# APPROXIMATION METHODS FOR SOLVING HIV INFECTION MODELS IN FUZZY ENVIRONMENT

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# APPROXIMATION METHODS FOR SOLVING HIV INFECTION MODELS IN FUZZY ENVIRONMENT

**by**

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## LIST OF SYMBOLS

| | |
|---|---|
| $\oplus$ | Addition operator on $\tilde{E}$ |
| $p$ | An embedding parameter belongs to [0,1] |
| $B$ | Banach space |
| $\tilde{f}(x)$ | Fuzzy function $f$ of independent variable $x$ |
| $\tilde{A}$ | Fuzzy set $A$ |
| $\lambda$ | General Lagrange multiplier |
| $\mathcal{H}$ | Homotopy function |
| $\ominus$ | Hukuhara difference |
| $\widetilde{f'}(x)$ | Hukuhara differentiable of $\tilde{f}(x)$ |
| $D_H$ | Hausdorff distance between two fuzzy set (or fuzzy numbers) |
| $L^{-1}$ | Inverse operator |
| $L$ | Linear operator |
| $t^*$ | Left end point of each subinterval |
| $\underline{f}(x)$ | Lower $r$-level representation of $\tilde{f}(x)$ |
| $\mu_{\tilde{A}}(x)$ | Membership function of a set $\tilde{A}$ |
| $\otimes$ | Multiplication operator on $\tilde{E}$ |
| $N$ | Nonlinear operator |
| $\hat{y_n}$ | Restricted variation of nth approximation |
| $[\tilde{f}(x)]_r$ | $r$-level function of $\tilde{f}(x)$ |
| $[\tilde{A}]_r$ | $r$-level set representation of a fuzzy set $\tilde{A}$ |
| $R$ | Set of all real number |
| $R_+$ | Set of all positive real number |
| $\tilde{E}$ | Set of all upper semi-continuous normal convex fuzzy numbers with bounded r-level sets. |
| $\overline{f}(x)$ | Upper $r$-level representation of $\tilde{f}(x)$ |

## LIST OF ABBREVIATIONS

| | |
|---|---|
| AIDS | Acquired Immune Deficiency Syndrome |
| ADM | Adomian Decomposition Method |
| ART | Anti Aetroviral Therapy |
| BCM | Bessel Collocation Method |
| CTLs | Cytotoxic T-Lymphocytes |
| DNA | Deoxyribonucleic Acid |
| DTM | Differential Transformation Method |
| EXACT | Exact Solution |
| FDM | Finite Difference Method |
| FADM | Fuzzy Adomian Decomposition Method |
| FBVPs | Fuzzy Boundary Value Problems |
| FCCs | Fuzzy constant coefficients |
| FDEs | Fuzzy Differential Equations |
| FHAM | Fuzzy homotopy analysis method |
| FHPM | Fuzzy Homotopy Perturbation Method |
| FIVPs | Fuzzy Initial Value Problems |
| FLDM | Fuzzy Laplace Decomposition Method |
| FLTM | Fuzzy Laplace transform Method |
| FLDEs | Fuzzy linear differential equations |
| FLC | Fuzzy logic controllers |
| FOCP | Fuzzy Optimal Control Problem |
| FOHAM | Fuzzy optimal homotopy analysis method |
| FODEs | Fuzzy Ordinary Differential Equations |
| FPDEs | Fuzzy Partial Differential Equations |
| FPSM | Fuzzy power series method |

| | |
|---|---|
| FRBS | Fuzzy rule-based system |
| FSCDEs | Fuzzy Set Control Differential Equations |
| FVIM | Fuzzy Variational Iteration Method |
| GPC | Generalized Predictive Control |
| GD | Gradient Descent |
| HAM | Homotopy Analysis Method |
| HPM | Homotopy Perturbation Method |
| HPTM | Homotopy Perturbation Transform Method |
| HIV | Human Immunodeficiency Virus |
| HFDEs | Hybrid Fuzzy Differential Equations |
| HTGA | Hybrid Taguchi Genetic Algorithm |
| RK4 | Runge-Kutta fourth-order method |
| LADM | Laplace Adomian Decomposition Method |
| LTDA | Laplace transform decomposition algorithm |
| LS | Least Squares |
| MF | Membership Function |
| MPC | Model Predictive Control |
| MFHPM | Multistage Fuzzy Homotopy Perturbation Method |
| MFVIM | Multistage Fuzzy Variational Iteration Method |
| MHPM | Multistage Homotopy Perturbation Method |
| MVIM | Multistage Variational Iteration Method |
| OHAM | Optimal Homotopy Analysis Method |
| ODEs | Ordinary Differential Equations |
| PP | Painleve' property |
| PIAM | Perturbation Iteration Algorithm Method |
| PSM | Power Series Method |
| PIs | Protease Inhibitor |
| RTIs | Reverse Transcriptase Inhibitor |

| | |
|---|---|
| SCSA | Shifted-Chebyshev Series Approach |
| STI | Structured Treatment Interruption |
| TSK | Takagi Sugeno Kang |
| TS | Takagi-Sugeno |
| TSR | Taylor's Series Representation |
| RNA | Transforms Ribonucleic Acid |
| TPFBVPs | Two points fuzzy boundary value problems |
| VIM | Variational Iteration Method |
| WCOG | Weighted Center of Gravity |
| CD4+T | White blood cells |

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**KAEDAH PENGHAMPIRAN UNTUK MENYELESAIKAN MODEL JANGKITAN HIV DALAM PERSEKITARAN KABUR**

