectiveness of atrazine herbicide in the environment. SBGN was utilized to assemble the relationship among different molecular species in the model-based upon previous studies minded form scientific literature and databases.The model consists of 11 compartments, 196 species, 20 proteins, 140 reactions, 12 genes, and 13 RNA (Figure 2).

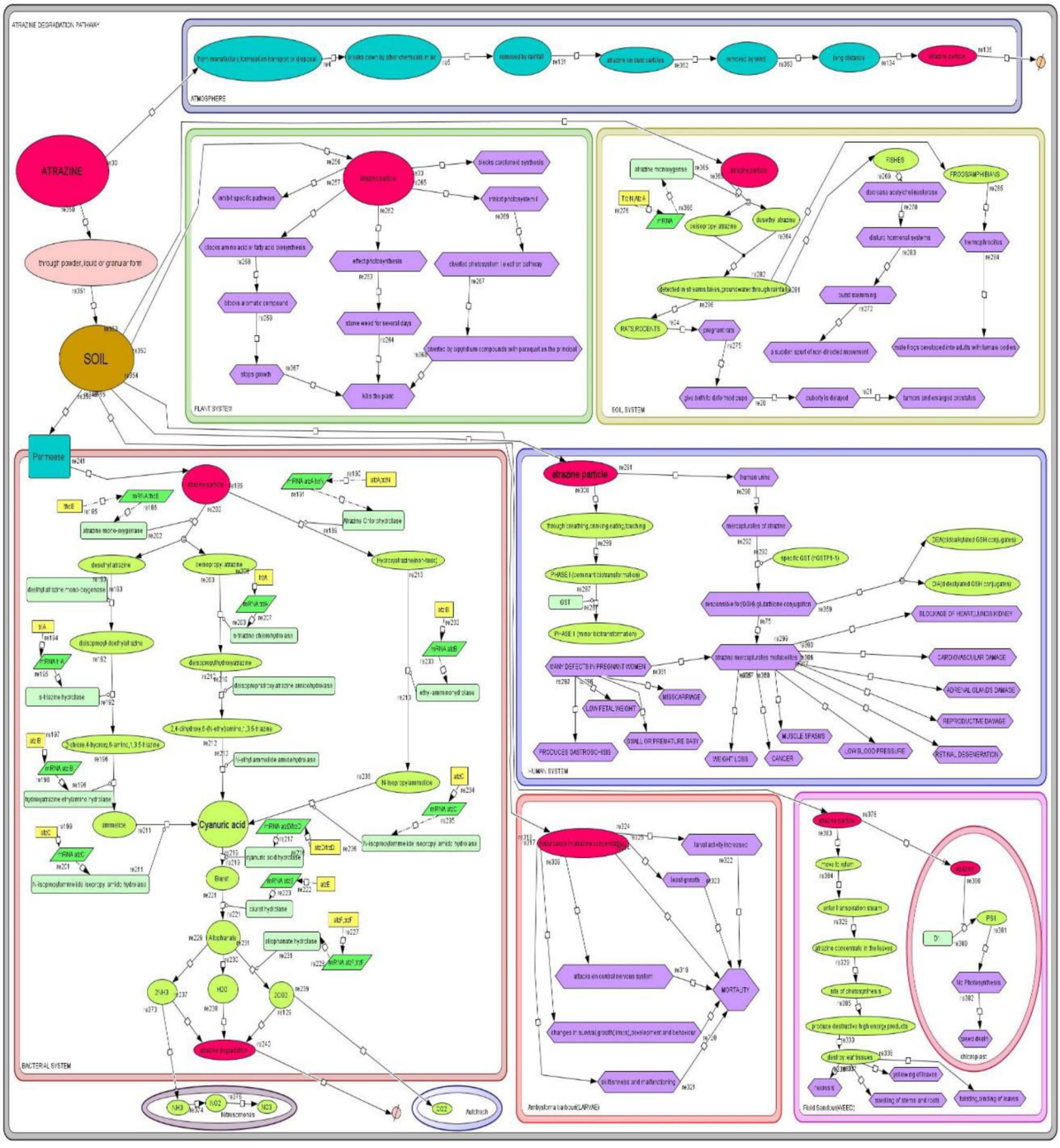
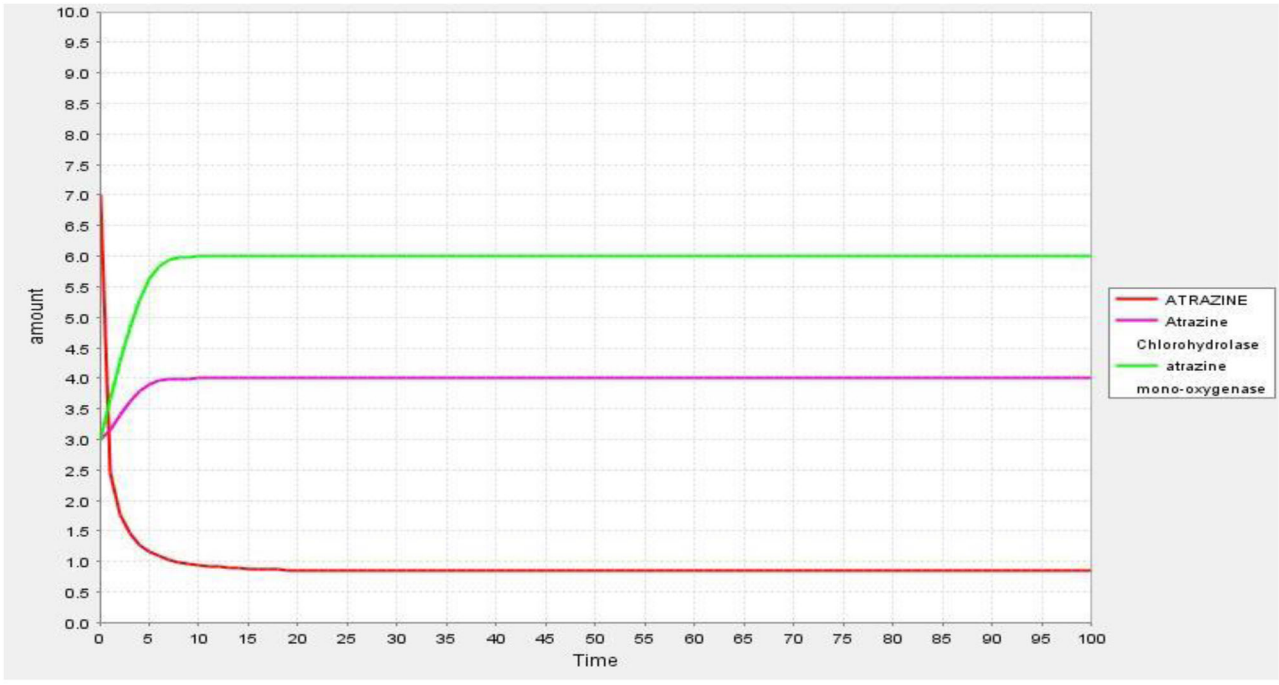


