CENTRO DE INVESTIGACIÓN EN MATEMÁTICAS.

DOCTORADO EN CIENCIAS CON ORIENTACIÓN EN MATEMÁTICAS APLICADAS.

NUMERICAL MODELING OF THE EVOLUTION OF INFECTED CELLS BY THE PAPILLOMA VIRUS

TESIS

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CIMAT

Go confidently in the direction of your dreams. Live the life you have imagined.
Henry David Thoreau

Twenty years from now you will be more disappointed by the things you did not do than by the ones you did do. So throw off the bowlines. Sail away from the safe harbor. Catch the trade winds in your sails. **Explore. Dream. Discover. To Love.**
Mark Twain

dedication

I dedicate this work all my heart to the person who helped me achieve this goal with your example showed me the way, the person who was always there to support me and give me your hand, who taught me patiently and dedication, professionalism and requirement, to which he has devoted his time to me and has always been there: my advisor.

Acknowledgement

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Summary

Cancer remains one of the most serious medical and health problems of human society. While there has been significant progress, especially in the prevention, mortality figures remain relatively stable. Therefore, it is very important to do research from different points of view. Cancer is a very complex disease that is multifactorial in origin, some types of cancer have a strong genetic component and others determined by environmental factors or unknown factors. Once the cancer is at an advanced stage there is no cure. In this work we are interested in early detection of cervical cancer, which is usually preceded by a long phase of preinvasive lesions, which are characterized microscopically by a series of changes ranging from cellular atypia to various grades dysplasia or cervical intraepithelial neoplasia. In our days, the best way to detect cervical cancer is to have regular screening with a Pap test. Most of the cervical cancer models proposed in the literature are based on a preventive approach, but for the diagnosis and development of precancerous lesions they are basically nonexistent.

Our principal goal in this dissertation is to propose models with a reliable interaction of Human Papillomanvirus (HPV) infected cells, that provide useful information on the evolution of these cells before they become cancerous. The objective is to contribute to early cancer detection and with the aid of other existing biological tests the diagnosis could be more successful and timely. We propose models for the interaction of HPV infected cells related to the different stages of the evolution of cervical cancer. Such models vary according to the quantitative information required. We analyze the models in order to provide tools to obtain biological information regarding the evolution of cervical cancer cells.

We propose two models for the interaction of cells infected by HPV. The first model consists in a discrete description of the virus invasion stages and we analize it by considering initial conditions according to characteristics of infection of a patient and respecting positivity conditions. The second model gives a continuous version of the first model and consists in a nonlinear advection-diffusion-reaction equation. We develop different numerical schemes to approximate the solution of the equation using the method non-standard finite differences. We also analyze the model from the perspective of perturbation theory, obtaining a numerical scheme which is sufficiently robust, accurate and efficient for larger time values. With the aid of these schemes implementation there is a possibility to understand the evolution of the different stages of the lesions of the cervix. This is an important aspect because the stage of the cancer is an important factor in selecting a treatment plan. Overall, this work may serve as a structural basis in the implementation of specific software to provide clinicians with a reliable benchmark.

Introduction

Cervical cancer is one of the most common cancer in women and is caused, among other factors, by several high-risk serotypes of the Human Papillomavirus (HPV) found in the majority of the clinical cases, [1]. The development of infected cells and the control mechanisms involved are very complex and the advance of mathematical models of HPV infected cell populations is relatively moderate. A number of models have been presented, most of them are based on a preventive approach [2, 3, 4, 5], but basically nonexistent for the diagnosis. Our main goal is to developed mathematical models for the interaction of infected cells of Human Papillomavirus. The models we consider are simple general interaction models between the number of infected cells in each stage of the natural evolution of the cancer. Their purpose is to illustrate some basic ideas and analysis used in the mathematical modeling of infected cell populations, and to provide a first step in the diagnosis in order to avoid taking small samples of surface cells of the cervix. First, important aspects of Human Papillomavirus (HPV) will be given next.

0.1 Human Papillomavirus (HPV) and Cervical Cancer (CC)

Human Papillomavirus (HPV) infection is associated with virtually all cases of cervical cancer. The virus is among the most common sexually transmitted diseases and most women clear the infection within two years without complications. Long term infection with high-risk strains of Human Papillomavirus can lead to the development of cervical dysplasia and cancer. Because of the very high correlation between HPV infection and cervical cancer, is important to describe the HPV in more detail. Human Papillomaviruses are small (55-nm-diameter), non-enveloped virions, with icosahedral capsid which contains two proteins L1 and L2. Its double-stranded circular DNA genome contains eight kilobase pairs encoding eight proteins. HPV Infection occurs in the basal cells or nearby epithelial basement membrane cells and the viral life cycle is closely related to maturation and differentiation of these cells [2]. Early diagnosis and control of HPV infection have become a pressing need, especially in developing countries, where more deaths are caused. It is important to be informed, since Cervical Cancer (CC) has no symptoms until it is at an advanced stage; therefore, it is very essential for women to be regularly screened for CC. The HPV detection methods are: papanicolaou test, colposcopic examination and molecular detection. The problem can be considered in three different approaches: epidemiological approach, preventive approach

(vaccines) and detection. More research is urgently needed in two significant areas: early detection of HPV through tests that accurately indicate abnormalities of the cervix before, during and after acquiring cervical cancer and preventing it by creating more effective vaccines, prophylactic as well as therapeutic. There are models related to the virus transmission, but not to its basal cells in cervix detection and evolution [5, 4]. Molecular Biology Studies (specialized tests to detect the viruses) have reported that almost 100% of cervical cancer tumors have HPV. For many years, HPV was considered a risk factor. However, it is currently accepted as the causal agent of cervical cancer. There are protocols that ensure that HPV is necessary but not enough to give rise to cervical cancer. This means, to start a HPV infection malignancy, it must be associated with one or several risk factors. There are about 130 HPV types, 30 of which affect the lower genital tract (cervix, vagina, vulva, and anus.) A number is assigned to each these viruses type, and according to its aggressiveness level to damage the epithelium (oncogenic risk), they may be low risk (types 6-11) or high risk (types 16-18-35-45.) The last mentioned have a greater capacity to produce epithelial damage and they are responsible for producing 80% of cervical cancers.The natural history of cervical cancer starts when women get HPV during sexual intercourse. HPV infection is more easily developed when there is a cofactor (a risk factor), in particular when the immune system is impaired. HPV causes damage to the cervix epithelium causing precursor lesions that may evolve if not corrected until invasive cancer. In the natural history of cervical cancer there are two stages pre-invasive stage and invasive stage. The pre-invasive stage is characterized by maintaining the whole basal membrane (membrane that protects the epithelium), which allows that cell changes, in despite of being malignant, are retained within the epithelial thickness (we could imagine that the lesion is encapsulated), so the possibility that these malignant cells to spread to other organs or lymph nodes are almost nil. Then we describe the precursor lesions: Cervical Intraepithelial Neoplasia grade I (CIN I) or mild dysplasia (the injury has spread to one third of the thickness of the epithelium); Cervical Intraepithelial Neoplasia grade II (CIN II) or moderate dysplasia (the injury has extended to two-thirds the thickness of the epithelium); Cervical Intraepithelial Neoplasia grade III (CIN III) or severe dysplasia (the injury has spread to more than two thirds of the thickness of the epithelium); and Carcinoma in situ (the injury has been extended to all the thickness of the epithelium) [9]. However, in the invasive stage, the injury to the cervix has caused basal membrane rupture, allowing the malignant cells to extend into the stroma (supporting tissue), capillaries, lymph nodes, adjacent or distant organs (metastases).

0.2 HPV vaccines

Protective immunity to HPV is directed to the major capsid (L1) protein. Immunity is type specific and there is little cross protection with other HPV types. After natural infection only 50-70% people develop detectable antibody and this takes many months to develop (as virus evasion delays onset and magnitude of specific immune response). This accounts for why people can be repeatedly infected with HPV throughout their sexual active life. A major breakthrough has been the development of subunit HPV vaccines, based on the L1 protein of specific HPV types. The vaccines consist of recombinant L1 protein. The L1 protein self assembles into virus-like particles (VLPs) which are highly immunogenic. A course of 3 doses induces high levels of type specific antibodies in vaccine recipients (much higher than is induced by natural HPV infection). To prevent infection, vaccine needs to be administered before onset of sexual activity (before first exposure to HPV), currently advised for pre-pubertal girls. Have been licensed two vaccines so far: the first vaccine is: Cervarix , this vaccine contains VLPs derived from HPV16 and 18. Together these high risk HPV types account for 70% of cervical cancers. The second vaccine is: Guardasil, this vaccine contains irus-like particles (VLPs) from HPV16 and 18 as well as for 6 and 11 (the last 2 are the major cause of genital warts). Clinical trials of these two vaccines have shown both vaccines to be highly effective at preventing type specific HPV infection in vaccine recipients. Many countries, including Mexico, have added this vaccine to their national immunization programmes (targeting pre-pubertal girls), but they are still very expensive and for example in South Africa they are not available to the public sector. However, it has not been demonstrated an effectiveness of these vaccines and therefore we must seek other methods to help improve the early detection with accurate diagnosis.

0.3 Importance of this dissertation

Early diagnosis and control of HPV infection have become a pressing need, especially in developing countries, where more deaths are caused. Mathematically, the modeling problem of Human Papillomavirus (HPV) has been considered using three different approaches: epidemiological approach, preventive approach (vaccines) and detection. To the best of my knowledge, in the literature there are many research articles in the prevention, transmission and epidemiological of HPV but none in the early detection [6, 7, 3, 4]. Thus, more research needs to be done in the early detection of HPV through tests that may accurately indicate abnormalities of the cervix before, during and after acquiring cervical cancer. The relevance of this dissertation is supported by the importance of the topic if we ask

the question What is the relevance of cancer research? there are many answers, the importance of research in cancer is in several aspects: on one hand, from the scientific perspective, cancer represents a group of diseases that are of great interest by itself and to help explain processes of importance in different areas of study. It is also a problem affecting global health economics, so their research is needed to reduce some of these problems. However, I think the primal importance of cancer research is our sensitivity for the human suffering and brotherhood with our fellow men. The present thesis is a first step to address the detection problem by proving mathematical models for HPV detection hopping that our approach provides an alternative method to existing ones and may open up new avenues to new modeling. It is our main goal to developed mathematical models of the interaction of infected cells of Human Papillomavirus. As a first step, we will derive a general interaction model between the number of infected cells in each stage. The approach is based in a discrete model for the cell cycle presented by Takahashi [8]. Then by considering a continuous description of the invasion stages, we will derive an advection diffusion reaction nonlinear model. For the sake of completeness, we develop nonstandard difference methods based on nonstandard finite difference methods.

0.4   Methodology

The methodology of the thesis varies in each chapter. In Chapter 1, we analyze the models that results from considering the evolution of HPV in discrete stages with ODE systems theory and solving the resulting systems with Runge Kutta method of order four. In Chapter 2, we build a continuous model, then by considering a continuous description of the invasion stages, we will derive an advection diffusion reaction nonlinear model. For the sake of completeness, we develop a nonstandard difference method based on nonstandard finite difference methods [9, 10, 11]. By testing our numerical scheme in some particular cases of our model, we show that this new method is robust and efficient. In Chapter 3, such model is approximated by a consistent explicit difference scheme which is based on Regular Perturbation Theory. In Chapter 4, we approximate the solutions of the model y constructing two different non standard schemes to obtain a better approximation for larger times than the ones obtained in Chapter 2.

0.5 Description of the thesis

The thesis comprises four chapters and five Appendices. In Chapter 1, we propose models for the interaction of Human Papillomanvirus infected cells related to the different stages of the evolution of cervical precancer. Such models will vary according to the quantitative information obtained. The models we consider are simple general interaction models between the number of infected cells in each stage of the natural evolution of the precancer stages. Their purpose is to illustrate some basic ideas and analysis used in the mathematical modeling of infected cell populations. We study the linear and nonlinear cases associated with our model. We obtain and analyze a nonlinear system of ordinary differential equations. Both the linear system and the nonlinear were considered and studied for important cases. In such analysis, initial conditions were chosen depending on the patient infection degree and considering positivity conditions. The results help us to understand the evolution of cells infected with HPV.

In Chapter 2, we develop a continuous mathematical model for the interaction of infected cells of Human Papillomavirus. Such model consists in an advection diffusion reaction nonlinear model. For the sake of completeness, we develop a nonstandard difference method based on nonstandard finite difference methods. By testing our numerical scheme in some particular cases of our model, we show that this new method is robust and efficient. The drawback of the obtained scheme is that we can not consider larger times.

In Chapter 3, we consider the equation of interest as a perturbation problem which evolves smoothly and slowly out of the initial solution. First we propose to analyze the continuous model under the perspective of perturbation theory by presenting first an unsatisfactory local approximation and then presenting a correct formal parametric approximation based on the original one. We analyze both cases: perturbed case and unperturbed case, and in the results we obtain that the behavior of the approximation are very similar. Such numerical scheme is sufficiently robust, accurate, and efficient for larger values of time. Later, we use a general framework to derive an analytical-numerical method using a special discretization of the domain and finally we analyze the approximations including numerical simulations and discuss the implications of the results.

In Chapter 4, we build two different schemes to approximate the solution of the proposed continuous model. These schemes were built with no standard finite difference method considering some subequations with schemes exact and some subequations with approximated schemes. The advantage of these schemes is that it could considerably increase the time as well as both schemes satisfies the conditions of positivity. Both schemes present very similar results for times smaller than t=200 and for values up to 250 we obtain only slight changes that are insignificant,

which shows that both approximations are reasonable. This fact is a consequence of using the discretization of the Duffing equation. It is important to remark that the only acceptable results have been reported only for times less than 150. As expected, both approximations deviate initially very slowly from initial data, which agrees with the fact that HPV infection takes very long time in transforming normal cervical cells into cancerous ones. Numerical results helped us understand the evolution of HPV-infected cells for very large times.

In Appendix A, we proof the uniqueness for some subequations of our model with the Energy method, while we study the monotone method for parabolic equation in Appendix B. Appendix C contains the details about the solution of the linear version of our model. Some properties of elliptic functions are given in Appendix D. In Appendix E some exact schemes of Differential Equations known are given.

In summary, we hope that this work is a motivation for further research in the area of detection of infected cells by Human Papillomavirus (HPV) before they turn cancerous. We have achieved with the results of our models and the detailed study of important special cases of these models to understand the evolution of HPV infected cells in short times and large times. This is a very good step forward in this context as there is scarce literature on this subject but we hope that in the near future increase research and interdisciplinary works and set of scientists from different areas converge to a single goal: to improve early accurate detection of infection of the virus in the basal cells of the cervix.

A model for HPV infected cells at different lesion discrete stages [1]

1.1 Introduction

Recently, early detection of uterine cervical cancer is based only on experimental tests. An important concern is the knowledge of the evolution of infected cells before they become cancerous in order to avoid such experimental evidence. The advantages consist of providing accurate and timely detection with less errors in the diagnosis of the stages in which a patient is diagnosed. Perhaps such goal is very ambitious and a more realistic aim will be to obtain models of a simplified stem in order to get a first step for early detection.

Our first goal of this chapter is to propose models for the interaction of Human Papillomanvirus infected cells related to the different stages of the evolution of cervical precancer. Such models will vary according to the quantitative information obtained. The models we consider are simple general interaction models between the number of infected cells in each stage of the natural evolution of the precancer stages.Their purpose is to illustrate some basic ideas and analysis used in the mathematical modeling of infected cell populations, and to provide a first step in the diagnosis in order to avoid taking small samples of cervix surface cells.

Our second goal is to analyze the obtained models in order to provide tools to obtain biological information regarding the evolution of cervical cancer cells. It is important too remark that the development of infected cells and the control mechanisms involved are very complex and the advance of mathematical modeling of HPV infected cell populations is relatively moderate. There are not works

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[1]This chapter is based on Francisco J. Solis and Luz M. Gonzalez, A model for HPV infected cells at different lesion discrete stages, International Journal of Complex Systems in Science, Vol. 2(1) (2012), pp. 7-10.

regarding the evolution of infected cells by HPV. Several models have been presented in the literature, most of them based on a preventive approach [2, 3, 4, 5] but basically nonexistent for the diagnosis.

The structure of this chapter is as follows: In Section 1.2 we present a discrete model for the cell cycle develop by Takahashi [8]. Such model considers the cell cycle stages in discrete steps, which is very important because it is the basis of our model. In Section 1.3 we construct our first model assuming that the evolution of the stages of uterine cervical precancer can be subdivided into discrete steps.The resulting model is a nonlinear system of m differential equations, where m is the number of stages. In section 1.4 we consider the linear approximation of such system and give the solution of the linear system associated studying different cases, and their asymptotic behavior. In section 1.5 we approximate the solution of the nonlinear system, using a fourth order Runge Kutta method. In this case the behavior of the solutions is studied for different times.We study some biologically important cases at the end of this section. Finally, conclusions are obtained in Section 1.6.

1.2 A model of cell cycle: a base for our model

In this section we will discuss a model of the cell cycle in discrete steps since our models will be based in similar ideas. Such model is very important since we want to understand the evolution and mechanisms of healthy cell in order to generate models for the evolution and mechanism of infected cells by HPV before it becomes cancerous cells. Cell cycle regulation was an early subject of biology inspired mathematical modeling. Even before the molecular regulators of the cell cycle were known, mathematical models of the cell cycle were already formulated [8]. As the molecular details of the underlying regulatory network were revealed, the modeling of the system became more and more sophisticated. Indeed cell cycle has been one of the pioneering examples of systems biology approaches, where experiments and mathematical modeling have guided each other. Thanks to these efforts now we are able to better understand the dynamics of the cell cycle regulation and to explain how the oscillations appear in different cell types and what roles positive and negative feedbacks play in cell cycle regulation. Different modeling methods were used to attack these questions at different levels of complexity.

The cell cycle is the process for which cells multiplicate or proliferate. Its correct execution in a pluricellular organism as the human, contribute to establish in an adequate functional and structural integration to face the environmental conditions. Proliferating cells perform a series of coordinated actions collectively referred to as the cell cycle. The complex network of regulatory enzymes and

cellular components that controls these processes enables cells to grow and divide, to co control or prevent growth when appropriate, to carry out the different stages of growth and division in the correct order, and to respond to DNA damage by arresting progression through the cycle so as to allow time for repair to occur before more DNA.

Since the development of cancer is associated with loss of control over this regulatory system, the study of the mechanisms and functions of the cell cycle has gained increased attention in the past decades. The detailed understanding of the mechanisms underlying tumor growth, DNA damage repair, intercellular signaling and other cell cycle related processes is therefore of paramount importance to diagnosis, treatment and prognosis of cancer. The discovery of controls that govern cell cycle has led us to understand many of the phenomena that occur in the cell life both health and disease, and this last point of particular interest for the study of potential therapeutic targets where they could cell cycle combat abnormalities that lead to tumors.Then, for us it is of great interest to study the cell cycle as a series of discrete events or stages as the basis for later construct a model for the evolution suffering HPV infected cells. The following simple discrete model for cell cycle, which is due to Takahashi will form our starting point .

1.2.1   The cell cycle

Cell division is a very important process in all living organism. Each cell undergoes a process of maturation that begins the moment they are created from parent cells and continues until they themselves are ready to divide and give rise to daughter cells. This process, known as the cell cycle, is traditionally divided into five main stages. Mature cells that are not committed to division are in G_0 phase. G_1 is a growth phase characterized by rapid synthesis of RNA and proteins. Following this is the S phase, during which DNA is synthesized. the G_2 phase is marked by further RNA and protein synthesis preparing for the M phase, in which mitosis occurs, see Figure 1.1.

1.2.2   A discrete model of the cell cycle (Takahashi)

We present the following discrete model for the cell cycle, which is due to Takhahashi, [8] which is a generalization of Kendall's [12] earlier work. Takahashi's model is specified by the following postulates.

1. Each cell must pass through a cycle of k discrete phases. A cell which has just been born is located in the first phase. A cell which is about to divide in the kth phase.
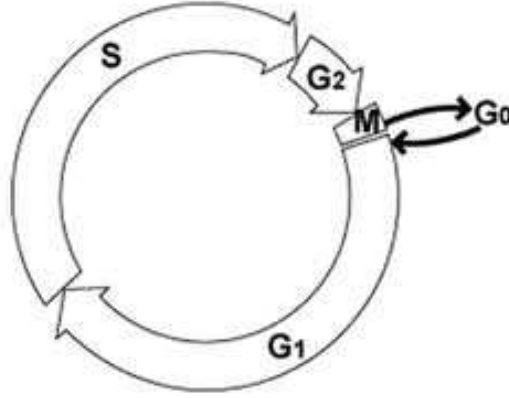
Figure 1.1: Cell cycle

2. The G_1, S, G_2 and M stages of the cell cycle also decomposed into g_1, s, g_2 and m phases respectively, where $g_1 + s + g_2 = k$.

3. Each cell transits from the jth phase to the $(j+1)th$ phase $j = 1, 2, \cdots, k-1$ with probability $\lambda_j \triangle t$.

4. Each cell in the kth phase gives birth to β daughter cells with probability $\lambda_k \triangle t$. These daughter cells pass into the first phase.

5. The probability of death in any phase is $\mu_j \triangle t$.

6. Each cell behaves independently of every other cell with regard to transit times, births and death.

With the aid of the previous postulates we can derive a model by letting N_j be the number of cells in the jth phase. The change $\triangle N_j$ during a time $\triangle t$ is given by

$$\triangle N_j(t) = \text{influx of cells into } jth \text{ phase - efflux of cells out of } jth \text{ phase}$$

by the Principle of cellular conservation $(j \neq 1)$. The influx (during a time interval $\triangle t$ the number of cells entering phase j) into the jth phase in $\triangle t$ is

$$\lambda_{j-1} N_{j-1}(t) \triangle t,$$

and the efflux (number of cells leaving) from it in $\triangle t$ is

$$(\lambda_j + \mu_j) N_j(t) \triangle t.$$

Hence

$$\triangle N_j(t) = \lambda_{j-1}N_{j-1}(t)\triangle t - (\lambda_j + \mu_j)N_j(t)\triangle t \quad j = 2, 3, \cdots, k. \qquad (1.1)$$

Since each cell leaving the last stage of mitoses ($j = k$) results in β cells in G_1 ($j = 1$), the conservation principle yields

$$\triangle N_1 = \beta\lambda_k N_k(t)\triangle t - (\lambda_1 + \mu_1)N_1(t)\triangle t. \qquad (1.2)$$

Dividing both sides of equations (1.1) and (1.2) by $\triangle t \to 0$ yields

$$\begin{aligned}
\frac{dN_j}{dt} &= \lambda_{j-1}N_{j-1} - (\lambda_j + \mu_j)N_j, \\
\frac{dN_1}{dt} &= \beta\lambda_k N_k - (\lambda_1 + \mu_1)N_1.
\end{aligned}$$

For example if we assume that transition probabilities $\lambda_j = \lambda$ are the same for all phases, that is, $\lambda_j = \lambda_{G_1} = \lambda_S = \lambda_{G_2} = \lambda_M$ during the corresponding phases and assume that $\mu_j = 0$ and that cell divides into two daughter cells $\beta = 2$ then the model can be written in the following way:

$$\begin{aligned}
\frac{dN_j}{dt} &= \lambda(N_{j-1}(t) - N_j(t)), \\
\frac{dN_1}{dt} &= \lambda(2N_k(t) - N_1(t)).
\end{aligned}$$

In the next section we develop a model for the evolution of uterine cervical precancer cells, which is based on this previous model.

1.3 A first HPV model

HPV infection requires epidermal or mucosal epithelial cells that are proliferating (basal cells). Following entry into the suprabasal layer, the viral genome replicates and in the upper layers of epidermis complete viral particles are released. HPV infection thus results in enhanced proliferation of the infected cells and their lateral expansion. Most often, cervical cancer is marked by a premalignant phase of various grades of Cervical Intraepithelial Neoplasia. which are characterized by a spectrum of histological abnormalities. On an average, it takes decades for cancer to arise. Cervical carcinogenesis thus is a multifactorial process and involves genetic, environmental, hormonal and immunological factors in addition to HPV [13].

1.3.1 Developing a model HPV

We assume that the stages of the evolution of cervical cancer can be subdivided in m discrete stages, where $N_1(t)$ and $N_j(t)$ $j = 2, \ldots, m$ represent the number of normal cells and the number of infected cells at time t in stage j, respectively. Let $f_1(N_1)$ be the reproductive rate depending only on the number of normal cells. Let $g_j(N_j)$, $j = 2, 3, \ldots, m$ be the rates of infected cells with HPV that cause injury intraepithelial that change from one stage to another. $M_j(N_j)$ represents the mortality rate associated to each stage. Following the approach based in a discrete model for the cell cycle presented in the previous section and assuming analyticity in the functions f and g, a general model can be written as:

$$
\begin{aligned}
\frac{dN_1(t)}{dt} &= f_1(N_1) - g_1(N_1) - M_1(N_1) \\
\frac{dN_2(t)}{dt} &= g_1(N_1) - g_2(N_2) - M_2(N_2) \\
&\vdots \\
\frac{dN_m(t)}{dt} &= g_{m-1}(N_{m-1}) - g_m(N_m) - M_m(N_m).
\end{aligned}
\tag{1.3}
$$

The system can be written in compact form as:

$$
\frac{dN_1}{dt} = H_1(N_1), \quad \frac{dN_j}{dt} = G_{j-1}(N_{j-1}) + H_j(N_j),
$$
$$
j = 2, 3, \ldots, m.
\tag{1.4}
$$

Without loss of generality we assume $G'_{j-1}(0) = H'_j(0)) \equiv \omega_j$ in the system. Otherwise

$$
\dot{N}_j = aN_{j-1} - bN_j + A_{j-1}N_{j-1}^2 + B_jN_j^2 + \cdots
$$

$$
\dot{N}_j = a(N_{j-1} - b/aN_j) + A_{j-1}N_{j-1}^2 + B_jN_j^2 + \cdots
$$

Let us do the following change of variable

$$
\dot{M}_j = b/a(\dot{N}_j),
$$

then we have

$$
\frac{dN_j}{dt} = \omega_j(N_{j-1} - N_j) + F(N_{j-1}) + G(N_j).
\tag{1.5}
$$

The system can be finally written as follows:

$$
\begin{aligned}
\frac{dN_1(t)}{dt} &= k_1 N_1 + A_0 N_1^2 + O(N_1^3), \\
\frac{dN_2(t)}{dt} &= k_2(N_1 - N_2) + A_1 N_1^2 + B_2 N_2^2 + O(N_1^3) + O(N_2^3), \\
&\vdots \\
\frac{dN_m(t)}{dt} &= k_m(N_{m-1} - N_m) + A_{m-1} N_{m-1}^2 + B_m N_m^2.
\end{aligned}
\tag{1.6}
$$

1.4 A simplified model: A linear system

The aim of this section is to study the system associated with our model. Since it is a very complex system we will consider as a first approach it is linear version which help us to understand the evolution of cells infected with HPV. This study is done in two cases considering the coefficients of our model, therefore the solution of the system associated to the model in each case will be different. We study the cases a) when all the coefficients of the associated linear system are different and b) when they are all equal. It is important to emphasize that not considered cases are reduced to the two studied cases (1.4.4). After obtaining the solution of the linear system in each of the above cases, we study the asymptotic behavior of these solutions. Finally, we consider a special case when the coefficient k_1 is negative in the system, in biology terms this case represents the presence of the immune system in the infectious process. For illustrative purposes we produce some graphs of the solutions obtained in order to observe the evolution of infected cells. In each case we choose the values of the constants in the linear system to satisfy the positivity condition.

