

A stochastic and state space model for tumour growth and applications

Wai-Yuan Tan^{a*}, Weiming Ke^b and G. Webb^c

^aDepartment of Mathematical Sciences, The University of Memphis, Memphis, TN, USA;

^bDepartment of Mathematics and Statistics, South Dakota State University, Brookings, SD, USA;

^cDepartment of Mathematics, Vanderbilt University, Nashville, TN, USA

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We develop a state space model documenting Gompertz behaviour of tumour growth. The state space model consists of two sub-models: a stochastic system model that is an extension of the deterministic model proposed by Gyllenberg and Webb (1991), and an observation model that is a statistical model based on data for the total number of tumour cells over time. In the stochastic system model we derive through stochastic equations the probability distributions of the numbers of different types of tumour cells. Combining with the statistic model, we use these distribution results to develop a generalized Bayesian method and a Gibbs sampling procedure to estimate the unknown parameters and to predict the state variables (number of tumour cells). We apply these models and methods to real data and to computer simulated data to illustrate the usefulness of the models, the methods, and the procedures.

Keywords: generalized Bayesian approach; Gompertz growth of cancer tumour; multilevel Gibbs sampling procedure; probability distributions; statistical model; state space model; stochastic model

1. Introduction

It has long been documented that the growth of cancer tumours follows a sigmoidal growth curve, exhibiting at first a phase of exponential growth and later a phase of slowed growth. The character of such curves is simulated by various mathematical formulations, including deterministic models, stochastic models, and cellular automata models. The most recognized pattern of tumour growth is Gompertz growth, which has been utilized by many researchers to provide a basis for description and prediction, including [6,7,8,14,15,27,33,35,37,38,40–42,44,45,73]. To explain the Gompertzian growth pattern of cancer tumours, many phenomenological rationales have been proposed based on tumour cell population heterogeneity, tumour mass geometry, or tumour environmental constraints [2,19,24,25,30,39]. The model in Refs. [24,25] demonstrated that the Gompertz growth of tumours resulted from the increased transition of proliferating cells (cancer stem cells) to quiescent cells (differentiated cells) as tumour mass increased. This model complies with the basic theoretical view of cancer as heterogeneous populations consisting of a minority of tumourigenic cancer stem cells and a majority of other non-tumourigenic cells ([4,5]). The number of these cancer stem cells may be as few as 100 and tumour growth is generated only by these cells ([4,5]). Furthermore, therapeutic intervention results in complex alteration of the growth characteristics of these

*Corresponding author. Email: waitan@memphis.edu

heterogeneous populations. Recent studies and observations from cancer molecular biology have provided strong support for the existence of quiescent cancer cells and cancer stem cells and for the dynamics as described in Refs. [24,25] in the growth of tumour, thus providing strong biological support for the model of Refs. [24,25]; see [20,31,34,43,46].

While various models provide a rational explanation of Gompertzian growth of tumours, application of these models to experimental and clinical tumours confront practical limitations. First, these models are typically deterministic, and assume that all response variables and input variables are deterministic functions of time, ignoring completely the randomness of these variables. Because the fundamental biological processes involved are stochastic, ignoring their inherent randomness may lead to misleading and erroneous results. Second, even if deterministic Gompertz growth models are theoretically sound, it is often difficult to fit the models to actual data and estimate their unknown parameters. The objective of this paper is to overcome these limitations by extending the deterministic model of Refs. [24,25] to a stochastic state space model for Gompertz growth of cancer tumours. In this stochastic state space model, the stochastic system model is a stochastic extension of the model by Refs. [24,25], whereas the observation model is statistical and is based on the count of the total number of tumour cells over time. By using this state space model, we will develop a generalized Bayesian approach to estimate the relevant cancer parameters, predict tumour growth patterns, and validate the models based on recent experimental data. We will apply this model to some experimental data to demonstrate the application and usefulness of the model and methods to assess growth of cancer tumours. We note in passing that stochastic Gompertz models of tumour growth have also been considered by the first author ([51,52]) and by others ([2,3,23]) but these models have never been combined with statistical models to estimate parameters and to predict state variables. Also these models were developed through stochastic birth–death processes and diffusion processes by incorporating the Gompertz behaviour of tumour growth into the proliferation rates and diffusion rates, ignoring the biological dynamic and the interaction between different types of cells.

In Section 2 we will develop a stochastic model for Gompertz growth of cancer tumours based on heterogeneity of tumour cell populations. In Section 3 we will develop a state space model for cancer tumours by combining the model in Section 2 with a statistical model based on the total number of tumour cells over time. In Section 4 we will develop procedures based on multi-level Gibbs sampling to estimate the unknown parameters and to predict the state variables. In Section 5 we will apply the model and the methods to real data, and illustrate the usefulness and application of the model and methods of this paper. Finally in Section 6 we will discuss further the basic model and methods proposed by this paper and suggest possible other applications.

2. A stochastic model for cancer tumour growth

To develop a stochastic model for tumour growth we follow [24,25] and assume that cancer tumours are heterogeneous populations consisting of two sub-populations of tumour cells: tumour stem cells and tumour quiescent cells. Only tumour stem cells can divide and proliferate giving rise to new tumour stem cells and new quiescent cells. Quiescent cells do not divide and hence do not proliferate; however, quiescent cells can be induced by some genetic or epigenetic change to become tumour stem cells. [24,25] have shown that the above mechanism of quiescent cells is a major driving force for generating Gompertz growth curves for tumours. (This mechanism is strongly supported by recent observations from cancer molecular biology; see [20,31,34,43,46].)

Let $N(t)$ denote the total number of tumour cells at time t , $P(t)$ the total number of tumour stem cells at time t , and $Q(t)$ the total number of tumour quiescent cells at time t . Thus, $N(t) = P(t) + Q(t)$. Set $\underline{X}(t) = \{P(t), Q(t)\}'$. To describe the stochastic growth of this tumour, we employ a two-dimensional stochastic process $\underline{X}(t)$ with continuous time $t \geq 0$, which is basically a two-dimensional Markov process with continuous time and discrete state space $S = \{(i, j), i, j = 0, 1, \dots, \infty\}$.

2.1 The traditional Kolmogorov approach

Denote by $P\{P(t) = i, Q(t) = j | P(0) = P_0, Q(0) = Q_0\} = P_{ij}(t)$ and $\phi(x, y; t)$ the probability generating function (PGF) of $P_{ij}(t)$. Let $\{b_p(t), d_p(t)\}$ denote the birth rate and the death rate of the tumour stem cells at time t respectively, and $d_q(t)$ the death rate of tumour quiescent cells at time t . Let $r_0(t)$ denote the transition rate of $P \rightarrow Q$ at time t for tumour stem cells to become tumour quiescent cells, and let $r_1(t)$ denote the transition rate of $Q \rightarrow P$ at time t for tumour quiescent cells to become tumour stem cells. Following [24,25], we assume $b_p(t) > 0$, $d_p(t)$ and $d_q(t)$ are non-negative constants, $r_0(t)$ is a non-negative non-decreasing function of $E\{N(t)\}$ and $r_1(t)$ a non-negative non-increasing function of $E\{N(t)\}$. Then it can be shown that $\phi(x, y; t)$ satisfies the following Kolmogorov forward equation (see Remark 1):

$$\begin{aligned} \frac{\partial}{\partial t} \phi(x, y; t) = & \{[x(x-1)b_p(t) - (x-1)d_p(t)] + (y-x)r_0(t)\} \frac{\partial}{\partial x} \phi(x, y; t) \\ & + \{(1-y)d_q(t) + (x-y)r_1(t)\} \frac{\partial}{\partial y} \phi(x, y; t), \end{aligned} \quad (1)$$

with initial condition $\phi(x, y; 0) = x^{P_0} y^{Q_0}$.

The above partial differential equation is quite difficult to solve. Furthermore, even if a solution is obtainable, it is often difficult to apply it to estimate parameters and to fit data. Thus, we use an alternative approach through stochastic differential equations. It is shown in the Appendix that the two approaches are equivalent, but the latter approach can yield more useful results than possible by the traditional approach. For example, as illustrated in Sections (2.3) and (2.4), the latter approach would not only provide equations for the expected numbers and the variances and covariances of the state variables, but also would provide a means to derive the probability distributions of the state variables.

