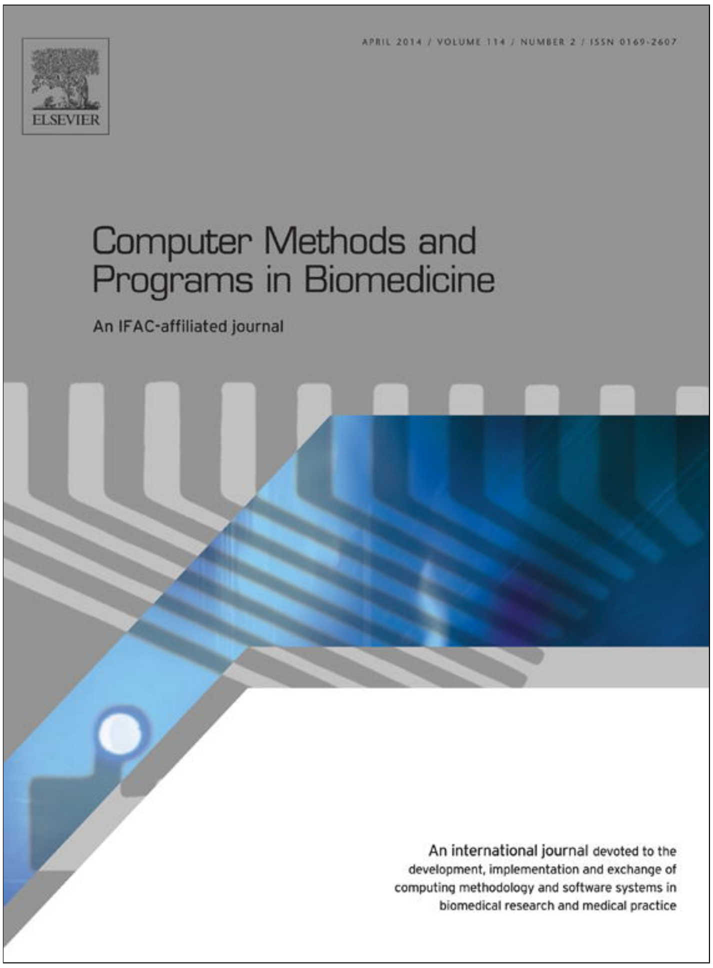
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CAROTID – A web-based platform for optimal personalized management of atherosclerotic patients

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A B S T R A C T

Carotid atherosclerosis is the main cause of fatal cerebral ischemic events, thereby posing a major burden for public health and state economies. We propose a web-based platform named CAROTID to address the need for optimal management of patients with carotid atherosclerosis in a twofold sense: (a) objective selection of patients who need carotid-revascularization (i.e., high-risk patients), using a multifaceted description of the disease consisting of ultrasound imaging, biochemical and clinical markers, and (b) effective storage and retrieval of patient data to facilitate frequent follow-ups and direct comparisons with related cases. These two services are achieved by two interconnected modules, namely the computer-aided diagnosis (CAD) tool and the intelligent archival system, in a unified, remotely accessible system. We present the design of the platform and we describe three main usage scenarios to demonstrate the CAROTID utilization in clinical practice. Additionally, the platform was evaluated in a real clinical environment in terms of CAD performance, end-user satisfaction and time spent on different functionalities. CAROTID

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classification of high- and low-risk cases was 87%; the corresponding stenosis-degree-based classification would have been 61%. Questionnaire-based user satisfaction showed encouraging results in terms of ease-of-use, clinical usefulness and patient data protection. Times for different CAROTID functionalities were generally short; as an example, the time spent for generating the diagnostic decision was 5 min in case of 4-s ultrasound video. Large datasets and future evaluation sessions in multiple medical institutions are still necessary to reveal with confidence the full potential of the platform.

1. Introduction

Atherosclerosis constitutes a chronic degenerative disease, which may affect all arterial beds (cardiac, cerebrovascular, etc.) and it is predominantly characterized by acellular products deposition (e.g. cholesterol and extracellular matrix) and cellular infiltration (e.g. inflammatory and smooth muscle cells) of the arterial wall. The gradual development of atherosclerotic lesions leads to arterial lumen encroachment with detrimental impact on blood supply. The prevalence of a carotid atherosclerotic stenosis increases with age and can be found in 6.9% of the elderly population (>65 years) [1]. It is well established that carotid atherosclerotic lesions (plaques) highly predispose to cerebral ischemic events, with the majority of stroke events being provoked due to the disease [1].

Stroke is one of the leading causes of morbidity, disability and mortality worldwide. Recent reports indicate that, annually, around one in every twelve men and one in ten women die from stroke in the European Union [2], while stroke accounts for 6% of all deaths in the United States [3]. If secular trends continue, 6.5 and 7.8 million stroke deaths globally are estimated by 2015 and 2030, respectively [4]. Stroke consequences, measured in disability-adjusted life years (DALYs), are also expected to rise to 53.8 and 63.8 million DALYs in 2015 and 2030, respectively [4]. These measures of both morbidity and mortality reveal the major economic and social burden posed by stroke, and hence, the need for optimal management of patients with carotid atherosclerosis.

Optimal management of established carotid atherosclerosis is a twofold concept consisting of (a) objective selection of patients who need carotid-revascularization (endarterectomy or carotid artery stenting) to prevent future cerebrovascular events and (b) effective storage and retrieval of patient data, which facilitates frequent follow-ups with the patient and assists diagnosis through easy comparisons with related cases.

