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P. Senthil Kumar
 Assistant Professor, Department
 of Mathematics, Rajah Serfoji
 Government College
 (Autonomous), Thanjavur,
 Tamilnadu, India. Pin:
 613005.

A. Dinesh Kumar
 Assistant Professor, Department
 of Mathematics, Dhanalakshmi
 Srinivasan Engineering College,
 Perambalur, Tamilnadu, India.
 Pin: 621212.

M. Vasuki
 Assistant Professor, Department
 of Mathematics, Srinivasan
 College of Arts and Science,
 Perambalur, Tamilnadu, India.
 Pin: 621212.

Correspondence:
A. Dinesh Kumar
 Assistant Professor,
 Department of Mathematics,
 Dhanalakshmi Srinivasan
 Engineering College,
 Perambalur, Tamilnadu, India.
 Pin: 621212.

Mathematical model by using birth death processes to estimate the gallbladder mean emptying curves

P. Senthil Kumar, A. Dinesh Kumar & M. Vasuki

Abstract

An impaired contractility has been suggested as a contributor to the increased incidence of gallstones in liver cirrhosis, but the few studies on gall bladder emptying in cirrhotics offered contradictory results. Ingestion of a meal triggers the physiological pathway of gall bladder emptying; therefore, it was decided to analyse postprandial kinetics by investigating simultaneously the rates of gastric and gall bladder emptying of a mixed meal in patients with liver cirrhosis. Using the birth death processes taking the values in $\mathbb{N} - \{0, 1, 2, \dots\}$ but allow the death rate in state 0 to be a positive so that escape from \mathbb{N} is possible.

Keywords: Gallbladder, Birth Death Process, Normal Distribution & Cholecystokinin

1. Introduction

Liver cirrhosis is associated with a high prevalence of gallstones, as a result of hypersplenism and alterations in hepatic metabolism. Impaired gall bladder motility has also been suggested as a contributor to this increased incidence of gallstones, but the few studies on gall bladder emptying in cirrhotics offered contradictory results [1] & [6]. Postprandial gall bladder emptying is mainly coordinated by the rate of gastric emptying of food into the duodenum, with subsequent cholecystokinin (CCK) release [2] & [7]. An accelerated gastric emptying in portal hypertension has been attributed to a decreased compliance and/or altered motility of the gastric antrum [8].

We have to find out whether gall bladder emptying was impaired in liver cirrhosis and to analyse the temporal and quantitative relation between gastric and gall bladder emptying in this disease. Sonography is increasingly used for the estimation of gastric emptying and is the gold standard for the study of gall bladder motility. We carried out real time ultrasonography for the simultaneous measurement of gastric and gall bladder emptying.

In this paper a birth death process [3-5] $X \equiv \{x(t), t \geq 0\}$, say will always be a process taking values in $\mathbb{N} \equiv \{0, 1, 2, \dots\}$ with birth rates $\{\lambda_n, n \in \mathbb{N}\}$ and death rates $\{\mu_n, n \in \mathbb{N}\}$. Two such processes with transition functions $\{P_{ij}(t)\}$ and $\{P'_{ij}(t)\}$ are said to be similar if for all $i, j \in \mathbb{N}$, there are constants c_{ij} such $\{P'_{ij}(t)\} = c_{ij}P_{ij}(t)$ for all $t \geq 0$

2. Birth Death Processes Model

In this paper a birth death process $X \equiv \{x(t), t \geq 0\}$, say will always be a process taking values in $\mathbb{N} \equiv \{0, 1, 2, \dots\}$ with birth rates $\{\lambda_n, n \in \mathbb{N}\}$ and death rates $\{\mu_n, n \in \mathbb{N}\}$. Two such processes with transition functions $\{P_{ij}(t)\}$ and $\{P'_{ij}(t)\}$ are said to be similar if for all $i, j \in \mathbb{N}$, there are constants c_{ij} such $\{P'_{ij}(t)\} = c_{ij}P_{ij}(t)$ for all $t \geq 0$. We will assume that the transition functions $\{P_{ij}(t), i, j \in \mathbb{N}\}$ of birth death process $X \equiv \{x(t), t \geq 0\}$, with birth rates $\{\lambda_n, n \in \mathbb{N}\}$ and death rates $\{\mu_n, n \in \mathbb{N}\}$ satisfy and, if $\mu_0 > 0$, are known. We let

$$\alpha_n \equiv \lambda_n + \mu_n, \beta_{n+1} \equiv \lambda_n \mu_{n+1}, n \in \mathbb{N} \quad (1)$$

