The Performance of Fixed Step Size and Adaptive Step Size Numerical Methods for Solving Deterministic Cell-Growth Models

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Abstract: - Deterministic cell-growth models describe the growth of cell populations using fixed mathematical rules, assuming no randomness in the system. These models are often based on differential equations that account for the rates of cell division, death, and other biological processes. The solution to the system is obtained via numerical methods. Most of the developed approaches are based on fixed step sizes. However, fixed step size implementation failed to offer the optimal solutions when dealing with stiff challenges. Fixed step size methods can be unstable for stiff equations, where some components of the solution change much more rapidly than others. The step size, h required to maintain stability can become impractically small. Thus, the adaptive step size method is required. Adaptive step size methods adjust the step size dynamically based on the behavior of the solution, aiming to maintain a desired level of accuracy while optimizing computational efficiency. These methods are particularly useful for solving ordinary differential equations (ODEs) where the solution can vary rapidly in some regions and slowly in others. This study is devoted to comparing the implementation of fixed step size and adaptive step size in solving ordinary differential equations (ODEs). The fixed step size and adaptive step size numerical method are solved in this study via the fourth order Runge-Kutta method (RK4) and Runge-Kutta Fehlberg 45 method (RKF45). The performance of both numerical methods used will be analyzed by comparing the numerical results approximated with the actual data. Subsequently, the absolute error, relative error, and rounding-off error will be calculated to compare both approaches. Based on the more precise findings, this work has shown that adaptive step size is predicted to be the optimal representation for solving ODEs. As a result, this may help mathematicians to choose the most effective numerical approach for solving ODEs.

Key-Words: - Adaptive step size; Ordinary differential equations; Fourth order Runge-Kutta method; Runge-Kutta Fehlberg 45.

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1 Introduction

Ordinary differential equations (ODEs) are essential tools for comprehending a wide range of physical phenomena in daily life, such as in biology, physics, chemical reactions, and mechanical systems. ODEs simplify real-world problems into mathematical language for analysis. Furthermore, structural equation modeling via ODEs can be used to study decision-making processes associated with life-risk avoidance behaviors, [1]. While there exist several analytical techniques for ODEs, quite a few of ODEs are not amenable to be solved by analytical approaches, [2]. Therefore, several numerical approximation methods are frequently implemented to resolve mathematical issues that are exceedingly challenging or potentially challenging to manage precisely. It works well for addressing mathematical problems with digital computer codes, by beginning with initial data to identify the optimum solutions.

Numerical analysis for deterministic differential equations is a method used widely in various fields such as engineering, science, economics, and physics for resolving complex mathematical systems in real-world situations. Number of numerical methods have been introduced for solving ODEs such as Euler's method with the lowest order of accuracy, as well as a family of Runge-Kutta methods that have proven to have good accuracy and also stability, [3]. In addition, a few types of numerical methods such as implicit methods and numerical methods for solving stiff ODEs have also been studied. Backward Euler, Trapezoidal Rule, Backward Differentiation formula, and also implicit Runge-Kutta methods are among the common numerical methods that have been used widely for approximating the solution to ODEs, [4]. There are several factors that may influence the choice of numerical method in solving ODEs which are the type of ODE presented, desired accuracy of the solution, and computational cost. Among developed numerical methods for ODEs, Runge-Kutta of order 4 (RK4) offers a relatively high degree of accuracy making it efficiently suitable for many cases. It has been shown can be applied to a wide range of ODE problems including those with complex dynamics. Unfortunately, this method is said to be very sensitive to step size where the large step size will result in the error to be accumulated rapidly. In this research, numerical methods for solving ODEs are implemented by using the step size, h and the solution for each step size isis thoroughly evaluated. This method also involves performing iterative calculations to approximate solutions, which often result in a numerical value, [5]. The numerical solutions obtained have been compared with the real data which leads to errors. By now, several mathematicians have proposed ways in the literature that rely on a fixed step size, [6], [7]. Unfortunately, there come many situations where the fixed step size does not really work as it has limitations especially when dealing with stiff problems. Although fixed step size variations are preferred for their rapid convergence, they may not always converge to the best solution. The step size h that required to maintain stability can become impractically small. Instead, they may approach a stationary distribution that is difficult to analyze analytically, [8]. Fixed step size implementation is inefficient in analyzing the behavior of the difficult areas. The step size would be limited only by the number of steps we are able to take within the given time frame and may result in the omission of any fluctuations. Furthermore, using a fixed step size for solving ODEs might result in high computational costs since we have to set up the step size as small as possible, [9]. It requires the use of large amounts of data to create solutions, and this requires a significant amount of computational capacity and time for calculation. Thus, the implementation of adaptive step size is required.

