

## State Space Models for Survival Analysis

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### 1. Introduction

Many diseases such as AIDS, cancer and infectious diseases are often very complicated biologically. Most of these diseases are complex stochastic processes where it is often very difficult to estimate the unknown parameters, especially in cases where not many data are available. In these cases, it would be very difficult to estimate the survival probabilities. To ease the estimation problem and to estimate the survival probabilities, in this article we propose a state space modeling approach by combining stochastic models with statistical models. Then one can readily apply the Gibbs sampling method and the Markov Chain and Monte Carlo approach (MCMC) to estimate the unknown parameters and the state variables. By using these estimates, one can validate the model and estimate the survival probabilities. We will illustrate the model and the method by using a birth–death–immigration–illness–cure process which involve stochastic birth–death processes with immigration and the illness and cure processes for a disease such as tuberculosis.

### 2. The state space models and the generalized Bayesian approach

To illustrate, consider a disease such as tuberculosis which is curable by drugs. Let  $\tilde{X}(t)$  be the vector of stochastic processes for key responses of the disease. Then,  $\tilde{X}(t)$  is the stochastic model for this disease and in many cases, one can derive stochastic equations for the state variables of the system by using basic biological mechanism of the disease; for some illustrations in cancer and AIDS, see (Tan, 2000; Tan, 2002; Tan and Chen, 1998; Tan et al., 2001). If some observed data are available from this system, then, one may derive some statistical models to relate the data to the system. Combining the stochastic model of the system with the statistical model, one has a state space model for the system. That is, the state space model of a system is a stochastic model 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. It extracts biological information from the system

1 via its stochastic system model and integrates this information with those from the data 1  
2 through its observation equation. 2

3  
4 *2.1. Some advantages of the state space models* 4

5 The state space model of the system is advantageous over the stochastic model of the 5  
6 system alone or the statistical model of the system alone in several aspects. The follow- 6  
7 ing are some specific advantages: 7  
8

- 9 (1) The statistical model alone or the stochastic model alone very often is not identi- 9  
10 fiable and can not provide information regarding some of the parameters and vari- 10  
11 ables. For some specific examples, [Brookmeyer and Gail \(1994\)](#); [Tan \(2000, Chap-](#) 11  
12 [ter 5\)](#) and [Tan and Ye \(2000, 2000\)](#). 12  
13 (2) State space model provides an optimal procedure to updating the model by new data 13  
14 which may become available in the future. This is the smoothing step of the state 14  
15 space models; see ([Catlin, 1989](#); [Gelb, 1974](#); [Sage and Melsa, 1971](#)). 15  
16 (3) The state space model provides an optimal procedure via Gibbs sampling to esti- 16  
17 mate simultaneously the unknown parameters and the state variables of interest; see 17  
18 [Tan and Ye \(2000, 2000\)](#). 18  
19 (4) The state space model provides an avenue to combine information from various 19  
20 sources. For some examples, see ([Tan et al., 2000](#)). 20  
21

22 The state space model was originally proposed by Kalman and his associates in the 22  
23 early 60s for engineering control and communication ([Kalman, 1960](#)). Since then it has 23  
24 been successfully used as a powerful tool in aerospace research, satellite research and 24  
25 military missile research. It has also been used by economists in econometrics research 25  
26 ([Harvey, 1994](#)) and by mathematicians and statisticians in time series research ([Aoki,](#) 26  
27 [1990](#)) for solving many difficult problems which appear to be extremely difficult from 27  
28 other approaches. It was first proposed by Tan and his associates for AIDS and cancer 28  
29 research ([Tan and Chen, 1998, 1999](#); [Tan et al., 2001, 2000, 2002](#); [Tan and Xiang, 1998](#); 29  
30 [Tan and Xiang, 1998](#); [Tan and Xiang, 1998](#); [Tan and Xiang, 1999](#); [Tan and Xiang,](#) 30  
31 [1999](#); [Tan and Ye, 2000](#); [Tan and Ye, 2000](#); [Wu and Tan, 1995](#); [Wu and Tan, 2000](#)). 31  
32 Apparently state space models can be extended to other diseases as well, including 32  
33 heart and infectious diseases. 33  
34

35 *2.2. A general Bayesian procedure for estimating unknown parameters and state* 35  
36 *variables via state space models* 36

37 Applying the state space models, [Tan and Ye \(2000, 2000\)](#) have developed a general 37  
38 Bayesian procedure to estimate simultaneously the unknown parameters and the state 38  
39 variables. These procedures would combine information from three sources: 39  
40

- 41 (1) previous information and experiences about the parameters in terms of the prior 41  
42 distribution of the parameters, 42  
43 (2) biological information via the stochastic system equations of the stochastic system, 43  
44 and 44  
45 (3) information from observed data via the statistical model from the system. 45

To illustrate, let  $\mathbf{X} = \{\tilde{X}(1), \dots, \tilde{X}(t_M)\}$  be the collection of all state variables,  $\Theta$  the collection of all unknown parameters and  $\mathbf{Y} = \{Y(t_1), \dots, Y(t_k)\}$  ( $0 \leq t_1 < \dots < t_k \leq t_M$ ) the collection of all vectors of observed data sets. Let  $P(\Theta)$  be the prior distribution of the parameters  $\Theta$ ,  $P(\mathbf{X} | \Theta)$  the conditional probability density of  $\mathbf{X}$  given the parameters  $\Theta$ , and  $P(\mathbf{Y} | \mathbf{X}, \Theta)$  the conditional probability density of  $\mathbf{Y}$  given  $\mathbf{X}$  and  $\Theta$ . Then the joint probability density function of  $(\mathbf{X}, \mathbf{Y}, \Theta)$  is  $P(\Theta, \mathbf{X}, \mathbf{Y}) = P(\Theta)P(\mathbf{X} | \Theta)P(\mathbf{Y} | \mathbf{X}, \Theta)$ . From this, one derives the conditional probability density function  $P(\mathbf{X} | \Theta, \mathbf{Y})$  of  $\mathbf{X}$  given  $(\Theta, \mathbf{Y})$  and the conditional probability density function  $P(\Theta | \mathbf{X}, \mathbf{Y})$  of  $\Theta$  given  $(\mathbf{X}, \mathbf{Y})$ , respectively, as:

$$P(\mathbf{X} | \Theta, \mathbf{Y}) \propto P(\mathbf{X} | \Theta)P(\mathbf{Y} | \mathbf{X}, \Theta); \quad (1)$$

$$P(\Theta | \mathbf{X}, \mathbf{Y}) \propto P(\Theta)P(\mathbf{X} | \Theta)P(\mathbf{Y} | \mathbf{X}, \Theta). \quad (2)$$

