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AN INTELLIGENT DECISION SUPPORT TOOL FOR EARLY DIAGNOSIS OF FUNCTIONAL PITUITARY ADENOMAS

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Abstract. In this work, a web based integrated Medical Decision Support System (MDSS) tool for mainly early diagnosis of functional pituitary adenomas (i.e., somatotrophinoma, corticotrophinoma and prolactinoma) is developed. In the MDSS tool, hormone diseases are described by means of well-classified set of attributes generated from the typical sign and symptoms of disorders.The proposed tool is based on a stationary linear stochastic system model which specifically predicts the selected hormone diseases employing certain system parameters. The MDSS tool is user friendly which includes questions and answers at the opening session of the self-test. Questions and answers session will be completed by "yes" or "no" type of simple-responses. Based on our clinical results, MDSS tool yields more than 99% correct decisions on the selected hormone diseases. It is expected that effective use of the proposed MDSS tool will save substantial amount of valuable time of an expert endocrinologists and minimizes the cost of diagnosis. Furthermore, it will provide the opportunity for early diagnosis for the patient and the expert medical doctor to take the necessary preventive measures.

Keywords: Acromegaly, Cushing's Disease, Endocrinology, Medical Decision Support System, MDSS Tool, Pituitary Adenomas, Prolactinoma.

AMS Subject Classification: 83-02, 99A00

1. Introduction

The exponential growth of the internet usage lies behind the advent of the personal computers [1]. Using computers and mobile technologies at work, at home, at school individuals can connect and find novel ways of accessing information, organizing memory, creating global communities and social networking. Web-based databases allow us to access information in new ways, often with remarkable ease. That is why internet has become a new domain of human activity. As a result of all these it is also a new domain for those who study human [2].

In 1984, a lecture given by Peter Reichertz was about the past, present and future of hospital systems [3]. In the meanwhile, there has been an enormous progress in medicine

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as well as informatics. Thirty years later from Peter Reichertz's lecture, there have been tremendous developments done in health information systems. With the increase of data in health care setting there has been a shift from paper-based to computer-based processing and storage. Also the shift from institution-centered hospital information systems towards regional and global health information systems (HIS), beside health care professionals and administrator patients and health consumers are included to health information systems as a user. Nowadays, HIS data are also used for health care planning as well as clinical and epidemiological research and medical decision support tools.

Medical decision support system (MDSS) tools aims to provide with valid, applicable, and useful information may result in care decisions that are more concordant with current recommendations based on some pre-coded domain knowledge [4] for family physicians, internists to guide the patients, Medical Emergency Services [5]-[7] and with the web-based self-test designs also for the patients [8]-[14]. With web-based questionnaires, medical lecture notes or medical groups, which periodically send medical information and reports, allow patients to be less dependent on clinicians for information [15]. Web-based MDSS tools can support this growing involvement of patients in clinical decision-making through interactive tools that allow patients to explore relevant information [16]-[17].

With relevant, high quality, and accessible web-based information tools people became more aware about the diseases which were not previously well-known such as pituitary adenomas. Moreover, it is very easy to face a surplus of medical information. On the other hand, symptoms of the pituitary disease can be confused with the different diseases. For this reason acquired information from internet may induce physiological distressed and finally they can reduce their life quality. Consequently, people may admit to different physicians that are related or unrelated to their complaints. So that when they admit to a non-specialist about their disease, symptoms can progress and become more complicated. Besides that, this will result loss of time and money.

On the basis of this knowledge, in this paper a reliable Medical Decision Support System (MDSS) that will be useful for the patients, for family physicians and internists to guide the patients to the endocrinology clinics for evaluation of pituitary adenoma namely, acromegaly, Cushing's disease and prolactinoma will be developed. If the patient coincides with a complete MDSS self-test tool, they may end up with a proper early diagnosis and directed to a specialist. The designed tool will also prevent malpractice for general physician and save time and reduce the cost [18].

The MDSS-tool is developed with basic decision making (or equivalently stochastic-mathematical) models and web programming techniques for some Endocrinology diseases based on the general classified information.

In the present research work, we verified that computer aided guidance can be provided with patients in the field of Endocrinology. The proposed MDSS tool is developed on three major excess hormone secreting diseases of Pituitary Gland; namely Acromegaly, Cushing's disease and Prolactinoma.

The proposed tool for early diagnosis consists of eight major blocks as listed below.

1. The Main Page,
2. News,
3. Forum,
4. Self-Test,
5. Links and Contact,
6. Information pages about Endocrinology (4 pages),
7. Three major diseases of pituitary gland; namely Acromegaly, Cushing's disease and Prolactinoma,

8. Admin module.

The main page is to guide the patients properly to determine their health state.

The second block includes the relevant news about the patients regarding the developments in pituitary-gland disease.

The third block is dedicated to patients to share their opinions and views regarding their symptoms.

The fourth block is assigned to the patients to make an early diagnosis about their health status if they have Acromegaly, Cushing's disease, Prolactinoma or none of them. This module is the essential S/W package to assess the major pituitary-gland diseases by means of a multi-dimensional stochastic model. The model is linear as explained in the following section.

The fifth module provides the patients with the relevant name of the medical-experts and institutions in the field.

The sixth module reveals the basic information about the Endocrine Systems of the human body.

The seventh block briefs the user about major hormone diseases such as Acromegaly, Cushing's disease and Prolactinoma.

The last block is for the administrators to add, change or remove information from the database wherever they are.

The complete computer package was prepared with software engineering concepts, concerned with all aspects of software production from the early stages of system specification through to maintaining the system after its life cycle.

During the software production and uploading, the following developments gadgets (or instruments) were employed.

- Apache server (for local hosting),
- PHP (for scripting),
- MySQL (for the database),
- Macromedia Dreamviewer MX,
- PHPEd,
- Homesite (as editors),
- CuteFTP (to upload files),
- MySQL-Front (to manage the database from the cyberspace).

Let us shortly introduce some of the major tools above.

