

Vessel Mathematical Model for Tumour Angiogenesis and its Fluctuation Characterization Equation

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ガン血管新生の脈管数理モデルとゆらぎ特徴付け方程式

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In this article we study a new tumour angiogenic mathematical model, which is described by the Itô type stochastic differential equation (SDE) driven by a Brownian motion. This mathematical model is able to describe the vessel dynamics of tips in tumour angiogenesis. We derive an explicit expression of the limit function in mean principle and an explicit representation of the characterization equation in fluctuation for the tumour angiogenic SDE model. In addition, we finally expand the stability argument for the stochastic system, and discuss a sufficient condition for instability of the corresponding random model. We think that this discussion guarantees some potential capability for our model to describe faithfully certain irregularity of the tumour angiogenesis in question.

この論文では、ブラウン運動不規則過程により駆動されたいわゆる伊藤型の確率微分方程式 (SDE) で記述される、ガンの血管新生に関する新しい数理モデルを考察する。この数理モデルは、ガンの血管新生における先端部分の脈管ダイナミクスを記述することができるものである。まず最初にガン血管新生確率微分方程式モデルの平均原理において出現する極限関数の具体的な表現を導出する。続いて同ランダム系におけるゆらぎ量を表す特徴付け方程式を具体的に求める。さらにそれに加えて、最後に確率システムの安定性解析の議論を展開し、対応するランダムなモデルが非安定であるための十分条件について議論を深める。このことは、我々がここで提案するモデルには問題にしているガン血管新生の特定の不規則性を忠実に表現する潜在的能力があるということを保証するであろうと考えている。

1 Introduction

In this article we consider the tumour angiogenesis and propose a new tumour angiogenic mathematical model, which is given by the so-called Itô type stochastic differential equation (SDE) driven by a Brownian random process, namely, a Wiener process. This mathematical model is able to describe the vessel dynamics of tips in tumour angiogenesis. Let us look at the figure 1. It is an illustration of cancer vessels, which is our target. If you only catch a glance at the lump of cancer cells in Figure 2, then there is no telling where the tumour vessels are. However, when you take a quick look at the photographs of



図 1 cancer vessels

blood vessels, even if vessels stand out themselves in green color from the background, you cannot tell which one is the tumour vessel (see Figure 3). Because they all consist of irregular complicated shapes. Actually, the left picture in Figure 3 is tumour vessel before medical treatment, and the middle is the one after proper medical treatment, while the right is normal vessel. We are eager to apply the random model theory to life science, especially in the field of medicine. We are aiming at providing with aids for medical diagnoses, in the near future, by supplying better information of tumour vessels based upon the

random models. In this article we study longtime asymptotic behavior of our SDE model, and derive an

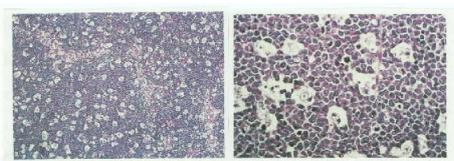


図 2 cancer cells (pa.2)

explicit expression of the limit function in mean principle. Moreover, we apply fluctuation analysis to the tumour angiogenic SDE model and derive an explicit representation of the characterization equation in fluctuation for the model. In addition, we finally expand the stability argument for the stochastic system, and discuss a sufficient condition for instability of the corresponding random model. We think that this

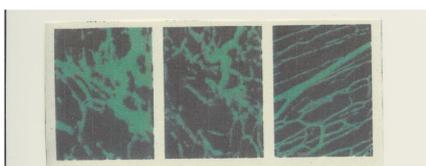


図 3 blood vessels

discussion guarantees some potential capability for our model to describe faithfully certain irregularity of the tumour angiogenesis in question. Lastly let us look at the figure 4. Now you shall see which is the normal one. Of course, so the left is. The middle is the one before treatment and the right is after treatment.

