CHAPTER - VII

STOCHASTIC REPRESENTATION OF BGTLN B MODEL FOR
THE EFFECT OF LIGNOCAINE ON ARGinine
VASOPRESSIN LEVEL

7.1 Introduction

For more than three decades, lignocaine, a local anaesthetic, has been used in therapeutics as an antiarrhythmic agent. Although, the electrophysiological properties of lignocaine are well known and acknowledged in the treatment of acute ventricular arrhythmias other effects of lignocaine, such as its influence on haemodynamics and on hepatic vascular resistance, are poorly characterized.

Concerning the effect of lignocaine on peripheral haemodynamics, in healthy subjects, low levels (<3.4μg ml⁻¹) of lignocaine produced a concentration-dependent elevation in peripheral blood flow resulting from a decrease in peripheral vascular resistance. On the other hand, venous capacitance rose until lignocaine concentrations were around 2μgml⁻¹, but decreased at higher concentrations when systolic blood pressure increased.
The net effect of lignocaine on haemodynamics appears modulated by individual baseline status, since in patients with cardiac failure, an intravenous dose of 50 or 100 mg of lignocaine induced a small decrease in the cardiac index, stroke volume and work indices, as well as in arterial blood pressure\textsuperscript{[31]}.

With respect to the effect of lignocaine on hepatic blood flow, in healthy volunteers, lignocaine appears to produce a concentration-dependent rise in hepatic blood flow, secondary to a fall in splanchnic vascular resistance and an increase in cardiac output\textsuperscript{[150]}. In anaesthetized dogs, the infusion of lignocaine for 24 h increases hepatic blood flow\textsuperscript{[91]}. These results contrast with those observed in other animals or in patients with heart failure, where lignocaine does not affect, hepatic, blood flow\textsuperscript{[22,42]}.

Theoretically, in healthy volunteers, the lignocaine-induced decrease in splanchnic vascular resistance could be caused by: (a) a direct effect on smooth muscle vasculature (b) an effect on the central nervous system \textsuperscript{[19]} or (c) an effect on factors regulating the tonus of the splanchnic vascular bed\textsuperscript{[144]}. 
Since in healthy volunteers, the effect of lignocaine is much more marked on hepatic blood flow than on peripheral resistance or cardiac output \(^{[150]}\). We hypothesized that lignocaine affects the release or effect of factors like arginine-vasopressin (AVP), the activity of which predominantly occurs on the splanchnic vascular bed.

The present study was designed to document in conscious healthy animals whether lignocaine alters (a) baseline plasma AVP levels, and (b) the secretion of AVP induced by a potent stimulus. Frusemide was used to induce AVP secretion, because the depletion of volume produced by
frusemide produces a rapid and potent increase in AVP plasma concentrations \[^{40}\]. Furthermore, the choice of frusemide was reinforced by the fact that in clinical practice, lignocaine and frusemide are frequently used simultaneously\[^{129,86}\].

In the current study, lignocaine diminished baseline\[^{105}\] AVP plasma levels almost sevenfold. This fall in AVP cannot be attributed to changes in plasma osmolality, since the latter remained stable, or to the infusion of sodium chloride-glucose. In the rabbit, exogenous AVP has a very high systemic clearance, about 45ml min\(^{-1}\)kg\(^{-1}\) and both the splanchnic bed and the liver appear to account for at least half of it. Therefore, the clearance of AVP should theoretically be considered as a blood-flow-dependent event. Accordingly, increases in splanchnic blood flow should enhance the clearance of AVP.

Since lignocaine did not increase hepatic blood flow, we believe that the lignocaine-induced decrease in AVP plasma concentrations is not associated with an increase in AVP clearance. Therefore, we must assume that lignocaine decreases the rate of secretion of AVP levels by changing liver blood flow is reasonable if we bear in mind that frusemide reduced liver blood flow significantly and following the administration of lignocaine, AVP plasma levels were reduced, instead of increased.
Lignocaine prevented the increase in AVP plasma concentrations induced by frusemide, probably because of a reduction in AVP secretion by the hypothalamo-neurohypophysial axis rather than an increase in AVP clearance. A 5 mg kg\(^{-1}\) dosage of frusemide resulted in a volume depletion of 58 ± 7ml in 1 h, equivalent to the diuresis produced.

