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Mathematical Analysis of Epidemiological Models using Fractional Derivative Operators

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■ Background of the study (Motivation)

Introduction to Mathematical Analysis of Epidemiological Models

Mathematical analysis is a crucial aspect of epidemiological modeling, as it provides a quantitative framework to understand the dynamics of disease spread in populations. Epidemiological models use mathematical equations to represent the interactions between different variables such as the number of susceptible, infected, and recovered individuals in a population. These models help in predicting the course of an epidemic, assessing the impact of interventions, and informing public health strategies.

Epidemiology Overview: The word epidemiology comes from the Greek words epi meaning "on or upon", demos meaning "people" and logos meaning "the study of". In other words, the word epidemiology has its roots in the study of what befalls a population. Epidemiology is the study of the distribution and determinants of health-related events or conditions in populations. It involves the application of scientific methods to investigate patterns, causes, and effects of diseases, ultimately contributing to the prevention and control of health problems.

Importance of Studying Epidemiological Models:

- **Prediction and Planning:** Epidemiological models allow for the prediction of disease trends, helping authorities plan and allocate resources effectively. This is crucial for managing healthcare infrastructure, personnel, and supplies during outbreaks.

- **Understanding Disease Dynamics:** Mathematical models help in understanding the dynamics of disease transmission, such as how infectious diseases spread through populations. This understanding is essential for developing targeted interventions.

- **Optimizing Interventions:** By simulating the effects of various interventions (e.g., vaccination, social distancing, quarantine), mathematical models assist in optimizing strategies to control and mitigate the impact of diseases.

- **Resource Allocation:** Models aid in the efficient allocation of resources by providing insights into the potential burden of diseases on healthcare systems and guiding decisionmakers on resource distribution.

- **Policy Development:** Epidemiological models contribute to evidence-based policymaking by providing quantitative insights into the effectiveness of different public health measures.

A Comprehensive Overview of Diseases and their Occurrence Patterns

Diseases characterized by abnormal conditions or disruptions in the structure or function of organisms, can be broadly classified into infectious and non-infectious categories. Infectious diseases are caused by pathogenic microorganisms, while non-infectious diseases result from various factors such as genetics, environment, and lifestyle choices. This comprehensive exploration aims to categorize diseases based on occurrence patterns, providing illustrative examples for better comprehension.

I. **Infectious Diseases:** Infectious diseases are caused by pathogens like bacteria, viruses, fungi, and parasites. They can be transmitted from person to person or from animals to humans. e.g. Influenza (Flu), Tuberculosis (TB), HIV/AIDS, Malaria, COVID-19.

II. **Non-Infectious Diseases:** Non-infectious diseases are not caused by pathogens and cannot be transmitted from person to person.e.g. Heart Disease, Cancer (Lung cancer, Breast cancer, Pancreatic cancer etc.), Diabetes.

III. **Classifying Diseases Based on Occurrence:** Diseases can be classified as follows:

   (a) **Endemic Diseases:** Consistently present at a stable level in a specific geographic area, illustrated by diseases like malaria in tropical regions.

   (b) **Epidemic Diseases:** Occur at a higher-than-normal rate within a population during a specific timeframe, as seen in seasonal influenza outbreaks.

   (c) **Pandemic Diseases:** Epidemics that spread across multiple countries or continents, exemplified by the global impact of the COVID-19 pandemic.

   (d) **Outbreaks:** Sudden occurrences of diseases in specific populations or regions, such as foodborne illness outbreaks (Listeria, Hepatitis A), Waterborne Disease Outbreaks (Cholera) in localized communities.

IV. **Conclusion:** Understanding the nature, causes, and patterns of diseases is essential for effective prevention, control, and treatment. This exploration provides insights into both infectious and non-infectious diseases, highlighting their occurrence patterns and offering real-world examples for a comprehensive understanding of the diverse landscape of human health challenges.

