OPTIMAL THERAPY POLICY FOR CANCER GROWTH WITH STOCHASTIC PERTURBATION

by

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A stochastic Gompertz model is proposed to study cancer growth with therapy. The model reveals that the therapy and environmental fluctuation can control the tumor size, but its extinction is impossible. Optimal therapy treatment is suggested, and its probability density function is elucidated clearly by the Fokker-Planck equation.

Key words**:** *optimal therapy policy, cancer, stochastic, equilibrium, permanent, persistent, Fokker-Planck equations, stationary distribution*

Introduction

Now cancer has become one of the major diseases threatening human life seriously, and millions of people die of cancer each year [1, 2]. On the other hand, the economic impact of medical treatment for cancer is also huge. For example, the overall cost of cancer in 2008 was around $ 228.1 billion in the US alone [3].

A biophysical model may prove to be useful in oncology not only in explaining basic phenomena but also in helping clinicians to plan a good and effective schedule of the therapy [1]. The most commonly used model is:

$$\frac{\mathrm{d}x(t)}{\mathrm{d}t} = rx(t)\ln\frac{k}{x(t)} \tag{1}$$

where $x(t)$ is the density of cancer cells at the time, t, r – the intrinsic growth rate of the tumor, and k – the largest tumor density that an organism can be tolerated.

Equation (1) is called as Gompertz model [4-11], which is not adequate to describe the growth of a small aggregate of tumors [8]. In this way, Gompertz law comes into play only for sufficiently large populations. Furthermore, the Gompertz model has been almost universally used to describe the growth of microorganisms [12] and the innovation diffusion such as digital cellular telephones [13, 14].

We notice that any solution $x(t)$ of eq. (1) with the initial value $x(0) > 0$ satisfies that $\lim_{t\to\infty} x(t) = k$.

The result shows that if we do not take any treatment, the tumor will grow the most number k for $0 < x(0) < k$.

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Taking tumor treatment into consideration, we now introduce one more term in eq. (1) in order to model the action of therapy [10, 15]. Let $e_0 > 0$ denotes the intensity of the therapy, h is a strictly increasing function and $h(0) = 0$. Then tumor growth model with therapy (constant or time depending) will then be:

$$\frac{\mathrm{d}x(t)}{\mathrm{d}t} = rx(t)\ln\frac{k}{x(t)} - h(e_0)x(t) \tag{2}$$

Equation (2) exists a unique positive equilibrium $x_2^* = k\exp[-h(e_0)/r]$.

Similarly, we can prove that $\lim_{t\to\infty} x(t) = x_2^*$ for any $x(0) > 0$. In this case, the tumor will grow the most number x_2^*.

Notice that $x_2^* = k\exp[-h(e_0)/r] < x_1^* = k$, $\lim_{h(e_0)\to\infty} k\exp[-h(e_0)/r] = 0$.

It means that therapy can make the largest tumor density smaller, and we can seemingly cure any tumor patient when $h(e_0)$ or e_0 is large enough for the fixed r and k. Now, we have another problem, which is a stochastic perturbation.

It should be stressed that quite often, discrepancies exist between clinical data and theoretical predictions due to environmental fluctuation [16, 17]. In practice, $h(e_0)$ is disturbed by the environment noise from nature or artificial factors, for example, the patient's individual differences, small changes on chemotherapy doses. Hence we could modify $h(e_0)$ to $h(e_0) + \rho\dot{\tilde{w}}(t)$ and eq. (2) can be rewritten as a stochastic differential equation of the form:

$$\mathrm{d}x(t) = \left[rx(t)\ln\frac{k}{x(t)} - h(e_0)x(t) \right]\mathrm{d}t - \rho x(t)\mathrm{d}\tilde{w}(t) \tag{3}$$

where $\tilde{w}(t)$ is white noise and $\rho > 0$ represents the disturbance intensity.