Remark 1 : The traditional approach in standard textbooks of stochastic processes (see for example, [9]) is to derive Kolmogorov forward equations for probabilities of the state variables. These are systems of infinitely many differential equations involving transition probabilities. By using these equations, one then derives partial differential equations for the probability generating functions. The transition probabilities of the processes are then derived by taking partial derivatives of these probability generating functions and by setting the dummy variable to be zero. This standard approach has been used by the first author ([52]) to derive partial differential equations for probability generating functions of transition probabilities, and consequently the probabilities of tumour cell counts and the time evolution of tumours. The same approach has been used to derive Equation (1) above. Because this approach is extremely complicated, the first author ([53,54]) has proposed an alternative approach through stochastic differential equations. This is the approach used here and given in the Appendix.

2.2 The stochastic differential equations of the state variables

To derive stochastic differential equations for the state variables $P(t)$ and $Q(t)$, we define the following transition variables:

- $B_p(t)$ = Number of births of proliferating cells during $[t, t + \Delta t)$;
- $F_p(t)$ = Number of proliferating cells that become quiescent during $[t, t + \Delta t)$;
- $F_q(t)$ = Number of quiescent cells that become proliferating during $[t, t + \Delta t)$;
- $D_p(t)$ = Number of deaths of proliferating cells during $[t, t + \Delta t)$;
- $D_q(t)$ = Number of deaths of quiescent cells during $[t, t + \Delta t)$.

Then it is easily seen that given $\bar{X}(t)$, to the order of $o(\Delta t)$, the conditional probability distribution of $\{B_p(t), D_p(t), F_p(t)\}$ and the conditional probability distribution of $\{D_q(t), F_q(t)\}$ are multinomial distributions with parameters given by $[P(t); b_p(t)\Delta t, d_p(t)\Delta t, r_0(t)\Delta t]$ and $[Q(t); d_q(t)\Delta t, r_1(t)\Delta t]$, respectively. That is, using standard probability and statistical notation ([26]), we have:

$$\{B_p(t), D_p(t), F_p(t)\} | \bar{X}(t) \sim \text{Multinomial} [P(t); b_p(t)\Delta t, d_p(t)\Delta t, r_0(t)\Delta t], \quad (2)$$

$$\{D_q(t), F_q(t)\} | \bar{X} \sim \text{Multinomial} [Q(t); d_q(t)\Delta t, r_1(t)\Delta t] \quad (3)$$

Equation (2) is equivalent to stating that the conditional probability of $\{B_p(t) = j_1, D_p(t) = j_2, F_p(t) = j_3\}$ given $\{P(t) = n_1, Q(t) = n_2\}$ is, with $j_4 = n_1 - \sum_{u=1}^3 j_u$:

$$P\{B_p(t) = j_1, D_p(t) = j_2, F_p(t) = j_3 | P(t) = n_1, Q(t) = n_2\} = \binom{n_1}{j_1, j_2, j_3} [b_p(t)\Delta t]^{j_1} \\ \times [d_p(t)\Delta t]^{j_2} [r_0(t)\Delta t]^{j_3} [1 - b_p(t)\Delta t - d_p(t)\Delta t - r_0(t)\Delta t]^{j_4},$$

where $\binom{n_1}{j_1, j_2, j_3} = \frac{n_1!}{\prod_{u=1}^3 j_u!}$.

Similarly, Equation (3) is equivalent to stating that the conditional probability of $\{D_q(t) = i_1, F_q(t) = i_2\}$ given $\{P(t) = n_1, Q(t) = n_2\}$ is, with $i_3 = n_2 - \sum_{u=1}^2 i_u$:

$$P\{D_q(t) = i_1, F_q(t) = i_2 | P(t) = n_1, Q(t) = n_2\} = \binom{n_2}{i_1, i_2} [d_q(t)\Delta t]^{i_1} \\ \times [r_1(t)\Delta t]^{i_2} [1 - d_q(t)\Delta t - r_1(t)\Delta t]^{i_3},$$

where

$$\binom{n_2}{i_1, i_2} = \frac{n_2!}{\prod_{u=1}^2 i_u!}.$$

From Equations (2) and (3), it follows that $E\{B_p(t) | \bar{X}(t)\} = P(t)b_p(t)\Delta t$, $E\{D_p(t) | \bar{X}(t)\} = P(t)d_p(t)\Delta t$, $E\{F_p(t) | \bar{X}(t)\} = P(t)r_0(t)\Delta t$, $E\{D_q(t) | \bar{X}(t)\} = Q(t)d_q(t)\Delta t$, and $E\{F_q(t) | \bar{X}(t)\} = Q(t)r_1(t)\Delta t$.

During the time interval $[t, t + \Delta t]$, define the following random noises:

$$\begin{aligned}\epsilon_1(t)\Delta t &= [B_p(t) - P(t)b_p(t)\Delta t] - [D_p(t) - P(t)d_p(t)\Delta t] \\ &\quad - [F_p(t) - P(t)r_0(t)\Delta t] + [F_q(t) - Q(t)r_1(t)\Delta t];\end{aligned}$$

$$\begin{aligned}\epsilon_2(t)\Delta t &= [F_p(t) - P(t)r_0(t)\Delta t] - [D_q(t) - Q(t)d_q(t)\Delta t] \\ &\quad - [F_q(t) - Q(t)r_1(t)\Delta t];\end{aligned}$$

From Equations (2) and (3), it is obvious that the above random noises are linear combinations of multinomial random variables. Further, by the conservation law, we have the following stochastic differential equations for $P(t)$ and $Q(t)$ (see Remark 2):

$$\begin{aligned}\Delta P(t) &= P(t + \Delta t) - P(t) = B_p(t) - D_p(t) - F_p(t) + F_q(t) \\ &= \{[b_p(t) - d_p(t) - r_0(t)]P(t) + r_1(t)Q(t)\}\Delta t + \epsilon_1(t)\Delta t,\end{aligned}\quad (4)$$

$$\begin{aligned}\Delta Q(t) &= Q(t + \Delta t) - Q(t) = F_p(t) - D_q(t) - F_q(t) \\ &= \{r_0(t)P(t) - [d_q(t) + r_1(t)]Q(t)\}\Delta t + \epsilon_2(t)\Delta t.\end{aligned}\quad (5)$$

In the above equations, it can easily be shown that the random noises $\epsilon_1(t)$ and $\epsilon_2(t)$ have expected value zero and are uncorrelated with the state variables $P(t)$ and $Q(t)$. Further, by using the above conditional probability distributions of $\{B_p(t), D_p(t), F_p(t)\}$ and $\{D_q(t), F_q(t)\}$ given $X(t)$, the variances and co-variance of these random variables are easily obtained as $\text{COV}\{\epsilon_i(t)\Delta t, \epsilon_j(t)\Delta t\} = Q_{ij}(t)\Delta t + o(\Delta t)$, where

$$Q_{11}(t) = [b_p(t) + d_p(t) + r_0(t)]E\{P(t)\} + r_1(t)E\{Q(t)\},$$

$$Q_{22}(t) = [d_q(t) + r_1(t)]E\{Q(t)\} + r_0(t)E\{P(t)\},$$

$$Q_{12}(t) = -r_0(t)E\{P(t)\} - r_1(t)E\{Q(t)\}.$$

Remark 2 : Equations (4) and (5) are stochastic equations because all variables in the equations are random variables as each equation contains a random noise term. These stochastic equations are derived through biological mechanisms and biological stochastic transitions. Notice that for fixed Δt , the random noises in the equations are linear combinations of multinomial random variables. In the limit as Δt goes to zero, in most cases these random noises may be approximated by Brownian motion and Wiener processes; in these cases the above equations reduce to Ito equations (see for example [70]).