Given these conditional distributions, one may then use the multi-level Gibb's sampler method (Liu and Chen, 1998; Shephard, 1994) to estimate simultaneously  $\Theta$  and  $\mathbf{X}$ . The multi-level Gibb's sampler method is a Monte Carlo method to estimate  $P(\mathbf{X} | \mathbf{Y})$  (the conditional density function of  $\mathbf{X}$  given  $\mathbf{Y}$ ) and  $P(\Theta | \mathbf{Y})$  (the posterior density function of  $\Theta$  given  $\mathbf{Y}$ ) through a sequential procedure by drawing from  $P(\mathbf{X} | \Theta, \mathbf{Y})$  and  $P(\Theta | \mathbf{X}, \mathbf{Y})$  alternatively and sequentially. The algorithm of this method iterates through the following loop:

- (1) Given  $\Theta^{(*)}$  and  $\mathbf{Y}$ , generate  $\mathbf{X}^{(*)}$  from  $P(\mathbf{X} | \mathbf{Y}, \Theta^{(*)})$ .
- (2) Generate  $\Theta^{(*)}$  from  $P(\Theta | \mathbf{Y}, \mathbf{X}^{(*)})$  where  $\mathbf{X}^{(*)}$  is the value obtained in (1).
- (3) Using  $\Theta^{(*)}$  obtained from (2) as initial values, go back to (1) and repeat the (1), (2) loop until convergence.

At convergence, the above procedure then leads to random samples of  $\mathbf{X}$  from the conditional density  $P(\mathbf{X} | \mathbf{Y})$  of  $\mathbf{X}$  given  $\mathbf{Y}$  independently of  $\Theta$  and to random samples of  $\Theta$  from the posterior density  $P(\Theta | \mathbf{Y})$  of  $\Theta$  independently of  $\mathbf{X}$ . Repeating these procedures we then generate a random sample of size  $n$  of  $\mathbf{X}$  and a random sample of size  $m$  of  $\Theta$ . One may then use the sample means to derive the estimates of  $\mathbf{X}$  and  $\Theta$  and use the sample variances as the variances of these estimates. The convergence of these procedures are proved by using the basic theory of homogeneous Markov chains; see (Tan, 2002, Chapter 3).

### 3. Stochastic modeling of the birth–death–immigration–illness–cure processes

Consider a population of individuals who are at risk for a disease and suppose that some drugs are available to treat the disease. One example is the tuberculosis. In this population, then there are two types of people: Normal healthy people (denote by  $N_1$ ) who do not have the disease and sick people (denote by  $N_2$ ) who have contracted the disease. When the population is at risk for the disease, normal people may contract the disease to become sick via contacts with sick people or disease agents. The sick people may die from the disease or die from other competing causes but normal healthy people can only die from other causes than the disease; sick people may also be cured by

1 drugs to become normal people. Besides death, suppose that there are births as well 1  
2 as immigration in the population. Then the stochastic system involves birth, death, 2  
3 immigration, illness and cure of the disease. Let  $N_i(t)$  ( $i = 1, 2$ ) denote the number 3  
4 of  $N_i$  ( $i = 1, 2$ ) people in the population at time  $t$  and put  $\tilde{X}(t) = \{N_1(t), N_2(t)\}'$ . 4  
5 Under treatment by a drug,  $\{\tilde{X}(t), t \geq 0\}$  is a birth–death–immigration–illness–cure 5  
6 process. This is a two-dimensional stochastic process with continuous time  $T = [0, \infty)$  6  
7 and discrete state space  $S = \{N_i(t) = j_i, i = 1, 2, j_i = 0, 1, \dots\}$  with initial condi- 7  
8 tions  $\{N_1(0) = n_1, N_2(0) = n_2\}$ . The initial condition is equivalent to assume that there 8  
9 are  $n_1$  healthy people at time 0 who are at risk for the disease and that there are  $n_2$  9  
10 sick people at time 0. If the numbers of  $\{N_i(t), i = 1, 2\}$  or of  $N(t) = N_1(t) + N_2(t)$  10  
11 are observed at times  $t_j, j = 1, \dots, n$ , then one can construct a state space model for 11  
12 this process. For this state space model, the stochastic system model is the stochastic 12  
13 model given by the stochastic process  $\tilde{X}(t)$  whereas the observation model is a statisti- 13  
14 cal model based on the observed numbers of  $N_i(t), i = 1, 2$  or based on  $N(t)$ . 14  
15

### 17 3.1. The traditional Kolmogorov approach 17

18 Denote by  $P\{N_1(t) = i, N_2(t) = j \mid N_1(0) = n_1, N_2(0) = n_2\} = P_{ij}(t)$  and  $\phi(x, y; t)$  18  
19 the probability generating function (PGF) of  $P_{ij}(t)$ . Let  $\{b_i(t), d_i(t)\}$  denote the birth 19  
20 rates and the death rates of the  $N_i$  people at time  $t$ , respectively,  $\alpha_1(t)$  the disease rate, 20  
21 and  $\alpha_2(t)$  the cure rate at time  $t$ , respectively. Then  $d_2(t) = d_1(t) + \mu(t)$ , and  $\alpha_1(t)$  21  
22 and  $\alpha_2(t)$  are the transition rates of  $N_1 \rightarrow N_2$  and  $N_2 \rightarrow N_1$  at time  $t$ , respectively. 22  
23 Assume that the number  $R_i(t)$  of immigration of  $N_i$  people during  $[t, t + \Delta t)$  follows 23  
24 a Poisson distribution with mean  $N_i(t)\delta_i(t)\Delta t + o(\Delta t)$ . Then it can be shown that 24  
25  $\phi(x, y; t)$  satisfies the following Kolmogorov forward equation: 25  
26

$$\begin{aligned}
 \frac{\partial}{\partial t}\phi(x, y; t) = & \{x(x-1)b_1(t) + (x-1)[\delta_1(t) - d_1(t)] \\
 & + (y-x)\alpha(t)\} \frac{\partial}{\partial x}\phi(x, y; t) \\
 & + \{y(y-1)b_2(t) + (y-1)[\delta_2(t) - d_2(t)] \\
 & + (x-y)\beta(t)\} \frac{\partial}{\partial y}\phi(x, y; t), \tag{3}
 \end{aligned}$$