Let $\dot{w}(t) = -\dot{\tilde{w}}(t)$, then $\dot{w}(t)$ is also a white noise. In this case, eq. (3) can be rewritten as

$$\mathrm{d}x(t) = \left[rx(t)\ln\frac{k}{x(t)} - h(e_0)x(t) \right]\mathrm{d}t + \rho x(t)\mathrm{d}w(t) \tag{4}$$

which is called the stochastic Gompertz model with therapy.

When $h(e_0) = 0$, eq. (4) is reduced to:

$$\mathrm{d}x(t) = rx(t)\ln\frac{k}{x(t)}\mathrm{d}t + \rho x(t)\mathrm{d}w(t) \tag{5}$$

The stochastic Gompertz model eq. (5) is suitable to model the growth of a population consisting of a group of individuals of one or more similar species in the absence of migration and interaction with other species [16]. On the other hand, some scholars [18-22] used the model eq. (5) to forecast energy consumption. For example, Gutierrez *et al.* [23] forecasted natural-gas consumption in Spain, Adam *et al.* [20] considered peak electricity demand in Mauritius, Gutierrez *et al.* [22] investigated the total consumption of electrical power in Morocco, *etc.* However, so far as we know, little research has been done on the stochastic Gompertz model with therapy eq. (4).

The optimal harvesting policy has been discussed by a number of authors [24-37]. In particular, Zou *et al.* [37] considered the optimal effort for a stochastic Gompertz model by using the ergodic theory. They gave the optimal policy but did not obtain the explicit solution for stationary distribution because they believed the corresponding Fokker-Planck equation could not be solved easily. General methods on stochastic optimal harvesting problems are re-

lated to Fokker-Planck equations, time-averaging methods, or stochastic calculus, see [24-26, 38] and references therein. In many cases, the probability density of nonlinear random systems is very difficult to obtain. Some scholars have done very meaningful research on it. Chen and Rui [39] did further work in solving the FPK equation. In [39], a high-dimensional FPK equation is reduced to a 1-D or 2-D PDE by invoking the concept of equivalent drift coefficient. Li *et al.* [40] introduced new advances in the probability density evolution method for nonlinear stochastic systems and derived the generalized density evolution equation (GDEE).

The present paper is stimulated by Zou *et al.* [37] which mainly gave some mathematical contributions. The related papers also see [7-11, 16-23]. However, we find that such a model is more suitable for tumor growth [5, 6]. On the other hand, [37] suppose that the term of harvesting is a linear function of effort. We think that the effect of the therapy (or the harvesting policy) should be an increasing function of effort, which increases rapidly at the beginning and gradually slows down later, see eq. (2). In general, the treatment efforts have an obvious effect in the early stage and then became less and less apparent. This is mainly caused by tumor resistance. At the same time, the noise should also be produced during treatment, see eqs. (3) or (4). In fact, the estimations of such parameters had been recently considered in Li *et al.* [41] and references therein. In this paper, we give many numerical simulations except for some mathematical contributions such that we can give some help for the cancer treatments.

Equilibrium state and long-term performance

First of all, we consider eq. (1). Clearly, $x_1^* = k$ is the unique positive equilibrium of eq. (1). Note that $\mathrm{d}x(t)/\mathrm{d}t>0$ for $x < k$ and that $\mathrm{d}x(t)/\mathrm{d}t<0$ for $x > k$, thus, the positive equilibrium $x_1^* = k$ is stable.

Similarly, in eq. (2), the equilibrium point is $x_2^* = k\exp[-h(e_0)/r]$, and the equilibrium point x_2^* is also stable. It means that if we take suitable therapy, the tumor will not grow too big, the patient has the chance to survive.

Noting that x_2^* is not already equilibrium of stochastic eq. (4). It is natural to discuss what will happen to the solution $x(t)$ in the mean when $t \to \infty$ in eq. (4). Our main result is stated in the following proposition.