Apache is a Unix-based, open-source web server that is used to host most sites on the Internet. The first version of Apache was developed by a group of programmers in 1995 [19]. Originally, it was a UNIX product, but now versions for Windows, OS/2 and other operating system platforms exist As with most open-source projects, there are numerous add-ons and tailored versions of the server available, which are created using the Apache module API. The name comes from its origins as "a patchy" web server. The name comes from its origins as a series of "patch files". As a result of its sophisticated features, excellent performance, and low price (it's free), Apache has become the world's most popular web server.

PHP (Personal Home Pages) is an open-source, Pre-Hypertext Preprocessor, server-side, cross-platform scripting language for creating dynamic Web pages **??**. A dynamic Web page is a page that interacts with the user, so that each user visiting the page sees customized information. The PHP commands embedded in HTML and processed on a web-server before sending the page to the client browser. Because PHP is embedded within tags, the author can jump between HTML and PHP instead of having to rely on heavy

amounts of code to output HTML. An HTML page with PHP script is typically given a file name suffix of ".php", ".php4" or ".phtml". PHP's strength lies in its compatibility with many types of databases. Also, PHP can talk across networks using IMAP, SNMP, NNTP, POP3, or HTTP. Today, PHP is shipped standard with a number of Web servers, including RedHat Linux and as an alternative to Microsoft's Active Server Pages (ASP) technology.

MySQL is an open source relational database management system that relies on SQL for processing the data in the database, which means that it stores data in separate tables rather than putting all the data in one big area [21]. This adds flexibility, as well as speed. A database is an organized collection of information that a computer uses to select and display data. Databases can help organize and enhance the site content. On the other hand the SQL part of MySQL stands for "Structured Query Language" which is the most common language used to access databases. The MySQL database server is most commonly used for Web applications and for embedded applications and a very popular database in the world because of unmatched speed, reliability, compactness, stability, and ease of customization due to its architecture. Their unique separation of the core server from the storage engine makes it possible to run with very strict control, or with fast disk access, whichever is more appropriate for the situation. MySQL can run on Windows, UNIX, Linux and Mac OS operating systems.

In the following section, we briefly introduce our verified decision making model.

2. A Multi-Dimensiona Stochastic-Model To Predict Major Pituitary Gland Diseases

From the mathematical-modelling point of view, a particular disease, say "A", may be associated with a random variable X or equivalently a random set X. For example, if X is the set of the members which possess the disease "A" for sure, then one can seek the probability $P(X)$ of a person to be a member of that set [22]-[24].

Disease "A" could be identified as the combination of some physical symptoms designated by $\{A_1, A_2, , A_N\}$ where the integer N designates the total number of symptoms which make up the disease "A".

Random variables $\{X_1, X_2, , X_N\}$ may be regarded as the mutually exclusive sets which are associated with the physical symptoms $\{A_1, A_2, , A_N\}$ respectively. More explicitly, X_k could be a set formed with the members who possess the symptom "A_k". At this point, we can assess the conditional probability $P(X|X_k)$ for a person having the disease "A" while possessing the symptom "A_k".

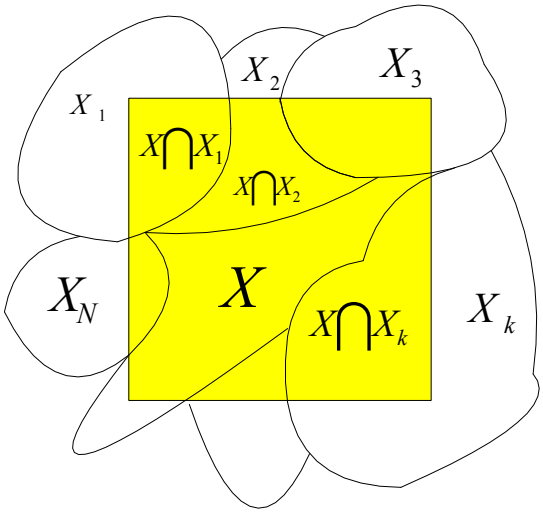
It is shown that conditional probabilities $P(X|X_k)$ are essential parameters to assess the probability $P(X)$ for a person who has the disease "A".

In order to determine conditional probabilities, it may be wise to select a sample set X_s which has total number of N_S members who for sure have the disease "A". Then, we construct a training set X_T out of the sample set X_s as follows.

Referring to Fig.1, let each independent set $\{X_T \cap X_k; k = 1, 2, .., N\}$ is formed on the patients of X_S who surely possess the disease "A" with symptom A_k with total number of n_k patients. In this case, total number of members of the training set X_T is given by

$$N_T = \sum_{k=1}^{N} n_k \tag{1}$$

In this regard, training set X_T is constructed on the union of the intersection-sets $(X_T \cap X_k)$ such that



(a) Event $X = (X \cap X_1) \cup ... \cup (X \cap X_N)$

$X_T \cap X_1$ n_1	$X_T \cap X_2$ n_2	...
...	...	$X_T \cap X_N$ n_N

(b) Formation of the training set X_T with $N_T = \sum_{k=1}^{N} n_k$ number of members

FIGURE 1

$$X_T = \bigcup_{k=1}^{N} X_T \cap X_k \tag{2}$$

Based on the above formation, for each member of X_T, probability of having disease "A" is unity ($i.e. P(X) = 1$). Furthermore, for each member of X_k probability of $P(X_k) = 1$ since all the members ofX_k possess the symptom A_k. Then, conditional probability $P(X|X_k)$ may be approximated employing the frequency count $f_k = n_k N_T$ such that

$$P(X \mid X_k) = \frac{P(X \cap X_k)}{P(X_k)} = \lim_{N_T \to \infty} \frac{n_k}{N_T} \cong \frac{n_k}{N_T} = f_k \tag{3}$$

In this context, by using clinical data run over 100 patients, it is verified that one may employ a Multi-Dimensional Stochastic Linear Model (MD-SLM) to assess the sicknesses due to mal-functioning of the pituitary-gland. Patients who possess a specific disease such as Acromegaly, Cushing or Prolactinoma, can be regarded as the members of an event set X. Here, the random function or equivalently the random set X may be described by means of mutually exclusive random sets $\{X_1, X_2, , X_N\}$ as shown in Fig.1.

