Article

A Generalized Net Model of the Prostate Gland's Functioning

Martin Lubich ^{1,†}, Velimir Papazov ^{2,†}, Elenko Popov ^{3,4,†} , Radostina Georgieva ^{3,4,†}, Dmitrii Dmitrenko ^{3,4,†}, Borislav Bojkov ^{3,4,†}, Chavdar Slavov ^{3,4,†}, Peter Vassilev ^{5,†} , Vassia Atanassova ^{5,†} , Lyudmila Todorova ^{5,†} and Krassimir T. Atanassov ^{5,*,†}

¹ Department of Nephrology, University Hospital Sofamed, 16 G. M. Dimitrov Blvd., 1797 Sofia, Bulgaria; martinlub11@abv.bg

² Department of Dialysis, University Hospital Alexandrovska, 1 Georgi Sofiiski Str., 1431 Sofia, Bulgaria; velibg@abv.bg

³ Faculty of Medicine, Medical University-Sofia, 15 Acad. Ivan Geshov Blvd., 1431 Sofia, Bulgaria; shennyp@yahoo.com (E.P.); rgeorgieva50@gmail.com (R.G.); dmitrii.dmitrenko@gmail.com (D.D.); b.b.bojkov@gmail.com (B.B.); ch.k.slavov@gmail.com (C.S.)

⁴ Department of Urology and Andrology, University Hospital Tsaritsa Yoanna-ISUL, 8 Byalo More Str., 1527 Sofia, Bulgaria

⁵ Department of Bioinformatics and Mathematical Modelling, Institute of Biophysics and Biomedical Engineering, Bulgarian Academy of Sciences, Acad. G. Bonchev Str., Bl. 105, 1113 Sofia, Bulgaria; peter.vassilev@gmail.com (P.V.); vassia.atanassova@gmail.com (V.A.); lpt@biomed.bas.bg (L.T.)

* Correspondence: krat@bas.bg

† These authors contributed equally to this work.

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Abstract: Over the last 20 years, many Generalized Net (GN) models of the ways of functioning of the different systems and organs in the human body and models related to the description of biomedical processes in living organisms have been constructed. In this paper, a GN model of the prostate gland's functioning was developed, as a continuation of the previous research. The model provides the possibility to trace the logical relations of the interactions of the prostate gland and various individual organs in the human body. The model shows the possibility for the existence of currently unknown feedback loops.

Keywords: endocrine system; generalized net; mathematical modelling; prostate

MSC: 68Q85; 92B05

1. Introduction: Basic Anatomy and Physiology of the Prostate Gland

The prostate gland is an organ with a dense consistency and the shape of a chestnut, which is located just below the bladder, covering the beginning of the urethra. It is an organ with a glandular structure, whose secretion is a part of semen. The gland is also characterized by an incretory function [1]. It weighs approximately 20–25 g and has the following dimensions: height 3 cm, thickness 2 cm, width 4 cm. The gland is surrounded by a capsule that sends to the interior of the prostate barriers of connective tissue of varying thickness and a high content of smooth muscle cells.

The prostate is made up of two main parts: glandular and muscular. The glandular part forms about 30–40 differently sized tubulo-alveolar glands, whose channels partially merge and open into the urethra. The glands are divided into two zones: external and internal. The secretory gland contains a large number of secretory units of the tubulo-alveolar type, which open sequentially in a long drainage channel with a gradually increasing caliber. The glands are surrounded by myoelastic stroma, which divides the parenchyma of the gland into separate partitions. In some cases, the prostate gland hypertrophies as the middle glands grow, developing an adenoma (a benign tumor of the gland) [2]. This formation protrudes into the area of the inner opening of the urethra, which impedes normal urination. Although topographically, the prostate gland is connected to the excretory system, it is

more of an endocrine organ that interacts closely with the hypothalamus, pituitary gland, testicles, and adrenal medulla of the adrenal gland [3].