27 with initial condition  $\phi(x, y; 0) = x^{n_1} y^{n_2}$ . 27

28 The solution of the above equation is extremely difficult if not impossible. Hence, 28  
29 this approach will not yield any useful results, especially in the non-homogeneous cases. 29  
30 We thus seek alternatively equivalent approach by stochastic differential equations. 30  
31

### 32 3.2. The stochastic differential equations for the state variables 32

33 The traditional approach by Markov theories is extremely difficult and manageable 33  
34 to yield useful results. Hence we use an alternatively equivalent approach through 34  
35 stochastic differential equations. Assume that during the time interval  $[t, t + \Delta t)$ , 35  
36

1 the birth–death–illness–cure processes follow the multinomial distributions with pa- 1  
2 rameters  $\{N_i(t), b_i(t)\Delta t, d_i(t)\Delta t, \alpha_i(t)\Delta t\}$  and the immigration processes the Poisson 2  
3 processes with means  $\lambda_i(t)\Delta t$ . Then, through the method of generating functions, it can 3  
4 readily be shown that the stochastic differential equation approach is equivalent to the 4  
5 classical Markov theory approach; see (Tan, 2002; Tan and Chen, 1998). 5

6 To derive stochastic differential equations for the state variables  $N_i(t)$ , observe 6  
7 that  $\tilde{X}(t + \Delta t)$  derive from  $\tilde{X}(t)$  stochastically through the birth–death–immigration 7  
8 process and the illness–cure process. Hence this transition is characterized by the fol- 8  
9 lowing transition variables: 9

10  $R_i(t)$  = Number of immigrants of  $N_i$  people during  $[t, t + \Delta t)$ ; 10  
11  $B_i(t)$  = Number of birth of  $N_i$  people during  $[t, t + \Delta t)$ ; 11  
12  $F_1(t)$  = Number of normal healthy people who become sick during  $[t, t + \Delta t)$ ; 12  
13  $F_2(t)$  = Number of sick people who are cured by the drug during  $[t, t + \Delta t)$ ; 13  
14  $D_i(t)$  = Number of deaths of  $N_i$  people during  $[t, t + \Delta t)$ ,  $i = 1, 2$ . 14  
15

16 Then, conditional on  $N_i(t)$ , the conditional probability distributions of  $R_i(t)$  and 16  
17  $\{B_i(t), D_i(t), F_i(t)\}$  are given respectively by: 17  
18

19  $R_i(t) | N_i(t) \sim$  Poisson with mean  $N_i(t)\lambda_i(t)\Delta t$ ,  $i = 1, 2$ ; 19  
20

21  $\{B_i(t), D_i(t), F_i(t)\} | N_i(t)$  21

22  $\sim$  Multinomial  $[N_i(t); b_i(t)\Delta t, d_i(t)\Delta t, \alpha_i(t)\Delta t]$ ,  $i = 1, 2$ . 22  
23

24 Given  $\tilde{X}(t)$ , conditionally  $\{R_i(t), i = 1, 2$ , and  $[B_j(t), B_j(t), F_j(t)], j = 1, 2\}$  are 24  
25 distributed independently of one another. 25

26 For  $i = 1, 2$ , define  $\varepsilon_i(t)$  by 26  
27

$$28 \varepsilon_i(t)\Delta t = [R_i(t) - N_i(t)\lambda_i(t)\Delta t] + [B_i(t) - b_i(t)N_i(t)\Delta t] 28  
29 - [F_i(t) - \alpha_i(t)N_i(t)\Delta t] - [D_i(t) - d_i(t)N_i(t)\Delta t]. \quad (4) 29  
30$$

31 Then, one has the following stochastic differential equations for  $N_i(t)$ ,  $i = 1, 2$ : 31  
32

$$33 \Delta N_1(t) = N_1(t + \Delta t) - N_1(t) 33  
34 = R_1(t) + F_2(t) + B_1(t) - F_1(t) - D_1(t) 34  
35 = \{[\lambda_1(t) + b_1(t) - d_1(t) - \alpha_1(t)]N_1(t) + \alpha_2(t)N_2(t)\}\Delta t 35  
36 + \varepsilon_1(t)\Delta t, \quad (5) 36  
37  
38  
39$$

$$40 \Delta N_2(t) = N_2(t + \Delta t) - N_2(t) 40  
41 = R_2(t) + F_1(t) + B_2(t) - F_2(t) - D_2(t) 41  
42 = \{[\lambda_2(t) + b_2(t) - d_2(t) - \alpha_2(t)]N_2(t) 42  
43 + \alpha_1(t)N_1(t)\}\Delta t + \varepsilon_2(t)\Delta t. \quad (6) 43  
44  
45$$

In Eqs. (5) and (6), the random noises  $\varepsilon_j(t)$ ,  $j = 1, 2$  have expectation zero and are uncorrelated with the state variables  $\{N_i(t), i = 1, 2\}$ . The variances and covariances of these random variables are easily obtained as  $\text{COV}\{\varepsilon_i(t)\Delta t, \varepsilon_j(t)\Delta t\} = Q_{ij}(t)\Delta t + o(\Delta t)$ , where

$$Q_{11}(t) = E\{[\lambda_1(t) + b_1(t) + d_1(t) + \alpha_1(t)]N_1(t) + \alpha_2(t)N_2(t)\},$$

$$Q_{22}(t) = E\{[\lambda_2(t) + b_2(t) + d_2(t) + \alpha_2(t)]N_2(t) + \alpha_1(t)N_1(t)\},$$

$$Q_{12}(t) = -E\left\{\sum_{i=1}^2 \alpha_i(t)N_i(t)\right\}.$$

#### 4. A state space model for the birth–death–immigration–illness–cure processes

The state space model of a system is a stochastic model consisting of two sub-models: The stochastic system model which is the stochastic model of the system and the observation model which is the statistical model relating available data from the system to the model. For the birth–death–immigration–illness–cure process, the state variables are  $\{N_i(t), i = 1, 2\}$  and the stochastic system model is represented by the stochastic differential equations given by (5), (6). Assuming that the number of sick people and/or the number of healthy people have been counted at times  $t_j$ ,  $j = 1, \dots, n$ . Then one can construct a statistical model and hence the observation model based on these observed numbers. Applying the MCMC procedures given above, one may then estimate the unknown parameters and the state variables as well as the survival probabilities.

