Regulation of Spermatogenesis Cycle — A Control Theory Approach

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We summarize the well-known spermatogenesis cycle once again, trying to present an equivalent control schema together with some questions, according to the motto "*If a question can be put at all, then it can also be answered*" (Ludwig Wittgenstein: Tractatus Logico-Philosophicus. 6.5)

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Issues of regulation and control are central to the study of biological and biochemical systems. The application of control theory to biological systems has a long history, dating back more than 60 years.

The field of control engineering grew out of the need to analyze and design regulatory mechanisms. To meet this need, a vast array of mathematical tools has been developed. Because of the conceptual similarities between engineering and biological regulatory mechanisms, it is not surprising that these tools are now being used to analyze biochemical and genetic networks.

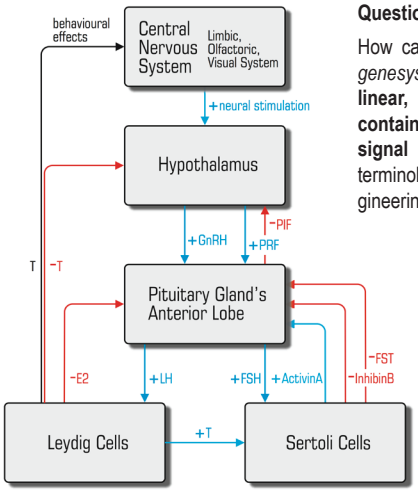

Figure 1: Regulation of Spermatogenesys Cycle

Question 1:

How can this *Regulation of Spermatogenesys Cycle* as **time-variant, non-linear, closed-loop control system containing mixed analogue/discrete signal flows** be represented with the terminology of regulating and control engineering as the Figure 2 tried to show ?

Remarks to Question 1:

Given a system with a time-dependent single output function $y(t)$, and a time-dependent input function $x(t)$; the system will be considered time-invariant if a time-delay on the input $x(t+\delta)$ directly equates to a time-delay of the output $y(t+\delta)$ function.

According to the definition above, the system which regulates the spermatogenesis cycle is *time-variant*.

As well as, this system is definitive non-linear because of the superposition principle is evidently not satisfied.

The continuous secretion of hormones can be seen as analogous signal flow, but the GenRH secreted from the hypothalamus is pulsatile: the producing is running 3..5 min long in every 1 to 3 hours. That is averaging a duty cycle from 1:12 to 1:60.

Question 2:

Can any type (longterm, carcadian, or any others) of oscillation/drift or any other type of changing (ageing) be observed in this control system ? Which robustness/stability refers the periodicities if any ?

Question 3:

Are there stable and unstable modes in that sytem ? Which abnormalities/disorders can be assigned to these modes ?

Question 4:

How can be the domain of the stability characterized ?

Question 5:

Can the following regulatory/controlling elements be identified ?

- comparing elements
- controlled variables
- disturbance variables
- feedback variables
- measuring elements

E.g. *Estradiol* (E2) is a feedback variable; reference range is 50..200 pmol/L in adult male. Estradiol is an estrogen steroid hormone is produced by action of estrogen synthetase in the Leydig cells of the testis, but also by some germ cells and the Sertoli cells. It functions to prevent the programmed cell death of male sperm cells (blocked apoptosis).

Question 6:

Are there stable and unstable modes in that sytem ? Which abnormalities/disorders can be assigned to these modes ?

Question 7:

What clinial applications can be deduced from a detailed control system architecture ?

Legend:

Activin A
Inhibin B

Activin and Inhibin are members of the Transforming Growth Factor-β (TGF-β) superfamily. Activins and inhibins are disulfide-linked dimeric proteins. Inhibin B is produced by Sertoli cells and Leydig cells in adult male. Inhibin B and Follistatin suppress selectively the release of FSH from the pituitary gland,

Central Nervous System

The Central Nervous System (CNS) is the core of the human existence by acting as the command center of the body. It interprets incoming sensory information, and then sends out instructions on how the body should react. The CNS consists of two major parts: the brain and the spinal cord.

E2

Estradiol (E2) is an estrogen steroid hormone is produced by action of estrogen synthetase in the Leydig cells of the testis, but also by some germ cells and the Sertoli cells. It functions to prevent the programmed cell death of male sperm cells (blocked apoptosis).

FSH

The follicle-stimulating hormone (FSH) is a gonadotropin, a glycoprotein polypeptide hormone. FSH is synthesized and secreted by the gonadotropic cells of the anterior pituitary lobe. FSH induces Sertoli cells to secrete androgen-binding proteins (ABPs), regulated by inhibin's negative feedback mechanism on the anterior pituitary lobe.

GnRH

The gonadotropin-releasing hormone (GnRH) enters the hypothalamic-pituitary portal system. It is characteristically secreted in a pulsatile mode and it stimulates the gonadotroph cells in the anterior pituitary expressing the GnRH receptors. The gonadotroph cells consequently secrete two gonadotrophins, FSH and LH, which act directly on the testis to stimulate the distinct somatic cells that support spermatogenesis.

Hypothalamus

Regulates the homeostasis (body temperature, food intake, water balance and thirst, sleep and the sleep cyle, etc). Conrols release of hormones by the anterior pituitary. Connects with neural stimulation to the other part of the Central Nervous System.

Leydig cells

Leydig cells produce and secrete testosterone. Leydig cells can be distinguished as stem Leydig cells as founder cell, progenitor Leydig cells as a committed stem cell, fetal Leydig cells as a terminally differentiated cell in the fetus, and adult Leydig cells as the terminally differentiated Leydig cell. Human testes contain approximately 2×10^8 Leydig cells.

