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Research Article

NUMERICAL SOLUTION OF THE MATHEMATICAL MODELLING OF TUMOR GROWTH DURING THE PROCESS OF ANGIOGENESIS

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ABSTRACT

The study focuses on mathematical modelling of tumor progress during angiogenesis process. It is the stage through which the tumor changes from being avascular to vascular. Nonlinear partial differential equations are used to describe the interactions between endothelial cells, fibronectin and tumor angiogenetic factors in the development of new blood vessels. The model aim to explain the spatial distribution of endothelial cells through diffusion, proliferation, chemotaxis, haptotaxis, and cell loss due to decay. The continuous equations obtained are solved using the Finite Difference method.

INTRODUCTION

Cancer is a life nasty disease of epidemic extents. World Cancer Reporthighlighted that trends in cancer escalating rate and mortality worldwide is growing quickly. The success of a tumor treatment be subject to on it being suitable for the type of tumor involved. Therefore it is very necessary to understand and recognize the different forms of tumors, and the processes and stages involved in their development and growth.

Tumor develop in three main stages, the avascular phase (benign), the vascular phase and the malignant phase (cancer). The stages are illustrated in Figure 1, and are described below.

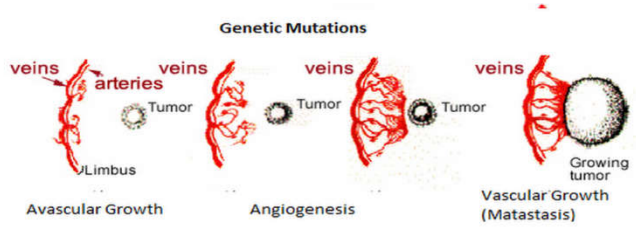

Figure 1 Stages of tumor invasion

A tumor in the avascular phase is non-cancerous (benign). In this stagethe tumor is less than about two millimeters in diameter, it is improbable to be harmful; if it grows in a critical body organ then it will only cause serious health problems or if it becomes too large. However without its own blood vessels the survival of any tumor is depends on diffusion of oxygen and nutrients from neighboring blood vessels and for removal of waste products to these blood vessels [1]. So at this stage, a tumor usually grows very slowly and does not proliferate or spread to other tissues or organs. In this early stage a tumor can usually be removed or be treated with radiation. When removed, benign tumors do not usually regrow. Though, if they are not treated or removed at this stage, they may develop into cancer.

MATHEMATICAL MODELLING

The largest blood vessels are arteries and veins, which have a thick, tough wall of connective tissue and many layers of smooth muscle cells. The wall is lined by an exceedingly thin single sheet of endothelial cells, the endothelium, separated from the surrounding outer layers by a basal lamina. Thus, endothelial cells line the entire vascular system, from the heart to the smallest capillary, and control the passage of materialsand the transit of white blood cells into and out of the bloodstream.

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Angiogenesis is initiated when a tumor discharges a diffusible tumor angiogenic factors into surrounding tissues (the extra cellular matrix), which eventually reach nearby blood vessels. These factors allow degradation of the basement membrane lining the blood vessels, thereby releasing endothelial cells from the lining. As the endothelial cells are stimulated to follow the chemical gradient of tumor angiogenic factors so they migrate towards the tumor until they form capillary sprouts which eventually penetrate it. This chemotatic response to the tumor angiogenic factors secreted by a tumor, is also enhanced by fibronectin, which is secreted by the endothelial cells.

We consider a situation in which a restricted tumor triggers an angiogenic response from a neighboring blood vessel. The process can be modelled in terms of concentration of tumor angiogenic factors, endothelial cell density and the concentration of fibronectin. Fick's law is used to model the diffusion of the tumor angiogenic factors, which creates the concentration gradient.

When formulating equations that model endothelial cell development, including authors like Anderson and Chaplain [1] and Holmes and Sleeman [2] consider the cell flux. Cell flux is a term used to describe the movement of endothelial cells. Some authors consider two factors which influence the cellular movement. These are first diffusion, which is the random molecular movement of chemicals, and then chemotaxis, which is a directional movement of cells along a chemical gradient [30].

