UNIVERSITI PUTRA MALAYSIA

THEORETICAL ADVANCEMENT IN DENGUE TRANSMISSION MODEL IN MALAYSIA USING FRACTIONAL ORDER DIFFERENTIAL EQUATIONS

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By

NUR IZZATI BINTI HAMDAN

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

July 2020

DEDICATIONS

To my beloved family,
my husband Mohamad Syafiq, my daughter Nia Zahraa, and my son Umar,
my parents and my siblings.
For their unconditional love, encouragement, support and prayers.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

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Chairman: Adem Kilicman, PhD
Faculty: Science

This thesis aims to deploy and develop fractional-order differential equations that possess hereditary properties in modelling the dengue transmission dynamics. Dengue models are generally of integer-order derivative systems, that cannot fully explain the behaviour of dengue transmission, which involves memory effect. In this study, three different deterministic fractional-order models are constructed, including the basic framework model, temperature-driven model, and dengue control model, using Caputo's derivative definition. The susceptible-infected-recovered (SIR) model is considered in the formulation. The significant differences between the integer-order model and the fractional-order model, and the relation of the order of the derivative with the dynamical behaviour of the dengue epidemic are addressed. Furthermore, this thesis discusses the effect of the temperature in the dengue transmission, and the efficacy of current dengue control measures, particularly in Malaysia. The theoretical analysis of the existence and stability of the equilibrium point is presented in detail. Additionally, sensitivity analysis is performed to assess the importance of model parameters in disease transmission and disease prevalence. The recorded dengue cases in Malaysia are used in numerical simulations. Numerical results reveal that the convergence rate of fractional-order models is more gradual compared to the integer-order model. A lower value of the order corresponds to a slower decaying time and reduction in the size of epidemics. The temperature-driven models show that the fractional-order model is more stable since there is no oscillatory behaviour observed in the solutions, unlike in the integer-order model. These models also predict that dengue can be persisted even in the non-optimal temperature condition. The dengue control model shows that vector control tools are the most efficient way to combat the spread of dengue viruses, and the combination of them with individual protection makes it more effective. In fact, with the massive

application of individual protection only, the number of cases can be reduced. Conversely, mechanical control alone cannot suppress the excessive number of cases in the population, although it can significantly reduce the number of *Aedes* mosquitoes. Overall, these findings have significant implications in understanding the transmission dynamics of dengue, and the proposed fractional-order models are found to be a great alternative in describing the real epidemic of dengue transmission.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

KEMAJUAN TEORI DALAM MODEL PENYEBARAN DENGGI DI MALAYSIA MENGGUNAKAN PERSAMAAN KEBEZAAN TERTIB PECAHAN

Oleh

NUR IZZATI BINTI HAMDAN

Julai 2020

Pengerusi: Adem Kilicman, PhD
Fakulti: Sains

Tesis ini bertujuan untuk menggunakan dan mengembangkan persamaan kebezaan tertib pecahan yang mempunyai sifat keturunan dalam memodelkan dinamika penularan denggi. Model denggi umumnya terdiri daripada sistem terbitan tertib integer, yang tidak dapat menjelaskan sepenuhnya tentang penularan denggi, yang melibatkan kesan ingatan. Dalam kajian ini, tiga model tertib pecahan deterministik yang berbeza dibina, termasuk model kerangka asas, model berdasarkan suhu, dan model kawalan denggi, menggunakan definisi terbitan Caputo. Model rentan-dijangkiti-pulih (SIR) dipertimbangkan dalam formulasi. Perbezaan yang signifikan antara model tertib integer dan model tertib pecahan, dan hubungan tertib terbitan dengan tingkah laku dinamik wabak denggi dibahaskan. Selanjutnya, tesis ini membincangkan pengaruh suhu pada penularan denggi, dan keberkesanan langkah-langkah kawalan denggi semasa, khususnya di Malaysia. Analisis teori mengenai kewujudan dan kestabilan titik keseimbangan dikemukakan secara terperinci. Selain itu, analisis kepekaan dilakukan untuk menilai kepentingan parameter model dalam penularan penyakit dan kelaziman penyakit. Kes denggi yang direkodkan di Malaysia digunakan dalam simulasi berangka. Hasil berangka menunjukkan bahawa kadar penumpuan model tertib pecahan lebih beransur-ansur dibandingkan dengan model tertib integer. Nilai tertib yang lebih rendah sepadan dengan masa pereputan yang lebih perlahan dan pengurangan saiz wabak. Model-model yang didorong oleh suhu menunjukkan bahawa model tertib pecahan lebih stabil kerana tidak ada tingkah laku berayun yang diperhatikan dalam penyelesaian, tidak seperti pada model tertib integer. Model-model ini juga meramalkan bahawa denggi dapat bertahan walaupun dalam keadaan suhu yang tidak optimum. Model kawalan denggi menunjukkan bahawa alat kawalan vektor adalah kaedah paling berkesan untuk memerangi penyebaran virus denggi, dan gabungannya dengan perlindungan individu menjadikan-