Following [4], we provide a concise description of the Hypothalamus, Pituitary, and Gonadal (HPG) axis. The functioning of the HPG axis is hierarchically orchestrated by the hypothalamus. Feedback control is the principal mechanism through which hormonal regulation occurs. Negative feedback is the main regulatory mechanism in the HPG axis, achieving the maintenance of homeostasis and essentially responsible for minimizing perturbations.

Hypothalamus: Being the integrative center of the HPG axis, the hypothalamus receives neuronal input from the amygdala, thalamus, pons, retina, olfactory cortex, and many other compartments of the brain. The hypothalamus represents a pace-maker for the cyclic secretion of pituitary hormones, and it is linked to the pituitary gland by a portal vascular system, as well as through neuronal pathways. Through the portal vascular system, the released hormones from the hypothalamus are delivered to the anterior pituitary. The main hypothalamic hormone regarding HPG function is Gonadotropin-Releasing Hormone (GnRH). GnRH stimulates the secretion of LH and FSH from the anterior pituitary. GnRH secretion is influenced by levels of stress, exercise, and some diet factors and is subjected to negative feedback regulation from pituitary gonadotropins, as well as from plasma levels of circulating sex hormones.

Anterior pituitary: The pituitary is composed of two anatomically and functionally distinct parts: posterior and anterior. The posterior part, the neurohypophysis, is responsible for the synthesis and secretion of two hormones, oxytocin and vasopressin, being under neuronal control. The anterior part, adenohypophysis, represents the classical endocrine gland, regulated by plasma levels of different bioactive substances, the main being GnRH. GnRH induces the synthesis and secretion of FSH and LH, which are the primary pituitary hormones regulating gonadal function. The circadian rhythm of LH includes between eight and sixteen pulses in 24 h, closely coupled to GnRH levels. Sex hormones exert negative feedback regulation on LH.

The gonads are the sole known site of action of FSH and LH. LH stimulates testicular steroidogenesis within Leydig cells, while FSH has a binding affinity to Sertoli cells and spermatogonial membranes and is a major stimulatory factor of seminiferous tubule growth. FSH is a critical initiating factor for spermatogenesis at puberty. During the adult life, FSH is a potent stimulator of normal spermatogenesis in terms of quantity.

Testis: Normal male development, functioning, and reproduction require the normal function of both the exocrine and endocrine compartments of the testis. The interstitially localized Leydig cells are responsible for steroidogenesis. The seminiferous tubules produce spermatozoa.

Testosterone is metabolized into two main active metabolites: (1) the main intracellular androgen Dihydrotestosterone (DHT), resulting from the action of the enzyme 5α -reductase, and, predominantly in fatty tissues, (2) the estrogen estradiol through the action of aromatases. DHT has much stronger androgen activity compared to testosterone.

The primary targets of FSH action are Sertoli cells located in seminiferous tubules. Under FSH influence, Sertoli cells produce Androgen-Binding Protein (ABP), transferrin, lactate, ceruloplasmin, clusterin, plasminogen activator, prostaglandins, and growth factors. These molecules exert a paracrine stimulatory effect on the growth of the seminiferous tubule and during puberty on the initiation of sperm production.

Inhibin and activin are two protein hormones secreted by the testis. Inhibin is made by Sertoli cells and has an inhibitory effect on FSH release from the pituitary. Inhibin production is stimulated by circulating FSH levels and represents a negative feedback loop to the pituitary and/or hypothalamus.

Activin has a stimulatory effect on FSH secretion. Activin receptors are found in a variety of tissues, suggesting that there could be some unknown growth factor or regulatory roles of this peptide hormone. Negative feedback inhibition of GnRH release is exerted by testosterone levels through binding with Androgen Receptors (ARs) in the hypothalamus and the pituitary.