The question of which birth death processes are similar to \mathcal{X} may now be phrased as follows. Can we identify, besides $\{\lambda_n, n \in N\}$ and $\{\mu_n, n \in N\}$ all other sets of birth rates $\{\tilde{\lambda}_n, n \in N\}$ and death rates $\{\tilde{\mu}_n, n \in N\}$ such that

$$\tilde{\lambda}_n + \tilde{\mu}_n = \alpha_n, \tilde{\lambda}_n \tilde{\mu}_{n+1} = \beta_{n+1}, n \in N \tag{2}$$

This problem can be transformed into a problem involving chain sequences. A sequence $\{A_n\}_{n=1}^\infty$ is a chain sequence if there exists a second sequence $\{G_n\}_{n=0}^\infty$ such that

$$\begin{aligned} (a) & 0 \leq G_0 < 1, 0 < G_n < 1, n = 1, 2, \dots \\ (b) & A_n = (1 - G_{n-1})G_n, n = 1, 2, \dots \end{aligned} \tag{3}$$

The sequence $\{G_n\}$ is called a parameter sequence for $\{A_n\}$. If both $\{G_n\}$ and $\{H_n\}$ are parameter sequences for $\{A_n\}$, then

$$G_n < H_n, n = 1, 2, \dots \text{ iff } G_0 < H_0 \tag{4}$$

Every chain sequence $\{A_n\}$ has a minimal parameter sequence $\{m_n\}$ uniquely determined by the condition $m_0 = 0$, and it has a maximal parameter sequence $\{M_n\}$ characterized by the fact that $M_0 > G_0$ for any other parameter sequence $\{G_n\}$. For every $x, 0 \leq x \leq M_0$, there is a unique parameter sequence $\{G_n\}$ for $\{A_n\}$ such that $G_0 = x$.

Returning to the context of the birth death process \mathcal{X} , we let

$$\gamma_n \equiv \frac{\beta_n}{\alpha_{n-1}\alpha_n}, n = 1, 2, \dots$$

and observe that $\{\gamma_n\}_{n=1}^\infty$ is a chain sequence. Since we can write

$$\gamma_n \equiv \left(1 - \frac{\mu_{n-1}}{\lambda_{n-1} + \mu_{n-1}}\right) \frac{\mu_n}{\lambda_n + \mu_n}$$

So that $\{\mu_n / (\lambda_n + \mu_n)\}$ constitutes a parameter sequence for the chain sequence $\{\gamma_n\}$. Our task is now to find all parameter sequences for the chain sequence $\{\gamma_n\}$, since there is a one to one correspondence between parameter sequence for $\{\gamma_n\}$ and sets of birth and death rates satisfying (2). Indeed, for every parameter sequence $G \equiv \{G_n\}$ we can construct the corresponding birth rates $\{\lambda_n^{(G)}\}$ and death rates $\{\mu_n^{(G)}\}$ by letting

$$\lambda_n^{(G)} = \alpha_n(1 - G_n), \mu_n^{(G)} = \alpha_n G_n, n \in N \tag{5}$$

The problem of identifying all parameter sequences for a chain sequence for which one parameter sequence is known, has been solved completely by [3]. In our setting the solution may be formulated as follows.

Case (i): $(\mu_0 = 0)$

$$\begin{aligned} \text{Let } S_{-1} & \equiv 0, S_n \equiv \lambda_0 \sum_{k=0}^n (\lambda_k \pi_k)^{-1}, n \in N \\ S & \equiv \lim_{n \rightarrow \infty} S_n \end{aligned} \tag{6}$$

(Possibly $S = \infty$). Then all the parameter sequences for $\{\gamma_n\}$ are given by $\{G_n(x)\}, 0 \leq x \leq 1/S$.

Where

$$G_0(x) = x, G_n(x) = \frac{\mu_n}{\lambda_n + \mu_n} \frac{1 - x S_{n-1}}{1 - x S_{n-2}}, n \geq 1 \tag{7}$$

It follows in particular that $\{\mu_n / (\lambda_n + \mu_n)\}$ is the only parameter sequence for $\{\gamma_n\}$ if $S = \infty$.

Case (ii): $(\mu_0 > 0)$

$$\begin{aligned} \text{Let } T_{-1} & \equiv 0, T_n \equiv \mu_0 \sum_{k=0}^n (\mu_k \pi_k)^{-1}, n \in N \\ T & \equiv \lim_{n \rightarrow \infty} T_n \end{aligned} \tag{8}$$

(Possibly $T = \infty$). Then all the parameter sequences for $\{\gamma_n\}$ are given by $\{G_n(x)\}, -\infty \leq x \leq 1/T$.

Where

$$G_n(x) = \frac{\mu_n}{\lambda_n + \mu_n} \frac{1 - x T_{n-1}}{1 - x T_n}, n \in N \tag{9}$$

It is interesting to observe that the maximal parameter sequence is obtained for $x = 1/T$. So the sequence $\{\mu_n / (\lambda_n + \mu_n)\}$ is the maximal parameter sequence for $\{\gamma_n\}$ if $T = \infty$.

