A new application of the kinetic type theory in immunology

Journal of Physics: Conference Series **2910** (2024) 012007 doi:10.1088/1742-6596/2910/1/012007

A new application of the kinetic type theory in immunology

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Abstract. The kinetic type theory for active particles is a methodology actively used for modeling processes and phenomena in biology and life sciences. One of the fields of its application is immunology, in particular the processes observed in the competition between immune system and foreign antigens. In this paper we present a new mathematical model describing such a complex system and possible occurrence of contemporary diseases. Preliminary qualitative analysis of the model is presented. The role of some of the main model parameters is studied using simulations.

1 Introduction

Knowing the regularities of the functioning of the immune system and the mechanisms of healing in viral infections at a time of continuous growth of chronic viral infections such as hepatitis B and C, cancers and AIDS, is one of the fundamental problems of modern medicine and immunology. Along with the developed theoretical, experimental and clinical immunological methods, an effective tool for studying these regularities is the mathematical modeling of the processes and systems [11, 12].

In recent decades, there has been a significant increase in the amount of work devoted to the modeling of immune processes. A large part of them have a rather formal character, which is why they cause a negative attitude of doctors and biologists. In these models, either the specificity of the studied phenomena is poorly reflected, or they are crowded with unjustified assumptions, the truth of which is quite doubtful. In the first case, the obtained results are trivial from the point of view of biology, and in the second case, it is difficult to separate the results that have a relation to reality from those that do not. Adequate mathematical models, quantitative and qualitative analysis, with an appropriate choice of initial conditions and parameter values, make it possible to obtain new information about the system, in particular, under conditions that have not been experimentally realized. It is also possible to predict different situations.

The problem of studying the occurrence and treatment of malignant neoplasms in the human body is not only medical. Methods from fundamental sciences such as physics, chemistry, mathematics, etc. are applied to study the growth and spread of cancer formations in the body [14].

By the middle of the 20th century, clinicians and immunologists had accumulated a huge amount of observational material on the course of various infectious diseases. As a result of the analyzes of this

material, fundamental results were obtained concerning the interaction between antigens and immunocompetent cells at different levels: macroscopic, intracellular and genetic. These results have made it possible to build numerous mathematical models of immune processes.

The immune system is a highly adaptive defense system that has evolved in vertebrates to protect against invading pathogens and cancer. The most important characteristics of an immune system are:

(i) the ability to distinguish one's own cells from foreign cells, molecules, particles, etc., which may enter the host's body;

(ii) ability to eliminate foreign invaders, some of which are very dangerous;

(iii) ability to recognize and destroy own cells, changed for some reasons such as injuries or diseases such as cancer.

The actions of the immune system against foreign pathogens and modified own cells are defined as an immune response.

Our environment is filled with numerous infectious agents of different shapes, sizes, structures and destructive power. In the absence of protective mechanisms, the human organism can be used as an environment for the development and reproduction of these agents.

The immune system functions as: a physical barrier to foreign cells, viruses and other particles, innate immunity and acquired immunity.

The simplest way to prevent infection is to prevent infectious agents from entering the body. This is accomplished by the physical barrier - the skin and the secretions released by the sweat and sebaceous glands and the mucus released by the internal organs [8]. The body's next defense against pathogens that have crossed the physical barrier is innate immunity. It has two components: the complement system - a group of over 20 proteins that provide the non-specific humoral protection of the body and the cellular protection that is carried out by phagocytes (macrophages and neutrophils). If phagocytosis is not possible (due to the large size of the pathogens, etc.), the so-called NK-cells or natural killers are activated. In the body's defense, there are two different mechanisms for extracellular destruction. For the own cells, which do not have thick envelopes and are capable of apoptosis, it is appropriate to be destroyed by cytotoxicity, which maximally spares the surrounding tissue. Degranulation, on the other hand, releases toxic compounds into the extracellular space. They damage not only the object to be destroyed, but also the surrounding tissue. Therefore, degranulation is used against parasites to which cytotoxicity is not applicable [8]. Another major part of innate non-specific immunity are interferons, which play an important role in protecting the body from foreign pathogens – especially viruses and cancer cells. Interferons are a group of proteins that act as warning signals for viral infection. After infecting the cell with a pathogen, it produces interferon, secretes it outside, and after binding it to the interferon receptors of the neighboring cells, the latter receive the signal of viral danger and react to this signal by stopping the production of proteins and degrading all the RNA available in the cell. When a virus enters such a cell, it cannot develop. Hepatitis B and C viruses do not allow infected cells to produce interferon and neutralize already produced, which is why it has to be injected from the outside. Interferon injections are part of the standard treatment for chronic hepatitis C. Innate immunity is non-specific because it is directed against pathogens in general and not against a specific pathogen. Moreover, it does not improve during the life of the individual, but acts equally on the first and all subsequent encounters with the pathogen. Innate immunity is very useful because its reaction is very fast (up to a few hours after infection), but it is not always effective enough. It acts against all possible pathogens and is often insufficiently adapted to one or another specific antigen. An individual approach to each causative agent can only be carried out by acquired immunity. Acquired immunity is carried out by lymphocytes, called B- and T-lymphocytes according to whether they differentiate in the bone marrow or in the thymus.

