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Endometrial Cancer Recognition via EEG Dependent upon 14-3-3 Protein Leading to an Ontological Diagnosis

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***Abstract*—**The purpose of my research proposal is to demonstrate that there is a relationship between EEG and endometrial cancer.

The above relationship is based on an Aristotelian Syllogism; since it is known that the 14-3-3 protein is related to the electrical activity of the brain via control of the flow of Na+ and K+ ions and since it is also known that many types of cancer are associated with 14-3-3 protein, it is possible that there is a relationship between EEG and cancer. This research will be carried out by well-defined diagnostic indicators, obtained via the EEG, using signal processing procedures and pattern recognition tools such as neural networks in order to recognize the endometrial cancer type. The current research shall compare the findings from EEG and hysteroscopy performed on women of a wide age range. Moreover, this practice could be expanded to other types of cancer. The implementation of this methodology will be completed with the creation of an ontology. This ontology shall define the concepts existing in this research's domain and the relationships between them. It will represent the types of relationships between hysteroscopy and EEG findings.

***Keywords*—**Bioinformatics, Protein 14-3-3, EEG, Endometrial cancer, Ontology.

I. State of the Art and Objectives

ENDOMETRIAL cancer consistently appears on the well-known list of the four most common cancers of females, following breast, lung, and colorectal cancers, in that order [1]. It has been found that it develops in normal, atrophic and hyperplastic endometrium [2], and it is defined as an epithelial tumor, usually with glandular differentiation, arising in the endometrium and having the potential to invade the myometrium and spread to distant sites [3]. Endometrioid adenocarcinoma accounts for 75–80% of all endometrial cancers. Other forms of endometrial cancer include papillary serous adenocarcinoma, clear cell adenocarcinoma, mucinous adenocarcinoma, squamous cell adenocarcinoma and mixed adenocarcinoma [4]. Endometrial hyperplasia may be a precursor to endometrial carcinoma [5] and has been categorised as follows: simple hyperplasia without atypia, complex hyperplasia without atypia, simple hyperplasia with atypia and complex hyperplasia with atypia [6].

This study aims to systematically decode some of the uncharted principles embedded in the association between EEG and endometrial cancer, such that the generated outcome can be controllably applied to a broad spectrum of hyperplasias and carcinomas. It must be stated that this association between EEG and endometrial cancer has not been directly analysed and documented in the existing medical/biochemical literature.

This research will be carried out using well-defined diagnostic indicators obtained via EEG using signal processing procedures and pattern recognition tools, such as neural networks, in order to recognise the different types of endometrial cancer. Finally, the current research shall focus on comparing the findings of EEGs and hysteroscopies performed on women of various ages.

Several research studies have proven an association between 14-3-3 protein and certain types of cancers (e.g. endometrial cancer [7], [8], [9]; uterine cervical cancer [10]; ovarian carcinoma [8], [9]; prostate cancer [8], [9]; breast cancer [9], [11], [12]; gastric cancer [11]; hepatocellular carcinomas [9], [11]; lung cancer [9], [13], [14]; and skin cancer [9]) and an association between 14-3-3 protein and the control of membrane localisation of ion channels [15].

Depending on the success of the outcome, the challenging possibility that this same practice can be applied to diagnose other types of cancers (e.g. uterine cervical cancer, breast cancer, ovarian cancer, prostate cancer, lung cancer, gastric cancer, hepatocellular carcinomas, skin cancer, etc.) may hold even greater potential from both a scientific and a humanitarian point of view. All gains could potentially be amplified through a future extension of the association between EEG and other proteins establishing a correlation between contributing membrane potential mechanisms and similar mechanisms for other types of cancer.

A. Objective I

The first objective is to investigate the possibility of utilising EEG as a new diagnostic and follow-up tool in

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endometrial cancer. An EEG records electrical currents of the brain caused primarily by Na+ and K+ ions, which are pumped through channels in neuron membranes in the direction governed by membrane potential. EEG is a totally noninvasive, safe and low-cost technique that has become a very important tool used widely in the fields of clinical medicine and research. Eighty years have elapsed since the first human electroencephalogram was recorded by Hans Berger. During this period of time, a great evolution has taken place in the field of technology that has enabled EEG to gradually assume a significant role in research, suggesting that its full potential has yet to be realised [16], [17].