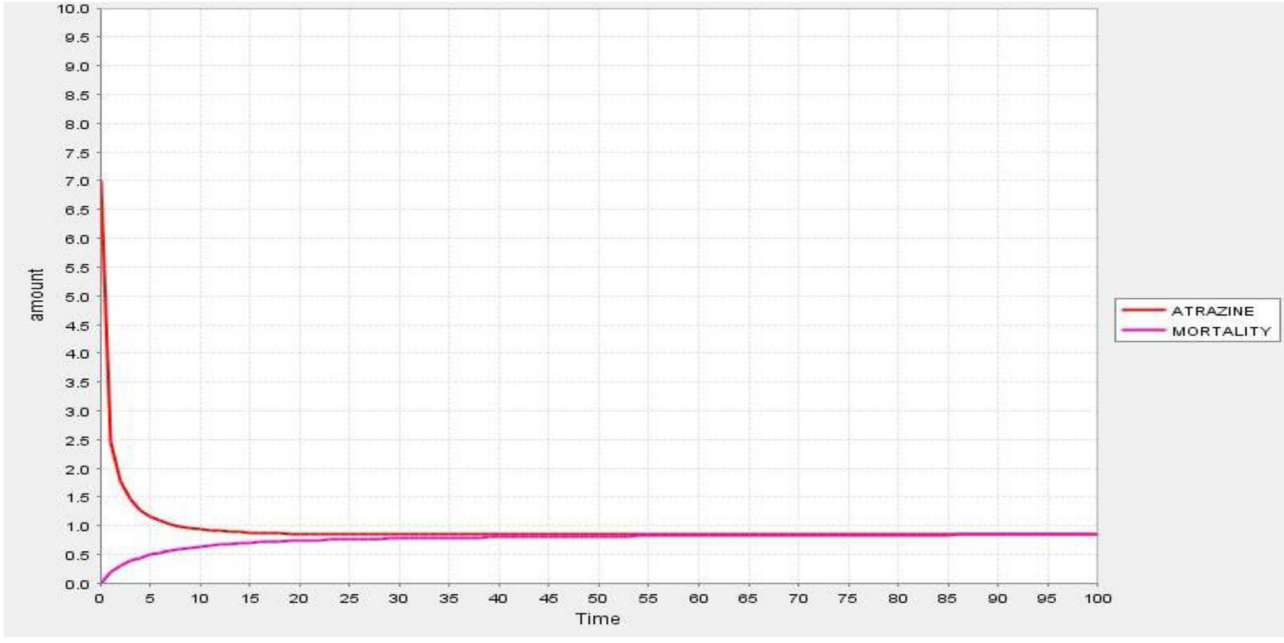
Figure 2. Atrazine degradation pathway in bacteria and its effect on the atmosphere, soil, plant, human, and weed systems. The figure is representing the DNA, RNA, proteins, compartments, catalysis and inhibition, and other molecular tools.

3.2. Dynamic behavior prediction of the constructed model through simulation analysis

The present study explains the outcome of an integrated systems-based approach that explored the intricate nature of the atrazine pathway during effectiveness in the environment at the molecular level. The rate laws produced by SBML squeezer were utilized to predict the dynamic behavior of the pathway.This could be useful for understanding the hazards of atrazine pesticide. The simulation jobs were run on hardware configuration comprises of intel corei7 processor of 2.40 GHz and 16GB RAM on 64-bit windows operating system. The real values for each molecular species in the model have not been used due to unavailability of experimental data for an individual cell. Simulation and dynamics can decipher the behavior of key molecular species. In the absence of quantitative molecular data of an individual cell, it is difficult to estimate the relationship between species. Therefore, quantity is occupied in terms of amount to confirm their existence.The values for each molecular species in the model ranged from 1 to 10. The value of pesticide atrazine is set at 1 to 10; The amounts of species are set at 1 to 10.The protein value are set as 2.5, and genes are set as 1 according to their activation and inactivation states.



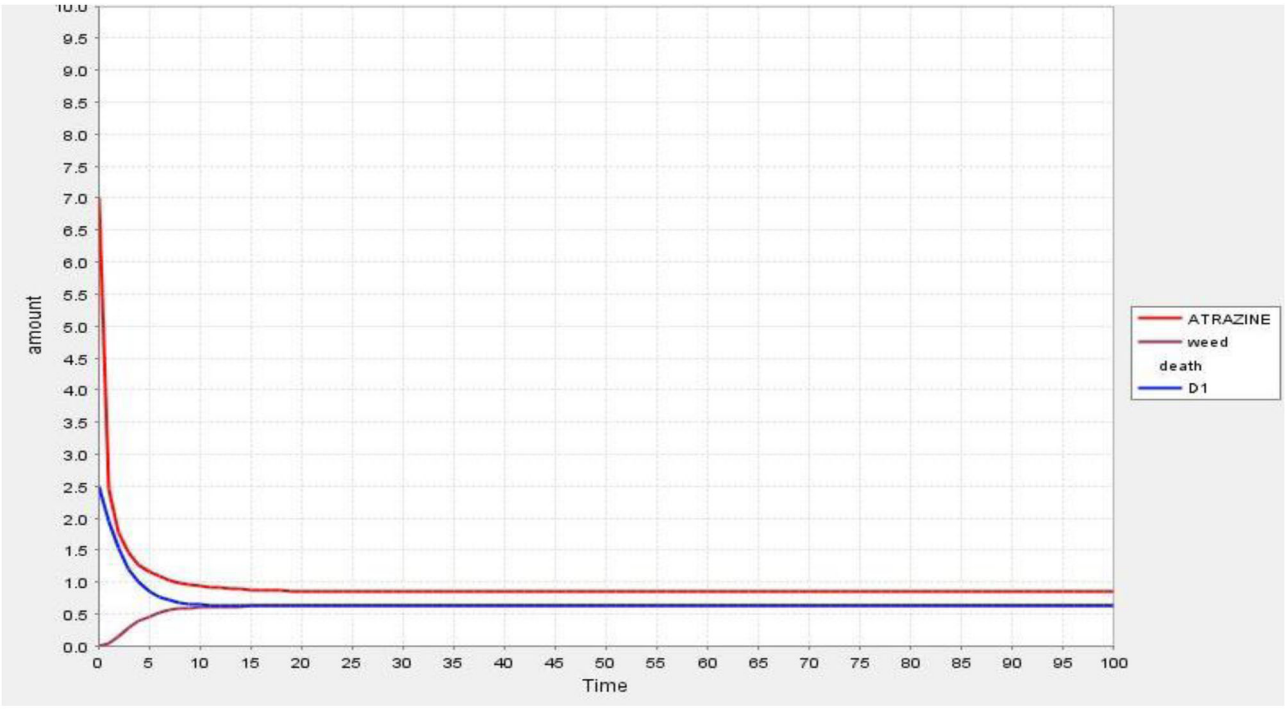
(a)



