Abstract

The model is a stochastic partial differential equation in three dimensional spaces with a multiplicative colored noise term. A stochastic model is developed to describe the growth of a tumor for dispersed cells regime. The main feature of the model is that it takes into account independent behavior of tumor cells as well as random interactions between tumor cells, immune system cells and anticancer drugs. Path-wise uniqueness and a convergence result are established. Some biomedical applications are suggested.

Keywords: path-wise uniqueness, convergence of approximated solutions, tumor growth, stochastic partial differential equation, colored noise

1. Introduction

We will study the growth of a heterogeneous tumor for dispersed cells regime. Following Bellomo, and Preziosi, the dispersed cells regime is a situation where the tumor cells are not yet packed in a macroscopically observable tumor and interact with immune cells, anticancer etc.
The interest in this topic is clearly motivated by medicine for two reasons. Firstly, after curative resection of a tumor, a small quantity of residual tumor cells can stay in an organism, which can grow into secondary tumors or dormant metastases. This is a consequence of viable tumor cells that have metastasized prior to curative resection and which are undetectable by current radiological techniques. Secondly, at the early stages of tumor growth when the tumor’s size is no more than small clumps of cells, the competition between tumor cells and immune cells can still be addressed towards the depletion of a tumor. Tumors that succeeded in growing and becoming clinically apparent were seen as the outcome of “errors” on the part of the immune system whereby it allowed the aberrant clone to escape as the result of aging or a subtle “corruption” exerted by the neoplastic cells themselves. Resistance to chemotherapy represents a well-organized barrier to the effective treatment of cancer. Response to adjuvant chemotherapy depends on the presence of drug resistant tumor cells. Resistance to anticancer drug is a combined characteristic of a specific drug, a specific tumor and a specific host. By emergence of drug resistance we mean the development of a new resistant subpopulation of tumor cells due to random genetic changes, independent on the dose. By induction of drug resistance we mean the dose dependent recruitment of a resistant subpopulation from a previously sensitive parent line. It is often inferred that acquired drug resistance results from a type of inductable or adaptive change in the tumor cells caused by the drug themselves. However, it is likely that this resistance arises as a consequence of a selection process acting on a heterogeneous cell population. The genetic irregularity displayed by the tumor cells from the beginning will lead to a great deal of biologic and molecular heterogeneity. The application of chemotherapy at this point will quickly select for cells that progressively show drug resistance. According to the epigenetic approach, the acquired drug resistance is the consequence of a large number of interacting biologic phenomena during the evolution of cancer: a) The development of random mutations in the key genes that influence drug sensitivity. Direct induction of molecular changes in the tumor cells in response to chemotherapeutic stress[32,34]. The paper is organized in 4 sections. After the introduction, section 2 analyses the pathwise uniqueness. Section 3 looks into the convergence of the approximated lattice solutions to the exact solution of the problem. Finally, section 4 is devoted to some applications.

2. Pathwise uniqueness

We consider the pathwise uniqueness of the SPDE

\[ \frac{\partial u}{\partial t} = \Delta u + f(u) + \sigma(u)W, \quad t \in \mathbb{R}_+, x \in \mathbb{R}^3 \]

with initial condition \( u(0, x) = u_0(x), \quad x \in \mathbb{R}^3 \), driven by a colored noise other than white. Here \( u = u(t, x) \) is a random field on \( \mathbb{R}_+ \times \mathbb{R}^3 \). The colored noise \( W = W(t, x) \) considered here is a Gaussian martingale measure on \( \mathbb{R}_+ \times \mathbb{R}^3 \) in the sense of
Stochastic model of tumor growth with colored noise

