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Συσχέτιση βιοδεικτών, παθοφυσιολογικών παραγόντων και συμπτωμάτων της Νόσου Alzheimer με χρήση Bayesian μοντελοποίησης

Bayesian model for biomarkers' and pathophysiological factors' correlation in Alzheimer's disease

Βασίλειος Δ. Μαντζαβίνος

ΠΤΥΧΙΑΚΗ ΕΡΓΑΣΙΑ

Επιβλέποτες
Αθανάσιος Αλεξίου
Παντελέημων Μπάγκος

Λαμία, 2016

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Με ατομική μου ευθύνη και γνωρίζοντας τις κυρώσεις [(1)], που προβλέπονται από της διατάξεις της παρ. 6 του άρθρου 22 του Ν. 1599/1986, δηλώνω ότι:

1. *Δεν παραθέτω κομμάτια βιβλίων ή άρθρων ή εργασιών άλλων αυτολεξεί* ***χωρίς να τα περικλείω σε εισαγωγικά*** *και χωρίς να αναφέρω το συγγραφέα, τη χρονολογία, τη σελίδα. Η αυτολεξεί παράθεση χωρίς εισαγωγικά χωρίς αναφορά στην πηγή, είναι λογοκλοπή. Πέραν της αυτολεξεί παράθεσης, λογοκλοπή θεωρείται και η παράφραση εδαφίων από έργα άλλων, συμπεριλαμβανομένων και έργων συμφοιτητών μου, καθώς και η παράθεση στοιχείων που άλλοι συνέλεξαν ή επεξεργάσθηκαν, χωρίς αναφορά στην πηγή. Αναφέρω πάντοτε με πληρότητα την πηγή κάτω από τον πίνακα ή σχέδιο, όπως στα παραθέματα.*

2. *Δέχομαι ότι η αυτολεξεί* ***παράθεση χωρίς εισαγωγικά****, ακόμα κι αν συνοδεύεται από αναφορά στην πηγή σε κάποιο άλλο σημείο του κειμένου ή στο τέλος του, είναι αντιγραφή. Η αναφορά στην πηγή στο τέλος π.χ. μιας παραγράφου ή μιας σελίδας, δεν δικαιολογεί συρραφή εδαφίων έργου άλλου συγγραφέα, έστω και παραφρασμένων, και παρουσίασή τους ως δική μου εργασία.*

3. *Δέχομαι ότι υπάρχει επίσης περιορισμός στο μέγεθος και στη συχνότητα των παραθεμάτων που μπορώ να εντάξω στην εργασία μου εντός εισαγωγικών. Κάθε μεγάλο παράθεμα (π.χ. σε πίνακα ή πλαίσιο, κλπ), προϋποθέτει ειδικές ρυθμίσεις, και όταν δημοσιεύεται προϋποθέτει την άδεια του συγγραφέα ή του εκδότη. Το ίδιο και οι πίνακες και τα σχέδια*

4. Δέχομαι όλες τις συνέπειες σε περίπτωση λογοκλοπής ή αντιγραφής.

Ημερομηνία 04/03/2016

Ο Δηλών

(Υπογραφή)

(1) «Όποιος εν γνώσει του δηλώνει ψευδή γεγονότα ή αρνείται ή αποκρύπτει τα αληθινά με έγγραφη υπεύθυνη δήλωση του άρθρου 8 παρ. 4 Ν. 1599/1986 τιμωρείται με φυλάκιση τουλάχιστον τριών μηνών. Εάν ο υπαίτιος αυτών των πράξεων σκόπευε να προσπορίσει στον εαυτόν του ή σε άλλον περιουσιακό όφελος βλάπτοντας τρίτον ή σκόπευε να βλάψει άλλον, τιμωρείται με κάθειρξη μέχρι 10 ετών.

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Μπάγκος Παντελεήμων

Τριανταφύλλου Ιωάννης

Summary in Greek

Η παρούσα εργασία αποτελεί μια προσπάθεια σύνδεσης των βασικών παραγόντων που προκαλούν τη νόσο του Alzheimer και της μη Κλασσικής ή Μπεϋζιανής Στατιστικής και Συμπερασματολογίας. Σύμφωνα με τη διεθνή βιβλιογραφία, έχουν ήδη συσχετισθεί με τη νόσο βιοδείκτες όπως οι πρωτείνες Tau και Amyloid βeta, η APOE-4 κ.α. που υποδεικνύουν την παθολογία του Alzheimer. Λαμβάνοντας υπόψη το ρόλο των δεικτών αυτών στην αναγνώριση των συμπτωμάτων της νόσου, δημιουργήθηκε ένα πιθανοθεωρητικό μοντέλο για την αναπαράσταση και συσχέτιση των βασικών κατηγοριών της νόσου Alzheimer με τη χρήση κατηγορικών κατανομών το οποίο προγραμματίστηκε στο Βιοστατιστικό λογισμικό Winbugs. Αν και η διάγνωση της νόσου θεωρείται ακόμη δύσκολη και περίπλοκη, συγκεντρώνοντας τα μέχρι τώρα διεθνώς αποδεκτά δεδομένα για την ανάπτυξη και εξέλιξη της νόσου, δημιουργήθηκε ένα 'Στατιστικό Ευφυές Σύστημα' που υπολογίζει την πιθανότητα παρουσίας τη νόσου στην περίπτωση που ένας ή περισσότερες βιοδείκτες έχουν διαγνωσθεί μη φυσιολογικοί. Παράλληλα δημιουργήθηκε μια πολύ απλή και φιλική ιστοσελίδα που θα μπορεί να δέχεται ανώνυμα δεδομένα για την μη αυτόματη εξαγωγή αποτελεσμάτων από τυχαίους χρήστες.

1. Introduction

Alzheimer's disease (AD) is referred as one of the most common cause of dementia and frailty [1]. Typically, the symptoms of the disease begin with mild memory difficulties and evolve towards cognitive impairment, dysfunctions in complex daily activities, and several other aspects of cognition [1]. By the time that AD is clinical diagnosed, neuronal loss and neuropathologic lesions occur in many brain regions [2]. Crucial role for the suspension of the potential damages is the timely drug delivery of neuroprotective medications before AD turn into mildly symptomatic [2].

To approach this goal, our capability to identify individuals with very mild symptoms prior to dementia needs to be improved [3]. A few diagnostic criteria concerning imaging techniques and cerebrospinal fluid biomarkers have been already published in order to establish a multivariate classification for AD [4]. With the pessimistic

projection of AD population and its corresponding social cost in the years between 2030 and 2050, the scientific and clinical research in the area of AD is nowadays directed to the early diagnosis of the transitional phase between normal aging, mild cognitive impairment (MCI) and dementia [4]. Lately, the concept of MCI has been expanded to address observed clinical heterogeneity. Two subtypes are recognized, amnesic and non-amnesic, with the later including deficits in executive functioning such as attention, planning, problem-solving, multitasking, monitoring and behavioral control, impaired mental flexibility, increased distractibility and difficulty in learning novel tasks. While amnesic syndromes are the most common symptoms of AD early onset, researchers are particularly focused on the analysis of the medial temporal lobe memory system [5]. When patients are diagnosed with AD dementia, memory impairments appear to be significantly correlated with medial temporal lobe atrophy and hypoactivation [5]. Mitochondrial electrophysiology or electrodermal activity skin conductance analysis may be particularly useful for detecting alterations in brain function that may be present very early in the progression of AD, possibly a long time before the development of clinical symptoms and even significant neuropathology [6-7].