## ABSTRAK

Persamaan pembezaan kabur (PPK) mempunyai pelbagai aplikasi dalam fizik, sains gunaan dan kejuruteraan dan telah menjadi alat penting untuk memodelkan pelbagai fenomena kehidupan sebenar, lebih-lebih lagi yang melibatkan ketidakpastian seperti model jangkitan HIV. Namun begitu, kebanyakan model matematik untuk jangkitan HIV kabur, seperti yang digambarkan dalam model tak linear, mengalami kemerosotan dalam penyelesaian analitik yang mana penyelesaian ini pada kebiasaannya sukar untuk difahami. Akibatnya, pendekatan lazim untuk menggambarkan model HIV kabur perlu melibatkan penggunaan kaedah penghampiran, biasanya melalui teknik berangka. Kaedah berangka sedemikian menghasilkan penyelesaian dalam nilai berangka. Walau bagaimanapun, adalah penting untuk ambil perhatian bahawa kaedah penghampiran berangka ini menghadapi had dalam menyelesaikan secara langsung model jangkitan HIV kabur dan memerlukan penggunaan pendiskretan atau pelinearan. Sebaliknya, kaedah penghampiran analitik terbukti boleh digunakan dengan beberapa cara yg berbeza, kerana ia bukan sahaja digunakan untuk model HIV kabur tanpa memerlukan pelinearan atau pendiskretan tetapi juga memberikan penyelesaian selanjar. Oleh itu, dalam tesis ini, penghampiran analitik seperti kaedah usikan homotopi kabur (KUHK), kaedah lelaran ubahan kabur (KLUK) serta versi yang terubahsuai telah dipertimbangkan untuk menyelesaikan beberapa model jangkitan HIV linear dan tak linear kabur di bawah konsep pendekatan kebolehbezaan Hukuhara untuk memberi penyelesaian penghampiran analitik dalam bentuk penyelesaian siri penumpuan. Kewujudan dan keunikan penyelesaian untuk model jangkitan HIV kabur linear dan

tak linear dalam kerja ini juga telah disiasat. Perbandingan berangka antara KUHK, KLUK dan penyelesaian tepat telah dilakukan, menunjukkan hasil ketepatan yang tinggi serta perbandingan dengan kaedah sedia ada yang lain. Kaedah tersebut didapati cekap dalam menyelesaikan model jangkitan HIV kabur linear. Sebaliknya, kerumitan sistem kabur tak linear menyukarkan untuk mendapatkan penyelesaian penghampiran analitik untuk tempoh yang panjang sekiranya menggunakan kaedah analisis anggaran semasa seperti KUHK dan KLUK. Untuk menangani perkara ini, penggunaan KUHK berperingkat (KUHKB) dan KLUK berperingkat (KLUKB) untuk menyelesaikan model jangkitan HIV tak linear kabur telah dicadangkan, dibina dan kemudiannya digunakan ke atas model tersebut. Tambahan pula, kesan ketidakpastian ke atas sistem imun yang berpadanan dengan umur, jantina dan pemakanan adalah parameter penting dalam rawatan penyakit HIV. Keadaan ini akan mengakibatkan keadaan awal yang tidak menentu, dan selalunya lebih sesuai untuk memodelkannya menggunakan nombor kabur, oleh itu, beberapa model jangkitan HIV tak linear telah diubah suai. daripada persekitaran klasik (crisp) kepada kabur dengan menggunakan konsep teori set kabur, dan kemudian diperiksa oleh semua kaedah yang dicadangkan. Perbandingan berangka telah dibuat antara KUHK, KUHKB, KLUK dan KLUKB dengan penyelesaian berangka yang diperoleh menggunakan kaedah Runge-Kutta peringkat empat (RK4) dan perbandingan dengan kaedah sedia ada yang lain. KUHKB dan KLUKB yang diubah suai telah ditunjukkan sebagai kaedah yang sangat tepat dan cekap untuk menyelesaikan masalah yang sama. Kaedah-kaedah tersebut juga telah terbukti berguna dalam menerangkan tahap ketidakpastian sel imun dan beban virus pada pesakit, dengan mengambil kira kategori pesakit dan kekuatan sistem imun mereka juga dalam menggambarkan ketidakpastian sel yang tidak dijangkiti dan dijangkiti, serta zarah

virus bebas. Dalam bentuk yang terubahsuai berdasarkan fungsi kawalan optimum, keputusan menunjukkan bahawa sistem sedang bergerak ke arah keseimbangan sihat yang diingini. Kesan set parameter peringkat-r telah diwakili secara grafik untuk menunjukkan kesahihan penyelesaian anggaran kabur. Melalui perwakilan jadual, rajah dan analisis penyelesaian, kaedah yang dicadangkan mempunyai beberapa kelebihan yang ketara berbanding yang sedia ada kerana kewujudan penyesaian siri dalam bentuk selanjar. Kaedah yang dibangunkan ini tidak memerlukan pelinearan atau andaian terbatas, menjadikannya kurang terdedah kepada ralat pengiraan. Ini boleh membantu penyelidik dan ahli penjagaan kesihatan professional mendapatkan pandangan tentang dinamik penyakit, membuat keputusan termaklum dan dalam menilai kesan pencegahan dan rawatan.

**APPROXIMATION METHODS FOR SOLVING HIV INFECTION MODELS IN FUZZY ENVIRONMENT**

## ABSTRACT

Fuzzy differential equations (FDEs) have a wide range of applications in physics, applied sciences, and engineering and has become undeniably an essential tool for modelling a wide range of real-life phenomena and even more so, those involved with uncertainties such as HIV infection models. Nevertheless, the majority of mathematical representations for fuzzy HIV infection, as depicted in nonlinear models, suffer from a deficiency in analytical solutions whereby these solutions are frequently elusive. Consequently, the prevalent approach to address fuzzy HIV models involves employing approximation methods, typically through numerical techniques. Such numerical methods yield solutions in numeric values. However, it's important to note that these approximate numerical methods face limitations in directly resolving fuzzy HIV infection models and necessitate the use of discretization or linearization. In contrast, approximate analytical methods prove versatile, as they not only apply to fuzzy HIV models without requiring linearization or discretization but also furnish continuous solutions. Therefore, in this thesis, the approximate analytical methods fuzzy homotopy perturbation method (FHPM), fuzzy variational iteration method (FVIM), and their modified versions are considered for solving several linear and nonlinear fuzzy HIV infection models under the concept of Hukuhara differentiability approach to provide approximate analytical solutions in the form of convergence series solution. The existence and uniqueness of the solution for linear and nonlinear fuzzy HIV infection models in this work have also been investigated. Numerical comparisons between the FHPM, FVIM, and the

