



Modelling the significance of feeding and mating related contact, optimal control and fractional order change on the long term dynamics of Devil Facial Tumour Disease

by

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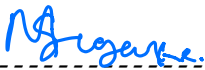
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Abstract

Tasmanian devils are the largest living carnivorous marsupial found in the wild of Tasmania. These species are being threatened by a cancerous tumour disease, the Devil Facial Tumour Disease (DFTD). The disease affects the facial areas and has led to a considerable population decline. In this thesis, mathematical models for transmission of DFTD are developed and analysed to investigate the significance of feeding and mating related contact, optimal control and fractional-order change on the long-term dynamics of the disease. The two-sex models consider two transmission pathways namely, feeding and mating related contact. The relative transmission rates through mating related contact from male devils to female devils and vice versa are assumed to be different. Model properties such as positivity and boundedness were proved to ensure that the models are analysed in a feasible regions of biological significance. The model disease thresholds were evaluated and used to analyse the model properties including existence and stability of steady states. Sensitivity analysis of the model parameters as input values and the reproduction number as the output values was carried out using the Latin Hypercube Sampling Scheme. Through sensitivity analysis of model parameters on the disease threshold, it was observed that feeding related contact rate has the greatest potential of making the disease epidemic worse when increased. In addition, the tumour induced death rate and the recovery rate for both male and female devils were observed to have a high potential of reducing the disease burden increased. Our numerical results indicated that, higher feeding and mating related contact for both male and female devils are associated with higher peak values of the infected devils. From optimal control numerical results, we observed that, the infection is considerably reduced in the presence of controls. However, the infection is predicted to remain in the population with a smaller number of devils affected. More still, in the absence of controls we observed that, the number of infected devils reaches very high and devastating proportions. It is therefore recommended that, controls be applied early in the epidemic so as to avert high peaks of the infection. The modelling work also considered a fractional-order model for the disease transmission dynamics with the presumption that future values of the infection depend on both the current and previous states, an aspect that constitutes memory of the system. Our results indicated that increased dependence on previous states predicted lower peaks of infected devils but higher long-term values in the population. From our results, we recommend that control measures such as isolation/quarantining be put in place to reduce contact between infected and healthy devils to reduce the disease burden. In addition culling infected devils and vaccination of the uninfected were predicted to be important in reducing the infection as well as avoid extinction of the devils population and therefore should be implemented to contain

the disease.



Dedications



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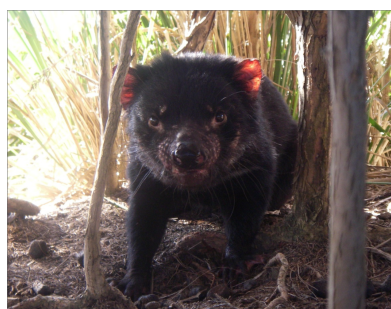
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Chapter 1

Introduction

Tasmanian devils are the largest living carnivorous marsupials that are unique to Tasmania [2, 3]. Hogg *et al.* (2013) [4] documented that, Tasmanian devils are found in the wild of Tasmania, but were once widespread all over Australia. The devils are black all over their body with white marks found on the chest [4]. Male devils are said to weigh upto 12 kilogrammes (with average weight of 8kg) and are larger than female devils weighing averagely 7 kilogrammes, a weight which they reach at the adult age of 2 years, and are believed to live longer than 5-6 years [4]. These species are now endangered by a cancerous transmissible Devil Facial Tumour Disease (DFTD) which was first reported from Tasmania in 1996, leading to more than 60% population decline once it spread over the wide range of species [2, 5]. McCallum (2008) [6] also supported that, DFTD threatens the largest surviving marsupial carnivore with extinction by spreading from one affected animal to another healthy one with the infective agents being the cancer cells themselves. Therefore, in that case, disease and conservation biology are some of the important general principles illustrated, including



(a) Healthy Devil



(b) Devil with Facial Tumour Disease.

Figure 1.1: 1.1(a) shows a figure of a healthy devil [1], 1.1(b) shows a figure of a Devil with Facial Tumour Disease Caused by DFTD [1].

the threat posed by loss of genetic diversity and the potential of pathogens with frequency-dependent transmission to cause extinction [6]. DFTD is said to be a clonal cell line that is transmitted from host to host, with atleast 60% mortality rate which occurs within six months once the tumour clinical signs have been detected, and has no known cure to date [5].

Low genetic diversity of the devil populations was first considered that it enabled the establishment of DFTD throughout subsequent devil populations, and recent evidence reveals that the animals which are genetically diverse are prone to the disease [5]. The lack of immune response against the disease is attributed to lack of immunogenicity of the tumor cells and this could facilitate transmission between devils [5]. The disease affects the devils causing ugly cancerous growths in the facial areas (around the mouth and face), which kills the animal within several months of infection [6]. The disease spreads from infected devils to healthy devils by bitings which occur during aggressive interactions over food when feeding on the same carcass and frequently during sexual encounters [6]. It was reported that, in the mating season, rates of biting mainly to the head are high and the infected devils die from starvation because of the inability of feeding due to the facial tumours [6]. DFTD is very rare among the sexually immature devils and it therefore appears to have many sexually transmitted disease characteristics that can be expected to have frequency-dependent transmission [6]. McCallum (2018) [6] indicated that, the prevalence of the disease has remained very high in the infected populations, even as the density has been reduced by up to 90%. Therefore, the disease is considered as one of the first examples in which it appears that an infectious disease with frequency-dependent transmission is likely to cause extinction [5, 6].

1.1 History and Infectious Diseases Management in Wildlife

The main findings of the study by Brown *et al.* (2014) [5] indicate that, DFTD cells are suitable targets for immuno-therapy. Therefore, to prevent extinction of the Tasmanian devil in the wild there is a need to develop a vaccine or treatment. It is believed that establishing isolation of uninfected devils from the infected devils reduces transimission of the infection [7]. Moreover, implementation of disease suppression by removal of infected devils can help to slow down the infection rate and hence eradicate the disease [7]. McCallum (2008) [6] also stresses that, possible tools to manage infectious diseases like DFTD are to isolate uninfected devils, culling to supress the disease, identifying or selecting resistant animals to be released into the wild and developing a vaccine. Therefore, isolation of uninfected animals from the threat of infectious disease enables matings to be controlled in order to maintain genetic di-

versity and evolutionary changes [6]. Disease suppression, that is, removing out by culling is the standard response to an exotic disease incursion in livestock that could remove the threat posed by the disease to the entire species in the population [6]. In line with vaccine administration, McCallum (2008) [6] indicated that, distributing a vaccine in a wild population on a broad scale would be a challenge even if it is developed.

A study by McCallum (2008) [6] established that, epidemiological theory suggests that extinction is unlikely to be caused by a host-specific pathogen. Most infectious diseases are believed to have a threshold host density with basic reproductive number less than one which then means that each case of infection is replaced in the next disease generation [6]. A reproduction number of less than one means that the pathogen should disappear from the population before extinction occurs [6]. If the contact rate between susceptible and infected hosts depends on host density, then a threshold host density exists [6]. McCallum (2008) indicated that, frequency dependent transmission of DFTD is often associated with sexually transmitted diseases in that, the mating system of the species determines the number of sexual partners per unit time rather than the population density. It should be noted that, there are limited tools in wildlife for managing any infectious disease [6].

It should be noted that, researches establish that it is necessary to determine the ecological impact of a disease in host populations for the implementation of management strategies that are effective. Ecological factors such as density or frequency dependence, pathogenicity of a disease and the host adaptive response, and existence of host reservoir species can significantly change the impact of a disease [1]. However, disease is a common and dynamic feature of wildlife populations and establishing its overall impact there is needed for long-term datasets [1].

A major disadvantage in identifying the emergent disease agents in wildlife is the lack of diagnostic capability for infectious diseases that do not affect domestic animals or humans [1]. Advances in diagnostic research and treatment as well as increased surveillance for wildlife diseases are required to enable a practical approach towards detection and management of diseases. Field, laboratory and theoretical research should provide new insights into the broader ecological processes of determining disease dynamics and their effects in the population as well as ecosystem levels [1].

The use of mathematical tools has become important in solving the real world problems. Mathematical modelling can be considered as the process of developing mathematical models to problems [8]. Mathematical models are useful in natural sciences, social sciences and political sciences to explain different systems, study the effects posed by its components and

prediction of the behaviour posed by the system [8]. In epidemiology, a model is formulated, and mathematical equations are obtained to be used determining the qualitative and quantitative behaviour of the population studied. Analytical solutions are obtained and numerical simulations done to determine the long-term behaviour of the system being studied. The obtained results from simulations can be discussed and predictions could be done. Simulations are more useful to describe, understand and predict future behaviour of the system or problem [8]. The most used mathematical concept in modelling is differentiation whereby derivatives are used [9]. Surveillance and monitoring of disease outbreaks are essential in order to understand the infectious diseases and designing management strategies that are effective [6]. Therefore, in this study, we develop a dynamic model highlighting the transmission pathways related to contact between infected and epidemiologically naive devils. The contact between devils usually occurs during feeding (mainly devils of the same sex) and during the mating season. We note that the disease is not known to be sexually transmitted. This work is aimed at ascertaining the significance of contact related to feeding and mating, optimal control and fractional-order change i.e. dependence of future values of the infected devil population on the current and previous states in the disease dynamics in addition to other parameters described in the constructed model.

1.2 Problem Statement

Devils were common and widespread across most of Tasmania, with a range up to 150 000 population size estimation, until the appearance of Tasmanian DFTD in 1996 which led to near extinction of devils [6]. The disease has now spread across the majority of the range of the species and within 5 to 10 years it is likely to occur across the entire range with continuing declination of up to 90% and virtual disappearance of older age groups [6]. Primary tumours occur on the face or in the oral cavity, but metastases elsewhere are common and also death is thought to occur due to combination of factors that includes inability to feed, secondary infections and metastases [6]. According to McCallum (2008) [6], there is very clear evidence on the case of devils that, loss of diversity is allowing DFTD to spread throughout the population in the east of Tasmania with threats to overall extinction of the species.

1.3 Justification of the Study

The population of devils has been decreased by an estimated 60% and no obvious cure or prevention was available for it. Scientists decided that the first step in saving the devil from extinction should be to establish disease-free populations of devils that are isolated from infected animals [2]. The animals are known as an insurance population and complete extinction of the species should be prevented [2]. In the meantime, scientists have been busy trying to find a preventative treatment for DFTD [2]. There is some hope that a vaccine will be developed to protect healthy devils due to recent discoveries about how the tumour cells become established in previously healthy devils [2]. Much is yet to be done in order to discover a means of preventing this disease as a means of protecting the remaining wild populations of devils. Thus, determining the significance of feeding and mating related contact, optimal control and fractional-order change (memory effect) are worth exploring and will give useful information on the transmission dynamics of the disease.

1.4 Aim

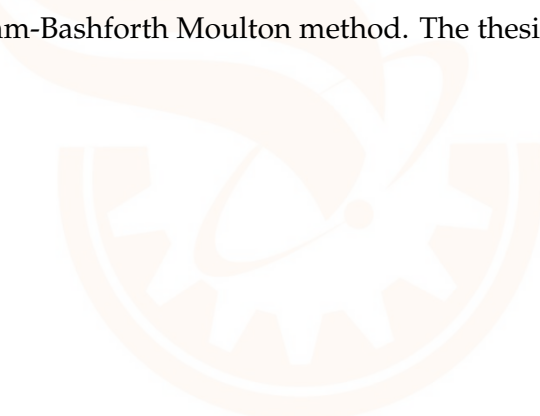
The research aim is to examine the significance of feeding and mating related contact, optimal control and fractional-order change on the long-term dynamics of DFTD.

1.5 Objectives

- Modelling the significance of feeding and mating related contact for female and male devils on the long term dynamics of DFTD.
- Identifying control measures and examine the optimal control strategies using an appropriate non-linear objective function.
- Analyse the Fractional-Order dynamics of DFTD presuming memory and non-local dynamics of the disease to ascertain the future disease trends with dependence on current and previous states.

1.6 Organisation of the thesis

The rest of the study is organised as follows: In Chapter 2, a review of literature and description of methods used is presented. A two sex mathematical model for DFTD is developed and analysed in Chapter 3. Positivity and boundedness are proved, the model disease threshold and equilibrium points evaluated as well as numerical simulations and sensitivity analysis results conducted using the Latin Hypercube Sampling technique are done in the same chapter. Chapter 4 contains an optimal control model for DFTD with controls. Control measures and a detailed qualitative optimal control model that minimizes the number of infected female and male devils with minimal cost of implementing the control measures is developed. In Chapter 5, we present a Fractional-order version of the DFTD model in Chapter 3 using a Caputo-Fabrizio fractional derivative type owing to its efficiency in solving initial value FDEs. Using the Mittag-Leffler function, the basics model properties such as positivity and boundedness are proved. Numerical simulations of the FDE model are also performed using the Adam-Bashforth Moulton method. The thesis is concluded in Chapter 6.



Chapter 2

Literature review and Mathematical Preliminaries

2.1 Literature Review

This chapter is an overview of available literature on the history and importance of modelling the significance of how the disease (Devil Facial Tumour Disease) spreads in a population. We give a brief explanation of methods used in carrying out the research. We also present an analysis of what other researchers have done and the results they have produced on transmission and prevention of DFTD.

2.1.1 Importance of modelling infectious diseases

Mathematical modelling is one of the most important tools for predicting disease spread and their impact on both human and animal. One of the vital roles of modelling is that it provides a bridge for integrating epidemiological and demographic data [1]. Hamede (2012) [1] states that, modelling epidemics to understand the processes by which an infectious agent spreads is the main purpose for the efficiency of different control actions and management strategies to be assessed. In the case of DFTD, it is observed that if one or more of the host species was relatively unaffected by the pathogen, then the host would function as a reservoir maintaining a high force of infection on the species threatened by extinction [6]. According to McCallum (2008) [6], direct evidence concerning the mechanism of the disease (DFTD) transimission in the wild is limited. However, there is need for accurate information in mathematical models on the nature and frequency of interactions to produce outcomes that are realistic [1]. It has been one of the major challenges to provide information for

wildlife epidemiologists [1]. Vaccines for some infectious diseases in wildlife, especially for diseases caused by viruses that also infect domestic livestock or humans are available and vaccination programs have been implemented to prevent the spread of diseases in several critically endangered species such as Ethiopian woles, African wild dogs and Iberian lynx [1]. However, as discussed earlier, vaccination programs are mainly used in preventing disease outbreaks rather than eliminating a disease once established or reducing its impacts on host populations [1].

Bashford *et al.* (2012) [10] stresses that, transimission of DFTD is by direct inoculation of tumour cells through biting or contact between infected and uninfected hosts. This is due to a process enabled by low host genetic diversity with reduced survival in populations that are affected which predicts that local extinctions are likely to occur within 10 years of disease arrival [10, 11]. The study by Bashford (2012) [10] simulated the spread of DFTD into naive populations of devils using weighted networks to incorporate mixing properties of gender and seasonal shifts in network metrics related to mating behaviour. Tuneable algorithms for growing virtual networks capable of recreating observed contact patterns of devils into epidemic simulations were used [10]. Epidemic simulations were used in the sense of including disease parameters and population into a susceptible-exposed-infected (SEI) network model for seasonal, sex and population based network metrics investigation on the spread of DFTD under different transmission rates and latent periods of the disease [10]. Finally, the results were compared and R_0 was estimated with those of a stochastic mean-field model, whereby every individual was equally likely to acquire or pass the infection through time [10]. Mean-field assumption can be made on most compartmental models of diseases to adequately model disease dynamics by assuming that individuals/organisms randomly get in contact with each other [11]. The basic reproduction number, R_0 , estimation derived from models forms the basis of most management strategies, since driving R_0 to below one eliminates the disease. Hence, it becomes clear that, for both wildlife and human diseases, the structure of many contact networks indicates that mean-field assumptions result in inaccurate R_0 estimation [10]. According to Bashford *et al.* (2012) [10], use of contact networks is becoming a powerful predictive epidemiological tool for modelling disease spread due to explicit account for non-random mixing patterns of hosts, by making assumptions about contact patterns between individuals, either by incorporating certain heterogeneities in contact or by assuming random mixing [10]. Assessing the validity of the assumption that the mean contact rate between individuals is adequate to describe transmission dynamics, can be done by using social network analysis [10]. The application of network theory in human epidemiology has been proved to be useful for individual heterogeneities estimation in con-

tact patterns and examining disease transmission dynamics implications for diseases that are both sexually and non-sexually transmitted [10]. Bashford *et al.* (2012) [10] asserts that, epidemiology wildlife diseases, particularly highly pathogenic ones, such as DFTD, strongly affect population size and for this reason they seem to be qualitatively different from most human diseases which may have a major influence on the structure of the network.

2.1.2 Description of Methods

Sensitivity Analysis

An abstraction of a real-world problem into a mathematical problem where disease models are created as tools for discovering underlying patterns in epidemiology is called mathematical modelling [12]. According to Gomero (2012) [12], a model becomes a tool for studying disease epidemiology along with the effect and targeting of various interventions. Moreover, in creation of models, simplifications and assumptions are made regarding the way the model is constructed and parameter values required [12]. Choices for parameter values can lead to uncertainty which also leads to introduction of variability to the model's prediction of resulting dynamics [12]. Therefore, understanding the effects of model parameter values on specific output measures is important [12]. Gomero (2012) [12] asserts that, variability depends on uncertainty of parameters. That is, the more uncertain parameters they are, the more significant the variability introduced [12]. Hence, sensitivity analysis can be performed to assess the variability in the model predictions [12].

Differential sensitivity analysis, one-at-a-time sensitivity measures, factorial design, sensitivity index, importance factors and subjective sensitivity analysis are various methods that have been used to carry out sensitivity analysis [13]. Subjective sensitivity analysis is the only qualitative method that relies on the opinion of experienced investigators amongst mentioned methods [13]. In this present study, we used Latin Hypercube Sampling technique discussed below to conduct our sensitivity.

Latin Hypercube Sampling

The Latin Hypercube Sampling scheme sensitivity analysis is an efficient tool that is frequently used in uncertainty analysis to explore the entire parameter space of a model with a minimum number of computer simulations [12]. The Latin hypercube sampling (LHS) is a scheme for simulating random parameter sets that adequately cover the parameter

space and can be used to identify the effect of uncertainty in model parameters together with Partial Rank Correlation Coefficient (PRCC) [14]. Moreover, it is a statistical sampling method allowing for efficient analysis of parameter variations across simultaneous uncertainty ranges in each parameter [15, 16]. Zi (2011) [14] asserts that, LHS is a method that is efficiently used to sample random parameter vectors while guaranteeing that the individual parameter ranges are evenly covered. The LHS can generate the output distribution with fewer sampling iterations than the simple Monte-Carlo sampling to achieve a similar accuracy. The tool involves the combination of two statistical techniques, which are Latin Hypercube Sampling and Partial Rank Correlation Coefficient analysis with the goal of identifying key parameters whose uncertainties contribute to prediction imprecision [12].

