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Integrating Sensitivity Analysis and Explicit Runge-Kutta Method for Modeling the Effect of Exposure Rate to Contaminated Water on Cholera Disease Spread

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ABSTRACT

Mathematical modeling and computer simulations aid in global transmission parameter estimation. Equations, tools, and behaviour assessments are vital in disease control modeling. The bacteria Vibrio cholera causes the waterborne infectious disease cholera, which causes severe diarrhoea and fast dehydration. Haiti; exemplifies cholera devastating impact. Although it has been acknowledged in history, there is a noticeable absence of efficient control strategies. In this paper, we review several papers on cholera models. First; it can answer important questions about global health care and provide useful recommendations. After that; we examine the cholera model using sensitivity analyses with numerical simulation for all states. Full normalizations, half normalizations, and non-normalizations are used to evaluate the local sensitivities to each model state about the model parameters. According to the sensitivity analysis, almost every model parameter might affect the virus's spread among susceptible, and the most sensitive parameters are a and λ(B), where a is the rate of contact with polluted water and $\lambda(B)$ depended on the state B (Density of toxigenic Vibrio cholera in water). So, to prevent the spread of this disease, depending on the simulations, the susceptible and infected people should be more careful about the parameters a and λ(B). Finally; we intend to solve the Cholera disease using both the fifth order and fourth order ERK methods. We aim to then juxtapose our outcomes with those achieved through the classical fourth order Runge-Kutta Method. This comparison will be facilitated by an assessment of their respective relative local truncation error estimators.

Keywords: Cholera Disease, Mathematical Modeling, Sensitivity Analysis, Explicit Runge-Kutta Method.

1. Introduction

The bacterium Vibrio cholera causes cholera; a serious infectious waterborne illness (V. cholera). In developing nations; such as Vietnam (2009), Cameroon (2010–2011), Haiti (2010–2011), Kenya (2010), the Democratic Republic of Congo (2008), Iraq (2008), Zimbabwe (2008–2009), and India (2008), cholera epidemics have been on the rise in recent years (2007)[1]. Because of its considerable impact on public health and its influence on societal and economic progress, cholera has been extensively studied through clinical trials, experiments, and theoretical investigations. It remains a noteworthy worldwide cause of infections and deaths, with the capacity to periodically trigger widespread disease outbreaks[2]. Cholera serves as an illustration of a bacterial infection that spreads through the body by an indirect path, which occurs when people consume feces-contaminated water carrying the bacterium V. cholera[2].

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Transmission of diseases between people and reservoirs means that disease transmission occurs via a pathway other than direct human-to-human contact. Education; is an important component of illness management that is sometimes ignored[3]. It necessitates a human commitment rather than a biological intervention, but it has the potential to yield huge advantages at a cheap cost. Indeed; behavioural treatments were exclusively responsible for Guinea Worm Disease's near-eradication[4,5]. On the other hand; a lack of knowledge might hasten the progression of the disease. For example; 60% of homosexual males in an urban South African STD clinic were uninformed that anal intercourse constituted an HIV risk factor[6].

Cholera-specific education involves encouraging individuals experiencing symptoms to seek medical help as soon as possible, as well as increasing sanitation and sanitary habits[7]. During the Guinea-Bissau cholera outbreak 1994, indigenous preventative rituals, radio, and word-of-mouth communication proved to be excellent instructional methods[7]. Messages were sent to research participants, who all sought medical help right away, but no one could figure out way the cholera epidemic was disseminated. The KwaZulu-Natal Department of Health in South Africa has

advised that educational messages concerning cholera should emphasize the importance of seeking prompt treatment at rehydration centres, clinics, or hospitals, along with practising self-care at home by consuming more fluids, especially sugar-salt solutions and oral rehydration salts[8].

In[9], they developed a mathematical model for cholera infection that assessed the impact of health education campaigns, vaccination, treatment, and water sanitation. They found that these interventions, especially expanded and improved vaccination, were crucial for reducing the cholera burden and recommended a combination of public health measures to eradicate cholera effectively. In the paper[10]; they presented a modified mathematical model for controlling cholera outbreaks in Nigeria, focusing on treatment, water hygiene, and environmental sanitation. They analyzed the model's stability and calculated the basic reproduction ratio (R_0) for different control measures, concluding that improving treatment, water hygiene, and environmental sanitation could effectively eradicate cholera epidemics. The researchers in[11] investigated cholera transmission through mathematical modeling, calculating the contact number and stability of infection-free and infection-present solutions. They formulated an optimal control problem to control disease spread based on sensitivity analysis and found that pre-exposure vaccination could significantly reduce the risk of cholera; with numerical results supporting the analytical findings.

Due to the intricate nature of solving a system of ordinary differential equations, precise analytical solutions are generally absent for most problems. Moreover; these problems exhibit diverse time scales that unfold concurrently. As a result; numerous researchers have shown considerable interest in tackling these problems, leading to the development of various numerical techniques throughout the years. These methods encompass the Euler method, the Runge-Kutta method, the Implicit-Explicit (IMEX) Runge-Kutta method, the Signal Diagonally Implicit Runge-Kutta (SDIRK) methods, and the Semi-Implicit and Explicit Runge-Kutta Methods[12-14]. Another approach involves the utilization of the Finite Difference method[15]. Among these techniques, the Explicit Runge-Kutta method (ERK) has gained significant prominence for resolving problems expressed in a differential equation system (equation 1). For a more comprehensive understanding, refer to[16, 17].

Around 1800, William Cumberland Cruikshank (in England) and Louis-Bernard Guyton de Morveau (in France) were the first scientists to advise disinfecting water with chlorine, when it was discovered that chlorine-treated water is efficient in the prevention of water-borne infections[18]. Chlorination can pose issues in certain cases due to reactions with organic compounds in water, leading to the creation of disinfection byproducts like trihalomethanes and haloacetic acids. These chemicals are potentially carcinogenic, so laws require regular monitoring in water systems. DBPs; which carry health risks, according to the World Health Organization, are relatively minor compared to inadequate disinfection[19]. Understanding the basic disease transmission process is critical for developing successful cholera preventive and management methods. As a result, mathematical modeling offers a one-of-a-kind way to learn about the dynamics of serious diseases. Hence; by considering the potential impacts of disease-control strategies such as water chlorination, mathematical modeling can predict the patterns of rapid epidemics such as cholera outbreaks.