exact solution have been performed, showing high accuracy results as well as comparisons with other existing methods. The methods have been found to be efficient in solving linear fuzzy HIV infection models. On the other hand, the complexity of nonlinear fuzzy systems makes it difficult to obtain an approximate analytical solution for an extended period using current approximate analytical methods such as the FHPM and FVIM. To address this, the use of the multistage fuzzy homotopy perturbation method (MFHPM) and multistage fuzzy variational iteration method (MFVIM) are proposed, constructed, and then applied to the models. Furthermore, the uncertainty effects on immune system corresponding to age, gender and feeding are important parameters in the HIV disease treatment. This implies to uncertain initial conditions, and often more suitable to model them using fuzzy numbers, therefore, some nonlinear HIV infection models were modified from classical (crisp) to fuzzy environment by using the concept of fuzzy set theories, and then examined by all proposed methods. Numerical comparisons have been made between the FHPM, MFHPM, FVIM, and MFVIM with numerical solutions obtained using Runge-Kutta fourth-order method (RK4) and comparisons with other existing methods. The modified MFHPM and MFVIM have been shown to be highly accurate and efficient methods for solving the same models. The methods have also been shown to be useful in describing the uncertain levels of immune cells and viral loads in patients, taking into account the patient's category and the strength of their immune system also in describing the uncertainty of uninfected and infected cells, as well as free virus particles. In modified forms based on optimal control functions, the results indicate that the system is moving towards a desired healthy balance. The parameters r-level sets effect has been graphically represented to demonstrate the validity of the fuzzy approximate solutions. Through the representation of tables,

figures and solution analysis, the proposed methods have some distinct advantages over existing ones due to the depiction of series solutions in continuous form. The proposed methods do not require linearization or restrictive assumptions, making them less prone to computation round off errors. This can help researchers and healthcare professionals gain insights into the dynamics of the disease, make decisions and in evaluating the impact of interventions and treatments.

# CHAPTER 1

# INTRODUCTION

Human Immunodeficiency Virus **(**HIV) infection can be modelled in linear and nonlinear ordinary differential equations (ODEs) to describe various aspects of the interaction between HIV and the immune cells. However, in the real world, there are various HIV infected patients with different strengths of immune system causing uncertainty as to the immune cells level and the viral load during the different stages of the disease. The uncertainty is modelled by fuzzy differential equations (FDEs). This thesis presents approximate analytical methods, fuzzy homotopy perturbation method (FHPM) and fuzzy variational iteration method (FVIM), as well as their modified versions, multistage fuzzy homotopy perturbation method (MFHPM) and multistage fuzzy variational iteration method (MFVIM) to solve linear and nonlinear fuzzy HIV infection models using Hukuhara differentiability approach. The introduction of the thesis provides background on FDEs including fuzzy HIV infection models and states the problem being addressed, research questions, objectives, scope, and significance of the research. The organization of the thesis is also outlined.

## 1.1 Fuzzy differential equations

ODEs play a major role in the modelling of physical phenomena in applied sciences and engineering. Researchers have extensively used classic ODEs to make many issues under study more understandable. Frequently, data related to physical phenomena often contains uncertainties due to various factors such as measurement errors, experimental uncertainties, and inaccuracies in data collection and initial value determination. These uncertainties can affect the accuracy and precision of the data and must be taken into account when analysing and interpreting the results.

Various attempts have been made to describe and measure the uncertainties. One of the approaches leads to fuzzy set theory, which was introduced by Zadeh in 1965, is a mathematical framework for dealing with uncertainty and vagueness in information. It uses fuzzy sets, which are sets whose elements have varying degrees of membership, as opposed to traditional sets in which elements have a binary membership of either belonging or not belonging to the set. From then on, properties and suggested applications have been revised by numerous researchers.

FDEs are a type of mathematical equation that involves uncertainty (Mazandarani & Najariyan, 2022). The most important part of history of FDEs is formed by different definitions of fuzzy derivatives. As a matter of fact, since the concept of derivative is the fundamental element of a differential equation, the evolution of fuzzy derivatives plays a key role in the evolution of FDEs (Mazandarani & Xiu, 2021). The concept of a fuzzy derivative was first introduced by Sheldon and Zadeh in 1972, and later refined by Dubois and Prade in 1982 using Zadeh's extension principle. Seikkala (1987) also presented the concept of fuzzy derivative as a generalization of the Hukuhara derivative. The use of fuzzy derivatives in differential equations often requires additional information, such as parameter values, initial conditions, or functional relationships (Mazandarani & Xiu, 2021).

Researchers have studied various aspects of FDEs, including the existence and uniqueness of solutions, and the initial value problem (IVP) for FDEs. In 1989, He and Yi provided a theorem of existence and uniqueness for the solution of FDEs, and later, in 1990, Kaleva conducted research on the existence and unique solution for the Cauchy problem for FDEs. Other researchers, such as Seikkala (1987) and Kaleva (1987), have also conducted research on IVP for FDEs. In 2005, Bede and

Gal developed a Newton–Leibnitz-type formula for FDEs using a concept of generalized differentiability. They also discussed the existence of solutions for FDEs and provided examples of applications to both partial and ordinary FDEs with fuzzy input data. In 2009, Nieto et al. further explained FDEs using a strongly generalized concept of differentiability which allowed for the examination of approximate solutions. They also showed that any numerical technique used for solving ODEs can also be applied to finding numerical solutions for FDEs under generalized differentiability. Khalilpour and Allahviranloo (2011) introduces the use of the initial value method for solving fuzzy boundary value problems (FBVPs) with two points and proves the existence and uniqueness of solutions under a strongly generalized concept of differentiability. This approach may provide a useful method for solving FBVPs in a variety of contexts. Abbasbandy et al. (2011a) introduced a new existence and uniqueness solution theorem for fuzzy initial value problems (FIVPs) using the extension principle of Zadeh and the concept of Hukuhara derivative. The Hukuhara derivative is used to ensure that the solution is unique and well-posed. This theorem provides a theoretical framework for solving FIVPs. Saberirad et al. (2018) introduced a highly effective approach for solving hybrid fuzzy differential equations (HFDE), employing the Hukuhara derivative to establish the existence and uniqueness of solutions.

Nowadays, FDEs play an important role in various applications related to civil engineering, medicine, population models and particle systems (Ali & Ibraheem, 2020), nuclear physics (Das et al., 2013; Salahshour et al., 2015), viscosity (Ahmadian et al., 2017; Sin et al., 2018), liquid kinetics (Ahmadian et al., 2015), robotics (Deng, 2019), and HIV infection models (Hussian and Suhhiem, 2015).