The scope of this study is to introduce a new process involving the analysing and decoding of indications obtained from EEGs to detect endometrial cancer using an intermediate logic involving the contribution of 14-3-3 protein. Beyond this core scope, the current study will establish a well-defined basis for re-introducing an existing, trustworthy, safe, time- and cost-efficient diagnosis technique (i.e. EEG) for this new purpose, which has remained unevaluated until now. Thus, EEG shall provide the means for developing a new approach for diagnosing endometrial cancer in the early stages (i.e. endometrial hyperplasia); it shall serve as an early diagnostic tool for a type of cancer that affects a significant portion of the population. Another aspect that should not be neglected is the possibility of utilising EEG as a clinical follow-up tool during the therapeutic process for associated cancers. A new horizon in medical research becomes visible with the prospect of establishing the basis for utilising EEG, with all its aforementioned advantages, in a new role as a tool for diagnosing numerous types of cancer in the early stages.

B. Objective II

The second objective is to create an ontology defining the concepts and relationships existing in the research domain that will lead to diagnosis and dissemination of the scientific results on the semantic web. Ontologies provide a semantic representation of the concepts existing in a certain domain, as well as their relationships, while keeping this information reusable and shareable. Ontologies have made a dynamic entry into the field of bio-medicine, providing services applicable to many cases.

The primary goal for creating a medical ontology for this study is to formally represent all research outcomes that correlate EEG signals with a diagnosis of endometrial cancer. This ontology, associated with the study's database storing experimental results, will contain all data derived from the research (bibliographic knowledge, experimental data and metadata) and their relationships, which will be processed by a linguistics expert who will provide lexical and semantic support to achieve formality. Furthermore, the ontology will constitute the basis for the development of a decision-making system capable of forming rules using ontology terms. All in all, the ontology and the decision-making system will constitute an innovative tool for the medical community capable of assisting doctors in making decisions regarding the diagnosis of endometrial cancer.

II. Methodology

The aim of this study is to demonstrate that there exists a correlation between EEG and endometrial cancer. The sequence of the logical steps made to reach this conclusion is based on Aristotelian syllogism: since it is known that electrical brain activity may be depicted using EEG, and given the fact that the 14-3-3 protein is related to the electrical activity of the brain via the control of the flow of Na+ and K+ ions, and also given that endometrial cancer and many other types of cancer are associated with 14-3-3 protein, it is possible that there exists a relationship between cancer and EEG. This proposal takes the following form: cancer is related to 14-3-3 protein → 14-3-3 protein is related to ion channels → ion channels are related to EEG → therefore, cancer is related to EEG.

The implementation of this study is based on a **literature review** (through which the aforementioned associations – cancer with 14-3-3, 14-3-3 with ion channels, ion channels with EEG – are confirmed and thus provide us with the means to make logical assumptions regarding the EEG-cancer correlation) and the **planning of the experimental part of the study**, in which the results shall be evaluated and shall undergo statistical processing (see Fig. 1).

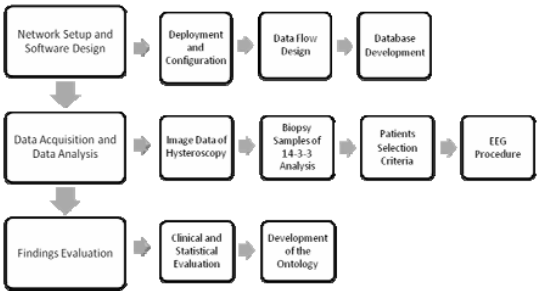

Fig. 1 Planning of the experimental part of the study

III. Literature Review

A. Cancer and 14-3-3

One of the most striking 'rags to riches' stories in the protein world is that of 14-3-3, originally identified in 1967 (Moore and Perez) as merely an abundant brain protein [11]. The first clues that 14-3-3 would play an important role in cell biology came almost 25 years later when it was found to interact with various proto-oncogene proteins and signaling proteins [11]. The subsequent identification of 14-3-3 as a phosphoserine/phosphothreonine-binding protein firmly established its importance in cell signaling. Members of the 14-3-3 family (30 kDa acidic proteins) are found in all eukaryotes – from plants to mammals – and more than 100 binding partners have been identified to date. The targets of 14-3-3 are found in all subcellular compartments and their functional diversity is overwhelming – they include

transcription factors, biosynthetic enzymes, cytoskeletal proteins, signaling molecules, apoptosis factors and tumor suppressors. Binding of 14-3-3 can alter the localisation, stability, phosphorylation state, activity and/or molecular interactions of a target protein. Recent studies indicate that the serine/threonine protein phosphatases PP1 and PP2A are important regulators of 14-3-3 binding interactions, and demonstrate a role for 14-3-3 in controlling the translocation of certain proteins from the cytoplasmic and endoplasmic reticulum to the plasma membrane [11].