##### 4.1. The stochastic system model and the probability distribution of the state variables

The stochastic system model is represented by the stochastic differential equations (5), (6) for the state variables  $\{N_i(t), i = 1, 2\}$ . Discretize the time scale by letting  $\Delta t \sim 1$  corresponding to a small time interval such as one month. Then, by using the multinomial distributions for the birth–death–illness–cure processes and using the Poisson processes for the immigration process, one may readily derive the probability distribution of the state variables. This probability distribution will be used through the multi-level Gibbs sampling method to estimate the state variables, the unknown parameters and the survival probabilities.

Let  $t_M$  be the current time or most recent time of interest. Then the collection of state variables is  $\mathbf{X} = \{X(t), t = 0, 1, \dots, t_M\}$ . Assume that the time interval  $[0, t_M]$  is partitioned into  $k$  non-overlapping sub-intervals  $L_s = [t_{s-1}, t_s)$ ,  $s = 1, \dots, k$  with  $t_0 = 0$  and  $t_k = t_M$  and that  $\{\lambda_i(t) = \lambda_i(s), b_i(t) = b_i(s), d_i(t) = d_i(s), \alpha_i(t) = \alpha_i(s), i = 1, 2, \text{ if } t \in L_s\}$ . Then the collection of parameters is  $\Theta = \{\Theta_s, s = 1, \dots, k\}$ , where  $\Theta_s = \{\lambda_i(s), b_i(s), d_i(s), \alpha_i(s), i = 1, 2\}$ . Then, the conditional density of  $\mathbf{X}$  given  $\Theta$  is

$$P\{\mathbf{X} | \Theta\} = P\{\mathbf{X}(0) | \Theta\} \prod_{j=1}^{t_M} P\{\tilde{X}(j) | \tilde{X}(j-1), \Theta\}. \quad (7)$$

Let  $g_i(j; t)$  denote the density of  $R_i(t)$ . Then  $P\{\tilde{X}(t+1) | \tilde{X}(t), \Theta\}$  is given by:

$$P\{\tilde{X}(t+1) | \tilde{X}(t), \Theta\} = \sum_{i=0}^{N_1(t)} \sum_{j=0}^{N_2(t)} \binom{N_1(t)}{i} \binom{N_2(t)}{j} [\alpha_1(t)]^i [\alpha_2(t)]^j h_1(i, j; t) h_2(i, j; t), \quad (8)$$

$$h_1(i, j; t) = \sum_{k=0}^{N_1(t+1)-N_1(t)+i-j} g_1(k; t) \sum_{r=0}^{N_1(t)-i} \binom{N_1(t)-i}{r} \binom{N_1(t)-i-r}{\xi_1(t)} \times [b_1(t)]^r [\mu_1(t)]^{\xi_1(t)} [1 - \alpha_1(t) - b_1(t) - \mu_1(t)]^{\xi_2(t)},$$

where  $\xi_1(t) = N_1(t) - N_1(t+1) - i + j + k + r$ ,  $\xi_2(t) = N_1(t+1) - j - k - 2r$ , and

$$h_2(i, j; t) = \sum_{k=0}^{N_2(t+1)-N_2(t)-i+j} g_2(k; t) \sum_{r=0}^{N_2(t)-j} \binom{N_2(t)-j}{r} \binom{N_2(t)-j-r}{\sigma_1(t)} \times [b_2(t)]^r [\mu_2(t)]^{\sigma_1(t)} [1 - \alpha_2(t) - b_2(t) - \mu_2(t)]^{\sigma_2(t)},$$

where  $\sigma_1(t) = N_2(t) - N_2(t+1) + i - j + k + r$ ,  $\sigma_2(t) = N_2(t+1) - i - k - 2r$ .

#### 4.2. The observation model

For the observation model, assume that observed numbers of  $N_i$  people at times  $\{t_j, j = 1, \dots, n\}$  are available. Let  $Y_i(j)$  be the observed number of  $N_i$  people at time  $t_j$ . Assume that  $[Y_i(j) - N_i(t_j)]/\sqrt{N_i(t_j)}$  is normal with mean 0 and variance  $\sigma_i^2$ , independently for  $i = 1, 2, j = 1, \dots, n$ . The observation model is represented by the statistical model given by:

$$Y_i(j) = N_i(t_j) + [N_i(t_j)]^{1/2} \varepsilon_i(j), \quad \text{for } i = 1, 2, j = 1, \dots, n, \quad (9)$$

where  $\varepsilon_i(j)$  are independently distributed as normal with mean 0 and variance  $\sigma_i^2$ .

Thus, the conditional likelihood function of  $\Theta$  given  $\mathbf{X}$  is

$$L(\Theta | \mathbf{X}) = \prod_{i=1}^2 \prod_{j=1}^n f_i\{Y_i(j); N_i(t_j)\},$$

where

$$f_i\{x; N_i(t_j), \sigma_i^2\} = \left\{ \sigma_i \sqrt{2\pi N_i(t_j)} \right\}^{-1} \exp \left\{ -\frac{1}{2\sigma_i^2 N_i(t_j)} [x - N_i(t_j)]^2 \right\}.$$

**5. The multi-level Gibbs sampling procedures for the birth–death–immigration–illness–cure processes**

To implement the multi-level Gibbs sampling method, denote by  $\underline{U}(t) = \{F_i(t), R_i(t), B_i(t), i = 1, 2\}$  and put  $\mathbf{U} = \{\underline{U}(t), t = 0, 1, \dots, t_M - 1\}$ . Then, given  $\underline{X}(0)$  and  $\Theta$ ,

$$P\{\mathbf{X}, \mathbf{U} | \underline{X}(0)\} = \prod_{i=1}^{t_M} P\{\underline{X}(i) | \underline{X}(i-1), \underline{U}(i-1)\} \times P\{\underline{U}(i-1) | \underline{X}(i-1)\}. \quad (10)$$