According to the latest National Institute on Aging and Alzheimer's Association workgroup, an accurate diagnosis can be based on the general clinical and pathophysiological conditions and the assessment of several in vivo biomarkers and memory tests (Figure 1). Albert et al. proposed a classification of 8 categories for AD: Prodromal AD, AD dementia, Typical AD, Atypical AD, Mixed AD, Preclinical States of AD, Alzheimer's Pathology and MCI [8]. The term Prodromal AD or Predementia Stage of AD is used for early symptomatic, predementia stage of AD where clinical symptoms such as episodic memory loss of the hippocampal type are visible, but do not affect the daily life activities and do not support dementia diagnosis. Also, in this stage the biomarkers existence from Cerebrospinal fluid (CSF) or imaging can proof AD pathology. In the case of AD dementia, several serious cognitive symptoms are present among with social functioning and instrumental activities of daily living consequences. The last state would be considered as a threshold between the episodic memory modifications and in another at least cognitive domain. Also, meaningful dementia threshold would be clinical trials or social/economic evaluations. The third category is called Typical AD and includes the most common clinical phenotype of AD. This phenotype characterized by early and progressive episodic memory deficit that dominates in the following stages of the disease and coexists with other cognitive disorders (executive dysfunction, language, praxis, and complex visual processing impairments). An incident integrates into this category if there is one or more in-vivo positive biomarker of AD pathology. The case of Atypical AD characterizes certain clinical phenotype of Alzheimer's pathology. Such incidents include primary progressive non-fluent aphasia, logopenic aphasia, frontal variant of AD, and posterior cortical atrophy. Also, strong in vivo evidence of amyloidosis in the brain or the CSF and one of the above clinical stages, it is certain the diagnosis of AD. The fifth category is called Mixed AD and refers to patients who fulfill the diagnostic criteria for Typical AD and present clinical and brain

imaging/biological evidence with other diseases which have a similar pattern with AD, such as cerebrovascular or Lewy Bodies diseases. The Preclinical States of AD is divided into two subcategories. This case consists of an asymptomatic period between the early pathogenic events such brain lesions of AD and the very first appearance of specific cognitive modifications. The first subcategory is characterized as Asymptomatic at-risk state for AD, where brain amyloidosis or amyloidosis in the CSF is the primary evidence. The second subcategory is called Presymptomatic AD, where patients are going to be evolved into AD. It referred that this state mainly appears in families that are carriers of a rare autosomal dominant monogenic AD mutation. Alzheimer's Pathology covers the very first pathogenic events in the brain such as synaptic loss, and vascular amyloid deposits. This term is used regardless of the clinical view. Finally, the last category contains incidents with measurable MCI. This state describes the case where there is no evidence for disease. It is a term of exclusion for individuals who have memory symptoms that do not match with AD pattern or have negative biomarkers of AD pathology [8].

This thesis aims to highlight the significance of several potential biomarkers of AD and their correlation with the attempt of an accurate diagnosis or even more an early prognosis. The proposed diagnostic model covers a broad range of AD biomarkers such as genetic mutations, hereditary risk factors, MCI and other comorbidities, referring both to the cases of sporadic and familial AD. At this direction, Bayesian Statistics constitutes an impressive tool for science and especially for Biomedical Informatics and Medical Decision Systems. Bayesian theory is based in probability theory and for several years many supporters of the Classical approach are opposed to the Bayesian one, due to the weak approach of prior distributions through the quantitative data analysis. Several times Markov Chain Monte Carlo (MCMC) theory was provided as a solution for this problem, for environmental or disease calculations with satisfactory results [9]. Bayesian statistics uses all the unknown parameters as random variables, in order to pre-define the prior distribution of the model and calculate the posterior distribution $f(\theta|y)$. The posterior distribution can be expressed as

$$f(\theta|y) = \frac{f(y|\theta)f(\theta)}{f(y)} \propto f(y|\theta)f(\theta), \quad (1)$$

including both the prior and the observed data by the expression of the prior distribution $f(\theta)$ and the likelihood $f(y|\theta)$ as follows:

$$f(y|\theta) = \prod_{i=1}^{n} f(y_i|\theta). \quad (2)$$

In this thesis Bayesian tools were used to create a probabilistic model describing the relationship between AD biomarkers, which may reveal and influence the disease's development, presence or progression. The algorithmic approach of AD prediction was coded with the WINBUGS biostatistics software [10] for Bayesian inference, data analysis and modeling. The model, the initial data and few examples are analytically described below.

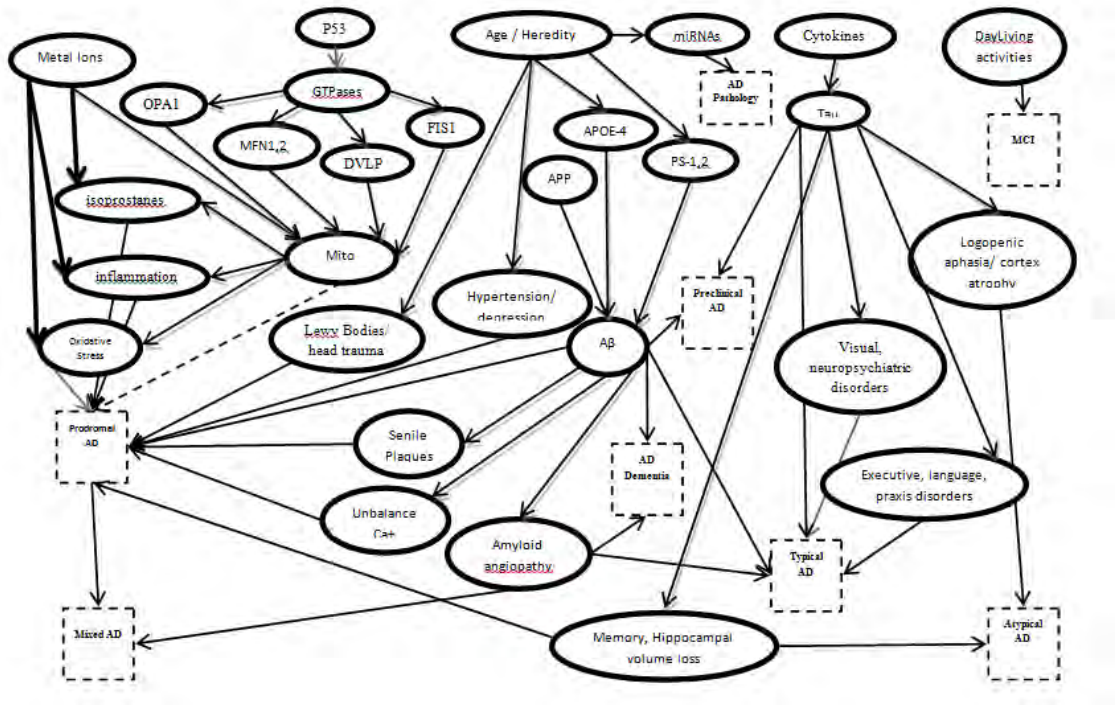

Figure 1: Biomarkers/nodes that reveal Alzheimer's disease presence, linked to the several Alzheimer's categories.

2. Biomarkers

When a patient presents visuospatial deficit and significant atrophy in the parietooccipital region on Magnetic Resonance Imaging (MRI), we can easily conclude to neurodegeneration, leading to posterior cortical atrophy or optical dysfunction of AD. Typically symptoms can be mentioned such as logopenia, aphasia, frontal form of AD, language, praxis and complicated visual process and neuropsychiatric changes in everyday activities [11-12]. Furthermore, patients with dementia and hemiparkinsonism have similar characteristics with AD pathology. However the coexistence of these two diseases it is rare while the one condition will prevail against the other [13-14].

At the same time biomarkers that reveal high probability of AD due to MCI could be more accurate if Amyloid-β (Aβ) and neuronal injury biomarkers were also positive tested. Exclusively the Aβ protein assessment can give us only an intermediary probability for developing AD due to MCI. In the case where only one biomarker of neurologic damage exists and Aβ cannot be measured, then these patients will be assumed with a lower probability to develop AD.

In another study related to age and the way that age influent the aggravation of AD, the density of the pathological lesions are mentioned about the age of the subject [15-16]. Moreover, the age marker exists as a primate factor in several studies [8, 17-18]. In conjunction with the above, AD can be also divided into early onset familial AD where the disease is mainly developed before the age of 60 years. In this case, the appearance of AD reveals a hereditary disease and is inherited an autosomal dominant manner [11, 19-20].

Alzheimer's disease is mainly characterized by the Aβ protein pathology that founded in amyloid precursor protein gene (APP, 21q21), of the long arm of chromosome 21 [20]. Aβ deposits lead to plaques creation, the amyloid fibrils accumulated in the cell's outer space and grouped into globe shape. Amyloid-β can also be deposit in media and adventitia of small and mid-sized arteries, in which case we refer to Cerebral Amyloid Angiopathy [21-22]. Besides, Aβ can be detected and quantified in CSF and plasma with Positron Emission Tomography scanning method, detecting fibrillar Aβ, while both techniques can detect neurological injury [23]. Few individuals with DS mutation due to trisomy 21, show high levels of Aβ and present the classic pathology by the age of 50 [20]. Another biomarker of neuronal injury is tau/phosphorylated tau protein. When the two biomarkers Aβ and tau/phosphorylated tau proteins are positively measured, the probability of AD development increases [11, 24]. Both Aβ and phosphorylated tau are conventional biomarkers for other disorders as well and can be detected in vivo or in vitro. In vitro Scanning Tunneling Microscopy detects Ab (1-42) and two Photon Rayleigh Scattering Assay technique can be also used for tau detection. In vivo with mMRI and Optical (Fluorescent) Imaging, we can detect Ab plaques [25].