As mentioned above, this volume depletion will stimulate several systems, all capable of enhancing the release of AVP. The fact that lignocaine was able to inhibit the stimuli responsible for the frusemide-induced secretion of AVP, supports the hypothesis that lignocaine inhibits AVP secretion directly at the hypothalamo-neurohypophysial axis.

7.2 Mathematical Model

In hydrology and climate research, the problem of estimating total stream flow, precipitation, Palmer Drought Severity Index, \textit{El Nino southern Oscillation (ENSO)} or pacific Decadal Oscillation indexes exceeding a threshold (e.g. long term mean or high percentile) is of primary importance to water resource managers and safe engineering design needing reasonable flood, drought, or water storage estimates\(^{17,18,27,99,140,155}\).
Long series of observations on environmental or hydrological processes are typically described in terms of positive and negative episodes.

An episode contains consecutive observations either above or below a reference (threshold) level. The episodes are quantified in terms of three variables; duration $N$, which is the number of time intervals in the episode, magnitude $X$, which is the sum of all process values for a given duration, and the peak value $Y$, which is the absolute maximum reached by the process within a given episode. In these applications the joint distributions involving the duration, magnitude, and maximum of an episode are of main interest.

Various univariate\cite{132,133} and multivariate\cite{28,51,76,122,135,152,153} stochastic models of duration, magnitude and maximum of episodes have appeared in the literature in recent years in the context of flood analysis and ENSO, several bivariate models have been proposed for duration and magnitude\cite{52,72,136,152,153} duration and maximum value\cite{28,135,152,153} and magnitude and maximum value\cite{51,76,122}. However, majority of existing model of episode characteristics have largely been selected according to the empirical fit to the data rather than theoretically derived from the mathematical properties of the process under consideration.
A natural mathematical interpretation of all three episode characteristics is connected with random sums and maxima of random variables. Following the work\(^{[17]}\) and we shall describe general models for the duration magnitude and maxima of episodes, which follow from the stochastic representation\(^{[74]}\).

\[
(X, Y, N) \overset{d}{=} \left( \sum_{i=1}^{N} E_i, \max_{i=1}^{N} E_i, N \right).
\] …(7.2.1)

Here, the \{E_i\} are the excesses of the process values within a positive episode of duration \(N\), and \(\max\) denotes the maximum. We focus on the bivariate distributions of \((X, N)\) and \((Y, N)\) in case where \(N\) has geometric distribution with the PDF

\[
P( N = n ) = p (1-p)^{n-1} n = 1,2 \ldots, \quad \ldots (7.2.2)
\]

and the \{E_i\} are independent and identically distributed (IID) exponential variables with the PDF

\[
f(x) = \beta e^{-\beta x}, \quad x > 0 \quad \quad \ldots (7.2.3)
\]

independent of \(N\). In the context of hydroclimatic events, the geometric distribution is often fit to univariate duration data\(^{[18,38,99,131,132]}\) which is justified by the theory of runs.
The exponential distribution is also a popular model for the magnitude of hydroclimatic episodes, mostly due to its simplicity and good empirical fit to the data although\textsuperscript{[18]} this model was justified within a stochastic framework as a limit of random number of IID random variables. Another reason why exponential distribution might provide a reasonable description of the values of a process above (or below) a threshold is the POT theory\textsuperscript{[12,33,113]}, which shows that suitably normalized excesses (of the process values above the threshold) converge to one of the POT distribution as the threshold increases. The fact that the exponential distribution is one of the three possible limits justifies its use in the context.

Another area where episodes with their duration, magnitude and maximum are of interest is finance and economics. Here, one is interested in \textit{periods of growth} (or decline), where consecutive (say, daily) values of a quantity such as a stock index, interest rate, or a currency exchange rate are increasing (or decreasing). In practice, one typically considers \textit{log returns}, which are the logarithms of two consecutive values, and the growth (decline) periods and episodes correspond to positive (negative) log returns.
In these applications, geometric distribution for the duration and exponential for the magnitude of the episodes were proposed\textsuperscript{[74]} following an empirical observation of the conditional stability property of the returns noted.\textsuperscript{[75]} The latter stipulates that the (random ) sum of the daily log returns over a growth period has the same distribution (up to the scale ) as that of the daily log returns within the period.