Walsh. W is defined on a filtered probability space \((\Omega, F, F_t, P)\) and satisfies this condition: The noise W can be characterized by its covariance functional

$$J_K(\phi, \psi) = \mathbb{E}[W(\phi)W(\psi)] = \int_0^\infty \int \phi(s, x)K(x, y)\psi(s, y)dx dy ds,$$

where \(K = K(x, y)\) is the correlation kernel of the noise W. The noise W can be characterized by its covariance functional

$$ \mathbb{E}[W(\phi)W(\psi)] = \int_0^\infty \int \phi(s, x)K(x, y)\psi(s, y)dx dy ds,$$

for \(\phi, \psi \in C^c_c(R, xR^3)\). The correlation kernel \(K = K(x, y)\) is bounded by a Riesz kernel

$$ |K(x, y)| \leq c(|x - y|^{-\alpha} + 1), \quad \forall x, y \in R^3, \quad \text{where } \alpha > 0 \text{ is an appropriate constant, and } (A)_q \text{ or } (A)_0.$$

We consider stochastically weak solutions to equation (1).

**Definition 1. (pathwise uniqueness)** The pathwise uniqueness holds for equation (1) in the space \(C(R, C_{tem})\) if, for every initial condition \(u_0 \in C_{tem}\), any two stochastically weak solutions to equation (28) with sample paths a.s. in \(C(R, C_{tem})\) must be equal with probability 1. That is, whenever \((u, W, u_0)\) and \((\bar{u}, \bar{W}, \bar{u}_0)\) are two stochastically weak solutions to equation (1) defined on the same filtered probability space \((\Omega, F, F_t, P)\) with \(W = \bar{W}\) and \(u_0 = \bar{u}_0\), then \(u(t, x) = \bar{u}(t, x)\) a.s. for all \(t > 0\) and \(x \in R^3\).

**Theorem 1.** Assume that the noise \(W\) is a Gaussian martingale measure on \(R \times R^3\) whose correlation kernel satisfies \((A)_q\). Assume that \(f(u)\) and \(\sigma(u)\) satisfy the growth condition

$$ |f(u)| + |\sigma(u)| \leq c(1 + |u|), \quad \forall u \in R.$$ Assume that the drift \(f(u)\) is Lipschitz continuous. Assume that the noise coefficient \(\sigma(u)\) is continuous and satisfies the Yamada-Watanabe condition: there exists a strictly increasing function \(\delta = \delta(x) : R_+ \rightarrow R_+\) such that

$$ |\sigma(u) - \sigma(v)| \leq \delta(|u - v|), \quad \forall u, v \in R \text{ and } \int_0^\infty \frac{dx}{\delta^2(x)} = \infty. $$

Assume further that the initial condition \(u_0(x) \in C_{tem}(R^3)\). Then pathwise uniqueness holds for stochastically weak solutions \(u = u(t, x)\) to equation

$$ u(t, x) = \int p(t, x, y)u_0(y)dy + \int_0^t \int p(t-s, x, y)f(u(s, y))dy ds + \int_0^t \int p(t-s, x, y)\sigma(u(s, y))W(ds, dy) \quad (2) $$

for almost all \(t \geq 0\) and \(x \in R^3\), where \(p(t, x, y)\) denotes the 3 dimensional heat kernel.

**Proof of Theorem 1.** The arguments given by Mytnik, Perkins and Sturm remain valid in our setting. A bit more care has been to be taken to justify the presence of the drift term \(f(u)\) and some of convergence results. This can be done using standard methods of SPDEs.
Remark 1a). Theorem 1 holds true if we consider the stochastically weak solutions to equation (2) with paths in the space $C(R_+, L^p(R^3))$, as was done in Viot’s work [80], who proved pathwise uniqueness on the bounded domains of $R^1$ for $\sigma(u) = \sqrt{u(1-u)}$, where the subscript + indicates that the positive part of the function $u(1-u)$ is taken. In this case, the stochastically weak solutions $u(t,x)$ to equation (2) are not necessarily continuous. The existence of stochastically weak solutions given by Theorem 2.