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nya lebih berkesan. Sebenarnya, dengan penggunaan perlindungan individu secara besar-besaran sahaja, jumlah kes dapat dikurangkan. Sebaliknya, kawalan mekanikal sahaja tidak dapat menekan jumlah kes yang berlebihan dalam populasi, walaupun secara signifikan dapat mengurangkan jumlah nyamuk *Aedes*. Secara keseluruhan, penemuan ini mempunyai implikasi yang signifikan dalam memahami dinamika penularan denggi, dan model tertib pecahan yang dicadangkan didapati menjadi alternatif yang baik dalam menggambarkan wabak sebenar penularan denggi.

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

BRDFE	Biologically Realistic Disease-free Equilibrium
DF	Dengue Fever
DFE	Disease-free Equilibrium
DHF	Dengue Hemorrhagic Fever
DSS	Dengue Shock Syndrome
DOSM	Department of Statistics Malaysia
EE	Endemic Equilibrium
GAS	Globally Asymptotically Stable
GM	Genetic Modified
LAS	Locally Asymptotically Stable
NCDC	National Climatic Data Center
ODE	Ordinary Differential Equation
PECE	Predict-Evaluate-Correct-Evaluate
SEI	Susceptible-Exposed-Infected
SEIS	Susceptible-Exposed-Infected-Susceptible
SEIR	Susceptible-Exposed-Infected-Recovered
SEIRS	Susceptible-Exposed-Infected-Recovered-Susceptible
SI	Susceptible-Infected
SIS	Susceptible-Infected-Susceptible
SIR	Susceptible-Infected-Recovered
SIRS	Susceptible-Infected-Recovered-Susceptible
ULV	Ultra-Low Volume
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

> *"I simply wish that, in a matter which closely concerns the wellbeing of the human race, no decision shall be made without all the knowledge which a little analysis and calculation can provide ".*
>
> by Daniel Bernoullli, 1760

The modern period features a plethora of social, technological, and biological epidemic phenomena. The spread of such epidemic is rapidly increasing each year due to the advances in technology, transportation and lifestyle. One of the crucial tools in understanding the epidemic is by formulating a mathematical model. Mathematical modelling plays a significant role in effective real-time decision making and management of the epidemic outbreaks. This research is motivated by the dengue outbreak in Malaysia, that has now become the most prevalent disease in the country. Currently, dengue is listed second after malaria, as the most severe vector-borne disease around the globe and about half of the people in this planet are in danger of the dengue viruses [161].

This study is focusing on the modelling of the dengue transmission disease using the approach of the fractional-order differential equation and comparing it with the classical integer order differential equation. The relationship between environmental factors, entomological factors, and epidemiological factors is explored in the modelling, to gain more insight on the transmission, and to assist in providing information in designing proper dengue control programs. The first chapter of this thesis begins by laying out the general knowledge on the epidemiology of dengue, specifically in Malaysia, the fundamental of modelling infectious disease and background on fractional calculus. It then goes on to specify the research objectives and concludes by introducing the structures for the next chapters of the thesis.

1.1 Dengue and its history

Dengue fever (DF) or acknowledged as dengue is a very well-known vector-borne disease that exists for more than 20 decades. The initially reported epidemics of dengue fever happened between the year of 1779-1780 in tropical regions, primarily in Asia, Africa, and North America [69]. During the earliest period of the existence of dengue, DF was regarded as a mild and non-fatal disease with low transmission rates. It was not easy to achieve major epidemics because of new serotypes only existed in a susceptible population when the mosquitoes and viruses can survive the slow transportation between the population. A contagion of dengue commenced in Southeast Asia following World War 2 and spreading globally ever since [69]. The number of dengue incidents has risen rapidly since then to the latest value of fifty to a hundred million cases yearly. The number of countries that get affected by the viruses has also grown substantively, with at least 100 countries is considered endemic, including in Americas and the Eastern Mediterranean [28] (see Figure 1.1).