This stability under geometric compounding is a fundamental property of the exponential distribution. Let us note that models for growth rates are of interest in many diverse areas, including modeling annual gross domestic product stock prices interest or foreign currency exchange rates\textsuperscript{[21]} and other processes.

Thus, we start our analysis of (7.2.1) assuming geometric distributions for N and exponential distribution for the \{E_{i}\}. The two main bivariate models derived from (7.2.1) are the \textit{Bivariate distribution with Exponential and Geometric marginal (\(\mathcal{BEG}\))} model and describing the joint distribution of duration and magnitude, and the \(\mathcal{BTLG}\) model for duration and maximum of episodes.
The latter are perhaps the most fundamental properties of the two models, extending those of their marginal geometric, exponential and truncated logistic distributions. Recall that geometric and exponential distributions are both stable with respect to geometric compounding: a geometric sum of IID exponential random variables is geometric and geometric sum of IID exponential random variables is exponential.

This property carries over to the bivariate case; a geometric sum of IID $\mathcal{BE}_G$ random vectors has $\mathcal{BE}_G$ distribution similarly, a geometric maximum of exponential random variables has a truncated logistic (TL) distribution, and geometric maximum of Identically Dependent Distributed TL, random variable is TL. We show that the mixed geometric maximum sum $\left( \bigwedge_{i=1}^{N} Y_i, \sum_{i=1}^{N} N_i \right)$ of IID $\mathcal{BT}_L G$ random vectors $(Y_i, N_i)_N$ has again a $\mathcal{BT}_L G$ distribution whenever $N$ has a geometric distribution independent of the $(Y_i, N_i)$ we consider extensions of the two models, connected with deterministic sums and maxima of IID $\mathcal{BE}_G$ and $\mathcal{BT}_L G$ random vectors. These generalizations are related to the tri-variate distribution of

$$(X, Y, Z) \sim \left( \sum_{i=1}^{n} X_i, \bigvee_{i=1}^{n} Y_i, \sum_{i=1}^{n} N_i \right) \quad \ldots (7.2.4)$$

where the $(X_i, Y_i, N_i)$ are IID random vectors admitting the stochastic representation (7.2.1).
It turns out that (7.2.4) can be embedded into continuous time stochastic processes. Our presentation will focus on the bivariate marginal distributions of this process, and include numerous new results related to the distribution of (Y,Z).

7.3 The BGNB model

With (X,Y,Z) defined in (7.2.4) the distribution of (X,Z) is the same as that of the sum of a n IID BEG random vectors, and it coincides with the marginal distribution at t=n of the bivariate Levy process \{(X(t),Z(t)), t \geq 0\} where (X(1), Z(1)). This process can be represented as

\[
\{(X(t),Z(t)), t \geq 0\} \overset{d}{=} \left\{ \sum_{i=1}^{NB(t)} E_i + G(t), NB(t) + t \right\}, t \geq 0 \right\} \ldots (7.3.1)
\]

where the \((E_i)\) are, as before, IID exponential variable with parameter \(\beta\), \{G(t), t \geq 0\} is a gamma Levy process starting at zero, based on the exponential distribution (7.2.3) and \{NB(t), t \geq 0\} is a Negative Binomial (NB) Levy process starting at zero, with the ChF

\[
E e^{i\chi_{NB(t)}} = \left( \frac{p}{1 - (1 - p)e^{is}} \right)^t, \quad s \in \mathbb{R} \ldots (7.3.2)
\]

This continuous time model, discussed\(^{74,75}\) along with three other related processes obtained by replacing either \(t\) or \(G(t)\) (or both) on the
right hand side of (7.3.2) by zero, has high potential use in stochastic modeling involving negative binomial sums of independent random quantities. Here we shall focus on the bivariate distribution of the process (7.3.2) with deleted t, which for t = 1 coincides with the BEG (β,p) distribution shifted by (0,-1). As shown in the joint pdf of this model is of the form

$$f(x,k) = \frac{\beta^{t+k}}{k!\Gamma(t)} x^{k+1} e^{-\beta x} p^t (1-p)^k, x > 0, k = 0,1,2, \ldots \ldots \ldots \ldots (7.3.3)$$