Importance of Mathematical Analysis in Epidemiological Models:

- **Model Calibration:** Mathematical analysis allows researchers to calibrate models using real-world data, ensuring that the model reflects the actual dynamics of the disease.
- **Parameter Estimation:** Mathematical analysis helps in estimating parameters such as the transmission rate, recovery rate, and other key variables, which are essential for making accurate predictions.
- **Sensitivity Analysis:** It helps identify which parameters have the most significant impact on the model's outcomes. This information is crucial for prioritizing interventions and resources.
- **Scenario Planning:** Mathematical models allow for the simulation of different scenarios, helping policymakers assess the potential outcomes of various interventions and make informed decisions.
- **Validation and Verification:** Through mathematical analysis, researchers can validate the accuracy of models by comparing their predictions with observed data. This ensures the reliability of the models for decision-making.

In conclusion, mathematical analysis is fundamental to the study of epidemiological models, providing a rigorous and quantitative framework for understanding, predicting, and controlling the spread of diseases in populations.

Introduction to Fractional Calculus

Fractional calculus has been used to model the real world problems. It plays a pivotal role in various domains such as science, engineering, finance and others. In the branch of fractional calculus, fractional derivatives and fractional integrals are important aspects. Fractional calculus, an emerging area of mathematics, addresses limitations in classical derivatives by employing non-integer or fractional-order differential operators. These operators possess memory properties, making them valuable for modeling natural phenomena with non-local dynamics and anomalous behavior [8]. The study of epidemiological dynamical processes with memory effects is particularly relevant as it involves fractional derivative operators.

Originating from a correspondence between Leibniz and L'Hospital in 1695, fractional calculus has evolved into a thriving field of research, extending beyond mathematics into physics, biology, and engineering. Leibniz's prediction of "useful consequences" has indeed materialized in various disciplines. Over the past decades, several fractional operators, such as Riemann–Liouville, Caputo, Marchaud, Weyle, Grunwald–Letnikov, Jumarie, Erdelyi–Kober, Katugampola, Hadamard, Riesz, conformable derivative, Caputo–Fabrizio, Atangana–Baleanu, Atangana–Koca, Atangana Gomez, and others, have been proposed. Each operator comes with its own set of advantages and disadvantages.

To gain better insights into model dynamics, various types of fractional operators have been employed to redesign classical models. Analytic, semi-analytic, and numerical methods are available for solving systems of fractional differential equations, accommodating different fractional derivative operators. Fractional calculus not only overcomes the limitations of classical derivatives but also provides a versatile toolkit for understanding and modeling complex systems with memory effects.

Mathematical Analysis of Epidemiological Models using Fractional Derivative Operators

The use of fractional derivative operators in the mathematical analysis of epidemiological models introduces a more nuanced and flexible approach to capturing complex behaviors in the dynamics of disease spread. Fractional calculus involves the use of derivatives and integrals of non-integer order, allowing for the incorporation of memory effects and long-range interactions. Here are some key reasons why the application of fractional calculus is important in modeling epidemiology:

- **Memory and Long-Range Dependence:** Traditional epidemiological models often assume instantaneous interactions between individuals, neglecting memory effects and long-range dependencies. Fractional calculus introduces fractional-order derivatives, enabling the incorporation of memory in the models. This is particularly relevant in situations where past interactions or exposures influence the current state of an individual's susceptibility or infectiousness.

- **Modeling Anomalous Diffusion:** Fractional calculus is well-suited for describing anomalous diffusion, where the spread of a disease may not follow standard diffusion processes. In epidemiology, this can be crucial when modeling the movement of individuals in populations that exhibit complex behaviors, such as subdiffusion or superdiffusion.

- **Capturing Heterogeneity:** Fractional-order models provide a more flexible framework for capturing heterogeneity in populations. Heterogeneity, such as variations in individual susceptibility or contact patterns, plays a significant role in the dynamics of infectious diseases. Fractional calculus allows for a more realistic representation of these variations.

- **Improved Accuracy in Model Predictions:** The inclusion of fractional derivatives can enhance the accuracy of epidemiological models by better capturing the underlying dynamics of disease spread. This can lead to more reliable predictions of outbreak patterns, optimal intervention strategies, and the impact of public health measures.