2. Mathematical Modeling for the Cholera Disease

The model considers the various dynamics of a cholera epidemic, which are driven by population-specific factors such as water chlorination and bacterium ingestion rates. The initial model compartment and flows are depicted in Figure (1)[20, 21]. Here; we have a complex web of interactions between the infected individual, virus, and environment. The model divides the human population $N(t)$ into two groups: susceptible people $S(t)$, infected individuals $I(t)$, (actually infected people recovered by reaction rate r); And the aquatic population of pathogenic bacteria $B(t)$, and the model states, parameters and their descriptions of their values are given in Table (1). For more details; see[19].

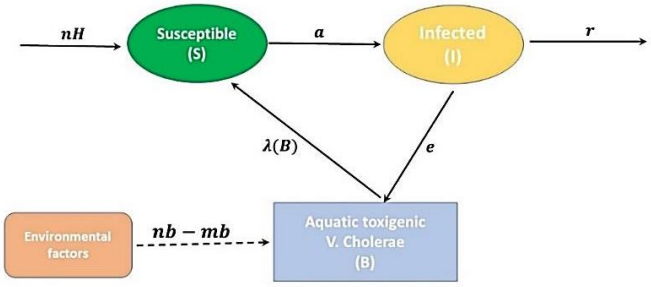

Figure 1: Model diagram for Cholera disease.

Then, the system of differential equations for diagram (1) can be defined as follows:

$$\frac{dS}{dt} = n(H - S) - a\lambda(B)S,$$

$$\frac{dI}{dt} = a\lambda(B)S - rI,$$

$$\frac{dB}{dt} = B(nb - mb) + eI, \quad \text{.....1}$$

where $\lambda(B) = \frac{B}{K+B}$[21].

Tabel 1: The list of symbols with their descriptions are used in the model [21,22.]

Symbol	Biological Descriptions	Values
State variables		
S	Quantity of individuals susceptible	10000
I	Quantity of individuals who have contracted the infection	0.2
B	Density of toxigenic Vibrio cholerae in water (cells per milliliter)	3
Parameter		
H	Overall human populace	10000
n	Rate of human births and deaths (day I)	0.0001
a	Rate of contact with polluted water (day I)	1
K	The density of Vibrio cholerae in water results in a 50% likelihood of	1 ∗ 10^6

	contracting cholera (cells per millilitre)	
r	Rate of cholera recovery among individuals (day I)	0.2
nb-mb	Rate of V. cholera growth and loss in the aquatic environment (day-I) correspondingly	-0.33
e	Impact of each infected individual on the population of V. cholera in the aquatic environment(cell/ml day I)	10

3. Explicit Runge-Kutta Method Algorithms

The conventional order of the explicit Runge-Kutta algorithm corresponds to an approximation of the initial terms found in an infinite Taylor series. This particular series is employed to compute the trajectory followed by a mobile point. Shampine and Gordon; thoroughly explored this concept in their research[23]. The local truncation error (LTE) refers to the remaining segment of the infinite sum that has been eradicated. These forecasting techniques are recognized as explicit Runge-Kutta (ERK) algorithms. Essentially; they predict a future point's location without relying on preceding phase data. Due to this characteristic; they necessitate only a small quantity of input data, rendering it uncomplicated for utilization and construction. The explicit Runge-Kutta (ERK) method of p-stages is used to find the solution to an initial value problem:

$$\frac{dv}{dt} = F(t, v) \quad \text{.....2}$$

where the initial condition is $v(t_0) = v_0$, will be determined as follows:

$$v_{n+1} = v_n + h\sum_{i=1}^{p} b_i k_i \quad \text{.....3}$$

where $k_i = F\left(t_n + c_i h, v_n + h\sum_{j=1}^{p} a_{ij} k_j\right)$ and $c_i = \sum_{j=1}^{p} a_{ij}$, $i = 1, 2, \ldots, p$.

Considering vectors c and b, both having p dimensions, along with the matrix $A(a_{ij})$ of size $p \times p$, the structure of the ERK algorithm for the system (1) can be described as follows [24]:

$$k_1 = hF(t_n, v_n),$$

$$k_2 = hF\left(t_n + \frac{h}{4}, v_n + \frac{k_1}{4}\right),$$

$$k_3 = hF\left(t_n + \frac{h}{4}, v_n + \frac{k_1}{8} + \frac{k_2}{8}\right),$$

$$k_4 = hF\left(t_n + \frac{h}{2}, v_n - \frac{k_2}{2} + k_3\right),$$

$$k_5 = hF\left(t_n + \frac{3h}{4}, v_n + \frac{3k_1}{16} + \frac{9k_4}{16}\right),$$

$$k_6 = hF\left(t_n + h, v_n - \frac{3k_1}{7} + \frac{2k_2}{7} + \frac{12k_3}{7} - \frac{12k_4}{7} + \frac{8k_5}{7}\right).$$

Predictor using a fifth order Explicit Runge-Kutta method:

$$v_{n+1} = v_n + \frac{1}{90}(7k_1 + 32k_3 + 12k_4 + 32k_5 + 7k_6) \quad \text{.....4}$$

Predictor using a fourth order Explicit Runge-Kutta method:

$$v_{n+1} = v_n + \frac{1}{6}(k_1 + 4k_4 + k_6) \quad \text{.....5}$$

The fourth order classical Runge-Kutta method is as follows:

$$v^*_{n+1} = v_n + \frac{1}{6}(kk_1 + 2kk_2 + 2kk_3 + kk_4) \quad \text{.....6}$$

where $kk_1 = hF(t_n, v_n)$, $kk_2 = hF\left(t_n + \frac{h}{2}, v_n + \frac{kk_1}{2}\right)$, $kk_3 = hF\left(t_n + \frac{h}{2}, v_n + \frac{kk_2}{2}\right)$ and $kk_4 = hF(t_n + h, v_n + kk_3)$.

Relative local truncation error estimator (REE) is defined as follows:

$$REE = \frac{|v_{n+1} - v^*_{n+1}|}{v_{n+1}} \quad \text{.....7}$$

You can find the REE for the Cholera disease system (1) by comparing the ERK solutions v of Equations (4) and (5) with the classical RK method v*, and the results are available in Table 3. The benefits of using high-order Runge-Kutta methods for solving differential equations include improved accuracy, reduced error, better stability (especially for stiff problems), increased computational efficiency, reduced sensitivity to step size choices, faster convergence, applicability to a wide range of problems, and the ability to use adaptive step size control.

