

Electrocardiographic Diagnosis of Cardiomyopathy in Postoperative Cardiovascular Patients

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Abstract: Cardiomyopathy refers to diseases of the heart muscle that becomes enlarged, thick, or rigid. These changes affect the electrical stability of the myocardial cells, which predisposes the heart to failure or arrhythmias. Cardiomyopathy in its two common forms, dilated and hypertrophic, implies enlargement of the atria. Therefore, computer intelligence techniques are proposed for the recognition and classification of P wave features for cardiomyopathy diagnosis. The technique that we propose is a neuro-fuzzy network. The neuro-fuzzy classifier will be trained with innovative evolutionary algorithms, which have recently been shown to be efficient global optimizers. The following aims are proposed: (1) develop a neuro-fuzzy model to diagnose cardiomyopathy using P wave features; and (2) train the network using a clinical database of ECG signals.

1. SPECIFIC AIMS

Cardiomyopathy is a significant clinical problem which is mainly generated by volume/diastolic overload. To accommodate the increased blood volume, the heart chambers may stretch or dilate. Valvular regurgitation and congestive heart failure are two conditions that contribute to chamber dilation.

Cardiomyopathy is generally diagnosed by an electrocardiographic (ECG) investigation. In the current standards published by the American Heart Association, chamber hypertrophy or enlargement is a separate diagnostic category which can be detected with ECG analysis [1]. Although many algorithms have been implemented for ECG analysis, the proposed research is unique in several ways.

- We propose the development of **non-invasive** and **automatic cardiomyopathy diagnosis**, which has not been reported in the literature.
- We propose the development of algorithms for **P wave analysis**, which have not been reported in the literature.
- We propose the use of **5-lead ECG data**, which is more readily available than 12-lead data.
- We propose the use of a powerful **neuro-fuzzy architecture** for ECG analysis, which has not been reported in the literature.
- We propose neuro-fuzzy ECG classifier optimization using **evolutionary algorithms**, which has not been reported in the literature.

Our preliminary studies of postoperative cardiovascular patients reveal our hypothesis: **the ECG presents different electrical activity for patients with cardiomyopathy, compared with patients who do not have cardiomyopathy.** This working hypothesis indicates that an automated method that selects the best ECG parameters to include in a cardiomyopathy diagnosis algorithm will be extremely valuable. Although such a method will not be fool-proof or 100% correct, and thus cannot replace medical doctors, it will help physicians diagnose or prognose life threatening conditions such as stroke or ventricular or atrial fibrillation. This will expedite the initiation of medical treatment as appropriate to minimize the risk of these conditions, or to prevent their onsets.

Although it has long been suggested that cardiomyopathy is reflected in modification of ECG characteristics, statistics-based attempts to classify cardiomyopathy from the ECG have been underwhelming [2, 3]. Motivated by the universal approximation theorem for neuro-fuzzy

networks discussed in Section 2.1, we hypothesize that earlier limitations may be overcome by a neuro-fuzzy classification model. To test this hypothesis the following aims are proposed.

(1) **The first aim** is to develop a neuro-fuzzy model to diagnose cardiomyopathy.

(2) **The second aim** is to train the network using a clinical database of ECG signals.

2. RESEARCH STRATEGY

2.1 SIGNIFICANCE

Cardiovascular diseases are the major cause of death in the western world, causing more than 800,000 deaths per year in the United States alone [4]. One in five Americans has some form of cardiovascular disease [5].

The term “cardiomyopathy” defines a group of diseases primarily affecting the cardiac muscle by weakening it or changing its structure. Cardiomyopathy can be acquired or inherited, and in many cases its cause is unknown. Hypertrophic cardiomyopathy is inherited and is supposed to be a result of defects of genes that regulate heart muscle growth. Abnormal cardiac enlargement can be due to an increase in length or diameter of existing cardiac muscle cells [6]. Cardiomyopathy, through electrical instability of myocardial cells, is associated with cardiac conduction abnormalities that can degenerate to arrhythmia or heart failure [7].

Cardiomyopathies, especially hypertrophic, are considered a common cause of sudden cardiac death in young adults and children [8, 9]. The Chagas and idiopathic dilated etiologies of cardiomyopathy led to Pereira et al.’s study in adults [10]; after 40 months, almost half of the cases studied (113 out of 284) registered deaths (104) or heart transplants (9).

