UNIVERSIDAD POLITÉCNICA DE VALENCIA

Departamento de Matemáticas Aplicadas
Instituto de Matemática Multidisciplinar

Mathematical modelling of virus RSV: Qualitative properties, numerical solutions and validation for the case of the region of Valencia

PhD THESIS

Presented by: **Abraham Jose Arenas Tawil**

Advisers: **PhD. Lucas Antonio Jódar Sánchez**
PhD. Rafael Jacinto Villanueva Micó

Valencia, May 2009

Lucas Antonio Jódar Sánchez and Rafael Jacinto Villanueva Micó, professors at the Valencia Polytechnic University,

Certify that the present thesis, *Mathematical modelling of virus RSV: Qualitative properties, numerical solutions and validation for the case of the region of Valencia* has been directed under our supervision in the Department of Applied Mathematics of the Valencia Polytechnic University by Abraham Jose Arenas Tawil and makes up him thesis to obtain the doctorate in Applied Mathematics.

As stated in the report, in compliance with the current legislation, we authorize the presentation of the above Ph.D thesis before the doctoral commission of the Valencia Polytechnic University, signing the present certificate

Valencia, May 2009

Lucas Antonio Jódar Sánchez   Rafael Jacinto Villanueva Micó

"... que se él fuera de su consejo al tiempo de la
general criación del mundo, i de lo que en él se
encierra, i se hallá ra con él, se huvieran producido
i formado algunas cosas mejor que fueran hechas,
i otras ni se hicieran, u se enmendaran i corrigieran."

Alphonso X (Alphonso the Wise), 1221–1284
King of Castile and Leon (attributed).

To my parents
Jose Maria, for your stoicism
Margarita Rosa for your support
and as example of breaking to my
daughters Vanessa Margarita
and Vanessa Inés

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Abstract

The primary purpose of this report is to model the behavior of seasonal diseases by systems of differential equations. It also deals with the study of the dynamic properties, such as positivity, periodicity and stability, of the analytical solutions and with the construction of numerical schemes for the calculation of approximate solutions of the systems of first order nonlinear differential equations, which model the behavior of seasonal infectious diseases such as the transmission of the Respiratory syncytial virus RSV.

Two mathematical models of seasonal diseases are generalized and we show that solutions are periodic using a Jean Mawhin's Theorem of Coincidence. To corroborate the analytical results, numerical schemes are developed using the non-standard finite difference techniques developed by Ronald Mickens and also by the differential transformation method, which allow us to reproduce the dynamic behavior of the analytical solutions, such as positivity and periodicity.

Finally, numerical simulations are performed using the implemented schemes with parameters derived from clinical data of the Region of Valencia in persons infected with the virus RSV. These results are compared with those produced using the methods of Euler, Runge-Kutta and the routine of ODE45 of Matlab. The new methods ensure better approximations using step sizes larger than those normally used by traditional schemes.

Resumen

El objetivo de esta memoria se centra en primer lugar en la modelización del comportamiento de enfermedades estacionales mediante sistemas de ecuaciones diferenciales y en el estudio de las propiedades dinámicas tales como positividad, periocidad, estabilidad de las soluciones analíticas y la construción de esquemas numéricos para las aproximaciones de las soluciones numéricas de sistemas de ecuaciones diferenciales de primer orden no lineales, los cuales modelan el comportamiento de enfermedades infecciosas estacionales tales como la transmisión del virus Respiratory Syncytial Virus *RSV*.

Se generalizan dos modelos matemáticos de enfermedades estacionales y se demuestran que tienen soluciones periódicas usando un Teorema de Coincidencia de Jean Mawhin. Para corroborar los resultados analíticos, se desarrollan esquemas numéricos usando las técnicas de diferencias finitas no estándar desarrolladas por Ronald Michens y el método de la transformada diferencial, los cuales permiten reproducir el comportamiento dinámico de las soluciones analíticas, tales como positividad y periocidad.

Finalmente, las simulaciones numéricas se realizan usando los esquemas implementados y parámetros deducidos de datos clínicos de la Región de Valencia de personas infectadas con el virus RSV. Se confrontan con las que arrojan los métodos de Euler, Runge Kutta y la rutina de ODE45 de Matlab, verificándose mejores aproximaciones para tamaños de paso mayor

a los que usan normalmente estos esquemas tradicionales.

Resum

L'objetiu d'esta memòria és l'estudi de les propietats dinàmiques, com la periodicitat, la positivitat o l'estabilitat de les solucions analíques i la construcció d'esquemes numèriques per a les aproximacions de les solucions numèriques de sistemes d'equacions diferencials de primer ordre no linials, que modelen el comportament de enfermetats infeccioses estacionals con és la transmissió del virus respiratori Sincitial (VRS).

Es generalitzen dos models matemàtics de enfermetats estacionals i es demostra que tenen solucions periòdiques utilitzant un Teorema de Coincidència de Jean Mawhin. Per a comprovar els resultats analitics, es desentrollen esquemes numèrics utilitzant les tècniques de diferències finites no-estàndar desentrollades per Ronald Michens i el mètode de la transformada diferencial, els quals permeten reproducir el comportament dinàmic de les solucions analítiques, tals com positivitat i periodicitat.

Finalment, les simulaciones numèriques es fan utilitzant els esquemes implementats i paràmetres deduits de dades clíniques de la regió de Valéncia de persones infectades amb el virus VRS. Estes es comparen amb les que donen els métodes d'Euler, Runge-Kutta i la rutina ODE45 de Matlab, verficant-se millors aproximacions per a tamanys de pas majors que els que utilitzen normalment els esquemes tradicionals.

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Basic notation

$\mathbb{R}$	Set of real numbers
$\mathbb{C}$	Set of real complex
$\mathbb{R}^n = \Big\{(x_1, ..., x_n)\Big\}$	$x_i \in \mathbb{R}$ for all $i = 1, ..., n$
$\mathbb{R}_+$	Set of positive real numbers
$\mathbb{R}_-$	Set of negative real numbers
$\mathbb{R}^n_+ = \Big\{(x_1, ..., x_n)\Big\}$	$x_i \in \mathbb{R}_+$ for all $i = 1, ..., n$
$\mathbb{R}^n_- = \Big\{(x_1, ..., x_n)\Big\}$	$x_i \in \mathbb{R}^-$ for all $i = 1, ..., n$
$B(x_0, R)$	Set $\Big\{x \in \mathbb{R}^n / \\|x - x_0\\| < R\Big\}$
$\overline{B(x_0, R)}$	Set $\Big\{x \in \mathbb{R}^n / \\|x - x_0\\| \leq R\Big\}$
$\partial B(x_0, R)$	Set $\Big\{x \in \mathbb{R}^n / \\|x - x_0\\| = R\Big\}$
$:=$	Defined as
$]a, b[$	Open interval $a < t < b$ in $\mathbb{R}$
$[a, b]$	Closed interval $a \leq t \leq b$ in $\mathbb{R}$
$C^k(I)$	Set $\Big\{f : I \subseteq \mathbb{R} \longrightarrow \mathbb{R} / \frac{d^i f(x)}{dx^i}$ exists and are continuous, for $i = 0, 1, ..., k\Big\}$
$C^k(\mathbb{R}, \mathbb{R}^n)$	Set $\Big\{f : \mathbb{R} \longrightarrow \mathbb{R}^n / f(t) = (f_1(t), ..., f_n(t))$ $f_i(t) \in C^k(\mathbb{R})$ for all $i = 0, 1, ..., k\Big\}$
$f^u = \sup\limits_{t \in [0, \infty[} f(t)$	$f : [0, \infty[\longrightarrow \mathbb{R}$ is a bounded continuous function
$f^l = \inf\limits_{t \in [0, \infty[} f(t)$	$f : [0, \infty[\longrightarrow \mathbb{R}$ is a bounded continuous function

Introduction

Seasonal infections of humans range from childhood diseases as measles, diphtheria and chickenpox, to faecal–oral infections, such as cholera and rotavirus as Respiratory syncytial virus (RSV), vector-borne diseases including malaria and even sexually transmitted gonorrhoea, see Grassly and Fraser (2006). In modeling of transmission of seasonal diseases, nonlinear systems of ordinary differential equations have been used with a coefficient given by a periodic continuous functions $\beta(t)$ (called sometimes seasonally-forced function) that incorporates the seasonality of the spread in the environment, see Diallo and Koné (2007), Anderson and May (1991), Keeling et al. (2001), White et al. (2005), White et al. (2007), Weber et al. (2001), Moneim and Greenhalgh (2005), Greenhalgh and Moneim (2003). Many authors take, as an example of seasonally-forced function, the expression $\beta(t) = b_0(1 + b_1 \cos(2\pi(t + \varphi))$, where $b_0 > 0$ is the baseline transmission parameter, $0 < b_1 \leq 1$ measures the amplitude of the seasonal variation in transmission and $0 \leq \varphi \leq 1$ is the normalized phase angle. For other examples of this type of functions see Keeling et al. (2001), Earn et al. (2000), Weber et al. (2001).

Within this type of seasonal infectious diseases, we can highlight the importance of the transmission of RSV: it is the cause of acute respiratory infections, outbreaks occur each year and the virus is highly contagious and essentially all children become infected within the first 2 years of life, (Cane, 2001), (Hall, 1992), (Craighead, 2000), (Sorce, 2008), (Nokes, 2006). This type of respiratory virus is, among other things, the most important cause of morbidity, incomplete immunity and repeated infections (Power, 2008). A comprehensive reference of the *RSV* epidemiology from a clinical pathogenesis point of view is Craighead (2000). This virus is known since 1957, but only recently the adult pathology has been established and it is the cause of the 18% of the hospitalizations due to pneumonia in adults older than 65 (Hall, 1992).

Transmission of virus *RSV* is a seasonal epidemic with minor variations each year and coincides in time with other infections such as influenza or rotavirus, producing a high number of hospitalizations and, consequently, a saturation of the Public Health Systems. Illness begins most frequently with fever, runny nose, cough, and sometimes wheezing. During the first *RSV* infection, between 25% and 40% of infants and young children have signs or symptoms of bronchiolitis or pneumonia, and between 0.5% to 2% require hospitalization. Most children recover from illness in 8 to 15 days and the majority of children hospitalized for *RSV* infection are under 6 months of age. *RSV* also causes repeated infections throughout life, usually associated with moderate-to-severe cold-like symptoms; however, severe lower respiratory tract disease may occur at any age, especially among the elderly or among those with compromised cardiac, pulmonary, or immune systems (CDC, 2007). *RSV* is spread from respiratory secretions through close contact with infected persons or contact with contaminated surfaces or objects. Infection can occur when infectious material contacts the mucous membranes of the eyes, mouth, or nose, and possibly through the inhalation of droplets generated by a sneeze or cough. In temperate climates, *RSV* infections usually occur during annual community outbreaks, often lasting 4 to 6 months, during the late fall, winter, or early spring months. The timing and severity of outbreaks in a community vary from year to year.

RSV spreads efficiently among children during the annual outbreaks and most children have serologic evidence of *RSV* infection by 2 years of age

(CDC, 2007). In Spain, there are 15.000 – 20.000 attentions in medical primary services due to RSV each year. As a particular case, in the Spanish region of Valencia, 1.500 children require hospitalization each year due to bronchiolitis caused by RSV. This is an incidence of 400 cases each 100.000 children younger than a year, with 6 hospitalization days as the average Díez et al. (2006). Only in pediatric hospitalizations, the cost to the Public Health System is about 3.5 millions of euros per year. Therefore, the research in RSV and other viruses and the developing of strategies to control epidemics are very important.

Mathematical modeling has been revealed as a powerful tool to analyze the epidemiology of the infectious illness, to understand its behavior, to predict its impact and to find out how external factors change the impact. A classical technique for modeling infectious diseases in the population is to use systems of ordinary differential equations, describing the evolution of the number of individuals in the different subpopulations. In this sense, mathematical models using system of nonlinear ordinary differential equations of the first order for RSV have been developed in Weber et al. (2001), White et al. (2005), White et al. (2007), Arenas et al. (2009c). These papers interpret the pattern of seasonal epidemics of RSV disease observed in different countries and estimate the epidemic and eradication thresholds for the RSV infection. The presented models are fitted to clinical data to estimate some parameters, and the mentioned papers only present numerical simulations using the Matlab package with particular data. They do not study the behavior of analytical solutions.

In the available literature there are two research fields for studying system of ordinary differential equations system of the first order involving the dynamical behavior Hirsch et al. (2004). The first one is for the case when the system of nonlinear ordinary differential equations is autonomous, and then the study of the eigenvalues of the associated Jacobian of the linearized system about the equilibria points determines the behavior of the solutions in time and identifies the local stability. The second approach use Lyapunov's functions global stability can sometimes be shown (Aranda et al., 2008), (Jódar et al., 2009), (Zhang and Teng, 2008). Moreover, infections disease models with pulse vaccination strategies and distributed time delay have been studied in Meng and Chen (2008), Gao et al. (2007) and Jianga and Wei (2008) where sufficient conditions for global asymptotic stability, bifurcations and permanence in the solutions are presented.

Now, if the system of nonlinear ordinary differential equations of the first order is non-autonomous, the above theory mentioned can not be applied because the equilibrium points depend on the time. The seasonal model with periodic parameters is non-autonomous. A very important problem in the study of infectious disease models with the population in a periodic environment is that of the global existence of positive periodic solutions, which plays a similar role as a globally stable equilibrium does in the autonomous case (Xu et al., 2004), (Chen, 2003), (Hui and Zhu, 2005). Hence, it is reasonable to seek conditions under which two generalized models for transmission of seasonal diseases would have a positive periodic solution. Thus, we conjecture that the analytical solutions of the models presented in (Weber et al., 2001), White et al. (2007), that model the behavior of the transmission of RSV, should be periodical. To do this, we use a Theorem of Continuation by Jean Mawhin, which, under conditions on the rate transmission $\beta(t)$ and the others parameters of the model, ensures the existence of positive periodic solutions.

In order to support our previous analytical results, we develop numerical schemes. These schemes are constructed using the nonstandard finite difference techniques developed by Ronald Mickens (see Mickens (1994), Mickens (2002)). With the differential transformation method (DTM) we approximate the solutions in a sequence of time intervals. In order to illustrate the accuracy of the schemes, the calculated results are compared with those produced by traditional schemes such as the fourth-order Runge-

Kutta method, the forward Euler method and the adaptive step Runge-Kutta method implemented in the Matlab package ODE45.

This thesis is organized as follows:

Chapter 1 is concerned with a general introduction to continuous, differentiable and integrable functions. It presents the construction of the Brouwer Degree. By means of the definitions of Fredholm mappings, it introduces coincidence degree theory and a Jean Mawhin's continuation theorem. In summary, the goal of this chapter is to provide the reader an adequate framework and sufficient tools for reading this dissertation.

In chapter 2, we generalize an epidemic model $SIRS$ (Susceptibles, Infected, Recovered and Susceptibles) for simulating the transmission of seasonal diseases which uses, as a transmission rate, a periodic continuous function $\beta(t)$. Using a Jean Mawhin's continuation theorem, we show that the solution of this kind of models are periodic continuous and positive. Moreover, under appropriate hypothesis the proposed model has a unique positive periodic solution which is globally asymptotically stable. As a particular case, numerical simulations of the transmission of RSV in some countries are presented.

In chapter 3, we generalize a nested seasonal model and again we use a Jean Mawhin's continuation theorem. It is shown that the solutions of this model are periodic, continuous and positive. We give some numerical simulations of the transmission of RSV in the regions of Madrid and Sao Paulo.

In chapter 4, we propose a numerical scheme for the epidemic model $SIRS$ using the nonstandard finite difference techniques developed by Ronald Mickens, which, as can be seen in the numerical simulations, has solutions that retain the properties of the solutions of the continuous model. Examples using the parameters of the transmission of RSV are proposed.

Finally, in chapter 5, using differential transformation techniques, we design numerical schemes to solve numerically the models proposed in chapters 2 and 3. The numerical simulations are performed with parameters obtained from the Valencia region and from other countries.

Chapter 1

Preliminaries

In this chapter we provide a brief overview general to continuous and differentiable functions, it presents the construction of Brouwer degree and with the definitions of Fredholm mappings one introduces the coincidence degree theory and the Jean Mawhin's Continuation Theorem. The aim of this chapter is to provide the reader an adequate framework and sufficient tools for the reading of this dissertation, more information can be found in O'Regan et al. (2006), Gaines and Mawhin (1977), Dieudonne (1969), Ward (2008).

1.1 Normed spaces

In this section we give some definitions on normed spaces.

Definition 1.1.1 *A complex (real) normed space is a complex (real) vector space X together with a map* $: X \longrightarrow \mathbb{R}$, *called the norm and denoted by* $\|\cdot\|$, *such that*

1. $\|x\| \geq 0$, *for all* $x \in X$, *and* $\|x\| = 0$ *if and only if* $x = 0$.
2. $\|\alpha x\| = |\alpha|\|x\|$, *for all* $x \in X$ *and all* $\alpha \in \mathbb{C}$ *(or* $\mathbb{R}$*).*
3. $\|x + y\| \leq \|x\| + \|y\|$, *for all* $x, y \in X$.

Remark 1.1.2 *If in 1 we only require that $\|x\| \geq 0$, for all $x \in X$, then $\|\cdot\|$ is called a seminorm.*

Remark 1.1.3 *If X is a normed space with norm $\|\cdot\|$, it is straightforward to check that the formula $d(x, y) = \|x - y\|$, for $x, y \in X$, defines a metric d on X. Thus a normed space is naturally a metric space and all metric space concepts are meaningful. For example, convergence of sequences in X means convergence with respect to the above metric.*

Definition 1.1.4 *A complete normed space is called a Banach space.*

Thus, a normed space X is a Banach space if every Cauchy sequence in X converges (where X is endowed the metric space structure as outlined underlined above). One may consider real or complex Banach spaces depending, of course, on whether X is a real or complex linear space.

Definition 1.1.5 *Two norms $\|\cdot\|_a$ and $\|\cdot\|_b$ are equivalent if only if there are positive constants μ, μ' such that*

$$\mu\|x\|_a \leq \|x\|_b \leq \mu'\|x\|_a$$

for all $x \in X$.

Consequently of above definition, we have the following result

Proposition 1.1.6 *Let X a normed space of finite dimension. Then all norms are equivalent.*

1.2 Continuous and Differentiable Functions

Here, we introduce the elemental concepts of continuous and differentiable functions.

Definition 1.2.1 *Let $\Omega \subset \mathbb{R}^n$ be an open subset and $f : \Omega \longrightarrow \mathbb{R}$ a function. We say that f has a local maximum at a point $x_0 \in \Omega$ if there exists $\delta > 0$ such that $f(x) \leq f(x_0)$ for all $x \in \Omega$ with $\|x - x_0\| < \delta$. Local minima are defined likewise.*

Definition 1.2.2 *Let $\Omega \subset \mathbb{R}^n$ be an open subset. We recall that a function $f : \Omega \longrightarrow \mathbb{R}^n$ is differentiable at $x_0 \in \Omega$ if there is a matrix $f'(x_0)$ such that $f(x_0 + h) = f(x_0) + f'(x_0)h + o(h)$, where $x_0 + h \in \Omega$ and $\frac{\|o(h)\|}{\|h\|}$ tends to zero as $\|h\| \longrightarrow 0$.*

Definition 1.2.3 *If f is differentiable at $x_0 \in \Omega$, we call $J_f(x_0) = det f'(x_0)$ the Jacobian of f at x_0. If $J_f(x_0) = 0$, then x_0 is said to be a critical point of f and we use $S_f(\Omega) = \Big\{x \in \Omega : J_f(x) = 0\Big\}$ to denote the set of critical points of f, in Ω. If $f^{-1}(y) \cap S_f(\Omega) = \emptyset$, then y is said to be a regular value of f. Otherwise, y is said to be a singular value of f.*

1.3 Some properties of the Riemann integral

Some properties of the Riemann integral used in this work are take from Rudin (1976), Wade (2000). Let f be a real function on interval $I \subseteq \mathbb{R}$. If f is Riemann integrable on I, then $\int_I f(x)dx < \infty$, and we write $f \in \mathcal{R}_I$.

Proposition 1.3.1 *If f is a continuous function on $I = [a, b]$, then $f \in \mathcal{R}_I$.*

Next, let f_1, f_2 be two functions on $I = [a, b]$. If $f_1, f_2 \in \mathcal{R}_I$, then the following properties it holds

1. $\int_I \big(c_1 f_1(x) + c_2 f_2(x)\big)dx = c_1 \int_I f_1(x)dx + c_2 \int_I f_2(x)dx$,
2. If $f_1(x) \leq f_2(x)$ on I, then $\int_I f_1(x)dx \leq \int_I f_2(x)dx$,
3. $\int_I f_1(x)f_2(x)dx = \int_I f_1(x)dx \int_I f_2(x)dx$.

As consequently of above is easy to prove the following statements:

Theorem 1.3.2 *[Mean value theorem for integrals] Suppose that $f, g \in \mathcal{R}_I$ where $I = [a, b]$ with $g(x) \geq 0$ for all $x \in I$. If*

$$m = \inf_{x \in I} f(x) \text{ and } M = \sup_{x \in I} f(x),$$

then there is $c \in [m, M]$ *such that*

$$\int_I f(x)g(x)dx = c\int_I g(x)dx.$$

In particular, if $f \in C(I)$*, then there is* $x_0 \in I$ *which satisfies*

$$\int_I f(x)g(x)dx = f(x_0)\int_I g(x)dx.$$

Proposition 1.3.3 *Suppose* $f \geq 0$*,* $f \in C(I)$*, and* $\int_I f(x)dx = 0$*, then* $f(x) = 0$ *for all* $x \in I$*.*

1.4 Construction of Brouwer Degree

Now, we give the necessary elements for the construction of Brouwer degree.

Definition 1.4.1 *Let* $\Omega \subset \mathbb{R}^n$ *be an open subset and* $f \in C^1(\overline{\Omega})$*. If* $p \notin f(\partial\Omega)$ *and* $J_f(p) \neq 0$*, then we define*

$$deg(f, \Omega, p) = \sum_{x \in f^{-1}(p)} sgn J_f(x),$$

with the agreement that the above sum is zero if $f^{-1}(y) = \emptyset$*.*

Definition 1.4.2 *Let* $\Omega \subset \mathbb{R}^n$ *be an open subset and* $f \in C^2(\overline{\Omega})$*. If* $p \notin f(\partial\Omega)$ *and* $J_f(p) \neq 0$*, then we define*

$$deg(f, \Omega, p) = deg(f, \Omega, p'),$$

where p' *is any regular value of* f *such that* $\|p' - p\| < d(p, \partial\Omega)$*.*

Finally, we are ready to introduce the following definition:

Definition 1.4.3 *Let* $\Omega \subset \mathbb{R}^n$ *be an open subset and* $f \in C^1(\overline{\Omega})$*. If* $p \notin f(\partial\Omega)$ *and* $J_f(p) \neq 0$*, then we define*

$$deg(f, \Omega, p) = deg(g, \Omega, p'),$$

where $g \in C^2(\overline{\Omega})$ *and* f *is such that* $\|f - g\| < d(p, \partial\Omega)$*.*

Now, one may check the following properties by a reduction to the regular case.

