Journal of Applied Mathematics and Physics, 2022, 10, 1013-1018
https://www.scirp.org/journal/jamp
ISSN Online: 2327-4379
ISSN Print: 2327-4352

Existence and Uniqueness of Almost Periodic Solution for a Mathematical Model of Tumor Growth

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How to cite this paper: Bu, C. (2022) Existence and Uniqueness of Almost Periodic Solution for a Mathematical Model of Tumor Growth. *Journal of Applied Mathematics and Physics*, **10**, 1013-1018.
https://doi.org/10.4236/jamp.2022.104068

Received: March 7, 2022
Accepted: April 3, 2022
Published: April 6, 2022

Abstract

This article is concerned with a mathematical model of tumor growth governed by 2nd order diffusion equation $\frac{\partial C}{\partial t} = f(C) + D\nabla^2 C + \lambda S(r,t)$. The source of mitotic inhibitor is almost periodic and time-dependent within the tissue. The system is set up with the initial condition $C(r,0) = C_0(r)$ and Robin type inhomogeneous boundary condition $D\frac{\partial C}{\partial n} + PC = K(r,t)$. Under certain conditions we show that there exists a unique solution for this model which is almost periodic.

Keywords

Mathematical Model of Tumor Growth, Almost Periodic Solution, Robin Boundary Condition, Pullback Attractor, Non-Autonomous Dynamics

1. Introduction

Since 1980, researchers in mathematics and biology have proposed and studied several deterministic mathematical models for tumor growth by diffusion equation. The main assumption is that these models serve as simplified but complementary description for one aspect of a complex biological phenomenon: the growth and stability of tissue. Given some simplified conditions, the study of these models is focused on describing qualitatively the early stages of growth of tissue. The diffusion equation is the type of a linear partial differential equation.

For example, Shymko, Glass [1] [2] and Adam [3] [4] proposed the following model governed by an inhomogeneous diffusion equation

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} - \lambda C + PS(x) \tag{1}$$

with the source term $S(x) = 1 - \frac{2}{L}|x|$ for $|x| \le \frac{L}{2}$ and 0 otherwise. Here L is the initial length of the chalone-producing tissue, being confined to the domain $|x| \le L/2$. The production rate of the chalone is $P > 0$ per unit length, the diffusion coefficient is D and the decay rate is λ which is proportional to its concentration $C(x,t)$. Since $S(x)$ is not constant, the source of mitotic inhibitor is not uniformly distributed within the tissue (in contrast to many earlier results). It was found that stable and unstable regimes of growth become significantly modified from the uniform-source case. Consequently, this model is very sensitive to the type of source term assumed. In fact, many of the existing deterministic models of tumor cell growth are proposed by an ordinary differential equation (ODE) coupled to one or more equations of reaction and diffusion type. The ODE derives from mass conservation applied to the tumor and describes the evolution of the tumor boundary and the reaction-diffusion equations describe the distribution of nutrients (oxygen and glucose) and growth inhibitory factors (chalones) [5] [6].

Clearly, a more realistic model requires a higher dimension because systems governing tumor growth are best served in a three dimensional domain. Consequently, Britton and Chaplain studied a more generalized system below [7].

$$\frac{\partial C}{\partial t} = f(C) + D\nabla^2 C + \lambda S(r) \text{ in } \Omega \times (0,\infty), \tag{2}$$

$$D\frac{\partial C}{\partial n} + PC = 0 \text{ in } \partial\Omega \times (0,\infty),\ P \ge 0 \tag{3}$$

$$C(r,0) = C_0(r) \ge 0 \text{ for } r \in \Omega \tag{4}$$

where $C = C(r,t)$ is the concentration of some chemical inhibitors in a bounded n-dimensional region Ω ($n = 1,2,3$). We note that $D, \lambda > 0, S \ge 0$, P is the permeability of the tissue surface. Using maximum principles for parabolic and elliptic operators, the authors examined the effect of growth inhibitory factor. It was shown that if f, C_0 and Ω satisfy the conditions of the parabolic comparison theorem, then C is always non-negative and unique. Also, the concentration decreases monotonically in the open interval $(0,R)$ provided that $S'(r) \le 0$ and f differentiable with $f' < 0$. This model is certainly a big improvement compared to one-dimensional system.

The following model adds a more general, time-dependent source function $S(r,t)$

$$\frac{\partial C}{\partial t} = f(C) + D\nabla^2 C + \lambda S(r,t) \text{ in } \Omega \times (0,\infty), \tag{5}$$

$$D\frac{\partial C}{\partial n} + PC = 0 \text{ in } \partial\Omega \times (0,\infty),\ P \ge 0, \tag{6}$$

$$C(r,0) = C_0(r) \in L^2(\Omega). \tag{7}$$

Here the source function is time-dependent. The boundary condition is of homogeneous Robin type. Existence and uniqueness of an almost periodic solution for this model were studied in [8] with the following result. If $C_0 \in L^2(\Omega)$ and $f'(C) \le -\alpha < 0, P > 0$, $f(\cdot): H^1(\Omega) \to L^2(\Omega)$ is local Lipschitz continuous, $L^2(\Omega)$-norm of K is uniformly bounded in time, and S is temporally almost periodic with its $L^2(\Omega)$-norm uniformly bounded in time. Then there exists a unique almost periodic solution for (5)-(7).