Up to now, the therapeutic modality for carotid atherosclerosis is driven by the degree of lumen stenosis and the history of symptoms (i.e. disease-induced neurological disorders) reported by the patient or diagnosed with computerized tomography (CT) or magnetic resonance imaging (MRI) of the brain [5]. However, there is evidence that this clinical practice does not assure valid identification of vulnerable atherosclerotic lesions [6]. The reason is that not all symptoms are always known, because they may not be realized by the patient, while CT/MRI scans are performed in limited cases that stroke or transient ischemic attack is suspected. Moreover, studies have suggested that factors other than stenosis are associated with plaque vulnerability [7] and that features such as the underlying plaque composition [8] and dynamic phenomena occurring within the arterial wall [9] should be also taken into consideration in treatment planning.

Therefore, during the last decade, research has been shifted toward investigating novel biochemical [10], [11] and image-analysis-based [12] markers, which, when incorporated in computer-aided diagnosis (CAD) systems, can aid vascular physicians to decide with higher confidence on plaque vulnerability. Given the high socio-economic burden of carotid atherosclerosis, the use of affordable imaging techniques has become particularly important. Hence, upgrading the role of ultrasound image analysis in this research field is considered a grand challenge by the scientific community [13]. Furthermore, given that ultrasound imaging is the imaging modality of choice for screening, diagnosing, and monitoring carotid atherosclerosis, CAD systems, which are based on ultrasound image analysis, can be easily incorporated in actual clinical practice.

Regarding the second aspect of optimal management of a patient, most hospitals and medical centers use information systems to organize medical data. However, in such systems data retrieval is achieved by querying by attributes (patient name, age or gender) stored either in medical records or in DICOM headers of images. Given that these attributes do not contain any (patho) physiological information, content-based queries to retrieve relevant patient cases remain a challenging task. The solution seems to be located in content-based data annotation [14]. In particular, ontologies and terminologies, and their incorporation in semantic web technologies, constitute a promising approach [15].

We propose a web-based platform named CAROTID as an integrated approach addressing both aspects of optimal management of patients with carotid atherosclerosis. CAROTID relies on a multifaceted phenotype of the atherosclerotic plaque, consisting of ultrasound-image-analysis-based, biochemical and clinical markers, to assist the therapeutic decision by providing objective and personalized clinical assessment. In addition, the embedded intelligent archival module incorporates semantically aided annotation of imaging data, thereby allowing structured data storage and content-based queries. The implementation of CAROTID as a web-based system provides numerous benefits including overcoming interoperability issues, enabling all-time access to the system functionalities, and promoting telematic collaboration in an attempt to reduce medical errors and increase patient safety.

2. Background

2.1. Project background

During the last decade, a major part of the authors' research work has been focused on investigating the potential of ultrasound image analysis in studying the (patho) physiology of the carotid arterial wall [16–25]. As a first step forward, they have applied ANALYSIS, which is an in-house personal-computer (PC)-based software for medical image interpretation, to ultrasound images of the carotid artery and they have demonstrated the applicability and usefulness of image-guided diagnosis for carotid atherosclerosis [16]. However, analyzing ultrasound images of the atherosclerotic vessels is a particularly challenging task due to the low quality, often encountered in ultrasound imaging, and the fuzzy appearance of atherosclerotic plaques [13]. This poses a need for image processing and analysis tools specialized at this clinical application.

Therefore, advanced methodologies have since been developed for quantifying texture and motion properties of the arterial wall from ultrasound image data, thereby providing valuable insights in (a) the allocation of echogenic (fibrous and calcified tissue) and anechoic (blood, lipids, inflammation) regions within the plaque [17,18], (b) strains and local deformations that occur within the arterial wall [9,19,20], (c) variations in motion activities between different plaque materials [21], (d) mechanical interactions of atherosclerotic plaque components [21], and (e) the ability of the collected information in discriminating vulnerable plaques [9,17,18,20] and evaluating their response to therapy [22].

Particular emphasis has been given on assuring the validity of image analysis results. Therefore, the authors have thoroughly investigated the effects of scanner settings [19,23], noise presence [9,19,20] and image normalization [23] on texture and motion analysis, and appropriate optimization procedures have been performed toward maximizing the algorithms' accuracy and robustness. Furthermore, automated, i.e. user-independent, methodologies have been developed to segment the arterial wall in ultrasound images [24,25], which allows more accurate measurements.

Significant steps have been also made by the authors to address the explosive growth in the storage of medical imaging data collected by radiologists [26,27]. Effective and efficient data management has been achieved through web-based approaches that offer semantically aided data annotation and retrieval.

CAROTID was embedded in a joint project of academic and clinical institutions and a commercial clinical software manufacturer. The goal was the conception and development of a system which incorporates the gained experience and research results of the involved partners on both CAD and data management to assist the clinical practice for carotid atherosclerosis.

2.2. Related work

Significant attempts have been made toward designing smart CAD tools for carotid atherosclerosis [13]. In all cases, the underlying idea was computer-assisted discrimination of "high-risk" atherosclerotic lesions from "low-risk" ones, through supervised training of sophisticated classifiers using ultrasound-image-analysis-based features of symptomatic and asymptomatic cases. It was concluded that support vector machines (SVM) are the most popular classification tool in this area. Moreover, it was noted that although motion characteristics are able to provide valuable functional information, they have been considered in limited classification attempts. The same stands for clinical and biochemical markers, for which studies have suggested that they may have a positive impact on the classification performance [8,10,11].