Theorem 1.4.4 *Let $\Omega \subset \mathbb{R}^n$ be an open subset and $f : \overline{\Omega} \longrightarrow \mathbb{R}^n$ be a continuous mapping. If $p \notin f(\partial\Omega)$, then there exists an integer $deg(f, \Omega, p)$ satisfying the following properties:*

1. *(Normality) $deg(I, \Omega, p) = 1$ if and only if $p \in \Omega$, where I denotes the identity mapping,*
2. *(Solvability) If $deg(f, \Omega, p) = 1$, then $f(x) = p$ has a solution in Ω,*
3. *(Homotopy) If $f_t(x) : [0, 1] \times \overline{\Omega} \longrightarrow \mathbb{R}^n$ is continuous and $p \notin \bigcup_{t\in[0,1]} f_t(\partial\Omega)$, then $deg(f_t, \Omega, p)$ does not depend on $t \in [0, 1]$,*
4. *(Additivity) Suppose that Ω_1, Ω_2 are two disjoint open subsets of Ω and $p \notin f(\partial\Omega - \Omega_1 \cup \Omega_2)$. Then $deg(f, \Omega, p) = deg(f, \Omega_1, p) + deg(f, \Omega_2, p)$,*
5. *$deg(f, \Omega, p)$ is a constant on any connected component of $\mathbb{R}^n - f(\partial\Omega)$.*

1.5 Coincidence degree theory

In the 1970s, Jean Mawhin systematically studied a class of mappings of the form $L + T$, where L is a Fredholm mapping of index zero and T is a nonlinear mapping, which he called a L-compact mapping. Based on the Lyapunov- Schmidt method, he was able to construct a degree theory for such mapping. The goal of this section is to introduce Mawhin's degree theory for L-compact mappings. We present some introductory material on Fredholm mappings, for more information to see O'Regan et al. (2006).

1.5.1 Fredholm Mappings

Next, we define the concepts of linear mapping in normed spaces.

Definition 1.5.1 *Let X and Y be normed spaces. A linear mapping $L : D(L) \subset X \longrightarrow Y$ is a mapping such that*

1. $L(x_1 + x_2) = L(x_1) + L(x_2),$ *for all* $x_1, x_2 \in D(L)$,

2. $L(\alpha x_1) = \alpha L(x_1),$ *for all* α *scalar,*

where $D(L) = Dom(L) = \Big\{ x \in X : L(x) = y,$ *for some* $y \in Y \Big\}$.

Definition 1.5.2 *Let X and Y be normed spaces and a linear mapping $L : D(L) \subset X \longrightarrow Y$, it defines*

1. $Ker(L) = \Big\{ x \in D(L) : L(x) = 0 \Big\}$,

2. $Im(L) = \Big\{ y \in Y : L(x) = y,$ *for* $x \in D(L) \Big\}$.

Definition 1.5.3 *Let X and Y be normed spaces. A linear mapping $L : D(L) \subset X \longrightarrow Y$ is called a Fredholm mapping if*

1. *$Ker(L)$ has finite dimension,*

2. *$Im(L)$ is closed and has finite codimension.*

Definition 1.5.4 *If W is a linear subspace of a finite-dimensional vector space V, then the codimension of W in V is the difference between the dimensions:*

$$\operatorname{codim}(W) = \dim(V) - \dim(W).$$

Definition 1.5.5 *It is the complement of the dimension of W, in that, with the dimension of W, it adds up to the dimension of the ambient space V:*

$$\dim(W) + \operatorname{codim}(W) = \dim(V).$$

Similarly, if N is a submanifold or subvariety in M, then the codimension of N in M is

$$\operatorname{codim}(N) = \dim(M) - \dim(N).$$

Just as the dimension of a manifold is the dimension of the tangent bundle (the number of dimensions that you can move on the submanifold), the codimension is the dimension of the normal bundle (the number of dimensions you can move off the submanifold). More generally, if W is a linear subspace of a (possibly infinite dimensional) vector space V then the codimension of W in V is the dimension (possibly infinite) of the quotient space V/W, which is more abstractly known as the cokernel *of the inclusion. For finite-dimensional vector spaces, this agrees with the previous definition*

$$\operatorname{codim}(W) = \dim(V/W) = \dim \operatorname{coker}(W \to V) = \dim(V) - \dim(W),$$

and is dual to the relative dimension as the dimension of the kernel.

Definition 1.5.6 *Let X and Y be normed spaces. A linear mapping $L : D(L) \subset X \longrightarrow Y$ is said to be bounded if there is some $k > 0$ such that*

$$\|Lx\| \leq k\|x\|$$

for all $x \in D(L)$. If L is bounded, we define $\|L\|$ to be

$$\|L\| = \inf\Big\{k : \|Lx\| \leq k\|x\|, x \in D(L)\Big\}.$$

Proposition 1.5.7 *Let X be a Banach space and $T : X \longrightarrow X$ be a linear bounded mapping. Then $dim(Ker(T)) < \infty$ and $Im(T)$ is closed if and only if, for $x_n \in \overline{B(0,1)}$ such that $Tx_n \longrightarrow y$, thus $\{x_n\}_{n=1}^{\infty}$ has a convergent subsequence.*

Proposition 1.5.8 *Let X be a Banach space, $T : X \longrightarrow X$ be a linear bounded Fredholm operator and $K : X \longrightarrow X$ be a linear continuous compact mapping. Then $T + K$ is a Fredholm mapping.*

1.5.2 Jean Mawhin's continuation theorem

Definition 1.5.9 *Let X and Y be normed vector spaces, let $L : DomL \subset X \longrightarrow Y$ be a linear mapping, and $N : X \longrightarrow Y$ be a continuous mapping. The mapping L is called a Fredholm mapping of index zero if $IndexL = dimKerL - codimImL = 0$ and ImL is closed in Y.*

Definition 1.5.10 *If L is a Fredholm mapping of index zero, there exist continuous projectors $P : X \longrightarrow X$ and $Q : Y \longrightarrow Y$ such that $ImP = KerL$, $KerQ = ImL = Im(I - Q)$ and $X = KerL \oplus KerP$, $Y = ImL \oplus ImQ$. It follows that $L \mid_{DomL \bigcap KerP}: (I - P)X \longrightarrow ImL$ is invertible. We denote the inverse of that map by K_P.*

Definition 1.5.11 *If Ω is an open bounded subset of X, the mapping N is called L-compact on $\overline{\Omega}$ if $QN(\overline{\Omega})$ is bounded and $K_P(I-Q)N : \overline{\Omega} \longrightarrow X$ is compact. Since ImQ is isomorphic to $KerL$ there exists an isomorphism $J : ImQ \longrightarrow KerL$.*

Let us recall the continuation theorem, that will help us to prove the existence of positive periodic solutions.

Theorem 1.5.12 *(Gaines and Mawhin, 1977, p.40) Let $\Omega \subset X$ be an open bounded set. Let L be a Fredholm mapping of index zero and N be L-compact on X. Assume that:*

1. *For each $\lambda \in]0, 1[$, $x \in \partial\Omega \cap DomL$, $Lx \neq \lambda Nx$,*
2. *For each $x \in \partial\Omega \cap KerL$, $QNx \neq 0$,*
3. *$deg\Big\{JQN, \Omega \cap KerL, 0\Big\} \neq 0$.*

Then the equation $Lx = Nx$ has at least one solution in $DomL \cap \overline{\Omega}$.

Chapter 2

Modeling the spread of seasonal epidemiological diseases: theory and applications†

This chapter studies the existence and uniqueness of periodic solutions of a seasonal epidemiological disease, by using a continuation theorem based on coincidence degree theory. Also it provides criteria for the existence, uniqueness and global asymptotic stability of the periodic solution of the system. As a particular case, it shows numerical simulations related to the transmission of respiratory syncytial virus RSV in different countries.

2.1 Introduction

Many epidemiological problems can be modeled by non-autonomous system of nonlinear differential equations. This is the case of the spread of infectious childhood diseases, where it has been argued that school system induces a time-heterogeneity in the per capita infection rate because of the

† This chapter is based on Jódar et al. (2008a)

interruption of the infections chain during vacations or the inclusion of new individuals at the beginning of each school year (Dietz and Schenzle, 1985). Some models use a time-varying contact rate $\beta(t)$ between susceptible and infected individuals called as seasonally-forced function (Diallo and Koné, 2007), (Anderson and May, 1991), (Keeling et al., 2001), (White et al., 2005), (White et al., 2007), (Weber et al., 2001), (Moneim and Greenhalgh, 2005), (Greenhalgh and Moneim, 2003). An example of seasonally-forced function is $\beta(t) = b_0(1 + b_1 \cos(2\pi(t + \varphi)))$ where $b_0 > 0$ is the baseline transmission parameter, $0 < b_1 \leq 1$ measures the amplitude of the seasonal variation in transmission and $0 \leq \varphi \leq 1$ is the phase angle normalized. Other examples of seasonally-forced functions may be found in Keeling et al. (2001), Earn et al. (2000), Weber et al. (2001).

Seasonality uses to be related to cold or rainy parts of the year. Transmission rate and other parameters are modeled after taking a series of clinic data and simulating the solutions fitting appropriately the involved parameters.

The aim of this chapter is to study the existence and the behavior of periodic solutions of a generalized epidemic $SIRS$ (Susceptibles, Infective, Recovered and Susceptibles) model, of the form

$$\dot{S}(t) = \mu(t) - \mu(t)S(t) - \beta(t)S(t)I(t) + \gamma(t)R(t), \quad S(0) = S_0 > 0 \tag{2.1}$$
$$\dot{I}(t) = \beta(t)S(t)I(t) - \nu(t)I(t) - \mu(t)I(t), \quad I(0) = I_0 > 0 \tag{2.2}$$
$$\dot{R}(t) = \nu(t)I(t) - \gamma(t)R(t) - \mu(t)R(t), \quad R(0) = R_0 > 0. \tag{2.3}$$

which is depicted in Figure 2.1 and modeling the spread of seasonal infectious diseases under the following hypotheses:

1. The population is divided in three classes:
    - Susceptibles $S(t)$, who are all individuals that have not the virus,
    - Infected $I(t)$, being all the infected individuals having the virus and able to transmit the illness,
    - Recovered $R(t)$, who are all the individuals not having the virus and with a temporary immunity.

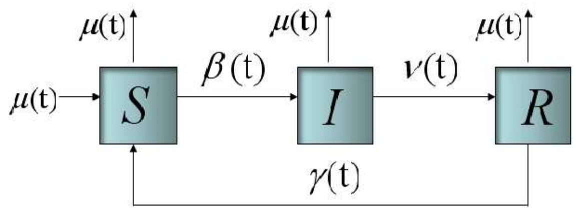


Figure 2.1: Compartmental model for $SIRS$ generalized.

2. The instantaneous birth rate $\mu(t) > 0$ with instantaneous death rate, being a continuous function. This mean that $\dot{S}(t) + \dot{I}(t) + \dot{R}(t) = 0$ and by (2.1)-(2.3) one gets $S(t) + I(t) + R(t) = 1$ is invariant with $S(t) \leq 1$, $I(t) \leq 1$, $R(t) \leq 1$, for all $t \geq 0$.

3. The meeting coefficient function $\beta(t)$ between classes $S(t)$ and $I(t)$, is a continuous T-periodic function, called the transmission rate that satisfies

$$0 < \beta^l := \min_{t \in [0,+\infty[} \beta(t) \leq \beta(t) \leq \beta^u := \max_{t \in [0,+\infty[} \beta(t).$$

   Periodicity of the $\beta(t)$ is a way to incorporate the seasonality of the spread in the environment.

4. The instantaneous per capita rate of leaving the infective class $I(t)$ is called $\nu(t)$ and the instantaneous per capita rate of recovered class $R(t)$ is $\gamma(t)$, are non-negative, continuous and bounded functions in $[0, \infty[$.

As $R(t) = 1 - S(t) - I(t)$, using this expression in (2.1) it obtains the following equivalent system

$$\dot{S}(t) = k(t) - k(t)S(t) - \beta(t)S(t)I(t) - \gamma(t)I(t), \tag{2.4}$$

$$\dot{I}(t) = \beta(t)S(t)I(t) - \omega(t)I(t), \tag{2.5}$$

with $S(0) = S_0 > 0$ and $I(0) = I_0 > 0$, where

$$k(t) = \mu(t) + \gamma(t) \text{ and } \omega(t) = \mu(t) + \nu(t). \tag{2.6}$$

It assumes that $\gamma(t) < \nu(t)$, for all $t \geq 0$, i. e., the per capita rate of recovered is greater than the per capita rate of leaving the infective and also that k^u, k^l, w^u and w^l are real numbers defined by

$$k^u = \sup_{t\in[0,+\infty)} (\mu(t) + \gamma(t)) \qquad k^l = \inf_{t\in[0,+\infty)} (\mu(t) + \gamma(t)), \tag{2.7}$$

$$\omega^u = \sup_{t\in[0,+\infty)} (\mu(t) + \nu(t)) \qquad \omega^l = \inf_{t\in[0,+\infty)} (\mu(t) + \nu(t)), \tag{2.8}$$

and for a continuous function $f(t)$ defined on $[0, T]$, we denote by $\overline{f}$ its mean value, i.e.,

$$\overline{f} = \frac{1}{T} \int_0^T f(t)dt. \tag{2.9}$$

The dynamical behavior of the solutions of this model will be analyzed on the set $D \subset \mathbb{R}^2_+$ where

$$D = \Big\{(S(t), I(t))/ \quad S(t) \geq 0, \quad I(t) \geq 0, \quad S(t) + I(t) \leq 1\Big\}. \tag{2.10}$$

The chapter is organized as follows. In Section 2.2, we show that the solutions of system (2.4)-(2.5) are positive and using Mawhin's continuation theorem a sufficient condition for the existence of a positive periodic solution of system (2.4)-(2.5) is established. In Section 2.3, by constructing a Lyapunov functional, we establish a sufficient condition for the global attractivity of the positive periodic solution of system (2.4)-(2.5). In Section 2.4, results are illustrated with two examples related to the transmission of respiratory syncytial virus.

2.2 Consistency and dynamical properties

2.2.1 Positive solutions

Let us start this section showing that a solution of problem (2.4)-(2.5) with positive initial conditions takes positive values.

Lemma 2.2.1 *Let $S(0) > 0$, $I(0) > 0$ and let $(S(t), I(t))$ be a solution of system (2.4)-(2.5) defined on an interval $[0, T]$. Then, $S(t) > 0$ and $I(t) > 0$, for all $t > 0$.*

Proof. Suppose that there is $t_1 \in]0, T[$ the first point that satisfies $S(t_1) \cdot I(t_1) = 0$. Firstly, we consider $I(t_1) = 0$ and note that $I(t) \geq 0$ for all $t \in [0, t_1]$ because $I(0) > 0$. Let C be defined as

$$C = \min_{t \in [0,t_1]} \Big\{ \beta(t)S(t) - \omega(t) \Big\},$$

where $\omega(t)$ is defined by (2.6). By (2.5) it follows that $\dot{I}(t) \geq I(t)C$, for all $t \in [0, t_1]$, and hence $I(t) \geq I(0)\exp(Ct)$ for all $t \in [0, t_1]$ in contradiction with the fact that $I(t_1) = 0$. Now, let us suppose that $S(t_1) = 0$ and note that $I(t) \geq 0$ for all $t \in [0, t_1]$ because $I(0) > 0$. Hence by (2.4)-(2.6)

$$\begin{aligned} \dot{S}(t_1) &= k(t_1) - k(t_1)S(t_1) - \beta(t_1)S(t_1)I(t_1) - \gamma(t_1)I(t_1) \\ &= \mu(t_1) + \gamma(t_1) - \gamma(t_1)I(t_1) = \mu(t_1) + \gamma(t_1)(1 - I(t_1)) \geq \mu(t_1) > 0. \end{aligned}$$

because $1 - I(t_1) \geq 0$. This is a contradiction with the fact that $S(0) > 0$ and $S(t) > 0$ for all $t \in [0, T[$ because it implies that $\dot{S}(t_1) \leq 0$.

Remark 2.2.2 *The solutions of (2.4)-(2.5) are restricted to the simplex $S(t) + I(t) \leq 1$ and since $R(t) = 1 - S(t) - I(t)$, then $0 < R(t) \leq 1$ for all $t \geq 0$.*

2.2.2 Existence of positive periodic solutions

We use the continuation theorem 1.5.12 of Gaines and Mawhin (1977) to obtain the existence of positive periodic solutions of system (2.4)-(2.5) in terms of the parameters linked with the model under an interval of common period. In order to do this, first we consider the following change of variables $S(t) = \exp(u_1(t))$, $I(t) = \exp(u_2(t))$. Thus the system (2.4)-(2.5) can be transformed into

$$\dot{u_1}(t) = k(t)e^{-u_1(t)} - k(t) - \beta(t)e^{u_2(t)} - \gamma(t)e^{u_2(t)-u_1(t)}, \tag{2.11}$$

$$\dot{u_2}(t) = \beta(t)e^{u_1(t)} - \omega(t), \tag{2.12}$$

with $u_1(0) = u_{1_0}$ and $u_2(0) = u_{2_0}$. Note that $u_1(t) \leq 0$, $u_2(t) \leq 0$ because $0 < S(t) \leq 1$ and $0 < I(t) \leq 1$. It is clear that if the system (2.11)-(2.12) admits a T-periodic solution, then the system (2.4)-(2.5) admits a positive T-periodic solution. Thus, we will study system (2.11)-(2.12). Consider the normed space $(X, \|\cdot\|)$ where

$$X = \Big\{u(t) = (u_1(t), u_2(t))^{\mathbf{T}} \in C(\mathbb{R}, \mathbb{R}^2_-)/\ u_i(T+t) = u_i(t);\ i = 1, 2; T > 0\Big\},$$

and for all $u \in X$ it uses the following norm

$$||u|| = ||(u_1(t), u_2(t))^{\mathbf{T}}|| = \max_{t\in[0,T]} |u_1(t)| + \max_{t\in[0,T]} |u_2(t)|,$$

where $|\cdot|$ is the Euclidean norm. Then X is a Banach space with the norm $||\cdot||$. Let L, N, P and Q be the operators defined on X by the expressions

$$L(u(t)) = \dot{u}(t); \qquad L : DomL \cap X \longrightarrow X,$$

$$P(u(t)) = Q(u(t)) = \tfrac{1}{T}\textstyle\int_0^T u(t)dt; \qquad P, Q : X \longrightarrow X,$$

$$N(u(t)) = \begin{bmatrix} k(t)e^{-u_1(t)} - k(t) - \beta(t)e^{u_2(t)} - \gamma(t)e^{u_2(t)-u_1(t)} \\ \beta(t)e^{u_1(t)} - \omega(t) \end{bmatrix}; \quad N : X \longrightarrow X,$$

where

$$DomL = \Big\{u(t) = (u_1(t), u_2(t))^{\mathbf{T}} \in C^1(\mathbb{R}, \mathbb{R}^2_-)/\ u(T+t) = u(t)\Big\} \subseteq X.$$

Note that

$$KerL = \mathbb{R}^2_-, \quad ImL = KerQ = Im(I - Q) = \Big\{u \in X\ /\frac{1}{T}\int_0^T u(t)dt = 0\Big\}.$$

Furthermore, ImL is closed in X and L is a Fredholm mapping of index zero because $IndexL = dimKerL - CodimImL = 0$, (see (1.5.9-1.5.11)). Also, the mapping

$$L|_{DomL\cap KerP} : (I-P)X \longrightarrow ImL$$

is invertible and the generalized inverse K_p of L, $K_p : ImL \longrightarrow DomL \cap KerP$, takes the expression

$$K_p(u) = \int_0^t u(s)ds - \frac{1}{T}\int_0^T \int_0^t u(s)dsdt, \quad t \in [0,T].$$

Thus, $QN : X \longrightarrow X$, where $QNu(t)$ is give by

$$\begin{bmatrix} \frac{1}{T}\int_0^T k(t)e^{-u_1(t)}dt - \frac{1}{T}\int_0^T k(t)dt - \frac{1}{T}\int_0^T \beta(t)e^{u_2(t)}dt - \frac{1}{T}\int_0^T \gamma(t)e^{u_2(t)-u_1(t)}dt \\ \frac{1}{T}\int_0^T \beta(t)e^{u_1(t)}dt - \frac{1}{T}\int_0^T \omega(t)dt \end{bmatrix}.$$

We have also that the operator $K_P(I-Q)N : X \longrightarrow X$ is defined by

$$K_P(I-Q)Nu(t) = \int_0^t Nu(s)ds - \frac{1}{T}\int_0^T \int_0^t Nu(s)dsdt - \left(\frac{t}{T} - \frac{1}{2}\right)\int_0^T Nu(s)ds.$$

Is clear that QN and $K_P(I-Q)N$ are continuous. If Ω is a open bounded set in X, then by the Arzela-Ascoli Theorem (Dieudonne, 1969), the set $\overline{K_P(I-Q)N(\overline{\Omega})}$ is compact and $QN(\overline{\Omega})$ is bounded. Thus, N is $L-$compact on $\overline{\Omega}$. As $ImQ = KerL$, the identity mapping from ImQ to $KerL$ is an isomorphism J between them.