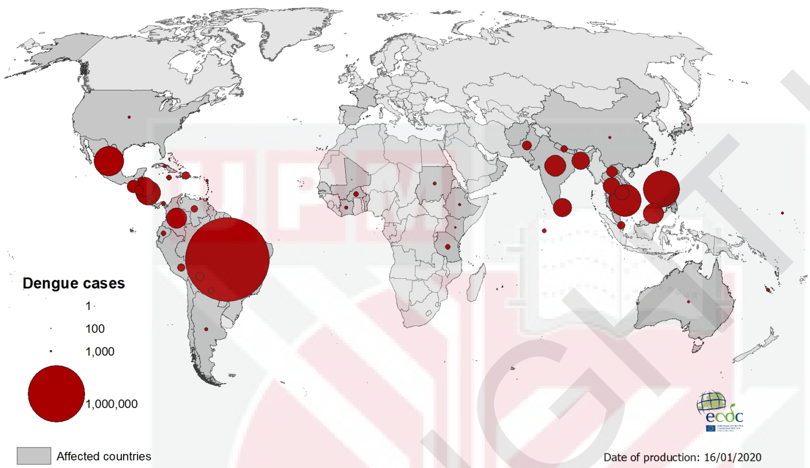

Figure 1.1: Distribution of dengue, worldwide, 2019. (Note: Reprinted from "European Centre for Disease Prevention and Control (ECDC)" [55])

DF is an acute mosquito-borne illness transferred through the bite of an adult female *Aedes aegypti* (primary vector) or *Aedes albopictus* (secondary vector) mosquitoes. Female mosquitoes get the infection after receiving a blood meal of an infected person, then transport the virus to the non-contagious individual through the blood meal process as well. The infection rates can reach up to 90% between individuals who have not yet been exposed or infected by the dengue virus [69]. There exist four different dengue serotypes specified as DENV-I, DENV-II, DENV-III, and DENV-IV. All serotypes come from the family Flaviviridae and genus *Flavivirus* [110]. Individuals who recover from one of the dengue serotypes will gain a lifetime resistance against the respective serotype but partly or momentary immunity to the other serotypes [159].

The typical dengue fever causes mild morbidity and mortality, at which the patients can recuperate within seven or fourteen days right after encountering the fever.

However, some individuals can progress into a severe condition that is dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS). DHF first emerged in the Philippines between 1953 to 1954, and in the mid-1970s, DHF has been a prominent cause of hospitalization and fatality, especially within children [69]. The World Health Organization (WHO) has reported nearly hundreds of thousands of DHF cases every year [159] worldwide.

Presently, no exclusive treatment or vaccine available for dengue. The standard approach taken to treat dengue fever is simply keeping the patients hydrated by drinking plenty of fluids, and they should be placed in a mosquitoes-free environment to prevent any transmission. For severe dengue-like DHF, maintaining the patient's body fluid volume is important, and at some stage, patients need to undergo blood transfusions to control the bleeding [159]. The development of a dengue vaccine is still in the stage of a clinical trial. According to WHO, at the clinical trial stage, the live attenuated dengue vaccine (CYD-TDV) showed a positive outcome. However, it is safe for the individual who had experienced dengue before but a high risk to those contracting the dengue virus for the first time after vaccination. Therefore, the vaccine has not yet be implemented and is considered as an imperfect vaccine.

At present, the main approaches to manage and prevent the spread of the dengue in the community is mostly through battling the vector mosquitoes by [159]:

- Preventing the adult female mosquitoes from having habitats to lay eggs by strategic environmental administration.
- Getting rid of solid waste properly.
- Emptying and cleaning the domestic water storage containers and covering the empty containers weekly.
- Using insecticides.
- Improving community participation and awareness.
- Active monitoring of *Aedes* mosquitoes to verify the efficiency of control measures.

Besides, rigorous clinical disclosure and supervision of dengue patients can significantly decrease the incidence rates and the mortality rates from DHF and DSS.

In general, dengue fever is one of a type of self-limited disease. It has a very low casualty with proper and prompt medical assessment (approximately less than 1%). Meanwhile, for severe dengue, the mortality rate is between 2%-5% when treated. However, the mortality rate can be as high as 20% when left untreated. According to WHO, about five hundred thousand individual diagnosed with severe dengue is required for hospitalization every year worldwide, and an estimated 2.5 percent of fatality rate cases, annually [161].

The first-ever dengue fever cases in Malaysia declared in 1902. Meanwhile, the DHF and DSS epidemic began in 1962 in Penang [155]. However, the DF cases only became notifiable in 1971 [126]. The first huge dengue outbreak in Malaysia happened in 1974, and later, it consequently happened every four to five years [155]. In the beginning years of the outbreaks, dengue cases in Malaysia were still under control and only occurred seasonally [150]. However, dengue cases have increased beyond control in the 21st century, and the number of deaths has also risen. A rapid increase in the incidents can be observed from 2012 onwards. An increment of 47% is recorded in the number of dengue fever in Malaysia throughout 2012 to 2013, and roughly 62% increase is recorded in 2013 and 2014 [155] (see Figure 1.2).