The ECG records the deflection of ionic current across myocardial cell membranes and through the extracellular space of the thoracic cavity tissues. The history of cardiomyopathy research reveals the evolution of the analysis of ECG correlations. Due to the left ventricle’s critical role, initial studies were focused only on the ECG features of the hypertrophic left ventricle [11]. The QRS and T waves, as the reflections of ventricular depolarization and repolarization respectively, were analyzed [12]. In the study by Sox et al., citing the Framingham Study, the left ventricular hypertrophy (LVH) was defined by a prolonged ventricular activation period of 0.05 s, tall R waves, depressed ST segments, and inverted T waves [11]. Ziegler was the first to analyze T waves related to LVH; he presented different patterns of the QRS and T configurations into left or right precordial limb leads [12]. The P wave portrays atrial electrical activity, so changes in the atrial action potential and substrate are reflected in P wave timing or morphology [13]. Bahl et al. presented the P wave changes associated with the type and stage of the disease [14]. Analyzing the four chamber enlargements, Johnson et al. presented P wave changes for enlarged left and right atria [15].

The atria, characterized by thin walls, respond to volume and pressure overload due to dilatation. Moreover, the enlargement of the associated ventricle is recognized as the cause of the enlargement of the atrium [2], [3]. The right atrium enlargement is recognized by the increased amplitude of the P wave (0.25 mV) while left atrial abnormality is reflected by the lengthened P wave duration (>120 ms) as well as a notched P wave.

The American Heart Association, American College of Cardiology Foundation, and the Heart Rhythm Society, recently concluded on standards to be used when interpreting ECG data related to cardiomyopathy [16]. In LVH, the P wave shape is mentioned as a criterion. In right ventricular hypertrophy, a P wave amplitude larger than 0.25 mV in lead II is presented as a threshold. Left atrial abnormality implies a prolongation of the total atrial activation time (>120 ms), widely notched P wave, and possible changes in P wave area. The right atrial abnormality list includes a larger P wave amplitude (> 0.25 mV) and a prolongation of the P wave in patients after cardiac surgery, which is the case for the patients in our proposed research.

Our proposed algorithm presents the advantage of compatibility with the clinical CVICU setting since it is designed to analyze P wave parameters from a 5-lead ECG, versus the

laboratory 12-lead ECG. P wave delineation is made automatically on the ECG signal using wavelet transforms. The P wave features obtained by the wavelets are then processed by a neuro-fuzzy system. Neuro-fuzzy systems are combinations of fuzzy systems and artificial neural networks (ANNs). Such combined systems have the advantage that they can learn faster and more accurately than an individual ANN or fuzzy logic system. A benefit over ANNs is that the rules that describe the system are explicit, thus permitting easy interpretation and validation.

Considering the frequent association of cardiomyopathy and atrial fibrillation, a future application of this successful classification process is the inclusion of the results in an automatic prediction algorithm for atrial fibrillation (AF). AF is a threatening arrhythmia that is encountered in 25% of post-cardiovascular surgical patients in the CVICU of the Cleveland Clinic.

2.2 INNOVATION

Cardiomyopathy diagnosis will be performed by a multivariate, neuro-fuzzy classification model that uses P wave parameters to generate a cardiomyopathy classification index. ANNs are universal approximators [17], and there has also been extensive work to prove that neuro-fuzzy systems can approximate any continuous function to any desired degree of accuracy [18]. Alvisi et al. [19] have studied the performances of fuzzy logic and ANNs, revealing the weaknesses and strengths of each of the methods. The strengths can be emphasized, and some of the weaknesses can be attenuated, by combining the techniques into a hybrid neuro-fuzzy model. **The universal approximation theorem is the reason that a neuro-fuzzy system may be able to overcome the limitations of previous statistics-based methods for ECG analysis.**