Acquired immunity arose after a long evolution in humans and higher mammals to counteract pathogens that manage to overcome innate defenses and enter the body. It is highly specialized and is based on recognition between molecules. When first infected with the relevant antigen, it takes some time (usually one or two days) for this type of immune reaction to occur. If the immune system is already familiar with this type of antigen, the acquired immunity is much faster and stronger. In this subsection, the functions of only the cells that are included in the mathematical model proposed in the following section are considered.

During their reactions against foreign pathogens, which are necessary for the protection of the body, defects sometimes occur that lead to the so-called autoimmune diseases. These are diseases in which the body's defense mechanisms attack its own uninfected elements. The prevalence of these diseases has increased in recent decades. It is estimated that more than one-fifth of the population in developed countries suffers from some autoimmune disease. One of the leading organizations in this field, the American Autoimmune Disease Association (AARDA) cites data that more than 50 million US citizens

have suffered from such diseases in recent years. To get a better idea of this amount, we can compare it to the number of Americans suffering from cancer, which is about 12 million, and those suffering from cardiovascular disease - about 25 million [3].

In researching diseases caused by a malfunctioning immune system against one's own tissues and organs, scientists have classified them into about 100 different diseases. Among them, some of the most widespread are insulin-dependent diabetes, Parkinson's disease, Alzheimer's disease, Meniere's disease, vitiligo, multiple sclerosis, psoriasis, psoriatic arthritis, Hashimoto's thyroiditis, and many others.

The causes of autoimmune diseases are diverse and not yet fully understood. Along with genetic factors, unfavorable environmental conditions (chemicals, pollutants, toxins), stress, infections, weakening of the immune system due to excessive use of drugs, as well as the relative cleanliness of the living environment play an important role [2, 10].

The role of nutrition is also important. On the one hand, the lack of important trace elements (vitamins and minerals) and on the other, the excessive use of gluten-containing foods can contribute to autoimmune diseases. Therefore, it is recommended to include high-quality meat and fish products, eggs, vegetables, fruits, nuts and seeds in the daily menu [3]. Among the factors that can help prevent or treat this type of diseases are stress control, normalizing sleep, avoiding a sedentary lifestyle, spending more time in nature, etc.

Recently mathematical modeling has been successfully used for the description and analysis of various diseases [1]. Among them are also autoimmune diseases [5, 6, 7]. During the process of modeling, information provided by immunology and medicine is used. Very important role plays the understanding and incorporation of the main components and functions of the body's systems of defense. As it is well known, they include physical barriers and the mechanisms of the immune system against foreign antigens [8].

In the long process of human evolution the defense system learned to produce specialized cells and molecules. Among them are lymphocytes, antibodies etc., which are able to destroy some of the foreign antigens and infected own cells. Usually, the immunological system must distinguish their own compartments from foreign agents. This feature of the immune system resulting in the fact that immunological response cannot be triggered against healthy own cells is known as immunological tolerance. Unfortunately, sometimes the mechanisms of tolerance fail and the immunological system attack the own compartments of the body. This is the main cause of autoimmune diseases [8].

The content of this paper is organized as follows:

We describe a kinetic model of autoimmune disease in Section 2. Further, in Section 3 we present a numerical scheme for solving approximately our model. In Section 4 results of numerical simulations are documented. Section 5 is devoted to conclusions.

