出國報告（出國類別：參加國際會議）

科技部研究計畫移地研究暨拜訪會商國際合作之出國報告

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派赴國家：馬來西亞

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摘 要

國際合作和訪問的對象是Monash University Malaysia 的Dr. Kenneth Lee 和 Dr. David Wu。他們協助我進行科技部研究計畫與開發模擬計算模式和比較模擬結果。因為他們對於亞洲人與馬來西亞人在使用藥物和經濟成本效益之特質和分析的經驗，以及比較了解相關文獻與資料。我向他們學習後，開發TreeAge 的模擬程式，如後頁所示。同時配合政大理學院的發展，介紹政大的師生在學術研究和學習方面的情形，加強招生宣傳。

目次

目的

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過程

於移地研究期間我特別拜訪幾位有興趣與臺灣合作的老師，名單如下。彼此一致的想法是，合作案必須持續推動。

一、 Professor Dr. Pervaiz Ahmed, Deputy Head of School and Director of Research, School of Business ，會談時間在2015-08-28 (週五) 下午2 點。另附相片於後頁。

二、 Prof Daniel Reidpath (Global Public Health) ，會談時間在2015-09-03 (週四) 下午2 點。

三、 Dr. Kuang Ye Chow, Associate Head of School (Research Training) School of Engineering，會談時間在2015-09-08 (週二) 下午2 點。

四、 Dr. Wong Chee Piau, Associate Professor, Jeffrey Cheah School of Medicine and Health Sciences，會談時間在2015-09-09 (週三) 下午 12 點。

另外也擔任在職班Dr. M Hafeezul Suraj A Wilson 的論文口試委員，時間在 2015-09-11 (週五) 下午2 點。而且於2015-08-27 (週四) 下午2 點 擔任論文專題演講人；於2015-09-10 (週四)擔任模擬課程工作坊主講人。也和下列幾位主要學術行政負責人討論合作事宜。

一、 Professor Dr. Iekhsan Othman, Jeffrey Cheah School of Medicine and Health Sciences

二、 Prof. Kenneth Lee, Dr. David Wu, Dr. Tahir Mehmood Khan, Dr. Shaun Lee, Department of Clinical Pharmacy.

心得及建議事項：

因為這個研究工作牽涉數學模式與理論、工程程式與工具開發撰寫、公共經濟與衛生專家、統計學家和臨牀專業醫生等不同背景的知識，本人是一邊學一邊做。同時感謝不同領域專家的協助，讓計畫得以進行。

未來，這個模式仍要繼續開發，同時也透過政大，希望建立與 Monash University Malaysia 的合作互訪機制，持續努力完成離散事件模擬法在藥物經濟成本效益分析的決策支援系統模型。馬來西亞方面對於和台灣的交流表示強烈的意願。本人僅獻棉薄之力。除了進行國民外交，與 Monash University 學者產生良好的互動，互相交換研究心得，增加彼此了解，加強友誼，對於未來的研究工作和國際交流有正面而且直接的影響。

附 錄(TreeAge 的模擬程式)

HBV Infection Prognosis Prolonged Simulation Models

ABSTRACT

Objectives: Chronic hepatitis B virus (HBV) infection is a dynamic process with an early replication phase and active liver disease. HBV can result in long-term infection causing a serious clinical problem, affecting 350-370 million individuals worldwide. Several unresolved issues are difficult to address using currently available clinical data. These include prognosis of hepatitis B with its natural history and the relative cost-effectiveness of the management procedures. Markov models and decision trees are commonly used in disease progression simulation. However, these methods cannot reflect the clinical appearance more flexibly and alternatively. Therefore, this requirement develops a discrete-event computer simulation model for the analysis of HBV disease progression. Discrete Event Simulation (DES) presents a flexible and powerful analysis tool for respective purposes in HBV studies. In this paper, we developed a DES model based on the natural course of HBV infection. The celebrated Gompertz function and the life table are applied the developed model. The model is effective by resembling individuals or cohorts of hypothetical patients while tracking disease progression and survival.

Methods: We consider that the disease progression is originally described by a Markov model, and propose a new method to approximate the HBV progression with clinical data. Instead of the additive assumption, this resulting model is established based on conditional probabilities and a life table.

Results: For a patient at age 25, the expected remaining life expectancy, and the maximal life year for him or she is 36.31 years and 80 years respectively. This patient has 16.37% probability of death/transplantation within 20 years because of HBV infection or population mortality.

Conclusion: Numerical results show that the proposed model can be applied to obtain a more realistic life expectancy, the survival probabilities at various initial ages, and mortalities from various initial symptoms to death. Meanwhile, its applications to derive the probabilities for patients' first experiencing critical medical status during a specified duration and its generalization to include multiple transition related factors are discussed.

Keywords: Markov chain, disease progression, life table, first passage time, survival probability.

Introduction

Simulation in healthcare as an academic subject has been widely explored and well doucmented. During the past decades, simulation modeling in healthcare has been referred to wide range of applications from health risk assesssment, cost-benefit analysis and policy evaluation of medical treatment, diesase menagement, planning of

healthcare services, training and healthcare decision support system, etc. [15], Computer simulation is a technique of informatics which allows stake holder to conduct experiments with model and ideally provides a communication platform in healthcare for administratiors and clinicians to to find better solutions for patients or tax payers.

Chronic hepatitis B virus (HBV) infection is a dynamic process with an early replication phase and active liver disease. HBV can result in long-term infection causing a serious clinical problem, affecting 350-370 million individuals worldwide. Disease progression modeling is generally recognized as a practical framework in considering related medical applications. Chronic hepatitis B inflicts an almost incredulous toll on the planet, affecting greater than 400 million people [11]. In Taiwan, chronic hepatitis B virus (HBV) infection and its potential adverse sequel are major causes of morbidity, mortality and medical expenditure. Chronic liver disease was the sixth leading cause of death in 2000 and hepatocellular carcinoma (HCC) was the most common cancer in 1997 [21]. According to Liver Disease Prevention & Treatment Research Foundation, there are 3 million people has been affected at a cost of more than US$ 3 million annually in Taiwan. Markov models and decision trees are most commonly used in disease progression simulation.

However, Markov models and decision trees are less able to reflect the clinical appearance more flexibly and alternatively. The risk of disease progression depends on the characteristics of the patients [3]. These models should take age, sex, disease severity, blood type, economical ability, and environmental factors into account simultaneously. Moreover, decisions about when a patient should take more aggressive medicine or when to have an operation are based not only on symptoms but also on social and environmental factors. Variables should be defined to contain factors that change over time to reflect the disease more naturally. Outcomes are costs, disease episodes and symptoms. Sensitivity analyses about cost or transition probabilities should be contained as well [4].

Therefore, this kind of requirement develops a discrete-event computer simulation model for the analysis of HBV disease progression. This paper describes the development of a model to assess the dependencies between a broad range of parameters in the treatment of disease. Discrete-event computer simulation has been widely used inside the management science and operations research contexts since it is already known as an important design tool for versatile applications. Importantly, this kind of simulation has been shown to be a fast and low-cost approach for health management modeling [2, 4]. The individual experience is modeled over time in terms of the events that occur and the consequences of those events. This approach is superior to the traditional Markov models. [3].

DES proceeds very efficiently because the clock is successively advanced to the time when the next event will occur, without wasting effort in unnecessary interim computations [2]. In other words, time advances in ‘discrete’ jumps. By making time explicit, a DES avoids one of the major problems of decision trees [2]. It also enables handling of time that is much more flexible than in Markov models since there is no need to declare a cycle length. Although cohort Markov models may involve fewer calculations, they require gross oversimplifications making them rarely suitable for informing real decisions.

1. Natural History

Chronic HBV infection is a dynamic process with an early replicative phase and active liver disease and a late low or nonreplicative phase with remission of liver disease. Persistence of HBsAg, hepatitis B e antigen (HBeAg) and HBV-DNA in high titer for more than 6 months implies progression to chronic HBV infection [1]. The variability in chronic hepatitis B has led to its classification into phases of disease based upon alanine aminotransferase (ALT) elevations, the presence of HBeAg, HBV-DNA levels and suspected immune status. The duration of typical HBeAg-positive chronic hepatitis B can be prolonged and severe and may result in cirrhosis [7,16].