Moreover, biomarkers of neurological injury are considered the hippocampal volume or medial temporal lobe atrophy in MRI, the temporoparietal/precuneus hypometabolism or the hypoperfusion on Positron Emission Tomography scanning method or single-photon emission computerized tomography [11]. In a recent study, increased levels of Aβ and abnormal tau were detected in neocortical regions [26-27], and the left precuneus, the superior temporal gyrus, and the fusiform gyrus have also observed with a decreased volume on MRI studies [28]. Family and population studies prove that individuals have increased the probability to develop AD with the fourth form of ApolipoproteinE gene of chromosome 14, while types 2 and 3 of this gene do not affect their carriers. Ages between 65 and 75 are also at high risk to develop AD [13,29-30]. In many recent studies, the CSF a-synuclein has been identified in samples of patients with AD or Parkinson's disease and is possibly correlated to other biochemical biomarkers [14,31.

Lately, scientists are also focused on mitochondrial function. The mitochondrion is a subcellular organelle that is responsible for ATP production and since neurons require high energy, low ATP levels signify cell's death. Mitochondrial fusion and fission occur continuously but in chaotic distributions and mutations in proteins that mediate their processes can cause irreparable loss. There are a few proteins that are involved in mitochondrial dynamics like the Optic Atrophy-1, the Dynamin-Related Protein-1 (DLP-1), the Mitochondrial Fission 1, the Mitofusin-1 and Mitofusin-2 [32]. Optic Atrophy-1 is founded in membrane's inner-space and mediate in fusion process of the inner mitochondrial membrane while DLP-1 is founded in mitochondrial membrane's interface to mediating during fission process. Dynamin Related Protein-1 is believed that concentrates long oligomers which use Guanosine Triphosphate hydrolysis to constrict mitochondrial tubules during fission process. Mitochondrial Fission 1 is an outer-membrane protein function with DLP-1 during the fission process. Mitofusin-1 and Mitofusin-2 belong to GTPases family, can be found in the outer membrane space

and mediate during the fusion process. Mitofusin-1 and Mitofusin-2 are also responsible for mitochondrial lashing [25,32]. Furthermore, mutations in Presenilin-1 and Presenilin-2 proteins, lead to AD expression. These two proteins encode amyloid precursor protein, and in the presence of Presenilin-1,2 mutations individuals have high probability to develop AD. Presenilin-1,2 mutations affect γ-secratase activity, which is responsible for disruption of amyloid precursor protein and Aβ cytotoxic accumulation [21,30-34]. Moreover mitochondrial phenotype present fragment, cristae structures are devastated, the number of mitochondria in dendrites is decreased, the mobility of mitochondria is decreased, and the KGDH-PDH-COX complexes present dysfunctions due to these proteins dysfunction. Additionally Aβ concentration interacts with DLP-1, Cyclin-Dependent Kinase 1 activity increases and Kinesin protein interacts with mitochondria in the cerebral cortex [18-21]. Individuals who inherit Presenilin-1,2 mutations present AD characteristics earlier than the age of 40-45. Families with these mutations present AD heredity which attends the autosomal dominant pattern with 50% probability for each generation to develop AD [13,35-36]. These mutations lead to plaque creation, tangles, cell loss and dementia. However the percentage of AD patients due to genetic mutations are less than 2% of the total AD population [13]. Education is referred as a controversial marker while individuals with high educational level have fewer probabilities to develop AD; the reason could be a network of highly stable neuronal synapses in their brain. Important AD risk factors are the metal ions, which can affect negatively the AD development. In any case that proteins and lipid membranes with toxic effect are affected, the main result is reactive oxygen species production or even more the presence of metalloprotein Aβ amyloid peptide. Zinc and Copper are released from brain's cortical neurons and cause Aβ accumulation and Aβ deposits, through histidine amino acid interactions. Additionally, Fe^{2+} and Cu^{2+} interactions with Aβ, lead to H2O2 production, H^2O^2 is partially responsible for the oxidative action. Also, Zn^{2+} and Cu^{2++} enhance Aβ interactions with cell's membranes, increasing Aβ toxicity. Furthermore Fe^{3+} and Cu^{2+} interacts with Aβ protein leading to oxidative stress, Aβ oligomerization lead to Calcium channels creation, these channels affect calcium homeostasis causing oxidative stress [25,37-38].

The p53 protein contributes to disease development, and specifically the unfolded p53 conformation leads to cell's death. Aβ peptides interact with HIPK-2 protein degradation affecting p53 conformation. Proteins p53 and tau are also related and founded in patients with AD. p53 induces phosphorylation of human 2N4R tau causing neuronal death and other tauopathies [39-41]. In a similar study BRCA1 and p53 accumulations have been detected in neurons at early AD onset [42]. Even if it has been reported in a few studies, gender seems to have been abandoned as a potential AD marker, due to women longer life expectancy. Also nationality does not appear to be a significant factor, however, certain people of the Asiatic origin appear to be differentiated [15]. Additionaly a new protein is under consideration, the YKL-40, which initially is characterized as brain cell injury biomarker, while it is increasingly detected in AD individuals between 50's and 70's years old [16]. D-serine levels have been identified and measured in higher levels in the hippocampus

and parietal cortex of AD patients and incriminated as a potential risk factor [43]. Four miRNAs, the miR-31, miR-93, miR-143, and miR-146a are observed to be decreased in AD patient's serum, therefore, are recently characterized as novel biomarkers of AD pathology and vascular dementia [44]. Blood pressure has been formulated as precursor marker for disease manifestation. Decades before the appearance of disease, high blood pressure can be observed when senile plaques, neurofibrillary tangles, and hippocampal atrophy are already present [45]. Also, it has been declared that the age and the blood pressure are related in AD development. As mentioned above high blood pressure revealed decades before AD diagnosis, however in later life of an AD patient low levels of blood pressure occur. Unfortunately, the way that blood pressure affects AD is still unknown, even though high blood pressure seems to be a lower risk factor for AD patients [46-48].

3. A Probabilistic Approach of Alzheimer's Disease

Let us recall some basic mathematical notations concerning the Bayesian approach [9,49-51]. Assume a random variable Y called response, which follows a probabilistic path f(y|θ), where θ is a parameter vector. We consider a sample y=[y1, y2,….,yn] of size n. If we assume two possible events A, B where A = A1∪A2∪….∪An, Ai ∩ Aj = ∅ ∀ i ≠j, Bayes Theorem calculates the probability to occur an event Ai given B,

$$(\mathrm{Ai}|\mathrm{B}) = \frac{\mathrm{P}(\mathrm{B}|\mathrm{Ai})\mathrm{P}(\mathrm{Ai})}{\mathrm{P}(\mathrm{B})} = \frac{\mathrm{P}(\mathrm{B}|\mathrm{Ai})\mathrm{P}(\mathrm{Ai})}{\sum_{\mathrm{i}=1}^{\mathrm{n}} \mathrm{P}(\mathrm{B}|\mathrm{Ai})\mathrm{P}(\mathrm{Ai})}. \quad (3)$$

In general,

$$\mathrm{P}(\mathrm{A}|\mathrm{B}) = \frac{\mathrm{P}(\mathrm{B}|\mathrm{A})\mathrm{P}(\mathrm{A})}{\mathrm{P}(\mathrm{B})} \propto \mathrm{P}(\mathrm{B}|\mathrm{A})\mathrm{P}(\mathrm{A}). \quad (4)$$