2 Mathematical model of autoimmune diseases

In this Section we describe a new mathematical model of autoimmune disease. It belongs to the kinetic type models. Kinetic models are characterized by the fact that the populations involved in the interactions are not considered homogeneous, but heterogeneous, due to the different biological activity of their various elements. Historically, kinetic models are influenced by the nonequilibrium statistical mechanics and generalized kinetic theory, see [4] for reference. We use a special variable, denoted by u, which belongs to the interval $[0,1]$ to describe the biological activity of some of the interacting populations. Using this variable, the distribution function of the population denoted by the index i at time t is represented as:

$$g_i(t,u), \quad g_i : [0,\infty) \times [0,1] \to R^+.$$

The functions:

$$n_i(t) = \int_0^1 g_i(t,u)du, \quad n_i : [0,\infty) \to R^+. \tag{1}$$

represent the concentrations of the respective populations.

We consider the following four interacting populations with respective subscripts:

(1) healthy or target cells, labeled by 1;

(2) damaged cells, labeled by 2;

(3) immune cells, labeled by 3;

(4) viral particles, labeled by 4.

The following mechanisms of autoimmune disease development are taken into account. Some healthy cells may be damaged as result of viral infection. This can activate mechanisms of immune defense, which may results in attacks of target cells by the immune cells.

In our model, the biological activity of the immunological cells represents their ability to destroy healthy cells.

In order to keep the model as simple as possible, we assume that the remaining populations corresponding to subscripts $i = 1$, $i = 2$ and $i = 4$ are homogeneous with respect to their biological activaty. Therefore, we assume that for the distribution functions $g_1(t,u)$, $g_2(t,u)$ and $g_4(t,u)$ the following identities hold:

$$g_i(t,u) = n_i(t), \quad i = 1,2,4 \quad \forall u \in [0,1], \quad t \geq 0.$$

As a result, our kinetic model of autoimmune disease has the form:

$$\begin{aligned} \frac{d}{dt}n_1(t) &= P_1(t) + p_{11}^{(1)} n_1(t) - \frac{p_{11}^{(1)}}{K_M} n_1^2(t) \\ &- d_{11} n_1(t) - d_{13} n_1(t) \int_0^1 v g_3(t,v) dv \end{aligned} \tag{2}$$

$$\frac{d}{dt}n_2(t) = d_{13} n_1(t) \int_0^1 v g_3(t,v) dv - d_{22} n_2(t) \tag{3}$$

$$\frac{\partial g_3}{\partial t}(t,u) = p_{23}^{(3)} n_2(t) + p_{34}^{(3)} n_4(t) - d_{33} g_3(t,u) \tag{4}$$

$$\frac{d}{dt}n_4(t) = p_{44}^{(4)} n_4(t) - d_{44} n_4(t) - d_{34} n_3(t) n_4(t) \tag{5}$$

with nonnegative initial conditions

$$n_i(0) = n_i^{(0)}, \quad i = 1,2,4, \quad g_3(0,u) = g_3^{(0)}(u).$$

The parameters of the system (2)-(5) are supposed to be nonnegative.

The equation (2) describes the time evolution of the concentration $n_1(t)$ of the healthy cells. The parameters in this equation have the following biological meaning:

- The function $P_1(t)$ characterizes the rate of production of healthy cells from inner sources;
- $p_{11}^{(1)}$ characterizes the maximal rate of proliferation of the healthy cells;
- K_M characterizes the concentration of the the healthy cells at which proliferation shuts off;
- d_{11} characterizes the rate of natural mortality of the healthy cells;
- d_{13} describes the rate of destruction of the healthy cells by the immune cells.

Equation (3) describes the time evolution of the concentration $n_2(t)$ of the damaged cells. The parameter d_{22} characterizes the rate of natural mortality of the damaged cells.

Equation (4) describes the temporary evolution of the distribution density $g_3(t,u)$ of the immune cells. The meaning of the parameters in this equation is the following:

- $p_{23}^{(3)}$ characterizes the rate of production of immunological cells due to self-antigens presented by damaged cells;
- $p_{34}^{(3)}$ characterizes the rate of production of immunological cells due to viral particles;
- d_{33} characterizes the rate of natural mortality of immune cells.

Equation (5) describes the evolution of the concentration $n_4(t)$ of the viral particles. The meaning of the parameters in this equation is the following:

- $p_{44}^{(4)}$ characterizes the rate of production of viruses;
- d_{34} characterizes the rate of destruction of the virusal particles to immune response;
- d_{44} describes the rate of natural mortality of the viruses.

Our model is more general version of our previous model [9]. In this previous model we did not consider the population of viruses. However, there are evidence that they can have important role in the process of development of autoimmune diseases [3].

3 Numerical scheme for solution

Here we present a numerical algorithm for finding the approximate solution for the unknown concentrations of the interacting populations $n_i(t)$, $i = 1, \ldots, 4$ for any time $t \geq 0$. The concentrations $n_1(t), n_2(t), n_4(t)$ will be computed from eqs. (2), (3) and (5), while the concentration $n_3(t)$ - from eq. (1) using the function $g_3(t, u)$. To obtain the approximate values of the functions $n_1(t), n_2(t), n_4(t)$ and $g_3(t, u)$, we carry out a discretization of the modeled problem (2) - (5) with regard to the activity $u \in [0, 1]$ by introducing a uniform grid using the grid-points

$$u_i = i\Delta u, \quad i = 0, \ldots, N,$$

where N is a positive integer and the step $\Delta u = 1/N$.

By using the constructed grid, we replace the values $g_3(t, u)$ in the modeled problem (2) - (5) with their approximations

$$g_3(t, u_i) \approx g_{3,i}(t), \tag{6}$$

at the state grid-points $u_i \in [0, 1]$.

For each $t > 0$ and each $u_i \in [0, 1]$ with $i = 0, \ldots, N$, we apply the approximations (6) for appropriate quadrature formulae in order to obtain approximations for the integrals:

$$\begin{array}{rcl} \int_0^1 g_3(t, v)dv & \approx & Q_0^N\Big[g_3(t, v)\Big], \\ \int_0^1 v g_3(t, v)dv & \approx & Q_0^N\Big[v g_3(t, v)\Big]. \end{array} \tag{7}$$

In the approximation formulae (7) arbitrary quadratures could be used. For instance, in Section 4, the values $Q_0^N\Big[g_3(t, v)\Big]$ and $Q_0^N\Big[v g_3(t, v)\Big]$ are computed using the composite Simpson's rule [15].

After application of the approximations (6) and (7) to the modeled problem (2) - (5), we obtain a system of ODEs.

The results of the solution of this system are presented in Section 4. As it is mentioned above, the obtained approximate solutions $g_{3,i}(t)$, for $i = 0, \ldots, N$, are used for computing the needed concentrations $n_3(t)$. For this aim we used the formulae

$$n_3(t) \approx Q_0^N\Big[g_3(t, v)\Big]. \tag{8}$$

4 Results of simulations

After performing the procedure described in the previous Section, we obtained a system of ordinary differential equations. This system was solved by the use of the solver `ode15s` from the Matlab ODE suite [13], where we set the parameters $RelTol = 10^{-4}$ and $AbsTol = 10^{-5}$. This solver has been used instead of `ode45` because for some parameter values the corresponding system occurred to be sharp.

The obtained approximate solutions for the function $g_{3,i}(t)$ for $i = 0, \ldots, N$, have been used in (8) for computing the needed concentrations $n_3(t)$.

As initial conditions we assume the presence of certain amount of target cells, small amount of damaged cells and very small amount of viruses and immune cells with low activation state:

$$n_1(0) = 100, \quad n_2(0) = 0.5, \quad n_4(0) = 0.01,$$

$$g_3(0, 0) = 0.01, \quad g_3(0, u) = 0.0, \quad \forall u \in (0, 1].$$

We used the following parameter values in our set of simulations:

$$P_1(t) = 10, \forall t \geq 0, \quad K_M = 100000,$$

$$p_{11}^{(1)} = 0.5, \quad d_{11} = 0.2, \quad d_{13} = 0.1, \quad d_{22} = 1.1,$$