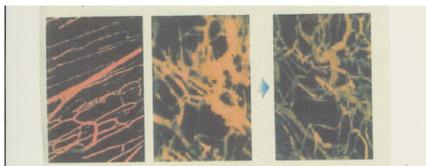


図 4 cancer vessels

2 Stochastic modelling

In Dôku-Misawa (2013) [9] we studied mean principle and fluctuation of SDE model for tumour angiogenesis, see also Dôku (2011) [7] and Misawa (2013) [14]. In this paper we propose a new mathematical model which is a generalization of the previous tumour angiogenic SDE model in Dôku-Misawa (2013) [9], and derive an explicit expression of the limit function in the mean principle of the model, as well as an explicit representation of the characterization equation in the fluctuation. We shall introduce below

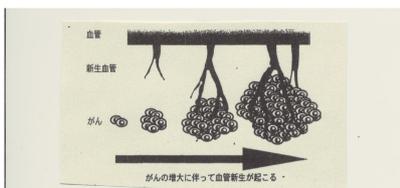


図 5 tumour angiogenesis

some notations, terminology and modelling of blood vessel networks in angiogenesis. Let N_0 be the initial

number of tips, $N(t)$ be the total number of tips at time t , $X^i(t) \in \mathbb{R}^d$ be the position of the i -th tip at time t with $d = 3$, and $v^i(t)$ be the moving velocity of the i -th tip at time t . Then the network of endothelial cells is expressed as the union of the trajectories of the tips, namely,

$$X(t) \equiv X(t, \omega) := \cup_{i=1}^{N(t)} \{X^i(s), T_i \leq s \leq t\}, \quad (1)$$

where T_i denotes the birth time of the i -th tip, that is to say, the time when an existing vessel branches and the i -th trajectory springs up. As is well known, the tip generating process is described by a marked point process. However, in the standpoint of its analysis and applications, it is more convenient to give

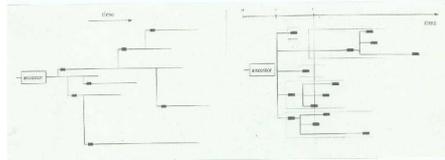


图 6 tip branching model

it as a probability measure on the product space between time space and position space. Hence, the corresponding process is given as a probability measure $G \equiv G(dt \times dx)$, i.e., $G(dt \times dx) = \sum_n \delta_{\{(T^n, Y^n)\}}$, where T^n is the birth time of the n -th tip and Y^n is the spatial position of the n -th tip that has been newly born. For each i we write

$$\tilde{X}_t^i \equiv \tilde{X}^i(t) = (X_1^i(t), X_2^i(t), X_3^i(t)) \in \mathbb{R}^3, \quad v_t^i \equiv v^i(t) = (v_1^i(t), v_2^i(t), v_3^i(t)) \in \mathbb{R}^3, \quad (2)$$

and for each j ($j = 1, 2, 3$) we have $X_j^i(t) \in \mathbb{R}$ and $v_j^i(t) \in \mathbb{R}$. Next we shall propose a new stochastic differential equation (SDE) model which describes the blood vessel dynamics. Under these circumstances

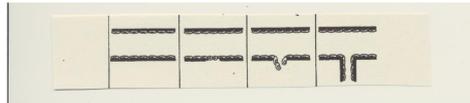


图 7 angiogenic process

the formulation via a random model (i.e., an SDE model) on the vessel motion is given by the following simultaneous equations. As a matter of fact, for each i ,

$$d\tilde{X}^i(t) = \Xi(t, \tilde{X})v_t^i dt, \quad \text{and} \quad dv^i(t) = a(t, \tilde{X}^i, v^i)dt + \sigma v_t^i dW_t^i, \quad (t > T_i) \quad (3)$$