2.3 The expected numbers and the variances and covariances of the state variables

Let $u_p(t) = E\{P(t)\}$ and $u_q(t) = E\{Q(t)\}$ denote the expected numbers of $P(t)$ and $Q(t)$, respectively. Then, by taking expectations of Equations (4) and (5) on both sides, we

obtain the following differential equations for $u_p(t)$ and $u_q(t)$:

$$\frac{d}{dt}u_p(t) = [b_p(t) - d_p(t) - r_0(t)]u_p(t) + r_1(t)u_q(t), \quad (6)$$

$$\frac{d}{dt}u_q(t) = r_0(t)u_p(t) - [d_q(t) + r_1(t)]u_q(t). \quad (7)$$

Equations (6) and (7) are exactly the same equations as the equations of $\{P(t), Q(t)\}$ from the deterministic model given in Refs. [24,25]. (In the deterministic model, $P(t) = u_p(-t), Q(t) = u_q(t)$.) It follows that the results for the deterministic model given by Refs. [24,25] are equivalent to working with the mean numbers of the stochastic model. In this sense one may consider the deterministic model of Refs. [24,25] as a special case of the above stochastic model. Notice, however, by working with the stochastic model one may derive many useful results which are not possible by working with the deterministic model. In particular, one may derive the variances and covariances of the state variables, which may be used to assess how some risk factors affect the variation of the state variables. (As an illustration, see [60].) In fact, by using the approach given by [60], we have the following equations for the variance $V_P(t) = \text{Var}\{P(t)\}$ of $P(t)$, the variance $V_Q(t) = \text{Var}\{Q(t)\}$ of $Q(t)$, and the covariance $C_{PQ}(t) = \text{Cov}\{P(t), Q(t)\}$ between $P(t)$ and $Q(t)$:

$$\frac{d}{dt}V_P(t) = 2[b_p(t) - d_p(t) - r_0(t)]V_P(t) + 2r_1(t)C_{PQ}(t) + Q_{11}(t),$$

$$\frac{d}{dt}V_Q(t) = 2r_0(t)C_{PQ}(t) - 2[d_q(t) + r_1(t)]V_Q(t) + Q_{22}(t),$$

$$\frac{d}{dt}C_{PQ}(t) = r_0(t)V_P(t) + [b_p(t) - d_p(t) - d_q(t) - r_0(t) - r_1(t)]C_{PQ}(t) + r_1(t)V_Q(t) + Q_{12}(t).$$

As in Ref. [60], one may use the above equations to assess how some risk factors affect the variances and covariance of the state variables. Similarly, it is straightforward to derive equations for higher moments and cumulants of the state variables ($P(t)$, $Q(t)$) but the formulae are too complicated to be of much use; we will thus not go any further here.

2.4 The probability distributions of the state variables

Using the stochastic equations of the state variables as given in (4) and (5), besides the expected values and the variances and covariance of the state variables, one may also derive probability distributions of the state variables. This provides a significant advantage of the stochastic model over the deterministic model, because one may not only use this probability distribution to assess the stochastic impact of the model but also provide a useful means to estimate efficiently unknown parameters, to predict outcomes of state variables, and to validate the model.

To derive this distribution, discretize the time scale by letting $\Delta t = 1$ correspond to some small time interval. Then the state variables are $X = \{X(t), t = 0, 1, \dots, t_n\}$, where t_n is the most recent time of interest. By Markov theory, the probability density

of \mathbf{X} is then:

$$P\{\mathbf{X}\} = P\{\underline{X}(0)\} \prod_{t=1}^{t_n} P\{\underline{X}(t)|\underline{X}(t-1)\}, \tag{8}$$

where $P\{\underline{X}(0)\}$ is the probability distribution density of $\underline{X}(0)$ and $P\{\underline{X}(t)|\underline{X}(t-1)\}$ the conditional probability density of $\underline{X}(t)$ given $\underline{X}(t-1)$.

By using the stochastic equations in (4) and (5) with $\Delta t = 1$ and by using the conditional probability distributions of $\{B_p(t), D_p(t), F_p(t)\}$ and $\{D_q(t), F_q(t)\}$ given $\underline{X}(t)$ as given in Equations (2) and (3), $P\{\underline{X}(t)|\underline{X}(t-1)\}$ is readily derived as (see Remark 3):

$$\begin{aligned} P\{\underline{X}(t)|\underline{X}(t-1)\} &= \sum_{i_1=0}^{P(t)} \sum_{i_2=0}^{P(t)-i_1} \sum_{j=0}^{Q(t)} \binom{P(t)}{i_1, i_2} \binom{Q(t)}{j} [b_p(t)]^{i_1} [r_0(t)]^{i_2} \\ &\times [d_p(t)]^{g_1(t)} [1 - b_p(t) - d_p(t) - r_0(t)]^{P(t+1)-j} \\ &\times [r_1(t)]^j [d_q(t)]^{g_2(t)} [1 - d_q(t) - r_1(t)]^{Q(t+1)-i_2}, \end{aligned} \tag{9}$$

where

$$\binom{P(t)}{i, j} = \frac{P(t)!}{(i!)(j!)[(P(t)-i-j)!]}, \binom{Q(t)}{j} = \frac{Q(t)!}{j![(Q(t)-j)!]}, g_1(t) = P(t) - P(t+1) - i_1 - i_2 + j,$$

and

$$g_2(t) = Q(t+1) - i_2.$$

Remark 3 : Equation (9) is the standard notation in probability and statistics for the probability density function that gives the probability values of the random variables ([26]). For example, the conditional probability of $\{P(t+1) = j_1, Q(t+1) = j_2\}$ given $\{P(t) = i_1, Q(t) = i_2\}$ is given by Equation (9) by substituting the values $\{P(t+1) = j_1, Q(t+1) = j_2\}$ and $\{P(t) = i_1, Q(t) = i_2\}$.

3. A state space model for cancer tumour growth

A state space model of a system is a stochastic model of the system consisting of two sub-models: The stochastic system model, which is the stochastic model of the system and the observation model, which is a statistical model relating some available data to the system. A state space model of a system combines a stochastic model of the system with a statistical model of the system based on some observed data from the system. As such, it extracts biological information from the system via its stochastic system model and integrates this information with data through its observation equation. Thus, as illustrated in the books by [53], Chapter 6; [54], Chapters 8 and 9) and in [61], a state space model of the system is advantageous over the stochastic model of the system alone and the statistical model of the system alone in several aspects. In particular, the state space model has the following advantages over the stochastic model used alone or statistical model used alone ([53], Chapter 6; [54], Chapters 8–9; [61]):

- (1) The statistical model alone or the stochastic model alone very often are not identifiable and cannot provide information regarding some of the parameters and variables. These problems usually disappear in state space models. For

some specific examples see [11,53], Chapter 5) and [67,68].

- (2) A state space model provides an optimal procedure to update the model by new data, which may become available in the future. This is the smoothing step of the state space models (see ([13,21,48])).
- (3) The state space model provides an optimal procedure via Gibbs sampling to estimate simultaneously the unknown parameters and the state variables of interest (see [67,68]).
- (4) The state space model provides a means to combine information from various sources. For some examples see [58].

Many natural systems are highly complex and require integration of information from many possible models and many data sources to be realistic and applicable. This complexity leads to the state space modelling approach (see Remark 4), which is made practical by the advance of biometric technology and bioinformatics.

For the growth of tumours, the available data are usually the observed total number of tumour cells in the tumour over time. It is thus possible to construct a statistical model for this observed data for tumour growth. Combining this statistical model with the stochastic model given in Section 2, we have then a state space model for the growth of a tumour. In this state space model, the stochastic system model is represented by the stochastic Equations (4) and (5) and the probability distributions given in Section (2.3); the observation model of this state space model is a statistical model based on data of the observed total number of tumour cells in the tumour over time.

Remark 4 : The state space model was originally proposed by Kalman in the early 1960s for engineering control and communication [32]. Since then it has been used successfully as a powerful tool in aero-space research, satellite research, and missile research. It has also been used by economists in econometrics research ([28]) and by mathematician and statisticians in time series research [1,16]) to solve many challenging problems, which appear to be extremely difficult with other approaches. It was first proposed by Tan and his associates for AIDS research and for cancer research [55,57–59,62–68,71–72].