Finally given the observed data y1,y2,…,yn the posterior distribution is calculated f(θ|y1,…,yn) from the prior distribution [51]. Bayesian Inference is based in the p(θ|y) factor which is used from MCMC methods. Markov Chain Monte Carlo methods are based on iterative sampling from the posterior distribution, using multiple chain probabilities of the sample parameters and resulting posterior means and variances of the parameters or functions of the parameters Δ = Δ(θ) as follows:

$$\mathrm{E}(\theta_{\mathrm{k}}|\mathrm{y}) = \int \theta_{\mathrm{k}} \mathrm{p}(\theta|\mathrm{y}) \mathrm{d}\theta, \quad (5)$$

$$\mathrm{Var}(\theta_{\mathrm{k}}|\mathrm{y}) = \int \theta_{\mathrm{k}}^2 \mathrm{p}(\theta|\mathrm{y}) \mathrm{d}\theta - [\mathrm{E}(\theta_{\mathrm{k}}|\mathrm{y})]2 = \mathrm{E}\left(\theta_{\mathrm{k}}^2|\mathrm{y}\right) - [\mathrm{E}(\theta_{\mathrm{k}}|\mathrm{y})]^2, \quad (6)$$

$$\mathrm{E}[\Delta(\theta)|\mathrm{y}] = \int \Delta(\theta) \mathrm{p}(\theta|\mathrm{y}) \mathrm{d}\theta, \quad (7)$$

$$\mathrm{Var}[\Delta(\theta)|\mathrm{y}] = \int \Delta^2 \, \mathrm{p}(\theta|\mathrm{y}) \mathrm{d}\theta - [\mathrm{E}(\Delta|\mathrm{y})]^2 = \mathrm{E}\left(\Delta^2|\mathrm{y}\right) - [\mathrm{E}(\Delta|\mathrm{y})]^2. \quad (8)$$

The most famous MCMC methods are the Metropolis-Hastings algorithm [52-54] and its special case the Gibbs Sampling [55]. In its general case the Metropolis-Hastings algorithm can be summarized in the following iterative steps [51], where vector x(t) contains the generated values in each t iteration of the algorithm:

1. *Set initial values* $x^{(0)}$.
2. *For* $t = 1,\ldots,T$ *repeat the following steps:*
   a) *Set* $x = x^{(t-1)}$

b) Generate new candidate values x' from a proposal distribution

$q(x \to x') = q(x'|x)$

c) Calculate $a = min\left(1, \frac{f(x')q(x|x')}{f(x)q(x|x')}\right)$

d) Update $x^{(t)} = x'$ *with probability a and* $x^{(t)} = x = x^{(t-1)}$ *with probability 1-a.*

In 1988, Lauritzen and Spiegelhalter presented for the first time a Bayesian expert system the well-known 'ASIA model', introducing a fictitious medical decision system for the explanation of dyspnea due to a patient's recent visit to Asia and the presence of several other symptoms [56]. The proposed AD prediction model was established based on the Bayesian Networks (BN). According to BN theory, if we assume a directed graph G with N nodes, each node n ∈ N has a number of paternal nodes pa(n), it may be linked with 'child' nodes and the joint distribution for such a network is given as follows:

$P(N) = \prod_{n \in N} p(n|pa(n))$. (9)

By taken into consideration the latest calculations for the relative probabilities of AD progression due to certain brain lesions (Table 2) [57-70], we designed a Bayesian model for the prediction of AD presence in relation to one or more biomarkers abnormal testing. The proposed model includes the main AD categories formulated by the categorical prior distribution

r~dcat(p[]) (10),

and all the known and accepted biomarkers that underlies AD severity. The corresponding graph is acyclic (figure 2), the AD categories are correlated using initial data true/false or the published probabilities based on Table 2 and in several cases a single biomarker can be related to more than one AD types.

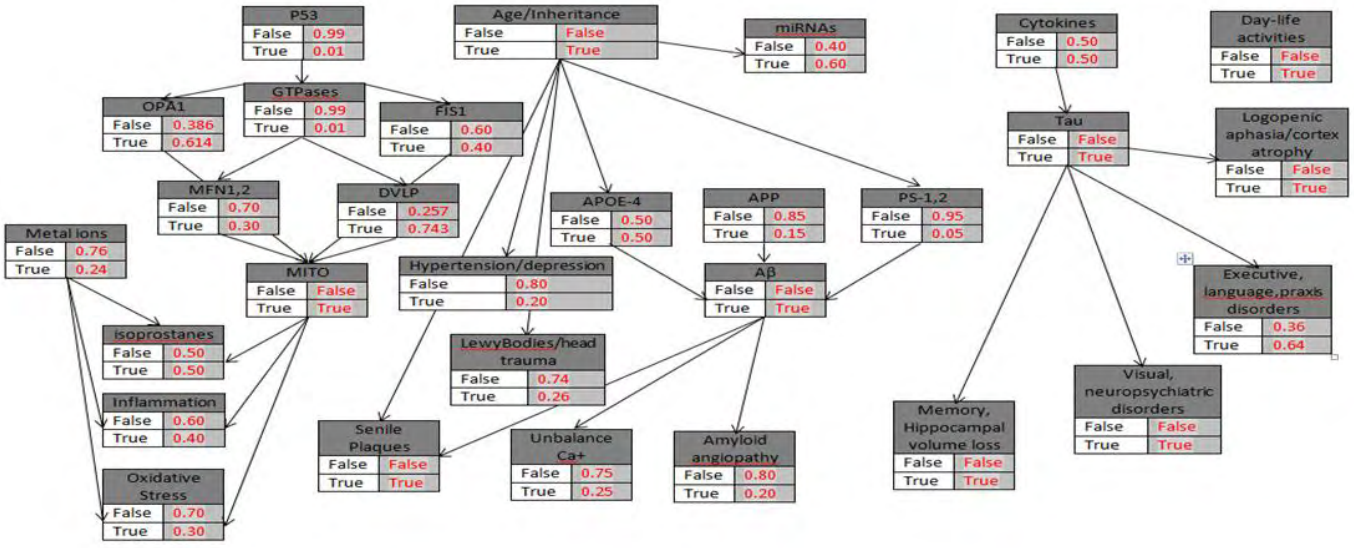

Figure 2. The general probabilistic model of Alzheimer's disease according to Bayesian Theory importing the Alzheimer's disease knowledge of probabilities.

Biomarker	Relevant Probability affecting AD progression	Reference
Age (>85)	38%	Alzheimer's Association Alzheimer's Disease Facts and Figures Alzheimer's & Dementia 2015 11(3):1-88 (2015)
Age (75-84)	43%	Alzheimer's Association Alzheimer's Disease Facts and Figures Alzheimer's & Dementia 2015 11(3):1-88 (2015)
Age (65-74)	15%	Alzheimer's Association Alzheimer's Disease Facts and Figures Alzheimer's & Dementia 2015 11(3):1-88 (2015)
Age (<65)	4%	Alzheimer's Association Alzheimer's Disease Facts and Figures Alzheimer's & Dementia 2015 11(3):1-88 (2015)
Lewy Body disease	10-20%	Alzheimer's Association Dementia with Lewy bodies (2015)
APP	10,15% - 50%	Bird DB Early-Onset Familial Alzheimer Disease ,GeneReviews (2012)
Hypertension	~20%	Israeli-Korn SD, Masarwa M, Schechtman E, Abuful A, Strugatsky R, Avni S, Farrer LA, Friedland RP, Inzelberga R Hypertension Increases the Probability of Alzheimer's Disease and of Mild Cognitive Impairment in an Arab Community in Northern Israel Neuroepidemiology 34(2): 99–105 (2010)
GTPases	<1%	Alzheimer's Association Alzheimer's Disease Facts and Figures Alzheimer's & Dementia 2015 11(3):1-88 (2015)
APOE4	30-70%	Thomas DB Early-Onset Familial Alzheimer Disease ,GeneReviews (2012)
PS 1,2	5%	Thomas DB Early-Onset Familial Alzheimer Disease ,GeneReviews (2012)
Amyloid Angiopathy	80%	Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT Neuropathological