- **Enhanced Sensitivity Analysis:** Fractional calculus allows for a more detailed sensitivity analysis of the model parameters. Researchers can better understand the influence of specific parameters on the model outcomes, helping to identify critical factors that affect disease dynamics.

- **Dynamic Response to Intervention Strategies:** Fractional-order models enable a more realistic representation of the dynamic response to intervention strategies over time. This is crucial for assessing the effectiveness of measures like vaccination campaigns, social distancing, and treatment protocols.

- **Flexibility in Model Development:** Fractional calculus provides a flexible framework that can be adapted to various scenarios and complexities in epidemiological systems. This adaptability is particularly valuable when modeling emerging infectious diseases or those with unique characteristics.

In summary, the importance of using fractional derivative operators in the mathematical analysis of epidemiological models lies in their ability to provide a more realistic representation of disease dynamics, incorporating memory effects, long-range dependencies, and capturing the complexities of heterogeneous populations. This can lead to more accurate predictions, improved understanding of disease spread, and better-informed public health decision-making.

■ Literature survey

Table 1: Application of various Fractional derivative operators

Authors	Year	Description	Ref.No.
Abro et al.	2019	An application to solar energy using CF operator	[1]
Agarwal et al.	2022	Analyzing fractional Covid-19 pandemic model	[2]
Baleanu et al.	2020	Mathematical modelling of human liver with CF operator	[3]
Evirgen	2023	Transmission of Nipah virus dynamics under Caputo operaator	[4]
El-Dessoky et al.	2021	Application of CF derivative to a Cancer model	[5]
Gómez-Aguilar et al.	2015	Modelling of a mass-spring-damper system by different fractional derivative operators	[6]
Hassani et al.	2023	Fractional tumor-immune interaction model related to lung cancer	[7]
Jena et al.	2021	Childhood diseases model through fractional operators	[9]
Khirsariya et al.	2023	Fractional diabetes model with and without complication class	[10]
Khirsariya et al.	2023	Fractional diabetes model involving glucose–insulin alliance scheme	[11]
Kumar et al.	2021	Transmission dynamics of HIV/AIDS model through fractional operators	[12]
Khan et al.	2021	A robust study on 2019-nCOV outbreaks through non-singular derivative	[13]
Khan et al.	2020	Modeling the dynamics of novel coronavirus (2019-nCov) with fractional derivative	[14]
Khan et al.	2020	Existence, uniqueness, and stability of fractional hepatitis B epidemic model	[15]
Liu et al.	2023	Monkeypox disease with the impact of vaccination using a fractional epidemiological modeling approach	[16]
Moore et al.	2019	HIV/AIDS with treatement compartment using CF operator	[17]
Muhammad et al.	2019	Dynamics of Ebola disease in the framework of different fractional derivatives	[18]
Ngungu et al.	2023	Monkeypox dynamism with non-pharmaceutical intervention using real data from UK	[19]
Pathak	2018	Lyapunov-type inequality for FBVPs with Hilfer derivative	[20]
Pathak	2019	Lyapunov-type inequality and eigenvalue analysis for a fractional problems of order α	[21]
Özköse et al.	2022	A fractional modeling of tumor–immune system interaction related to Lung cancer with real data	[22]
Peter et al.	2023	Mathematical dynamics of measles transmission with real data from Pakistan	[23]
Qureshi et al.	2019	Fractional modeling of blood ethanol concentration system with real data application	[24]
Qureshi et al.	2019	Dengue fever outbreak by novel fractional operators with field dada	[25]
Qureshi et al.	2019	Modeling chickenpox disease with fractional derivatives	[26]
Qureshi et al.	2019	Varicella zoster virus modeled by classical and novel fractional operators using real statistical data	[27]
Qureshi et al.	2019	Modelling diarrhea transmission dynamics under real statistical data	[28]
Shah et al.	2023	Investigating a smoking tobacco cancer model with fractional operator	[29]
Shah et al.	2022	dynamical behaviour of financial system via fractional calculus	[30]
Sinam et al.	2022	Fractional order mathematical modeling of typhoid fever disease	[31]
Singh et al.	2018	A fractional epidemiological model for computer viruses	[32]
Sweilam et al.	2020	Optimal control for cancer treatment mathematical model using ABC operator	[33]
Tang et al.	2022	Modelling and analysis of breast cancer dynamics through fractional derivative	[34]
Ullah et al.	2018	A fractional model for the dynamics of TB	[35]
Yousef et al.	2020	Mathematical modeling of the immune-chemotherapeutic treatment of breast cancer under some control parameters	[36]

