A Support System for Diagnosis of Dementia, Alzheimer or Mild Cognitive Impairment

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Introduction

• Population aging has occurred as a **global phenomenon**.

• In 2020, Brazilian population aged 60 years old and over will be **beyond 32 million**.

• In Canada, the number of seniors aged 65 and over **increased 14.1%** between. This rate of growth was **higher than all others** segments (The Canadian Population: Age and Sex – Statistic Canada).

• **High prevalence of diseases related to aging**.
What Is Dementia?

• Dementia is a general term for a decline in mental ability severe enough to interfere with daily life (Memory loss is an example).

• Dementia symptoms gradually worsen.

• Early dementia detection and treatment allows better clinical results.
Alzheimer's and dementia basics

- **Alzheimer's is the most common type of dementia** (60 to 80% of cases).

- Others are vascular dementia, front temporal dementia, etc.

- By 2025, the number of elderly people with Alzheimer’s disease is estimated to reach **6.7 millions**.

- Up to 5% of people with the disease have **early onset** of Alzheimer's (it often appears when someone is in 40s or 50s).
Alzheimer's is progressive disease

It is the **sixth** leading cause of **death** in the **United States**.

Those with Alzheimer's live an average of **8 years after symptoms become noticeable**, but survival can range from 4 to 20 years.

Although current Alzheimer's treatments cannot stop progressing, they can temporarily **slow the worsening** of dementia symptoms and **improve quality of life**.
7 Stages of Alzheimer's

Stage 1: No impairment (normal function)

Stage 2: Very mild decline (only the person may feel symptoms).

Stage 3: Mild decline (Friends, family or co-workers begin to notice difficulties)

Stage 4: Moderate decline (medical interview should be able to detect)

Stage 5: Moderately severe decline (begin to need help with day-to-day activities)

Stage 6: Severe decline (personality changes may take place and individuals need extensive help with daily activities)

Stage 7: Very severe decline (individuals lose the ability to respond to their environment, to carry on a conversation and, eventually, to control movement, need help with daily personal care, lose the ability to smile, to sit without support and to hold their heads up. Reflexes become abnormal. Muscles grow rigid. Swallowing impaired.)
Neurons are the chief type of cell destroyed by Alzheimer's disease.

Signals that form memories and thoughts move through nerve cell as electric charge.

Nerve cells connect to one another at synapses. When a charge reaches a synapse, it bursts destroying neurotransmitters.

Alzheimer's disease disrupts both the way electrical charges travel within cells and the activity of neurotransmitters.
The **positron emission tomography** (PET) scan shows typical patterns of brain activity associated with oxygen and fuel carry by blood.

The **normal patterns change** when **Alzheimer's disease** or a related disorder **disrupts nerve cells and their connections**.
Alzheimer's disease leads to nerve cell death and tissue loss throughout the brain.

- Over time, the brain shrinks dramatically, affecting nearly all its functions.

A brain with advanced Alzheimer's

A normal brain

two brains merged
Alzheimer's brain:

The **cortex shrivels up**, damaging areas involved in **thinking, planning and remembering**.

**Ventricles** (fluid-filled spaces within the brain) grow larger.

**Shrinkage** is especially severe in the **hippocampus** (an area of the cortex that plays a key role in formation of **new memories**).
What **causes** cell death and tissue loss in the Alzheimer's brain are **yet not well known**, but plaques and tangles are prime suspects.

Alzheimer's tissue has fewer nerve cells and synapses than a healthy brain. **Plaques**, abnormal clusters of protein fragments, build up between nerve cells. **Dead and dying nerve cells contain tangles**, which are made up of twisted strands of proteins.
Plaques and tangles tend to spread through the cortex as Alzheimer's disease progresses.

The rate of progression varies greatly.

The course of the disease depends in part on age at diagnosis (+ treatments) and whether a person has other health conditions.
Clinical Decision Support Systems (CDSS) are interactive Computer software designed to assist health professionals in determining diagnosis from all of patient data at the point of care.