2.2.1 Model Development

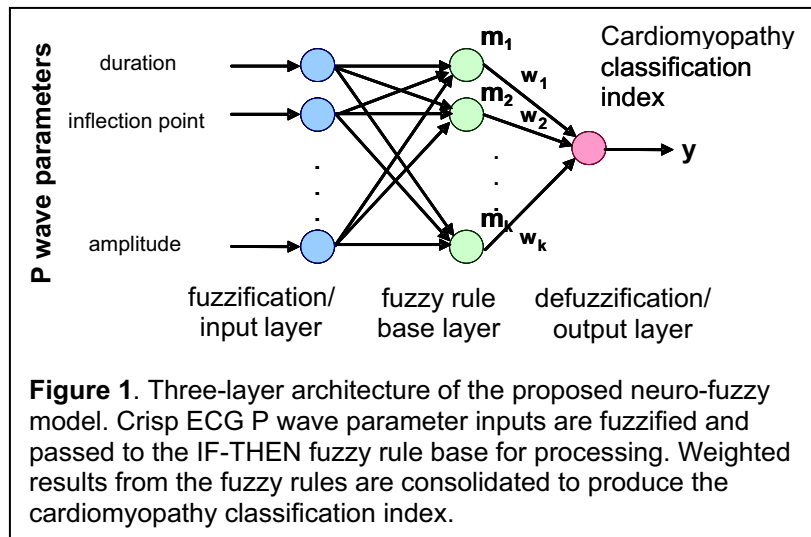
The initial model is a multi-input single-output fuzzy inference system with a simplified three-layer architecture as shown in Figure 1. The fuzzy modeling problem is to obtain the minimum number of fuzzy rules and optimal parameters with a minimum error. Model development involves a series of inter-dependent steps as shown in Figure 2.

Fuzzy Rule Selection -

Determination of the optimal number of rules will be decided

by a trade-off between compactness within clusters and separation among clusters. For this, a fuzzy c-means clustering algorithm will be used [20, 21].

Parameter Learning - Training of the neuro-fuzzy system will be performed in a supervised manner due to the availability of training data with known outcomes. This step will involve optimization of the parameters and inter-nodal weights with the goal of improving classification performance. A back propagation (BP) learning algorithm with learning rate and momentum parameters will be used [20, 21, 22]. Other parameter optimization approaches will be used include Kalman filtering [23], [24], constrained state estimation [25], H-infinity estimation [26], and evolutionary algorithms such as genetic algorithms and swarm intelligence [27]. One of the PI's has developed a new optimization algorithm called biogeography-based optimization (BBO) which has shown advantages over traditional optimization approaches [28]. These methods are global optimization approaches, while BP is a local optimization approach. Therefore, computer intelligence promises to provide superior parameter learning compared to BP.



Model Simplification - Some of the membership functions may be similar, resulting in difficulty interpreting the model. The similarity between fuzzy sets will be used to remove some of the sets.

2.2.2 Data Analysis

The presence or absence of cardiomyopathy is extracted from the electronic medical record and compared to the output of the classification model. The model will be evaluated for performance in terms of accuracy, sensitivity, and specificity.

- **Accuracy** – ratio of number of correct decisions to total number of patients.
- **Sensitivity** – ratio of number of true positive decisions to number of actually positive cases.
- **Specificity** – ratio of number of true negative decisions to number of actually negative cases.

To minimize training error and generalize the model, cross-validation will be used. The objective is to select an error cutoff with sufficiently high sensitivity and specificity for classification. The relationship between sensitivity and specificity for various cutoff points can be plotted as a receiver operating characteristic (ROC) curve. Various logistic models will be compared based on the area under their ROC curves (the C-statistic). The model with the highest C-statistic will be considered to have the best ability to properly classify the patients. Our aim is to obtain a success rate in the range 70%–90% for sensitivity and specificity.

2.2.3 Model Refinement

The main technical difficulty that may be encountered is poor model classification performance. Fortunately, there are multiple stages in the process that can be modified to improve accuracy if necessary. For example, the need for more input data can be alleviated by altering classification thresholds or by simplifying the model. Better performance could be obtained by including risk factors as neuro-fuzzy system inputs, such as demographics and surgical information [3, 5, 15].

2.3 APPROACH

2.3.1 Preliminary Training Data

In preparation for the testing of a cardiomyopathy diagnosis model, a database of long duration ECG signals was collected. The database includes 55 consecutive patients, 18 of them with cardiomyopathy. The cardiomyopathy group contained 10 males and 8 females with a mean age of 54 years (range 23–88). The control group contained 22 males and 15 females with a mean age of 60 years (range 27–77). The inclusion criteria were the same for both groups: no chronic or paroxysmic atrial fibrillation and no perioperative pacing.