Several research papers emphasize the importance of adaptive step size controllers in various contexts, including their application in solving diffusion equations in heat conduction [10] and implementing a nonlinear explicit integration algorithm for ordinary differential equations with adaptive step size, [11]. These studies highlight the significance and effectiveness of adaptive step size techniques in efficiently solving ordinary differential equations (ODEs) in many fields. Adaptive step size is considered as flexible since it can be automatically adjusted to decrease the step size when meeting the challenging parts or to increase the step size when dealing with easy areas, [12]. This leads to enhanced computational solutions and convergence towards parametrized equilibrium viscosity solutions. Additionally, it is crucial for problem-solving as it may lead to more efficient solutions with fewer errors and less computational time in various research areas. Therefore, the adaptive step size numerical method has a great performance in approximating solutions to the system of ODEs.

2 Problem Formulation

2.1 Mathematical Models

From the literature review analysis, modeling physical processes and biological systems incorporating ODEs has been an enormous rise in research. It proves that the mathematical model approaches are widely used to understand the behaviour of the cell growths especially in the context of tumor development and biopharmaceutical production. Deterministic cell growth models describe the growth of cell populations using fixed mathematical rules, assuming no randomness in the system. These models are often based on differential equations that account for the rates of cell division, death, and other biological processes. In previous research, it has been mentioned that a deterministic model, specifically in the field of ordinary differential equations (ODE), is a mathematical framework used to analyze the transmission dynamics of illnesses such as COVID-19, [13]. Furthermore, the examination of microbial growth patterns, such as yeast, is essential for a range of industrial procedures, resulting in the development of deterministic models that can forecast the growth trajectories of microorganisms from the point of introduction until their death, [14]. Deterministic models play an important part in estimating and validating parameters, emphasizing the significance of exposed and infected classes in defining the dynamics of an epidemic, [15].

2.1.1 Deterministic Model of Cell Growth of C. *acetobutylicum* P262

Several mathematical models for the cell growth process of C. *acetobutylicum* P262 have been formulated in the literature. The deterministic model used for cell growth in C. *acetobutylicum* P262 utilizes logistic equations to elucidate its growth dynamics, [16]. This model is crucial for comprehending the population dynamics and metabolic activities of C. *acetobutylicum* in fermentation systems. C. *acetobutylicum* P262 is a Gram-positive anaerobic bacterium that forms endospores. It has been widely used in industrial fermentation procedures to produce acetone and butanol from carbohydrate substrates. Furthermore, C. *acetobutylicum*, which is used in fermentation operations has undergone thorough investigation using diverse mathematical models in order to comprehend its development and dynamics of solvent production. The cell growth of C. *acetobutylicum* in the form of ODEs had been modeled by [17]. The deterministic model of cell growth of C. *acetobutylicum* P262 can be written as:

$$dx(t) = \mu_{\max}\left(1 - \frac{x(t)}{x_{\max}}\right)x(t)dt \qquad t \in [0, 288] \tag{1}$$

Equation above can be written in integral form as:

$$x(t) = x(t_0) + \int_0^t \mu_{\max}\left(1 - \frac{x(t)}{x_{\max}}\right)x(t)dt \tag{2}$$

where x is the cell concentration, $x_{\max}$ denotes the maximum value of cell growth and $\mu_{\max}$ represents the maximum specific growth rate, h^{-1}.

2.1.2 Deterministic Gompertz Model

Various studies have explored the use of differential equations to model tumor growth, with the Gompertzian model showing the effectiveness in describing tumor growth over time, [18]. The mathematical model began with Gompertz, who developed the model to describe his law of human mortality, [19]. This model has the capability to depict undetected stages of a cancerous tumor. The sigmoidal curve was used to accurately represent the overall cell development of the organisms. It demonstrated remarkable predictive accuracy for the progression of breast and lung cancer, [18]. There has been a wide range of applications of the Gompertz model in predicting the growth of tumor cells. The deterministic Gompartz model can be written as:

$$dS(t) = (\alpha S(t) - \beta S(t)\ln(S(t)))dt \tag{3}$$

where $S(t)$ represent the area in cm of the tumor at time, t, α is a parameter related to the initial mitosis rate representing the intrinsic growth rate of the tumor and β which is the growth rate deceleration factor is related to the process known as the antiangiogenic process.

