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Cardiac ScoreCard: A diagnostic multivariate index assay system for predicting a spectrum of cardiovascular disease

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ABSTRACT

Clinical decision support systems (CDSSs) have the potential to save lives and reduce unnecessary costs through early detection and frequent monitoring of both traditional risk factors and novel biomarkers for cardiovascular disease (CVD). However, the widespread adoption of CDSSs for the identification of heart diseases has been limited, likely due to the poor interpretability of clinically relevant results and the lack of seamless integration between measurements and disease predictions. In this paper we present the Cardiac ScoreCard—a multivariate index assay system with the potential to assist in the diagnosis and prognosis of a spectrum of CVD. The Cardiac ScoreCard system is based on lasso logistic regression techniques which utilize both patient demographics and novel biomarker data for the prediction of heart failure (HF) and cardiac wellness. Lasso logistic regression models were trained on a merged clinical dataset comprising 579 patients with 6 traditional risk factors and 14 biomarker measurements. The prediction performance of the Cardiac ScoreCard was assessed with 5-fold cross-validation and compared with reference methods. The experimental results reveal that the ScoreCard models improved performance in discriminating disease versus non-case (AUC = 0.8403 and 0.9412 for cardiac wellness and HF, respectively), and the models exhibit good calibration. Clinical insights to the prediction of HF and cardiac wellness are provided in the form of logistic regression coefficients which suggest that augmenting the traditional risk factors with a multimarker panel spanning a diverse cardiovascular pathophysiology provides improved performance over reference methods. Additionally, a framework is provided for seamless integration with biomarker measurements from point-of-care medical microdevices, and a lasso-based feature selection process is described for the down-selection of biomarkers in multimarker panels.

1. Introduction

Cardiovascular disease (CVD) is a diverse class of diseases affecting the cardiovascular system. Although mortality rates are declining somewhat, CVD remains the leading cause of death and serious illness in the United States, accounting for nearly one of every three deaths (Go et al., 2014). With staggering direct and indirect costs, CVD is a major contributor to rising healthcare expenditure in the U.S. For instance, heart failure (HF) costs alone are projected to double by 2030, with every US taxpayer paying up to $244 each year (Heidenreich et al., 2013). The most common type of CVD is coronary artery disease (CAD), which is character-

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ized by atherosclerotic plaque buildup that begins early in life and slowly progresses over time. About 50% of cardiovascular deaths occur due to sudden cardiac death, and a vast majority due to CAD (Mehta, Curwin, Gomes & Fuster, 1997). In a significant proportion of these events, sudden cardiac death occurs without any history of CVD. These individuals may have only one, or none, of the traditional risk factors. Thus, novel biomarkers approaches may be necessary to supplement traditional risk factors in CVD diagnosis and prognosis. Early detection and frequent monitoring of both traditional risk factors and novel biomarkers has the potential to save lives and reduce unnecessary costs due to CVD morbidity and mortality.

To aid in disease identification and patient monitoring, clinical decision support systems (CDSSs) are being increasingly adopted to provide clinicians with personalized assessments or recommendations to assist in medical decisions. A popular topic in expert systems and artificial intelligence in medicine, a CDSS is defined as “any electronic system which aids in the clinical decision making process in which data from individual patients are used to generate personalized assessments or recommendations that are then presented to clinicians for consideration” (Kawamoto, Houlihan, Balas & Lobach, 2005). The CDSSs have several advantages relative to standard of care including the potential for faster diagnosis, improved prediction performance, and reduced medical costs via elimination of unnecessary testing. However, clinicians may be reluctant to adopt certain CDSSs which are based on “black box” methods and provide results that are not easily interpreted in a clinical context. Likewise, lack of seamless integration between biomarker measurements and disease predictions may serve as a barrier to the broad-scale uptake of CDSS technologies. In an attempt to bridge this gap in this paper we present a CDSS for the prediction of a spectrum of CVD called the Cardiac ScoreCard. Based on a lasso logistic regression approach, the Cardiac ScoreCard algorithms combine patient demographics and novel protein biomarker data to form a single-valued “cardiac score” and clinically interpretable logistic regression coefficients. When fully developed, the Cardiac ScoreCard is intended to provide individualized assessments of cardiac health that are seamlessly integrated with biomarker measurements from point-of-care medical microdevices (McRae et al., 2015).