Let $\lambda \in]0,1[$ and let us write the continuation operator equation $Lu = \lambda Nu$ as follows

$$\dot{u_1}(t) = \lambda\left(k(t)e^{-u_1(t)} - k(t) - \beta(t)e^{u_2(t)} - \gamma(t)e^{u_2(t)-u_1(t)}\right), \tag{2.13}$$

$$\dot{u_2}(t) = \lambda\left(\beta(t)e^{u_1(t)} - \omega(t)\right). \tag{2.14}$$

Suppose that $u(t) = (u_1(t), u_2(t))^{\mathbf{T}} \in X$ is a solution of system (2.11)-(2.12) for some $\lambda \in (0,1)$. Let $\xi_i, \eta_i \in [0,T]$ for $i = 1,2$, defined as

$$u_1(\xi_1) = \min_{t\in[0,T]} u_1(t), \qquad u_2(\xi_2) = \min_{t\in[0,T]} u_2(t), \tag{2.15}$$

and

$$u_1(\eta_1) = \max_{t\in[0,T]} u_1(t), \qquad u_2(\eta_2) = \max_{t\in[0,T]} u_2(t), \tag{2.16}$$

and note that $\dot{u_1}(\xi_i) = 0$, $\dot{u_2}(\eta_i) = 0$, for $i = 1, 2$, due to their periodicity. Assume that

$$\omega^u < \beta^l, \tag{2.17}$$

from equations (2.13)-(2.16) it follows that

$$\begin{aligned} \omega^u &\geq \omega(\xi_2) = \beta(\xi_2)e^{u_1(\xi_2)} \geq \beta^l e^{u_1(\xi_1)}, \\ \omega^l &\leq \omega(\xi_2) = \beta(\xi_2)e^{u_1(\xi_2)} \leq \beta^u e^{u_1(\eta_1)}, \end{aligned}$$

and

$$\begin{aligned} k(\xi_1) &= k(\xi_1)e^{u_1(\xi_1)} + \beta(\xi_1)e^{u_2(\xi_1)}e^{u_1(\xi_1)} + \gamma(\xi_1)e^{u_2(\xi_1)} \\ &\leq \frac{k(\xi_1)\omega^u}{\beta^l} + \frac{\beta^u e^{u_2(\eta_2)}\omega^u}{\beta^l} + \gamma^u e^{u_2(\eta_2)}, \end{aligned}$$

and

$$\begin{aligned} k(\eta_1) &= k(\eta_1)e^{u_1(\eta_1)} + \beta(\eta_1)e^{u_2(\eta_1)}e^{u_1(\eta_1)} + \gamma(u_1)e^{u_2(\eta_1)} \\ &\geq \frac{k(\eta_1)\omega^l}{\beta^u} + \frac{\beta^l e^{u_2(\xi_2)}\omega^l}{\beta^u} + \gamma^l e^{u_2(\xi_2)}. \end{aligned}$$

Therefore, we obtain that

$$e^{u_1(\xi_1)} \leq \frac{\omega^u}{\beta^l}, \qquad \text{i.e.,} \qquad u_1(\xi_1) \leq \ln\left(\frac{\omega^u}{\beta^l}\right), \tag{2.18}$$

$$e^{u_1(\eta_1)} \geq \frac{\omega^l}{\beta^u}, \qquad \text{i.e.,} \qquad u_1(\eta_1) \geq \ln\left(\frac{\omega^l}{\beta^u}\right), \tag{2.19}$$

$$e^{u_2(\eta_2)} \geq \frac{k^l\left(1 - \frac{\omega^u}{\beta^l}\right)}{\left(\gamma^u + \frac{\beta^u\omega^u}{\beta^l}\right)}, \quad \text{i.e.,} \quad u_2(\eta_2) \geq \ln\left(\frac{k^l\left(1 - \frac{\omega^u}{\beta^l}\right)}{\left(\gamma^u + \frac{\beta^u\omega^u}{\beta^l}\right)}\right), \tag{2.20}$$

$$e^{u_2(\xi_2)} \leq \frac{k^u\left(1-\frac{\omega^l}{\beta^u}\right)}{\left(\gamma^l+\frac{\beta^l\omega^l}{\beta^u}\right)}, \quad \text{i.e.,} \quad u_2(\xi_2) \leq \ln\left(\frac{k^u\left(1-\frac{\omega^l}{\beta^u}\right)}{\left(\gamma^l+\frac{\beta^l\omega^l}{\beta^u}\right)}\right). \tag{2.21}$$

By integrating the equation (2.13) on the interval $[0,T]$, we have that

$$\int_0^T k(t)e^{-u_1(t)}dt = \int_0^T k(t)dt + \int_0^T \beta(t)e^{u_2(t)}dt + \int_0^T \gamma(t)e^{u_2(t)-u_1(t)}dt,$$

but $u_2(t) \leq 0$ for all $t \in [0,T]$, then $e^{u_2(t)} \leq 1$ for all $t \in [0,T]$ and

$$\int_0^T k(t)e^{-u_1(t)}dt \leq k^uT + \overline{\beta}T + \int_0^T \gamma(t)e^{-u_1(t)}dt,$$

hence

$$\int_0^T e^{-u_1(t)}dt \leq \frac{\left(k^u+\overline{\beta}\right)T}{\mu^l}. \tag{2.22}$$

In an analogous way, by integrating (2.14) one gets that

$$\int_0^T \beta(t)e^{u_1(t)}dt = \overline{\omega}T. \tag{2.23}$$

Let $t \in [0,T]$. Then from (2.13) it follows that

$$\begin{aligned} u_1(t) &\leq u_1(\xi_1) + \int_0^T |\dot{u_1}(t)|dt \\ &= u_1(\xi_1) + \lambda\int_0^T |k(t)e^{-u_1(t)} - k(t) - \beta(t)e^{u_2(t)} - \gamma(t)e^{u_2(t)-u_1(t)}|dt \\ &< u_1(\xi_1) + 2\int_0^T k(t)e^{-u_1(t)}dt, \end{aligned}$$

and by (2.18) and (2.22) one gets that

$$u_1(t) < \ln\left(\frac{\omega^u}{\beta^l}\right) + \frac{2k^u\left(k^u+\overline{\beta}\right)T}{\mu^l} := \rho_1. \tag{2.24}$$

In an analogous way, we have that

$$u_1(t) > \ln\left(\frac{\omega^l}{\beta^u}\right) - \frac{2k^u\left(k^u+\overline{\beta}\right)T}{\mu^l} := \rho_2. \tag{2.25}$$

Let $M_1 = \max\Big\{|\rho_1|, |\rho_2|\Big\}$, then

$$\max_{t\in[0,T]} |u_1(t)| < M_1. \tag{2.26}$$

By (2.20)-(2.21) and (2.23) it is easy show that

$$u_2(t) < \ln\left(\frac{k^u\left(1-\frac{\omega^l}{\beta^u}\right)}{\left(\gamma^l+\frac{\beta^l\omega^l}{\beta^u}\right)}\right) + 2\overline{\omega}T := \rho_3, \tag{2.27}$$

and

$$u_2(t) > \ln\left(\frac{k^l\left(1-\frac{\omega^u}{\beta^l}\right)}{\left(\gamma^u+\frac{\beta^u\omega^u}{\beta^l}\right)}\right) - 2\overline{\omega}T := \rho_4. \tag{2.28}$$

By (2.27) and (2.28) one gets

$$\max_{t\in[0,T]} |u_2(t)| \le \max\Big\{|\rho_3|, |\rho_4|\Big\} := M_2. \tag{2.29}$$

Note that M_1 and M_2 defined in (2.26) and (2.29) are independent of λ. Let us take M_0 large enough so that the only solution $(n, m) \in \mathbb{R}^2_-$ of the algebraic equation

$$\overline{k}e^n - \overline{k} - \overline{\beta}e^n e^m - \overline{\gamma}e^m = 0, \tag{2.30}$$

$$\overline{\beta}e^n - \overline{\omega} = 0, \tag{2.31}$$

where

$$0 < e^n = \frac{\overline{\omega}}{\overline{\overline{\beta}}} < 1, \qquad 0 < e^m = \frac{\overline{k}\left[1-\frac{\overline{\omega}}{\overline{\overline{\beta}}}\right]}{\overline{\omega}+\overline{\gamma}} < 1,$$

and satisfy $\|(n, m)^{\mathbf{T}}\| = |n| + |m| < M_0$. Let M defined as $M = M_0 + M_1 + M_2$, and let Ω be the open set defined by

$$\Omega = \Big\{u(t) = (u_1(t), u_2(t))^{\mathbf{T}} \in X \text{ such that } \|u\| < M\Big\}. \tag{2.32}$$

Note that this set Ω satisfies condition 1 of the theorem 1.5.12. If $u = (u_1, u_2)^{\mathbf{T}} \in \partial\Omega \cap KerL = \partial\Omega \cap \mathbb{R}^2_-$, then u is a constant vector in $\mathbb{R}^2$ with $\|u\| = M$ and

$$QNu = \begin{bmatrix} \overline{k}e^{-u_1} - \overline{k} - \overline{\beta}e^{u_2} - \overline{\gamma}e^{u_2-u_1} \\ \overline{\beta}e^{u_1} - \overline{\omega} \end{bmatrix} \neq 0,$$

and the condition 2 in theorem 1.5.12 holds.
Taking $J = I : ImQ \longrightarrow KerL$, $(u_1, u_2)^{\mathbf{T}} \longrightarrow (u_1, u_2)^{\mathbf{T}}$, a direct calculation shows that

$$\begin{aligned}
& deg\left(JQN((u_1,u_2)^{\mathbf{T}}), \partial\Omega \cap KerL, (0,0)^T\right) \\
& = deg\left(JQN((u_1,u_2)^{\mathbf{T}}), \Omega \cap R^- \times R^-, (0,0)^{\mathbf{T}}\right) \\
& = deg\left((\overline{k}e^{-u_1} - \overline{k} - e^{u_2}\overline{\beta} - \overline{\gamma}e^{u_2-u_1}, e^{u_1}\overline{\beta} - \overline{\omega}), \partial\Omega \cap KerL, (0,0)^T\right) \\
& = sgn\left(det \begin{pmatrix} -\overline{k}e^{-u_1} + \overline{\gamma}e^{u_2}e^{-u_1} & -\overline{\beta}e^{u_2} - \overline{\gamma}e^{u_2}e^{-u_1} \\ \overline{\beta}e^{u_1} & 0 \end{pmatrix}_{(n,m)} \right) \\
& = sgn\left(\left(e^{u_1}e^{u_2}\overline{\beta}^2 + \overline{\gamma}e^{u_2}\overline{\beta} \right)_{(n,m)} \right) \\
& = sgn\left(e^{n}e^{m}\overline{\beta}^2 + \overline{\gamma}e^{m}\overline{\beta} \right) = 1,
\end{aligned}$$

where (n, m) is the unique solution of system (2.28)-(2.29). By theorem 1.5.12, the system (2.9)-(2.10) admits at least one T-periodic solution $(u_1^*(t), u_2^*(t))^{\mathbf{T}} \in DomL \cap \overline{\Omega}$. Summarizing, the following result has been established:

Theorem 2.2.3 *If $\omega^u < \beta^l$, then the system (2.4)-(2.5) has at least one positive T-periodic solution.*

2.3 Uniqueness and global stability

Now, let us study the uniqueness and global stability of system (2.4)-(2.5). The strategy of the proof is the construction of a suitable Lyapunov function and the application of the following Lemma.

Lemma 2.3.1 *Let $(S(t), I(t))^{\mathbf{T}}$ denote any positive solution of system (2.4)-(2.5) with initial conditions. If the conditions of the Theorem 2.2.3 holds, then there exists a $T > 0$, and $m_S^1, M_S^1, m_I^2, M_I^2 \in]0,1[$ such that*

$$m_S^1 \leq S(t) \leq M_S^1,\ m_I^2 \leq I(t) \leq M_I^2, \quad \text{for all } t \geq T. \tag{2.33}$$

Proof *See Chen (2003).*

Definition 2.3.2 *A bounded positive solution* $(S^*(t), I^*(t))^{\mathbf{T}}$ *of system (2.4)-(2.5) is said to be globally asymptotically stable (or globally attractive) if, for any other solution* $(S(t), I(t))^{\mathbf{T}}$ *of (2.4)-(2.5) with positive initial values, the following holds*

$$\lim_{t \longrightarrow +\infty} (|S(t) - S^*(t)| + |I(t) - I^*(t)|) = 0, \text{ (Fan et al., 2003).} \quad (2.34)$$

Remark 2.3.3 *If (2.3.1) holds for any two solutions with positive initial values, then we say system (2.4)-(2.5) has a bounded positive solution globally asymptotically stable, and therefore the system (2.4)-(2.5) is globally asymptotically stable. Conversely, if the system (2.4)-(2.5) is globally asymptotically stable, then equality (2.34) holds. Moreover, from Theorem 2.2.3 and Lemma 2.3.1, is easy to see that there exists* $m_p > 0$ *and* $M_p > 0$*, such that* $m_p < S(t), I(t) < M_p$ *for all* $t \geq 0$*.*

Theorem 2.3.4 *If the hypothesis of the Theorem 2.2.3 holds, and also that* $sgn(S(t) - z)$=$sgn(I(t) - z)$*, for all* $z \in [m_p, M_p]$*, then the system (2.4)-(2.5) with initial positive conditions, has a unique positive* T*-periodic solution which is globally asymptotically stable.*

Proof Let $(S^*(t), I^*(t))^{\mathbf{T}}$ be a positive T-periodic solution of (2.4)-(2.5), and $(S(t), I(t))^{\mathbf{T}}$ be any positive solution of system (2.4)-(2.5) with initial condition $S(0) > 0, I(0) > 0$. We define

$$V(t) = |S(t) - S^*(t)| + |I(t) - I^*(t)|.$$

Calculating the upper right derivative of $V(t)$ along the solutions of system (2.4)-(2.5), it follows that

$$\begin{aligned} D^+V(t) &= sgn(S(t) - S^*(t))\Big(\dot{S}(t) - \dot{S}^*(t)) + sgn(I(t) - I^*(t))(\dot{I}(t) - \dot{I}^*(t)\Big) \\ &= sgn(S(t) - S^*(t))\Big(-k(t)(S(t) - S^*(t)) - \beta(t)(S(t)I(t) \\ &\quad - S^*(t)I^*(t)) - \gamma(t)(I(t) - I^*(t))\Big) + sgn(I(t) - I^*(t))\Big(-\omega(t)(I(t) \\ &\quad - I^*(t)) - \beta(t)(S(t)I(t) - S^*(t)I^*(t))\Big), \end{aligned}$$

$$\begin{aligned}D^+V(t) \leq & -k^l|S(t)-S^*(t)| - sgn(S(t)-S^*(t))\beta(t)\Big(S(t)I(t)-S^*(t)I^*(t)\Big) \\ & - \gamma^l sgn(S(t)-S^*(t))(I(t)-I^*(t)) - \omega^l|I(t)-I^*(t)| \\ & + sgn(S(t)-S^*(t))\beta(t)\Big(S(t)I(t)-S^*(t)I^*(t)\Big),\end{aligned}$$

$$\begin{aligned}D^+V(t) &\leq -k^l|S(t)-S^*(t)| - \gamma^l(I(t)-I^*(t)) - \omega^l|I(t)-I^*(t)| \\ &\leq -k^l|S(t)-S^*(t)| - (\omega^l-\gamma^l)|I(t)-I^*(t)| \\ &\leq -\alpha\Big(|S(t)-S^*(t)| + |I(t)-I^*(t)|\Big),\end{aligned}$$

and we get that

$$D^+V(t) \leq -\alpha\Big(|S(t)-S^*(t)| + |I(t)-I^*(t)|\Big), \tag{2.35}$$

where $0 < \alpha = \min\Big\{k^l, \omega^l - \gamma^l\Big\}$. Integrating both sides of (2.35) on the interval $[0,t]$, it follows that for all $t \geq 0$,

$$\begin{aligned}V(t) + \alpha\int_0^t |S(t)-S^*(t)|dt &+ \int_0^t |I(t)-I^*(t)|dt \\ &\leq V(0) = |S(0)-S^*(0)| + |I(0)-I^*(0)| < +\infty. \end{aligned} \tag{2.36}$$

Therefore, $V(t)$ is bounded on $[0,t]$ and also

$$\int_0^{+\infty} |S(t)-S^*(t)|dt < +\infty \quad \text{and} \quad \int_0^{+\infty} |I(t)-I^*(t)|dt < +\infty. \tag{2.37}$$

Thus, $|S(t)-S^*(t)| \in L^1[0,\infty[$ and $|I(t)-I^*(t)| \in L^1[0,\infty[$. On the other hand, since $(S^*(t), I^*(t))^{\mathbf{T}}$ and $(S(t), I(t))^{\mathbf{T}}$ are bounded for $[T,+\infty[$ and from (2.4)-(2.5) their derivatives are also bounded, then $|S(t)-S^*(t)|$ and $|I(t)-I^*(t)|$ are uniformly continuous on $[T,+\infty[$. By Barbalat's Lemma (Barbălat, 1959), we conclude that

$$\lim_{t \longrightarrow +\infty} |S(t)-S^*(t)| = 0, \qquad \lim_{t \longrightarrow +\infty} |I(t)-I^*(t)| = 0.$$

2.4 Applications

Finally, we give two examples to illustrate the feasibility of the main results.

Example 2.4.1 *Let us consider the model $SIRS$ for the transmission of respiratory syncytial virus (RSV)*

$$\begin{aligned}
\dot{S}(t) &= 0.0041 - 0.0041S(t) - 60\left(1 + 0.16\cos(2\pi t + 0.15)\right) S(t)I(t) + 1.8R(t),\\
\dot{I}(t) &= 60\left(1 + 0.16\cos(2\pi t + 0.15)\right) S(t)I(t) - 36I(t) - 0.0041I(t),\\
\dot{R}(t) &= 36I(t) - 1.8R(t) - 0.0041R(t),
\end{aligned} \tag{2.38}$$

studied in Weber et al. (2001) for the country of Gambia. RSV has long been recognized as the single most important virus causing acute severe respiratory-tract infections causing symptoms ranging from rhinitis to bronchitis in children who require hospitalization. It is easy to check that the coefficients in system (2.38) satisfy all the assumptions in Theorem 1.5.12. Thus, the system (2.38) has a unique positive 1-periodic solution which is globally stable. Using the program $ode45$ of Matlab for solving, the numerical simulation shows that system (2.38) has a unique 1-periodic solution which is globally asymptotically stable (see Figure 2.2).

Example 2.4.2 *We consider the periodic SIRS model, now for the transmission of virus RSV in the country of Finland (Weber et al., 2001),*

$$\begin{aligned}
\dot{S}(t) &= 0.0013 - 0.0013S(t) - 44\left(1 + 0.36\cos(2\pi t + 0.60)\right) S(t)I(t) + 1.8R(t)\\
\dot{I}(t) &= 44\left(1 + 0.36\cos(2\pi t + 0.60)\right) S(t)I(t) - 36I(t) - 0.0013I(t)\\
\dot{R}(t) &= 36I(t) - 1.8R(t) - 0.0013R(t).
\end{aligned} \tag{2.39}$$

Clearly, the conditions of Theorem 1.5.12 holds for system (2.39). Again we use the program $ode45$ of Matlab for obtaining numerical simulations it can be seen in Figure 2.3.

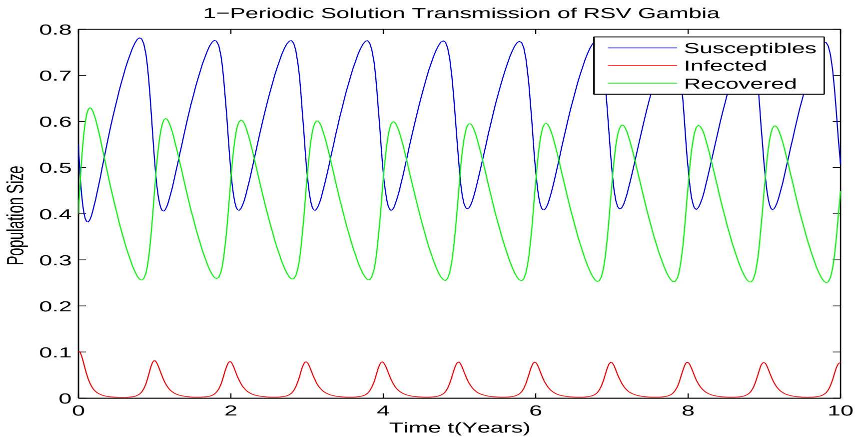


Figure 2.2: The existence of 1-periodic solution of system (2.38) with initial conditions (0.50 0.10 0.40).

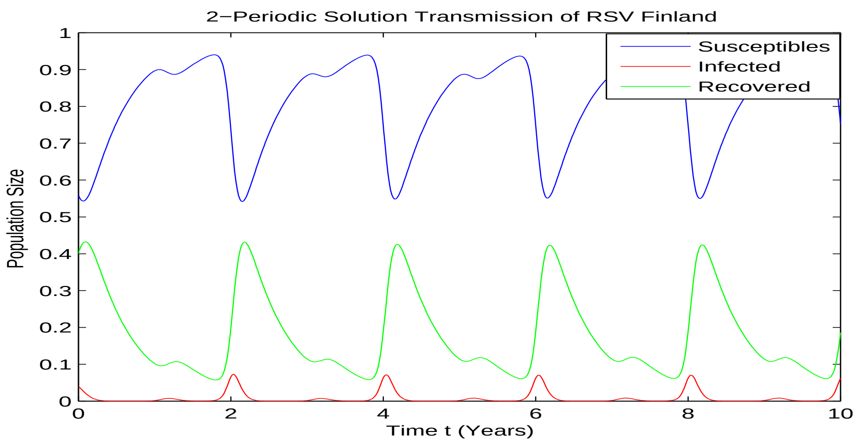


Figure 2.3: The existence of 2-periodic solution of system (2.39) with initial conditions (0.56 0.04 0.40).

Chapter 3

Existence of periodic solutions in nested models of respiratory syncytial virus $RSV^{\dagger}$

In this chapter, we study the existence of a positive periodic solutions for a generalized nested models by using a continuation theorem based on coincidence degree theory. Conditions for the existence of periodic solutions in the model are given. Numerical simulations related to the transmission of respiratory syncytial virus RSV in Madrid and Rio Janeiro are included.

3.1 Introduction

Respiratory syncytial virus (RSV) has long been recognized as the most important virus causing acute severe respiratory-tract infections, give rise to symptoms ranging from rhinitis to bronchitis in children who require hospitalization. RSV has been also implicated in severe lung diseases in adults, especially in the elderly. Infections with RSV frequently occur in

†This chapter is based on Arenas et al. (2008b) the early years of life and repeated infections are common in all age groups. Outbreaks of RSV occur each year and, because the virus is highly contagious, essentially all children become infected within the first 2 years of life (Cane, 2001), (Hall, 1992), (Craighead, 2000), (Sorce, 2008), (Nokes, 2006). This type of respiratory virus is among other things is the most important causes of morbidity, incomplete immunity and repeated infections (Power, 2008). A comprehensive reference of the RSV epidemiology from a clinical pathogenesis point of view is Craighead (2000). The transmission dynamics of RSV are strongly seasonal with a pronounced annual or biannual component in many countries. Epidemics occur each winter in many temperate climates and are often coincident with seasonal rainfall and religious festivals in tropical countries (White et al., 2007), (White et al., 2005).

A classical technique for model infectious diseases in the population is by means of systems of ordinary differential equations, describing the evolution of the number of individuals in the different subpopulations. In this way, recently the SIR infections disease model with pulse vaccination strategy and distributed time delay has been studied in Meng and Chen (2008), Gao et al. (2007), Jianga and Wei (2008) where it presents sufficient conditions of global asymptotic stability, bifurcations and permanence in the solutions. Also the $SIRS$ epidemic model with time delay and infection-age dependence has been analyzed in Zhang and Teng (2008), Zhang and Teng (2007), where the contact rate is nonlinear. Now, in most epidemic models, the transmission rate is a general periodic contact rate due to seasonal variation. In Hui and Zhu (2005) a SIS epidemic models and in Jódar et al. (2008a) a $SIRS$ epidemic model generalized are presented with a general continuous, bounded, positive and periodic function with period T and the authors shown the existence of positive periodic solution with the help of the continuation theorem based on coincidence degree.