2.2 Numerical Method

Applying numerical methods is required in approximating the solutions for ODEs due to the lack of accessible analytical solutions in various conditions. In ODEs, there exists a variety of established methods for solving ODE issues. Runge-Kutta (RK) methods are widely used as numerical solvers in solving ordinary differential equations (ODEs). The RK method is considered a free-derivative method since it does not rely on high-order derivatives of functions. Instead, it is able to construct highly accurate numerical methods only based on the functions themselves. Somehow, these features of the RK methods contribute to the solution convergence to the ODEs, [20]. Additionally, this method is well recognized for its stability, high accuracy level, and ease of coding.

Among a family of Runge-Kutta methods, RK4 is one of the known numerical methods that provide better accuracy and efficiency of the solutions approximated. The general solution for the RK4 method is:

$$y_{n+1}(x) = y_n(x) + \frac{1}{6}(k_1 + 2k_2 + 2k_3 + k_4), \quad n = 0, 1, 2, \dots \tag{4}$$

where

$$\begin{aligned} k_1 &= hf(x, y) \\ k_2 &= hf\left(x + \frac{h}{2}, y + \frac{k_1}{2}\right) \\ k_3 &= hf\left(x + \frac{h}{2}, y + \frac{k_2}{2}\right) \\ k_4 &= hf(x + h, y + k_3) \end{aligned} \tag{5}$$

The RK4 method is a popular choice due to its balance of accuracy and efficiency. However, it is essential to consider the specific characteristics of the ODE problem and the computational resources available to determine if it is the most appropriate method. Therefore, in this study, the adaptive Runge-Kutta method known as Runge-Kutta Fehlberg (RKF) will be compared to the approximate solutions via the RK4 method.

For the Runge-Kutta Fehlberg method, each of the following six values is necessary for each step as follows:

$$\begin{aligned}
k_1 &= hf\left(t_k, y_k\right) \\
k_2 &= hf\left(t_k + \frac{1}{4}h, y_k + \frac{1}{4}k_1\right) \\
k_3 &= hf\left(t_k + \frac{3}{8}h, y_k + \frac{3}{32}k_1 + \frac{9}{32}k_2\right) \\
k_4 &= hf\left(t_k + \frac{12}{13}h, y_k + \frac{1932}{2197}k_1 - \frac{7200}{2197}k_2 + \frac{7296}{2197}k_3\right) \\
k_5 &= hf\left(t_k + h, y_k + \frac{439}{216}k_1 - 8k_2 + \frac{3680}{513}k_3 - \frac{845}{4104}k_4\right) \\
k_6 &= hf\left(t_k + \frac{1}{2}h, y_k - \frac{8}{27}k_1 + 2k_2 - \frac{3544}{2565}k_3 + \frac{1859}{4104}k_4 - \frac{11}{40}k_5\right)
\end{aligned} \tag{6}$$

Then, an approximation to the solution of the IVP is made using the Runge-Kutta method of order 4:

$$y_{n+1} = y_n + \frac{25}{216}k_1 + \frac{1408}{2565}k_3 + \frac{2197}{4104}k_4 - \frac{1}{5}k_5 \tag{7}$$

where the four function values k_1, k_3, k_4 and k_5 are used. A better value for the solution is determined using a Runge-Kutta method of order 5:

$$z_{n+1} = y_n + \frac{16}{135}k_1 + \frac{6656}{12825}k_3 + \frac{28561}{56430}k_4 - \frac{9}{50}k_5 + \frac{2}{55}k_6 \tag{8}$$

The optimal step size can be determined by multiplying the scalar s times the current step size, h. The scalar s is:

$$s = \left(\frac{tol\, h}{2\left|z_{k+1} - y_{k+1}\right|}\right)^{1/4} \approx 0.84\left(\frac{tol\, h}{\left|z_{k+1} - y_{k+1}\right|}\right)^{1/4} \tag{9}$$

A thorough analysis of the solutions for each step size is conducted for both fourth-order Runge-Kutta and Runge-Kutta Fehlberg methods using the Maple program. The approximation values for both models are obtained using the fourth-order Runge-Kutta algorithm and the Runge-Kutta Fehlberg algorithm. Maple will be used to formulate and solve the nonlinear system of equations for the coefficients of the Runge-Kutta formulas, facilitating the numerical solution of ordinary differential equations with a high level of complexity, [21]. This method can ensure the accuracy and precision of the obtained results. Then, the approximation solutions for the deterministic model in (1) will be compared with the real data. We will also compare the estimated solutions for the deterministic Gompertz model in (3) with the real data. Here, we can see the best performance among fixed step size and adaptive steps.