In this paper, we study a similar system similar to (5)-(7) under non-homogeneous Robin boundary condition $D\frac{\partial C}{\partial n} + PC = K(r,t)$ in $\partial\Omega \times (0,\infty)$ and initial condition $C(r,0) = C_0(r) \in L^2(\Omega)$. We prove that, under certain conditions of initial and boundary data, there exists a unique solution which is almost periodic. The existence is obtained via continuous contraction semigroup and fixed point theorem and uniqueness is obtained via integral estimates on L^2 norm of C.

2. Existence and Uniqueness of the Almost Periodic Solution

In this section, we discuss the existence and uniqueness of almost periodic solution when the source function is almost periodic and the dynamics of the system. We consider the following system with a time-dependent source function $S(r,t)$ and Robin inhomogeneous boundary data:

$$\frac{\partial C}{\partial t} = f(C) + D\nabla^2 C + \lambda S(r,t) \text{ in } \Omega \times (0,\infty), \tag{8}$$

$$D\frac{\partial C}{\partial n} + PC = K(r,t) \text{ in } \partial\Omega \times (0,\infty), \tag{9}$$

$$C(r,0) = C_0(r) \in L^2(\Omega). \tag{10}$$

Here $D, P > 0$, $K(r,t) \in C^2(\Omega \times [0,T])$ for any $T > 0$. First, we prove the following existence theorem for (8)-(10).

Theorem 2.1. *Assume that* $C_0 \in L^2(\Omega)$ *and* $f'(C) \le -\alpha < 0, P > 0$. *Let* $f(\cdot): H^1(\Omega) \to L^2(\Omega)$ *be local Lipschitz continuous,* $L^2(\Omega)$*-norm of K is uniformly bounded in time, and S is temporally almost periodic with its* $L^2(\Omega)$*-norm uniformly bounded in time. Then there exists a unique almost periodic solution for* (8)-(10) *such that* $C \in L^\infty(0,T;L^2) \cap L^2(0,T;H^1(\Omega))$ *for any* $T > 0$.

PROOF. We use a transformation $C = G + H$ where H is a smooth function in Ω satisfying the boundary condition $D\frac{\partial H}{\partial n} + PH = K(r,t)$ on $\partial\Omega$. Then (8) is converted to

$$\frac{\partial G}{\partial t} = f(G+H) + D\nabla^2 G + \lambda S(r,t) + D\nabla^2 H - \frac{\partial H}{\partial t} \tag{11}$$

where G satisfies the homogeneous boundary condition $D\frac{\partial G}{\partial n} + PG = 0$. Similar to the system studied in [8], local existence for (11) can be obtained by [9] [10] [11]. Consequently this establishes local existence for (8)-(10).

Let $\|S\|_\infty$ be the L^∞ norm of S and $\|C\|,\|\nabla C\|$ be the L^2 norms of C and ∇C. We differentiate $\|C\|^2$ and substitute (10) to get

$$\begin{aligned}\frac{1}{2}\frac{\mathrm{d}}{\mathrm{d}t}\|C\|^2 &= \int_\Omega C\cdot C_t\mathrm{d}x = \int_\Omega f(C)\cdot C\mathrm{d}x + D\int_\Omega \nabla C\cdot C\mathrm{d}x + \lambda\int_\Omega SC\mathrm{d}x \\ &= \int_\Omega f(C)C\mathrm{d}x - D\|\nabla C\|^2 + \int_{\partial\Omega} K(r,t)C\mathrm{d}S \\ &\quad - P\int_{\partial\Omega}|C|^2\mathrm{d}S + \lambda\int_\Omega S(r,t)C\mathrm{d}x\end{aligned} \tag{12}$$

Since $L^2(\Omega)$-norm of K is uniformly bounded in time, there exists a number c_0 such that

$$\begin{aligned}&\int_{\partial\Omega} K(r,t)C\mathrm{d}S - P\int_{\partial\Omega}|C|^2\mathrm{d}S \\ &\le \frac{1}{2P}\int_{\partial\Omega}|K|^2\mathrm{d}S + \frac{P}{2}\int_{\partial\Omega}|C|^2\mathrm{d}S - P\int_{\partial\Omega}|C|^2\mathrm{d}S\mathrm{d}S \le c_0\end{aligned} \tag{13}$$

