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A model for HVP infected cells at different lesion discrete stages

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Abstract. In this work we propose models for the interaction of Human Papillomanvirus 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.

Keywords: Human Papillomavirus, cervical cancer model, Discrete stages.
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1. 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, [5]. The development of infected cells and the control mechanisms involved are very complex and the advance of mathematical models of HVP infected cell populations is relatively moderate. A number of models have been presented, most of them are based on a preventive approach [1, 2, 3, 4], 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.

2. The Model

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 an approach based in a discrete model for the cell cycle presented by Takahashi [8] and assuming analyticity in the functions f and g, a general model can be written as:

$$\begin{aligned}
\frac{dN_1(t)}{dt} &= f_1(N_1) - g_1(N_1) - M_1(N_1) = k_1 N_1 + A_1 N_1^2 + O(N_1^3), \\
\frac{dN_2(t)}{dt} &= g_1(N_1) - g_2(N_2) - M_2(N_2) = k_2(N_1 - N_2) + A_1 N_1^2 - B_2 N_2^2 + O(N_1^3) + O(N_2^3), \\
&\vdots \\
\frac{dN_m(t)}{dt} &= g_m(N_{m-1}) - g_m(N_m) - M_m(N_m) = k_m(N_{m-1} - N_m) + A_{m-1} N_{m-1}^2 - B_m N_m^2.
\end{aligned} \tag{1}$$

3. Results

Consider the linear model obtained from (1) (by choosing $A_j = B_j = 0$). The solutions of this homogeneous linear system are of the form

$$\begin{pmatrix} N_1(t) \\ \vdots \\ N_m \end{pmatrix} = \begin{cases} c_0 \mathrm{e}^{k_1 t}\mathbf{v}_1 + \sum_{s=1}^{m-1} c_s \mathrm{e}^{-k_s t}\mathbf{v}_s, & \text{if } k_s \text{ are different} \\ c_1 \mathrm{e}^{kt}\mathbf{w}_0 + \mathrm{e}^{-kt}\sum_{j=2}^{m}\left(\sum_{s=j}^{m-1} c_s \frac{t^{s-j}}{(s-j)!}\right)\mathbf{w}_j, & \text{if } k_s \text{ are equal.} \end{cases}$$

Those solutions exponentially diverge in the direction of $\mathbf{v}_1$, namely $\left(\frac{2\prod_{n=1}^{m-1}(k_1+k_{n+1})}{\prod_{n=2}^{m-1} k_n}, \frac{\prod_{n=1}^{m-1}(k_1+k_{n+1})}{\prod_{n=2}^{m-1} k_n}, \frac{\prod_{n=2}^{m-1}(k_1+k_{n+1})}{\prod_{n=3}^{m-1} k_n}, \frac{\prod_{n=3}^{m-1}(k_1+k_{n+1})}{\prod_{n=4}^{m-1} k_n}, \ldots, 1\right)^T$ in the case of different eigenvalues and in the direction of $\mathbf{w}_0 = (2, 1, \ldots, 1/2^m)^T$ for equal eigenvalues.From this result we immediately conclude that the number of infected cells growth exponentially for all time, 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 this linear model has been analyzed in the context of pursuit in [7]. Meaning that N_1 follows an independent path in phase space and the rest follows him in a cyclical fashion, that is,

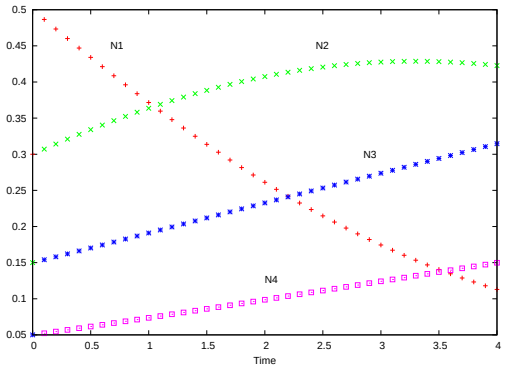

Figure 1: Evolution of different stages varying time

N_j follows N_{j-1} for $j = 2, \ldots, m$. In this way, if we replace the first equation in system (1) 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.

Considering the linear and quadratic terms in (1) we obtain a more realistic model. Considering A_1 negative in the first equation of (1) 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. It is important to remark that the total number of cells is almost constant, so we impose the condition that $\sum_{j=1}^{m} N_j(t)$ =constant. The coupled differential equations in the model were analyzed numerically by using a classical Runge-Kutta method of order 4. In Figure 1 we present the time evolution of the solution of system for $m = 4$. The initial conditions are $N_1 = 0.5$, $N_2 = 0.3$, $N_3 = 0.15$, $N_4 = 0.05$, which correspond to initial conditions for a patient with mild dysplasia. As can be seen, 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. Similar qualitative behavior is obtained for models with higher nonlinear terms included.

4. Conclusions

In this work, we presented a reliable model for the interaction of HPV infected cells. The model provide useful information regarding the evolution of the infected cells. It is only a first step to provide clinicians with a reliable benchmark. More research needs to be done to refine our presented model. A step in this direction is the development of models with a continuous number of stages for the natural history of cervical cancer [6].

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