Generic evidence-based disease profiling for predicting outcomes: Application to Alzheimer's disease and Traumatic Brain Injuries

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Background: When assessing complex diseases, the state of a patient is characterised using multiple different measurements, for example clinical tests, imaging data, laboratory measurements, and electrophysiological measurements. As the amount of data available for patients is continuously increasing in modern hospitals, forming a reliable and holistic view about the state of the patient is becoming a real challenge. Currently, the integration of all these data is based on clinicians' expertise containing subjective reasoning, and the availability of objective tools for supporting the decision making is still very limited. The focus of the PredictAD (www.predictad.eu, 6/2008-11/2011) and TBIcare (www.tbicare.eu, 2/2011-1/2014) VPH EU-projects has been on developing systematic and evidence-based tools for this challenge. The approach used in these projects is based on phenomenological disease profile models meeting the clinical needs. The use of the approach is demonstrated in two major neurological disorders: Alzheimer's disease (AD) and traumatic brain injuries (TBI).

Methods: A disease state index (DSI) was developed based on comparing the patient's measurements with measurements of other subjects (healthy and diseased) from large databases [1,2]. DSI is a risk score, a value in the interval [0,1], indicating a patient's disease state, i.e., the location or rank based on data, in relation to previously known control (healthy) and positive (disease) populations. It is intended to be used mainly with quantitative features, such as standardized questionnaire answers, laboratory analysis results, automatically quantified biomedical data, and outputs of personalized disease model simulations. It can be considered a supervised classifier, where patient data are compared to previously diagnosed data. In addition to DSI, a disease state fingerprint (DSF), a graphical counterpart of DSI, was developed. This disease profile visualises the relevance of each biomarker or measure in diagnosing the disease (the size of the box in DSF) and the fitness of the patient measurements against the study populations (the color of the box in DSF). The use of DSF keeps the computation of the index transparent and a clinician can find reasons and understand why the index is high or low. This is not the case with many existing classifiers, and they remain more or less black-boxes for the user. The basic principles of DSF and DSI are described in Fig. 1.

Results: In one clinical study performed in PredictAD, three clinicians predicted the conversion to Alzheimer's disease for 140 mild cognitive impairment (MCI) cases from the ADNI cohort using only baseline clinical, imaging, and CSF biomarker data. In addition to the prediction, the clinicians rated each case using a 6-level scale from clear non-Alzheimer's case to clear Alzheimer's case. The use of the tool was compared with the situation where exactly the same measurement data were shown printed on paper. The prediction accuracies with and without the tool were 70 % and 63 %, respectively (difference statistically significant with $p<0.05$). If only clear cases were studied, the prediction accuracy increased to 86 % (covering 33 % of cases) with the tool and to 82 % (covering 26 % of cases) when only paper prints were used. Our recent results show that clear cases can be selected also automatically based on the disease state index value. The results indicate that the prediction can

be performed in the accuracy of 87 % for about 50 % of cases already 12 months before the diagnosis is made currently.

The approach was tested also using data from 81 cases with traumatic brain injury from a patient cohort from Cambridge. The objective was to predict the outcome, measured by the Glasgow Outcome Scale, using the data obtained immediately after entering the hospital after accident. As only clinical measures, e.g., not including imaging data, were used, the results are still preliminary. The disease state index was able to predict the outcome, i.e., good recovery & moderate outcome vs. vegetative state & dead, with the accuracy of 68 % (Fig. 2).

Conclusions: The PredictAD and TBIcare projects have developed and demonstrated a generic disease profiling technology that allows clinicians to evaluate the state of their patients in an objective way. The approach is evidence-based as the patient data are compared to large number of previously diagnosed database cases. In the Alzheimer's disease application, the use of a continuous disease state index allows stratification of patient populations and automatic selection of clear cases for which the Alzheimer's disease can be predicted with high accuracy (> 85 %). The accuracy of 85 % represents the level that can be obtained with clinical diagnosis at later stages of the disease when compared with the ground truth from post-mortem samples. In addition to the index, the profiling technology allows to evaluate also visually the match of the patient to the profile of a certain disease. The work for its application in traumatic brain injury is still in the early phase, but already this shows potential usefulness. As combining forces in modeling highly complex human body is essential, the PredictAD and TBIcare projects provide a successful example of collaboration between VPH projects.

