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Study of Birth-Death Processes with Immigration

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Abstract. Birth-death processes are applied in the modelling of many biological populations, such as tumour cells and viruses. Various studies have established that birth-death processes, which occur when the population size is zero, are not in-line with reality in many situations. Therefore, in this study, the birth-death processes with immigration were investigated. We considered two immigration policies. First, immigration is allowed if and only if the population size is zero. Second, immigration at a constant rate is allowed irrespective of the population size. Birth and death rates were chosen such that the mean population size is a Gompertz function when the immigration rate is zero. The transient population size probability was obtained for both cases. Several tumour growth datasets were fitted using the mean population size of the above models and standard birth-death model without immigration. The two models with immigration provided entirely different probabilities of the population size being zero at an arbitrary epoch when compared with the model without immigration. Moreover, all three models provided a similar fit to the data. For each of the datasets studied, the models that allowed immigration produced less variance than the non-immigration model.

Keywords: birth-death process; Gompertz function; immigration; tumour growth

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1. Introduction

Birth-death processes are considerably important tools in modelling many real-world phenomena, such as queues, inventory, evolution, population biology, and epidemiology. General inputs to the birth-death process are the birth and death rates. Although assuming these rates to be independent of time simplifies the analysis of the modelling stochastic process, in real-world applications, the above rates are often time- dependent. Kendall [15] studied a birth-death process in which birth and death rates were assumed as functions of time. The author provided the explicit expression for the expected population size, its variance, and the probability of extinction, and also discussed the possibility of a model with minimum variance, depending on the nature of the birth and death rates.

Often, biological applications demand the modelling of large populations. For example, studies have reported that tumours with a diameter of 1 mm may contain 10^6 tumour cells [13]. A mathematical model intended to predict the time when the tumour is 2 mm in diameter would need to address a significantly large population size. In such cases, the probability that the population size is equal to a particular value (e.g., 10^6) may not be significantly important to biologists. This could be the reason deterministic models are the first choice for a tumour mathematical model [26]. Some popular deterministic models include exponential, power law, Gompertz, logistic, generalised logistic, and von Bertalanffy models [4]. The growth pattern of human breast cancer shows that tumours do not grow exponentially after a certain period,

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and this is incorporated in the Gompertz model of cell growth [21]. Although this is the case, to obtain more details such as the variability in the size of the tumour or the probability of the tumour disappearing before gaining detectable size, a natural choice for a mathematical model would be a stochastic model [5, 26]. Speer et al. [25] developed a stochastic numerical model of breast cancer growth. This model suggests that Gomperzian kinetics govern tumour growth; however, from time to time, there is a random change in the growth rate. Mazlan and Rosli [19] described the growth process of breast cancer by including noisy behaviour in the Gomperzian model, and obtained better results for this stochastic model compared with those of its deterministic counterpart. Lo [17] proposed a stochastic nonlinear model of tumour growth based on the Gompertz growth law, in which the probability density function of the tumour size obeys a nonlinear Fokker-Planck equation that can be solved analytically. Lo [16] proposed a stochastic model of tumour cell growth based on the deterministic Gompertz law of cell growth, which assumes a bound on the number of tumour cells. Tumour growth was studied as a diffusion approximation of a continuous time and density-dependent branching process with the Gompertz law as the deterministic counterpart [2, 14]. Hence, all the above studies can be considered as attempts to combine the advantages of a deterministic model with a more informative stochastic model.

Before we discuss some similar attempts in the case of birth-death processes, let us discuss the idea of combining deterministic models with a birth-death model. For example, consider the Gompertz model defined by the differential equation:

$$\frac{dN}{dt} = N(\beta - \alpha \log N), \quad t > 0,\ \alpha, \beta > 0 \tag{1}$$

where $N(t)$ is the population size at time t. The solution to Eq. (1) is given by:

$$N(t) = e^{(\frac{\beta}{\alpha} - (\frac{\beta - \alpha \log N_0}{\alpha})e^{-\alpha t})} \tag{2}$$

A random analogue of the above Gompertz model can be considered as a birth-death process in which a transition from state i can occur only to states $i-1$ or $i+1$ in a small interval of time. The transition from state i to $i-1$ is considered death, and the transition from i to $i+1$ is considered birth. Taking the birth rate as $\lambda(t) = \beta e^{-\alpha t}$ and $\mu(t) = \alpha \log N_0 e^{-\alpha t}$, the random analogue becomes Kendall's birth–death process [15].

Gompertz's birth-death process is shown as a special case of the non-homogeneous birth-death process in [27], which obtained the first four cumulants and absorption probabilities. The density-dependent birth-death process with a mean satisfying the logistic equation was given, and expressions for the probability generating function and stationary distributions were obtained in [22]. The solution of the associated Fokker-Planck equation was used to build a likelihood function for the unknown parameters. In the above study, the stochastic counterparts and relevant properties of the logistic growth model were considered and compared with those of other growth models.