1.4.1 Solution of the model with different eigenvalues

Consider the linear model obtained from (1.6) (by choosing $A_j = B_j = 0$). We can rewrite the linear system in matrix form as

$$
\dot{\mathbf{N}} = \mathbf{A}\mathbf{N}
\tag{1.7}
$$

where

$$
\mathbf{N} = (N_1(t), N_2(t), N_3(t), \ldots, N_m(t))^T
$$

and

$$\mathbf{A} = \begin{pmatrix} k_1 & 0 & 0 & 0 & 0 & \cdots \\ k_2 & -k_2 & 0 & 0 & 0 & \cdots \\ 0 & k_3 & -k_3 & 0 & 0 & \cdots \\ 0 & 0 & k_4 & -k_4 & 0 & \cdots \\ \vdots & 0 & 0 & \ddots & \ddots & \vdots \\ 0 & 0 & 0 & \ddots & k_m & -k_m \end{pmatrix}. \tag{1.8}$$

The solution of homogeneous linear system is given by the following basic theorem

Theorem 1.4.1 *If A has m linearly independent eigenvectors $\mathbf{v_1}, \mathbf{v_2} \cdots \mathbf{v}_m$ with eigenvalues $k_1, -k_2, \cdots - k_m$, then the solution to the linear system $\dot{\mathbf{N}} = \mathbf{A}\mathbf{N}$ is given by*

$$\mathbf{N}(t) = c_1 e^{k_1 t} \mathbf{v}_1 + c_2 e^{-k_2 t} \mathbf{v}_2 + c_3 e^{-k_3 t} \mathbf{v}_3 + c_4 e^{-k_4 t} \mathbf{v}_4 + \cdots + c_m e^{-k_m t} \mathbf{v}_m. \tag{1.9}$$

We have obtained the explicit solution of the system where the only important eigenvector is $\mathbf{v}_1$ and that indicates the direction in which the solution diverges. It is important to note that due to the special shape of the matrix A eigenvectors obtained are special and because of that we find all explicitly, the eigenvector $\mathbf{v}_1$ associated to the eigenvalue k_1 is given by

$$\mathbf{v}_1 = \left(\frac{\prod_{n=1}^m (k_1 + k_{n+1})}{\prod_{n=2}^m k_n}, \frac{\prod_{n=2}^m (k_1 + k_{n+1})}{\prod_{n=3}^m k_n}, \frac{\prod_{n=3}^m (k_1 + k_{n+1})}{\prod_{n=4}^m k_n}, \ldots, 1 \right)^T,$$

the eigenvector $\mathbf{v}_p$ associated to the eigenvalue $-k_p$ with $p = 2, \ldots, m-1$ is given by

$$\mathbf{v}_p = \left(\frac{\prod_{n=2}^{m-p-1}(k_p - k_{n+p})}{\prod_{n=3}^{m-1} k_n}, -\frac{\prod_{n=3}^{j-p-1}(k_p - k_{n+p})}{\prod_{n=4}^{m-1} k_n}, \frac{\prod_{n=4}^{j-p-1}(k_p - k_{n+p})}{\prod_{n=5}^{m-1} k_n}, \ldots, 1 \right)^T.$$

Finally, the eigenvector $\mathbf{v}_m$ associated to the eigenvalue $-k_m$ is given by

$$\mathbf{v}_m = (0, 0, 0, 0, \ldots, 1)^T.$$

Remark If at least two k_j approximate to a common value then the set of their corresponding associated eigenvectors approximates a set of linearly dependent eigenvectors. We will study this limit case on the next subsection.

1.4.2 Solution of the model with equal eigenvalues

If we consider that k_s are equal, then the matrix $\mathbf{A}$ in linear system (1.7) is

$$\mathbf{A} = \begin{pmatrix} k & 0 & 0 & 0 & 0 & \cdots \\ k & -k & 0 & 0 & 0 & \cdots \\ 0 & k & -k & 0 & 0 & \cdots \\ 0 & 0 & k & -k & 0 & \cdots \\ \vdots & 0 & 0 & \ddots & \ddots & \vdots \\ 0 & 0 & 0 & \ddots & k & -k \end{pmatrix}, \tag{1.10}$$

and the solution of homogeneous system (1.7) is

$$\mathbf{N} = c_1 e^{kt} \mathbf{w}_0 + e^{-kt} \sum_{j=1}^{m} \left(\sum_{s=j}^{m-1} c_s \frac{t^{s-j}}{(s-j)!} \right) \mathbf{w}_j,$$

where $c_j, j = 1, \ldots m$ are some arbitrary constants and

$$\mathbf{w}_0 = \begin{pmatrix} 2 \\ 1 \\ 1/2 \\ 1/4 \\ 1/8 \\ \vdots \\ \frac{1}{2^{m-1}} \end{pmatrix}, \mathbf{w}_1 = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ \vdots \\ 0 \\ 1 \end{pmatrix}, \mathbf{w}_2 = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ \vdots \\ 0 \\ 1 \\ 1 \end{pmatrix}, \mathbf{w}_3 = \begin{pmatrix} 0 \\ 0 \\ 0 \\ \vdots \\ 0 \\ 1 \\ 1 \\ 1 \end{pmatrix}, \ldots, \mathbf{w}_m = \begin{pmatrix} 1 \\ 1 \\ \vdots \\ 1 \\ 1 \\ 1 \\ 1 \end{pmatrix} \text{ are}$$

the eigenvectors.

In the following theorem it proved that the functions $N_j(t)$ are solutions of system (1.7).

Theorem 1.4.2 *Let $-k$ be an eigenvalue with multiplicity $r = m - 1$ of the matrix A associated to linear system (1.7), then the functions*

$$N_1(t) = \mathbf{w}_1 e^{-kt},$$

$$N_2(t) = (t\mathbf{w}_1 + \mathbf{w}_2)e^{-kt},$$

$$N_3(t) = (t^2\mathbf{w}_1 + t\mathbf{w}_2 + \mathbf{w}_3)e^{-kt},$$

$$\cdots$$

(a)   (b)
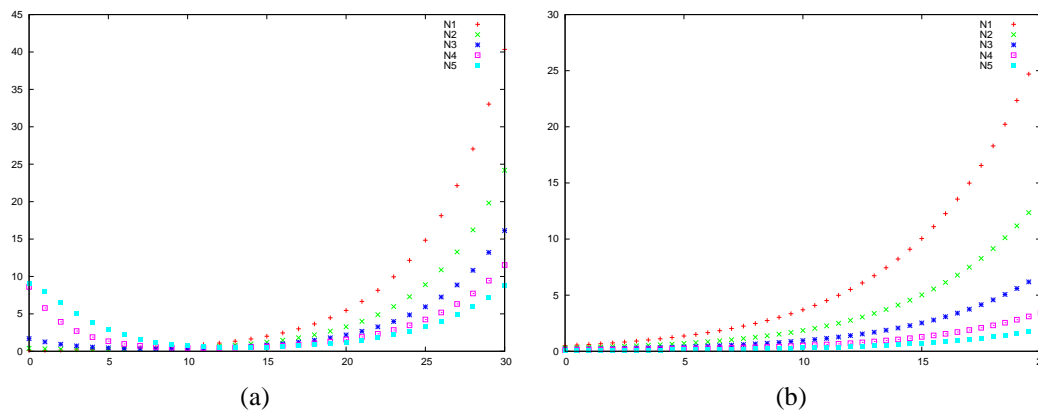
Figure 1.2: (a) Graph of the solution of the linear system with $m = 5$ different eigenvalues and k_1 positive and (b) Graph of the solution of linear system for m=5 for equal eigenvalues and k positive.

$$N_r(t) = \left(\frac{t^{r-1}}{(r-1)!} \mathbf{w}_1 + \cdots + \frac{t^2}{2} \mathbf{w}_{r-2} + t\mathbf{w}_{r-1} + \mathbf{w}_r \right) e^{-kt},$$

are r solutions of the system $\dot{\mathbf{N}} = \mathbf{AN}$.

For the proof of this theorem see appendix C.

1.4.3 Asymptotic behavior of the linear system

The solution of homogeneous linear system (1.7) are the form

$$\begin{pmatrix} N_1(t) \\ \vdots \\ N_m \end{pmatrix} = \begin{cases} c_1 e^{k_1 t} \mathbf{v}_1 + \sum_{s=2}^{m} c_s e^{-k_s t} \mathbf{v}_s, & \text{if } k_s \text{ are different} \\ c_1 e^{kt} \mathbf{w}_0 + e^{-kt} \sum_{j=1}^{m} \left(\sum_{s=j}^{m-1} c_s \frac{t^{s-j}}{(s-j)!} \right) \mathbf{w}_j, & \text{if } k_s \text{ are equal.} \end{cases}$$

Those solutions exponentially diverge in the direction of $\mathbf{v}_1$, namely

$$\left(\frac{\prod_{n=1}^{m}(k_1+k_{n+1})}{\prod_{n=2}^{m} k_n}, \frac{\prod_{n=2}^{m}(k_1+k_{n+1})}{\prod_{n=3}^{m} k_n}, \frac{\prod_{n=3}^{m}(k_1+k_{n+1})}{\prod_{n=4}^{m} k_n}, \frac{\prod_{n=4}^{m}(k_1+k_{n+1})}{\prod_{n=5}^{m} k_n}, \ldots, 1 \right)^T$$

in the case of different eigenvalues, see Figure 1.2a, and in the direction of

$$\mathbf{w}_0 = (2, 1, \ldots, 1/2^m)^T$$

for equal eigenvalues, see Figure 1.2b. From this result we immediately conclude that the number of infected cells grow exponentially, which is an undesirable

characteristic of the linear model. Therefore, we have to take in consideration the nonlinear terms.

It is important to remark that a similar case of this linear model (when $k_1 < 0$) has been analyzed in the context of pursuit in [14]. Meaning that N_1 considered a moving particle follows an independent path in phase space and the rest follows him in a cyclical fashion, that is, N_j follows N_{j-1} for $j = 2, \ldots, m$. In this way, if we replace the first equation in system (1.6) for one with N_1 settling in a bounded region, for example a closed trajectory, then the rest of the functions will exponentially settle into that region.

1.4.4 Effect of the immune system

The immune response is regarded as an effector mechanism in tumors and resistance is related from the initiation phase to the growth and progression of these. evidence suggests that important system involved in the elimination of malignant cells that appear in the host, probably as a result of spontaneous mutations, exposure to carcinogens and environmental viral activation. It also has a crucial involvement in progression of established tumors are more aggressive, generally in patients who suffer from immunosuppression. Many reports state that the host response to infection cellular and humoral components of the immune system involves both. The immune system has the ability to detect and neutralize or remove any external agent poses a threat to the body. The answer is complex and based on many signals that activate one or more routes rejection and attack foreign agent. When the integrity of this response is not compromised, success is safe and not affected body function. The papilloma virus infection, most young women without immune compromise, goes unnoticed. However, the confrontation between the immune system and HPV infection is complex, both possess highly effective mechanisms to overcome the other and the slightest advantage or defect in the system immune is used by the virus to replicate and develop their oncogenic potential and induce cancer. The solutions of the system converge to zero as time increases, this means that the number of infected cells in each stage decreases because of the immune system [15], [35]. Consider the linear system with k_1 negative. In this case the solution of linear system is given by

$$\mathbf{N}_m(t) = \sum_{s=1}^{m} c_s \mathrm{e}^{-k_s t} \mathbf{v}_s \tag{1.11}$$

and converges to zero as time increases, this means that the number of infected cells in each stage decreases because of the immune system. In Figure 1.3 we took the initial conditions as $N_1 = 0.1$, $N_2 = 0.4$, $N_3 = 1.7$, $N_4 = 8.6$, with the condition

(a)   (b)
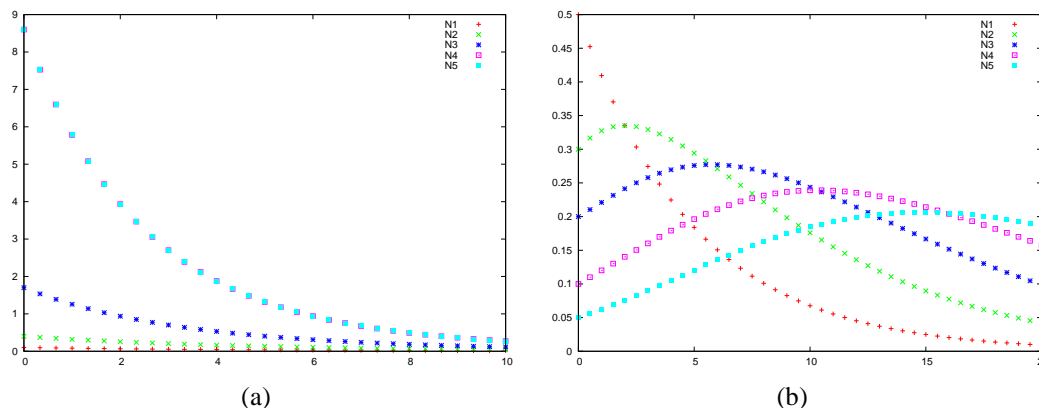
Figure 1.3: Evolution of different stages case: (a) different eigenvalues k_1 negative and (b) equal eigenvalues k negative.

of positivity

$$c_n = N_n(0) - \sum_{j=1}^{n-1} \frac{\Pi_{j=2}^n k_i}{\Pi_{i=j+1}^n (k_i - k_j)} c_j \geq 0,$$

where $c_1 = N_1(0)$ for $n = 2, 3, \ldots, m$.

Remark If the matrix A of m by m of the linear system associated with our model 1.7 has a square submatrix R of r by r where $(r < m)$ and ks different and other submatrix of A is P of p by p $(p < m)$ with equal ks such that $r + p = m$ then the solution to the system 1.7 is given by combining the solutions studied in paragraphs 1 and 2 then the solution has the form:

$$N(t) = c_1 e^{k_1 t} \mathbf{v}_1 + \sum_{s=2}^{r-1} c_s e^{-k_s t} \mathbf{v}_s + e^{-kt} \sum_{j=2}^{p} \left(\sum_{s=j}^{p-1} c_s \frac{t^{s-j}}{(s-j)!} \right) \mathbf{w}_j.$$

1.5 A simple nonlinear system (up to quadratic terms)

In this section it will be studied a nonlinear system by considering only the linear and quadratic terms in (1.6) in order to obtain a more realistic model. By taking A_1 negative in the first equation of (1.6) we obtain a logistic growth for the normal cells. In general, we take A_j negative and B_j positive for $j = 2, \ldots m$ in the model. This study will be divide into three parts, on the first part we consider the hypothesis

Figure 1.4: Evolution of different stages varying time and considering number of cells equal to constant (a) m=4 and (b) m=5.

that the number of cells is a constant and we will study the behavior of the solution for short times. On the second part we want to understand the asymptotic behavior of solutions. In the third part we consider some special cases depending on the initial conditions. This study will be conducted by approximating the solutions in all cases using Runge Kutta method of order 4 for $m = 4$ and $m = 5$.

1.5.1 Short time evolution of the system

First, we consider that the total number of cells is almost constant, so we impose the condition that $\sum_{j=1}^{m} N_j(t) = $ constant. In this case we want to understand the evolution of infected cells for short times, also we want our numerical method is stable. The coupled differential equations in the model were analyzed numerically by using classical Runge-Kutta method of order 4, these method were chosen because both methods are relatively simple to use and precise. We present the time evolution of the solution of system for $m = 4$, in this particular case the initial conditions are $N_1 = 0.5$, $N_2 = 0.3$, $N_3 = 0.15$, $N_4 = 0.05$, see Figure 1.4a and we present the time evolution of the solution of system for $m = 5$ with initial conditions $N_1 = 0.3$, $N_2 = 0.25$, $N_3 = 0.2$, $N_4 = 0.15$, $N_5 = 0.1$, see Figure 1.4b, which correspond to initial conditions for a patient with mild dysplasia. Notice that the number of infected cells growths slowly implying that cervical usually develops very slowly, which is an important fact. This nonlinear model is more reliable than the linear one since gives us information on the evolution of infected cells at each stage. Similar qualitative behavior is obtained for models with higher nonlinear terms included.

1.5.2 The evolution in time of the system for large times

Next, we want to understand the evolution of cells for larger times, in this case, we do not consider the assumption of a constant number of cells, only approximate the solution with Runge-Kutta method of order 4, see Figure 1.5 we present the time evolution of the solution of system for $m = 5$. In this case the initial conditions are $N_1 = 0.5$, $N_2 = 0.3$, $N_3 = 0.20$, $N_4 = 0.05$, $N_5 = 0.01$. We get the following behavior: as time passes the number of infected cells in each stage grows to a maximum and then decreases, as some of them are infecting even more and become the next stage and others die; well as the time of maximum grows number of cells in stage j is less than the maximum number of cells in stage $j + 1$, this means that the number of infected cells in advanced stages grows faster than in early stages. Notice in the graph largest 1.5-c) maximum value of infected cells in larger time $t = 20$ is much larger than in previous times.

1.5.3 Some special cases for nonlinear system

Now let us consider some special cases considering the initial conditions, the degree of infection of a patient at the initial time. These cases arise depending on the degree of dysplasia of a patient: first, the patients with very small degree of infection; second, the patients with similar levels of infection in each stage and finally, the patients with the same number of infected cells at each stage.

1. *All initial conditions are small.*
   This case is important because we can observe the evolution of the solution curves when the degree of infection is very small at the initial time. We consider in this case the initial conditions: $N_1 = 0.01, N_2 = 0.02, N_3 = 0.03, N_4 = 0.04, N_5 = 0.05$ that corresponds to patients with very mild dysplasia. In this case the solution curves of the nonlinear system are decreasing, and converge to zero as time increases see Figure 1.6. This means that the immune system eliminates the HPV infection.

2. *All initial conditions are significantly similar*
   In this case, the patient has about the same number of infected cells in each stage. We consider the initial conditions: $N_1 = 0.24, N_2 = 0.2, N_3 = 0.16, N_4 = 0.12, N_5 = 0.08$ see Figure 1.7a and the initial conditions: $N_1 = 0.25, N_2 = 0.21, N_3 = 0.17, N_4 = 0.13, N_5 = 0.09$ see Figure 1.7b. In this case, the patient has infected cells at different stages with a very similar degree of infection. The solution curves have a very similar behavior, that is, they start increasing, reach their maximum and then decrease. As
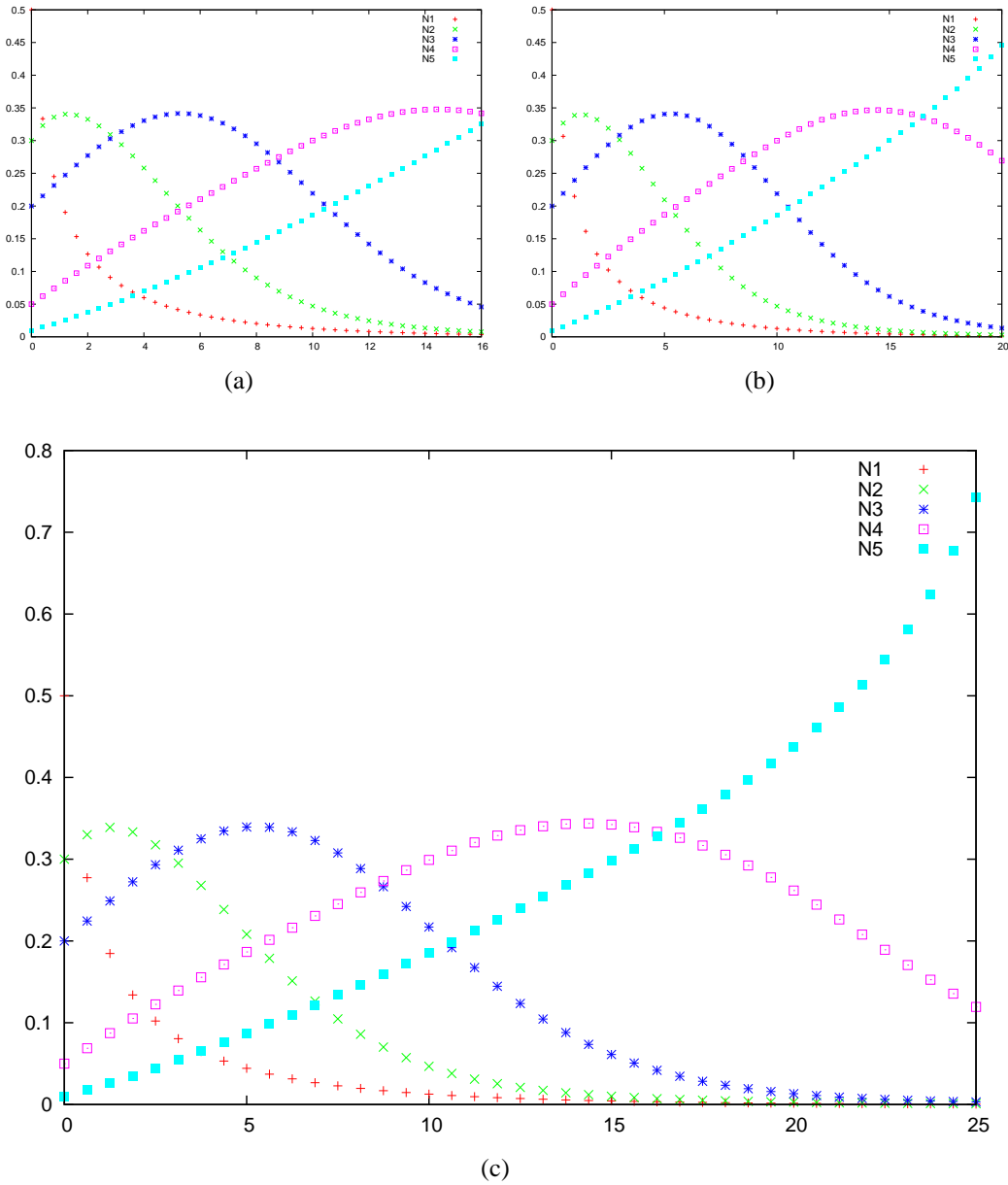
Figure 1.5: Evolution of different stages varying time, for great times: (a) up t=16 (b) up t=20 and (c) up t=25.
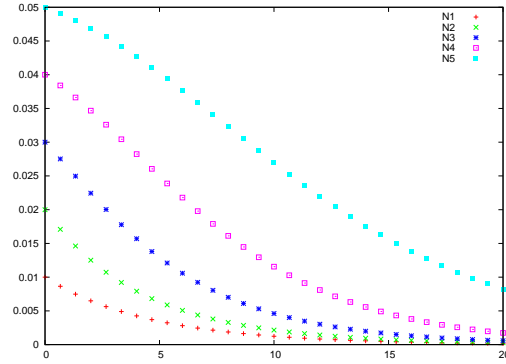
Figure 1.6: Evolution of different stages with initial conditions very small
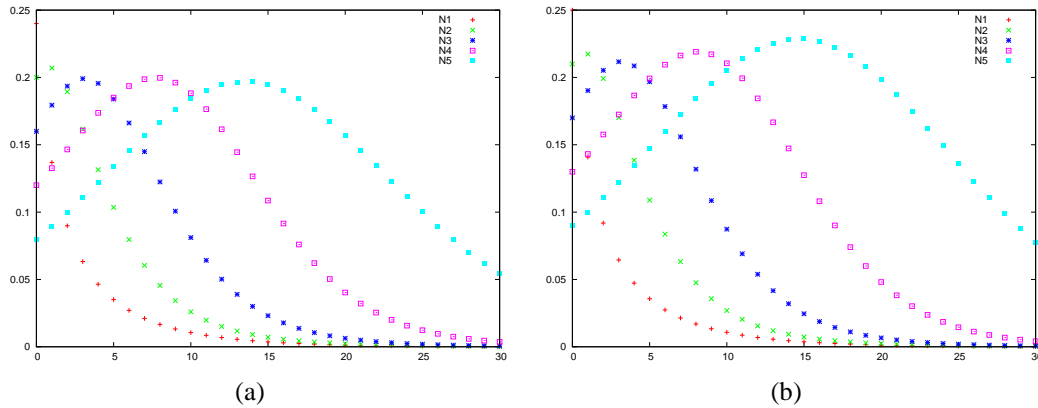
Figure 1.7: Evolution of different stages with initial conditions similar

time increases, the maximum value of each of these curves is similar to the previous one.

3. *All initial conditions are equal*
   In this case the initial conditions indicate that the infection degree of the patient is the same in each stage. We note that each solution curve grows to a maximum and then decreases at later stages. The maximum is significantly larger than each previous solution curve, see Figure 1.8.
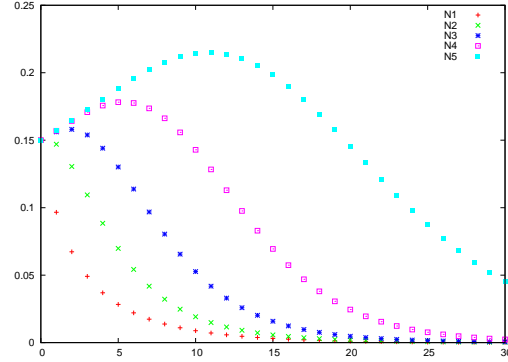
Figure 1.8: Evolution of different stages with equal initial conditions

1.6 Conclusions

In this chapter, we presented a reliable model for the interaction of HPV infected cells. The model provides useful information regarding the evolution of the infected cells. This model is the first model known in the literature regarding the evolution of cells infected with HPV that cause lesions in the cervix before they become cancerous. We studied the linear and nonlinear cases associated with our model. We solved the linear system and approximate the solution of the nonlinear system with Runge Kutta method of order 4 for $m = 4$ and $m = 5$. Both the linear and the nonlinear system were considered and studied for important cases. In such analysis, initial conditions were chosen depending on the patient infection degree and considering positivity conditions. The results help us to understand the evolution of cells infected with HPV. It is only a first step to provide clinicians with a reliable benchmark. More research needs to be done to refine the present model. A step in this direction is the development of models with a continuous number of stages for the natural history of cervical cancer which we will do in the next chapter.

Chapter 2

Modeling the effects of Human Papillomavirus in cervical cells [1]

2.1 Introduction

The present chapter is a second step to address the detection problem for HPV by proving mathematical models hopping that our approach provides an alternative method to existing ones and open up new avenues to new modeling. It is our main goal to developed mathematical models of the interaction of infected cells of Human Papillomavirus. A first step was developed in chapter 1 where we built a model considering the stages of HPV infection as discrete stages. By considering a continuous description of the invasion stages, we will derive a general interaction model between the number of infected cells in each stage, resulting in an advection diffusion reaction nonlinear model. For the sake of completeness, we develop a nonstandard difference method based on nonstandard finite difference methods. By testing our numerical scheme in some particular cases of our model, we show that this new method is robust and efficient.

This chapter is organized as follows. In Section 2.2, we propose a general framework of structure models, from which we derive a family of models. In Section 2.3, we present some particular cases of our models in order to provide insight into biological factors. In Section 2.4, we develop a nonstandard numerical scheme for our models, we include numerical simulations and also interpret the biological implications of the results. Finally, conclusions are given in Section 2.5.

