CHAPTER 9

MATHEMATICAL MODELLING ON LAMPREY GnRH-III USING AUTOREGRESSIVE LOGISTIC PROCESSES

9.1 Introduction

In applied work in economics and political science, there is increased attention to the importance of spatial or network interdependence between observations. Not only does this violate the assumption of independence underlying may econometric methodologies for cross-section data, there is also growing interest is estimating strength of independence itself. While the econometric literature on linear regression models with spatial interdependence is well established, in particular since the publication of Anselin's seminal work, the literature on regression models with binary dependent variables and spatial interdependence is still relatively limited**[3].**

Autoregressive logistic processes was originally defined as a technique to model dependent binary responses , with repeated observation of an outcome variable within the same individual as a special case of dependence , with Repeated measurements, previous response are used as a covariate predicting

the future responses. By decomposing the joint probabilities into a product of successive joint survival function, conditional logistically modeled probabilities, the initially multivariate problem can be solved with ordinary univariate logistic regression using standard statistical software first, reviewing the basic ideas of autoregressive logistic processes as applied to medical problem, and then the autoregressive logistic processes is discussed, including markov process.

As an application of these logistic process models a set of data is fitted. The analysis of the data on the lamprey GnRH –III in LH\FSH concentrations were transformed logarithmically, and differenced. Since the LH has shown a fairly steady downward trend against the FSH. These transformations will fit in a power-logistic process **[144].**

The aim of the present paper was to develop a model that predicts the outcome of the dose dependent manner with lamprey GnRH-III involved in LH and FSH concentration. In the analysis using a modelling technique that enables fitting various type a multistate transition including markov models.

9.2 Mathematical model

A random variable X has a logistic distribution with location parameter $\alpha \in (0,1]$ and scale parameter σ (> 0) if

$$f_X(x)=\left\{1+\exp\left[-\left(\frac{x-\alpha}{\sigma}\right)\right]\right\}^{-1} \quad -\infty<x<\infty \tag{9.1}$$

In such a case writing $X_n \sim \mathbb{F}(0,\alpha)$. In particular the conditional mean and variance of such a random variable are given by

$$E(X)=\alpha^j x \tag{9.2}$$

And

$$vax(x)=\frac{\left(1-\alpha^{2j}\right)\pi^2}{3} \tag{9.3}$$

The basic logistic process introduced in **[142]** is defined in the following manner. L et $\{\xi_n\}^{\infty}{}_{n=0}$ be a sequence of independent identically distributed (i.i.d.) random variables with common distribution (9.1) . Define a Markov process $\{X_n\}^{\infty}{}_{n=0}$ by

$$\begin{aligned} X_{n+1} &= X_n - \log\beta \ \ w.p.\beta \\ &= \min\{X_n - \log\beta, \xi_{n+1}\} \ \ w.p\, 1-\beta \end{aligned} \tag{9.4}$$

Here β is a parameter with range [0, 1). Straightforward conditioning leads to the conclusion that $X_n \approx \mathbb{F}(0,\sigma), \forall n$, i.e. results in a completely stationary Markov process with logistic marginal. It is convenient to define

$$\mathbb{Z}_{n-1} = \frac{X_{n-1} - \mu}{\sigma}, \quad n = 1, 2, 3... \tag{9.5}$$

The process $\{\mathbb{Z}_n\}_{n=0}^{\infty}$ may be called a standard logistic process. Distributional properties of the process $\{X_n\}$ are readily deduced from those of the standard process $\{\mathbb{Z}_n\}$ for which a standard logistic marginal distribution is obtained, i.e. $\mathbb{Z}_n \approx \mathbb{F}(0,\sigma)$ n= 0, 1, 2… By conditioning on $\mathbb{Z}_n$ and using the joint survival function of $(\mathbb{Z}_n\mathbb{Z}_{n+1})$ is readily obtained. Thus

$$P(\mathbb{Z}_n > z_n, \mathbb{Z}_{n+1} > z_{n+1}) = \frac{\left(1+\beta\exp\left(z_{n+1}\right)\right)}{\left(1+\beta\exp\left(z_{n+1}\right)\right)\left(1+\max\left[\exp\left(z_{n+1}\right), \beta\exp\left(z_{n+1}\right)\right]\right)} \tag{9.6}$$

The correlation between $\mathbb{Z}_n$ and $\mathbb{Z}_{n+1}$ may be evaluated as follows:

$$E\left(\mathbb{Z}_{n-1}\left(\mathbb{Z}_{n-1} - \log\beta\right)\right) + (1-\beta) \iint\limits_{y>x-\log\beta} (x - \log\beta) x f(x) f(y)\, dxdy + (1-\beta) \iint\limits_{y>x-\log\beta} yx f(x) f(y)\, dxdy \tag{9.7}$$