Immune tolerance phase:

The presence of circulating HBsAg, HBeAg and high levels of serum HBV-DNA identifies the first immunotolerant phase. Perinatally acquired HBV infection is characterized by a prolonged "immunotolerant" phase with HBeAg positivity, high levels of serum HBV-DNA, normal levels of aminotransferases, minimal liver damage and very low rates of spontaneous HBeAg clearance. A proportion of HBeAg-positive persons, have no ALT elevations and scant histological activity. In Asia, it is most common in children, adolescent, and young adults [11].

Immune clearance phase:

The second immunoactive phase which is associated with a decrease in HBV-DNA concentrations and increased ALT levels and histological activity reflects the host immune mediated lysis of infected hepatocytes [7]. Patients with childhood or adult acquired infection and chronic hepatitis B usually present in the "immunoactive" phase with elevated aminotransferases and liver necroinflammation at histology and approximately 50% will clear HBeAg within 5 years. This phase marks the incubation period of acute HBV infection and lasts about two to four weeks, in contrast with perinatal infection this phase often lasts for decades in which patients with chronic HBV infection has a variable duration from months to years [11]. Hepatitis flares during treatment were defined as elevations in the alanine aminotransferase level to more than twice the baseline level and to more than 10 times the upper limit of normal [13].

Residual phase is the third low or non-replicative phase involves seroconversion from HBeAg to antibody to HBeAg (anti-HBe) usually preceeded by a marked reduction of serum HBV-DNA levels below 105 copies per ml, that are not detecTable Ay hybridization techniques, and followed by normalization of ALT levels and resolution of liver necroinflammation. Serum HBV-DNA remains detectable only by ultrasensitive technique of polymerase chain reaction (PCR) in many patients. In chronic HBV infection this phase is also referred as the inactive HBsAg carrier state. The inactive chronic HBV infection may last for lifetime, but a proportion of patients may undergo subsequent spontaneous or immunosuppression induced reactivation of HBV replication with reappearance of high levels of HBV-DNA with or without HBeAg seroreversion and rise in ALT levels [11, 16].

HBV can be classified into 7 genotypes A-G and recent studies, all from Asia, have indicated that HBV genotype B is associated with earlier HBeAg seroconversion than genotype C, thus most likely explaining the less

progressive disease in patients with genotype B [6, 8, 19]. HBeAg seroconversion associated with liver disease remission marks the transition from chronic hepatitis B to the inactive HBsAg carrier state, however a small percentage of patients (approximately 5%) may continue to show biochemical activity and high levels of serum HBV-DNA at the time of HBeAg seroconversion [1, 12, 14]. These patients as well those undergoing reactivation of hepatitis B after HBeAg seroconversion may generate the group of patients with HBeAg negative chronic hepatitis B.

Figure 1 presents a model with a slight modification by Liaw and Chu [27]. Here we take numerical experiments based on Figure 1 by some required approximations and modifications stated in the following. First, we assume that several estimates in Figure 1 are annual transition probabilities rather than percentages. Second, the state "curative therapy" is combined with the state "death/transplantation." and replaced with the state "death". Besides, no treatments are applied to patients. Third, in Figure 1, the annual transition probability from "HBeAg(+) hepatitis HBV-DNA> $2\times10^{6\sim7}$ IU/ml" to "HBeAg(+) hepatitis HBV-DNA> $2\times10^{4\sim5}$ IU/ml" and "HBeAg seroconversion" is assumed to be 15% per year.

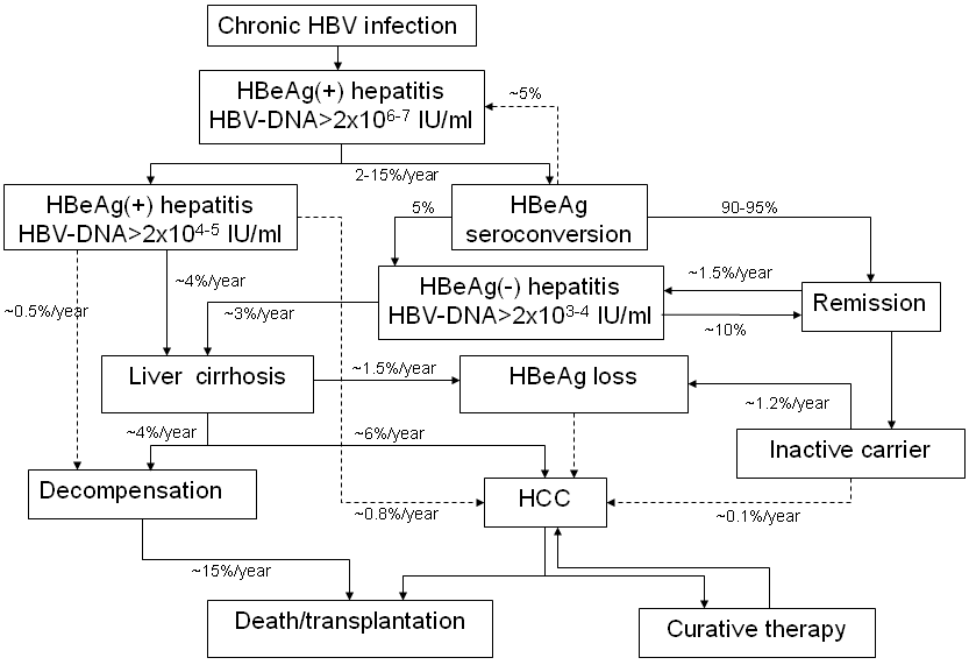

Figure 1: A transition diagram of chronic HBV progression from Liaw and Chu [27].

The outward annual transition probability from state "HBeAg(+) hepatitis HBV-DNA> $2\times10^{6\sim7}$ IU/ml" is assumed to be 15% per year. We may assume that the ratio between transitions to "HBeAg(+) hepatitis HBV-DNA> $2\times10^{4\sim5}$ IU/ml" and transitions to "HBeAg seroconversion" is approximately 2:1. In other words, annual transition probability to "HBeAg(+) hepatitis HBV-DNA> $2\times10^{4\sim5}$ IU/ml" is 10% per year and annual transition probability to "HBeAg seroconversion" is 5% per year. Figure 2 summarizes the modifications.

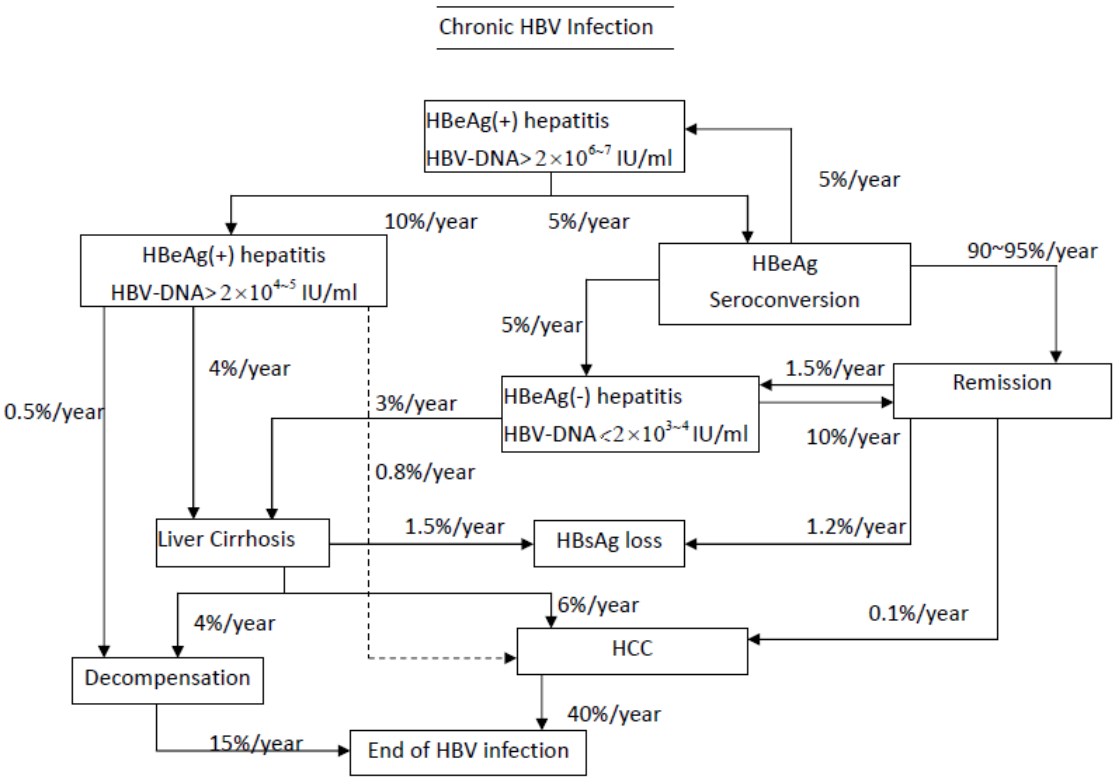

Figure 2: The modified transition diagram of Chronic HBV progression.