Theorem 1. For the arbitrary initial value $x(0) = x_0 > 0$, assume that $x(t)$ is a solution of eq. (4), then:

$$\lim_{t\to\infty} E[x(t)] = k\exp\left[-\frac{h(e_0)}{r} - \frac{0.25\rho^2}{r}\right]$$

and

$$\lim_{t\to\infty} D[x(t)] = k^2\,\mathrm{e}^{-\frac{2h(e_0)}{r}}\left(1-\mathrm{e}^{-\frac{\rho^2}{r}}\right)$$

Proof. By using Ito's formula, we can obtain a solution:

$$x(t) = \exp\left\{\mathrm{e}^{-rt}\ln x_0 + (1-\mathrm{e}^{-rt})\left[\ln k - \frac{h(e_0)}{r} - \frac{\rho^2}{2r}\right] + \rho\int_0^t \mathrm{e}^{-r(t-\tau)}\mathrm{d}w_\tau\right\}$$

of eq. (4) with the initial condition $P[x(0) = x_0] = 1$.

Let:

$$z_t = \rho \int_0^t \mathrm{e}^{-r(t-\tau)} \mathrm{d}w_\tau$$

then z_t is martingale, so $E(z_t) = 0$. By using the isometry property [42], we can also get that:

$$D(z_t) = \rho^2 E\left[\int_0^t \mathrm{e}^{-r(t-\tau)} \mathrm{d}w_\tau\right]^2 = \rho^2 \int_0^t \mathrm{e}^{-2r(t-\tau)} \mathrm{d}\tau = \frac{\rho^2}{2r}(1-\mathrm{e}^{-2rt})$$

That is, we have:

$$z_t \sim N\left[0, \frac{\rho^2}{2r}(1-\mathrm{e}^{-2rt})\right]$$

Denote:

$$\theta(t) = \exp\left\{e^{-rt}\ln x_0 + (1-e^{-rt})\left[\ln k - \frac{h(e_0)}{r} - \frac{\rho^2}{2r}\right]\right\}, \quad \text{then} \quad x(t) = \theta(t)e^{z_t}$$

Note that:

$$E[\exp(z_t)] = \exp\left(\frac{1}{2}Ez_t^2\right) = \exp\left[\frac{\rho^2}{4r}(1-\mathrm{e}^{-2rt})\right]$$

which implies that:

$$E[x(t)] = \exp\left\{\mathrm{e}^{-rt}\ln x_0 + (1-\mathrm{e}^{-rt})\left[\ln k - \frac{h(e_0)}{r} - \frac{\rho^2}{2r}\right] + \frac{\rho^2}{4r}(1-\mathrm{e}^{-2rt})\right\}$$

and that

$$\lim_{t\to\infty} E[x(t)] = k\mathrm{e}^{-\frac{h(e_0)}{r}-\frac{\rho^2}{4r}}$$

Similarly:

$$E[x(t)^2] = \exp\left\{\mathrm{e}^{-rt}\ln x_0^2 + (1-\mathrm{e}^{-rt})\left[\ln k^2 - \frac{2h(e_0)}{r} - \frac{\rho^2}{r}\right] + \frac{\rho^2}{r}(1-\mathrm{e}^{-2rt})\right\}$$

and

$$D[x(t)] = \exp\left\{\mathrm{e}^{-rt}\ln x_0^2 + (1-\mathrm{e}^{-rt})\left[\ln k^2 - \frac{2h(e_0)}{r} - \frac{\rho^2}{r}\right]\right\} \cdot$$
$$\cdot\left[\exp\frac{\rho^2}{r}(1-\mathrm{e}^{-2rt}) - \exp\frac{\rho^2}{2r}(1-\mathrm{e}^{-2rt})\right]$$

which implies that:

$$\lim_{t\to\infty} D[x(t)] = k^2 \mathrm{e}^{-\frac{2h(e_0)}{r}}\left(1-\mathrm{e}^{-\frac{\rho^2}{2r}}\right)$$

The proof is complete.