In CDSS, characteristics of individual patients are matched to a knowledge base and an algorithm generates patient-specific assessments and recommendations.
<table>
<thead>
<tr>
<th>Objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>This work describes a <strong>CDSS</strong> for diagnosis of dementia and related disorder (as Alzheimer’s Disease - <strong>AD</strong> and Mild Cognitive Impairment – <strong>MCI</strong>).</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>• Proper disease identification;</td>
</tr>
<tr>
<td>• Prevention of diagnostic error and diagnostic error rate;</td>
</tr>
<tr>
<td>• Delay in detection; and</td>
</tr>
<tr>
<td>• Improvement of clinical decision.</td>
</tr>
</tbody>
</table>
• The most commonly used criteria for diagnoses were established by DSM-IV (Diagnostic and Statistical Manual for Mental Disorders 4th edition) published by American Psychiatric Association

• For such diseases there is no single test to prove a person has Alzheimer's or other types of dementia. Diagnosing these requires careful medical evaluation, including:
  • Medical history (physician)
  • Mental status tests (psychology)
  • A physical and neurological exam (medical doctors)
  • Clinics and laboratorial tests (such as blood tests and brain imaging) to rule out other causes of dementia-like symptoms.
Alois Alzheimer (1864–1915)

Former works:


Some criteria used for diagnosis

<table>
<thead>
<tr>
<th>Dementia</th>
<th>AD</th>
<th>MCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Decrease cognitive activities</td>
<td>• Smelling deficiency</td>
<td>• Difficulties with new information</td>
</tr>
<tr>
<td>• Difficulties with complex work</td>
<td>• Difficulties with space and visual recognitions</td>
<td>• Difficulties with remembering names</td>
</tr>
<tr>
<td>• Behavior changes</td>
<td>• Neuropsychological tests</td>
<td>• Alteration of the biomarkers</td>
</tr>
<tr>
<td>• <strong>Hippocampus</strong> atrophy</td>
<td>• History of AD in relatives</td>
<td></td>
</tr>
</tbody>
</table>
• The decision theoretic model was built on a **Bayesian network** using a data-driven approach.

• The Bayesian network structure was built with **the support of a disease domain expert** and a three-level generic structure.

• Probability distribution was estimated using a **supervised learning** method and a training base containing real patient cases and normal controls.

• The **training attributes** are composed of **predisposal factors**, **neuropsychiatry tests**, **patient data**, **symptoms** and **signs**.
Used Bayesian network

Diseases: MCI, AD, D

Predisposing factors

Symptoms, signals, results of tests

Bayesiana 3 level nets

Decision box
Clinical Decision Support System components

**Bayesian network modeling phase**

- Patients’ dataset
- Systems analyst (responsible for decision model tests and validation)
- Supervised learning.
- Performance measures.

**Clinical Decision Support System (CDSS)**

- Knowledge base
- Inference engine
- Communication interface

**Clinical routine**

- Health Information Systems (HIS)
- Electronic Health Record (EHR)
- User interface

**Semantic interoperability**

- Evidences set.
- The most probably diagnosis and the most sensitive items.
- Request assistance from CDSS.
- View, insert, edit and query subject data.

- Physician

- Request assistance from CDSS.

- Systems analyst (responsible for decision model tests and validation)

- Patient's dataset

- Physician
The training database

• Real clinical cases of patients and normal controls from:
  – Duke University Medical Center (USA)
  +
  – Center for Alzheimer Disease and Related Disorder, Institute of Psychiatric of Federal University of Rio de Janeiro (Rio de Janeiro, Brazil).