Where f denotes a standard logistic density (i.e. $f(x) = \frac{e^{-x}}{\left(1+e^{-x}\right)^2}$). After some manipulation (9.7) gives

$$E\left(\mathbb{Z}_n\mathbb{Z}_{n+1}\right) = \frac{\beta\pi^2}{3} + (1-\beta)\varphi(\beta) \tag{9.8}$$

Where

$$\varphi(\beta)=\int_0^{\infty}\frac{\log\omega\log(1+\beta\omega)}{(1+\omega)^2}d\omega \qquad 9.9$$

The integral (9.9) may be evaluated numerically for various values of β . The correlation between $\mathbb{Z}_n$ and $\mathbb{Z}_{n+1}$ is then given by

$$\rho(\mathbb{Z}_n,\mathbb{Z}_{n+1})=4\frac{E(\mathbb{Z}_n\mathbb{Z}_{n+1})}{\alpha^j\pi^2} \qquad 9.10$$

A simple computation gives

$$P(X_{n+1}>x_n)=P(\mathbb{Z}_{n+1}>z_n) \qquad 9.11$$

$$=\frac{(1+\beta)}{2}$$

Find the further

$$P(X_{n+2}>x_n)=P(\mathbb{Z}_{n+2}>z_n)=\frac{(1+\beta^2)}{2} \qquad 9.12$$

$$P(X_{n+3}>x_n)=P(\mathbb{Z}_{n+3}>z_n)=\frac{(1+\beta^3)}{2} \qquad 9.13$$

Like (9.10), these may be proved by expressing $\mathbb{Z}_{n+1}\,\mathbb{Z}_{n+2}$ in terms of $\mathbb{Z}_n$. An unusual feature of the calculation is that the probabilities, conditional on taking a particular branch, are sometimes much more complex than the final answers above. Results (9.10)-(9.12) yield convenient consistent estimators of β Thus,

for example, writing $U_n = 1$ for $X_{n+1} > X_n$, and 0 otherwise, a consistent estimator of β is $\left(\frac{4}{n}\sum_{i=0}^{n} U_i\right) - 1$. The related observation that

$$P((\mathbb{Z}_n \mathbb{Z}_{n+1} > 0) = \frac{(1+\beta)}{2} \qquad 9.14$$

Does not seem to be as useful for estimation purposes (since α and σ will be unknown). Based on a particular realization $\{X_0, X_1, X_2, ...X_n\}$ of the basic logistic process **[137,140],** convenient consistent estimators are available for all three parameters. Natural candidates are

$$\hat{\mu} = \frac{1}{n+1}\sum_{i=0}^{n} X_i \qquad 9.15$$

$$\hat{\alpha} = \left(\frac{3}{\pi^2 (n+1)}\sum_{i=0}^{n} (X_i - \hat{\mu})^2\right)^{\frac{1}{2}} \qquad 9.16$$

$$\hat{\beta} = \left(\frac{2}{n}\sum_{i=0}^{n} U_i\right) - 1 \qquad 9.17$$

Where U_i is defined in the previous paragraph. Alternative estimators for α and σ can be obtained using order statistics. Since the median of $\mathbb{F}(0,\sigma)$ is σ and the interquartile range is α log 16, consistent estimators can be found from the sample median and interquartile range. The sampling distributions of all these estimators is considered in **[77,92 ,98].**

Inspection of (9.6) leads to the realization that the joint distribution of (X_{n-1}, X_n) will be singular. In fact there is positive probability that the sequence $(X_n - X_{n+1})$ contains ties. A straightforward modification in (9.4) will eliminate this potentially troublesome phenomenon. Instead of using the same value of β at every stage, a random of β is generated. The resulting logistic process is discussed in section 9.5.

9.3 Application

Among these isoforms, GnRH-III has a substantial anti proliferative effect on several cancer cell lines. The physiologic role played by GnRH-III on gonadotropin secretion in mammalian species is controversial. Although GnRH-III is a weak GnRH agonist, early research in mammalian species suggested that lGnRH-III can selectively stimulate the secretion of FSH without changing concentration of LH. In rodents, lGnRH-III significantly increased FSH concentrations in a dose-dependent manner when using anterior pituitaries at $(10^{-9} to 10^{-4})$ M concentrations. In contrast, LH concentrations were affected only when the highest doses of lGnRH-III $(10^{-6} to 10^{-4})M.$ were used **[1].** Intravenous infusion of lGnRH-III also increased FSH without changes in LH concentrations **[103,144].**

Subsequently, data from the same laboratory reported the isolation of a FSH-releasing factor (RF) obtained from the stalk-median eminence of rats. The FSHRF was associated with lGnRH-III, and had the ability to interact with a putative receptor to selectively release FSH. These data and that from other non-traditional sources suggest that lGnRH-III is a potent and specific FSH-releasing peptide. However, other lines of research have raised questions about the ability of GnRH-III to selectively secrete FSH in rodents.