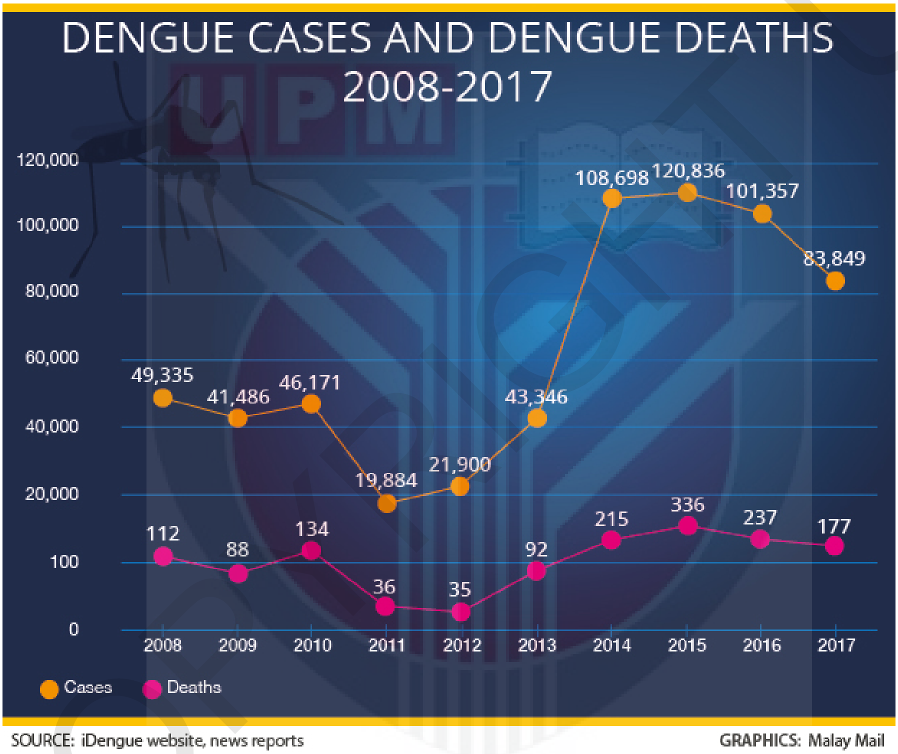

Figure 1.2: Dengue cases recorded in Malaysia for year 2008 to 2017. (Note: Reprinted from "Malaysia records three-year low with 11 dengue deaths in January", by Malay Mail [101]).

All four serotypes of dengue viruses coexist in Malaysia. The DENV-I, DENV-II, and DENV-III are the predominant virus in different periods in Malaysia, while DENV-4 shows less influence [109]. According to a recent study, major dengue outbreaks in Malaysia during the period of 2013 and 2014 were possibly caused by changes in the predominant serotypes to 6 months before each outbreak [109]. Although the government of Malaysia managed to lower the number of dengue cases and death nationwide, in two consecutive years, by 16% (17%) in cases and 29%

(25%) in the number of deaths in 2016 (2017) (see Figure 1.3), dengue is still claimed as the most prevalent disease in Malaysia.

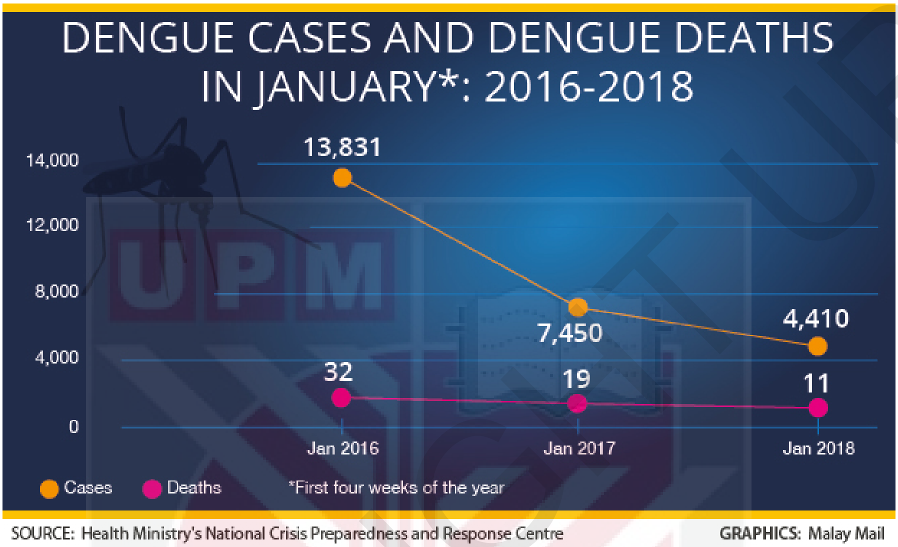

Figure 1.3: Dengue cases in Malaysia January 2016-2018. (Note: Reprinted from "Malaysia records three-year low with 11 dengue deaths in January", by Malay Mail [101]).