According to [10], the absorbing state at zero in Kendall's process fails to mimic a real-world situation in which the reduction of cell size to zero does not occur. Therefore, the authors considered a random analogue of the Gompertz model as a pure birth process with an average value that was the same as that of the deterministic Gompertz model. A similar technique was considered in the logistic growth model [12]. According to Weedon-Fekjær et al. [30], Gompertz's and logistic models are popular for modelling tumour growth data. They did not consider the exponential growth model to be reliable. Because the logistic model behaves as an exponential model, when the maximum tumour volume is significantly large, the Gompertz model is more suitable for modelling tumour growth data. Motivated by these studies, we consider a birth–death analogue of the Gompertz model and the immigration of a single cell if and only if the cell size becomes zero to avoid the absorbing state. The model obtained differs

from the usual immigration model where immigration is allowed for any population size [9, 11]. Our immigration policy may be considered as a special case to the one studied by [23], which assumes that the immigration of particles occurs at a rate λb_k whenever the population size is zero. However, the birth and death rates are assumed to be $\frac{a_2}{n}$ and $\frac{a_0}{n}$, respectively, such that the cumulative birth and death rates remain constant. Conversely, the cumulative birth and death rates in this study were $n\lambda$ and $n\mu$ respectively. Thus, the analysis of modelled Markov chain becomes entirely different. We conducted a transient study of the resulting model. The type of immigration policy discussed in this study can be seen in polling models without switchover lines, which can be considered a multitype branching process with immigration only in state zero [1, 6]. Zheng et al. [31] considered a similar immigration policy with time-independent birth and death rates. This study differs from the aforementioned studies in that the birth and death rates are of the Gompertz type, which is time- dependent. Moreover, the average cell population size, which emerges from the stochastic model, was applied to model tumour growth data, such as to obtain a less variant stochastic model. Hence a comparison of three stochastic models, namely: i) a model with no immigration; ii) a model with immigration if and only if the population size is zero; and iii) a model with immigration irrespective of the population size, was conducted.

The reminder of this paper is organised as follows. In Section 2, we introduce the Markov chain model and study its transient characteristics. In Section 3, we compare the models with and without immigration by fitting the models to tumour growth data. Finally, Section 4 concludes the study.

2. Methodology

2.1. Birth-Death process with immigration only when the population size is zero

Here, we consider Kendall's birth-death process [15] in which immigration is allowed only when the population size is zero. We discuss two cases: first, constant birth and death rates, and second, time-dependent Gompertzian birth and death rates.

2.1.1. Constant birth and death rare case

Consider a Kendall's birth–death process $\{N(t); t \geq 0\}$ [15] in which immigration is allowed only when the population size is zero. Let γ, λ and μ denote constant immigration, birth, and death rates, respectively. The transition probabilities in $\{N(t)\}$ over an infinitesimal interval of length h are given by:

$$\begin{aligned} &P[N(t+h) = 1/N(t) = 0] = \gamma \\ &P[N(t+h) = j+1/N(t) = j] = j\lambda h + o(h), \quad j \geq 1, \\ &P[N(t+h) = j-1/N(t) = j] = j\mu h + o(h), \quad j \geq 1 \end{aligned} \tag{3}$$

where $o(h) \to 0$ as $h \to 0$.

It follows that $p_n(t)$ satisfies the differential difference equations:

$$p_0'(t) = -\gamma p_0(t) + \mu p_1(t) \tag{4}$$

$$p_1'(t) = \gamma p_0(t) - (\lambda + \mu)p_1(t) + 2\mu p_2(t) \tag{5}$$

$$p_n'(t) = (n-1)\lambda p_{n-1}(t) - n(\lambda + \mu)p_n(t) + (n+1)\mu p_{n+1}(t), \ n \geq 2. \tag{6}$$

We assume that $N(0) = 1$, such that:

$$p_1(0) = 1. \tag{7}$$

Consider the generating function:

$$P(z,t) = \sum_{n=0}^{\infty} p_n(t) z^n. \tag{8}$$

Equations (4)–(7) imply that $P(z,t)$ satisfies the partial differential equation:

$$\frac{\partial}{\partial t} P(z,t) - (\lambda z^2 - (\lambda+\mu)z + \mu) \frac{\partial}{\partial z} P(z,t) = \gamma(z-1)p_0(t), \tag{9}$$

with initial condition:

$$P(1,t) = 1, \; P(z,0) = z. \tag{10}$$

To find the solution of this equation, we introduce the auxiliary variable ζ such that:

$$\frac{dt}{d\zeta} = 1 \text{ and } \frac{dz}{d\zeta} = -(\lambda z^2 - (\lambda+\mu)z + \mu), \tag{11}$$

with initial conditions:

$$t = 0, \; z = \xi, \text{ when } \zeta = 0. \tag{12}$$

Eq. (11) yields:

$$t = \zeta \text{ and } \frac{dz}{(\lambda z^2 - (\lambda+\mu)z + \mu)} = -d\zeta. \tag{13}$$

By partial fractioning the left-hand side of Eq. (13), we obtain:

$$dz \left[\frac{1}{1-\frac{\mu}{\lambda}} \frac{1}{z-1} - \frac{1}{1-\frac{\mu}{\lambda}} \frac{1}{z-\frac{\mu}{\lambda}} \right] = -\lambda d\zeta, \tag{14}$$

which implies:

$$\log\left(\frac{z-1}{z-\frac{\mu}{\lambda}}\right) = (\mu-\lambda)\zeta + c_1. \tag{15}$$

Applying the initial condition in Eq. (12), we obtain:

$$\frac{z-1}{z-\frac{\mu}{\lambda}} = \exp((\mu-\lambda)\zeta) \left(\frac{\zeta-1}{\zeta-\frac{\mu}{\lambda}}\right), \tag{16}$$

which gives:

$$(z-1) = \frac{\phi(\zeta)}{1-\phi(\zeta)} \left(1-\frac{\mu}{\lambda}\right), \tag{17}$$

where:

$$\phi(\zeta) = \exp((\mu-\lambda)\zeta) \left(\frac{\zeta-1}{\zeta-\frac{\mu}{\lambda}}\right). \tag{18}$$

Now, Eq. (9) is reduced to the form:

$$\frac{dP}{dt}\frac{dt}{d\zeta} + \frac{dP}{dz}\frac{dz}{d\zeta} = \gamma(z(\zeta)-1)p_0(\zeta), \tag{19}$$

$$\frac{dP}{d\zeta} = \gamma(z(\zeta)-1)p_0(\zeta). \tag{20}$$

By integrating, we obtain:

$$P(z,t) = \int_0^{\zeta} \gamma \frac{\phi(u)}{1-\phi(u)} \left(1-\frac{\mu}{\lambda}\right) p_0(u)du + k, \tag{21}$$

where k is an integration constant. The initial conditions in Eq. (12) implies that $P(z,t) = \xi$, when $\xi = 0$, which gives $k = \xi$. Thus:

$$P(z,t) = \int_0^{\zeta} \gamma \frac{\phi(u)}{1-\phi(u)} \left(1 - \frac{\mu}{\lambda}\right) p_0(u)du + \xi. \tag{22}$$

Substituting ζ as t, we obtain:

$$P(z,t) = \int_0^{t} \gamma \frac{\phi(u)}{1-\phi(u)} \left(1 - \frac{\mu}{\lambda}\right) p_0(u)du + \xi. \tag{23}$$

To determine $p_0(t)$, we note that $P(0,t) = p_0(t)$. Hence, for a given t, $p_0(t)$ is obtained by selecting ξ such that $z = 0$ in Eq. (23).

From Eq. (16), it follows that when $z = 0$:

$$\xi = \frac{1}{1 - \frac{\lambda}{\mu}\exp(\lambda - \mu)t} - \frac{\mu}{\lambda}. \tag{24}$$

For the above ξ, Eq. (23) gives:

$$p_0(t) = \int_0^{t} \gamma \frac{\phi(u)}{1-\phi(u)} (1 - \frac{\mu}{\lambda}) p_0(u)du + \frac{1}{1 - \frac{\lambda}{\mu}\exp(\lambda - \mu)t} - \frac{\mu}{\lambda} \tag{25}$$

which is a Volterra integral equation of the second type. Efficient numerical methods are available for solving such equations (please refer to Brunner et al. [7]).

Note that Eq. (4) can be solved to obtain:

$$\exp(\gamma t)p_0(t) = \int_0^{t} \exp(\gamma u)\mu p_1(u)du. \tag{26}$$

Because $p_0(t)$ is known, the above equation can be considered a Volterra integral equation of the first type, which can be solved to obtain $p_1(t)$. Mirzaee [20] described a numerical procedure for solving the Volterra integral equations of the first type.

Expected value of $N(t)$.
Let $E(t) = E(N(t)) = \sum_{n=0}^{\infty} np_n(t)$.
Partially differentiating Eq. (9) with respect to z, we obtain:

$$\frac{\partial^2 P(z,t)}{\partial z \partial t} = \gamma p_0(t) + (\lambda z^2 - (\lambda + \mu)z + \mu)\frac{\partial^2 P(z,t)}{\partial z^2} + \frac{\partial P(z,t)}{\partial z}(2\lambda z - (\lambda + \mu)). \tag{27}$$

Note that $\frac{\partial P(z,t)}{\partial z}$ is $E(t)$, when $z = 1$.
When $z = 1$, we obtain the differential equation for expectation as:

$$E'(t) = \gamma p_0(t) + (\lambda - \mu)E(t). \tag{28}$$

By integrating, we obtain:

$$E(t)\exp((\mu - \lambda)t) = \int_0^{t} \gamma \exp((\mu - \lambda)u)p_0(u)du + c. \tag{29}$$

The initial condition, $E(0) = 1$, gives $c = 1$.

$$E(t) = \exp((\lambda - \mu)t)\left[\int_0^{t} \gamma \exp((\mu - \lambda)u)p_0(u)du + 1\right]. \tag{30}$$

Variance of $N(t)$.
Let $V(t) = V(N(t))$ be the variance of $N(t)$.
Partially differentiating Eq. (27) with respect to z, we obtain:

$$\frac{\partial^3 P(z,t)}{\partial z^2 \partial t} = (\lambda z^2 - (\lambda+\mu)z + \mu)\frac{\partial^3 P(z,t)}{\partial z^3} + 2\frac{\partial^2 P(z,t)}{\partial z^2}(2\lambda z - (\lambda+\mu)) + \frac{\partial P(z,t)}{\partial z}(2\lambda). \quad (31)$$

Note that $\frac{\partial^2 P(z,t)}{\partial z^2} - E(t) - E(t)^2$ is $V(t)$ when $z = 1$, which leads to the differential equation:

$$V'(t) - 2(\lambda - \mu)V(t) = \gamma p_0(t)(1 - 2E(t)) + (\lambda + \mu)E(t). \quad (32)$$

Thus, we obtain:

$$V(t) = \exp(2(\lambda-\mu)t)\left(\int_0^t (\gamma p_0(u)(1-2E(u)) + (\lambda+\mu)E(u))\exp(2(\mu-\lambda)u)du + c_1\right) \quad (33)$$

$V(0) = 0$, implies $c_1 = 0$.

2.1.2. Time-dependent Gompertzian birth and death rate case

Here, we assume that the birth and death rates are time-dependent, as given by $\lambda(t) = \beta e^{-\alpha t}$ and $\mu(t) = \alpha \log N_0 e^{-\alpha t}$. Note that Kendall's birth–death process [15] with these rates and without immigration implies that the expected value of $N(t)$ is a Gompertz function [10]. However, under the assumption of immigration, these rates yield a different $E(t)$. For more generality, we assume that $N(0) = N_0$. In this case, $P(z,t)$ satisfies the partial differential equation:

$$\frac{\partial}{\partial t}P(z,t) - \exp(-\alpha t)(\beta z^2 - (\beta + \alpha \log N_0)z + \alpha \log N_0)\frac{\partial}{\partial z}P(z,t) = \gamma(z-1)p_0(t) \quad (34)$$

with initial and boundary conditions:

$$p(\xi, 0) = \xi^{N_0},\ P(1,t) = 1,\ P(0,t) = p_0(t). \quad (35)$$

Proceeding in lines similar to those in the previous subsection, the generating functions $p_0(t)$, $p_1(t)$, expectation, and variance are obtained as:

$$P(z,t) = \int_0^t \gamma \frac{\phi(u)}{1-\phi(u)}\left(1 - \frac{\alpha \log N_0}{\beta}\right)p_0(u)du + \xi^{N_0} \quad (36)$$

where

$$\phi(u) = \exp\left(\frac{\beta - \alpha \log N_0}{\alpha}(\exp(-\alpha u) - 1)\right)\left[\frac{\xi - 1}{\xi - \frac{\alpha \log N_0}{\beta}}\right], \quad (37)$$

where ξ is given by:

$$\xi = \frac{1 - \exp(\frac{\beta - \alpha \log N_0}{\alpha}(1 - \exp(-\alpha t)))}{1 - \frac{\beta}{\alpha \log N_0}\exp(\frac{\beta - \alpha \log N_0}{\alpha}(1 - \exp(-\alpha t)))} \quad (38)$$

$\phi(u)$ is given by Eq. (37) for the above ξ, and $p_0(t)$ satisfies the Volterra integral equation of the second type:

$$\begin{aligned} p_0(t) = &\int_0^t \gamma \frac{\phi(u)}{1-\phi(u)}(1 - \frac{\alpha \log N_0}{\beta})p_0(u)du \\ &+ \left(\frac{1 - \exp(\frac{\beta - \alpha \log N_0}{\alpha}(1 - \exp(-\alpha t)))}{1 - \frac{\beta}{\alpha \log N_0}\exp(\frac{\beta - \alpha \log N_0}{\alpha}(1 - \exp(-\alpha t)))}\right)^{N_0} \end{aligned} \quad (39)$$

Further, $p_1(t)$ satisfies the Volterra integral equation of the first type:

$$\exp(\gamma t)p_0(t) = \int_0^t \exp(\gamma u)\alpha \log N_0 \exp(-\alpha u)p_1(u)du \tag{40}$$

$$E(t) = \exp\left(\frac{\alpha \log N_0 - \beta}{\alpha}\exp(-\alpha t)\right) \times \left[\int_0^t \gamma p_0(u)\exp(\frac{\beta - \alpha \log N_0}{\alpha}\exp(-\alpha u))du + N_0 \exp(\frac{\beta - \alpha \log N_0}{\alpha})\right] \tag{41}$$

$$V(t) = \exp\left(2\left(\frac{\alpha \log N_0 - \beta}{\alpha}\right)\exp(-\alpha t)\right)\vartheta(t), \tag{42}$$

where:

$$\vartheta(t) = \int_0^t (\gamma p_0(u)[1 - 2E(u)] + \exp(-\alpha u)(\beta + \alpha \log N_0)E(u)) \exp(2(\frac{\beta - \alpha \log N_0}{\alpha})\exp(-\alpha u)du) \tag{43}$$

2.2. Birth and Death process with immigration in all states

Here, we consider the birth–death process in which immigration occurs at a constant rate, irrespective of the population size. The immigration, birth, and death rates are described in Subsection 2.1.2. The transition probabilities over an infinitesimal interval of length h are given by:

$$\begin{aligned} P[N(t+h) = j+1/N(t) = j] &= j\lambda h + \gamma + o(h),\ j \geq 1 \\ P[N(t+h) = j-1/N(t) = j] &= j\mu h + o(h),\ j \geq 1 \end{aligned} \tag{44}$$

It follows that $p_n(t)$ satisfies the differential difference equations:

$$p_0'(t) = -\gamma p_0(t) + \alpha \log N_0 \exp(-\alpha t)p_1(t) \tag{45}$$

$$p_1'(t) = \gamma p_0(t) - (\beta \exp(-\alpha t) + \alpha \log N_0 \exp(-\alpha t) + \gamma)p_1(t) + 2\alpha \log N_0 \exp(-\alpha t)p_2(t) \tag{46}$$

$$p_n'(t) = ((n-1)\beta \exp(-\alpha t) + \gamma)p_{n-1}(t) - (n(\beta \exp(-\alpha t) + \alpha \log N_0 \exp(-\alpha t)) + \gamma)p_n(t) + (n+1)\alpha \log N_0 \exp(-\alpha t)p_{n+1}(t),\ n \geq 2 \tag{47}$$

Equations (44–47) imply that the generating function $P(z,t)$ satisfy the partial differential equation:

$$\frac{\partial}{\partial t}P(z,t) - \exp(-\alpha t)(\beta z^2 - (\beta + \alpha \log N_0)z + \alpha \log N_0)\frac{\partial}{\partial z}P(z,t) = \gamma(z-1)P(z,t). \tag{48}$$

To determine the solution of this equation, we introduce the auxiliary variable ζ such that:

$$\frac{dt}{d\zeta} = 1 \text{ and } \frac{dz}{d\zeta} = -(\exp(-\alpha t)(\beta z^2 - (\beta + \alpha \log N_0)z + \alpha \log N_0)), \tag{49}$$

with initial conditions:

$$t = 0,\ z = \xi^{N_0},\ \text{when } \zeta = 0. \tag{50}$$

Now, Eq. (48) reduces to the form:

$$\frac{dP}{d\zeta} = \gamma(z-1)P. \tag{51}$$

A similar procedure as in Subsection 2.1.1 gives:

$$P(z,t) = \exp\left(\gamma \int_0^t \frac{\phi(u)}{1-\phi(u)} \left(1 - \frac{\alpha \log N_0}{\beta}\right) du\right) \xi^{N_0}, \tag{52}$$

where ϕ is the same as in Eq. (37).

With ξ as given by Eq. (38), and $\phi(u)$ as given by Eq. (37) for this ξ, $p_0(t)$ satisfies the Volterra integral equation of the second type:

$$p_0(t) = \exp\left(\gamma \int_0^t \frac{\phi(u)}{1-\phi} \left(1 - \frac{\alpha \log N_0}{\beta}\right) du\right) \left(\frac{1 - \exp(\frac{\beta - \alpha \log N_0}{\alpha}(1 - \exp(-\alpha t)))}{1 - \frac{\beta}{\alpha \log N_0} \exp(\frac{\beta - \alpha \log N_0}{\alpha}(1 - \exp(-\alpha t)))}\right)^{N_0} \tag{53}$$

Furthermore, $p_1(t)$ satisfies the Volterra integral equation of the first type:

$$\exp(\gamma t) p_0(t) = \int_0^t \exp(\gamma u) \alpha \log N_0 \exp(-\alpha u) p_1(u) du. \tag{54}$$

The expectation and variance of $N(t)$ are given by:

$$E(t) = \exp\left(\frac{\alpha \log N_0 - \beta}{\alpha} \exp(-\alpha t)\right) \left(\int_0^t \gamma \exp\left(\frac{\beta - \alpha \log N_0}{\alpha} \exp(-\alpha u)\right) du + N_0 \exp\left(\frac{\beta - \alpha \log N_0}{\alpha}\right)\right) \tag{55}$$

$$V(t) = \exp\left(2\left(\frac{\alpha \log N_0 - \beta}{\alpha}\right) \exp(-\alpha t)\right) \vartheta_1(t) \tag{56}$$

$$\vartheta_1(t) = \int_0^t (\gamma + \exp(-\alpha u)(\beta + \alpha \log N_0) E(t)) \exp\left(2\left(\frac{\beta - \alpha \log N_0}{\alpha}\right) \exp(-\alpha u) du\right). \tag{57}$$

2.3. Birth and death processes with no immigration

To compare the models with and without immigration, we discuss the case of a birth–death process with 0 as the absorbing state. We derive their transient solution when the birth and death rates are of Gompertz nature using a method similar to that described in the previous section. We note that a solution to the above problem is given in [8] by exploiting the theory of the continued fraction to obtain the Laplace transforms of the transient probabilities.

We consider the birth–death process in Subsection 2.1.2 and assume that the immigration rate is zero. In lines similar to those in Subsection 2.1.2, the generating function is obtained as:

$$P(z,t) = \xi^{N_0}, \tag{58}$$

where:

$$\xi = \frac{z[\beta - \alpha \log N_0 f(t)] + \alpha \log N_0 (f(t) - 1)}{z(1 - f(t))\beta + [f(t)\beta - \alpha \log N_0]}, \tag{59}$$

with

$$f(t) = \exp\left(\frac{\alpha \log N_0 - \beta}{\alpha}(\exp(-\alpha t) - 1)\right) \tag{60}$$

By expanding the right-hand side of Eq. (59) as a Taylor series and equating the constant term and coefficient of z, we obtain $p_0(t)$ and $p_1(t)$ as:

$$p_0(t) = \left(\frac{\alpha \log N_0 (f(t) - 1)}{f(t)\beta - \alpha \log N_0}\right)^{N_0} \tag{61}$$

$$\text{and } p_1(t) = N_0 p_0(t) \left(\frac{(f(t) - 1)\beta}{f(t)\beta - \alpha \log N_0} + \frac{\beta - \alpha \log N_0 f(t)}{\alpha \log N_0 (f(t) - 1)}\right). \tag{62}$$

The expected value and variance of $N(t)$ are given by:

$$E(t) = N_0 \exp\left(\frac{\alpha \log N_0 - \beta}{\alpha}(\exp(-\alpha t) - 1)\right) \tag{63}$$

$$V(t) = N_0 \frac{\beta + \alpha \log N_0}{\alpha \log N_0 - \beta} \exp\left(\frac{\beta - \alpha \log N_0}{\alpha}\right) \exp\left(\frac{\alpha \log N_0 - \beta}{\alpha} \exp(-\alpha t)\right) \tag{64}$$

3. Numerical Examples

The computations of various performance measures were performed using MATLAB R2019b. Curve fitting was performed by applying the nonlinear least-squares method with a trust-region-reflective algorithm in MATLAB R2019b.

3.1. Tumour growth data in Tan et al.

A comparison of the birth-death models with and without immigration was performed based on the tumour growth data given in [28] in terms of the number of tumour cells in different epochs, to identify the model that best mimics reality. The number of tumour cells at various epochs was fitted using the mean population size given by Eqs. (41), (55) and (63). Figure 1 shows the fit. The parameter values that provide the fit are listed in Table 1. As shown in the figure, all three models produced a similar data fit. This may be attributed to the large tumour population size $N(t)$ to the tune of 768,720, such that the averages produced by each of the three stochastic models converge to the deterministic model. It is important to note that the probability $p_0(t)$ does not tend to zero in the case of the model with no immigration, which is the main difference between the three models. More precisely, this probability increased for the model with no immigration, as depicted in Figure 2, which is the opposite for models with immigration. This is expected because in the case of the no immigration model, the presence of the absorbing state at zero continues to add some mass to the probability $p_0(t)$ as t increases. Figure 3 shows that the probability $p_1(t)$ continues to decrease with increasing t in all three models. The behaviour of probabilities $p_0(t)$ and $p_1(t)$ together suggest that allowing immigration is more realistic for the stochastic tumour model. Figure 4 shows the variances of the three models. As observed, the models with immigration produce less variance than the non-immigration model. These facts suggest that immigration models are more realistic when compared with the non-immigration model in the case of the data in [28]. Figure 5 shows that the time-dependent birth and death rates decrease with time rather than remain constant, which further justifies the choice of the Gompertz model.

Model	Immigration when and only when population size is 0	All state immigration model	No immigration model
β	1.5948	1.4259	1.5925
α	0.0966	0.0919	0.0966
N_0	2.0386	6.0000	2.0000
γ	99.1902	12.9519	

Table 1: Gompertzian parameters for the fit of the tumour cell count data [28].

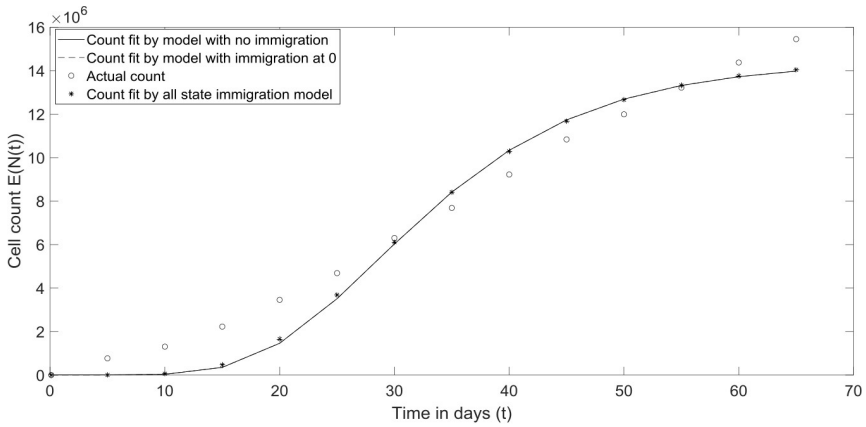

Figure 1: Fit of the tumour cell count [28] by the expected cell population size obtained from the birth–death models with and without immigration.

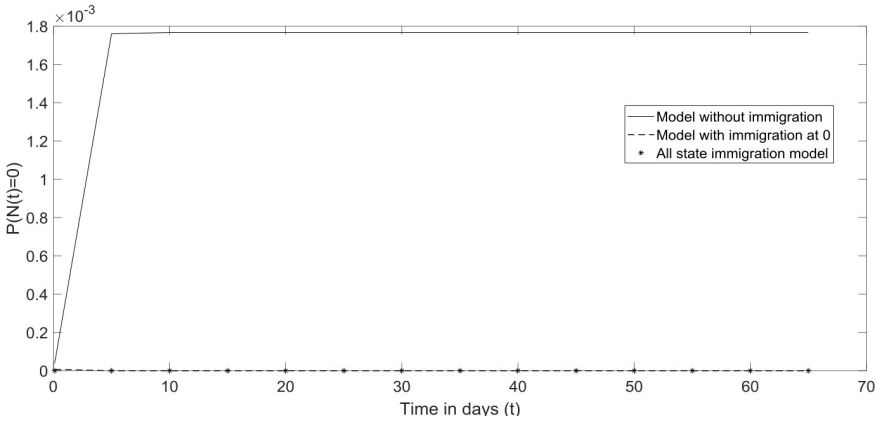

Figure 2: Comparison of the probability of the cell population size being zero at an arbitrary epoch t in the case of birth–death models with and without immigration based on the data in [28].

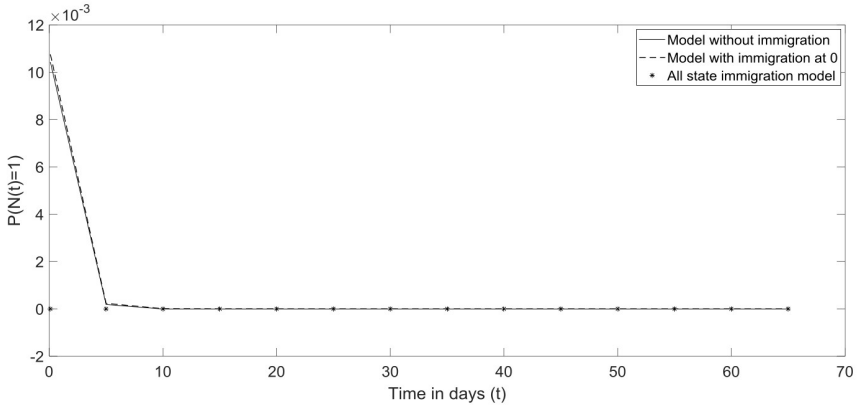

Figure 3: Comparison of the probability of the cell population size being one at an arbitrary epoch t in the case of birth–death models with and without immigration based on the data in [28].