		Alterations in Alzheimer Disease Cold Spring Harb Perspect Med. 1(1): a006189 (2011)
Oxidative Stress	25-30%	Yves Christen Oxidative stress and Alzheimer disease1,2 American Society for Clinical Nutrition 71(2):621-629 (2000)
Inflammation	30-40%	J.C. de la Torre Alzheimer Disease as a Vascular Disorder
Nosological Evidence 33(4):1152-62 (2002)		
Isoprostanes	50%	Praticò D, Clark CM, Liun F, Lee VYM, Trojanowski JQ Increase of Brain Oxidative Stress in Mild Cognitive Impairment
A Possible Predictor of Alzheimer Disease 59(6) (2002)		
P53	75%	Hooper C, Meimaridou E, Tavassoli M, Melino G, Lovestone S, Killicka R p53 is upregulated in Alzheimer's disease and induces tau phosphorylation in HEK293a cells 418(1):34-37 (2007)
Cytokines	50%	Chakrabarty P, Li A, Ceballos-Diaz C, Eddy JA, Funk CC, Moore B, DiNunno N, Rosario AM, Cruz PE, Verbeeck C, Sacino A, Nix S, Janus C, Price ND, Das P, GOLDE TE IL-10 Alters Immunoproteostasis in APP Mice, Increasing Plaque Burden and Worsening Cognitive Behavior Neuron (2015)
miRNAs	60%	Wang X, Su B, Lee Hg, Li X, Perry G, Smith MA, Zhu X Impaired Balance of Mitochondrial Fission and Fusion in Alzheimer's Disease The Journal of Neuroscience 29(28): 9090-9103 (2009)
DVLP	74.3%	Wang X, Su B, Lee Hg, Li X, Perry G, Smith MA, Zhu X Impaired Balance of Mitochondrial Fission and Fusion in Alzheimer's

		Disease The Journal of Neuroscience 29(28): 9090-9103 (2009)
OPA1	61.4%	Wang X, Su B, Lee Hg, Li X, Perry G, Smith MA, Zhu X Impaired Balance of Mitochondrial Fission and Fusion in Alzheimer's Disease The Journal of Neuroscience 29(28): 9090-9103 (2009)
MFN1	27.8%	Wang X, Su B, Lee Hg, Li X, Perry G, Smith MA, Zhu X Impaired Balance of Mitochondrial Fission and Fusion in Alzheimer's Disease The Journal of Neuroscience 29(28): 9090-9103 (2009)
MFN2	33.6%	Wang X, Su B, Lee Hg, Li X, Perry G, Smith MA, Zhu X Impaired Balance of Mitochondrial Fission and Fusion in Alzheimer's Disease The Journal of Neuroscience 29(28): 9090-9103 (2009)
FIS1	60%	Wang X, Su B, Lee Hg, Li X, Perry G, Smith MA, Zhu X Impaired Balance of Mitochondrial Fission and Fusion in Alzheimer's Disease The Journal of Neuroscience 29(28): 9090-9103 (2009)
Visual, neuropsychiatric disorders	5%	Alzheimer’s Association Alzheimer’s Disease Facts and Figures Alzheimer’s & Dementia 2015 11(3):1-88 (2015)
Executive, language, praxis disorders	40%	Alzheimer’s Association Alzheimer’s Disease Facts and Figures Alzheimer’s & Dementia 2015 11(3):1-88 (2015)
DayLiving disorders	10-20%	Alzheimer’s Association Alzheimer’s Disease Facts and Figures Alzheimer’s & Dementia 2015 11(3):1-88 (2015)

Table 2. Alzheimer's disease biomarkers, biomarkers probabilistic impact on Alzheimer's disease presence and the corresponding bibliographic reference.

4. Experimental

In the general case of the model, all the biomarkers/variables are assigned to discrete priors and they are repeated as many times as the different AD categories belong to. The so called 'max' variables are presented in a tree structure, resulting to the maximum probability for each AD category path.

```
pseudomodel{
Age~ dcat( [1:2] )
Ab~dcat( APOE4,PS1-2, APP  [1:2] )
Tau,Phospho ~ dcat( Cytokines 1:2] )
MetalIons ~ dcat( [1:2] )
LewyBodies ~dcat( Age [1:2] )
Hypertension,depression ~ dcat( Age [1:2] )
APP ~ dcat( [1:2] )
GTP ~ dcat( p53 [1:2] )
APOE4 ~ dcat( Age [1:2] )
PS1-2 ~ dcat( Age [1:2] )
Cytokines ~ dcat( [1:2] )
SenilePlaques ~ dcat( Ab [1:2] )
UnbalanceCa ~ dcat( Ab [1:2] )
Vascular ~ dcat( Ab, Tau,Phospho [1:2] )
LogopenicAphasia,CortexAtrophy~dcat( Tau,Phospho [1:2] )
Memory,HippocampalLoss~dcat( Tau,Phospho [1:2] )
ExecLangPrax~dcat( Tau,Phospho [1:2] )
Visual,Neuropsychiatric~dcat( Tau,Phospho [1:2] )
DailyActivities ~ dcat( [1:2] )
OxidStress~dcat( Mito,MetalIons [1:2] )
Inflamation~dcat( Mito,MetalIons [1:2] )
Isoprostanes~dcat( Mito,MetalIons [1:2] )
Mito ~dcat( MetalIons,OPA1, MFN1,DVLP, FIS1 [1:2] )
MFN1~dcat( GTP [1:2] )
OPA1~dcat( GTP [1:2] )
DVLP~dcat( GTP [1:2] )
FIS1~dcat( GTP [1:2] )
p53 ~ dcat( [1:2] )
miRNAs~dcat( Age [1:2] )
MCI~dcat( DailyAct [1:2] )
max1←max( Ab,LewyBodies, Mito, OxidStress, Memory_Hippocampal_loss,SenilePlaques,
Unbalance_Ca, Hypertension_depression, Inflamation, Isoprostanes,Mito )
ProdromalAD ←max( max1,OxidStress )
ADdementia ←max( Ab, Vascular )
max2 ←max( Ab,Tau,Phospho,Vascular,ExecLangPrax )
TypicalAD ← max( max2,Visual,Neuropsychiatric )
AtypicalAD ←max( LogopenicAphasia,CortexAtrophy,Memory,HippocampalLoss )
MixedAD ←max( Vascular,Category1 )
PreclinicalAD ←max( Ab, Tau,Phospho )
ADPathology ←miRNAs
MildCognitiveImpairment ←MCI
}
```

Data

```
list(Age =2, MetalIons=2, APP=2, Cytokines=2, DailyAct=2, p53=2,
 Age =(0.99,0.01),
 Ab=  (  (0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,1,0,1,0)  ),
 Tau_Phospho = (  (1,0,1,0)  ),
 MetalIons = (0.76, 0.24),
 LewyBodies = (  (0.884,0.116,0.884,0.116)  ),
 Hypertension,depression = (  (0.884,0.116,0.884,0.116)  ),
 APP  = (0.98,0.02),
 GTP = (  (1,0,1,0)  ),
 APOE4  =  (  (1,0,1,0)  ),
 PS1,2 = (  (1,0,1,0)  ),
 Cytokines  (1,0),
 SenilePlaques =  (  (1,0,1,0)  ),
 UnbalanceCa =  (  (1,0,1,0)  ),
 Vascular =  (  (1,0,1,0,1,0,1,0)  ),
 LogopenicAaphasia,CortexAtrophy  = (  (1,0,1,0)  ),
 Memory,HippocampalLoss =  (  (1,0,1,0)  ),
 ExecLangPrax = (  (1,0,1,0)  ),
 Visual,Neuropsychiatric = (  (1,0,1,0)  ),
 DailyActivities = (0,1),
 OxidStress = (  (1,0,1,0,1,0,1,0,1,0,1,0,1,0,1,0)  ),
 Inflamation = (  (1,0,1,0,1,0,1,0,1,0,1,0,1,0,1,0)  ),
 Isoprostanes = (  (1,0,1,0,1,0,1,0, 1,0,1,0,1,0,1,0)  ),
 Mito1 = (  (1,0,1,0,1,0,1,0, 1,0,1,0,1,0,1,0, 1,0,1,0)  ),
 Mito2 = (  (1,0,1,0,1,0,1,0)  ),
 MFN1 = (  (1,0,1,0)  ),
 OPA1= (  (1,0,1,0)  ),
 DVLP= (  (1,0,1,0)  ),
 FIS1 = (  (1,0,1,0)  ),
 p53 =  (0.75,0.25),
miRNAs = ( (1,0,1,0)  ),
MCI = ( (0,1,0,1)  ))
```

The model can be easily extended or adjusted to new biomarkers or new relations between the symptoms, the lesions and the exported AD categories. Three examples are discussed below with the resulted statistics from the Winbugs software concerning different cases of abnormal biomarkers testing, revealing potential AD presence.