In White et al. (2007) a nested model is presented for study the dynamical transmission of virus RSV. This model is structured with a set of four ordinary differential equations that include homotopy parameters which provide paths for different types of RSV transmission models and the transmission rate is a continuous positive periodic function. The models presented in White et al. (2005), Jódar et al. (2008a), Weber et al. (2001) are particular

case of this nested model with suitable parameters.
A very important problem in the study of infectious disease models with population-growth in a periodic environment, is the global existence of positive periodic solutions, which plays a similar role as a globally stable equilibrium does in the autonomous model (Xu et al., 2004), (Chen, 2003), (Hui and Zhu, 2005). Hence, it is reasonable to seek conditions under which the system would have a positive periodic solution.

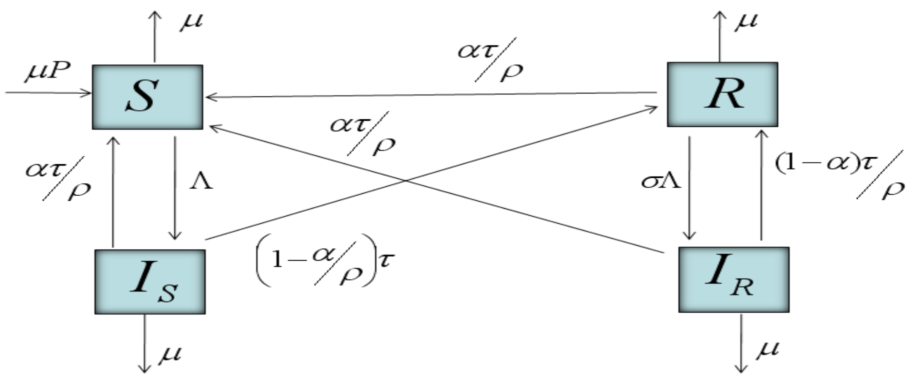
Motivated by the work in White et al. (2007), in this chapter, we study systematically the existence and the analytical behavior of the periodic solutions of a nested epidemic model generalized by a transmission rate continuous positive T-periodic function, of the form

$$\begin{aligned}
\dot{S}(t) &= \mu P - \frac{\Lambda(t)S(t)}{P} + \frac{\alpha\tau}{\rho}(I_S(t) + I_R(t) + R(t)) - \mu S(t), \\
\dot{I_S}(t) &= \frac{\Lambda(t)S(t)}{P} - (\tau+\mu)I_S(t), \\
\dot{I_R}(t) &= \frac{\sigma\Lambda(t)R(t)}{P} - \left(\frac{\tau}{\rho} + \mu\right) I_R(t), \\
\dot{R}(t) &= \left(1 - \frac{\alpha}{\rho}\right)\tau I_S(t) + \frac{(1-\alpha)\tau}{\rho} I_R(t) - R(t)\left(\frac{\sigma\Lambda(t)}{P} + \frac{\alpha\tau}{\rho} + \mu\right).
\end{aligned} \tag{3.1}$$

The full model (within which all others are nested) is illustrated by the flow diagram in Fig.3.1 and the following assumptions are made:

1. $S(t)$ denotes the number of susceptibles at time t (Individuals that have not the virus) and can be infected at a rate $\Lambda > 0$. $I_S(t)$ is the number of infected at time t (Individuals that have the virus and can infect) and their infection is lost at a rate $\tau > 0$. $R(t)$ is the number of recovered at time t (They have a temporary immunity). $I_R(t)$ are the individuals that were in the $R(t)$ class prior to infection, with potentially reduced infectiousness by a factor η and potentially reduced infectious period by a factor ρ, i.e. infectivity being lost at a rate τ/ρ. The homotopy parameters σ, η and ρ determine the differences between primary subsequent infections in terms of susceptibility, infectiousness and duration of infection respectively, see White et al. (2007).

Figure 3.1: The boxes represent the state variables of the model for each of which there is an ordinary differential equation and the arrows the flow between the states of the model (White et al., 2007).



2. The per capita birth rate is a constant $\mu > 0$. As births balance deaths, we must have that the per capita death rate is also μ and $\dot{S}(t) + \dot{I}_S(t) + \dot{I}_R(t) + \dot{R}(t) = 0$. From (3.1) we have that $S(t) + I_S(t) + I_R(t) + R(t) = P$ is invariant. Thus $S(t) \leq P$, $I_S(t) \leq P$, $I_R(t) \leq P$, $R(t) \leq P$, for all $t \geq 0$.

3. The rate of infection $\Lambda = \beta(t)\,(I_S(t) + \eta I_R(t))$, is the product of transmission coefficient and the total effective infectiousness, where $\beta(t)$ is a continuous T-periodic function such that

$$0 < \beta^l := \min_{t\in[0,+\infty[} \beta(t) \leq \beta(t) \leq \beta^u := \max_{t\in[0,+\infty[} \beta(t)$$

and is defined by

$$\beta(t) = b\left(1 + a\cos\left(\frac{2\pi}{T}(t-\phi)\right)\right),$$

where a is the relative amplitude and varying between 0 and 1, b is the mean transmission coefficient and ϕ is the peak transmission and is given in a fraction of a year. The assumption of periodicity for the parameter $\beta(t)$ is a way of to incorporate the seasonality of the spread of RSV in the environment and have been used in several epidemiological models (White et al., 2005), (Weber et al., 2001).

4. The parameters $\Big\{\sigma, \rho, \eta, \alpha\Big\}$ take values between 0 and 1 and by setting some of them to the extremes and estimating others, it possible to obtain different models, see White et al. (2007).

For the sake convenience, we shall use the following notations:

- Denote mean value $\overline{f}$ as in (2.9),
- moreover, we set

$$C_1 = \frac{\alpha\tau}{\rho}, \quad C_2 = \frac{\tau}{\rho}, \quad \text{and} \tag{3.2}$$

$$x_1(t) = S(t)/P,\ x_2(t) = I_S(t)/P,\ x_3(t) = I_R(t)/P,\ x_4(t) = R(t)/P.$$

Therefore, the model (3.1) is normalized and with (3.2) leads to the following equivalent non-homogeneous system

$$\begin{aligned}
\dot{x_1}(t) &= \mu + C_1 - \beta(t)x_1(t)x_2(t) - \eta\beta(t)x_1(t)x_3(t) - (C_1+\mu)x_1(t),\\
\dot{x_2}(t) &= \beta(t)x_1(t)x_2(t) + \eta\beta(t)x_1(t)x_3(t) - (\tau+\mu)x_2(t),\\
\dot{x_3}(t) &= \sigma\beta(t)x_2(t)x_4(t) + \sigma\eta\beta(t)x_3(t)x_4(t) - (C_2+\mu)x_3(t),\\
\dot{x_4}(t) &= (\tau - C_1)x_2(t) + (C_2 - C_1)x_3(t) - \sigma\beta(t)x_2(t)x_4(t)\\
&\quad - \sigma\eta\beta(t)x_3(t)x_4(t) - (C_1+\mu)x_4(t),
\end{aligned} \tag{3.3}$$

where

$$x_1(t) + x_2(t) + x_3(t) + x_4(t) = 1,$$

and the dynamical behavior of the solutions of this model will be analyzed on the set $D \subset \mathbb{R}^4_+$ where

$$D = \Big\{(x_1, x_2, x_3, x_4) \in R^4_+ \,/\, x_1 + x_2 + x_3 + x_4 = 1\Big\}$$

and the set D is invariant for system (3.3).

We suppose that the following conditions for the system (3.3) are satisfied:

(H_1) The parameters $\sigma, \rho, \eta, \alpha \in]0, 1]$,

(H_2) $\alpha < \rho$,

(H_3) and $\overline{\beta} > \tau + \mu > 0$.

The chapter is organized as follows. In Section 3.2, using a Mawhin's continuation theorem, it is proved that the system (3.3) has at least one positive periodic solution. In Section 3.3, results are illustrated with two examples related to the transmission of respiratory syncytial virus. Finally conclusions are presented in Section 3.4.

3.2 Existence of Positive Periodic Solutions

In this section, based on the Mawhin's continuation theorem (Gaines and Mawhin, 1977, p.40), we study the existence of at least one positive periodic solution of (3.3), in terms of the parameters linked with the model under an interval of common period. We main result is the following

Theorem 3.2.1 *Assume that the above conditions H_1, H_2 and H_3 are satisfied, then the system (3.3) has at least one positive T-periodic solution.*

Proof. In order to prove the existence of positive periodic solutions of system (3.3), first we consider the following change of variables:

$$x_i(t) = e^{u_i(t)}, \text{ for all } i = 1, ..., 4 \text{ and } t \geq 0. \tag{3.4}$$

(Since $x_i(t) \leq 1$, for all $t \geq 0$, then $u_i(t) \leq 0$, for all $i = 1, ..., 4$ and $t \geq 0$). Thus system (3.3) can be written in the from

$$\begin{aligned}
\dot{u_1}(t) &= (\mu + C_1)e^{-u_1(t)} - \beta(t)e^{u_2(t)} - \beta(t)\eta e^{u_3(t)} - (C_1 + \mu), \\
\dot{u_2}(t) &= \beta(t)e^{u_1(t)} + \beta(t)\eta e^{u_1(t)}e^{u_3(t)-u_2(t)} - (\tau + \mu), \\
\dot{u_3}(t) &= \sigma\beta(t)e^{u_2(t)}e^{u_4(t)-u_3(t)} + \sigma\eta\beta(t)e^{u_4(t)} - (C_2 + \mu), \\
\dot{u_4}(t) &= (\tau - C_1)e^{u_2(t)-u_4(t)} + (C_2 - C_1)e^{u_3(t)-u_4(t)} \\
&\quad - \sigma\beta(t)e^{u_2(t)} - \sigma\eta\beta(t)e^{u_3(t)} - (C_1 + \mu).
\end{aligned} \tag{3.5}$$

It is easy to see from (3.4) that if (3.5) has one T-periodic solution $(u_1^*(t), u_2^*(t), u_3^*(t), u_3^*(t))^{\mathbf{T}}$, then $(x_1^*(t), x_2^*(t), x_3^*(t), x_4^*(t))^{\mathbf{T}}$ is a positive T-periodic solution of the system (3.3), and consequently the system (3.1) has at least one positive T-periodic solution. Therefore, to complete the proof, it suffices to show that the system (3.5) has at least one T-periodic solution. Let us introduce the following normed space

$$X = Y = \Big\{ u(t) = (u_1(t), u_2(t), u_3(t), u_4(t))^{\mathbf{T}} \in C(\mathbb{R}, \mathbb{R}_-^4)/u(T+t) = u(t) \Big\},$$

with the following norm

$$||u|| = ||(u_1(t), u_2(t), u_3(t), u_4(t))^{\mathbf{T}}|| = \sum_{i=1}^{4} \max_{t\in[0,T]} |u_i(t)|,$$

for any $u \in X$, where $|\cdot|$ is the Euclidean norm. Then X and Y are both Banach spaces with the norm $||\cdot||$. Let $u \in X$, and define

$$\begin{aligned}
\delta_1(u(t), t) &= (\mu + C_1)e^{-u_1(t)} - \beta(t)e^{u_2(t)} - \beta(t)\eta e^{u_3(t)} - (C_1 + \mu),\\
\delta_2(u(t), t) &= \beta(t)e^{u_1(t)} + \beta(t)\eta e^{u_1(t)} e^{u_3(t)-u_2(t)} - (\tau + \mu),\\
\delta_3(u(t), t) &= \sigma\beta(t)e^{u_2(t)}e^{u_4(t)-u_3(t)} + \sigma\eta\beta(t)e^{u_4(t)} - (C_2 + \mu),\\
\delta_4(u(t), t) &= (\tau - C_1)e^{u_2(t)-u_4(t)} + (C_2 - C_1)e^{u_3(t)-u_4(t)}\\
&\quad - \sigma\beta(t)e^{u_2(t)} - \sigma\eta\beta(t)e^{u_3(t)} - (C_1 + \mu).
\end{aligned}$$

Is it clear that $\delta_i(u(t), t) \in C(\mathbb{R}, \mathbb{R})$ for $i = 1, ..., 4$ and are all T-periodic. Let

$$L : DomL \cap X \longrightarrow X, \text{ such that } L(u(t)) = \dot{u}(t) = \frac{du(t)}{dt},$$

where

$$DomL = \Big\{ u(t) \in C^1(\mathbb{R}, \mathbb{R}_-^4)/u(T+t) = u(t) \Big\} \subseteq X \quad \text{and } N : X \longrightarrow X,$$

such that

$$Nu(t) = \Big(\delta_1(u(t), t),\ \delta_2(u(t), t),\ \delta_3(u(t), t),\ \delta_4(u(t), t) \Big)^{\mathbf{T}}, u \in X.$$

Let $P : X \longrightarrow X$ and $Q : Y \longrightarrow Y$ are continuous projectors such that

$$Pu(t) = Qu(t) = \frac{1}{T}\int_0^T u(t)dt.$$

Then

$$KerL = \mathbb{R}^4_-, \;\; ImL = KerQ = Im(I-Q) = \Big\{u \in X \;/ \frac{1}{T}\int_0^T u(t)dt = 0\Big\},$$

is closed in X and $IndiceL = dimKerL - CodimImL = 0$, thus L is a Fredholm mapping of index zero. Therefore, the mapping

$$L_p = L|_{DomL\cap KerP} : (I-P)X \longrightarrow ImL$$

is invertible (see (1.5.9)-(1.5.11)). Furthermore, the inverse (to L_p), $K_p : ImL \longrightarrow DomL \cap KerP$, exists and has the form

$$K_p(u) = \int_0^t u(s)ds - \frac{1}{T}\int_0^T\int_0^t u(s)dsdt, \quad t \in [0,T].$$

Thus, $QN : X \longrightarrow X$ is $QNu(t) = (q_1, q_2, q_3, q_4)^{\mathbf{T}}$ where

$$q_i = \frac{1}{T}\int_0^T \delta_i(u(\tau),\tau)d\tau, \quad \text{for } i = 1,...,4.$$

Now $K_P(I-Q)N : X \longrightarrow X$ is given by

$$K_P(I-Q)Nu(t) = \big(\varphi_1(u(t),t), \varphi_2(u(t),t), \varphi_3(u(t),t), \varphi_4(u(t),t)\big)^{\mathbf{T}},$$

where

$$\begin{aligned}\varphi_i(u(t),t) = &\int_0^t \delta_i(u(s),s)ds - \frac{1}{T}\int_0^T\int_0^t \delta_i(u(s),s)dsdt \\ &- \Big(\frac{t}{T} - \frac{1}{2}\Big)\int_0^T \delta_i(u(s),s)ds,\end{aligned}$$

for $i = 1,...,4$. Is clear that QN and $K_P(I-Q)N$ are continuous. Using the Arzela-Ascoli Theorem (Dieudonne, 1969) it is not difficult to show that $\overline{K_P(I-Q)N(\overline{\Omega})}$ is compact for any open bounded set $\Omega \subset X$. Moreover, $QN(\overline{\Omega})$ is bounded. Thus, N is $L-$compact under $\overline{\Omega}$ with any open

bounded set $\Omega \subset X$. The isomorphism J from ImQ under $KerL$ can be the identity mapping, since that $ImQ = KerL$.
To apply the continuation theorem, we need to search an appropriate open bounded subset Ω. In order to do it, we use the operator equation $Lu = \lambda Nu$ with $\lambda \in]0,1[$, we derive

$$\begin{aligned}
\dot{u_1}(t) &= \lambda\Big((\mu + C_1)e^{-u_1(t)} - \beta(t)e^{u_2(t)} - \beta(t)\eta e^{u_3(t)} - (C_1+\mu)\Big), \\
\dot{u_2}(t) &= \lambda\Big(\beta(t)e^{u_1(t)} + \beta(t)\eta e^{u_1(t)}e^{u_3(t)-u_2(t)} - (\tau+\mu)\Big), \\
\dot{u_3}(t) &= \lambda\Big(\sigma\beta(t)e^{u_2(t)}e^{u_4(t)-u_3(t)} + \sigma\eta\beta(t)e^{u_4(t)} - (C_2+\mu)\Big), \\
\dot{u_4}(t) &= \lambda\Big((\tau - C_1)e^{u_2(t)-u_4(t)} + (C_2 - C_1)e^{u_3(t)-u_4(t)} - \sigma\beta(t)e^{u_2(t)} \\
&\qquad - \sigma\eta\beta(t)e^{u_3(t)} - (C_1+\mu)\Big).
\end{aligned} \tag{3.6}$$

Suppose that $u(t) = (u_1(t), u_2(t), u_3(t), u_4(t))^{\mathbf{T}} \in X$ is any solution of system (3.6) for a certain $\lambda \in]0,1[$. Integrating (3.6) on both sides from 0 to T with respect to t, we obtain that

$$\begin{aligned}
&\int_0^T \beta(t)e^{u_2(t)}dt + \eta\int_0^T \beta(t)e^{u_3(t)}dt + (C_1+\mu)T = (\mu + C_1)\int_0^T e^{-u_1(t)}dt, \\
&\int_0^T \beta(t)e^{u_1(t)}dt + \eta\int_0^T \beta(t)e^{u_1(t)}e^{u_3(t)-u_2(t)}dt = (\tau+\mu)T, \\
&\int_0^T \sigma\beta(t)e^{u_2(t)}e^{u_4(t)-u_3(t)}dt + \sigma\eta\int_0^T \beta(t)e^{u_4(t)}dt = (C_2+\mu)T, \\
&\int_0^T \sigma\beta(t)e^{u_2(t)}dt + \sigma\eta\int_0^T \beta(t)e^{u_3(t)}dt = -(C_1+\mu)T \\
&+ (\tau - C_1)\int_0^T e^{u_2(t)-u_4(t)}dt + (C_2 - C_1)\int_0^T e^{u_3(t)-u_4(t)}dt.
\end{aligned} \tag{3.7}$$

Since $e^{u_i(t)} \leq 1$ for all $t \geq 0$ (with $i = 1,2,3,4$), from (3.6) and (3.7), we obtain

$$\begin{aligned}
\int_0^T |\dot{u_1}(t)|dt \leq \lambda\Bigg[&(\mu + C_1)\int_0^T e^{-u_1(t)}dt + \int_0^T \beta(t)e^{u_2(t)}dt \\
&+ \eta\int_0^T \beta(t)e^{u_3(t)}dt + (C_1+\mu)T\Bigg].
\end{aligned}$$

Thus

$$\begin{aligned}\int_0^T |\dot{u_1}(t)|dt &< 2\left[\int_0^T \beta(t)e^{u_2(t)}dt + \eta\int_0^T \beta(t)e^{u_3(t)}dt + (C_1+\mu)T\right]\\ &< 2T\left[\overline{\beta} + \eta\overline{\beta} + (C_1+\mu)\right] := K_1. \end{aligned} \tag{3.8}$$

$$\begin{aligned}\int_0^T |\dot{u_2}(t)|dt &\leq \lambda\left[\int_0^T \beta(t)e^{u_1(t)}dt + \eta\int_0^T \beta(t)e^{u_1(t)}e^{u_3(t)-u_2(t)}dt\right.\\ &\left. + (\tau+\mu)T\right] < 2T\left[(\tau+\mu)\right] := K_2. \end{aligned} \tag{3.9}$$

$$\begin{aligned}\int_0^T |\dot{u_3}(t)|dt &\leq \lambda\left[\sigma\int_0^T \beta(t)e^{u_2(t)}e^{u_4(t)-u_3(t)}dt + \sigma\eta\int_0^T \beta(t)e^{u_4(t)}dt\right.\\ &\left. + (C_2+\mu)T\right] < 2T\left[(C_2+\mu)\right] := K_3. \end{aligned} \tag{3.10}$$

$$\begin{aligned}\int_0^T |\dot{u_4}(t)|dt \leq \lambda&\left[(\tau - C_1)\int_0^T e^{u_2(t)-u_4(t)}dt + (C_2 - C_1)\int_0^T e^{u_3(t)-u_4(t)}dt\right.\\ &\left. + \sigma\int_0^T \beta(t)e^{u_2(t)}dt + \sigma\eta\int_0^T \beta(t)e^{u_3(t)}dt + (C_1+\mu)T\right], \end{aligned}$$

and thus it follows that

$$\int_0^T |\dot{u_4}(t)|dt < 2T\left[\sigma\overline{\beta} + \sigma\eta\overline{\beta} + (C_1+\mu)\right] := K_4. \tag{3.11}$$

Next, multiplying the first equation of systems (3.5) by $e^{u_1(t)}$, the second equation by $e^{u_2(t)}$, the third equation by $e^{u_3(t)}$, the fourth equation by $e^{u_4(t)}$ and integrating over the interval $[0,T]$, it follows that

$$
\begin{aligned}
&\int_0^T \beta(t)e^{u_1(t)}e^{u_2(t)}dt + \int_0^T \eta\beta(t)e^{u_1(t)}e^{u_3(t)}dt = (\mu + C_1)T \\
&- (C_1+\mu)\int_0^T e^{u_1(t)}dt, \\
&\int_0^T \beta(t)e^{u_1(t)}e^{u_2(t)}dt + \int_0^T \eta\beta(t)e^{u_1(t)}e^{u_3(t)}dt = (\tau+\mu)\int_0^T e^{u_2(t)}dt, \\
&\int_0^T \sigma\beta(t)e^{u_2(t)}e^{u_4(t)}dt + \sigma\eta\int_0^T \beta(t)e^{u_3(t)}e^{u_4(t)}dt = (C_2+\mu)\int_0^T e^{u_3(t)}dt, \\
&\int_0^T (\tau - C_1)e^{u_2(t)}dt + (C_2 - C_1)\int_0^T e^{u_3(t)}dt = \sigma\int_0^T \beta(t)e^{u_2(t)}e^{u_4(t)}dt \\
&+ \sigma\eta\int_0^T \beta(t)e^{u_3(t)}e^{u_4(t)}dt + (C_1+\mu)\int_0^T e^{u_4(t)}dt. \qquad (3.12)
\end{aligned}
$$

Since we are considering the solution $u(t) \in X$ in the interval $[0, T]$, there exist $\xi_i, \eta_i \in [0, T]$ for $i = 1, 2, 3, 4$, such that

$$
u_i(\xi_i) = \min_{t\in[0,T]} u_i(t), \qquad u_i(\eta_i) = \max_{t\in[0,T]} u_i(t), \qquad i = 1, 2, 3, 4.
$$

Thus, from second equation of (3.12) gives

$$
(\tau+\mu)\int_0^T e^{u_2(t)}dt \leq \int_0^T \beta(t)e^{u_1(t)}(t)dt + \int_0^T \beta(t)e^{u_1(t)}dt
$$

and there exist $\theta_2^* \in [0, T]$ such that

$$
T(\tau+\mu)e^{u_2(\theta_2^*)} \leq 2T\overline{\beta}e^{u_1(\eta_1)} < 2T\left(\overline{\beta} + (\tau+\mu)\right)e^{u_1(\eta_1)}.
$$

Therefore $e^{u_1(\eta_1)} > \frac{(\tau+\mu)e^{u_2(\theta_2^*)}}{2\left(\overline{\beta}+(\tau+\mu)\right)}$, thus

$$
u_1(\eta_1) > \ln\left(\frac{(\tau+\mu)e^{u_2(\theta_2^*)}}{2\left(\overline{\beta}+(\tau+\mu)\right)}\right) = M_1. \qquad (3.13)
$$