In the LHS, probability distributions are assigned to parameters, thus so called stratified scheme [12]. The intervals in the distribution are divided into equiprobable regions and then each interval is sampled without replacement [12]. The LHS procedure has an advantage in that, the parameters are sampled independently of one another and the sampling procedure requires random samples to be taken one at a time, while taking into account the row and column of the previously generated sample points, and requires to achieve the same level of accuracy [12]. The advantage that LHS has over simple random sampling is that, it guarantees that the parameters are uniformly sampled from the corresponding distribution [14]. In addition, correlation is a statistical procedure used to measure the strength of the relationship between the output measures and the parameters in a model using the residuals obtained from the regression procedure [12]. It is also considered to be more significant at determining the sensitivity of a parameter that is strongly monotonic yet highly non-linear as compared to ordinary Partial Correlation Coefficient procedure [12].

PRCC analysis is a sensitivity analysis method that calculates the partial rank correlation coefficients for the model inputs and outputs that are sampled by the LHS method [14]. This method assumes a monotonic relationship between the model input parameters and the model outputs [14]. Therefore, this makes it qualify to be used mainly when the model outputs are monotonically related to the model input parameters [14]. Input–output scatter plots can therefore be used to examine the monotone relationship between the input and output [17]. The qualitative relationship between the model input and output can be determined by the sign of the PRCC values [14]. A PRCC value that is positive implies that, when the corresponding model parameter increases, the model output will also increase whilst a negative PRCC value indicates a decrease in the model output when the parameters are increased [14]. The magnitude of the PRCC sensitivity measures the importance of the model input in contributing to the model output [14, 15].

When using PRCCs, to reduce the effect of non-linear data, rank-transformation is done on which it is preferable to work better when there is a monotonic relationship between the parameter of interest and outcome measure [12]. Therefore, the level of monotonicity between the LHS parameters and the outcome measures when rank-transformation is used is indicated by the rank correlation coefficient [12].

Optimal Control

Optimal control theory is regarded as a powerful mathematical tool for making decisions that involve complex dynamical systems and is a standard method for solving dynamic optimization problems when they are expressed in continuous time [18]. Optimal control theory was developed by the Russian mathematician Lev S. Pontryagin (1908–1988) and his coworkers with the formulation and proof of the Pontryagin Maximum Principle [19]. According to Kahuru *et al.* (2017) [18], optimal control is also a process of determining control and state trajectories for a dynamic system over a period of time to minimize a performance index. In line with epidemiological modelling, Mu'tamar (2018) [20] stresses that, optimal control is used to prevent interaction between susceptible and infected individuals. Moreover, optimal control has been used to make decisions that involve biological and medical models whereby a set of differential equations is generated describing the paths of the control variables that minimize the cost functional [20]. In an optimal control problem formulation, the following are required; i.e. a mathematical model of the system should be controlled, a specification of the performance index, i.e. cost function, and a specification of all boundary conditions on states and constraints to be satisfied by states and controls [18]. Transformation of the constrained dynamic optimization problem into an unconstrained problem is the principle technique in optimal control and this is done by allowing each of the adjoint variables to correspond to each of the state variables accordingly and combining the results with the objective functional [18]. The resulting function which is used to solve a set of necessary conditions that an optimal problem and the corresponding state variables must satisfy is known as the Hamiltonian [18].

In epidemiology, optimal control has been applied in various problems that include tungiasis disease [18], alcoholism [20], HIV/AIDS prevention [21] and cholera transmission [22], to cite just a few. From the research by Kahuru *et al.* [18], a mathematical model of tungiasis was presented based on the interaction between humans, animal reservoirs and flea contaminated environment. The model was formulated to derive five optimal control measures with minimal implementation cost to reduce the disease after a period of time. From the

study, it was observed that, the control strategies have significant impact on the tungiasis disease [18]. Therefore, it was advised that, on-host and off-host control measures which include focal spraying, application of insecticidal dust, personal hygiene, application of repellents, use of closed footwear and education campaign should be implemented [18]. In a research by Mu'tamar (2018) [20], optimal control was used for alcoholism model with two infected compartments to prevent interaction between susceptible individuals and infected individuals in order to minimise the infected individuals. The main findings from the study indicated that, the use of controls decrease the infected individuals and increase the susceptible individuals [20]. In addition, optimal control was applied in a study for cholera transmission in communities linked by immigration [22]. The aim was to minimise the number of infected individuals at the same time minimising the costs of implementing the controls. The results indicated that, the use of controls reduces the infection in adjacent communities [22].

Fractional Order in Modelling Infectious Diseases

Fractional differential equations (FDE) are an extension of ODEs and are one of the best tools for modelling in science and engineering [23]. Fractional Differential Equations are good in approaching solutions of differential equations whereby the integer order derivative is replaced by a fractional derivative [23]. In a paper by Shaher *et al.* (2013)[23], Fractional Order System was used in an analytic numeric solution for SIRC model to show positivity of solutions and the approximate solution obtained by the multi-step generalized differential transform method were considered highly accurate and valid for a long time in the integer case. Fractional derivatives have recently been used in compartmental models in a physically consistent way by modelling the dynamics of transitions between compartments as a stochastic process [24]. Fractional calculus applies the use of fractional derivatives that include Riemann-Liouville, Caputo-Fabrizio, Liouville-Caputo and Atangana-Baleanu among others. The Riemann-Liouville fractional derivatives can be applied in theories of elasticity and many other fields [8]. The Riemann-Liouville in Caputo sense was reported to be good owing to the fact that, it involves the inclusion of memory effect since the memory is not always associative and commutative [8]. Memory effects involve aspects such as learning and model dependence on previous states. To determine the basic properties of the model, Mittag-Leffler functions are used. The Mittag-Leffler function is a generalization of the exponential function that was first introduced as a one-parameter function by a series and later two parameter generalization [25]. This two-parameter generalization is considered to be of great importance in fractional calculus [25]. The two-parameter function of Mittag-Leffler

type was reported to improve the limitations posed by the power-law [26]. According to Aguilar and Atangana [26], Liouville-Caputo fractional derivative involves the power-law function and allows initial conditions when working with the integral transform for example Laplace transform. A fractional-order model for dengue transmission was presented in a research by Hamdan *et al.* [27] to understand the dynamic of dengue disease. The main findings of the study indicated that, the solution of fractional-order model tends to a fixed point over a longer period of time and as the fractional-order approaches zero, the dengue disease needs longer time to be eliminated in the population [27]. Also increasing the mosquito and human memory can reduce the intensity of the dengue transmission [27]. Moreover, fractional calculus was applied in a research for the dynamics of the Hepatitis B virus using Caputo-Fabrizio derivatives [28]. The aim of the study was to describe the Hepatitis B virus with an arbitrary order derivative [28]. The main findings showed that, the un-immunised children born to carrier mothers show a significant decrease on the number of infected individuals by decreasing their values when the fractional-order value decreases [28]. Ullah *et al.* [28] advised that, vaccination is a useful tool for Hepatitis B in the community.

Chapter 3

Significance of contact and mating in DFTD

3.1 Introduction

In this chapter, we develop a dynamic model highlighting the transmission pathways related to contact between infected and epidemiologically naive devils. The contact between devils usually occurs during feeding (mainly devils of the same sex) and during the mating season. We note that the disease is not sexually transmitted. This work is aimed at ascertaining the significance of contact related to feeding and mating in the disease dynamics in addition to other parameters described in the constructed model. Calculation of reproduction number, equilibrium points and their stability is done in this chapter to determine the stability of our model. In addition, sensitivity analysis using LHS Technique and numerical simulations are also conducted.

3.2 The Model

The model describes the spread of DFTD in devil population. A population of N devils where the disease spreads due to contact related to feeding and mating between devils is considered in this study. We assume that the devils in specific compartments mix homogeneously and the probability a susceptible devil gets infected is proportional to the number of infected devils (that is, the infected devils only gets in contact with a proportion of susceptible devils). We note that the devils that are infected either die due to the disease or recover and then those that recover can still be infected again once they get to contact with

the infected devils after the acquired temporary immunity wanes. Thus, the population is divided into 6 compartments, that is, susceptible male and female (S_m and S_f), infected male and female (I_m and I_f) and recovered male and female (R_m and R_f) devils. Infections in compartments I_m and I_f arise by contact related to feeding and mating between susceptible devils in compartments S_m and S_f at the forces of infection λ_m and λ_f respectively, where $\lambda_m = \beta \left(\frac{I_m + \eta_1 I_f}{N} \right)$, $\lambda_f = \beta \left(\frac{I_f + \eta_2 I_m}{N} \right)$ and $N = S_m + S_f + I_m + I_f + R_m + R_f$ (the total devil population). The rate at which the disease is spread through mating related contact is η_1 and η_2 respectively. Once infected, the devils progress from compartment I_m and I_f at rates σ_1 and σ_2 respectively to compartment R_m and R_f upon recovery or die due to disease at rates δ_1 and δ_2 respectively. There is also natural death rate, μ , which occurs from each compartment. Devils from compartment R_m and R_f develop temporary immunity which wanes at rates ω_1 and ω_2 respectively and will be infected again after a long period of time if they get in contact with infected devils. The model assumes a constant recruitment rate from new births with proportions ρ and $(1-\rho)$ for males and females respectively.

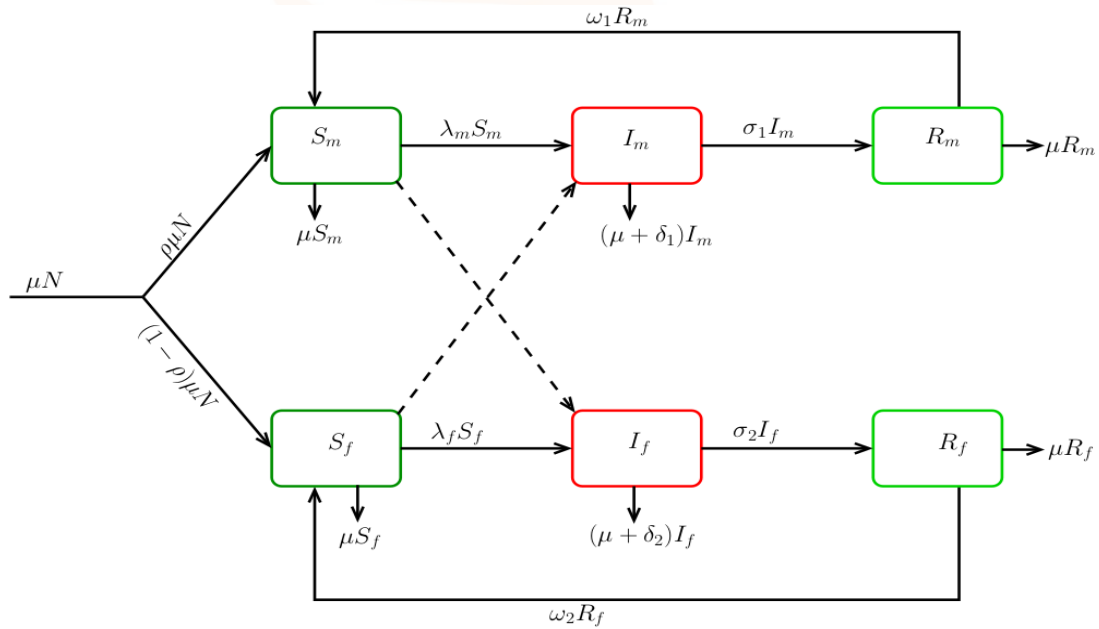


Figure 3.1: A compartmental representation of the model of Devil Facial Tumour Disease, $0.4 \leq \rho \leq 0.6$.

System of equations

$$\frac{dS_m}{dt} = \rho\mu N + \omega_1 R_m - \lambda_m S_m - \mu S_m, \quad (3.1a)$$

$$\frac{dI_m}{dt} = \lambda_m S_m - Q_1 I_m, \quad (3.1b)$$

$$\frac{dR_m}{dt} = \sigma_1 I_m - Q_2 R_m, \quad (3.1c)$$

$$\frac{dS_f}{dt} = (1 - \rho)\mu N + \omega_2 R_f - \lambda_f S_f - \mu S_f, \quad (3.1d)$$

$$\frac{dI_f}{dt} = \lambda_f S_f - Q_3 I_f, \quad (3.1e)$$

$$\frac{dR_f}{dt} = \sigma_2 I_f - Q_4 R_f, \quad (3.1f)$$

where $Q_1 = (\mu + \delta_1 + \sigma_1)$, $Q_2 = (\mu + \omega_1)$, $Q_3 = (\mu + \delta_2 + \sigma_2)$ and $Q_4 = (\mu + \omega_2)$.

The flow diagram of the DFTD model is given in Figure 3.1 and the model that governs the system of differential equations is given on equation (3.1a)-(3.1f).

State variable	Description
S_m	Susceptible male devils
S_f	Susceptible female devils
I_m	Infected male devils
I_f	Infected female devils
R_m	Recovered male devils
R_f	Recovered female devils

Table 3.1: List of state variables used in the model and their description

Symbol	Description
ρ	Proportion of new borns that are males
μ	Natural death rate
$1-\rho$	Proportion of new borns that are females
η_1	Transmission in males through mating related contact relative to feeding
η_2	Transmission in females through mating related contact relative to feeding
β	Contact rate between devils
σ_1	Rate of recovery of male devils
σ_2	Rate of recovery of female devils
ω_1	Rate at which recovered male devils become susceptible again
ω_2	Rate at which recovered female devils become susceptible again
δ_1	Tumour induced death rate of male Devils
δ_2	Tumour induced death rate of female Devils

Table 3.2: Parameters used in the model and their description

3.3 Model Analysis

Non Dimensionalisation of the Model

To non-dimensionalise the model of equation system (3.1a)-(3.1f), we let $\frac{S_m}{N} = s_m$, $\frac{I_m}{N} = i_m$, $\frac{R_m}{N} = r_m$, $\frac{S_f}{N} = s_f$, $\frac{I_f}{N} = i_f$, and $\frac{R_f}{N} = r_f$. We non-dimensionalise the state variables. Therefore, we substitute into the system (3.1) and maintain the upper case for the state variables for the non dimensionalised system which then reduces to

$$\begin{aligned}
 \frac{dS_m}{dt} &= \rho\mu + \omega_1 R_m - \hat{\lambda}_m S_m - \mu S_m, \\
 \frac{dI_m}{dt} &= \hat{\lambda}_m S_m - Q_1 I_m, \\
 \frac{dR_m}{dt} &= \sigma_1 I_m - Q_2 R_m, \\
 \frac{dS_f}{dt} &= (1 - \rho)\mu + \omega_2 R_f - \hat{\lambda}_f S_f - \mu S_f, \\
 \frac{dI_f}{dt} &= \hat{\lambda}_f S_f - Q_3 I_f, \\
 \frac{dR_f}{dt} &= \sigma_2 I_f - Q_4 R_f,
 \end{aligned} \tag{3.2}$$

where $\hat{\lambda}_m = \beta(I_m + \eta_1 I_f)$ and $\hat{\lambda}_f = \beta(I_f + \eta_1 I_m)$.

All the model parameters are positive and the initial conditions of the model system (3.2) are non-negative, given by $S_m(0) = S_m^0 > 0$, $I_m(0) = I_m^0 > 0$, $R_m(0) = R_m^0 > 0$, $S_f(0) = S_f^0 > 0$, $I_f(0) = I_f^0 > 0$, $R_f(0) = R_f^0 > 0$.

3.3.1 Basic Properties of the model

Positivity of Solutions

Since the model describes the infection dynamics of living organisms, it is imperative to ensure that all the state variables are non-negative for all $t \geq 0$. We thus state the following lemma.

Lemma 3.3.1. *Given the initial conditions of the system (3.2) such that $S_m^0 > 0$, $I_m^0 \geq 0$, $R_m^0 \geq 0$, $S_f^0 > 0$, $I_f^0 \geq 0$, and $R_f^0 \geq 0$, the solutions $S_m(t)$, $I_m(t)$, $R_m(t)$, $S_f(t)$, $I_f(t)$, and $R_f(t)$ are non-negative for $t > 0$*

Proof. Assume that

$\hat{t} = \sup\{t > 0: S_m(t) > 0, I_m(t) > 0, R_m(t) > 0, S_f(t) > 0, I_f(t) > 0, \text{ and } R_f(t) > 0\} \in [0, t]$.

Thus, $\hat{t} > 0$, from the first equation of the system (3.2), it follows that

$$\begin{aligned} \frac{dS_m}{dt} &= \rho\mu - \beta(I_m + \eta_1 I_f)S_m - \mu S_m, \\ &\geq -\beta(I_m + \eta_1 I_f)S_m - \mu S_m. \end{aligned}$$

Separating variables in the equation gives

$$\frac{dS_m}{S_m} \geq [-\beta(I_m + \eta_1 I_f) - \mu].$$

Integrating both sides with respect to corresponding variables and applying corresponding limits, we obtain

$$\begin{aligned} S_m(t) &\geq S_m^0 e^{-\beta[\int_0^t (I_m(z) + \eta_1 I_f(z))dz] - \mu t}, \\ &= S_m^0 e^{-[\beta \int_0^t (I_m(z) + \eta_1 I_f(z))dz + \mu t]}. \end{aligned} \tag{3.3}$$

From the second equation of the system (3.2),

$$\begin{aligned} \frac{dI_m}{dt} &= \beta(I_m + \eta_1 I_f)S_m - Q_1 I_m, \\ &\geq -Q_1 I_m. \end{aligned} \tag{3.4}$$

Using separation of variables, and integrating the resulting inequality with respect to appropriate variables, we obtain

$$I_m(t) \geq I_m^0 e^{-Q_1 t} > 0.$$

Similarly, using the same approach for the rest of the state variables, we obtain

$$\begin{cases} R_m &\geq R_m^0 e^{-Q_2 t} > 0, \\ S_f &\geq S_f^0 e^{-[\beta \int_0^t (I_f(z) + \eta_2 I_m(z))dz + \mu t]} > 0, \\ I_f &\geq I_f^0 \exp(-Q_3 t) > 0, \\ R_f &\geq R_f^0 \exp(-Q_4 t) > 0. \end{cases}$$

Taking the limit as t approaches infinity on each of the obtained state variable expressions, it is clear that $S_m(t) > 0$, $I_m(t) > 0$, $R_m(t) > 0$, $S_f(t) > 0$, $I_f(t) > 0$, and $R_f(t) > 0$ for all $t > 0$. This completes the proof. $\square$

Invariant region

Since the model monitors changes in a population, the state variables are shown to be non-negative for all $t > 0$. Therefore, the analysis of the system (3.2) will be performed in a region D of biological significance. We ought to show that the total population is bounded above to ensure that the model does not grow without bound and is within a region D of biological significance. The following lemma presents the region on which the system (3.2) is restricted.