Following, we say that a random vector (X,N) with the pdf (7.3.3) has a $BGNB$ distribution with parameters $t > 0$, $\beta > 0$ and $p \in (0,1)$ denoted by $BGNB (t, \beta,p)$ The name reflects the marginal distribution X has a gamma distribution with shape parameter t and scale $p\beta$, while N has a negative binomial distribution supported on non negative integers, given by the pdf

$$P(N = k) = \frac{\Gamma(k+t)}{k!\Gamma(t)} p^t (1-p)^k, k = 0,1,2, \ldots \ldots \ldots \ldots \ldots (7.3.4)$$

As shown in the CDF and the survival function of $BGNB (t, \beta,p)$ are

$$P(X \leq x, N \leq y) = \frac{p^t}{\Gamma(t)} \sum_{j=0}^{\lfloor y \rfloor} \frac{(1-p)^j}{j!} \{\Gamma(j+t) - \Gamma(j+t, \beta x)\} \ldots (7.3.5)$$

and
respectively where \( x, y \geq 0, \lfloor y \rfloor \) is the integer part of \( y \), and the quantity

\[
P(X > x, N > y) = \frac{\Gamma(t, p\beta x)}{\Gamma(t)} - \frac{p'}{\Gamma(t)} \sum_{j=0}^{\lfloor y \rfloor} \frac{(1-p)^j}{j!} \Gamma(j + t, \beta x) \quad \ldots (7.3.6)
\]

is the incomplete gamma function.

### 7.4 Conditional distributions

The Conditional distribution of \( X \) given \( V = k \), \( k = 0,1,2, \ldots \) is gamma with shape parameter \( t + k \) and scale \( \beta \), so that the conditional pdf is

\[
f_{\mathbf{X} \mid \mathbf{V} = k}(x) = \frac{\beta^{k+t} x^{k+t-1} e^{-\beta x}}{\Gamma(t+k)} \quad x > 0 \quad \ldots (7.4.1)
\]

The conditional PDF of \( N \) given \( X = x \) is given by

\[
f_{\mathbf{N} \mid \mathbf{X} = x}(k) = \frac{[\beta (1-p)x]^k e^{-\beta (1-p)x}}{k!}, \quad k = 0,1, \ldots \quad \ldots (7.4.2)
\]

which is a Poisson distribution with mean \( \beta(1-p)x \). Further, for any real \( x > 0 \) and integers \( m, n \geq 0 \), we have

\[
\mathbb{P}(X > x, N > m \mid N > n) = \frac{1}{c_n} \left\{ \frac{\Gamma(t, p\beta x)}{\Gamma(t)} - \frac{p'}{\Gamma(t)} \sum_{j=0}^{m+n} \frac{(1-p)^j}{j!} \Gamma(j + t, \beta x) \right\}
\]

where

\[
c_n = \mathbb{P}(N > n) = 1 - \sum_{j=0}^{n} \frac{\Gamma(j+t)}{j!\Gamma(t)} p'(1-p)^j \quad \ldots (7.4.3)
\]
For $0 \leq m \leq n$ this gives the survival function of $X$ given $N > n$.

Similarly, for any integers $n \geq 0$ and real $x,u > 0$ we have

$$P(X > x, N > n \mid X > u) = \frac{\Gamma(t, p\beta(x \vee u))}{\Gamma(t, p\beta u)} - \frac{p^t}{\Gamma(t, p\beta u)} \sum_{j=0}^{n} \frac{(1-p)^j}{j!} \Gamma(j + t, \beta(x \vee u))$$

which coincides with the survival function of $N$ given $X > u$ when $u \geq x > 0$