In this study, the deterministic model of cell growth of C. *acetobutylicum* P262 has been solved via a fixed step size approach by using the fourth order Runge-Kutta (RK4) method and the Runge-Kutta Fehlberg (RKF45) method. The step size will be fixed for every suggested time. If the step size is small, it takes many steps to approach the ideal weights. Additionally, it becomes difficult to achieve significant progress beyond the step size. This issue becomes more apparent when using big step sizes.

Furthermore, the fourth-order Runge-Kutta (RK4) method and the Runge-Kutta Fehlberg (RKF45) method also have been used in solving the deterministic Gompertz model via the adaptive step size approach. This step size has the capability of adjusting the step size automatically during numerical computations based on several criteria. The process applied will verify whether the correct step size is being executed. Two distinct approximations for the answer are generated and compared at every step. The approximation is considered valid whenever there is a significant level of concurrence between the two responses. If there is a discrepancy between the two responses to a certain level of precision, the step size will be lowered. If the solutions agree to more significant digits than required, the step size will be raised.

3 Result & Discussion

In this section, the numerical problems have been solved by the proposed methods using different types of step sizes. Numerical results and errors are computed with the real data using the Maple programming language. Both the RK4 method and RKF45 method have been used in solving the deterministic model of cell growth for C. *acetobutylicum* P262 yeasts, labeled as Yeast 1, Yeast 2, and Yeast 3. Similarly, both methods have been implemented to solve the deterministic Gompertzian model of cancer cell growth for cancer patients, defined as Patient 1 and Patient 2. These methods have been solved and compared with the real data and the results have been presented graphically as follows.

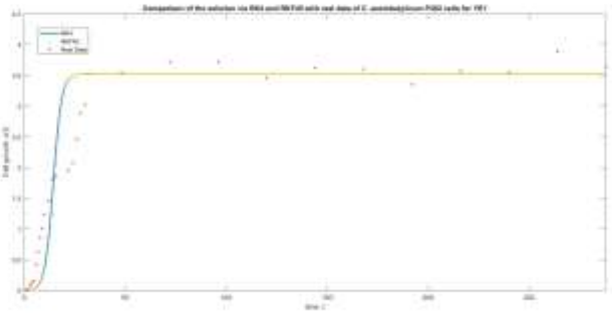

Fig. 1: The comparison of the solutions via fourth-order Runge-Kutta, Runge-Kutta Fehlberg, and real data of C. *acetobutylicum* P262 for Yeast 1

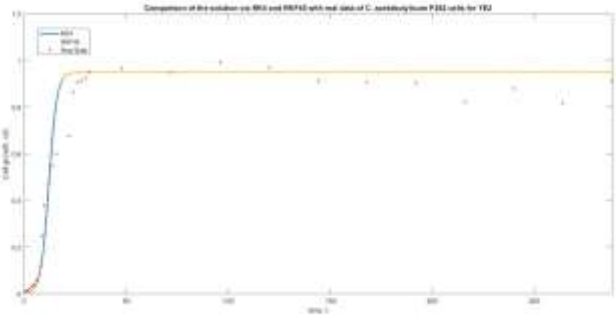

Fig. 2: The comparison of the solutions via fourth-order Runge-Kutta, Runge-Kutta Fehlberg, and real data of C. *acetobutylicum* P262 for Yeast 2