Lemma 3.3.2. *The feasible region D defined by*

$$D = \{(S_m(t), I_m(t), R_m(t), S_f(t), I_f(t), R_f(t)) \in \mathbb{R}_+^6 | 0 \leq N \leq 1\},$$

with initial conditions $S_m^0 > 0, I_m^0 \geq 0, R_m^0 \geq 0, S_f^0 > 0, I_f^0 \geq 0, R_f^0 \geq 0$ is positively invariant and attracting with respect to the system (3.2) for all $t > 0$.

Proof. The total population in this model is clearly not constant. The equation for the change in the population is given by

$$\begin{aligned} \frac{dN}{dt} &= \mu - \mu N - \delta_1 I_m - \delta_2 I_f, \\ &\leq \mu - \mu N. \end{aligned} \tag{3.5}$$

Solving the resulting inequality by the method of separation of variables, it can be easily shown that

$$N \leq 1 + (N_0 - 1)e^{-\mu t}, \tag{3.6}$$

where $N(0) = N_0$. From equation (3.6), we observe that as $t \rightarrow \infty, N(t) \rightarrow 1$. So if $N_0 \leq 1$ then $\lim_{t \rightarrow \infty} N(t) = 1$. This implies that the upper bound of N is 1. On the other hand, if $N_0 > 1$, then N will decrease to 1 as $t \rightarrow \infty$. This implies that if $N_0 > 1$, then the solution $(S_m(t), I_m(t), R_m(t), S_f(t), I_f(t), R_f(t))$ enters D or approaches D asymptotically. Hence, D is positively invariant under the flow induced by the system (3.2). Therefore, it is sufficient to study the dynamics of the model since it is well-posed in D .

□

The disease free equilibrium and the basic reproduction number

The model system (3.2) has a steady state solution called the disease free equilibrium (DFE). In the absence of DFTD infection, the total population will reduce to $N = S_m + S_f$ and the

system of equations (3.2) will reduce to

$$\begin{aligned}\frac{dS_m}{dt} &= \rho\mu - \mu S_m, \\ \frac{dS_f}{dt} &= (1 - \rho)\mu - \mu S_f.\end{aligned}\tag{3.7}$$

The DFE is obtained by equating the right-hand side of the equation (3.7) to zero and solving for the steady state. Hence, the DFE is given by

$$E_0 = (S_m^*, 0, 0, S_f^*, 0, 0) = (\rho^*, 0, 0, (1 - \rho^*), 0, 0),\tag{3.8}$$

where $0.4 < \rho \leq 0.6$. The reproduction number, R_0 , is the expected number of secondary cases produced in a completely susceptible population by a typical infective individual [29]. If $R_0 < 1$, then on average an infected devil produces less than one new infected devil over the course of its infectious period, and thus the infection cannot grow. In the case of the DFTD model, if $R_0 < 1$ then the successive number of infected devils will be less than their predecessors and thus the disease can not establish in the community. On the other hand, if $R_0 > 1$, then each infected devil produces more than one new infectious case on average which means the disease can remain prevalent in the population [29]. On this case, the general basic reproduction number is defined as the number of new infections produced by a typical infective devil in a population at a DFE considering the dynamics of the linearised system [29]. The DFE is locally asymptotically stable if all the eigenvalues of the Jacobian matrix evaluated at DFE have negative real parts and unstable if any eigenvalue has a positive real part [29].

The reproduction number is obtained by the method of the next generation matrix approach outlined in [29]. A reproduction number obtained by this method determines the local stability of the disease free equilibrium point. Hence, adopting the matrix notations in [29], the new infection terms and the transition terms matrices of the compartments at the DFE are given by

$$\mathcal{F} = \begin{bmatrix} \beta(I_m + \eta_1 I_f)S_m \\ \beta(I_f + \eta_2 I_m)S_f \end{bmatrix} \text{ and } \mathcal{V} = \begin{bmatrix} Q_1 I_m \\ Q_3 I_f \end{bmatrix}.$$

The infected compartments are I_m and I_f . An equilibrium solution with $I_m = I_f = 0$ has the form $E_0 = (\rho^*, 0, 0, (1 - \rho^*), 0, 0)$ where E_0 is any positive solution. Then the Jacobi of the

new infection terms and transition terms are given by

$$F = \begin{bmatrix} \beta S_m & \beta \eta_1 S_m \\ \beta \eta_2 S_f & \beta S_f \end{bmatrix} \text{ and } V = \begin{bmatrix} Q_1 & 0 \\ 0 & Q_3 \end{bmatrix}.$$

Evaluating the matrix of new infection at the disease free equilibrium and the inverse of the transition matrix, we obtain

$$F = \begin{bmatrix} \beta \rho & \beta \eta_1 \rho \\ \beta \eta_2 (1 - \rho) & \beta (1 - \rho) \end{bmatrix} \text{ and } V^{-1} = \begin{bmatrix} \frac{1}{Q_1} & 0 \\ 0 & \frac{1}{Q_3} \end{bmatrix}.$$

The reproduction number, R_0 , is given as the spectral radius (the largest eigenvalue) of the matrix

$$FV^{-1} = \begin{bmatrix} \frac{\beta \rho}{Q_1} & \frac{\beta \rho \eta_1}{Q_3} \\ \frac{\beta \eta_2 (1 - \rho)}{Q_1} & \frac{\beta (1 - \rho)}{Q_3} \end{bmatrix},$$

such that

$$R_0 = \frac{R_{0c} + \sqrt{(R_{0cm} - R_{0cf})^2 + 4R_{0mf}R_{0fm}}}{2}$$

where

$$\begin{cases} R_{0c} &= \frac{\beta \rho}{Q_1} + \frac{\beta (1 - \rho)}{Q_3}, \\ R_{0cm} &= \frac{\beta \rho}{Q_1}, \\ R_{0cf} &= \frac{\beta (1 - \rho)}{Q_3}, \\ R_{0mf} &= \frac{\beta \rho \eta_1}{Q_1}, \\ R_{0fm} &= \frac{\beta (1 - \rho) \eta_2}{Q_3}. \end{cases}$$

Case 1: Assuming no interaction between male and female devils in the population.

- (a) If the disease is localised only in the male population then we have $R_{0mf} = R_{0fm} = 0$ and $R_0 = R_{0cm}$.
- (b) If the disease is localised within the female population then we have $R_0 = R_{0cf}$.

Case 2: If the disease is only transmitted through feeding related contact, amongst the independent sexes, the expression for R_0 reduces to

$$R_0 = R_{0_c} = \frac{\beta\rho}{Q_1} + \frac{\beta(1-\rho)}{Q_3}.$$

Case 3: If the disease is only transmitted through contact during mating (not sexually), the value of R_0 reduces to

$$R_0 = \sqrt{R_{0_{mf}} R_{0_{fm}}}.$$

Case 4: Accounting for both feeding and mating related contact, the value of R_0 is given by

$$R_0 = \frac{R_{0_c} + \sqrt{(R_{0_{cm}} - R_{0_{cf}})^2 + 4R_{0_{mf}} R_{0_{fm}}}}{2}.$$

The square root in the reproduction number, R_0 , appears owing to the two "generations" of mating male and female devils that it would take for the disease to replicate itself in either subgroup.

Local stability of the disease free equilibrium point

Following the major assumptions of the next generation method [29] in line with local stability of the DFE, we state the following theorem.

Theorem 3.3.1. *The disease free-equilibrium of the system (3.2) is locally asymptotically stable whenever $R_0 < 1$ and unstable if otherwise.*

Proof. To conduct an analysis of the stability at Disease Free Equilibrium, we consider a Jacobian matrix. We can now linearise the system (3.2) giving;

$$\mathcal{J} = \begin{bmatrix} -\beta(I_m + \eta_1 I_f) - \mu & -\beta S_m & \omega_1 & 0 & -\beta\eta_1 S_m & 0 \\ \beta(I_m + \eta_1 I_f) & \beta S_m - Q_1 & 0 & 0 & \beta\eta_1 S_m & 0 \\ 0 & \sigma_1 & -Q_2 & 0 & 0 & 0 \\ 0 & -\beta\eta_2 S_f & 0 & -\beta(I_f + \eta_2 I_m) - \mu & -\beta S_f & \omega_2 \\ 0 & \beta\eta_2 S_f & 0 & \beta(I_f + \eta_2 I_m) & \beta S_f - Q_3 & 0 \\ 0 & 0 & 0 & 0 & \sigma_2 & -Q_4 \end{bmatrix}$$

Evaluating the associated linearised system at the Disease Free Equilibrium point E_0 we obtain

$$\mathcal{J}_{(\rho, 0, 0, (1-\rho), 0, 0)} = \begin{bmatrix} -\mu & -\beta\rho & \omega_1 & 0 & -\beta\eta_1\rho & 0 \\ 0 & \beta\rho - Q_1 & 0 & 0 & \beta\eta_1\rho & 0 \\ 0 & \sigma_1 & -Q_2 & 0 & 0 & 0 \\ 0 & -\beta\eta_2(1-\rho) & 0 & -\mu & -\beta(1-\rho) & \omega_2 \\ 0 & \beta\eta_2(1-\rho) & 0 & 0 & \beta(1-\rho) - Q_3 & 0 \\ 0 & 0 & 0 & 0 & \sigma_2 & -Q_4 \end{bmatrix}$$

The eigenvalues are:

$\lambda_1 = \lambda_2 = -\mu$, $\lambda_3 = -Q_2$, $\lambda_4 = -Q_4$ and the roots of the quadratic equation

$$\lambda^2 + B\lambda + C = 0 \quad (3.9)$$

where

$$\begin{cases} B = Q_1(1 - R_{0_{cm}}) + Q_3(1 - R_{0_{cf}}), \\ C = Q_1Q_3(1 - R_{0_c}) + Q_1Q_3R_{0_{cm}}R_{0_{cf}}(1 - \eta_1\eta_2). \end{cases}$$

When $R_0 < 1$, then $R_{0_c} < 1$, $R_{0_{cm}} < 0$ and $R_{0_{cf}} < 0$. Also since $1 < \eta_1 < \eta_2 < 0$, then $0 < \eta_1\eta_2 < 1$. Clearly $C > 0$, $B > 0$ and hence, the roots of the quadratic equation (3.9) are negative. Hence, the disease free equilibrium point E_0 is locally asymptotically stable when $R_0 < 1$. $\square$

Global stability of the disease free equilibrium point

We prove the global stability of the disease-free equilibrium E_0 when $R_0 < 1$ in this section and we have the following theorem.

Theorem 3.3.2. *The disease free equilibrium E_0 of the system (3.2) is globally asymptotically stable when $R_0 < 1$ and unstable when $R_0 > 1$.*

Proof. To prove global stability of the model, we use a suitable candidate Lyapunov function and show that its derivative is negative for a given set of constants. Let

$$V(I_m, R_m, I_f, R_f) = aI_m + bR_m + cI_f + dR_f,$$

be a candidate Lyapunov function for some non-negative constants of a , b , c , and d . The time derivative of V is given by

$$\begin{aligned}
\frac{dV}{dt} &= a \frac{dI_m}{dt} + b \frac{dR_m}{dt} + c \frac{dI_f}{dt} + d \frac{dR_f}{dt}, \\
&= a[\beta(I_m + \eta_1 I_f)S_m - Q_1 I_m] + b[\sigma_1 I_m - Q_2 R_m] \\
&\quad + c[\beta(I_f + \eta_2 I_m)S_f - Q_3 I_f] + d[\sigma_2 I_f - Q_4 R_f], \\
&\leq a[\beta(I_m + \eta_1 I_f)\rho - Q_1 I_m] + b[\sigma_1 I_m - Q_2 R_m] \\
&\quad + c[\beta(I_f + \eta_2 I_m)(1 - \rho) - Q_3 I_f] + d[\sigma_2 I_f - Q_4 R_f], \\
&= [a\rho\beta - aQ_1 + b\sigma_1 + c(1 - \rho)\beta\eta_2]I_m \\
&\quad + [a\rho\beta\eta_1 + c(1 - \rho)\beta - cQ_3 + d\sigma_2]I_f - bQ_2 R_m - dQ_4 R_f.
\end{aligned} \tag{3.10}$$

We now evaluate the coefficients of the suitable Lyapunov function such that the coefficients of R_m and R_f are equal to zero. Thus, we obtain $b = 0$, $d = 0$. Let $a = Q_3$ and $c = Q_1$, then we have

$$\begin{aligned}
\frac{dV}{dt} &= [Q_3\beta\rho - Q_1Q_3 + Q_1\beta\eta_2(1 - \rho)]I_m \\
&\quad + [Q_3\beta\rho\eta_1 + Q_1\beta(1 - \rho) - Q_1Q_3]I_f.
\end{aligned} \tag{3.11}$$

Simplifying equation (3.11), we obtain

$$\frac{dV}{dt} = -Q_1Q_3 \left[\left(1 - (R_{0_{cm}} + R_{0_{fm}})\right) I_m + \left(1 - (R_{0_{cf}} + R_{0_{mf}})\right) I_f \right]. \tag{3.12}$$

Clearly, when $R_0 < 1$, then each of the components of R_0 will be less than 1. Therefore, the derivative of the Lyapunov function is negative when $R_0 < 1$. Thus, the disease free equilibrium E_0 is stable and $\frac{dV}{dt} = 0$ if and only if both I_m and I_f are equal to zero. Therefore, from the LaSalle invariance principle [30], E_0 is globally asymptotically stable. $\square$

The disease-persistent equilibrium

Let the steady state be $E_1 = (S_m^*, I_m^*, R_m^*, S_f^*, I_f^*, R_f^*)$. At the steady state, the system of equation (3.2) reduces to

$$0 = \rho\mu + \omega_1 R_m^* - \beta(I_m^* + \eta_1 I_f^*)S_m^* - \mu S_m^*, \tag{3.13a}$$

$$0 = \beta(I_m^* + \eta_1 I_f^*)S_m^* - Q_1 I_m^*, \tag{3.13b}$$

$$0 = \sigma_1 I_m^* - Q_2 R_m^*, \tag{3.13c}$$

$$0 = (1 - \rho)\mu + \omega_2 R_f^* - \beta(I_f^* + \eta_2 I_m^*)S_f^* - \mu S_f^*, \tag{3.13d}$$

$$0 = \beta(I_f^* + \eta_2 I_m^*)S_f^* - Q_3 I_f^*, \tag{3.13e}$$

$$0 = \sigma_2 I_f^* - Q_4 R_f^*. \tag{3.13f}$$

From equation (3.13c),

$$R_m^* = \frac{\sigma_1 I_m^*}{Q_2} \quad (3.14)$$

and from equation (3.13f),

$$R_f^* = \frac{\sigma_2 I_f^*}{Q_4}. \quad (3.15)$$

Substituting equation (3.14) into equation (3.13a) to get

$$0 = \rho\mu + \frac{\omega_1\sigma_1}{Q_2} I_m^* - \beta(I_m^* + \eta_1 I_f^*) S_m^* - \mu S_m^*, \quad (3.16)$$

and substituting equation (3.15) into equation (3.13d) to get

$$0 = (1 - \rho)\mu + \frac{\omega_2\sigma_2}{Q_4} I_f^* - \beta(I_f^* + \eta_2 I_m^*) S_f^* - \mu S_f^*. \quad (3.17)$$

From equation (3.13b),

$$S_m^* = \frac{Q_1 I_m^*}{\beta(I_m^* + \eta_1 I_f^*)}. \quad (3.18)$$

Substituting for S_m^* in equation (3.16) we get

$$0 = \rho\mu + \frac{\omega_1\sigma_1}{Q_2} I_m^* - Q_1 I_m^* - \frac{\mu Q_1 I_m^*}{\beta(I_m^* + \eta_1 I_f^*)}. \quad (3.19)$$

Rearranging the equation, we obtain

$$I_f^* = \frac{(1 - R_{0_{cm}}) I_m^* + \Phi_1 I_m^{*2}}{R_{0_{mf}} - \eta_1 \Phi_1 I_m^*}, \quad (3.20)$$

where $\Phi_1 = \frac{\beta}{\mu} \left(1 - \frac{\omega_1\sigma_1}{Q_1 Q_2} \right)$. From equation (3.13e),

$$S_f^* = \frac{Q_3 I_f^*}{\beta(I_f^* + \eta_2 I_m^*)}. \quad (3.21)$$

Substituting equation (3.21) into equation (3.17) we get

$$0 = (1 - \rho)\mu + \frac{\omega_2\sigma_2}{Q_4} I_f^* - Q_3 I_f^* - \frac{\mu Q_3 I_f^*}{\beta(I_f^* + \eta_2 I_m^*)}. \quad (3.22)$$

Rearranging the equation, we obtain

$$I_m^* = \frac{(1 - R_{0_{cf}}) I_f^* + \Phi_2 I_f^{*2}}{R_{0_{fm}} - \eta_2 \Phi_2 I_f^*}, \quad (3.23)$$

where $\Phi_1 = \frac{\beta}{\mu} \left(1 - \frac{\omega_2 \sigma_2}{Q_3 Q_4}\right)$. From equation (3.23),

$$\Phi_2 I_f^{*2} + \left[(1 - R_{0_{cf}}) + \eta_2 \Phi_2 I_m^*\right] I_f^* - R_{0_{fm}} I_m^* = 0. \quad (3.24)$$

Since $\Phi_2 > 0$, then I_f will have only one positive solution in terms of I_m . Similarly from equation (3.20)

$$\Phi_1 I_m^{*2} + \left[(1 - R_{0_{cm}}) + \eta_1 \Phi_1 I_f^*\right] I_m^* - R_{0_{mf}} I_f^* = 0. \quad (3.25)$$

Since $\Phi_1 > 0$, then I_m will have only one positive solution in terms of I_f . Therefore, the model has a unique co-existence solution. We can consider substituting equation (3.20) into equation (3.24) to get

$$\Phi_2 \left[\frac{(1 - R_{0_{cm}}) I_m^* + \Phi_1 I_m^{*2}}{R_{0_{mf}} - \eta_1 \Phi_1 I_m^*} \right]^2 + \left[(1 - R_{0_{cf}}) + \eta_2 \Phi_2 I_m^*\right] \left[\frac{(1 - R_{0_{cm}}) I_m^* + \Phi_1 I_m^{*2}}{R_{0_{mf}} - \eta_1 \Phi_1 I_m^*} \right] - R_{0_{fm}} I_m^* = 0. \quad (3.26)$$

Factor out I_m , we notice that either $I_m = 0$, DFE or if $I_m \neq 0$, then we have

$$\begin{aligned} & \Phi_2 \left[(1 - R_{0_{cm}}) + \Phi_1 I_m^*\right]^2 I_m^* + \left[(1 - R_{0_{cf}}) + \eta_2 \Phi_2 I_m^*\right] \left[(1 - R_{0_{cm}}) + \Phi_1 I_m^*\right] \left[R_{0_{mf}} - \eta_1 \Phi_1 I_m^*\right] \\ & - R_{0_{fm}} \left[R_{0_{mf}} - \eta_1 \Phi_1 I_m^*\right]^2 = 0. \end{aligned} \quad (3.27)$$