where $W_t^i \equiv W^i(t) = (W_1^i(t), W_2^i(t), W_3^i(t)) \in \mathbb{R}^3$ is a three-dimensional Brownian motion (or Wiener process). Next we refer to the concrete components of the afore-mentioned equations. Namely, $C(t, x)$ denotes the concentration rate of TAF (tumour angiogenic factors), and $f(t, x)$ is the fibronectin and/or their gradients. The positive constant $\sigma > 0$ is a diffusion coefficient, and the term Ξ is given by $\Xi(t, \tilde{X}) := 1 - p_a \mathbb{I}_{\tilde{X}_t} \{\tilde{X}_t^k\}$, where p_a is a switching parameter, and the parameter p_a takes only the 0 and 1 values. Actually, the state $p_a = 0$ indicates that no impingement is considered, while $p_a = 1$ means that the phenomenon of anastosis is taken into account. $\mathbb{I}_{(\cdot)}\{\cdot\}$ is the indicator or characteristic function associated with the existing blood network status. According to several system biological or molecular biological observations, the coefficient term (or the drift term) $a(t, x, v)$ of (3) is thought to be a function of $C(t, x)$ and $f(t, x)$. Here we suppose that it is given by $a(t, \tilde{X}^i, v^i) := -kv^i + \Phi(C(t, \tilde{X}_t^i), f(t, \tilde{X}_t^i))$, $k > 0$. There are surely various discussions for the term Φ to be described. Suggested by considerations of the bias depending on TAF and the fibronectin field of Plank-Sleeman (2004) [15], and also inspired

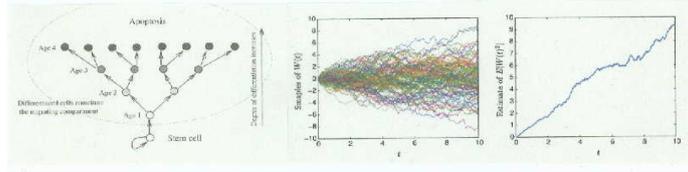


Fig 8 branching mechanism and simulation

by the argument on the magnitude of the chemotactic and haptotactic gradient for the reorientation of the cell increase of Stéphanou et al. (2006) [17], we adopt the function Φ of the following form:

$$\Phi(C, f) \equiv \Phi(C(t, \tilde{X}_t^i), f(t, \tilde{X}_t^i)) = d_C \cdot \nabla C(t, \tilde{X}_t^i) + d_f \cdot \nabla f(t, \tilde{X}_t^i) \quad (4)$$

with $d_1 > 0$, $d_2 > 0$, $\gamma > 0$, $q > 0$,

$$d_C = d_1 \frac{|\nabla C(t, \tilde{X}_t^i)|}{(1 + \gamma C(t, \tilde{X}_t^i))^q}, \quad \text{and} \quad d_f = d_2 |\nabla f(t, \tilde{X}_t^i)|. \quad (5)$$

Note that

$$\begin{aligned} \nabla C &= (\partial_1 C, \partial_2 C, \partial_3 C) = \left(\frac{\partial C}{\partial x_1}, \frac{\partial C}{\partial x_2}, \frac{\partial C}{\partial x_3} \right) \quad \text{and} \\ \nabla f &= (\partial_1 f, \partial_2 f, \partial_3 f) = \left(\frac{\partial f}{\partial x_1}, \frac{\partial f}{\partial x_2}, \frac{\partial f}{\partial x_3} \right) \quad \text{with} \quad \partial_i g = \frac{\partial g}{\partial x_i} \quad (i = 1, 2, 3), \end{aligned} \quad (6)$$

and also that the term $\Phi = (\Phi_1, \Phi_2, \Phi_3)$ is considered to have a form

$$\Phi_j \equiv \Phi_j(C(t, x), f(t, x)) = K_1 \frac{\partial C}{\partial x_j} + K_2 \frac{\partial f}{\partial x_j}, \quad \text{with} \quad (j = 1, 2, 3). \quad (7)$$

For brevity's sake, we abbreviate its individual tag number i in what follows. We also use the following notations.

$$X_t = (\tilde{X}_t, v_t) = (X_t^1, X_t^2, X_t^3, v_t^1, v_t^2, v_t^3) \quad \text{and} \quad B_t = (\tilde{B}_t, W_t) = (\tilde{B}_t^1, \tilde{B}_t^2, \tilde{B}_t^3, W_t^1, W_t^2, W_t^3)$$

where $\tilde{B}_t = (\tilde{B}_t^i, i = 1, 2, 3)$ is a three-dimensional Brownian motion independent of W_t . Then our newly proposed tumour angiogenic SDE model for vessel tip dynamics (4) is equivalent to

