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Diagnostic Biomarkers for Alzheimer's Disease using Dynamic Nonlinear Models based on Principal Dynamic Modes

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***Abstract*—Sensitive and robust diagnostic biomarkers for Alzheimer's disease (AD) were sought using dynamic nonlinear models of the causal interrelationships among time-series (beat-to-beat) data of arterial blood pressure, end-tidal CO_2 and cerebral blood flow velocity collected in human subjects (4 AD patients and 4 control subjects). These models were based on Principal Dynamic Modes (PDM) and yielded a reliable biomarker for AD diagnosis in the form of the "Effective CO_2 Reactivity Index" (ECRI). The results from this initial set of subjects corroborated the efficacy of the ECRI biomarker for accurate AD diagnosis.**

I. Introduction

ALZHEIMER'S disease (AD) is a critical national health priority. At present, there are about 5.3 million AD patients in the US who suffer gravely and cause an economic burden on society of about $148 billion/yr. Owing to the aging population, the number of people affected by AD and the attendant cost are expected to rise rapidly, if no effective treatments or preventive interventions are found. AD is a progressive brain disease which is initiated many years before its drastic symptoms appear – upon which current diagnostic methods rely. Therefore, the development of biomarkers for *early* diagnosis of AD is fundamentally important, because potential treatment or prevention of AD may be effective only at the early stages of the disease.

Similar to other chronic diseases, AD involves both genetic and environmental factors. Large epidemiologic studies have shown that the presence of cardiovascular risk factors such as hypertension, diabetes and dyslipidemia are also risk factors for AD. Postmortem studies of AD brains have documented extensive vascular abnormalities due to amyloid plaques and neurofibrillary tangles, such as cerebral amyloid angiopathy, atherosclerosis and microcirculatory degeneration. Carefully controlled studies in transgenic animal model of AD have demonstrated that cerebrovascular function is impaired even before deposition of Aβ amyloid in the brain parenchyma, suggesting that cerebrovascular dysfunction may occur at the early stages of AD. Previous studies have also suggested that vascular abnormalities and/or AD pathology may lead to changes in cerebral hemodynamics that may be detectable by the pressure-flow relationship in cerebral circulation. However, the quantitative study of cerebral hemodynamics has been confounded by the fact that cerebral blood flow variations depend on multiple physiological factors, including variations in blood perfusion pressure and CO_2 tension, in a manner that is dynamic, nonlinear and time-varying. Because of the underlying physiological complexity, the use of conventional linear modeling for cerebral hemodynamics has serious limitations. This motivates the proposed use of nonlinear (and dynamic) modeling methods in a practical context to address the true complexity of the problem. These methods require beat-to-beat measurements of the relevant variables: arterial blood pressure (ABP), end-tidal CO_2 ($ETCO_2$) and cerebral blood flow velocity (CBFV). The latter measurements are feasible using transcranial Doppler (a non-invasive method of high temporal resolution that has been used in our previous studies), but are not possible with either PET or fMRI which have low temporal resolution.

We present a modeling approach to quantifying the effects of AD on cerebral hemodynamics through "cerebrovascular biomarkers" that can be useful for AD diagnosis and the assessment of efficacy of pharmaceutical and therapeutic procedures in future studies. We propose the use of the novel concept of Principal Dynamic Modes (PDM) to construct robust models of the combined dynamic nonlinear effect of beat-to-beat variations in arterial blood pressure and end-tidal CO_2 upon cerebral blood flow velocity in the middle cerebral artery. This modeling methodology has been developed in recent years and has been applied successfully to various physiological domains [4]. Its use in this context is expected to improve our diagnostic means for AD at low cost relative to alternative methods (e.g. fMRI, PET etc.).

Our working hypothesis is that CBFV depends on certain fundamental aspects of the AD pathophysiology that affect the cerebrovascular elasticity and compliance, either through passive or active mechanisms of microcirculation involving endothelial and/or neural processes (local, regional and central) and their coupling to the cerebral vasculature. The functional characteristics of these complex physiological mechanisms are captured by the quantitative models that are estimated from the time-series data and, therefore, these models can be used to derive biomarkers for AD diagnosis.