By the above distribution results with  $i \neq j; i, j = 1, 2$ :

$$P\{\underline{U}(t) | \underline{X}(t)\} = C_1(t) \prod_{i=1}^2 g_i\{R_i(t); t\} [\alpha_i(t)]^{F_i(t)} [b_i(t)]^{B_i(t)} \times [1 - \alpha_i(t) - b_i(t)]^{N_i(t) - F_i(t) - B_i(t)}, \quad (11)$$

where

$$C_1(t) = \prod_{i=1}^2 \binom{N_i(t)}{F_i(t)} \binom{N_i(t) - F_i(t)}{B_i(t)},$$

$$P\{\underline{X}(t+1) | \underline{X}(t), \underline{U}(t)\} = \prod_{i=1}^2 \binom{N_i(t) - F_i(t) - B_i(t)}{\eta_i(t)} \times \left[ \frac{\mu_i(t)}{1 - \alpha_i(t) - b_i(t)} \right]^{\eta_i(t)} \left[ 1 - \frac{\mu_i(t)}{1 - \alpha_i(t) - b_i(t)} \right]^{\zeta_i(t)},$$

where  $\eta_i(t) = N_i(t) - N_i(t+1) - F_i(t) + F_j(t) + R_i(t) + B_i(t)$ ,  $i \neq j$ ,  $i, j = 1, 2$ , and  $\zeta_i(t) = N_i(t+1) - F_j(t) - R_i(t) - 2B_i(t)$ ,  $i \neq j$ ,  $i, j = 1, 2$ .

These distribution results indicate that given the parameters and given  $\mathbf{X}$ , one can readily generate  $\mathbf{U}$ ; similarly, given the parameters and given  $\mathbf{U}$ , one can readily generate  $\mathbf{X}$ .

Let  $\mathbf{Y} = \{Y_i(j), i = 1, 2, j = 1, \dots, n\}$ . Then the joint density of  $\{\mathbf{X}, \mathbf{U}, \mathbf{Y}\}$  give the parameters  $\Omega = \{\Theta, \sigma_i^2, i = 1, 2\}$  is:

$$P\{\mathbf{X}, \mathbf{U}, \mathbf{Y} | \Omega\} = P\{\underline{X}(0) | \Theta(0)\} P\{\underline{U}(0) | \underline{X}(0)\} \times \prod_{j=1}^n \left\{ \prod_{i=1}^2 f_i[Y_i(j); N_i(t_j), \sigma_i^2] \right\}$$

$$\begin{aligned}
& \times \prod_{r=t_{j-1}+1}^{t_j} P\{\tilde{X}(r) | U(r-1), \tilde{X}(r-1)\} \\
& \times P\{U(r-1) | \tilde{X}(r-1)\}. \tag{12}
\end{aligned}$$

Let  $P\{\Omega\} = P\{\Theta\}P\{\sigma_i^2, i = 1, 2\}$  be the density of the prior distribution of  $\Omega$ . Then the density of the conditional posterior distribution of  $\Omega$  given  $\{\mathbf{X}, \mathbf{U}, \mathbf{Y}\}$  is

$$\begin{aligned}
P\{\Omega | \mathbf{X}, \mathbf{U}, \mathbf{Y}\} & \propto P\{\Omega\} \prod_{i=1}^2 [\sigma_i^2]^{-n/2} \exp\left\{-\frac{S_i}{\sigma_i^2}\right\} \prod_{s=1}^m \{\exp\{-m(s)\lambda_i(s)\}\} \\
& \times [\lambda_i(s)]^{\hat{R}_i(s)} [\alpha_i(s)]^{\hat{F}_i(s)} [b_i(s)]^{\hat{B}_i(s)} [d_i(s)]^{\hat{\eta}_i(s)} \\
& \times [1 - \alpha_i(s) - b_i(s) - d_i(s)]^{\hat{\zeta}_i(s)}, \tag{13}
\end{aligned}$$

where  $m(s) = t_s - t_{s-1}$  and for  $i = 1, 2$ ,

$$\begin{aligned}
S_i & = \frac{1}{2} \sum_{j=1}^n \frac{1}{N_i(t_j)} [Y_i(j) - N_i(t_j)]^2 \\
\hat{R}_i(s) & = \sum_{t=t_{s-1}+1}^{t_s} R_i(t), \quad \hat{F}_i(s) = \sum_{t=t_{s-1}+1}^{t_s} F_i(t), \\
\hat{B}_i(s) & = \sum_{t=t_{s-1}+1}^{t_s} B_i(t), \quad \hat{\eta}_i(s) = \sum_{t=t_{s-1}+1}^{t_s} \eta_i(t), \\
\hat{\zeta}_i(s) & = \sum_{t=t_{s-1}+1}^{t_s} \zeta_i(t).
\end{aligned}$$

Using the above distribution results, the multi-level Gibbs sampling procedures for estimating the unknown parameters  $\Omega$  and the state variables  $\mathbf{X}$  are given by the following loop:

- (1) Combining a large sample from  $P\{\mathbf{U} | \mathbf{X}, \Omega\}$  for given  $\mathbf{X}$  with  $P\{\mathbf{Y} | \Omega, \mathbf{X}\}$  through the weighted Bootstrap method due to **Smith and Gelfand (1992)**, generate  $\mathbf{U}$  (denote the generated sample  $\mathbf{U}^{(*)}$ ) from  $P\{\mathbf{U} | \Omega, \mathbf{X}, \mathbf{Y}\}$  although the latter density is unknown.
- (2) Combining a large sample from  $P\{\mathbf{X} | \mathbf{U}^{(*)}, \Omega\}$  with  $P\{\mathbf{Y} | \Omega, \mathbf{X}\}$  through the weighted Bootstrap method due to **Smith and Gelfand (1992)**, generate  $\mathbf{X}$  (denote the generated sample by  $\mathbf{X}^{(*)}$ ) from  $P\{\mathbf{X} | \Omega, \mathbf{U}^{(*)}, \mathbf{Y}\}$  although the latter density is unknown.
- (3) On substituting  $\{\mathbf{U}^{(*)}, \mathbf{X}^{(*)}\}$  which are generated numbers from the above two steps and assuming non-informative uniform priors, generate  $\Theta$  from the conditional density  $P\{\Omega | \mathbf{X}^{(*)}, \mathbf{U}^{(*)}, \mathbf{Y}\}$  given by **Eq. (13)**.

(4) On substituting  $\mathbf{X}^{(*)}$  generated from Step 2 above and with  $\Omega$  being generated from Step 3 above, go back to Step 1 and repeat the above (Aoki, 1990; Brookmeyer and Gail, 1994; Catlin, 1989) loop until convergence.