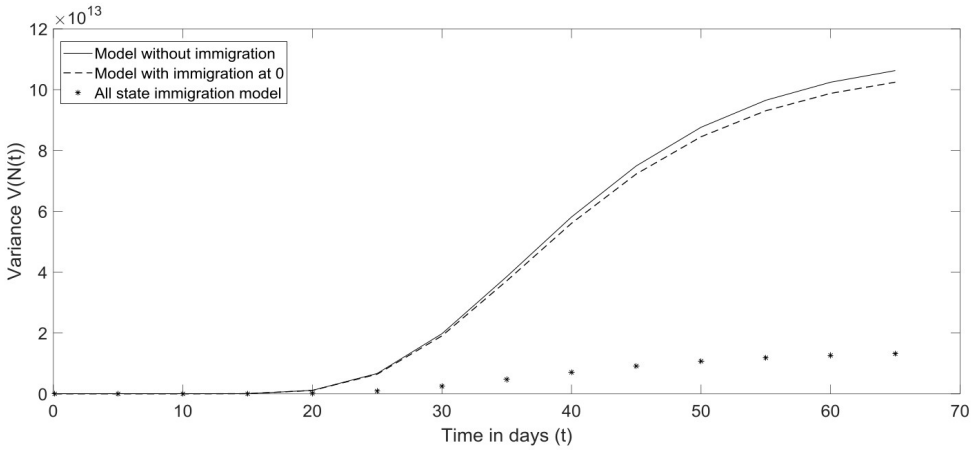

Figure 4: Comparison of the variance in the cell population size in the case of birth–death models with and without immigration based on the data in [28].

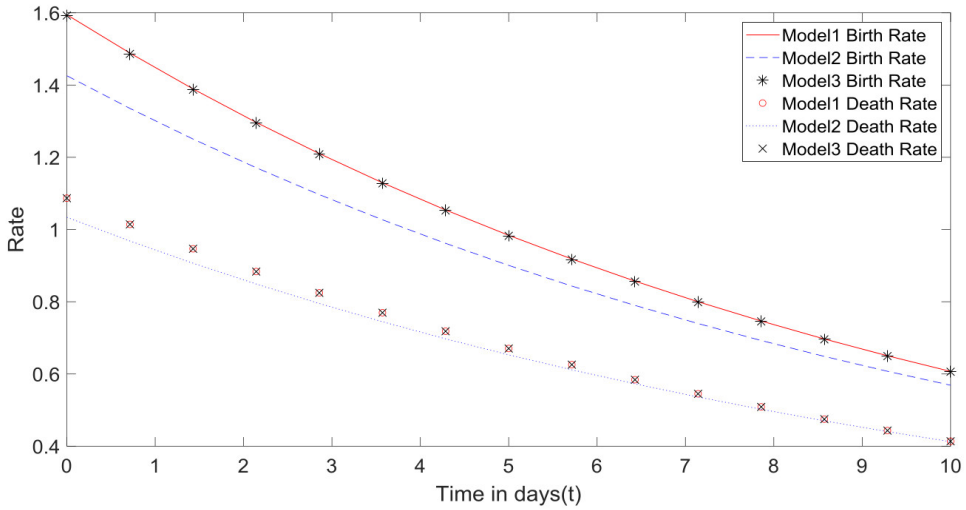

Figure 5: Birth and death rates in the case of birth–death models with and without immigration based on the data in [28].

3.2. Tumour growth data in Mastri et al.

Here, we consider the tumour growth data given by [18]. These data were obtained from studies performed on mice after injecting 10^6 tumour cells and periodically measuring the tumour size in mm^3. The data consisted of the number of tumour cells in 66 animals at different epochs and are available at https://zenodo.org/record/3574531.

We repeated the comparison performed in the previous section for the above data. The parameter values that provided the fit in the case of eight animals (animal identification number 1–8 in the study) are given in Table 2. In the case of each animal, a conclusion similar to that in Section 3.1 is obtained. Figures showing the cell count fit, behaviour of the probabilities $p_0(t)$ and $p_1(t)$, behaviour of the cell count variance, and the birth and death rates in the case

of animal 1 are given in the supplementary material. Therefore, in the case of the data in [18], the immigration models are more realistic than the non-immigration model.