In this work we will derive the total cell flux through on spatial position *x* during time *t*. $G(x,t)$ represents a tumor angiogenic factor concentration. Similarly, $F(x,t)$ and $C(x,t)$ will represents fibronectin and endothelial concentration respectively. [1,2,5,6]. Following the work of Anderson and Chaplain [1] and Edelstein-Keshet [7], we formulated an equation governing the total cell flux as follows:

$$C_{Total} = C_{Random} + C_{Chemo} + C_{Hapto} \tag{1}$$

where C_{Total} represents the total collection of endothelial cells present, C_{Random} represents endothelial cells due to random diffusion, C_{Chemo} represents endothelial cells due to chemotaxis, C_{Hapto} represent cells due to haptostaxis. The random flux is given as

$$C_{Random} = -D_c \nabla C, \tag{2}$$

Where D_E represents a cell random positive constant and ∇A is the rate of change of the concentration of of endothelial cells. The chemotatic flux is given by:

$$C_{Chemo} = B(C) C \nabla G \tag{3}$$

Where $B(C)$ is the term for chemotaticfunction. C is a term for endothelial cells and $\nabla G$is the rate of change of tumor angiogenic factors. Following a receptor kinetic law, the chemotatic function can then be defines as:

$$B(C) = B_o \frac{K_1}{K_1 + C} \tag{4}$$

where B_o is the chemotatic coefficient and K_1 is a positive constant. The haptotatic flux can also be defined as follows:

$$C_{Hapto} = \rho_1 C \nabla F \tag{5}$$

where ρ_1 is a positive constant called the haptotatic coefficient and ∇F is the rate of change of fibronection concentration. By substituting Equations (2), (3), (4) and (5) into (1) we get the equation for the total cell flux as:

$$C_{Total} = -D_c \nabla C + B(C) C \nabla G + \rho_1 C \nabla F \tag{6}$$

where μ is a positive constant associated to maximum loss rate. It can be concluded that the rate of increase of endothelial cell concentration can be written as follows: if $G \le G^*$ no proliferation will take place and

$$\frac{\partial C}{\partial t} = D_C \nabla^2 C - \nabla B_1 \frac{K_1}{K_1 + C} C \nabla G - \nabla \rho_C C \nabla F - \mu C \tag{7}$$

but if $G > G^*$ mitosis will take place and

$$\frac{\partial C}{\partial t} = D_c \nabla^2 C - \nabla B_1 \frac{K_1}{K_1 + C} C \nabla G - \nabla \rho_1 C \nabla F + \rho_2 C \left(1 - \frac{C}{C_o}\right)\left(\frac{G^* - G}{G_o}\right) - \mu C \tag{8}$$

for $G^* \le G_o$.

We accept that the tumor angiogenic factors diffuses, depletes and decays. Thus the rate of change of tumor angiogenic factors concentration in a specific region can be denoted by:

$$\frac{\partial G}{\partial t} = D_G \nabla^2 G - f(G) g(C) - h(G) \tag{9}$$

where D_G , is tumor angiogenic factors diffusion coefficient. The function $f(G)$ represents the local uptake of tumor angiogenic factor by endothelial cells, which is linearly dependent on cell density and so it can be expressed as follows:

$$f(G) = \frac{QG}{K_{\max} + G} \tag{10}$$

where $K_{\max}$ is the Michaelis–Menten kinetic law constant which is equivalent to the concentration of tumor angiogenic factors required to achieve a reaction rate of $Q/2$, where Q is maximum reaction uptake rate.

The function $g(C)$ is a strongly increasing function which can be expressed as $g(C) = C/C_o$, where C_o is the maximum amount of endothelial cells that can use the tumor angiogenic factors within the specified boundary with zero flux boundary condition. $h(G)$ is the decay rate for tumor angiogenic factors which are taken as:

$$h(G) = dG \tag{11}$$

where d is the tumor angiogenic factors decay rate. The rate of change of the tumor angiogenic factor then written as: [1, 2, 3]

$$\frac{\partial G}{\partial t} = D_G \nabla^2 G - \left(\frac{QG}{K_{\max} + G} \right) C/C_o - dG \tag{12}$$

Now, we assume that the equation governing the rate of change of fibronectin concentration has terms for: diffusion, secretion by endothelial cells, loss due to cell-cell adhesion and loss due to decay. Thus it can be expressed as follows:

$$\frac{\partial F}{\partial t} = D_F \nabla^2 F + \frac{\alpha_F C_F}{\beta + F} - s_F CF - \lambda_F Fa \tag{13}$$

where α_F is the secretion rate, β is a positive constant, s_F is the uptake rate of fibronectin by endothelial cells and λ_F is the decay rate of fibronectin. The term $\frac{\alpha_F C_F}{\beta + F} a$ represents the concentration of fibronectin which is secreted by endothelial cells. Models already developed do not consider concentration of oxygen and glucose because as Ward and King [11] suggest it can be neglected in the interior of larger spheroids.