The arrangement of the Butcher array in equation (3) assumes the subsequent configuration:

$$\begin{array}{c|cccccc}
0 & & & & & & \\
\frac{1}{4} & \frac{1}{4} & & & & & \\
\frac{1}{4} & \frac{1}{8} & \frac{1}{8} & & & & \\
\frac{1}{2} & 0 & -\frac{1}{2} & 1 & & & \\
\frac{3}{4} & \frac{3}{16} & 0 & 0 & \frac{9}{16} & & \\
0 & -\frac{3}{7} & \frac{2}{7} & \frac{12}{7} & -\frac{12}{7} & \frac{8}{7} & \\
\hline
 & \frac{7}{90} & 0 & \frac{32}{90} & \frac{12}{90} & \frac{32}{90} & \frac{7}{90} \\
 & \frac{1}{6} & 0 & 0 & \frac{4}{6} & 0 & \frac{1}{6}
\end{array}$$

4. Analysis of the Cholera Disease System

To solve the Cholera disease system numerically, we typically need to make assumptions or simplifications to obtain an approximate solution. Without specific values for the parameters $(n, a, \lambda, r, nb - mb, e)$ and initial conditions, it is challenging to provide a specific solution. Now; we will do some general steps that will be taken to analyze the system (1):

4.1 Equilibrium Points

To find the equilibrium points of the given differential equation system (1), we need to set the derivatives of each variable concerning time (dS/dt, dI/dt, and dB/dt) equal to zero and solve for the values of S, I, and B that satisfy these conditions. Equilibrium points are the points where the rates of change of all variables are zero, indicating a stable state.

$$\frac{dS}{dt} = 0 \implies n(H - S) - a\lambda(B)S = 0,$$

$$\frac{dI}{dt} = 0 \implies a\lambda(B)S - rI = 0,$$

$$\frac{dB}{dt} = 0 \implies B(nb - mb) + eI = 0 \quad \text{.....8}$$

After solving this non-linear system and putting $\lambda(B) = \frac{B_{eq}}{K+B_{eq}}$. Then; we get the equilibrium points:

$$S_{eq} = \frac{nH}{n + a*\frac{B_{eq}}{K+B_{eq}}} \quad \text{.....9}$$

$$I_{eq} = \frac{aB_{eq}S_{eq}}{r\,(K + B_{eq})} \quad \text{.....10}$$

$$B_{eq} = \frac{eI_{eq}}{nb - mb} \quad \text{.....11}$$

After solving this set of non-linear equations, we find that it has two equilibrium points, namely $E_1 = (H, 0, 0)$and

$E_2 = \left(\frac{Hen - K(nb-mb)r}{e(a+n)}, \frac{Haen + K(nb-mb)nr}{aer + enr}, -\frac{Haen + K(nb-mb)nr}{amr + (nb-mb)nr}\right)$.

4.2 Linearization

Linearization begins by approximating the system's behaviour near its equilibrium points and subsequently examining the stability of these points. This procedure entails the determination of the Jacobian matrix for the differential equation system (1) and its subsequent assessment at every equilibrium point.

To analyze the stability of the equilibrium points, we can use linear stability analysis, which involves finding the Jacobian matrix's eigenvalues at each equilibrium point. The eigenvalues will furnish us with information regarding the stability of the system. To calculate the Jacobian matrix for the given differential equation system (1) at the equilibrium point (S_{eq}, I_{eq}, B_{eq}), we will need to compute the partial derivatives of each equation concerning the variables S, I, and B, and then evaluate these derivatives at (S_{eq}, I_{eq}, B_{eq}). The Jacobian matrix will have the form:

$$\text{Jacobian} = \begin{bmatrix} \frac{\partial\left(\frac{dS}{dt}\right)}{\partial S} & \frac{\partial\left(\frac{dS}{dt}\right)}{\partial I} & \frac{\partial\left(\frac{dS}{dt}\right)}{\partial B} \\ \frac{\partial\left(\frac{dI}{dt}\right)}{\partial S} & \frac{\partial\left(\frac{dI}{dt}\right)}{\partial I} & \frac{\partial\left(\frac{dI}{dt}\right)}{\partial B} \\ \frac{\partial\left(\frac{dB}{dt}\right)}{\partial S} & \frac{\partial\left(\frac{dB}{dt}\right)}{\partial I} & \frac{\partial\left(\frac{dB}{dt}\right)}{\partial B} \end{bmatrix} \quad \text{.....12}$$

We will compute the partial derivatives of each equation in the system (1) concerning S, I, and B, and then evaluate them at the equilibrium point, substitute these values into the computed partial derivatives to get the entries of the Jacobian matrix:

$$\text{Jacobian} = \begin{bmatrix} -n - \frac{aB}{K+B} & 0 & -\frac{aSK}{(K+B)^2} \\ \frac{aB}{K+B} & -r & \frac{aSK}{(K+B)^2} \\ 0 & e & m \end{bmatrix} \quad \text{.....13}$$

Substitute the equilibrium values (S_{eq}, I_{eq}, B_{eq}) into the Jacobian matrix:

Firstly, at $E_1 = (S_{eq}, I_{eq}, B_{eq}) = (H, 0, 0)$.

$$\text{Jacobian} = \begin{bmatrix} -n - \frac{a\times 0}{K+0} & 0 & -\frac{aHK}{(K+0)^2} \\ \frac{a\times 0}{K+0} & -r & \frac{aHK}{(K+0)^2} \\ 0 & e & nb - mb \end{bmatrix} = \begin{bmatrix} -n & 0 & -\frac{aH}{K} \\ 0 & -r & \frac{aH}{K} \\ 0 & e & nb - mb \end{bmatrix} \quad \text{.....14}$$

We must solve the characteristic equation $\det(\text{Jacobian} - \lambda I_d) = 0$ in order to determine the eigenvalues of this matrix, where I_d is the identity matrix, and λ represents the eigenvalues.

$$|\text{Jacobian} - \lambda I_d| = \begin{vmatrix} -n - \lambda & 0 & -\frac{aH}{K} \\ 0 & -r - \lambda & \frac{aH}{K} \\ 0 & e & nb - mb - \lambda \end{vmatrix} \quad \text{... (15)}$$

Setting $\det(\text{Jacobian} - \lambda I_d) = 0$, we will get the Eigen values:

$\lambda_1 = -n,$

$$\lambda_2 = \frac{nb - mb}{2} - \frac{r}{2} - \frac{\left((nb - mb)^2 + 2(nb - mb)r + r^2 + \frac{4Hae}{K}\right)^{\frac{1}{2}}}{2}.$$

$$\lambda_3 = \frac{nb - mb}{2} - \frac{r}{2} + \frac{\left((nb - mb)^2 + 2(nb - mb)r + r^2 + \frac{4Hae}{K}\right)^{\frac{1}{2}}}{2},$$

Substitute the values of the parameters as given in Table 1 and solve for λ. Then, we will get the Eigenvalues for the given differential equation system (1) at the equilibrium point E_1.