Theorem 2. Assume that $u_0 \in C_{term}$, the drift term $f(u)$ and the noise coefficient $\sigma(u)$ are continuous functions satisfying the growth condition $|f(u)| + |\sigma(u)| \leq c(1+|u|)$ for all $u \in R$. Assume further holds for some $\alpha \in (0,2)$. Then there exists a weak solution with sample paths a.s. and the pathwise uniqueness conclusion of Theorem 1 imply the existence of stochastically strong solution to equation (2). That is, a solution which is adapted with respect to canonical filtration of colored noise $W$. The proof follows just as in the classical stochastic differential equations argument of Yamada and Watanabe.

Remark 2a). The function $\sigma(u) = \sqrt{u}$, $u \in R$, clearly satisfies the Yamada-Watanabe condition. For any $u \geq 0$ and $v \geq 0$ the following inequality holds $|\sqrt{u} - \sqrt{v}| \leq \sqrt{|u-v|}$.

Remark 2b). Under the hypothesis of Theorem 2, weak solutions to equation (2) with continuous $C_{term}$-valued paths are also weak solutions to equation (1) in its distributional form, for suitable test functions $\phi(x)$ More specifically, for $\phi(x) \in C_c^\infty (R^3)$ the following formula is valid

$$\int_{R^3} u(t,x)\phi(x)dx = \int_{R^3} u_0(x)\phi(x)dx + \int_{0}^{t} \int_{R^3} u(s,x)\Delta\phi(x)dxds$$

$$+ \int_{0}^{t} \int_{R^3} f(u(s,x))\phi(x)dxds + \int_{0}^{t} \int_{R^3} \sigma(u(s,x))\phi(x)W(ds,dx), \forall t \geq 0 \text{ a.s.}$$

In fact, given an appropriate class of test functions, the two notions of weak solutions are equivalent. In our case, a suitable class of test functions is $\{\phi(x) \in C_c^\infty (R^3) : \phi(x) \leq Ce^{-|x|}, \forall x \in R^3\}$ where $C > 0$ is a constant. For the details of the proof (of equivalence).

3. Convergence in probability of the approximations

The following theorem investigates the convergence in probability of the approximating lattice systems (18) to the stochastically weak solution of equation (2), providing the pathwise uniqueness holds.
Theorem 3. Assume that \( f(u) \) and \( \sigma(u) \) satisfy the growth condition 
\[
|f(u)| + |\sigma(u)| \leq c(1 + |u|)
\]
for all \( u \in \mathbb{R} \), \( f(u) \) is Lipschitz continuous, \( \sigma(u) \) is continuous and satisfies Yamada-Watanabe condition. Assume further that \( W(t,x) \) is a colored noise such that its correlation kernel \( K(x,y) \) satisfies the condition \( (A)_0 \). Assume, in addition, that there exist stochastically strong solutions \( u^n(t,x) \) to the approximating lattice systems (18). Finally, assume that \( \mathbb{E}[\|u_0\|_p^p] < \infty \) for some \( p > 2 \). Then convergence in probability of \( u^n(t,x) \) to \( u(t,x) \) on the space \( C(\mathbb{R}, L^p_0(\mathbb{R}^3)) \) holds for equation (2). When the existence of stochastically strong solutions to approximating lattice systems (18) and the pathwise uniqueness of stochastic equation (2) are known, Theorem 3 establishes the convergence in probability of the approximations \( u^n(t,x) \) to the weak solutions \( u(t,x) \).

Proof of Theorem 3. By the assumptions in Theorem 3, there exist stochastically strong solutions \( u^n \) to (18) with initial condition \( u_0 \). We set 
\[
f(u) = f(u(t,x)), \quad \sigma(u) = \sigma(u(t,x)),
\]
\( \tilde{f}^n(t,x,u) = f(u(t,K_n(x))) \), and \( \tilde{\sigma}^n = \sigma(u(t,K_n(x))) \).

By the given continuity of the functions \( f(u) \) and \( \sigma(u) \) we obtain pointwise convergence \( \lim_{n \to \infty} \tilde{f}^n(t,x,u) = f(u(t,K_n(x))) \) and \( \lim_{n \to \infty} \tilde{\sigma}^n = \sigma(u(t,K_n(x))) \) for all \( (t,x,u) \in \mathbb{R}, \mathbb{R}^3 \times \mathbb{R} \).