■ Brief about our work

Our research spans various chapters, each contributing to the application of fractional calculus. Chapter 2 explores innovative mathematical techniques for analyzing fractional boundary value problems. In Chapter 3, we introduce novel mathematical models for breast cancer dynamics using Caputo, Caputo–Fabrizio (CF), Atangana–Baleanu-Caputo (ABC) fractional derivatives, demonstrating their superiority through stability analyses and numerical simulations. Chapter 4 focuses on Chikungunya virus contamination dynamics, employing Caputo fractional derivatives and numerical simulations. Chapter 5 presents a model for smoking-related cancer disease, emphasizing the impact of fractional order on transmission dynamics. Chapter 6 investigates into a fractional-order compartmental model for hard water disease, capturing the transmission dynamics of renal disease. Chapter 7 introduces fractional models for pancreatic cancer, utilizing both Caputo and Atangana-Baleanu fractional derivatives. Chapter 8 investigates arbitrary-order tumor growth models, showcasing the superiority of fractional-order models through numerical simulations and stability analyses. Our future scope suggests avenues for multidisciplinary applications, experimental validation, optimization of treatment strategies, and real-time monitoring systems. Overall, our work significantly contributes to the understanding of complex systems and offers potential implications for medical applications and treatment strategies.

■ Formation of the thesis

We have structured our thesis into eight chapters.

Chapter 1:

Introduction and Preliminaries

This chapter serves as an introduction, providing preliminary insights into Fractional Calculus and Epidemiology.

Chapter 2:

Eigen Value Estimates for Fractional Sturm-Liouville Boundary Value Problem

This chapter delves into studying a Cauchy-Schwarz-type inequality for a fractional Sturm-Liouville boundary value problem that involves a Caputo derivative of order α, where $1 < \alpha \leq 2$. We use this inequality to find a lower bound for the smallest eigenvalue. By comparing this smallest eigenvalue with its lower bound obtained from both Lyapunov-type and Cauchy-Schwarz-type inequalities, we gain insights into the properties of these eigenvalues. This comparison sheds light on the characteristics and behaviors of the eigenvalues in the context of our problem.

Chapter 3:

Fractional Modeling of Breast Cancer Dynamics

In the first part of this chapter, a novel approach is introduced to model breast cancer dynamics using the Caputo fractional derivative operator. The study includes an analysis of breast cancer growth and control through chemotherapy treatment with three control parameters. Sadovskii's fixed-point theorem establishes the existence and uniqueness of solutions, and stability is examined using the Routh-Hurwitz criteria and Hyers-Ulam criteria. Numerical simulations illustrate the model's superiority over integer-order models.

The second part focuses on modeling and analyzing various phases of breast cancer in a fractional framework, utilizing a CF derivative. Simulations with real data from breast cancer incidences in Saudi Arabia from 2004 to 2016 demonstrate the efficacy of the CF model compared to classical models. The Picard-Lindelof method is employed for existence and uniqueness, and the two-step Adams-Bashforth technique is used for simulation. Graphical representations highlight the impact of fractional order on breast cancer behavior and chemotherapy rates.