LH

Luteinising Hormone (LH) is a heterodimeric glycoprotein, produced by the anterior lobe of pituitary gland. LH acts upon the Leydig cells of the testis and is regulated by GnRH. The Leydig cells produce testosterone under the control of LH.

Prolactin

A peptid hormone. Elevated levels of prolactin, decrease the levels of testosterone in adult male. PRF: prolactin-releasing factor. PIF: prolactin-inhibiting factor.

Sertoli cells

The Sertoli cells are unique polarized epithelial cells that are the main structural element of the seminiferous epithelium. Sertoli cells are known for their structural role in the establishment of the blood-testis barrier, and for the active nurturing of germ cells.

T

The Testosterone (T) is an androgen steroid hormone that in the testis is produced by Leydig cells, as a consequence of LH stimulation. Androgens play the central role in masculinization of the reproductive tract and genitalia during the sexual differentiation process in the male. Testosterone inhibits the secretion of GnRH and gonadotropins.

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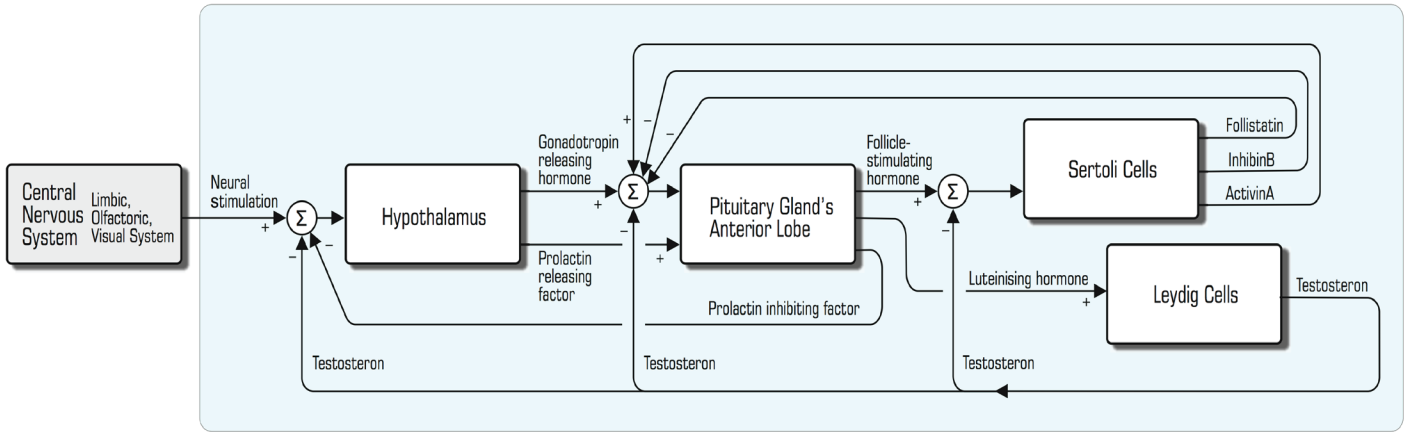

Figure 2: Regulation of Spermatogenesys Cycle — from control engineering viewpoint

The block diagrams shown on Figure 1 and Figure 2 are topologically equivalents, however the signal pathway are top-down directed on the Figure 1, merely on historical grounds. Similarly, a left-right signal pathway is preferred in the control and regulation technology (Figure 2).

The block diagrams shown on Figure 1 and Figure 2 are topologically equivalents, however the signal pathway are top-down directed on the Figure 1, merely on historical grounds. Similarly, a left-right signal pathway is preferred in the control and regulation technology (Figure 2).

To elaborate the transfer function for each building block, we can assume that the feedback mechanisms operate via proportional control with corresponding controller gains.

Time-domain analysis would probably the best way to prefer, instead of the frequency-domain one. Further information and methodology skills can be obtained from [3].

This kind of interdisciplinary approach is being actively investigated by the authors; this yellow paper tried to summarize the most important questions the way they point out us : "*Human and Herbal Spermatogenesis - a Comparative Study*".

However there are several limitation of time domain analysis, such as the noise and disturbance characteristics are not understood as good as it is understood in frequency domain analysis. But, in time-domain, the interpretation is direct. It works on more accurate mathematical model that can be well visualized. For stability analysis: two most preferred methods are the Root Locus and Routh Hurtwitz Criteria. Performance parameters are: Poles-Zeros Location, Rise Time, Peak Time, Settling Time, Delay Time, Damping Factor, Natural and Damped Frequencies etc.

So, control system analysis can be carried out in either time-domain or in frequency-domain. Every advantage the frequency domain analysis has can be viewed as a disadvantage for the time domain analysis. This is our choice: *Est difficultatum paene omnium diligens ratio vitrix multa menta versans et varia*.

Resources:

[1] David L. Nelson, Michael M. Cox: Lehninger Principles of Biochemistry. ISBN-13: 978-1464126116. W.H.Freeman & Co; Januar 2017.

[2] Aurélio Gouveia Alves, Marco. Biochemistry of Andrology (Andrology: Current and Future Developments, Book 1). Bentham Science Publishers. Kindle Edition. 2017.

[3] Pablo A. Iglesias and Brian P. Ingalls (ed): Control Theory and Systems Biology. The MIT Press Cambridge, Massachusetts London, England, 2010.

[4] Eberhard Nieschlag, Hermann M. Behre, Susan Nieschlag (ed): Andrology Male Reproductive Health and Dysfunction, 3rd Edition. Springer-Verlag Berlin Heidelberg 2010.

[5] Michael A. Savageau, Eberhard O. Voit, Douglas H. Irvine: Biochemical Systems Theory and Metabolic Control Theory: Fundamental Similarities and Differences. Department of Microbiology and Immunology. The University of Michingan. Ann Arbor, Michingan 48109. 18 June 1987.

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