$$p_{23}^{(3)} = 0.001, \quad p_{34}^{(3)} = 0.001, \quad d_{33} = 0.1,$$

$$d_{34} = 0.001, \quad d_{44} = 0.001$$

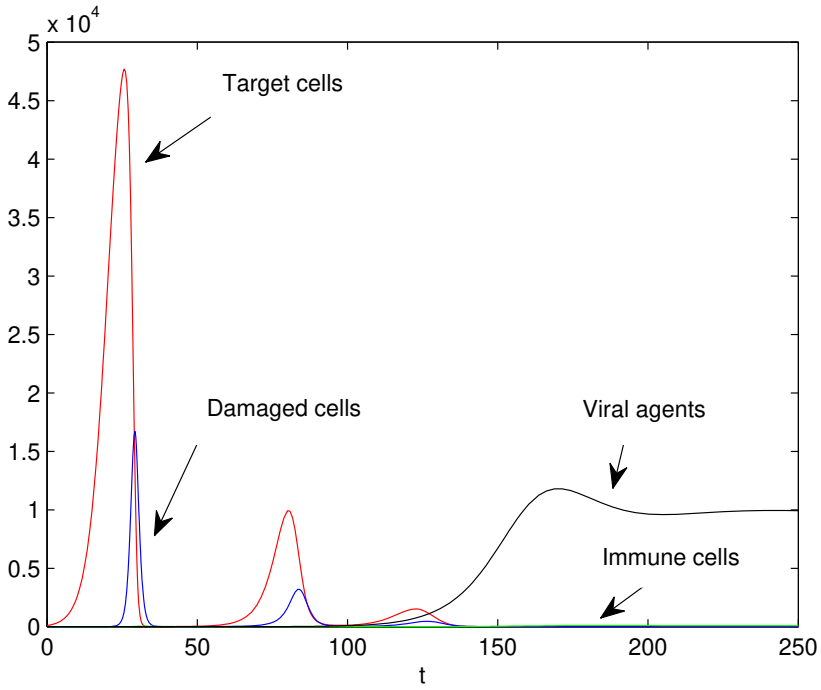

Figure 1: Autoimmune response with high aggressiveness: $p_{44}^{(4)} = 0.1$

The values of parameter $p_{44}^{(4)}$ were different in every case.

The goal of our simulations was to investigate the role of the viruses for the outcome of the interactions. Our numerical experiments show that in some cases, when the rate of production of viral particles $p_{44}^{(4)}$ is significantly bigger than the values of parameters of destruction of viruses d_{34} and d_{44}, the viruses can induce aggressive autoimmune response that destroys too many healthy cells, which can result even in death of a patient. Corresponding results are shown in Fig. 1, where $p_{44}^{(4)} = 0.1$. When the advantage of $p_{44}^{(4)}$ is not so large, more time is necessary for the autoimmune response to cause substantial damages to the organism (see Fig. 2, where $p_{44}^{(4)} = 0.02$). On the contrary, when the mentioned difference is even less, the autoimmune response is not very aggressive and the body tends to equilibrium state which can be considered as chronic autoimmune disease with mild symptoms or even as a healthy state (see Fig. 3, where $p_{44}^{(4)} = 0.001$).

For the new model with viruses (2))-(5)) we obtained the above scenarios for certain values of parameters. In addition, we studied the role of the viruses for the outcome of the interactions. Our numerical experiments show that in some cases, when the rate of production of viruses $p_{44}^{(4)}$ is significantly bigger than values of parameters of destruction of viruses d_{34} and d_{44}, the viral agents can induce strong autoimmune response that destroys too many healthy cells, which can lead even to death. Results for such case are presented in Fig. 1. When the advantage of $p_{44}^{(4)}$ is not so large, more time is necessary for the autoimmune response to cause substantial damages to the organism (see Fig. 2). On the contrary, when the mentioned difference is even less, the autoimmune response is not very strong and the organism tends to equilibrium state which can be considered as chronic autoimmune disease with mild symptoms or even as a healthy state (see Fig. 3).

5 Conclusions

The creation of adequate mathematical models reflecting the behavior of viral infections and tumors and the impact of the immune system on them is extremely useful.

A good mathematical model allows, without doing experiments, to study, analyze and even predict some new properties and changes in the behavior of the studied system.