Substitute (13) in (12) we have

$$\begin{aligned}\frac{1}{2}\frac{\mathrm{d}}{\mathrm{d}t}\|C\|^2 &= \int_\Omega f(C)\cdot C\mathrm{d}x + D\int_\Omega \nabla C\cdot C\mathrm{d}x + \int_{\partial\Omega} K(r,t)C\mathrm{d}S \\ &\quad - P\int_{\partial\Omega}|C|^2\mathrm{d}S + \lambda\int_\Omega SC\mathrm{d}x \\ &\le -\alpha\|C\|^2 - D\|\nabla C\|^2 + c_0 + \frac{\lambda^2}{2\alpha}\|S\|^2 + \frac{\alpha}{2}\|C\|^2 \\ &\le -\frac{\alpha}{2}\|C\|^2 - D\|\nabla C\|^2 + c_0 + \frac{\lambda^2}{2\alpha}\|S\|^2.\end{aligned} \tag{14}$$

This implies that

$$\begin{aligned}\|C\|^2 &\le \mathrm{e}^{-\alpha t}\|C_0\|^2 + \left(1-\mathrm{e}^{-\alpha t}\right)\left(\frac{2c_0}{\alpha} + \frac{\lambda^2}{\alpha^2}\|S\|^2\right) \\ &\le \|C_0\|^2 + \left(2c_0 + \frac{\lambda^2}{\alpha^2}\|S\|^2\right) = M\end{aligned} \tag{15}$$

when $t \ge T$ for some sufficiently large T. Therefore, all solutions C enter the following bounded set in $L^2(\Omega)$

$$\mathcal{B} = \left\{C : \|C\| \le \sqrt{M}\right\}. \tag{16}$$

Suppose that C_1 and C_2 are two solutions with same initial value $C_0(r)$ and boundary value $K(r,t)$. Then $C = C_1 - C_2$ satisfies the following system

$$\frac{\partial C}{\partial t} = f(C_1) - f(C_2) + D\nabla^2 C \tag{17}$$

$$D\frac{\partial C}{\partial n} + PC = 0 \ \text{ in } \partial\Omega\times(0,\infty),\ P > 0 \tag{18}$$

with $C(r,0) = 0$.

A quick calculation shows

$$\frac{1}{2}\frac{\mathrm{d}}{\mathrm{d}t}\|C\|^2 = \int_\Omega f'(\eta)|C|^2\mathrm{d}x - D\|\nabla C\|^2 - P\int_{\partial\Omega}|C|^2\mathrm{d}S \le -\alpha\|C\|^2 - D\|\nabla C\|^2 \tag{19}$$

This implies that

$$\frac{1}{2}\frac{\mathrm{d}}{\mathrm{d}t}\|C\|^2+\alpha\|C\|^2\le 0 \tag{20}$$

therefore we know $C\equiv 0$ and the solution is unique since $C(r,0)=0$.

On the other hand, if we assume that C_1 and C_2 are two solutions with C_{01}, C_{02} as initial values respectively and same boundary value. Then $C=C_1-C_2$ satisfies (17) and (18) with initial value $C(r,0)=C_{01}(r)-C_{02}(r)$. It is easy to check that C satisfies (19) and (20). Therefore,

$$\|C\|^2\le \mathrm{e}^{-2\alpha t}\|C_{01}-C_{02}\|^2. \tag{21}$$

Define the solution operator $S_{t,0}:L^2\to L^2$ by $S_{t,0}C_0=C(t)$ for $t\ge 0$, where $C(t)$ is the solution of (8)-(10). By (21), $S_{t,0}$ possesses strong contraction property with absorbing sets (16).

Recall that a function $\varphi:\mathbb{R}\to X$ where (X,d_X) is a metric space, is called *almost periodic* [12] [13] if for every $\varepsilon>0$ there exists a relatively dense subset M_ε of $\mathbb{R}$ such that

$$d_X\left(\varphi(t+\tau),\varphi(t)\right)\le\varepsilon \tag{22}$$

for all $t\in\mathbb{R}$ and $\tau\in M_\varepsilon$. Almost periodic functions play an important role in the theory of nonautonomous dynamical systems.

By similar arguments in [14] [15] [16], Theorem 2.2 in [8] holds for system (8)-(10) and the corresponding pullback attractor defines a unique almost periodic solution. Therefore the proof of Theorem 2.1 is now completed.

3. Conclusion

We study a mathematical model of tumor growth presented by a diffusion equation with appropriate initial and boundary conditions. The boundary value is of Robin type and is inhomogeneous. We show that there exists a unique solution that is almost periodic. The main method is to show that a pullback attractor defines a unique almost periodic solution for the system.

Acknowledgements

This research was supported by William R. Kenan Jr. Professorship, Staley Small Grant and Wellesley College Faculty Award.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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