### 7.5 Moments and related parameters

The joint moments of $(X, N) \sim \mathcal{BGNB}(t, \beta, p)$ are given by,

$$E_{X^n N^t} = \frac{\Gamma(\eta + t)}{\Gamma(t)} \left( \frac{1}{\beta \eta} \right)^{\mu_{\gamma}}$$

where $\mu_{\gamma} = E W^\gamma$ and $W$ has NB distribution with parameters $\eta + t > 0$ and $p \in (0, 1)$. In particular $EX = t(\beta p)^{-1}$, $EN = t(1-p)p^{-1}$ $EXN = (1+t^2)(1-p)/(\beta p^2)$ and the covariance matrix of $(X, N)$ is

$$\sum = t \begin{bmatrix}
1 & 1 - p \\
\beta^2 p^2 & \beta p^2 \\
1 - p & 1 - p \\
\beta p^2 & \beta^2 p^2
\end{bmatrix}$$

(7.5.2)

The correlation coefficient of $X$ and $N$ is the same as that of the $\mathcal{BEG}$ model

$$\rho = \sqrt{1 - p}$$
7.6 Representations

By definition, a $\mathcal{BGNB}$ random vector with parameters $t > 0$, $\beta > 0$ and $p \in (0,1)$ admits the stochastic representation

$$(X, N) \xdef \left( \sum_{i=1}^{N} E_i + G, N \right),$$

...(7.6.1)

where all the variables on the right-hand-side of (7.5.3) are mutually independent, the $\{E_i\}$ are IID exponential variables with pdf (7.2.3), $G$ has a gamma distribution with shape parameter $t$ and scale $\beta$, and $N$ is a NB variable with the pdf (7.3.4). In addition we have two related representations in terms of randomly stopped gamma and poisson processes, which follow from more general results established\(^{[74]}\). The first representation of $(X, N) \sim \mathcal{BGNB}(t, \beta, p)$ is

$$(X, N) \xdef (G(N + t), N)$$

...(7.6.2)

Here, $\{G(t), t \geq 0\}$ is a gamma Levy process, where $G(1)$ has the exponential distribution with pdf (7.2.3) and $N$ is an independent negative binomial variable with pdf (7.3.4). The second representation is

$$(X, N) \xdef (X, N(X)),$$

where $\{N(t), t \geq 0\}$ is a Poisson process with parameter $\lambda = \gamma(1 - p)/p$ while $X$ is an independent gamma variable with parameter $p\beta$. 

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7.7 Definition: A random vector \((Y, N)\) with the stochastic representation

\[
(Y, N) = \left( \sum_{i=1}^{N} E_i \lor R, N \right)
\]  

(7.7.1)

where the \(\{E_i\}\) are IID exponential variables \(f(x) = \beta e^{-\beta x}, x>0\), \(R\) is a generalized exponential variable with the CDF \(P(R \leq x) = (1 - e^{-\beta x})^t\), and \(N\) is a NB variable. \(P(N = k) = \frac{\Gamma(k + t)}{k!\Gamma(t)} p^k (1 - p)^{k - 1}, k = 0, 1, 2, \ldots\) with all the variables mutually independent, is said to have a \(BGTLNB\) distribution with parameters \(t > 0, \beta > 0\) and \(p \in (0, 1)\). This distribution is denoted by \(BGTLNB(t, \beta, p)\).

The joint pdf of \((Y, N) \sim BGTLNB(t, \beta, p)\) can be derived through a conditioning argument. Given \(N = n\), \(Y\) is the maximum of \(n\) IID \(\text{EXP}(\beta)\) variables and a generalized exponential variable with CDF \(P(R \leq x) = (1 - e^{-\beta x})^t\) so that the CDF and the PDF of \(Y\) are

\[
F_{Y/N}(y/n) = (1 - e^{-\beta y})^{n+t}, y > 0, \quad \ldots(7.7.2)
\]

and

\[
f_{Y/N}(y/n) = (n + t)\beta e^{-\beta y} (1 - e^{-\beta y})^{n+t - 1}, y > 0 \quad \ldots(7.7.3)
\]

respectively. Since \(N\) is a NB variable with the pdf \(P(N = k) = \frac{\Gamma(k + t)}{k!\Gamma(t)} p^k (1 - p)^{k - 1}, k = 0, 1, 2, \ldots\) the joint PDF of this model is of the form,
\[ f(y,n) = \frac{\beta(n + t)\Gamma(n + t)}{n!\Gamma(t)} e^{-\beta y} (1 - e^{-\beta y})^{n-1} p'(1 - p)^n, \quad y > 0, \quad n = 0,1,2,\ldots \quad (7.7.4) \]