In Malaysia, it became public health practitioners responsibility to inform the Local Health Office every case diagnosed with either dengue fever, DHF, or DSS within 24 hours. Such increment in the dengue cases is related to many factors. Among the general factors suggested globally are due to the high rates of population growth and rapid and relatively unorganized urbanization. Besides, alteration in public health, global warming, and the rise in global commerce and tourism contribute to the dengue spread in the country [69]. As of now, there are no drugs or vaccine available in Malaysia. There is no option other than vector control to resist the spread of dengue. In controlling the larva population, the control tools taken were focusing on environment administration, source reduction, usages of larvicides, such as temephos (Abate), the house inspection, and enforcement of Destruction of Disease-Bearing Insect Act 1975 [118]. Meanwhile, fogging was executed based on the immediate viral cases reported, to control adult mosquitoes. The other alternatives vector control are by using the microbes *Bacillus thuringiensis* H-14, attractant trap, and genetic modified (GM) mosquito.

1.2 Dengue epidemiology

1.2.1 Ecology of *Aedes* mosquito

Aedes aegypti is the primary vector of transmitting the dengue virus. They are prone to the urban environment where human capacity is large. The life cycle of the *Aedes aegypti* involves four distinct stages, namely eggs, larvae, pupa, and adult. The mosquitoes lay their eggs in a wet environment, such as tree holes and redundant. The eggs will then hatch into larva form after a rain takes place. Within a week, the larvae will change into a pupa and become a mosquito in 2 days. Only the matures adult female mosquito gets blood meals from humans or animals, while, the male mosquito feeds on plants and flowers. On average *Aedes* mosquitoes can live up to 12 to 15 days [62]. *Aedes aegypti* mosquitoes have good adaptations to nature that makes them capable of immediately recover to their original numbers following any disruption occurring from a natural disaster such as droughts or human interferences. One of the adaptations is the eggs can tolerate dryness. *Aedes aegypti* may continue responding and adapting to the environmental change. For instance, in the recent study, it was found that *Aedes aegypti* can undergo the immature stage in broken or open septic tanks resulting in the formation of large amount of *Aedes aegypti* adult per day [87].

Temperature is very significant in the survival of the larval population and the competence of the *Aedes aegypti*. In a warmer climate with longer light exposure, a shorter growth period is required from eggs hatch to the development of the adult mosquito [32]. These explain the widespread distribution of *Aedes aegypti* in tropical and subtropical regions, particularly in Malaysia. Moreover, the study suggests that increasing the abundance of *Aedes aegypti* mosquito in urban areas leading to outbreaks [87]. The developing countries, like Malaysia, are becoming more citified. However, due to poor town planning and cleanliness, it leads to an increase in mosquito breeding sites.

Aedes albopictus referred to as the Asian tiger mosquito is a type of mosquito that innate to the tropical and subtropical zones in Southeast Asia. Their eggs are very much resistant to dryness, which develops their durability in inhospitable habitats [83]. This type of *Aedes* mosquito is among the competitive species, and they bite in the daylight by attacking not only humans but also livestock, amphibians, reptiles, and birds [51]. They have a high biting rate level that could go up to 30 to 48 bites per hour, and they can survive in a broad array of temperatures [17, 35]. *Aedes albopictus* is a tree hole mosquito, and thus, the reproduction process normally takes place in natural or suburban forested regions. However, their ecological adaptability enables them to lay eggs in various types of man-made water-holding containers, particularly discarded tires, flowerpots, and abandoned containers [87]. *Aedes albopictus* can also produce and survive in urban regions, where artificial containers are rarely found, thus, raising an additional public-health concern, especially in rural districts [51].

1.2.2 Dengue transmission

There are three types of dengue virus transmission cycle, specifically, enzootic, epizootic, and epidemic [87]. The enzootic cycle includes transmission between mosquito and monkey (monkey-Aedes-monkey). This cycle is primeval and can be found in Africa and South Asia [69]. Meanwhile, the epizootic cycle includes the transmission from non-human primates to the subsequent human in the epidemic cycles by the *Aedes* mosquito [87]. The last cycle, which is the epidemic, involves the transmission among humans and *Aedes* mosquito. Here, we will only discuss the transmission in the epidemic cycle.

In the epidemic cycle, the transmission of the dengue virus happens if the uninfected female mosquito gets the virus from an infected individual during the blood-feeding activity or if the infected mosquito has contact with susceptible individuals at the time of the blood meal. Once the mosquito gets infected by the virus, the extrinsic incubation period is within 14 days, and the infected mosquito will remain infected and dies [69]. Dengue virus cannot spread directly from human to another human. The incubation period varies from one virus to another, but in general, the dengue virus appears between two to fifteen days from inoculation to the development of clinical symptoms [87]. At this stage, an uninfected mosquito can get the virus once she feeds on this individual.