$\lambda_1 = -0.000,$

$\lambda_2 = +0.0578,$

$\lambda_3 = -0.5878.$

Since one eigenvalue has a positive real part. So; the equilibrium point $E_1 = (H.0.0)$ is unstable.

At the second equilibrium point $E_2 = (S_{eq}.I_{eq}.B_{eq})$,

$$\text{Jacobian} = \begin{bmatrix} -n - \frac{aB_{eq}}{K+B_{eq}} & 0 & -\frac{aS_{eq}K}{(K+B_{eq})^2} \\ \frac{aB_{eq}}{K+B_{eq}} & -r & \frac{aS_{eq}K}{(K+B_{eq})^2} \\ 0 & e & nb - mb \end{bmatrix} \quad \text{.....16}$$

where $S_{eq} = \frac{Hen - K(nb-mb)r}{e(a+n)}$, $I_{eq} = \frac{Haen + K(nb-mb)nr}{aer + enr}$, and $B_{eq} = -\frac{Haen + K(nb-mb)nr}{amr + (nb-mb)nr}$.

So, we can get the Eigenvalues for the Jacobian matrix of the given differential equation system (1) at the second equilibrium point E_2 will become:

$$\lambda_1 = -0.0001 + 0.0025i,$$
$$\lambda_2 = -0.0001 - 0.0025i,$$
$$\lambda_3 = -0.53.$$

Given that the real parts of all eigenvalues are negative, this characteristic holds across all parameter values outlined in Table 1. Consequently; it can be deduced that the equilibrium point E_2 is stable.

To perform a phase plane analysis and visualize the behaviour of the system, we will plot trajectories in the $(S-I).(S-B)$, and $(I-B)$ planes. This phase plane will help us understand how the variables S, I, and B change over time and how the system evolves. Since; these plots can be complex, we will give you a general idea of how to create these phase plane plots using numerical simulations, as shown in Figure 2.

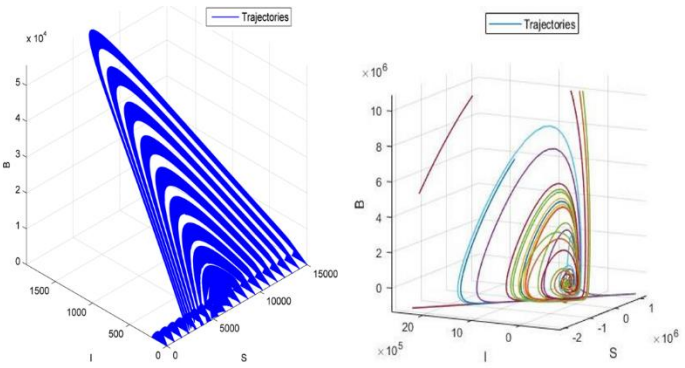

Figure 2: Phase Plane Analysis of the differential equation system (1).

5. Sensitivity Analysis

Sensitivity analysis using mass action law is one of the finest techniques to better understand the issues of the biological process and analyze the output of the mathematical model. The following is a simple version of a sensitivity analysis technique with m reversible processes and n components [25]:

$$\sum_{j=1}^{n} \alpha_{ij}\, \mathcal{C}_j \underset{\mathcal{R}_i^b}{\overset{\mathcal{R}_i^f}{\rightleftharpoons}} \sum_{j=1}^{n} \beta_{ij}\, \mathcal{C}_j\,, \quad i = 1.2.\ldots.m, \quad \ldots\ldots\ldots\ldots 17$$

Where $\mathcal{C}_j, j = 1.2.\ldots.n$ are species (components), α_{ij} and β_{ij} are non-negative integers. And the constant reactions (forward and backward reactions) $R_i^f > 0$ and $R_i^b \geq 0$. The reaction rates may be described as follows using the mass action law:

$$r_i = \mathcal{R}_i^f \prod_{j=1}^{n} \mathcal{C}_j^{\alpha_{ij}}(t) - \mathcal{R}_i^b \prod_{j=1}^{n} \mathcal{C}_j^{\beta_{ij}}(t) \ldots\ldots\ldots\ldots 18$$

Thus, the system of differential equations is formulated below:

$$\frac{d\mathcal{C}}{dt} = \sum_{i\in J\subset\mathbb{R}} \gamma_i\, r_i \ldots\ldots\ldots\ldots 19$$

Where $\gamma_i = \beta_{ij} - \alpha_{ij}$, for $i = 1.2.\ldots.m$ and $j = 1.2.\ldots.n$. Equation (18) it is possible to write it in the form of:

$$\frac{d\mathcal{C}_j}{dt} = \ell_j(\mathcal{C}, \mathcal{R}) \ldots\ldots\ldots\ldots 20$$

Where $\mathcal{C} \in \mathbb{R}^n$ and $\mathcal{R} \in \mathbb{R}^m$. So, model inputs and outputs are represented by the vector of parameters and variables (components)[25]. Local sensitivity is also defined as the change in model states $\mathcal{C}_j, j = 1.2.\ldots.n$ as a function of model parameters $\mathcal{R}_p$, $p = 1.2.\ldots.m$. The sensitivity mathematical formulation for each variable about the parameters is provided in general. After some calculations, we get the following equation, and the Jacobian matrix is being used in the local sensitivity equation as follows:

$$\dot{\mathcal{S}} = \mathcal{L}_{\mathcal{R}_p} + \mathcal{J}.\mathcal{S}, \quad p = 1.2.\ldots.m \ldots\ldots\ldots\ldots 21$$

where the matrices $\mathcal{S}.\mathcal{L}_{\mathcal{R}_p}$ and $\mathcal{J}$ are provided as follows:

$$\mathcal{S} = \begin{pmatrix} \frac{\partial \mathcal{C}_1}{\partial \mathcal{R}_p} \\ \frac{\partial \mathcal{C}_2}{\partial \mathcal{R}_p} \\ \vdots \\ \frac{\partial \mathcal{C}_n}{\partial \mathcal{R}_p} \end{pmatrix}, \quad \mathcal{L}_{\mathcal{R}_p} = \begin{pmatrix} \frac{\partial \ell_1}{\partial \mathcal{R}_p} \\ \frac{\partial \ell_2}{\partial \mathcal{R}_p} \\ \vdots \\ \frac{\partial \ell_n}{\partial \mathcal{R}_p} \end{pmatrix}, \text{and } \mathcal{J} = \begin{pmatrix} \frac{\partial \ell_1}{\partial \mathcal{C}_1} & \frac{\partial \ell_1}{\partial \mathcal{C}_2} & \cdots & \frac{\partial \ell_1}{\partial \mathcal{C}_n} \\ \frac{\partial \ell_2}{\partial \mathcal{C}_1} & \frac{\partial \ell_2}{\partial \mathcal{C}_2} & \cdots & \frac{\partial \ell_2}{\partial \mathcal{C}_n} \\ \vdots & \vdots & \ddots & \vdots \\ \frac{\partial \ell_n}{\partial \mathcal{C}_1} & \frac{\partial \ell_n}{\partial \mathcal{C}_2} & \cdots & \frac{\partial \ell_n}{\partial \mathcal{C}_n} \end{pmatrix}.$$

By inputting parameters $\mathcal{R}_p$ with initial conditions for output components $\mathcal{C}_j$, the initial conditions for the system (20) are calculated. Readers could see more details in[25-33]. Using SimBiology Toolbox in MATLAB, the values of local sensitivity in equation (21) can be calculated with three different methods: full normalization, half normalization, and non-normalization. It is very important to pay attention and care to sensitivity analysis in a wide and accurate complex modeling case such as cholera. Therefore; we analyze the equations for cholera defined in the system (1) and computed all three different cases of local sensitivities for the model compartments with regard to model parameters.

Using the approach of local sensitivity analysis, as described in equation (21), is a step forward in further study and model building. To compute the local sensitivity for every model state to model parameters, we apply the SimBiology Toolbox for MATLAB. We use three approaches to evaluate these model sensitivities: full-normalizations, half-normalizations, and non-normalizations; See Figures (3-5). Surprisingly; the outcomes provide us with a better understanding of the model and also allow us to determine key critical parameters of the model. Figure (3) shows that the set of $\{a.e\}$ is the most sensitive group of parameters on the Cholera disease, especially a (Rate of exposure to contaminated water) is very sensitive to the state variables S and I (Susceptible and infected individuals), and the parameter $\{nH\}$ is less effective model parameters, whereas the set $\{r.nb - mb.\lambda(B)\}$ has not any effective on the model states. Figure (4); provides us with that model parameters nH, r, e and $nb - mb$ are the least critical, but a and $\lambda(B)$ are typically critical to a model, especially $\lambda(B)$ is very sensitive to the state variables S and I

(Susceptible and infected individuals). Figure (5); also shows that the group $\{nH.e.nb - mb\}$ model parameters are the lowest critical, whilst the set of a model parameter $\{a.r.\lambda(B)\}$ becomes sensitive for the model states, especially $\lambda(B)$ is very sensitive to the state variables S and B (Susceptible individuals and Concentration of toxigenic V. cholera in water). Figures (7-9); are numerical simulations for each state variable. Figure (9); provides us with the numerical simulation for all state variables here as time passes through state B (Concentration of toxigenic V. cholera in water) growing more and the number of susceptible individuals become infected and then they become less, so we see that the vibrio cholera spread and all susceptible people become infected.

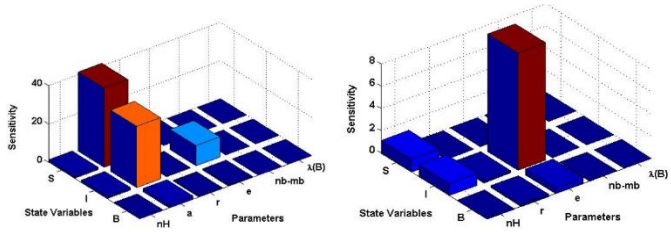

Figure 3: The two figures are local sensitivity analysis for cholera computed with full normalizations using MATLAB. In this approach, these two parameters {a, e} are extremely sensitive compared with other parameters, especially a is very sensitive to the state variable S and I (Susceptible and Infected people), (I) Each compartment's sensitivity to each parameter, (II) Each compartment's sensitivity to each parameter except a.

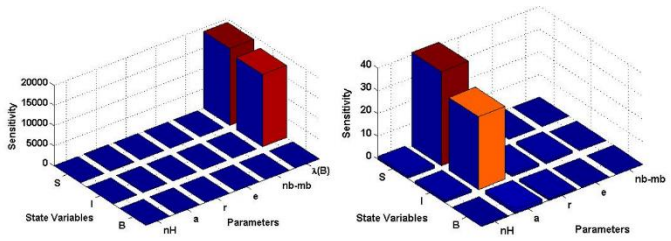

Figure 4: The three figures are local sensitivity analysis for cholera computed with half normalizations using MATLAB. In this approach, the parameter λ(B) very sensitive for state variables S and I, by eliminating λ(B), the parameter a is sensitive to S and I, and if we eliminate a and $\lambda(B)$, other parameters are become sensitive for all state variables, (I) Each compartment's sensitivity to each parameter, (II) Each compartment's sensitivity to each parameter except $\lambda(B)$.

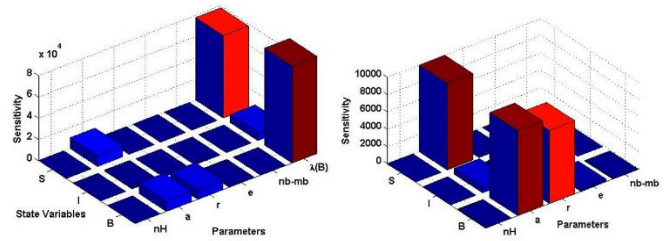

Figure 5: The two figures are local sensitivity analysis for cholera computed with non-normalizations using MATLAB. In this approach; the group of parameters $\{a, r, \lambda(B)\}$ are very sensitive compared with other parameters, especially $\lambda(B)$ is very sensitive to the state variable S and B, (I) Each compartment's sensitivity to each parameter, (II) Each compartment's sensitivity to each parameter except $\lambda(B)$.