$$d \begin{pmatrix} \tilde{X}_t \\ v_t \end{pmatrix} = \begin{pmatrix} (1 - p_a \mathbb{I}_{\tilde{X}_t}(\tilde{X}_t^k)) v_t \\ a(t, \tilde{X}_t, v) \end{pmatrix} dt + \begin{pmatrix} 0 & 0 \\ 0 & \sigma \end{pmatrix} \begin{pmatrix} \tilde{X}_t \\ v_t \end{pmatrix} d \begin{pmatrix} \tilde{B}_t \\ W_t \end{pmatrix}, \quad (8)$$

and furthermore, for simplicity, we shall write it as follows:

$$dX_t = F(t, X_t)dt + G(X_t)dB_t, \quad \text{and} \quad X_0 = Z, \quad (9)$$

with, for $T > 0$, $F(t, x) : [0, T] \times \mathbb{R}^6 \rightarrow \mathbb{R}^6$, and $G(x) : \mathbb{R}^6 \rightarrow (\mathbb{R}^6 \otimes \mathbb{R}^6) \times \mathbb{R}^6 \cong \mathbb{R}^6$. This is nothing but an Itô type stochastic differential equation with respect to a Brownian motion, to which the usual stochastic calculus (or Iô calculus) can be applied.

3 Assumptions and main results

According to the general theory on stochastic differential equations (cf. Øksendal (1998) or Ikeda-Watanabe (1989)), in order to obtain the existence and uniqueness result for solutions to the stochastic differential equation (SDE) of Itô type (9), we have only to assume the following conditions. For the function $G(t, x) = G(x)$ by convention, we assume:

(A.1) There exists a proper positive constant $C > 0$ such that for $\forall t \in [0, T]$ and $\forall x \in \mathbb{R}^6$

$$|F(t, x)| + \|G(t, x)\| \leq C(1 + |x|). \quad (10)$$

(A.2) There exists a proper positive constant $D > 0$ such that for $\forall t \in [0, T]$ and $\forall x, y \in \mathbb{R}^6$

$$|F(t, x) - F(t, y)| + \|G(t, x) - G(t, y)\| \leq D|x - y|. \quad (11)$$

Here note that $G(t, x) = (G_{ij}(t, x)) \in M(6 \times 6)$ and $\|G(t, x)\| = \sum_{i,j} |G_{ij}(t, x)|^2 = \sum_{i=1}^6 \sum_{j=1}^6 G_{ij}^2(t, x)$, where $M(6 \times 6)$ denotes the totality of $(6, 6)$ -type square matrices.

(A.3) The initial value Z is a random variable and is independent of the σ -algebra $\mathcal{F}_\infty^B = \sigma(B_s : s \geq 0)$, and satisfies the integrability condition $\mathbb{E}|Z|^2 < +\infty$.

Then it is well known as the theorem on existence and uniqueness of solutions to SDEs that under the assumptions (A.1), (A.2) and (A.3), the SDE (9) possesses the unique solution which is t -continuous and satisfies (i) X_t is \mathcal{F}_t^Z -adapted where $\mathcal{F}_t^Z \equiv \sigma(Z) \vee \sigma(B_s : s \leq t)$; and (ii) $\mathbb{E} \int_0^T |X_t|^2 dt < \infty$. On this account, we can prove the following first main result. For simplicity we set $\Upsilon^{[f]}(t, x, y) := f(t, x) - f(t, y)$ and $\mathcal{F}_t^Z := \sigma(Z) \vee \sigma(B_s : s \leq t)$.

THEOREM 1. (Existence and uniqueness of solution to SDE) *Assume (A.3). We also suppose that*

$$|\nabla C(t, x)| + |\nabla f(t, x)| \leq C_1(1 + |x|), \quad \text{for } \exists C_1 > 0, \forall t \geq 0, \forall x \quad (12)$$

$$|\Upsilon^{[\nabla C]}(t, x, y)| + |\Upsilon^{[\nabla f]}(t, x, y)| \leq C_2|x - y|, \quad \text{for } \exists C_2 > 0, \forall t > 0, \forall x, y. \quad (13)$$

Then SDE (11) possesses the unique solution $X = (X_t) \in \mathbb{R}^6$ such that (a) X_t is t -continuous, (b) X_t is \mathcal{F}_t^Z -adapted, and (c) X_t satisfies the integrability condition $\mathbb{E} \int_0^T |X_t|^2 dt < +\infty$.