Example 1: *In the first case study, a patient is assumed to be diagnosed with problems on daily living activities, with no other evidence of abnormal biomarkers. Additionally, the patient does not belong to a risk group due to the age factor. Therefore, while there are evidences only for abnormal daily-living activities, the corresponding node becomes true and all the other nodes take the false value (figure 3). The model calculates the P(MCI|DailyLivingActivities), the probability that Mild Cognitive Impairment is true given the DailyLivingActivities variable, which can be written as follows:*

$$P(MCI|DailyLivingActivities) = \frac{P(MCI|DailyLivingActivities)P(MCI)}{P(DailyLivingActivities)}$$

$$P(MCI|DailyLivingActivities) = 0.999. \quad (11)$$

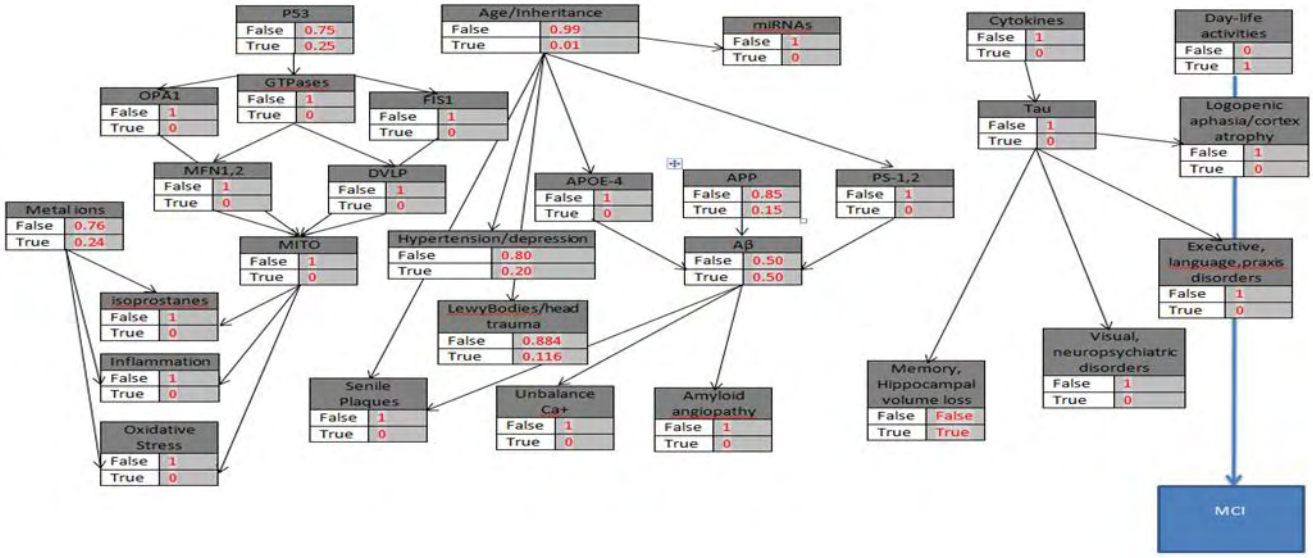

Figure 3. The probabilistic model that can be used for MCI validation.

Executing the code in Winbugs, the result for MCI category is the same as calculated above. For each stochastic variable of the generated probabilistic model, Winbugs defines the interval [1,2] as the probabilities range based on the categorical distribution ~dcat, which receives only positive values. The posterior summary estimations, mean, standard deviation and error are exported as MCMC results, where the estimation of the MCMC error is implemented by the batch mean method (Tables 3-5). After 3000 iterations of the current MCMC Winbugs algorithms, the mean value of MCI category can be described as

$$EMCI = 2 * p_{MCI} + 1 . (1 - p_{MCI}) = 2\ P(MCI|DailyLivingActivities) = p_{MCI} = 2 - 1.999 = 0.999. \quad (12)$$

DayLiving Activities		**Mild Cognitive Impairment**	
		False	True
	False	0.999	0.001
	True	0.001	0.999

Table 3: The probabilities array of Mild Cognitive Impairment presence due to possible alterations in DayLiving Activities. The probability is 0.999 in both the cases of strong true/false evidences

Node	Mean	Sd	MC error	2.5%	Median	97.5%	Start	Sample
Prodromal AD	1.612	0.4872	0.009333	1.0	2.0	2.0	1	3000
AD dementia	1.501	0.5	0.008188	1.0	2.0	2.0	1	3000
Typical AD	1.501	0.5	0.008188	1.0	2.0	2.0	1	3000
Atypical AD	1.0	0.0	1.826E-12	1.0	1.0	1.0	1	3000
Mixed AD	1.612	0.4872	0.009333	1.0	2.0	2.0	1	3000
Preclinical states of AD	1.501	0.5	0.008188	1.0	2.0	2.0	1	3000
Alzheimer's Pathology	1.0	0.0	1.826E-12	1.0	1.0	1.0	1	3000
Mild Cognitive Impairment	1.999	0.03161	5.625E-4	2.0	2.0	2.0	1	3000

Table 4: The WINBUGS results for every Alzheimer's disease category, according to Example 1

Alzheimer's disease classification	Probability of Alzheimer's disease presence (in response to DayLiving Activities biomarker)
Prodromal AD	0.612
AD dementia	0.501
Typical AD	0.501
Atypical AD	0.0
Mixed AD	0.612
Preclinical states of AD	0.501
Alzheimer's Pathology	0.0
Mild Cognitive Impairment	0.999

Table 5: The total probability value for Alzheimer's disease presence due to alterations in DayLiving Activities of the patient. The results revealed the highest probability 0.999 for the case of Mild Cognitive Impairment, while Prodromal AD and Mixed AD show also high scores.

Example 2: In a similar case where miRNAs biomarker is true and there is no other evidence of heredity concerning AD (figure 4) the model calculates the $P(\text{ADPathology}|\text{miRNAs})$. However, while miRNAs node is also linked to the age/heredity node, there is a probabilistic relation between the age/heredity and miRNAs nodes (Tables 6-10).

$$P(\text{ADPathology}|\text{miRNAs}) = \frac{P(\text{ADPathology}|\text{miRNAs})P(\text{ADPathology})}{P(\text{miRNAs})}$$

$P(\text{ADPathology} \mid \text{miRNAs})=1.0$. (13)

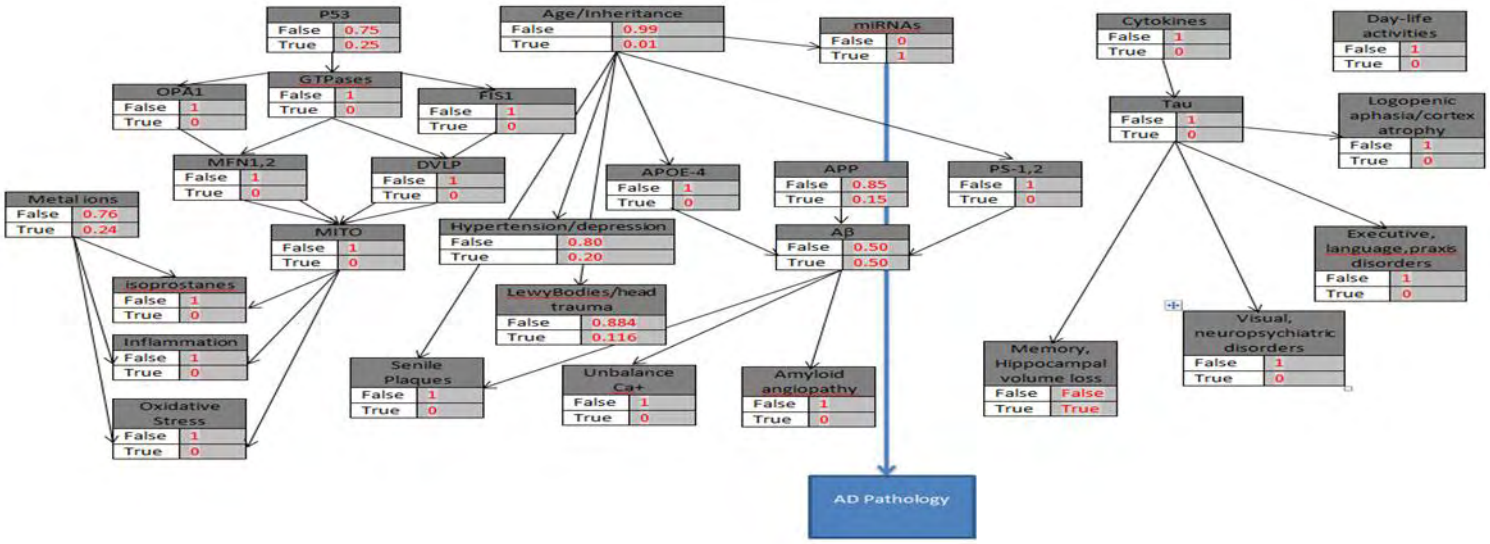

Figure 4. The probabilistic model that can be used for AD Pathology validation.