In Fig.1, event-set X is constructed by means of N- mutually exclusive sets X_k such that

$$X = (X \cap X_1) \cup (X \cap X_2) \cup ... \cup (X \cap X_N) \tag{4}$$

In this case, probability of having the event X is given by

$$P(X) = P(X \cap X_1) + P(X \cap X_2) + ... + P(X \cap X_N) = \sum_{k=1}^{N} P(X \cap X_k) \tag{5}$$

It should be noted that, while event X_k occurs, conditional probability of having event X is given by

$$PX \mid X_k = \frac{P(X \cap X_k)}{P(X_k)} \tag{6}$$

$$P(X \cap X_k) = P(X \mid X_k)P(X_k) \tag{7}$$

Let us designate the conditional probability $P(X|X_k)$ by w_k. Then,

$$P(X) = \sum_{k=1}^{N} w_k P(X_k) \tag{8}$$

Let us elaborate on (8) as follows.

When event X occurs; $P(X)$ must be equal to one, which in turn makes all $P(X_k)$ equal to one. Therefore, $\sum_{k=1}^{N} w_k$ must add-up to one. Hence,

$$w_{sum} = \sum_{k=1}^{N} w_k = 1 \tag{9}$$

The above equation can be expressed as a theorem.

2.1. **Theorem on Conditional Probabilities.** If an event X is generically made out of N-mutually exclusive complete-events $X_1, X_2, , X_N$ as shown in Fig.1, then sum of conditional probabilities $w_k = P(X|X_k)$ must be equal to one such that

$$\sum_{k=1}^{N} w_k = 1 \tag{10}$$

Definition 1: *Utility Score or Probability of Occurence*
Let $y = P(X)$. Let $x_k = P(X_k)$. Then, we say that y is the utility score of the random event X which describes the probability of occurrence for event X.
Definition 2: *Utility Score or Probability of Occurence*
The random variable y is called the outcome of a stationary Linear Stochastic System LSS which is described by

$$y = \sum_{k=1}^{N} w_k x_k \tag{11}$$

Definition 3: *Utility Score or Probability of Occurence*
In LSS, x_k is called the independent random input variables whereas y is called the random output variable of LSS as shown in Fig.2.
Definition 4: *Utility Score or Probability of Occurence*
In LSS, $w_k s$ are called the system parameters. They are predicted on the occurred event X using the conditional probabilities $w_k = P(X|X_k)$. In fact, if the set $X = (X \cap X_1) \cup$

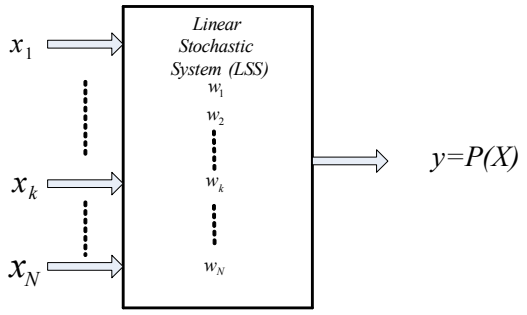


FIGURE 2. Stationary Linear Stochastic System LSS

$(X \cap X_2) \cup \cup (X \cap X_N)$ is complete, the system parameters w_k uniquely determine the probability of occurrence for the random event X.

Definition 5: *Utility Score or Probability of Occurence*

By (11), the outcome $y = P(X)$ is the weighted sum of the random inputs $x_k s$. In this regard, the system parameters $w_k s$ of LSS are also called weight coefficients which operate on the random-input variables $x_k s$ as depicted in Fig.2.

$$y = \sum_{k=1}^{N} w_k x_k \tag{12}$$

Based on above derivations and definitions we can now propose a main statement to model hormone diseases.

2.2. Main Statement: Stationary Linear Stochastic System (LSS) Model for a Hormone Disease.

Disease "A" may be described by means of a stationary linear stochastic system LSS as shown in Fig.2. The system parameters are the weight coefficients w_ks which works on the random inputs w_ks over a linear operator as specified by (11) and they are predicted employing a training set X_T as introduced by (3).

The above systematic approach can be combined under two major design algorithms. In the first one, we estimate and store the complete set of LSS parameters w_ks for the hormone disease under consideration. The second algorithm is devoted to run a self-test. In the following section brief outline of the algorithms are presented.

3. S/W Design Algorithms For MDSS

The proposed MDSS tool consists of two major blocks. The first one is the training block to construct a stationary LSS Model for diagnosis purpose. The second one is the self-test block. These bocks are developed module by module in a sequential manner as described in the following algorithms.

3.1. S/W Design Algorithm for Block 1: Determination of the Complete Set of Attributes and Estimation of the Weight Coefficients to Describe the LSS for Hormone Diseases.

Module 1: Develop a module to collect the clinical data from the patients for sure they have the disease "A" under consideration.

Module 2: Develop a module to classify the collected clinical data to extract complete set of attributes $\{A_k; k = 1, 2, , N\}$.

Module 3: Develop a module to construct a sample set X_S using the collected clinical data.

Module 4: Develop a module to decompose the sample set X_S into its attribute sets $\{(X_T \cap X_k); k = 1, 2, , N\}$

Module 5: Develop a module to generate the training set X_T with $\sum_k^N n_k$ members as shown in Fig.1b where $X_T = \bigcup_{k=1}^N (X_T \cap X_k)$

Module 6: Develop a module to estimate the LSS parameters as $w_k = n_k/N_T$ and store them for future use in self-tests.

Module 7: Develop a module to combine all the above modules in a sequential manner under the training Block (S/W Block 1) as shown in Fig. 3(a-b)

3.2. **S/W Design Algorithm for Block 2: Development of the Self-Test Modules.**

Module 1: Develop a module which enables user to enter attribute scores $P(X_k)$. It should be noted $P(X_k)$ s are either 1 or 0 depending on the existence of the attribute that belongs to the patient.