When fully developed, mass produced, and validated clinically, lab-on-a-chip systems have the potential to simplify lab analysis routines, reduce sample and reagent volumes, shorten analysis times, and lower the cost of healthcare. There is a strong need for these medical microdevices that are both cost-effective and analytically robust. The programmable bio-nano-chip (p-BNC) is a flexible detection platform that rivals established remote laboratory methods (Jokerst et al., 2011; McRae et al., 2015). Recent work has demonstrated the ‘macro’ laboratory based p-BNC’s multiplexed analyses of diverse analyte classes across several disease applications (Chou et al., 2012; Jokerst & McDevitt, 2009; Jokerst et al., 2010), for example, in the areas of HIV immune function (Rodriguez et al., 2005), cardiac heart disease (Christodoulides et al., 2005a; Christodoulides et al., 2005b; Christodoulides et al., 2012; Floriano et al., 2009), ovarian cancer (Raamanathan et al., 2012), oral cancer (McDevitt et al., 2011), prostate cancer, and the detection of drugs of abuse (Christodoulides et al., 2015). While the p-BNC sensor platform offers a solution to the acquisition of cardiac biomarker measurements, the scope of this manuscript primarily covers the methods of converting biomarker and risk factor data streams into clinically usable and interpretable results. The various Cardiac ScoreCard models are intended to be used in conjunction with the p-BNC, but they may act as standalone calculators when provided the necessary input parameters.

The objective of this work is to develop predictive models for a spectrum of CVD and do so in a manner that can be integrated seamlessly with multi-parameter biomarker measurements. This paper will describe the process of developing the Cardiac ScoreCard and summarize the initial performance characteristics observed for two areas of cardiac disease, that is (i) cardiac wellness and (ii) HF diagnosis. The remainder of this paper is organized as follows. Section 2 reviews the literature for work related to CVD prediction models. Section 3 introduces the Cardiac ScoreCard approach and the role of biomarkers in CVD prediction. Descriptions of the clinical study data and the lasso logistic regression methods are provided in Section 4. Results and discussion for the cardiac wellness and HF models are covered in Section 5. Lastly, Section 6 concludes the paper with a brief summary of the models developed, their significance, and future directions.

2. Related work

2.1. Literature review

Clinical decision support tools are powerful expert systems with the potential to provide faster diagnoses, improved prediction performance, and reduced medical costs by eliminating unnecessary testing. Several clinical decision support systems and related prediction models for the identification of heart diseases have been developed over the years, implementing a variety of techniques. One of the most commonly used techniques is artificial neural networks (ANN) due to its superior prediction performance and ability to identify complex nonlinear patterns in the data (Kurt, Ture & Kurum, 2008). In one of the first implementations for heart disease applications, an ANN was trained on chest pain patients presenting to the emergency room for the diagnosis of AMI (Baxt, 1991). Similarly, Furlong, Dupuy and Heinsimer (1991) developed an ANN for diagnosing AMI using serial cardiac enzyme data. Yan, Jiang, Zheng, Peng and Li (2006) implemented a multilayer perceptron-based model that can differentially diagnose five different cardiac outcomes. Mehrabi, Maghsoudloo, Arabalibeik, Noormand and Nozari (2009) compared multilayer perceptron and radial basis function neural networks for the discrimination of HF and COPD in 266 patients and 42 clinical variables.

Aside from neural networks, various other techniques have been successfully implemented. Conforti and Guido (2005) used a Support Vector Machine (SVM) approach to classify AMI and non-case patients. Ion Titapiccolo et al. (2013) supported the use of random forest models in predicting cardiovascular outcomes in hemodialysis patients due to their ability to learn non-linear patterns in the feature space. Vila-Francés et al. (2013) employed a Bayesian network for the prediction of unstable angina (UA). Bayesian models are attractive for clinical use because the relationships among variables are represented by a graph and are, thus, easily interpreted by clinicians. Ensemble methods are a useful strategy for increasing the generalization performance by combining the posterior probabilities or predicted values from several base learners. Das, Turkoglu and Sengur (2009) improved prediction performance using an ANN ensemble method for heart disease diagnosis on the Cleveland heart disease database. Wang, An, Chen, Li and Alterovitz (2015) developed a low-cost and non-invasive screening system for hypertension based on a hybrid logistic regression and an ANN model using only simple demographic data from questionnaire responses.

Feature selection is an important step in developing predictive models that eliminates irrelevant or redundant input parameters, resulting in reduced model complexity and improved generalization ability. Various feature selection methods have been attempted within the context of diagnosing heart diseases. For example, Nahar, Imam, Tickle and Chen (2013) identified several key risk factors which contribute to heart disease using an association