Numerical Solution

The systems of equations shown in Equations (8), (12) and (13) are all nonlinear parabolic differential equations. They are one space dimensional, because x is the only independent spatial variable involved. Solving them needs that they are first nondimensionalized as in Holmes and Sleeman [2]. The distance from the parent blood vessel to tumor is given to be L is, and the time $\tau = L^2 / D_G$, and by setting appropriate reference variables. Therefore, we obtain

$$\bar{G} = \frac{G}{G_o}, \bar{C} = \frac{C}{C_o}, \bar{F} = \frac{F}{F_o}, \bar{x} = \frac{x}{L}, \bar{t} = \frac{t}{\tau},$$

We also

$$\omega = \frac{TQ}{G_o}, \gamma = \frac{k_m}{G_o}, \sigma = \frac{Td}{G_o}, \xi = \frac{\beta}{F_o},$$

$$\varepsilon = \frac{\alpha_F T C_o}{F_o}, \eta = TS_F C_o, \kappa = \lambda_F T, \psi = \mu T,$$

$$\rho = \frac{\rho_1 T G_o}{L^2}, \rho_o = \rho_2 T, B(1) = \frac{B_o T G_o}{L^2}, d_F = \frac{TD_F}{L^2}, d_G = \frac{TD_G}{L^2}, d_C = \frac{TD_C}{L^2}$$ [2].

Dropping the bars, the following non-dimensionalized systems are obtained from (12), (13) and (8) respectively:

$$\frac{\partial F}{\partial t} = d_F \frac{\partial^2 F}{\partial x^2} + \frac{\varepsilon CF}{\xi + F} - \eta CF - \kappa F, \tag{14}$$

$$\frac{\partial G}{\partial t} = d_G \frac{\partial^2 G}{\partial x^2} - \left(\frac{\omega CG}{\gamma + G} \right) - \sigma G, \tag{15}$$

$$\frac{\partial C}{\partial t} = d_C \frac{\partial^2 C}{\partial x^2} - B_o \frac{K_1}{K_1 + C} \frac{\partial C \partial G}{\partial x \partial x} - C \frac{\partial^2 G}{\partial x^2} - \rho \frac{\partial C \partial F}{\partial x \partial x} - C \frac{\partial^2 F}{\partial x^2} + \rho_o C(1 - C) I(G) - \psi C \tag{16}$$

The initial condition that will be used in this work are derived from those given by Holmes and Sleeman [2] and Eleondou [3].

Finite Difference Scheme to the Model for Fibronectin

When solving equation (18) using the finite difference scheme it becomes:

$$\frac{F_i^{i+1} - F_i^j}{\Delta t} = d_F \frac{\left[F_{i-1}^{j+1} - 2F_i^{j+1} + F_{i+1}^{j+1} + F_{i-1}^j - 2F_i^j + F_{i+1}^j \right]}{2\Delta x^2} + \varepsilon \frac{C_i^j F_i^j}{\xi + F_i^j} - \eta C_i^j F_i^j - k \frac{F_i^{j+1} - F_i^j}{2}$$