Theorem

A birth death process \mathcal{X} with birth rates $\{\lambda_n, n \in N\}$ and death rates $\{\mu_n, n \in N\}$ is not similar to any other birth death process if and only if $\mu_0 = 0$ and $\sum_{n=0}^\infty (\lambda_n \pi_n)^{-1} = \infty$. In the opposite case the process is similar to any member of an infinite, one parameter family of birth death processes $\{\mathcal{X}^{(x)} / 0 \leq x \leq 1/S\}$ if $\mu_0 = 0$ and $\{\mathcal{X}^{(x)} / -\infty \leq x \leq 1/T\}$ if $\mu_0 > 0$. The birth rates $\lambda_n(x), n \in N$ and death rates $\mu_n(x), n \in N$ of $\mathcal{X}^{(x)}$ are given by

$$\begin{aligned} \mu_0(x) &= \lambda_0(x) \\ \lambda_n(x) &\equiv \lambda_n \frac{1-x S_n}{1-x S_{n-1}} \\ \mu_{n+1}(x) &\equiv \mu_{n-1} \frac{1-x S_{n-1}}{1-x S_n}, n \geq 0 \\ \mu_0 &= 0 \text{ and } \lambda_n(x) \equiv \lambda_n \frac{1-x T_{n+1}}{1-x T_n} \\ \mu_n(x) &\equiv \mu_n \frac{1-x T_{n-1}}{1-x T_n}, n \geq 0, \mu_0 > 0 \end{aligned}$$

If $\mu_0 > 0$, The quantities

$$S_n \equiv \lambda_0 \sum_{k=0}^n (\lambda_k \pi_k)^{-1}, n \in N \text{ and } S \equiv n \rightarrow \infty S_n$$

If $\mu_0 > 0$, The quantities

$$T_n \equiv \mu_0 \sum_{k=0}^n (\mu_k \pi_k)^{-1}, n \in N \text{ and } T \equiv n \rightarrow \infty T_n$$

We first want to make some additional remarks on the example already discussed by [4]. So let $\mathcal{X} = \{x(t), t \geq 0\}$ be the birth death process with constant birth rates $\lambda_n \equiv \lambda, n \in N$ and constant death rates $\mu_n \equiv \mu, n \in N$. Since $\mu_0 > 0$ this process is transient. The first to that its transition functions can be represented by

$$P_{ij}(t) = (\sqrt{\lambda/\mu})^{j-1} e^{-(\lambda+\mu)t} \{I_{j-1}(2t\sqrt{\lambda\mu}) - I_{j+i+2}(2t\sqrt{\lambda\mu})\}, t \geq 0$$

Where $I_n(\cdot)$ is the n^{th} modified Bessel function, It is readily seen that the quantities T_n of (8) are now given by

$$T_n = \frac{\lambda^{n+1} - \mu^{n+1}}{(\lambda - \mu)\lambda^n}, n \in N, \text{ while } T = \begin{cases} \frac{\lambda}{\lambda - \mu}, & \text{if } \lambda > \mu \\ \infty, & \text{if } \lambda \leq \mu \end{cases}$$

Hence, we conclude from Theorem that for each x in the interval $-\infty \leq x \leq 1/T$, the process $\mathcal{X}^{(x)}$ with rates

$$\lambda_n(x) = \lambda + \mu - \mu_n(x)$$

$$\mu_n(x) = 95.344 \frac{0.718 \lambda^{n-1} - x(\lambda^n - \mu^n)}{0.718 \lambda^n - x(\lambda^{n+1} - \mu^{n+1})}, n \in N$$

is similar to \mathcal{X} , in accordance with [4].

3. Example

Gastric and gall bladder emptying were measured using ultrasound techniques after a solid liquid meal (14 g fat, 425 kcal) in 24 patients with liver cirrhosis and in 12 controls. None took any medication 24 hours before the study which might have influenced gastrointestinal motility, and none smoked on the morning of the investigation. None of the subjects had gall bladder disease. Sequential changes in cross sectional area of the gastric antrum and in gall bladder volume were represented as a monoexponential process after the test meal between time 0 to 60 (or 45) minutes. Cirrhotic patients were analysed according to the severity of disease [1-2] & [6-8].

Patients were instructed to assume the upright position between measuring periods. After measuring the basal antral

area and gallbladder volume, each subject was requested to consume a mixed (solid liquid meal) consisting of one slice of bread (30 g), 10 g butter, one boiled egg, 300 ml tea with 25 g sucrose. This was equivalent to 14 g fat and 465 kcal. The test meal was finished within 3 or 4 minutes. The following variables for gastric emptying were evaluated immediately (time 0) and every 15 minutes until 90 minutes after the test meal.