The third part explores the development, analysis, and simulation of fractional mathematical models investigating the transmission dynamics of different phases of breast cancer. Incorporating Caputo, Caputo-Fabrizio-Caputo, and Atangana-Baleanu-Caputo operators, the study establishes solutions' existence and uniqueness using Krasnoselskii's fixed-point theory. Equilibrium points and stability are analyzed with the Routh-Hurwitz criterion. Model verification is done using reported occurrences of stage IV breast cancer in Saudi Arabia, and parameters are estimated using least squares methodology. Numerical simulations offer insights into each suggested fractional order model.

Chapter 4:

Novel Fractional Mathematical Models for Chikungunya Virus Dynamics

The focus of this chapter is to present two novel mathematical models that elucidate the dynamics of Chikungunya virus contamination. Leveraging the Caputo fractional derivative, we apply a recently developed numerical technique to approximate solutions for the Chikungunya virus system, providing valuable insights. A meticulous analysis of the numerical and graphical solutions unravels the profound impact of fractional orders on infection dynamics. The chapter also delves into the investigation of the existence, uniqueness, and stability properties of solutions, offering a deeper understanding of key parameters influencing the spread and persistence of the infection.

Chapter 5:

Quantifying Cancer Risk from Smoking: A Fractional Mathematical Approach

This chapter aims to shed light on a mathematical model assessing the risk of smoking-related cancer. This model employs fractional-order derivatives with seven compartments, utilizing the ABC fractional derivative to portray the transmission dynamics of cancer induced by smoking.

Our numerical results, computed through the Adams-Bashforth-Moulton Method, demonstrate a high level of accuracy. We establish the model's solution's existence and uniqueness using Banach's fixed-point theory, exploring steady state points and determining the basic reproduction number. The model's stability is discussed using the Hyers-Ulam criterion. To enhance comprehension, 2D and 3D simulations are conducted across diverse compartments and fractional-order parameters, shedding light on the intricate dynamics of the system.

Chapter 6:

Hard Water-Induced Renal Disease: A Fractional-Order Model

This chapter centers on a fractional-order compartmental model describing the transmission dynamics of renal disease caused by hard water usage. The model considers both human and water components. Humans are categorized into susceptible, infected, and recovered, while the water component is based on calcium and magnesium levels. The study investigates steady state points, including disease-free and endemic equilibrium points. Utilizing Sadovskii's fixed-point theory, we establish the existence and uniqueness of the model solution. The model's stability is assessed through the Hyers-Ulam criterion. Numerical simulations, employing the Adomian decomposition General transform method, illustrate the results for different compartments and fractional-order parameters. Graphical visualizations depict magnesium and calcium concentrations, along with water treatment efficiency. The findings highlight the importance of enhanced water treatment methods to reduce magnesium and calcium levels.

Chapter 7:

Qualitative Analysis of Fractional Modeling of Pancreatic Cancer Dynamics

Within this chapter, we divide our exploration into two parts:

In the first part, we unveil a fractional mathematical model that intricately depicts the interplay between immune system components and pancreatic cancer, employing the Caputo fractional derivative operator. We ensure the system's well-posed nature using Sadovskii's fixed-point theorem and delve into the stability of solutions through Ulam Stability results, offering crucial insights into the nuanced dynamics of pancreatic cancer.

Shifting focus to the second part, we concentrate on crafting and scrutinizing a fractional mathematical model for pancreatic cancer utilizing the Atangana-Baleanu fractional derivative. Encompassing pancreatic ductal adenocarcinoma, the model strives to establish the existence and uniqueness of the solution system. Employing a fixed-point theorem and the Lipschitz condition for robustness, we delve into the model's stability using the Hyers-Ulam criteria. These findings deepen our comprehension of the model's behavior, showcasing its ability to accurately represent the intricacies of pancreatic cancer dynamics. This research not only contributes valuable insights into understanding pancreatic cancer but also holds potential implications for the development of innovative treatments and therapies in the future.

Chapter 8:

Advanced Fractional Mathematical Model for Tumor Growth Dynamics

This chapter explores a refined mathematical model for tumor growth dynamics. Our fractional-order approach, based on the Hahnfeldt et al. model with Caputo fractional derivatives, incorporates relevant factors. We validate the model's existence and uniqueness through the Lipschitz condition and employ the fractional Euler method for numerical solutions. Evaluating against various cancers, we calculate the root mean square error (RMSE) for different α values. The results underscore the fractional-order model's superiority over the classical model, enhancing our understanding and prediction of tumor growth dynamics.