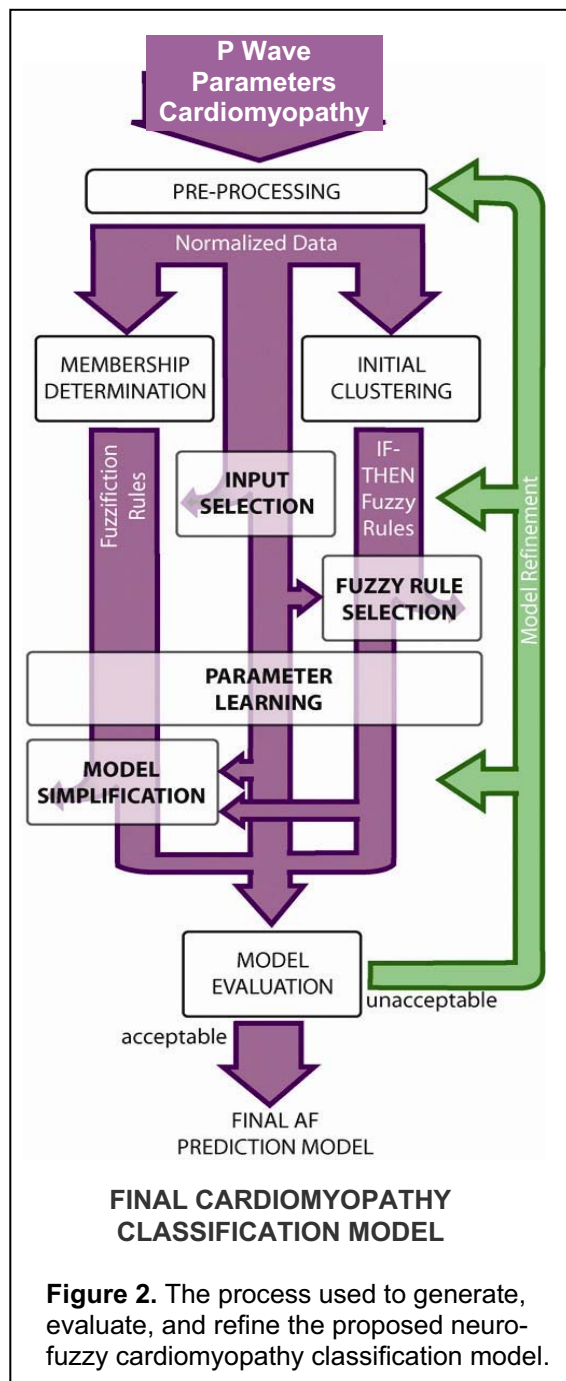


Figure 2. The process used to generate, evaluate, and refine the proposed neuro-fuzzy cardiomyopathy classification model.

ECG parameters describing P wave morphology were computed for each minute of data recording for all patients in the training data set. These parameters are duration; amplitude; a shape parameter which represents monophasic or biphasic P waves; inflection point, which is the duration of the P wave between the onset and the peak points; and energy ratio, defined as the ratio of right atrial excitation to total atrial excitation energy [29]–[32]. These parameters constitute the input of the training data set for neuro-fuzzy model development. P wave detection was performed with the PI’s wavelet-based method [31]. Average P wave parameters were computed every minute. Differences of P wave morphology parameters between cardiomyopathy and control patients in the training database are presented in Figure 3. The use of these differences in identifying patients with cardiomyopathy is presented below.

2.3.2 Preliminary Results

Figure 4 shows initial results for a neuro-fuzzy cardiomyopathy classification network [34, 35]. We used data from the 55 test subjects described above, including 37 control patients and 18 cardiomyopathy patients. We randomly divided the patients into approximately equal numbers of training and test patients, so we have 9 cardiomyopathy patients and 19 control patients for network training, and 9 cardiomyopathy patients and 18 control patients for network testing. The training outputs were defined to be +1 for cardiomyopathy and -1 for control. We randomly chose 200 ECG data points from a 700-minute interval for each patient for training and testing. Therefore, we have $200 \times (9+19) = 5600$ training data, and $200 \times (9+18) = 5400$ testing data.

The training objective was to minimize RMS output error. Biogeography-based optimization (BBO) was used to optimize the parameters of a neuro-fuzzy network with four inputs and three hidden neurons (see Figure 1). The BBO population size was 200. The top plot in Figure 4 shows that the minimum RMS error (over all 200 BBO individuals) is nonincreasing. This is guaranteed due to the use of elitism in the BBO algorithm [33]. The average in the top plot of Figure 4 is the average RMS output error of all 200 members of the BBO population.