The 14-3-3 protein family is highly conserved and ubiquitously expressed. In mammals, there are at least seven isoforms: β, ε, γ, η, σ, θ and ζ: the phosphorylated forms of β and γ initially being described as α and δ respectively, each encoded by a distinct gene [11]. In the past, candidate approaches led to the identification of a few proteins associated with 14-3-3σ: CDC2, BAX, p53, the glucocorticoid receptor, WEE1, EFP, CDK2 and CDK4, BAD and TBC2 were shown to interact with 14-3-3σ [9]. New reports also link 14-3-3 to several neoplastic and neurological disorders, where it might contribute to the pathogenesis and progression of these diseases [11].

Several research studies have proven an association between 14-3-3 protein and certain types of cancer (e.g. endometrial cancer [7], [8], [9]; uterine cervical cancer [10]; ovarian carcinoma [8], [9]; prostate cancer [8], [9]; breast cancer [9], [11], [12]; gastric cancer [11]; hepatocellular carcinomas [9], [11]; lung cancer [9], [13], [14]; and skin cancer [9]). Endometrial carcinoma is the most common malignancy of the female genital tract. Approximately 80% to 90% of all cases are in the clinical early stage and the incidences have recently increased. In normal endometrium, 14-3-3σ protein is expressed weakly in epithelial glandular cells. However, the status of 14-3-3σ protein and its possible roles have never been examined in endometrial carcinoma. The prognostic significance of p53 overexpression in endometrial cancer has been reported. Therefore, decreased expression of 14-3-3σ may possibly have an important role in the development of endometrial cancer, because 14-3-3σ is directly regulated by p53 [18]. In order to study the possible correlation between the status of 14-3-3σ protein and a patient's prognosis, immunoreactivity was observed in 103 cases of endometrioid endometrial cancer and the findings were correlated with the clinical outcomes of the patients [18]. This was the first study to examine the status of 14-3-3σ protein and its possible roles in determining the clinical outcome of a patient with endometrial carcinoma. It is well known that the 14-3-3σ gene is induced after DNA damage in a p53-dependent manner and that it plays an important role in the G2 checkpoint by sequestering the CDC2/cyclin B1 complex. It is currently believed that an inactivation of 14-3-3σ plays an important role in tumor development and/or progression. However, it is also true that 14-3-3σ may play different roles in tumor development and/or progression in different human organs. For example, 14-3-3σ is highly up-regulated in pure squamous cell urinary bladder carcinoma, whereas it is down-regulated in invasive bladder urothelial cell carcinoma. Loss or absence of 14-3-3σ expression is generally considered an early event during carcinogenesis in breast and prostate carcinoma. It has recently been shown that the loss of 14-3-3σ expression is correlated with advanced disease and/or high-grade tumors and significantly associated with poor prognosis in epithelial ovarian carcinoma. In the present study, the results suggest that the loss of 14-3-3σ expression in endometrioid endometrial cancer may be associated with aggressive biological characteristics, which play an important role in prognosis and/or recurrence, although it could be a relatively early event that takes place during carcinogenesis [18].

These findings indicate that the absence of 14-3-3σ protein, as determined by immunohistochemistry, could be a very important tool for identifying endometrial cancer cases at high risk of recurrence and/or death, which are otherwise not detected by current clinical and pathologic evaluation, especially those in the early stages of endometrial carcinoma. In addition, results of 14-3-3σ immunohistochemistry in the early stages of endometrial carcinoma could contribute to planning postoperative follow-up and adjuvant therapy [18].