Let $1 + 2M + D = \upsilon_o$ and $(\zeta_1)_i^j = 1 - 2P + R_i^j - V_i^j + R$. We then obtain a tridiagonal matrix like this for $j = 0,1,2....n$

$$\begin{pmatrix} \zeta_o & -P & o & o & o & o \\ -P & \zeta_o & -P & o & o & o \\ o & -P & \zeta_o & -P & o & o \\ . & . & . & . & . & . \\ . & . & . & . & . & . \\ o & o & o & -P & \zeta_o & -P \\ o & o & o & o & -P & \zeta_o \end{pmatrix} \begin{pmatrix} F_1^{j+1} \\ F_2^{j+1} \\ F_3^{j+1} \\ . \\ . \\ F_{i-1}^{j+1} \\ F_i^{j+1} \end{pmatrix}$$

$$= \begin{pmatrix} (\upsilon_1)_i^j & P & o & o & o & o \\ P & (\upsilon_1)_i^j & P & o & o & o \\ o & P & (\upsilon_1)_i^j & P & o & o \\ . & . & . & . & . & . \\ . & . & . & . & . & . \\ o & o & o & P & (\upsilon_1)_i^j & P \\ o & o & o & o & P & (\upsilon_1)_i^j \end{pmatrix} \times \begin{pmatrix} F_1^j \\ F_2^j \\ F_3^j \\ . \\ . \\ F_{i-1}^j \\ F_i^j \end{pmatrix} + \begin{pmatrix} 2P \times F_1^j \\ o \\ o \\ . \\ . \\ o \\ 2P \times F_i^j \end{pmatrix} \tag{17}$$

Finite Difference Scheme to the Model for Tumor Angiogenic Factors

As in the previous section, the solution of equation (15) is obtained by applying the Finite difference scheme in discrete form as:

$$\frac{G_i^{i+1}-G_i^j}{\Delta t}=d_A\frac{\left[G_{i-1}^{j+1}-2G_i^{j+1}+G_{i+1}^{j+1}+G_{i-1}^j-2G_i^j+G_{i+1}^j\right]}{2\Delta x^2}+\omega\frac{C_i^jG_i^j}{\gamma+G_i^j}-\sigma\frac{G_i^{j+1}-G_i^j}{2} \quad (18)$$

Let $1+2M+D=\upsilon_o$ and

$(\upsilon_1)_i^j=1-2M+X_i^j+D$ *For* $j=0,1,2,3,....n$, Equation (18) can be written as a tridiagonal matrix, like shown below:

$$\begin{pmatrix}\upsilon_o & -M & o & o & o & o\\ -M & \upsilon_o & -M & o & o & o\\ o & -M & \upsilon_o & -M & o & o\\ . & . & . & . & . & .\\ . & . & . & . & . & .\\ o & o & o & -M & \upsilon_o & -M\\ o & o & o & o & -M & \upsilon_o\end{pmatrix}\begin{pmatrix}G_1^{j+1}\\ G_2^{j+1}\\ G_3^{j+1}\\ .\\ .\\ G_{i-1}^{j+1}\\ G_i^{j+1}\end{pmatrix}$$

$$=\begin{pmatrix}(\upsilon_1)_i^j & M & o & o & o & o\\ M & (\upsilon_1)_i^j & M & o & o & o\\ o & M & (\upsilon_1)_i^j & M & o & o\\ . & . & . & . & . & .\\ . & . & . & . & . & .\\ o & o & o & M & (\upsilon_1)_i^j & M\\ o & o & o & o & M & (\upsilon_1)_i^j\end{pmatrix}\times\begin{pmatrix}G_1^j\\ G_2^j\\ G_3^j\\ .\\ .\\ G_{i-1}^j\\ G_i^j\end{pmatrix}+\begin{pmatrix}2M\times G_1^j\\ o\\ o\\ .\\ .\\ o\\ 2M\times G_i^j\end{pmatrix} \quad (19)$$