At convergence, one then generates a random sample of  $\mathbf{X}$  from the conditional distribution  $P\{\mathbf{X} | \mathbf{Y}\}$  of  $\mathbf{X}$  given  $\mathbf{Y}$ , independent of  $\mathbf{U}$  and  $\Theta$  and a random sample of  $\Theta$  from the posterior distribution  $P\{\Theta | \mathbf{Y}\}$  of  $\Theta$  given  $\mathbf{Y}$ , independent of  $\{\mathbf{X}, \mathbf{U}\}$ . Repeat these procedures one then generates a random sample of size  $N$  of  $\mathbf{X}$  and a random sample of size  $M$  of  $\Theta$ . One may then use the sample means to derive the estimates of  $\mathbf{X}$  and  $\Theta$  and use the sample variances as the variances of these estimates. Alternatively, one may also use Efron's bootstrap method (Efron, 1982) to derive estimates of the standard errors of the estimates.

## 6. The survival probabilities of normal and sick people

Let  $S_i(t)$  denote the survival probability that an  $N_i$  person at time 0 will survive at least  $t$  months when the population is at risk for the disease. Then, under the conditions given in Section 3, one has, to order of  $o(\Delta t)$ ,

$$S_i(t + \Delta t) = \alpha_i(t)\Delta t S_j(t) + \{1 - d_i(t)\Delta t - \alpha_i(t)\Delta t\}S_i(t),$$

$$\text{for all } i \neq j, i, j = 1, 2.$$

It follows that the  $S_i(t)$ 's satisfy the following system of equations:

$$\frac{d}{dt}S_1(t) = \alpha_1(t)S_2(t) - [\alpha_1(t) + d_1(t)]S_1(t), \quad (14)$$

$$\frac{d}{dt}S_2(t) = \alpha_2(t)S_1(t) - [\alpha_2(t) + d_2(t)]S_2(t). \quad (15)$$

The initial condition is  $\{S_i(0) = 1, i = 1, 2\}$ .

Let  $\tilde{S}(t) = \{S_1(t), S_2(t)\}'$ . Then, in matrix notation,

$$\frac{d}{dt}\tilde{S}(t) = -F(t)\tilde{S}(t),$$

where  $F(t)$  is given by

$$F(t) = \begin{bmatrix} \alpha_1(t) + d_1(t) & -\alpha_1(t) \\ -\alpha_2(t) & \alpha_2(t) + d_2(t) \end{bmatrix}.$$

The initial condition is  $\tilde{S}(0) = \mathbf{1}_2$ , a  $2 \times 1$  column of 1's.

Assume that  $\{\alpha_i(t) = \alpha_i(s), d_i(t) = d_i(s), i = 1, 2\}$  for  $t \in L_s = [t_{s-1}, t_s)$ ,  $s = 1, \dots, k$  with  $t_0 = 0$  and  $t_{k+1} = \infty$ . Then the solution of Eqs. (14), (15) are given by:

$$\tilde{S}(t) = e^{-F(m)(t-t_{m-1})} \prod_{i=1}^{m-1} e^{-F(m-i)\xi_{m-i}} \mathbf{1}_2, \quad (16)$$

if  $t \in [t_{m-1}, t_m)$ ,  $m = 1, \dots, k + 1$ ,

where  $\xi_i = t_i - t_{i-1}$  and the  $e^{-F(i)x}$  are matrix exponential functions defined by

$$e^{-F(i)x} = \sum_{j=0}^{\infty} \frac{(-1)^j}{j!} [F(i)]^j x^j. \quad (17)$$

Now the eigenvalues of  $F(t)$  are  $\lambda_i(t) = \frac{1}{2}\{\alpha_1(t) + \alpha_2(t) + d_1(t) + d_2(t) \pm w(t)\}$ , where  $w(t) = \{[\alpha_1(t) + \alpha_2(t) + d_1(t) - d_2(t)]^2 + 4\alpha_2(t)[d_2(t) - d_1(t)]\}^{1/2}$ . Let

$$E_i(t) = \frac{1}{\lambda_i(t) - \lambda_j(t)} (F(t) - \lambda_j(t)I_2), \quad i \neq j, \quad i, j = 1, 2.$$

Then  $e^{-F(t)x} = \sum_{i=1}^2 e^{-\lambda_i(t)x} E_i(t)$ . Hence, for  $t \in [t_{m-1}, t_m)$ ,  $m = 1, \dots, k+1$ :

$$\begin{aligned} \tilde{S}(t) = & \{e^{-\lambda_1(m)(t-t_{m-1})} E_1(m) + e^{-\lambda_2(m)(t-t_{m-1})} E_2(m)\} \\ & \times \left\{ \prod_{i=1}^{m-1} [e^{-\lambda_1(m-i)(\xi_{m-i})} E_1(m-i) \right. \\ & \left. + e^{-\lambda_2(m-i)(\xi_{m-i})} E_2(m-i)] \right\} \tilde{1}_2. \quad (18) \end{aligned}$$

If further  $\alpha_i(t) = \alpha_i$  and  $d_i(t) = d_i$  for  $i = 1, 2$ , then the solution of Eqs. (14), (15) are given by:

$$S_1(t) = \frac{1}{\omega} \{(d_1 - \lambda_2)e^{-\lambda_1 t} + (\lambda_1 - d_1)e^{-\lambda_2 t}\} \quad (19)$$

$$S_2(t) = \frac{1}{\omega} \{(d_2 - \lambda_2)e^{-\lambda_1 t} + (\lambda_1 - d_2)e^{-\lambda_2 t}\}, \quad (20)$$

where  $\{\omega(t) = \omega, \lambda_i(t) = \lambda_i\}$ .