B. 14-3-3 and Ions

A study by Rajan et al. (2002) published in *The Journal of Physiology* provides a novel protocol whereby 14-3-3 plays an essential role in the control of membrane localisation of ion channels [15]. Two-pore-domain potassium channels (K_{2P} channels) are a family of potassium channels strongly expressed in the central nervous system and characterized by very complex regulation. TASK-1, TASK-3 and TASK-5 are members of a subfamily of the K_{2P} channels. The defining property of the TASK (Two-pore-domain Acid Sensitive K^+ channel) subfamily is the inhibition of the trans-membrane K^+ currents by extracellular acidification. TASK-1 and TASK-3 are differentially expressed in the central nervous system, with high mRNA levels found in spinal cord motoneurons, in cerebellar granule cells and in neurons of the brain stem. Recently it has been shown that in certain neurons TASK-1 and/or TASK-3 can be inhibited by activation of heptahelical receptors coupled to G proteins of the αq/11 subtype, and it has been suggested that K_{2P} channels are the likely effectors of slow excitatory postsynaptic potentials elicited by activation of metabotropic receptors. Transcripts of TASK-5 were found in olfactory bulb mitral cells and in cerebellar Purkinje cells, but were predominantly associated with central auditory pathways in the brain [19].

K^+ channels control excitability, action potential waveforms and firing patterns of neuronal cells. Each population of neurons expresses a specific set of K^+ channels, resulting in distinct input/output characteristics. The open probability of most K^+ channels can be modulated by neurotransmitters which activate G-protein coupled receptors and mobilise intracellular second messengers. Recently it has been found that the gene expression of different subtypes of K^+ channels may also be subject to regulation, and that the resulting

change in outward current amplitude is associated with profound changes in neuronal function. Furthermore, both the functional properties and the density of channels in the surface membrane can be modulated at the post-transcriptional level by glycosylation and by interaction with β-subunits or anchoring proteins. Variable (possibly phosphorylation dependent) interaction with different isoforms of 14-3-3 may represent a mechanism for regulating the assembly and/or the trafficking of TASK channels to the surface membrane. The resulting variation in K^+ conductance is expected to alter the input/output characteristics of neuronal cells and may thus play a role in the dynamic regulation of information processing in the central nervous system [19].

C. Ions and EEG

1) Volume Conduction

An EEG records the flow of currents flowing through the tissues between an electrical generator and a recording electrode. This is called volume conduction. EEG provides a two-dimensional study of a three-dimensional reality [20].

2) Synaptic Sources of EEG

To visualize and monitor minute (in the microvolt range) cerebral electrical activity, it must be of sufficient duration and sustained strength. To put it facetiously, one has to find a platform on which both the examiner and the examined brain find themselves in the same time-space continuum. Only synaptic activity readily fulfills those criteria and is the most significant source of EEG potentials. Each synapse acts like a battery driving current in a small loop. Both excitatory postsynaptic potentials (EPSPs) and inhibitory postsynaptic potentials (IPSPs) contribute to the synaptic activity recorded as EEG. The summation of extracellular currents is slow enough to be able to generate EEG potentials. The current flowing across the external resistance of the cortex sums with the loop currents of the neighboring neurons to constitute a local mean field. Viewed from outside the cells, membrane areas where current flows in or out of the cells are called sinks and sources. Excitatory currents, involving Na^+ or Ca^{2+} ions, flow inward toward an excitatory synapse and outward away from it. The outward current is referred to as a passive return current (from intracellular to extracellular space). Inhibitory loop currents, involving Cl^- and K^+ ions, flow in the opposite direction. Scalp electrodes record potential differences that are caused by postsynaptic potentials in the cell membrane of cortical neurons. The two scalp electrodes record the difference between the summation of extracellular currents produced by the postsynaptic potentials and the points having the same voltage level [20].

3) Nonsynaptic Contributions to EEG

The nonsynaptic activity is a less significant source of extracellular current flow that produces EEG potentials. Intrinsic neuronal activity, such as fast action potentials, is usually too short to affect EEG. Nonsynaptic intercellular interactions may potentially contribute to EEG [20].

4) Intrinsic Neuronal Sources of EEG

Short-lasting (< 2 μs) high-amplitude individual fast (Na^+) action potentials do not contribute to scalp recorded potentials except during synchronous events – both physiological, such as sleep transients, and pathological, such as epileptic activity. Calcium-mediated action potentials (calcium spikes) are voltage generated and occur synchronously with dendritic EPSPs. They can contribute to the creation of the dendritic field sinks, especially during epileptiform activity [20].