Although major efforts have been made toward the computerization of diagnosis for the disease, only a few integrated systems have been developed in the field. Specifically, the "Plaque Texture Analysis" software has been presented for image-intensity normalization and texture measurements in ultrasound images of the carotid artery [28]. Furthermore, the recently developed "Atheromatic" estimates textural plaque features from carotid ultrasound images, feeds them to an offline-trained SVM and provides a CAD response [29]. Both systems are PC-based software packages with promising performances. However, studies in different research areas have demonstrated the numerous advantages offered by web-based CAD systems [30–32], especially when cooperating with advanced archival modules [31].

CAROTID incorporates the valuable lessons which are provided by the related work and moves a step forward in integrated CAD systems for carotid atherosclerosis by (a) including motion-based features in ultrasound image analysis, (b) adding biochemical and clinical markers in CAD, (c) combining CAD with an intelligent archival tool in a unified system, (d) considering continuous re-optimization of the CAD tool as the data repository is enriched, and (e) being implemented as a web-based platform.

3. Design considerations

CAROTID allows access via Internet or intranet. The architecture of the platform is based on LAMP, which is a broadly open-source software bundle (Linux, Apache, MySql, PHP) for web applications. The two aspects of optimal management of patients with carotid atherosclerosis are addressed by two interconnected components, namely the CAD module and the intelligent archival system (Fig. 1). Both components are connected to the data repository, where multi-source patient data are stored.

CAROTID user requirements were specified in collaboration with a local advisory board consisting of five potential end users (vascular physicians). The recorded requests ranked on top priority the following features: (a) ease-of-use by less-experienced users, (b) computational efficiency, (c) security in patient data, and (d) error minimization in data entry.

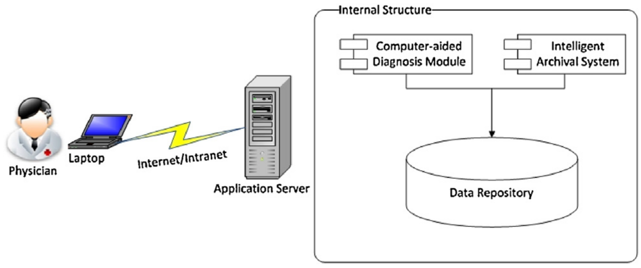


Fig. 1 – High-level design of the CAROTID platform.

4. Description of the platform

4.1. *Architecture*

The CAD module includes the data-driven diagnosis component (Fig. 2), which processes the available patient data, estimates a number of features representing the disease phenotype, and generates a diagnostic decision (CAD response) on plaque vulnerability. More details on the data-driven diagnosis module are presented in Section 5. The generated information is stored at the data repository and the CAD response is available upon request to the user via a modal dialog. The algorithms that form the CAD module have been developed in Matlab and ported into C++ libraries using the Matlab compiler deployment tool.

The intelligent archival system offers two basic functionalities, namely data input and retrieval, served by data-entry and querying interfaces, respectively (Fig. 3). Through the data-entry interfaces, imaging data are annotated with semantic features and, together with biochemical markers and clinical information, are uploaded to the platform. Image annotation consists in specifying the imaged region of the carotid artery, i.e. the anatomic position of the atherosclerotic plaque, and the imaging modality. This task is performed using the FMA ontology [33], which describes the anatomy of human body, and the RadLex terminology [34], which describes imaging modalities. Both FMA and RadLex are available via web service through the NCBO bioportal (http://bioportal.bioontology.org/).

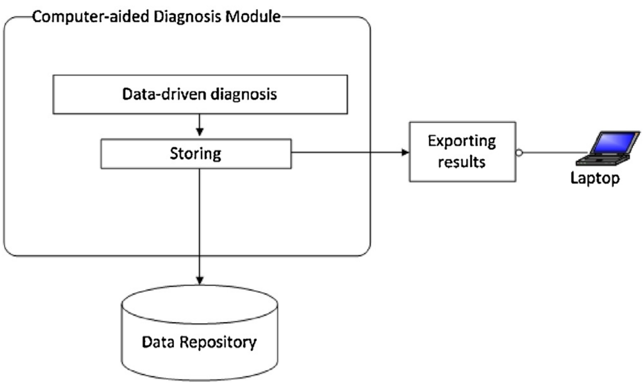


Fig. 2 – Design of the computer-aided risk diagnosis module.

The querying interfaces are used to retrieve medical data based on criteria, which are specified by the user. Through a separate search-interface, the platform offers conventional and more complex patient-based queries. Moreover, in the CAD module, the user can easily retrieve related, in terms of disease phenotype and/or plaque vulnerability, cases. Data annotation with arterial region and imaging modality also allows selective imaging data retrieval for the related cases.

4.2. *Usage scenarios*

CAROTID utilization by potential final users is enlightened through three usage scenarios, including clinical decision support, development of a rich data repository which can be used to design future studies, and educational services.

The typical usage scenario involves CAROTID as a support tool of clinical decision which advices on treatment modality. Once logged on to the platform, the user is able to enter patient's medical data through the data-entry interfaces. Moreover, the user is offered the possibility to consult the CAD response characterizing the atherosclerotic plaque as "high-risk" or "low-risk" and, accordingly, decide if either carotid-revascularization or conservative therapy is required. Furthermore, the user is urged to retrieve similar past cases, so that the diagnosis at hand is more easily taken by comparison. This service enhances the trust of the user in the platform, because it provides him with case-based evidence, thereby acting as a physician with accumulated empirical knowledge.