Module 2: Develop a module which called the LSS parameters w_k from the relevant data-base developed for the disease under consideration

Module 3: Develop a module to compute the outcome of the LSS such that the outcome y is given by $y = P(X) = \sum_{k=1}^N w_k P(X_k)$

Module 4: Develop a module to check If $y = P(X) \geq 50\%$. If yes, branch to a data-base where the detail information about the sickness and expert doctors is provided.

Module 5: Develop a module to check if $y = P(X) < 50\%$. If $P(X) < 0.5$ then branch to a data base prepared for the persons who does not have the hormone disease under consideration. In this case, the directed data-base should include regular medical advises such as no need to get worry about your health etc.

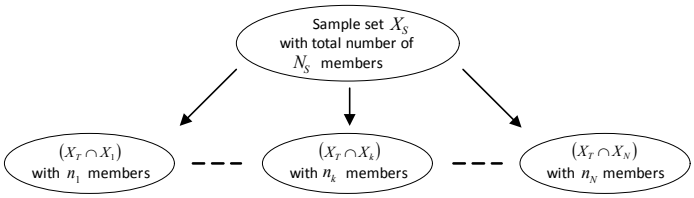
Module 6: Develop a module to combine all the above modules in a sequential manner under the self-test block (S/W Block 2) as shown in Fig. 3(a-b)

In the following section, we run a case study to construct a linear stochastic model to assess the probability P(X) for a person who may be acromegaly.

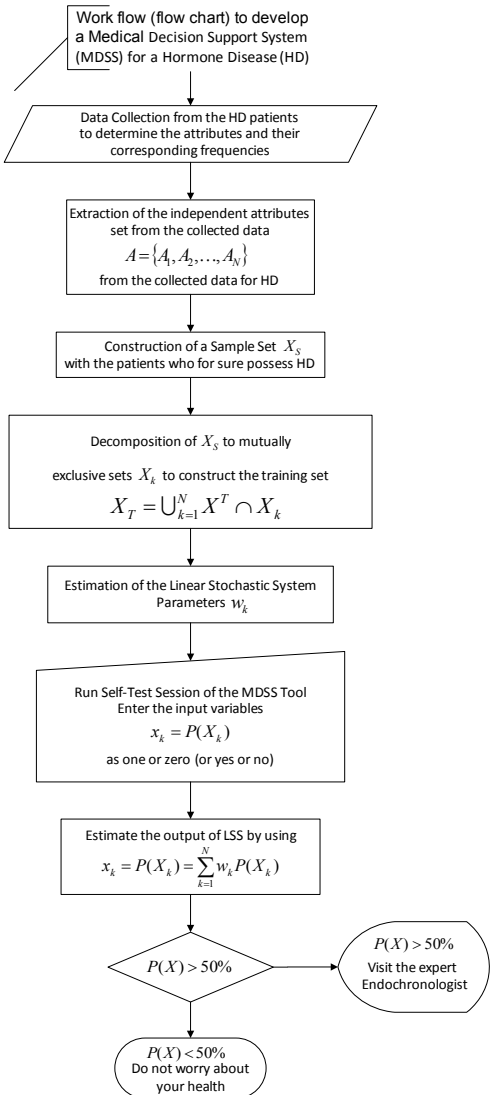
4. Case Study 1: LSS Model For Acromegaly

Pituitary adenomas are common benign tumors of the pituitary gland. About half of adenomas secrete too much of one of the pituitary hormones, which are called by functional pituitary adenomas. Therefore due to hormonal imbalances that affect bodily functions it can be detected at any age and most of them arise from the anterior lobe of the pituitary gland. These adenomas have specific signs and symptoms that are primarily related to the hypersecretion of pituitary hormones, diseases namely, acromegaly (growth hormone secreting adenoma), Prolactinoma (prolactine secreting adenoma) and Cushing Disease (Adrenocorticotropic hormone secreting adenoma) [25]-[29].

Acromegaly is caused by increase of growth hormone secretion, with a prevalence of 58130 cases/million people. The most common sign is the enlargement of hands and foot (change in ring or shoe size), coarsening of facial features, spreading teeth, tongue enlargement, Carpal tunnel syndrome, excessive perspiration (sweating), oily skin, sleep apnoea, small outgrowths of skin tissue (skin tags), fatigue and muscle weakness, a deepened and husky voice, snoring, joint and bone aches, impotence and menstrual irregularities. Acromegaly can be associated with hypertension, diabetes mellitus and cardiovascular disease [30]-[38].

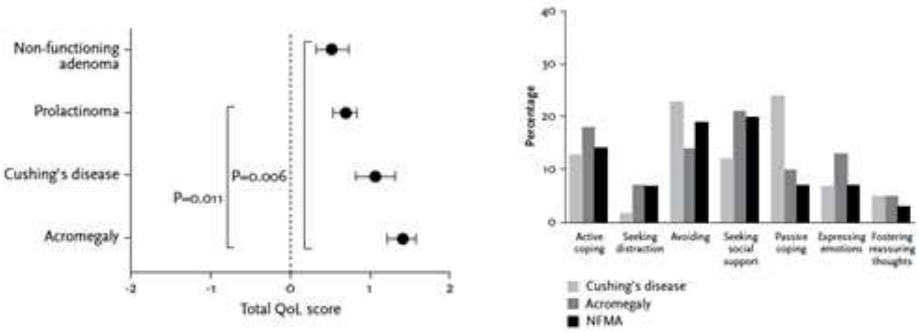


(a) Selection of the sample set X_S with N_S number of patients who for sure have the hormone disease "A" with N distinct attributes.



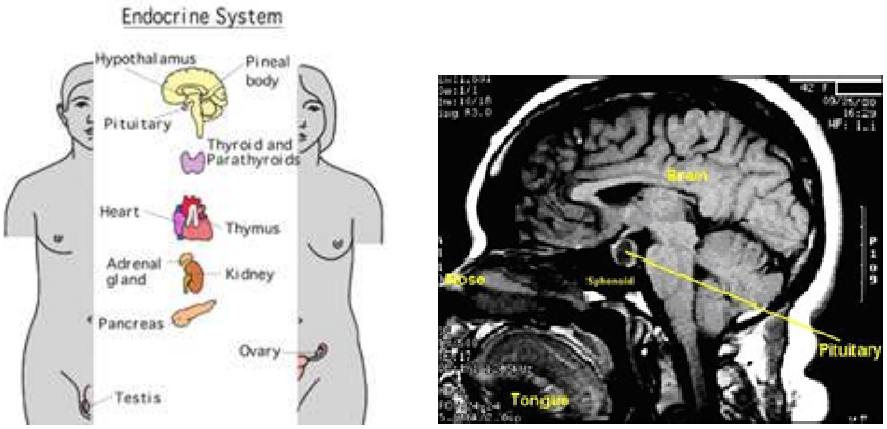
(b) Flow chart of self-test module.

FIGURE 3



(a) Quality of life in Pituitary Adenomas (b) Different personality traits result in different coping strategies.

FIGURE 4



(a) Endocrine system of the human body (b) MR of a human brain with emphasis of Pituitary Gland

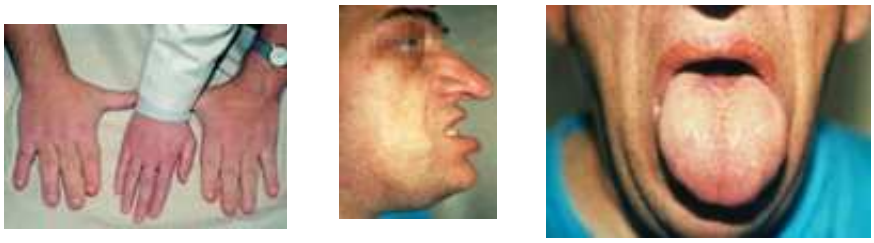
FIGURE 5

The pituitary gland (sometimes called the master gland) plays a critical role in regulating growth, development, metabolism, and reproduction of a human body. It produces variety of key hormones like growth hormone, which regulates growth; ACTH (corticotrophin), which stimulates the adrenal glands to produce cortisol; TSH (thyroid stimulation hormone), which stimulates the thyroid gland to produce thyroid hormone; Luteinizing hormone and follicle-stimulating hormone, which regulate ovulation and estrogen and progesterone production in women as well as sperm formation and testosterone production in men. Prolactin hormone stimulates the mammary glands to produce milk production. When the pituitary gland produces excess growth hormone, this result in excessive growth called Acromegaly [39].

In Fig.5a, endocrine system of the human body is shown. In Fig. 5b, an actual brain MR with emphasis of pituitary gland is presented.

Some selected symptoms of acromegaly may be listed as follows.

- swelling of the hands and feet ($A_1 \to X_1$)
- facial features become coarse as bones grow ($A_1 \to X_1$)



(a) $X_1 \rightarrow$ swelling Hands and feet (b) $X_2 \rightarrow$ Coarse Facial Features (c) $X_3 \rightarrow$ Enlarged lip and tongue

FIGURE 6. Problem steps for edge cell users

- enlarged lips, nose, and tongue ($A_1 \rightarrow X_1$)

In view of our proposed linear stochastic system model introduced in Fig.2, the above symptoms may be regarded as mutually exclusive events or equivalently attributes which are seen in acromegaly patients. For example, the symptom swelling of hands and feet may be associated with a random event set X_1 constructed by the members of that particular attribute ($i.e.A_1$). The symptom course facial features as bones grow may be referred with the random event set X_2 formed by the members of attributeA_2. Similarly, enlarged lips, nose and tongue is connected with a random event set X_3 constructed with the members of attribute A_3. Some pictures from these events are shown in Fig.6.

Our extensive clinical research reveals that Acromegaly disease may be identified roughly by means of 19 distinct attributes as listed in Table I. LSS parameters for Acromegaly can be predicted from a training set X_T which is constructed employing a sample set X_S consist of $N_S = 100$ Acromegaly patients for sure having distinct attributes. For example, out of 100 Acromegaly patients, all of them (i.e. 100 of them) show swelling hands and feet. In other words, the set $(X_T X_1)$ is built on $n_1 = 100$ acromegaly patients having attribute A_1. On the other hand, in the sample set X_S, 88 patients has Coarse facial features as bones grow attribute. That is to say, the set $(X_T \mid X_2)$ includes $n_2 = 88$ patients. Similarly, the set $(X_T \mid X_3)$ which refers to attribute enlarged lips, nose and tongue includes $n_3 = 96$ patients. The complete list of attributes and their corresponding populations (n_k) of the sets $(X_T \mid X_k)$ are listed in Table I.

Close examination of Table I reveals that the training set X_T includes total of $N_T = 1175$ members.

Based on the parameters $\{w_k; k = 1, 2, , 19\}$ given in Table I, a self-test for Acromegaly can be run by setting up a utility function described by (10) such that

$$P(X) = \sum_{k=1}^{N} w_k P(X_k) \tag{13}$$

In (12), one should ask if the attribute A_k prevails or not. If the answer is yes, then $P(X_k)$ must be selected as 1. Otherwise, $P(X_k)$ is zero.

Referring to Table II, let us run an example to show the usage of (12).