Note that when \( t = 1 \) this reduces to the pdf of the \( BTLG(\beta, p) \) distribution shifted by \((0,-1)\). Similar conditioning leads to the CDF of \( Y \):

\[
P(Y \leq y) = \sum_{n=0}^{\infty} P\left( \bigvee_{j=1}^{n} E_j \land R \leq y \right) P(N = n) = (F(y))^t G_N(F(y))
\]

where \( F(.) \) is the CDF of the \( \{E_i\} \) and \( G_N(.) \) is the generating function of \( N \). After further simplifications we obtain

\[
F_t(y) = \left( \frac{P(1 - e^{-\beta y})}{P + (1 - P)e^{-\beta y}} \right)^t = \left( \frac{p \ 1-q}{q \ 1-p} \right)^t \quad y \geq 0 \quad \ldots (7.7.5)
\]

with \( q \) defined in \( q = q(p, \beta, y) = p + (1-p) e^{\beta y} \in (0,1) \). Since this is a power of the truncated logistic CDF \( F_t(y) = \left( \frac{p(1 - e^{-\beta y})}{p + (1 - p)e^{-\beta y}} \right)^t = \left( \frac{p \ 1-q}{q \ 1-p} \right)^t y \geq 0 \) in analogy to the generalized exponential distribution, we shall refer to this as a generalized truncated logistic distribution (\( GTL \)) with shape parameter \( t>0 \) and scale parameter \( \beta > 0 \).
To obtain the joint CDF of the BGTLNB model, we start by writing
\[
P(Y \leq y, N \leq n) = \sum_{k=0}^{n} \frac{\Gamma(k+t)}{k!\Gamma(t)} p^k (1-p)^k \int_0^y \beta(k-t)e^{-\beta x} (1-e^{-\beta x})^{t-k-1} dx
\]
for any \( y > 0 \) and \( n = 0,1,2,\ldots \). Since the integral above simplifies to
\((1-e^{-\beta y})^{k+t}\), after further simplifications we obtain

\[
P(Y \leq y, N \leq n) = \left( \frac{1-q}{q-\beta} \right) \sum_{k=0}^{n} \frac{\Gamma(k+t)}{k!\Gamma(t)} q^k (1-q)^k \text{  } y>0, \text{  } n=0,1,2,\ldots \quad \quad (7.7.6)
\]

with \( q \) given by \( q(p,\beta,y) = p+(1-p)e^{-\beta y} \in (0,1) \) as before. Note that the summation above is the same as the probability \( P(N_q \leq n) \), where \( N_q \) is a NB variable with parameter \( t > 0 \) and \( q \in (0,1) \).

Fig 7.7.1
7.8 Conclusion

In this model a random vector \((Y,N)\) with the stochastic representation \((Y,N)\overset{d}{=}\left(\bigvee_{i=1}^{N} E_i \lor R \lor N\right)\) is discussed, where the \(\{E_i\}\) are IID exponential variable, \(R\) is a generalized exponential variable with CDF \(P(R \leq x) = (1-e^{\beta x})\) and \(N\) is a negative binomial, with all the variables are mutually independent. This distribution is known as \(BGTLNB\) distribution with parameters \(t > 0, \beta > 0\) and \(p \in (0,1)\).

This model is used for our application part. Here effect of the infusion of lignocaine on frusemide-induced Arginine vasopressin, the infusion of lignocaine generated mean steady state serum concentration levels, compared to the influence of frusemide alone on average Arginine vasopressin plasma levels are taken as random variables. Here we conclude that the infusion of lignocaine generated mean steady state serum concentration increases for certain levels and reached the maximum levels at the time point (280 minutes) and then decreases suddenly at the time axis in consecutive times. The other two variables simultaneously decreases to the time axis from the certain highest time.