Since CAROTID is a web-based platform, input and retrieval processes are available both locally, i.e. at the hospital where the medical examination takes place, and remotely. As a result, the physician is offered an all-time access both to the

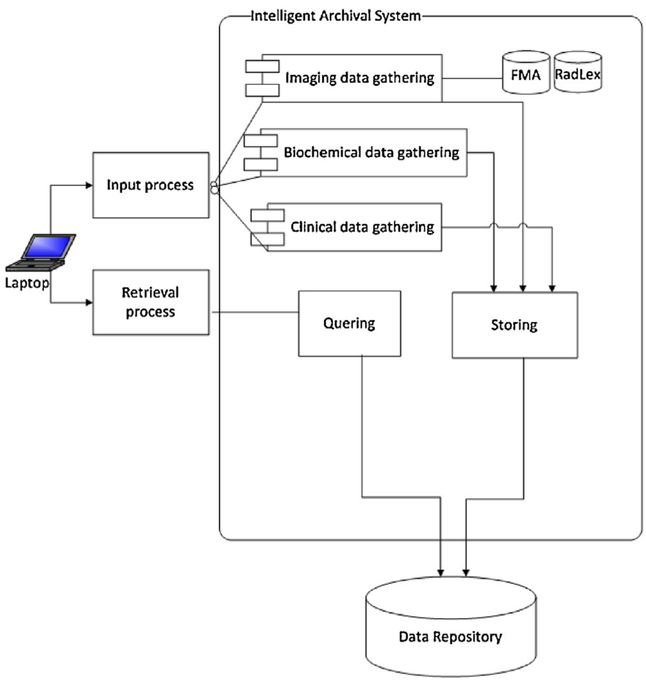


Fig. 3 – Design of the intelligent archival system.

diagnostic services and the stored data of patients, and can collaborate with other remote experts.

Another interesting CAROTID usage scenario is the collection of data and findings regarding carotid atherosclerosis worldwide. This continuously growing repository of imaging, biochemical and clinical data is accessible by collaborating clinicians and researchers. Given the lack of large databases of patients with carotid atherosclerosis and the difficulties in carrying out prospective cohort studies, this repository is expected to facilitate the design and implementation of future studies investigating causative factors and risk markers for the disease. Moreover, the use of the same dataset by different research groups allows direct and unbiased comparisons and associations, which enhances coherence in related studies and eventually leads to more valid and accurate conclusions.

Finally, CAROTID serves two educational scenarios: (a) CAROTID users share the accumulated knowledge for carotid atherosclerosis, which offers a multi-scientific view of the disease, and (b) by retrieving stored cases, vascular physicians are trained in identifying the phenotype of severe atherosclerotic lesions.

4.3. *Implementation issues*

CAROTID implementation followed the design specifications. Particular emphasis was put on developing user-friendly interfaces, which offer intuitive navigation to the different modules of the platform. In the same line of work, one-button CAD services were considered and the platform offers bilingual (English and Greek) user-interfaces. The request for enhanced computational efficiency was considered in the selection of the server which hosts CAROTID, while time-consuming repetitions, when different users request the CAD "opinion" for the same clinical case, are avoided by storing the output of the CAD module.

Data security and integrity were ensured through data anonymization and encryption, SSL data exchange, monitoring of the users' actions, and granting different administrative and view rights according to the user and the usage. Additionally, patient data are managed according to the personal data protection laws of the Greek state (DL 2472/1997, DL 2479/1997), which are harmonized with the EU regulations. Finally, range and consistency checking was included to avoid errors in data-entry (duplicates and invalid values). The use of semantic data annotation is also very important toward error minimization, because it allows for standardized data-entry.

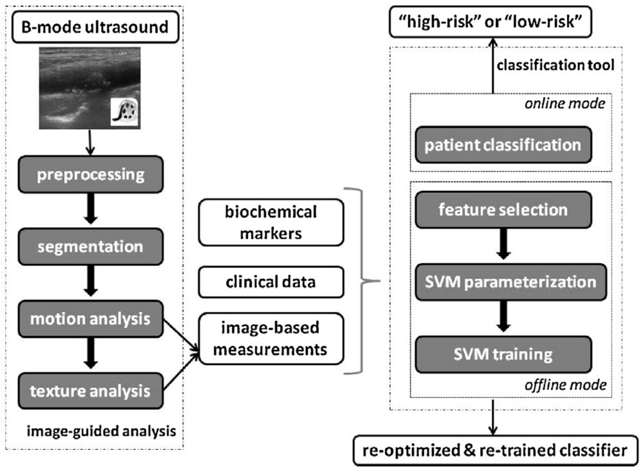
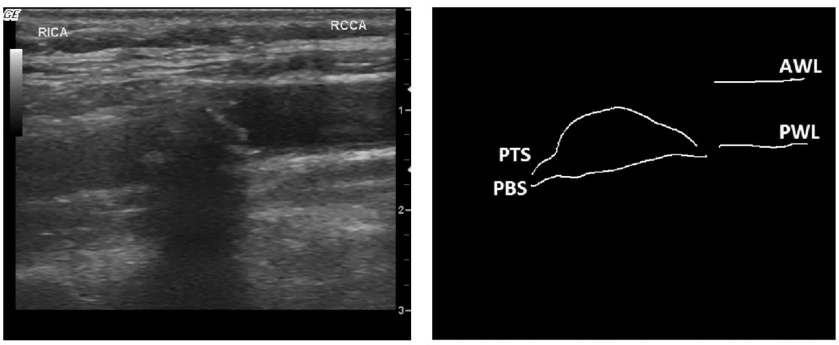


Fig. 4 – Workflow for computer-aided data-driven diagnosis.