3.1 The stochastic system model, the expanded model and the probability distributions

To apply the stochastic system model and to implement the Gibbs sampling procedure to estimate unknown parameters, we expand the model by defining dummy state unobservable variables $\underline{U}(t) = \{B_p(t), F_p(t), F_q(t)\}'$ and put $\underline{U} = \{\underline{U}(t), t = 0, 1, \dots, t_n - 1\}$. Then, by using the conditional probability distributions of $\{B_p(t), D_p(t), F_p(t)\}$ and $\{D_q(t), F_q(t)\}$ given $\underline{X}(t)$ as given in Section (2.2), one can easily generate $\underline{U}(t)$ stochastically; and given $\{\underline{X}(t), \underline{U}(t)\}$ one can easily generate $\underline{X}(t + 1)$ stochastically. The conditional probability density of $\underline{U}(t)$ given $\underline{X}(t)$ is:

$$\begin{aligned}
 P\{\underline{U}(t)|\underline{X}(t)\} &= \binom{P(t)}{B_p(t), F_p(t)} [b_p(t)]^{B_p(t)} [r_0(t)]^{F_p(t)} [1 - b_p(t) - r_0(t)]^{P(t) - B_p(t) - F_p(t)} \\
 &\times \binom{Q(t)}{F_q(t)} [r_1(t)]^{F_q(t)} [1 - r_1(t)]^{Q(t) - F_q(t)}. \tag{10}
 \end{aligned}$$

The conditional probability density of $X(t+1)$ given $\{X(t), U(t)\}$ is:

$$\begin{aligned}
 P\{U(t+1)|X(t), U(t)\} &= \binom{P(t) - B_p(t) - F_p(t)}{\xi(t)} \left(\frac{d_p(t)}{1 - b_p(t) - r_0(t)} \right)^{\xi(t)} \\
 &\times \left(1 - \frac{d_p(t)}{1 - b_p(t) - r_0(t)} \right)^{P(t+1) - F_q(t)} \binom{Q(t) - F_q(t)}{\eta(t)} \\
 &\times \left(\frac{d_q(t)}{1 - r_1(t)} \right)^{\eta(t)} \left(1 - \frac{d_q(t)}{1 - r_1(t)} \right)^{Q(t+1) - F_p(t)}, \quad (11)
 \end{aligned}$$

where $\xi(t) = P(t) - P(t+1) - B_p(t) - F_p(t) + F_q(t)$, and $\eta(t) = Q(t) - Q(t+1) + (t) = Q(t) - Q(t+1) + F_p(t) - F_q(t)$.

The joint probability density of $\{\mathbf{X}, \mathbf{U}\}$ is:

$$P\{\mathbf{X}, \mathbf{U}\} = P\{X(0)\} \prod_{t=1}^{t_n} P\{X(t)|X(t-1), U(t-1)\} \times P\{U(t-1)|X(t-1)\}. \quad (12)$$

Notice that by summing over all elements of $U(t)$ in $P\{X(t+1)|X(t), U(t)\}P\{U(t)|X(t)\}$ over the sample space of $U(t)$, one obtains $P\{X(t+1)|X(t)\}$ as given in Equation (9). Thus one may derive $P\{\mathbf{X}\}$ as given in Equation (8) by summing over all elements of \mathbf{U} over the sample space of \mathbf{U} .

3.2 The observation model

Assume that the observed number of tumour cells in the tumour are counted at times $\{t_j, j = 1, \dots, n\}$ and denote these observed numbers by $\{Y(j), j = 1, \dots, n\}$. Then the observation model is represented by the following statistical model:

$$\begin{aligned}
 Y(j) &= N(t_j) + [N(t_j)]^{1/2}e(j) = [P(t_j) + Q(t_j)] + [P(t_j) + Q(t_j)]^{1/2}e(j), \quad j \\
 &= 1, \dots, n, \quad (13)
 \end{aligned}$$

where $e(j)$ is the random measurement error for measuring $Y(j)$.

One may assume that the $e(j)$'s are independently distributed as normal variables with mean 0 and variance σ^2 and that the $e(j)$'s are independently distributed of the random noises $\epsilon_i(t)$'s. Put $\mathbf{Y} = \{Y(j), j = 1, \dots, n\}$. Then, the conditional probability density of \mathbf{Y} given $\{\mathbf{X}, \mathbf{U}\}$ and given the parameters Θ is, with $t_0 = 0$:

$$P\{\mathbf{Y}|\mathbf{X}, \mathbf{U}, \Theta\} = \prod_{j=1}^n f\{Y(j); N(t_j), \sigma^2\}, \quad (14)$$

where

$$f(x; N(t_j), \sigma^2) = \{\sigma\sqrt{2\pi N(t_j)}\}^{-1} \exp\left\{-\frac{1}{2\sigma^2 N(t_j)}[x - N(t_j)]^2\right\}. \quad (15)$$

The joint probability density of $\{\mathbf{X}, \mathbf{U}, \mathbf{Y}\}$ given the parameters Θ is:

$$P\{\mathbf{X}, \mathbf{U}, \mathbf{Y}|\Theta\} = P\{\underline{X}(0)\} \prod_{j=1}^n f\{Y(j); N(t_j), \sigma^2\} \times \prod_{t=t_{j-1}+1}^{t_j} P\{\underline{X}(t)|\underline{X}(t-1), \underline{U}(t-1)\} \\ \times P\{\underline{U}(t-1)|\underline{X}(t-1)\}. \quad (16)$$

In the above density, the unknown parameters are $\Theta = \{b_p(t), d_p(t), d_q(t), r_0(t), r_1(t), \sigma^2\}$. It is reasonable to assume $\{b_p(t) = b_p, d_p(t) = d_p, d_q(t) = d_q\}$ ([25]). One may also assume that during the time interval $L_j = [s_{j-1}, s_j)$ ($s_j > s_{j-1}, j = 1, \dots, m; s_0 = 0, s_m = t_n$), we have $\{r_0(t) = r_0(j), r_1(t) = r_1(j)\}$ for all $t \in L_j$. Then the unknown parameters are $\Theta = \{b_p, d_p, d_q, \sigma^2, r_0(j), r_1(j), j = 1, \dots, m\}$.

Using the density of Equation (16), the likelihood function of Θ given $\{\mathbf{X}, \mathbf{U}, \mathbf{Y}\}$ is:

$$L\{\Theta|\mathbf{X}, \mathbf{U}, \mathbf{Y}\} \propto \prod_{t=1}^{t_n} \{b_p^{B_p(t)} d_p^{\xi(t)} [r_0(t)^{F_p(t)} [1 - b_p - d_p - r_0(t)]^{P(t+1)-F_q(t)} d_q^{\eta(t)} \\ \times [r_1(t)]^{F_q(t)} [1 - d_q - r_1(t)]^{Q(t+1)-F_p(t)}\} \{\sigma^2\}^{-n/2} \exp\left\{-\frac{n}{2\sigma^2} \hat{\sigma}^2\right\} \\ = [b_p]^{\sum_{t=1}^{t_n} B_p(t)} [d_p]^{\sum_{t=1}^{t_n} \xi(t)} [1 - b_p - d_p]^{\sum_{t=1}^{t_n} [P(t+1)+F_p(t)-F_q(t)]} \\ \times [d_p]^{\sum_{t=1}^{t_n} \eta(t)} [1 - d_q]^{\sum_{t=1}^{t_n} [Q(t+1)-F_p(t)+F_q(t)]} \\ \times \prod_{j=1}^m \left(\frac{r_0(j)}{1 - b_p - d_p}\right)^{\sum_{i=s_{j-1}+1}^{s_j} F_p(i)} \left(1 - \frac{r_0(j)}{1 - b_p - d_p}\right)^{\sum_{i=s_{j-1}+1}^{s_j} [P(t+1)-F_q(t)]} \\ \times \prod_{j=1}^m \left(\frac{r_1(j)}{1 - d_q}\right)^{\sum_{i=s_{j-1}+1}^{s_j} F_q(i)} \left(1 - \frac{r_1(j)}{1 - d_q}\right)^{\sum_{i=s_{j-1}+1}^{s_j} [Q(t+1)-F_p(t)]} \\ \times \{\sigma^2\}^{-n/2} \exp\left\{-\frac{n}{2\sigma^2} \hat{\sigma}^2\right\}, \quad (17)$$

where $\hat{\sigma}^2 = 1/n \sum_{j=1}^n (1/N(t_j)) [Y(j) - N(t_j)]^2$.

4. The generalized Bayesian procedure for estimating unknown parameters

In this section, we propose a generalized Bayesian approach to estimate the unknown parameters, to predict state variables, and to validate the model. This approach combines the prior distribution of the parameters with the joint density of $\{\mathbf{Y}, \mathbf{X}, \mathbf{U}\}$ given by Equation (16). It follows that besides drawing information from the statistical model via the probability distribution of \mathbf{Y} and information from the prior distribution of Θ , this approach also incorporates and integrates information from the stochastic system model via the probability distribution of $\{\mathbf{X}, \mathbf{U}\}$. This additional information from $\{\mathbf{X}, \mathbf{U}\}$ provides a significant advantage of the generalized Bayesian approach over the traditional Bayesian approach, which in turn is advantageous over the classical sampling theory approach (see [12]).

To illustrate the approach, let $P\{\Theta\}$ be the prior distribution of Θ . Then using Equation (17), the conditional posterior distribution of Θ given $\{\mathbf{X}, \mathbf{U}, \mathbf{Y}\}$ is:

$$P\{\Theta|\mathbf{X}, \mathbf{U}, \mathbf{Y}\} \propto P\{\Theta\} L\{\Theta|\mathbf{X}, \mathbf{U}, \mathbf{Y}\}. \quad (18)$$

Using Equations (12), (16) and (18), one may then generate Θ from the posterior distribution $P\{\Theta|\mathbf{Y}\}$ via the multi-level Gibbs sampling procedure given in Refs. [49] and

[54]. Similarly, by using the Gibbs sampling procedure, one may also generate the state variables $\{\mathbf{X}, \mathbf{U}\}$ given \mathbf{Y} . Given $\{\mathbf{X}, \mathbf{U}\}$ and given Θ , the predicted \mathbf{Y} 's are then generated by using Equation (14).

4.1 The prior distribution of Θ

For the prior distribution of Θ , we will basically use conjugate prior if previous studies are available. That is, we assume $P(\Theta)$ as:

$$\begin{aligned}
 P(\Theta) &\propto [b_p]^{m_b-1} [d_p]^{m_d-1} [1 - b_p - d_p]^{k_f-1} [d_q]^{m_q-1} [1 - d_q]^{k_q-1} \\
 &\times \prod_{j=1}^m \left(\frac{r_0(j)}{1 - b_p - d_p} \right)^{m_{r_0}-1} \left(1 - \frac{r_0(j)}{1 - b_p - d_p} \right)^{k_{r_0}-1} \\
 &\times \prod_{j=1}^m \left(\frac{r_1(j)}{1 - d_q} \right)^{m_{r_1}-1} \left(1 - \frac{r_1(j)}{1 - d_q} \right)^{k_{r_1}-1} \\
 &\times \{\sigma^2\}^{-n_0/2} \exp \left\{ -\frac{1}{2\sigma^2} \sigma_0^2 \right\}, \tag{19}
 \end{aligned}$$

where $\{m_b, m_d, m_{r_0}, m_{r_1}, k_f, k_q, k_{r_0}, k_{r_1}, n_0, \sigma_0^2\}$ are hyper-parameters.

In the above prior distribution, the hyper-parameters are positive constants and can be estimated by data from previous studies or prior information if such previous studies are available. In the event that our prior knowledge is vague and imprecise, we then follow [10] to assume a non-informative prior $P\{\Theta\} \propto \{\sigma^2\}^{-1}$, unless otherwise stated.

From Equation (17), if one assumes a non-informative prior distribution for Θ as above, then the conditional posterior distribution of $(n/\sigma^2)\hat{\sigma}^2$ given $\{\mathbf{X}, \mathbf{U}, \mathbf{Y}\}$ is a central chi-square variate with degrees of freedom n ; the conditional posterior distribution of (b_p, d_p) given $\{\mathbf{X}, \mathbf{U}, \mathbf{Y}\}$ is a bi-variate beta vector with parameters

$$\left\{ \sum_{t=1}^{t_n} B_p(t) + 1, \sum_{t=1}^{t_n} \xi(t) + 1, \sum_{t=1}^{t_n} [P(t+1) + F_p(t) - F_q(t)] + 1 \right\};$$

the conditional posterior distribution of d_q given $\{\mathbf{X}, \mathbf{U}, \mathbf{Y}\}$ is a beta variate with parameters

$$\left\{ \sum_{t=1}^{t_n} \eta(t) + 1, \sum_{t=1}^{t_n} [Q(t+1) - F_p(t) + F_q(t)] + 1 \right\};$$

the conditional posterior distribution of $(r_0(j))/(1 - b_p - d_p)$ given $\{\mathbf{X}, \mathbf{U}, \mathbf{Y}\}$ is a beta variate with parameters

$$\left\{ \sum_{t=s_{j-1}+1}^{s_j} F_p(t) + 1, \sum_{t=s_{j-1}+1}^{s_j} [P(t+1) - F_q(t)] + 1 \right\};$$

the conditional posterior distribution of $(r_1(j))/(1 - d_q)$ given $\{\mathbf{X}, \mathbf{U}, \mathbf{Y}\}$ is a beta variate with parameters

$$\left\{ \sum_{t=s_{j-1}+1}^{s_j} F_q(t) + 1, \sum_{t=s_{j-1}+1}^{s_j} [Q(t+1) - F_p(t)] + 1 \right\}.$$

4.2 The multilevel Gibbs sampling procedure

Using the distribution results given in Section 3, one may use the multi-level Gibbs sampling procedures to estimate the unknown parameters Θ and to predict the state variables. These Gibbs sampling procedures ([49,54]) are given by the following loop:

- Given $\{\Theta, \mathbf{Y}\}$, generate $\{\mathbf{X}, \mathbf{U}\}$ from the conditional probability distribution of $\{\mathbf{X}, \mathbf{U}\}$ given $\{\mathbf{Y}, \Theta\}$. Since this conditional distribution is very complicated and not available, we use an indirect procedure due to [50] to implement this step. Given Θ , this indirect procedure first generates a large sample $\{\mathbf{X}^{(i)}, \mathbf{U}^{(i)}, i = 1, \dots, N\}$ of $\{\mathbf{X}, \mathbf{U}\}$ by using the stochastic equations (4) and (5), the probability distributions in Section 2 and in Equation (12); then by combining this large sample with the conditional density of \mathbf{Y} given $\{\mathbf{X}, \mathbf{U}, \Theta\}$ as given by Equation (14), one selects a $\{\mathbf{X}, \mathbf{U}\}$, say $\{X^{(*)}, U^{(*)}\}$, from the sample through the weighted Bootstrap method due to [50]. Then it can be shown that $\{X^{(*)}, U^{(*)}\}$ is a sample of size one from the density $P\{\mathbf{X}, \mathbf{U}|\mathbf{Y}, \Theta\}$ although the latter is not available; for proof and the weighted bootstrap procedure, see [54], Chapter 3).
- Using $\{X^{(*)}, U^{(*)}\}$ from Step 1, generate Θ (say $\Theta^{(*)}$) from the posterior distribution of Θ given $\{X = X^{(*)}, U = U^{(*)}, \mathbf{Y}\}$ given by Equation (18). As shown in Section (4.1) and in Equation (18), under non-informative prior this step can readily be implemented by using central chi-square variate and beta variate.
- With $\Theta = \Theta^{(*)}$ generated in Step 2, go to Step 1 and continue until convergence.

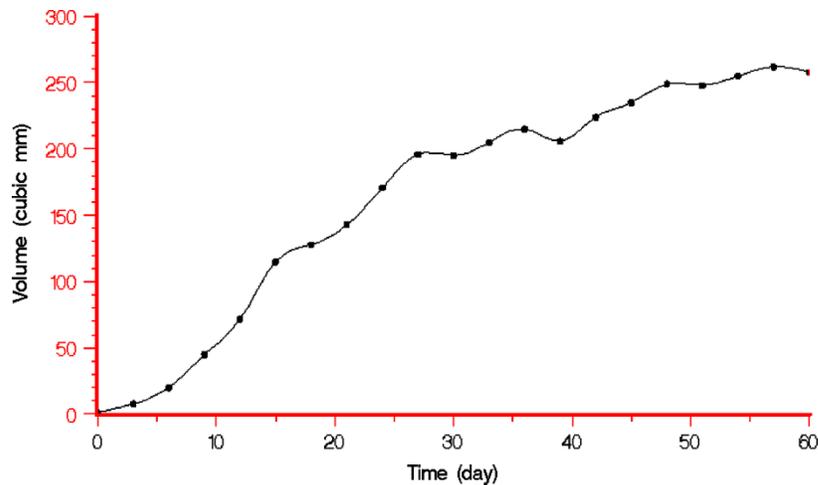


Figure 1. The growth curve of tumour induced by T53cl4 cells in a nude mouse treated with PNU153429.

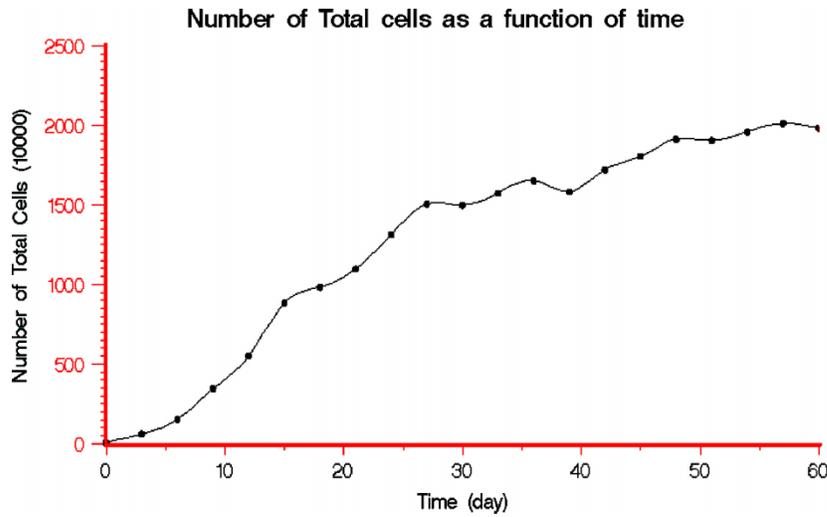


Figure 2. Modified growth curve of tumour induced by T53cl4 cells in a nude mouse treated with PNU153429.

The convergence of the above procedures have been proved in Chapter 3 of Ref. [54] and by Ref. [69]. At convergence, one then generates a random sample of $\{X, U\}$ from the conditional distribution $P\{X, U|Y\}$ of $\{X, U\}$ given Y , independently of Θ and a random sample of Θ from the posterior distribution $P\{\Theta|Y\}$ of Θ given Y , independently of $\{X, U\}$. Repeat these procedures and one then generates a random sample of size N of $\{X, U\}$ and a random sample of size M of Θ . One may then use the sample mean of Θ as estimate of Θ and the sample mean of $\{X, U\}$ as predicted values of $\{X, U\}$ and use the sample variances as the variances of these estimates and predicted values. Alternatively, one may also use Efron’s bootstrap method ([17]) to derive estimates of the standard errors of the estimates and predicted values.

Table 1. Estimates of parameters and standard errors.

Time (day)	Parameter	Estimate	Standard error	Minimum	Maximum
0–60	b_p	0.4203	0.0378	0.3866	0.4547
0–60	d_p	0.1213	0.0104	0.1028	0.1414
0–60	d_q	0.0716	0.0088	0.0575	0.0861
0–3	$r_0(t)$	0.0822	0.0063	0.0756	0.0908
4–6		0.1215	0.0112	0.1095	0.1334
7–9		0.1712	0.0207	0.1532	0.1912
10–12		0.2283	0.0213	0.2079	0.2488
13–18		0.2826	0.0265	0.2627	0.3179
19–36		0.3325	0.0284	0.3093	0.3615
37–60		0.3849	0.0326	0.3523	0.4176
0–3	$r_1(t)$	0.4123	0.0512	0.3987	0.4332
4–6		0.3574	0.0413	0.3382	0.3854
7–9		0.2912	0.0338	0.2725	0.3131
10–12		0.2357	0.0219	0.2107	0.2512
13–18		0.1687	0.0187	0.1375	0.1787
19–36		0.1149	0.0123	0.1043	0.1398
37–60		0.0751	0.0091	0.0612	0.0945

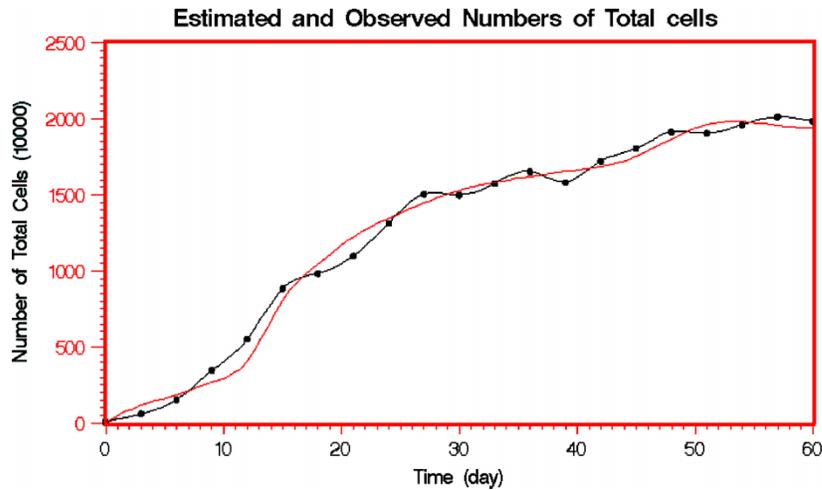


Figure 3. Estimated and observed numbers of total cells (—: estimated; -•-•-: observed).

Notice that these estimates of the parameters are equivalent to the posterior mean values of these parameters. As such, these estimates minimize the Bayesian risk under squared loss function, for proof, see [26].

5. An illustrative example

In this section we use the actual data from [47] to illustrate the application of the above model and methods. This data set gives the growth of tumours developed in nude mice inoculated with the T53 cell line. In this experiment, similar mice (equal age, equal weight and equal size) were examined daily until the appearance of a tumour with initial volume equal to 1 mm^3 . Afterward, the mouse was treated with PNU153429 (100 mg/kg of body weight) given intraperitoneally, and the tumour volume was measured every 3 days for 2 months. The growth curve of the tumours is given in Figure 1. The picture in Figure 1 clearly shows that the growth curve of cancer tumour fits a typical S-shape of the Gompertz curve.

The growth curve of the tumour given in Figure 1 is expressed using the volume (mm^3) of the tumour as its size. To apply the above state space model, we follow [29] to transform the three dimensional volume into number of cells by noting that on the average, 1 mm^3 volume contains 76,872 cells (see p. 36, [29]). This is presented in Figure 2.

Using the data in Figure 2 and assuming a non-informative uniform prior for the parameters, we have applied the multi-level Gibbs sampling procedure and the weighted Bootstrap procedure given in Section 4 to estimate the unknown parameters and the state variables. The parameters are the birth or division rate b_p of the proliferating cells, the

Table 2. Generated total numbers of proliferating and quiescent cells.