Remark 1. We find that:

$$x_3^* = k\mathrm{e}^{-\frac{h(e_0)}{r}-\frac{\rho^2}{4r}} < x_2^* = k\mathrm{e}^{-\frac{h(e_0)}{r}} < x_1^* = k$$

It means that both therapy and environmental fluctuations can make the tumor small in the mean.

Using the data given in [5, 6], $k = 2\cdot 10^6$, $x_0 = 10^3$, $r = 0.16$, $h(e_0) = 0.16$, $\rho = 0.2$, we can characterize the growth of tumors under three models, model (1) no therapy, model (2) with therapy, model (4) with therapy and fluctuations, see fig. 1.

As we know, we can seemingly cure any tumor patient now. The tumor cannot be gotten rid of completely in a long time. Maybe permanent and persistent of eq. (4) we will discuss in the following can show this phenomenon.

Definition 1. Equation (4) is said to be stochastically permanent [43] if for any $\varepsilon \in (0,1)$, there exist positive constants $\delta = \delta(\varepsilon)$ and $\xi = \xi(\varepsilon)$ such that

$$\liminf_{t\to+\infty} \inf P[x(t) \ge \delta(\varepsilon)] \ge 1-\varepsilon$$

and

$$\liminf_{t\to+\infty} P[x(t) \le \xi(\varepsilon)] \ge 1-\varepsilon$$

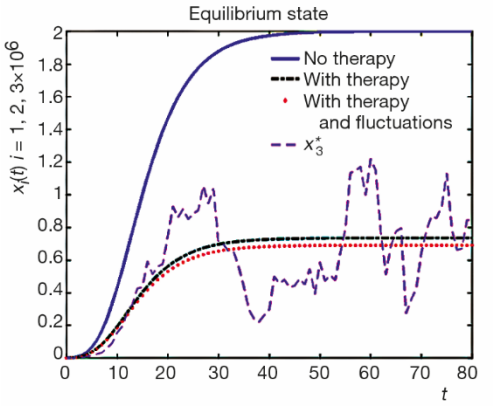

Figure1. Tumor growth under three models

where $x(t)$ is a solution of eq. (4) with the arbitrary initial value $x(0) = x_0 > 0$.

Theorem 2. Equation (4) is stochastically permanent.

Proof. For $\alpha > 0$, we have:

$$P[x(t) \le \alpha] = P[\theta(t)\mathrm{e}^{z_t} \le \alpha] = \Phi\left[\frac{\ln\alpha - \ln\theta(t)}{\sqrt{D(z_t)}}\right]$$

Note that:

$$\lim_{t\to+\infty} \ln\theta(t) = \ln k - \frac{h(e_0)}{r} - \frac{\rho^2}{2r}, \quad \text{and} \quad \lim_{t\to+\infty} \sqrt{D(z_t)} = \frac{\rho}{\sqrt{2r}}$$

Thus, we can get that:

$$\lim_{t\to+\infty} P[x(t) \le \alpha] = \Phi\left\{\frac{\ln\alpha - \left[\ln k - \frac{h(e_0)}{r} - \frac{0.5\rho^2}{r}\right]}{\frac{\rho}{\sqrt{2r}}}\right\}$$

For any $\varepsilon \in (0,1)$, we choose that:

$$0 < \delta(\varepsilon) \le \exp\left\{\Phi^{-1}(\varepsilon)\frac{\rho}{\sqrt{2r}} + \ln k - \frac{h(e_0)}{r} - \frac{\rho^2}{2r}\right\}$$

then:

$$\lim_{t\to+\infty} P[x(t) \ge \delta(\varepsilon)] = 1 - \Phi\left\{\frac{\ln\delta(\varepsilon) - \left[\ln k - \frac{h(e_0)}{r} - \frac{0.5\rho^2}{r}\right]}{\frac{\rho}{\sqrt{2r}}}\right\} \ge 1-\varepsilon$$