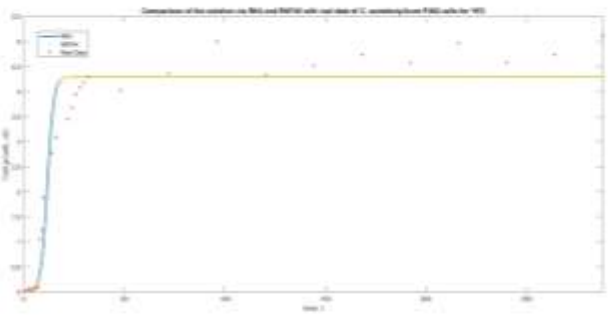

Fig. 3: The comparison of the solutions via fourth-order Runge-Kutta, Runge-Kutta Fehlberg and real data of C. *acetobutylicum* P262 for Yeast 3

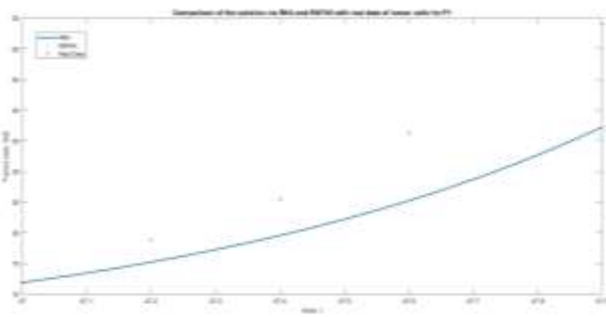

Fig. 4: The comparison of the solutions via fourth-order Runge-Kutta, Runge-Kutta Fehlberg, and real data of cancer cell growth for Patient 1

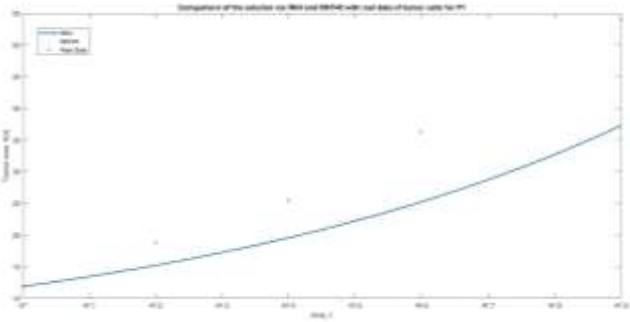

Fig. 5: The comparison of the solutions via fourth-order Runge-Kutta, Runge-Kutta Fehlberg, and real data of cancer cell growth for Patient 2

Figure 1, Figure 2 and Figure 3 describe the deterministic cell growth model of C. *acetobutylicum* P262 for Yeast 1, Yeast 2, and Yeast 3, respectively while Figure 4 and Figure 5 illustrate the deterministic Gompertz model of cancer cell growth for Patient 1 and Patient 2, respectively. Both models were analyzed based on fixed and adaptive step sizes, and the graphs were plotted using the Matlab programming language, allowing for a visual representation of how well the numerical methods approximate the real data in the cell growth models.

These five graphs consist of two different methods used which are RK4 and RKF45 methods, which will be compared with the real data of the models. The blue line stands for fourth order Runge-Kutta, the yellow star stands for Runge-Kutta Fehlberg and the red diamond is the real data of the models.

Here, we can see that Figure 1, Figure 2, Figure 3, Figure 4 and Figure 5 shows the Runge-Kutta Fehlberg method has a better performance compared to fourth order Runge-Kutta method for both the deterministic model of cell growth for C. *acetobutylicum* P262 and deterministic Gompertzian model of cancer cell growth for cancer patients. RKF45 values are close to the real data. This is because RKF45 via the adaptive step size approach can accurately depict the system of the C. *acetobutylicum* P262 cell and the cancer cell proliferation even when dealing with difficult areas since the step size will be adjusted automatically. The adaptability of the step size in the adaptive method allows for more precise solutions, especially in ODEs where the solution varies significantly in different regions.

This agreement can be supported by implementing the comparison of absolute error, relative error, and rounding off the error for all models. The absolute error is calculated by taking the absolute value of the difference between the precise value and the approximate value. This error quantifies the degree of accuracy or precision of the measurement. Meanwhile, the relative error is defined as the ratio of the absolute error and the precise value, where the absolute error is divided by the data value. Subsequently, the round-off error may be used to convert a number into an integer or one with a fewer number of decimal places. Anastasiia and Eva have mentioned that rounding off error, a prevalent problem in computational mathematics, may have an influence on the accuracy of results, particularly in methods such as Cody's approximation, which seeks to strike a compromise between computational complexity and precision when approximating error functions, [22]. Here, the tables below represent the analysis of the results that were obtained.