However, until FDEs are solved, they will continue to be impractical. This is due to the fact that having answers to FDEs would enable researchers to make accurate predictions regarding the phenomena that are being investigated. The solution of FDEs is regarded challenging due to the parameters of uncertainty that are involved.

The analytical approach and the approximation approach are the two primary methods that can be utilized in the solution of FDEs. The analytical method aims to provide solutions in the form of closed systems, which are mathematical expressions that can be written as the sum of fundamental functions, such as polynomials, exponentials, trigonometric, and hyperbolic functions. Closed form solutions are considered to be the best possible answer to a problem as they provide a comprehensive understanding of the solution (Kudryashov, 2020). Additionally, closed form solutions tend to require less computational work during the analysis process (Bulut et al., 2013). Nevertheless, the obtained solutions are generally limited to the linear category of FDEs (Panahi, 2017). It is unfortunate that most of the complex physical phenomena described using nonlinear FDEs lack analytical solutions (Hasan et al., 2017). In many instances, analytical solutions cannot be found (Ghanbari & Akgul, 2021; Verma & Kumar, 2020). Therefore, to deal with such instances in a more realistic manner, FDEs are commonly solved using the approximation approach (Hasan et al., 2017).

Approximation approach can generally be divided into two categories: approximate numerical methods and approximate analytical methods. According to Moore and Ertürk's research from 2020, the approximate numerical methods provide answers that are approximately expressed in the form of numerical values, and the assessment of error makes use of mathematical operations. However, approximate

numerical methods cannot solve FDEs directly, instead they require transformation to linear system or discretization to convert the continuous problem into a discrete problem. The objective of the approximation methods is to arrive at a solution that is close to the true one; more specifically, these methods seek an open form solution rather than a closed form one.

The approximate analytical methods are another subcategory of methods that fall under the umbrella of the approximation approach. This family of methods, in contrast to the approximate numerical class of methods, can be applied to linear and nonlinear models of FDEs without the necessity of linearization or discretization (Hasan et al., 2017; Khodadadi & Celik, 2013). The solutions of these equations will be presented in the form of a polynomial function series. This will make it simple to demonstrate the degree of solution and convergence of the solution through its presentation in graphical form. The methods have the capacity to determine the accuracy of the solution that was achieved without necessitating the use of the exact solution (close form) as a point of comparison.

In reality, various mathematical models have been devised to depict the progression of HIV infection to AIDS (Sohaib, 2020). Typically, these models employ FDEs to characterize the dynamics of the virus within the body and the subsequent response of the immune system. Najariyan et al. (2011) proposed an HIV infection model using FDEs that incorporates factors such as gender, age, and feeding habits, known to influence the disease's progression. They also introduced a fuzzy control model to maximize uninfected cells in HIV disease. The utilization of fuzzy variables and fuzzy dynamical systems in this model enables a more precise and realistic representation of the intricate dynamics of HIV infection. Furthermore, Zarei et al. (2012) presented a fuzzy mathematical model of HIV infection deploying

fuzzy linear differential equations (FLDEs) to portray the uncertain levels of immune cells and viral load in HIV infected patients. This model accommodates the inherent fuzziness of the immune system's strength in these patients. Additionally, the proposed model integrates a fuzzy control function to determine drug dosage, and a fuzzy optimal control problem (FOCP) is formulated to minimize both viral load and drug costs.

Solving these models aids researchers in comprehending the underlying mechanisms of the disease and serves as a means to evaluate the efficacy of diverse treatment strategies (Younus, 2021). In the study by Najariyan et al. (2011) employed numerical methods based on the generalized Euler method to solve a fuzzy nonlinear HIV infection model, and Fitting-based methods were applied to a fuzzy linear HIV infection model in Zarei et al. (2012). Furthermore, Maan and Ramle (2017) developed a numerical solution for the fuzzy linear HIV model introduced by Zarei et al. (2012) using the Runge-Kutta fourth-order method (RK4).

Consequently, the aim of this study is to modify and improve approximate analytical methods for fuzzy HIV infection models, eliminating the necessity for linearization or discretization while delivering a continuous solution. The utilization of these methods enables graphical representation of solutions through series solutions, facilitating researchers and healthcare professionals in gaining a deeper understanding of the disease dynamics. This approach aids in making informed decisions and evaluating the effectiveness of interventions and treatments.

## 1.2 Problem statement

In the fuzzy HIV infection models, the solution of these models can help researchers understand the underlying mechanisms of the disease and can also be used to test the effectiveness of different treatment strategies (Younus, 2021). FDEs

including fuzzy HIV infection are commonly solved using the approximation approach (Hasan et al., 2017).

However, the existing approximate numerical methods necessitate the transformation of fuzzy HIV infection models into linear systems or discrete problems, providing results at discrete points without an explicit functional representation, hindering graphical representation. In contrast, the proposed approximate analytical methods prove versatile, as they not only apply to fuzzy HIV models without requiring linearization or discretization but also furnish continuous solutions and allow for graphical representation of solutions (Khodadadi & Celik, 2013; Hasan et al., 2017).

Certain approximate analytical methods within ODEs, such as the homotopy perturbation method (HPM) and variational iteration method (VIM), have shown promise in ensuring solution convergence (Yang, 2022; Timothy et al., 2019). These methods require less computational effort compared to other approximate analytical methods such as Adomian decomposition method (ADM) and homotopy analysis method (HAM) (Shakil et al., 2013; Paliivets et al.,2021; Omar, 2021; Liao & Zhao, 2016; AL-Juaifri & Mechee; 2018). However, they are generally less suitable for solving nonlinear ODEs over extended time spans due to the intricate dynamics of hyperchaotic systems (Razali 2015; Heydari et al., 2015; Gokyildirim et al., 2018; Timothy et al., 2019; Yang, 2022).

The modified methods, multistage homotopy perturbation method (MHPM) and multistage variational iteration method (MVIM), have demonstrated efficacy in solving nonlinear ODEs for prolonged periods, particularly in the context of HIV infection models (Merdan et al., 2011; Vazquez et al., 2014; Bastani, 2014; Kamboj & Sharma, 2016).