In Table II, attribute A_1 is absent. That means the person running the self-test does not have excess hair growth. Therefore, we set $P(X_1) = 0$. Similarly, the person neither has swelling hands, nose and feet nor obesity. Therefore, corresponding probabilities $P(X_6)$ and $P(X_15)$ are set to zero. Thus, (11) yields $P(X) = 0.83$. Hence, we say that, the person who used the self-test has % 83 chance to be Acromegaly. Therefore, he/she must

TABLE 1. Complete Set of Attributes for Acromegaly and its Predicted LSS Parameters W_K

Event Sets	Descriptions for the attributes $A_k \to X_k$	Total number of members (n_k) in the sampled set X_s with attribute A_k	Weight Coefficients $w_k = P(X \mid X_k) = n_k/N_T$
$X \cap X_1$	Swelling of hands nose and feet	100	$w_1 = 0,085106383$
$X \cap X_2$	Coarse Facial features by bones nose and feet	88	$w_2 = 0,074893617$
$X \cap X_3$	Enlarged lip, nose, and tongue nose and feet	96	$w_3 = 0,081702128$
$X \cap X_4$	Excess hair growth nose and feet	59	$w_4 = 0,050212766$
$X \cap X_5$	Headaches nose and feet	84	$w_5 = 0,071489362$
$X \cap X_6$	Osteolysis nose and feet	64	$w_6 = 0,054468085$
$X \cap X_7$	Joint pain nose and feet	64	$w_7 = 0,054468085$
$X \cap X_8$	Impotence in men nose and feet	36	$w_8 = 0,030638298$
$X \cap X_9$	Reduced sex drive in men nose and feet	35	$w_9 = 0,029787234$
$X \cap X_{10}$	Loss of vision nose and feet	30	$w_{10} = 0,025531915$
$X \cap X_{11}$	Irregular menstrual cycles in women nose and feet	71	$w_{11} = 0,060425532$
$X \cap X_{12}$	Stopped menstrual cycles in women nose and feet	49	$w_{12} = 0,041702128$
$X \cap X_{13}$	Breast milk production in women nose and feet	48	$w_{13} = 0,040851064$
$X \cap X_{14}$	Muscle weakness nose and feet	18	$w_{14} = 0,015319149$
$X \cap X_{15}$	Voice deepening nose and feet	73	$w_{15} = 0,06212766$
$X \cap X_{16}$	Obesity nose and feet	46	$w_{16} = 0,039148936$
$X \cap X_{17}$	Excess perspire nose and feet	79	$w_{17} = 0,067234043$
$X \cap X_{18}$	High blood pressure nose and feet	35	$w_{18} = 0,029787234$
$X \cap X_{19}$	Non-fitting ring nose and feet	100	$w_{19} = 0,085106383$

N_T = Total number of Certain Acromegaly Patients in the training set X_T
$N_T = 1175$
$w_{sum} = 1$

immediately visit an expert endocrinologist and run further Lab tests and take an MR of the pituitary gland as guided by the expert doctor etc.

In the following section, we introduce the second case study for Cushing Syndrome

5. Case Study 2: LSS Model For Cushing Syndrome

Cushings disease is one form of Cushings syndrome, which the body produces high level of cortisol (hypercortisolism) caused by pituitary adenoma. In other words, Cushing Syndrome is a disease caused by an excess of cortisol production due to pituitary gland or by excessive use of cortisol or other similar steroid hormones. The symptoms of hypercortisolism are including changes in physical characteristics of the body such as obesity, round

TABLE 2. Result of the Self-Test for Pre-Acromegaly Diagnosis

Attributes	Event Sets	Descriptions for the attributes $A_k \to X_k$	Weight Coefficients $P(X \mid X_k) = n_k/N_T$	$P(X_k)$	$w_k P(X_k)$
A_1	$X \cap X_1$	Excess hair growth	$w_1 = 0,085106383$	0	0
A_2	$X \cap X_2$	Headaches	$w_2 = 0,074893617$	1	0,0714894
A_3	$X \cap X_3$	Osteolysis	$w_3 = 0,081702128$	1	0,0544681
A_4	$X \cap X_4$	Enlarged lip, nose, and tongue	$w_4 = 0,050212766$	1	0,0817021
A_5	$X \cap X_5$	Joint pain	$w_5 = 0,071489362$	1	0,0544681
A_6	$X \cap X_6$	Swelling of the hands and feet	$w_6 = 0,054468085$	0	0
A_7	$X \cap X_7$	Impotence in men	$w_7 = 0,054468085$	1	0,0306383
A_8	$X \cap X_8$	Reduced sex drive in men	$w_8 = 0,030638298$	1	0,0297872
A_9	$X \cap X_9$	Loss of vision	$w_9 = 0,029787234$	1	0,0255319
A_{10}	$X \cap X_{10}$	Irregular menstrual cycles in women	$w_{10} = 0,025531915$	1	0,0604255
A_{11}	$X \cap X_{11}$	Stopped menstrual cycles in women	$w_{11} = 0,060425532$	1	0,0417021
A_{12}	$X \cap X_{12}$	Breast milk production in women	$w_{12} = 0,041702128$	1	0,0408511
A_{13}	$X \cap X_{13}$	Muscle weakness	$w_{13} = 0,040851064$	1	0,0153191
A_{14}	$X \cap X_{14}$	Voice deepening	$w_{14} = 0,015319149$	1	0,0621277
A_{15}	$X \cap X_{15}$	Obesity	$w_{15} = 0,06212766$	0	0
A_{16}	$X \cap X_{16}$	Excess perspire	$w_{16} = 0,039148936$	1	0,067234
A_{17}	$X \cap X_{17}$	High blood pressure	$w_{17} = 0,067234043$	1	0,0297872
A_{18}	$X \cap X_{18}$	Facial features become coarse	$w_{18} = 0,029787234$	1	0,0748936
A_{19}	$X \cap X_{19}$	Non-fitting ring	$w_{19} = 0,085106383$	1	0,0851064
Result of the test			$w_{sum} = 1$	$P(X) = \sum_{k=1}^{19} \sum w_k x_k = 0.83$	

or moon face, plethora (red cheeks), added fat on back of neck (buffalo hump) and abdominal excessive weight gain, while the arms and legs to become relatively thin, and thin skin that bruises easily, abdominal striae, Generalized weakness and fatigue; wasting of muscles, most noticeably in the upper thighs, osteoporosis and vertebral compression fractures, backache, hypertension, excess hair growth on the face, neck, chest, abdomen and thighs (hirsutism), menstrual disorders, decreased fertility and/or sex drive, high blood pressure, diabetes mellitus, mood and behaviour disorders [40]-[44]. All the symptoms of the Cushing Syndrome are shown in Table III.

Some of the basic symptoms of Cushing Syndrome are given as follows.

- upper body obesity ($A_1 \to X_1$)
- round face ($A_2 \to X_2$)
- thinning arms and legs ($A_3 \to X_3$)
- stretch marks on abdomen ($A_4 \to X_4$)
- high blood pressure ($A_5 \to X_5$)
- high blood sugar ($A_6 \to X_6$)
- irritability and anxiety ($A_7 \to X_7$)

In view of our proposed mathematical model introduced in Fig.2, the above symptoms may be regarded as mutually exclusive events or equivalently attributes $X_k s$ which are observed on the patients possessing Cushing Syndromes.

Some pictures from these attributes are shown in Fig.7.

Based on our clinical experience, Cushing Syndrome may be identified roughly by means of 14 distinct attributes as listed in Table IV. LSS-Parameters for the Cushing Syndrome may be predicted forming a training set X_T as in the previous case study. For this purpose, we use a sample set X_S with 100 Cushing Syndrome patients. For example, out of 100 Cushing Syndrome patients, 82 of them show Chapped skin. In other words, intersection set $(X_T \cap X_1)$ includes $n_1 = 82$ patients with chapped skin. In the same sample set, 51 patients have Excess hair growth. That is to say, the intersection set $(X_T \cap X_2)$ includes $n_2 = 51$ patients. Similarly, the set $(X_T \cap X_3)$, which refers to attribute Headaches has $n_3 = 49$ patients. The complete list of attributes and their corresponding

(a) Cushing Syndrome with upper body obesity, round face and thinning arms and legs

(b) Stretch marks on abdomen

FIGURE 7

TABLE 3. Clinical Features of Cushing Syndrome (All Ages)

Symptoms/Sign	Frequency, %
Obesity or weight gain (> 115% ideal body weight)	80
Thin Skin (> 115% ideal body weight)	80
Moon facies (> 115% ideal body weight)	75
Hypertension (> 115% ideal body weight)	75
Purple skin stria (> 115% ideal body weight)	65
Hirsutism (> 115% ideal body weight)	65
Abnormal glucose tolerance (> 115% ideal body weight)	55
Impotence (> 115% ideal body weight)	55
Menstrual disorders (usually amenorrhea) (> 115% ideal body weight)	60
Plethora (> 115% ideal body weight)	60
Proximal muscle weakness (> 115% ideal body weight)	50
Truncal obesity (> 115% ideal body weight)	50
Acne (> 115% ideal body weight)	45
Brusing (> 115% ideal body weight)	45
Mental changes (> 115% ideal body weight)	45
Osteoporosis (> 115% ideal body weight)	40
Edema of lower extremities (> 115% ideal body weight)	30
Hyperpigmentation (> 115% ideal body weight)	20
Hypokalemic alkalosis (> 115% ideal body weight)	15
Diabetes mellitus (> 115% ideal body weight)	15

populations (n_k) of ($X_T \cap X_k$) s are listed in Table IV. As in Table I, weight coefficients for LSS is approximated using the frequency calculations over $N_T = 836$ patients such that $w_1 = 82(836 = 0.098)$, $w_2 = 51/836 = 0.061$, $w_3 = 49(836 = 0.058)$ etc.

In Table V, a self- test was run for a person who was suspicious to have the Cushing Syndrome. He selected $P(X_1) = P(X_2) = P(X_3) = P(X_{11}) = P(X_{12}) = P(X_{13}) = P(X_{14}) = 0$ and the rest of $P(X_k)$ were set to 1. Thus, it is found that his chance to have Cushing Syndrome is 39.8%. Our threshold level is 50%. Therefore, he does not need to bother to visit an endocrinologist for Cushing Syndrome. Finally, in the following section we present the case study on Prolactinoma.

TABLE 4. Complete Attributes Extracted From Cushing Syndrome Patients and Computations of Their Corresponding Weight Coefficients

Attributes	Event Sets for Cushing Syndrome	Descriptions for the attributes $(A_k \to X_k)$	Total number of members (n_k) in the sample set X_s with attribute A_k	Weight Coefficients $w_k = P(X \mid X_k) = n_k/N_T$
A_1	$X \cap X_1$	Chapped Skin	82	$w_1 = 0,098086124$
A_2	$X \cap X_2$	Excess hair growth	51	$w_2 = 0,061004785$
A_3	$X \cap X_3$	Headaches	49	$w_3 = 0,05861244$
A_4	$X \cap X_4$	Depression (discomfort, stress, anxiety)	33	$w_4 = 0,039473684$
A_5	$X \cap X_5$	Fragile skin	51	$w_5 = 0,061004785$
A_6	$X \cap X_6$	Increased fat around neck	75	$w_6 = 0,089712919$
A_7	$X \cap X_7$	Impotence in men	10	$w_7 = 0,011961722$
A_8	$X \cap X_8$	Irregular menstrual cycles in women	53	$w_8 = 0,063397129$
A_9	$X \cap X_9$	Muscle weakness	61	$w_9 = 0,072966507$
A_{10}	$X \cap X_{10}$	High blood sugar	50	$w_{10} = 0,059808612$
A_{11}	$X \cap X_{11}$	Obesity	77	$w_{11} = 0,092105263$
A_{12}	$X \cap X_{12}$	Acnes	82	$w_{12} = 0,098086124$
A_{13}	$X \cap X_{13}$	High blood pressure	80	$w_{13} = 0,095693784$
A_{14}	$X \cap X_{14}$	Red round face	82	$w_{14} = 0,098086124$
N_T =Total number of Certain Cushing Syndrome Patients in the training set X_T			$N_T = 836$	$w_{sum} = 1$

6. Case Study 3: LSS Model For Prolactinoma

A Prolactinoma is a benign tumor of the pituitary gland. Symptoms of prolactinoma are caused by too much prolactin in the blood or by pressure on the tumor by the surrounding tissues. Prolactin stimulates the breast to produce milk during pregnancy and nursing period after delivery.