(b)

Figure 3. (a) Dynamic Behaviour of atrazine with two main bacterial enzymes. These two enzymes are essential for the degradation of atrazine in a bacterial system. (b) Simulation of atrazine concerning its toxic action on the larval system. (c) Simulation of atrazine correlated with weed death, and expression of D1 (PSII protein) in weed system.

Phenotypic value are set as 3, Soil value are set as 7, Permease value is set as 2.5, and all the enzymes involved in the biosynthetic pathway are set at 2.5. The value of CO_2, H_2O, NH_3 are considered as 0.5,0.5,1.2 to observe the dynamic behavior of the system in presence of these molecules. The amount of transcription factors is set to 1, and proteins is set to 2.5 as well as the amount of phenotypic response is set equal to 3. Previous studies clearly demonstrated that when the intensity of abiotic and biotic stresses increases, the defense responses decrease rapidly in time-dependent manner. Here, the dynamic behavior of the different species in the model was visualized during simulation with the course of time.The system C1, C3, C5, C8, C9, C10, C11 is denoted as Atmosphere, Plant system, bacterial



(c)

Figure 3. (Continued).

system, autotroph, atrazine degradation, human system, *Ambystoma barbourin* (LARVAE) and C12 system is named as Field Sandbur (weed). Soil system is also known here, C13. Similarly, C14 and C15 are accordingly known here chloroplast, *Nitrosomonas*. In overall pathway contains 11 compartments, 196 species, 20 proteins, 140 reactions, 12 genes, and 13 RNA. The simulation-based results confirmed that during degradation of the atrazine, the enzyme chlorohydrolase and mono-oxygenase expression was higher (Figure 3(a)). The atrazine concentration was linked with the mortality of the larvae (Figure 3(b)). In addition to these studies, the simulation confirmed that atrazine inhibits the photosystem protein D1 of the weeds (Figure 3(c)).

3.3. Topological analysis of the atrazine degradation

The atrazine model stored in a cell designer after simulation used for the topological analysis with the Cytoscape. The network of the atrazine degradation and connected pathways consisted of 289 nodes and 300 edges (Figure 4). The network contains the undirected edges during interpretation. Results of the parameters calculated the clustering coefficient 0.0, connected component 1, network diameter 41, network centralization 0.031, characteristics pathlength 16.50, network density 0.007 and network heterogeneity 0.471 (Table 1).

The visualization style for the map node size is "Degree," whereas the map node color to "Betweenness Centrality" (Figure 5). The mapping of the atrazine degradation and its effect on cellular systems described in the map generated by Cytoscape tool. The hub nodes mainly represented by red, green, and yellow color. The red color is showing the most important reactions of the network pathways and green representing the common effect on atrazine degradation. Whereas the yellow nodes denoted the least effect on atrazine degradation and effect on different cellular systems. Our results indicated the specific degradation pathways and regulatory steps in the degradation of atrazine.