5. Data-driven diagnosis

This section gives a detailed description of the tasks composing the CAD functionality of CAROTID (Fig. 4). The CAD module has two functionality modes. The online mode is activated when medical data for a new patient are uploaded to the platform and the user asks for a diagnostic decision. A number of image-based measurements are then estimated and, combined with biochemical markers and the clinical profile of the patient, are fed to the classifier. Subsequently, the offline-trained classifier responds on the severity of the atherosclerotic lesion.

The offline mode is activated when the user enters both medical data for a new patient and sufficient information about plaque characterization as symptomatic or asymptomatic. Sufficiency lies in validated presence or absence of disease-induced disorders. In this case, the estimated



(a) (b)

Fig. 5 – (a) B-mode ultrasound image of a longitudinal section of a carotid artery with an atherosclerotic plaque on the posterior (farthest from the probe) wall. (b) Defined regions of interest for the same case.

image-based, biochemical and clinical indices are used to improve the performance of the classifier.

5.1. *Image-guided analysis*

Image-based measurements are estimated with a series of image processing and analysis procedures, which are applied to a temporal sequence (video) of digitized B-mode ultrasound images of a longitudinal section of the carotid artery (Fig. 5(a)). B-mode ultrasound is a two-dimensional presentation of echo-producing interfaces. In B-mode ultrasound images of a longitudinal section of the artery, the three different layers of the wall (intima, media, and adventitia) are recognized as three echo zones. Moreover, dynamic B-mode ultrasound imaging of longitudinal sections of the arterial wall allows the estimation of tissue motion in two dimensions, namely longitudinal, i.e. along the vessel axis, and radial, i.e. along the vessel radius, and perpendicular to the longitudinal one.

Firstly, in order to assure comparable measurements in case of images obtained by different operators or using different equipments, image intensities ([0: black, 255: white]) are linearly adjusted so that the median gray level value of the blood is 0, and the median gray level value of the adventitia is 190 [21].

Afterwards, four regions of interest (ROIs), namely the posterior (PWL) and anterior wall-lumen (AWL) interfaces and the plaque top (PTS) and bottom surfaces (PBS), are semi-automatically defined in the first image of the sequence (Fig. 5(b)); PTS and PBS correspond to the region of the plaque, while PWL and AWL are healthy parts of the arterial wall. The segmentation step consists of three main stages. The first stage is the automatic selection of the image area containing the carotid artery [24]. This stage is important because it reduces the computational cost of subsequent image-analysis tasks. At the second stage, PWL and AWL are automatically identified using an active-contour-based algorithm previously presented in [25]. Briefly, using an initial contour approximation, a Hough Transform methodology [24] generates initial active contours, which are then processed and deformed by minimizing an energy function, which consists of external forces, internal forces and user-defined constraints [25]. At the third stage, the user manually traces PTS and PBS via a modal window and is also allowed to refine the identified PWL and AWL.

For the purpose of motion analysis, all pixels composing the four identified ROIs, as well as the whole plaque region (i.e., the region contoured by PTS and PBS), are selected as motion targets and the $OF_{LK(WLS)}$ algorithm [20] is used to estimate their radial and longitudinal positions across time. From the produced waveforms, pixel-wise indices representing radial, longitudinal, and total motion amplitudes, velocities, and diastole-to-systole displacements are estimated [21]. Moreover, the relative movements between (a) PTS and PBS, (b) PWL and AWL, (c) PTS and PWL, and (d) PBS and PWL, are expressed in strain indices by repeating the methodologies described in [9,20] for multiple pairs of pixels of the selected ROIs. A number of descriptive statistical measures (minimum, maximum, mean, median, standard deviation, skewness, kurtosis, entropy) of the estimated kinematic and strain indices are used as the final motion-based measurements.

The last step in image-guided analysis is the estimation of textural features of the plaque. Plaque texture is measured using first and second-order statistical properties [21], as well as multiresolution features [17] of image intensities corresponding to the region of the plaque. These features are estimated for specific instants of the cardiac cycle, namely, systole and diastole, which are identified as the time points corresponding to the maximum and minimum radial distance, respectively, between PWL and AWL.

5.2. *Biochemical markers and clinical data*

The biochemical markers which are recorded for each patient are blood-derived agents, some of which have been associated with plaque stability and risk stratification [35]: red/white-blood-cells indices, hemoglobin, hematocrit, lymphocyte surface markers, platelet indices, urea, creatinine, transaminases, fasting total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglycerides, glucose, C-reactive protein, fibrinogen, matrix metalloproteinases (MMP-1, MMP-2, MMP-7, MMP-9), tissue inhibitors of metalloproteinases (TIMP-1, TIMP-2), cytokines (IL-1β, IL-6, TNF-a), and insulin resistance (HOMA-IR).

In CAROTID, the clinical profile of the patient consists of the following data: age, gender, personal and family medical history, body mass index, waist circumference, fat mass, ankle-brachial index, cardiac hemodynamic parameters (heart rate, systolic and diastolic arterial pressures), and habits (smoking, diet, and physical exercise). Body mass index, waist circumference, fat mass, and ankle-brachial index form the set of candidate clinical markers for patient characterization as “high-risk” or “low-risk”.

5.3. *Classification tool*

The classification tool is an implementation of SVM, which, compared to other classification methods, is less affected by the so-called “curse of dimensionality” and, therefore, is suitable for large sets of features [36]. SVM are learning machines based on intuitive geometric principles, aiming to the definition of an optimal hyper plane which separates the training data so that a minimum expected risk is achieved [37]. The training method is based on a nonlinear mapping of the dataset, using kernels that have to satisfy Mercer’s theorem. In this study, a Gaussian radial basis function (RBF) kernel was used. In this case, the SVM training algorithm is affected by the parameter s, a scaling factor of the Gaussian kernel, which has to be appropriately adjusted to optimize the performance of the classifier.

In the offline mode, the SVM is re-optimized and re-trained using all the stored cases for which, at that time point, there is sufficient information on disease-induced disorders. The first step of the re-optimization process is feature selection, in which an optimal subset of the whole feature representation is selected. Specifically, considering the extracted features for the patients, the Wilcoxon rank sum test is applied on each feature vector and the *p*-value is used as a measure of how effective the feature is at separating “symptomatic”

Table 1 – List of selected features which are used in patient characterization as "high-risk" or "low-risk" in the current version of the platform.

Motion-based (N = 23)	Over PWL: LSI [9] skewness Over PWL: LSI [9] kurtosis Over AWL: median of MV_{rad} [21] Over AWL: median of *MVA* [21] Over AWL: median of MD_{long} [21] Over AWL: max of *MDA* [21] Over whole plaque region: MD_{rad} [21] kurtosis Over whole plaque region: MV_{long} [21] kurtosis Over whole plaque region: MD_{long} [21]kurtosis Over PTS: *AmA* [21] kurtosis Over PTS: *RMA* [21] kurtosis Over PTS: *LMA* [21] kurtosis	Over PTS: MD_{rad} [21] skewness Over PTS: MD_{rad} [21] kurtosis Over PTS/PWL pairs of pixels: max of LSI [20] Over PTS/PWL pairs of pixels: mean of LSI [20] Over PTS/PWL pairs of pixels: std of LSI [20] Over PTS/PWL pairs of pixels: LSI [20] skewness Over PTS/PWL pairs of pixels: LSI [20] kurtosis Over PTB/PWL pairs of pixels: mean of LSI [20] Over PTB/PWL pairs of pixels: median of LSI [20] Over PBS/PWL pairs of pixels: LSI [20] skewness Over PBS/PWL pairs of pixels: LSI [20] kurtosis
Textural (N = 12)	Systolic images: energy, $\theta = 0°$ [21] Systolic images: energy, $\theta = 45°$ [21] Systolic images: energy, $\theta = 90°$ [21] Systolic images: energy, $\theta = 135°$ [21] Systolic images: mean of Dh3Dh2Dh1 [17] Systolic images: std of Dh2A1 [17]	Diastolic images: energy, $\theta = 0°$ [21] Diastolic images: energy, $\theta = 45°$ [21] Diastolic images: energy, $\theta = 90°$ [21] Diastolic images: energy, $\theta = 135°$ [21] Diastolic images: homogeneity, $\theta = 0°$ [21] Diastolic images: mean of Dh3A2A1 [17]
Biochemical (N = 4)	Fibrinogen White-blood-cells count	Platelet count Plateletcrit

and "asymptomatic" groups. Features having strong discrimination power (i.e. p-values ≤ 0.05) are selected and principal component analysis is then used to identify and remove correlations among them. In the second step, the set of selected features is used to parameterize, in terms of s, the SVM using leave-one-out cross validation. Specifically, classification performance is measured in terms of accuracy (degree of veracity of the diagnostic decision) for different values of s in the range of [0.1–10], and the value that gives the highest classification performance is selected. In leave-one-out, a single observation (patient) is used as the testing sample, and the remaining observations compose the training dataset; this is repeated such that each observation is used once as the testing sample. Leave-one-out is a popular re-sampling technique for performance evaluation for classification schemes, because it preserves unbiased results for small-sized samples [38]. After re-optimization, the SVM is re-trained using the selected feature subset and value of s. It is noted that in re-training, patients are not separated in training and testing datasets.

In the online mode, the offline optimized and trained SVM is fed with the collected features (image-based measurements, biochemical indices and clinical markers) for a new patient, separates the indicated, by the optimization process, subset of features, and classifies the case as "high-risk" or "low-risk".

6. Status report

The development of both the intelligent archival system and the computer-aided risk stratification tool has been completed, while the authors' ongoing work focuses on systematically evaluating and improving the different modules. CAROTID was used by vascular physicians at the "Attikon" university hospital of Greece and complete sets of imaging, biochemical, and clinical data for 96 patients (aged 50–80 years) with established carotid atherosclerosis (diagnosed carotid stenosis > 30%) were successfully imported in the platform. Among those patients, 24 had experienced an ischemic cerebrovascular event (stroke or transient ischemic attack) associated with the carotid stenosis ("symptomatic" group), while 72 had no neurological symptoms ("asymptomatic" group) within a 6-month time period from the time of examination. In all cases, the presence or absence of symptoms was validated with CT/MRI scans of the brain. No statistically significant difference was found in the degrees of stenosis (Wilcoxon rank sum test p-value = 0.10), nor in the ages between the two groups (Wilcoxon rank sum test p-value = 0.45). All patients included in the platform gave their informed consent to the scientific use of the data.

The classification tool was optimized and trained, using the estimated features for the 96 stored cases, as described in Section 5. The step of feature selection generated an optimal subset of features, consisting of 23 motion-based, 12 textural, and 4 biochemical indices (Table 1). The feature subset does not include any clinical data, because no statistically significant differences in clinical markers were found between the two groups of patients. Using this subset of features for the 96 patients and the leave-one-out cross-validation process, SVM was parameterized with $s = 3.9$. At this point, the SVM classification accuracy was 87%, which was very satisfying, considering that related attempts have reached 73.1–99.1% accuracy values [13] and that, if only the stenosis-degree was considered, the CAD performance in the same dataset would have been 61%. Classification performance in terms of sensitivity and specificity were also measured and found equal to 75% and 97%, respectively.

To evaluate the computational efficiency of CAROTID, the internal execution time for the main CAROTID functionalities was measured 100 times and the average values of the corresponding measurements were recorded in each case. The elapsed time between the upload of patient data and the generation of the diagnostic decision depends on the time duration of the B-mode ultrasound video; for a 4 s video, the average elapsed time was 5 min. The average query time for retrieving stored cases through the search-module was

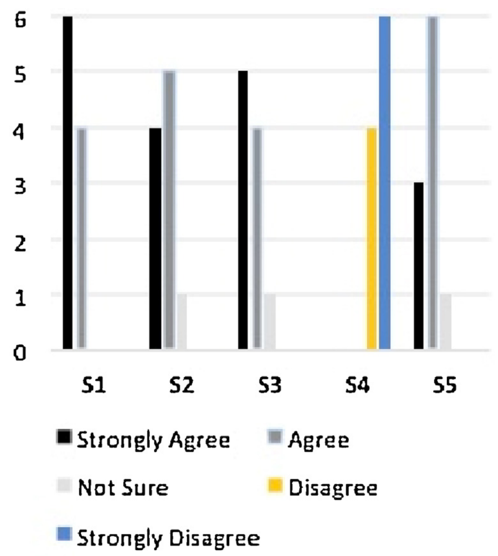


Fig. 6 – Bar charts representing end-users satisfaction. The height of each bar represents the number of users who selected the corresponding answer to the statement Si (i = 1–5).

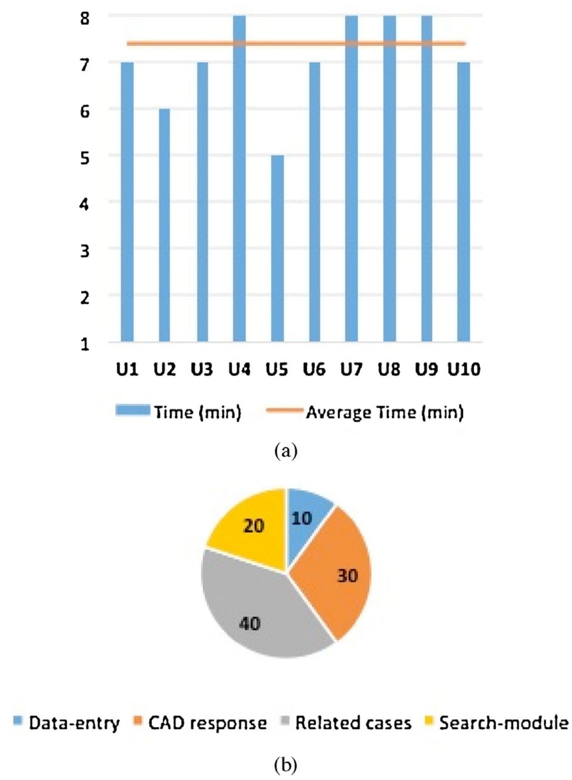


Fig. 7 – Statistics for a typical CAROTID use representing (a) the total time spent by each user Uj (j = 1–10) and (b) % percentage of time spent by all users in each of the four CAROTID functionalities.

118 ms, while the average time for retrieving related cases through the CAD module was 1.73 ms.

The end-user satisfaction from CAROTID and CAROTID use-statistics were evaluated by distributing a questionnaire to ten potential users (U1-U10) who were granted a 3-month free access to the platform. The physicians were asked to select among 'strongly agree', 'agree', 'not sure', 'disagree', and 'strongly disagree' for five statements representing user satisfaction: (S1) CAROTID is easy to navigate, (S2) The computational performance of CAROTID is satisfactory, (S3) CAROTID is useful in clinical diagnosis, (S4) Patient data are misused, (S5) CAROTID meets my expectations. The answers are summarized in Fig. 6, revealing an overall user satisfaction from the platform.

Moreover, the users were asked about the amount of time they spent in each CAROTID functionality (data-entry, CAD response, retrieval of related cases, and search-module) in a typical use. Based on their answers, it was concluded that the duration of a typical CAROTID use ranged from 5 min to 8 min (Fig. 7(a)) and data retrieval, either as a typical search functionality or as a CAD service, mostly attracted the users' attention (Fig. 7(b)).

Fig. 8 depicts snapshots of CAROTID usage. Specifically, Fig. 8(a) corresponds to data entry for a new patient at the stage of importing and annotating ultrasound image data. Fig. 8(b)

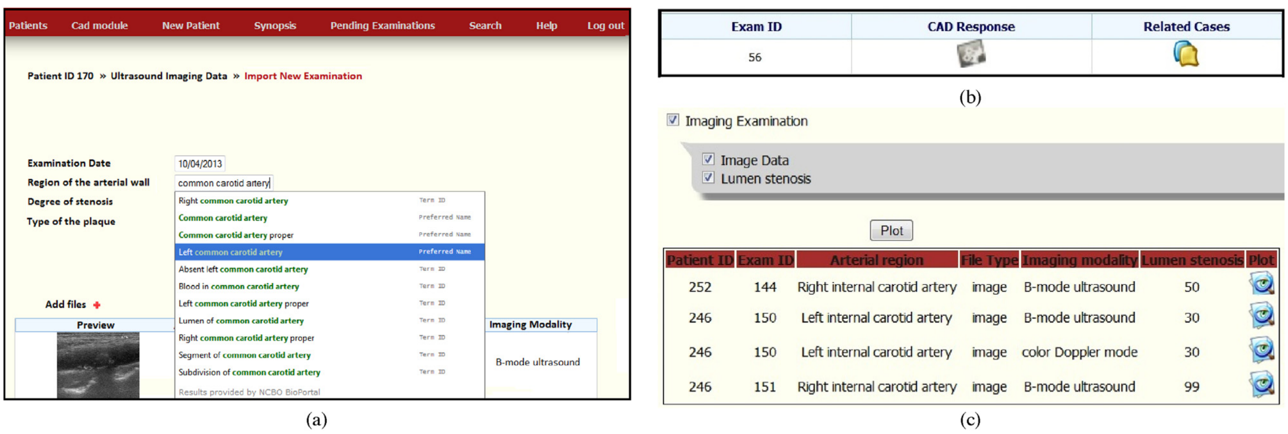


Fig. 8 – Snapshots of CAROTID usage at the stage of (a) importing ultrasound imaging data for a new patient, completing the examination date, degree of stenosis, and type of the plaque [39], and annotating the position of the atherosclerotic plaque using FMA ontology, (b) navigating to the one-button CAD services and (c) retrieving imaging data for stored cases.

illustrates the user navigation to the one-button CAD services and Fig. 8(c) presents the stage of retrieving imaging data for stored cases.

7. Lessons learned

The design and implementation of the CAROTID platform constitute an attempt to address the challenge of optimal management of atherosclerotic patients and assist the clinical practice for carotid atherosclerosis by serving both as a diagnostic advice system and as a tool to effectively store and retrieve patient data. This twofold functionality is a significant advantage of CAROTID in comparison with other integrated CAD systems for carotid atherosclerosis [28,29] which offer only a classification response.

In terms of CAD functionalities, CAROTID assists the diagnostic process by additionally encouraging the retrieval of similar past cases, which enhances the trust of the physician in the generated diagnostic decision. Moreover, the CAROTID diagnostic decision is based on a multifaceted description of the disease which includes image-based, biochemical and clinical features. Regarding image-based features, CAROTID also first considers dynamic phenomena occurring within the arterial wall, expressed in terms of kinematic and strain features, in the classification scheme.

However, the major strength of CAROTID lies in its web-oriented implementation, which allows the use of the platform by multiple health-care providers. This offers a number of privileges which are summarized to the following. Firstly, given that multi-center data collection is facilitated and the data repository is enriched with large volumes of multi-origin data, the continuously re-optimized classification tool can achieve its full potential. Secondly, CAROTID allows the physician to gain access to and consult more data than a single health care provider possesses in his local setting. Furthermore, collaborative clinical decisions are promoted, which is of particular significance for both the patient safety and the support of less-experienced physicians.

The preliminary evaluation results (Section 6), including (a) questionnaire-based end-user satisfaction in terms of ease-of-use, clinical usefulness and patient data protection, and (b) short times for various platform functionalities, form an encouraging feedback on the expectations posed by CAROTID design. However, large datasets and extensive assessment tests on the platform are still necessary to demonstrate its potential with adequate confidence and make valid comparisons with other CAD tools. Moreover, technical issues need to be addressed to (a) provide fully automated segmentation of ROIs and (b) reduce the required time for generating the CAD decision.

8. Mode of availability of the platform

CAROTID platform in its current status is available at carotid.vidavo.eu. Access rights are granted upon request.

9. Future plans

Future steps include the beta release of CAROTID to be used by multiple vascular physicians in international medical institutions. Remarks and recommendations that will be gathered at the end of the trial period will form a valuable feedback for future versions of the platform. Moreover, the collection of large volumes of patient data is expected to reveal the full potential of the classification tool and enhance the capability of the platform to provide trustful CAD services for carotid atherosclerosis.

Moreover, a number of future actions will further enhance the efficiency, interoperability, feasibility, and functionalities of CAROTID. Firstly, automatic methodologies for segmenting the region of the plaque will be developed and incorporated in the platform. Furthermore, algorithms will be transferred into new web technologies, such as HTML5 and WebGL, which is expected to make (a) the data processing algorithms lighter and faster and (b) CAROTID functionalities compatible with future technical progress in browsers and portable devices.

Finally, inspired by similar attempts on CAD for coronary-artery [40] and urinary-system [41] diseases, the derived conclusions on risk markers for carotid atherosclerosis will be described with the use of semantic web. All risk factors will be expressed as classes and properties of a medical ontology specially designed for the disease. This ontology will facilitate the re-use and discovering of new knowledge and will also achieve clarity, unambiguity, proof tracing, and interoperability among institutions.

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