To prove the convergence in probability \( u^n(t,x) \to u(t,x) \) as \( n \to \infty \), when the pathwise uniqueness holds for equation (2), we consider a pair of subsequences \( u'(t,x) \) and \( u''(t,x) \) of \( u^n(t,x) \).

By the tightness arguments presented in the proof of Theorem 1*, there exist further subsequences denoted by \( u^{(k)}(t,x) \) and \( u^{(m)}(t,x) \) with weak convergence on the space \( C(\mathbb{R}, L^p_0(\mathbb{R}^3)) \) to the limits \( u = u(t,x) \) and \( \bar{u} = \bar{u}(t,x) \), respectively. Similar calculations as in the proof of Theorem 1*.

Theorem 1*. Assume that the coefficients \( f = f(t,x,u) \) and \( \sigma = \sigma(t,x,u) : \mathbb{R}_+ \times \mathbb{R}^3 \times \mathbb{R} \to \mathbb{R} \) are continuous functions. Assume further that \( \mathbb{E}[\|u_0\|_p^p] < \infty \) for some \( p > 2 \). Let \( W \) be a colored noise such that its correlation kernel \( K = K(x,y) \) satisfies the condition \( (A)_0 \). For any \( T > 0 \) there exists a constant \( c(T) \) such that 
\[
\mathbb{E}[\sup_{0 \leq s \leq T} \|u(t,x)\|_{p,v}^p] \leq c(T).
\]
show that \( u \) and \( \bar{u} \) are stochastically weak solutions to equation (2) with respect to the colored noise \( W \). The pathwise uniqueness results implies \( u(t,x) = \bar{u}(t,x) \) a.s. for all \( t > 0 \) and \( x \in \mathbb{R}^3 \). Thus, \( u(t,x) = \bar{u}(t,x) \) a.s. on the diagonal of \( \mathbb{E} \), with \( E = C(\mathbb{R}_+, L^p_0(\mathbb{R}^3)) \) and Theorem 3. Under suitable assumptions, we prove the continuity of construct-
ed stochastically weak solutions $u(t,x)$ to equation (2). Let $C_\lambda(R^3)$ be the space of continuous functions $u(x): R^3 \rightarrow R$ endowed with supremum norm $\|u\|_{\lambda,\infty} = \sup_{x \in R^3} |u(x)| \gamma(x)$, where $\gamma(x) = e^{-\lambda |x|}$ for $\lambda > 0$.

**Theorem 4.** Let $u(t,x)$ be a stochastically weak solution to equation (2) with coefficients $f(u)$ and $\sigma(u)$ that satisfy the growth condition

$$|f(u)| + |\sigma(u)| \leq c(1 + |u|)$$

for all $u \in R$. Assume that $p > 5$ and $E[\|u_0\|_{\lambda,\infty}^p] < \infty$.

Assume further that for each $T > 0$ there exists a constant $c(T)$ so that

$$E[\sup_{0 \leq t \leq T} \|u(t,x)\|_{r,p}^p] \leq c(T)$$

(3)

Then $u(t,x) \in C(R_+, C_\lambda(R^3))$ and for any $T > 0$ there exists a constant $c(T)$ so that

$$E[\sup_{0 \leq t \leq T} \|u\|_{\lambda,\infty}^p] < \infty$$

(4)

**Proof of Theorem 4.** The arguments follow along the lines of those given in Sturm [80] or Brezniak and Peszat [10]. We first show that, under the assumptions of Theorem 4, the inequality (3) implies (4). Then we apply Theorem 1*, Jensen’s Inequality, Cauchy-Schwartz Inequality, Lebesgue’s Dominated Theorem, and Taylor’s Theorem. We show that $u(t,x) \in C([0,T], C_\lambda(R^3))$ for any $t \in [0,T]$. We end the proof by showing that $u(t,x) \in C([0,T], C_\lambda(R^3))$ for any $T > 0$, therefore $u(t,x) \in C(R_+, C_\lambda(R^3))$.