From equation (3.25), we make I_m the subject to get

$$I_m^* = \frac{\Phi_2 I_f^{*2} + (1 - R_{0_{cf}}) I_f^*}{R_{0_{fm}} - \eta_2 \Phi_2 I_f^*}. \quad (3.28)$$

Substituting for I_m in equation (3.25) to get

$$\Phi_1 \left[\frac{\Phi_2 I_f^* + (1 - R_{0_{cf}})}{R_{0_{fm}} - \eta_2 \Phi_2 I_f^*} \right]^2 I_f^{*2} + \left[(1 - R_{0_{cm}}) + \eta_1 \Phi_1 I_f^*\right] \left[\frac{\Phi_2 I_f^* + (1 - R_{0_{cf}})}{R_{0_{fm}} - \eta_2 \Phi_2 I_f^*} \right] I_f^* - R_{0_{fm}} I_f^* = 0. \quad (3.29)$$

We recognise that one of the roots of the equation is $I_f^* = 0$ which corresponds to the disease free equilibrium. If $I_f^* \neq 0$, then we obtain a cubic equation

$$A I_f^{*3} + B I_f^{*2} + C I_f^* + D = 0, \quad (3.30)$$

where

$$\begin{cases} A &= \Phi_1\Phi_2^2 - \eta_1\eta_2\Phi_1\Phi_2^2 = \Phi_1\Phi_2^2(1 - \eta_1\eta_2) > 0, \\ B &= 2\Phi_1\Phi_2(1 - R_{0_{cf}}) + (R_{0_{fm}} - \eta_2(1 - R_{0_{cf}}))\eta_1\Phi_1\Phi_2 - \eta_2(1 - R_{0_{cm}})\Phi_2^2 - \eta_2\Phi_1R_{0_{mf}}, \\ C &= (1 - R_{0_{cf}})^2\Phi_1 + \eta_1\Phi_1R_{0_{fm}}(1 - R_{0_{cf}}) + (1 - R_{0_{cf}})(R_{0_{fm}} - \eta_2(1 - R_{0_{cf}}))\Phi_2 + 2\eta_2R_{0_{mf}}R_{0_{fm}}\Phi_2, \\ D &= [1 - (R_{0_{cm}} + R_{0_{cf}} + R_{0_{mf}}R_{0_{fm}}) + R_{0_{cm}}R_{0_{cf}}]R_{0_{fm}}. \end{cases}$$

To confirm whether the polynomial equation (3.30) above has a positive root, we use Descartes rule of signs on the terms A, B, C and D. We note that the term A is positive. Given the complexity of the terms B, C and D it is not easy to analytically confirm their signs in terms of the components of R_0 . However, if the feeding related contact reproduction number is greater than 1, there is at least 1 change of sign which indicates existence of at least an endemic equilibrium point.

3.4 Numerical simulations

3.4.1 Parameter Estimation

We estimate the model parameters used in the model numerical simulations in this section. The parameter values were considered in units of per day and nominal values selected from within the specified range of intervals obtained. The DFTD was reported as a unique case of a transmissible cancer with a devastating effect on the Tasmanian devil [31]. According to Siska *et al.* (2018) [31], estimates of its density are currently at roughly 20% of the pre-disease state, and epidemiological models have predicted the likely extinction of the Tasmanian devils. From the previous researches, the population size of devils in the wild is estimated at 10 000 to 25 000 devils [32]. The annual recruitment was recorded within the range from 1-2 offspring female devils [10]. We choose a sex proportional value of 0.5 per year from a range (0.4-0.6). From the research by Hansen *et al.*, (2018), the disease induced mortality rate i.e. death due to DFTD infection was reported to occur within 6 months or less once the tumours are discovered [33, 34]. During the mating season, the disease spread is high since males fight against each other for females [32]. We thus consider values for both δ_1 and δ_2 as 0.0055 per day. Devils were assumed to have a life expectancy of 7-8 years (males) and 5-6 years (females) in the wild [34, 35]. We estimated the value of natural mortality rate (μ) between the range of (0.000342 – 0.000548) with a nominal value of 0.0004 per day. We estimated the general recovery rates for both male and female devils population i.e. σ_1 and σ_2 as 0.04 and 0.045 per day respectively. In the research by Bashford *et al.* (2012) [10], the

mean mating rate per season for devils was 0.39. It was reported that female devils can mate with several males if not guarded [32]. Thus, we choose a range from 0 to 1 and estimated η_1 and η_2 to be 0.8 and 0.6 respectively. The contact rate of devils was observed to be within the range 0-0.5 in [10] hence, we choose $\beta = (0.005; 0.02; 0.021; 0.025)$ per day as varied rates for simulations. The summary for parameter values used in model numerical simulations are given in Table 3.3.

Parameter	Unit	Range	Nominal Value	Source
β	day ⁻¹	0 - 0.5	0.021	[10]
η_1	-	0 - 1	0.8	[10]
η_2	-	0 - 1	0.6	[10]
σ_1	day ⁻¹	0 - 0.01	0.004	estimated
σ_2	day ⁻¹	0 - 0.01	0.0045	estimated
δ_1	day ⁻¹	0 - 0.01	0.0055	[33, 34]
δ_2	day ⁻¹	0 - 0.01	0.0055	[33, 34]
ω_1	day ⁻¹	0 - 0.01	0.0056	estimated
ω_2	day ⁻¹	0 - 0.01	0.0056	estimated
μ	day ⁻¹	0.000342-0.00055	0.0004	[34, 35]
ρ	proportion	0.4-0.6	0.5	[10]

Table 3.3: Parameter values used in simulations and sensitivity analysis

3.4.2 Sensitivity analysis using Latin Hypercube Sampling (LHS)/Partial Rank Coefficient Analysis (PRCC)

The major issue in mathematical biology models construction is estimation of precise parameter values and sometimes the model behaviour may be strongly dependent on the parameters [14]. Therefore, according to Zi (2011) [14], uncertainty must be considered when drawing conclusions from the model output for parameters that are uncertain using sensitivity analysis. The use of sensitivity analysis was well established in mathematical modelling in many fields which include biology for cellular signalling and also one of the best-known examples is the use of metabolic control analysis (MCA) in the study of metabolism [14]. There are many different methods that have been used to carry out sensitivity analysis that includes differential SA, one at a time SA, factorial design, sensitivity index and subjective SA [13]. Also, some of the popular techniques in sensitivity analysis include various graphical methods such as scatter plots and cobweb plots, correlation measures i.e. partial and rank correlation, and regression methods such as step wise, rank and non-parametric regression [17]. However, in this research, we use the Latin Hypercube Sampling Sensitivity Analysis referring to more general literature where appropriate owing to its efficient analysis of

variations of parameters across simultaneously uncertain ranges of individual parameters [16].

We present the PRCCs on R_0 for each of the input parameters. The aim of this analysis is to identify the parameters that have the most effects on reproduction number as PRCCs illustrate the degree of effect that each parameter has on the outcome [15].

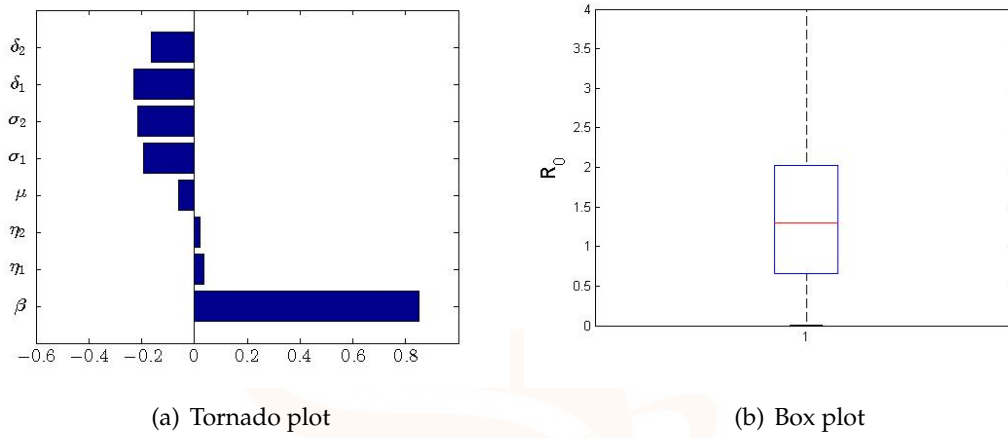


Figure 3.2: 3.2(a) Shows the Tornado plot, 3.2(b) the Box plot.

When parameters with positive PRCC are increased they will increase R_0 whilst those with negative PRCC will reduce R_0 when increased [15]. In Figure 3.2(a), we illustrated the PRCCs Tornado plot for the parameters $\delta_1, \delta_2, \sigma_1, \sigma_2, \mu, \eta_1, \eta_2$ and β used in the model and Figure 3.2(b), a Box plot which gives the five number summary (min, lower quartile, median, upper quartile and maximum value) of the reproduction number. It was observed that, the general contact rate, β is the parameter with the greatest potential of making the disease epidemic worse when increased. Therefore, isolation of uninfected devils to avoid contact with the infected devils may reduce the disease transmission and hence reduce the reproduction number to below 1. The disease is reported to attack more of the adult devils as they are the ones active and exposed to feeding and mating related contact [35]. The young devils are usually localised at one place since the mothers feed them, so they are not involved in contact with other infected devils [35].

The disease induced death rates of both male and female devils (δ_1 and δ_2) and recovery rates for both male and female devils (σ_1 and σ_2) are some of the parameters with the potential to contain the epidemic when maximised. An increase in death rates and the number of recoveries result in low number of infected devils, hence, resulting in the reduction of the reproduction number to below 1. The parameters that include mating related contact for

both male and female devils (η_1 and η_2) and death rate (μ) have a low effect on the reproduction number since they have small magnitudes of PRCCs. We note however that these parameters may still produce significant changes in the disease burden for the devil population if in combination with other processes. The rates at which the male and female devils become susceptible again (ω_1 and ω_2 respectively) does not have effects on the reproduction number.

We computed p-values for simulated parameters to identify the most important parameters describing processes that either contain or make the epidemic worse. The PRCCs computed are bounded between the interval $[-1,1]$ and some sampling distribution of variables that are highly correlated is skewed [16]. We computed p-values for each of the parameters based on PRCCs and transforming the skew distribution to a normal distribution using Fisher's Transformation ($p(r) = 0.5 \log \left(\frac{1+r}{1-r} \right)$) [36]. Indicated in Table 3.4 are the PRCCs for the parameters together with their p-values. The parameter values whose p-values are significant are indicated "True" for keep and those whose p-values are not significant with "False".

Variable(Parameter)	PRCCs	p-value	Keep
β	0.8552	0.0000	True
η_1	0.0358	0.2598	False
η_2	0.0204	0.5209	False
μ	-0.0615	0.05268	False
σ_1	-0.1914	0.0000	True
σ_2	-0.2157	0.0000	True
δ_1	-0.2282	0.0000	True
δ_2	-0.1644	0.0000	True

Table 3.4: Parameter PRCC Significance (Unadjusted P-value)

	β	σ_1	σ_2	δ_1	δ_2
β		0	0	0	0
σ_1			0.5727	0.3917	0.4909
σ_2				0.7699	0.2102
δ_1					0.1222
δ_2					

Table 3.5: Pairwise PRCC Comparisons (Unadjusted P-values)

There is significant correlation for the parameters β , σ_1 , σ_2 , δ_1 and δ_2 with the output values of R_0 . The p-values indicated as zeros in Table 3.4 are not necessarily zeros but are numbers that are very small closer to zero. In Table 3.5, pairwise PRCCs comparisons of significant parameters are shown to determine whether the underlying processes are significantly different. We performed Pairwise Comparisons to describe fully the pattern of the parameter

	β	σ_1	σ_2	δ_1	δ_2
β		0	0	0	0
σ_1			0.6363	0.5596	0.6136
σ_2				0.7699	0.3503
δ_1					0.2444
δ_2					

Table 3.6: Pairwise PRCC Comparisons (FDR Adjusted P-values)

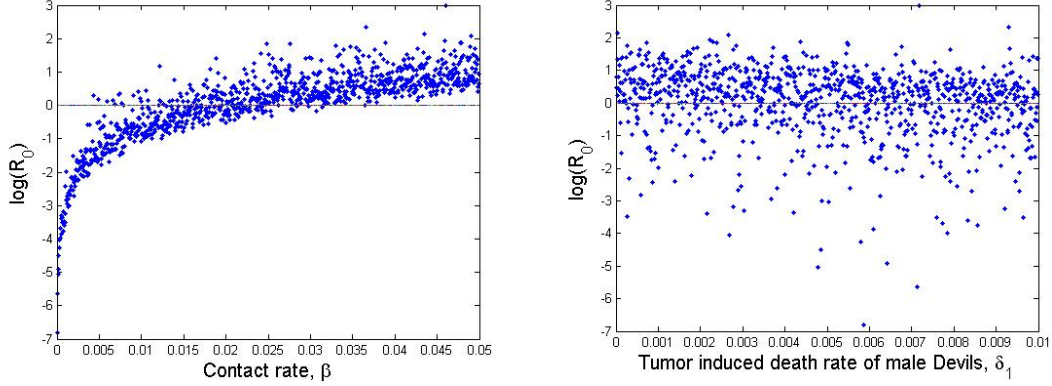
	β	σ_1	σ_2	δ_1	δ_2
β		TRUE	TRUE	TRUE	TRUE
σ_1			FALSE	FALSE	FALSE
σ_2				FALSE	FALSE
δ_1					FALSE
δ_2					

Table 3.7: Parameters different after FDR adjustment?

differences with the null hypothesis H_0 : stating that all the parameters are significantly different. Therefore, the great difference was observed from the parameter β with all the other significant parameters that include σ_1 , σ_2 , δ_1 and δ_2 . There is no significant difference between the rest of the pairs of significant parameter. When computing pairwise comparisons, there is a possibility of making Type 1 statistical error. Therefore, we perform the Pairwise with False discovery rate adjustment and the results for (FDR Adjusted p-values) are shown in Table 3.6. In Table 3.7, we summarise the parameters observed to be significantly different after FDR adjustment. The table shows the parameters that are statistically different, where "True" indicates the parameters which are different and "False" indicating otherwise. We observed that, for the infection to be contained, introduction of disease suppression that is stamping by culling should be implemented as well as isolation of devils that are uninfected to reduce contact rate with the infected devils so as to reduce the reproduction number to below one. More still, developing and administering a vaccine to the newly recruited devils in the population is another method to avoid extinction of the devils although there would be a challenge in administering the vaccine in the wild population [6].

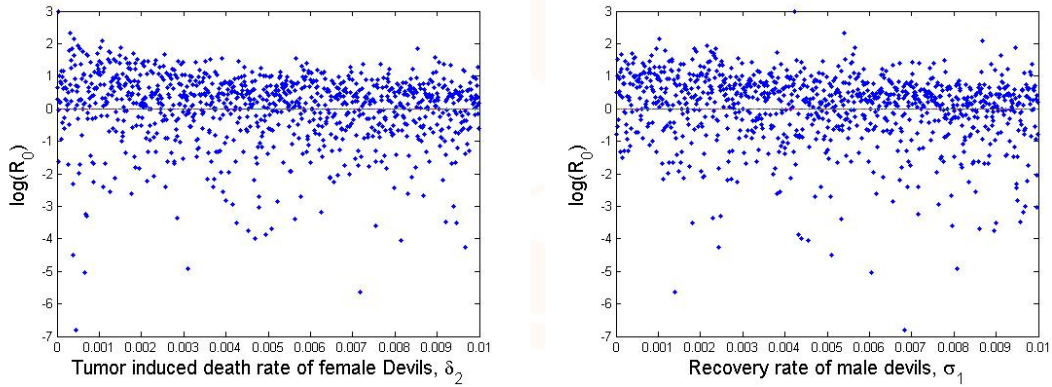
Scatter-plots for parameters with significant PRCCs were generated to examine the assumption of monotonicity. Figures 3.3 to 3.5 show the scatter plots for variation in the reproduction number, R_0 , against the parameters with significant PRCCs. The parameters were varied according to the range of values given in the Table 3.3. According to the results, we observed that the feeding related contact rate, β , the tumour induced death rate for both male and female devils, (δ_1 and δ_2), male and female devils recovery rate, (σ_1 and σ_2), are the parameters which are most monotonically related to the reproduction number as compared

to other parameters.



(a) Variation of $\mathcal{R}_0$ with feeding related contact rate (b) Variation of $\mathcal{R}_0$ with the disease induced death rate for male Devils

Figure 3.3: 3.3(a) Shows the variation of $\mathcal{R}_0$ with feeding related contact rate, 3.3(b) the variation of $\mathcal{R}_0$ with the disease induced death rate for male devils.



(a) Variation of $\mathcal{R}_0$ with Tumour disease induced death rate of female Devils (b) Variation of $\mathcal{R}_0$ with Recovered rate for male Devils

Figure 3.4: 3.4(a) Shows the variation of $\mathcal{R}_0$ with Tumour disease induced death rate of female Devils, 3.4(b) the variation of $\mathcal{R}_0$ with Recovered rate for male Devil.