miRNAs		**Alzheimer's Pathology**	
		False	True
	False	1.0	0.0
	True	0.0	1.0

Table 6: The miRNAs compared with Alzheimer's Pathology

Age/Heredity	
False	True
1	0

Table 7: The Age/Heredity probability array

Age/Heredity		miRNAs	
		False	True
	False	0.0	1.0
	True	1.0	0.0

Table 8: The Age/Heredity compared with miRNAs

Node	Mean	Sd	MC error	2.5%	Median	97.5%	Start	Sample
Prodromal AD	1.613	0.4872	0.005404	1.0	2.0	2.0	1	10000
AD dementia	1.504	0.5	0.005197	1.0	2.0	2.0	1	10000
Typical AD	1.504	0.5	0.005197	1.0	2.0	2.0	1	10000
Atypical AD	1.0	0.0	1.0E-12	1.0	1.0	1.0	1	10000
Mixed AD	1.613	0.4872	0.005404	1.0	2.0	2.0	1	10000
Preclinical states of AD	1.504	0.5	0.005197	1.0	2.0	2.0	1	10000
Alzheimer's Pathology	2.0	0.0	1.0E-12	2.0	2.0	2.0	1	10000
Mild Cognitive Impairment	1.0	0.0	1.0E-12	1.0	1.0	1.0	1	10000

Table 9: The WINBUGS results for every Alzheimer's disease category, according to Example 2

Alzheimer's disease classification	Probability of Alzheimer's disease presence (in response to miRNAs biomarker)
Prodromal AD	0.613
AD dementia	0.504
Typical AD	0.504
Atypical AD	0.0
Mixed AD	0.613
Preclinical states of AD	0.504
Alzheimer's Pathology	1.0
Mild Cognitive Impairment	0.0

Table 10: The total probability value for Alzheimer's disease presence due to alterations in miRNAs biomarker of the patient. The results revealed the highest probability 1 for the case of AD Pathology, while Prodromal AD and Mixed AD show also high scores

Thus, importing the initial data below to Winbugs, in the case of AD Pathology given that the miRNAs variable is true, the exported probability is 1.

Data

```
List(Age =2, MetalIons=2, APP=2, Cytokines=2, DailyAct=2, p53=2,
 Age = (0.99,0.01),
 Ab = (  (0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,1,0,1,0) ),
 Tau,Phospho = (  (1,0,1,0)  ),
 MetalIons = (0.76, 0.24),
 LewyBodies = (  (0.884,0.116,0.884,0.116)  ),
 Hypertensiondepression = (  (0.80,0.20,0.80,0.20)  ),
 APP = (0.98,0.02),
 GTP = (  (1,0,1,0)  ),
 APOE4 = (  (1,0,1,0)  ),
```

PS1,2 = ((1,0,1,0)),
Cytokines = (1,0),
SenilePlaques = ((1,0,1,0)),
UnbalanceCa = ((1,0,1,0)),
Vascular = ((1,0,1,0,1,0,1,0)),
LogopenicAphasia,CortexAtrophy = ((1,0,1,0)),
Memory,HippocampalLoss = ((1,0,1,0)),
ExecLangPrax = ((1,0,1,0)),
Visual,Neuropsychiatric = ((1,0,1,0)),
DailyActivities = (0,1),
OxidStress = ((1,0,1,0,1,0,1,0,1,0,1,0,1,0,1,0,)),
Inflamation = ((1,0,1,0,1,0,1,0,1,0,1,0,1,0,1,0)),
Isoprostanes = ((1,0,1,0,1,0,1,0,1,0,1,0,1,0,1,0)),
Mito = ((1,0,1,0,1,0,1,0,1,0,1,0,1,0,1,0, 1,0,1,0)),
MFN1 = ((1,0,1,0)),
OPA1 = ((1,0,1,0)),
DVLP = ((1,0,1,0)),
FIS1 = ((1,0,1,0)),
p53 = (0.75,0.25),
miRNAs = ((0,1,0,1)),
MCI = ((1,0,1,0),))

After 10000 iterations the mean value of ADPathology can be described as

$$\mathrm{EADPathology} = 2 * \mathrm{p}_{\mathrm{ADPathology}} + 1 \,.\left(1 - \mathrm{p}_{\mathrm{ADPathology}}\right) = 2,$$

$$\mathrm{P(ADPathology|miRNAs)} = \mathrm{p}_{\mathrm{ADPathology}} = 2 - 1 = 1. \quad (14)$$

Example 3: In this last example the most common case is presented, where both Amyloid beta and Tau proteins abnormalities occur, with additional true values in the Age_Inheritance, APP, APOE4 and Vascular variables of the probabilistic model (figure 5).

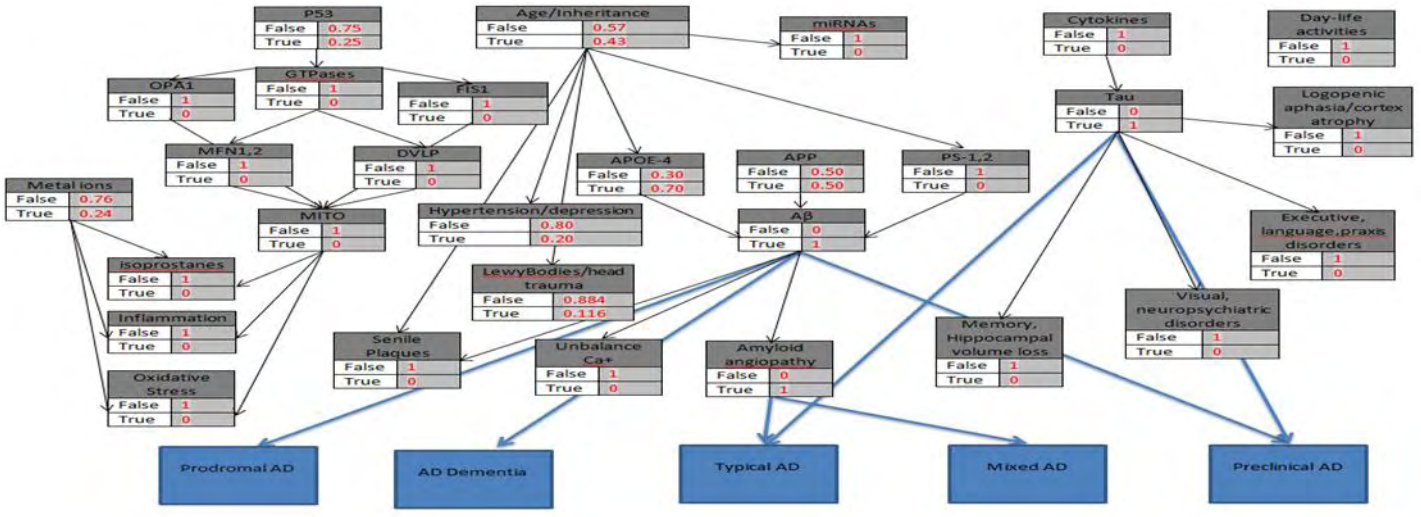

Figure 5. The probabilistic model that shows an incident which can belong to more than one categories of Alzheimer's disease groups.