5) Intrinsic Spike Afterhyperpolarization

Intrinsic spike afterhyperpolarization (AHP) following dendritic Ca^{2+} spikes results in suppression of fast spikes and hyperpolarization of the membrane caused by activation of the Ca^{2+}-mediated K^+ conductance. These AHPs are comparable in amplitude and duration to the synaptic events, and as such, may contribute to extracellularly recorded EEG potentials. An example of AHPs may be the generation of delta waves in sleep. In the awake brain, subcortical neurotransmitters, such as acetylcholine, catecholamines and histamine, reduce the calcium-mediated potassium conductance, blocking AHP-related delta waves [20].

6) Nonsynaptic Cellular Interactions

Evoked "ephaptic" effects may change transmembrane potentials creating extracellular current loops that can recruit neurons to fire even with insufficient activation by synaptic inputs. Ultrafast cortical rhythms result from short-lived interactions between interneurons and pyramidal cells that may produce a short-lived oscillatory field potential (ripple) in both the hippocampus and neocortex. Although not recorded by standard EEG equipment, they may be diagnostically significant harbingers of seizure onset and offset [20].

D. Summary

The Aristotelian core logic approach of the study is depicted in Fig. 2. From the aforementioned literature review, the associations between cancer and 14-3-3, 14-3-3 and ion channels and ion channels and EEG become obvious. These associations provide the foundation upon which an association between cancer and EEG can be hypothesised. This hypothesis shall be proven for endometrial cancer.

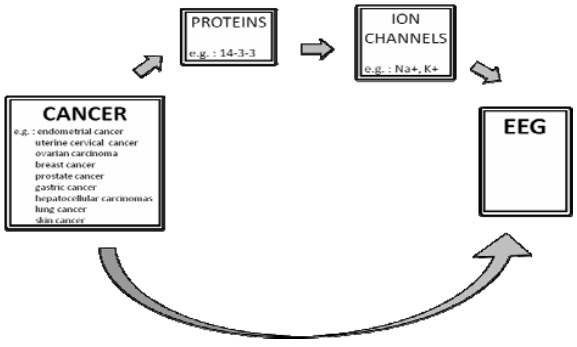

Fig. 2 Possible correlation between cancer and EEG

IV. Planning of the Experimental Part of the Study

This section is divided into three main phases (Fig. 1). The **first phase** includes network set up and software design (deployment and configuration, data flow design, database development), the **second phase** includes data acquisition and data analysis (hysteroscopy image data, analysis of biopsy samples of 14-3-3, patient selection criteria, EEG procedure) and the **third phase** includes evaluating findings (clinical and statistical evaluation) and development of the ontology.

A. Network Set Up and Software Design

Network set up and software design will constitute the first phase of this study. In this phase, the whole research team will cooperate in order to accomplish the following steps:

- **Deployment and configuration** of the equipment of the host and participating institutions. (For more information see the Resources section.)
- **Data flow design** will begin in the initial phase of the study and continue until the final phase with the evaluation of findings. Import portals and information processing positions will be defined in the various workshops. (For more information see the Resources section.)
- **Database development** will involve developing a database for storing the study's data and identifying the types of management applications to be used in the points of data entry and findings processing. Implementation of the database will be accomplished by the system and network administrators and will take into account the flexibility required for the experimental period.

B. Data Acquisition and Analysis

1) Hysteroscopy Image Data

In this phase, the "primary information" (the data received when a patient is subject to a hysteroscopy procedure) will be recorded in the database. At this point, it must be stated that the hysteroscopy images, which will be acquired in very high resolution by a hysteroscope, are critical and may contain embedded metadata from various semantic medical systems, such as DICOM. The technical characteristics of this instrument offer stability in image acquisition (focal length, angle-making, etc.), and create significant opportunities for digital image comparison. The captured images are automatically processed in a special digital analysis form, based on algorithms developed using concepts established in studies that focused on searching for morphological characteristics of medical interest (deformities, cancers, etc.) [21]. The medical staff of the laboratory will be able to record any medical comments deemed to have research interest while the research moves forward, and will automatically embed their comments as private metadata within the image. All cases will be divided into three main categories: 'normal endometrium', 'endometrial hyperplasia' and 'endometrial cancer'.