3.4.3 Numerical Results

We conducted several numerical simulations of the model system of equations (3.2) using the nominal values of the parameter values provided in the Table 3.3. The proportion for the initial conditions used are as $(S_m, I_m, R_m, S_f, I_f, R_f) = (0.45, 0.045, 0.005, 0.45, 0.045, 0.005)$. We presented proportions of infected devils with respect to time considering the reproduction number, R_0 , below 1 and above 1 in Figure 3.6. The proportion of infected male and

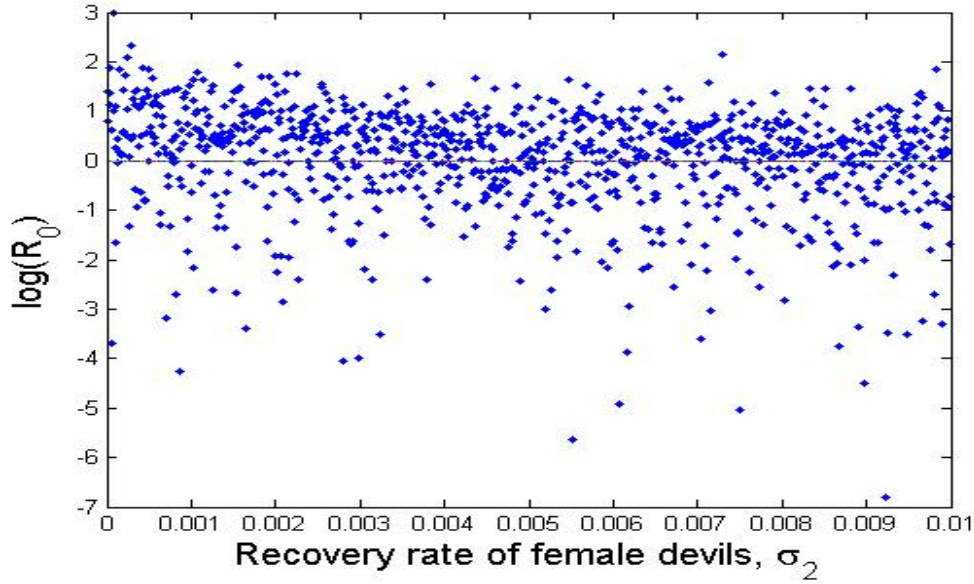
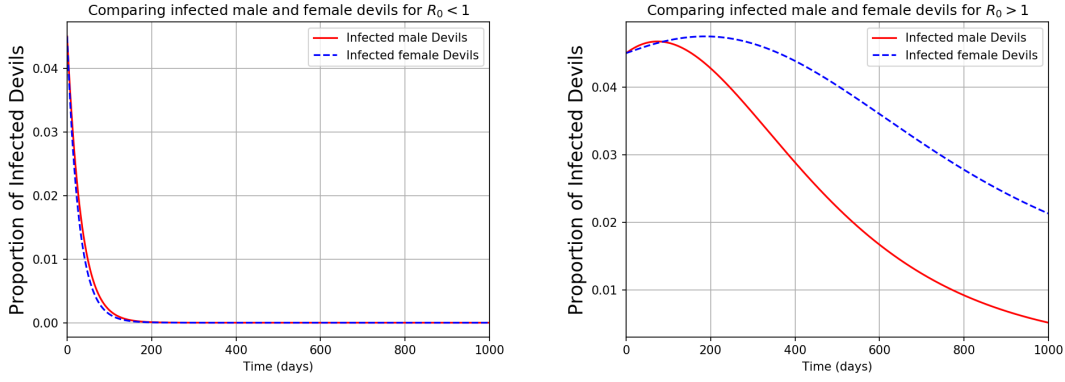


Figure 3.5: Variation of $\mathcal{R}_0$ with Recovered rate for female Devils.

female devils with the change in contact rate of individuals related to feeding in Figure 3.7. The simulations were carried out with varying values of the infection rate $\beta \in [0.005, 0.025]$ as in Table 3.3. From Figure 3.6, we indicated the comparison of male and female devil proportions for R_0 below one in Figure 3.6(a), and for R_0 above one in Figure 3.6(b). The infection was observed to devastate more the female devil population than male devils from both figures where reproduction number is below and above one. For R_0 below one, we observed that the proportion for both male and female infected devils is reduced in less than 200 days which is likely to show that the disease will not get established in the whole population in the future. For R_0 above one (i.e. $R_0 = 1.055$), the population for both male and female infected devils remain significantly high compared to the case when $R_0 < 1$. Therefore, for $R_0 > 1$, the disease is likely to stay long in the devil population, but may not necessarily wipe out the population.

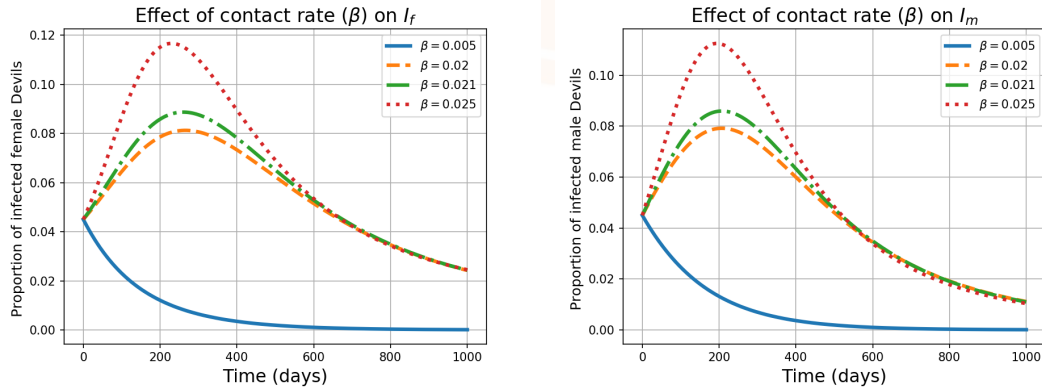
From Figure 3.7, it is observed that the higher the feeding related contact rate, the faster (and the higher) the peak values are reached and then followed by a decline for both male and female devils. This decline may be also due to the disease's self-limitation since there will be a low number of susceptible devils to be infected.

Figures 3.8 and 3.9 indicate the effect of the relative contact during mating (i.e. from male to female and from female to male). Figure 3.8(a) shows the effect of mating related contact rate from male to female and Figure 3.8(b) shows the effect of mating related contact rate from



(a) Variation of infected devil population when R_0 is below 1 (b) Variation of infected devil population when R_0 is above 1

Figure 3.6: 3.6(a) Shows the comparison of male and female Devil proportions for R_0 below 1, 3.6(b) the comparison of male and female Devil proportions for R_0 above 1.



(a) Variation of Time (days) with proportion of Infected female Devils (b) Variation of Time(days) with proportion of Infected male Devils

Figure 3.7: 3.7(a) Shows the variation of Infected female Devils with the change in effective contact rate of devils, 3.7(b) the variation of Infected male Devils with the change in effective contact rate of devils.

male to female on the male devil population. For values of the relative mating related rate from male to female devils, $\eta_1 = \{0.25, 0.48, 0.65, 0.8\}$ we obtained the reproduction number, $R_0 = \{1.4016, 1.4022, 1.4026, 1.403\}$. Figure 3.9(a) indicates the effect of relative mating related infection rate from male to female devils on the female devil. Figure 3.9(b) indicates the effect of mating related infection rate from male to female on the male devil population. For values of the mating infection rate from female to male devils, $\eta_2 = \{0.18, 0.32, 0.45, 0.6\}$, we obtained the reproduction number, $R_0 = \{1.4015, 1.402, 1.4025, 1.403\}$. From Figures 3.8(a) and 3.9(b), we observed that large change in η_1 and η_2 are associated with directly proportional marginal changes in the reproduction number, R_0 . Figures 3.8(b) and 3.9(a) show that there is marginal effect of the mating related contact rate from the female to male and male to male devils respectively.

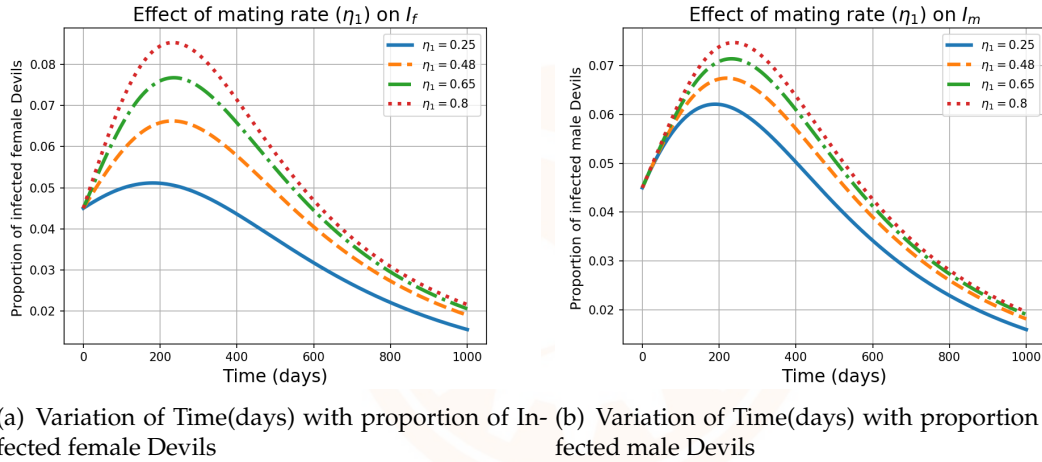
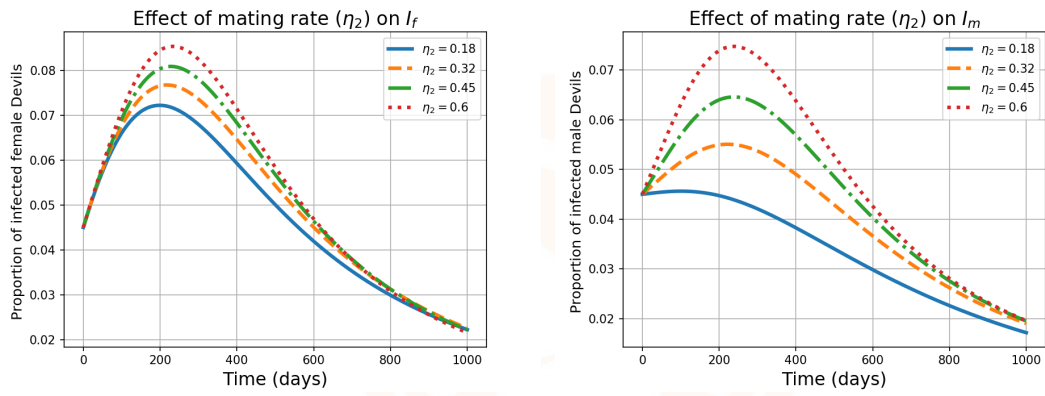


Figure 3.8: 3.8(a) Shows the variation of Infected female devils with the change in the mating related relative transmission from female to male devils, 3.8(b) the variation of Infected male devils with the change in the mating related relative transmission from female to male devils.



(a) Variation of Time(days) with proportion of Infected female Devils (b) Variation of Time(days) with proportion of Infected male Devils

Figure 3.9: 3.9(a) Shows the variation of Infected female Devils with the change in the mating related contact of male to female devils, 3.9(b) the variation of Infected male Devils with the change in the mating related infection rate from male to female devils.

Chapter 4

Optimal Control

4.1 Introduction

In this chapter the Devil Facial Tumour disease dynamical model (3.2) with controls is presented. Control measures and a detailed qualitative optimal control model that minimizes the number of infected female and male devils with minimal cost of implementing the control measures is developed. We analyse the optimal control problem in order to determine the necessary conditions for optimality using the same method as in Njagarah *et al.* 2015 [22]. Optimal control has been studied in models of Cholera transmission [22], Tungiasis transmission [18], Alcoholism [20] and many more models.

According to The Save the Tasmanian Devil Organisation and from past researches, there are various controls of DFTD recommended such as isolation, culling, selection of resistant animal to be released in the wild and developing a vaccine as discussed in Chapter 1 [6]. These preventive measures are aimed at reducing the infections by reducing contact rates between the infected and uninfected devils or reducing infected devils coming into contact with the uninfected devils. In this chapter, we discuss three preventive and control measures that include isolation, culling and vaccination. We consider model (4.1) with controls in this chapter, where we denote isolation of devils at any time t by $p(t)$. We note that devils once isolated, there will be selection of resistant ones to be released into the wild. We assume that the infection is reduced by fractions $q(t)$ and $r(t)$ which are culling and vaccination respectively. Therefore, the general procedure of optimal control process in an epidemiological model involves processes that include the following; (i.) identifying permissible controls applicable to the model, (ii.) setting up the objective function with controls, (iii.) constructing the Hamiltonian, and (iv.) evaluating costate variables (adjoint functions), and (v.) lastly

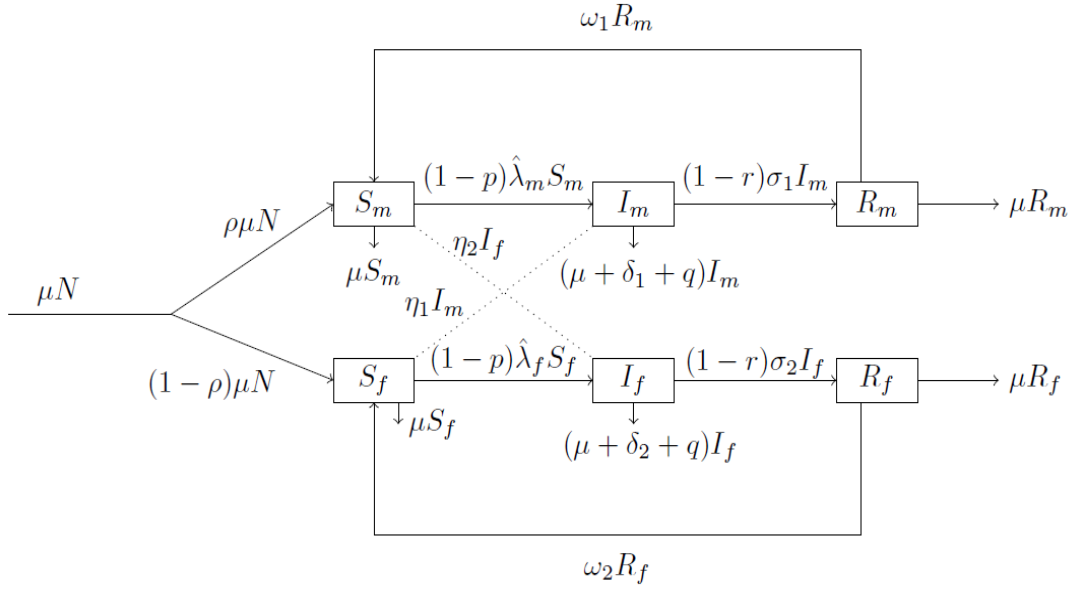


Figure 4.1: A compartmental representation of the model of Devil Facial Tumour Disease with controls

identify the threshold controls that minimise the Hamiltonian [22]. This optimal control minimisation procedure follows Pontryagin's Maximum/Minimum principle [22, 37]. The flow diagram of the DFTD model with controls is given in Figure 4.1 and the model that governs the system of differential system is given on equation (4.1).

4.2 The Model with Controls

System of Equations

$$\begin{aligned}
 \frac{dS_m}{dt} &= \rho\mu + \omega_1 R_m - (1-p)\hat{\lambda}_m S_m - \mu S_m, \\
 \frac{dI_m}{dt} &= (1-p)\hat{\lambda}_m S_m - (1-r)\sigma_1 I_m - (\mu + \delta_1 + q)I_m, \\
 \frac{dR_m}{dt} &= (1-r)\sigma_1 I_m - (\omega_1 + \mu)R_m, \\
 \frac{dS_f}{dt} &= (1-\rho)\mu + \omega_2 R_f - (1-p)\hat{\lambda}_f S_f - \mu S_f, \\
 \frac{dI_f}{dt} &= (1-p)\hat{\lambda}_f S_f - (1-r)\sigma_2 I_f - (\mu + \delta_2 + q)I_f, \\
 \frac{dR_f}{dt} &= (1-r)\sigma_2 I_f - (\omega_2 + \mu)R_f.
 \end{aligned} \tag{4.1}$$

The objective function for our minimisation problem is given by:

$$f(p, q, r) = \int_0^T (\xi_1 I_m + \xi_2 I_f + xp^2 + yq^2 + zr^2) dt \quad (4.2)$$

subjected to

$$\begin{aligned} \frac{dS_m}{dt} &= \rho\mu + \omega_1 R_m - (1-p)\hat{\lambda}_m S_m - \mu S_m, \quad S_m(0) = S_m^0 \geq 0, \\ \frac{dI_m}{dt} &= (1-p)\hat{\lambda}_m S_m - (1-r)\sigma_1 I_m - (\mu + \delta_1 + q)I_m, \quad I_m(0) = I_m^0 \geq 0, \\ \frac{dR_m}{dt} &= (1-r)\sigma_1 I_m - (\omega_1 + \mu)R_m, \quad R_m(0) = R_m^0 \geq 0, \\ \frac{dS_f}{dt} &= (1-\rho)\mu + \omega_2 R_f - (1-p)\hat{\lambda}_f S_f - \mu S_f, \quad S_f(0) = S_f^0 \geq 0, \\ \frac{dI_f}{dt} &= (1-p)\hat{\lambda}_f S_f - (1-r)\sigma_2 I_f - (\mu + \delta_2 + q)I_f, \quad I_f(0) = I_f^0 \geq 0, \\ \frac{dR_f}{dt} &= (1-r)\sigma_2 I_f - (\omega_2 + \mu)R_f, \quad R_f(0) = R_f^0 \geq 0. \end{aligned}$$

The coefficients associated with the costs over a finite period T are ξ_1 , ξ_2 , x , y , and z . $\xi_1 I_m$ and $\xi_2 I_f$ indicate the cost associated with minimising the infection in the male and female devil populations, respectively. Relative cost weights for the respective control measures which include isolation, culling and vaccination are represented by x , y , and z . We consider the use of quadratic terms due to the assumption that the cost of controls is non-linear. We construct the optimal control problem with the aim of investigating the effect of control strategies in the interaction of the susceptible and infected devils so as to minimise the number of infected devils at the same time minimising the cost of implementing the controls. In this case, we seek optimal controls p^* , q^* , and r^* such that:

$$f(p^*, q^*, r^*) = \min_{p, q, r} \{f(p, q, r) / p, q, r \in U\}, \quad (4.3)$$

where

$$U = \{(p, q, r) / p, q, r : [0, T] \rightarrow [0, 1]\}.$$

We use the Hamiltonian constructed for the model system of equations with the necessary adjoint functions to evaluate the integral in (4.2). Let λ_{S_m} , λ_{I_m} , λ_{R_m} , λ_{S_f} , λ_{I_f} and λ_{R_f} be the adjoint functions or costate variables associated with the evolution of the corresponding state variables. We multiply each of the adjoint functions with the right side of the equation describing the evolution of each state variable to obtain

$$\begin{aligned}
H = & \xi_1 I_m + \xi_2 I_f + xp^2 + yq^2 + zr^2 \\
& + \lambda_{S_m} [\rho\mu + \omega_1 R_m - (1-p)\beta(I_m + \eta_1 I_f)S_m - \mu S_m] \\
& + \lambda_{I_m} [(1-p)\beta(I_m + \eta_1 I_f)S_m - (1-r)\sigma_1 I_m - (\mu + \delta_1 + q)I_m] \\
& + \lambda_{R_m} [(1-r)\sigma_1 I_m - (\omega_1 + \mu)R_m] \\
& + \lambda_{S_f} [(1-\rho)\mu + \omega_2 R_f - (1-p)\beta(I_f + \eta_2 I_m)S_f - \mu S_f] \\
& + \lambda_{I_f} [(1-p)\beta(I_f + \eta_2 I_m)S_f - (1-r)\sigma_2 I_f - (\mu + \delta_2 + q)I_f] \\
& + \lambda_{R_f} [(1-r)\sigma_2 I_f - (\omega_2 + \mu)R_f].
\end{aligned} \tag{4.4}$$