Approval of the “Comissão Nacional de Ética em Pesquisa” Brazilian Ministry of Health nº 284/2010.
Bayesian network for diagnosis of Dementia
Bayesian network for diagnosis of Alzheimer’s Disease

[Diagram showing various factors and their relationships related to Alzheimer's Disease diagnosis.]
Bayesian network for diagnosis of Mild Cognitive Impairment
Relationship between decision points considering diagnostic process

- **Patient care**
  - Does the patient have possible Dementia?
    - No: Treatment for other diseases
    - Yes: Carry out neuropsychological tests for Dementia
  - Diagnosis of Dementia
    - Yes: Carry out neuropsychological and exams for Dementia due to Alzheimer's Disease
    - No: Diagnosis of Mild Cognitive Impairment
      - Yes: Treatment for Mild Cognitive Impairment
      - No: Treatment for other diseases

- **Alzheimer's Disease?**
  - Yes: Treatment for Dementia due to Alzheimer's Disease
  - No: Treatment for other diseases

- **Mild Cognitive Impairment?**
  - Yes: Treatment for Mild Cognitive Impairment
  - No: Treatment for other diseases
Multi-Level Healthcare Information Modelling (MLHIM) is an approach to creating portable concept definitions based on XML Schema in order to facilitate semantic interoperability.

Do you know why interoperability is hard? With traditional software design approaches, the semantics are locked in the application code and database schema. Having access to the semantics of the data is essential for clinical and epidemiological decision support.

Unlock Your Semantics!

MLHIM is first a concept. Based on this concept are frameworks, applications and tools used to develop healthcare applications and the governance of knowledge artifacts using a multi-level information model. MLHIM is an implementation-independent model. The reference implementation is expressed in XML Schema Language v1.1.

It is multi-level in regards to a reference model that is developed in software with the conceptual knowledge models implemented using XML schemas that express constraints on the reference model. The XML schemas can then be easily shared between systems so that the semantic context is made available to the data in any conforming application. These XML schema knowledge models can be aggregated in order to form queries, messages, screen forms, reports, etc.

It is important, in the context of the current global world of health informatics, to describe what MLHIM *IS NOT*.

MLHIM is not an EMR/EHR specification. MLHIM is not a messaging specification.

MLHIM is the foundation of these and other healthcare IT applications. It is the foundation that provides the ontological model that is the basis for the development of this body of knowledge.
1. Please, set the clinical evidence

**Background Information:**

- **Age:** no evidence
- **Gender:** no evidence
- **Education:** no evidence
- **Diagnosis of Dementia:** no evidence

**Symptoms, Signs and Test Results:**

- **Mini-mental state score:** no evidence
- **Clinical dementia rating scale:** no evidence
- **Verbal fluency test score:** no evidence
- **Pfeffer questionnaire score:** no evidence
- **Clock drawing test scale:** no evidence
- **Trail making test:** no evidence
- **Stroop color word test:** no evidence
Interface

2. Query CDSS:

Please, select the diagnosis: Dementia

Query CDSS (generate XML instance and send to CDSS server)

3. CDSS Response:

Probability of positive diagnosis: 0.5396
<table>
<thead>
<tr>
<th>Number</th>
<th>Interface Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Selection of factor for the patient.</td>
</tr>
<tr>
<td>2</td>
<td>Selection of symptoms, signals, and results of tests</td>
</tr>
<tr>
<td>3</td>
<td>Selection of diseases</td>
</tr>
<tr>
<td>4</td>
<td>Results</td>
</tr>
</tbody>
</table>

**Assessment scales**

1. Please, set the clinical evidence

---

**Background Information:**
- **Age:** 0-72
- **Gender:** no evidence
- **Education:** no evidence
- **Diagnosis of Dementia:** positive

---

**Symptoms, Signs, and Test Results:**
- **Mini-mental state score:** 20-27
- **Clinical dementia rating scale:** no evidence
- **Verbal fluency test score:** no evidence
- **Pfeffer questionnaire score:** no evidence
- **Clock drawing test scale:** 1
- **Trail making test:** no evidence
- **Stroop color word test:** no evidence
- **Lawton scale:** no evidence
- **IQCode score:** no evidence
- **Berg balance scale:** 0-54
- **Depression:** no evidence

---

2. Query CDSS:

Please, select the diagnosis: Alzheimer’s Disease

3. CDSS Response:

Probability of positive diagnosis:
Considerations:

- **TP:** Disease patients correctly classified as diseased;
- **TN:** Healthy patients correctly identified as diseased;
- **FP:** Healthy patients incorrectly classified as healthy;
- **FN:** Disease patients incorrectly identified as healthy.