In Figure 2, consider a random variable sequence $X=\{X_n, n\in \mathrm{N}\}$ and $T=\{T_n, n\in \mathrm{N}\}$ defined on a probability space (Ω, F, P) with a finite set $E=\{s_1, s_{2,}, \cdots, s_m\}$, $m\in \mathrm{N}$, where N is the set of all positive integers. For example, s_1 denotes the health status of HBeAg(+) hepatitis HBD-DNA> $2\times10^{6\sim7}$ IU/mL; s_2 denotes the health status of HBeAg(-) hepatitis HBD-DNA> $2\times10^{3\sim4}$ IU/mL, and so on. X_n represents the state at the n^{th} transition and T_n denotes the time before the n^{th} transition. If $X_n=i$ and $i\in E$, then the process is said to be in state i at time n. For any nonnegative integer n and any state $i, j, i_0, \cdots, i_{n-1}$, we have:

$$p_{i,j}=P(X_{n+1}=j \mid X_0=i_0, X_1=i_1, \cdots, X_{n-1}=i_{n-1}, X_n=i)=P(X_{n+1}=j \mid X_n=i).$$

In addition, if state j is not adjacent to state i in the HBV disease progression model, then the probability $p_{i,j}$ is assumed to be 0. We define

$$p_i=\sum_{j=1}^{m} p_{i,j},$$

where p_i denotes the probability for a patient to leave state i in one year.

2. Gompertz Distributions

The principal focus of the analysis was to determine the relative transitions of hepatic liver disease in patients with clinical symptoms. An analysis with best estimates for all model parameters and event probabilities was carried out from a societal perspective following the consensus recommendations of Liaw and Chu [27]. Instead of the conventional Markov Model in most published papers on such outcome studies, the methodology is to use discrete

event simulation for prognosis of HBV modeling. The model tracks the liver disease status, virus activity, clinical symptoms, and age of each patient. Survival life is predicted on the basis of disease extent.

The celebrated Gompertz distribution [18] is introduced in the DES model. We assume that each state i follows the Gompertz distribution with different parameters a_i and b_i. The probability density function of Gompertz distribution is given as

$$f_i(t;\ a_i,\ b_i) = b_i \cdot e^{a_i t} \exp[\frac{b_i}{a_i}(1-e^{a_i t})]$$

for $0 < t < \infty$, $a_i > 0$, and $b_i > 0$ (0 otherwise). The corresponding cumulative distribution function is

$$F_i(t;\ a_i,\ b_i) = 1 - \exp[\frac{b_i}{a_i}(1-e^{a_i t})].$$

In every state, it is essential to estimate the time interval of such a health state in simulation. Denoting by T the time interval of a specific state i, the probability of an incidence occurrence before time t where $T \le t$ is

$$P(T_{n+1} - T_n \le t | \mathrm{X}_n = i,\ X_{n+1} \ne i) = F_i(t;\ a_i,\ b_i) = 1 - \exp[\frac{b_i}{a_i}(1-e^{a_i t})]. .$$

In particular, for every state i, the probability of an incidence occurrence within one year is $T \le 1$. Hence, we have

$$P(T_{n+1} - T_n \le 1 | \mathrm{X}_n = i,\ X_{n+1} \ne i)) = 1 - \exp[\frac{b_i}{a_i}(1-e^{a_i})] = p_i.$$

For given transition probability p_i and a_i in state i, we have b_i as a function of a_i written as

$$b_i = f(a_i) = \frac{a_i \ln(1-p_i)}{1-e^{a_i}}.$$

In DES, the average length of time intervals of the nonabsorbing state is estimated by $1/p_i$. For each simulation run, we converted all available data into annual probability estimates for use in the DES model. We calculated these annual estimates of each time period that a state will experience. Hence, we know that

$$P(T_{n+1} - T_n \le t | \mathrm{X}_n = i,\ X_{n+1} \ne i) = F_i(t;\ a_i) = 1 - \exp[\frac{\ln(1-p_i)}{1-e^{a_i}}(1-e^{a_i t})].$$

According to Yousef [18], the mean $u_t|_i$ of the distribution is

$$u_t|_i = \frac{1}{a_i} e^{\frac{b_i}{a_i}} \left[\ln a_i - \ln b_i - \gamma - \sum_{k=1}^{\infty} \frac{\left(-\frac{b_i}{a_i}\right)^k}{k \cdot k!} \right],$$

where $\gamma \sim 0.5772$ is an Euler's constant. Hence, the equation of $u_t|_i$ for each status can be rewritten as

$$u_t|_i = \frac{1}{a_i} e^{\frac{\ln(1-p_i)}{1-e^{a_i}}} \left[\ln \frac{1-e^{a_i}}{\ln(1-p_i)} - \gamma - \sum_{k=1}^{\infty} \frac{\left(-\frac{\ln(1-p_i)}{1-e^{a_i}}\right)^k}{k \cdot k!} \right].$$

We want to choose proper a_i for each state to fit that $u_t|_i \approx 1/p_i$, so we solve the equation $u_t|_i - 1/p_i = 0$ for a_i for different status. Table 1 summarizes the results of a_i and b_i. Note that the status "Death/Transplantation" is the absorbing state. In addition, for the state "HBeAg seroconversion", every patient in this symptom is assumed to stay for one year and then transfers to another states. For patients at "HBsAg loss", he will follows the population mortality instead of the Gompertz distribution.

Table 1: The symbols and parameters a_i and b_i of states in Figure 2.

Symptoms	State symbol	a_i	b_i
HBeAg(+) hepatitis HBD-DNA> $2 \times 10^{6\sim7}$ IU/mL	s_1	0.11	0.0004
HBeAg(+) hepatitis HBD-DNA> $2 \times 10^{4\sim5}$ IU/mL	s_2	0.4	0.0001

HBeAg seroconversion	s_3	None	None
HBeAg(-) hepatitis HBD-DNA< $2\times10^{3\sim4}$ IU/mL	s_4	0.095	0.0004
Remission	s_5	0.02	0.0001
Liver cirrhosis	s_6	0.081	0.0003
HBsAg loss	s_7	None	None
Decompensation	s_8	0.11	0.0004
HCC	s_9	0.28	0.0011
Death/Transplantation	s_{10}	None	None

3. Model Overview

To articulate the natural course of chronic HBV, a discrete-event simulation model was developed with the ProModel [20]. This model is based on the concepts of entities, locations, processes, time of events and attributes. In this study, an entity represents a patient in the disease progression. Locations are liver status where the processes are the routines that connect locations. Processes will decide how an entity will work in every location, where the Gompertz distribution [18] and the life table [22] are embedded. Attributes are the possible clinical symptoms of patients which are presented by entities. These elements, taken together with discrete time of every possible events of a system, allow for the construction of computer models that represent the system actual operating conditions. Basic system parameters are excerpted from the literature given in Liaw and Chu [27], and the life table [22] is described in Appendix.

We developed a Discrete Event Simulation model based on the natural course of Chronic HBV [9, 16, 27]. In this section, the proposed DES model will be expounded in detail. Flow diagram of the computation process for a discrete event simulation is also discussed. The life table [22] is also concluded in the DES model, which is given in Appendix.

3.1 Entities

A central component of DES is the entity which denotes the patient in modeling. In contrast to decision trees and Markov models, which do not specify the patient but instead focus exclusively on outcomes or states, the patient is an explicit element in a DES. A DES model allows introducing interactions between patients or different status while a Markov Monte-Carlo microsimulation deals with one health status at a time. It is important while modeling for infectious diseases.

Patients have attributes of which individual has a specific value for each characteristic. These values are defined at the start of the simulation and updated at particular points in time. Two important attributes of patients are the time to reach the significant status and the sojourn time in status. When patients start infected with HBV, they are concerned about how much time they have to reach the worse status, how much time they could stay healthy, what the remaining life expectancy is for them, or what the survival probability is in the future. Attributes in DES play an important part in

estimating.