We use the scaling to the model relative to $\varepsilon > 0$, and consider a scaled process $X_t^\varepsilon(\omega) \equiv X^\varepsilon(t, \omega) := X(\frac{t}{\varepsilon}, \omega)$. In this stage we are very concerned on the asymptotic behavior of $X^\varepsilon(t, \omega)$ as $\varepsilon \rightarrow 0$. In order to analyze the asymptotic behaviors and derive the mean principle for our SDE model, we need the following conditions.

$$\sup_{t>0} |v_t(\omega)| < +\infty, \quad \mathbb{P} - a.s. \quad (14)$$

$$\sup_{t>0} |\nabla C(t, x)| < +\infty, \quad \text{and} \quad \sup_{t>0} |\nabla f(t, x)| < +\infty, \quad \text{uniformly in } x. \quad (15)$$

For $\forall s, u$ such that $0 < s < u$, $\lim_{\varepsilon \rightarrow 0} \int_s^u F^\varepsilon(t, y) dt = \int_s^u F^0(t, y) dt$, where $F^\varepsilon(t, y)$ is defined by $F(\frac{t}{\varepsilon}, y)$. Then we call F^ε is integrally continuous at $\varepsilon = 0$ with respect to (t, y) .

We are now in a position to state the second main result in this paper, which supplies with an explicit expression of the limit function in mean principle. Although our SDE model (3) (or (8), (9)) is an extension of the tumour angiogenic model treated in Dôku-Misawa (2013) [9] and Misawa (2013) [14], this result sharpens the previous mean principle theorem (cf. Theorem 22, §4.2 in [9]).

THEOREM 2. *Suppose the same conditions (12) and (13) as in Theorem 1. In addition, we assume (14), (15) and integral continuity.*

(a) *Under the hypothesis that $X_s(\omega) = y = (\tilde{y}, \hat{y}) \in \mathbb{R}^6 \cong \mathbb{R}^3 \times \mathbb{R}^3$, \mathbb{P} -a.s., there exists a proper function $\tilde{F}(y) : \mathbb{R}^6 \rightarrow \mathbb{R}^6$ such that*

$$\lim_{T \rightarrow \infty} \frac{1}{T} \int_0^T F(s, y) ds = \tilde{F}(y) \quad (16)$$

holds uniformly in y .

(b) *Moreover, if $u \equiv u(t)$ is a solution of the Cauchy problem for deterministic dynamic differential equation*

$$\frac{du}{dt}(t) = \tilde{F}(u(t)) \quad \text{with} \quad u(t)|_{t=0} = z, \quad (17)$$

then the convergence in law $X(\frac{t}{\varepsilon}) \implies u(t)$ holds as ε approaches to zero.

(c) The limit function \tilde{F} is given concretely by

$$\tilde{F} := \begin{pmatrix} c_0 \cdot \hat{y} \\ -k\hat{y} + \alpha(\infty) \cdot \nabla C(\infty, \hat{y}) + \beta(\infty) \cdot \nabla f(\infty, \hat{y}) \end{pmatrix} \quad (18)$$

with $\alpha(\infty) = d_C(\infty, \hat{y})$, $\beta(\infty) = d_f(\infty, \hat{y})$ for $d_C \equiv d_C(t, \tilde{X}_t)$ and $d_f \equiv d_f(t, \tilde{X}_t)$. Here we set $c_0 = 1 - p_a \mathbb{I}_{\tilde{X}}\{\tilde{X}^k\}$.