4. Discussion

Atrazine is used throughout the world due to its effective weedicidal action and less prices. Due to its broad applications, environmental traces are increasing from time to time in recent decades. These residues are harmful to the living systems in the environment and can cause severe illness in humans and other animals. Microorganisms are found to degrade these chemicals from the environment in a cost-effective manner. Previous research has focused on the biodegradation of the atrazine using the bacterial and fungal strains. However, no one has given the complete system biology analysis of the atrazine in terms of the biomagnification study. In this study, we have investigated the biodegradation with comparative effect on other cellular systems. The main concepts behind the study to understand how many systems are working at a time in the environment in the presence of the atrazine. Previously few of the researchers applied the system biology tools for the understanding of the detailed degradation and metabolic networks (Pathak et al., 2017).

After the application of the atrazine in the environment, it interacted within various living systems. In bacterial cells, atrazine come inside the cell using the enzyme permease. Inside the bacterial, it is converted into the desethyl atrazine and deisopropyl atrazine. Through the metabolic pathway,

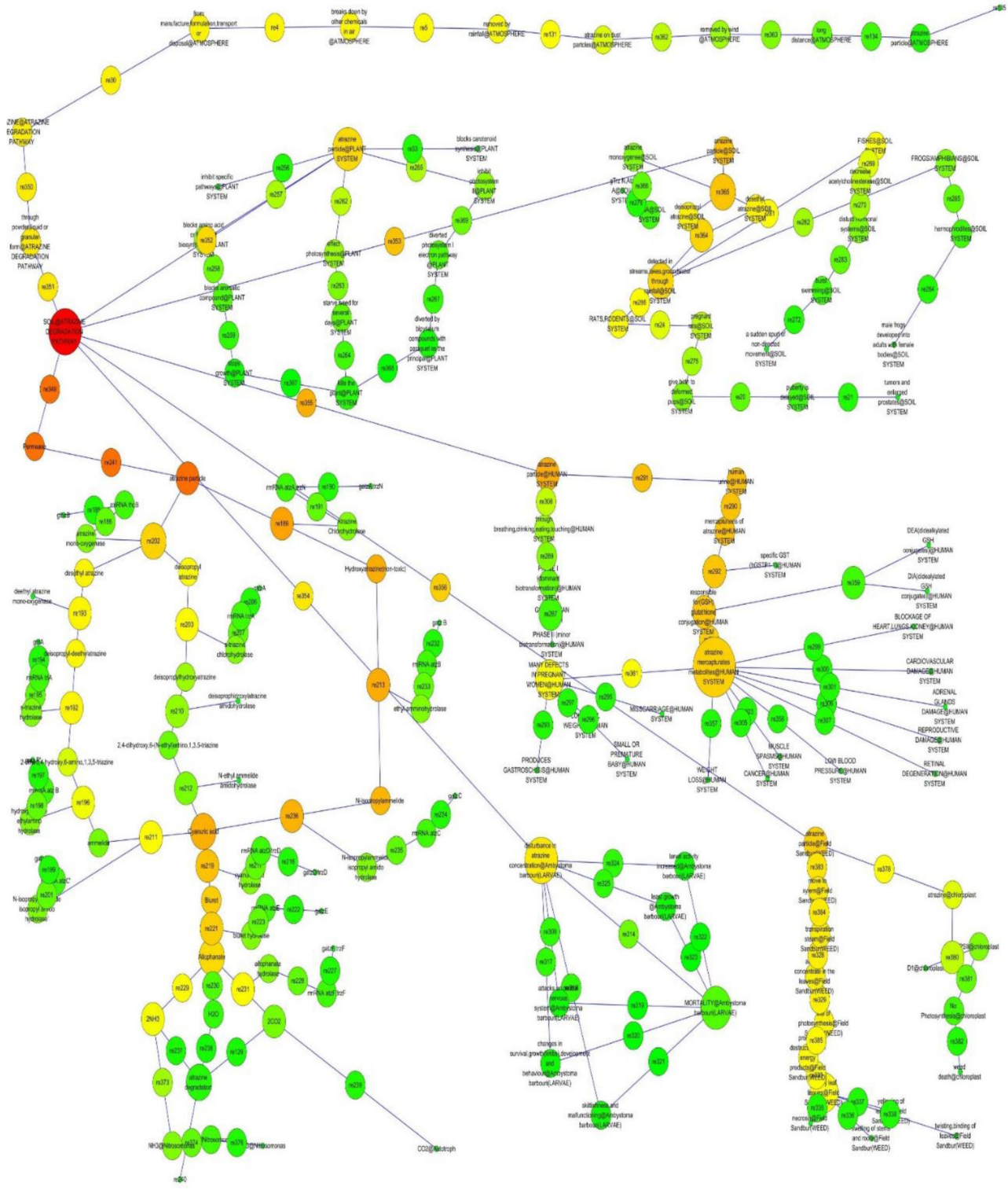


Figure 4. A network analysis of atrazine biodegradation and its effect on other cellular systems.

Table 1. Topological analysis of atrazine signaling network.

Node	289	CPL	16.50
Edge	300	ND	26
CC	1	MENP	0
ANN	2.076	IN	0
SP	4869(5%)	NR	21

Values of topological parameters for Atrazne signaling networks.
CC, connected component; ANN, average number of neighbors; SP, shortest path; CPL, characteristics path length; ND, network diameter; MENP, multiedge node pair; IN, isolated node; NR, network radius.

bacterial cells produce the marker metabolite called cyanuric acid (Porrúa et al., 2010). Monooxygenases and hydrolases are the main enzymes that are playing an important role in atrazine degradation in bacteria. The genes that encoded for the atrazine monooxygenase is *thc*B. The others that are coding for different hydrolases are *atz*ABC and *atz*DEF (Lihl et al., 2020). The cyanuric acid formed after atrazine degradation can be converted into CO_2 and NH_3 (Fernandes et al.,