Time	0	5	10	15	20	25	30	35	40	45	50
Y	10	17	29	45	61	82	100	120	141	156	172
Time	55	60	65	70	75	80	85	90	95	100	
Y	187	201	211	221	231	239	244	250	258	265	

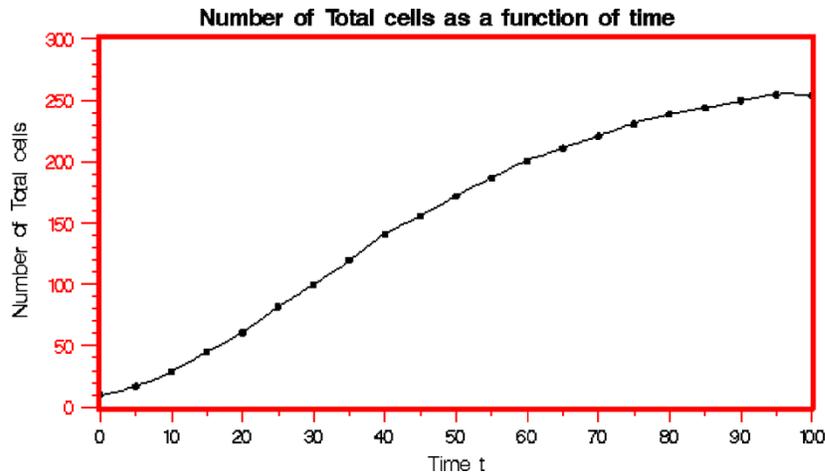


Figure 4. Generated numbers of total cancer tumour cells.

death rate of the proliferating cells d_p , the death rate of quiescent cells d_q , the transition rate $r_0(t)$ by which proliferating cells become quiescent cells, and the transition rate $r_1(t)$ by which the quiescent cells change into proliferating cells. Given in Table 1 are the estimates of the unknown parameters with the standard errors of the estimates obtained by using Efron’s bootstrap method ([17]). Plotted in Figure 3 are the predicted numbers of the state variables together with the respective observed numbers. From Figure 3, it is apparent that the predicted numbers of the total cells are very close to the observed numbers.

From results in Table 1, we have also observed the following interesting results:

- (1) The proliferation rate $\gamma_p = b_p - d_p$ is positive. It follows that the number of proliferating cells would increase with time. However, $r_0(t)$ also increases with

Table 3. Estimates of parameters and standard errors.

Time (day)	Parameter	Estimate	Standard error	Minimum	Maximum
0–100	b_p	0.2817	0.0266	0.2538	0.3074
0–100	d_p	0.1628	0.0141	0.1385	0.1903
0–100	d_q	0.0327	0.0047	0.0275	0.0462
0–5	$r_0(t)$	0.1242	0.0116	0.1126	0.1408
6–10		0.1851	0.0212	0.1675	0.1934
11–15		0.2442	0.0235	0.2232	0.2712
16–20		0.2853	0.0279	0.2579	0.2988
21–30		0.3364	0.0364	0.3227	0.3679
31–50		0.3841	0.0388	0.3593	0.4015
51–100		0.4253	0.0376	0.4023	0.4576
0–5	$r_1(t)$	0.3852	0.0401	0.3689	0.4131
6–10		0.3127	0.0322	0.2982	0.3353
11–15		0.2542	0.0306	0.2265	0.2732
16–20		0.2179	0.0224	0.1987	0.2433
21–30		0.1663	0.0155	0.1465	0.1797
31–50		0.1248	0.0112	0.1076	0.1486
51–100		0.0741	0.0082	0.0612	0.0978

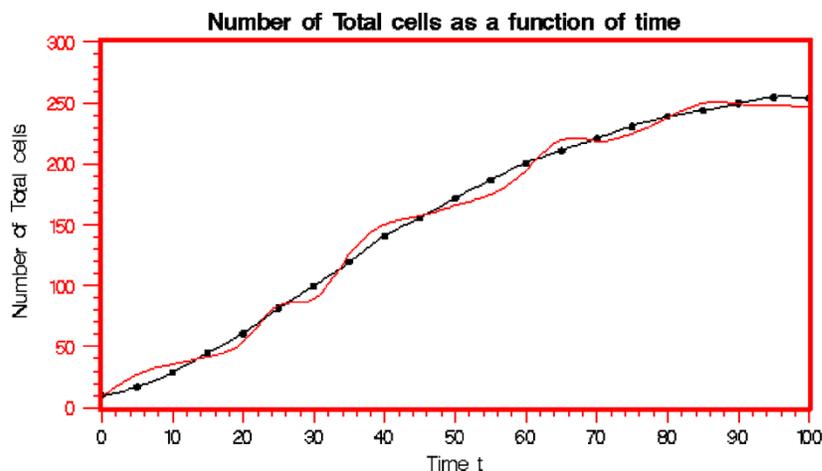


Figure 5. Estimated and observed numbers of total cancer tumour cells (—: estimated; -●-●-: observed).

time so that as time increases, more P cell will become Q cells. This will lead to the situation that the number of proliferating cells (P cells) would not change significantly with time.

- (2) $r_0(t)$ is a monotone increasing function of time with very small value $r_0(t) = 0.0822$ during the first 3 days, but increases to 0.3849 by 60 days. On the other hand, $r_1(t)$ is a monotone decreasing function of time with $r_1(t) = 0.4123$ during the first 3 days, but decreases to $r(t) = 0.0751$ by day 60. Notice also that $r_0(t) < r_1(t)$ during the first 12 days but $r_0(t) > r_1(t)$ during days 13–60. It follows that during the first 12 days, more Q cells would become P cells but the opposite is true during days 13–60. These results help explain why the population of cancer stem cells in tumours is in general not very large.

5.1 Simulation study

To further examine our approach, in this Section we have assumed some parameter values and generated some computer Monte Carlo data. Since the transition rate $r_0(t)$ at which proliferating cells become quiescent is a non-negative non-decreasing function of $N(t)$ and the transition rate $r_1(t)$ at which quiescent cells become proliferating is a non-negative non-increasing function of $N(t)$, we assumed that

$$r_0(t) = r_0(N(t)) = \frac{r_{00} \times N(t)}{r_{01} + N(t)}, \quad r_1(t) = r_1(N(t)) = \frac{r_{10} \times r_{11}}{r_{11} + N(t)},$$

where r_{00} , r_{01} , r_{10} , r_{11} are constants.

The generated numbers are given in Table 2 and plotted in Figure 4. The parameter values for generating these data are taken as $\{b = 0.3, d_p = 0.15, d_q = 0.03, r_{00} = 0.5, r_{01} = 40, r_{10} = 0.5, r_{11} = 40, P(0) = 5, Q(0) = 5\}$.

Using the data in Table 2 and assuming a non-informative uniform prior for the parameters, we have applied the procedures of Section 3 to estimate the unknown parameters and the state variables. Given in Table 3 are the estimates of the unknown

parameters. Plotted in Figure 5 are the predicted numbers of the state variables together with the generated numbers. It is apparent from results in Table 3 that the estimates are very close to its true values. From Figure 5, it is also apparent that the predicted numbers of the state variables are very close to the generated numbers. These results indicate that the methods we propose are quite promising and useful.

6. Discussion

In 1825 Benjamin Gompertz published an empirical law for the growth of populations given by the formula $N(t) = \alpha e^{\beta e^{-\gamma t}}$, which is a solution of the ordinary differential equation

$$\frac{d}{dt}N(t) = N(t)(\delta - \gamma \log(N(t))) \quad (20)$$

with $\alpha = e^{\delta/\gamma}$, $\beta = -\delta/\gamma$, and the initial value $N(0) = 1$. In Ref. [25] it was shown that the solution of the system of ordinary differential equations given by (6) and (7) with $b_p > d_p$, $\delta = b_p - d_p$, $d_q = 0$, $r_0(N) = \gamma(1 + \log(N))$, $r_1(N) \equiv 0$, $u_p(0) = 1$, and $u_q(0) = 0$ yields a solution $N(t)$ of (20) with $N(t) = u_p(t) + u_q(t)$. With $u_p(t)$ interpreted as the population of proliferating cells and $u_q(t)$ interpreted as the population of quiescent cells, the system of Equations (6) and (7) provides a rationale for the characteristic Gompertz form of tumour growth. Consequently, the principal mechanism driving the Gompertz growth form is the transition of proliferating cells to non-proliferating cells as the total cell count increases.

We have developed a stochastic model of tumour growth by following the basic mechanism given in Refs. [24,25]. We have shown that the deterministic model and the defining system of equations given in Refs. [24,25] are equivalent to the mean numbers of a corresponding stochastic model. Working with the stochastic model, however, provides several advantages: (a) the stochastic model allows derivation of the variances and covariances of the state variables, which may be used to assess risk factors effecting variation in the state variables and in prediction; (b) the stochastic model provides a formal means to assess effects of many stochastic input variables on the model and the system; (c) the stochastic model provides a formal means to give efficient estimates of unknown parameters and to validate the model through predicted numbers.