Sex hormones' negative feedback is a result mainly of testosterone binding to ARs, with a lesser role played by estradiol. The main anatomical site of testosterone feedback is the hypothalamus, while estrogens act predominantly on the pituitary. Testosterone is the main regulatory factor for LH secretion, while estradiol (and also inhibin) is the primary regulatory molecule for FSH secretion.

At the present time, there are no defined molecule or molecules that have proven feedback regulatory action on the other participants in the sex hormone axis. Much research on this subject has been performed on Prostate-Specific Antigen (PSA) and other members of the human kallikrein family and a number of paracrine substances in the prostate such as dihydrotestosterone—without a definitive conclusion at the present time [5]. These relationships are not well studied and form the basis for understanding the process of benign prostatic hypertrophy and prostate gland carcinoma [6,7].

After these brief remarks, we note that in Section 2, we propose a GN model of the prostate gland for the first time. In Section 3, we demonstrate how this model would change under the conjectured relations between the prostate gland and the hypothalamus, hypophysis, testes, and adrenal gland.

2. A Generalized Net Model

Generalized Nets (GNs) [8–11] are one of the tools for modeling parallel processes running in real time. GNs are an extension of the classical Petri nets. The complete theory of GNs was presented in [9,10], while a short and concise description was given in [12]. All models described by different types of Petri nets may be represented in terms of GNs. As stated in [13], GN models are most appropriate in the areas of biology and medicine. Indeed, the presence of predicates in the index matrices of the transitions determining the direction of the tokens' movement and the initial and current characteristics obtained by the tokens, respectively, provide the possibility to model the logical connections in the described process, as well as to gather its evaluations in numerical or linguistic form. For this reason, the process of the prostate gland's functioning is described through a GN, and the benefit of such a model is discussed. This model is the first generalized net model of the functioning of and the result of work on the prostate gland from the physiological point of view. It is a basis for investigating the changes in the prostate and the interactions of other organ systems as a result of pathological changes. Similar types of models describing the functioning of the excretory and a part of the vascular systems can be found in [14,15], respectively.

The GN model contains 7 transitions, 20 places, and 15 types of tokens. These GN components are as follows (see Figure 1):

- χ —token representing the current status of the hypothalamus;
- φ —token representing the current status of the hypophysis;
- τ —token representing the current status of the testes;
- α —token representing the current status of the adrenal gland;
- π —token representing the current status of the prostate gland;
- π' —token representing the process of the enlargement of the prostate gland;
- $\sigma_{1,1}, \sigma_{1,2}, \dots$ —tokens representing the signals from the hypothalamus to the hypophysis;
- $\sigma_{2,1}, \sigma_{2,2}, \dots$ —tokens representing the signals from the hypophysis to the hypothalamus;
- $\sigma_{3,1}, \sigma_{3,2}, \dots$ —tokens representing the signals from the hypophysis to the testes;
- $\sigma_{4,1}, \sigma_{4,2}, \dots$ —tokens representing the signals from the hypophysis to the adrenal gland;
- $\sigma_{5,1}, \sigma_{5,2}, \dots$ —tokens representing the signals from the testes to the hypophysis;
- $\sigma_{6,1}, \sigma_{6,2}, \dots$ —tokens representing the signals from the testes to the prostate gland;
- $\sigma_{7,1}, \sigma_{7,2}, \dots$ —tokens representing the signals from the adrenal gland to the prostate gland;

- $\sigma_{8,1}, \sigma_{8,2}, \dots$ —tokens representing the signals from the adrenal gland to the hypophysis;
- $\mu_1, \mu_2, \dots$ —tokens representing the signals from the prostate gland to the hypothalamus, hypophysis, testes, and adrenal gland, respectively.

We must mention that the tokens are denoted by Greek letters related to the model by the tokens' objects. The letter σ corresponds to the biological signals, of which there are of eight types. This is represented by the first index. Since the individual organs sequentially emit signals, the order of the consecutive signals is denoted by the second index of the respective token. The same is valid for tokens μ generated by the prostate.

Here, by signals, we understand any type of biochemical compound produced in one organ effectively impacting another.