It was found that gastric emptying after the solid liquid meal was delayed in cirrhotic patients compared with controls. Gall bladder emptying was significantly diminished in cirrhotic patients. No correlation was found between the variables of gastric and gall bladder emptying. Gall bladder refilling began earlier in cirrhotics than in controls, before completion of gastric emptying [9-11].

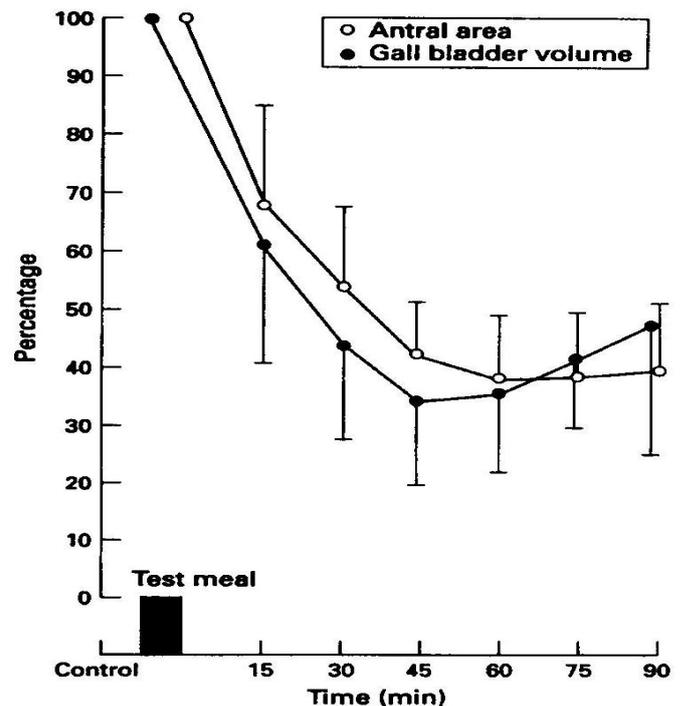


Fig 1: Mean Emptying Curves of the Stomach and the Gallbladder determined by Sonography in Controls.

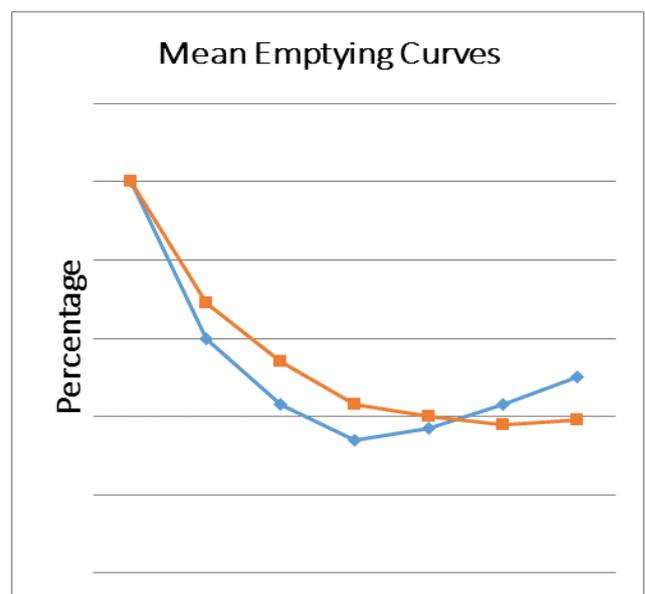


Fig 1: Mean Emptying Curves of the Stomach and the Gallbladder determined by Sonography in Controls (Using Normal Distribution).

4. Conclusion

The results indicate the lack of coordination between gastric and gallbladder emptying in liver cirrhosis. They also support the hypothesis that diminished gall bladder contractility might contribute to the increased gallstone formation in liver cirrhosis. So we consider a birth death process $X \equiv \{x(t), t \geq 0\}$ taking values in the finite set $N = \{0, 1, 2, \dots, N\}$ with birth rates $\{\lambda_n, n \in N\}$ and death rates $\{\mu_n, n \in N\}$ all strictly positive except μ_0 and λ_N which may be equal to 0. When $\mu_0 > 0$ the process may escape from N , via 0, to an absorbing state -1 and when $\lambda_N > 0$ the process may escape from N , via N , to an absorbing state $N+1$. The model is fitted with the birth death processes taking the values in $N = \{0, 1, 2, \dots\}$ but allow the death rate in state 0 to be a positive so that escape from N is possible. The model is beautifully fitted with birth and death process and gives good results than the medical report.

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