Now, subtracting the first equation from the second equation of systems (3.12), one gets

$$
T(C_1+\mu) = (\tau+\mu)\int_0^T e^{u_2(t)}dt + (C_1+\mu)\int_0^T e^{u_1(t)}dt. \qquad (3.14)
$$

From (3.14) there exist $\theta_1^* \in [0,T]$ such that

$$T(C_1+\mu) = (\tau+\mu)\int_0^T e^{u_2(t)}dt + (C_1+\mu)e^{u_1(\theta_1^*)}T,$$

and with $1 > M = 1 - e^{u_1(\theta_1^*)} > 0$, we have

$$T(C_1+\mu)M \leq T(\tau+\mu)e^{u_2(\eta_2)} < T(\tau+(C_1+\mu))e^{u_2(\eta_2)}.$$

Therefore $e^{u_2(\eta_2)} > \frac{(C_1+\mu)M}{(\tau+(C_1+\mu))}$, thus

$$u_2(\eta_2) > \ln\left(\frac{(C_1+\mu)M}{(\tau+(C_1+\mu))}\right) = M_2. \tag{3.15}$$

Now, from third equation of (3.12) there are $\theta_3^*, \theta_3^\circ \in [0,T]$ such that

$$\begin{aligned}\sigma T\overline{\beta}e^{(u_2+u_4)(\theta_3^*)} &\leq (C_2+\mu)\int_0^T e^{u_3(t)}dt \\ &< T(\sigma\overline{\beta}e^{(u_2+u_4)(\theta_3^*)} + C_2+\mu)e^{u_3(\eta_3)},\end{aligned}$$

therefore $e^{u_3(\eta_3)} > \frac{\sigma\overline{\beta}e^{(u_2+u_4)(\theta_3^*)}}{\sigma\overline{\beta}e^{(u_2+u_4)(\theta_3^*)}+C_2+\mu}$, thus

$$u_3(\eta_3) > \ln\left(\frac{\sigma\overline{\beta}e^{(u_2+u_4)(\theta_3^*)}}{\sigma\overline{\beta}e^{(u_2+u_4)(\theta_3^*)}+C_2+\mu}\right) = M_3, \tag{3.16}$$

and also $T(C_2+\mu)e^{u_3(\theta_3^\circ)} \leq 2T\overline{\beta}e^{u_4(\eta_4)} < 2T\left(\overline{\beta}+(C_2+\mu)\right)e^{u_4(\eta_4)}$. It follows that $e^{u_4(\eta_4)} > \frac{(C_2+\mu)e^{u_3(\theta_3^\circ)}}{2\left(\overline{\beta}+(C_2+\mu)\right)}$ and consequently

$$u_4(\eta_4) > \ln\left(\frac{(C_2+\mu)e^{u_3(\theta_3^\circ)}}{2\left(\overline{\beta}+(C_2+\mu)\right)}\right) = M_4. \tag{3.17}$$

Now, summing the third and the last equation of (1.5.10) it follows that

$$(\tau - C_1)\int_0^T e^{u_2(t)}dt = (C_1+\mu)\int_0^T e^{u_4(t)}dt + (\mu+C_1)\int_0^T e^{u_3(t)}dt. \tag{3.18}$$

We subtract (3.14) from (3.18) and simplifying we get that

$$\int_0^T e^{u_1(t)}dt + \int_0^T e^{u_2(t)}dt + \int_0^T e^{u_3(t)}dt + \int_0^T e^{u_4(t)}dt = T. \tag{3.19}$$

We derive from (3.19) that there exists $\theta_i \in [0,T]$ such that $e^{u_i(\xi_i)} < 1 - e^{u_j(\theta_i)}$, thus

$$u_i(\xi_i) < \ln\left(1 - e^{u_j(\theta_i)}\right) =: m_i \tag{3.20}$$

where $0 < 1 - e^{u_j(\theta_i)} < 1$, for $i \neq j$ and $i, j = 1,2,3,4$. For $t \in [0,T]$, from (3.8,3.9,3.10,3.11) and (3.20) one gets

$$u_i(t) \leq u_i(\xi_i) + \int_{\xi_i}^T |\dot{u}_i(t)|dt \leq u_i(\xi_i) + \int_0^T |\dot{u}_i(t)|dt < m_i + K_i, \tag{3.21}$$

for $i = 1,2,3,4$. Using the same argument, with (3.13,3.15,3.16,3.17) we obtain

$$u_i(t) \geq u_i(\eta_i) - \int_0^T |\dot{u}_i(t)|dt > M_i - K_i, \tag{3.22}$$

for $i = 1,2,3,4$. Thus, from (3.21) and (3.22) leads to

$$\max_{t\in[0,T]} |u_i(t)| < \max\Big\{|m_i + K_i|, |M_i - K_i|\Big\} = R_i, \text{ for } i = 1,2,3,4. \tag{3.23}$$

Clearly, the R_i $(i = 1,2,3,4)$ are independent of λ. On the other hand, for $\mu_0 \in [0,1]$, we consider the following algebraic equations

$$\begin{aligned}
&(\mu + C_1)e^{-u_1} - \overline{\beta}e^{u_2} - \mu_0\big(\overline{\beta}\eta e^{u_3} + (C_1 + \mu)\big) = 0,\\
&\overline{\beta}e^{u_1} - (\tau + \mu) + \mu_0\overline{\beta}\eta e^{u_1}e^{u_3 - u_2} = 0,\\
&\sigma\overline{\beta}e^{u_2}e^{u_4 - u_3} - (C_2 + \mu) + \mu_0\sigma\eta\overline{\beta}e^{u_4} = 0,\\
&(\tau - C_1)e^{u_2 - u_4} - (C_1 + \mu) + \mu_0\big((C_2 - C_1)e^{u_3 - u_4} - \sigma\overline{\beta}e^{u_2} - \sigma\eta\overline{\beta}e^{u_3}\big) = 0,
\end{aligned} \tag{3.24}$$

where $(u_1, u_2, u_3, u_4)^{\mathbf{T}} \in \mathbb{R}^4_-$. From the second equation of (3.24), we have

$$e^{u_1} \leq \frac{\tau + \mu}{\overline{\beta}} = B_1. \tag{3.25}$$

Now, from first and second equation of (3.24), one gets that

$$\mu + C_1 = \mu_0(\mu + C_1)e^{u_1} + (\mu + \tau)e^{u_2}, \tag{3.26}$$

from which we derive

$$e^{u_2} \leq \frac{\mu + C_1}{\mu + \tau} = B_2, \tag{3.27}$$

and together with (3.25) so we have

$$e^{u_2} \geq B_2 \frac{(\overline{\beta} - (\mu + \tau))}{\overline{\beta}} = b_2. \tag{3.28}$$

Next, from third equation of (3.24), we obtain

$$\mu_0\sigma\beta e^{u_2}e^{u_4} + \mu_0\sigma\beta e^{u_3}e^{u_4} \geq \mu_0(C_2 + \mu)e^{u_3},$$

and with the fourth equation of (3.24) one gets that

$$(\tau - C_1)e^{u_2} \geq \mu_0(\mu + C_1)e^{u_3} + (\mu + C_1)e^{u_4}. \tag{3.29}$$

Thus, using (3.27) in (3.29), it follows that

$$e^{u_4} \leq \frac{\tau - C_1}{\tau + \mu} = B_4. \tag{3.30}$$

Now, multiplying the second equation of (3.24) by $\sigma e^{u_2}e^{u_4}$ and the third equation of (3.24) by $e^{u_1}e^{u_3}$, one gets

$$e^{u_1}e^{u_3} \leq \frac{\tau + \mu}{C_2 + \mu}. \tag{3.31}$$

From (3.25) it is easy to see that

$$e^{u_3} \leq \frac{\overline{\beta}}{\overline{\beta} + C_2 + \mu} = B_3, \tag{3.32}$$

satisfy (3.31). Thus, multiplying the first equation of (3.24) by e^{u_1}, the last equation of (3.24) by e^{u_4}, using (3.27) and (3.32) we can see that

$$(\mu + C_1) \leq \overline{\beta}e^{u_1} + \overline{\beta}e^{u_1} + (C_1 + \mu)e^{u_1}$$

and

$$(\tau - C_1) \le (C_1 + \mu)e^{u_4} + \overline{\beta}e^{u_4} + \overline{\beta}e^{u_4}.$$

Therefore, we obtain that

$$e^{u_1} > \frac{\mu + C_1}{3\overline{\beta}} = b_1, \tag{3.33}$$

and

$$e^{u_4} > \frac{\tau - C_1}{3\overline{\beta} + \tau - C_1} b_2 = b_4. \tag{3.34}$$

Finally, from third equation of (3.24), we get that

$$(C_2 + \mu + \sigma\overline{\beta})e^{u_3} > \sigma\overline{\beta}e^{u_2}e^{u_4},$$

and with (3.28) and (3.34) one gets that

$$e^{u_3} > \frac{\sigma\overline{\beta}}{C_2 + \mu + \sigma\overline{\beta}} b_2 b_4 = b_3. \tag{3.35}$$

If we select $R = \max\limits_{i\in\{1,\ldots,4\}} \Big\{ |\ln(B_i)|, |\ln(b_i)| \Big\}$, then

$$|u_1| + |u_2| + |u_3| + |u_4| < 4R = R_0. \tag{3.36}$$

We choose $R_T = \sum_{i=0}^{4} R_i$, and we take

$$\Omega = \Big\{ u(t) = (u_1(t), u_2(t), u_3(t), u_4(t))^{\mathbf{T}} \in X : \|u\| < R_T \Big\}, \tag{3.37}$$

since, for each $\lambda \in]0,1[$, $u \in \partial\Omega \cap DomL$, $Lu \neq \lambda Nu$, then Ω verifies requirement 1 of the Theorem 1.5.12. When $u = (u_1, u_2, u_3, u_4)^{\mathbf{T}} \in \partial\Omega \cap KerL = \partial\Omega \cap \mathbb{R}^4_-$, u is a constant vector in $\mathbb{R}^4_-$ with $\|u\| = R_T$. If $QNu = 0$, then $(u_1, u_2, u_3, u_4)^{\mathbf{T}}$ is a constant solution of the system

$$\begin{aligned}
&(\mu + C_1)e^{-u_1} - \overline{\beta}e^{u_2} - \mu_0\big(\overline{\beta}\eta e^{u_3} + (C_1 + \mu)\big) = 0,\\
&\overline{\beta}e^{u_1} - (\tau + \mu) + \mu_0\overline{\beta}\eta e^{u_1}e^{u_3 - u_2} = 0,\\
&\sigma\overline{\beta}e^{u_2}e^{u_4 - u_3} - (C_2 + \mu) + \mu_0\sigma\eta\overline{\beta}e^{u_4} = 0,\\
&(\tau - C_1)e^{u_2 - u_4} - (C_1 + \mu) + \mu_0\big((C_2 - C_1)e^{u_3 - u_4} - \sigma\overline{\beta}e^{u_2} - \sigma\eta\overline{\beta}e^{u_3}\big) = 0,
\end{aligned}$$

with $\mu_0 = 1$. From (3.36) we have that $\|(u_1, u_2, u_3, u_4)^{\mathbf{T}}\| < R_0$ which is in contradiction to $\|(u_1, u_2, u_3, u_4)^{\mathbf{T}}\| = R_T$. It follows that for each $u \in \partial\Omega \cap KerL$, $QNu \neq 0$. This shows that condition 2 of the Theorem 1.5.12 is satisfied. In order to verify the condition 3 of Theorem 1.5.12, we define $\phi : (DomL \cap KerL) \times [0,1] \longrightarrow X$ by

$$\phi(u_1, u_2, u_3, u_4, \mu_0) = \begin{bmatrix} (\mu + C_1)e^{-u_1} - \overline{\beta}e^{u_2} \\ \overline{\beta}e^{u_1} - (\tau + \mu) \\ \sigma\overline{\beta}e^{u_2}e^{u_4 - u_3} - (C_2 + \mu) \\ (\tau - C_1)e^{u_2 - u_4} - (C_1 + \mu) \end{bmatrix} + \mu_0 \begin{bmatrix} -\overline{\beta}\eta e^{u_3} - (C_1 + \mu) \\ \overline{\beta}\eta e^{u_1}e^{u_3 - u_2} \\ \sigma\eta\overline{\beta}e^{u_4} \\ (C_2 - C_1)e^{u_3 - u_4} - \sigma\eta\overline{\beta}e^{u_3} - \sigma\overline{\beta}e^{u_2} \end{bmatrix},$$

where $\mu_0 \in [0,1]$ is a parameter. When $u = (u_1, u_2, u_3, u_4)^{\mathbf{T}} \in \partial\Omega \cap KerL = \partial\Omega \cap \mathbb{R}^4_-$, u is a constant vector in $\mathbb{R}^4_-$ with $\|u\| = R_T$ and $\phi(u_1, u_2, u_3, u_4, \mu_0) \neq 0$. So, due to homotopy invariance of topology degree (Gaines and Mawhin, 1977) we have

$$\begin{aligned}
&deg\left(JQN((u_1, u_2, u_3, u_4)^{\mathbf{T}}), \partial\Omega \cap KerL, (0,0,0,0)^{\mathbf{T}}\right) \\
&= deg\left(\phi(u_1, u_2, u_3, u_4, 1), \Omega \cap KerL, (0,0,0,0)^{\mathbf{T}}\right) \\
&= deg\left(\phi(u_1, u_2, u_3, u_4, 0), \Omega \cap KerL, (0,0,0,0)^{\mathbf{T}}\right) \\
&= deg\Bigg\{\Big((\mu + C_1)e^{-u_1} - \overline{\beta}e^{u_2},\ \overline{\beta}e^{u_1} - (\tau + \mu),\ \sigma\overline{\beta}e^{u_2}e^{u_4 - u_3} - (C_2 + \mu), \\
&\qquad (\tau - C_1)e^{u_2 - u_4} - (C_1 + \mu)\Big)^{\mathbf{T}},\ \Omega \cap KerL,\ (0,0,0,0)^{\mathbf{T}}\Bigg\}.
\end{aligned}$$

If the conditions of Theorem 3.2.1 are satisfied, it follows that the system of algebraic equations

$$\begin{aligned}(\mu+C_1)x^{-1}-\overline{\beta}y &= 0,\\ \overline{\beta}x-(\tau+\mu) &= 0,\\ \sigma\overline{\beta}yzw^{-1}-(C_2+\mu) &= 0,\\ (\tau-C_1)yz^{-1}-(C_1+\mu) &= 0,\end{aligned}$$

has a unique solution $(x,y,w,z)^{\mathbf{T}}$=$(e^{u_1^*},e^{u_2^*},e^{u_3^*},e^{u_4^*})^{\mathbf{T}}$ which satisfies

$$e^{u_1^*}=\frac{(\tau+\mu)}{\overline{\beta}}>0,\ e^{u_2^*}=\frac{(\mu+C_1)}{\tau+\mu}>0,$$

$$e^{u_3^*}=\frac{(\tau-C_1)(\mu+C_1)\sigma\overline{\beta}}{(C_2+\mu)(\tau+\mu)^2}>0,\ e^{u_4^*}=\frac{(\tau-C_1)}{(\tau+\mu)}>0.$$

Hence,

$$deg\Big(JQN((u_1,u_2,u_3,u_4)^{\mathbf{T}}),\partial\Omega\cap KerL,(0,0,0,0)^{\mathbf{T}}\Big)=$$

$$=sign\begin{vmatrix}-(\mu+C_1)e^{-u_1^*} & -\overline{\beta}e^{u_2^*} & 0 & 0\\ \overline{\beta}e^{u_1^*} & 0 & 0 & 0\\ 0 & \sigma\overline{\beta}e^{u_2^*}e^{-u_3^*}e^{u_4^*} & -\sigma\overline{\beta}e^{u_2^*}e^{-u_3^*}e^{u_4^*} & \sigma\overline{\beta}e^{u_2^*}e^{-u_3^*}e^{u_4^*}\\ 0 & (\tau-C_1)e^{u_2^*}e^{-u_4^*} & 0 & -(\tau-C_1)e^{u_2^*}e^{-u_4^*}\end{vmatrix}$$

$$=sgn\{\sigma\overline{\beta}^3(\tau-C_1)e^{u_1^*+2u_2^*-u_3^*}\}=1.$$

This completes the proof of condition (3) of theorem 1.5.12. Therefore, by continuation theorem the system (3.5) has at least one T-periodic solution $(u_1^*(t),u_2^*(t),u_3^*(t),u_4^*(t))^{\mathbf{T}}\in DomL\cap\overline{\Omega}$. Thus the result has been established.

3.3 Numerical Simulations

Finally, we give two examples to illustrate the feasibility of the main results. To illustrate the periodic behavior of the solution of the model (3.3), we perform numerical simulations using the biologically feasible parameter values given in Table 3.1. In Fig.3.2 can be observed the periodic behavior of the model with parameters values for the city Madrid in regard to the infected population and in Fig. 3.3 for the city of Rio de Janeiro.

Table 3.1: Parameter values α, ρ, σ and η are fixed and others μ, τ, b, a, ϕ and T are taken from White et al. (2007)

City	μ	τ	b	a	ϕ	α	ρ	σ	η	T
Madrid	0.0120	9	11.716	0.29	0.92	0.1	0.3	0.1	0.1	1
Rio de Janeiro	0.0145	9	15.324	0.22	0.36	0.2	0.3	0.2	0.2	1

Figure 3.2: Numerical approximations of solutions of system (3.2) in Madrid using the adaptive MatLab solver ode45.

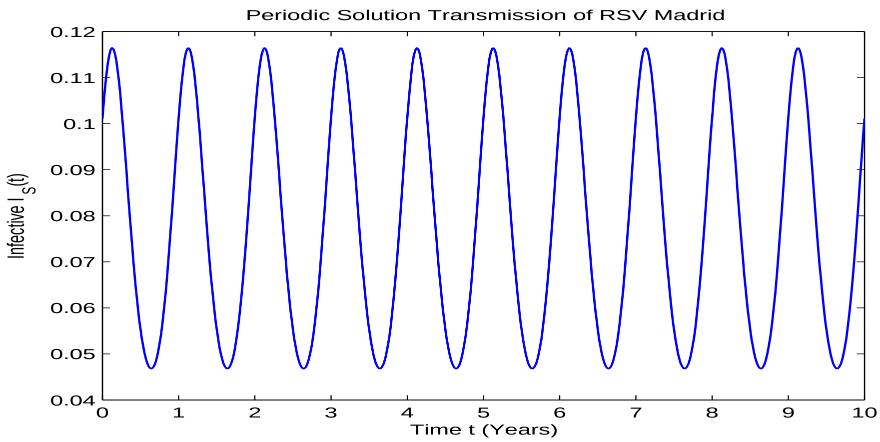
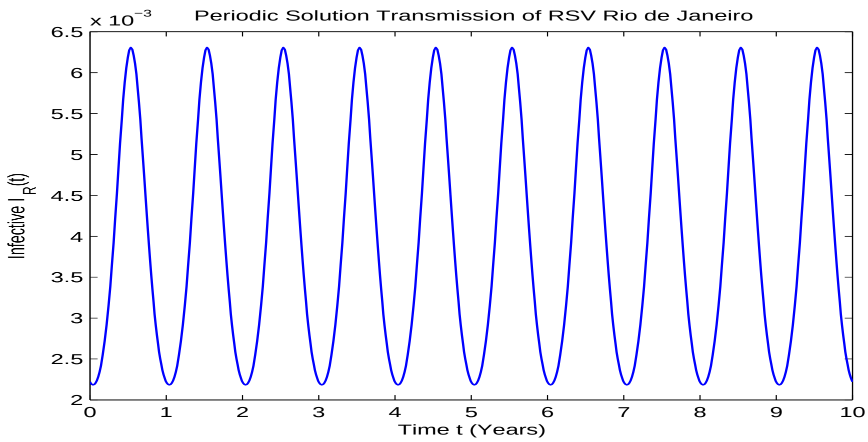


Figure 3.3: Numerical approximations of solutions of system (3.2) in Rio de Janeiro using the adaptive MatLab solver ode45.



3.4 Conclusion

In this chapter, we applied the method of coincidence degree in order to obtain verifiable sufficient criteria for the existence of positive periodic solution of a nested mathematical model of the dynamical transmission of respiratory syncytial virus presented in White et al. (2007). This result guarantees that this type of population models with seasonal forcing $\Lambda = \beta(t)\,(I_S(t) + \eta I_R(t))$, where $\beta(t)$ is a continuous T-periodic function, has positive periodic solution. As an application, two numerical simulation were done using reported data of infected population in the cities of Madrid and Rio de Janeiro, in order to illustrate the periodic behavior of system (3.1).

Chapter 4

Nonstandard numerical method for a mathematical model of *RSV* epidemiological transmission†

In this chapter we develop a nonstandard numerical scheme for a $SIRS$ seasonal epidemiological model for RSV transmission. This nonstandard numerical scheme preserves the positivity of the continuous model and is applied to approximate the solution using different sizes of step. Finally this method is compared with some well-known explicit methods and simulations with data from Gambia and Finland are carried out.

†This chapter is based on Arenas et al. (2008c)

4.1 Introduction

Mathematical models have been revealed as a powerful tool to analyze the epidemiology of the infectious illness, to understand its behavior, to predict its impact and to find out how external factors change the impact. In the case of RSV, the building of a reliable model is a priority objective to predict the medical care requirements needed in next seasons. Mathematical models for RSV have been developed previously. For instance, in Weber et al. (2001), a $SIRS$ (susceptible - infectious - recovered - susceptible) and a $MSEIRS$ (maternally derived immunity - susceptible - latent - infectious - recovered - susceptible) mathematical models with four possible re-infections are studied and applied with data from Gambia, Singapore, Florida and Finland. In White et al. (2007) a nested RSV model, stochastic simulations and fitting data from several countries are presented.

In Mathematical epidemiologic and others areas, models are non-linear IVP (initial value problem) systems. But, they do not have solution in closed form (in term of the model parameters only) or it can locally predict the behavior of systems. It is very important to design robust numerical methods to observe the behavior of the numerical solutions numerically of the systems for several time steps. It is well known that the traditional schemes like forward Euler, Runge-Kutta and so others to solve nonlinear initial values problems, sometimes fail, generating oscillations, bifurcations, chaos and spurious states (Lambert, 1973), (Solis and Chen-Charpentier, 2004), (Arenas et al., 2009b), (Arenas et al., 2009a). Moreover some methods despite using adaptative step sizes still fail (see for instance Moghadas et al. (2003)). One alternative way to prevent all this class of numerical instabilities is the construction of schemes of finite differences using different techniques. The nonstandard finite difference techniques developed by Ronald Mickens (see (Mickens, 1994), (Mickens, 2002)) have brought a creation of new methods, see Moghadas et al. (2004), Anguelov and Lubuma (2003), Gumel et al. (2003), Piyawong et al. (2003), Dimitrov and Kojouharov (2005), Dimitrov and Kojouharov (2006), Jódar et al. (2008b), Villanueva et al. (0154).