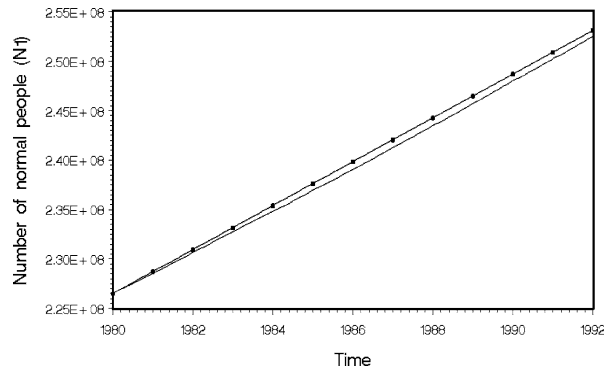
## 7. Some illustrative examples

To illustrate the above methods, consider the disease – tuberculosis (TB) which is curable by drugs. Given in Table 1 are the numbers of TB cases in US from 1980 to 1992 reported by CDC together with the total US population sizes over these years (CDC Report, 1993). In this data set, it is clear that the curve of TB cases in US is declining to the lowest level in 1985 and then increases due presumably to the effects of HIV (CDC Report, 1993). To fit this data, we thus assume  $\alpha_1(t) = \alpha_1(1)$  before January 1985 and assume  $\alpha_1(t) = \alpha_1(2)$  after January 1985. Assume that other parameters are not affected by HIV and other factors. Because the TBs are rare in children, we may ignore birth so that the unknown parameters are  $\Theta = \{\lambda_i, d_i, \alpha_i(1), \alpha_i(2), i = 1, 2\}$ . Let  $t_0 = 0$  denote January 1980 so that  $N_1(0) = 226517805$  and  $N_2(0) = 28000$ .

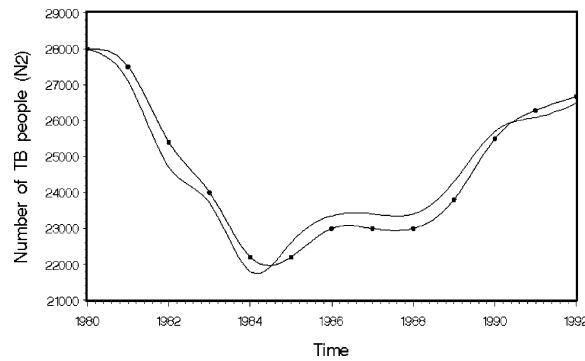
Using the data given in Table 1, one may readily apply the method of Section 6 to estimate the unknown parameters and the state variables. Because we do not have

Table 1  
Observed numbers of total people, TB people and normal people

Time	Total people	TB people	Normal people
1980	226545805	28000	226517805
1981	228762212	27500	228734712
1982	230978619	25400	230953219
1983	233195025	24000	233171025
1984	235411432	22201	235389231
1985	237627839	22201	237605638
1986	239844246	23000	239821246
1987	242060653	23000	242037653
1988	244277059	23000	244254059
1989	246493466	23800	246469666
1990	248709873	25500	248684373
1991	250926280	26283	250899997
1992	253142687	26673	253116014



(a)

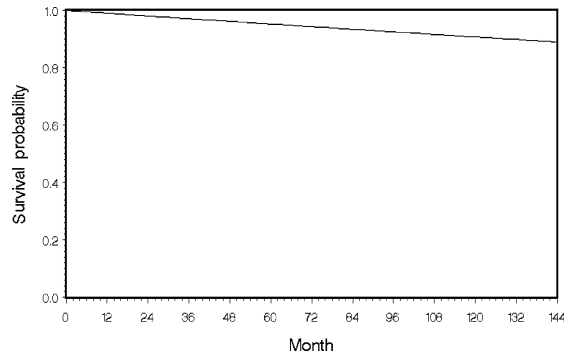


(b)

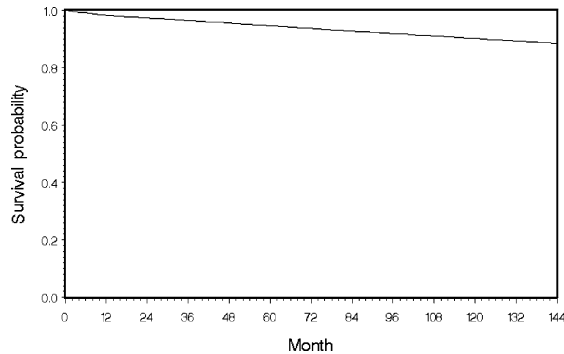
Fig. 1. The estimated number and observed number of (a) normal people, and (b) TB people. (—: estimates; —●—: observed.)

Table 2  
Estimates of parameters and standard errors

Parameters	Mean	Standard error	Minimum	Maximum
$\lambda_1$	0.0014990	2.0113312E-7	0.0014986	0.0014996
$\lambda_2$	0.0011764	0.000017760	0.0011363	0.0012171
$d_1$	0.000803630	1.4315684E-7	0.000803242	0.000803936
$d_2$	0.0037722	0.000027462	0.0037019	0.0038617
$\alpha_1(1)$	0.000045527	5.0690768E-7	0.000040545	0.000045720
$\alpha_2(2)$	0.000045570	4.4691119E-8	0.000045448	0.000045679
$\alpha_2$	0.4343895	0.000255445	0.4336948	0.4349698



(a)



(b)

Fig. 2. The survival probabilities of (a) normal people, and (b) TB people with Jan. 1980 = 0.

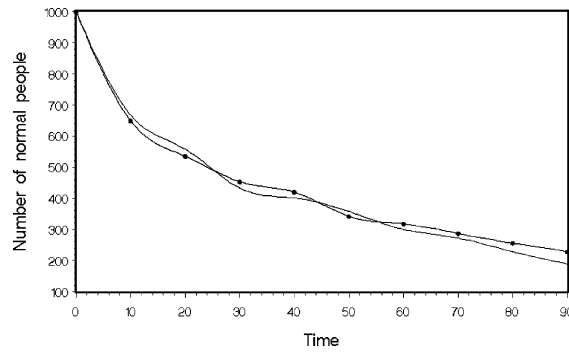
previous knowledge and data on US TB, to implement the procedures of Section 6 we assumed a non-informative uniform prior for the parameters. Using the method in Section 6 with  $b_i(t) = 0$  ( $i = 1, 2$ ), the estimates of the parameters are given in Table 2 with the standard errors of the estimates obtained by using Efron's bootstrap method (Efron, 1982). In Figures 1(a), (b), the estimates of the state variables are plotted together with

Table 3

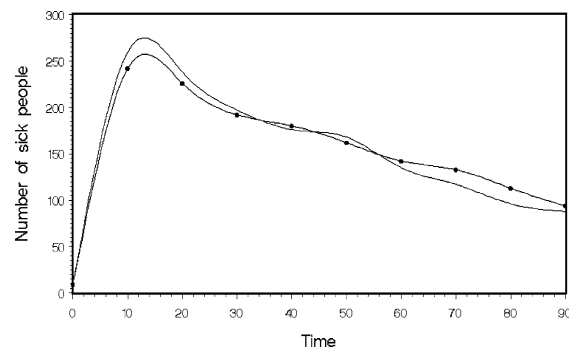
The generated numbers of normal (YN) and sick people (YI)

T	YN	YI
0	1000	9
10	649	242
20	535	226
30	453	192
40	420	180
50	342	162
60	318	142
70	287	133
80	256	113
90	228	94

The parameter values for generating these data are:  $\lambda_1 = 0.05$ ,  $\lambda_2 = 0.03$ ,  $d_1 = 0.04$ ,  $d_2 = 0.1$ ,  $\alpha_1 = 0.2$ ,  $\alpha_2 = 0.4$ ,  $N(0) = 1000$ ,  $I(0) = 10$ .