Data

```
list(Age =2, MetalIons=2, APP=2, Cytokines=2, DailyAct=2, p53=2,
 Age = (0.57,0.43),
Ab = ( (0,1, 0,1, 0,1, 0,1,1,0,1,0), ),
Tau,Phospho = ( (0,1, 0,1), ),
MetalIons = (0.76, 0.24),
LewyBodies = ( (0.884,0.116,0.884,0.116), ),
Hypertension,depression = ( (0.80,0.20,0.80,0.20), ),
APP = (0.50,0.50),
GTP = ( (1,0,1,0), ),
APOE4 = ( (0.30,0.70,0.30,0.70), ),
PS1,2 = ( (1,0,1,0), ),
Cytokines = (1,0),
SenilePlaques ( (1,0,1,0), ),
UnbalanceCa = ( (1,0,1,0), ),
Vascular = ( (0,1,0,1,0,1,0,1), ),
LogopenicAphasia,CortexAtrophy = ( (1,0,1,0), ),
Memory,HippocampalLoss = ( (1,0,1,0), ),
ExecLangPrax = ( (1,0,1,0), ),
Visual,Neuropsychiatric = ( (1,0,1,0), ),
DailyActivities = (0,1),
OxidStress=( (1,0,1,0,1,0,1,0,1,0,1,0,1,0,1,0), ),
Inflamation=( (1,0,1,0,1,0,1,0,1,0,1,0,1,0,1,0), ),
Isoprostanes=( (1,0,1,0,1,0,1,0,1,0,1,0,1,0,1,0), ),
Mito=( (1,0,1,0,1,0,1,0, 1,0,1,0,1,0,1,0, 1,0,1,0), ),
MFN1 = ( (1,0,1,0), ),
OPA1 = ( (1,0,1,0), ),
DVLP = ( (1,0,1,0), ),
FIS1 = ( (1,0,1,0), ),
p53 = (0.75,0.25),
miRNAs = ((1,0,1,0), ),
MCI = ((1,0,1,0), ))
```

Given the initial data set above, after 10,000 iterations, the probability values of the eight categories (Tables 11-12) reveals high risk for AD presence. The results highlight the role of Amyloid beta and Tau proteins and emphasize to their importance and effectiveness in AD aggravation.

Node	Mean	Sd	MC error	2.5%	Median	97.5%	Start	Sample
Prodromal AD	2.0	0.0	1.0E-12	2.0	2.0	2.0	1	10000
AD dementia	2.0	0.0	1.0E-12	2.0	2.0	2.0	1	10000
Typical AD	2.0	0.0	1.0E-12	2.0	2.0	2.0	1	10000
Atypical AD	1.0	0.0	1.0E-12	1.0	1.0	1.0	1	10000
Mixed AD	2.0	0.0	1.0E-12	2.0	2.0	2.0	1	10000
Preclinical states of AD	2.0	0.0	1.0E-12	2.0	2.0	2.0	1	10000
Alzheimer's Pathology	1.0	0.0	1.0E-12	1.0	1.0	1.0	1	10000
Mild Cognitive Impairment	1.0	0.0	1.0E-12	1.0	1.0	1.0	1	10000

Table 11: The WINBUGS results for every Alzheimer's disease category, according to Example 3

Alzheimer's disease classification	Probability of Alzheimer's disease presence (in response to Ab, Tau Activities biomarker)
Prodromal AD	1.0
AD dementia	1.0
Typical AD	1.0
Atypical AD	0.0
Mixed AD	1.0
Preclinical states of AD	1.0
Alzheimer's Pathology	0.0
Mild Cognitive Impairment	0.0

Table 12: The total probability value for Alzheimer's disease presence due to alterations in Ab, Tau/TotalTau, age/inheritance, APP, APOE4 and Vascular disorders of the patient. The results revealed high probabilities for the cases of Prodromal AD, AD dementia, Typical AD, Mixed AD, Preclinical states of AD

5. Conclusion

Since a definitive and accurate diagnosis for AD and other related disorders can be made only at autopsy, neuroimaging techniques face challenges related to clinicopathologic heterogeneity. Although all patients with AD progress through some form of an MCI phase before dementia, the converse is not true. That is some patients who fulfill MCI criteria may have non-AD disease states [71]. Furthermore, the rate at which individuals with MCI will develop dementia may also vary considerably. Thus, although prodromal AD may be clinically identifiable as MCI [72], it is important to recognize the heterogeneity within this clinical construct. Cerebrospinal fluid and plasma biomarkers, as well as amyloid imaging markers, can offer information about neuropathological symptoms of AD, when no evidence markers for hippocampal volume loss can be accurately exported from MRI scanning [73]. In AD patients who have been tested in structural imaging biomarker's detection, left and right hippocampal gradings, cortical thicknesses of the left precuneus, left superior temporal sulcus and right anterior part of the parahippocampal gyrus, offer 72% accuracy in AD diagnosis [74]. Additionally, genetic mutations affect less than 2% of total AD patients and age seems to play a dominant role in the aggravation of disease even though it has been observed that the first lesions begin at least 20 years earlier from the first symptoms. The educational level shows some resistance in the disease, but it should not be considered as a valid marker. Mitochondrial dynamics is a latest crucial element in the puzzle of AD etiology and development, concerning metal ions concentrations in the brain and metal ions interactions with Aβ protein, increasing cells and brain toxicity [75-77]. In this thesis an extensive reference of biomarkers was taken place, that affect in a negative way the development and the progress of Alzheimer's disease. Also, markers was identified from a wide range of scientific papers, and their relation offering a view for the behavior of the disease. Continuing,

with Bayesian theory and inference achieved the attempt of WINBUGS application, creating in that base a relation scheme of the disease according to literal and later a probabilistic model. The exported probabilistic model is based on conditional probabilities, therefore it must be noted that the calculated error is the Monte Carlo error that measures the variability of each estimation due to the simulation. The proposed AD Bayesian model uses the WinBUGS 1.4.3 software, which cannot be used online. Therefore a website was also designed for individuals users and medical staff for the submission of anonymous AD tests results. Users are able to fill AD results in the form of 1 (true) or 2 (false) and receive the exported statistics in their email account. This new educational website is the http://alzheimers.edu.gr. Obviously this Bayesian approach can be extended in several other diseases where the early recognition of symptoms is a crucial factor for an efficient treatment. [78-81].
The proposed AD Bayesian model uses the WinBUGS 1.4.3 software, which cannot be used online. Therefore a website was designed for individuals users and medical personnel for the submission of anonymous AD tests results. Users will have to fill AD biomarkers results in the form of true/false-1/2 (figure 6) and we will execute the calculations afterwards and forward back the exported statistics. The new website is http://alzheimers.edu.gr

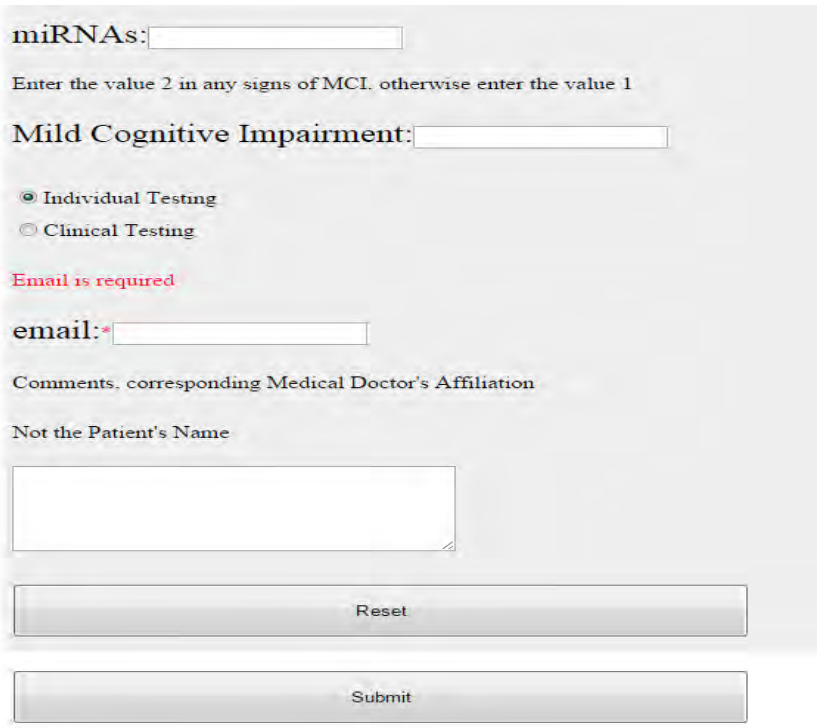

Figure 6. The new website for Alzheimer's disease probabilistic prediction

6. References

[1] Kukull WA, Bowen JD. Dementia epidemiology. Med Clin North Am. 86:573–590 (2002).

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Publications in the thesis

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