Theorem 4.2.1. According to [22], we let p^* , q^* , and r^* be the optimal controls for the system of equations (4.1), x^* the state space at equilibrium and $\lambda_{(\bullet)}$ positive semi-definite piecewise differentiable functions for all t . Suppose that for all $t \in [0, T]$

$$\begin{aligned}
0 = & H_p(t, x^*, p^*, q^*, r^*, \lambda(t)) \\
= & H_q(t, x^*, p^*, q^*, r^*, \lambda(t)) \\
= & H_r(t, x^*, p^*, q^*, r^*, \lambda(t)),
\end{aligned} \tag{4.5}$$

then the following holds for optimal controls p^* , q^* , and r^*

$$H(t, x^*, p^*(t), q^*(t), r^*(t), \lambda(t)) \leq H(t, x^*, p(t), q(t), r(t), \lambda(t)). \tag{4.6}$$

We differentiate the Hamiltonian with respect to each of the state variables to find the differential equations of the associated adjoint functions such that

$$\begin{aligned}
\frac{d\lambda_{S_m}}{dt} &= (1-p)\beta(I_m + \eta_1 I_f)[\lambda_{S_m} - \lambda_{I_m}] + \mu\lambda_{S_m}, \\
\frac{d\lambda_{I_m}}{dt} &= (1-p)\beta S_m[\lambda_{S_m} - \lambda_{I_m}] + (1-p)\beta\eta_2 S_f[\lambda_{S_f} - \lambda_{I_f}] + (\mu + \delta_1 + q)\lambda_{I_m} + (1-r)\sigma_1[\lambda_{I_m} - \lambda_{R_m}], \\
\frac{d\lambda_{R_m}}{dt} &= (\omega_1 + \mu)\lambda_{R_m} - \omega_1\lambda_{S_m}, \\
\frac{d\lambda_{S_f}}{dt} &= (1-p)\beta(I_f + \eta_2 I_m)[\lambda_{S_f} - \lambda_{I_f}] + \mu\lambda_{S_f}, \\
\frac{d\lambda_{I_f}}{dt} &= (1-p)\beta\eta_1 S_m[\lambda_{S_m} - \lambda_{I_m}] + (1-p)\beta S_f[\lambda_{S_f} - \lambda_{I_f}] + (\mu + \delta_2 + q)\lambda_{I_f} + (1-r)\sigma_2[\lambda_{I_f} - \lambda_{R_f}], \\
\frac{d\lambda_{R_f}}{dt} &= (\omega_2 + \mu)\lambda_{R_f} - \omega_2\lambda_{S_f},
\end{aligned} \tag{4.7}$$

with a transversality condition given by

$$\lambda_{S_m(T)} = \lambda_{I_m(T)} = \lambda_{R_m(T)} = \lambda_{S_f(T)} = \lambda_{I_f(T)} = \lambda_{R_f(T)} = 0. \tag{4.8}$$

For the condition (4.8), the following hold

$$\begin{aligned}
\frac{d\lambda_{S_m}}{dt} &= -\frac{dH}{dS_m} \\
&\bullet \\
&\bullet \\
&\bullet \\
\frac{d\lambda_{R_f}}{dR_f} &= -\frac{H}{dR_f}.
\end{aligned} \tag{4.9}$$

The following conditions illustrate the optimal controls

$$\begin{aligned}
p^*(t) &= \max(0, \min(\hat{p}(t), 1)), \\
q^*(t) &= \max(0, \min(\hat{q}(t), 1)), \\
r^*(t) &= \max(0, \min(\hat{r}(t), 1)).
\end{aligned} \tag{4.10}$$

As in [22], the standard control arguments on the controls are such that

$$p^* = \begin{cases} 0 & \text{if } \hat{p} \leq 0, \\ \hat{p} & \text{if } 0 < \hat{p} < 1, \\ 1 & \text{if } \hat{p} \geq 1. \end{cases} \tag{4.11}$$

The upper bound of p^* clearly indicates that, isolating the devils that are uninfected is likely to reduce the transmission of the infection. This is especially if all the devils isolated are uninfected i.e. no infected devils taken to be isolated together with the uninfected devils and there are no uninfected devils that are left to be isolated. This results in no interaction or contact between infected and uninfected thereby, reducing transmission of DFTD.

$$q^* = \begin{cases} 0 & \text{if } \hat{q} \leq 0, \\ \hat{q} & \text{if } 0 < \hat{q} < 1, \\ 1 & \text{if } \hat{q} \geq 1. \end{cases} \quad (4.12)$$

The upper bound of q^* is characterised by culling. This involves killing of the most extremely infected devils in the population as a mechanism to reduce risk of infection in the population.

$$r^* = \begin{cases} 0 & \text{if } \hat{r} \leq 0, \\ \hat{r} & \text{if } 0 < \hat{r} < 1, \\ 1 & \text{if } \hat{r} \geq 1. \end{cases} \quad (4.13)$$

The value $r^* = 1$ indicates a perfect vaccine of DFTD. Developing a perfect vaccine for devils would reduce the infection although if the immunity wanes the devils will be likely to get infected again. We have not found any information relating to the time frame over which the vaccine stays in the system once the devils are vaccinated. We note that the upper bound ($r^* = 1$) can only be attained in a case of a perfect vaccine.

Now we differentiate the Hamiltonian, H , with respect to our controls p , q , and r thus we obtain,

$$\begin{aligned} \frac{dH}{dp} &= 2xp + \beta(I_m + \eta_1 I_f)S_m[\lambda_{S_m} - \lambda_{I_m}] + \beta(I_f + \eta_2 I_m)S_f[\lambda_{S_f} - \lambda_{I_f}], \\ \frac{dH}{dq} &= 2yq - I_m\lambda_{I_m} - I_f\lambda_{I_f}, \\ \frac{dH}{dr} &= 2zr + \sigma_1 I_m[\lambda_{I_m} - \lambda_{R_m}] + \sigma_2 I_f[\lambda_{I_f} - \lambda_{R_f}]. \end{aligned} \quad (4.14)$$

We obtain the control characterisations $\hat{p}$, $\hat{q}$, and $\hat{r}$ of the optimal controls p^* , q^* , and r^* by equating the right hand side of the system of equations (4.14) to zero i.e. $\frac{dH}{dp} = \frac{dH}{dq} = \frac{dH}{dr} = 0$:

Thus we have,

$$\begin{aligned}\hat{p} &= \frac{\beta(I_m + \eta_1 I_f)S_m[\lambda_{I_m} - \lambda_{S_m}] + \beta(I_f + \eta_2 I_m)S_f[\lambda_{I_f} - \lambda_{S_f}]}{2x}, \\ \hat{q} &= \frac{I_m \lambda_{I_m} + I_f \lambda_{I_f}}{2y}, \\ \hat{r} &= \frac{\sigma_1 I_m[\lambda_{R_m} - \lambda_{I_m}] + \sigma_2 I_f[\lambda_{R_f} - \lambda_{I_f}]}{2z}.\end{aligned}\tag{4.15}$$

From the equation (4.15), it can be observed that the control characterisations have an inverse proportion with the associated costs.

4.3 Numerical simulations

4.3.1 Parameter estimation

We conducted numerical simulations using the parameter values given in Table 3.3 of Chapter 3 and Table 4.1 for control costs to determine the necessary conditions for optimality.

Coefficient	Cost	Source
ξ_1	\$20	estimated
ξ_2	\$12	estimated
X	\$8	estimated
Y	\$5	estimated
Z	\$5	estimated

Table 4.1: Permissible control costs

4.3.2 Numerical Results

We conducted numerical simulations to investigate the significance of optimal control strategies in the devil population. Isolation, culling and vaccination are the 3 control strategies that are commonly practised. If the controls are efficient, the transmission of the infection in the population of devils will be reduced.

From Figure 4.2, we present the results based on the effect of controls on the susceptible female and male devil populations. With optimal controls, the susceptible devils in both populations are isolated and vaccinated to reduce contact with infected devils. Therefore, the number of devils at risk of contracting the infection is reduced which leads to a low

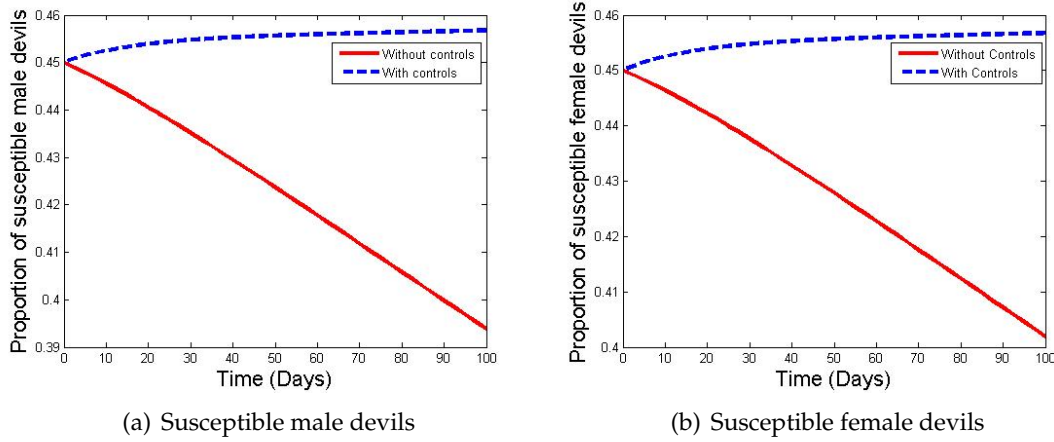


Figure 4.2: 4.2(a) Shows the proportion of susceptible male devils in the population with controls and without controls, 4.2(b) the proportion of susceptible female devils in the population with controls and without controls.

number of recoveries. The number of infected devils is also reduced. In the presence of controls, the population of susceptible devils remain relatively constant.

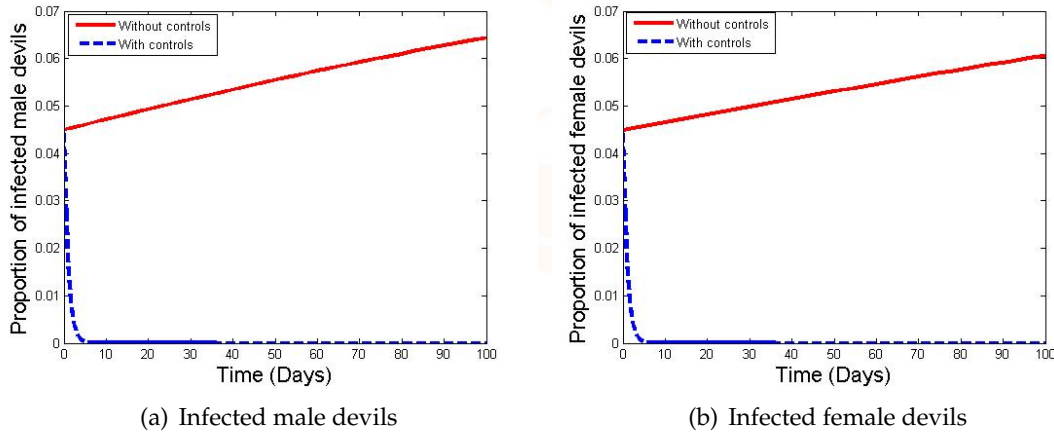


Figure 4.3: 4.3(a) Shows the proportion of infected male devils in the population with controls and without controls, 4.3(b) the proportion of infected female devils in the population with controls and without controls.

In the presence of controls, culling and vaccination are implemented in the infected female and male populations. From the results in Figure 4.3, it is indicated that the infection is reduced in the presence of controls in both female and male devil populations. However, the infection remain in the population with a lower number of devils affected. We also observe that, in the absence of controls the number of recovered devils reached to high population levels this is partly because the model assumes a high rate of recovery. The female and male

devils are threatened equally by the infection.

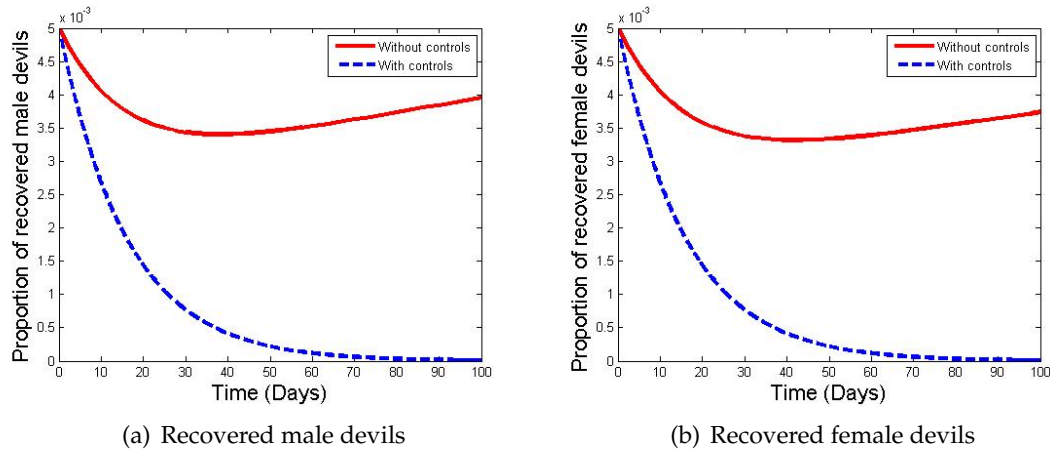


Figure 4.4: 4.4(a) Shows the proportion of recovered male and female devils in the population with controls and without controls, 4.4(b) the proportion of recovered female devils in the population with controls and without controls.

Figure 4.4 indicates that, with controls in the population of devils, the number of recoveries is reduced since the infection is also reduced. In the absence of controls the number of recoveries are high as a result of natural recovery.

Chapter 5

Fractional-Order Model for DFTD

5.1 Introduction

In this chapter we employ Fractional-order calculus to study DFTD dynamics of the model presented in Chapter 3. In epidemic models, it is assumed that the memory effect is little when the order of the derivative is an integer and when the derivative is a fractional order, the memory has a great influence in the dynamics of the disease [38]. There are challenges faced in gathering data on how transmission occurs in the wild populations. In previous researches [39], it was observed that when the disease spreads, the affected animals may become lethargic and seek isolation. Moreover, they avoid contact with other animals or sometimes they increase their aggressive behaviour [39]. Once they seek isolation, chances of the healthy animals to get infected are minimized. Based on this, the use of Fractional-Order Derivative is useful to model problems that involve memory effect. Fractional Calculus has been used in different fields that include Science, Engineering and Finance. It has also been used in epidemiology and mathematical biology, for example in [28, 40, 41] to solve problems of epidemiological models of infections such as Whooping cough, Dengue fever [27], ebola [42], HBV infection [43], HIV dynamics [44] and Metapopulation Cholera transmission [45]. In this chapter, we present a DFTD model system (3.2) using a Caputo-Fabrizio fractional derivative type owing to its efficiency in solving initial value FDEs. Using the Mittag-Leffler functions, we prove the basic model properties such as positivity and boundedness. The Caputo-Fabrizio fractional derivatives of our model for the system of equations used are given in equations (5.1a) -(5.1f). Model formulation and description as well as the reproduction number are the same as in Chapter 3, except that the integer order derivative

has been replaced with a general fractional-order derivative.

$${}_0^c D_t^\alpha S_m = \rho\mu + \omega_1 R_m - \beta(I_m + \eta_1 I_f)S_m - \mu S_m, \quad (5.1a)$$

$${}_0^c D_t^\alpha I_m = \beta(I_m + \eta_1 I_f)S_m - Q_1 I_m, \quad (5.1b)$$

$${}_0^c D_t^\alpha R_m = \sigma_1 I_m - Q_2 R_m, \quad (5.1c)$$

$${}_0^c D_t^\alpha S_f = (1 - \rho)\mu + \omega_2 R_f - \beta(I_f + \eta_2 I_m)S_f - \mu S_f, \quad (5.1d)$$

$${}_0^c D_t^\alpha I_f = \beta(I_f + \eta_2 I_m)S_f - Q_3 I_f, \quad (5.1e)$$

$${}_0^c D_t^\alpha R_f = \sigma_2 I_f - Q_4 R_f. \quad (5.1f)$$

The order of the fractional derivative is represented by α where $\alpha \in (0,1]$.

5.2 Positivity and boundedness

In dealing with a biological model, we need to make sure that the system is well posed with the assumption that all solutions of the state variables are non negative and bounded. We use Mittag-Leffler function to prove positivity of solutions of the DFTD dynamics model. We consider the following lemma.

Lemma 5.2.1. *Given that the initial conditions of the system of equations (5.1a) - (5.1f) are $S_m^0 > 0$, $I_m^0 \geq 0$, $R_m^0 \geq 0$, $S_f^0 > 0$, $I_f^0 \geq 0$, and $R_f^0 \geq 0$, the solutions $S_m(t)$, $I_m(t)$, $R_m(t)$, $S_f(t)$, $I_f(t)$, and $R_f(t)$ are non-negative for all $t > 0$.*

To prove Lemma 5.2.1, we use solutions of the respective (inequalities) detailed in [46]

Proof. Let

$$\hat{t} = \sup \{t > 0: S_m(t) \geq 0, I_m(t) \geq 0, R_m(t) \geq 0, S_f(t) \geq 0, I_f(t) \geq 0, \text{ and } R_f(t) \geq 0\} \in [0, t].$$

Thus, for $\hat{t} > 0$, from equation (5.1a) of the model system it follows that

$$D_t^\alpha S_m = \rho\mu + \omega_1 R_m - \beta(I_m + \eta_1 I_f)S_m - \mu S_m, \quad S_m(0) \in \mathbb{R}. \quad (5.2)$$

The equation (5.2) can be expressed as the following Cauchy problem;

$$\begin{aligned} D^\alpha S_m(t) &\geq -[\beta(I_m(t) + \eta_1 I_f(t)) + \mu]S_m(t), \\ &\geq (\hat{\lambda}_m(t) + \mu)S_m(t), \quad S_m(0) \in \mathbb{R}, \end{aligned} \quad (5.3)$$

where $\hat{\lambda}_m = \sup_{t \geq 0} \{\hat{\lambda}_m\}$.

The solution of the Cauchy problem (5.3) in terms of a Mittag-Leffler Function is given as

$$S_m(t) \geq S_m(0)E_\alpha(-[\hat{\lambda}_m + \mu]t^\alpha), \quad (5.4)$$

where $E_\alpha(t) = \sum_{k=0}^{\infty} \frac{t^k}{\Gamma(k\alpha + 1)}$ is the Mittag-Leffler function for $0 < \alpha < 1$.