Similarly, we take:

$$\xi(\varepsilon) \ge \exp\left[\Phi^{-1}(1-\varepsilon)\frac{\rho}{\sqrt{2r}} + \ln k - \frac{h(e_0)}{r} - \frac{\rho^2}{2r}\right]$$

then:

$$\lim_{t\to+\infty} P[x(t) \le \xi(\varepsilon)] = \Phi\left\{\frac{\ln\xi(\varepsilon) - \left[\ln k - \frac{h(e_0)}{r} - \frac{0.5\rho^2}{r}\right]}{\frac{\rho}{\sqrt{2r}}}\right\} \ge 1-\varepsilon$$

The proof is completed.

Remark 2. In the study of population systems, permanence is one of the most important and interesting characteristics, meaning that the population system will survive in the future. Although the tumor cannot be removed completely, many patients can survive with tumors.

Definition 2. Equation (4) is said to be persistent in mean [44] if:

$$\liminf_{t\to+\infty} \frac{1}{t}\int_0^t x(s)\mathrm{d}s > 0 \quad \text{a.s.}$$

where $x(t)$ is a solution of eq. (4) with the arbitrary initial value $x(0) = x_0 > 0$.

Theorem 3. Equation (4) is persistent in the mean.

Indeed, we can conclude it from *Theorem 2* of [37]:

$$\lim_{t\to+\infty} \frac{1}{t}\int_0^t x(s)\mathrm{d}s = \lim_{t\to+\infty} E[x(t)] = ke^{-\frac{h(e_0)}{r}-\frac{\rho^2}{4r}} > 0$$

Remark 3. Persistence is another expression of survival of the population.

From *Theorem 2* and *Theorem 3*, and Remarks 3 and 4, even if we take therapy and there are environmental fluctuations, the tumor does not go extinct. Well-known, current chemotherapy or radiotherapy treatments is a double-edged sword. It can kill not only tumor cells but also normal cells. In most cases, cancer cannot be cured. So in cases that are beyond cure, the clinical prerogative is changed to extending life. This means that the tumor is no

longer aggressively attacked, and instead, only the drugs necessary to prevent patient death are applied until the inevitable occurs. Perhaps this mindset shift is unnecessary; instead, the goal could always be control of the tumor, whether that be successful eradication or not, this would be a more realistic yardstick for treatment success [15].

Optimal therapy policy

The very natural question is, how much do we pay the efforts of therapy in order to achieve the best therapeutic effect? The problem is similar to that of the optimal harvesting policy of renewable resources. Classical methods on stochastic optimal harvesting problems are related to Fokker-Planck equations, time-averaging methods ergodic theory, or stochastic calculus, such as [24-38] and references therein. In what follows, we will discuss the optimal therapy policy of eq. (4) by using Fokker-Planck equation [45, 46].

Let $m(x) = rx(t)\ln k/[x(t)] - h(e_0)x(t)$, $\sigma(x) = \rho x$.

Therefore, the Fokker-Planck equation corresponding to eq. (4) is:

$$\frac{\partial p(x,t,e_0)}{\partial t} = -\frac{\partial}{\partial x}[m(x)p(x,t,e_0)] + \frac{1}{2}\frac{\partial^2}{\partial x^2}[\sigma^2(x)p(x,t,e_0)]$$

Thus, the equation satisfied by the stationary distribution is:

$$\frac{\mathrm{d}}{\mathrm{d}x}[m(x)p(x,e_0)] - \frac{1}{2}\frac{\mathrm{d}^2}{\mathrm{d}x^2}[\sigma^2(x)p(x,e_0)] = 0$$