4. Applications

We can apply Theorems, 1, 3 and 4 as well as Remarks 1 and 2 to investigate the tumor growth for dispersed cells regime, considering several special cases of $\phi(u), l(u), d(u)$ and $\sigma(u)$. Let $b \approx 10^6 \text{cells/mm}^3$ represent the carrying capacity of the host.

4.1 The proliferative rate of drug sensitive tumor cells

The logistic proliferative rate term is given by the formula

$$\phi(u) = \begin{cases} au(b - u), & \text{for } 0 \leq u \leq b, \\ 0, & \text{otherwise} \end{cases}$$

The proliferative rate term corresponding to activation of sensitive tumor cells is (see [1])

$$\phi(u) = \begin{cases} au(b^2 - u^2), & \text{for } 0 \leq u \leq b \\ 0, & \text{otherwise} \end{cases}$$
The proliferative rate term corresponding to inhibition is (see [1])
\[ \varphi(u) = \begin{cases} 
  au(b-u)^2 & \text{for } 0 \leq u \leq b, \\
  0 & \text{otherwise.}
\end{cases} \]

The proliferative rate term corresponding to activation-inhibition is (see [1])
\[ \varphi(u) = \begin{cases} 
  ab^n u - au^{n+1} & \text{for } 0 \leq u \leq b \\
  0 & \text{otherwise, with } n \geq 2.
\end{cases} \]

The von-Bertalanfy-Richard’s proliferative rate term is
\[ \varphi(u) = \begin{cases} 
  au''(b-u)^n & \text{for } 0 \leq u \leq b \\
  0 & \text{otherwise,}
\end{cases} \]

Where \( m > 1 \) and \( n > 1 \) are two parameters.

The Gompertz’s proliferative rate term is
\[ \varphi(u) = \begin{cases} 
  au^m (\ln b - \ln u) & \text{for } 0 \leq u \leq b \\
  0 & \text{otherwise, with } m > 1.
\end{cases} \]

Note that, except Gompertz’s model, all other proliferative rate terms are Lipschitz continuous.

### 4.2 The lysis rate term

We consider four different models for lysis rate term,

- **Michaelis-Menten’s model**
  \[ l(u) = \begin{cases} 
  0 & \text{for } u < 0 \\
  c_u(c_u + u)^{-1} & \text{for } 0 \leq u \leq b \\
  l(b) & \text{for } u > b.
\end{cases} \]

- **Lefever’s model**
  \[ l(u) = \begin{cases} 
  0 & \text{for } u < 0 \\
  \alpha u(1 + \beta u)(\gamma u^2 + \delta u + 1)^{-1} & \text{for } 0 \leq u \leq b \\
  l(b) & \text{for } u > b
\end{cases} \]

- **Kusnetsov’s model**
  \[ l(u) = \begin{cases} 
  0 & \text{for } u < 0 \\
  \alpha u & \text{for } 0 \leq u \leq b \\
  l(b) & \text{for } u > b
\end{cases} \]

Freundlich’s model
\[ l(u) = \begin{cases} 
  0 & \text{for } u < 0 \\
  \alpha u^2 & \text{for } 0 \leq u \leq b \\
  l(b) & \text{for } u > b
\end{cases} \]

### 4.3 The rate of sensitive tumor cell lost due to the anticancer drugs

The common expression for the drug loss function \( d(u) \) is where it is proportional to the drug concentration within tumor (in some cases, within sensitive tumor cell) and the current sensitive tumor cells population size, Hence,
Where $\mu$ represents the drug concentration within the tumor and $K$ denotes the killing parameter of the drug, see [13,16], and [62]. Another expression for $d(u)$ is proposed by Costa et.al

$$d(u) = \begin{cases} 0 & \text{for } u < 0 \\ K\mu u & \text{for } 0 \leq u \leq b \\ d(b) & \text{for } u > b \end{cases}$$