Finite Difference Scheme to the Model for Endothelial Cells

Then applying the Finite difference approximation to equation, We get

$$\frac{C_i^{j+1}-C_i^j}{\Delta t}=d_C\frac{\left[C_{i-1}^{j+1}-2C_i^{j+1}+C_{i+1}^{j+1}+C_{i-1}^j-2C_i^j+C_{i+1}^j\right]}{2(\Delta x)^2}$$
$$-\frac{B(1)K_1}{K_1+C_i^j}\times-\frac{\left[C_{i+1}^{j+1}-C_{i-1}^{j+1}+C_{i+1}^j+C_{i-1}^j\right]}{4(\Delta x)}\times\frac{\left[G_{i+1}^{j+1}-G_{i-1}^{j+1}+G_{i+1}^j+G_{i-1}^j\right]}{4(\Delta x)}$$
$$+C_i^jB(1)K_1\frac{\left[G_{i-1}^{j+1}-2G_i^{j+1}+G_{i+1}^{j+1}+G_{i-1}^j-2G_i^j+G_{i+1}^j\right]}{2(\Delta x)^2}$$
$$-\rho\frac{\left[C_{i+1}^{j+1}-C_{i-1}^{j+1}+C_{i+1}^j+C_{i-1}^j\right]}{4(\Delta x)}\times\frac{\left[F_{i+1}^{j+1}-F_{i-1}^{j+1}+F_{i+1}^j+F_{i-1}^j\right]}{4(\Delta x)}$$
$$+C_i^j-\rho\frac{\left[F_{i-1}^{j+1}-2F_i^{j+1}+F_{i+1}^{j+1}+F_{i-1}^j-2F_i^j+F_{i+1}^j\right]}{2(\Delta x)^2}$$
$$+\rho_oC_i^j\left(1-C_i^j\right)I\left(G_i^j\right)-\psi\frac{C_i^{j+1}-C_i^j}{2} \quad (20)$$

Using equation (20), which is the conservation equation for endothelial cells,After substituting for for $j=1,2,3,.....,n$ in equation (34) then we got system of linear equations which is then expressed as this tridiagonal matrix:

$$\begin{pmatrix}\alpha_o & (\alpha_2)_i^j & o & o & o & o\\ (\alpha_1)_i^j & \alpha_o & (\alpha_2)_i^j & o & o & o\\ o & (\alpha_1)_i^j & \alpha_o & (\alpha_2)_i^j & o & o\\ . & . & . & . & . & .\\ . & . & . & . & . & .\\ o & o & o & (\alpha_1)_i^j & \alpha_o & (\alpha_2)_i^j\\ o & o & o & o & (\alpha_1)_i^j & \alpha_o\end{pmatrix}\begin{pmatrix}C_1^{j+1}\\ C_2^{j+1}\\ C_3^{j+1}\\ .\\ .\\ C_{i-1}^{j+1}\\ C_i^{j+1}\end{pmatrix}=$$
$$\begin{pmatrix}(\alpha_3)_i^j & (\alpha_5)_i^j & o & o & o & o\\ (\alpha_4)_i^j & (\alpha_3)_i^j & (\alpha_5)_i^j & o & o & o\\ o & (\alpha_4)_i^j & (\alpha_3)_i^j & (\alpha_5)_i^j & o & o\\ . & . & . & . & . & .\\ . & . & . & . & . & .\\ o & o & o & (\alpha_4)_i^j & (\alpha_3)_i^j & (\alpha_5)_i^j\\ o & o & o & o & (\alpha_4)_i^j & (\alpha_3)_i^j\end{pmatrix}\times\begin{pmatrix}C_1^j\\ C_2^j\\ C_3^j\\ .\\ .\\ C_{i-1}^j\\ C_i^j\end{pmatrix}+\begin{pmatrix}2Q\times C_1^j\\ o\\ o\\ .\\ .\\ o\\ 2Q\times C_i^j\end{pmatrix}$$
(21)

The Method has been proved to be stable and reliable. Its stability has been proved in [40].

RESULTS AND DISCUSSION

Matrices (17), (19) and (21), were solved numerically using Matlab software. Parameter values, boundary and initial conditions are taken from published literature, and the results obtained are discussed below.Matrix (19) generated earlier in this chapter was then converted to Matlab codes, following previously published approaches [4,8] for generating Matlab codes. Accordingly Figure 1 illustrates the concentration of tumor angiogenic factors in the space between the tumor and blood vessel during angiogenesis specifically at 1, 3, 7, 9 and 10 days from the start. In this work we assume the angiogenesis process is completed after 10 days. Results indicate that the concentration of tumor angiogenic factor in the space between the tumor and blood vessel at different times. Results indicate that as time progresses, that is as the value of *t* increases, the level of tumor angiogenic factors decreases. This would occur because some of the tumor angiogenic factors was used to degrade the basement membrane on the blood vessel and other chemical is lost due to decay.