II. Methodology

We have employed the PDM modeling methodology [4] to obtain dynamic nonlinear models of the causal

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relationships among arterial blood pressure (ABP), end-tidal CO_2 (ETCO2) and cerebral blood flow velocity (CBFV) time-series data. The data were collected as continuous recordings at the Institute for Exercise and Environmental Medicine in the Presbyterian Hospital of Dallas and were reduced to beat-to-beat data (resampled every second and de-trended) using the recorded RR intervals. Data from 4 control subjects (CS) and 4 Alzheimer's patients (AP) in supine position over 6 min were used in this study. Figure 1 shows the preprocessed data for control subject #1.

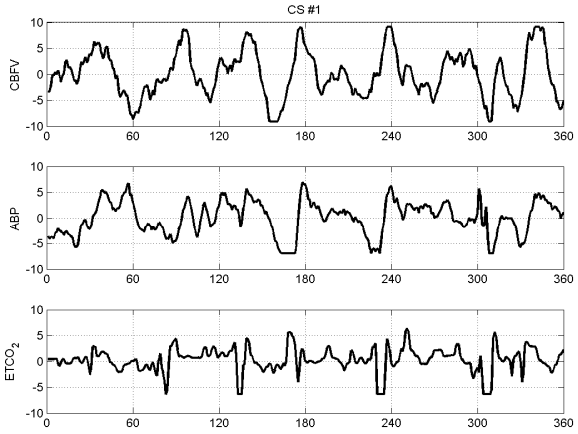

Fig. 1. Preprocessed beat-to-beat data samples of CBFV (first row), ABP (second row), and ETCO2 (third row) for the control subject #1.

Our previous work on the related subject of cerebral autoregulation has demonstrated the feasibility and utility of obtaining dynamic nonlinear (3rd order Volterra) models from the same type of data [5-6]. It was shown that significant nonlinearities exist in the lower frequencies (below 0.07 Hz) and strong interactions take place between arterial pressure and CO_2 tension variations in the way they influence cerebral blood flow [5-8]. This is the only known method that can identify and separate the cross-interaction term in the data, as well as identify and separate the linear and the nonlinear components. The characteristics of these dynamic nonlinear models were shown to be altered by orthostatic stress (low body negative pressure) and pharmaceutical interventions [7-8].

In this study, the reliable estimation of dynamic nonlinear models of cerebrovascular function from these experimental data relies on the use of PDMs. According to the proposed methodology, we estimate a set of "global" PDMs from the data that represent a "functional coordinate system" or "basis of functions" for the efficient representation of the Volterra kernels [4] which account for the dynamic characteristics of the system. Subsequently, we estimate the static nonlinearities associated with the PDMs that complete the model. The practical ability of estimating these dynamic nonlinear models from relatively short data-records (6 min of beat-to-beat data) is one of the contributions of this work. Another is the utilization of these models for developing effective diagnostic biomarkers for AD, as described below.

The obtained models are subject-specific and can be used to classify unambiguously each subject as an AD patient or non-AD control using the model-derived biomarkers.

III. Results

We begin with the estimation of the PDMs using the preprocessed beat-to-beat data of ABP and $ETCO_2$ as the two inputs and CBFV as the output. The PDMs of each subject were obtained through Laguerre expansions of the kernels using 7 and 5 Laguerre functions for the ABP and $ETCO_2$ inputs respectively. Three significant PDMs were found for each of the two inputs. The "global PDM template" comprised of 3 PDMs for each input was formed by merging (through SVD) the PDMs of two subjects from each group. Note that the form of these "global PDMs" did not change much when different subjects were used for this purpose, corroborating the claim of a "global PDM template" that can be used for all subjects. Figure 2 shows the obtained global PDM templates for the ABP and ETCO2 inputs in the time-domain. Figure 3 shows the same PDM templates in the frequency-domain, so that their spectral characteristics can be observed.

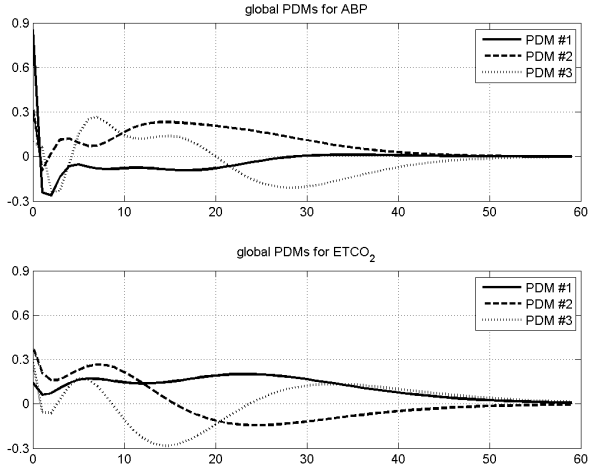

Fig. 2. The global PDMs obtained for both CS and AP in the time-domain for the ABP input (top) and the $ETCO_2$ input (bottom), plotted over 60 sec of "system memory" (α_1 =0.5, L_1 = 7 and α_2 =0.65, L_2 = 5).

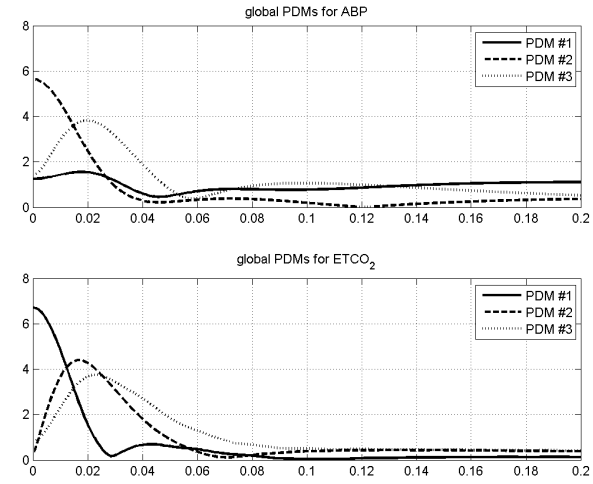

Fig. 3. The global PDMs obtained for both CS and AP in the frequency-domain for the ABP input (top) and the $ETCO_2$ input (bottom), plotted over a frequency range from 0 to 0.2 Hz.

Our previous studies have shown that the frequency range from 0.01 to 0.08 Hz is most critical in terms of cerebral flow autoregulation [5-8] – a fact that is consistent with the higher values of the PDMs in this range. It was also shown that most of the nonlinear characteristics of cerebral flow autoregulation were exhibited in the range from 0.01 to 0.04 Hz [5-8] – a fact that suggests significant nonlinearities associated with these PDMs. It is worth noting that 4 out of 6 PDMs exhibit spectral peaks around 0.02 Hz – a frequency band that seems to attain critical importance in cerebral circulation. Secondary spectral peaks of the PDMs are seen around the frequencies 0.04, 0.06 and 1.0 Hz.

Previous studies of cerebral autoregulation have utilized the transfer function measurement of cerebrovascular impedance based on linear system theory [1-3]. Figure 4 shows the gain functions (i.e. the FFT magnitudes of the transfer functions) for the best linear models of the pressure-to-flow dynamic relationship for the four CS and four AP datasets, which are the frequency-dependent cerebrovascular admittances (the inverse of the impedances) for these subjects. The mean and the standard deviation of the prediction NMSE (Normalized Mean Square Errors) of these linear models are: 46.4% (6.8%) for CS and 47.7% (16.8%) for AP. Note that these prediction NMSE values drop to 29.2% (6.7%) for CS and 31.1% (14.8%) for AP when the nonlinear models are used that are obtained with the use of the global PDMs of Figure 2 (i.e. about two-thirds of the NMSE for the linear models) – a fact that corroborates the importance of nonlinear modeling in this case.

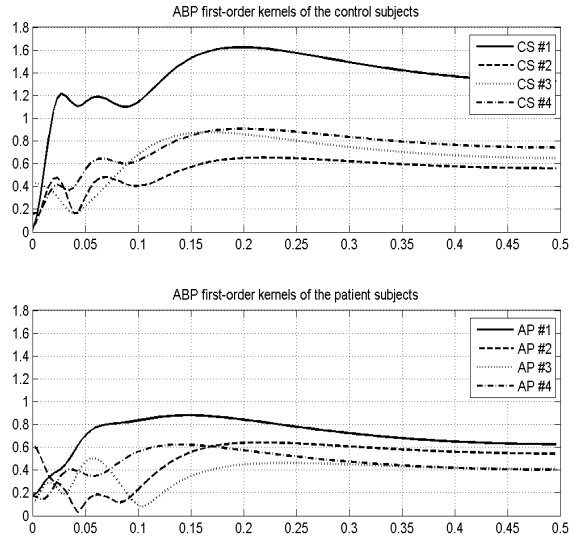

Fig. 4. The gain functions (i.e. the FFT magnitudes of the transfer functions) for the best linear models of the pressure-to-flow dynamic relationship for the four CS (top) and four AP (bottom) of this study.

It is evident that these gain functions generally exhibit higher values at high frequencies for the CS relative to the AP, but this observation does not delineate unambiguously the two groups. For this reason, we explore the potential utility of the nonlinear models in delineating the two groups.

In order to visualize the nonlinear model characteristics, we computed the asymptotic step responses of the nonlinear model (steady-state responses) for step inputs of ABP and $ETCO_2$ with various magnitudes. This process eliminates the effect of the detailed form of the PDM dynamics (since each PDM is integrated to yield the respective steady-state response) and preserves only the nonlinear features of the model/system – modulated by the integral of the respective PDM. The resulting nonlinear response surfaces are shown in Figures 5 and 6 for the four CS and the four AP, respectively. It is evident that the surfaces for the CS have similar morphology – viz. strong cubic dependence on $ETCO_2$ with positive trend and weak dependence on ABP (for given $ETCO_2$ value), as expected when cerebral autoregulation functions properly to preserve homeostasis – while the surfaces for all AP do not exhibit these characteristics and have variable features.

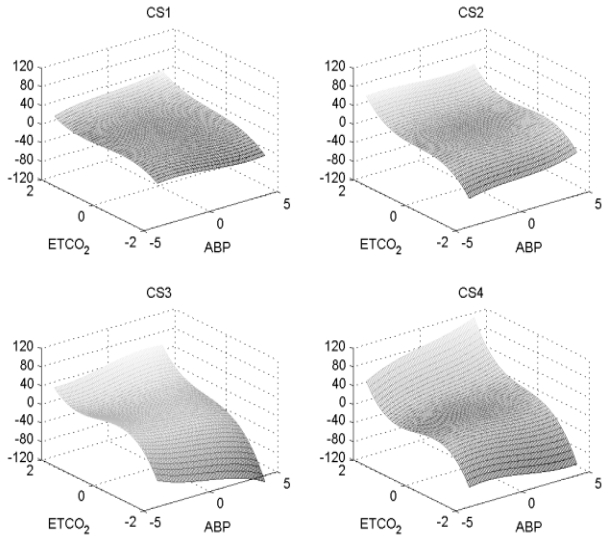

Fig. 5. The nonlinear response surfaces for the four CS computed from the steady-state responses of the nonlinear model.

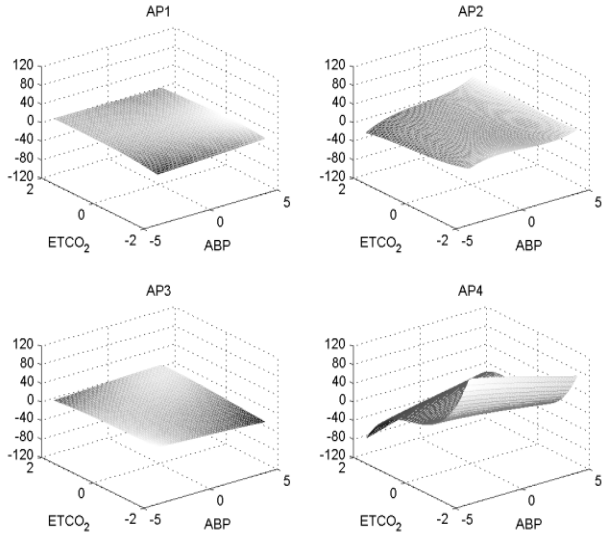

Fig. 6. The nonlinear response surfaces for the four AP computed from the steady-state responses of the nonlinear model.