For brevity, below, we omit the second indices of the tokens, because they represent the current number of the respective signal.

Transition Z_1 denotes the hypothalamus. It contains the place l_2 in which token χ stays permanently with the initial and current characteristic “the current status of the hypothalamus and its parameters (in the current time moment)”.

Transition Z_2 denotes the hypophysis. It contains the place l_6 in which token φ stays permanently with the initial and current characteristic “the current status of the hypophysis and its parameters (in the current time moment)”.

Transition Z_3 denotes the testes. It contains the place l_{10} in which token τ stays permanently with the initial and current characteristic “the current status of the testes and their parameters (in the current time moment)”.

Transition Z_4 denotes the adrenal gland. It contains the place l_{14} in which token α stays permanently with the initial and current characteristic “the current status of the adrenal gland and its parameters (in the current time moment)”.

Transition Z_5 denotes the prostate gland. It contains the place l_{16} in which token π stays permanently with the initial and current characteristic “the current status of the prostate gland and its parameters (in the current time moment)”.

Transition Z_6 denotes the process of the synthesis of messenger RNA in the prostate gland. It contains the place l_{18} in which token π' stays permanently with the initial and current characteristic “the current status of the synthesized messenger RNA in the prostate gland and its parameters (in the current time moment)”.

Transition Z_7 denotes the process of the generation of initiation factors in the prostate gland. It contains the place l_{20} in which token π' stays permanently with the initial and current characteristic “the current status of the generation of initiation factors in the prostate gland and its parameters (in the current time moment)”.

- “adrenocorticotrophic hormone, parameters (e.g., quantity)”.

$$Z_3 = \left\langle \{l_4, l_{10}, l_{11}\}, \{l_7, l_8, l_9, l_{10}\}, \begin{array}{c|ccc} & l_7 & l_8 & l_9 & l_{10} \\ \hline l_4 & false & false & false & true \\ l_{10} & W_{10,7} & W_{10,8} & W_{10,9} & true \\ l_{11} & false & false & false & true \end{array} \right\rangle,$$

where:

- $W_{10,7}$ = “a signal from the testes to the hypophysis is generated”;
- $W_{10,8}$ = “a signal from the testes to the prostate gland is generated”;
- $W_{10,9}$ = “a signal from the testes to the adrenal gland is generated”.

The token τ in place l_{10} splits into two, three, or four tokens with respect to the validity of the predicates $W_{10,7}$, $W_{10,8}$, and $W_{10,9}$: the original token τ that continues to stay in place l_6 and the tokens $\sigma_5, \sigma_6, \sigma_7$ that obtain the equal characteristic “currently generated testosterone, parameters (e.g., quantity)”.

$$Z_4 = \left\langle \{l_5, l_9, l_{14}\}, \{l_{11}, l_{12}, l_{13}, l_{14}\}, \begin{array}{c|cccc} & l_{11} & l_{12} & l_{13} & l_{14} \\ \hline l_5 & false & false & false & true \\ l_9 & false & false & false & true \\ l_{14} & W_{14,11} & W_{14,12} & W_{14,13} & true \end{array} \right\rangle,$$

where:

- $W_{14,11}$ = “a signal from the adrenal gland to the testes is generated”;
- $W_{14,12}$ = “a signal from the adrenal gland to the prostate gland is generated”;
- $W_{14,13}$ = “a signal from the adrenal gland to the hypophysis is generated”.

The token τ in place l_{14} splits into two, three, or four tokens with respect to the validity of the predicates $W_{14,11}$, $W_{14,12}$, and $W_{14,13}$: the original token τ that continues to stay in place l_6 and the tokens $\sigma_8, \sigma_9, \sigma_{10}$ that obtain the equal characteristic “currently generated adrenocorticotrophic hormone, parameters (e.g., quantity)”.

$$Z_5 = \left\langle \{l_9, l_{11}, l_{16}, l_{19}\}, \{l_{15}, l_{16}\}, \begin{array}{c|cc} & l_{15} & l_{16} \\ \hline l_9 & false & true \\ l_{11} & false & true \\ l_{16} & W_{16,15} & true \\ l_{19} & false & true \end{array} \right\rangle,$$

where $W_{16,15}$ = “there is increasing of testosterone.”