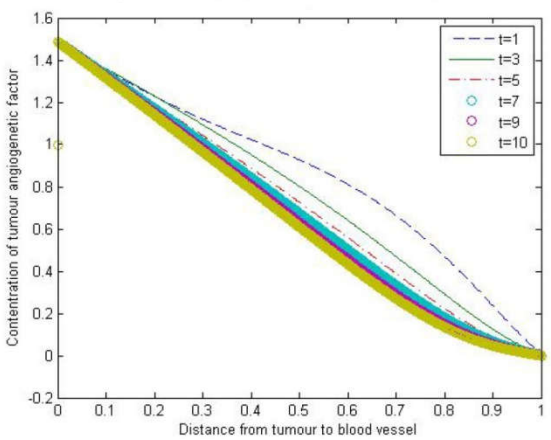

Figure 1 Spatial Distribution of the Concentration of Tumor Angiogenic Factors at different times

Matrix (17) generated earlier in this chapter was then converted to matlab codes, following previously published approaches [4,8] for generating Matlab codes.Figure 2 illustrates the concentration of fibronectin in the region during different times of angiogenesis; that is 1, 3, 5, 7, 9 and 10 days. The graphs indicates that, fibronectin behaved in the same way as endothelial cells. Graphs indicate that as time progresses, fibronectin concentration decreases with distance away from the blood vessel.

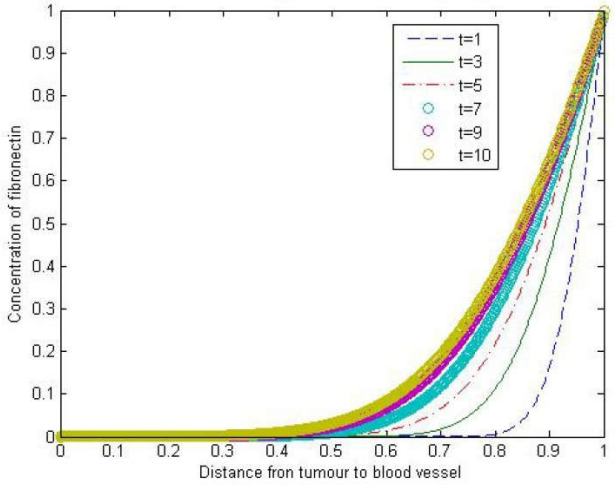

Figure 2 Spatial Distribution of Fibronectin concentration at Different Times

Matrix (21) producedprevious in this section was then converted to Matlab codes, following previously published methodologies [4,8] for generating Matlab codes. Figure 3explains the concentration of endothelial cells in the region during these different times of angiogenesis; 1, 3, 5, 7, 9 and 10 days.

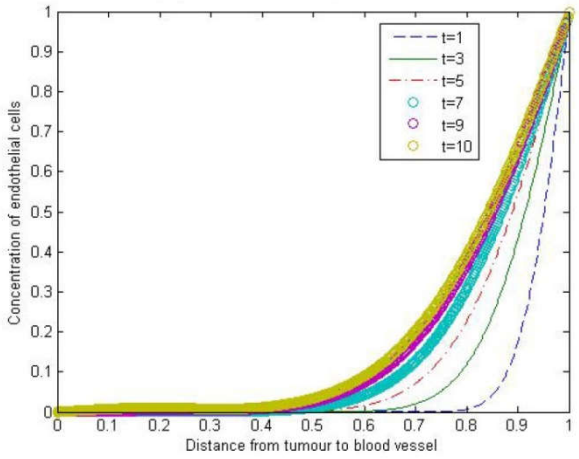

Figure 3 Concentration of Endothelial Cells at Different Times

Results shows that the endothelial cells discharge from the blood vessel and they migrate towards the tumor. It is noticed that as time progresses the distance between the endothelial cells and the tumor decreases until and they ultimately reach the tumor. In this way they complete the process of angiogenesis.

CONCLUSION

Parabolic partial differential equations governing the conservation of tumor angiogenic factors, fibronectin and endothelial cells have been developed. A finite difference method, is applied to solve them. The matrices acquired are then simulated with the help of Matlab, using parametric values already published or those chosen to suit this study. The results designate the concentration of tumor angiogenic factors is greater nearby the tumor boundary, but moves towards the blood vessel as time progresses. At the same spellfibronectin and endothelial cells are also detected to migrate towards the tumor, and eventually reach it. That indicates that angiogenesis is the process of transition for the tumor from being avascular to become vascular. As such this confirms that our model is realistic.

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