The presence of lGnRH-III in the brain of rats was identified by immunocytochemistry and subsequently localized in the dorsomedial preoptic area of the brain and colocalized with mGnRH **[1].** However, lGnRH-III was not detected in rats and other rodents by reverse-phase-HPLC followed by RIA, or by performing two successive HPLC steps to prevent the coelution of GnRH peptides .Similarly, when rat pituitary cells were perfused with lGnRH-III or mGnRH $\left(10^{-9}\, to 10^{-6}\right)$ *M*, lGnRH-III was 1,000 fold less active in releasing LH than mGnRH. Moreover, when rat pituitary cells were perfused with doses $\left(10^{-7}\, to 10^{-5}\right)$M of lGnRH-III, gonadotropin secretion was increased without any indication of a selective secretion of FSH. These data is in agreement with in vitro results obtained from rat hemipituitaries incubated with doses $\left(10^{-9}\, to 10^{-7}\right)$ *M* of lGnRH-III. The contradictory results obtained by different laboratories, may be explained by experimental condition, the influence of the presence or absence of steroid in the in vivo models, and data interpretation **[92].**

In addition to the information provided above, other areas of investigation have stressed the need to reconsider the traditional conjecture that a single GnRH molecule controls reproduction [**72, 74]**. Briefly, lesions to the median eminence (ME) of castrated male rats suppressed LH but not FSH pulses, while animals with posterior to mid- median eminence lesions had no FSH pulses but maintained LH episodic releases. Similarly, ablation of the dorsal anterior hypothalamus of ovariectomized rats suppressed FSH pulses but not LH **[1,103].** These results raise the possibility that another form of GnRH may contribute nontraditionally to the control of reproductive function or may take part in an important neuroendocrine role.

The nature of episodic FSH secretion in portal blood cannot be accounted completely by changes in GnRH secretion.when infused with doses (0.055, to 1.1 mg/kg BW) of lGnRH-III. Higher doses (4.4 mg/kg BW) released LH but not FSH. Similarly, in vitro doses $\left(10^{-7}\, to 10^{-6}\right) M$ of lGnRH-III elicited a non-selective increase of LH and FSH, while lower doses $\left(10^{-9}\, to 10^{-8}\right)\, M$ were not associated with gonadotropin secretion in bovine adenohypophyseal cells .A clear and unbiased interpretation of the discordant results observed in cattle is difficult. Reagents (RIAs) used in both laboratories to evaluate LH and FSH were provided by the National Hormone and Pituitary Program. Thus, it is unlikely that differences can be attributed to the ability of a particular RIA to detect FSH concentrations **[92].** This concludes that lGnRH-III is a weak GnRH

agonist, and at high doses, lGnRH-III has the ability to release LH but not FSH in barrows. Similar findings were also obtained in gilts that were infused (i.m.) with a synthetic lGnRH-III product. In Lamprey, lGnRH-III significantly increased FSH concentrations in a dose-dependent manner when using anterior pituitaries at $\left(10^{-1}\, to 10^{-10}\right) M$ concentrations **[144].**

9.4 Results

As an application of these logistic process models a set of data is fitted. A analyzed data on the lamprey GnRH –III in LH\FSH concentrations. The data were transformed logarithmically, and differenced, since the LH has shown a fairly steady downward trend against the FSH (in figure 9.4.1).