So:

$$J(x) = m(x)p(x,e_0) - \frac{1}{2}\frac{\mathrm{d}}{\mathrm{d}x}[\sigma^2(x)p(x,e_0)]$$

must be constant. It is easy to see that $\lim_{x\to 0} J(x) = 0$. Equation (4) has an explicit solution:

$$p(x,e_0) = N(e_0)x^{\frac{2r\ln k - 2h(e_0)}{\rho^2} - 2 - \frac{r}{\rho^2}\ln x}$$

where

$$N(e_0) = \frac{\sigma^2(x_0)p(x_0,e_0)}{\rho^2}\exp\left[-\frac{2r\ln k - h(e_0)}{\rho^2}\ln x_0 + \frac{r}{\rho^2}\ln^2(x_0)\right], \quad x_0 > 0$$

$N(e_0)$ is determined by $1 = \int_0^{+\infty} N(e_0)x^{\frac{2r\ln k - 2h(e_0)}{\rho^2} - 2 - \frac{r}{\rho^2}\ln x}\mathrm{d}x$. Obviously:

$$N(e_0) = \left[\int_0^{+\infty} x^{\frac{2r\ln k - 2h(e_0)}{\rho^2} - 2 - \frac{r}{\rho^2}\ln x}\mathrm{d}x\right]^{-1}$$

The improper integral is convergent for all the $h(e_0) \in [0, +\infty)$. Let $\ln x = t$, then:

$$\int_0^{+\infty} x^{\frac{2r\ln k - 2h(e_0)}{\rho^2} - 2 - \frac{r}{\rho^2}\ln x}\mathrm{d}x = \rho\sqrt{\frac{\pi}{r}}\mathrm{e}^{\frac{[r\ln k - h(e_0) - \frac{\rho^2}{2}]^2}{\rho^2 r}}$$

Then:

$$p(x,e_0)=\frac{1}{\rho}\sqrt{\frac{r}{\pi}}\mathrm{e}^{-\frac{r}{\rho^2}b_1^2}x^{\frac{2r\ln k-2h(e_0)}{\rho^2}-2-\frac{r}{\rho^2}\ln x} \tag{6}$$

Similar to [24-28, 37] and references therein, we will give the curative effect of therapy expressed

$$F(e_0)=E[h(e_0)X]=\int_0^{+\infty}h(e_0)xp(x,e_0)\mathrm{d}x=ke^{-\frac{\rho^2}{4r}}h(e_0)\mathrm{e}^{-\frac{h(e_0)}{r}}$$

Since:

$$\lim_{h(e_0)\to 0}h(e_0)\mathrm{e}^{-\frac{h(e_0)}{r}}=0 \quad \text{and} \quad \lim_{h(e_0)\to+\infty}h(e_0)\mathrm{e}^{-\frac{h(e_0)}{r}}=0$$

then $F(0) = 0$ and $F(+\infty) = 0$.

Let $f(y) = y\mathrm{e}^{(-y/r)}$. So $f(y)$ is increasing as $y<r;$ and decreasing as $y>r$. It is easy to see:

$$r=\arg\max_y f(y)$$

Hence:

$$F(e_0)=k\mathrm{e}^{-\frac{\rho^2}{4r}}f[h(e_0)]$$

reach the maximum at $e_0^*=h^{-1}(r),$ and:

$$F(e_0^*)=rk\mathrm{e}^{-\frac{\rho^2}{4r}-1}$$

At last, the corresponding variance of the curative effect of chemotherapy is:

$$D_s^*=E^2[h(e_0^*)X]-\{E[h(e_0^*)X]\}^2=\int_0^{+\infty}x^2h^2(e_0^*)p(x,e_0^*)\mathrm{d}x-\left(rke^{-\frac{\rho^2}{4r}-1}\right)^2=$$

$$=r^2k^2e^{-2}\left(1-e^{-\frac{\rho^2}{2r}}\right)$$

The result show when therapeutic agents item $h(e_0)$ equals to the intrinsic growth rate, the tumor growth is slowest.