We note that for a special case when $\alpha = 1$, the equation (5.4) reduces to an exponential function given below

$$\begin{aligned} S_m(t) &> S_m(0)E_1(-[\hat{\lambda}_m + \mu]t), \quad S_m(0) \in \mathbb{R}, \\ &= S_m(0)\exp\{-(\hat{\lambda}_m + \mu)t\} \geq 0 \quad \forall t \in [0, \infty). \end{aligned} \quad (5.5)$$

From equation (5.1b), we have

$$D_t^\alpha I_m = \hat{\lambda}_m S_m - Q_1 I_m. \quad (5.6)$$

The equation (5.6) can be expressed as an inequality of the following Cauchy problem

$$D^\alpha I_m(t) \geq -Q_1 I_m, \quad I_m(0) \in \mathbb{R}, \quad (5.7)$$

whose solution is given in terms of a Mittag-Leffler function as

$$I_m(t) \geq I_m(0)E_\alpha[-Q_1 t^\alpha], \quad I_m(0) \in \mathbb{R}. \quad (5.8)$$

We note that for a special case when $\alpha = 1$, equation (5.8) reduces to an exponential function

$$I_m(t) \geq I_m(0)e^{-Q_1 t} \geq 0 \quad \forall t \in [0, \infty). \quad (5.9)$$

From equation (5.1d) of the model system, it follows that

$$D_t^\alpha S_f = (1 - \rho)\mu + \omega_2 R_f - \beta(I_f + \eta_2 I_m)S_f - \mu S_f, \quad S_f(0) \in \mathbb{R}, \quad (5.10)$$

which gives a fractional-order inequality that can be expressed as the following Cauchy problem

$$\begin{aligned} D^\alpha S_f(t) &\geq -[\beta(I_f(t) + \eta_2 I_m(t)) + \mu]S_f(t), \\ &\geq (\hat{\lambda}_f + \mu)S_f(t), \quad S_f(0) \in \mathbb{R}, \end{aligned} \quad (5.11)$$

where $\hat{\lambda}_f = \sup_{t \geq 0} \{\hat{\lambda}_f\}$. Hence, the solution of the Cauchy problem in terms of a Mittag-Leffler

function is given as

$$S_f(t) \geq S_f(0)E_\alpha[-(\hat{\lambda}_f + \mu)t^\alpha]. \quad (5.12)$$

Furthermore, we note that for a special case when $\alpha = 1$, the equation (5.12) reduces to

$$\begin{aligned} S_f(t) &\geq S_f(0)E_1[-(\hat{\lambda}_f + \mu)t^1], \\ &\geq S_f(0)\exp\{-(\hat{\lambda}_f + \mu)t\} > 0. \end{aligned} \quad (5.13)$$

Similarly, for the rest of the state variables, we apply the same approach to show that the solutions of their corresponding Cauchy problems are given by the following equations

$$\begin{cases} R_m(t) &\geq R_m(0)E_\alpha[-Q_2t^\alpha], R_m(0) \in \mathbb{R}, \\ I_f(t) &\geq I_f(0)E_\alpha[-Q_3t^\alpha], I_f(0) \in \mathbb{R}, \\ R_f(t) &\geq R_f(0)E_\alpha[-Q_4t^\alpha], R_f(0) \in \mathbb{R}. \end{cases} \quad (5.14)$$

Therefore, from this proof we observed that the solutions of the system of equations (5.1a) - (5.1f) are non-negative for all non negative initial conditions. This completes the proof. $\square$

Proposition 5.2.1. *Given that all the parameters $\rho, \mu, \beta, \eta_1, \eta_2, \sigma_1, \sigma_2, \omega_1, \omega_2, \delta_1$ and δ_2 as well as all the state variables are non negative, then the domain of biological significance Ω defined by*

$$\Omega = \{(S_m(t), I_m(t), R_m(t), S_f(t), I_f(t), R_f(t)) \in \mathbb{R}_+^6 \mid 0 \leq t \leq 1\},$$

with initial conditions $S_m^0 > 0, I_m^0 \geq 0, R_m^0 \geq 0, S_f^0 > 0, I_f^0 \geq 0, R_f^0 \geq 0$ is positively invariant and attracting with respect to the system of equations (5.1a) - (5.1f) for all $t > 0$.

Proof. By considering the general equation for the total devil population, we have

$$D_t^\alpha N = \mu - \mu N - \delta_1 I_m - \delta_2 I_f, \quad (5.15)$$

which can be reduced to the inequality and a Cauchy problem as

$$D_t^\alpha N \leq \mu - \mu N, N(0) = N_0 \in \mathbb{R}^+.$$

The solution to the resulting Cauchy problem in terms of a Mittag-Leffler function is given as

$$N(t) \leq 1 + (N_0 - 1)E_\alpha(-\mu)t^\alpha. \quad (5.16)$$

In addition, we note that for a special case when $\alpha = 1$, the solution (5.16) reduces to

$$N(t) \leq 1 + (N_0 - 1)e^{-(\mu t)}, \quad (5.17)$$

from which we obtain

$$\lim_{t \rightarrow \infty} N(t) \leq \lim_{t \rightarrow \infty} [1 + (N_0 - 1)e^{-(\mu t)}] \leq 1. \quad (5.18)$$

Thus, the feasible region Ω is positively invariant under the flow induced by the system of equations (5.1a) - (5.1f) which makes it feasible to study the dynamics of the model in Ω . $\square$

5.3 Numerical simulations

Several numerical techniques have been proposed to solve fractional differential equations. These include the Adomian Decomposition Method, Homotopy Decomposition Method, Adams-Bashforth-Moulton Method, among others. Here, we use the Adams-Bashforth-Moulton method to provide an approximate solution for the DFTD dynamic model based on the Predator-Corrector algorithm. We set $h = \frac{T}{N}$, $t_n = nh$ and $n = 0, 1, 2, \dots, N \in \mathbb{Z}^+$ [47, 48]. Then DFTD model system can be discretized as follows.

The corrector values

$$\begin{aligned} S_{m_{n+1}} &= S_{m_0} + \frac{h^\alpha}{\Gamma(\alpha + 2)} \left(\rho\mu + \omega_1 R_{m_{n+1}}^p - \beta(I_{m_{n+1}}^p + \eta_1 I_{f_{n+1}}^p) S_{m_{n+1}}^p - \mu S_{m_{n+1}}^p \right) \\ &\quad + \frac{h^\alpha}{\Gamma(\alpha + 2)} \sum_{j=0}^n x_{j,n+1} \left(\rho\mu + \omega_1 R_{m_j} - \beta(I_{m_j} + \eta_1 I_{f_j}) S_{m_j} - \mu S_{m_j} \right), \\ I_{m_{n+1}} &= I_{m_0} + \frac{h^\alpha}{\Gamma(\alpha + 2)} \left(\beta(I_{m_{n+1}}^p + \eta_1 I_{f_{n+1}}^p) S_{m_{n+1}}^p - Q_1 I_{m_{n+1}}^p \right) \\ &\quad + \frac{h^\alpha}{\Gamma(\alpha + 2)} \sum_{j=0}^n x_{j,n+1} \left(\beta(I_{m_j} + \eta_1 I_{f_j}) S_{m_j} - Q_1 I_{m_j} \right), \\ R_{m_{n+1}} &= R_{m_0} + \frac{h^\alpha}{\Gamma(\alpha + 2)} \left(\sigma_1 I_{m_{n+1}}^p - Q_2 R_{m_{n+1}}^p \right) + \frac{h^\alpha}{\Gamma(\alpha + 2)} \sum_{j=0}^n x_{j,n+1} \left(\sigma_1 I_{m_j} - Q_2 R_{m_j} \right), \\ S_{f_{n+1}} &= S_{f_0} + \frac{h^\alpha}{\Gamma(\alpha + 2)} \left((1 - \rho)\mu + \omega_2 R_{f_{n+1}}^p - \beta(I_{f_{n+1}}^p + \eta_2 I_{m_{n+1}}^p) S_{f_{n+1}}^p - \mu S_{f_{n+1}}^p \right) \\ &\quad + \frac{h^\alpha}{\Gamma(\alpha + 2)} \sum_{j=0}^n x_{j,n+1} \left((1 - \rho)\mu + \omega_2 R_{f_j} - \beta(I_{f_j} + \eta_2 I_{m_j}) S_{f_j} - \mu S_{f_j} \right), \\ I_{f_{n+1}} &= I_{f_0} + \frac{h^\alpha}{\Gamma(\alpha + 2)} \left(\beta(I_{f_{n+1}}^p + \eta_2 I_{m_{n+1}}^p) S_{f_{n+1}}^p - Q_3 I_{f_{n+1}}^p \right) \\ &\quad + \frac{h^\alpha}{\Gamma(\alpha + 2)} \sum_{j=0}^n x_{j,n+1} \left(\beta(I_{f_j} + \eta_2 I_{m_j}) S_{f_j} - Q_3 I_{f_j} \right), \\ R_{f_{n+1}} &= R_{f_0} + \frac{h^\alpha}{\Gamma(\alpha + 2)} \left(\sigma_2 I_{f_{n+1}}^p - Q_4 R_{f_{n+1}}^p \right) + \frac{h^\alpha}{\Gamma(\alpha + 2)} \sum_{j=0}^n x_{j,n+1} \left(\sigma_2 I_{f_j} - Q_4 R_{f_j} \right). \end{aligned} \quad (5.19)$$

where

$$\begin{aligned}
 S_{m_{n+1}}^p &= S_{m_0} + \frac{1}{\Gamma(\alpha)} \sum_{j=0}^n y_{j,n+1} \left(\rho\mu + \omega_1 R_{m_j} - \beta(I_{m_j} + \eta_1 I_{f_j}) S_{m_j} - \mu S_{m_j} \right), \\
 I_{m_{n+1}}^p &= I_{m_0} + \frac{1}{\Gamma(\alpha)} \sum_{j=0}^n y_{j,n+1} \left(\beta(I_{m_j} + \eta_1 I_{f_j}) S_{m_j} - Q_1 I_{m_j} \right), \\
 R_{m_{n+1}}^p &= R_{m_0} + \frac{1}{\Gamma(\alpha)} \sum_{j=0}^n y_{j,n+1} \left(\sigma_1 I_{m_j} - Q_2 R_{m_j} \right), \\
 S_{f_{n+1}}^p &= S_{f_0} + \frac{1}{\Gamma(\alpha)} \sum_{j=0}^n y_{j,n+1} \left(\rho\mu + \omega_2 R_{f_j} - \beta(I_{f_j} + \eta_2 I_{m_j}) S_{f_j} - \mu S_{f_j} \right), \\
 I_{f_{n+1}}^p &= I_{f_0} + \frac{1}{\Gamma(\alpha)} \sum_{j=0}^n y_{j,n+1} \left(\beta(I_{f_j} + \eta_2 I_{m_j}) S_{f_j} - Q_3 I_{m_j} \right), \\
 R_{f_{n+1}}^p &= R_{f_0} + \frac{1}{\Gamma(\alpha)} \sum_{j=0}^n y_{j,n+1} \left(\sigma_2 I_{m_j} - Q_4 R_{f_j} \right)
 \end{aligned} \tag{5.20}$$

are the predictor values, such that

$$x_{j,n+1} = \begin{cases} n^{\alpha+1} - (n - \alpha)(n + 1), & \text{if } j = 0, \\ (n - j + 2)^{\alpha+1} + (n - j)^{\alpha+1} - 2(n - j + 1)^{\alpha+1} & \text{if } 1 \leq j \leq n, \\ 1 & \text{if } j = n + 1 \end{cases} \tag{5.21}$$

and

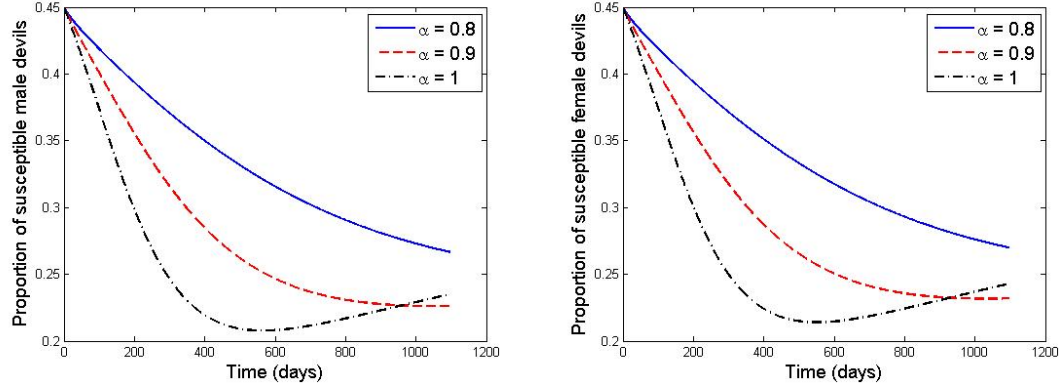
$$y_{j,n+1} = \frac{h^\alpha}{\alpha} ((n - j + 1)^\alpha - (n - j)^\alpha), \quad 0 \leq j \leq n.$$

where p is the order of accuracy such that $p = \min(2, 1 + \alpha)$ [48].

Numerical results

We conducted numerical simulations of the DFTD model system (5.1a) - (5.1f) to determine the long term dynamics of the devil population. We used parameters that are displayed in Table 3.3 of Chapter 3 to conduct the simulations with initial conditions $(S_m, I_m, R_m, S_f, I_f, R_f) = (0.45, 0.045, 0.005, 0.45, 0.045, 0.005)$. The simulations were also conducted taking the values of the fractional-orders in the interval $\alpha \in [0.8, 1]$. We presented the dynamic of the susceptible, infected and recovered populations for both male and female devils in Figures 5.1 - 5.3. The simulations in each figure employed the order α value of 0.8 (blue-dash line), 0.9 (black-dash line) and 1 (red-solid line). In addition, we presented Figures 5.4- 5.13 indicating variations of contact rate, β , disease induced death rate for male and female devils, δ_1 and δ_2 , male and female devils recovery rate, σ_1 and σ_2 , for different values of order α (0.8,

0.9 and 1.0) in the infected populations of male and female devils.



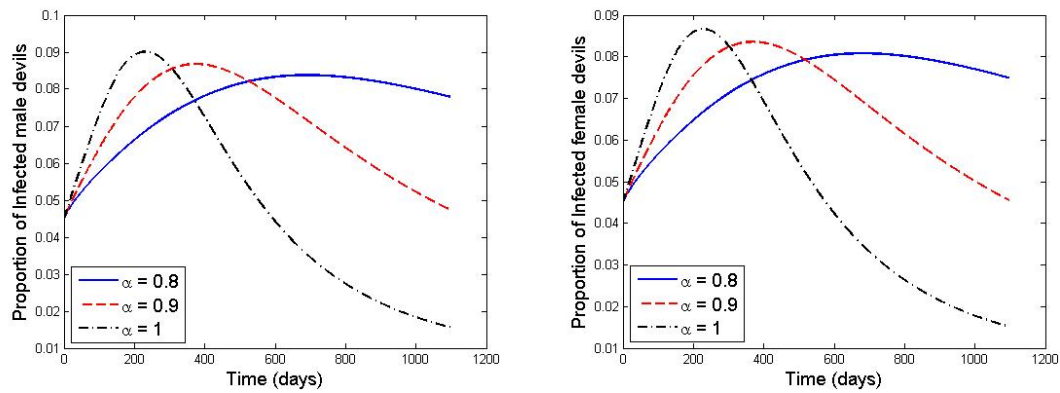
(a) Variation of α with the proportion of susceptible males (b) Variation of α with the proportion of susceptible females

Figure 5.1: 5.1(a) Shows the variation of the proportion of susceptible male Devils with α , 5.1(b) the variation of the proportion of susceptible female Devils with α .

From Figure 5.1, the results indicate that, as the fractional-order α is increased, the faster the populations of the susceptible male and female devils is reduced in a short period of time. The lower orders α are characterised by high memory effect and high proportions of both the susceptible male and female devils in the population as compared to higher orders α . Higher orders of the fractional derivative (α) are characterised by near extinction in the populations of male and female devils. The increase in the susceptible devil populations is due new births and waning of acquired immunity for the recovered devils. This is the case in both the female and male devil populations. Moreover, the results show that, the male and female devil populations are more likely to be threatened the same by the disease.

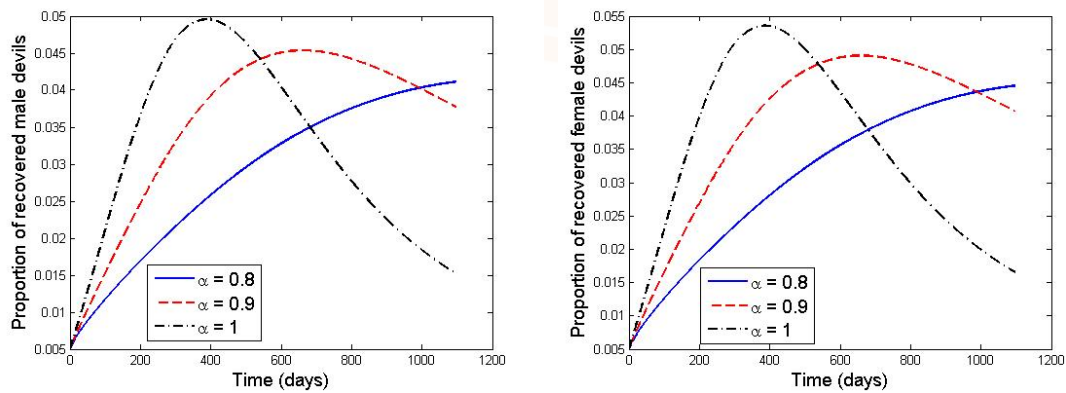
As the fractional-order α is increased, the infection reaches the maximum population in few days followed by a quick decline due to self regulation. From Figure 5.2, it was observed that the higher the order α value, the faster the convergence speed and the smaller the fractional order value α the slower the convergence speed for all the devil populations. Therefore, higher fractional-orders are characterised by high peak values reached in fewer days followed by a decline. When the fractional-orders α decreases from 1, the memory effect of DFTD system increases and the infection stays longer in the population. As fractional-orders are reduced towards zero, the peak values of the proportions of infected devils are also reduced in both the female and male devils. However, the long-term proportions are higher when compared to higher fractional-order values.

From Figure 5.3, the results show that when the fractional-orders are increased, the faster



(a) Variation of α with the proportion of infected males (b) Variation of α with the proportion of infected females

Figure 5.2: 5.2(a) Shows the variation of the proportion of infected male Devils with α , 5.2(b) the variation of the proportion of infected female Devils with α .



(a) Variation of α with the proportion of recovered males (b) Variation of α with the proportion of recovered females

Figure 5.3: 5.3(a) Shows the variation of the proportion of recovered male Devils with α , 5.3(b) the variation of the proportion of recovered female Devils with α .

the peak values are reached in early stages followed by a decline. As the fractional-orders α are reduced, the number of recoveries is reduced in both female and male devil populations. We also varied the parameters with the different values of the fractional-order α values on the infected population of male and female devils to determine how the system behaves.