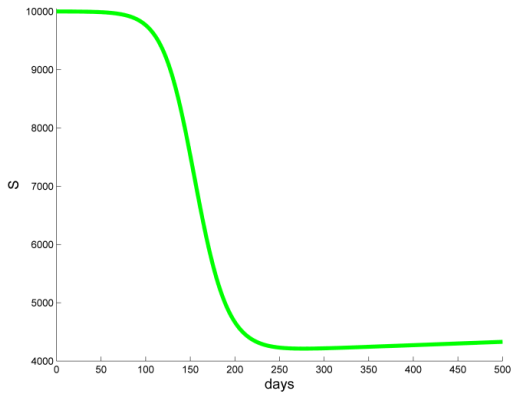

Figure 6: ERK solution for state S.

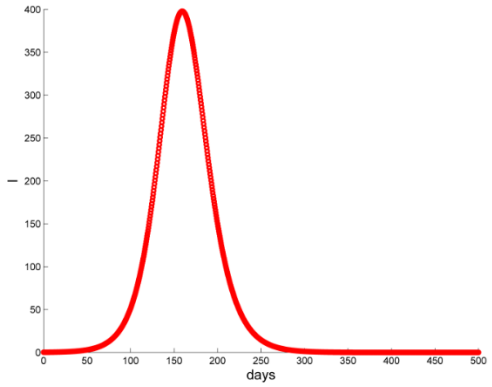

Figure 7: ERK solution for state I.

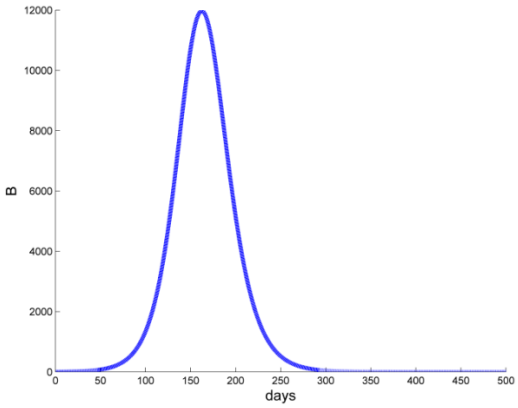

Figure 8: ERK solution for state B.

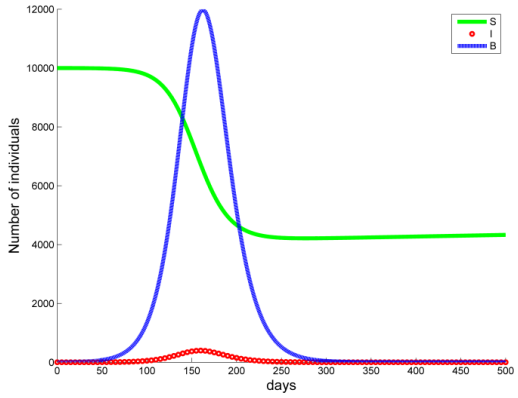

Figure 9: ERK solution for all state variables.

6. Numerical Experiments

The objective of this section is to demonstrate the effectiveness of the introduced technique using an implementation carried out in the Matlab programming language. The specific parameter values and initial conditions can be found in Table 1.

Tabel 2: Comparison between the ERK solution of fifth and fourth order for the cholera disease system (1).

Time (days)	*S*		*I*		*B*	
	ERK 5th Order	ERK 4th Order	ERK 5th Order	ERK 4th Order	ERK 5th Order	ERK 4th Order
0	1.0000e+4	1.0000e+4	0.2	0.2	3	3
50	0.9987e+4	0.9988e+4	3.0288	2.9268	7.8133e+1	7.5499e+1
100	0.9765e+4	0.9779e+4	51.6059	48.4650	1.3430e+3	1.2605e+3
150	0.7527e+4	0.7644e+4	372.6154	365.8305	1.0708e+4	1.0452e+4
200	0.4667e+4	0.4680e+4	150.2237	158.7689	5.1572e+3	5.4447e+3
250	0.4230e+4	0.4216e+4	14.6497	15.0380	5.2180e+2	5.3628e+2
300	0.4219e+4	0.4203e+4	1.2360	1.2155	4.4077e+1	4.3403e+1
350	0.4244e+4	0.4229e+4	0.1062	0.1000	3.7783	3.5650
400	0.4272e+4	0.4257e+4	0.0094	0.0085	3.3424e-1	3.0244e-1
450	0.4301e+4	0.4286e+4	0.0009	0.0007	3.0550e-2	2.6531e-2
500	0.4329e+4	0.4314e+4	0.0001	0.0001	2.8847e-3	2.4062e-3

Tabel 3: Relative local truncation error estimator (REE) between ERK solution and classical RK method for the cholera disease system (1).

Time (days)	REE between the fifth order ERK and classical fourth order RK methods			REE between the fourth order ERK and classical fourth order RK methods		
	S	*I*	*B*	*S*	*I*	*B*
0	0	0	0	0	0	0
50	0.0000	0.0115	0.0115	0.0000	0.0230	0.0230
100	0.0005	0.0209	0.0211	0.0010	0.0426	0.0430
150	0.0052	0.0054	0.0074	0.0102	0.0131	0.0170
200	0.0007	0.0183	0.0180	0.0021	0.0365	0.0357
250	0.0013	0.0069	0.0073	0.0022	0.0191	0.0199
300	0.0013	0.0087	0.0082	0.0024	0.0080	0.0072
350	0.0013	0.0239	0.0235	0.0023	0.0358	0.0350
400	0.0013	0.0386	0.0382	0.0023	0.0638	0.0630
450	0.0013	0.0528	0.0524	0.0023	0.0921	0.0912
500	0.0012	0.0665	0.0661	0.0023	0.1205	0.1196

Furthermore, we will do the parameter analysis, which involves exploring how changes in the values of system parameters affect the behaviour of the system (1). In our case, we are interested in the effects of changing parameters like the transmission rate (a) and recovery rate (r) in the ranges $[0, 2]$ and $[0, 0.5]$, respectively. See Figure 10.