- **Sensitivity:** measures the proportion of positive cases which are correctly identified as positive;
- **Specificity:** measures the proportion of negative cases which are correctly identified as negative;
- **Accuracy:** percentage of correct classification.

- **Area under Receiver Operating Characteristic - ROC curve:**
  \[ \text{Sensitivity} \times (1 - \text{Specificity}) \]
- **F1 measure**
Cont.

Sensitivity or True Positive Ratio: \[ TPR = \frac{TP}{TP + FN} \]

Specificity or True Negative Ratio: \[ TNR = \frac{TN}{TN + FP} \]

Precision: \[ TP = \frac{TP}{TP + FP} \]

\[ F_1 = 2 \cdot \frac{Precision \cdot Recall}{Precision + Recall} \]

\[ MSE = \frac{1}{n} \sum_{i=1}^{n} [y_i - P(x = 1)]^2 \]

\[ MXE = \frac{1}{n} \sum_{i=1}^{n} - y_i \cdot \log[P(x = 1)] - (1 - y_i) \cdot \log[1 - P(x = 1)] \]
Results: Dementia

Performance measures and results obtained for each fold considering the proposed Bayesian network for Dementia (D)

<table>
<thead>
<tr>
<th>Fold</th>
<th>AUC</th>
<th>$F_1$</th>
<th>TPR</th>
<th>TNR</th>
<th>TP</th>
<th>FP</th>
<th>TN</th>
<th>FN</th>
<th>MSE</th>
<th>MXE</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>0.93</td>
<td>0.89</td>
<td>0.91</td>
<td>0.63</td>
<td>41</td>
<td>6</td>
<td>10</td>
<td>4</td>
<td>0.11</td>
<td>0.20</td>
</tr>
<tr>
<td>2</td>
<td>0.94</td>
<td>0.93</td>
<td>0.93</td>
<td>0.82</td>
<td>42</td>
<td>3</td>
<td>14</td>
<td>3</td>
<td>0.09</td>
<td>0.18</td>
</tr>
<tr>
<td>3</td>
<td>0.91</td>
<td>0.94</td>
<td>0.98</td>
<td>0.71</td>
<td>44</td>
<td>5</td>
<td>12</td>
<td>1</td>
<td>0.09</td>
<td>0.21</td>
</tr>
<tr>
<td>4</td>
<td>0.89</td>
<td>0.89</td>
<td>0.89</td>
<td>0.71</td>
<td>40</td>
<td>5</td>
<td>12</td>
<td>5</td>
<td>0.15</td>
<td>0.32</td>
</tr>
<tr>
<td>Av</td>
<td>0.92</td>
<td>0.91</td>
<td>0.93</td>
<td>0.72</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.11</td>
<td>0.23</td>
</tr>
<tr>
<td>(St)</td>
<td>(0.02)</td>
<td>(0.03)</td>
<td>(0.04)</td>
<td>(0.08)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>(0.03)</td>
<td>(0.06)</td>
</tr>
</tbody>
</table>

<sup>b</sup> Av (St) = average (standard deviation). Fold = sub set used for Cross Validation. AUC = area under ROC (Receiver Operating Characteristics), Best result = 1. $F_1$ Best result = 1. TPR = Best result =1. TNR Best result = 1. MSE Best result = 0 (zero). MXE Best result = 0 (zero).
Results: AD

Performance measures and results obtained for each fold considering the proposed Bayesian network for Alzheimer's disease (AD):