Next we shall introduce the third main result in this paper, which provides with an explicit representation of the characterization equation for the fluctuation of the rescaled tumour angiogenic SDE model. Before stating the theorem, we define the fluctuation quantity based upon the fundamental results (cf. Lemma 6 in §4 of [13]): i.e., (i) vanishing of the Itô type stochastic integral of rescaled function

$$\sqrt{\varepsilon} \int_0^t G^\varepsilon(y) dB_s^\varepsilon \implies 0 \quad (\text{as } \varepsilon \rightarrow 0); \quad (19)$$

(ii) the limiting equality of the SDE model: $\lim_{\varepsilon \searrow 0} X(\frac{t}{\varepsilon}) = z + \int_0^t \tilde{F}(\lim_{\varepsilon \searrow 0} X(\frac{s}{\varepsilon})) ds$. As a matter of fact, we define the fluctuation as

$$V_t^\varepsilon \equiv V^\varepsilon(t, \omega) := \frac{1}{\sqrt{\varepsilon}} \left\{ X\left(\frac{t}{\varepsilon}, \omega\right) - u(t) \right\}, \quad \mathbb{P} - \text{a.s. for } t > 0 \text{ and } \varepsilon > 0. \quad (20)$$

THEOREM 3. *We assume (12), (13), (14), (15) and integral continuity.*

(a) *There exist some proper functions $\xi(t, \omega) \in L^1(0, T)$, \mathbb{P} -a.s., and $\Psi(t, \omega) \in L^2(0, T)$, \mathbb{P} -a.s. such that*

$$\lim_{\varepsilon \rightarrow 0} \int_0^t (\nabla \cdot F(\frac{s}{\varepsilon}, z)) \cdot y ds = \int_0^t \xi(s) \cdot y ds, \quad \text{and} \quad \lim_{\varepsilon \rightarrow 0} \int_0^t G^\varepsilon(X^\varepsilon(s)) ds = \int_0^t \Psi(s) ds. \quad (21)$$

(b) *The fluctuation V_t^ε converges in law to some process Z_t as $\varepsilon \rightarrow 0$.*

(c) *The limit process Z_t satisfies the following SDE: $dZ_t = \xi(t)Z_t dt + \Psi(t)dB_t$.*

(d) *Actually, the limit functions in (21) which determine the characterization equation of the fluctuation, are explicitly presented as*

$$\xi(s, \omega) = \nabla \cdot F(\infty, u(s)) \quad \text{and} \quad \Psi(s, \omega) = G(\infty, u(s)) = \begin{pmatrix} 0 & 0 \\ 0 & \sigma \end{pmatrix} u(s) = \begin{pmatrix} 0 & 0 \\ 0 & \sigma \end{pmatrix} \begin{pmatrix} \tilde{u}(s) \\ \hat{u}(s) \end{pmatrix} = \begin{pmatrix} 0 \\ \hat{u}(s) \end{pmatrix}. \quad (22)$$

If we rewrite the definition (20) of fluctuation, then we immediately obtain $X(\frac{t}{\varepsilon}) = u(t) + \sqrt{\varepsilon}V^\varepsilon(t)$. Here $u(t)$ is the solution of the ordinary differential equation like $\frac{d}{dt}u(t) = \tilde{F}(u(t))$, so that, the solution curve (parametrized by time t) is a smooth curve with respect to t . The above expression suggests that the rescaled process $X(\frac{t}{\varepsilon})$ (which satisfies a SDE (23) below) is obtained by adding a random quantity (fluctuation) $\sqrt{\varepsilon}V^\varepsilon(t)$ to the curve $u(t)$ additively for each t . In other words, the random quantity $X(\frac{t}{\varepsilon})$ (controlled by our SDE model) can be regarded as the sum structure being decomposed as the deterministic term $u(t)$ and randomly perturbed term. Note that the rescaled process $X(\frac{t}{\varepsilon})$ satisfies

$$X\left(\frac{t}{\varepsilon}\right) = z + \int_0^t F\left(\frac{s}{\varepsilon}, X\left(\frac{s}{\varepsilon}\right)\right) ds + \sqrt{\varepsilon} \int_0^t G\left(X\left(\frac{s}{\varepsilon}\right)\right) dB_s^\varepsilon(\omega). \quad (23)$$

4 Stability argument

In this section we discuss the stability analysis for the stochastic model. The solution $X_t = 0$ of SDE (9): $dX_t = F(t, X_t)dt + G(X_t)dB_t$ is stable in probability for $t \geq 0$ if for $\forall s \geq 0, \forall \varepsilon > 0$,

$$\lim_{x \rightarrow 0} \mathbb{P}(\sup_{t > s} |X_t^{s,x}(\omega)| > \varepsilon) = 0 \quad (24)$$