As well as in fuzzy ordinary differential equations (FODEs), FHPM and FVIM have been found to be capable of generating accuracy approximate analytical solution for FODEs. The convergence solution of FHPM for FODEs has been proven by (Najafi et al., 2013; Saberirad et al.,2018; Anakira, 2019). Besides, the convergence solution of FVIM for FODEs has been proven by many authors such as (Fard & Ghal, 2011; Abbasbandy et al., 2011b; Allahviranloo et al, 2014). During this study, we seek to obtain approximate analytical solutions for fuzzy HIV infection models, which are one of the real-life systems. This study utilizes systems of FODEs to examine the dynamics of fuzzy HIV infection models.

As a result, this research aims to modify and improve approximate analytical methods FHPM and FVIM to directly solve linear fuzzy HIV models. The modified methods, called multistage fuzzy homotopy perturbation method (MFHPM) and multistage fuzzy variational iteration method (MFVIM), will be used to solve nonlinear fuzzy HIV infection models over a prolonged period.

These methods provide a convergence series solution for a long-time interval. They do not require linearization or restrictive assumptions, making them less prone to computation round off errors. The proposed methods allow for graphical representation of solutions, providing a visual representation of the results that because of the series solutions. This can help researchers and healthcare professionals gain insights into the dynamics of the disease, make informed decisions and in evaluating the impact of interventions and treatments. The research will systematically investigate the existence and uniqueness of solutions for these models, in addition to assessing the convergence of these solutions, with the aim of evaluating the effectiveness of the proposed methods.

## 1.3 Research questions

This study will address the following research questions:

1. What methods are appropriate for solving a dynamic system of first-order linear and nonlinear fuzzy HIV infection models without discretizing variable?
2. What are suitable methods for solving a dynamic system of first-order nonlinear fuzzy HIV infection models with long-time span?
3. Are the modified and extended methods feasible for solving fuzzy HIV infectious models in the presence of treatment?
4. How to measure the performance of the modified and extended methods?

## 1.4 Research objectives

The objectives of this thesis are:

1. To modify approximate analytical methods in parametric form of fuzzy numbers based on FHPM and FVIM in approximating the solutions of first- order linear and nonlinear fuzzy HIV infection models.
2. To extend the modified methods in (1) in approximating the solutions of first-order nonlinear fuzzy HIV infection models in the context of dynamic systems over a long-time span.
3. To apply the modified and extended methods in (1) for solving linear and nonlinear fuzzy optimal control of HIV infectious models.
4. To compare the performance of the modified and extended methods with the exact solution and existing methods in terms of accuracy.

## 1.5 Research scope

This research, within the framework of fuzzy sets theory, concentrates on modification FHPM, FVIM, MFHPM, and MFVIM to address two categories of problems related to FIVPs: linear and nonlinear fuzzy models of HIV infection employing Hukuhara derivatives, and the conversion of certain crisp nonlinear HIV infection models into fuzzy representations. Furthermore, this thesis investigates the existence and uniqueness of solutions for these models, along with assessing the convergence of the solutions to gauge the effectiveness of the proposed methods in the Chapters four and five. The experimental analysis of the models proposed in this study will be carried out using Mathematica 12 software.

## 1.6 Research significance

The proposed methods FHPM, FVIM, MFHPM, and MFVIM, represent approximate analytical methods aimed to surmount the limitations inherent in existing numerical methods such as RK4 method and the generalized Euler method. These proposed methods yield convergent series solutions applicable over extended time intervals. Notably, they obviate the need for linearization or restrictive assumptions, minimizing susceptibility to computation round-off errors. Furthermore, they enable the graphical representation of solutions, offering a visual depiction of outcomes facilitated by the series solutions. This visual representation can aid researchers and healthcare professionals in comprehending the disease dynamics, facilitating informed decision-making, and assessing the impact of interventions and treatments. The research will systematically investigate the existence and uniqueness of solutions for these models, in addition to assessing the convergence of these solutions, with the aim of evaluating the effectiveness of the proposed methods.

## 1.7 Thesis organization

This thesis has six chapters. Chapter 1 introduces the main research framework. Chapter 2 reviews previous literature. Chapter 3 provides the mathematical background, description of approximate analytical methods, and introduction of fuzzy set theory. It also covers the analysis of FIVPs systems, description of the methods in a fuzzy environment as well as convergence analysis of the methods, models under study and research methodology used in this study. Chapter 4 discusses various approximate analytical methods for solving a first-order linear fuzzy HIV infection model and its modification. These methods are based on FHPM and FVIM and take into account fuzzy initial conditions under Hukuhara derivatives. The chapter also covers the existence and uniqueness of the solutions for the proposed models and includes a detailed analysis of the solutions. Chapter 5 presents methods for solving nonlinear fuzzy HIV infection models, using modified approximate analytical methods based on FHPM, MFHPM, FVIM, and MFVIM. It also discusses the process of converting some nonlinear HIV infection models from crisp to fuzzy, with a focus on the existence and uniqueness of the solutions and the convergence of the methods. The chapter also includes an analysis of the solutions obtained. Finally, Chapter 6 presents the conclusions of this study and some suggestions for future work.

# CHAPTER 2

# LITERATURE REVIEW

## 2.1 Introduction

FDEs are popular among mathematical researchers since they can be used in many branches of application, such as physics, astronomy, biology, and population dynamics. Finding the exact solution to FDEs is difficult, due to the complexity of parameters of uncertainty. Therefore, FDEs are commonly solved using the approximation approach which includes the approximate numerical and approximate analytical methods. This work marks the first implementation of the strategy to modify and apply approximate analytical methods FHPM, MFHPM, FVIM, and MFVIM, in the investigation of fuzzy HIV infection models. Therefore, this chapter discusses fuzzy HIV models in the form of a system of FIVPs and the approaches to solving them.

## 2.2 Human Immunodeficiency Virus

HIV is an infection that the virus attacks the immune system, which is the body's natural defense against illness and infection. A healthy immune system is one that is able to effectively defend the body against harmful pathogens and infections. This is achieved through a combination of physical barriers, such as the skin, and the activity of immune cells, which can identify and neutralize invading organisms. An unhealthy immune system, on the other hand, may be weakened or compromised in some way, making the body more susceptible to infection and disease. This can be caused by a variety of factors, including poor nutrition, chronic stress, and certain medical conditions (Gombart et al., 2020). HIV continues to pose a significant challenge to global public health, having led to the loss of 51.3 million lives to date.