The most notable among these response-surface features that distinguish the AP surfaces from their CS counterparts is the reduced "effective positive slope with respect to ETCO2 changes", i.e. the "effective CO2 reactivity" that quantifies the degree to which the cerebral flow velocity increases in response to a step increase in ETCO2. This observation (and measurable fact) suggests that the pathophysiology of AD impairs the physiological mechanism by which the homeostatic mechanism of CO2 reactivity is implemented during normal cerebral flow autoregulation. Our working hypothesis is that the AD pathology impairs the perivascular muscle tone of cerebral arteries which may affect the normal autoregulation of cerebral blood flow in response to changes in the CO2 tension in the blood.

A possible biomarker can be constructed from these nonlinear response surfaces that represents an "Effective CO_2 Reactivity Index" (ECRI) – i.e. the overall trend of the nonlinear surface with respect to $ETCO_2$ which is shown in the index-value line of Fig. 7. It is evident that all CS in this set of data have high positive ECRI values, while all AP have very small or negative ECRI values. The mean (and standard deviation) values of the ECRI for two groups are: 17.21 (7.44) for the CS and -7.32 (13.86) for the AP group.

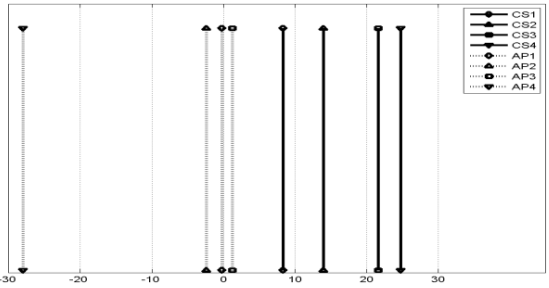

Fig. 7. The values of the "Effective CO_2 Reactivity Index" (ECRI), which is the overall linear trend of the nonlinear response surface with respect to $ETCO_2$, for the four CS (dark) and four AP (light). It is evident that all CS in this set of data have high positive ECRI values, while all AP have very small or negative ECRI values.

It is evident that this index separates clearly the two groups and, therefore, shows great promise as an effective biomarker for early AD diagnosis. Plausible physiological mechanisms that can explain these differences in ECRI are briefly discussed in the following section.

IV. Discussion and Conclusion

We presented a novel biomarker for AD diagnosis that is based on dynamic nonlinear models employing the concept of Principal Dynamic Modes (PDMs). The models are estimated from beat-to-beat time-series data of ABP, $ETCO_2$ and CBFV measurements collected non-invasively in human subjects over a few minutes. The obtained models allow the computation of the nonlinear steady-state response surfaces that are subsequently used to compute the "Effective CO_2 Reactivity Index" (ECRI). The latter was shown to delineate clearly the control subjects from the Alzheimer's patients in this initial set of data and, therefore, constitutes a promising biomarker for AD diagnosis.

Plausible physiological mechanisms that can explain these differences in ECRI include the effect of amyloid deposition on the cerebral vasculature that may impair the normal processes of cerebral flow autoregulation or effects on the endothelial feedback mechanisms of sensing the intravascular CO_2 tension that constitutes the afferent pathway of CO_2 reactivity in cerebral flow autoregulation. The specific attribution of the observed model changes to detailed physiological mechanisms will require future studies in which the physiological interpretation of the obtained PDM models will be the first critical step. It is intriguing to note that the distinctive differences between the two groups (CS and AD) are manifested in the computed nonlinear response surfaces and not in the form of the PDMs that are employed for the estimation of the nonlinear models. In fact, the form of the three PDMs (for each of the two inputs) that were found to be sufficient for the purposes of this modeling task, was found to be invariant across the ensemble. This allowed the determination and utilization of a"global PDM template" that represents the key tool for the implementation of the advocated approach in a practical context. It is evident that the form of the "global PDMs" attains considerable physiological importance and future studies should seek to examine the specific physiological mechanisms that give rise to these specific PDM waveforms (e.g. the prominent spectral peak around 0.02 Hz in 4 of the 6 global PDMs).

Further study is also needed in a larger population of AD patients and control subjects in order to establish the reliability and robustness of these results for potential clinical use, as well as to define the range of operational parameters (e.g. length of collected data) for the proper use of this methodology in a clinical setting.

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