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[1]This chapter is based on Francisco J. Solis and Luz Maria Gonzalez, Modelling the effects of human papillomavirus in cervical cells, International Journal of Computer Mathematics, Vol. 91(2) (2014), pp. 179-187.
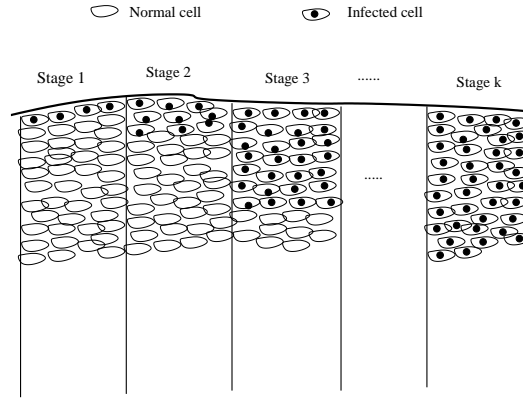
Figure 2.1: A schematic distribution of the different stages of the lesions.

2.2 Model development

The aim of this section is to derive first a general interaction model between the number of infected cells in each stage. Then by considering a continuous description of the invasion stages, we proceed to the derivation of a family of advection diffusion reaction models.

The evolution of cervical cancer is divided into several stages. The first stage, called pre-invasive stage, is characterized by maintaining the whole basal membrane, which allows that cell changes, in despite of being malignant, are retained within the epithelial thickness. The latter stages, called invasive stages are subdivided in three stages (or more). The first one, known as mild dysplasia has spread to approximately one third of the thickness of the epithelium, the second one, known as moderate dysplasia, is where the injury has extended to two-thirds the thickness of the epithelium and the last one, known as severe dysplasia, the injury has been extended to all the thickness of the epithelium, for more detail see [2]. However, in the invasive stages, the injury to the cervix has caused basal membrane rupture, allowing the malignant cells to spread into the the supporting or interior tissue. It is important to establish that this classification on three invasive stages depends on how deep the epithelium is penetrated by the infected cells, thus the number of stages may vary depending of the degree of resolution required.

2.2.1 Model with a discrete number of stages

Let us recall the model, with its assumptions, that we introduced in the previous chapter. Let us assume that the stages of the natural history of cervical cancer can be subdivided in k discrete stages, see Figure 2.1, where $N_j(t)$ represents the number

of infected cells in stage j, at time t, $j = 1, 2, \ldots, k$. Let $f_j(N_j)$ be reproductive rates depending only on the number of infected cells. Let $g_j(N_j)$, $j = 2, 3, \ldots, k$ be rates of cells infected with HPV that cause injury intraepithelial that change from one stage to another. $M_j(N_j)$ represents the mortality rate associate to each stage.

The system can be written as follows:

$$
\begin{aligned}
\frac{dN_1}{dt} &= f_1(N_1) - g_1(N_1) - M_1(N_1), \\
\frac{dN_2(t)}{dt} &= g_1(N_1) - g_2(N_2) - M_2(N_2), \\
&\vdots \qquad\qquad \vdots \\
\frac{dN_{k-1}(t)}{dt} &= g_{k-2}(N_{k-2}) - g_{k-1}(N_{k-1}) - M_{k-1}(N_{k-1}), \\
\frac{dN_k(t)}{dt} &= g_{k-1}(N_{k-1}) - g_k(N_k) - M_k(N_k),
\end{aligned}
$$

where functions f_j and g_j are continuous, their derivatives exist and are bounded to ensure that the system has a unique solution for any initial condition for any particular initial condition. For different cell division models see for example [16, 17]. The system can be written in a compact form as:

$$
\frac{dN_1}{dt} = H_1(N_1), \quad \frac{dN_j}{dt} = G_{j-1}(N_{j-1}) + H_j(N_j), \quad j = 2, 3, \ldots, k \qquad (2.1)
$$

where G_{j-1} and H_j are given by $g_{j-1}(N_{j-1})$ and $-g_j(N_j) - M_j(N_j)$, respectively and $j = 2, 3, \ldots, k$. Without loss in generality we can assume that $G'_{j-1}(0) = H'_j(0)) \equiv \omega_j$ in (2.1), since we can rescale the original variables. One assumption that we make in the following is that $\omega_j = \omega$ for all $j > 1$. Thus,

$$
\frac{dN_j}{dt} = \omega(N_{j-1} - N_j) + F(N_{j-1}) + G(N_j), \qquad (2.2)
$$

where F and G are of order $O(N_{j-1}^2)$ and $O(N_j^2)$, respectively.

System (2.2) has been already analyzed in [18] for proper functions F and G. Furthermore, the system obtained from (2.2) by considering only the linear part has been analyzed in the context of cycle pursuit in [14]. It has been shown that this linear system contain a globally attracting equilibrium point characterized by the arithmetic mean of the initial conditions, or in geometric terms by the barycenter of the initial conditions.

2.2.2 Models with a continuous number of stages

The previous model has the drawback that one requires to quantify the number of cells in each stage, which in most cases there is only a qualitative description of the distribution of infected cells. One may take some averages on the number of infected cells depending on the information available. A better way to deal with some incomplete data is to use a continuous model, which only requires the initial distribution along with some boundary conditions. Now, let us develop a continuous model. We begin by assuming the natural history of cervical cancer can be subdivided in k discrete equal stages with length $h = 1/k$ and by defining

$$\eta(\alpha_j, t) = N_j(t)/h, \text{ with } \alpha_j = jh \text{ for } j = 1, 2, \ldots, k,$$

which represents infected cell density per time unit in each stage j. Assuming that h is small enough, we can expand $\eta(\alpha_{j-1}, t)$ in a Taylor series, obtaining

$$
\begin{aligned}
\eta(\alpha_{j-1}, t) &= \eta(\alpha_j - h, t) \\
&= \eta(\alpha_j, t) - \left.\frac{\partial \eta}{\partial \alpha}\right|_{\alpha=\alpha_j} h + \left.\frac{\partial^2 \eta}{\partial \alpha^2}\right|_{\alpha=\alpha_j} h^2/2 - \left.\frac{\partial^3 \eta}{\partial \alpha^3}\right|_{\alpha=\alpha_j} h^3/6 + \cdots
\end{aligned}
\tag{2.3}
$$

Dividing by h and substituting (2.3) in (2.2), we get

$$
\begin{aligned}
\frac{\partial \eta}{\partial t}(\alpha_j, t) &= \omega[\eta(\alpha_{j-1}, t) - \eta(\alpha_j, t)] + \frac{1}{h}\left[F\left(\eta(\alpha_{j-1}, t)h\right) + G\left(\eta(\alpha_j, t)h\right)\right] \\
&= \omega[\eta(\alpha_{j-1}, t) - \eta(\alpha_j, t)] + \frac{1}{h}\left[\sum_{s=2}^{l} f_s(\eta(\alpha_{j-1}, t)h)^s\right] + \\
&\quad \frac{1}{h}\left[\sum_{s=2}^{l} g_s(\eta(\alpha_j, t)h)^s\right] + O((\eta h)^{l+1}) \\
&= \omega\left[-\left.\frac{\partial \eta}{\partial \alpha}\right|_{\alpha=\alpha_j} h + \left.\frac{\partial^2 \eta}{\partial \alpha^2}\right|_{\alpha=\alpha_j} h^2/2 + \cdots\right] + \sum_{s=2}^{l} f_s h^{s-1} \eta^s(\alpha_{j-1}, t) + \\
&\quad \sum_{s=2}^{l} g_s h^{s-1} \eta^s(\alpha_j, t) \\
\frac{\partial \eta}{\partial t}(\alpha_j, t) &= \omega\left[-\frac{\partial \eta}{\partial \alpha} h + \frac{\partial^2 \eta}{\partial \alpha^2} h^2/2 + \cdots\right] + \sum_{s=2}^{l} g_s h^{s-1} \eta^s(\alpha_j, t) + \\
&\quad \sum_{s=2}^{l} f_s h^{s-1}\left(\eta - \frac{\partial \eta}{\partial \alpha} h + \frac{\partial^2 \eta}{\partial \alpha^2} h^2/2 + \cdots\right)^s.
\end{aligned}
\tag{2.4}
$$

From the equation 2.4, we can obtain a series of models depending on the resolution (powers of h) required. Considering only the linear terms in h we find

$$\frac{\partial \eta}{\partial t} = -\omega h \frac{\partial \eta}{\partial \alpha} + (g_2 + f_2)h\eta^2 + O(h^2), \tag{2.5}$$

which is a standard transport equation with a quadratic reaction term. Let us note that the velocity is small of order h, Which in a numerical setting means that it will take a long time for the transient behavior to settle into its asymptotic behavior. From this simple model we realize that the invasive stage takes a large period of time to develop. The analytical solution of this model is given in the next section.

Carrying the nonlinearities to second order only and neglecting third and higher order terms in h, we get the following equation

$$\frac{\partial \eta}{\partial t} = \omega h(\alpha)\left(-\frac{\partial \eta}{\partial \alpha} + \frac{\partial^2 \eta}{\partial \alpha^2}\frac{h}{2}\right) + (g_2 + f_2)h(\eta^2) - 2f_2\eta\frac{\partial \eta}{\partial \alpha}h^2 + (f_3 + g_3)h^2\eta^3 \tag{2.6}$$

which can be rewritten as

$$\frac{\partial \eta}{\partial t} = c_1(\alpha)\frac{\partial \eta}{\partial \alpha} + c_2(\alpha)\frac{\partial^2 \eta}{\partial \alpha^2} + c_3\eta\frac{\partial \eta}{\partial \alpha} + c_4\eta^2 + c_5\eta^3. \tag{2.7}$$

Let us remark that this model can be written in conservative form as follows:

$$\frac{\partial \eta}{\partial t} + \frac{\partial f(\eta)}{\partial \alpha} = c_2\frac{\partial \eta}{\partial \alpha^2} + \eta^2(c_4 + c_5\eta) - c_1'(\alpha)\eta \tag{2.8}$$

with

$$f(\eta) = -\frac{c_3}{2}\eta^2 - c_1\eta, \tag{2.9}$$

where η is the conservative variable and $f(\eta)$ is the flux function.

In general if we keep nonlinearities to order N in h neglecting higher order terms we get

$$\frac{\partial \eta}{\partial t} = \sum_{j=1}^{N} a_j(\alpha)\frac{\partial^j \eta}{\partial \alpha^j} + P_{N+1}(\eta) + \frac{\partial \eta}{\partial \alpha}Q_{n-1}(\eta), \tag{2.10}$$

where P_{N+1} and Q_{N-1} are polynomials in α of degree $N+1$ and $N-1$, respectively, for $N \geq 2$. For example for $N = 3$ we obtain:

$$\frac{\partial \eta}{\partial t} = c_1(\alpha)\frac{\partial \eta}{\partial \alpha} + c_2(\alpha)\frac{\partial^2 \eta}{\partial \alpha^2} + c_2(\alpha)\frac{\partial^3 \eta}{\partial \alpha^3} + \frac{\partial \eta}{\partial \alpha}(-h^2\eta)(2f_2 + 3hf_3\eta) \tag{2.11}$$
$$+\eta^2 h[f_2 + g_2 + \eta h(f_3 + g_3) + f_4 h^2\eta^2].$$

Notice how for $N \geq 3$ the complexity of the models increases dramatically. The model for $N = 1$ can be solved explicitly by using the splitting operator technique which basically consists in decomposing a partial differential equation into simpler subproblems and treat them individually, see for details [19]. The solution of such equation is given by

$$\eta(\alpha, t) = \frac{f(\int (1/hw(\alpha))d\alpha - t)}{1 - h(f_2 + g_2)tf(\int (1/hw\alpha))d\alpha - t)}, \quad (2.12)$$

where f is an arbitrary function (initial profile). Therefore the initial profile moves with time without alteration for very short periods of time, changing the shape of the initial profile slowly for larger times up to a singularity. In Figure 2.2, we show the temporary evolution of a patient with a pre-invasive stage, for values of time (given in months) of $t = 10$, $t = 20$ and $t = 30$.

Our next step is to analyze the nonlinear model (2.7). Solving partial differential equations similar to Equation (2.7) is very complicated, although some one-dimensional analytical solutions to some particular equations have been given by transforming the nonlinear equation into a linear one. So our approach to analyze the model is via numerical analysis, but before developing a numerical scheme let us mention that Equation (2.7) includes some well known partial differential equations as the nonlinear transport equation with polynomial reaction term, the diffusion equation and the viscous Burgers equation. The knowledge of these particular cases are essential to understand the behavior of our model, its complexity and its potential difficulty in numerical integration. It is important to remark that there are many incomplete biological models that do not include non-constant velocity and diffusion terms leading to some discrepancies. To alleviate this dilemma, some modification of those previous models have been made, see for example [20]. In our case, we know exactly the origin of all the terms and we can regard our model as complete in the sense discussed previously. It is important to keep in mind that the constants in Equation (2.7) are not independent, for example $c_4/(g_2 + f_2) = (c_5/f_3)^{1/2}$ and so on.

2.3 Particular continuous submodels

Solving similar partial differential equations to our model remains a difficult task, although some one-dimensional analytical solutions to some particular equations have been given by transforming the non-linear equation into a linear one, as we show next. So our approach to analyze the model is via numerical analysis, but before developing a numerical scheme, we review some particular cases of equation (2.7) along with their formal solutions. These particular cases are essential to
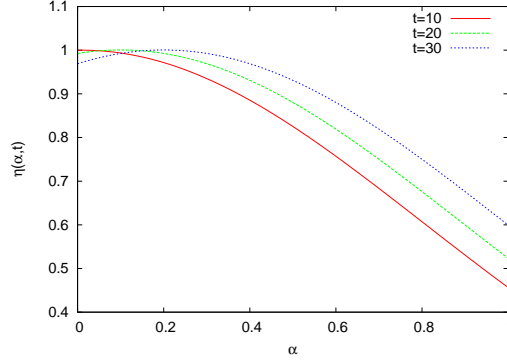
Figure 2.2: Time evolution of the solution (2.12) at times t = 10, t = 20 and t = 30.

understand the behavior of our model, its complexity and its potential difficulty in numerical integration.

2.3.1 Transport equation

First, by setting $g(\eta) = c_1 + c_3\eta$ and eliminating the diffusion term ($c_2 = 0$) we get the following transport equation with linear velocity and with a quadratic and cubic reaction term, namely

$$\frac{\partial \eta}{\partial t} + g(\eta)\frac{\partial \eta}{\partial \alpha} = c_1\eta^2 + c_2\eta^3.$$

We have two cases

1. Consider the nonlinear partial differential equation of order one

$$\frac{\partial \eta}{\partial t} + c_0\eta\frac{\partial \eta}{\partial \alpha} = c_1\eta^2 + c_2\eta^3, t > 0.$$

By taking $\eta(\alpha, 0) = f(\alpha)$ the solution is given by

$$\frac{c_2}{c_1{}^2} \ln \left| \frac{c_1 + c_2 f(\alpha - c_0\eta t)}{c_1 f(\alpha - c_0\eta t)} \right| - \frac{1}{c_1 f(\alpha - c_0\eta t)} = t + k_1, \qquad (2.13)$$

where k_1 is a constant.

2. Consider the nonlinear partial differential equation

$$\frac{\partial \eta}{\partial t} + c\frac{\partial \eta}{\partial \alpha} = -\eta^2.$$

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By taking $\eta(\alpha, 0) = f(\alpha)$, the solution is

$$\eta(\alpha, t) = \frac{f(\alpha - ct)}{tf(\alpha - ct) + 1}.$$ (2.14)

From these two examples we realize that an exact numerical scheme for our model (if exists) must have a rational form.

2.3.2 Diffusion equation

The diffusion equation describes the diffusion of species or energy starting at an initial time, with an initial spatial distribution and progressing over time. Setting $c_1 = c$ and $c_3 = c_4 = c_5 = 0$ we get

$$\frac{\partial \eta}{\partial t} + c\frac{\partial \eta}{\partial \alpha} = c_2\frac{\partial^2 \eta}{\partial \alpha^2},$$ (2.15)

with solution

$$\eta(\alpha, t) = \frac{e^{\frac{c}{2c_2}\alpha - \frac{c^2}{4c_2}t}}{(4\pi c_2 t)^{1/2}} \int_{-\infty}^{\infty} e^{-\frac{(\alpha-y)^2}{4kt}} f(y) e^{\frac{-c}{2k}y} dy$$ (2.16)

2.3.3 Viscous Burgers' equation

Let us set $c_1 = c_4 = c_5 = 0$, $c_3 = -1$ and $c_2 = \epsilon$ to obtain Burgers' equation, namely

$$\frac{\partial \eta}{\partial t} + \eta\frac{\partial \eta}{\partial \alpha} - \epsilon\frac{\partial^2 \eta}{\partial \alpha^2} = 0.$$ (2.17)

We impose the condition $\eta(\alpha, 0) = f(\alpha)$. Burgers' equation is an important partial differential equation from fluid mechanics, which appears in many applications, such as modeling of gas dynamics and traffic flow. Its importance also resides in the fact that it is one of the simplest models of non linear system outside equilibrium. It is also used to test new numerical resolution methods for nonlinear conservation laws because it belongs to this kind of laws and its solution can be found easily.

Using the Cole-Hopf transformation (see [21]) $\eta \equiv \frac{-2\epsilon}{V}\frac{\partial V}{\partial \alpha}$ and substituting it in (2.17), we get

$$\frac{1}{V}\frac{\partial V}{\partial \alpha}\left(\epsilon\frac{\partial^2 V}{\partial \alpha^2} - \frac{\partial V}{\partial t}\right) - \frac{\partial}{\partial \alpha}\left(\epsilon\frac{\partial^2 V}{\partial \alpha^2} - \frac{\partial V}{\partial t}\right) = 0$$ (2.18)

Thus, equation (2.18) is satisfied if we select V to satisfy the diffusion equation (2.15).

$$\epsilon \frac{\partial^2 V}{\partial \alpha^2} - \frac{\partial V}{\partial t} = 0, \qquad V(\alpha, 0) = \alpha e^{\frac{-1}{2}\epsilon \int_0^\alpha f(s)ds}.$$

Therefore, by using (2.16) we get

$$\eta(\alpha, t) = \frac{\int_{-\infty}^{\infty} \frac{g(\xi)(\alpha - \xi)}{t} e^{-(\alpha - \xi)^2/4\epsilon t} d\xi}{\int_{-\infty}^{\infty} g(\xi) e^{-(\alpha - \xi)^2/4\epsilon t} d\xi}, \tag{2.19}$$

where $g(\alpha) = e^{\frac{-1}{2}\epsilon \int_0^\alpha f(s)ds}$.

From these examples we realize that a numerical scheme must be of a rational form.

2.4 Numerical scheme and results

The aim of this section is first to develop a nonstandard numerical method to solve (2.7) and then provide with some numerical results that illustrate the behavior of our model. The development of the numerical scheme is based on Mickens' ideas, [11].

Let us recall our derived model

$$\frac{\partial \eta}{\partial t} = c_1 \frac{\partial \eta}{\partial \alpha} + c_2 \frac{\partial^2 \eta}{\partial \alpha^2} + c_3 \eta \frac{\partial \eta}{\partial \alpha} + c_4 \eta^2 + c_5 \eta^3. \tag{2.20}$$

Our strategy to derive a numerical scheme is to obtain an exact scheme for some subequations of (2.20) (see Appendix E) whenever possible and nonstandard schemes when the previous is no feasible. A subequation of (2.20) is basically the same equation with some of the involved constants set equal to zero.

Let $\lambda = c_4$, $\beta = c_5/c_4$, $\gamma = c_4/c_2 = \lambda/c_2$ and $\delta = c_4/c_3$. The propose subequations are the following:

Let us first consider the special case without reaction rate. Setting $c_1 = c_3 = c_2 = 0$ in (2.20), we get

$$\frac{d\eta_1}{\partial t} = \lambda \eta_1^2 (1 + \beta \eta_1). \tag{2.21}$$

Setting $c_1 = c_2 = 0$ and $\frac{\partial \eta}{\partial t} = 0$ in (2.20), we get

$$\frac{d\eta_2}{d\alpha} + \delta \eta_2 (1 + \beta \eta_2) = 0. \tag{2.22}$$

Setting $c_1 = c_3 = 0$ and $\frac{\partial \eta}{\partial t} = 0$ in (2.20), we get

$$\frac{d^2 \eta_3}{d\alpha^2} + \gamma \eta_3^2 (1 + \beta \eta_3) = 0. \tag{2.23}$$

Equations (2.21) and (2.22) are ordinary differential equations with known exact solutions. Dividing the spatial and time domains in intervals of selected length ($\Delta\alpha$ and Δt), defining $\eta_1(t_k) = \eta^k$ and $\eta_2(x_m) = \eta_m$ for $k = 1, 2, \ldots$ and $m = 1, 2, \ldots$ and using the exact solution, we obtain the following two exact schemes:

$$\frac{\eta^{k+1} - \eta^k}{\frac{e^{\lambda\Delta t}-1}{\lambda}} = \eta^{2k}\left(1 + \beta\eta^{k+1}\right), \tag{2.24}$$

$$\frac{\eta_{m+1} - \eta_m}{\frac{1-e^{-\delta\Delta\alpha}}{\delta}} + \eta_m(1 + \beta\eta_m) = 0. \tag{2.25}$$

For (2.23) we propose the nonstandard scheme taken from [22], which is exact for second order quadratic ordinary differential equations of the form $\frac{dw}{d\alpha^2} = aw^2 + bw$. Such scheme is achieve by a discretization of the second derivative as

$$\frac{d^2 w}{d\alpha^2} \approx \frac{w(\alpha + h) - 2w(\alpha) + w(\alpha - h)}{\phi(h)},$$

where $\phi(h) = \frac{1}{b}\left(e^{h\sqrt{b}} - 2 + e^{-h\sqrt{b}}\right)$.

Using this nonstandard scheme in (2.23) and setting $\eta_3(\alpha_m) = \eta_m$, we obtain

$$\frac{\eta_{m+1} - 2\eta_m + \eta_{m-1}}{(e^{\gamma^{1/2}\Delta\alpha} - 2 + e^{-\gamma^{1/2}\Delta\alpha})/\gamma} + \eta_m^2\left(1 + \beta\eta_m\right) = 0. \tag{2.26}$$

Combining equations (2.24), (2.25) and (2.26) and setting $\eta(\alpha_m, t_k) = \eta_m^k$, we obtain a numerical scheme for our model:

$$\begin{aligned}
\frac{\eta_m^{k+1} - \eta_m^k}{\frac{e^{\lambda\Delta t}-1}{\lambda}} &= c_1 \frac{\eta_{m+1}^k - \eta_m^k}{\frac{1-e^{-\delta\Delta\alpha}}{\delta}} + c_2 \frac{\eta_{m+1}^k - 2\eta_m^k + \eta_{m-1}^k}{(e^{\gamma^{1/2}\Delta\alpha} - 2 + e^{-\gamma^{1/2}\Delta\alpha})/\gamma} \\
&\quad + c_3\eta_m^{k+1}\left(\frac{\eta_{m+1}^k - \eta_m^k}{\frac{1-e^{-\delta\Delta\alpha}}{\delta}}\right) + c_4\eta_m^{2k}\left(1 + \beta\eta_m^{k+1}\right).
\end{aligned}$$

Denoting by $\alpha_1 = \frac{c_1\delta}{\lambda}\left(\frac{e^{\lambda\Delta t}-1}{1-e^{-\delta\Delta\alpha}}\right)$, $\alpha_2 = \frac{c_2\gamma(e^{\lambda\Delta t}-1)}{\lambda(e^{\gamma^{1/2}\Delta\alpha}-2+e^{-\gamma^{1/2}\Delta\alpha})}$, $\alpha_3 = \frac{c_3\alpha_1}{c_1}$, $\alpha_4 = \frac{c_4\left(e^{\lambda\Delta t}-1\right)}{\lambda}$, we get the following explicit scheme

$$\begin{aligned}
\eta_m^{k+1} - \eta_m^k &= \alpha_1\left(\eta_{m+1}^k - \eta_m^k\right) + \alpha_2\left(\eta_{m+1}^k - 2\eta_m^k + \eta_{m-1}^k\right) + \alpha_3\eta_m^{k+1}\left(\eta_{m+1}^k - \eta_m^k\right) \\
&\quad + \alpha_4(\eta_m^k)^2\left(1 + \beta\eta_m^{k+1}\right).
\end{aligned}$$

Which can be explicitly written as
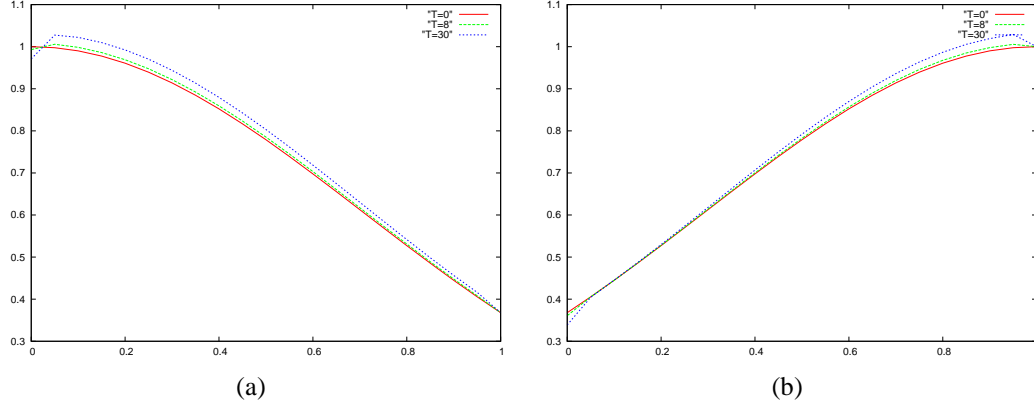
Figure 2.3: Two approximations of the solution η for different values of time

$$\eta_m^{k+1} = \frac{(1 - \alpha_1 - 2\alpha_2)\eta_m^k + (\alpha_1 + \alpha_2)\eta_{m+1}^k + \alpha_4(\eta_m^k)^2 + \alpha_2\eta_{m-1}^k}{1 - \alpha_3(\eta_{m+1}^k - \eta_m^k) - \alpha_4\beta(\eta_m^k)^2}. \qquad (2.27)$$

Notice that the structure of (2.27) was expected by the explicit solution of (2.7). It is important to remark that our numerical scheme is positive only in an large region of the first positive quadrant of the domain, so a careful selection of the spatial and temporal steps sizes must be done.

2.4.1 Numerical results

Now let us give some numerical results by applying (2.27). Since we do not have actual data, we will only present a numerical simulation for illustration purposes. We use $\eta(\alpha, 0) = e^{-\alpha^2}$ as initial condition see Figure 2.3a along with some values of the constants namely, $c_1 = 0.01$, $c_2 = 0.00005$, $c_3 = 0.0002$, $c_4 = 0.01$ and $c_5 = 0.0001$, we use $\eta(\alpha, 0) = e^{-(\alpha-1)^2}$ in Figure 2.3b in both cases we show the evolution of the approximation for times $t = 8$ and $t = 30$. In the Figure 2.4 we consider the constants $c_1 = 0.0117$, $c_2 = 0.00006$, $c_3 = 0.00046$, $c_4 = 0.0231$ and $c_5 = 0.00089$ we show the evolution of the approximation for times $t = 10$, $t = 30$ $t = 50$ y $t = 70$ and use the same initial conditions than previous graphics. Clearly, we could manipulate the constants to modify the shape of the approximation, but such parametric adjustment will be worthy only in a real data simulation. As expected, the approximation deviates very slowly from initial data, which agrees with the fact that HPV infection takes very long time in transforming normal cervical cells into cancerous ones.