3.2 Locations

The model contains ten liver statuses as in Table 1: HBeAg(+) hepatitis HBD-DNA> $2\times10^{6\sim7}$ IU/mL, HBeAg(+) hepatitis HBD-DNA> $2\times10^{4\sim5}$ IU/mL, HBeAg seroconversion, HBeAg(-) hepatitis HBD-DNA> $2\times10^{3\sim4}$ IU/mL, remission, liver cirrhosis, HBsAg loss, decompensation, hepatocellular carcinoma, and death/transplantation. Each liver status is defined as a location in this model. All patients begin in the Chronic HBV infection and enter HBeAg(+) hepatitis HBD-DNA> $2\times10^{6\sim7}$ IU/mL immediately. Patients change to any of the liver statuses with given probability according the Gompertz function. When entities entered a location, they will follow the rule of processing defined on each location to decide how long they would stay in this location and where to go for the next. A demonstration of DES model is shown as Figure 3.

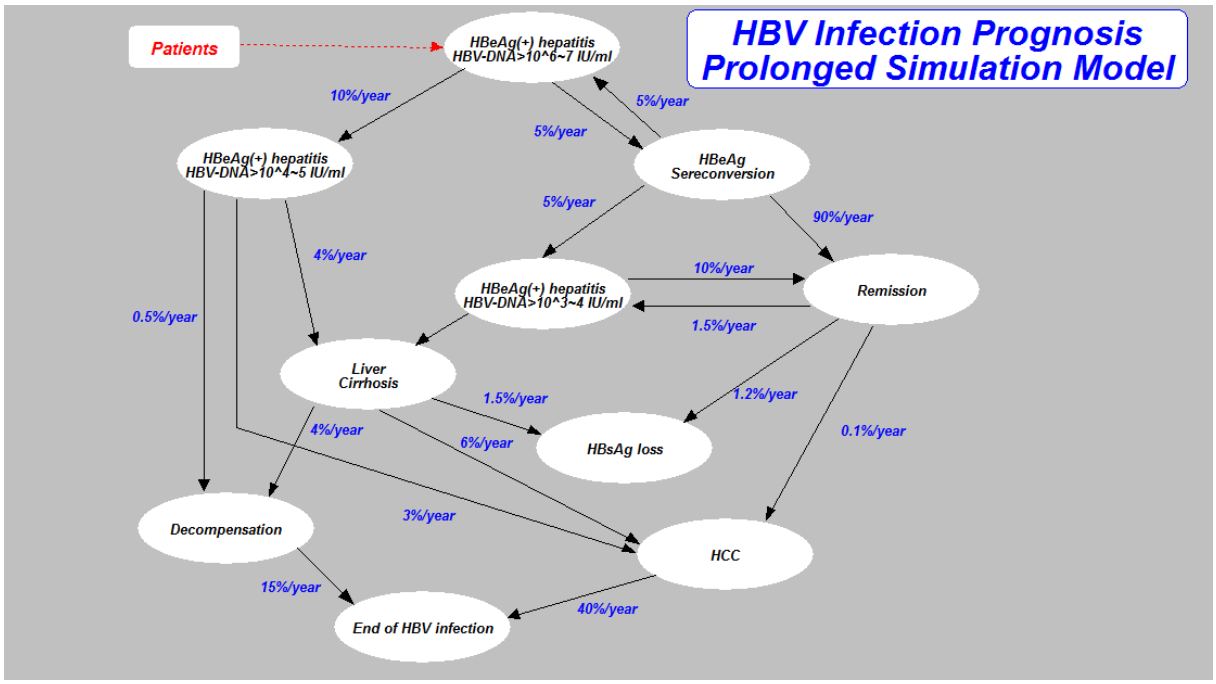

Figure 3: A demonstration of DES model

3.3 Processing

Processing guides how an entity acts in a location. Figure 4 shows how a patient will move in this DES disease progression. First, a HBV patient is created and then he starts his own HBV disease progression. Generally speaking, an entity will reach the status "HBeAg(+) hepatitis HBD-DNA> $2\times10^{6\sim7}$ IU/mL". Then the entity will decide how long he will stay at the state "HBeAg(+) hepatitis HBD-DNA> $2\times10^{6\sim7}$ IU/mL" according to the Gompertz function given in Section 5. For a entity at this status, given a random number $0 \le r \le 1$, we have the waiting time T_1 for this patient at this state by

$$T_1 = \frac{1}{a_1}\ln(\ln\frac{e}{(1-r)^{1-e^{a_1}/\ln(1-p_1)}}).$$

That is, this patient will spend time T_1 at current state. After waiting time T_1 in the state "HBeAg(+) hepatitis

HBD-DNA> $2\times10^{6\sim7}$ IU/mL" for a while, the entity will decide whether he will die or not according to the population mortality or disease progression. If the entity died, then he simply reaches the final status "Death". If the entity does not die, he will leave the current state and reach another state s_j, $j \sim i$. Then the entity repeats the progression rule for another state s_j again until he reaches the final state "Death".

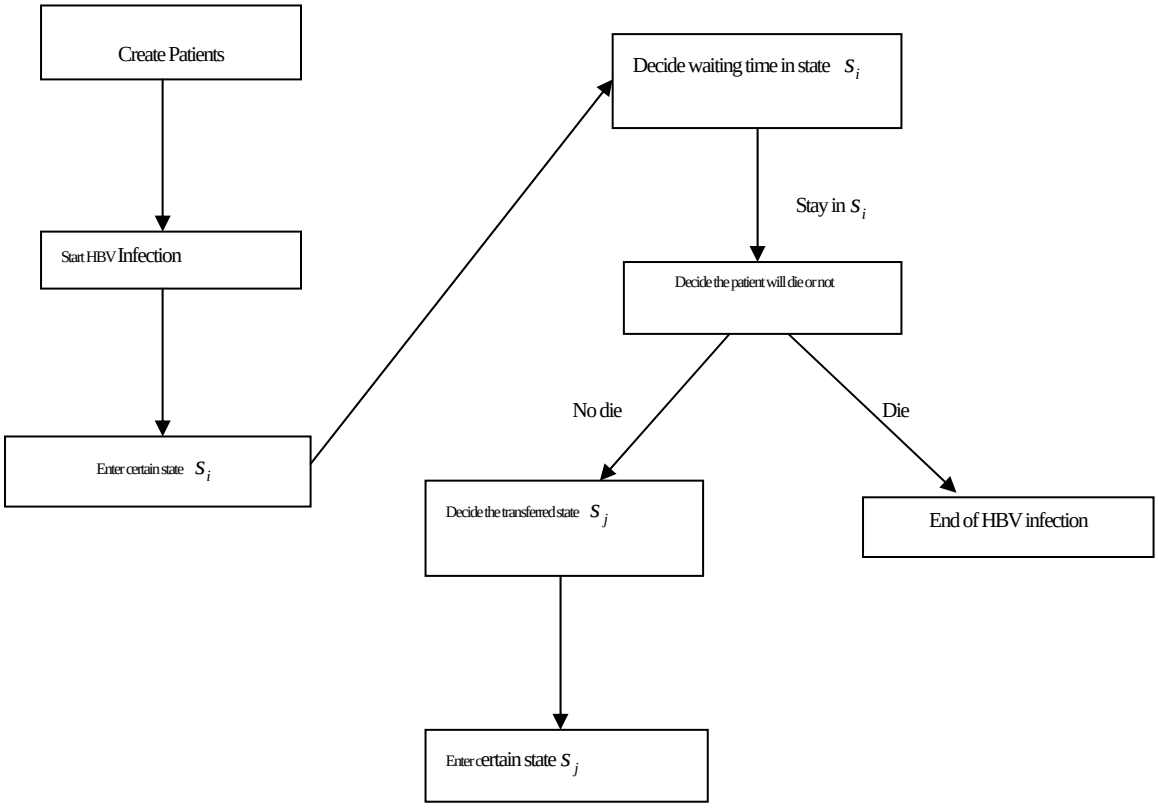

Figure 4: The flow chart of the DES disease progression.

4. The Outcome of DES Model

4.1 The outcome of DES model

This process continues until a predetermined time is reached, at which point the simulation is terminated. The basic model includes only a generic setting and no treatment strategy. The model is effective by simulating cohorts of hypothetical patients while tracking disease progression, complications, and survival. For each set of model assumptions under consideration, we may simulate hypothetical cohorts of patients.