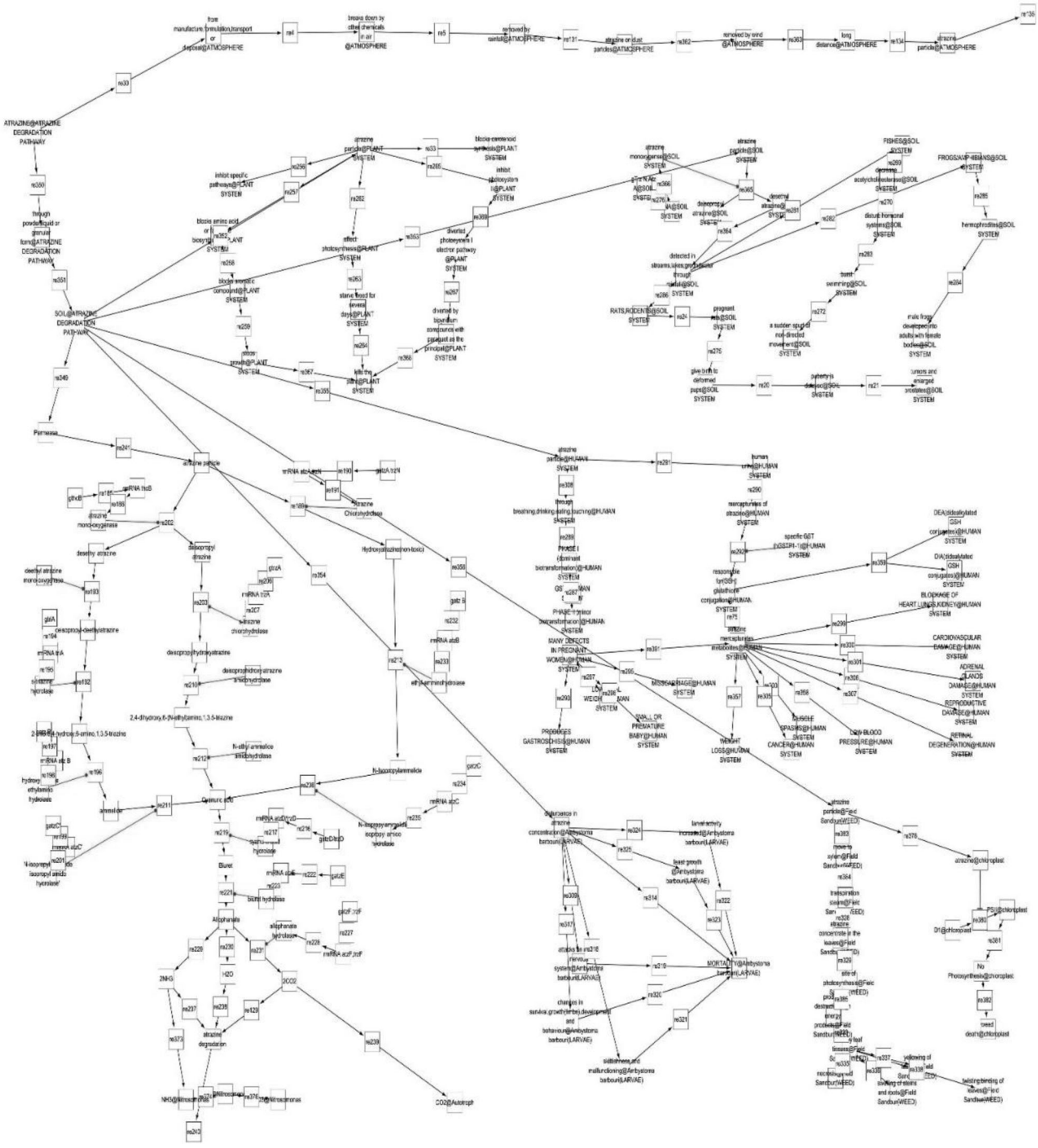


Figure 5. Module view of the atrazine degradation and affects other living systems with physical simulation and catalysis.

2020). These low molecular weight can be used by the soil bacteria like *Nitrosomonas*. Atrazine is acting as both nitrogen and carbon source for the growth of the microbial cells due to the presence in atrazine molecular structure.

The biodegradation of the atrazine reported well in many previous investigations (Singh et al., 2018). But the information about degradation is not sufficient to understand the real facts about their environmental fate. The development of the networking sciences proves these studies can be possible with the modeling and simulation tools. In this study, we have made the network of all the information together for the easy understanding of the atrazine degradation. In our simulation study of atrazine, we have investigated various nodes that are responsible for degradation and toxic effects pathways (Pathak et al., 2017; Vehlow, 2015). On the basis of the color in the module view, we have predicted the red one for most regulatory and yellow hub nodes for the least regulatory function in the degradation network (Barabási & Oltvai, 2004; Kohl et al., 2011). Previously for methyl halide degradation, the hub nodes and their functions were explained (Bhatt et al., 2019b). Our results are in line with the previous findings of modeling and simulations (Pathak et al., 2017).

The herbicide atrazine affects the plant system by inhibiting several metabolic pathways. It mainly blocks the amino acid biosynthesis, inhibits the plant photosynthesis by blocking the electron transport chain. In the soil system, atrazine disturbs all the soil and water ecosystem. In high concentrations, it acts as a toxic chemical for frogs and fishes. The small traces of the atrazine also contaminated the air of the atmosphere where it can be degraded due to rainfall and wind action physically. In humans, several adverse actions of the atrazine reported, such as low fetal weight, cancer, muscle spasms, contaminated urine, and cardiovascular damage. Insects showed mortality for the atrazine due to the disturbance of the central nervous system. In the weeds, tissue damage was observed in the presence of atrazine. It mainly inhibits the function of the D1 protein of the photosystem II of weeds.

5. Conclusion

The present research work investigated the complete system biology analysis of atrazine degradation. Modeling and simulations of the atrazine helps to understand the complex biological network within various cellular systems. This study investigates the toxic effect of atrazine in living system and biodegradation using bacterial strains. The correlated dynamics study of atrazine degrading chlorohydrolase and monooxygenase suggested important role in atrazine bioremediation. The findings of the present study could be helpful in understanding the degradation and fate of the atrazine and similar toxic compounds in the environment.

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Authors contribution

PB designed the experiment and analyses the data writing of the manuscript. KS analyzed the data SG, GB, AV, MA, YS, and SC revised the manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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