This phase can be described as the cornerstone of this research, due to the fact that all data are recorded in the system and the basic registration information portal will be used in subsequent phases. Finally, the medical image analysis, the EEG signal analysis, as well as the clinical evaluation (for the creation of the ontological approach of the research program) will be correlated.

2) Analysis of Biopsy Samples for 14-3-3

Quantification and characterisation of the 14-3-3 protein expression will be carried out using three different kinds of tissues (normal-cycling endometrium, endometrial hyperplasia and endometrial cancer). Immunohistochemical analysis will be used to examine 14-3-3 protein levels in each kind of tissue. Tissue samples obtained from patients during a hysteroscopy procedure will be immediately placed in formalin fixative in the operating theater and embedded in paraffin. Immunohistochemical analysis will be done employing the streptavidin-biotin amplification method using a Histofine kit. Polyclonal antibodies for 14-3-3 will be purchased from Santa Cruz Biotechnology, Inc. Moreover, this step will involve the colligation of 14-3-3 protein levels with a pH or temperature of cancer tissues with normal tissues [22]. Changes in the expression of 14-3-3 will be studied in relation to the different EEG and finally a statistical analysis will be carried out.

3) Patient Selection Criteria

The selection of patients via the EEG procedure will need to conform to a specific protocol with inclusive and exclusive criteria. For instance, a certain spectrum of drugs and mental disorders might affect the brain's electrical activity, and therefore the reliability of an EEG. Other criteria stem from the bioethical field and will be considered so as to ensure the confidentiality of a patient's sensitive personal data. In addition, the creation of two forms is required: a patient's history form and a questionnaire for the diagnosis of depression among cancer patients. Depression is a relatively common but regrettably under-diagnosed condition among cancer patients. Thus, comprehensive care should encompass not only a good understanding of the physical domains of patient care, but attentiveness to the psychological, spiritual and existential concerns of patients facing malignant illnesses [23]. It is known that prefrontal cortex (PFC) EEG alpha asymmetry has been found in individuals with major depression and studies indicate that specific symptoms of depression are uniquely associated with patterns of PFC EEG alpha activity [24]. However, EEG activity has never been examined with regard to specific depressive symptoms. Cancer is a serious illness that affects a large number of women, and as with other serious illnesses, such as HIV, the disease can be accompanied by depression from the initial diagnosis through treatment and to the end of life. Depression can affect the mind, body and behaviour of a patient. Depression can exist before the diagnosis of cancer or may develop after the cancer is identified. Even if there is no evidence to support a causal role for depression in cancer, depressive symptoms not only impair quality of life for cancer patients, but constitute an independent risk factor for

increased mortality. In this proposed research study, undertaking the investigation of a possible relationship between cancer and EEG, depression cannot be avoided. Thus, in order to accurately and efficiently identify depression in cancer patients, we propose to use the 21-item, observer-rated Hamilton rating scale for depression (Ham-D) that will optimise the diagnosis of depression among cancer patients. This questionnaire is a valid, accurate instrument for the diagnosis of major depression in cancer populations [25].

4) EEG Procedure

All individuals participating in the study belonging to either the "normal endometrium" category, the "endometrial hyperplasia" category or the "endometrial cancer" category shall undergo EEG and hysteroscopy at the same time. The recording of the EEGs will be based on the 10-20 international system of electrode placement using at least 16 channels and a sampling frequency higher than 256Hz. Furthermore, in the processing stage, each EEG will be submitted to parametric and non-parametric processes with linear and non-linear approaches. These processes will be carried out in the specific spectral segments of each EEG covering a frequency band of 1-64 Hz, where the basic rhythms of the EEG will be investigated exhaustively. The aim of this procedure will be to extract semantic features suitable to classify the EEGs successfully into the three aforementioned categories. Various types of neural networks, such as LVQ, RBF and other supervised and unsupervised expert classification systems will be tested as potential classification systems for this task. In this phase, the experiment will be implemented using successfully tested EEG signal processing and classification methods, which are based on our previous studies [26], [27].

C. Evaluation of Findings

1) Clinical and Statistical Evaluation

The study's participants will be divided into five categories:

- The control group with normal cycling endometrium.
- Patients with endometrial hyperplasia (low-grade, high-grade).
- Patients at high risk of developing endometrial cancer due to other medical conditions (e.g., diabetes, obesity, etc.).
- Patients undergoing tamoxifen therapy for breast cancer (tamoxifen has been found to increase the risk of endometrial cancer [28], [29]).
- Patients with endometrial cancer (histologically diagnosed).