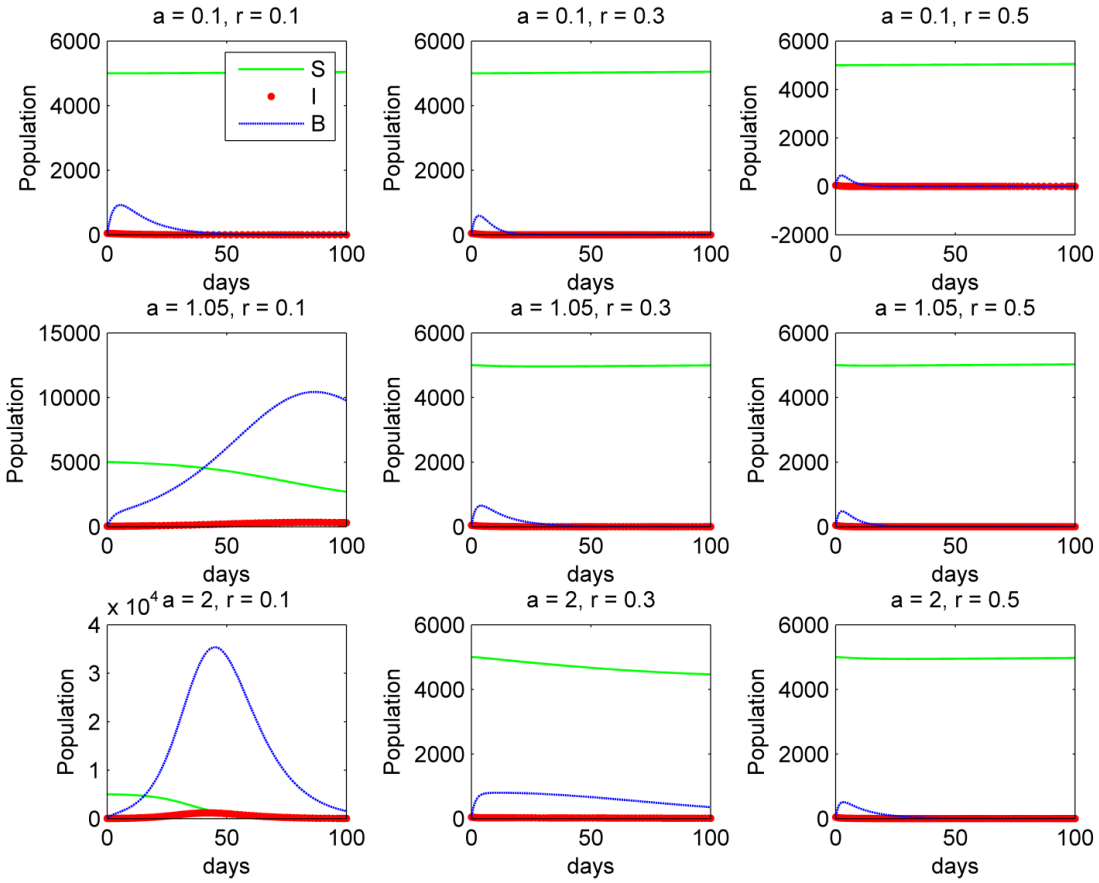

Figure 10: Parameter Analysis: Effects of Changing the parameters a and r.

Conclusion

As a result, using numerical simulations to identify the most critical parameters of the model within that investigation is the reasonable and best option to investigate the model in both a practical and theoretical way, as well as make some recommendations for future improvements to Cholera disease prevention efforts and vaccinations, treatments, and disease control. Additionally; we solved this Cholera disease by fifth order and fourth order ERK methods, compared our results with the fourth order classical Runge-Kutta Method. We got a good result by evaluating their relative local truncation error estimator (REE). Based on the results of the sensitivity analysis, it is evident that nearly all the parameters in the model exert significant influence on the transmission of the virus among vulnerable individuals. Notably; the parameter a representing the rate of exposure to contaminated water and the parameter $\lambda(B)$ associated with the state B (the density of toxigenic Vibrio cholera in water), have emerged as the most impactful factors. The findings strongly suggest that in order to effectively mitigate the spread of this disease, susceptible and infected individuals must exercise heightened caution concerning parameters a and $\lambda(B)$ and the parameter K (Density of Vibrio cholera in water resulting in a 50% likelihood of contracting cholera), whereas it inversely changes with the parameter K.

Conflict of interests

None

Author contribution

The authors contributed equally to this work; form the implementation and design of the research, to the analysis of the results and to the writing of the manuscript.

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References

1. Tuite, A. R., Tien, J., Eisenberg, M., Earn, D. J., Ma, J., & Fisman, D. N. Cholera epidemic in Haiti, 2010: using a transmission model to explain spatial spread of disease and identify optimal control interventions. Annals of internal medicine, 154(9), 593-601 (2011). https://doi.org/10.7326/0003-4819-154-9-201105030-00334
2. Mukandavire, Z., Liao, S., Wang, J., Gaff, H., Smith, D. L., & Morris Jr, J. G. Estimating the reproductive numbers for the 2008–2009 cholera outbreaks in Zimbabwe. Proceedings of the National Academy of Sciences, 108(21), 8767-8772 (2011). https://doi.org/10.1073/pnas.1019712108
3. Hargreaves, J.R., Bonell, C.P., Boler, T., Boccia, D., Birdthistle, I., Fletcher, A., Pronyk, P.M. and Glynn, J.R. Systematic review exploring time trends in the association between educational attainment and risk of HIV infection in sub-Saharan Africa. Aids, 22(3), pp.403-414. (2008). https://doi.org/10.1097/QAD.0b013e3282f2aac3
4. Barry, M. The tail end of guinea worm—global eradication without a drug or a vaccine. New England Journal of Medicine, 356(25), 2561-2564 (2007). https://doi.org/10.1056/NEJMp078089