Mathematical modeling of the object under study allows the often unsuccessful experimentation with the real object to be replaced by targeted research using a mathematical model, allowing the experiment

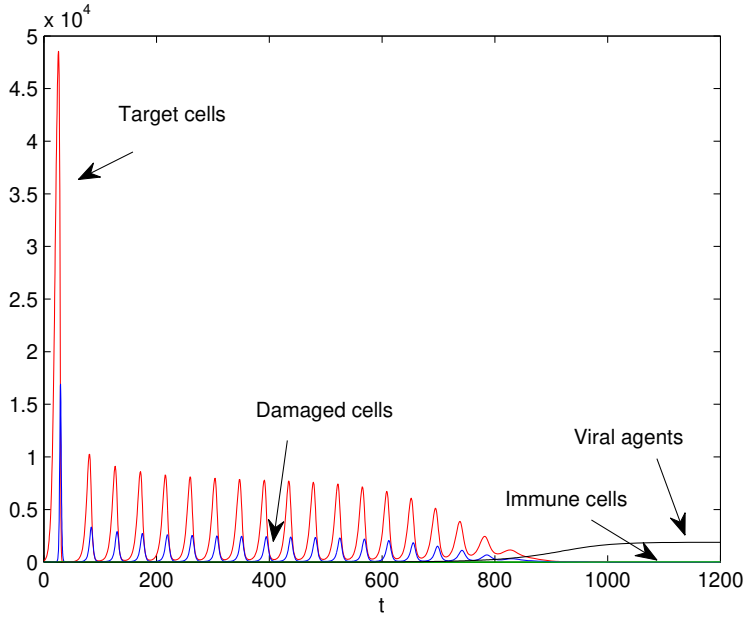

Figure 2: More prolonged aggressive autoimmune response: $p_{44}^{(4)} = 0.02$

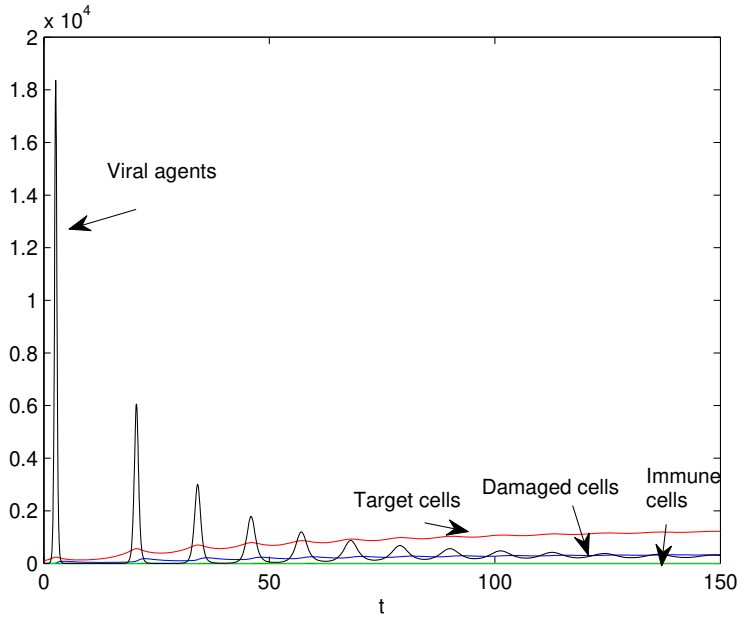

Figure 3: Weak autoimmune response: $p_{44}^{(4)} = 0.001$

to be performed on the model using a computer program.

Thus, mathematics from a means of calculation becomes a necessary method of modern research, and at certain stages it can be the only means of revealing the internal properties of the objects under consideration.

In our paper we propose a new mathematical model of autoimmune disease. The model takes into account the role of viral agents for occurrence and development of autoimmune disease. The modelled problem is solved numerically. The numerical solutions represent several typical dynamics of autoimmune disease.

Our future plans include analysis of the role of other model parameters as well as the development of the model through inclusion of activity for the populations of healthy cells, damaged cells and viral agents. In addition we plan to study the problem whether virus infections can lead to decrease of autoimmune reaction.

Acknowledgements
Mikhail Kolev and Iveta Nikolova thank to the financial support of European Union-NextGenerationEU, through the National Recovery and Resilience Plan of the Republic of Bulgaria, project № BG-RRP-2.004-0002-C01, "BiOrgaMCT".

CRediT roles: Conceptualization, M.L.; methodology, I.N. and M.L.; software, I.N.; validation, M.K. and I.N.; formal analysis, M.L.; investigation, S.S. and M.K.; resources, M.L. and S.S.; data curation, I.N. and S.S.; writing – original draft preparation, I.N. and M.K.; writing – review and editing, M.L. and I.N.; visualization, I.N. and M.K.; supervision, M.L.; project administration, S.S.; funding acquisition, S.S. and I.N.

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