<table>
<thead>
<tr>
<th>Fold</th>
<th>AUC</th>
<th>$F_1$</th>
<th>TPR</th>
<th>TNR</th>
<th>TP</th>
<th>FP</th>
<th>TN</th>
<th>FN</th>
<th>MSE</th>
<th>MXE</th>
</tr>
</thead>
<tbody>
<tr>
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<td>0.82</td>
<td>0.88</td>
<td>0.18</td>
<td>30</td>
<td>9</td>
<td>2</td>
<td>4</td>
<td>0.16</td>
<td>0.21</td>
</tr>
<tr>
<td>2</td>
<td>0.77</td>
<td>0.86</td>
<td>0.94</td>
<td>0.27</td>
<td>32</td>
<td>8</td>
<td>3</td>
<td>2</td>
<td>0.15</td>
<td>0.20</td>
</tr>
<tr>
<td>3</td>
<td>0.88</td>
<td>0.85</td>
<td>0.97</td>
<td>0.17</td>
<td>32</td>
<td>10</td>
<td>2</td>
<td>1</td>
<td>0.14</td>
<td>0.17</td>
</tr>
<tr>
<td>4</td>
<td>0.80</td>
<td>0.86</td>
<td>0.97</td>
<td>0.09</td>
<td>33</td>
<td>10</td>
<td>1</td>
<td>1</td>
<td>0.15</td>
<td>0.22</td>
</tr>
<tr>
<td>Av</td>
<td>0.80</td>
<td>0.85</td>
<td>0.94</td>
<td>0.18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.15</td>
<td>0.20</td>
</tr>
<tr>
<td>(St)</td>
<td>(0.06)</td>
<td>(0.02)</td>
<td>(0.04)</td>
<td>(0.07)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>(0.01)</td>
<td>(0.02)</td>
</tr>
</tbody>
</table>

$^b$ Av (St) = average (standard deviation). Fold = sub set used for Cross Validation. AUC = area under ROC (Receiver Operating Characteristics). Best result = 1. $F_1$ Best result = 1. TPR = Best result = 1. TNR Best result = 1. MSE Best result = 0 (zero). MXE Best result = 0 (zero).
Results: MCI

Performance measures and results obtained for each fold considering the proposed Bayesian network for mild cognitive impairment (MCI)\(^b\).

<table>
<thead>
<tr>
<th>Fold</th>
<th>AUC</th>
<th>(F_1)</th>
<th>TPR</th>
<th>TNR</th>
<th>TP</th>
<th>FP</th>
<th>TN</th>
<th>FN</th>
<th>MSE</th>
<th>MXE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.00</td>
<td>0.94</td>
<td>1.00</td>
<td>0.89</td>
<td>8</td>
<td>1</td>
<td>8</td>
<td>0</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>2</td>
<td>0.95</td>
<td>0.77</td>
<td>0.63</td>
<td>1.00</td>
<td>5</td>
<td>0</td>
<td>8</td>
<td>3</td>
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<td>6</td>
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</tr>
<tr>
<td>4</td>
<td>0.96</td>
<td>0.94</td>
<td>1.00</td>
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<tr>
<td>Av</td>
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<td>0.87</td>
<td>0.91</td>
<td>0.86</td>
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<td>0.24</td>
</tr>
<tr>
<td>(St)</td>
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<td>(0.19)</td>
<td>(0.14)</td>
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<td>(0.07)</td>
<td>(0.2)</td>
</tr>
</tbody>
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\(^b\) Av (St) = average (standard deviation). Fold = sub set used for Cross Validation. AUC = area under ROC (Receiver Operating Characteristics). Best result = 1. \(F_1\) Best result = 1. TPR = Best result = 1. TNR Best result = 1. MSE Best result = 0 (zero). MXE Best result = 0 (zero).
• We have constructed the structure of Bayesian network, data-driven base of clinical cases.
• The patients are assisted by Center for Treatment of Alzheimer's (CDA), Federal University of Rio de Janeiro (UFRJ).
• The clinical concepts of Bayesian network are modeled using MLHIM (Multilevel Healthcare Information Model).
• The decision model is represented by a graphical diagram, which facilitates its ongoing review.
• Modeling of a network decision based on Bayesian network and influence diagram is feasible and consistent.

• As future work, we intend to improve the database of clinical cases.
Thank you!

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