4.4 The driving noise term

We consider the following expressions for the coefficient of the noise term

$$\sigma(u) = \begin{cases} 0 & \text{for } u < 0 \\ \sqrt{c} \sqrt{u} & \text{for } 0 \leq u \leq b \text{ and } \sigma(b) & \text{for } u > b \end{cases}$$

$$\sigma(u) = \begin{cases} a \sqrt{\mu (b - u)} & \text{for } 0 \leq u \leq b \\ 0 & \text{for } u \in (-\infty, \infty) \setminus [0,b] \end{cases}$$

We give some representative values of the parameters:

$b = 10^6$ cells/mm$^3$, $D = 10^{-10}$ cm$^2$/s, $\lambda = 1.1$ day$^{-1}$, $\alpha = 10^{-6}$

We suggest also some applications of our mathematical results in immunotherapy or gene therapy for cancer. The important discovery that tumor antigen can invoke tumor specific immune response in cancer patients has given new impetus for the possibility of treating patients with immunotherapy [7, 8, 24, 28, 70]. To be more concrete, we will consider dentritic cells (DCs) which are highly effective antigen presenting cells. They are capable of efficiently priming class I and class II tumor specific immune response [9, 29 and 52]. Human colorectal cancers are infiltrated by DCs. In addition, in these tumors has been shown the local production of one cytokine, GM-CSF (one homotopeietic growth factor), that promotes the differentiation of peripheral blood monocytes in DCs. These last years DCs are used in cancer immunotherapy clinical trials. WE can apply our stochastic model of tumor growth for dispersed cells regime to evaluate the impact of DCs on combined treatment chemotherapy +immunotherapy of human colorectal cancer. Molecular chemotherapy strategies attempt to achieve selective delivery or expression of a toxic gene in stormal cells to induce their eradication or alternatively to increase their sensitivity to adjuvant chemotherapy. Genetic chemosensitivation can be achieved by inducing apoptosis, by inhibiting intracellular molecules involved in induced drug resistance or by enhancing intratumoral production of cytotoxic drugs. To facilitate apoptosis, genes such as p53 may be administered to tumor cells to enhance the mechanisms of apoptosis induced by drugs [26,35]. Genetic down regulation of cellular factors related to drug resistance has been shown to enhance drug sensitivity [34]. Alternatively, genes can be administered intratumorally to enhance metabolic conversion of anticancer drugs. For example, transfer of a liver cytochrome P450 gene, CYP2B1, into human breast cancer cells greatly sensitized these cells to the anticancer drug cyclophosphamide as a consequence of the acquired capacity for
intracellular drug activation. This effect produced a substantially enhanced antitumor activity in vivo [14]. Also, attempts have been made to deliver genetic sequences that protect bone marrow cells from the toxic effects of anticancer drugs, thus allowing the administration of higher drug doses [25,35] . We can apply our stochastic model with colored noise to evaluate the effects of the above mentioned methods of molecular chemotherapy in terms of survival advantage and the reduction of the risk of recurrence in cancer patients.

Conclusions

The success in the mathematical study of tumor growth for dispersed cell regime expected to be largely due to independence: For dispersed cells regime all tumor cells behave independently of each other, starting from their birthplace and time [32,34]. After reviewing various publications concerning stochastic modeling of tumor growth, we conclude that the proposed model is probably the first model of tumor growth for dispersed cells regime by stochastic partial differential equations with multiplicative colored noise. We investigate the convergence in probability of the approximating lattice systems to the exact solution $u(t,x)$, assuming that the colored noise $W$ satisfies the condition $(A)_0$. Our mathematical modeling of tumor growth for dispersed cells regime is developed through a careful analysis of in vivo biomedical system. The framework for collaboration and communication between the oncologist, cancer biologist, immunologist, mathematician and computer scientists is clear. The development of a specific computer program and simulations lead to a better understanding of the key parameters that influence the overall health of patients in medium to long terms. Also, these computer simulations will enable medical staff to determine the best treatment and medications for cancer patients.

References


**Received: January 21, 2020; Published: February 5, 2020**