Research & Reviews: Journal of Veterinary Science and Technology
ISSN: 2319-3441(online), ISSN: 2349-3690(print)
Volume 4, Issue 3
www.stmjournals.com

Development of an Endocrine Profiles Based Mathematical Model for the Estrous Cycle in Indian Crossbred Cows

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Abstract

Declined fertility of the high-yielding dairy cows reared under intensive condition of management is of great concern not only for India but for the whole world. The bovine estrous cycle, particularly the estrus, is tightly controlled by the complex interplay of various organs and hormones. Mathematical modeling of the bovine estrous cycle could help in understanding the dynamics of this complex biological system. The authors, therefore, developed a mechanistic mathematical model for the estrous cycle of Indian crossbred cows that exclusively includes the key hormones that interact to control these processes. The authors used the data generated by them for approximately 163 estrous cycles having 1793 readings related to different hormones like LH, FSH, progesterone, estrogen, etc., under the control of the hypothalamo-pituitary-gonadal (ovarian) axis. The developed model was capable enough to generate successive estrous cycles of 21-day length. The model contains seven differential equations and 34 parameters. By simulating the developed model, a set of equations and parameters that were obtained were found to describe vividly the system consistent with empirical knowledge. In conclusion, the authors for the first time developed a mechanistic mathematical model of the estrous cycle for the Indian crossbred cows and it can be used for predicting hormonal inter milieu of the complex biological system without spending much time and money towards laboratory estimation. The developed model may also be used as a basis for more elaborate models that can predict the effects of external manipulations and genetic differences in Indian bovines.

Keywords: *Indian crossbred cow, hormones, differential equations, systems biology*

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INTRODUCTION

Understanding the various components of a biological system together is an important aspect than investigating only individual parts of it. Here comes the "System biology," a new research area in the field of animal sciences. One of the many approaches is the translation of a conceptual biological model into a set of mathematical equations representing the dynamic relations between system components.

The aim of developing such mathematical models is to interpret and predict the dynamics of complex biological systems, and to identify new research questions [1]. One vibrant example of a dynamic biological system is the bovine estrous cycle that is tightly controlled by the hormonal *inter milieu* of the cow. In recent times, declined fertility of high-yielding dairy cows is a great concern to the dairy producers and farmers [2].

The decline in fertility is due to alterations in hormone patterns during the estrous cycle, reduced expression of estrous behavior and lower conception rates [3]. However, it is very difficult to understand the exact cause(s) underlying this decline in fertility in the complex biological system. The regulation of estrus is controlled by the interplay of various organs and hormones. Mathematical modeling of the involved mechanisms is expected to improve insight in the biological processes

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underlying the bovine estrous cycle, and could thereby help to find causes of declined fertility in dairy cows [1]. Though a lot of information is available on the endocrine and physiological regulation of the bovine estrous cycle, development of mathematical models of cycle regulation are hardly available in Indian cows. The objective of the present study was, therefore, to develop mathematical models of the dynamics of the bovine estrous cycle based on the fluctuations in hormone concentrations during the cyclicity.

METHODS FOR MATHEMATICAL FORMULATION OF THE ESTROUS CYCLE

Basics

The bovine estrous cycle is controlled through the functions of the hypothalamus, pituitary and ovaries. Therefore, these natural control mechanisms were considered for developing mathematical models and later the authors showed that the hormone levels predicted by their model are consistent with experimental data. They used the data generated by them for approximately 163 estrous cycles having 1793 readings related to different hormones like LH, FSH, progesterone, estrogen, etc., under the control of the hypothalamo-pituitary-gonadal (ovarian) axis. The models are developed based on the differential equations to describe rates of change in hormone concentrations during the estrous cycle.

The biological feedback mechanisms which control hormone concentrations are modelled using Hill functions [4], which have a value between 0 and 1. For negative feedback, the generic Hill function is defined as

$$\boldsymbol{H}\text{-}(\boldsymbol{x},\boldsymbol{n},\boldsymbol{T}) = \frac{\mathbf{1}}{\mathbf{1}+\left(\frac{x}{T}\right)^{n}}$$

and for positive feedback the generic Hill function is defined as:

$$H+(x,n,T) = \frac{\left(\frac{x}{T}\right)^{n}}{1+\left(\frac{x}{T}\right)^{n}}$$

where, *x*=the concentration of the hormone providing feedback,

T=the threshold concentration at which feedback is switched on or off, and

n=the sharpness or suddenness of the switch with larger values of n giving a sharper on/off switching effect.

Regulation by Hypothalamo-Pituitary Axis

The hypothalamus-pituitary axis plays a crucial role in regulating the bovine estrous cycle through release of gonadotropin-releasing hormone (GnRH), which in turn controls FSH and LH release from the pituitary gland. These hormones are important for the growth and development of the follicles and ultimately the ovulation.