Some of the references used in the thesis are provided in the bibliography section.

■ List of publications

Published Articles:

- Anil Chavada & Nimisha Pathak (2021), Eigen Value Estimates for Fractional Sturm-Liouville Boundary Value Problem, *Springer Proceedings in Mathematics & Statistics, Springer, Singapore*, Vol. 344, pp 231–238, ISBN: 978-981-33-4646-8, Indexed in : **Scopus**.

- Anil Chavada & Nimisha Pathak (2021), A Note on Lyapunov-type Inequalities for Fractional Boundary Value Problems with Sturm-Liouville Boundary Conditions, *Journal of Mathematical Extension*, Vol. 15, No. 4, pp 1-12, ISSN: 1735-8299, Indexed in : **Web of Science**.

- Anil Chavada, Mihir Thakkar & Nimisha Pathak (2023), Mathematical analysis of a Pancreatic cancer with Atangana-Baleanu derivative, *Proceedings of International Conference RAISE 2023: Vol. III Computer Science & Engg., Applied Mathematics, Electrical Engineering, Applied Physics*, ISBN: 978-81-962938-3-3.

- Anil Chavada, Nimisha Pathak, Bhavyata Patel & Geeta Chaudhary (2023), Numerical Simulation of Fractional Mathematical Model of Tumor Growth, *Proceedings of International Conference RAISE 2023: Vol. III Computer Science & Engg., Applied Mathematics, Electrical Engineering, Applied Physics*, ISBN: 978-81-962938-3-3.

- Anil Chavada & Nimisha Pathak (2024), Transmission dynamics of breast cancer through Caputo Fabrizio fractional derivative operator with real data, *Mathematical Modelling and Control, AIMS Press*, **Accepted**, Indexed in : **Scopus, Web of Science**.

Communicated Papers in International Journals (Under Review):

- Anil Chavada, Nimisha Pathak (2023), Fractional Mathematical Modelling of Breast Cancer Stages with True data from Saudi Arabia, *Results in Control and Optimization*, Elsevier, (**Under revision**), Indexed in : **Scopus, Web of Science**.

- Anil Chavada, Nimisha Pathak (2023), Fractional order mathematical modelling and analysis of Breast cancer epidemiology under control parameters,*Researches in Mathematics, Dnipro University Mathematics Bulletin,* Indexed in : **Scopus**.

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- Anil Chavada, Nimisha Pathak, Sagar R Khirsariya (2024), A Fractional Mathematical Model for Assessing the Cancer Risk due to Smoking habit. *Mathematical Modelling and Control*, AIMS Press, Indexed in : **Scopus, Web of Science**.

Paper Presentations in Conferences:

- International Conference on Fractional Calculus:Theory, Applications and Numerics (ICFTAN–2023) Organized by Department of Mathematics, National Institute of Technology Puducherry, Karaikal, India, during 27^{th} - 28^{th} January, 2023.

  Title : Numerical simulation of fractional initial value problems with atangana baleanu fractional derivative operator

- International Conference on Recent Advances in (Applied) Sciences & Engineering (Raise-2023) organized by Faculty of Technology & Engineering, The Maharaja Sayajirao University of Baroda, Vadodara, Gujarat, India, during 12^{th} - 13^{th} April, 2023.

  Title : Numerical Simulation of Fractional Mathematical Model of Tumor Growth

- International Symposium on Mathematical Analysis of Fractals and Dynamical System-2023 (ISMAFDS-2023) organized by the Department of Mathematics, School of Advanced Sciences, Vellore Institute of Technology, Vellore, Tamil Nadu, India held from 24^{th} - 25^{th}, August 2023.

  Title : Fractional order mathematical modelling and analysis of Breast cancer epidemiology under control parameters

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