(a)   (b)
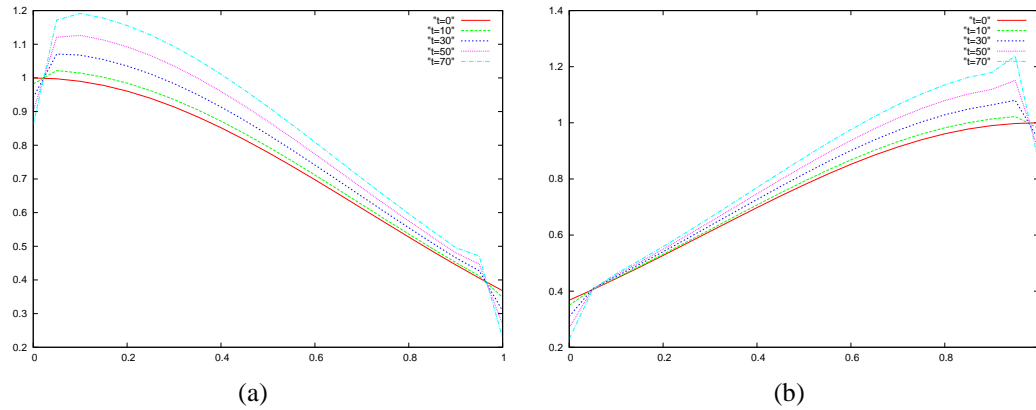
Figure 2.4: Two approximations of the solution η for different values of time

2.5 Conclusions

In this chapter we have presented a family of models for the interaction of infected cells of Human Papillomavirus. Those models are classified with a degree of resolution required. By assuming (2.4), we obtained a family of generalized advection diffusion reaction models, which have biological foundation. We also give a nonstandard numerical method, which is not exact but have better numerical properties than the usual difference standard methods. Future work will focus on obtaining spatial models and numerical methods.The numerical approximations were made for times up to $t = 60$ and if this time is increased then numerical problems arise. In the next chapter our approach is based on a new trend in numerical analysis that consists in the development of numerical techniques for perturbation problems.

Chapter 3

A regular perturbation analytical numerical method for the evolution of precancerous lesions caused by the human papillomavirus [1]

3.1 Introduction

The development of infected cells and the control mechanisms involved are complex processes, which is one of the reasons that the progress in mathematics models for the evolution of HPV infected cells is relatively scarce. Most of the proposed models are based on a preventive approach, [2, 3, 4, 5], but for the diagnosis and for the development of precancerous lesions are basically non-existent. A first step to amend this situation has been taken in our previous chapters, where reliable interaction of HPV infected cells models were presented, providing useful information on the evolution of the infected cells. Also in chapter 2, a nonstandard numerical method was developed in order to extract basic biological information. Such numerical method was shown to be efficient but was only valid for small values of time. It was only a first initiative in providing health professionals with a reliable quantity reference and more research needs to be done to refine such numerical schemes. A measure in this direction is the development of new numerical methods such that theirs approximations follow the exact solution for large values of time.

The goal of this chapter is to construct a numerical scheme that it is

reliable and provide accurate approximations for large values of time in order to obtain information on the evolution of precancerous lesions at the cervical cells caused by human papillomavirus. The numerical scheme is developed to obtain approximations to the solution of one of the models presented in chapter 2, which consists of one nonlinear advection-diffusion-reaction equation for a continuous description of the invasion stages. We consider the equation of interest as a perturbation problem which evolves smoothly and slowly out of the initial solution. It is important to remark that our approach is based on a new trend in numerical analysis that consists in the development of numerical techniques for perturbation problems. To achieve our goal, we propose in section 3.2 to analyze such model under the perspective of perturbation theory by presenting first an unsatisfactory local approximation and then presenting a correct formal parametric approximation based on the original one. In section 3.3, we use a general framework in order to derive an analytical-numerical method by using a special discretization of the domain. In section 3.4, we analyze the approximations including Numerical Methods and Mathematical Modeling in Biology, Medicine and Social Sciences numerical simulations and discuss the implications of the results. Finally, conclusions are given in section 3.5.

3.2 Models approximations via regular perturbation

The process of establishing how far the cancer has spread is known as staging. Information from laboratory tests is used to determine how deeply the tumor has invaded tissues within and around the cervix, and the spread to lymph nodes or nearby organs. The evolution of cervical cancer historically has been divided into several stages, or phases, characterized with potentially premalignant transformation and abnormal growth of cells on the surface of the cervix that can either progress, or regress. For example the Bethesda reporting system, used mostly in the United States, bases its classification in four levels. The first stage called pre-invasive stage, is distinguished by maintaining the whole basal membrane, which allows cell changes to be retained within the epithelial thickness. The posterior phases, called invasive stages are subdivided in three or more phases, say m phases. The first phase represents only mild dysplasia, or abnormal cell growth. It is confined to the first $1/m$ of the thickness of the epithelium, which may eliminated by the immune system in several years, indicating that the whole process is very slow. The second phase, known as moderate dysplasia, is where the injury has extended to $2/m$ the thickness of the epithelium and so on, for more detail see [2].

Here we will assume that the number of stages of phases is large enough to

produce an exact indicator of the cancer spread. We denote by $\eta(\alpha, t)$ the density of cells that are at stage α at time t, where $\alpha \in [0, 1]$ and $t \geq 0$. Our starting point is to consider the general family of models (given in [23]) that describes the evolution of $\eta(\alpha, t)$ such that for any natural number k we have the following model:

$$
\begin{aligned}
\frac{\partial \eta}{\partial t}(\alpha, t) &= \omega(\alpha) \left[-\frac{\partial \eta}{\partial \alpha} \epsilon + \frac{\partial^2 \eta}{\partial \alpha^2} \epsilon^2/2 + \cdots \right] + \sum_{s=2}^{k} g_s \epsilon^{s-1} \eta^s(\alpha, t) + \\
&\qquad \sum_{s=2}^{k} f_s \epsilon^{s-1} \left(\eta - \frac{\partial \eta}{\partial \alpha} \epsilon + \frac{\partial^2 \eta}{\partial \alpha^2} \epsilon^2/2 + \cdots \right)^s.
\end{aligned}
\tag{3.1}
$$

Where h has been replaced by the parameter ϵ and ω is the coefficient of the linear transition of infected cells to a different stage, henceforth we consider it constant and ϵ is a small parameter that indicates the length of each stage. It is assumed that ω and ϵ are relatively small to obtain parabolic equations to guarantee the existence and uniqueness of solutions and to avoid discontinuities. The first summation term in (3.1) indicates the nonlinear rate of infected cells that gets to a specific α-stage and the second summation represents the nonlinear rate of the infected cells that leave that particular stage including the mortality rate.

Our first step is to extract basic information of this model and to get a benchmark to propose numerical schemes. For practical purposes and simplicity we only consider the model up to quadratic terms in ϵ. So truncating (3.1) and keeping only up to quadratic terms in ϵ we obtain:

$$
\frac{\partial \eta}{\partial t} = \left(-\omega(\alpha) \frac{\partial \eta}{\partial \alpha} + (f_2 + g_2)\eta^2 \right) \epsilon + \left(\frac{\omega}{2} \frac{\partial^2 \eta}{\partial \alpha^2} + (f_3 + g_3)\eta^3 - 2\eta \frac{\partial \eta}{\partial \alpha} \right) \epsilon^2,
\tag{3.2}
$$

with an initial condition given by

$$
\eta(\alpha, 0) = F_0(\alpha) + \epsilon F_1(\alpha).
$$

Here the initial value $F_0(\alpha)$ refers to the patient conditions to the clinic arrival and F_1 accounts for the potential initial error measurements. Notice that model (3.2) consists in a general transport equation given by a one dimensional nonlinear advection-diffusion equation with a quadratic and a cubic reaction term. Such type of equations have been used to describe physical, chemical and biological phenomena where a quantity of interest is transferred inside a system due to two processes: diffusion and advection. Equation (3.2) can be written compactly as

$$
\frac{\partial \eta}{\partial t} = L(\eta)\epsilon + M(\eta)\epsilon^2,
\tag{3.3}
$$

where L is the differential operator defined by $L(\eta) = -\omega(\alpha)\frac{\partial \eta}{\partial \alpha} + (f_2 + g_2)\eta^2$ and M is given by $M(\eta) = \frac{\omega}{2}\frac{\partial^2 \eta}{\partial \alpha^2} + (f_3 + g_3)\eta^3 - 2\eta\frac{\partial \eta}{\partial \alpha}$.

Let us start the analysis of equation (3.3) by performing a regular perturbation [24], that is, let us assume that such equation has a solution $U(\alpha, t, \epsilon)$ which is analytical in the parameter ϵ and seek for solutions of the form

$$U(\alpha, t, \epsilon) = U_0(\alpha, t) + \epsilon U_1(\alpha, t) + \epsilon^2 U_2(\alpha, t) + \mathcal{O}(\epsilon^3), \tag{3.4}$$

with initial conditions given by

$$U_0(\alpha, 0) = F_0(\alpha), \quad U_1(\alpha, 0) = F_1(\alpha) \text{ and } U_j(\alpha, 0) = 0 \text{ for } j \geq 2.$$

It would be understood that the neglected terms in (3.4) should be small over the entire interval for which we want the expansion to be valid. We find after some algebraic manipulations that

$$U(\alpha, t, \epsilon) = \eta(\alpha, 0) + \epsilon t \left[L(F_0(\alpha) + \epsilon M(F_0(\alpha)) + 2F_0(\alpha)\epsilon F_1(\alpha) + \omega \epsilon F_1{}'(\alpha) \right]$$
$$+ (\epsilon t)^2 \left(F_0(\alpha) L(F_0(\alpha)) + \frac{\omega}{2}\frac{\partial L(F_0(\alpha))}{\partial \alpha} \right) + \mathcal{O}(\epsilon^3). \tag{3.5}$$

We emphasize that the solution of (3.3) as given by (3.4) is formal and is separated into three initial terms: The first one represents the initial condition and is independent of t; the second one is proportional to $t\epsilon$; also note that its value is t times the right hand side of (3.3) evaluated at the true initial solution, $F_0(\alpha)$, plus an additional expression indicating the propagation of error in the initial measurements. The third term is proportional to $(t\epsilon)^2$ and is given by the linearization of the operator L around $F_0(\alpha)$. The higher order terms in the expansion, which are not shown in equation (3.5), can be generated by continuing the substitution procedure in the regular perturbation scheme.

So far we have developed a solution that intermixes terms depending only in α and ϵ in its perturbation expansion. It is basically a time Taylor expansion of the solution, which is local in time. Thus such implementation of the solution is developing an approximation by using an incorrect time-measuring scheme. To guide us toward a correct perturbation expansion we remark that there is a coupling between ϵ and t and we are only able to truncate the approximation if the time interval under consideration is such that $|t\epsilon| << 1$. Which suggest that ϵt should be the new time scale. What we learned from this perturbation expansion is that the inconvenience originates in our decision to use the given time as the basic time signal that generates the perturbation expansion. Thus, we obtain a partial correct view of the behavior of the system. We conclude that such expansion is unsatisfactory, specially for longer times. Therefore we would like to develop

a systematic perturbation expansion that would give the solution in the correct time-scale.

3.2.1 Regular perturbation with correct time-scale

We now introduce a transformation of the time variable to a new time that incorporates a correction to the time scale which will be sufficient for the development of a consistent perturbation scheme. Such requirement motivates us to rescale the time variable as $\tau = \epsilon t$ and thus equation (3.3) becomes:

$$\frac{\partial \eta}{\partial \tau} - L(\eta) = M(\eta)\epsilon. \tag{3.6}$$

Now we seek solutions of the form:

$$\bar{U}(\alpha, \tau, \epsilon) = \bar{U}_0(\alpha, \tau) + \epsilon \bar{U}_1(\alpha, \tau) + \epsilon^2 \bar{U}_2(\alpha, \tau) + \mathcal{O}(\epsilon^3),$$

with initial conditions given by

$$\bar{U}_0(\alpha, 0) = F_0(\alpha), \quad \bar{U}_1(\alpha, 0) = F_1(\alpha), \text{ and } \bar{U}_j(\alpha, 0) = 0 \text{ for } j \geq 2.$$

Let us consider first the approximation to the lowest order in the small parameter ϵ, that is:

$$\frac{\partial \bar{U}_0}{\partial \tau} + \omega(\alpha)\frac{\partial \bar{U}_0}{\partial \alpha} = (f_2 + g_2)\bar{U}_0^2. \tag{3.7}$$

Which is an inhomogeneous parabolic transport equation without diffusion. If $f_2 + g_2 = 0$, the solution becomes $\bar{U}_0(\alpha, \tau) = F_0(\alpha - \omega\tau)$ which implies that the initial profile is unchanged in shape at later times, and it is simply translated to the right as time increases. Now if $f_2 + g_2 \neq 0$ (which is the correct assumption) we get:

$$\bar{U}_0(\alpha, \tau) = \frac{-\frac{1}{(f_2+g_2)}F_0(\alpha - \omega\tau)}{\tau F_0(\alpha - \omega\tau) + 1},$$

which still has the transportation properties but with a deformation on the initial profile consisting in a reduction on its amplitude.

To first order in ϵ we obtain that $\bar{U}_1$ satisfies the following equation:

$$\frac{\partial \bar{U}_1}{\partial \tau} + \omega(\alpha)\frac{\partial \bar{U}_1}{\partial \alpha} = 2(f_2 + g_2)\bar{U}_0\bar{U}_1 - 2(f_2 + g_2)\bar{U}_0\frac{\partial \bar{U}_0}{\partial \alpha} + (f_3 + g_3)\bar{U}_0^3 + \frac{\omega(\alpha)}{2}\frac{\partial^2 \bar{U}_0}{\partial \alpha^2},$$

that is,

$$\frac{\partial \bar{U}_1}{\partial \tau} + \omega(\alpha)\frac{\partial \bar{U}_1}{\partial \alpha} = G_1(\alpha, \tau)\bar{U}_1 + G_2(\alpha, \tau), \tag{3.8}$$

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where

$$G_1(\alpha, \tau) = \frac{-2F_0(\alpha - \omega\tau)}{\tau F_0(\alpha - \omega\tau) + 1}$$

and

$$G_2(\alpha, \tau) = -2(f_2 + g_2)\bar{U}_0\frac{\partial \bar{U}_0}{\partial \alpha} + (f_3 + g_3)\bar{U}_0^3 + \frac{\omega(\alpha)}{2}\frac{\partial^2 \bar{U}_0}{\partial \alpha^2}.$$

Using the method of characteristics, the solution of equation (3.8) can be written as:

$$\bar{U}_1(\alpha, \tau) = F_1(\alpha - \omega\tau)e^{\int_0^\tau G_1(\alpha+\omega(\xi-\tau),\xi)\,d\xi} + \int_0^\tau G_2(\alpha + \omega(\xi - \tau), \xi)\,d\xi,$$

notice that $\bar{U}_1(\alpha, 0) = F_1(\alpha)$ as required. Therefore the approximation becomes:

$$\begin{aligned}\bar{U}(\alpha, \tau, \epsilon) &= \frac{-\frac{1}{(f_2+g_2)}F_0(\alpha - \omega\tau)}{\tau F_0(\alpha - \omega\tau) + 1} + \epsilon[F_1(\alpha - \omega\tau)e^{\int_0^\tau G_1(\alpha+\omega(\xi-\tau),\xi)\,d\xi} \\ &\quad + \int_0^\tau G_2(\alpha + \omega(\xi - \tau), \xi)\,d\xi] + O(\epsilon^2).\end{aligned} \qquad (3.9)$$

Approximation (3.9) has the following behavior: The lowest approximation is a solution of a transport equation with a deformed initial profile moving with a velocity given by $\omega\tau$ which in the original time scale becomes $\omega\epsilon t$ indicating that the velocity of the evolution of lesion in the cervix is a slow process. The density of healthy cell is diminished gradually and the initial profile will be moving to the right with a decreasing amplitude. These facts confirm the results obtained in [23, 18], but the numerical approximation in that case was only valid for small values of t and the continuation for larger times was not possible. In this case the continuation of the approximation is viable and valid for larger values of t. We expect that the second term $\epsilon\bar{U}_1$ to make only a small correction to the approximation. In section 3.4, we will analyze the influence of this correction term.

3.3 Numerical scheme development

The aim of this section is first to develop a numerical method to approximate the solutions of (3.6) and then provide some numerical results that illustrate the behavior of the model for a particular initial condition. Our strategy to derive such numerical scheme is to obtain different approximations according to the ϵ-scale, meaning that we will obtain an exact scheme to the lowest order in ϵ and a correction

to next order which will be an approximation that yields a contribution that cancels the potential secular terms.

Let us start the discretization process by subdividing the domain $[0, 1] \times [0, \infty)$ into a rectangular mesh with step sizes given by $\Delta\alpha = k$ and $\Delta\tau = h$. In order to state and prove our main result, we need two intermediate steps given by the following two lemmas:

Lemma 3.3.1 *For a particular discretization of the domain, that is choosing $k = wh$, we have that*

$$U_0(\alpha + k, \tau + h) = \frac{U_0(\alpha, \tau)}{1 - h(f_2 + g_2)U_0(\alpha, \tau)}, \quad \forall h.$$

Proof For a general rectangular regular mesh we have that

$$U_0(\alpha + k, \tau + h) = \frac{\frac{-1}{(f_2+g_2)}F_0(\alpha + k - \omega(\tau + h))}{(\tau + h)F_0(\alpha + k - \omega(\tau + h)) + 1}.$$

If we choose $k = wh$ we get

$$U_0(\alpha + k, \tau + h) = \frac{\frac{-1}{(f_2+g_2)}F_0(\alpha - \omega\tau)}{(\tau + h)F_0(\alpha - \omega\tau) + 1} = \frac{\frac{-1}{(f_2+g_2)}}{\frac{-1}{(f_2+g_2)U_0(\alpha,\tau)} + h},$$

therefore

$$U_0(\alpha + k, \tau + h) = \frac{U_0(\alpha, \tau)(1 + \tau F_0(\alpha - \omega\tau))}{1 - (f_2 + g_2)}.$$

Lemma 3.3.2 *There exist two real numbers ϕ_1^* and $\phi_2^* \in [0, h]$ with $k = wh$ such that for every point in the mesh*

$$
\begin{aligned}
U_1(\alpha + k, \tau + h) &= U_1(\alpha, \tau) + G_2(\alpha + \omega\phi_1^*, \tau + \phi_1^*)h \\
&\quad + F_1(\alpha - \omega\tau)e^{G_1(\alpha+\omega\phi_2^*, \phi_2^*+\tau)h}, \quad \forall h.
\end{aligned}
$$

Proof Consider

$$U_1(\alpha, \tau) = F_1(\alpha - \omega\tau)e^{\int_0^\tau G_1(\alpha+\omega(\xi-\tau),\xi)\, d\xi} + \int_0^\tau G_2(\alpha + \omega(\xi - \tau), \xi)\, d\xi.$$

For any k, h in the mesh we have that

$$
\begin{aligned}
U_1(\alpha + k, \tau + h) &= \int_0^{\tau+h} G_2(\alpha + k + \omega(\xi - \tau + h), \xi)\, d\xi + \\
&\quad F_1(\alpha + k - \omega(\tau + h))e^{\int_0^{\tau+h} G_2(\alpha+k+\omega(\xi-\tau+h),\xi)\, d\xi}.
\end{aligned}
$$

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Now if $k = wh$ we obtain

$$
\begin{aligned}
U_1(\alpha + k, \tau + h) &= \int_0^{\tau+h} G_2(\alpha + \omega(\xi - \tau), \xi)\, d\xi \\
&\quad + F_1(\alpha - \omega\tau)e^{\int_0^{\tau+h} G_1(\alpha+\omega(\xi-\tau),\xi)\, d\xi} \\
&= U_1(\alpha, \tau) + \int_0^h G_2(\alpha + \omega\phi, \phi + \tau)\, d\phi \\
&\quad + F_1(\alpha - \omega\tau)e^{\int_0^h G_1(\alpha+\omega\phi,\phi+\tau)\, d\phi} \\
&= U_1(\alpha, \tau) + G_2(\alpha + \omega\phi_1^*, \tau + \phi_1^*)h \\
&\quad + F_1(\alpha - \omega\tau)e^{G_1(\alpha+\omega\phi_2^*,\phi_2^*+\tau)h},
\end{aligned}
$$

where in the last equality we have used the mean value theorem for integrals.

Therefore we obtain the following proposition:

Proposition 3.3.3 *Consider equation* (3.6)*, then there exist two real numbers ϕ_1^* and $\phi_2^* \in [0, h]$ such that its solution satisfies*

$$
\begin{aligned}
\bar{U}(\alpha + k, \tau + h, \epsilon) &= \frac{U_0(\alpha, \tau)}{1 + hU_0(\alpha, \tau)} + \epsilon U_1(\alpha, \tau) + \epsilon h G_2\left(\alpha + \omega\phi_1^*, \tau + \phi_1^*\right) \\
&\quad + \epsilon F_1(\alpha - \omega\tau)e^{G_1(\alpha+\omega\phi_2^*,\tau+\phi_2^*)h} + \mathcal{O}(\epsilon^2).
\end{aligned}
$$

A central question is how to choose the intermediate points ϕ_1^* and ϕ_1^* from proposition 3.3.3. If the functions $G_1(\alpha + \omega\phi, \phi + \tau)$ and $G_2(\alpha + \omega\phi, \phi + \tau)$ are continuous functions of ϕ and as long as h remains small, the points ϕ_1^* and ϕ_2^* are very close to $\frac{h}{2}$. Moreover, the following proposition, see [25] for details, gives a better estimate for the limiting value of each ϕ_1^* and ϕ_2^*.

Proposition 3.3.4 *If $G(\alpha + \omega\phi, \phi + \tau)$ is a continuous function of ϕ for fixed α, ω and τ and is n-times differentiable at $\phi = 0$ with $\frac{\partial^j G(\alpha,\tau)}{\partial \phi^j} = 0$ for $j = 1, 2, \ldots, n-1$ but $\frac{\partial^n G(\alpha,\tau)}{\partial \phi^n} \neq 0$, then*

$$
\lim_{h \to 0} \frac{\phi^*}{h} = \frac{1}{(n+1)^{\frac{1}{n}}},
$$

where ϕ^* is the point required by the mean value theorem for integrals for the function $f(\phi) = G(\alpha + \omega\phi, \phi + \tau)$.

Let us now present the numerical scheme. From proposition (3.3.3) the differentiability of the functions G_1 and G_2 are required and they both depend only on the initial data. Therefore assuming that G_j is n_j-times differentiable at zero for $j = 1, 2$ then, the desired scheme becomes:

$$
\begin{aligned}
\bar{U}(\alpha + k, \tau + h, \epsilon) \;\cong\;& \frac{U_0(\alpha, \tau)}{1 + h\,U_0(\alpha, \tau)} + \epsilon U_1(\alpha, \tau) + \\
& \epsilon h G_2\left(\alpha + \frac{\omega h}{(n_2 + 1)^{\frac{1}{n_2}}}, \tau + \frac{h}{(n_2 + 1)^{\frac{1}{n_2}}}\right) + \\
& \epsilon F_1(\alpha - \omega\tau)e^{\displaystyle h G_1\left(\alpha + \frac{\omega h}{(n_1+1)^{\frac{1}{n_1}}}, \tau + \frac{h}{(n_1+1)^{\frac{1}{n_1}}}\right)},
\end{aligned} \tag{3.10}
$$

where $k = \omega h$ and h is arbitrary small parameter.

3.4 Numerical results

To serve as a baseline for analyzing the behavior of the evolution of the lesions at the cervical cells caused by human papillomavirus, we have implemented scheme (3.10). Specifically, the mesh size parameter, h, is fixed at successful time iterations, only differentiability is assuming on the functions G_1 and G_2 thus we select $\phi^* = \frac{h}{2}$. We have tested a number of particular cases for the validation of the implementation.

It is important to remark that scheme (3.10) will be specialized to initial conditions that reflect different stages of the infection. For example for an early infection we will use functions of the form $\eta(0, \alpha) = \exp(-c\alpha^2)$ to illustrate a typical condition of a person with an infection presenting lesion only in the first levels (a mild dysplasia). Here c reflects the full width at half maximum of the peak of the infection meaning the difference between the two extreme values of α at which $\eta(0, \alpha)$ is equal to half of its maximum value. Mathematically, the parameter c can also be interpreted as the position where the two inflection points of the initial function occurs (at $\pm\frac{1}{c}$).

Let us first consider the unperturbed case ($\epsilon = 0$ in (3.10)) to illustrate, grosso modo, the behavior of the solution. As expected, the approximation obtained deviates very slowly from initial data. The previous observation agrees with the fact that HPV infection takes very long time in transforming normal cervical cells into cancerous ones, presumably due to actions of the immune system in maintaining in check further developments of the infection. Moreover such approximation is valid for larger values of time. In Figure 3.1 on the left, we show the evolution of the
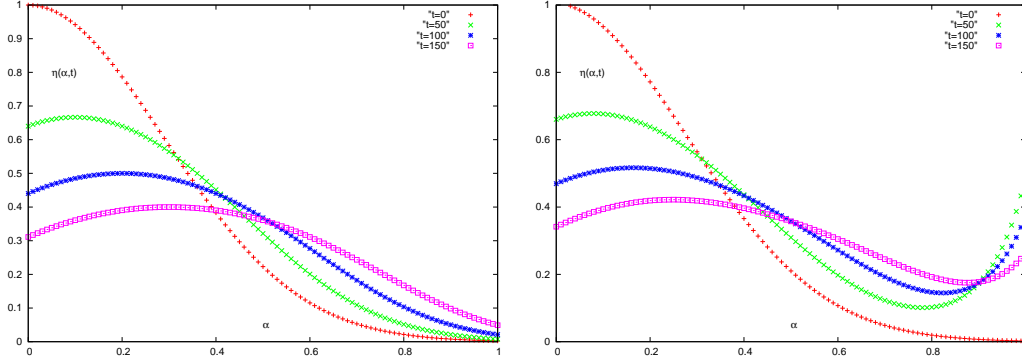
Figure 3.1: Numerical simulations of evolution of equation with $\epsilon = 0$ (left) and $\epsilon = 0.01$ (right).

approximation for the parameter values $\omega = 0.2$, $c = 6.0$, $-(f_2 + g_2) = f_3 + g_3 = 1.0$ and times $t = 0$, $t = 50$, $t = 100$ and $t = 150$. In previous schemes the approximations obtained were valid only up to $t = 70$. It is important to remark that there is also a non pleasant behavior of the unperturbed approximation: It decays to zero for values of α closer to one. A feature that is incorrect since the level of cancer cells increases for such values of α. Therefore in order to accept the proposed scheme a lower order perturbation term must correct this behavior.

For the perturbed case, the behavior of the approximation is very similar to the unperturbed case for all values of α except for those values closer to one. For such values of α, we have a pleasant characteristic: The approximation do not decay to zero, it changes its concavity from downward to upward after a large value of α and from there it starts increasing. In Figure 3.1 on the left, we show the evolution of the approximation for the same values of time that the unperturbed case. Notice how the correction starts for the particular case t= 50 at about $\alpha = 0.8$. Therefore the next correction term in the approximation of ϵ will also correct those behaviors for larger values of α.

3.5 Conclusions

In this chapter we have developed a numerical scheme for a model of the evolution of precancerous lesions at the cervical cells caused by human papillomavirus. Such numerical scheme is sufficiently robust, accurate, and efficient for larger values of time. With the aid of the scheme implementation there is a possibility to understand the evolution of the different stages of the lesions of the cervix. This is an important aspect because the stage of the cancer is an important factor in selecting a treatment

plan. Overall, this work may serve as a structural basis in the implementation of specific software to provide clinicians with a reliable benchmark. The drawback of this work consists in the validation of some of the parameter values with real data and the continuation for large times, a problem that we will overcome in the next chapter.

Efficient Numerical schemes for the precancer lesions [1]

4.1 Introduction

In previous chapters we have presented mathematical models for the evolution of HPV-infected cells. These models have been analyzed using different formulations regarding from classical approximations of ODE and new numerical methods such as nonstandard finite differences and perturbation theory obtaining good results for a reasonable time. Now, we are interested in creating better approaches to our model which give us results reliable for even larger times. In order to achieve this goal, this chapter proposes two non-standard schemes to approximate the solution of our model. Finally we obtain that these two schemes presented in this chapter give us a better approximation to the solution of our model.

It is very important to remember that Human Papillomavirus (HPV) is responsible for over five per cent of all cancers worldwide and of 15% of cancer in women in developing countries [2]. HPV is the necessary cause of cervical cancer [4], and is thought to be the necessary cause for anal cancer [4]. A certain number of models have been presented in order to study the evolution of infected cells by HPV, most of them are based on a preventive approach [2, 3, 4, 5], but basically nonexistent for the diagnosis. For example there are several works about how vaccines can reduce the number of infections and deaths due to cervical cancer, using a stability analysis to determine the stability of the disease-free and endemic equilibria for different vaccination programs, [3].

In this chapter we develop two numerical methods to approximate the solutions of a pioneer model of the evolution of the lesions at the cervical cells caused

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[1]This chapter is based on Solís Francisco, González Luz, Numerical approach for a model of the precancer lesions caused by HPV (2015).

by the human papillomavirus (HPV). Such model is given by a a nonlinear advection-diffusion-reaction partial differential equation and the goal of the schemes is to analyze the behavior of the evolution of the lesions at the cervical cells caused by the HPV. The developed schemes consist of two explicit NSFD numerical schemes, which satisfy positivity conditions, by using the subequation method in the context of the NSFD scheme methodology. Our approach provides an alternative method to the early diagnosis of the disease and may open up new avenues of research.

The structure of this chapter is: in Section 4.2, we consider some sub-equations of the HPV model with the aim to obtain exact schemes for most sub-model equations and approximated ones when the exact schemes are not available. A special sub-equation is the Duffing equation [28], thus, in section 4.3, we construct a nonstandard function $\phi(h)$ by calculating the exact solution of a second order differential equation. Our method produces discrete solutions that are exact for particular equations and therefore have the same properties as their analytical solutions, [9]. In section 4.4, we develop two different schemes with finite differences nonstandard to approximate the solution of a nonlinear advection diffusion reaction equation of the HPV model. In both schemes we preoved positivity properties. In section 4.5, we analyze use the schemes to provide approximations and interpret the results. Finally, conclusions are given in section 4.6.

4.2 A HPV Model

Here we will assume that the number of stages of phases is large enough to produce an exact indicator of the cancer spread. We denote by $\eta(\alpha, t)$ the density of cells that are at stage α at time t, where $\alpha \in [0, 1]$ and $t \geq 0$. Our starting point is to consider the general family of models (given in [18]) that describes the evolution of $\eta(\alpha, t)$ such that for any natural number k we have the following model:

$$
\begin{aligned}
\frac{\partial \eta}{\partial t}(\alpha, t) &= \omega(\alpha) \left[-\frac{\partial \eta}{\partial \alpha}\epsilon + \frac{\partial^2 \eta}{\partial \alpha^2}\epsilon^2/2 + \cdots \right] + \sum_{s=2}^{k} g_s \epsilon^{s-1} \eta^s(\alpha, t) + \\
&\quad \sum_{s=2}^{k} f_s \epsilon^{s-1} \left(\eta - \frac{\partial \eta}{\partial \alpha}\epsilon + \frac{\partial^2 \eta}{\partial \alpha^2}\epsilon^2/2 + \cdots \right)^s,
\end{aligned}
\tag{4.1}
$$

where ω is the coefficient of the linear transition of infected cells to a different stage, henceforth we consider it a positive constant and ϵ is a small parameter that indicates the length of each stage. It is assumed that ω and ϵ are relatively small to obtain

parabolic equations to guarantee the existence and uniqueness of solutions and to avoid discontinuities. The first summation term in (4.1) indicates the nonlinear rate of infected cells that gets to a specific α-stage and the second summation represents the nonlinear rate of the infected cells that leave that particular stage including the mortality rate. We truncated model (4.1) up to quadratic terms in ϵ, namely

$$\frac{\partial \eta}{\partial t} = \omega\epsilon\left(-\frac{\partial \eta}{\partial \alpha} + \frac{\partial^2 \eta}{\partial \alpha^2}\frac{\epsilon}{2}\right) + (f_2 + g_2)\epsilon(\eta^2) - 2f_2\epsilon^2\eta\frac{\partial \eta}{\partial \alpha} + (f_3 + g_3)\epsilon^2\eta^3, \quad (4.2)$$

Our strategy to derive a numerical scheme is to obtain an exact scheme and approximated schemes (when there are not exact) for some subequations of (4.2). A subequation of (4.2) is an ordinary or partial differential equation obtained by dropping one or more terms appearing in the full equation. Using the change of variable $\eta = w + 1/\epsilon$ and by assuming that $f_2 + g_2 = -3(f_3 + g_3)$, then equation (4.2) can be written as

$$\frac{\partial w}{\partial t} = \alpha_1\frac{\partial w}{\partial \alpha} + \alpha_2\frac{\partial^2 w}{\partial \alpha^2} + \alpha_3 w\frac{\partial w}{\partial \alpha} + \alpha_4 w + \alpha_5 w^3 + \alpha_6, \quad (4.3)$$

where $\alpha_1 = (2f_2 - \omega)\epsilon$, $\alpha_2 = \frac{\omega\epsilon^2}{2}$, $\alpha_3 = 2f_2\epsilon^2$, $\alpha_4 = 9(f_3 + g_3)$, $\alpha_5 = (f_3 + g_3)\epsilon^2$ and $\alpha_6 = -2(f_3 + g_3)/\epsilon$.

Remark The form of equation (4.3) was achieved since it is a standard step in solving algebraic cubic equations and also to obtain the duffing equation as subequation.

The aim of this section is to develop an exact schemes for some subequations of (4.3) whenever possible and nonstandard schemes when the previous is no feasible for others sub-equations. A subequation of (4.3) is basically the same equation with some of the involved constants set equal to zero.

4.2.1 Exact schemes for some sub-equations HPV Model

In this section we construct an exact schemes for the some subequations of model (4.3). An exact finite difference scheme is one for which the solution to the difference equation has the same general solution as the associated differential equation. By setting values of $\alpha's$ in (4.3), we get the following two subequations (Exponential equation and the Linear Harmonic Oscillator equation):

$$\frac{dw}{\partial t} = \alpha_4 w \quad \text{and} \quad \alpha_2\frac{d^2 w}{d\alpha^2} + \alpha_4 w = 0.$$

which both have exact finite difference schemes, given respectively by

$$\frac{W^{k+1} - W^k}{\frac{e^{\alpha_4 \Delta t} - 1}{\alpha_4}} = \alpha_4 W^k, \tag{4.4}$$

$$\alpha_2 \frac{W_{m+1} - 2W_m + W_{m-1}}{\left(\frac{4\alpha_2}{\alpha_4}\right) \sin^2[(\frac{\alpha_4}{\alpha_2})^{1/2}(\frac{\Delta \alpha}{2})]} + \alpha_4 W_m = 0 \tag{4.5}$$

where $w(\alpha, t_k) = W^k$ and $w(\alpha_m, t) = W_m$. Also by choosing appropriate values of the α's we get the following subequation, known as the cubic Advection-Reaction Equation

$$\frac{\partial w}{\partial t} - \alpha_1 \frac{\partial w}{\partial \alpha} = \alpha_4 w + \alpha_5 w^3 \tag{4.6}$$

which can be put in dimensionless form by making the following substitutions $w = (\frac{\alpha_4}{-\alpha_5})^{1/2} W$, $\bar{t} = \alpha_4 t$ $\bar{\alpha} = (\frac{\alpha_4}{-\alpha_1})\alpha$ obtaining the partial differential equation:

$$\frac{\partial W}{\partial \bar{t}} + \frac{\partial W}{\partial \bar{\alpha}} = W(1 - W^2) \tag{4.7}$$

with an exact finite difference scheme given by

$$\frac{B(m,k)}{\phi(\triangle t)} + \left(\frac{W_m^k + W_{m-1}^k}{A(m,k)}\right) \frac{B(m,k)}{\phi(\triangle \alpha)} = 2\left(\frac{W_{m-1}^k}{A(m,k)}\right) W_{m-1}^k [1 - (W_m^{k+1})^2],$$

where $A(m,k) = W_m^{k+1} + W_m^k$ and $B(m,k) = W_m^{k+1} - W_m^k$, see [29] for details.

4.2.2 Nonstandard schemes for some sub-equations of HPV Model

So far all the subequations presented have exact difference schemes. In this section we present some non-standard finite differences schemes for some nonlinear subequations of (4.3). The first three that we presented have been treated in the literature, see [9].

Choosing appropriate the values of the constant we obtain the following three subequations:

$$\frac{dw}{\partial t} = \alpha_4 w \left(1 + \beta w^2\right),$$

$$\frac{dw}{d\alpha} + \frac{\alpha_4}{\alpha_1} w(1 + \beta w^2) = 0,$$

$$\frac{\partial w}{\partial t} = \alpha_4 w + \alpha_5 w^3,$$

where $\beta = \frac{\alpha_5}{\alpha_4}$.

For the first two subequations we divide the spatial and time domains in intervals of selected length ($\Delta\alpha$ and Δt), and defining $w(\alpha, t_k) = W^k$ and $w(\alpha_m, t) = W_m$ for $k = 1, 2, \ldots$ and $m = 1, 2, \ldots$ we obtain the following two approximate schemes:

$$\frac{W^{k+1} - W^k}{\frac{e^{\alpha_4 \Delta t} - 1}{\alpha_4}} = \alpha_4 W^{k+1} \left(1 + \beta W^{2k}\right), \tag{4.8}$$

$$\frac{W_{m+1} - W_m}{\frac{1 - e^{-\delta \Delta \alpha}}{\delta}} + \delta W_{m+1}(1 + \beta W_m^{2k}) = 0. \tag{4.9}$$

The finite-difference scheme for the third sub-equation is given by

$$\frac{W_m^{k+1} - W_m^k}{\frac{e^{\alpha_4 \Delta t} - 1}{\alpha_4}} = \alpha_4 W_m^k + \alpha_5 W_m^{2k} \left(\frac{W_m^{k+1} + W_m^{k-1}}{2}\right). \tag{4.10}$$

4.2.3 Special subequation of HPV model:The Duffing Equation

In this section we will study a special subequation of our model: The Duffing equation. First solve the equation analytically second term build discretization duffing equation and obtain a nonstandard finite difference scheme for this equation. Setting $\alpha_1 = \alpha_3 = \alpha_6 = 0$ and $\frac{\partial W}{\partial t} = 0$ in (4.3), we get the Duffing Equation

$$\frac{d^2 w}{d\alpha^2} + aw + bw^3 = 0 \text{ with } a = \frac{\alpha_4}{\alpha_2} \text{ and } b = \frac{\alpha_5}{\alpha_2} \tag{4.11}$$

The Duffing equation in its various forms is used to describe many nonlinear systems. Although most physical systems cannot be described accurately in this way for a wide range of operating conditions, such as frequency and amplitude of excitation, in many cases it is possible to use this equation as an approximate description so that their behavior can be studied qualitatively. In this section, we will study the Duffing equation, see [28], first find the analytical solution and then we get a non-standard scheme to approximate the solution of the Duffing equation.

4.2.4 Exact solution of Duffing equation

The differential equation:

$$\frac{d^2 w}{d\alpha^2} + aw + bw^3 = 0 \text{ with } b \neq 0 \tag{4.12}$$

is called the Duffing oscillator, which is a model of a structural system that includes nonlinear restoring forces (for example springs). To solve the Duffing equation we consider the initial conditions $y(0) = A, y'(0) = 0$. Let $v = \frac{dw}{d\alpha}$, then

$$\frac{d^2w}{d\alpha^2} = \frac{dv}{d\alpha} = \frac{dw}{d\alpha}\frac{dv}{dw} = v\frac{dv}{dw},$$

to rewrite the equation (4.12)

$$v\frac{dv}{dw} + aw + bw^3 = 0.$$

Integration of this equation gives the first-integral

$$v^2 + aw^2 + \left(\frac{b}{2}\right)w^4 = aA^2 + \left(\frac{b}{2}\right)A^4,$$

where the integration constant was evaluated using the initial conditions.

Solving for $v(w)$ gives

$$v = \pm \left\{(A^2 - w^2)(a + (b/2)(A^2 + w^2))\right\}^{\frac{1}{2}}. \tag{4.13}$$

The value of α to go from point $(A, 0)$ to the point (w, v) in the lower half-plane is

$$\alpha(w) = -\int_A^w \frac{ds}{\left\{(A^2 - s^2)(a + (b/2)(A^2 + s^2))\right\}^{\frac{1}{2}}}. \tag{4.14}$$

Let $s = Az$, then the previous equation becomes

$$\alpha(w) = (1/A)(2/b)^{\frac{1}{2}} \int_{w/A}^1 \frac{dz}{\left\{(1 - z^2)\left(\frac{2a + bA^2}{bA^2} + z^2\right)\right\}^{\frac{1}{2}}}. \tag{4.15}$$

The integral can be written in terms of an elliptic integral of the first kind, denoted by F,

$$\alpha(w) = \frac{F(\arccos(w/A), \theta)}{[a + bA^2]^{\frac{1}{2}}}, \tag{4.16}$$

where

$$\theta = \left[\frac{bA^2}{2(a + bA^2)}\right]^{\frac{1}{2}}.$$

Equation (4.16) can be inverted to give w as a function of α. Doing this gives

$$w(\alpha) = A \operatorname{cn}\left((a + bA^2)^{\frac{1}{2}}\alpha, \theta\right)$$

Therefore we obtain that

Theorem 4.2.1 *The exact solution of (4.11) with initial conditions $w(0) = A, w'(0) = 0$ is given by*

$$w(\alpha) = A \operatorname{cn}\left((a + bA^2)^{\frac{1}{2}}\alpha, \left[\frac{bA^2}{2(a + bA^2)}\right]^{\frac{1}{2}}\right). \tag{4.17}$$

Proof. We substitute (4.17) into (4.11) and use the foregoing elliptic function identities (see Appendix D). To begin with, let us take the derivative of (4.17) with respect to α and consider that $a_2 = (a + bA^2)^{\frac{1}{2}}$

$$\frac{dy}{d\alpha} = Aa_2 \frac{\partial}{\partial u} \operatorname{cn} = Aa_2 \operatorname{sn} \operatorname{dn} \tag{4.18}$$

where for brevity we write $\operatorname{cn} = \operatorname{cn}(u, \theta)$, $\operatorname{sn} = \operatorname{sn}(u, \theta)$ and $\operatorname{dn} = \operatorname{dn}(u, \theta)$. Differentiating (4.18),

$$\frac{d^2y}{d\alpha^2} = -Aa_2^2(\operatorname{sn}\frac{\partial}{\partial u}\operatorname{dn} + \operatorname{dn}\frac{\partial}{\partial u}\operatorname{sn}) = -Aa_2^2(\operatorname{cn}\operatorname{dn}^2 - k^2 \operatorname{sn}^2 \operatorname{cn})$$
$$= -Aa_2^2(\operatorname{cn}(1 - \theta^2 \operatorname{sn}^2) - \theta^2(1 - \operatorname{cn}^2)\operatorname{cn})$$

After simplifications of we have

$$\frac{d^2y}{d\alpha^2} = -Aa_2^2 \operatorname{cn}(1 - 2\theta^2 - 2\theta^2 \operatorname{cn}^2) \tag{4.19}$$

Substituting (4.19) and (4.17) into Duffings equation (4.11) and equating to zero the coefficients of cn and cn^3 gives two equations relating A, a_2 and θ:

$$- Aa_2^2(\operatorname{cn}(1 - 2\theta^2) - 2\theta^2 \operatorname{cn}^3) + aA\operatorname{cn} + bA^3 \operatorname{cn}^3 = 0 \tag{4.20}$$
$$(-Aa_2^2(1 - 2\theta^2) + aA)\operatorname{cn} + (-Aa_2^2 2\theta^2 + bA^3)\operatorname{cn}^3 = 0$$
$$A(2a_2^2\theta^2 - a_2^2 + a) = 0$$
$$-A(2a_2^2\theta^2 - bA^2) = 0$$

These may be solved for a_2 and k in terms of a_1:

$$a_2^2 = a + A^2b, \quad \theta^2 = \frac{A^2b}{2(a + A^2b)} \tag{4.21}$$

Equations (4.21) together with (4.17) is the exact solution to Duffings equation (4.11).

4.2.5 A NSFD for the Duffing Equation

The finite difference algorithm that we develop in this section is based in the nonstandard difference method introduced by Mickens [9, 10, 11, 27]. The idea in our case is to use the generalized form of the discretization of the second derivative, and obtains a nonstandard function $\varphi(h)$ by calculating the exact solution of a second order differential equation. Since the discrete second-order derivative takes the form

$$\frac{\partial^2 w}{\partial \alpha^2} = \lim_{\Delta\alpha \to 0} \frac{w(\alpha + \Delta\alpha, t) - 2w(\alpha, t) + w(\alpha - \Delta\alpha, t)}{\varphi(\Delta\alpha)},$$

then the first stage is to find a nonstandard function, $\varphi(\Delta\alpha)$ assuming that our approximated solution, $\eta(\alpha, t) = w_t(\alpha)$ of (4.3), satisfies the following differential equation:

$$\frac{\partial^2 w_t}{\partial \alpha^2} = aw_t^3 + bw_t \text{ with } \frac{dw_t}{d\alpha}(0) = 0 \tag{4.22}$$

where a and b are constant coefficients. We recall that the exact solution of (4.22) is

$$w_t(\alpha) = w_t(0) \, \text{cn}(z, \theta) \tag{4.23}$$

where $z = (a + bw_t^2(0))^{\frac{1}{2}}\alpha$ and $\theta = \left[\frac{bw_t^2(0)}{2(a+bw_t^2(0))}\right]^{\frac{1}{2}}$.

Since

$$\frac{w_t(\alpha + \Delta\alpha) - 2w_t(\alpha) + w_t(\alpha - \Delta\alpha)}{w_t(0)}$$

$$= \text{cn}(z + a_2\Delta\alpha, \theta) - 2\,\text{cn}(z, \theta) + \text{cn}(z - a_2\Delta\alpha, \theta)$$

$$= [cn(z + a_2\Delta\alpha, \theta) - 2cn(z, \theta) + cn(z - a_2\Delta\alpha, \theta)]$$

$$= \left[\frac{(cn(z, \theta)cn(a_2\Delta\alpha, \theta) - sn(z, \theta)sn(a_2\Delta\alpha, \theta)dn(z, \theta)dn(a_2\Delta\alpha, \theta) + cn(z, \theta)cn(a_2\Delta\alpha, \theta)}{1 - \theta^2 sn^2(z, \theta)sn^2(a_2\Delta\alpha, \theta)}\right]$$

$$+ \left[\frac{sn(z, \theta)sn(a_2\Delta\alpha, \theta)dn(z, \theta)dn(a_2\Delta\alpha, \theta)}{1 - \theta^2 sn^2(z, \theta)sn^2(a_2\Delta\alpha, \theta)}\right] - 2cn(z, \theta)$$

$$= \frac{2\,\text{cn}(z, \theta)\,\text{cn}(a_2\Delta\alpha, \theta)}{1 - \theta^2\,\text{sn}^2(z, \theta)\,\text{sn}^2(a_2\Delta\alpha, \theta)} - 2\,\text{cn}(z, \theta)$$

$$= -2\,\text{cn}(z, \theta)\left(1 - \frac{\text{cn}(a_2\Delta\alpha, \theta)}{1 - \theta^2\,\text{sn}^2(z, \theta)\,\text{sn}^2(a_2\Delta\alpha, \theta)}\right)$$

$$\approx -2\,\text{cn}(z, \theta)(1 - \text{cn}(a_2\Delta\alpha, \theta)) + O(\Delta\alpha^2)),$$

then we obtain that

$$\varphi(\Delta\alpha) = \frac{2}{a_2^2}(1 - \text{cn}(a_2\Delta\alpha, \theta)) \text{ with } a_2 = (a + bA^2)^{\frac{1}{2}}.$$

Finally, setting $w_{t_k}(\alpha_m) = W_m^k$, we obtain a nonstandard scheme for equation (4.22)

$$\frac{W_{m+1}^k - 2W_m^k + W_{m-1}^k}{\frac{2}{a_2^2}(1 - \operatorname{cn}(a_2 \Delta\alpha, \theta))} = bW_{m+1}^k \left(1 + (a/b)(W_m^k)^2\right), \qquad (4.24)$$

with $a = -\alpha_5/\alpha_2, b = -\alpha_4/\alpha_2$.

4.3 NSFD schemes for HPV Model

In this section we develop two different non-standard schemes to approximate the solution of nonlinear equation model of HPV. In both schemes the property of positivity is satisfied.

4.3.1 Scheme 1

Combining the discretizations from equations (4.4) (4.8) (4.24) we obtain a NSFD for the HPV Model. Denoting by $A_1 = \frac{e^{\alpha_4 \Delta t} - 1}{1 - e^{-\delta\Delta\alpha}}$, $A_2 = \frac{\alpha_2 a_2^2 (e^{\alpha_4 \Delta t} - 1)}{2\alpha_4 (1 - \operatorname{cn}(a_2 \Delta\alpha, \theta))}$ $A_3 = \frac{\alpha_3 A_1}{\alpha_1}$, $A_4 = e^{\alpha_4 \Delta t} - 1$ and $A_5 = (\alpha_6/\alpha_4)(e^{\alpha_4 \Delta t} - 1)$, we get the following explicit scheme

$$\begin{aligned}
W_m^{k+1} - W_m^k &= A_1 \left(W_{m+1}^k - W_m^k\right) + A_2 \left(W_{m+1}^k - 2W_m^k + W_{m-1}^k\right) + \\
&\quad A_3 W_m^{k+1} \left(W_{m+1}^k - W_m^k\right) + A_4 (W_m^{k+1}) \left(1 + \beta W_m^{2k}\right) + A_5.
\end{aligned}$$

Which can be explicitly written as

$$W_m^{k+1} = \frac{(1 - A_1 - 2A_2)W_m^k + (A_1 + A_2)W_{m+1}^k + A_2 W_{m-1}^k + A_5}{1 - A_3(W_{m+1}^k - W_m^k) - A_4(1 + \beta(W_m^k)^2)}. \qquad (4.25)$$

Notice that the structure of (4.25) was expected by having (4.6) as a subequation.

Positivity of Scheme 1

It is important to remark that our numerical scheme is positive only in an large region of the first positive quadrant of the domain, so a careful selection of the spatial and temporal steps sizes must be done. The corresponding positivity requirement for our discrete scheme is $W_m^k \geq 0 \geq 0$ implies that $W_m^{k+1} \geq 0$ for k fixed and all relevant values of m. Notice that in our case we have to show that for any value of k and for an arbitrary but fixed value of m we have $W_m^{k+1} \geq 0$ given that W_m^k, W_{m-1}^k and W_{m+1}^k are nonnegative. We have the following result:

Theorem 4.3.1 *The scheme (4.25) is positive, that is, $W_m^k \geq 0$ for all m and k if*

1.

$$1 - A_1 - 2A_2 \geq 0, \quad A_1 + A_2 \geq 0, \quad A_2 \geq 0, \quad A_5 \geq 0$$

2. For all m,

$$\max\left\{0, \frac{1}{2Q} - \sqrt{\frac{P}{Q}}\right\} < W_m^1 < \frac{1}{2Q} + \sqrt{\frac{P}{Q}},$$

$$0 < W_{m+1}^1 < P - Q\left(W_m^1 - \frac{1}{2Q}\right)^2,$$

with $P = \frac{4\beta A_4(1-A_4)+A_3^2}{4\beta A_3 A_4}$ and $Q = \frac{\beta A_4}{A_3}$.

3.

$$V_1 + A_5 \leq V_2\left(1 - A_4(1 + \beta V_2^2 + A_3 V_2)\right),$$

where $V_1 = \frac{1}{2Q} + \sqrt{\frac{P}{Q}}$ and $V_2 = \min\{V_1, P\}$.

Remark Assumptions 1 and 2 are required in order to show that the numerator and denominator of (4.25) are positive respectively, whereas assumption 3 is required to prove invariance.

Proof.

Consider the numerator and denominator of (4.25) separately. Such numerator is

$$(1 - A_1 - 2A_2)W_m^k + (A_1 + A_2)W_{m+1}^k + A_2 W_{m-1}^k + A_5, \qquad (4.26)$$

where $A_1 = \frac{e^{\alpha_4 \Delta t}-1}{1-e^{-\delta \Delta \alpha}}$, $A_2 = \frac{\alpha_2 a_2^2(e^{\alpha_4 \Delta t}-1)}{2\alpha_4(1-\text{cn}(a_2\Delta\alpha,\theta))}$ $A_3 = \frac{\alpha_3 A_1}{\alpha_1}$, $A_4 = e^{\alpha_4 \Delta t} - 1$ and $A_5 = (\alpha_6/\alpha_4)(e^{\alpha_4 \Delta t} - 1)$. Then positivity of the numerator is assured if the coefficients of this expression are non-negative, namely:

$$1 - A_1 - 2A_2 \geq 0, \quad A_1 + A_2 \geq 0, \quad A_2 \geq 0, \text{ and } A_5 \geq 0.$$

The denominator can not have a definite sign everywhere, but we will construct a region where the denominator is positive. In the following lemma, we show the details of this idea.

Lemma 4.3.2 *Let $y = W_{m+1}^k$ and $x = W_m^k$. The denominator is positive for the region of points (x, y) with*

$$\max\left\{0, \frac{A_3}{2\beta A_4} - \sqrt{\frac{P}{Q}}\right\} < x < \frac{A_3}{2\beta A_4} + \sqrt{\frac{P}{Q}},$$

$$0 < y < P - Q \left(x - \frac{A_3}{2\beta A_4} \right)^2,$$

with $P = \frac{4\beta A_4 + a_3^2}{\beta^2 A_3 A_4^2}$ *and* $Q = \frac{\beta A_4}{A_3}$.

Proof. Consider the denominator of (4.25)

$$1 - A_3(W_{m+1}^k - W_m^k) - A_4(1 + \beta(W_m^k)^2).$$

To show that this expression is positive is equivalent to show that the following inequality holds:

$$(1 - A_4) - AY + AX - BX^2 > 0$$

After some straightforward calculations we obtain that

$$y < P - Q \left(x - \frac{A_3}{2\beta A_4} \right)^2.$$

Finally we need to prove invariance of the region, that is, if we start in such region, then each iteration will remain in such place. Since $(1 - A_1 - 2A_2)W_m^k + (A_1 + A_2)W_{m+1}^k + A_2 W_{m-1}^k + A_5 \le V_1 + A_5$ and since $1 - A_3(W_{m+1}^k - W_m^k) - A_4(1 + \beta(W_m^k)^2) > 1 - A_4(1 + \beta V_2^2) + A_3 V_2$, then $0 < W_m^k < V_3$ for all k and for all m.

Dynamical consistency of scheme 1.