The biological studies on the vector-borne disease like dengue and malaria showed that memory and associative learning behaviour of the vectors (mosquitoes), in general, are important in the disease transmission process [24, 104, 148]. Recent studies revealed that the behaviour during oviposition site-selection, host location, and host selection are dependent not only on the environment but also in the experience after eclosion [104]. Thus, it is significant to consider modelling the dengue transmission using a system that passes the information of its former state.

1.2.3 Seasonality and intensity of transmission

The ongoing risk of dengue virus is caused by the growth of geographical distribution, including climate shift and the evolution of the epidemic cycle to endemic with seasonal patterns [90]. Climate variability has a significant contribution to the development of the mosquito population, both in immature and mature stages. Environmental factors like precipitation, temperature, and humidity could affect the growth and survivability of the mosquitoes as well as their behaviour and habitats [73, 129]. The former study showed that temperature and precipitation have significant relationships in the transmission of dengue virus. However, such associations have not consistently described [30, 39, 91]. In general, dengue transmission takes place during rainy seasons with proper temperature and humidity to make sure that adult and larval mosquito can survive in that environment. In dry areas, where rainfall is insufficient, *Aedes* mosquito opted for the man-made containers as their breeding sites, thus, can also increase the transmission rate.

1.3 Mathematical deterministic models

Mathematical modelling has been gradually recognized in the public health community as one of the important research tools in understanding the epidemiology of an infectious disease [6]. The main purpose of the mathematical modelling of infectious disease including the vector-borne disease is to identify mechanisms that cause the outbreaks as well as to evaluate the effectiveness of control strategies. There are two approaches in mathematical modelling that is widely used in infectious disease epidemiology namely deterministic model and stochastic model. The deterministic models involve models based on the differential equation, integral, or functional differential equations. The deterministic model of an infectious disease was discovered in the 20th century by the work of Bailey [12], Hamer [75], Kermack and McKendrick [84], and Ross [135]. Since then, deterministic models have had an important role in the description of the spread of disease. In the deterministic model, the outcomes of the model are determined from the parameter values and the initial conditions, and it is possible to obtain a unique solution. On the other hand, stochastic models possess random characteristics, where the same set of parameter values and initial conditions can result in different output values.

In simple deterministic epidemic models, a threshold value is obtained that allows us to determine whether the epidemic or outbreaks will occur or will not occur. However, a different approach is taken in the stochastic model, where the probability is used to determine the visibility of epidemics. Clearly, the natural world is buffed by stochasticity. However, modelling an infectious disease using a stochastic model can be quite complicated and challenging. The deterministic model is relatively easy to parametrize and rapid to simulate. They are useful for predictions in a large population. A stochastic model, on the other hand, is more appropriate to model disease in a small population.

Example 1.3.1 *A simple susceptible-infected (SI) epidemic model. This model presumes that the host population is either susceptible or infectious. The infectious hosts will never recover, and it is assumed to be a closed population. The SI compartmental model is expressed by the ordinary differential equations:*

$$\begin{aligned}\dot{S} &= -\lambda S \\ \dot{I} &= \lambda S \qquad (1.3.1)\end{aligned}$$

where λ is the force of infection, that is, the rate where the susceptible population *acquires the infection.*

The force of infection relies on:

- The frequent contact between human and mosquito.
- The probability that a given contact is with infections individuals.
- The probability that a given contact leads to a transmission of the infection.

1.4 Fundamental concepts in epidemic models

1.4.1 Disease incidence

In the epidemiological model, the incidence of a disease is described in terms of the rate when the new infection occurs or can be defined as the number of people acquire the infection per time [93]. This quantity has a significant part in ensuring that the proposed mathematical model is able to provide a realistic qualitative analysis of the dynamic of a disease. There are few types of incidence rate that are commonly used in the epidemic model, such as the standard incidence rate, bilinear incidence rate (mass-action) and non-linear incidence rate with saturation [40, 59, 77, 84, 136].

Suppose that $S(t), I(t)$, and $N(t)$ represent the susceptible population, infectious population, and the total number of population at a given time t, sequentially. Assume that $\beta(N)$ represents the effective contact rate for each individual at time t. Then, the mean of contacts a susceptible person does with an infectious person per unit of time is equivalent to $\beta(N)\frac{I}{N}$. Therefore, the number of new incidents from susceptible individuals (S) is presented by λS, where $\lambda = \beta(N)\frac{I}{N}$ is the force of infection. Then, we consider the following two cases:

1) If the effective contact rate $\beta(N) = \beta$, is a constant and independent of the total population size, then, λS is considered to be a standard incidence form.
2) If the effective contact rate relies on the total population size, $\beta(N) = \beta N$, then λS is known as the mass action incidence.