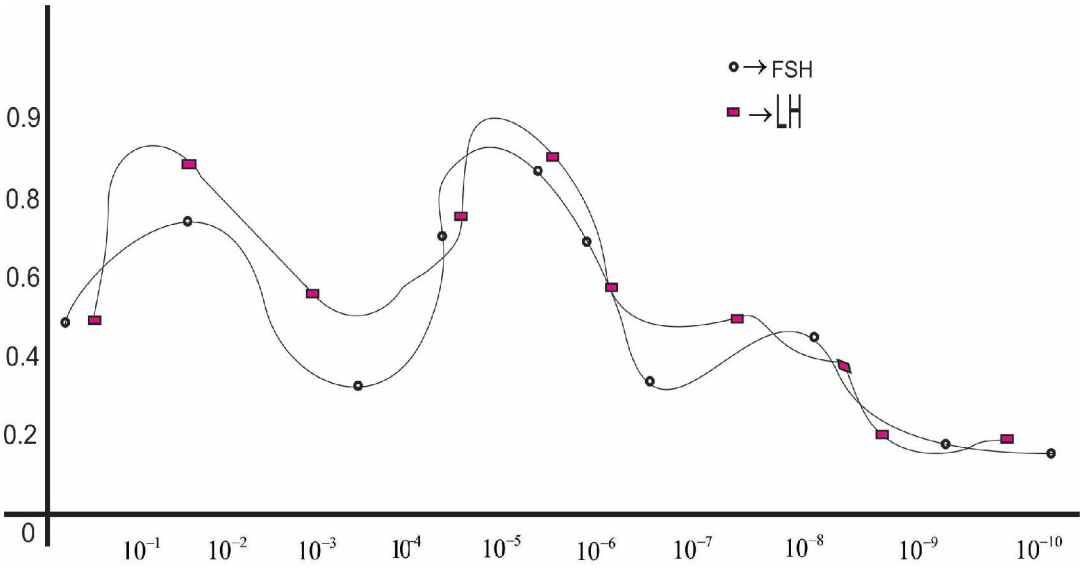

FIGURE 9.4.1 Concentration of LH and FSH on lamprey GnRH-III

9.5 The Autoregressive power logistic processes

A parameter family of distribution which may play the role of G, the distribution of β in section 9.3, is provided by the power function distributions. Specifically

$$G_\alpha(\beta) = \beta^\alpha, 0 < \beta < 1 \tag{9.18}$$

Where α > 0, substituting this distribution in (9.3) and (9.5) the following expression for the joint survival function of $(\mathbb{Z}_n \mathbb{Z}_{n+1})$ in the standard process is obtained:

$$P(\mathbb{Z}_n > z_n, \mathbb{Z}_{n+1} > z_{n+1}) = \frac{\left(1+\beta\exp\left(z_{n+1}\right)\right)}{\left(1+\exp\left(z_{n+1}\right)\right)\left(1+\left[\exp\left(z_n\right)\right]\right)}, z_n > z_{n+1} \tag{9.19}$$

And for $z_n \le z_{n+1}$

$$\left(1+\exp\left(z_{n+1}\right)\right)^{-1} - \frac{1}{\alpha+1}\frac{\left(\exp\left(\alpha+1\right)z_n \exp\left(-\alpha z_n\right)\right)}{\left(1+\exp\left(z_{n+1}\right)\right)\left(1+\left[\exp\left(z_n\right)\right]\right)} \tag{9.20}$$

It is evident that the joint distribution of $(\mathbb{Z}_n \mathbb{Z}_{n+1})$ is absolutely continuous. For reference the corresponding rather cumbersome expression for the joint density function is included.

$$f_{z_n z_{n+1}}(z_n, z_{n+1}) = \frac{\left(\exp-(z_n + z_{n+1})\right)}{(\alpha+1)\left(1+\exp(z_{n+1})\right)^2 \left(1+\left[\exp(z_n)\right]\right)^2}, z_n \le z_{n+1} \quad 9.21$$

While for $z_n \le z_{n+1}$

$$f_{z_n z_{n+1}}(z_n, z_{n+1}) = \frac{\exp\left(-(1-\alpha)z_n + (1+\alpha)z_{n+1}\right)\left(1+\frac{\alpha}{\alpha-1}\exp(z_n)\right)\left(1+\frac{\alpha}{\alpha-1}\exp(z_{n+1})\right)}{(\alpha+1)\left(1+\exp(z_{n+1})\right)^2 \left(1+\left[\exp(z_n)\right]\right)^2} \quad 9.22$$

Note that for the power-logistic process the mean of the distribution G, denoted by $\mathbf{b} \in (0, 0.9)$ is a simple function of α:

$$\hat{\alpha} = \frac{\left(\frac{4}{n}\sum_{i=0}^{n} U_i\right) - 1}{4 - \left(\frac{4}{n}\sum_{i=0}^{n} U_i\right)} \quad 9.23$$

$$b = \frac{\alpha}{\alpha - 1} \quad 9.24$$

Where U_n is defined in (9.11) **[4, 55, 86].**

9.6 Conclusion

A mathematical model, based on clinical data has been constructed with a statistical system approach, with the aim of analyzing the performance, and predicting the effects that possible readjustments and/or interventions on the structure may produce on it. When amphibians were infused with doses of

GnRH-III, gonadotropin secretion was increased in a dose dependent manner with a greater increase in LH than FSH concentrations.

The contradictory results obtained by different laboratories, may be explained by experimental condition, the influence of the presence or absence of steroid in the in vivo models, and data interpretation. Undoubtedly, more research is needed to clarify the existence of GnRH-III or a FSH that may be involved in the differential secretion of gonadotropins in mammals.