Mickens Mickens (2002) introduced a nonstandard difference method that produces solutions that are exact, and therefore, have the same properties as the analytical solutions. So, while his method is ideal, it is not obvious how to derive related methods for the majority of equations. He gave the method for linear differential equations, both first-order and higher-order, for equations with a quadratic right-hand side, including the logistic equation, and others for which there is an exact analytical solution. Mickens' method has two main differences with standard difference methods. The first is that the first derivative usually is replaced by $(u_{k+l} - u_k)/\phi(h)$, where $u_k = u(kh)$ with h the uniform time step and $\phi(h) = h + \mathcal{O}(h^2)$. The second is that some of the terms in the righthand side at evaluated at different time steps. But the question is how to generalize Mickens' method to other equations where there is no exact solution. Sometimes, the straightforward generalizations of changing the derivative for the difference approximation with the different denominator and using the two time levels for the different terms in the right-hand side of the equation works and produces solutions that, even though they are no longer exact, have the same stability properties. But, sometimes, this generalization does not work, see (Solis and Chen-Charpentier, 2004). The aim of this chapter is to present the construction of a nonstandard finite difference scheme for the numerical solution of the $SIRS$ model for modeling transmission of respiratory syncytial virus RSV presented by Weber et al. (2001), in which we combine a nonstandard difference method and a predictor-corrector. We analyze its behavior for different parameter values of the model.

The organization of this chapter is as follows. In Section 4.2, some mathematical preliminaries and the model of transmission of RSV are proposed. In Section 4.3 we build the numerical scheme numerical using the nonstandard difference techniques. In Section 4.4 numerical simulations for different parameter values of the model and different steps sizes of the numerical scheme are reported and finally, in Section 4.5 ends the chapter with discussion and conclusions are presented.

4.2 Mathematical model

In this section, we presented the continuous mathematical model for the transmission of virus RSV showed by Weber et al. (2001), which is a particular case of (2.1)-(2.3) when the following parameters are constants, i.e., $\mu(t) := \mu$, $\nu(t) = \nu$, $\gamma(t) = \gamma$. Thus, it obtains the following $SIRS$ (Susceptibles, Infected, Recovered and Susceptibles) with the hypothesis given in Section 2.1 of the form

$$\begin{aligned}
\dot{S}(t) &= \mu - \mu S(t) - \beta(t)S(t)I(t) + \gamma R(t), & S(0) &= S_0 > 0\\
\dot{I}(t) &= \beta(t)S(t)I(t) - \nu I(t) - \mu I(t), & I(0) &= I_0 > 0\\
\dot{R}(t) &= \nu I(t) - \gamma R(t) - \mu R(t), & R(0) &= R_0 > 0.
\end{aligned} \tag{4.1}$$

From Section 2.1 we have that $R(t) + S(t) + I(t) = 1$ and using this expression in (4.1) we have the following equivalent system

$$\begin{aligned}
\dot{S}(t) &= k - kS(t) - \beta(t)S(t)I(t) - \gamma I(t), & S(0) &= S_0 > 0\\
\dot{I}(t) &= \beta(t)S(t)I(t) - \omega I(t), & I(0) &= I_0 > 0,\\
R(t) &= 1 - S(t) - I(t), \text{ for all } t \geq 0,
\end{aligned} \tag{4.2}$$

where $k = \mu + \gamma$ and $\omega = \mu + \nu$. We assume that

$$\gamma < \nu, \tag{4.3}$$

see Section 2.1.

4.3 Scheme construction

In this section we develop a numerical scheme that it will be used in the next section to solve the system of ordinary differential equations representing the evolution of the different subpopulations in regard to transmission of virus RSV. The construction of the scheme is based on non-standard techniques developed by Ronald Mickens, (More information see Mickens (1994), and Mickens (2002)). Let us denote by S^n, I^n, β^n and R^n the approximations of $S(nh)$, $I(nh)$, $R(nh)$ and $\beta(nh)$ respectively for $n = 0, 1, 2...$, and $h > 0$ the step size of the scheme. The discretization of the system (4.2) and the developing of the numerical method is based on the approximations of the temporal derivatives by a first order forward scheme, using the non-standard difference techniques as we mentioned previously. If $f(t) \in C^1(\mathbb{R})$, we define the derivative as

$$\frac{df(t)}{dt} = \frac{f(t+h) - f(t)}{\varphi(h)} + \mathcal{O}(h) \text{ as } h \longrightarrow 0, \tag{4.4}$$

where $\varphi(h)$ are called the denominator function. An example of this type of function, is

$$\varphi(h) = 1 - \exp(-h),$$

see for instance (Mickens, 2002, p.19). Thus, for the first equation of (4.2), we have

$$\frac{S^{n+1} - S^n}{\varphi(h)} = k - kS^{n+1} - \beta^n S^{n+1} I^n - \gamma I^n, \tag{4.5}$$

where the second term on the right-side of (4.5), has the discrete form

$$\begin{aligned} -S &\to -\ S^{n+1}, \\ -\beta SI &\to -\ \beta^n S^{n+1} I^n, \\ -I &\to -\ I^n. \end{aligned}$$

A way to determine convergence schemes with an arbitrary high order of accuracy is *suggested* by converting the original differential equation into an equivalent integral equation (E. Isaacson, 1994). Thus, taking the second equation of (4.2) as a differential equation of first order in $I(t)$, we have the solution in the interval $[t_0, t]$ for $t > t_0$ given by

$$I(t) = I(t_0) \exp\left(\int_{t_0}^{t} \big(\beta(u)S(u) - \omega\big) du \right),$$

and using the ideas of (Mickens, 1994, p.148), we can obtain a scheme by making in the equation above the following substitutions:

$$\begin{cases} t_0 \longrightarrow t_n = \varphi(h)n, \\ t \longrightarrow t_{n+1} = \varphi(h)(n+1), \\ I(t_0) \longrightarrow I^n, \\ I(t) \longrightarrow I^{n+1}, \\ S(t_0) \longrightarrow S^n, \\ S(t) \longrightarrow S^{n+1}. \end{cases}$$

Thus, one gets

$$I^{n+1} = I^n \exp\left(\int_{t_n}^{t_{n+1}} \big(\beta(u)S(u) - \omega\big)du\right),$$

and using the quadrature trapezoidal formula, we concluded that

$$I^{n+1} = I^n \exp\left(\frac{\varphi(h)}{2}(\beta^{n+1}S^{n+1} + \beta^n S^n) - \varphi(h)\omega\right). \tag{4.6}$$

Finally, on the same way, we have

$$\begin{aligned} S(t) = {} & \exp\left(-\int_{t_0}^{t} \big(k + \beta(u)I(u)du\big)\right)S_0 \\ & + \exp\left(-\int_{t_0}^{t} \big(k + \beta(u)I(u)du\big)\right)\int_{t_0}^{t} (k - \gamma I(\tau)) \\ & \times \exp\left(\int_{t_0}^{\tau} \big(k + \beta(u)I(u)du\big)\right)d\tau \end{aligned}$$

and we present the following scheme as a corrector of (4.5)

$$\begin{aligned} S^{n+1} = {} & S^n \exp\left(-\frac{\varphi(h)}{2}(2k + \beta^{n+1}I^{n+1} + \beta^n I^n)\right) + \frac{\varphi(h)}{2}(k - \gamma I^{n+1}) \\ & + \frac{\varphi(h)}{2}(k - \gamma I^n)\exp\left(-\frac{\varphi(h)}{2}(2k + \beta^{n+1}I^{n+1} + \beta^n I^n)\right). \end{aligned} \tag{4.7}$$

After rearranging the explicit formulations, we obtain the following discrete system:

$$S_p^{n+1} = \frac{\varphi(h)(k-\gamma I^n)+S^n}{1+\varphi(h)k+\varphi(h)\beta^n I^n}, \tag{4.8i}$$

$$I^{n+1} = I^n \exp\left(\frac{\varphi(h)}{2}(\beta^{n+1}S_p^{n+1}+\beta^n S^n)-\varphi(h)\omega\right), \tag{4.8ii}$$

$$\begin{aligned} S_c^{n+1} &= S^n \exp(-\frac{\varphi(h)}{2}(2k+\beta^{n+1}I^{n+1}+\beta^n I^n)) + \frac{\varphi(h)}{2}(k-\gamma I^{n+1}) \\ &\quad + \frac{\varphi(h)}{2}(k-\gamma I^n)\exp(-\frac{\varphi(h)}{2}(2k+\beta^{n+1}I^{n+1}+\beta^n I^n)), \end{aligned} \tag{4.8iii}$$

and

$$R^{n+1} = 1 - S_c^{n+1} - I^{n+1}. \tag{4.8iv}$$

From the systems (4.8), we can see that the positivity requirement is satisfied if $S(t) \leq \omega/\beta^l$ for all $t \geq 0$ ($\beta^l = \min_{t\in[0,T]} \beta(t)$) and $0 < h < h_c$, where h_c is a critical value, that for this case we obtain $h_c \leq 0.1$, see (Mickens, 2006). To calculate, using this scheme, we proceed as follows:

(i) Select values S^0, I^0, R^0, such that $S^0 + I^0 + R^0 = 1$.

(ii) Calculate S^1 from (4.8i).

(iii) Using this value of S^1 and I^0, calculate I^1 from (4.8ii).

(iv) Correct the value S_c^1, using S^0, I^1 and the equation (4.8iii).

(v) Calculate R^1 from (4.8iv).

(vi) Repeat all of the above steps, for n=1,2,3....

Thus, we get the numerical solution of system (4.2).

4.4 Numerical Simulations

To illustrate the behavior of the numerical solution of scheme (4.8), we perform several simulations. In a sequence of executions runs, we change the parameters of the model using the set of biologically feasible parameter values given in Table 4.1.

Table 4.1: The values μ, ν,γ are expressed in rates per year. The phase angle in years is denoted by ϕ. (Weber et al., 2001)

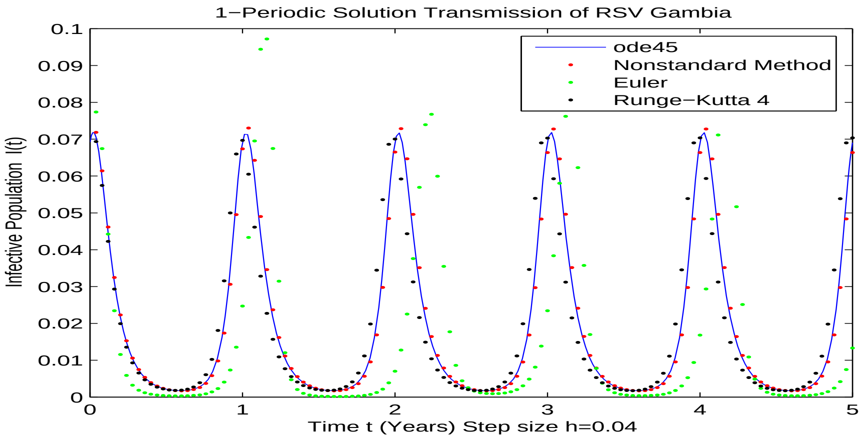
Country	μ	ν	γ	b_0	b_1	φ
Gambia	0.041	36	1.8	60	0.16	0.15
Florida	0.016	36	1.8	62	0.10	0.14
Finland	0.013	36	1.8	44	0.36	0.60
Singapore	0.016	36	1.8	77	0.14	0.28

Parameters μ, b_0, b_1, φ correspond, respectively, to the birth and death rate both are equal, average of transmission parameter and amplitude of the seasonal fluctuation in the transmission rate $\beta(t)$ and $0 \leq \varphi \leq 1$ is the phase angle normalized. γ, ν are the rate of immunity lost and the rate of recovered of the transmission of virus RSV.

4.4.1 Numerical results and comparison with other schemes

In order to test convergence and stability properties of the schemes, we perform several numerical simulations with different values for the parameters of the model according to the Table 4.1 with different step sizes. We compare the performance of the method (4.8), the explicit Euler method, the explicit 4th Order Runge-Kutta using $h = 0.04$ and they were compared with the solution computed via the adaptive MatLab solver ode45. Solutions of the Euler and 4th Order Runge-Kutta methods are not the correct, Figures 4.1-4.4, show this fact. Now, for a relatively small stepsize $h = 0.001$ all three methods achieve the correct solution, (see Figure 4.5).

Figure 4.1: Numerical approximations of solutions to system (4.2) in Gambia, using the scheme (4.8), the explicit Euler, 4th Order Runge-Kutta and the adaptive MatLab solver ode45.



4.4.2 Numerical results for very large time

We present further simulations of the method with larger values of the time as $t = 10, 20, 30$ years and h such as: $h = 0.001, 0.01, 0.1$ respectively, and it shows that preserve positivity periodic solutions. The profiles of infective populations for $h = 0.001, 0.01, 0.1$ portrayed in the graphics of Figure 4.6 for Gambia, confirm that the scheme (4.8) is stable for step sizes less than $h = 0.1$. This simulation verify the behavior positive T-periodic of the solution and is globally asymptotically stable (Jódar et al., 2008a). Furthermore, in the rate of transmission $\beta(t)$, the parameter $b_0 > 0$ is extremely changed and we make simulation with $b_0 = 44, 80, 120$ and the value parameter for Finland. In Figure 4.7 we can see that the scheme preserve the positivity of the solutions, although the periodicity of solutions change.

Figure 4.2: Numerical approximations of solutions to system (4.2) in Finland, using the scheme (4.8), the explicit Euler, 4th Order Runge-Kutta and the adaptive MatLab solver ode45.

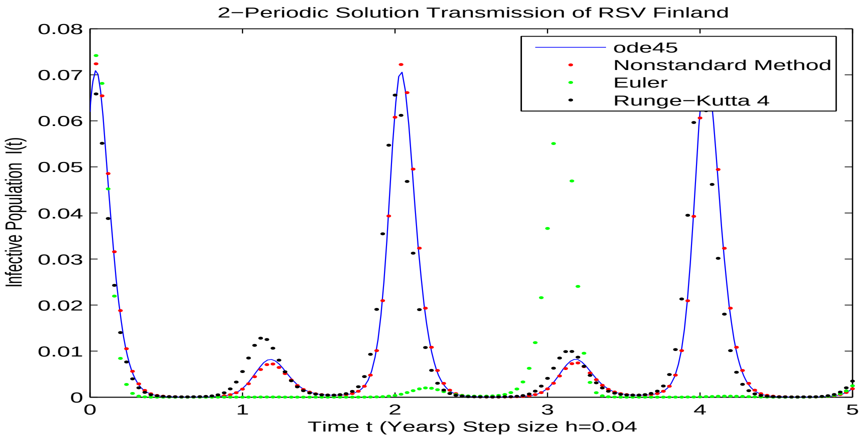


Figure 4.3: Numerical approximations of solutions to system (4.2) in Florida, using the scheme (4.8), the explicit Euler, 4th Order Runge-Kutta and the adaptive MatLab solver ode45.

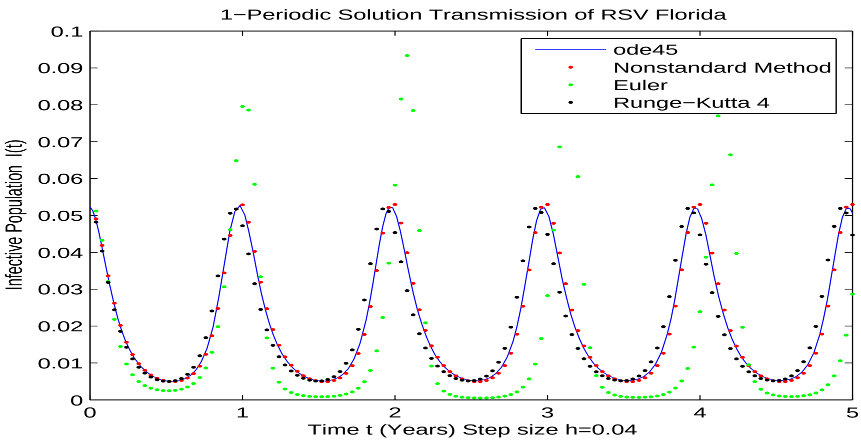


Figure 4.4: Numerical approximations of solutions to system (4.2) in Singapore, using the scheme (4.8), the explicit Euler, 4th Order Runge-Kutta and the adaptive MatLab solver ode45.

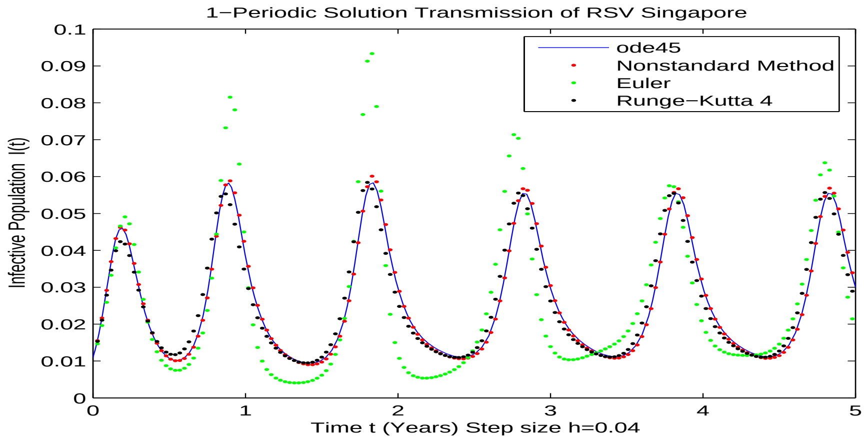


Figure 4.5: Numerical solutions to (4.2) in Gambia with all methods.

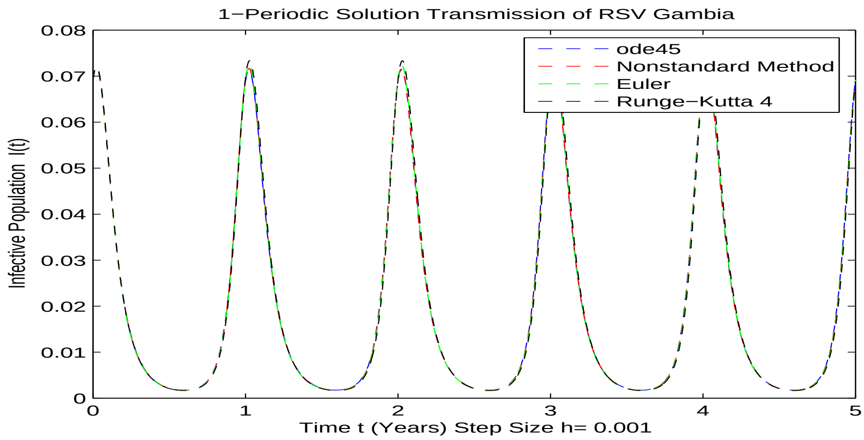


Figure 4.6: Numerical approximations of solutions to system (4.2) in Gambia, using the scheme (4.8) with larger values of the time as $t = 10, 20, 30$ years.

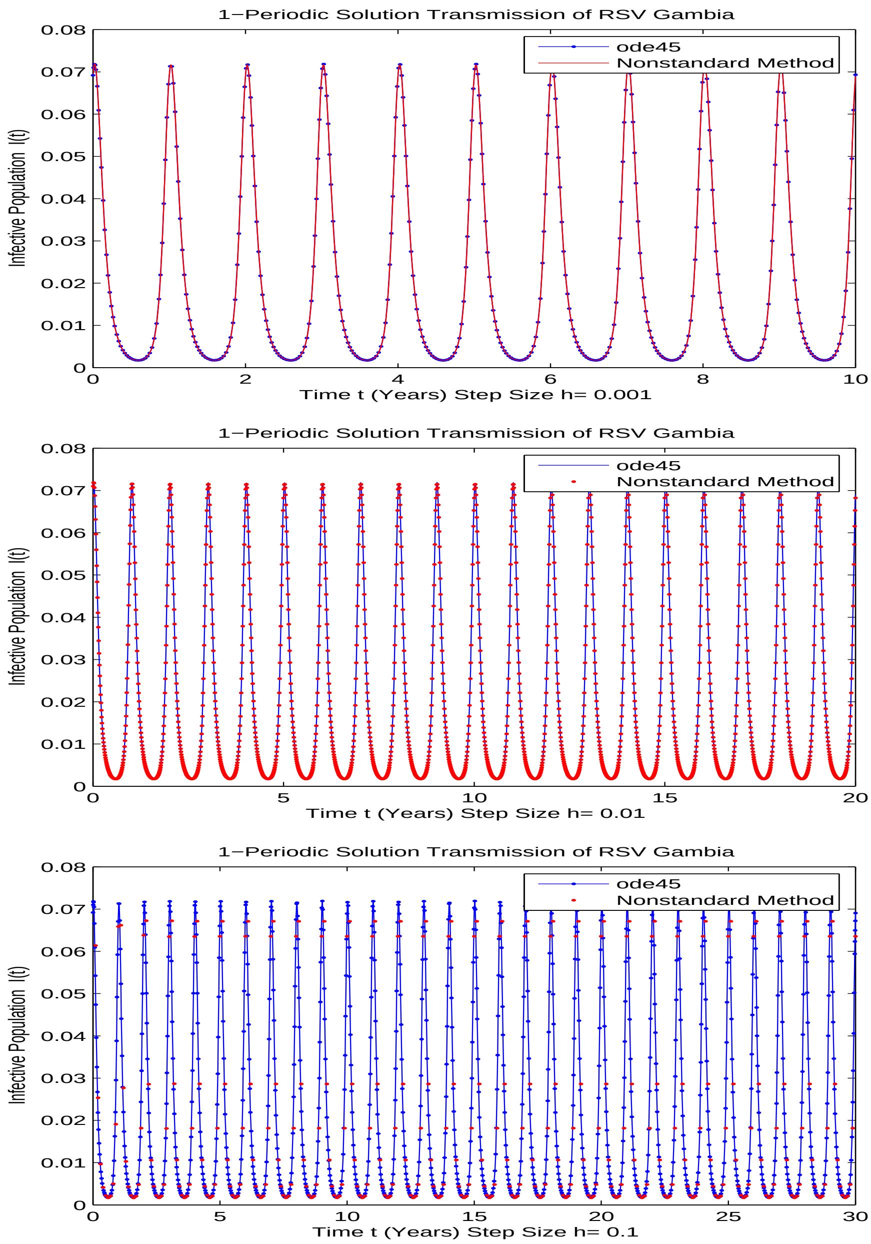
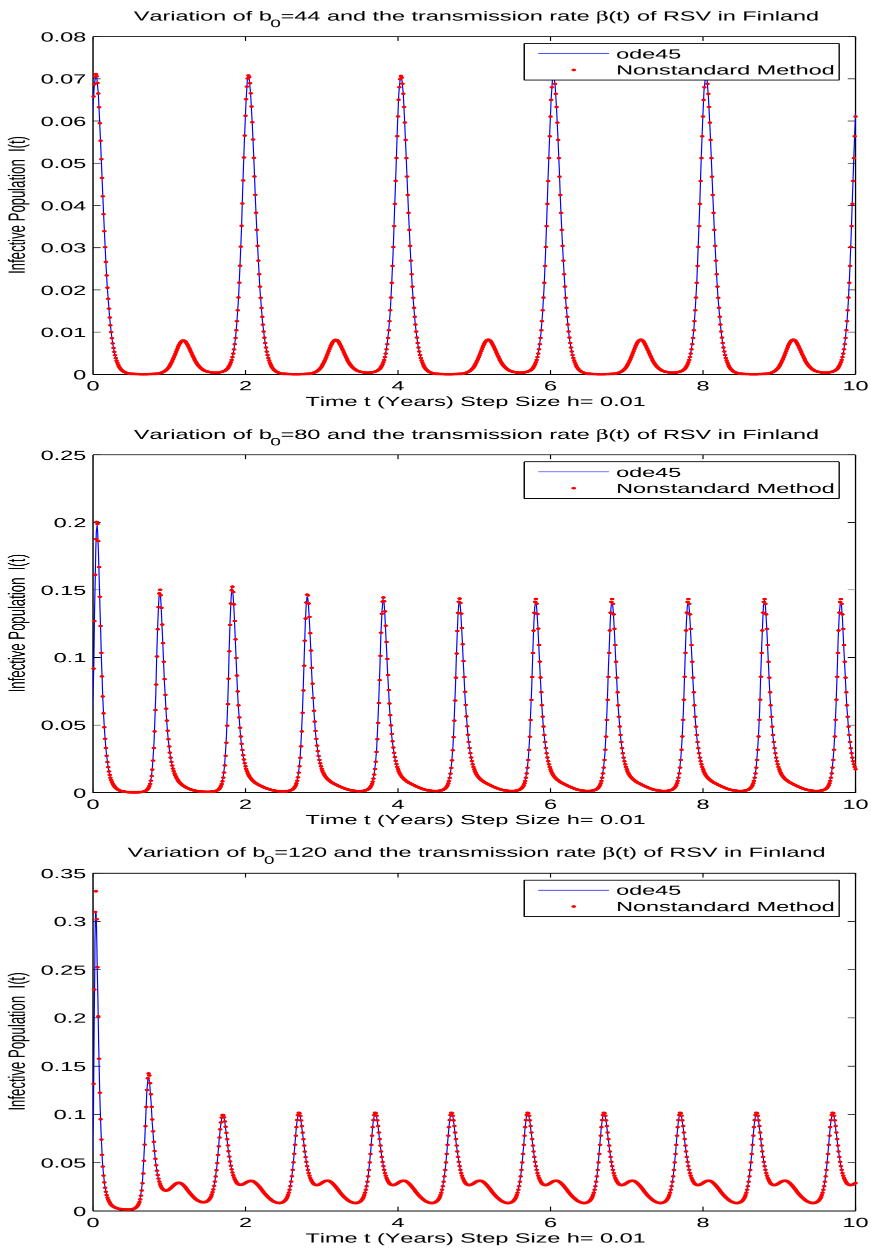


Figure 4.7: Numerical approximations of solutions to system (4.2), using the scheme (4.8) with the variation of b_0 for Finland.