1.4.2 Basic reproduction number

The basic reproduction number generally expressed by R_0, is also called the basic reproductive number and the basic reproductive ratio. This parameter measures "the average number of secondary infections given by an infected person in a susceptible population during the infectious period" [93]. Generally, if R_0 is lower than unity, such that $R_0 < 1$, then disease outbreaks or epidemic would not be occurring. Thus, disease eradication in the population can be achieved in the long run. In such a case, the associate's disease-free equilibrium point (DFE) is said to be stable. Conversely, if R_0 is beyond unity ($R_0 > 1$), then an epidemic will take place and leads to the disease persistence over time. Thus, a positive endemic equilibrium point (EE) exists, and it is said to be stable if it satisfies the stability property. This is the example of the forward bifurcation where DFE and EE shift their stability at $R_0 = 1$.

The forward bifurcation was first discovered by Kermack and McKendrick [84] and later can be seen in many infectious disease models. If the model exhibits forward bifurcation, it is necessary and sufficient to have a condition of $R_0 < 1$ for disease elimination. However, this may not be required and adequate to eradicate the disease if the model demonstrates the occurrence of backward bifurcation. This appears when a stable DFE coincides with a stable EE whenever $R_0 < 1$. This special case has been discussed in great details in many epidemic model paper, see for instance in [59, 70].

1.5 Fractional calculus

The differentiation operator $\frac{d}{dx}$ is a fundamental form of derivative in the calculus subject. For a proper function denoted by f, the nth derivative of such function can be written as $\frac{d^n f(x)}{dx^n}$ where n is a positive integer. However, this is not the case in the fractional calculus. Fractional calculus involves integrals and derivatives of an arbitrary real number or even complex order. It can be seen as a generalization of classical calculus. Hence, it preserves many of the classical basic properties.

1.5.1 Historical background of fractional calculus

The beginning of the fractional calculus theory dates to Leibniz's note in his letter to L'Hospital in 1695 [43]. Leibniz presented a symbol $\frac{d^n}{dx^n} f(x)$ to express the nth derivative of a function of f with the assumption that $n \in \mathbb{N}$. L'Hospital then answered back his letter by a question of "What does $\frac{d^n}{dx^n} f(x)$ mean if $n = 1/2$?" This letter is commonly accepted as the first appearance of a fractional derivative in a mathematics world. Nowadays, the order of the fractional operator is not restricted to only fractions but also arbitrary real numbers and even complex numbers. Nonetheless, the name 'fractional calculus' is kept for historical reasons. Several leading mathematicians have contributed to the advancement of the theory of fractional calculus, for instance, Laplace (1812), Fourier (1822), Abel (1823-1826), Liouville (1832-1837), Riemann (1847), Grunwald (1867-1872), Letnikov (1868-1872), Heaviside (1892-1912), and many others [67].

1.5.2 Geometric and physical interpretation

In the classical calculus, integer-order integrals and derivatives have a clear geometric and physical interpretation, which can describe different concepts in the various field of science. For instance, a distance can be expressed as a function of time, the first derivative can be associated with the velocity, and the second derivative represents the acceleration. Even though fractional integrals and derivatives are the generalizations of the classical integrals and derivatives, up until today, there is still no definite physical interpretation of the fractional cases. Since the appearance of the idea of fractional calculus, there was not any satisfactory geometric and physical explanation of these operations for over 30 decades [124]. This problem has been widely acknowledged and has been listed as an open problem [134].

Several authors attempted to provide a general physical and geometric interpretation of the fractional operators [13, 108, 115, 124]. For example, in [108], the interpretation is based upon the fractal geometry, linear filters, Cantor set, and physical realization of fractional operators. It has been presumed that fractional operators can be classified as filters with partial memory that includes in between complete memory and no memory. However, Podlubny in [124] claimed that such consideration is only small portions of chosen examples of applications of fractional operators. Thus, it cannot be recognized as a certain answer to the posed question. He then gave a physical description of the fractional integrals in terms of two different time scales, i.e., the homogeneous and the inhomogeneous time scale [124].

Du et al. discovered that in modelling different types of memory problems, the memory process normally consists of two stages, and one of them is governed by a simple fractional-order derivative model [47]. The numerical results indicate that the fractional model perfectly fits the test data represent the memory phenomena, not only in mechanics but also in biology and psychology. The authors conclude that the fractional-order can be physically associated with an index of memory. In this study, we will associate the fractional-order operator with the index of memory following the results by Du et al.