The model tracks up to 10 individual hepatic clinical symptoms in each patient, specifying and updating liver disease status shown in Table 1. Percentages of occurrences at different liver status are given in Figure 2. For each hypothetical patient, the type of virus activity is chosen at random from a population distribution conditioned on a previous liver status and other variables. The type of virus activity is then distributed throughout the simulation. We assume that each patient has an independent, equal probability of being infected by virus**.** The clinical symptom of

each patient is similarly selected at random from a population distribution but mainly depending on the previous condition. We assume time advances with Gompertz distributions and that no new liver disease develops between any two occurrences, since all events are assumed to happen at discrete time manner. Events can happen in any logical sequence and even simultaneously. They can recur if that happens in reality and they can change the course of a given patient's experience by influencing that patient's attributes and the occurrence of future events with no restriction on 'memory'.

In the DES, the model is assumed to have a lifetime horizon and a cycle length of 75 years with patients with HBV at age 25. In ProModel, one year is assumed to be 360 days, so we setup the time limit to be $75 \times 360 = 27000$ days. Note that the unit of the results is days. The simulation is repeated for 10 times, and in every simulation 20000 patients are involved. The simulated results are shown in Figure 5.

Variable Name	Total Changes	Average Hours Per Change	Minimum Value	Maximum Value	Current Value	Average Value	
remission time*	8880.6	3.03	0.69	25919.5	13776.6	4831.26	(Average)
remission time*	129.30	0.04	0.84	313.71	4938.26	90.49	(Std. Dev.)
e loss time*	6784.1	2.15	365	365	365	365	(Average)
e loss time*	71.86	0.34	0	0	0	0	(Std. Dev.)
decompensation time*	4942	5.42	0.45	10934.9	3806.35	2400.5	(Average)
decompensation time*	86.77	0.09	0.32	12.61	2715.02	24.00	(Std. Dev.)
cirrhosis time*	10924	2.46	0.21	10942.6	2108.21	2754.7	(Average)
cirrhosis time*	99.49	0.02	0.22	5.28	1137.31	22.45	(Std. Dev.)
DNA1034 time*	4628.4	5.82	0.75	10937.3	3256.45	2604.57	(Average)
DNA1034 time*	114.03	0.14	0.46	11.36	2957.59	26.53	(Std. Dev.)
DNA1045 time*	13441.5	1.65	0.19	10945.7	9643.12	3966	(Average)
DNA1045 time*	72.97	0.08	0.18	3.66	807.24	22.76	(Std. Dev.)
HCC time*	7789.7	3.44	0.48	10936.9	2530.07	2162.96	(Average)
HCC time*	58.67	0.03	0.39	11.49	4026.27	24.65	(Std. Dev.)
sloss time*	4661.4	5.79	365	25258	18469	11424.7	(Average)
sloss time*	86.69	0.10	0	335.41	3025.56	91.99	(Std. Dev.)
DNA1067 time*	20337.4	0.76	0.08	10838.5	9350.77	1979.67	(Average)
DNA1067 time*	12.60	0.11	0.07	90.59	1381.96	6.92	(Std. Dev.)
time 2 DNA1045*	13441.5	1.65	2.85	15246.5	12667.8	2023.43	(Average)
time 2 DNA1045*	72.97	0.08	0.09	1695.3	1397.07	11.31	(Std. Dev.)
time 2 DNA1034*	4628.4	5.82	376.98	26266.4	14561	6648.72	(Average)
time 2 DNA1034*	114.03	0.14	6.22	436.95	10504.6	90.68	(Std. Dev.)
time 2 DNA1067*	20337.4	0.76	1	1	1	1	(Average)
time 2 DNA1067*	12.60	0.11	0	0	0	0	(Std. Dev.)
time 2 HCC*	7789.7	3.44	165.99	26318.9	24307.3	8268.19	(Average)
time 2 HCC*	58.67	0.03	76.35	368.78	4071.7	33.37	(Std. Dev.)
time 2 decompensation*	4942	5.42	253.8	25383.3	22995.2	8259.16	(Average)
time 2 decompensation*	86.77	0.09	93.94	583.24	2868.77	74.37	(Std. Dev.)
time 2 cirrhosis*	10924	2.46	61.96	25639.1	24771.3	6379.1	(Average)
time 2 cirrhosis*	99.49	0.02	34.14	650.03	1101.41	38.73	(Std. Dev.)
time 2 eloss*	6784.1	2.15	3.03	7661.08	3004.72	1951.19	(Average)
time 2 eloss*	71.86	0.34	0.23	383.03	755.08	18.34	(Std. Dev.)
time 2 sloss*	153932	0.17	472.56	26592.2	9441.76	7331.55	(Average)
time 2 sloss*	2985.81	0.00	125.83	34.23	4471.74	50.30	(Std. Dev.)
time 2 remission*	8880.6	3.03	369.12	14833.5	1934.34	2504.89	(Average)
time 2 remission*	129.30	0.04	0.24	736.14	1009.92	21.98	(Std. Dev.)
time to death*	19134.3	1.41	21.21	26995.4	26995.4	13070.5	(Average)
time to death*	24.59	0.00	12.68	4.18	4.18	53.37	(Std. Dev.)

Figure 5: The results of the HBV disease progression model.

From Figure 5, there are the results of the HBV disease progression model. The results are classified into 2 parts. Take the status "remission" for example, one is the word "remission time", and the other is "time 2 remission". "Remission time" represents the time a patient spent in status remission, whereas "time 2 remission" means the time a patient spent before reaching the status "remission" for the first time. The time unit in Figure As the titles in Figure

5, we focus on the average value. The average value for "remission time" is 4831.26 days, and 90.49 days is the standard deviation for the results. The average value for "Time 2 remission" is 2504.89 days with standard deviation 21.98 days. In other words, the average value for "remission time" and "Time 2 remission" is 4831.26/360=13.42 years and 2504.89/360=6.96 years respectively. Table 2 summarized the results of Figure 5. Note that the time unit in Figure 5 is days, and the time unit in Table 2 is years.

Table 2: The average sojourn time in different liver status and the average time to reach different liver status in Figure 2

Symptoms	The average sojourn time	The average time
HBeAg(+) hepatitis HBD-DNA> $2\times10^{6\sim7}$ IU/mL	5.50 years	None
HBeAg(+) hepatitis HBD-DNA> $2\times10^{4\sim5}$ IU/mL	11.02 years	5.62 years
HBeAg seroconversion	1 year	5.42 years
HBeAg(-) hepatitis HBD-DNA> $2\times10^{3\sim4}$ IU/mL	7.23 years	18.46 years
Remission	13.42 years	6.96 years
Liver cirrhosis	7.65 years	17.72 years
HBsAg loss	31.74 years	20.37 years
Decompensation	6.67 years	22.94 years
HCC	6.01 years	22.97 years
Death	None	36.31 years

This model was constructed by a systematic search of the literature to identify source materials on the natural history, epidemiology of HBV, and demography. In the state transition model, patients with HBV may remain in that state, move on to more progressive stages of liver disease or may clear the disease. The model has a lifetime horizon and a cycle length of 75 years, assuming a patient with HBV at age 25. Table 2 demonstrates the average sojourn time in each liver status and the average time for a patient at age 25 to reach different liver status. The patients are estimated to wait 7.65 years at the liver status liver cirrhosis and 31.74 years at HBsAg loss respectively. Moreover, it is approximated about 17.72 years for a patient at age 25 to reach the liver status liver cirrhosis. The remaining life expectancy is predicted about 36.31 years for a patient at age 25 at the beginning of HBV infection. The outcomes analysis of our study presents a byproduct of the development of DES, which illustrates the usage of DES.

4.2 DES versus Markov

In this section, we compare the results of a DES model and a Markov model for chronic HBV disease progression. The results are based on assuming that the patients are at state s_1 starting at age 25. Table 3 represents the outcome of a DES model and Table 4 shows the result of a Markov model.

Table 3: The simulated disease progression probabilities distribution for a DES model

States / Ages	s_1	s_2	s_3	s_4	s_5	s_6	s_7	s_8	s_9	s_{10}
25	1	0	0	0	0	0	0	0	0	0
30	0.4864	0.3059	0.0308	0.0130	0.1104	0.0306	0.0061	0.0044	0.0072	0.0054
35	0.1452	0.4126	0.0177	0.0367	0.1814	0.1028	0.0308	0.0200	0.0312	0.0221
40	0.1448	0.4126	0.0177	0.0367	0.1814	0.1030	0.0308	0.0196	0.0312	0.0221
45	0.0065	0.2146	0.0007	0.0623	0.1273	0.1667	0.1137	0.0570	0.0877	0.1637
50	0.0036	0.1202	0.0006	0.0540	0.0931	0.1426	0.1534	0.0590	0.0872	0.2872

55	0.0005	0.0135	0.0002	0.0340	0.0425	0.0699	0.2054	0.0410	0.0562	0.5370
60	0.0001	0.0023	0	0.0231	0.0327	0.0381	0.2094	0.0273	0.0349	0.6320
65	0	0.0007	0	0.0148	0.0266	0.0181	0.2014	0.0159	0.0187	0.7039
70	0	0.0003	0	0.0091	0.0221	0.0093	0.1814	0.0094	0.0091	0.7593
75	0	0.0002	0	0.0056	0.0188	0.0047	0.1497	0.0049	0.0040	0.8122
80	0	0.0001	0	0.0040	0.0141	0.0023	0.1101	0.0025	0.0019	0.8659

Table 4: The simulated disease progression probabilities distribution for a Markov model

States / Ages	s_1	s_2	s_3	s_4	s_5	s_6	s_7	s_8	s_9	s_{10}
25	1	0	0	0	0	0	0	0	0	0
30	0.4479	0.3275	0.0263	0.0096	0.1379	0.0289	0.0034	0.0047	0.006	0.0078
35	0.201	0.3948	0.0118	0.0185	0.2075	0.076	0.0173	0.0166	0.0158	0.0407
40	0.09	0.3639	0.0053	0.0233	0.225	0.1044	0.0367	0.0279	0.0218	0.1017
45	0.0401	0.3031	0.0024	0.0251	0.2206	0.1122	0.0578	0.0345	0.0234	0.1808
50	0.0178	0.2399	0.001	0.0249	0.2072	0.106	0.0778	0.0363	0.0222	0.2669
55	0.0078	0.1841	0.0005	0.0237	0.1901	0.0926	0.0952	0.0343	0.0194	0.3524
60	0.0034	0.1375	0.0002	0.0217	0.1707	0.0763	0.1086	0.0299	0.016	0.4358
65	0.0015	0.1	0.0001	0.0193	0.15	0.0599	0.1171	0.0245	0.0126	0.5151
70	0.0006	0.07	0	0.0164	0.1272	0.0447	0.1187	0.0189	0.0094	0.5941
75	0.0002	0.0463	0	0.0133	0.1022	0.0312	0.1119	0.0134	0.0066	0.6748
80	0.0001	0.0282	0	0.0098	0.0755	0.0199	0.0955	0.0087	0.0042	0.7582

Table 3 and Table 4 show the simulated disease progression probabilities distribution. After ten years, about 14.52% it will be in s_1 and 18.14% in s_5, and 2.2% in s_{10} in a DES model, whiles about 9% it will be in s_1 and 20.75% in s_5, and 4% in s_{10} in a Markov model. Likewise, the other probabilities can be interpreted in the same manner. Figure 6 and Figure 7 show the corresponding survival probability simulated from a DES and a Markov model respectively. Moreover, the remaining life expectancy for DES model and Markov model are 36.31 years and 39.48 years.

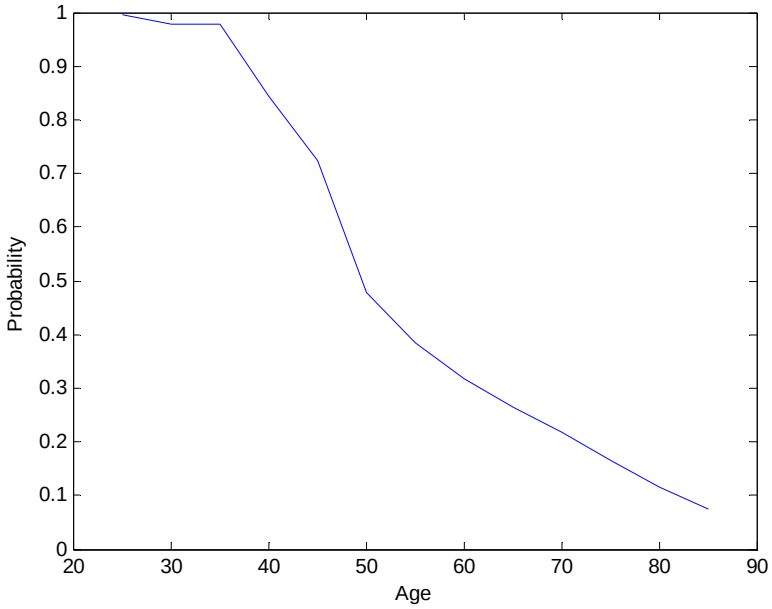

Figure 6: The survival probability of different ages starting at age 25

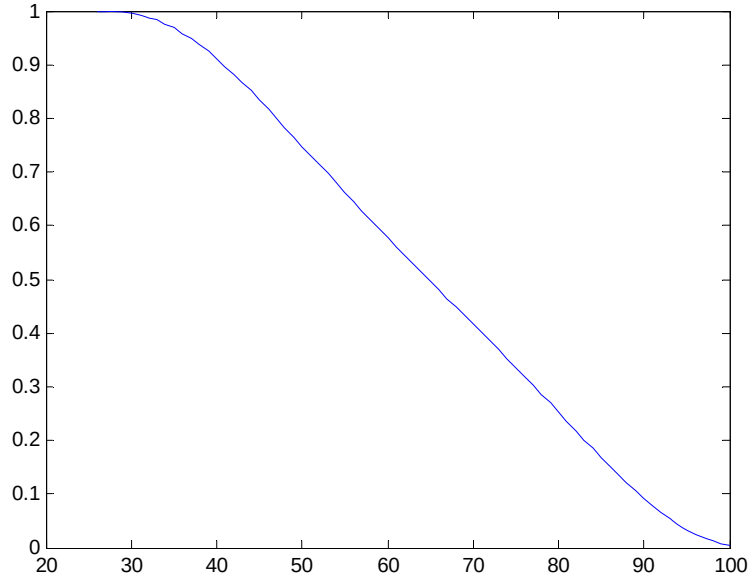

Figure 7: The survival probability of different ages starting at age 25

5. Conclusion

A model of DES is a tool for decision support system. The key feature of any decision model is to be "fit for purpose" for decision-making [25]. A model is a logic mathematical framework that permits the integration of facts and values and that links these data to outcomes for decision makers. If a model built at human disease processes to reasonably inform decision-makers and deal with uncertainty, variability, and heterogeneity, interaction, etc., simulation can appropriately handle the realities to correctly model it at the required depth, although it may involve a large number of computations which may be a hindrance to conducting DES. However, as computing techniques emerge dramatically, DES becomes easy and powerful for various managerial purposes.

Our analysis has two strengths. First, to our knowledge, our study is the first discrete event simulation model of decision analysis to compare competing strategies for chronic HBV infection. Previous models have focus on either the Markov model or decision tree analysis. Second, our model acknowledges the increasing prevalence of simulation models. This approach increases the generalizability of modeling flexibility in light of statistical data.

Our study only demonstrates a possible construction for a DES used in analysis of chronic HBV. Our model has several limitations. First, several of our estimates are based on literature which may depend on different design, patient population, follow-up and quality. Our estimates of patient health preferences may be limited because we adopted utilities for cirrhosis health states in HBV from limited sources. However, it is reasonable to assume that a patient who develops cirrhosis or related complications would have the same quality of life decrement regardless of time. Second, the time period of health states were estimated and adjusted accordingly to systematical consistence of

simulation. More conditional health statuses could be included for better results and decision-making processes.

However, as mentioned in [10], the impact that simulation has on policy-making or at clinician level, managerial decision-making is weak although simulation has been successfully usedin military and manufacturing sectors. Information Technology (IT) systems and high quality of data may play key roles.

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References

1. Bortolotti F, Jara P, Crivellaro C, Hierro L, Cadrobbi P, Frauca E, Camarena C, De La Vega A, Diaz C, De Moliner L, Noventa F. Outcome of chronic hepatitis B in Caucasian children during a 20-year observation period. J Hepatol 1998; 29: 184-190.

2. Brennan A, Chick SE, Davis R. A taxonomy of model structures for economic evaluation of health technologies Health Economics 15: 1295-1310 2006.

3. Caro JJ, Möller J, Getsios D., Discrete Event Simulation: The Preferred Technique for Health Economic Evaluations? Value Health. 2010 Dec; 13(8):1056-60.

4. Caro JJ., Pharmacoeconomic analyses using discrete event simulation, Pharmacoeconomics, 2005:23(4), 323-332.

5. Chen CH, Chen YY, Chen GH, Yang SS,Tang HS, Lin HH, Lin DY, Lo SK, Du JM, Chang TT, Chen SC, Liao LY, Kuo CH, Lin KC, Tai DI, Changchien CS, Chang WY, Sheu JC, Chen DS, Liaw YF, Sung JL. Hepatitis B virus transmission and epatocarcinogenesis: a 9 year retrospective cohort of 13 676 relatives with hepatocellular carcinoma. Journal of Hepatology 2004; 40: 653-659.

6. Chu CJ, Hussain M, Lok ASF. Hepatitis B virus genotype B is associated with earlier HBeAg seroconversion compared to hepatitis B virus genotype C. Gastroenterology 2002; 122: 1756-1762.

7. Chu CM, Hung SJ, Lin J, Tai DI, Liaw YF. Natural history of hepatitis B e antigen to antibody seroconversion in patients with normal serum aminotransferase Levels. The American Journal of Medicine 2004; 116: 829-834.

8. Chu CM, Liaw YF. Genotype C hepatitis B virus infection is associated with a higher risk of reactivation of hepatitis B and progression to cirrhosis than genotype B: A longitudinal study of hepatitis B e antigen-positive patients with normal aminotransferase levels at baseline. Journal of Hepatology 2005; 43: 411-417.

9. Chu CM, Liaw YF. Hepatitis B virus-related cirrhosis: natural history and treatment. Seminars in Liver Disease 2006; 26 (2): 142-152.

10. Eldabi T, Paul RJ, Young T. Simulation modeling in healthcare: reviewing legacies and investigating futures. Journal of the Operational Research Society 2007; 58, 262-270.

11. Fattovich, G. Natural history and prognosis of hepatitis B. Seminar in Liver Disease 2003 Feb;23(1):47-58.

12. Fattovich G, Rugge M, Brollo L, Pontisso P, Noventa F, Guido M, Alberti A, Realdi G. Clinical, virologic and histologic outcome following seroconversion from HBeAg to anti-HBe in chronic hepatitis type B. Hepatology 1986; 6: 167-172.

13. Gambarin-Gelwan M, Jacobson I. Treatment of chronic hepatitis B infection, 2007; www.gastro.org/.../Documents/08_Publications/06_GIHep_Annual_Review/Articles/GambarinGelwan-Jacobson.pdf.

14. Hsu YS, Chien RN, Yeh CT, Sheen IS, Chiou HY, Chu CM, Liaw YF. Long-term outcome after spontaneous HBeAg seroconversion in patients with chronic hepatitis B. Hepatology 2002; 35: 1522-1527.

15. Katsaliaki K, Mustafee N. Applications of simulation within the healthcare context, Journal of the Operational Research Society 2011; 62, 1431-1451.

16. Liaw YF. Hepatitis B virus replication and liver and disease progression: the impact of antiviral therapy. Antiviral Theory 2006; 11: 669-679.

17. Matlab, Version R2008b, The MathWorks, Inc., USA, 2008.

18. M.H. AI Yousef, Estimation of Parameters and Truncation Point for the Truncated Gompertz Distribution, J. of King Saud Univ., Vol. 5, Admin Sci. (2), 35-48.

19. Orito E, Mizokami M, Sakugawa H, Michitaka K, Ishikawa K, Ichida T, Okanoue T, Yotsuyanagi H, Iino S. A case-control study for clinical and molecular biological diffferences between hepatitis B viruses of genotype B and C. Japan HBV Genotype Research Group. Hepatology 2001; 33: 218-223.

20. ProModel software 4.1 (Promodel Co.), 2001.

21. Pwu RF, Chan KA. Cost-effectiveness analysis of interferon-alpha therapy in the treatment of chronic hepatitis B in Taiwan, J Formos Med Assoc 2002;101:632-41.

22. Taiwan life table (1999-2001), Department of Statistics, Ministry of the Interior of Taiwan. http://www.moi.gov.tw/stat/life.aspx

23. The analysis of the main cause of death in Taiwan, 2011. Department of Health, Executive Yuan,

R.O.C.,http://www.doh.gov.tw/CHT2006/DM/DM2_2.aspx?now_fod_list_no=11962&class_no=440&level_no=4

24. TreeAge Pro Suite 2009, version 2009, TreeAge Software, Inc., 2009.

25. Weinstein MC, O'Brien B, Hornberger J, Jackson J, Johannesson M, McCabe C, Luce BR, Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices--Modeling Studies, Value in Health, 2003, 6(1), 9-16.

26. Yeh CT, Sheen IS, Chen TC, Hsien SY, Chu CM, Liaw YF. Prednisolone modulates the therapeutic effect of interferon to eliminate preferentially the hepatitis B virus precore stop mutant. Journal of Hepatology 2000; 32:829-836.

27. Y. F. Liaw and C. M. Chu, "Hepatitis B virus Infection," The Lancet, Vol.373, No.9663, 582-592, Feb., 2009.

Appendix A

A Chronic Hepatitis B Virus Infection Model on TreeAge

We use the software TreeAge [24] as a computing tool to compare results of the HBV disease progression with that calculated by the proposed model in this paper. The Markov model in TreeAge [24] is shown as a tree in Figure A. The transitional probabilities between symptoms are defined in the first box of the tree based on Figure 2. For each Markov node, first it will decide that whether or not the patient will die by population mortality or disease progression. If the patient died, then the disease progression will end up with death; if the patient does not die of population mortality, then the patient will make a transfer to another state or simply stay at the previous state. In Figure A, the symbols pDie, pDieDecompensation, and pDieHCC represent the population mortality, the probabilities of death at state decompensation and at state HCC respectively. Besides, pDNA1067_DNA1045 means the transitional probability from state "HBeAg(+) hepatitis HBV-DNA $>2\times10^{6\sim7}$ IU/ml" to "HBeAg(+) hepatitis HBV-DNA$>2\times10^{4\sim5}$ IU/ml". The interpretations for the other transition probabilities are similar. The symbol "#" represents the probability of one subtracting the total probabilities of other transitions above. Note in the first block named "HBV problem", pDie is defined to be that calculated by one subtracting the survival probability in the life table at different ages.

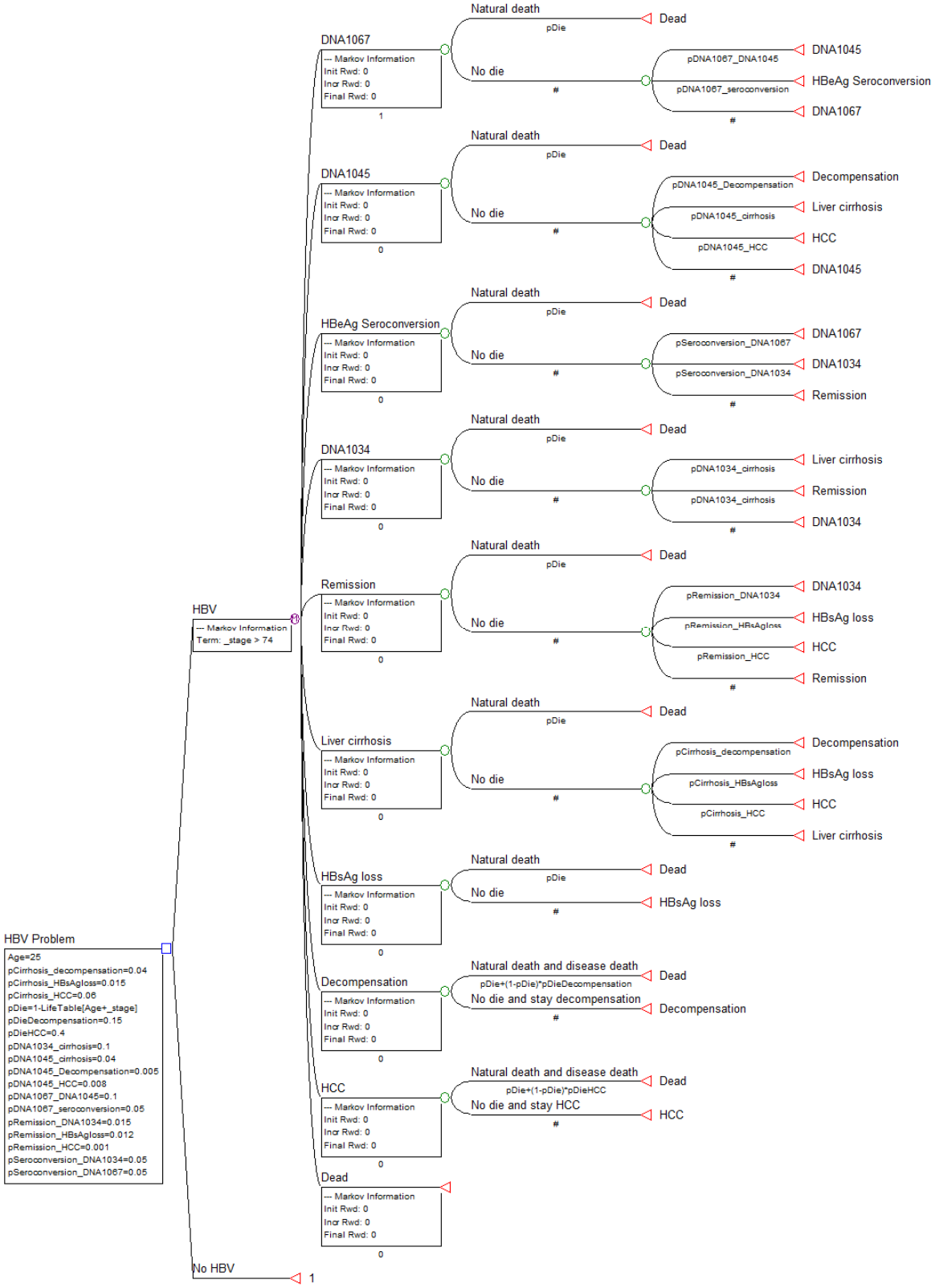

Figure A: The HBV disease progression model in TreeAge.

The survival probability at different ages in Table A is applied to the Markov model with TreeAge as well. Table A shows the simulated disease progression probabilities distribution, which is similar to the result in Table A. The

simulated disease progression probability distributions are plotted in Figure B. Moreover, the corresponding survival probability can be computed simultaneously. Figure D shows the survival curve for the patients infected HBV starting at age 25.

Table A: The simulated disease progression probabilities distribution by using TreeAge

States / Ages	s_1	s_2	s_3	s_4	s_5	s_6	s_7	s_8	s_9	s_{10}
25	1	0	0	0	0	0	0	0	0	0
30	0.4478	0.3274	0.0263	0.0087	0.1378	0.0298	0.0034	0.0047	0.0060	0.0081
35	0.2009	0.3946	0.0118	0.0148	0.2063	0.0795	0.0174	0.0169	0.0162	0.0417
40	0.0899	0.3635	0.0053	0.0170	0.2216	0.1100	0.0371	0.0287	0.0225	0.1046
45	0.0400	0.3024	0.0023	0.0171	0.2142	0.1189	0.0582	0.0358	0.0243	0.1867
50	0.0177	0.2392	0.0010	0.0161	0.1975	0.1130	0.0782	0.0378	0.0232	0.2763
55	0.0078	0.1831	0.0005	0.0146	0.1773	0.0991	0.0953	0.0358	0.0203	0.3662
60	0.0034	0.1363	0.0002	0.0129	0.1554	0.0820	0.1080	0.0314	0.0168	0.4537
65	0.0014	0.0986	0.0001	0.0110	0.1328	0.0646	0.1154	0.0258	0.0132	0.5371
70	0.0006	0.0684	0.0001	0.0091	0.1091	0.0482	0.1155	0.0198	0.0099	0.6197
75	0.0002	0.0447	0.0000	0.0070	0.0844	0.0336	0.1069	0.0140	0.0068	0.7023
80	0.0001	0.0265	0.0000	0.0050	0.0595	0.0212	0.0888	0.0089	0.0043	0.7857

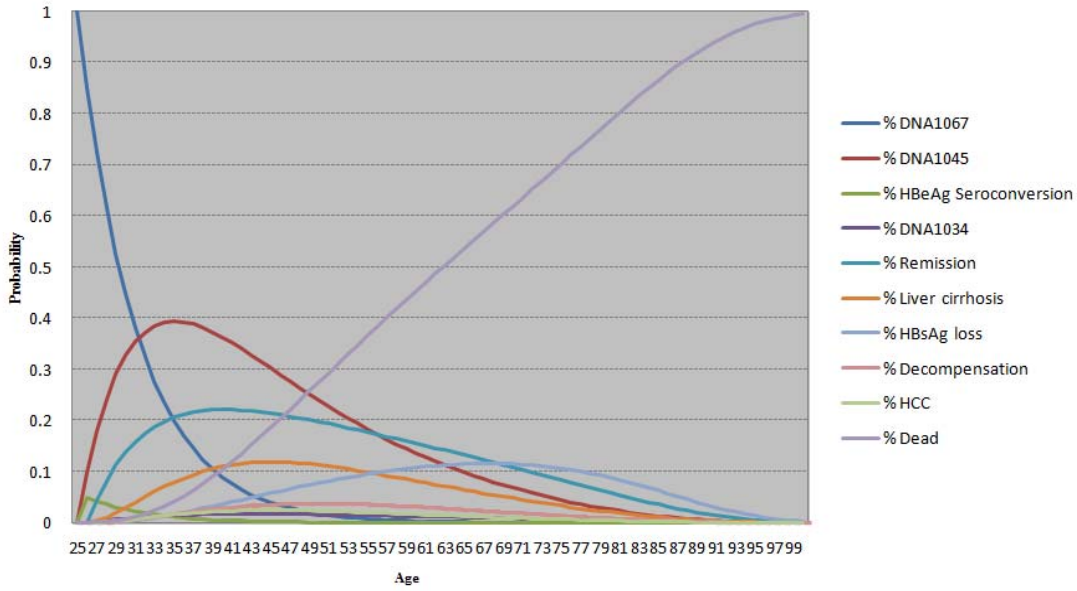

Figure B: Starting from s_1, the simulated disease progression with probabilities at different states by using TreeAge

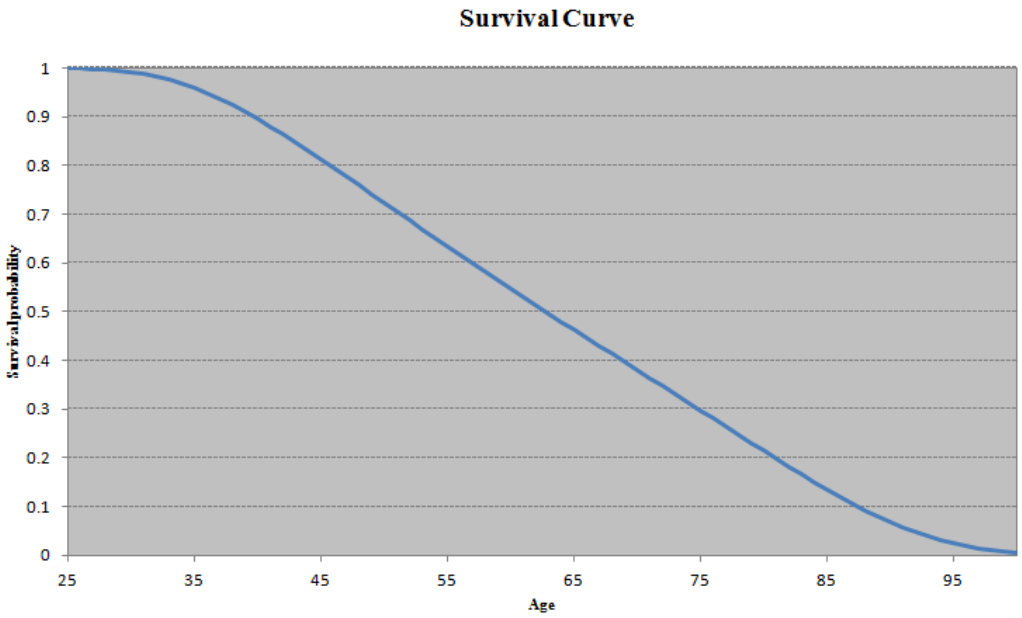

Figure C: The survival curve starting from s_1 computed by using TreeAge