4.5 Conclusions

In this chapter, we propose a numerical scheme to solve a $SIRS$ model for the transmission of virus RSV which is a first-order ODE system and we analyze its behavior. We applied the theory of nonstandard numerical methods based on Mickens' ideas for constructing numerical scheme approximating the solution of problem modeled by ordinary differential equations.

For nonlinear equations, the schemes are not exact, but have better stability properties than the usual Runge-Kutta and Euler schemes. We showed how to construct the schemes and studied their stability properties.

We combined nonlocal approximations to transform the original system of differential equation (4.2) into an equivalent system of integral equation, for solving the $SIRS$ model for the transmission of virus RSV.

This numerical scheme is analyzed and tested in several numerical simulations and we can see that the scheme preserves essential positivity properties of exact solutions of the $SIRS$ model.

The classical explicit Euler and explicit four order Runge-Kutta schemes are compared with the scheme proposed in (4.8). The forward Euler and four order Runge-Kutta schemes diverge for small step-sizes, in general for $h > 0.01$. On the other hand, the scheme proposed in (4.8), shows convergence in all the numerical simulations performed for step size less than $h_c = 0.1$ and any initial condition.

We can see from the numerical simulations, that this $SIRS$ model predicts the endemic effect of the transmission of virus RSV for realistic parameter values taken from (Weber et al., 2001), in special for Gambia, Finland, Florida and Singapore and are illustrated in Figures 4.1-4.7 where we simulate for large time and different step size. This epidemic model of temporary immunity is interesting to understand the evolution of virus *RSV* as well other diseases of similar characteristics.

Chapter 5

Numerical solutions for the transmission of virus RSV using the differential transformation method[†]

The aim of this chapter is to apply the differential transformation method (DTM) to solve systems of nonautonomous nonlinear differential equations that describe the transmission of virus RSV, where the solutions exhibit periodic behavior due to the seasonal transmission rate. These models describe the dynamics of the different classes of populations. Here the concept of DTM is introduced and then it is employed to derive a set of difference equations for these kinds of epidemic models. The DTM is used here as an algorithm for approximating the solutions of the epidemic models in a sequence of time intervals. In order to show the efficiency of the method, the obtained numerical results are compared with the fourth-order Runge-Kutta method solutions. The numerical comparisons show that the DTM is accurate, easy to apply and the calculated solutions preserve the proper-

[†]This chapter is based on Arenas et al. (2008a)

ties of the continuous models, such as the periodic behavior. Furthermore, it is showed that the DTM avoids large computational work and symbolic computation.

5.1 Introduction

Ordinary differential initial value problems appear in biological applications and commonly in the modeling of infectious diseases. These models describe the behavior and relationship between the different subpopulations: susceptible, infective and recovered, which together constitute the total population of a certain region o environment. Generally, the exact solutions of these models are unavailable and usually are very complex. Therefore, it is necessary to obtain accurate numerical approximations to the solutions to be able to understand the dynamics of the systems. Many epidemiological models have been studied using computer simulations to examine the effect of a seasonally varying contact rate on the behavior of the disease. Most of these models performed computer simulations using sinusoidal functions of period 1 year ($\beta(t) = \beta_0 + \beta_1 \cos(\omega t + \phi)$) for the seasonal varying contact rate. Examples of such studies include Ma and Ma (2006), Grossman (1980), Moneim and Greenhalgh (2005), Dowell (2005), Schwartz (1992), Weber et al. (2001), White et al. (2007). The numerical solution of seasonal epidemic models has been obtained in several papers in order to investigate numerically the reliability and efficiency of the different methods. For instance in Piyawong et al. (2003), a nonstandard numerical method was tested numerically using a seasonally forced epidemic model. Additionally, in Roberts and Grenfell (1992) a Fourier transform method was studied and applied to analyze the population dynamics of nematode infections of ruminants with the effect of seasonality in the free-living stages. Also, in Arenas et al. (2008c) a nonstandard numerical method for the solution of a mathematical model for the RSV epidemiological transmission is used to investigate the numerical efficiency of the method.

In this chapter seasonal epidemiological models are solved using the

DTM for approximating the solutions in a sequence of time intervals. In order to illustrate the accuracy of the DTM, the obtained results are compared with the fourth-order Runge-Kutta method. It is showed that the DTM is easy to apply and their numerical solutions preserve the properties of the continuous models, such as periodic behavior, positivity and boundedness. Furthermore, the proposed numerical method is used in some cases with arbitrarily large time step sizes, saving computational cost when integrating over long time periods. In fact Euler's method and other well-known methods produce bad approximations in the simulation of the numerical solutions for the models when using large time step sizes. It is important to remark that this method is applied directly to system of nonlinear ordinary differential equations without requiring linearization, discretization or perturbation.

The DTM is a semi-analytical numerical technique depending on Taylor series that promises to be useful in various fields of mathematics. The DTM derives from the differential equation system with initial conditions a system of recurrence equations that finally leads to a system of algebraic equations whose solutions are the coefficients of a power series solution. However, the classical DTM has some drawbacks: the obtained truncated series solution does not exhibit the periodic behavior which is characteristic of seasonal disease models and gives a good approximation to the true solution, only in a small region. Therefore, in order to accelerate the rate of convergence and improve the accuracy of the calculations, it is necessary to divide the entire domain H into n subdomains. The main advantage of domain split process is that only a few series terms are required to get the solution in a small time interval H_i. Therefore, the system of differential equations can then be solved in each subdomain (Chen et al., 1996). After the system of recurrence equations has been solved, each solution $x^j(t)$ can be obtained by a finite-term Taylor series. Thus this proposed DTM does not have the above drawbacks.

The differential transformation technique is applied here to solve (3.1) and (4.1), which are different systems nonlinear of differential equations that arise from seasonal epidemiological models, that are related with the *RSV* epidemiological transmission (Weber et al., 2001), (White et al., 2007), (Jódar et al., 2008a), (Arenas et al., 2008b). The seasonality of these models are given by a transmission rate $\beta(t)$.

The organization of this chapter is as follows. In Section 5.2, basic definitions of the differential transform method are presented. Some basic properties of the differential transform method are introduced in Section 5.3. Section 5.4 is devoted to present the numerical results of the application of the method to the seasonal epidemiological models. Comparisons between the differential transform method and the fourth-order Runge-Kutta (RK4) solutions are included in Section 5.5. Finally in Section 5.6 conclusions are presented.

5.2 Basic definitions of DTM

Pukhov (1980), proposed the concept of differential transformation, where the image of a transformed function is computed by differential operations, which is different from the traditional integral transforms as are Laplace and Fourier. Thus, this method becomes a numerical-analytic technique that formalizes the Taylor series in a totally different manner. The differential transformation is a computational method that can be used to solve linear (or non-linear) ordinary (or partial) differential equations with their corresponding boundary conditions. A pioneer using this method to solve initial value problems is Zhou (1986), who introduced it in a study of electrical circuits. Additionally, differential transformation has been applied to solve a variety of problems that are modeled with differential equations (Chen et al., 1996), (Yeh et al., 2007), (Hassan, 2008), (Jang and Chen, 1997).

The method consists of, given a system of differential equations and related initial conditions, these are transformed into a system of recurrence equation that finally leads to a system of algebraic equations whose solutions are the coefficients of a power series solution. The numerical solution of the system of differential equation in the time domain can be obtained in the form of a finite-term series in terms of a chosen basis system. For this case, we take $\{t^k\}_{k=0}^{+\infty}$ as a basis system, therefore the solution is obtained in the form of the Taylor series. Other bases may be chosen, see Hwang et al. (2008). The advantage of this method is that it is not necessary to do linearization or perturbations. Furthermore, large computational work and round-off errors are avoided. It has been used to solve effectively, easily and accurately a large class of linear and nonlinear problems with approximations. However, to the best of our knowledge, the differential transformation has not been applied yet in seasonal epidemic models. For the sake of clarity in the presentation of the DTM and in order to help to the reader we summarize the main issues of the method that may be found in Zhou (1986).

Definition 5.2.1 *Let $x(t)$ be analytic in the time domain D, then it has derivatives of all orders with respect to time t. Let*

$$\varphi(t,k) = \frac{d^k x(t)}{dt^k}, \qquad \forall t \in D. \tag{5.1}$$

For $t = t_i$, then $\varphi(t,k) = \varphi(t_i,k)$, where k belongs to a set of non-negative integers, denoted as the K domain. Therefore, (5.1) can be rewritten as

$$X(k) = \varphi(t_i,k) = \left[\frac{d^k x(t)}{dt^k}\right]_{t=t_i} \tag{5.2}$$

where $X(k)$ is called the spectrum of $x(t)$ at $t = t_i$.

Definition 5.2.2 *Suppose that $x(t)$ is analytic in the time domain D, then it can be represented as*

$$x(t) = \sum_{k=0}^{\infty} \frac{(t-t_i)^k}{k!} X(k). \tag{5.3}$$

Thus, the equation (5.3) represents the inverse transformation of $X(k)$.

Definition 5.2.3 *If $X(k)$ is defined as*

$$X(k) = M(k)\left[\frac{d^k x(t)}{dt^k}\right]_{t=t_i} \tag{5.4}$$

where $k \in \mathbb{Z}^+ \cup \{0\}$, then the function $x(t)$ can be described as

$$x(t) = \frac{1}{q(t)} \sum_{k=0}^{\infty} \frac{(t-t_i)^k}{k!} \frac{X(k)}{M(k)}, \tag{5.5}$$

where $M(k) \neq 0$ and $q(t) \neq 0$. $M(k)$is the weighting factor and $q(t)$ is regarded as a kernel corresponding to $x(t)$.

Note, that if $M(k) = 1$ and $q(t) = 1$, then Eqs. (5.2) and (5.3) and (5.4) and (5.5) are equivalent.

Definition 5.2.4 *Let $[0, H]$ the interval of simulation with H the time horizon of interest. We take a partition of the bounded interval $[0, H]$ as $\Big\{0 = t_0, t_1, \ldots, t_n = H\Big\}$ such that $t_i < t_{i+1}$ and $H_i = t_{i+1} - t_i$ for $i = 0, \ldots, n$. Let $M(k) = \frac{H_i^k}{k!}$, $q(t) = 1$ and $x(t)$ be a analytic function in $[0, H]$. It then defines the differential transformation as*

$$X(k) = \frac{H_i^k}{k!}\left[\frac{d^k x(t)}{dt^k}\right]_{t=t_i} \quad \text{where } k \in \mathbb{Z}^+ \cup \{0\}, \tag{5.6}$$

and its differential inverse transformation of $X(k)$ is defined as follow

$$x(t) = \sum_{k=0}^{\infty} \left(\frac{t}{H_i}\right)^k X(k), \ \text{ for } t \in [t_i, t_{i+1}]. \tag{5.7}$$

From the definitions above, we can see that the concept of differential transformation is based upon the Taylor series expansion. Note that, the original functions are denoted by lowercase and their transformed functions are indicated by uppercase letter. The DTM can solve a system of differential equation with initial-value of the form:

$$\dot{x}(t) = f\big(x(t), t\big) \quad t \in [a, b], \ \text{ with the initial condition } x(a) = x_a,$$

where $x(t) = (x^1(t), x^2(t), ..., x^j(t), ..., x^n(t))^T$ (T transposed) and that are well-posed. Thus, applying the DTM a system of differential equations in the domain of interest can be transformed to a algebraic equation system in the K domain and each $x^j(t)$ can be obtained by the finite-term Taylor series plus a remainder, i.e.,

$$x^j(t) = \frac{1}{q(t)} \sum_{k=0}^{n} \frac{(t-t_i)^k}{k!} \frac{X^j(k)}{M(k)} + R_{n+1} = \sum_{k=0}^{n} \left(\frac{t}{H}\right)^k X^j(k) + R_{n+1}, \quad (5.8)$$

where

$$R_{n+1} = \sum_{k=n+1}^{\infty} \left(\frac{t}{H}\right)^k X^j(k), \text{ and } R_{n+1} \to 0 \text{ as } n \to \infty.$$

For practical problems of simulation, the computation interval $[0, H]$ is not always small, and to accelerate the rate of convergence and improve the accuracy of the calculations, it is necessary to divide the entire domain H into n subdomains, as shown in Fig. 5.1. The main advantage of domain split process is that only a few Taylor series terms are required to construct the solution in a small time interval H_i, where $H = \sum_{i=1}^{n} H_i$. It is important to remark that, H_i can be chosen arbitrarily small if necessary. Thus, the system of differential equations can then be solved in each subdomain (Chen et al., 1996). The approach described above is known as the D spectra method. Considering the function $x^j(t)$ in the first sub-domain ($0 \leq t \leq t_1$, $t_0 = 0$), the one dimensional differential transformation is given by

$$x^j(t) = \sum_{k=0}^{n} \left(\frac{t}{H_0}\right)^k X_0^j(k)\,, \text{ where } X_0^j(0) = x_0^j(0). \quad (5.9)$$

Therefore, the differential transformation and system dynamic equations can be solved for the first subdomain and X_0^j can be solved entirely in the first subdomain. The end point of function $x^j(t)$ in the first subdomain is x_1^j, and the value of t is H_0. Thus, $x_1^j(t)$ is obtained by the differential transformation method as

$$x_1^j(H_0) = x^j(H_0) = \sum_{k=0}^{n} X_0^j(k). \quad (5.10)$$

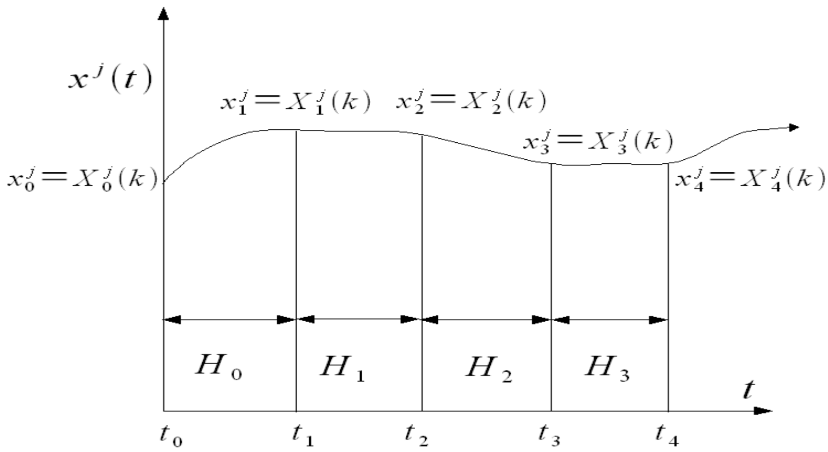


Figure 5.1: Time step diagram.

Since that $x_1^j(H_0)$ represents the initial condition in the second subdomain, then $X_1^j(0) = x_1^j(H_0)$. And so the function $x^j(t)$ can be expressed in the second sub-domain as

$$x_2^j(H_1) = x^j(H_1) = \sum_{k=0}^{n} X_1^j(k). \tag{5.11}$$

In general, the function $x^j(t)$ can be expressed in the $i-1$ subdomain as

$$x_i^j(H_i) = x_{i-1}^j(H_{i-1}) + \sum_{k=1}^{n} X_{i-1}^j(k) = X_{i-1}^j(0) + \sum_{k=1}^{n} X_{i-1}^j(k), \; i = 1, 2, ..., n. \tag{5.12}$$

Using the D spectra method described above, the functions $x^j(t)$ can be obtained throughout the entire domain, for all j.

5.3 The operation properties of the differential transformation

We consider $q(t) = 1$, $M(k) = \frac{H_i^k}{k!}$ and $x^1(t)$, $x^2(t)$, $x^3(t)$ three uncorrelated functions of time t and $X^1(k)$, $X^2(k)$, $X^2(k)$ the transformed functions corresponding to $x^1(t)$, $x^2(t)$, $x^2(t)$. With $\mathcal{D}$ we denote the Differential Transformation Operator. Thus, the following basic properties hold:

1. **Linearity**. If $X^1(k) = \mathcal{D}[x^1(t)]$, $X^2(k) = \mathcal{D}[x^2(t)]$ and c_1 and c_2 are independent of t and k then

$$\mathcal{D}[c_1x^1(t) \pm c_2x^2(t)] = c_1X^1(k) \pm c_2X^2(k). \tag{5.13}$$

   Thus, if c is a constant, then $\mathcal{D}[c] = c\delta(k)$, where $\delta(k)$ is the Dirac delta function.

2. **Convolution**. If $X^1(k) = \mathcal{D}[x^1(t)]$, $X^2(k) = \mathcal{D}[x^2(t)]$, then

$$\mathcal{D}[x^1(t)x^2(t)] = X^1(k) * X^2(k) = \sum_{l=0}^{k} X^1(l)X^2(k-l). \text{ Therefore,}$$

$$\begin{aligned}\mathcal{D}[x^1(t)x^2(t)x^3(t)] &= X^1(k) * \Big(X^2(k) * X^3(k)\Big) \\ &= \sum_{k_2=0}^{k} \sum_{k_1=0}^{k_2} X^1(k_1)X^2(k_2-k_1)X^3(k-k_2).\end{aligned} \tag{5.14}$$

3. **Derivative**. If $x^1(t) \in C^n[0, H]$, then

$$\mathcal{D}\left[\frac{d^n x^1(t)}{dt^n}\right] = \frac{(k+1)(k+2)\cdots(k+n)}{H_i^n} X^1(k+n). \tag{5.15}$$

4. If $x^1(t) = \cos(\omega t + \alpha)$, then

$$\mathcal{D}[x^1(t)] = \frac{(H_i\omega)^k}{k!} \cos\left(\frac{\pi k}{2} + \alpha + 2\pi i H_i\right), \tag{5.16}$$

   where i denotes the i-th split domain.

The proof of the above properties is deduced from the definition of the differential transformation.

5.4 Applications to seasonal epidemic models

In this section, the differential transformation technique is applied to solve several nonlinear differential equations system that arise from seasonal epidemiological models. The seasonality of the models is given by the transmission rate $\beta(t)$ and biological considerations mean that must be a continuous function, positive, nonconstant and periodic of period T. Thus, $0 < \beta^l := \min_{t\in[0,+\infty[} \beta(t) \leq \beta(t) \leq \beta^u := \max_{t\in[0,+\infty[} \beta(t)$. In this paper,

$$\beta(t) = b_0 \left(1 + b_1\, cos\left(\frac{2\pi}{T}(t+\phi)\right)\right), \tag{5.17}$$

where $b_0 > 0$ is the baseline transmission parameter, $0 < b_1 \leq 1$ measures the amplitude of the seasonal variation in the transmission and $0 \leq \varphi \leq 1$ is the phase angle normalized.