1.5.3 Application

The first application of a fractional derivative is found in the work of Abel in 1823, where the order of the derivative is chosen to be half (1/2) and related to the tautochrone problem [117]. The interest in applications of the fractional calculus, particularly fractional derivatives in modelling various engineering systems, diffusion phenomena including heat transfer, viscoelasticity, and in many other physic systems, has widely increased in recent decades [96, 99] and has found to be a great success. This results in a growing interest in the mathematical biology field, especially in the subject of infectious diseases. Area et al. in [9] have shown that the proposed fractional model fits the considered real data accurately. In [66], a fractional-order dynamic of influenza A (H1N1) is analyzed numerically. In 2013, Diethelm [44] developed a fractional-order system for the dengue outbreak, and the simulation results agreed with the actual dengue data in Cape Verde Island in 2009.

The purpose of the application of the fractional derivative in the literature is to obtain comprehensive knowledge and understanding of the complex behavioural pattern of the biological systems [19]. The memory feature in the fractional-order systems enables the integration of the previous state, that gives more realistic and accurate prognostications of the models, that cannot be done by the classical integer order model. Moreover, these have found to benefit the public health authorities by providing data in terms of the behaviour predictions of the model to suit their patient's data with the most suitable order index.

1.6 Research objectives

The majority of the epidemic models are developed using the classical integer-order differential equation (Markovian system), where the current state of the systems not in any way affected by their former state. However, in reality, once the disease circulates in the human community, people's experience and knowledge of the state of the disease will eventually affect their response. This tells us that memory has a major contribution in the evolution of the epidemic process. Therefore, researchers suggest that models based on the fractional-order derivative (non-Markovian system) are more realistic and suitable to study the dynamics of the epidemiological system or any system with memory. This is our main motivation in setting up the goals for this research.

The main objectives of the study are summarized as follows:

1) To develop and analyze various deterministic mathematical models of dengue transmission dynamics with the approach of the fractional-order differential equation.
2) To examine significance differences between modelling the dengue transmission dynamics by the fractional-order differential equation as compared to the classical integer-order differential equation.
3) To study the significance of the order of the derivative with the dynamical behaviour of the dengue epidemic that interprets the consequence of memory in the dengue transmission dynamics. .

These include the following:

(i) a basic deterministic dengue model using the approach of the fractional-order differential equation will be developed. This model will be constructed based on the susceptible-infected-recovered (SIR) model for humans and the susceptible-infected (SI) model for vectors. This model will include the aquatic stages of the vector population that has not been considered in any of the related literature of the fractional-order dengue model. The model will be categorized into two order dynamics, i.e., similar order dynamics and different order dynamics on the humans and vectors. Stability and sensitivity analysis will be conducted for the model. A suitable range of fractional order values for the dengue transmission model is examined so that the models provide a realistic and useful approximation with the real data.

(ii) a new dengue transmission model will be first developed using the classical integer-order differential equation. This model will consider the existence of a relationship among the entomological (immature phase of vector population), epidemiological (notified data cases), and environmental factors (temperature). Phenomena, like the backward bifurcation, will be further investigated. Then, this model will be fractionalized, and the numerical results of the ODE and the fractional-order model will be compared.

(iii) a fractional-order dengue model with control measures will be formulated and analyzed. In this model, we consider additional parameters for the vector compartments related to the mortality rate due to the mosquito control action taken and the common-practice of individual protections.

1.7 The structure of the thesis

This thesis contains seven chapters in total. The first chapter of the thesis begins by emphasizing the fundamental background of the study and its objectives. In Chapter 2, we present the literature reviews of the previous related studies on the dengue transmission dynamics, both for the classical integer-order and the fractional-order model. Under Chapter 3, we provide some of the required basic mathematical properties. In the next three chapters, different chapters present distinct models but constructed on the same themes as the previous chapters.

In Chapter 4, we present a basic dengue transmission model that incorporates the immature stage of the *Aedes* mosquito population using the fractional-order differential equation approach. The main focus of this chapter is to introduce the fractional-order derivative in modelling the dengue transmission disease. We study the significance of the order to the dynamical behaviour of the dengue transmission. In Chapter 5, we extend the basic model in the previous chapter by incorporating the temperature effect into the modelling of the transmission of the dengue virus and introducing a new infectious class known as the notified infected human population. We begin this chapter by formulating and analyze the new dengue model in the sense of integer-order differential equation, and later we fractionalize the integer-order model using the Caputo definition. We then compare the numerical results of the integer-order model and the fractional-order model.

In Chapter 6, we present and analyze a fractional-order dengue model that incorporates vector control tools and an individual protection tool. The effectiveness of different control tools is analyzed, and the effect of the order is studied. In Chapter

7, we summarize the main mathematical and epidemiological contributions of the thesis. We also provide relevant suggestions for future works. Chapters 4, 5, and 6 of this thesis represent a study that may stand on its own.

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LIST OF PUBLICATIONS

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