The token π in place l_{16} splits into two tokens: the original token π that continues to stay in place l_{16} with the characteristic “change of prostate gland volume, parameters”, and the token π' that obtains the characteristic “moment of starting the process of transcription and synthesis of messenger RNA”.

$$Z_6 = \left\langle \{l_{15}, l_{16}\}, \{l_{17}, l_{18}\}, \begin{array}{c|cc} & l_{17} & l_{18} \\ \hline l_{15} & false & true \\ l_{18} & true & false \end{array} \right\rangle.$$

The token π' from place l_{15} enters place l_{18} with the characteristic “process of the transcription and synthesis of messenger RNA, parameters (e.g., quantity)”.

After this, it enters place l_{17} , and there, it obtains the characteristic “moment of starting the process of translation”.

$$Z_7 = \left\langle \{l_{17}, l_{20}\}, \{l_{19}, l_{20}\}, \begin{array}{c|cc} & l_{19} & l_{20} \\ \hline l_{17} & false & true \\ l_{20} & true & false \end{array} \right\rangle.$$

The token π' from place l_7 enters place l_{20} with the characteristic “protein and growth hormone, parameters (e.g., quantity)”.

After this, it enters place l_{19} , and there, it obtains the characteristic “a process of translation, results”.

3. Conclusions or a New Perspective

As discussed in the literature (see, e.g., [16]), at the present moment, it is not known whether there are signals from the prostate gland and the other objects in our model (hypothalamus, hypophysis, testes, and adrenal gland). The above GN model suggests the idea that we can represent these hypothetical connections. In this case, the model from Figure 1 will have the form shown Figure 2, and transition Z_5 will have the form:

$$Z_5 = \langle \{l_9, l_{11}, l_{16}, l_{19}\}, \{l_{15}, l_{16}, m_1, m_2, m_3, m_4\},$$

	l_{15}	l_{16}	m_1	m_2	m_3	m_4
l_9	false	true	false	false	false	false
l_{11}	false	true	false	false	false	false
l_{16}	$W_{16,15}$	true	$W_{16,1}$	$W_{16,2}$	$W_{16,3}$	$W_{16,4}$
l_{19}	false	true	false	false	false	false

$$\rangle,$$

where:

- $W_{16,15}$ = “there is an increase in testosterone”;
- $W_{16,1}$ = “a signal from the prostate gland to the testes is generated”;
- $W_{16,2}$ = “a signal from the prostate gland to the hypophysis is generated”;
- $W_{16,3}$ = “a signal from the prostate gland to the hypothalamus is generated”;
- $W_{16,4}$ = “a signal from the prostate gland to the adrenal gland is generated”.

Figure 2. Second generalized net model.

Now, the token π in place l_{16} splits into six tokens: the original token π that continues to stay in place l_{16} and the tokens π' (as before), $\rho_1, \rho_2, \rho_3, \rho_4$ that obtain the same characteristic “substance secreted by the prostate, exerting a biofeedback effect on the other objects in the model” at places m_1, m_2, m_3, m_4 .

In the future, if such connections are indeed observed in practice, the first model will be replaced by the second one, which will have to be further expanded. In the near future, a GN model of pathological processes in the prostate and their impact on the human body will be investigated.

As was mentioned at the beginning of Section 2, the first model reflects only the physiology of the prostate gland and the logical connections between it and other organs and systems. The external influences on the human organism and in particular on the prostate will be considered for investigation in future studies. Currently, a software product is being developed to implement the generalized net models. Through it, the processes described in the above models can be simulated with the data of a particular patient.

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