Here we will show that equation (4.3) and its discretization (4.25) have the same equilibrium points and also they have the same local dynamical behavior. The equilibrium points of (4.3) satisfy:

$$\alpha_5 w^3 + \alpha_4 w + \alpha_6 = 0, \tag{4.27}$$

whereas the equilibrium points of (4.25) satisfy:

$$A_4 \beta w^3 + A_4 w + A_5 = 0. \tag{4.28}$$

But since $\frac{A_4 \beta}{\Delta t} = \alpha_5 + \alpha_4 \Delta t + O(\Delta^2 t)$, $\frac{A_4}{\Delta t} = \alpha_4 + \alpha_4^2 \Delta t + O(\Delta^2 t)$ and $\frac{A_5}{\Delta t} = \alpha_6 + \alpha_4 \alpha_6 \Delta t + O(\Delta^2 t)$ we have that for arbitrary small Δt both equations have the same roots. Now since

$$\frac{\alpha_4^3}{27\alpha_5^3} + \frac{\alpha_6^2}{4\alpha_5^2} > 0,$$

then both (4.27) and (4.28) have only one real root which is negative and therefore of non biological interest.

4.3.2 Scheme 2

Now let us we construct a new NSFD scheme for HPV model considering the cubic term approximated by the discretization (4.10) combined with the discretizations from equations (4.4) and (4.24). Thus,

$$
\frac{W_m^{k+1} - W_m^k}{\frac{e^{\alpha_4 \Delta t}-1}{\alpha_4}} = \alpha_1 \frac{W_{m+1}^k - W_m^k}{\frac{1-e^{-\delta \Delta \alpha}}{\delta}} + \alpha_2 \frac{W_{m+1}^k - 2W_m^k + W_{m-1}^k}{\frac{2}{a_2^2}(1 - \mathrm{cn}(a_2 h, \theta))} + \alpha_6 + \alpha_4 W_m^k
$$

$$
+ \alpha_3 W_m^{k+1} \left(\frac{W_{m+1}^k - W_m^k}{\frac{1-e^{-\delta \Delta \alpha}}{\delta}} \right) + \alpha_5 W_m^{2k} \left(\frac{W_m^{k+1} + W_m^{k-1}}{2} \right).
$$

Denoting by $A_1 = \frac{\alpha_1 \delta}{\alpha_4} \left(\frac{e^{\alpha_4 \Delta t}-1}{1-e^{-\delta \Delta \alpha}} \right)$, $A_2 = \frac{\alpha_2 a_2^2 (e^{\alpha_4 \Delta t}-1)}{\alpha_4 2(1-\mathrm{cn}(a_2 \Delta \alpha, \theta))}$, $A_3 = \frac{\alpha_3 A_1}{\alpha_1}$, $A_4 = e^{\alpha_4 \Delta t} - 1$, $A_5 = (\alpha_6/\alpha_4)(e^{\alpha_4 \Delta t} - 1)$ and $\beta = \frac{\alpha_5}{\alpha_4}$, we get the following explicit scheme:

$$
W_m^{k+1} - W_m^k = A_1 \left(W_{m+1}^k - W_m^k \right) + A_2 \left(W_{m+1}^k - 2W_m^k + W_{m-1}^k \right) + A_4 W_m^k +
$$

$$
A_3 W_m^{k+1} \left(W_{m+1}^k - W_m^k \right) + A_4 \beta W_m^{2k} \left(\frac{W_m^{k+1} + W_m^{k-1}}{2} \right) + A_5.
$$

Which can be explicitly written as

$$
W_m^{k+1} = \frac{\bar{A}_1 W_m^k + \bar{A}_2 W_{m+1}^k + A_2 W_{m-1}^k + A_4 \beta/2 W_m^{2k} W_m^{k-1} + A_5}{1 - A_3 (W_{m+1}^k - W_m^k) - A_4 \beta/2 W_m^{2k}}, \qquad (4.29)
$$

with $\bar{A}_1 = 1 - A_1 - 2A_2 + A_4$ and $\bar{A}_2 = A_1 + A_2$.

Positivity of Scheme 2

Consider the *numerator* of equation (4.29), positivity is assured if the coefficients of this expression are non-negative, that is,

Theorem 4.3.3 *The scheme (4.29) is positive, that is, $W_m^{k+1} \geq 0$ if*

$$
1 - A_1 - 2A_2 + A_4 \geq 0, \ A_1 + A_2 \geq 0, \ A_2 \geq 0, \ A_4 \beta/2 \geq 0, \ A_5 \geq 0
$$

and for all m

$$
\max \left\{ 0, \frac{1}{Q} - \sqrt{\frac{2P}{Q}} \right\} < W_m^1 < \frac{1}{Q} + \sqrt{\frac{2P}{Q}},
$$

$$0 < W_{m+1}^1 < P - \frac{Q}{2}\left(W_m^1 - \frac{1}{Q}\right)^2,$$

with $P = \frac{4\beta A_4 + A_3^2}{4\beta A_3 A_4}$ *and* $Q = \frac{\beta A_4}{A_3}$.

The proof is analogous as the one for theorem 4.3.1.

Remark The dynamical consistency of scheme 2 is basically the same as the one from scheme 1 since the equilibrium points of both schemes satisfy the same condition, namely (4.28).

4.4 Numerical results

Now let us give some numerical results by applying (4.25) y (4.29). Since we do not have actual data, we will only present numerical simulations for illustration purposes. We use $\eta(\alpha, 0) = e^{-8\alpha^2}$ as initial condition to represent an infected patient with a mild dysplasia. The values of the constants were chosen to satisfy positivity conditions and they are given by $\alpha_1 = 0.01164$, $\alpha_2 = 0.06$, $\alpha_3 = 0.00046$, $\alpha_4 = -0.0267$, and $\alpha_5 = 0.00089$ and $\alpha_6 = 0.00356$. Clearly, we could adjust the values of the constants in a real data simulation.

Both schemes present very similar results for times smaller than t=200 and for values up to 250 we obtain only slight changes that are insignificant, which shows that both approximations are reasonable, see Figure 4.1. This fact is a consequence to have used the discretization of the Duffing equation. It is important to remark that the only acceptable results have been reported only for times less than 150. As expected, both approximations deviate initially very slowly from initial data, which agrees with the fact that HPV infection takes very long time in transforming normal cervical cells into cancerous ones. As time increases, we observe a slowly formation of a parabolic shape denoting the increment of mature infected cells. Finally in Figure 4.2, we show the deviation of both approximations for larger times.

4.5 Conclusions

Two different NSFD schemes was constructed for the nonlinear advection-diffusion-reaction model of HPV. This new schemes satisfies positivity conditions. Such numerical schemes are sufficiently efficient for larger values of time. The simulations show that the numerical solutions of our methods help us understand the behavior and evolution of infected cells for very large times. In
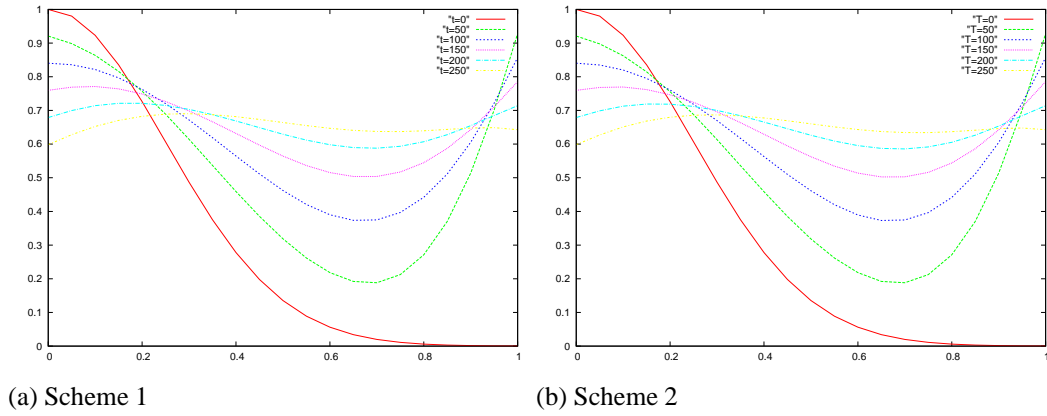
(a) Scheme 1
(b) Scheme 2

Figure 4.1: Numerical approximations of the model using both schemes for different times.

(a) $t = 200$
(b) $t = 250$
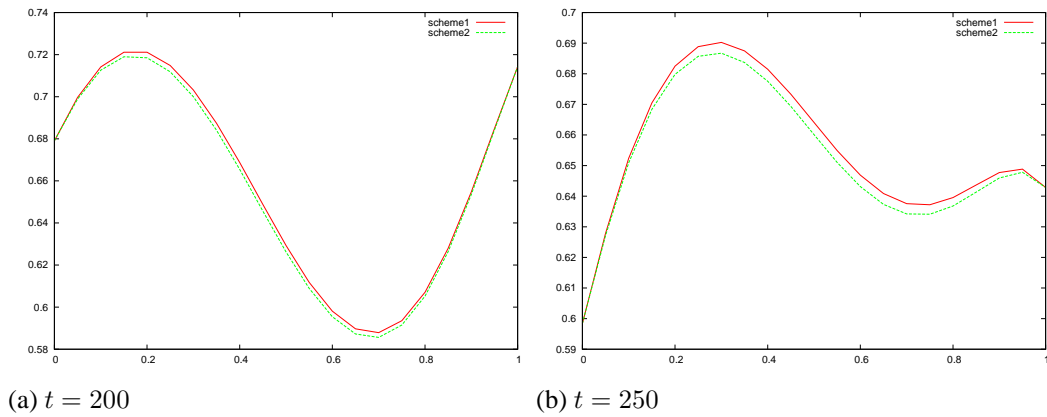
Figure 4.2: Numerical approximations of the model using both schemes at different times.

both schemes, we obtained similar results, however the second scheme allows us to continue the simulation for larger times.

Finally we note that these two schemes presented in this chapter give us a better approximation to the solution of our model as we increase the time for values up to 250, this helps us to understand the detailed evolution of HPV-infected cells for larger times.

Chapter 5

Conclusions and Future Research

In this dissertation we have presented a family of models for the interaction of infected cells of HPV. We also have proposed and analyzed two different models for the evolution of these cells.

We presented a family of models considering that precancer stages are given by discrete stages, thus obtaining a nonlinear system of differential equations. We solved the linearized systems and we approximated the solution of the nonlinear system. Both systems have been analyzed for several important cases. In such analysis, initial conditions were chosen depending on the infection degree of the patient and technically considering positivity conditions. Such family of models has the drawback that one requires to quantify the number of cells in each stage, which in most cases, there is only a qualitative description of the distribution of infected cells. In this case, one may take some averages on the number of infected cells depending on the information available.

A better way to deal with some incomplete data is to use a continuous model, which only requires the initial distribution along with some boundary conditions. Thus, we developed and analyzed a family of continuous models, the family of generalized advection diffusion reaction models, which have a biological foundation. We developed these models using nonstandard finite difference schemes which are dynamically consistent and present advantages over the classic methods because low computational time is required. In this case different numerical schemes were constructed to approximate the solutions of our continuous model of the evolution of precancerous lesions at the cervical cells caused by human papillomavirus. As a first approximation to the solution of the continuous model we gave a nonstandard numerical method, which is not exact but have good numerical efficient properties, but was only valid for small values of time. To overcome this issue, we approximate the solution of our second family of models using perturbation theory, in order to construct reliable numerical schemes that provide accurate approximations for large values of time. So we considered the equation

of interest as a perturbation problem which evolves smoothly and slowly out of the initial solution. It is important to remark that our approach is based on a new trend in numerical analysis that consists in the development of numerical techniques for perturbation problems. The numerical schemes were sufficiently robust, accurate, and efficient for larger values of time.

Finally, we built two more efficient schemes to approximate the solution of our continuous model using the non standard finite difference method with a pre-scaling of the problem. For this, first we constructed special schemes for some sub-equations that includes the Duffing equation. Some of these subequations have exact schemes and satisfy the positivity conditions. With these two new schemes we increased the approximation time, which allowed us to understand the evolution of HPV-infected cells for greater times values than the ones obtained from our previous schemes.

The results have helped us to understand the evolution of cells infected with HPV. So far, it is only a first step to provide clinicians with a reliable benchmark, hoping that our approach gives a desirable method and may open up new avenues to new modeling.

Regarding future research after this work, there are some interesting projects that we may address and we briefly list them as follows:

- Obtaining spatial models with efficient numerical methods.

- Implementation of specific software to provide clinicians with a reliable benchmark.

Uniqueness with energy method

In this appendix we use the energy method to prove the uniqueness of some sub-equations of our HPV model

$$\frac{\partial w}{\partial t} = \alpha_1 \frac{\partial w}{\partial \alpha} + \alpha_2 \frac{\partial^2 w}{\partial \alpha^2} + \alpha_3 w \frac{\partial w}{\partial \alpha} + \alpha_4 w + \alpha_5 w^3 + \alpha_6 \qquad \text{(A.0.1)}$$

Theorem A.0.1 *The boundary-initial value problem,*

$$
\begin{aligned}
\frac{\partial u}{\partial t} &= \frac{\partial^2 u}{\partial \alpha^2} + au, \quad 0 < \alpha < 1, \qquad 0 < t < T, \ a > 0 \quad \text{(A.0.2)} \\
u(\alpha, 0) &= f(\alpha), \qquad 0 < \alpha < 1, \\
u(0, t) &= g(t), \qquad u(1, t) = h(t), \quad 0 < t < T.
\end{aligned}
$$

where $f \in C[0, 1]$ and $g, h \in C[0, T]$ has a unique solution $u(\alpha, t)$ on the rectangle $R : 0 \le \alpha \le l,\ 0 \le t \le T$, for any $T > 0$.

Proof By way of contradiction assume solutions are not unique and there are two distinct solutions $u_1(\alpha, t)$ and $u_2(\alpha, t)$ to A.0.2.Then their difference $U(\alpha, t) \equiv u_1(\alpha, t) - u_2(\alpha, t)$ must satisfy the boundary value problem

$$
\begin{aligned}
\frac{\partial U}{\partial t} &= \frac{\partial^2 U}{\partial \alpha^2} + aU, \qquad 0 < \alpha < 1, \quad 0 < t < T, \ a > 0 \quad \text{(A.0.3)} \\
U(\alpha, 0) &= 0, \qquad\qquad 0 < \alpha < 1, \\
U(0, t) &= U(1, t) = 0, \qquad 0 < t < T.
\end{aligned}
$$

If we show $U(\alpha, t) \equiv 0$ on R, then $u_1(\alpha, t) = u_2(\alpha, t)$ on R, wich is a contradiction. Multiply the differential equation A.0.3 by U and integrate over $(0, 1)$ to find

$$\int_0^1 U \frac{\partial U}{\partial t} d\alpha = \int_0^1 U \frac{\partial^2 U}{\partial \alpha^2} d\alpha + a \int_0^1 U^2 d\alpha \qquad \text{(A.0.4)}$$

and consider the function of time

$$E(t) = \frac{1}{2} \|U(t)\|^2, \qquad \left(E(t) = \frac{1}{2} \int_0^1 U^2(\alpha, t) d\alpha \right),$$

(such that $E(0) = 0$ and $E(t) \geq 0$ which represents the energy of the function U). Integrate by parts in the second integral of equation A.0.4 we have:

$$\int_0^1 U \frac{\partial^2 U}{\partial \alpha^2} d\alpha = -\int_0^1 \left(\frac{\partial U}{\partial \alpha} \right)^2 d\alpha + U \frac{\partial U}{\partial \alpha} \big]_0^1 = -\|U_x\|^2 \qquad \text{(A.0.5)}$$

then, the equation A.0.4 becomes

$$\begin{aligned}
\frac{dE}{dt} &= -\|U_x\|^2 + a\|U\|^2, \qquad (\|U_\alpha\|^2 \neq 0), \\
&= -a\|U_\alpha\|^2 \left(\frac{1}{a} - \frac{\|U\|^2}{\|U_\alpha\|^2} \right), \\
&\leq -a\|U_x\|^2 \left(\frac{1}{a} - max_H \frac{\|U\|^2}{\|U_\alpha\|^2} \right). \qquad \text{(A.0.6)}
\end{aligned}$$

where H is the space of admissible functions over which we seek a maximum. Set

$$H = \left\{ U \in C^2(0,1) | \ U = 0 \ \text{ when } \ \alpha = 0, 1 \right\}.$$

Now define R_E by

$$\frac{1}{R_E} = max_H \frac{\|U\|^2}{\|U_\alpha\|^2};$$

then the energy inequality may be rewritten

$$\frac{dE}{dt} \leq -a\|U_\alpha\|^2 \left(\frac{1}{a} - \frac{1}{R_E} \right).$$

If $a < R_E$, then $1/a - 1/R_E > 0$, say $1/a - 1/R_E = c(> 0)$, and so

$$\frac{dE}{dt} \leq -ac\|U_\alpha\|^2 \leq 0.$$

Since $\frac{dE}{dt} < 0$ so $E(t) = 0$, and $U \equiv 0$, then $u_1(\alpha, t) = u_2(\alpha, t), \ \forall t > 0$.

Theorem A.0.2 *The boundary-initial value problem,*

$$\frac{\partial u}{\partial t} + u\frac{\partial u}{\partial \alpha} = \frac{\partial^2 u}{\partial \alpha^2} + \beta u^2, \qquad 0 < \alpha < 1, \qquad 0 < t < T, \quad \beta > 0 \quad \text{(A.0.7)}$$

$$\begin{aligned} u(\alpha, 0) &= f(\alpha), & 0 < \alpha < 1, \\ u(0, t) &= g(t), & u(1, t) = h(t), & \quad 0 < t < T, \end{aligned}$$

where $f \in C[0, 1]$ and $g, h \in C[0, T]$ has a unique solution $u(\alpha, t)$ on the rectangle $R : 0 \le \alpha \le 1$, $0 \le t \le T$, for any $T > 0$.

Proof A way to find a contradiction suppose $u_1(\alpha, t)$ y $u_2(\alpha, t)$ are two solutions of A.0.7 then their difference $U(\alpha, t) = u_1(\alpha, t) - u_2(\alpha, t)$ must satisfy the problem initial boundary conditions:

$$\frac{\partial U}{\partial t} + U\frac{\partial U}{\partial \alpha} = \frac{\partial^2 U}{\partial \alpha^2} + \beta U^2, \quad 0 < \alpha < 1, \quad 0 < t < T, \quad \beta > 0 \qquad \text{(A.0.8)}$$

$$\begin{aligned} U(\alpha, 0) &= 0, & 0 < \alpha < 1, \\ U(0, t) = U(1, t) &= 0, & 0 < t < T. \end{aligned}$$

If we show that $U(\alpha, t) \equiv 0$ en R then $u_1(\alpha, t) = u_2(\alpha, t)$ en R, which is a contradiction. Consider the function of time

$$E(t) = \frac{1}{2}\|U(t)\|^2, \qquad \left(E(t) = \frac{1}{2}\int_0^1 U^2(\alpha, t)d\alpha \right) \qquad \text{(A.0.9)}$$

(such that $E(0) = 0$ and $E(t) \ge 0$ which represents the Energy of the function U) We multiply the differential equation by U and integrate over $(0, 1)$ to obtain

$$\frac{1}{2}\frac{d}{dt}\|U\|^2 = \int_0^1 U\frac{\partial^2 U}{\partial \alpha^2} + \beta \int_0^1 U^3 d\alpha. \qquad \text{(A.0.10)}$$

We have

$$\int_0^1 U^2\frac{\partial U}{\partial \alpha}d\alpha = 0, \qquad \text{(A.0.11)}$$

and integrating by parts,

$$\int_0^1 U\frac{\partial^2 U}{\partial \alpha^2}d\alpha = -\|U_\alpha\|^2. \qquad \text{(A.0.12)}$$

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The Energy equation

$$\frac{1}{2}\frac{d}{dt}\|U\|^2 = -\|U_\alpha\|^2 + \beta \int_0^1 U^3 d\alpha. \tag{A.0.13}$$

We write

$$\int_0^1 U^3 d\alpha = \int_0^1 U^2 U d\alpha \leq \left(\int_0^1 U^4 d\alpha\right)^{1/2} \left(\int_0^1 U^2 d\alpha\right)^{1/2}, \tag{A.0.14}$$

by use of the Cauchy-Schwarz inequality. From the Sobolev embedding inequality we know that

$$\int_0^1 U^4 d\alpha \leq \frac{1}{4} \left(\int_0^1 U_\alpha^2 d\alpha\right)^2. \tag{A.0.15}$$

Using this leads to

$$\int_0^1 U^3 dx \leq \left(\int_0^1 U_\alpha^2 d\alpha\right) \left(\int_0^1 U^2 d\alpha\right)^{1/2} = \frac{1}{2}\|U\|\|U_\alpha\|^2. \tag{A.0.16}$$

Put A.0.16 into A.0.13 to find

$$\frac{1}{2}\frac{d}{dt}\|U\|^2 \leq -\|U_x\|^2 \left(1 - \frac{1}{2}\beta\|U(t)\|\right). \tag{A.0.17}$$

Next, assume that

$$\|U_0\| < 2\beta^{-1} \qquad \left(i.e, \int_0^1 U_0(\alpha)d\alpha < 4\beta^2\right).$$

Then either
  i) $\|U(t)\| < 2\beta^{-1}, \qquad \forall t > 0,$
  or
  ii) there exists an $\eta < \infty$ such that $\|U(\eta)\| = 2\beta^{-1}$, with

$$\|U(\eta)\| < 2\beta^{-1}, \text{on} \quad [0, \eta).$$

Suppose (ii) holds.Then on $[0, \eta)$, $1 - \beta\|U(t)\| > 0$, so A.0.17 shows

$$\frac{d}{dt}\|U\|^2 < 0, \quad \text{for} \quad 0 \leq t < \eta. \tag{A.0.18}$$

Hence

$$\|U(t)\|^2 \leq \|U(0)\|^2 = \|U_0\|^2 < 4\beta^{-2}, t \in [0, \eta).$$

Since $\|U(t)\|$ is assumed continuous in t, this means $\|U(\eta)\| \neq 2/\beta$, a contradiction. Hence, (ii) is false and (i) holds. (We are assuming the solutions we are dealing with are "classical", and so $U \in C^2$, in α, $U \in C^1$ in t). Therefore, provided

$$\|U_0\| < 2/\beta,$$

it follows that

$$\|U(t)\| \leq 2/\beta, \qquad \forall t \geq 0.$$

Further, A.0.18, now holds $\forall t \geq 0$, and hence,

$$\|U(t)\|^2 \leq \|U_0\|^2, \forall t \geq 0.$$

We have shown that $1 - \beta\|U(t)\| \geq 1 - \beta\|U_0\|(> 0)$. Now, use this in A.0.17

$$\frac{1}{2}\frac{d}{dt}\|U\|^2 \leq -\|U_\alpha\|^2 \left(1 - \frac{1}{2}\beta\|U(t)\|\right) \leq -\|U_\alpha\|^2 \left(1 - \frac{1}{2}\beta\|U_0\|\right). \quad \text{(A.0.19)}$$

Next, from Poincare's inequality, $\|U_\alpha\|^2 \geq \pi^2\|U\|^2$ and since $1 - \beta\|U_0\| > 0$, we find

$$\frac{1}{2}\frac{d}{dt}\|U\|^2 \leq -\pi^2 \left(1 - \frac{1}{2}\beta\|U_0\|\right) \|U\|^2 = -A\|U\|^2, \quad \text{(A.0.20)}$$

then

$$\frac{1}{2}\frac{d\|U\|^2}{dt} \leq 0$$

and $E(t)$ it is not growing, together with the facts that $E(t) \geq 0$ and $E(0) = 0$ then $E(t) = 0$. Therefore the integrand in A.0.9 must be 0 in $0 < \alpha \leq l$ and $0 \leq t \leq T$ since U is continuous, then $U \equiv 0$ en R and uniqueness is showed.

Theorem A.0.3 *The problem with boundary value*

$$\frac{\partial w}{\partial t} - \alpha_1 \frac{\partial w}{\partial \alpha} - \alpha_2 \frac{\partial^2 w}{\partial \alpha^2} - \alpha_3 w \frac{\partial w}{\partial \alpha} - \alpha_4 w - \alpha_5 w^3 = 0, \quad \text{(A.0.21)}$$

$$\text{(A.0.22)}$$

$$0 < \alpha < 1, \qquad 0 < t < T,$$

$$\begin{aligned} w(\alpha, 0) &= f(\alpha), & 0 < \alpha < 1, \\ w(0, t) &= g(t), & w(1, t) = h(t), & 0 < t < T, \end{aligned}$$

where $f \in C[0,1]$ and $g, h \in C[0,T]$ has a unique solution $u(\alpha, t)$ on the rectangle $R : 0 \leq \alpha \leq 1$, $0 \leq t \leq T$, for any $T > 0$.

Proof A way to find a contradiction suppose $w_1(\alpha, t)$ y $w_2(\alpha, t)$ are two solutions of A.0.21 then their difference $W(\alpha, t) = w_1(\alpha, t) - w_2(\alpha, t)$ must satisfy the problem initial boundary conditions

$$\frac{\partial W}{\partial t} - \alpha_1 \frac{\partial W}{\partial \alpha} - \alpha_2 \frac{\partial^2 W}{\partial \alpha^2} - \alpha_3 W \frac{\partial W}{\partial \alpha} - \alpha_4 W - \alpha_5 W^3 = 0. \qquad (A.0.23)$$

$$W(\alpha, 0) = 0, \qquad 0 < \alpha < 1,$$
$$W(0, t) = W(1, t) = 0, \qquad 0 < t < T.$$

If we show that $W(\alpha, t) \equiv 0$ en R then $w_1(\alpha, t) = w_2(\alpha, t)$ en R, which is a contradiction. We define the integral of energy

$$E(t) = \int_0^1 W^2(\alpha, t) d\alpha, \qquad (A.0.24)$$

we have $E(t) \geq 0$ y $E(0) = 0$, then

$$\frac{dE}{dt} = \int_0^1 2W W_t d\alpha \qquad (A.0.25)$$

and

$$\frac{1}{2} \frac{dE}{dt} = \int_0^l W \left[\alpha_1 \frac{\partial W}{\partial \alpha} + \alpha_2 \frac{\partial^2 W}{\partial \alpha^2} + \alpha_3 W \frac{\partial W}{\partial \alpha} + \alpha_4 W + \alpha_5 W^3 \right] d\alpha. \quad (A.0.26)$$

For the last equality we consider each integral separately. In the first integral, we integrated by parts and use the boundary conditions

$$\alpha_1 \int_0^l W W_\alpha d\alpha \;=\; \alpha_1 \left([W^2]_0^l - \int_0^l W W_\alpha d\alpha \right) \qquad (A.0.27)$$

$$(2\alpha_2) \int_0^1 W W_\alpha d\alpha \;=\; 0. \qquad (A.0.28)$$

We solve the second integral for parts,

$$\alpha_2 \int_0^1 W W_{\alpha\alpha} d\alpha \;=\; \alpha_2 \left([W W_\alpha]_0^1 - \int_0^1 W_\alpha^2 d\alpha \right) \qquad (A.0.29)$$

$$\alpha_2 \int_0^1 W W_{\alpha\alpha} d\alpha \;=\; -\alpha_2 \int_0^1 W_\alpha^2 d\alpha = -\alpha_2 \|W_\alpha\|^2 \qquad (A.0.30)$$

The third integral we have

$$\alpha_3 \int_0^1 W^2 W_\alpha d\alpha \;=\; \alpha_3 \left([W^3]_0^1 - 2 \int_0^1 W^2 W_\alpha d\alpha \right) \qquad \text{(A.0.31)}$$

$$(3\alpha_3) \int_0^1 W^2 W_\alpha d\alpha \;=\; 0, \qquad\qquad\qquad \text{(A.0.32)}$$

the fourth integral

$$\alpha_4 \int_0^1 W^2 d\alpha = \alpha_4 \|W\|^2, \qquad\qquad\qquad \text{(A.0.33)}$$

donde $\alpha_4 < 0$ the fifth integral and From the Sobolev embedding inequality we know that

$$\alpha_5 \int_0^1 W^4 d\alpha \le \frac{\alpha_5}{4} \left\{ \int_0^1 W_\alpha^2 d\alpha \right\}^2, \qquad\qquad \text{(A.0.34)}$$

then

$$\frac{1}{2}\frac{dE}{dt} \;=\; -\alpha_2 \|W_\alpha\|^2 + \alpha_4 \|W\|^2 + \alpha_5 \int_0^l W^4 d\alpha \qquad \text{(A.0.35)}$$

$$\le \;-\alpha_2 \|W_\alpha\|^2 + \alpha_4 \|W\|^2 + \alpha_5/4 \|W_\alpha\|^4 \qquad \text{(A.0.36)}$$

$$\le \;-\alpha_2 \|W_\alpha\|^2 \left(1 - \frac{\alpha_4 \|W\|^2}{\alpha_2 \|W_\alpha\|^2} - \frac{\alpha_5}{4\alpha_2} \|W_\alpha\|^2 \right), \qquad \text{(A.0.37)}$$

where we choose the coeficients such that

$$\left(1 - \frac{\alpha_4 \|W\|^2}{\alpha_2 \|W_\alpha\|^2} - \frac{\alpha_5}{4\alpha_2} \|W_\alpha\|^2 \right) > 0,$$

where $\|W_\alpha\|^2 \ne 0$ then $E(t)$ it is not growing, together with the facts that $E(t) \ge 0$ and $E(0) = 0$ then $E(t) = 0$.Therefore the integrand in A.0.24 must be 0 in $0 < \alpha \le l$ and $0 \le t \le T$ since W is continuous, then $W \equiv 0$ en R and uniqueness is showed.