In this research, all participants shall undergo an initial hysteroscopy (Gynecology Department, University Hospital of Ioannina). The individuals belonging to any of the above categories (should they meet the specified criteria) shall also undergo EEG (Neurology Department, University Hospital of Ioannina). The EEG findings corresponding to the 'endometrial hyperplasia' and 'endometrial cancer' categories shall be compared against those of the "normal endometrium" category in order to detect possible alterations in the EEGs of both pathological categories.

The indications obtained from hysteroscopy shall then be evaluated against the results of the EEGs. Alterations detected in the EEGs of individuals belonging to the "hyperplasia" and "cancer" categories (as compared to EEGs of participants in the normal category) shall be the first targeted findings. Such findings will trigger the investigation of the dependency of the alterations on the type of endometrial hyperplasia and/or stage of endometrial cancer. All findings that result from this procedure shall be processed through a statistical model in order to eventually evaluate the validity of the study's hypothesis.

2) Development of the Ontology

The implementation of the methodology will be completed with the creation of an ontology. An ontology is defined as a formal and explicit specification of a shared conceptualization [30]. In other words, it is a shared understanding of some domain interest, which is often realised as a set of classes (concepts), relations, functions, axioms and instances. Ontologies try to capture the semantics of domain expertise by deploying knowledge representation primitives enabling a machine to understand the relationships between concepts in a domain [31]. They are complex knowledge representation artifacts intended for the development of intelligent applications and also social constructions for communication and crystallisation of domain-specific knowledge [32].

In recent years, ontologies have moved from the artificial intelligence (AI) research community into real-word applications in a number of domains. In many disciplines, standardised ontologies have been developed, so that domain experts can use them to share and annotate information in their fields. In the field of medicine, ontologies are becoming increasingly important, since they enable knowledge sharing in a formal, homogeneous and unambiguous way. Knowledge, in a rapidly growing field such as biomedicine, is usually evolving; therefore, an ontology maintenance process is required to keep ontological knowledge up to date.

The ultimate goal of this research is to build a formally defined ontology based on information (data and metadata) stored in a database, such as medical images obtained through hysteroscopy and EEG procedures and clinical evaluations of testing results, which will define the concepts existing in this research domain. Moreover, the relationships between them will be established (e.g., relationships between hysteroscopy and EEG findings) and maintained exploiting machine learning techniques and domain specific corpora, and evaluated using a well-defined experimental setting. The innovation will be to make diagnoses using the knowledge represented by the ontology. All levels of this decision-making process will be based on a set of rules that will determine the way that a decision is made and will be applied on existing knowledge represented by the ontology. Finally, this ontology shall be published on the web.

V. Concluding Remarks

We propose to investigate the possibility that there exists a correlation between EEG and endometrial cancer, with the

prospect that EEG can be used as a tool to assist endometrial cancer diagnosis. For this purpose, our research will be divided into three critical phases:

- Network set up and software design will be achieved in the first step of the proposed study. The basis of this step will be the deployment and configuration of the equipment and software that will be used, as well as the networking of these components.
- Data acquisition and data analysis will be accomplished in the second phase, which will include the collection of all necessary data, such as images obtained through hysteroscopy and EEG procedures, the results of analyses of biopsy samples for 14-3-3 protein, and patient selection criteria. In addition, a database will be created, which will store all the data.
- Finally, the evaluation of the findings phase will involve the clinical and statistical evaluation of hysteroscopy and EEG testing results. Moreover, this phase will involve the creation and development of the ontology, which will represent research findings, thus providing not only semantic understanding of this research, but a significant and powerful tool for the diagnosis of endometrial cancer.

VI. Future Plans

It is anticipated that this research program will lead to future work in the following areas:

- The correlation of the quality and quantity of 14-3-3 proteins of cancer tissues with the 14-3-3 protein levels of the brain, which are associated with EEG.
- By using EEG as an 'eye' to see and identify the primary steps of cancer, functionalised nanomaterials (e.g. dendrimers, nanotubes) or chemical substances with pharmaceutical action can be provided in areas showing encephalic disorders to indirectly control and decrease the proliferation of cancer cells, thereby creating a 'self-remedy' mechanism [33], [34], [35].

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