Rate of change in blood concentration of LH, dLH/dt, is a function of the amount of LH released from the pituitary gland into the bloodstream and the amount cleared from the bloodstream, either by the liver or through normal degradation of the hormone. Release of LH from the pituitary gland is controlled by episodic release of GnRH from the hypothalamus [5] and clearance of LH from the bloodstream is assumed to be proportional to the concentration of LH in the bloodstream. To model the positive effect of GnRH on release of LH, the authors used a positive Hill function H+. Thus, the rate of change in concentration of LH is given by the Eq. (1):

$$\frac{dLH}{dt} = kLH + \left(GnRH; P_{LH,GnRH}.T_{LH,GnRH}\right) \text{---} \delta_{LH} L \quad (1)$$

Here, the rate of clearance of LH from the bloodstream is parameterized by δ_{LH}. The term $kLH + \left(GnRH; P_{LH,GnRH}.T_{LH,GnRH}\right)$ denotes release of LH (as a function of GnRH) and since $0 \leq H + \left(GnRH; P_{LH,GnRH}.T_{LH,GnRH}\right) < 1$ then parameter *kLH* mathematically represents the maximum release rate of LH from the pituitary gland into the bloodstream.

Release of GnRH from the hypothalamus occurs in a series of pulses, with its release being a function of the ovarian hormones progesterone and estradiol [6]. It is assumed that release of GnRH is a function of concentrations of progesterone and estradiol in the bloodstream [7] with progesterone having a negative feedback effect and estradiol having a positive effect. Clearance rate of GnRH is assumed to be proportional to bloodstream concentration of GnRH. The model also includes the biological phenomenon whereby a surge of GnRH is released when estradiol reaches a critical level. To model effects of these negative and positive feedback mechanisms on GnRH, the authors have used Eq. (2):

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$$\frac{dGnRH}{dt} = K_{GnRH} H_{-}(P4(t); P_{GnRH.P4}, T_{GnRH.P4}) H_{+} (E2(t); P_{GnRH.E2}, T_{GnRH.E2}) - \delta_{GnRH} GnRH \quad (2)$$

It is noted that multiplying the two Hill functions, H_{-} and H_{+}, in the Eq. (2) has the effect that a surge in GnRH release in response to estradiol (E2) can only occur if progesterone (P4) levels are sufficiently low.
FSH is synthesized in the pituitary and released into the blood,

$$\frac{d}{dt} FSH_{pit}(t) = Syn_{FSH}(t) - Cl_{FSH}(t) \quad (3)$$

Concluding, FSH serum level is a result of the difference between the released amount from the pituitary and clearance in the blood,

$$\frac{d}{dt} FSH_{Blood}(t) = Rel_{FSH}(t) - C_{FSH}.FSH_{Blood}(t) \quad (4)$$

Where, C_{FSH} is the *FSH* clearance rate constant.

$$\frac{d}{dt} LH_{Pit}(t) = Syn_{LH}(t) - Rel_{LH}(t) \quad (5)$$

LH synthesis in the pituitary is stimulated by E2 and inhibited by P4,

$$Syn_{LH}(t) = H + (E2) + H - (P4) \quad (6)$$

Summarizing, LH in the blood is obtained as

$$\frac{d}{dt} LH_{Blood}(t) = Rel_{LH}(t) - C_{LH}.LH_{Blood}(t) \quad (7)$$

Where, C_{LH} is the LH clearance rate constant.

RESULTS AND DISCUSSION

Using the models as developed in the present study, hormone concentrations over three estrous cycles, considering its length as 21 days, were calculated. Concentration of LH was found to increase sharply prior to ovulation concomitant with fall of progesterone concentrations.

The concentrations of FSH and estradiol were found to rise on three occasions during entire estrous cycle indicating three follicular waves per estrous cycle. Predicted progesterone concentration follows the peculiar pattern of changes as seen in bovine estrous cycle with concentration declining from day 16 until ovulation. All predicted hormone concentrations were found to be in line both qualitatively and quantitatively [8, 9] as in live animals.

The current mathematical model describes the interaction between a number of key physiological processes of the bovine estrous cycle. The model is able to simulate the dynamics of the associated hormone level changes in consecutive cycles. The proposed model comprises 7 equations and 34 parameters. The estrous cycles generated in the model are not only entirely identical within a cycle but also between the cycles.

The modeling method as used for the present study with the bovine estrous cycle was also used for the model of the human menstrual cycle [10]. As the authors aimed at the development of a model for the dynamical changes of a biological system, including the information about how components influence the rates of change of other components, the authors' approach to model the system with differential equations appears to be the most reasonable.

CONCLUSIONS

In conclusion, the authors for the first time developed a mechanistic mathematical model of the estrous cycle for the Indian crossbred cows using their data generated during estrous cycle in the Indian crossbred cows.

The developed model can be used for predicting hormonal *inter milieu* of the complex biological system without spending much time and money toward laboratory estimation. The developed model may also be used as a basis for more elaborate models that can predict the effects of external manipulations and genetic differences in Indian bovines.

ACKNOWLEDGMENTS

The authors are grateful to the Director, ICAR-National Dairy Research Institute, India, for providing the facilities for the present work. The authors also acknowledge the funding received from the Department of Biotechnology, Government of India, for conducting the present work.

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Cite this Article

Mondal M, Karunakaran M, Ghosh MK *et al.* Development of an Endocrine Profiles Based Mathematical Model for The Estrous Cycle in Indian Crossbred Cows. *Research & Reviews: Journal of Veterinary Science and Technology*. 2015; 4(3): 35–38p.