5. Edward, S., & Nyerere, N.. A mathematical model for the dynamics of cholera with control measures. Applied and Computational Mathematics, 4(2), 53-63 (2015). https://doi.org/10.11648/j.acm.20150402.14
6. Ramjee, G., Gouws, E., Andrews, A., Myer, L. and Weber, A.E., 2001. The acceptability of a vaginal microbicide among South African men. International Family Planning Perspectives, pp.164-170 (2001). https://doi.org/10.2307/2673851.
7. Einarsdóttir, J., A. Passa, and G. Gunnlaugsson, Health education and cholera in rural Guinea-Bissau. International Journal of infectious diseases, 2001. 5(3): p. 133-138.
8. Mugero, C. and A. Hoque, Review of cholera epidemic in South Africa, with focus on KwaZulu-Natal Province. Provincial DoH KwaZulu-Natal (2001). URL: http://www.kznhealth.gov.za/cholerareview.pdf
9. Okolo, P.N., Magaji, A.S., Joshua, I. and Useini, P.F. Mathematical modelling and analysis of cholera disease dynamics with control. Fudma Journal of Sciences, 4(4), pp.363-381 (2020). https://doi.org/10.33003/fjs-2020-0404-494
10. Maliki, O.S. and Chibuike, O.C. A Mathematical Model for the Control of Cholera Epidemic without Natural Recovery. Applied Mathematics, 12(08), pp.655-668 (2021). https://doi.org/10.4236/am.2021.128046
11. Albalawi, W., Nisar, K.S., Aslam, A., Ozair, M., Hussain, T., Shoaib, M. and Zahran, H.Y. Mathematical modelling approach to cholera transmission with vaccination strategy. Alexandria Engineering Journal, 75, pp.191-207 (2023). https://doi.org/10.1016/j.aej.2023.05.053
12. Pirdawood, M. A., Rasool, H. M., Sabawi, Y. A., & Azeez, B. F. Mathematical modeling and analysis for COVID-19 model by using implicit-explicit Rung-Kutta methods. Academic Journal of Nawroz University, 11(3), 65-73 (2022). https://doi.org/10.25007/ajnu.v11n3a1244
13. Sabawi, Y. A., Pirdawood, M. A., & Khalaf, A. D. Semi-implicit and explicit runge kutta methods for stiff ordinary differential equations. In Journal of Physics: Conference series (Vol. 1999, No. 1, p. 012100). IOP Publishing (2021). https://doi.org/10.1088/1742-6596/1999/1/012100
14. Sabawi, Y. A., Pirdawood, M. A., & Khalaf, A. D. Signal diagonally implicit Runge Kutta (SDIRK) methods for solving stiff ordinary problems. In AIP Conference Proceedings (Vol. 2457, No. 1). AIP Publishing (2023). https://doi.org/10.1063/5.0118644
15. SADEEQ, M. I., OMAR, F. M., & PIRDAWOOD, M. A. Numerical solution of Hirota-Satsuma coupled Kdv system By Rbf-Ps method. Journal of Duhok University, 25(2), 164-175 (2022). https://doi.org/10.26682/sjuod.2022.25.2.15
16. Rasool, H. M., Pirdawood, M. A., Sabawi, Y. A., Mahmood, R. H., & Khalil, P. A. Model reduction and analysis for ERK cell signalling pathway using implicit-explicit Rung-Kutta methods. Passer Journal of Basic and Applied Sciences, 4(Special issue), 160-178 (2022). https://doi.org/10.24271/psr.2022.161692
17. Sabawi, Y. A., Pirdawood, M. A., & Sadeeq, M. I. A compact fourth-order implicit-explicit Runge-Kutta type method for solving diffusive Lotka–Volterra system. In Journal of Physics: Conference Series (Vol. 1999, No. 1, p. 012103). IOP Publishing (2021). https://doi.org/10.1088/1742-6596/1999/1/012103
18. Rideal, S. Disinfection and disinfectants (an introduction to the study of): Together with an account of the chemical substances used as antiseptics and preservatives. London, Charles Griffin and Company Limited: Exeter Street, Strand (1895).
19. Al-Arydah, M. T., Mwasa, A., Tchuenche, J. M., & SMITH?, R. J. Modeling cholera disease with education and chlorination. Journal of Biological systems, 21(04), 1340007 (2013). https://doi.org/10.1142/S021833901340007X
20. Capasso, V., & Paveri-Fontana, S. L. A mathematical model for the 1973 cholera epidemic in the European Mediterranean region. Revue d'epidemiologie et de sante publique, 27(2), 121-132 (1979).
21. Codeço, C. T. Endemic and epidemic dynamics of cholera: the role of the aquatic reservoir. BMC Infectious Diseases, 1(1), 1-14 (2001).
22. Adewole, M. O., & Faniran, T. S. Analysis of Cholera model with treatment noncompliance. International Journal of Nonlinear Analysis and Applications, 13(1), 29-43 (2022). http://dx.doi.org/10.22075/ijnaa.2021.23626.2568
23. Shampine, L.F. and Gordon, M.K. Computer Solution of Ordinary Differential Equations-The Initial Value Problem, W.H. Freeman & Co, San Francisco, USA (1975).
24. Park, J.Y., Evans, D.J., Murugesan, K., Sekar, S. and Murugesh, V. Optimal control of singular systems using the RK–Butcher algorithm. International Journal of Computer Mathematics, 81(2), pp.239-249 (2004).
25. Khoshnaw, S. H. A. Model reductions in biochemical reaction networks (Doctoral dissertation, University of Leicester) (2015).
26. Babtie, A. C., Kirk, P., & Stumpf, M. P. Topological sensitivity analysis for systems biology. Proceedings of the National Academy of Sciences, 111(52), 18507-18512 (2014). https://doi.org/10.1073/pnas.1414026112
27. Kiparissides, A., Kucherenko, S. S., Mantalaris, A., & Pistikopoulos, E. N. Global sensitivity analysis challenges in biological systems modeling. Industrial & Engineering Chemistry Research, 48(15), 7168-7180 (2009). https://doi.org/10.1021/ie900139x
28. Powell, D. R., Fair, J., LeClaire, R. J., Moore, L. M., & Thompson, D. Sensitivity analysis of an infectious disease model. In Proceedings of the International System Dynamics Conference (2005).
29. Zi, Z. Sensitivity analysis approaches applied to systems biology models. IET systems biology, 5(6), 336-346 (2011). https://doi.org/10.1049/iet-syb.2011.0015
30. Akgül, A., Khoshnaw, S. H., & Rasool, H. M. Minimizing cell signalling pathway elements using lumping parameters. Alexandria Engineering Journal, 59(4), 2161-2169(2020). https://doi.org/10.1016/j.aej.2020.01.041
31. Khoshnaw, S. H., & Rasool, H. M. Mathematical modelling for complex biochemical networks and identification of fast and slow reactions. The International Conference on Mathematical and Related Sciences (pp. 55-69). Cham: Springer International Publishing (2019).
32. Khoshnaw, S. H., & Rasool, H. M. Model reduction for non-linear protein translation pathways using slow and fast subsystems. ZANCO Journal of Pure and Applied Sciences, 31, 14-24 (2019).
33. Rasool, H. M., & Khoshnaw, S. H. Minimizing IL-6 and IL-10 signalling pathway elements using lumping species and parameters. *Physica Scripta*, *96*(12), 124077 (2021). https://doi.org/10.1088/1402-4896/ac42a7