Monotone method for parabolic equations

The basic idea of the monotone method is that by using an upper solution or a lower solution as the initial iteration in a suitable iterative process the resulting sequence of iterations is monotone and converges to a solution of the problem. This appendix shows limit of the monotone sequence is indeed the solution of the parabolic problem for each of the three basic boundary conditions. First we need to review some results already established for linear parabolic equations.

B.1   A Review of the Linear Parabolic Problem

The Hölder function spaces

Let Ω be either a bounded or an unbounded open domain in R^n, and let $\partial\Omega$ be the boundary of Ω. For each $T > 0$, let $D_T = (0, T] \times \Omega$, $S_T = (0, T] \times \partial\Omega$. Denote by $C^m(\Omega)$ the set of all continuous functions whose partial derivatives up to the mth order are continuous in Ω, and by $C^{l,m}(D_T)$ the set of functions whose l-times derivatives in t and m-times derivatives in x are continuous in D_T. In particular, the set $C^{1,2}(D_T)$ consists of all functions that are once continuously differentiable in t and twice continuously differentiable in x for all $(t, x) \in D_T$. Similar notations are used for $C^m(\bar{\Omega})$ and $C^{l,m}(\bar{D}_T)$, where $\bar{\Omega}$, $\bar{D}_T$ are the respective closures of Ω and D_T. When $m = 0$ we denote by $C(\Omega)$, $C(\bar{\Omega})$, $C(\bar{D}_T)$, and the set of continuous functions in Ω, $\bar{\Omega}$, D_T , and $\bar{D}_T$, respectively. In the following discussion we state some basic definitions and collect some facts from the theory of linear parabolic equations.

Parabolic Problem

The monotone method, can be used to parabolic boundary-value problems.To justify that the limit of the monotone sequence is a classical solution we need

to review some of the well established results for the following linear parabolic equation:

$$u_t - Lu + cu = g(t,x) \ in \ D_T \tag{B.1.1}$$

under the boundary and initial conditions

$$Bu \equiv \alpha_0(t,x)\frac{\partial u}{\partial v} + \beta_0(t,x)u = h(t,x) \ on \ S_T \tag{B.1.2}$$

$$u(0,x) = u_0(x) \ in \ \Omega$$

where $D_T = (0,T] \times \Omega$, $S_T = (0,T] \times \partial\Omega$ and $\Omega \in \mathbb{R}^n$ open and bounded. Furthermore, c is a continuous function and the functions g, h, and u_0 are given functions and assumed Hölder continuous in their respective domains. and for each fixed t, L is a uniformly elliptic operator given by

$$Lu = \sum_{i,j=1}^{n} a_{ij}(t,x)\frac{\partial^2 u}{\partial x_i \partial x_j} + \sum_{i=1}^{n} b_i(t,x)\frac{\partial u}{\partial x}$$

where $\equiv$ denotes definition or identity. L uniformly elliptical is in the sense that the matrix (a_{ij}) is positive definite in $\bar{D}^T$ that is, there exist positive constants d_0, d_1 such that for every vector $\xi = (\xi_1, \xi_2 \cdots, \xi_n) \ in \ \mathbb{R}^n$

$$d_0|\xi|^2 \leq \sum_{i,j=1}^{n} a_{ij}(t,x)\xi_i\xi_j \leq d_1|\xi|^2 \ (t,x) \in \bar{D}_T$$

where

$$|\xi|^2 = \xi_1{}^2 + \xi_2{}^2 + \ldots + \xi_n{}^2.$$

We assume that the coefficients of L and c are Hölder continuous in D_T, α_0 y β_0 are continuous on S_T with $\alpha_0 \geq 0$, and $\alpha_0 + \beta_0 \geq 0$. We call problem B.1.1 the first (or Dirichlet) boundary-value problem when $\alpha_0 = 0$, $\beta_0 > 0$, and the second B.1.2(or Neumann) boundary-value problem when $\alpha_0 > 0$, $\beta_0 \geq 0$.

(1) Fundamental solution

A function $\Gamma(t,x;\tau,\xi)$ is called a fundamental solution of the parabolic operator

$$L_c \equiv (\partial/\partial t - L + c) \ in (0,T] \times \mathbb{R}^n$$

if for any fixed $(\tau,\xi)\epsilon(0,T] \times R^n$, Γ satisfies the equation

$$L_c[\Gamma] \equiv \Gamma_t - L\Gamma + c\Gamma = \delta(t-\tau)\delta(x-\xi)$$

where δ is the Dirac δ-function. If $L = D\nabla^2$ and $c = c_0$ is a constant, is given by:

$$\Gamma(t, x; \tau, \xi) = [4\pi D(t - \tau)]^{-n/2} exp[-(c_0 t + |x - \xi|^2 / 4D|t - \tau|)]$$

For the general parabolic operator L_c , is a positive function in $(0, T] \times \mathbb{R}^n$ except at the singular point (τ, ξ). Furthermore, for any x, ξ in $\mathbb{R}^n$ and $0 \leq \tau < t \leq T$ it has the estimates

$$\Gamma(t, x; \tau, \xi) \leq \frac{K_0}{(t - \tau)^\mu} \frac{1}{|x - \xi|^{n-2+\mu}}, \quad (0 < \mu < 1)$$

$$\frac{\partial \Gamma}{\partial v_x}(t, x; \tau, \xi) \leq \frac{K_0}{(t - \tau)^\mu}, \quad \frac{1}{|x - \xi|^{n+1-2\mu-\gamma}}, \quad (1 - \gamma/2 < \mu < 1)$$

where $\frac{\partial}{\partial v_x}$; is the outward normal derivative with respect to the x variable and K_0 is a constant independent of (t, x) and (τ, ξ).

B.2 Upper and lower sequence

We consider the semilinear parabolic equation:

$$u_t - Lu \quad = \quad f(t, x, u) \ in \ D_T \tag{B.2.1}$$

under the initial and boundary conditions

$$Bu \equiv \alpha_0(t, x)\frac{\partial u}{\partial v} + \beta_0(t, x)u \quad = \quad g(t, x, u) \ on \ S_T \tag{B.2.2}$$
$$u(0, x) \quad = \quad u_0(x) \ in \ \Omega$$

where $g(t, x, u)$ is in general nonlinear in u. We assume that g is continuous on $S_T \times J$ and that f, β_0, u_0 and L are assumed Hölder continuous in their respective domains. Where J is the sector between upper and lower solutions. The definition of upper and lower solutions is given by:

Definition A function $\tilde{u} \in C(\bar{D}_T) \cap C^{1,2}(D_T)$ is called an **Upper solution** of (B.2.1) if it satisfies all the inequalities

$$\tilde{u}_t - L\tilde{u} \quad \geq \quad f(t, x, \tilde{u}) \ in \ D_T \tag{B.2.3}$$
$$B\tilde{u} \quad \geq \quad g(t, x, \tilde{u}) \ on \ S_T$$
$$\tilde{u}(0, x) \quad \geq \quad u_0(x) \ in \ \Omega$$

Definition A function $\hat{u} \in C(\bar{D}_T) \cap C^{1,2}(D_T)$ is called an **Lower solution** of (B.2.1) if it satisfies all the inequalities

$$
\begin{aligned}
\hat{u}_t - L\hat{u} &\leq f(t, x, \hat{u}) \; in \; D_T \\
B\hat{u} &\leq g(t, x, \hat{u}) \; on \; S_T \\
\hat{u}(0, x) &\leq u_0(x) \; in \; \Omega
\end{aligned}
\tag{B.2.4}
$$

It is clear from the above definition that every solution of (B.2.1) is an upper solution as well as a lower solution. For a given pair of ordered upper and lower solutions $\tilde{u}$ y $\hat{u}$, in $\bar{D}_T$ We assume that there exist bounded functions $\bar{c} = \bar{c}(t, x)$, $\underline{c} = \underline{c}(t, x)$ and $\bar{b}$, $\underline{b}$ en $C(S_T)$ such that

$$
\begin{aligned}
-\underline{c}(u_1 - u_2) &\leq f(t, x, u_1) - f(t, x, u_2) \leq \bar{c}(u_1 - u_2) \\
-\underline{b}(u_1 - u_2) &\leq f(t, x, u_1) - f(t, x, u_2) \leq \bar{b}(u_1 - u_2) \\
&\qquad for \; \hat{u} \leq u_2 \leq u_1 \leq \tilde{u}
\end{aligned}
\tag{B.2.5}
$$

The above condition implies that the functions

$$
\begin{aligned}
F(t, x, u) &\equiv \underline{c}(t, x)u + f(t, x, u) \\
G(t, x, u) &\equiv \underline{b}(t, x)u + g(t, x, u)
\end{aligned}
\tag{B.2.6}
$$

are monotone nondecreasing in u and satisfy the Lipschitz condition

$$
\begin{aligned}
|F(t, x, u_1) - F(t, x, u_2)| &\leq K|u_1 - u_2| \\
|G(t, x, u_1) - G(t, x, u_2)| &\leq K|u_1 - u_2| \\
(for \quad u_1, u_2 &\in \langle \hat{u}, \tilde{u} \rangle)
\end{aligned}
\tag{B.2.7}
$$

Where K may be taken as an upper bound of $|\underline{c}(t, x)| + |\bar{c}(t, x)|$ in D_T. Note that (B.2.4) holds when f is Lipschitz continuous in u. However, in the construction of the monotonous succession only the left side of the Lispchitz condition in (B.2.4) is needed; the right side of the condition Lipschitz is used to ensure the uniqueness of the solution. In terms of F and G, problem (B.2.1) may be written as

$$
\begin{aligned}
L_c u &= F(t, x, u) \; in \; D_T \\
Bu + \underline{b}u &= G(t, x, u) \; on \; S_T \\
u(0, x) &= u_0(x) \; in \; \Omega
\end{aligned}
\tag{B.2.8}
$$

We consider the same initial and boundary conditions as in (B.2.2) where F is a given by (B.2.6) and $L_c u$ is given by (B.2.8) with $c = \underline{c}$. Starting from an initial

iteration appropriate $u^{(0)}$ is possible to construct a sequence $u^{(k)}$ Then consider the iteration process

$$
\begin{aligned}
L_c u^{(k)} &= F(t, x, u^{(k-1)}) \ \ in \ \ D_T \\
Bu^{(k)} + \underline{b}u^{(k)} &= G(t, x, u^{(k-1)}) \ \ on \ \ S_T \\
u^{(k)}(0, x) &= u_0(x) \ \ in \ \ \Omega
\end{aligned}
\tag{B.2.9}
$$

where $k = 1, 2, 3 \ldots$. We denote the sequences with $u^{(0)} = \tilde{u}$ and $u_0 = \hat{u}$ by $\bar{u}^{(k)}$ and $\underline{u}^{(k)}$, respectively, and refer to them as upper and lower sequences. We show that under the condition on (B.2.5) each of the sequences converge monotonically on a unique solution of (B.2.1). The following lemma gives the monotone property of these two sequences.

Lemma B.2.1 *Let f, g satisfy condition (B.2.5). Then the sequences $\bar{u}^{(k)}$, $\underline{u}^{(k)}$, are well defined and possess the monotone property. Moreover $\bar{u}^{(k)}$ and $\underline{u}^{(k)}$ are ordered upper and lower solutions of (B.2.1) for every k.*

Proof Let

$$
w = \bar{u}^{(0)} - \bar{u}^{(1)} = \tilde{u} - \bar{u}^{(1)}
$$

From the definition of superior solution and (B.2.9) we have

$$
\begin{aligned}
L_c w = L_c \tilde{u} - F(t, x, \bar{u}^{(0)}) &= \tilde{u}_t - L\tilde{u} - f(t, x, \tilde{u}) \geq 0 \quad \text{(B.2.10)} \\
Bw + \underline{b}w &= B\tilde{u} + b\tilde{u} - G(t, x, \bar{u}^{(0)}) \\
&= B\tilde{u} - g(t, x, \tilde{u}) \geq 0 \\
w(0, x) &= \tilde{u}(0, x) = u_0(x) \geq 0.
\end{aligned}
$$

The positivity lemma implies that $w \geq 0$ that is, $\bar{u}^{(1)} \leq \bar{u}^{(0)}$. A similar argument gives $\underline{u}^{(1)} \geq \underline{u}^{(0)}$. Let $w^{(1)} = \bar{u}^{(1)} - \underline{u}^{(1)}$. By (B.2.9) and the monotone property of F, G, $u^{(0)} \geq 0$ It follows from $w^{(1)}(0, x) = 0$ that $w^{(1)} \geq 0$ The above conclusion shows that $\underline{u}^{(0)} \leq \underline{u}^{(1)} \leq \bar{u}^{(1)} \leq \bar{u}^{(0)}$ Assume by induction that

$$
\underline{u}^{(k-1)} \leq \underline{u}^{(k)} \leq \bar{u}^{(k)} \leq \bar{u}^{(k-1)} \quad \text{in} \quad \bar{D}_T.
$$

Then by (B.2.9) and the monotone property of F, the function $w^{(k)} = \bar{u}^{(k)} - \bar{u}^{(k+1)}$ satisfies the relation

$$
L_c w^{(k)} = F(t, x, \bar{u}^{(k-1)}) - F(t, x, \bar{u}^{(k)}) \geq 0
$$

and the boundary and initial conditions as for $w^{(1)}$. This leads to the conclusion $w^{(k)} \geq 0$ and thus $\bar{u}^{(k+1)} \leq \bar{u}^{(k)}$. The same argument gives $\underline{u}^{(k+1)} \geq \underline{u}^{(k)}$ and $\bar{u}^{(k+1)} \geq \underline{u}^{(k)}$. The conclusion of the lemma follows by the principle of induction.

Lemma B.2.2 *The pointwise limits*

$$\lim_{k \to \infty} \bar{u}^{(k)}(t, x) = \bar{u}(t, x) \quad and \quad \lim_{k \to \infty} \underline{u}^{(k)}(t, x) = \underline{u}(t, x) \qquad \text{(B.2.11)}$$

exist and satisfy the relation

$$\hat{u} \le \underline{u}^{(k)} \le \underline{u}^{(k+1)} \le \underline{u} \le \bar{u} \le \bar{u}^{(k+1)} \le \bar{u}^{(k)} \le \tilde{u} \quad in \quad \bar{D}_T \qquad \text{(B.2.12)}$$

where $k = 1, 2, \ldots$

Proof Since by lemma B.2.1 the sequence $\bar{u}^{(k)}$ is monotone non increasing and is bounded from below and the sequence $\underline{u}^{(k)}$ is monotone nondecreasing and is bounded from above, the point wise limits of these sequences exist and their limits are denoted by $\bar{u}$ and $\underline{u}$ as in (B.2.11). Moreover, by lemma (B.2.1) the limits $\bar{u}$ and $\underline{u}$ satisfy the relation B.2.12.

Lemma B.2.3 *If the limits $\bar{u}$ and $\underline{u}$ are solutions of (B.2.1) then $\bar{u} = \underline{u}$ is the solution in $< \hat{u}, \tilde{u} >$.*

Proof Let $w = \underline{u} - \bar{u}$.Then w satisfies the relation

$$w_t - Lw = f(t, x, \underline{u}) - f(t, x, \bar{u}) \ge -\bar{c}(\bar{u} - \underline{u}) = cw$$

and the boundary and initial conditions $Bw = 0$ on D_T , $w(0, x) = 0$ in S_T, where $c = c(t, x)$ is the function in (B.2.5). For the positivity lemma, $w \ge 0$ in D_T , which ensures that $\bar{u} = \underline{u}$. Now if u^* is any other solution in the sector $< \hat{u}, \tilde{u} >$ then by considering u^*, $\hat{u}$ and $\tilde{u}$, u^* as ordered upper and lower solutions then $u^* \ge \underline{u}$ and $u^* \le \bar{u}$. This implies that $\bar{u} = u^* = \underline{u}$ and u^* is the unique solution of B.2.1.

We next show that $\bar{u}^{(k)}$ and $\underline{u}^{(k)}$ are ordered upper and lower solutions of B.2.1.

Lemma B.2.4 *For each k, $\bar{u}^{(k)}$ is an upper solution, $\underline{u}^{(k)}$ is a lower solution, and $\underline{u}^{(k)} \le \bar{u}^{(k)}$ in D_T.*

Proof By the iteration process B.2.9 and the conditions B.2.5 and B.2.12, $\bar{u}^{(k)}$ satisfies the relation

$$\begin{aligned} \bar{u}_t^{(k)} - L\bar{u}^{(k)} &= \underline{c}(\bar{u}^{(k-1)} - \bar{u}^{(k)}) + (f(t, x, \bar{u}^{(k-1)}) && \text{(B.2.13)} \\ &= \underline{c}(\bar{u}^{(k-1)} - \bar{u}^{(k)}) + (f(t, x, \bar{u}^{(k-1)}) - f(t, x, \bar{u}^{(k)})) + f(t, x, \bar{u}^{(k)}) \\ &\ge f(t, x, \bar{u}^{(k)}) \end{aligned}$$

and $\underline{u}^{(k)}$ satisfies the relation

$$
\begin{aligned}
\underline{u}_t^{(k)} - L\underline{u}^{(k)} &= -\underline{c}(\underline{u}^{(k)} - \bar{u}^{(k-1)}) + (f(t,x,\underline{u}^{(k-1)})) \qquad \text{(B.2.14)} \\
&= -\underline{c}[(\underline{u}^{(k)} - \bar{u}^{(k-1)}) + f(t,x,\underline{u}^{(k)}) - f(t,x,\underline{u}^{(k-1)})] + f(t,x,\underline{u}^{(k)}) \\
&\geq f(t,x,\underline{u}^{(k)})
\end{aligned}
$$

It follows from the boundary and initial conditions in B.2.9 that $\bar{u}^{(k)}$ and $\underline{u}^{(k)}$ are upper and lower solutions, respectively. The relation $\underline{u}^{(k)} \leq \bar{u}^{(k)}$ follows from lemma B.2.1

In lemma B.2.4 it is assumed that the upper and lower solutions $\tilde{u}$, $\hat{u}$ are ordered. The following lemma states that if f is a C^1-function (or is Lipschitz continuous) in u then $\tilde{u}$ and $\hat{u}$ are necessarily ordered.

Lemma B.2.5 *Let $\tilde{u}$, $\hat{u}$ be upper and lower solutions of B.2.1, and let f be a C^1 function in u. Then $\tilde{u} \geq \hat{u}$. In particular, if $\tilde{u}$ is an upper solution (resp., $\hat{u}$ is a lower solution) and u is the solution of B.2.1, then $\tilde{u} \geq u^*$ (resp., $\hat{u} \leq u^*$).*

Proof Let $w = \tilde{u} - \hat{u}$.Then by the definition of $\tilde{u}$, $\hat{u}$ and the mean value theorem,

$$
\begin{aligned}
w_t - Lw &\geq f(t,x,\tilde{u}) - f(t,x,\hat{u}) = f_u(t,x,\hat{\eta}(t,x))w \qquad \text{(B.2.15)} \\
Bw &\geq h - h = 0 \\
w(0,x) &\geq u_0 - u_0 = 0
\end{aligned}
$$

where $\hat{\eta}$ is an intermediate value between $\tilde{u}$ and $\hat{u}$. By Lemma B.2.1, $\tilde{u} \geq \hat{u}$. Since every solution u^* may be considered as a lower solution or an upper solution the relations $\tilde{u} \geq \hat{u}$ and $\tilde{u} \leq \hat{u}$ follow immediately.

For details of this method see [30], and [31].

Solution of the linear version of the model

Theorem C.0.6 *Let* $-k$ *eigenvalue with multiplicity* $r = m - 1$ *of the matrix* A *associated to linear system (1.7), then the functions*

$$N_1(t) = \mathbf{w}_1 e^{-kt},$$

$$N_2(t) = (t\mathbf{w}_1 + \mathbf{w}_2)e^{-kt},$$

$$N_3(t) = (t^2\mathbf{w}_1 + t\mathbf{w}_2 + \mathbf{w}_3)e^{-kt},$$

$$\cdots$$

$$N_r(t) = \left(\frac{t^{r-1}}{(r-1)!}\mathbf{w}_1 + \cdots + \frac{t^2}{2}\mathbf{w}_{r-2} + t\mathbf{w}_{r-1} + \mathbf{w}_r \right) e^{-kt},$$

are r *solutions of the system* $\dot{\mathbf{N}} = \mathbf{A}\mathbf{N}$.

Proof A chain of generalized eigenvectors of length r gives us r independent solutions, then we only will proof that the functions $N_j(t)$ are solutions of the system (1.7). We have

$$\mathbf{N}_j = e^{-kt}\left(\sum_{i=1}^{j} \frac{t^{j-i}}{(j-i)!}\mathbf{w}_i \right) \tag{C.0.1}$$

and

$$\dot{\mathbf{N}}_j = e^{-kt}\left(\sum_{i=1}^{j} \frac{t^{j-i-1}}{(j-i-1)!}\mathbf{w}_i \right) + e^{-kt}\left(\sum_{i=1}^{j}(-k)\frac{t^{j-1}}{(j-i)!}\mathbf{w}_i \right) \tag{C.0.2}$$

on the other hand,

$$A\mathbf{N}_j = e^{-kt} \sum_{i=1}^{j} \frac{t^{j-i}}{(j-i)!} A\mathbf{w}_i \tag{C.0.3}$$

and we have

$$
\begin{aligned}
(A + kI)\mathbf{w}_1 &= 0, \\
(A + kI)\mathbf{w}_2 &= \mathbf{w}_1, \\
&\vdots \\
(A + kI)\mathbf{w}_r &= \mathbf{w}_{r-1}
\end{aligned} \tag{C.0.4}
$$

then $A\mathbf{w}_i = \mathbf{w}_{i-1} - k\mathbf{w}_i$ for $i = 1, 2, \cdots, r$ and

$$
\begin{aligned}
A\mathbf{N}_j(t) &= e^{-kt} \sum_{i=1}^{j} \frac{t^{j-i}}{(j-i)!} (\mathbf{w}_{i-1} - k\mathbf{w}_i) \\
&= e^{-kt} \sum_{i=1}^{j} \frac{t^{j-i}}{(j-i)!} \mathbf{w}_{i-i} + e^{-kt} \sum_{i=1}^{j} \frac{t^{j-i}}{(j-i)!} \mathbf{w}_i \\
&= e^{-kt} \sum_{i=1}^{j-i} \frac{t^{j-i-1}}{(j-i-1)!} \mathbf{w}_i + e^{-kt} \sum_{i=1}^{j} (-k) \frac{t^{j-i}}{(j-i)!} \mathbf{w}_i
\end{aligned} \tag{C.0.5}
$$

Then, $N_j(t)_{j=1}^{r}$ are r linearly independent solutions of system (1.7).

Elliptic functions

The Jacobi elliptic functions are defined as the inverses of the elliptic integral of the firt kind. Let

$$u = \int_0^\phi \frac{d\theta}{\sqrt{1 - k^2 \sin^2(\theta)}},$$

$0 \le k^2 \le 1$ and define the indicated functions as follows:

$$
\begin{aligned}
\text{sn}(u, k) &\equiv \sin(\phi), \\
\text{cn}(u, k) &\equiv \cos(\phi), \\
\text{dn}(u, k) &\equiv \sqrt{1 - k^2 sin^2(\phi)}, \\
\text{am}(u, k) &\equiv \phi, \\
\tan(u, k) &\equiv \frac{\text{sn}(u, k)}{\text{cn}(u, k)} = \tan(\phi).
\end{aligned}
\tag{D.0.1}
$$

These functions have the associated names:
    $\text{sn}(u, k)$: Jacobi sine functions,
    $\text{cn}(u, k)$: Jacobi cosine functions,
    $\text{am}(u, k)$: Amplitude of u.
    Note that if $k^2 = 0$ then $u = \phi$ and

$$
\begin{aligned}
\text{sn}(u, 0) &= \sin(u), \\
\text{cn}(u, 0) &= \cos(u), \\
\text{dn}(u, 0) &= 1, \\
\text{am}(u, 0) &= u.
\end{aligned}
\tag{D.0.2}
$$

These result suggest that the Jacobi sine and cosine functions are generalization of the sine cosine trigonometric functions. The following properties of the Jacobi

elliptic functions are a direct consecuence of their definitions given by D.0.1

$$\begin{aligned}
\operatorname{sn}(0, k) &= 0, & \text{(D.0.3)} \\
\operatorname{cn}(0, k) &= 1, \\
\operatorname{dn}(0, k) &= 1, \\
\operatorname{am}(u, 0) &= 0.
\end{aligned}$$

Each of the Jacobi elliptic functions depend on a parameter k, called the modulus. We also have the complementary modulus k defined by $(k)^2 + (k')^2 = 1$

$$\begin{aligned}
\operatorname{sn}^2(u, k) + \operatorname{cn}^2(u, k) &= 1, & \text{(D.0.4)} \\
k^2 \operatorname{sn}^2(u, k) + \operatorname{dn}^2(u, k) &= 1, \\
\operatorname{dn}^2(u, k) - k^2 \operatorname{cn}^2(u, k) &= 1 - k^2 = (k')^2.
\end{aligned}$$

$$\begin{aligned}
\operatorname{sn}(-u, k) &= -\operatorname{sn}(u, k), & \text{(D.0.5)} \\
\operatorname{dn}(-u, k) &= \operatorname{dn}(u, k), \\
\operatorname{am}(-u, k) &= -am(u, k).
\end{aligned}$$

$$\begin{aligned}
\operatorname{sn}(u, 1) &= tanh(u), & \text{(D.0.6)} \\
\operatorname{cn}(u, 1) &= \operatorname{dn}(u, 1), \\
\operatorname{cn}(u, 1) &= sech(u).
\end{aligned}$$

Theorem D.0.7 *From now on we will ommit the second argument in the functions. The derivatives of the Jacobi elliptic functions are*

$$\begin{aligned}
\frac{d}{du}(\operatorname{sn}(u)) &= \operatorname{cn}(u) \operatorname{dn}(u), & \text{(D.0.7)} \\
\frac{d}{du}(\operatorname{cn}(u)) &= \operatorname{sn}(u) \operatorname{dn}(u), \\
\frac{d}{du}(\operatorname{dn}(u)) &= k^2 \operatorname{sn}(u) \operatorname{dn}(u),
\end{aligned}$$

Proof By differentiation of D.0.1 we have,

$$\frac{du}{d(\phi)} = \frac{1}{\sqrt{1 - k^2 \sin^2(\phi)}} = \frac{1}{(\operatorname{dn}(u))},$$

and using $\text{sn}(u,k) \equiv \sin(\phi)$ we obtain

$$\frac{d}{du}(\text{sn}(u)) = \frac{d(\sin(\phi))}{du} = (\cos(\phi))\frac{d(\phi)}{du} = (\text{cn}(u))(\text{dn}(u)).$$

Similarly, it follows that

$$\frac{d}{du}(\text{cn}(u)) = \frac{d(\cos(\phi))}{du} = (-\sin(\phi))\frac{d\phi}{du} = (-\text{sn}(u))\,\text{dn}(u)$$

and $\frac{d}{du}(\text{dn}(u)) = -k^2(\text{sn}(u))(\text{cn}(u))$.