		β	α	γ	N_0
Animal 1	Model 1	2.99092113	0.14219634	36.38902689	2.00066629
	Model 2	2.98946308	0.14185352	1.00007742	2.00000000
	Model 3	2.98946321	0.14212689		2.00000000
Animal 2	Model 1	2.70223853	0.12400724	14.78321876	2.01204108
	Model 2	2.70028587	0.12363064	0.99940879	2.00000000
	Model 3	2.70028597	0.12394977		2.00000000
Animal 3	Model 1	2.97523983	0.14082930	14.22743179	1.99066115
	Model 2	2.97362404	0.14044251	0.99952214	2.00000000
	Model 3	2.97362406	0.14071604		2.00000000
Animal 4	Model 1	2.80828457	0.13254888	0.19390893	1.99941087
	Model 2	2.80692204	0.13217717	0.99976647	2.00000000
	Model 3	2.80692219	0.13248052		2.00000000
Animal 5	Model 1	3.15561319	0.15206211	0.17662123	1.99974785
	Model 2	3.15406158	0.15159687	0.99899721	2.00000000
	Model 3	3.15406164	0.15198512		2.00000000
Animal 6	Model 1	2.52228960	0.11787264	51.69518522	2.00158947
	Model 2	2.52100299	0.11745620	1.00022790	2.00000000
	Model 3	2.52100308	0.11781404		2.00000000
Animal 7	Model 1	2.94661214	0.14079881	6.86245272	1.99955558
	Model 2	2.94522122	0.14044876	0.99995963	
	Model 3	2.94522134	0.14072858		2.00000000
Animal 8	Model 1	2.99742413	0.14451661	15.95860856	2.00010829
	Model 2	2.99600019	0.14417569	1.00001095	2.00000000
	Model 3	2.99600030	0.14444600		2.00000000

Table 2: Gompertzian parameters for the fit of the tumour cell count data [18]. In the table, Model 1 denotes birth–death model with immigration only when the population size is zero, Model 2 denotes birth–death model with immigration in all states, and Model 3 denotes birth–death model with no immigration.

3.3. Tumour growth data in Rodallec et al.

An additional comparison of the birth-death models with and without immigration was performed based on the tumour growth data given by [24]. To obtain this data, mice were initially injected with 80,000 tumour cells, and the tumour size was measured using optical imaging. Therefore, these data consisted of measurements of the number of photons and can be obtained from the website: https://zenodo.org/record/3593919.

Vaghi et al. [29], which had previously analysed the above data, noted that the initial 80,000 cells corresponded to 1.22×10^7 photons. Hence, to convert the number of photons to the number of cells, we multiplied the former by a factor of 0.0065574.

The parameter values, when the comparison of the three models was conducted in the case of eight animals (animal identification number 0–7 in the study), are given in Table 3. Figures showing the cell count fit, behaviour of the probabilities $p_0(t)$ and $p_1(t)$, behaviour of the cell count variance, and the birth and death rates in the case of animal 0 are given in the supplementary material. These results are similar to those obtained by [18]. This further strengthens the conclusion that immigration models are more realistic than non-immigration models.

		β	α	γ	N_0
Animal 0	Model 1	3.06496	0.14928	25.53077	2.00231
	Model 2	3.06322	0.14888	0.99953	2.00000
	Model 3	3.06322	0.14920		2.00000
Animal 1	Model 1	2.43777	0.11668	37.92036	2.00120
	Model 2	2.43655	0.11666	1.00001	2.00000
	Model 3	2.43655	0.11662		2.00000
Animal 2	Model 1	2.60459	0.12584	0.50000	1.99983
	Model 2	2.60347	0.12541	0.99979	2.00000
	Model 3	2.60347	0.12578		2.00000
Animal 3	Model 1	1.90257	0.08840	94.78272	2.00569
	Model 2	1.90216	0.08839	1.00001	2.00000
	Model 3	1.90216	0.08839		2.00000
Animal 4	Model 1	2.62651	0.12769	86.13296	2.00220
	Model 2	2.62504	0.12724	1.00021	2.00000
	Model 3	2.62504	0.12762		2.00000
Animal 5	Model 1	2.91604	0.14090	9.63470	1.99984
	Model 2	2.91599	0.14057	0.99894	2.00000
	Model 3	2.91599	0.14090		2.00000
Animal 6	Model 1	3.98557	0.19566	40.88037	2.00040
	Model 2	3.98339	0.19520	1.00085	2.00000
	Model 3	3.98339	0.19556		2.00000
Animal 7	Model 1	1.99909	0.09379	98.50918	2.01848
	Model 2	1.99747	0.09369	1.00023	2.00000
	Model 3	1.99747	0.09375		2.00000

Table 3: Gompertzian parameters for the fit of the tumour cell count data [24]. Models 1, 2, and 3 have the same definition as for Table 2.

4. Conclusions

In this study, two birth-death processes with immigration were considered. First, immigration is allowed if and only if the population size becomes zero. Second, immigration is allowed irrespective of the population size. The birth and death rates were considered such that the mean population size is a Gompertz function when immigration is not allowed. These results were in time-dependent transition rates in modelling the Markov chain. The generating function of the transient probabilities was obtained by solving a Volterra integral when immigration was allowed only when the population size was zero. The expected population size suitable for fitting real-world data was obtained. We compared the models with and without immigration by fitting the respective mean population sizes to several tumour growth datasets. In each case, all three models produced a similar fit for the data. Moreover, the models in which immigration was allowed produced less variance compared to non-immigration model. The probability of the population size being zero at an arbitrary epoch was found to decrease with time in the case of the two immigration models. The same probability was found to increase with time in the case of the birth-death model without immigration. Thus, the models with immigration were more realistic than the non-immigration model.

Although the assumption that the birth and death rates depend on time brings some generality in the modelling, assuming them as also depending on the present population size would be more realistic. Furthermore, considering the logistic model instead of the Gompertz model would be interesting. Most of the tumour data that we could find started with a large population size. Analysis of tumour growth data that starts with a population size of less than

1,000 cells would also be interesting. With improvements in tumour detection techniques and frequent screening, such data may become common in the future.

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