By using a stochastic equation approach and by discretizing the time scale, we have derived for the first time the probability distributions for the numbers of various types of tumour cells in Gompertz tumour growth. Such a derivation using the classical approach is extremely difficult and has not been attempted previously. By incorporating these probability distributions into state space models, we are then able to derive efficient procedures to estimate unknown parameters to predict state variables and to validate the model.

Our state space model combines a stochastic system model with a statistical model of data as data from the system become available. Because the available data for tumour growth are typically the total tumour cell count number over time, the observation model of our state model is based on this type of data set. Based on this state space model, we have further developed a generalized Bayesian approach to estimate the unknown parameters and to predict the state variables. This approach combines the joint density of observed data, state variables, and expanded state variables of the stochastic system with the prior distribution of the parameters. Because the approach we proposed draws information from three sources (the statistical model and data, the stochastic system

model, and the prior distribution of parameters), it can overcome many difficulties which would normally be encountered in estimating a large number of unknown parameters. For example, in many practical situations, if one uses the statistical model of data alone or stochastic model of state variables alone or deterministic model with least squares method to estimate unknown parameters, one usually encounters many problems of identifiability of parameters; that is, because of the limited amount of information, one can at most estimate functions of these parameters and cannot estimate all parameters. This has been illustrated in detail by [53], [54] for many AIDS and cancer problems. Notice that in the example in Section 5, there are 19 unknown parameters and the observed data points (> 20) are barely sufficient. Hence, using a statistical model alone would be very difficult and inefficient, as the information from the data is very limited. In our approach, the stochastic system model provides additional information besides the information from the statistical model and data, and the prior distribution of the parameters.

To illustrate the application of our model and methods, we used the data in Ref. [47] as an illustrative example. We obtained an excellent fit to this experimental data, due presumably to efficient estimation of the unknown parameters by the generalized Bayesian approach. The estimated parameters indicated that the population size of the proliferating cells (cancer stem cells) is stable and does not change significantly over time. To further illustrate the usefulness and effectiveness of our model and methods, we have generated some simulation data by computer. For the simulated data, the model and methods in this paper gave estimates which are very close to the true assumed values; also the predicted total number of cells are very close to the generated numbers. From these analyses, we believe that our model and methods will provide a useful approach to prediction of experimental and clinical tumour growth. For further applications more research is needed, and some key questions are: (1) Given available prior data or previous experiments, how can the prior distribution of the unknown parameters be constructed from these previous data sets? (2) How can one apply the model and methods to assess effects of cancer chemotherapy? (3) How can one apply the model and methods to develop efficient procedures for controlling tumour growth?

Acknowledgements

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Appendix: Equivalence of the traditional Markov theory approach and the stochastic differential equation approach

To prove the equivalence of the Markov theory approach and the stochastic differential equation approach, it suffices to show that the probability generating function of the probabilities of $\underline{X}(t)$ can be derived by the stochastic differential equations in (4) and (5). Notice that applying the stochastic equations in (4) and (5) we obtain:

$$\begin{aligned} \phi(x, y; t + \Delta t) &= E[x^{P(t+\Delta t)} y^{Q(t+\Delta t)}] \\ &= E\{x^{P(t)+B_p(t)-F_p(t)-D_p(t)+F_q(t)y^{Q(t)+F_p(t)-D_q(t)-F_q(t)}}\} \\ &= E\{(x^{P(t)} y^{Q(t)} x^{B_p(t)} (x^{-1})^{D_p(t)} (yx^{-1})^{F_p(t)} (y^{-1})^{D_q(t)} (xy^{-1})^{F_q(t)}\} \\ &= E\{(x^{P(t)} y^{Q(t)}) f_1(x, y; t, \Delta t) f_2(x, y; t, \Delta t)\}, \end{aligned}$$

where

$$\begin{aligned} f_1(x, y; t, \Delta t) &= E\{x^{B_p(t)} (x^{-1})^{D_p(t)} (yx^{-1})^{F_p(t)} | P(t)\} \\ &= \{1 + [(x-1)b_p(t) + (x^{-1}-1)d_p(t) + (yx^{-1}-1)r_0(t)]\Delta t\}^{P(t)} \\ &= 1 + P(t)h_1(x, y; t)\Delta t + o(\Delta t), \end{aligned} \quad (21)$$

where $h_1(x, y; t) = [(x-1)b_p(t) + (x^{-1}-1)d_p(t) + (yx^{-1}-1)r_0(t)]$, and $o(\Delta t)$ is defined by $\lim_{\Delta t \rightarrow 0} o(\Delta t)/\Delta t = 0$;

$$\begin{aligned} f_2(x, y; t, \Delta t) &= E\{(y^{-1})^{D_q(t)} (xy^{-1})^{F_q(t)} | Q(t)\} \\ &= \{1 + [(y^{-1}-1)d_q(t) + (xy^{-1}-1)r_1(t)]\Delta t\}^{Q(t)} \\ &= 1 + Q(t)h_2(x, y; t)\Delta t + o(\Delta t), \end{aligned}$$

where $h_2(x, y; t) = (y^{-1}-1)d_q(t) + (xy^{-1}-1)r_1(t)$.

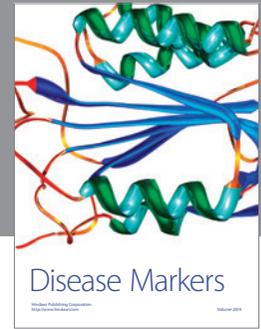
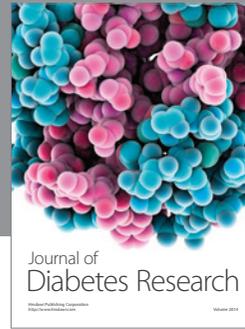
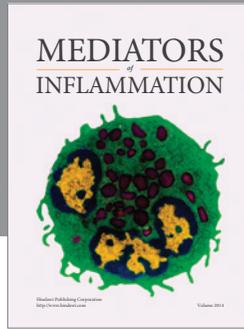
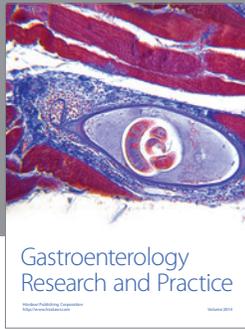
It follows that

$$\begin{aligned}\phi(x, y; t + \Delta t) &= E\{(x^{P(t)}y^{Q(t)})[1 + P(t)h_1(x, y; t)\Delta t + o(\Delta t)] \\ &\quad \times [1 + Q(t)h_2(x, y; t)\Delta t + o(\Delta t)]\} = E\{(x^{P(t)}y^{Q(t)}) \\ &\quad \times [1 + P(t)h_1(x, y; t)\Delta t + Q(t)h_2(x, y; t)\Delta t + o(\Delta t)]\} = \phi(x, y; t) \\ &\quad + xh_1(x, y; t)\left\{\frac{\partial}{\partial y}\phi(x, y; t)\right\}\Delta t + yh_2(x, y; t)\left\{\frac{\partial}{\partial y}\phi(x, y; t)\right\}\Delta t + o(\Delta t).\end{aligned}$$

In the above equation, notice that $xh_1(x, y; t) = x(x - 1)b_p(t) + (1 - x)d_p(t) + (y - x)r_0(t)$ and $yh_2(x, y; t) = (1 - y)d_q(t) + (x - y)r_1(t)$. On both sides of the above equation, subtracting $\phi(x, y; t)$, dividing by Δt and letting $\Delta t \rightarrow 0$, we obtain the partial differential equation for $\phi(x, y; t)$:

$$\begin{aligned}\frac{\partial}{\partial t}\phi(x, y; t) &= \{[x(x - 1)b_p(t) - (x - 1)d_p(t)] + (y - x)r_0(t)\}\frac{\partial}{\partial x}\phi(x, y; t) \\ &\quad + \{(1 - y)d_q(t) + (x - y)r_1(t)\}\frac{\partial}{\partial y}\phi(x, y; t),\end{aligned}\tag{22}$$

with initial condition $\phi(x, y; 0) = x^P y^Q$.



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