Given data of Ehrilich under three situations [5, 6],

– $r=h(e_0),\ k=2\cdot10^6,\ x_0=10^3,\ r=0.16,\ h(e_0)=0.16,\ \rho=0.2,$
– $r>h(e_0),\ k=2\cdot10^6,\ x_0=10^3,\ r=0.16,\ h(e_0)=0.08,\ \rho=0.2,$
– $r<h(e_0),\ k=2\cdot10^6,\ x_0=10^3,\ r=0.16,\ h(e_0)=0.32,\ \rho=0.2.$

The curative effect of chemotherapy is characterized by fig. 2.

Remark 4. By eq. (6), the stationary distribution x^* of Model (4) is lognormal distribution, *i.e.*:

$$\ln x^* \sim N\left[\ln k - \frac{h(e_0)}{r} - \frac{\rho^2}{2r}, \frac{\rho^2}{2r}\right]$$

If we take the following values:

– $k = 2\cdot 10^6$, $r = 0.16$, $h(e_0) = 0.16$, $\rho^2 = 0.04$;
– $k = 10^6$, $r = 0.16$, $h(e_0) = 0.16$, $\rho^2 = 0.04$; the distributions of $\ln x^*$ have different mean but the same standard deviation.

If we take the following values:

– $k = 2\cdot 10^6$, $r = 0.16$, $h(e_0) = 0.16$, $\rho^2 = 0.32$;
– $k = 5.436\cdot 10^6$, $r = 0.16$, $h(e_0) = 0.16$, $\rho^2 = 0.64$; the distributions of $\ln x^*$ have different standard deviation but the same mean, fig. 3.

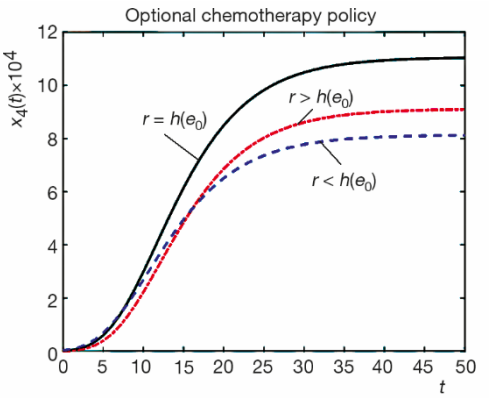

Figure 2. Therapy effect on cancer growth

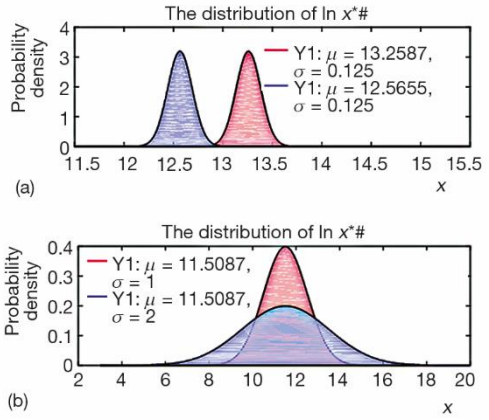

Figure 3. The distributions of lnx^*

Conclusions

The size of the tumor described by the Gompertz Model (4) with therapy and environmental fluctuations will oscillate around the mean $x_3^* = k\exp[-h(e_0)r^{-1} - 0.25\rho^2 r^{-1}]$ as $t \to +\infty$, and its equilibrium point is greater than that of the Gompertz Model (2) with therapy. It concludes that both therapy and environmental fluctuations can make the tumor small for a long time.

The tumor model given in eq. (4) is stochastically permanent and persistent. It means even if we take therapy and there are environmental fluctuations, the tumor does not go extinct.

When the intensity of the chemotherapy e_0 takes $h^{-1}(r)$ in eq. (4), the treatment effect is the best. The stationary distribution of Model (4) is lognormal distribution.

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