5.4.1 $SIRS$ model for the transmission of Respiratory Syncytial Virus (RSV)

As a first case, it presents a epidemiological mathematical model for the transmission of RSV (Weber et al., 2001), which was presented in (4.1) as a $SIRS$, where the total population is normalized and divided into three classes namely: Susceptibles $S(t)$, who are all individuals that have not the virus, Infected $I(t)$, being all the infected individuals having the virus and able to transmit the illness and Recovered $R(t)$ who are all the individuals not having the virus and with a temporary immunity. The model is presented as follows

$$\begin{aligned}
\dot{S}(t) &= \mu - \mu S(t) - \beta(t)S(t)I(t) + \gamma R(t), & S(0) &= S_0 > 0\\
\dot{I}(t) &= \beta(t)S(t)I(t) - \nu I(t) - \mu I(t), & I(0) &= I_0 > 0\\
\dot{R}(t) &= \nu I(t) - \gamma R(t) - \mu R(t), & R(0) &= R_0 > 0,
\end{aligned} \tag{5.18}$$

where the parameters are given as in (4.1),and $\beta(t)$ is the transmission rate, which is represented by (5.17) with $T = 1$. Taking the differential transformation of system (5.18) with respect to time t, one gets

$$\begin{aligned}
\mathbf{S}(k+1) &= \frac{H_i}{k+1}\Bigg\{\mu(\delta(k)-\mathbf{S}(k))+\gamma\mathbf{R}(k) \\
&\quad -\sum_{k_2=0}^{k}\sum_{k_1=0}^{k_2}\mathbf{B}(k_1)\mathbf{S}(k_2-k_1)\mathbf{I}(k-k_2)\Bigg\} \qquad (5.19)\\
\mathbf{I}(k+1) &= \frac{H_i}{k+1}\Bigg\{\sum_{k_2=0}^{k}\sum_{k_1=0}^{k_2}\mathbf{B}(k_1)\mathbf{S}(k_2-k_1)\mathbf{I}(k-k_2)-(\mu+\nu)\mathbf{I}(k)\Bigg\},\\
\mathbf{R}(k+1) &= \frac{H_i}{k+1}\Bigg\{\nu\mathbf{I}(k)-(\mu+\gamma)\mathbf{R}(k)\Bigg\},
\end{aligned}$$

with $\mathbf{S}(0)=S_0$, $\mathbf{I}(0)=I_0$, $\mathbf{R}(0)=R_0$ and

$$\mathbf{B}(k_1)=b_0\delta(k)+b_0b_1\frac{(H_i\omega)^k}{k!}\cos\left(\frac{\pi k}{2}+\phi+2\pi i H_i\right), \qquad (5.20)$$

where, bold uppercase letters are for the transformed functions. Thus, from a process of inverse differential transformation, it can be obtained the solutions of each sub-domain taking $n+1$ terms for the power series like Eq. (5.9), i.e.,

$$\begin{aligned}
S_i(t) &= \sum_{k=0}^{n}\left(\frac{t}{H_i}\right)^k\mathbf{S}_i(k),\ 0\le t\le H_i,\\
I_i(t) &= \sum_{k=0}^{n}\left(\frac{t}{H_i}\right)^k\mathbf{I}_i(k),\ 0\le t\le H_i, \qquad (5.21)\\
R_i(t) &= \sum_{k=0}^{n}\left(\frac{t}{H_i}\right)^k\mathbf{R}_i(k),\ 0\le t\le H_i,
\end{aligned}$$

provided that the solutions holds with:

$$S(t)=\sum_{i=0}^{n}S_i(t),\ I(t)=\sum_{i=0}^{n}I_i(t),\ R(t)=\sum_{i=0}^{n}R_i(t). \qquad (5.22)$$

5.4.2 Nested model for the transmission of Respiratory Syncytial Virus (RSV)

As a second case, in White et al. (2007) a nested model was presented for study the dynamical transmission of RSV at the population level. This model is also a particular case of (3.1) when $T = 1$. The model is as follows

$$\begin{aligned}
\dot{S}(t) &= \mu P - \frac{\Lambda(t)S(t)}{P} + \frac{\alpha\tau}{\rho}(I_S(t) + I_R(t) + R(t)) - \mu S(t),\\
\dot{I_S}(t) &= \frac{\Lambda(t)S(t)}{P} - (\tau+\mu)I_S(t),\\
\dot{I_R}(t) &= \frac{\sigma\Lambda(t)R(t)}{P} - \left(\frac{\tau}{\rho} + \mu\right) I_R(t),\\
\dot{R}(t) &= \left(1 - \frac{\alpha}{\rho}\right)\tau I_S(t) + \frac{(1-\alpha)\tau}{\rho} I_R(t) - R(t)\left(\frac{\sigma\Lambda(t)}{P} + \frac{\alpha\tau}{\rho} + \mu\right),
\end{aligned} \tag{5.23}$$

where the parameters are given as in (3.1). For the sake of convenience it uses the following systems

$$\begin{aligned}
\dot{x_1}(t) &= \mu + C_1 - \beta(t)x_1(t)x_2(t) - \eta\beta(t)x_1(t)x_3(t) - (C_1+\mu)x_1(t),\\
\dot{x_2}(t) &= \beta(t)x_1(t)x_2(t) + \eta\beta(t)x_1(t)x_3(t) - (\tau+\mu)x_2(t),\\
\dot{x_3}(t) &= \sigma\beta(t)x_2(t)x_4(t) + \sigma\eta\beta(t)x_3(t)x_4(t) - (C_2+\mu)x_3(t),\\
\dot{x_4}(t) &= (\tau - C_1)x_2(t) + (C_2 - C_1)x_3(t) - \sigma\beta(t)x_2(t)x_4(t)\\
&\quad - \sigma\eta\beta(t)x_3(t)x_4(t) - (C_1+\mu)x_4(t),
\end{aligned} \tag{5.24}$$

where $x_1(t) + x_2(t) + x_3(t) + x_4(t) = 1$. The system of algebraic recurrence given by the differential transformation applied to system (5.24) is the following

$$\begin{aligned}
\mathbf{X}_1(k+1) = \frac{H_i}{k+1}\Big\{&(\mu + C_1)\,\delta(k) - \sum_{k_2=0}^{k}\sum_{k_1=0}^{k_2}\mathbf{B}(k_1)\,\mathbf{X}_1(k_2-k_1)\,\mathbf{X}_2(k-k_2)\\
&- \eta\sum_{k_2=0}^{k}\sum_{k_1=0}^{k_2}\mathbf{B}(k_1)\,\mathbf{X}_1(k_2-k_1)\,\mathbf{X}_3(k-k_2) - (C_1+\mu)\,\mathbf{X}_1(k)\Big\},
\end{aligned}$$

$$\begin{aligned}
\mathbf{X}_2(k+1) = \frac{H_i}{k+1}\Big\{&\sum_{k_2=0}^{k}\sum_{k_1=0}^{k_2}\mathbf{B}(k_1)\,\mathbf{X}_1(k_2-k_1)\,\mathbf{X}_2(k-k_2)\\
&+ \eta\sum_{k_2=0}^{k}\sum_{k_1=0}^{k_2}\mathbf{B}(k_1)\,\mathbf{X}_1(k_2-k_1)\,\mathbf{X}_3(k-k_2) - (\tau+\mu)\,\mathbf{X}_2(k)\Big\},
\end{aligned}$$

$$\mathbf{X}_3(k+1) = \frac{H_i}{k+1}\Bigg\{\sigma \sum_{k_2=0}^{k}\sum_{k_1=0}^{k_2} \mathbf{B}(k_1)\,\mathbf{X}_2(k_2-k_1)\,\mathbf{X}_4(k-k_2)$$

$$+\,\sigma\eta \sum_{k_2=0}^{k}\sum_{k_1=0}^{k_2} \mathbf{B}(k_1)\,\mathbf{X}_3(k_2-k_1)\,\mathbf{X}_4(k-k_2) - (C_2+\mu)\,\mathbf{X}_3(k)\Bigg\},$$

$$\mathbf{X}_4(k+1) = \frac{H_i}{k+1}\Bigg\{(\tau - C_1)\,\mathbf{X}_2(k) + (C_2 - C_1)\,\mathbf{X}_3(k)$$

$$-\,\sigma \sum_{k_2=0}^{k}\sum_{k_1=0}^{k_2} \mathbf{B}(k_1)\,\mathbf{X}_2(k_2-k_1)\,\mathbf{X}_4(k-k_2)$$

$$-\,\sigma\eta \sum_{k_2=0}^{k}\sum_{k_1=0}^{k_2} \mathbf{B}(k_1)\,\mathbf{X}_3(k_2-k_1)\,\mathbf{X}_4(k-k_2) - (C_1+\mu)\,\mathbf{X}_4(k)\Bigg\},$$

where the initial conditions are given by $\mathbf{X}_1(0) = x_1(0)$, $\mathbf{X}_2(0) = x_2(0)$, $\mathbf{X}_3(0) = x_3(0)$, $\mathbf{X}_4(0) = x_4(0)$, and $\mathbf{B}(k_1)$ as in (5.20), and again as in (5.21) and (5.22), it gives the numerical solutions in the respective interval of time.

5.5 Numerical results

The numerical simulations were made using the parameter values showed in Table 5.1, 5.2 and the DTM algorithm is coded in the computer using Fortran and the variables are in double precision in all the calculations done in this chapter. Moreover the calculations are based upon a value of $n = 5$ in the Taylor series. From Figs. 5.2, 5.3 it can be seen that the numerical solutions given by DTM reproduce the correct periodic behavior, positivity and boundedness of the different subpopulations for the seasonal models, which are in line with the periodic behavior of the continuous model shown in Jódar et al. (2008a), Arenas et al. (2008b).

Fig. 5.2(a), 5.2(b), and 5.2(c) represent the transmission of RSV, in the region of Valencia for the hospitalized population, according to data supplied from the database of the Spanish region of Valencia (IVE, 2007).

Moreover, it is clear from Figs. 5.2, 5.3 that excellent agreement exists between the two sets of results, i.e., that the numerical solutions obtained are as accurate as the 4-th order Runge-Kutta method solution, which shows that the results obtained from the DTM are highly consistent with those obtained from the Runge-Kutta method.

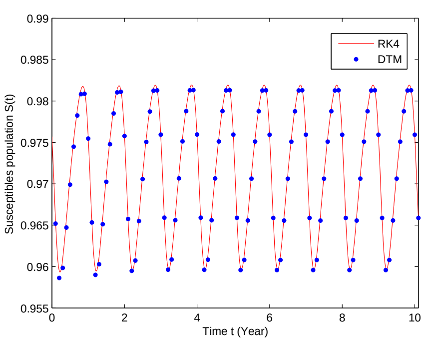
In Table 5.3 we present the absolute errors between the 5-term DTM solutions on time steps $h = 0.1, 0.001$ and the Runge-Kutta solutions on time step $h = 0.001$: here the parameters used in system (5.18) are from the region of Valencia as given in Table 5.1. Table 5.4 provides a quantitative comparison of the two methods with step size $h = 0.1, 0.001$ for the DTM and $h = 0.001, 0.0001$ for Runge-Kutta method respectively we can see that both methods are consistent between 2 and 4 decimal places for a step size $h = 0.5$ for DTM and step size $h = 0.01$ for the Runge-Kutta method.

Table 5.1: Parameters values for the system (5.18).

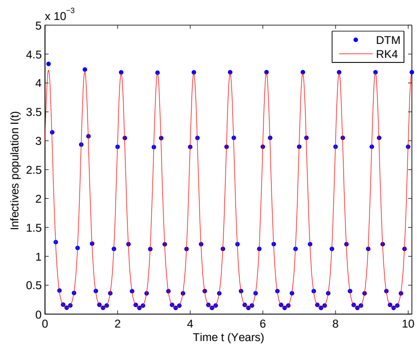
$Region$	b_0	b_1	ϕ	μ	ν	γ
$Valencia$	37	0.31	0.9	0.009	36	1.8
$Gambia$	60	0.16	0.15	0.041	36	1.8

Table 5.2: Parameter values α, ρ, σ and η are fixed and others μ, τ, b_0, b_1, ϕ and T are taken from White et al. (2007), Arenas et al. (2008c) to the system (5.23).

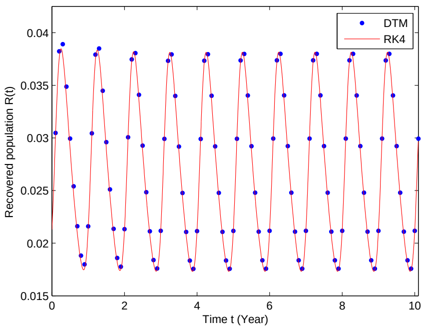
$City$	μ	τ	b_0	b_1	ϕ	α	ρ	σ	η	T
$Madrid$	0.2013	9	11.716	0.29	0.92	0.1	0.3	0.1	0.1	1



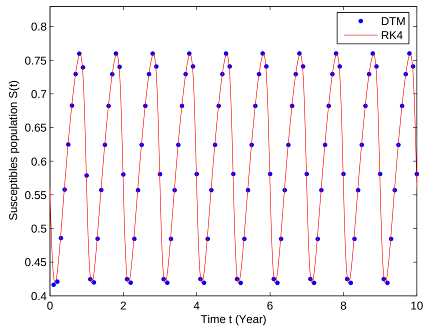
(a)$h = 0.1,\ S_0 = 0.9757,\ H_i = 0.1$



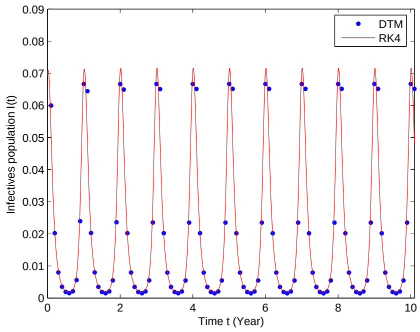
(b)$h = 0.1,\ I_0 = 0.0030,\ H_i = 0.1$



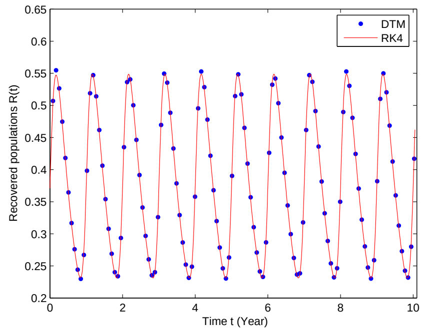
(c) $h = 0.1,\ R_0 = 0.0213,\ H_i = 0.1$



(d) $h = 0.1,\ S_0 = 0.56,\ H_i = 0.1$

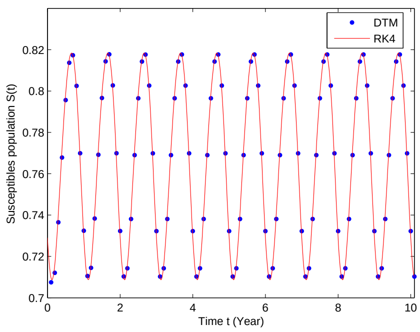


(e) $h = 0.1,\ I_0 = 0.069,\ H_i = 0.1$

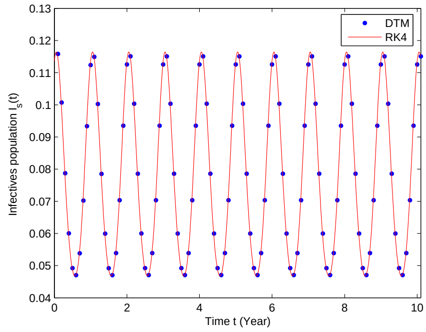


(f) $h = 0.1,\ R_0 = 0.371,\ H_i = 0.1$

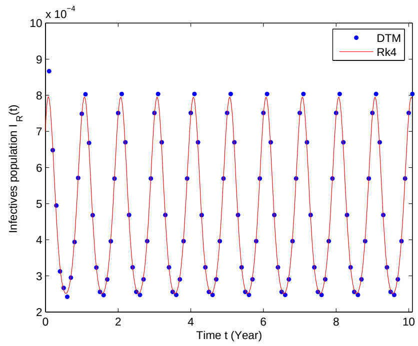
Figure 5.2: Comparison of the numerical approximations of solutions between the differential transformation and Runge-Kutta results with $n = 5$ to the system (5.18).



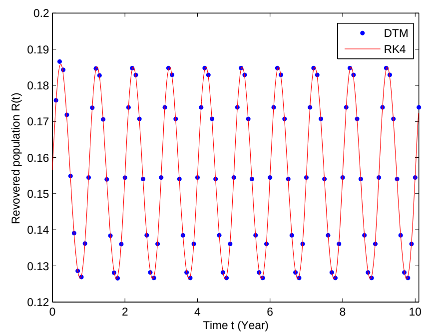
(a) $h = 0.1,\ S_0 = 0.729,\ H_i = 0.1$



(b) $h = 0.1,\ I_{S0} = 0.1137,\ H_i = 0.1$



(c) $h = 0.1,\ I_{R0} = 0.0007,\ H_i = 0.1$



(d) $h = 0.1,\ R_0 = 0.1516,\ H_i = 0.1$

Figure 5.3: Comparison of the numerical approximations of solutions between the differential transformation and Runge-Kutta results with $n = 5$ to the system (5.23).

Table 5.3: Differences between the 5-term DTM and $RK4$ solutions to the system (5.18).

	$\Delta = \lvert DTM_{0.1} - RK4_{0.001}\rvert$			$\Delta = \lvert DTM_{0.001} - RK4_{0.001}\rvert$		
$Time$	ΔS	ΔI	ΔR	ΔS	ΔI	ΔR
0	$.0000E+00$	$.0000E+00$	$.0000E+00$	$.0000E+00$	$.0000E+00$	$.0000E+00$
1	$.1346E-03$	$.1484E-04$	$.1198E-03$	$.4148E-05$	$.1478E-04$	$.1893E-04$
2	$.1956E-03$	$.1645E-04$	$.1792E-03$	$.6245E-04$	$.2099E-04$	$.4146E-04$
3	$.2008E-03$	$.1502E-04$	$.1858E-03$	$.8979E-04$	$.2138E-04$	$.6841E-04$
4	$.1941E-03$	$.1417E-04$	$.1799E-03$	$.9104E-04$	$.2060E-04$	$.7045E-04$
5	$.1904E-03$	$.1402E-04$	$.1764E-03$	$.8732E-04$	$.2020E-04$	$.6712E-04$
6	$.1899E-03$	$.1408E-04$	$.1758E-03$	$.8552E-04$	$.2015E-04$	$.6537E-04$
7	$.1902E-03$	$.1413E-04$	$.1760E-03$	$.8533E-04$	$.2019E-04$	$.6514E-04$
8	$.1904E-03$	$.1414E-04$	$.1762E-03$	$.8553E-04$	$.2022E-04$	$.6532E-04$
9	$.1904E-03$	$.1414E-04$	$.1763E-03$	$.8565E-04$	$.2022E-04$	$.6543E-04$
10	$.1904E-03$	$.1414E-04$	$.1763E-03$	$.8566E-04$	$.2022E-04$	$.6545E-04$

Table 5.4: Differences between the 5-term DTM and $RK4$ solutions to the system (5.23).

	$\Delta = \lvert DTM_{0.1} - RK4_{0.001}\rvert$				$\Delta = \lvert DTM_{0.001} - RK4_{0.001}\rvert$			
$Time$	ΔS	ΔI_R	ΔI_S	ΔR	ΔS	ΔI_R	ΔI_S	ΔR
0	$.0000E+00$	$.0000E+00$	$.0000E+00$	$.0000E+00$	$.0000E+00$	$.0000E+00$	$.0000E+00$	$.0000E+00$
1	$.3905E-03$	$.1714E-03$	$.1449E-05$	$.6474E-04$	$.3464E-04$	$.1394E-04$	$.3828E-07$	$.5513E-05$
2	$.3818E-03$	$.1521E-03$	$.2177E-06$	$.6730E-04$	$.3334E-04$	$.1212E-04$	$.5142E-07$	$.5095E-05$
3	$.3753E-03$	$.1514E-03$	$.1597E-06$	$.6134E-04$	$.3283E-04$	$.1210E-04$	$.5452E-07$	$.4594E-05$
4	$.3764E-03$	$.1518E-03$	$.1654E-06$	$.6188E-04$	$.3293E-04$	$.1214E-04$	$.5398E-07$	$.4646E-05$
5	$.3764E-03$	$.1518E-03$	$.1653E-06$	$.6192E-04$	$.3292E-04$	$.1213E-04$	$.5399E-07$	$.4648E-05$
6	$.3763E-03$	$.1518E-03$	$.1652E-06$	$.6190E-04$	$.3292E-04$	$.1213E-04$	$.5400E-07$	$.4647E-05$
7	$.3763E-03$	$.1518E-03$	$.1652E-06$	$.6190E-04$	$.3292E-04$	$.1213E-04$	$.5400E-07$	$.4647E-05$
8	$.3763E-03$	$.1518E-03$	$.1652E-06$	$.6190E-04$	$.3292E-04$	$.1213E-04$	$.5400E-07$	$.4647E-05$
9	$.3763E-03$	$.1518E-03$	$.1652E-06$	$.6190E-04$	$.3292E-04$	$.1213E-04$	$.5400E-07$	$.4647E-05$
10	$.3763E-03$	$.1518E-03$	$.1652E-06$	$.6190E-04$	$.3292E-04$	$.1213E-04$	$.5400E-07$	$.4647E-05$

5.6 Conclusion

In this chapter, seasonal epidemiological models are solved numerically using the DTM for approximating the solutions in a sequence of time intervals. In order to obtain very accurate solutions, the domain region has been splitted into subintervals and the approximating solutions are obtained in a sequence of time intervals. The DTM produces from the system of differential equations with initial conditions a system of recurrence equations that finally leads to a system of algebraic equations whose solutions are the coefficients of a power series solution, and applying a process of inverse transformations it obtain the solutions. Moreover, the DTM does not evaluate the derivatives symbolically and this give advantages over other methods such Taylor, power series or Adomian method. In order to illustrate the accuracy of the DTM, the obtained results were compared with the fourth-order Runge-Kutta method. For the seasonal epidemiological models studied we found that the 5-term DTM solutions on a larger time step achieved comparable results with the $RK4$ solutions on a much smaller time step. Here, it is showed that the DTM is easy to apply and their numerical solutions preserves the properties of the continuous models, such as periodic behavior, positivity and boundedness, which when using Runge-Kutta and other numerical methods, we cannot guarantee these properties especially with step size h relatively large. Furthermore, the calculated results demonstrate the reliability and efficiency of the method when is applied to seasonal epidemiological models. It is important to remark that this method is applied directly to the system of nonlinear ordinary differential equations without requiring linearization, discretization or perturbation. Based on the numerical results it can be concluded that the DTM is mathematical tool to find approximate accurate analytical solutions for seasonal epidemiological models represented by systems of nonautonomous nonlinear ordinary differential equations. In general, by splitting the time domain, the numerical solutions can be approximated quite well using a small number of terms and small time interval H_i. Furthermore, high accuracy can be obtained without using large computer power and the DTM has the advantage of giving an analytical form of the solution within each time interval which is not possible in purely numerical techniques like $RK4$. Since the Taylor series is an infinite series, the differential transformation should theoretically consist of an infinite series, but the numerical results shown that a small number of terms of the series are sufficient to provided an accurate solution in practice.

Chapter 6

Conclusions

The work presented in this thesis contributes to the study of systems of nonlinear of ordinary differential equations of the first order and includes the analytical demonstration of the periodicity of the solutions of some generalized seasonal epidemic models, which uses as transmission rate a function $\beta(t)$ periodic. The proof is based on Jean Mawhin's Theorem of Coincidence. Moreover, using the nonstandard finite difference method of Ronald Mickens and Differential Transformation Method, new numerical schemes are developed in order to support our analytical results for the transmission of RSV in the region of Valencia (Spain) and other countries.

As future work, we will develop new seasonal models, where parameters of vaccination, such as pulse vaccination or booster vaccination, are included, and thus to determine the incidence of the disease under different vaccination policies. Another interesting possibility for future research is to consider epidemic mathematical models using random differential equations, where, for instance, the initial conditions are random because the data of the initial population is not known with certainty.

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