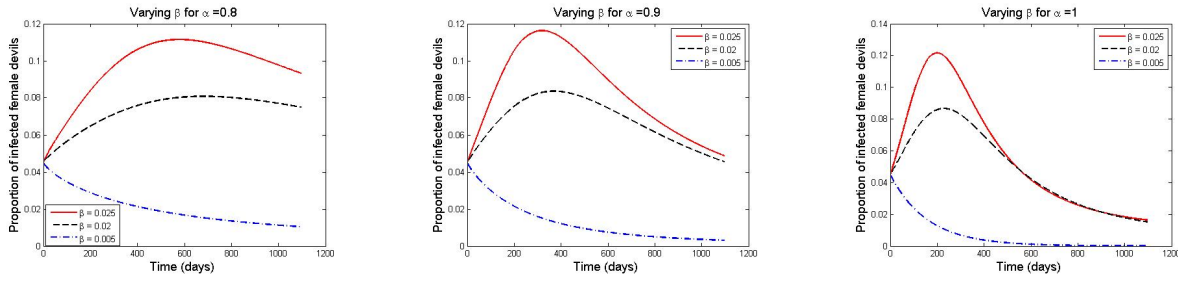


Figure 5.4: Varying β for $\alpha=0.8, 0.9$ and 1 on the Infected female devil proportion.

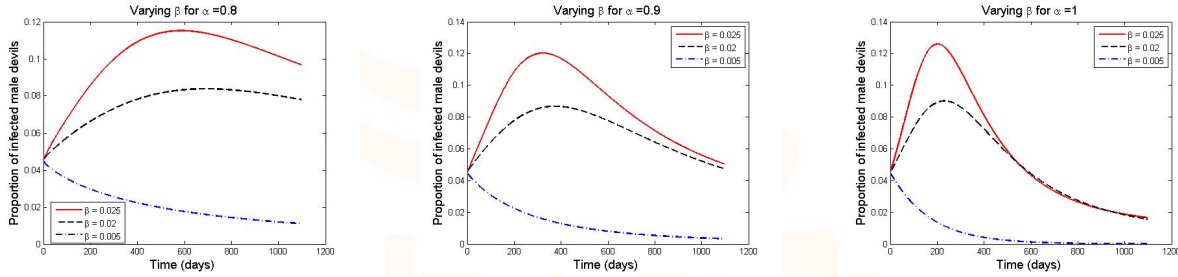


Figure 5.5: Varying β for $\alpha=0.8, 0.9$ and 1 on the Infected male devil proportion.

From Figure 5.4 and 5.5, we observed that, the higher the contact rate the more severe the infection gets in both populations of male and female devils for all the different values of the fractional-orders α . We also observed that, the higher the fractional-orders and the contact rate, the faster the disease spreads in both populations. We also observed that there is an average of more than 60% decrease of the infection from $\beta = 0.02$ to 0.005 on all the fractional-orders from both the female and male devil populations. Moreover, higher fractional-orders predict near extinction in later stages. As the fractional-orders are reduced from 1, the model predicts that the infection will stay long in the populations but the devils will not reach extinction.

Figures 5.6 and 5.7, showed that, higher recovery rates for male devils, σ_1 , in both the female and male devil populations are characterised by low proportions of both the infected female and male devils. Moreover, higher fractional-orders α and the recovery rates for male devils are characterised by lower infections in the populations due to increased recovery.

Figures 5.8 and 5.9, show that, higher recovery rates for female devils, σ_2 , are characterised by low proportions of both the infected female and male devils. In addition, the results

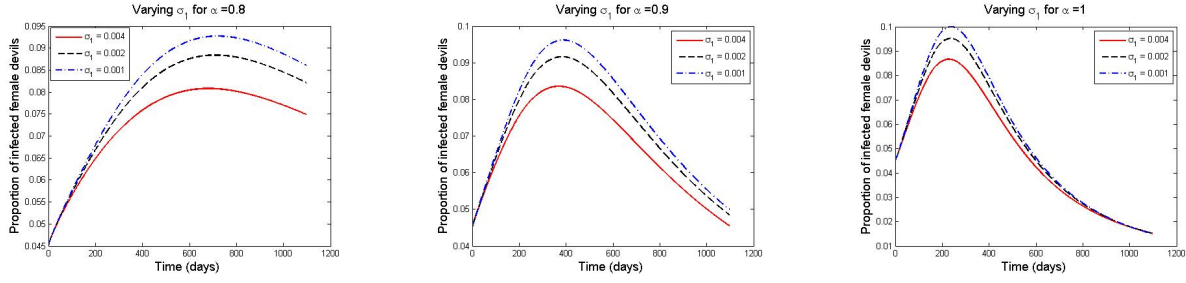


Figure 5.6: Varying σ_1 for $\alpha=0.8, 0.9$ and 1 on the Infected female devil proportion.

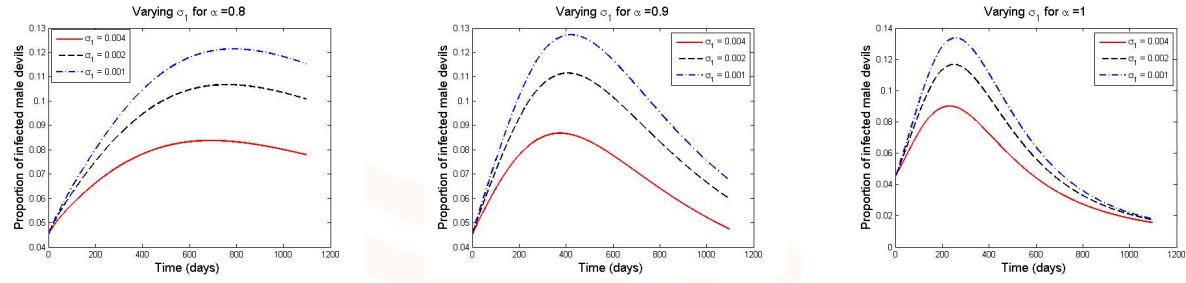


Figure 5.7: Varying σ_1 for $\alpha=0.8, 0.9$ and 1 on the Infected male devil proportion.

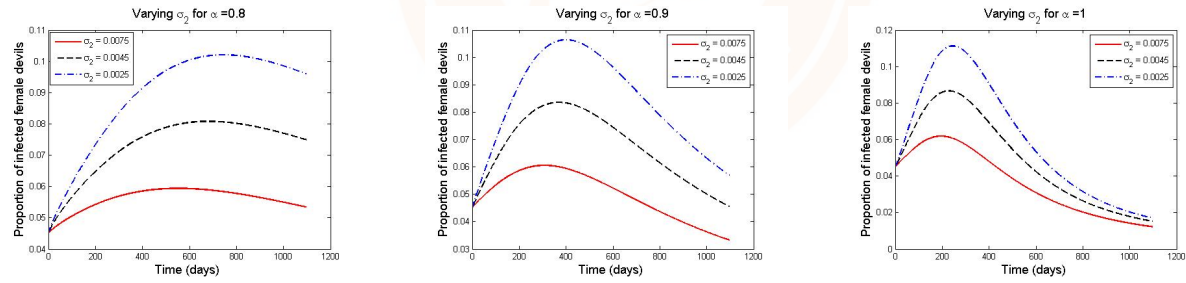


Figure 5.8: Varying σ_2 for $\alpha=0.8, 0.9$ and 1 on the Infected female devil proportion.

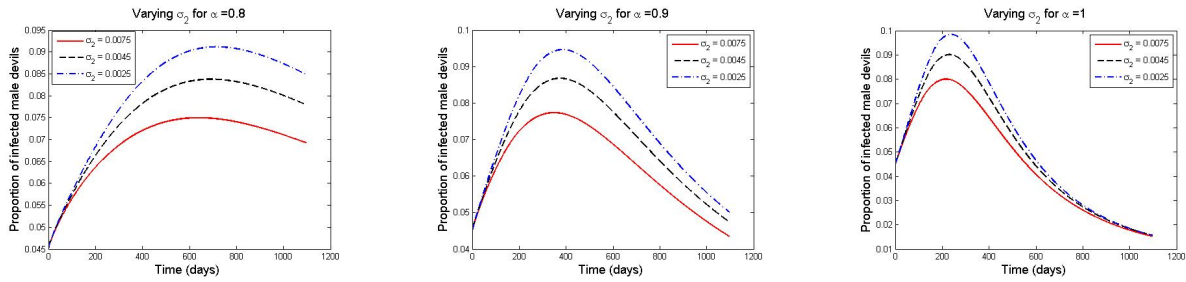


Figure 5.9: Varying σ_2 for $\alpha=0.8, 0.9$ and 1 on the Infected male devil proportion.

indicate that, high fractional-orders are associated with high infection in the female and male populations as compared to low fractional-orders. Moreover, the higher fractional-orders are associated with higher peak values of recoveries for all recoveries rates.

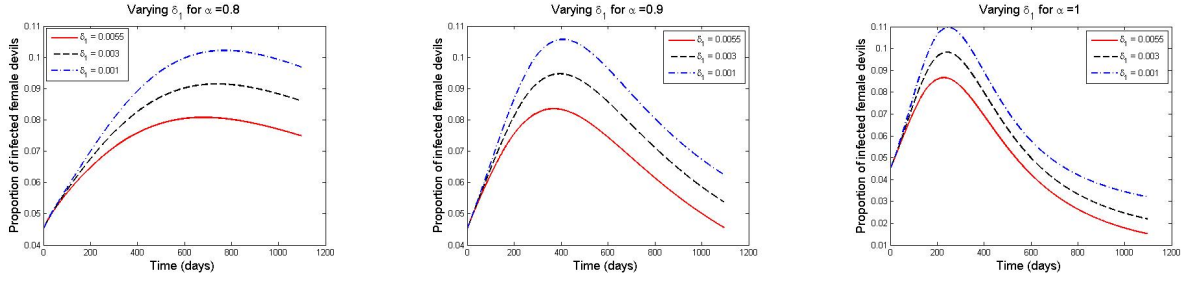


Figure 5.10: Varying δ_1 for $\alpha=0.8, 0.9$ and 1 on the Infected female devil proportion.

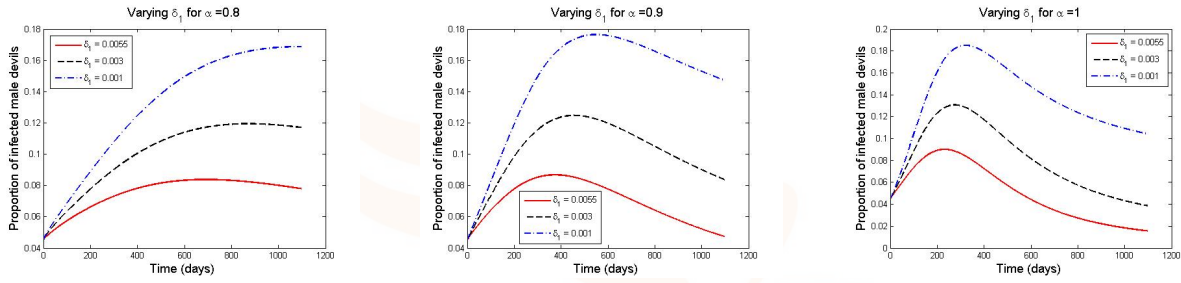


Figure 5.11: Varying δ_1 for $\alpha=0.8, 0.9$ and 1 on the Infected male devil proportion.

High disease induced death rate for male devils, δ_1 , is characterised by a depletion of the population of the female and male devils as shown in Figure 5.10 and 5.11. It was also observed that, high fractional-orders are associated with high infection values in the short term but low long-term infected cases. As the fractional-order values are reduced from 1, the longer the disease persist in the infected male and female devil populations.

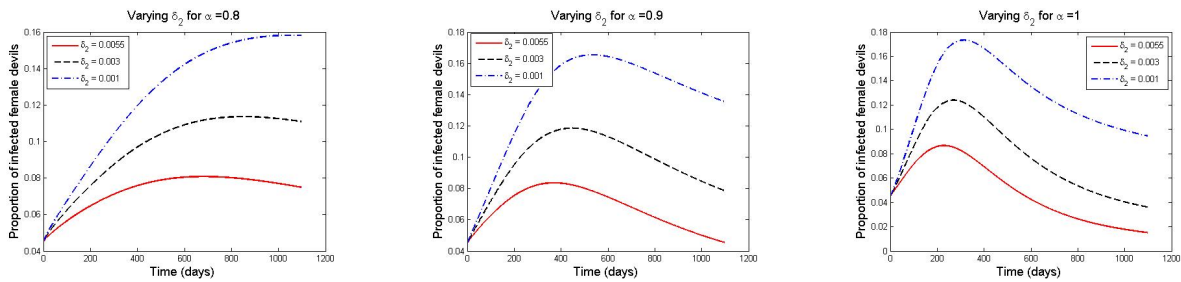


Figure 5.12: Varying δ_2 for $\alpha=0.8, 0.9$ and 1 on the Infected female devil proportion.

From Figure 5.12 and 5.13, we observe that, when the disease induced death rate for female devils, δ_2 , are high the infection is reduced. We also observed that, higher fractional-orders and increased disease induced death rate for female devils are characterised by higher numbers of devils in the infected populations. Moreover, comparing the Figures 5.4 - 5.13, it is

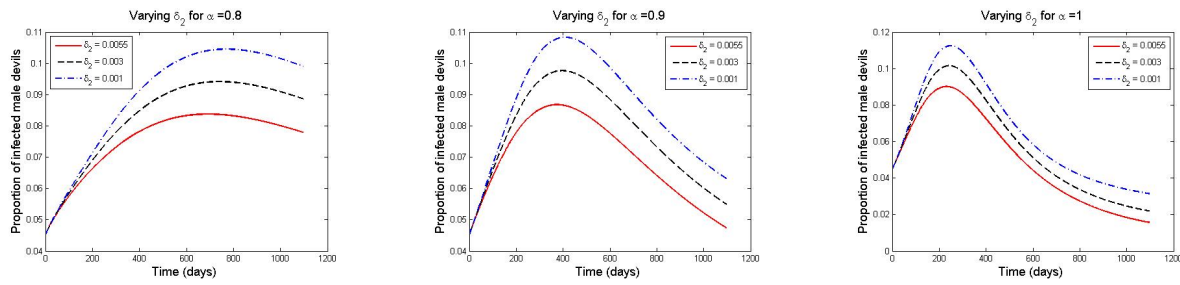


Figure 5.13: Varying δ_2 for $\alpha=0.8, 0.9$ and 1 on the Infected male devil proportion.

observed that as the fractional-orders are reduced, the model predicts higher peak values in the initial stages of the disease for values of α and higher long-term values of the infected for lower values of α .



Chapter 6

Conclusion and Discussion

DFTD is an infection transmitted from infected to healthy devil via biting which occurs during feeding and mating. A DFTD model has been developed and analysed to study the significance of feeding and mating related contact, optimal control and fractional order change on the long term dynamics of disease among devils. From Chapter 3, the basic reproduction number, R_0 , was computed and it was used to determine the local and global stability of the disease free equilibrium (DFE), as well as existence of the endemic equilibrium. The DFE globally asymptotically stable when $R_0 < 1$. Sensitivity analysis was done using the LHS. From the sensitivity analysis results, we observed that, the spread of the disease through feeding related contact in the population of devils was the most significant while the spread of the disease through mating related contact was not significant. When contact in the population is increased, the reproduction number also increases, therefore, it is plausible to isolate healthy devils to prevent contact with infected ones. The tumour disease induced death rate for both female and male devils reduce the reproduction number when increased. Therefore, there could be need to implement culling of the infected devils so as to minimise the infection in the population. In addition, we observed that the recovery rate for both female and male devils can reduce the reproduction number to below 1 when increased. Hence, the disease can be contained. Although mating related contact was not significant, it may still produce some changes in the disease burden for the devil population. The devils are believed to mate during a particular season. Thus, mating has a less effect on the reproduction number due to less relative transmission as compared to feeding related contact that occurs during the whole year. We also observed that there is a no difference for the parameters σ_1 , σ_1 , δ_1 and δ_2 with the parameter β (contact rate) from the PRCC pairwise comparisons. From the numerical results, we observed that, the higher the contact rate, the higher and peak of the infection in the devil population. The numerical results show also that there is

less effect on the transmission rate through mating related contact from female to male or male to female devils in the population.

We employed an optimal control model for DFTD transmission in Chapter 4 to investigate the impact of using the control measures/strategies to reduce the infection in the population of devils. The control strategies include isolation, vaccination and culling. The basic reproduction number, R_0 , was computed following the assumption that the control values are constant. We used an objective/cost functional to minimise the numbers of infected devils along with the cost associated for saving the Tasmanian devils. We used a quadratic objective function since the intervention controls are non linear. From the numerical results, we observed that, when all the controls are implemented effectively, the infection is reduced in the population. Therefore, the devils will not get to extinction in the long term which is an advantage for the ecosystem. In the presence of controls, the uninfected devils are isolated from the infected devils. This helps to reduce contact with the infected devils in the female and male susceptible populations, and also reduce the transmission of the infection. In the presence of controls, the population of female and male susceptible devils is less affected. However, due to the absence of controls, the susceptible devil populations can be depleted considerably. In the presence of controls, culling and vaccination are implemented in the infected female and male populations. We observed that the infection is reduced if the controls are efficient. Although the infection remains in the population, we observed that a lower number of devils are affected leading to lower numbers of recoveries. Therefore, culling the most affected devils, isolation of uninfected devils from infected ones could be advantageous in minimising the transmission rate of the infection from the infected to the healthy devils in the population.

More still, from Chapter 5, a DFTD model from Chapter 3 was investigated introducing a fractional-order generalisation of an integer-order model. We proved the positivity and boundedness of the solutions using Mittag-Leffler functions. We performed the numerical simulations and results showed that the larger the order α value, the faster the convergence speed compared to the smaller value of order α . The results show that from the infected populations of both female and male devils, there is an explosive outbreak during the early days followed by a decline as a result of self regulation and or application of treatments. As the fractional-order is reduced from one, the number of recoveries are reduced in the populations. High fractional-orders are associated with higher number of recoveries. We note that the model assumes that recovered devils become susceptible again once the acquired immunity wanes. The infection in both populations of female and male devils is relatively the same. From the devil populations, it was observed that when the fractional-orders are

reduced from one, the model predicts higher long-term numbers of infected devils but lower peak values. The results also provides the effect of contact rate on the infected devils. It was observed that the higher the fractional-orders and the contact rate, β , the faster the disease spread in the populations within short period. High contact rate can lead to near extinction of the devils. Therefore, there is need for certain measures to be practised such as isolation of uninfected/healthy devils to reduce contact with the infected devils. The results also provide more insight of disease induced death for both female and male devils. High fractional-orders and the disease induced death rates are characterised by lower infected cases in the long-term. Therefore, practising culling would help reduce transmission of the infection. In general, the application of control measures such as culling, isolation and vaccination would be highly recommended to minimise the infection so as to avoid extinction of devils.

This work provides dynamical models that can be used to understand the transmission dynamics in the long term dynamics of DFTD. This will help to design or come up with proper control methods of the disease so as to reduce the mortality rate of devils in the endemic population. In addition, information about the advantage of practising control strategies to reduce high mortality and extinction of devils in the wild population is provided. Our research only considered the proportions of devil population compared to the exact numbers in population since the model is non-dimensionalised. Moreover, lack of numerical data for conducting model validation was also a challenge. Hence, there is need for carrying out more researches related to the biology of Devil Facial Tumour Disease.

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