References:

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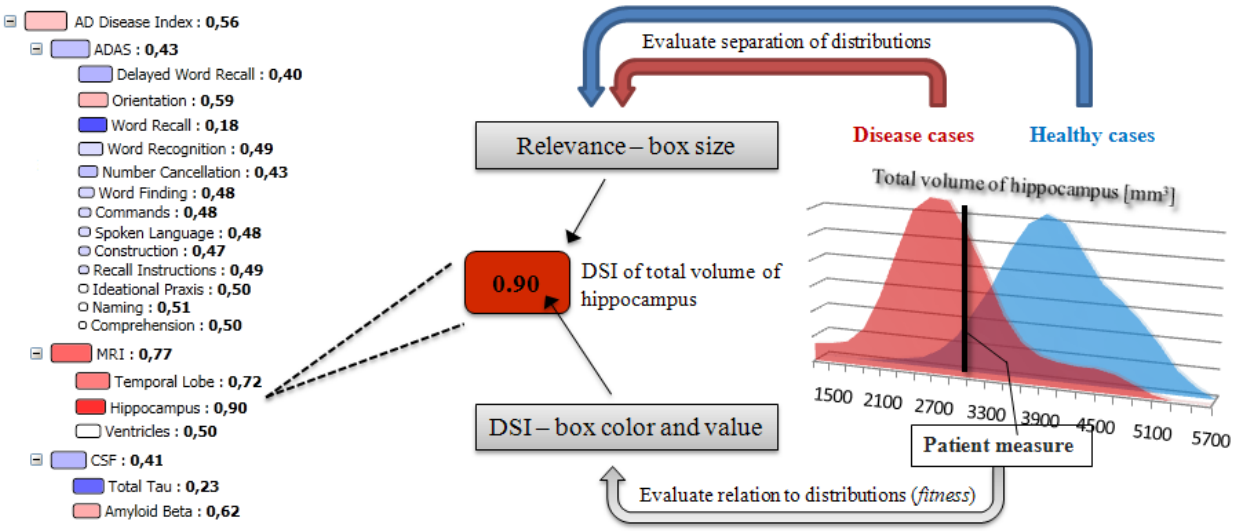

Fig. 1. Disease State Fingerprint (DSF) and Disease State Index (DSI) concept**.** The red and blue distributions on the right show the probability density distributions of the hippocampus volume in AD patients and healthy controls, respectively, computed from a database of several hundreds of cases. The more separated the peaks are the better and more relevant the biomarker is in diagnostics. The relevance of the biomarker is indicated by the size of the box in DSF (on the left). The black vertical line on the right shows the value measured from the patient studied. It can be seen that the probability of belonging to the AD population is much higher than to the healthy control population. This is indicated by the color of the box and the DSI value (deep red and DSI values close to one indicate high probability of AD and blue shades and DSI values close to zero indicate high probability of healthy). In addition to single biomarkers, DSF contains a hierarchical representation showing the relevance and fitness for combined measures, such as, MRI imaging and CSF biomarkers.

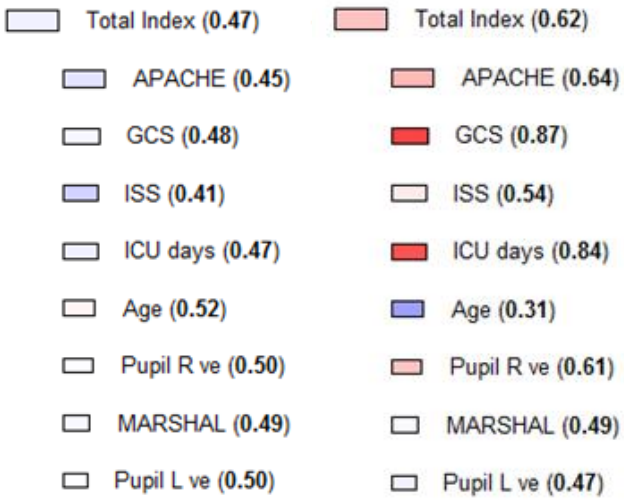

Fig. 2. Disease state index and fingerprint for moderately disabled and vegetative patient groups.