The corresponding second derivatives are,

$$
\begin{aligned}
\frac{d^2}{du^2}(\text{sn}(u)) &= 2k^2(\text{sn}^3(u)) - (1+k^2)(\text{sn}(u)), \qquad \text{(D.0.8)}\\
\frac{d^2}{du^2}(\text{cn}(u)) &= (2k^2-1)(\text{cn}(u)) - 2k^2(\text{cn}^3(u)),\\
\frac{d^2}{du^2}(\text{dn}(u)) &= 2(2-k^2) - 2(\text{dn}^3(u)).
\end{aligned}
$$

Theorem D.0.8 *The addition formulas for the Jacobi elliptic functions are*

$$
\begin{aligned}
\text{sn}(u_1+u_2) &= \frac{(\text{sn}(u_1))(\text{cn}(u_2))(\text{dn}(u_2)) + (\text{sn}(u_2))(\text{cn}(u_1))(\text{dn}(u_1))}{1 - k^2(\text{sn}^2(u_1))(\text{sn}^2(u_2))},\\
\text{cn}(u_1+u_2) &= \frac{(\text{cn}(u_1))(\text{cn}(u_2)) - (\text{sn}(u_1))(\text{sn}(u_2))(\text{dn}(u_1))(\text{dn}(u_2))}{1 - k^2(\text{sn}^2(u_1))(\text{sn}^2(u_2))},\\
\text{dn}(u_1+u_2) &= \frac{(\text{dn}(u_1))(\text{dn}(u_2)) - k^2(\text{sn}(u_1))(\text{sn}(u_2))(\text{cn}(u_1))(\text{cn}(u_2))}{1 - k^2(\text{sn}^2(u_1))(\text{sn}^2(u_2))}.
\end{aligned}
$$

Proof We denote $s_1 = (\text{sn}(u_1))$, $s_2 = (\text{sn}(u_2))$, $c_1 = (\text{cn}(u_1))$, $c_2 = (\text{cn}(u_2))$, $d_1 = (\text{dn}(u_1))$ and $d_2 = (\text{dn}(u_2))$. Let

$$w = \frac{s_1 c_2 d_2 + s_2 c_1 d_1}{1 - k^2 s_1^2 s_2^2}$$

Then, by partial differentiation with respect to u_1, and after simplification we have,

$$\frac{dw}{du_1} = \frac{c_1 d_1 c_2 d_2(1 + k_2 s_1^2 s_2^2) - s_1 s_2(d_1^2 d_2^2 + k^2 c_1^2 c_2^2)}{(1 - k^2 s_1^2 s_2^2)^2}$$

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Therefore, dw/du_1 is symmetric in u_1 and u_2, and as w is symmetric, it follows that dw/du_2 is equal to dw/du_1. Hence, for a function $f(u_1 + u_2)$ of $u_1 + u_2$, we have $w = f(u_1 + u_2)$, and it follows that

$$f(u_1 + u_2) = \frac{s_1 c_2 d_2 + s_2 c_1 d_1}{(1 - k^2 s_1^2 s_2^2)}$$

Putting $u_2 = 0$ gives $f(u_1) = s_1$, while $u_1 = 0$ gives $f(u_2) = s_2$. Therefore, $f(u_1 + u_2) = \mathrm{sn}(u_1 + u_2)$. Now, we have

$$\mathrm{cn}^2(u_1 + u_2) = 1 - \mathrm{sn}^2(u_1 + u_2) = \frac{(1 - k^2 s_1^2 s_2^2) - (s_1 c_2 d_2 + s^2 c_1 d_1)^2}{(1 - k^2 s_1^2 s_2^2)^2}$$

If we express $(1 - k^2 s_1^2 s_2^2)^2$ in the form $(c_1^2 + s_1^2 d_2^2)(c_2^2 + s_2^2 d_1^2)$, then

$$\mathrm{cn}^2(u_1 + u_2) = \frac{(c_1 c_2 - s_1 s_2 d_1 d_2)^2}{(1 - k^2 s_1^2 s_2^2)^2}.$$

We then take the square root, and to remove the ambiguity in sign we note that both of these expressions are one-valued functions of u_1 except at isolated poles, so, by the theory of analytic continuation, either the positive sign, or else the negative sign must always be taken. By setting $u_2 = 0$, it follows that the positive sign must be taken. The formula for $\mathrm{dn}(u_1 + u_2)$ follows by a similar argument.
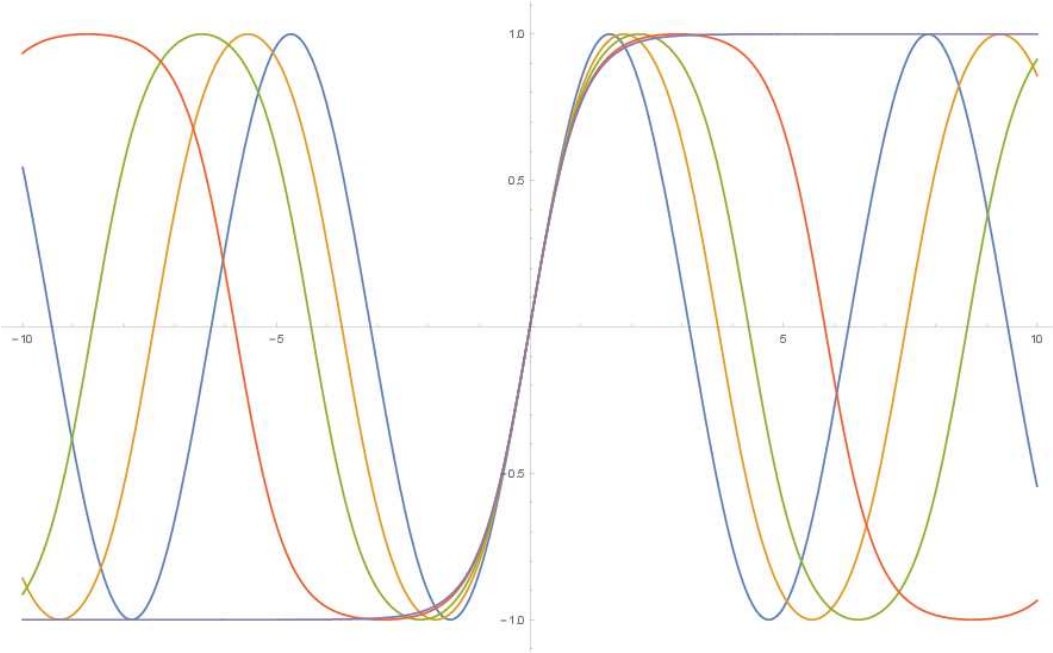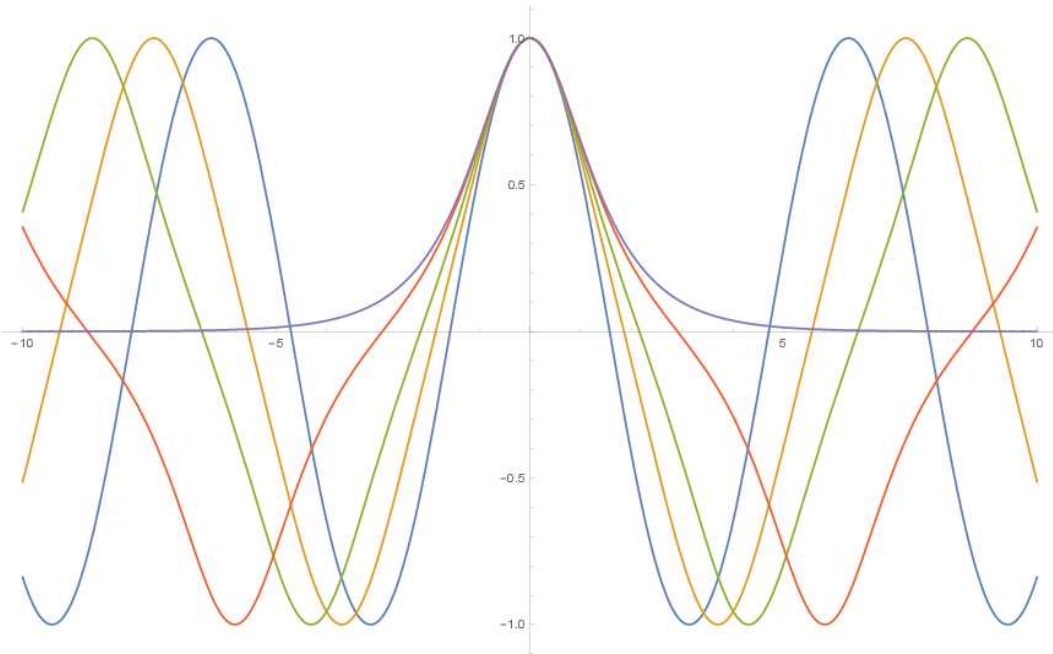
Figure D.1: Jacobi sn; for k=0, 0.5, 0.75, 0.95, 1
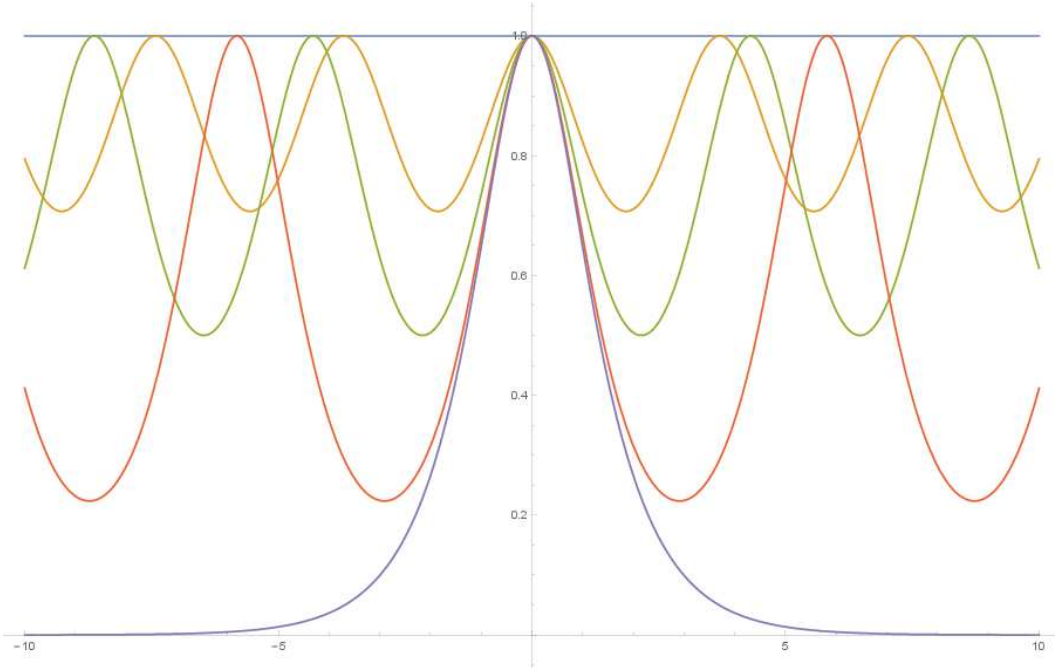

Figure D.2: Jacobi cn; for k=0, 0.5, 0.75, 0.95, 1
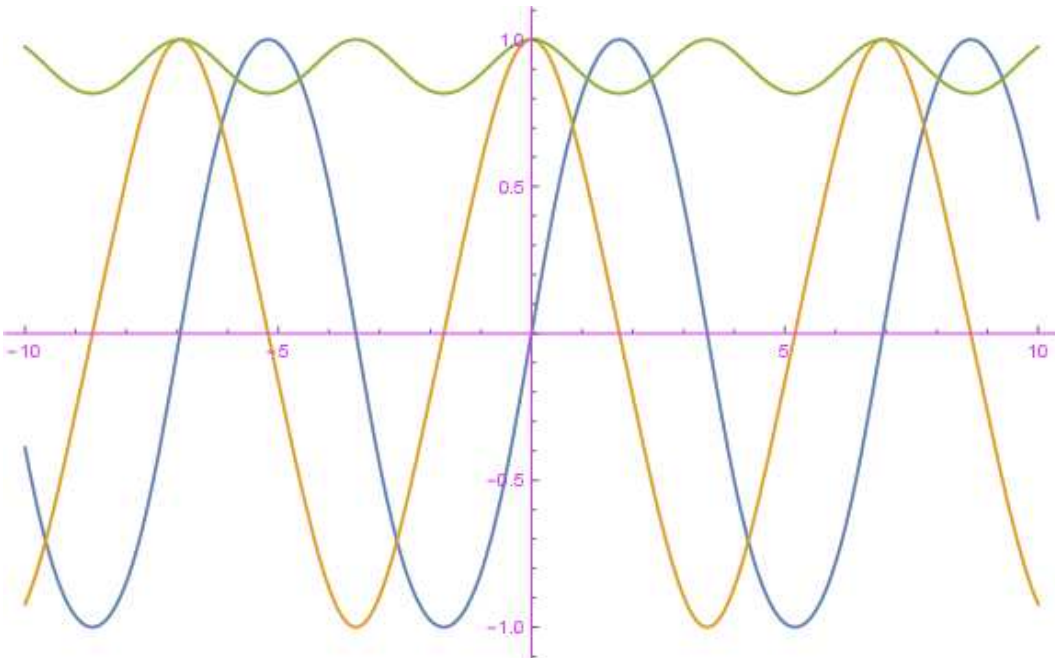
Figure D.3: Jacobi dn; for k=0, 0.5, 0.75, 0.95, 1

Figure D.4: Jacobi Functions k=1/3

Appendix E

Exact finite differences schemes for ODE and PDE

E.1 Exact Finite-difference schemes

Consider a dynamical system described by a first-order scalar equation

$$\frac{du}{dt} = f(u, t, \lambda), \quad u(t_0) = u_0 \tag{E.1.1}$$

where λ is the system parameters and $f(u, t, \lambda)$ is such that a unique solution exists for $0 \leq t < T$. Let the solution to Eq. E.1.1 be

$$u(t) = \phi(\lambda, u_0, t_0, t), \tag{E.1.2}$$

with

$$\phi(\lambda, u_0, t_0, t_0) = u_0. \tag{E.1.3}$$

Denote a finite difference model of Eq.E.1.1

$$u_{k+1} = F(\lambda, h, u_k, t_k), \tag{E.1.4}$$

where $h = \triangle t$; $t_k = hk$; and $u_k \approx u(t_k)$. Let the solution of Eq. E.1.4 written

$$u_k = \psi(\lambda, h, u_0, t_0, t_k), \tag{E.1.5}$$

where

$$\psi(\lambda, h, u_0, t_0, t_k) = u_0. \tag{E.1.6}$$

Definition Equations (E.1.1) and (E.1.4) are said to have the same general solution if and only if

$$u_k = u(t_k) \tag{E.1.7}$$

for $h > 0$

Definition An exact finite difference scheme is one for which the solution of the difference equation has the same general solution as the associated differential equation.

Theorem E.1.1 *The first order differential equation*

$$\frac{du}{dt} = f(u, t, \lambda), \quad u(t_0) = u_0 \tag{E.1.8}$$

has an exact finite difference scheme given by

$$u_{k+1} = \phi[\lambda, u_k, t_k, t_{k+1}] \tag{E.1.9}$$

where the function ϕ is the same as that in equation E.1.2

Proof The group property of the solutions to E.1.8 gives (Appendixe D of [32])

$$u(t + h) = \phi[\lambda, u(t), t, t + h]. \tag{E.1.10}$$

If we make the identifications

$$t \rightarrow t_k, \quad u(t) \rightarrow u_k, \tag{E.1.11}$$

then eq.E.1.10 becomes

$$u_{k+1} = \phi(\lambda, y_k, t_k, t_{k+1}). \tag{E.1.12}$$

This is the required ordinary difference equation that has the same general solution as eq. E.1.8.

E.2 Examples of Exact Schemes for ODE

The following interesting result is often useful in the construction of exact schemes for linear ODE's [33]. Let $u^{(i)}(t)$; $i = 1, 2, ..., N$; be the set of linearly independent functions. It is possible to construct an $N - th$ order linear difference equation that

has the corresponding discrete functions as solutions. $\{u_k^{(i)} \equiv u^{(i)}(t_k)\}$ $t_k =\triangle tk = hk$, The required equation is given by the following determinant

$$
\begin{vmatrix}
u_k & u_k^{(1)} & u_k^{(2)} & \cdots & u_k^{(N)} \\
u_{k+1} & u_{k+1}^{(1)} & u_{k+1}^{(2)} & \cdots & u_{k+1}^{(N)} \\
\vdots & \vdots & \vdots & \vdots & \vdots \\
u_{k+N} & u_{k+N}^{(1)} & u_{k+N}^{(2)} & \cdots & u_{k+N}^{(N)}
\end{vmatrix} = 0
\tag{E.2.1}
$$

As an elementary illustration of the above procedure consider the following examples [10, 11]:

E.2.1 Decay equation

$$
\frac{du}{dt} = -\lambda u, \quad u(0) = u_0
\tag{E.2.2}
$$

with solution $u(t) = u_0 e^{-\lambda u(t)}$ Therefore,

$$
\begin{vmatrix}
u_k & e^{-\lambda t_k} \\
u_{k+1} & e^{-\lambda t_{k+1}}
\end{vmatrix}
\tag{E.2.3}
$$

$$
= e^{-\lambda t_k}
\begin{vmatrix}
u_k & 1 \\
u_{k+1} & e^{-\lambda th}
\end{vmatrix} = 0
\tag{E.2.4}
$$

and the exact scheme for Eq.E.2.2 is

$$
u_{k+1} = e^{-\lambda h} u_k
\tag{E.2.5}
$$

However, a more instructive form can be obtained by subtracting u_k from both sides of Eq.E.2.5

$$
u_{k+1} - u_k = (e^{-\lambda h} - 1)u_k = -\lambda \left(\frac{1 - e^{-\lambda h}}{\lambda} \right) u_k
\tag{E.2.6}
$$

and finally,

$$
\frac{u_{k+1} - u_k}{\left(\frac{1-e^{-\lambda h}}{\lambda} \right)} = -\lambda u_k
\tag{E.2.7}
$$

The discrete first-derivative for the decay equation is given by the expression

$$
\frac{du}{dt} \rightarrow \frac{u_{k+1} - u_k}{\phi}
\tag{E.2.8}
$$

where the denominator function ϕ is

$$\phi = \left(\frac{1 - e^{-\lambda h}}{\lambda} \right)$$

and has the property

$$\phi(\lambda, h) = h + O(\lambda h^2) \tag{E.2.9}$$

We consider the simplest differential equation, the exponential equation,

$$\frac{du}{dt} = \lambda u; \quad u(t_0) = u_0, \tag{E.2.10}$$

where λ is a number not equal to 0. The solution of this equation is given by,

$$u(t) = u_0 e^{\lambda(t-t_0)}.$$

We assume that the initial condition is $u(t_k) = u_k$ and evaluating the solution in $k + 1$, $u(t_{k+1}) = u_{k+1}$, we get that the equation (E.2.10) is equivalent to the following difference equation:

$$u_{k+1} = u(t_{k+1}) = u_k e^{\lambda(\Delta t)}, \tag{E.2.11}$$

where $\Delta t = t_{k+1} - t_k$. Subtracting u_k on both sides of the equation (E.2.11), multiplying by λ, and doing some algebraic manipulations, we get,

$$\frac{u_{k+1} - u_k}{(e^{\lambda \Delta t} - 1)/\lambda} = \lambda u_k. \tag{E.2.12}$$

With an analogous process, we obtain this equivalent equation,

$$\frac{u_{k+1} - u_k}{(1 - e^{-\lambda \Delta t})/\lambda} = \lambda u_{k+1}. \tag{E.2.13}$$

So, equations (E.2.12) and (E.2.13) correspond to two exact nonstandard finite difference schemes.

For these schemes the discrete representation for the first order derivative is,

$$\frac{du}{dt} \approx \frac{u_{k+1} - u_k}{\varphi(\Delta t)},$$

where

$$\varphi(\Delta t) = \frac{e^{\lambda \Delta t} - 1}{\lambda} \quad o \quad \varphi(\Delta t) = \frac{1 - e^{-\lambda \Delta t}}{\lambda}$$

and u can be replaced by u_k in the scheme (E.2.12) or by u_{k+1} in the scheme (E.2.13).

E.2.2   The harmonic oscillator differential equation

We consider the harmonic oscillator differential equation

$$\frac{d^2u}{dt^2} + w^2u = 0 \tag{E.2.14}$$

where w is a real constant. The two linearly independent solutions are

$$u^{(1)}(t) = cos(wt), \ \ and \ \ u^{(2)}(t) = sin(wt),$$

or in complex form

$$\bar{u}^{(1)}(t) = e^{iwt}, \ \ and \ \ \bar{u}^{(2)}(t) = e^{-iwt}.$$

Therefore

$$\begin{vmatrix} u_k & e^{iwhk} & e^{-iwhk} \\ u_{k+1} & e^{iwh(k+1)} & e^{-iwh(k+1)} \\ u_{k+2} & e^{iwh(k+2)} & e^{-iwh(k+2)} \end{vmatrix} = 0, \tag{E.2.15}$$

and

$$u_{k+2} - [2cos(wh)u_{k+1}] + u_k = 0. \tag{E.2.16}$$

Shifting downward the index k by one unit and using the identity

$$2cos(wh) = 2 - 4sin^2(wh/2),$$

Eq.E.2.16 can be put in the form

$$\frac{u_{k+1} - 2u_k + u_{k-1}}{(4/w^2)sin^2(hw/2)} + w^2u_k = 0. \tag{E.2.17}$$

This is the exact finite difference scheme for E.2.14

E.3   Examples of Exact Schemes for PDE

We now turn to some examples of partial differential equations for which exact discrete models exists.

E.3.1 Non linear reaction-advection equation

Consider the nonlinear reaction-advection equation

$$u_t + u_x = u(1 - u), \tag{E.3.1}$$

with the initial value

$$u(x, 0) = f(x) \tag{E.3.2}$$

where $f(z)$ is bounded with a bounded derivative. The nonlinear transformation

$$u(x, t) = \frac{1}{w(x, t)} \tag{E.3.3}$$

reduces Eq.E.3.1 to the linear equation

$$w_t + w_x = 1 - w. \tag{E.3.4}$$

The general solution of this equation can be easily determined by standard methods [34]. It is

$$w(x, t) = g(x - t)e^{-t} + 1, \tag{E.3.5}$$

where g(z) is an arbitrary function of z having a bounded firs derivative. Imposing the initial condition of Eq. E.3.2 allows g to be calculated, i.e,

$$g(x) + 1 = \frac{1}{f(x)} \tag{E.3.6}$$

or

$$g(x) = \frac{1 - f(x)}{f(x)}. \tag{E.3.7}$$

Using this result with Eqs.E.3.3 and E.3.5, we can obtain the solution to Eqs E.3.1 and E.3.2; it is given by the expresion

$$u(x, t) = \frac{f(x - t)}{e^{-t} + (1 - e^{-t})f(x - t)}. \tag{E.3.8}$$

To proceed, we firt construc the exact finite-difference scheme for the unidirectional wavw equation

$$u_t + u_x = 0. \tag{E.3.9}$$

the general solution of this equation is [34]

$$u(x, t) = H(x - t), \tag{E.3.10}$$

where H is an arbitrary function. Now the partial difference equation

$$u_m^{k+1} = u_{m-1}^k \tag{E.3.11}$$

has as its general solution an arbitrary function of $(m - k)$ [33], i.e.,

$$u_m^k = F(m - k). \tag{E.3.12}$$

if we impose the condition

$$\triangle x = \triangle t, \tag{E.3.13}$$

then Eq. E.3.11 can be rewritten in the following form

$$\frac{u^{k+1} - u_m^k}{\beta(\triangle t)} + \frac{u_m^k - u_{m-1}^k}{\beta(\triangle x)} = 0, \tag{E.3.14}$$

where $\beta(z)$ has the property

$$\beta(z) = z + O(z^2), \quad z \to 0. \tag{E.3.15}$$

The general solution of Eq.E.3.14, which is formally equivalent to Eq.E.3.11, is

$$u_m^k = F_1[h(m - k)] = F_1(x_m - t_k), \tag{E.3.16}$$

donde $(h = \triangle x = \triangle t)$ and F_1 is an arbitrary function of its argument. Thus, the exact difference scheme for de unidirectional wave equation is Eq.E.3.14. We can use this result to calculate the exact difference scheme for Eq.E.3.1. Solving Eq.E.3.8 for $f(x - t)$ gives

$$f(x - t) = \frac{e^{-t}u(x, t)}{1 - (1 - e^{-t})u(x - t)}. \tag{E.3.17}$$

Now make the following substitutions in the last equation

$$x \to x_m = (\triangle x)m, \quad t \to t_k = (\triangle t)k, \quad \triangle x = \triangle t = h,$$
$$u(x, t) = u_m^k,$$
$$f(x - t) \to f[h(m - k)] = f_m^k.$$

Doing this gives

$$f_m^k = \frac{e^{-hk}u_m^k}{1 - (1 - e^{-hk})u_m^k}. \tag{E.3.18}$$

However,from Eqs.E.3.11 and E.3.12, we know that f_m^k satisfies the following partial difference equation

$$f_m^{k+1} = f_{m-1}^k.$$

Therefore, we have

$$\frac{e^{-h(k+1)}u_m^{k+1}}{1 - (1 - e^{-h(k+1)})u_m^{k+1}} = \frac{e^{-hk}u_{m-1}^k}{1 - (1 - e^{-hk})u_{m-1}^k}. \qquad \text{(E.3.19)}$$

After some algebraic manipulations, this expression becomes

$$\frac{u_m^{k+1} - u_m^k}{e^{\triangle t} - 1} + \frac{u_m^k - u_{m-1}^k}{e^{\triangle x} - 1} = u_{m-1}^k(1 - u_m^{k+1}),$$

$$\triangle t = \triangle x.$$

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