Prolactin-secretion adenomas are the most common, and account for approximately 30% of all pituitary tumors. Symptoms of prolactinoma depend on the excessive secretion of prolactin hormone (hyperprolactinaemia) from the tumor and pressure of the tumor on adjacent tissues. Therefore hyperprolactinemia induced galactorrhea (milky breast discharge), absent or irregular menstrual periods, low sex drive, vaginal dryness and difficulty achieving pregnancy. Controversially, macro-adenomas cause visual field defect (pressure in optic nerves), headaches and cause sexual dysfunction and infertility mainly in men [46]-[48].

Some of the basic symptoms of prolactinoma is given as follows.

- Infertility $(A_1 \to X_1)$
- Headaches $(A_2 \to X_2)$
- Impotence, reduced sex drive and enlargement of breasts in men $(A_3 \to X_3)$
- Breast milk production; irregular or stopped or non-menstrual cycles in women $(A_4 \to X_4)$

Our extensive clinical studies indicate that Prolactinoma can be pre-diagnosed by means 9 distinct attributes as listed in Table VI.

LSS parameters for Prolactinoma are predicted employing a training set X_T. The set X_T was constructed on the sample set X_S formed among the $N_S = 100$ patients who have for sure Prolactinoma. For example, in the sample set $X_S, n_1 = 67$ number of patients exhibit attribute *Headaches*; $n_2 = 22$ number of patients show impotence etc. Thus, we end up with total of $N_T = 279$ members in the training set X_T. Then, parameters $w_k = n_k N_T$ are estimated. In this regards, $w_1 = 67279 = 0.24, w_2 = 22279 = 0.0788$ etc. Hence, we up with all the LSS parameters as listed in column 5 of Table VI. Using Table VI, anyone can run a self-test as described in the previous study cases.

TABLE 5. Self-Test For Cushing Syndrome

Attributes	Event Sets for Cushing Syndrome	Explanation for the attributes	Weight Coefficients $w_k = P(X \mid X_k) = n_k/N_T$	$P(X_k)$	$w_k = P(X_k)$
A_1	$X \cap X_1$	Chapped Skin	0,098086124	0	0
A_2	$X \cap X_2$	Excess hair growth	0,061004785	0	0
A_3	$X \cap X_3$	Headaches	0,05861244	0	0
A_4	$X \cap X_4$	Depression (discomfort, stress, anxiety)	0,039473684	1	0,039473684
A_5	$X \cap X_5$	Fragile skin	0,061004785	1	0,061004785
A_6	$X \cap X_6$	Increased fat around neck	0,089712919	1	0,089712919
A_7	$X \cap X_7$	Impotence in men	0,011961722	1	0,011961722
A_8	$X \cap X_8$	Irregular menstrual cycles in women	0,063397129	1	0,063397129
A_9	$X \cap X_9$	Muscle weakness	0,072966507	1	0,072966507
A_{10}	$X \cap X_{10}$	High blood sugar	0,059808612	1	0,059808612
A_{11}	$X \cap X_{11}$	Obesity	0,092105263	0	0
A_{12}	$X \cap X_{12}$	Acnes	0,098086124	0	0
A_{13}	$X \cap X_{13}$	High blood pressure	0,09569378	0	0
A_{14}	$X \cap X_{14}$	Red round face	0,098086124	0	0
Test result run for the person for the pre-diagnosis of Cushing Syndrome			$w_{sum} = 1$	$P(X) = 0,398$	

TABLE 6. Complete Attributes Extracted Cushing Syndrome Patients and Computations of Their Corresponding Weight Coefficients

Attributes	Event Sets for Cushing Syndrome	Descriptions for the attributes $A_k \to X_k$	Total number of members (n_k) in the sample set X_s with attribute A_k	Weight Coefficients $w_k = P(X \mid X_k) = n_k/N_T$
A_1	$X \cap X_1$	Headaches	67	$w_1 = 0,240143369$
A_2	$X \cap X_2$	Impotence in men	22	$w_2 = 0,078853047$
A_3	$X \cap X_3$	Reduced sex drive in men	11	$w_3 = 0,039426523$
A_4	$X \cap X_4$	Enlargement of breast in men	6	$w_4 = 0,021505376$
A_5	$X \cap X_5$	Infertility	28	$w_5 = 0,100358423$
A_6	$X \cap X_6$	Irregular menstrual cycles in women	6	$w_6 = 0,021505376$
A_7	$X \cap X_7$	Stopped menstrual cycles in women	44	$w_7 = 0,157706093$
A_8	$X \cap X_8$	No menstrual cycles in women	17	$w_8 = 0,0609319$
A_9	$X \cap X_9$	Breast milk production in women	78	$w_9 = 0,279569892$
N_T =Total number of Certain Prolactinoma Patients in Set X			$N_T = 279$	$w_{sum} = 1$

7. Closing Remarks and Conclusion

In these days, whenever we complaint about our health, we immediately surf on the internet to search for the symptoms we feel. In the course of search process, it is very easy to face medical information pollution which confuses us where to go and whom to look for to receive proper medical help. This fact may create psychological stress and anxiety which may further aggravate our sickness and rush us to seek for the relevant and the irrelevant medical care. The end result is loss of "health", "aggravation of the illness", loss of "time" and "money". On the other hand, if the patient coincides with a complete medical self-test tool, he/she may end up with early diagnosis and perhaps directed to a proper medical center. In this regard, Medical Decision Support Systems may be useful for family practitioners to guide the patients to the correct addresses.

In this work, we have chosen the liberty to develop a reliable medical decision support tool for early diagnosis of hormone diseases namely, acromegaly, cushing and prolactinoma. The tool prevents malpractice, saves time, effort and money both for patients and expert medical doctors.

The proposed tool is based on a Stationary Linear Stochastic System to model hormone diseases. In the model, hormone diseases are described by means of their complete set of attributes. Attributes stems from the physical symptoms and they are quantified by calculating their portion on the overall disease by estimating conditional probabilities.

Outcome of the system is the probability of having the specific disease by the person who is running the self-test. It is verified that the model proposed in this research work results in more than 99% accurate decisions for early diagnosis of the particular disease under consideration. As the continuation of this work, our intension is to wide spread the pre-diagnostic decision support tool on mobile platforms in Europe and Associated Countries by means of an EU Horizon 2020 project.

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