The goal of the neuro-fuzzy network is maximum classification percentage. If the neuro-fuzzy output is positive, then the ECG is classified as cardiomyopathy; otherwise, it is classified as non-cardiomyopathy. The bottom plot in Figure 4 shows that test classification reaches its maximum at about 40 BBO generations. After that, training performance continues to improve, but test performance gets worse. This implies that

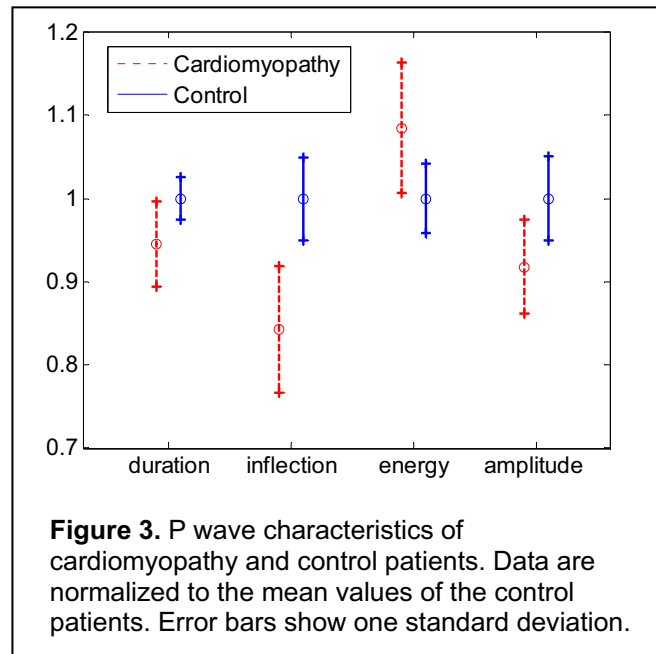


Figure 3. P wave characteristics of cardiomyopathy and control patients. Data are normalized to the mean values of the control patients. Error bars show one standard deviation.

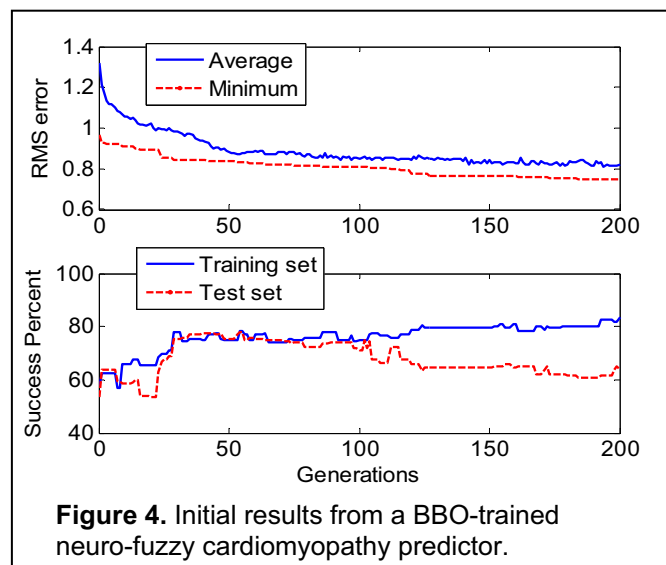


Figure 4. Initial results from a BBO-trained neuro-fuzzy cardiomyopathy predictor.

we are “overtraining” after about 40 generations. That is, the algorithm is “memorizing” the training inputs instead of learning a general classification rule. This is a typical result often seen in neuro-fuzzy training programs.

Test classification peaks at around 78% after about 40 BBO generations. These preliminary results are promising, but there are many enhancements that need to be explored with further research. For example, the training criteria should not be RMS error, but classification success rate. Also, demographic information may need to be included with the ECG data. Some of the test ECGs were correctly classified 100% of the time, while others had a success rate of less than 50%. This indicates that demographic data may be important, and that we should group patients into similar sets for testing and training (e.g., gender, race, medication usage, and age).

Finally, we note that these results are based on snapshots of the data at single instants of time. We could get much better results by using a “majority rules” strategy for data collected over several minutes. For example, if test accuracy is 60% for a given patient and a given time interval, we could use ECG data over three separate time intervals, and predict cardiomyopathy if the neuro-fuzzy network predicts cardiomyopathy two of the three time intervals. This would boost test accuracy from 60% to 65%, assuming that the probability of correct classification is independent between time intervals.