Ongoing transmission persists across all nations, with certain countries witnessing a resurgence in new infections after previous declines. HIV is transmitted through body fluids, such as blood, semen, vaginal fluids, and breast milk. When a person is infected with HIV, the virus attacks and destroys a type of immune cell called CD4 cells, which are also known as T-cells. These cells play a crucial role in helping the body fight off infections and diseases. As HIV destroys more and more CD4 cells, the immune system becomes weaker and less able to fight off other infections and diseases. This is why HIV is such a serious disease and can lead to Acquired Immune Deficiency Syndrome (AIDS), which is the most advanced stage of HIV infection (Franjic, 2020). What do CD4 cells do? What is AIDS? How is HIV transmitted? What happens to the body when HIV infection occurs? Hussian and Suhhiem (2015), and later Franjic (2020) have discussed these questions in more detail. In Perrin et al. (1996), the first model proposed for HIV infection was introduced in the early 1980s by Dr. William McLean and colleagues at the Centers for Disease Control and Prevention in the United States. This model estimated the number of secondary infections that would arise from a single infected individual in a susceptible population and was used to predict the spread of the HIV epidemic in the early years of the epidemic. Since then, many other models have been developed to describe the dynamics of HIV transmission and the impact of interventions such as antiretroviral therapy and behavioral interventions.

There are several mathematical models that have been developed to describe various aspects of the interaction between HIV and the immune cells. These models can help researchers better understand how the virus infects and spreads within the body, as well as how the immune system responds to the virus. They can also be used to predict the course of the disease and to evaluate the effectiveness of different

treatment strategies. The basic and simple model of HIV infection that contains three state variables: healthy CD4+ T cells, infected CD4+ T cells, and viruses, is presented by Nowak and May (1991) which is a basic model of HIV dynamic. In Capistran and Solis (2009) is proposed a class of models based on the Nowak and May model to study reactivation of resting infected T-cells, $T_r$, during long-term HIV infection. These models incorporate classes of $T_r$ cells and cytotoxic T-cells, $T_c$ . In addition, a number of mathematical models have been proposed to understand HIV dynamics, disease process, anti-retroviral response in (Nowak & May, 2000; Perelson & Nelson, 1999; Perelson et al., 1993; Perelson et al., 1996; Perelson, 1989).

The dynamic multidrug therapy problem is modelled in Wein et al., (1997) as an optimal control model that maximizes the inhibition of HIV. In Kirchner et al. (1997), finite horizon open loop control tools are applied to an HIV chemotherapy model using an objective function based on a combination of maximizing T-cells count and minimizing the systemic cost of chemotherapy.

In study by Mhawej et al. (2010), the authors introduced a control and drug dosage for the HIV infection. The study applied on an HIV mathematical model proposed by Perelson et al. (1993), in Croicu (2015) aimed to develop a theoretical optimal control treatment for HIV infection of CD4+ T cells using Pontryagin's classical control theory. The goal of the treatment was to decrease the concentration of free HIV virus particles in the blood while minimizing toxicity to patients. The mathematical model used in the study was a system of nonlinear differential equations that modelled the concentration of susceptible CD4+ T cells, infected CD4+ T cells, and free HIV virus particles in the blood. Next section (2.3) focuses on reviewing the existing concept of non-fuzzy HIV models, which serves as the basis for the proposed methods for solving the suggested fuzzy HIV models in this work.

## 2.3 Existing methods of crisp HIV infection models

The models in the crisp case of HIV infection models have been validated by many methods, which can be summarized as follows. In the research conducted by Ghoreishi et al. (2011), the HAM has been effectively developed and employed to address a model for HIV infection of CD4+ T-cells, utilizing the time interval [0,1] as proposed by Perelson (1989). The HAM solution incorporates the auxiliary parameter providing a straightforward means to adjust and govern the convergence region of the resulting infinite series. The results obtained indicate that HAM is a precise and efficient technique for approximating the solution of HIV infection in CD4+ T cells. Nevertheless, it's crucial to note that the convergence of the series in HAM may be influenced by the selection of the convergence control parameter. The accuracy of the solution is contingent upon this parameter, and determining an optimal value can be a challenging task. HAM may encounter convergence challenges, particularly for highly nonlinear or intricate systems.

The study by Merdan et al. (2011) explore the utilization of the VIM and its modified version, MVIM, for approximating and analytically solving nonlinear ODE systems, exemplified by a model representing HIV infection of CD4+ T cells (Perelson & Nelson, 1999) over the time interval [0,3]. The VIM method relies on Laplace transformation and Padé approximants. The authors introduce the MVIM method, incorporating Padé approximants to enhance the precision of the VIM approach. The study showcases the outcomes of applying these methods to solve ODE systems, comparing them with the RK4 method. The results demonstrate the accuracy and efficiency of both VIM and MVIM methods, which notably do not necessitate variable discretization. Moreover, the approach is conceptually straightforward and easily implementable, involving the construction of a correction functional and

employing an iterative process for solution refinement. VIM has found successful applications in diverse types of differential equations, encompassing both ODEs and PDEs. The theoretical establishment of convergence for specific problem types underpins the method's reliability under certain conditions. However, despite existing convergence theory in some instances, VIM may encounter challenges, particularly in highly nonlinear or complex systems, with convergence behaviours contingent on the nature of the differential equation. On the other hand, MVIM exhibits success in solving hyperchaotic systems, demonstrating high accuracy, particularly for large time domain sizes.

Additionally, Ongun (2011) discusses the application of the Laplace Adomian Decomposition Method (LADM) in solving nonlinear ODEs, such as those modelling the HIV infection of CD4+ T cells (Perelson et al., 1993) within the time interval [0,1]. The author illustrates that LADM can generate highly accurate approximate solutions with minimal iterations, making it a viable approach for solving nonlinear systems without resorting to linearization, perturbation, or discretization. The paper presents numerical examples and plots to underscore the method's reliability and simplicity. Nevertheless, the precision of LADM is contingent on the selection of Adomian polynomials compared with RK4. The convergence of the method may be influenced by the accuracy of these polynomials, posing a challenge in identifying suitable ones for certain problems. Despite its versatility, LADM might not be the most efficient choice for specific types of differential equations or boundary value problems, leading to limited applicability in certain instances. Particularly for highly nonlinear problems, LADM may exhibit slow convergence or fail to converge in some cases.

