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Analytical and numerical modeling of the evolution of human papillomavirus infected cells

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ABSTRACT

In this paper analytical properties of solutions of a novel human papillomavirus (HPV) infected cells model is investigated. We show existence, uniqueness and stability of solutions by using standard techniques based on the energy method and the method of upper and lower solutions. For the numerical counterpart, we develop and implement one efficient numerical algorithm scheme which satisfies nonnegative conditions and dynamical consistency. Efficiency of this method is shown by its longtime approximations, which are of paramount importance for a slow process like the evolution of HPV infected cells.

1. Introduction

Human papilloma virus infection is an important disease since it is believed to be the main cause for cervical cancer. The propagation of this infection has been studied and modeled mathematically by many authors, see for example [4,5,7,8,13]. These studies include the use of molecular tools and novel statistical approaches to understand HPV transmission and key steps in the natural history of HPV related malignancies [20]. In general, such models have contributed to understand this serious disease from different perspectives. Moreover, organized arrangements to detect and treat precancerous abnormalities at the early stages of cancer prevent most of cervical cancers in developed countries. However, effective screening programs have been difficult to implement in low-resource settings, which is one reason why cervical cancer mortality rates are much higher in some developing countries.

In the literature there are just few mathematical models of the detection of HPV infection and the evolution of infected cells. In previous works we have developed a family of models for the evolution of infected cells, their detailed formulation can be found in [17,18]. Subsequent works have been devoted to develop analytical and numerical methods in order to obtain approximations that can be used to supply additional information about the evolution of HPV infected cells [9]. Given that such evolution is a slow process, algorithms that can provide reliable long time approximation are heavily required.

The goal of this work is to exhibit the analytical (existence, uniqueness, stability) and numerical (nonnegative, dynamical consistency) properties of solutions for a specific nontrivial model of the evolution of HPV infected cells. The resulting equation consists in an initial-boundary value nonlinear advection–diffusion–reaction problem. The analysis of the model consists in two stages, one analytical and one numerical. Thus, in Section 2, we use standard techniques to show uniqueness and analytical nonlinear stability of the model, see [2,6,14,15]. The existence requires a balance between diffusion and reaction and it is obtained as a consequence of a theorem given in [1]. In Section 3, our purpose is to construct a numerical scheme

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with properties such as nonnegativity and dynamical consistency, in the sense that the approximations and solutions have the same dynamical characteristics. It is important to remark that the proposed numerical algorithm must provide good asymptotic approximations. Therefore, at the end of the section we provide some numerical results in order to illustrate the behavior of our model. Finally, conclusions are given in Section 4.

2. Analytical modeling: nonlinear stability, existence and uniqueness

For any natural number $N \geq 2$ there is a family of equations that models the evolution of HPV infected cells, see [17], given by

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

where $\eta(\alpha, t)$ represents the density of HPV infected cells at the level of infection α at time t and P_{N+1} and Q_{N-1} are polynomials in η of degree $N+1$ and $N-1$ respectively.

From that family we consider the following initial boundary problem

$$\frac{\partial \eta}{\partial t} = c_1\frac{\partial \eta}{\partial \alpha} + c_2\frac{\partial^2 \eta}{\partial c^2} + c_3\eta\frac{\partial \eta}{\partial \alpha} + c_4\eta^2 + c_5\eta^3, \quad 0<\alpha<1, \quad 0<t<T. \tag{1}$$

$$\eta(\alpha,0) = f(\alpha), \qquad 0<\alpha<1,$$
$$\eta(0,t) = g(t), \quad \eta(1,t) = h(t), \quad 0<t<T.$$

Where c_2, c_4 and c_5 are positive constants, c_1 and c_3 are negative and the function η_0 describes the profile of an initial patient stage. It is important to remark that in the literature there are many application from different areas where these type of problems appear, see for example [10,16].

2.1. Nonlinear conditional stability

Let us start by defining the concept of conditional nonlinear stability, see [12]. An equilibrium point η_e (in our case $\eta_e = 0$) of a dynamical system is said to be nonlinearly stable if or every $\epsilon > 0$ there is a $\delta > 0$ such that if $||\eta(0) - \eta_e|| < \delta$, then $|\eta(t) - \eta_e|| < \epsilon$ for $t > 0$. This concept is more general than the concept of linear stability, Moreover linear stability does not imply nonlinear stability. Let us prove that $\eta = 0$ is nonlinear stable.

Let us assume that $\| \frac{df}{d\alpha} \|_{L_2[0,1]} < \frac{2c_2}{c_5}$ and that $\|f\|_{L_2[0,1]} < \frac{c_4}{c_2}$. To prove the nonlinear conditional stability we use the Poincaré inequality and the fact that $1 - \frac{c_5}{4c_2}\| \frac{\partial \eta}{\partial \alpha}(\alpha,0)\|^2_{L_2[0,1]} > 0$ to get that

$$\frac{1}{2}\frac{d}{dt}\|\eta\|^2_{L_2[0,1]} \leq -\pi^2\left(1 - \frac{c_5}{4c_2}\left\|\frac{\partial \eta}{\partial \alpha}(\alpha,0)\right\|^2_{L_2[0,1]}\right)\|\eta\|^2_{L_2[0,1]}.$$

Setting $K = -\pi^2\left(1 - \frac{c_5}{4c_2}\left\|\frac{\partial \eta}{\partial \alpha}(\alpha,0)\right\|^2_{L_2[0,1]}\right)\|\eta\|^2_{L_2[0,1]}$ we obtain

$$\|\eta\|^2_{L_2[0,1]} \leq e^{-2Kt}\|f\|^2_{L_2[0,1]}.$$

Which implies that

$$\|\eta(\alpha,t)\|_{L_2[0,1]} \to 0 \text{ as } t \to \infty,$$

at least exponentially fast.

This nonlinear conditional stability property is very important since it reflects the fact that the immune system is able to get rid of the HPV infection as long as the initial profile is small enough. In practical terms, such property does not establish how small the initial condition must be.

2.2. Existence and uniqueness

2.2.1. Existence

Given that the coefficients in (1) and the reaction terms are smooth functions, the existence of solutions can be obtained directly from the following theorem proven in [1]:

Theorem 2.1. *Let G be a smooth, bounded domain in the Euclidean n-space. Consider the differential equation*

$$\sum_{i,j=1} a_{ij}(x,u,\text{grad}\,u)\frac{\partial^2 u}{\partial x_i \partial x_j} + \sum_{k=1} b_k(x,u,\text{grad}\,u)\frac{\partial u}{\partial x_k} = f(x,u,\text{grad}\,u)$$

with the following assumptions: