行政院國家科學委員會專題研究計畫 成果報告

慢性病程模型最佳化-以B型肝炎為例
研究成果報告(精簡版)

計 畫 類 別 ：個別型
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執 行 期 間 ：98年10月01日至99年10月31日
執 行 單 位 ：國立政治大學應用數學學系

計 畫 主 持 人：陳政輝

計畫參與人員：碩士班研究生-兼任助理人員：陳玫芳
碩士班研究生-兼任助理人員：陳盈穎

處 理 方 式 ：本計畫可公開查詢

中 華 民 國 100年01月31日

行政院國家科學委員會補助專題研究計畫成果報告

慢性病程模型最佳化-以 B 型肝炎為例

Optimal Modeling of Chronic Disease Dynamics — with Examples on Chronic Hepatitis B Virus Infection

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計畫參與人員：陳盈穎、陳玫芳

成果報告類型(依經費核定清單規定繳交)：精簡報告
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中 華 民 國 100 年 1 月 27 日

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一、中文摘要

慢性病的病程研究具有基本的重要性，因為藉由這些研究，研究人員可以更了解病程發展的機制，進而發展出更有效的治療方法，改善患者的病況或延長其壽命。根據統計，臺灣地區的慢性B型肝炎約有超過三百萬的帶原者。隨著病程進展，將來可能發展為肝硬化或肝癌，不但嚴重影響國人健康，也造成健保的沉重負擔。因此，藉由研究慢性B型肝炎自然病程，提供病患相關資訊及醫療專家精確病程模型，對衛生保健、醫學研究及健保給付評估為相當重要之工作。

文獻中，有許多由醫學觀點建立之病程模型。然而，在許多應用中，由於模型簡化如未適當考慮年齡因素，結果將造成相當大的誤差。本研究考慮生命年表，將模型適切修正，使模型能更貼近真實狀況，並進行嚴格數學分析。所發展之數值工具，可估算在一定年限下，病程發展至特定狀態之機率，達到提供病患相關資訊，有助其後續醫療選擇及保健。

關鍵詞：馬可夫模型，慢性 B 型肝炎，存活分析

Abstract

The progression of chronic diseases plays an important role on their research. Through related studies, researchers can frequently extract information to design better clinic protocols to extend or improve patients' lives. According to statistics, there are more than 3 million carriers of hepatitis B virus infection in Taiwan. Its adverse sequelae could be liver cirrhosis or hepatocellular carcinoma (HCC). This greatly threatens people's lives and also leads to significant burden to national health insurance. Therefore, the study on progression of chronic HBV infection is of fundamental importance to Taiwanese society.

In the literature, several disease progression models on HBV have been proposed. However, due to over-simplification such as non -age-dependence, these models can lead to significant errors

in related applications. In this project, data from life table is embedded into the models to provide a better approximation to the realistic progression of HBV. Furthermore, numerical tools are developed to estimate the probability that patients will reach some critical medical statuses. This provides patients and the health administrations essential information for the management of chronic HBV infection.

Keywords: Markov Models, Chronic Hepatitis B Virus Infection, Survival Analysis.

二、緣由與目的

2.1 Background

The progression of chronic diseases is usually described as occurrence of successive discrete events. Studying the underlying dynamics, which specify the order of occurrence of these events and their interrelations, is of fundamental importance since it can provide a better understanding to the development of these diseases. Frequently, researchers can benefit from the dynamics-related information to design better clinic protocols to extend or improve patients' lives.

One serious chronic disease is hepatitis B virus (HBV) infection. It leads to the risk of hepatic decompensation, cirrhosis and hepatocellular carcinoma (HCC) [1]. In Taiwan, chronic liver disease is one of the leading causes of death [2]. Moreover, HCC, one of potential adverse sequelae of chronic HBV infection, was the most common cancer in 1997 [2]. Based on the statistics of Liver Disease Prevention and Treatment Research Foundation, it costs more than 3 million US dollars annually and is one of the major medical expenditure in Taiwan [3].

Based on these facts, our goal of this project is to develop a more realistic mathematical model on the natural history of chronic HBV infection. Numerical tools for subsequent analysis such as the probability of the occurrence of critical medical events and survival functions are developed. This provides patients and the health administrations essential information for the management of chronic HBV.

三、研究報告應含的內容

3.1 Mathematical Model Development

A recent survey paper in [1] provides one progression model on the natural history of chronic HBV infection (see Figure 1.) From medical viewpoints, this is a very good reference for medical practitioners. However, it is not a mathematically valid Markov model. In addition, based on this model, chronic HBV patients can possess longer expected life span than disease-free people.

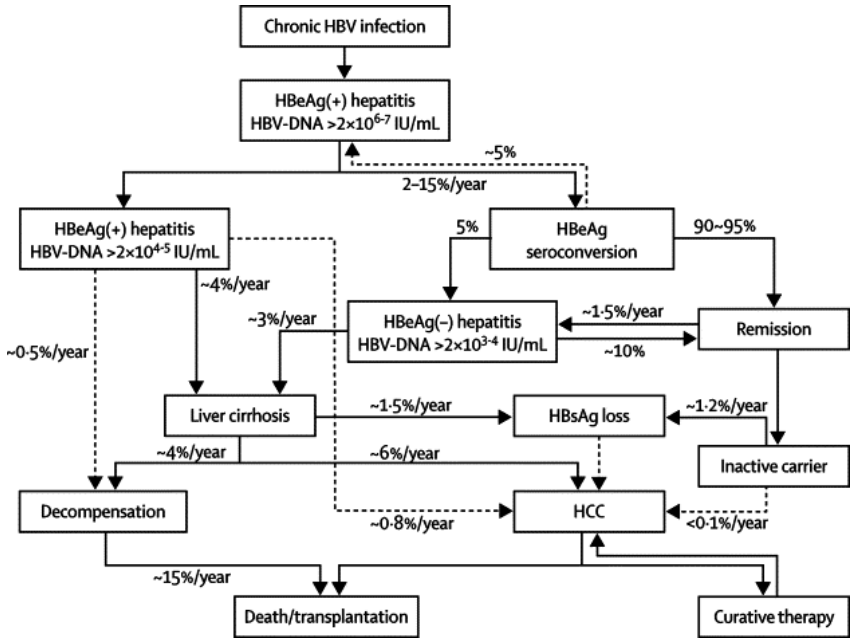

Figure 1. A model on HBV infection from Liaw and Chu [1]

To correct these disadvantages of the original model, we improve it with the following two steps. First, based on the understanding to HBV progression, the model is transformed into a valid Markov model. Secondly, data from life table is incorporated into this model to provide adjustments and offers a more realistic approximation to disease progression on HBV [5][6].

To facilitate our presentation on how data in life table is incorporated into the model, we illustrate by focusing on one specific transition in Figure 1 (i.e. state "HBeAg(+) hepatitis and HBV-DNA> $2\times10^{4\sim5}$ IU/mL" to state "Liver cirrhosis.") Such a transition is only possible under the condition that the patient survives up to the following year. Therefore, data from life table can be embedded based on conditional probability. For instance, suppose that one 18-year-old patient is with the state "HBeAg(+) hepatitis and HBV-DNA> $2\times10^{4\sim5}$ IU/mL." Denote p^{18} the probability in life table that a 18-year-old person will survive up to the following year. Transitions from this initial state and age in Figure 1 and their associated probabilities can be summarized as follows.

(1) With probability $1-p^{18}$, the patient will die in the following year.
(2) With probability $0.04p^{18}$, the next state of this patient will be "Liver cirrhosis."
(3) With probability $0.005p^{18}$, the next state will be "Decomposition."
(4) With probability $0.008p^{18}$, the next state will be "HCC."
(5) With probability (1-0.04-0.005-0.08) p^{18}, the next state will be the original state.

These transitions are summarized as Figure 2.

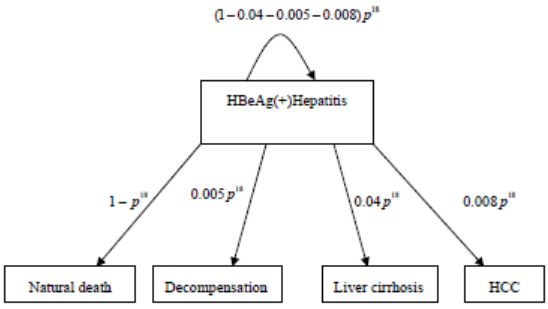

Figure 2: An illustrated example.

With such a construction, we obtain an age dependent model. Each element in the transition probability matrix under a Markov model, denoted as $P_{i,j}^{k,k+1}$, represents that the annual probability of a transition from the state i to the state j with initial age k.

3.3 Transitions between Critical Events and Survival Analysis

With the developed model, the probability of a transition between any two pre-specified states can be analyzed. Moreover, the survival function can be obtained accordingly. We have implemented numerical procedures to compute the desirable probabilities based on the following formula. If the transition probability $P_{i,j}^{t,t+n}$ is denoted as $P_{i,j}^{(n)}(t)$, the following result can be easily extended from the first passage time in [4].

(1) [5][6] Let $f_{i,j}^{(n)}$ be the probability that a person with age t and at the state i reaches the state j for the first time after n years. That is,

$$f_{i,m}^{(n)}(t) = \Pr\{Y_{t+n} = m \mid Y_{t+n-1} = i_{t+n-1}, ..., Y_{t+1} = i_{t+1},\ Y_t = i,\ i_k \neq m,\ t \leq k \leq t+n-1\}.$$

Then, we have the first passage time formula:

$$f_{i,j}^{(n)}(t) = P_{i,j}^{(n)}(t) - \sum_{k=1}^{n-1} f_{i,j}^{(k)}(t) P_{j,j}^{(n-k)}(t+k).$$

The survival function can also be obtained and expressed as function of $f_{i,j}^{(n)}(t)$ [5][6].

3.4 Error Analysis

The difference of the life expectance between the models with and without embedded data from life table can be analyzed. Let L_1 and L_2 denote the life expectance without and with embedded data from life table, respectively. Suppose that L_1 is finite. Our derivations arrive the

following conclusions: L_2 is finite and $L_2 \le L_1$. We also provide exact mathematical formulae of the upper and lower bounds on $L_1 - L_2$. From our study, it shows that when the death rate varies significantly with age, the variation between these two models will increase accordingly. The detailed results may be referred to our subsequently submitted papers [7].

3.5 Applications

The developed model and tools can be applied to study several related applications. For instance, it can be used to compute the probability that a patient arrives one specific health status from a given initial age and initial health state. The following examples demonstrate how our numerical procedures can provide such information.

Example 1:[5][6]

Suppose that a patient is infected with HBV at aged 25. Our developed tool provides the information of that he or she will undergo disease progression to critical medical events when he or she is at age 40. The result is summarized in the Table 1.

In Table 1, each probability on the right column indicates the possibility that the patient will reach the corresponding events shown on the left column at aged 40.

Critical medical events	Probability
Seroconversion & Sustained Remission	25%
Decompensation	4%
Liver cirrhosis	16%
HBsAg loss	3%
HCC	7%
Death/Transplantation	37%

Table 1. Probabilities of critical events.

Example 2.[5][6]

A patient at aged 40 is diagnosed as “liver cirrhosis.” The probabilities that he or she will reach the listed health states at the age of 60 are summarized in Table. 2

	Probability
Decompensation	23%
HBsAg loss	9%
HCC	34%
Death/Transplantation	90%

Table 2. Probabilities of critical events.

3.6 Evaluation on the Outcomes

Our principal goal of this project is to provide a more accurate model on the natural history of chronic HBV infection. Towards this goal, we have accomplished three major tasks in this project:

(1) Compared with the original model, we provide a more realistic life-table embedded model on the natural history of chronic HBV infection. In addition, we conduct rigorous mathematical analysis on the difference of the original and the new model. This offers a clearer picture of age-dependent property on the progression on chronic HBV.

(2) To answer the questions of the probability and life-years that patients may go through transitions between critical heath states, we develop numerical procedures to provide such computation. This offers chronic HBV patients crucial medical information for their follow-up treatment options and health management.

(3) Through cooperation with Chang Gang Memorial Hospital, we process original paper-based medical data (with protection on patients' privacy) and establish an electronic database for these valuable information. It is worth mentioning that we continuously expand our database and this will help us further improve the accuracy and applicability of our model.

One Master's Thesis of NCCU [6] is based on the research of this project. The results have been reviewed by specialists on chronic HBV infection. Moreover, these results have been prepared as two journal papers [5][7] and will be submitted after revision.

四、參考文獻

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國科會補助計畫衍生研發成果推廣資料表

日期:2011/01/25

國科會補助計畫	計畫名稱: 慢性病程模型最佳化-以B型肝炎為例
	計畫主持人: 陳政輝
	計畫編號: 98-2218-E-004-002- 學門領域: 作業研究

無研發成果推廣資料

98 年度專題研究計畫研究成果彙整表

計畫主持人：陳政輝	計畫編號：98-2218-E-004-002-
計畫名稱：慢性病程模型最佳化-以 B 型肝炎為例	

成果項目			量化			單位	備註（質化說明：如數個計畫共同成果、成果列為該期刊之封面故事...等）
			實際已達成數（被接受或已發表）	預期總達成數(含實際已達成數)	本計畫實際貢獻百分比		
國內	論文著作	期刊論文	0	0	0%	篇	
		研究報告/技術報告	1	1	100%		本計畫結果，已被用於撰寫一碩士論文
		研討會論文	1	0	0%		
		專書	0	0	0%		
	專利	申請中件數	0	0	0%	件	
		已獲得件數	0	0	0%		
	技術移轉	件數	0	0	0%	件	
		權利金	0	0	0%	千元	
	參與計畫人力（本國籍）	碩士生	2	2	100%	人次	
		博士生	0	0	0%		
		博士後研究員	0	0	0%		
		專任助理	0	0	0%		
國外	論文著作	期刊論文	0	0	0%	篇	根據本計畫研究成果，撰寫兩篇期刊論文. 第一篇已完成,將於修改後投稿至期刊. 第二篇已完成部份初稿，目前仍撰寫中，論文題目與部份細節可參考成果報告.
		研究報告/技術報告	0	0	0%		
		研討會論文	0	0	0%		
		專書	1	0	0%	章/本	
	專利	申請中件數	0	0	0%	件	
		已獲得件數	0	0	0%		
	技術移轉	件數	0	0	0%	件	
		權利金	0	0	0%	千元	
	參與計畫人力（外國籍）	碩士生	0	0	0%	人次	
		博士生	0	0	0%		
		博士後研究員	0	0	0%		

		專任助理	0	0	0%		
其他成果 (無法以量化表達之成果如辦理學術活動、獲得獎項、重要國際合作、研究成果國際影響力及其他協助產業技術發展之具體效益事項等，請以文字敘述填列。)		將基隆長庚部份 B 型肝炎紙本原始就診資料建立為電子資料庫，未來可持續進行研究.					

	成果項目	量化	名稱或內容性質簡述
科教處計畫加填項目	測驗工具(含質性與量性)	0	
	課程/模組	0	
	電腦及網路系統或工具	0	
	教材	0	
	舉辦之活動/競賽	0	
	研討會/工作坊	0	
	電子報、網站	0	
	計畫成果推廣之參與（閱聽）人數	0	

國科會補助專題研究計畫成果報告自評表

請就研究內容與原計畫相符程度、達成預期目標情況、研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性）、是否適合在學術期刊發表或申請專利、主要發現或其他有關價值等，作一綜合評估。

1. 請就研究內容與原計畫相符程度、達成預期目標情況作一綜合評估

■達成目標

□未達成目標（請說明，以 100 字為限）

□實驗失敗

□因故實驗中斷

□其他原因

說明：

2. 研究成果在學術期刊發表或申請專利等情形：

論文：□已發表 ■未發表之文稿 □撰寫中 □無

專利：□已獲得 □申請中 ■無

技轉：□已技轉 □洽談中 ■無

其他：（以 100 字為限）

根據本計畫研究成果，撰寫兩篇期刊論文. 第一篇已完成，將於修改後投稿至期刊. 第二篇已完成部份初稿，目前仍撰寫中，論文題目與部份細節可參考成果報告.

3. 請依學術成就、技術創新、社會影響等方面，評估研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性）（以500 字為限）

本計畫與基隆長庚醫院合作,研究 B 型肝炎自然進程之模型, 其主要貢獻可簡述如下:

(1) 資料庫建立

透過與長庚合作, 經適當病患隱私保護措施下, 收集約 3500-4000 患者長期就診記錄. 在本計畫支持下, 已將部份原始就診資料電子化並儲存於資料庫中. 目前仍持續與基隆長庚醫院合作,預計將所有資料建立為一完整資料庫, 以便提供 B 型肝炎病程發展更進一步瞭解. 由於 B 型肝炎有不同基因型, 國人所感染之 B 型肝炎與國外資料不盡相同, 因此,利用本土病患資料所分析之結果,將能提供較準確模型.

(2) 模型改進與分析

傳統的模型中,較少考慮年齡或僅做片段的分析. 然而,當模型被運用於存活或平均餘命分析時, 可能產生較大之誤差. 本計畫與醫師合作, 對病程發展作較整體的考量, 提出模型改進方法, 並以數學方法進行嚴謹之分析. 由研究結果顯示, 改進後模型用於存活或平均餘命計算時, 可得較準確結果.

本計畫成果可能之影響與進一步發展

(1) 本計畫支持下所建立之資料庫因來自病患原始就診記錄,含有豐富 B 型肝炎進程醫療資訊,未來可持續分析, 以便對 B 型肝炎進程有更進一步瞭解.

(2) 本計畫建立之模型,可提供病患存活與平均生命年限相關資訊,有助於病患瞭解自身健康狀況與管理.