In Yüzbaş's study (2012), the Bessel Collocation Method (BCM) is introduced for approximating solutions to a set of nonlinear ODEs, specifically addressing the HIV infection model of CD4+ T cells (Perelson et al., 1993) within the time range [0,1]. The methodology involves transforming the problem into a system of nonlinear algebraic equations by expanding the approximations using Bessel polynomials and unknown coefficients. The determination of these unknown coefficients employs matrix operations and the collocation method. The proposed approach is showcased as reliable and efficient through a numerical example and comparison with alternative methods like VIM, MVIM, LADM, and RK4. The computations can be readily executed using programming platforms such as MATLAB, Maple, and Mathematica. The fundamental concept of the method is anticipated to be applicable to analogous nonlinear problems. Nevertheless, the study's tabulated results indicate that the method exhibits high accuracy within the interval [0,7], diverging from the outcomes obtained by MVIM and RK4 beyond that point. Additionally, the tables suggest that the validation of VIM, LADM, and BCM is effective only for short time intervals. Moreover, certain issues may give rise to ill-conditioned matrices, potentially impacting the stability and accuracy of the method.

Furthermore, Vazquez et al. (2014) detail the application of a mathematical approach known as the Multistage Homotopy-Perturbation Method (MHPM) to characterize the behaviour of CD4+ T cells during an HIV infection (Perelson et al., 1993) spanning the time interval [0,70]. The study includes numerical comparisons between the MHPM, the standard HPM, MVIM, and the RK4. The findings indicate that the MHPM method exhibits greater accuracy than other methods (MVIM and HPM) in forecasting the progression of the infection over an extended period of 70 days compared to the alternative techniques. These comparisons highlight the MHPM

as a highly accurate and effective algorithm for solving HIV models and other hyperchaotic systems. Additionally, simulations demonstrate that the validity of the method can be maintained for an extended duration.

In 2014, Bastani applied the MVIM to address a diverse set of first-order ODEs. The study introduced a theorem that established the convergence of this method. Subsequently, MVIM was employed to tackle a model related to the HIV infection of CD4+ T cells within the time interval [0,1]. The numerical results showcased the remarkable effectiveness of MVIM, surpassing the performance of the LADM method when compared to the RK4 method. However, the computation of the correction functional after a few iterations in subintervals posed challenges, making it difficult to obtain accurate values. To address this issue, the study suggests performing only a minimal number of iterations (e.g., one or two) in each subinterval and employing a large number of subintervals (small time step size) to achieve greater accuracy in the solution. The proposed method presents distinct advantages over RK4, being utilized without imposing restrictive assumptions and remaining unaffected by computation round-off errors. Furthermore, the method provides a continuous form solution.

Moreover, Khalid et al. (2015) introduced a novel Iteration Algorithm known as the Perturbation Iteration Algorithm method (PIAM) and applied it to solve a model describing the HIV infection of CD4+ T Cells over the time interval [0,1]. The algorithm utilizes an infinite series to compute the solution of the governing differential equation, with components that are easily calculable. The reliability and efficiency of this proposed approach were demonstrated through numerical examples and compared with other methods such as Euler's, Differential Transform, and RK4. The PIAM was identified as a straightforward yet potent mathematical tool suitable

for solving nonlinear problems in systems of nonlinear differential equations and dynamical systems. It proved to be an accurate and efficient method, particularly when applied to the HIV infection model of CD4+ T-Cells in comparison to alternative methods. However, it is worth noting that the method may involve intricate mathematical manipulations and computations, especially when dealing with higher-order perturbations and series expansions, rendering it computationally intensive. Additionally, the success of the PIAM depends on the convergence of the iterative process, which, in some cases, may be challenging to achieve, making the method inapplicable.

In the investigation conducted by Kamboj and Sharma (2016), mathematical models and the MVIM are employed to explore the impact of combined drug therapy on the growth of HIV and the dynamics of the CD4+ T-cell population within the time span [0,700]. The model is employed to gain insights into the existence and stability of both infected and uninfected steady states in HIV growth. The MVIM is adapted to yield rapidly convergent successive approximations of the exact solution, with no alterations or constraints imposed on the physical behavior of the problem. Numerical simulations are utilized to elucidate the consequences of the proposed drug therapy on the progression or decline of the infection.

Later, AL-Juaifri and Mechee (2018) employed mathematical modeling to examine the HIV infection of CD4+ T cells over the time interval [0,1]. They utilized a set of nonlinear ODEs to depict the IVPs and subsequently employed two methods, HPM and VIM, to assess the population of uninfected CD4+ T cells in the organism. By comparing the outcomes derived from these two methods in relation to accuracy and computational time, they demonstrated the superiority and efficiency of these approaches.

Senthamarai et al. (2018) proposed a mathematical model for the dynamics of HIV infection over the time interval [0,1] using the HPM to obtain an analytical solution. The authors used the MATLAB software to generate graphical and numerical solutions and found that the HPM provided an approximate analytical solution for each compartment of the model. The analytical results were compared to simulation results and a satisfactory agreement was observed. The authors also noted that the HPM is a relatively simple method and can be used to solve other nonlinear equations.

Additionally, Perturbation (2018) investigates a mathematical model portraying the HIV infection of CD4+ T cells over the interval [0,1] through the use of nonlinear ODEs. The primary goal is to employ the HPM and VIM techniques to assess the population of uninfected CD4+ T cells within the organism. The study includes a comparison of these two methods in relation to accuracy and computational time, demonstrating their efficiency in approximating solutions for the systems of ODEs.

The study by Timothy et al. (2019) developed a linear mathematical model of HIV/AIDS dynamics that considers counselling and anti-retroviral therapy (ART) using ODEs over the interval [0,50]. The study used VIM to obtain solutions for the model and sub-models, which provided continuous solutions that can be used for further analysis. The solution when it exists is found in a rapidly converging series form. The results showed that the VIM method was an alternative to the RK4 method and that for effective counselling and ART to lead to eradication, it is necessary for the same proportion of males and females to be involved in ART. The study also found that the equilibrium state of the general model was locally and asymptotically stable.