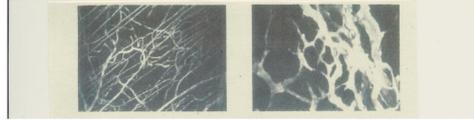


图 9 cancer vessels

holds. The solution is asymptotically stable in probability if the solution is stable in probability and

$$\lim_{x \rightarrow 0} \mathbb{P}(\lim_{t \rightarrow \infty} X_t^{s,x}(\omega) = 0) = 1 \quad (25)$$

holds. Condition [D] is that any solution of SDE (9) beginning in the domain $\varepsilon < |x| < r$, almost surely reaches the boundary of this domain in a finite time, for any sufficiently small r and $\varepsilon > 0$. Let $U \subset \mathbb{R}^\ell$ be a domain, and $E = (0, \infty) \times U$ be a domain including $\{x = 0\}$. Let $A(x) = (a_{ij}(x))$ such that $A(x) = G(x)G^*(x)$. We assume that there exists a function $V(t, x) \in C_{t,x}^{1,2}(E)$ being positive definite in Lyapunov's sense, and satisfying

$$LV = \frac{\partial V}{\partial t} + \sum_i F_i(t, x) \partial_i V + \frac{1}{2} \sum_{ij} a_{ij}(x) \partial_{ij}^2 V \leq 0. \quad (26)$$

Then the solution is stable in probability. Furthermore, suppose that there exists a positive definite function $V(t, x) \in C_{t,x}^{1,2}(E)$ such that $\lim_{x \rightarrow 0} \sup_{t > 0} V(t, x) = 0$ and $LV \leq 0$. Then under the condition [D] the solution of SDE is asymptotically stable in probability.

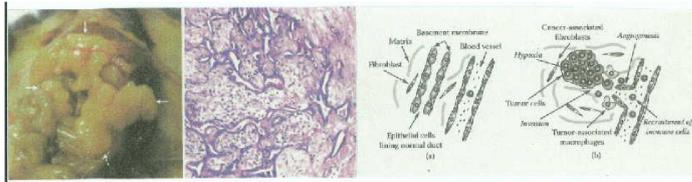


图 10 cancer cells

5 Instability for the stochastic system

In this section we state the instability for the random model. Assume the condition [D]. We suppose that there exists $V(t, x) \in C_{t,x}^{1,2}(E_r)$ with $E_r = (0, \infty) \times B_r$ such that (i) $LV \leq 0$ in $B_r \setminus \{0\}$; and (ii) $\lim_{x \rightarrow 0} \inf_{t > 0} V(t, x) = \infty$. Then the solution of SDE is not stable in probability. Moreover, the event $\{\sup_{t > 0} |X_t^{s,x}(\omega)| < r\}$ has probability zero for all $s > 0$, $x \in B_r$. We can state a more precise result for instability. Suppose that the expansions $F_i(t, x) = \sum_j \tilde{F}_i^j(t) x_j + o(|x|)$ uniformly in t , and $a_{ij}(x) = \sum_k \tilde{a}_{ij}^k x_k + o(|x|)$ hold in the neighborhood of $x = 0$, where $\tilde{F}_i^j(t)$, \tilde{a}_{ij}^k are bounded. In addition, we assume that for $\exists \varepsilon > 0$, $\ell > 0$ and $\forall t > 0$

$$\Gamma_{ij}^k(t) = \int_0^t (\tilde{F}_i^j(s) - \frac{1}{2}(\tilde{a}_{ij}^k)^2 - \varepsilon) ds > -\ell. \quad (27)$$

Then we can show that the auxiliary function $V_{ij}^k(t, x) = -\log |x| + \Gamma_{ij}^k(t)$ satisfies the conditions on V in the above-mentioned result. Hence the solution of SDE is not stable in probability.

Acknowledgements. This work is supported in part by Japan MEXT Grant-in Aids SR(C) No.24540114 and also by ISM Coop. Res. No.24-CR-5008. The figures are all taken from [1], [9], and [15–17].

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