Table 1. Absolute error between solution obtained via RKF45 and RK4 methods with the real data for cell growth of C. *acetobutylicum* P262 model and Gompertzian model for cancer cell growth

Model	Method	
	RK4	RKF45
Yeast 1 (YE1)	0.368653	0.368652
Yeast 2 (YE2)	0.056084	0.056084
Yeast 3 (YE3)	0.322312	0.322311
Patient 1 (P1)	7.460073	7.460071
Patient 2 (P2)	105.729645	105.729648

Table 2. Relative error between solution obtained via RKF45 and RK4 methods with the real data for cell growth of C. *acetobutylicum* P262 model and Gompertzian model for cancer cell growth

Model	Method	
	RK4	RKF45
Yeast 1 (YE1)	0.353465	0.353464
Yeast 2 (YE2)	0.195734	0.195733
Yeast 3 (YE3)	0.237638	0.237637
Patient 1 (P1)	0.207606	0.207606
Patient 2 (P2)	1.815439	1.815440

Table 3. Rounding off error between solution obtained via RKF45 and RK4 methods with the real data for cell growth of C. *acetobutylicum* P262 model and Gompertzian model for cancer cell growth

Model	Method	
	RKF45	RK4
Yeast 1 (YE1)	0.353465	0.353464
Yeast 2 (YE2)	0.195734	0.195733
Yeast 3 (YE3)	0.237638	0.237637
Patient 1 (P1)	0.207607	0.207606
Patient 2 (P2)	1.815441	1.815440

Low values of absolute error, relative error, and rounding off error, as shown in Table 1, Table 2 and Table 3, which suggest good fits, are produced when the solution is obtained using Runge-Kutta Fehlberg for all models. This method used adaptive step size techniques which it can help mitigate rounding off errors by adjusting the step size to better capture the varying behavior of the solution, hence reducing the accumulation of errors over time. Furthermore, it has the ability to reduce the incidence of rounding errors in computations. Effective management of rounding errors is essential in numerical computations as it improves the dependability and precision of the outcomes. Thus, researchers may enhance the dependability and precision of numerical computations by understanding and effectively managing certain kinds of errors.

4 Conclusion

In this research, the purpose is to compare the fixed step size and adaptive step size numerical methods for solving ordinary differential equations (ODEs) using RK4 and RKF45 methods. The Runge-Kutta Fehlberg method is better as it is able to describe the presented data than the fourth order Runge-Kutta method as seen by the graphs and the low values of absolute error, relative error, and rounding off error for both deterministic model of cell growth for C. *acetobutylicum* P262 and deterministic Gompertzian model of cancer cell growth for patients. Many studies on the development of cell cancer and cell yeast have applied fourth-order Runge-Kutta. However, there are always discrepancies between the curve predicted by the RK4 method and the real data because of the fixed step size where it may miss fluctuations, including the crucial point of the solution. Furthermore, the fixed step size method can struggle with stiff equations, where some solution components change rapidly, necessitating adaptive step size methods that adjust dynamically based on solution behavior. Consequently, a more mathematical model using the accurate numerical method to predict cell growth was created. It is crucial to bear in mind that the Runge-Kutta Fehlberg method provides more accurate approximation solutions, making it very valuable for future applications including personalization and optimization. As a result, this study will expand the use of adaptive step size numerical methods in stochastic modeling, specifically in solving stochastic differential equations (SDEs).

This study focuses on the performance of fixed step size and adaptive step size numerical methods in approximating the solution to the differential equations. This can be a guide to other researchers in identifying which one is the optimal method while revealing the limitations of the methods discussed.

In conclusion, research comparing fixed and adaptive step size methods for ODEs provides valuable insights into the strengths and weaknesses of these methods. By understanding their suitability and limitations, researchers and practitioners can make informed decisions and advance the field of numerical analysis.

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Declaration of Generative AI and AI-assisted Technologies in the Writing Process
During the preparation of this work the authors used ChatGPT in order to improve language and copy editing. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Contribution of Individual Authors to the Creation of a Scientific Article (Ghostwriting Policy)

The authors equally contributed in the present research, at all stages from the formulation of the problem to the final findings and solution.

Sources of Funding for Research Presented in a Scientific Article or Scientific Article Itself

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Conflict of Interest

The authors have no conflicts of interest to declare.