Ali et al. (2019) employed the ADM to solve a model describing HIV infection in chronically infected CD4+T cells over the time interval [0,50]. The ADM was applied to a deterministic mathematical model featuring four compartments that represent latently infected CD4+T cells. The effectiveness and dependability of this method were illustrated through numerical examples, revealing that the ADM is capable of providing approximate solutions in a more efficient and reliable manner. Additionally, the ADM stands out for its practicality, as it does not necessitate specialized equipment or extensive time when implemented with computer programs. However, it's worth noting that the results lack a comparison with alternative methods in terms of accuracy. Furthermore, the accuracy of the ADM is contingent on the choice of Adomian polynomials, and the convergence of the method may be influenced by the precision of these polynomials. Selecting appropriate polynomials could pose a challenge for certain problems.

In study by Bunga and Ndii (2020) the authors present a mathematical model of HIV with antiviral treatment and use the differential transformation method (DTM) to solve the model within the time span [0,50]. DTM is a semi-analytical technique that provides an iterative procedure to obtain the power series of the solution in terms of initial value parameters. The results of the DTM are compared to those of the RK4 method and it is found that the DTM gives good agreement with the RK4 method for smaller time steps but fails for larger time steps. The authors suggest that some modifications may be required to enhance the performance of the DTM for larger time steps, but this is not the focus of the paper.

Afterward, Shah and Sheoran (2022), studies the co-infection dynamics of pneumonia and HIV/AIDS through a mathematical model that includes different equilibrium points for each disease and co-infections. The main focus of the study is

to demonstrate the efficiency of the HPM in solving nonlinear ODEs within the time span [0,1]. The results obtained from the numerical simulations indicate that the HPM is reliable and converges quickly. The results also show the importance of preventive measures for HIV-infected individuals to protect themselves from co-infection with pneumonia. It is emphasized that HIV-infected individuals should be more aware of their health conditions and take the proper medications to avoid other infections. In addition, it is also stressed that individuals suffering from either disease should take their treatments at the right time to prevent the spread of co-infections.

In summarizing this section, various methods utilized in HIV infection models, such as HAM, HPM, BCM, ADM, LADM, PIAM, DTM, and VIM, have proven effective in addressing nonlinear HIV infection models for short time intervals. However, their suitability diminishes when applied to nonlinear ODEs governing HIV infection models over extended durations due to the complex dynamics of hyperchaotic systems (Razali 2015; Heydari et al., 2015; Liao & Zhao, 2016; Gokyildirim et al., 2018; Timothy et al., 2019; Yang, 2022). An advantage of HPM and VIM is their lower computational requirements compared to other approximate analytical methods like ADM and HAM (Shakil et al., 2013; Paliivets et al., 2021; Omar, 2021; Liao & Zhao, 2016; AL-Juaifri & Mechee; 2018). In addition, they have shown promise in ensuring solution convergence (Yang, 2022; Timothy et al., 2019). Modified methods, MHPM and MVIM, have demonstrated effectiveness in solving nonlinear ODEs for extended periods, particularly in the context of HIV infection models (Merdan et al., 2011; Vazquez et al., 2014; Bastani, 2014; Kamboj & Sharma, 2016).

However, in the real world, there are various HIV infected patients with different strengths of immune system causing uncertainty as to the immune cells level

and the viral load during the different stages of the disease (Zarei et al., 2012). None of the previous models can mirror the mentioned uncertainties. Proposing a mathematical model with fuzzy parameters which could reflect such ambiguities would be desirable (Hussian & Suhhiem., 2015).

## 2.4 Fuzzy HIV infection models

In HIV the uncertainty is modelled by fuzzy subsets, where two approaches are used to study continuous fuzzy dynamical systems in these models with several types of derivatives to represent the continuous variation rate that will appear. The fundamental difference of each one of the methods is the treatment given to the variation rate and/or how it is related to the state variables. The first approach evolves the derivative. Originally developed for functions with values in classical sets and subsequently adapted for functions with values in fuzzy sets (FDEs). The second approach differs from the other one because the rate is related to the state variables given by some fuzzy rules instead of an equation (Fuzzy Rule-Based Systems) (De Barros et al. 2017). In this work we will use the first approach to study fuzzy dynamical systems in fuzzy HIV infection models. The solution of fuzzy HIV infection models can help researchers understand the underlying mechanisms of the disease and can also be used to test the effectiveness of different treatment strategies and should provide useful information for the healthcare of the nation, as stated in the section of Ministry of Health Malaysia (2015) in the national strategic plan for ending AIDS (2016-2030).

### 2.4.1 Derivative approach for solving fuzzy HIV infection models

Once the concept of differentiability is defined for fuzzy mappings, it becomes possible to study FDEs and develop techniques for solving them. This is an active area of research, with ongoing efforts to better understand the behaviour of fuzzy systems.

In this approach, there are numerous existing methods to solve FODEs of type FIVPs including fuzzy HIV infection models. In general, the methods can be divided into two approaches: fuzzy approximate numerical and fuzzy approximate analytical.

### 2.4.1(a) Fuzzy approximate numerical methods

The fuzzy approximate numerical methods are a class of computational methods that are used to solve problems in fields such as physics, engineering, and other areas where real-world problems need to be modelled and analysed (Li & Chen, 2018). The approximate numerical methods give solutions approximately in numeric value form, and the error in the solution can be estimated using arithmetic operations (Moore & Ertürk, 2020). This class of methods is described in more detail in Moore and Ertürk (2020). The classes of existing approximate numerical methods for fuzzy HIV infection models are available in some articles.

In the study of Najariyan et al. (2011) suggested a nonlinear model of HIV infection with FDEs. Since the proportion of the disease depend on the gender, age, feeding, one needs to consider the variables in equations as fuzzy variables. Also, a fuzzy dynamical system is considered to control HIV disease. They used α-cuts to convert the system into two non-fuzzy ODEs, then used a discretization approach, and applied generalized Euler method for solving two systems. The authors suggest that treating the equation variables as fuzzy variables can lead to a more accurate representation of the HIV infection and can also help to manage the disease through the use of a fuzzy dynamic system. In addition, Euler method is a one-step numerical method that belongs to the family of Runge-Kutta methods and directly computes the values of the solution at discrete points. It is suitable for both linear and nonlinear problems. The method is generally accurate for a wide range of problems, especially when the step size is appropriately chosen. typically has a moderate computational