(a)



(b)

Fig. 3. The estimated and observed numbers of the (a) normal people and (b) sick people. (—: estimates; -●-: observed.)

Table 4  
Estimates of parameters and standard errors

Parameters	Mean	Standard error	Minimum	Maximum
$\lambda_1$	0.0407253	0.0014776	0.0376655	0.0447270
$\lambda_2$	0.0262105	0.0016861	0.0218033	0.0314858
$d_1$	0.0517746	0.0017989	0.0475090	0.0561725
$d_2$	0.1395334	0.0040820	0.1293103	0.1522202
$\alpha_1$	0.2198501	0.0034795	0.2123125	0.2280998
$\alpha_2$	0.3802137	0.0054955	0.3652281	0.3927149

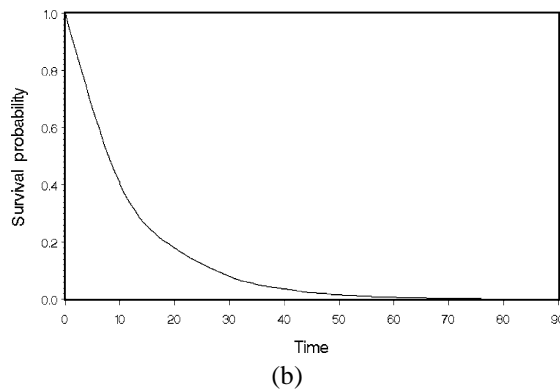
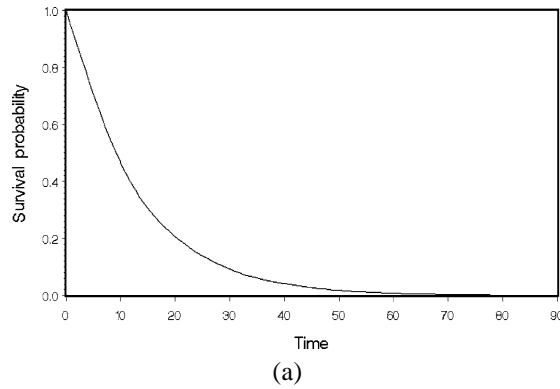


Fig. 4. The estimated survival probabilities of (a) normal people and (b) sick people.

the respective observed numbers. The estimates of the survival probabilities of normal people and sick people are plotted in Figures 2(a), (b). From Figure 1, apparently the estimated numbers of the  $N_i$  people are close to its observed numbers. From results in Table 2, it turned out that the estimate of  $\alpha_1(2)$  is only slightly greater than  $\alpha_1(1)$  but the standard error of the estimate of  $\alpha_1(2)$  is 10 times smaller than that of the estimate

1 of  $\alpha_1(1)$ , indicating that HIV and/or other causes have increased the infection rate of 1  
2 TB slightly. 2

3 To further examine the approach, we have assumed some parameter values and gener- 3  
4 ated some computer Monte Carlo data. The generated numbers are given in [Table 3](#) 4  
5 and the parameter values for generating these data are  $\{\lambda_1 = 0.05, \lambda_2 = 0.03, d_1 =$  5  
6  $0.04, d_2 = 0.1, \alpha_1 = 0.2, \alpha_2 = 0.4, N_1(0) = 1000, N_2(0) = 10\}$ . As in the TB exam- 6  
7 ple, we have ignored birth so that we are restricting ourselves to adults. 7

8 Using the data in [Table 3](#) and assuming a non-informative uniform prior for the param- 8  
9 eters, we have applied the procedures of [Section 6](#) to estimate the unknown parameters 9  
10 and the state variables. Given in [Table 4](#) are the estimates of the unknown parameters. 10  
11 Plotted in [Figures 3 and 4](#) are the estimates of the state variables together with the gener- 11  
12 ated numbers, and the estimates of the survival probabilities, respectively. From results 12  
13 in [Table 4](#), apparently, the estimates are very close to its true values. From [Figure 3](#), 13  
14 it is also apparent that the estimates of the state variables are very close to the gener- 14  
15 ated numbers. These results indicate that the methods proposed in this article are quite 15  
16 promising and useful. 16

## 17 18 19 **8. Conclusions** 19

20  
21 In this article, we have developed a state space model for the birth–death–immigration– 21  
22 illness–cure process. We have developed a generalized Bayesian method to estimate 22  
23 the unknown parameters and the state variables, and hence the survival probabilities. 23  
24 The numerical examples indicate that the methods are useful and promising. Of course, 24  
25 more studies are needed to further confirm the usefulness of the method and to check 25  
26 the efficiency of the method. 26

27 In the past 5 years, we have developed some state space models for cancers and for 27  
28 AIDS ([Tan and Chen, 1998](#); [Tan et al., 1999](#); [Tan et al., 2001](#); [Tan et al., 2000](#); [Tan et al.,](#) 28  
29 [2002](#); [Tan and Xiang, 1998](#); [Tan and Xiang, 1998](#); [Tan and Xiang, 1998](#), [Tan and Xiang,](#) 29  
30 [1999](#); [Tan and Xiang, 1999](#); [Tan and Ye, 2000](#); [Tan and Ye, 2000](#); [Wu and Tan, 1995](#); 30  
31 [Wu and Tan, 2000](#)). The present article extends this modeling approach to other human 31  
32 diseases such as tuberculosis. This type of modeling approach is definitely useful for 32  
33 other diseases such as the heart disease and to risk assessment of environmental agents 33  
34 as well. In this respect, more research work are needed. 34

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