2.3.3 Research Plan

To obtain the best neuro-fuzzy network for ECG classification, several steps will be taken as detailed below. All network testing will be done using cross validation techniques to obtain a good estimate of how the network generalizes to independent data sets. The statistical measures discussed in Section 2.2.2 will be used to obtain a high measure of confidence in the significance of the performance differences between various network settings.

(1) Evolutionary training will be done with a genetic algorithm (GA, the standard baseline), a particle swarm optimization (a competitive evolutionary algorithm based on a different paradigm than a GA), and biogeography-based optimization (one of the PI’s contribution to evolutionary computing). Following this task, the best evolutionary algorithm trained network will be available for task (2), which follows.

(2) Gradient-based training will be done with gradient descent (the standard baseline), Kalman filtering (second order training), and H-infinity training (one of the PI’s unique contributions to analytical neuro-fuzzy optimization). Gradient-based training will be initialized randomly, and also with the results of task (1) above.

(3) Various sets of inputs to the neuro-fuzzy network will be used to determine the effect of input selection on network performance. Inputs can include ECG features and patient demographics. Statistical tests on network performance will show which inputs are important for good classification. Tasks (1) and (2) above will be repeated for each input set that is tested.

(4) Various settings for the number of hidden units will be used to determine its effect on network performance (e.g., Figure 1 shows k hidden units). Task (3) above will be repeated for each hidden layer size. Following this task, the best combination of evolutionary training, gradient training, input set, and hidden layer size, will be available for task (5) below.

(5) Network pruning will be implemented to simplify the network without reducing classification performance, using various pruning methods discussed in the neural network literature.

2.3.4 Project Management Plan

The research will be jointly supervised by Dr. Ovreiu (formerly Visinescu), who has expertise in cardiology, and Dr. Simon, who has expertise in computer intelligence. Two engineering graduate students at CSU will work on this project under the supervision of Drs. Ovreiu and Simon. The graduate students will each work 40 hours per week during the summer, and 20 hours per week during the academic year. The work will be managed through weekly meetings between the PIs and the graduate students. A general schedule for this project follows.

2011 May–June: Preprocess input data for more convenient organization and use.
 2011 June–July: Normalize and cluster the input data. Determine initial estimates for fuzzy input data categories and membership functions.
 2011 July–Aug: Determine initial fuzzy if-then rules using unsupervised learning.
 2011 Aug–Sep: Implement back propagation for parameter learning.
 2011 Oct–Nov: Use statistical analyses to determine the effectiveness of the neuro-fuzzy cardiomyopathy classifier network.
 2011 Nov–Dec: Implement and tune evolutionary algorithms for parameter learning.
 2012 Jan–Feb: Conduct a systematic comparison and tradeoff analysis of back propagation training results and evolutionary training results.
 2012 March–May: Prepare publications and proposals.

3. OUTCOMES

Publications: The outcomes of this work will be presented at biomedical and computer intelligence conferences and journals. The interdisciplinary nature of this work makes it suitable for a variety of publication venues, including those that focus on biomedical engineering, computer intelligence, and engineering applications. The results of this work will put the investigators in a position to submit grant proposals to external funding agencies. This will enable the investigators to continue their collaboration on a long-term basis.

Preliminary, Current Outcomes: The PIs have published one peer-reviewed conference paper [34] and have made presentations at two venues [35, 36] of their initial results. The PIs received \$197,588 from the National Science Foundation for the research project “Non-contact ECG Monitoring and Diagnosis,” August 2010–August 2013. The NSF grant is closely related to the research proposed here, but the NSF grant emphasizes simple diagnosis algorithms with sophisticated non-contact carbon nanotube ECG sensors, while the project proposed here emphasizes a more challenging diagnosis goal with a more traditional ECG.

National Institutes of Health: The National Heart, Lung, and Blood Institute is a possible sponsor of this research. The current NHLBI program announcement most related to this proposed work is PA-07-355, Improving Heart Failure Disease Management. The National Institute of Biomedical Imaging and Bioengineering is also a possible funding agency. Current NIBIB announcements which are related to this work are PAR-07-352, Bioengineering Research Partnerships (BRP); and PAR-10-009, Bioengineering Research Grants.

National Science Foundation: Another likely funding source for this work is the Chemical, Bioengineering, Environmental, and Transport Systems Division (CBET) of the NSF. Programs of interest in CBET include Biomedical Engineering, Biophotonics, Biosensing, and Biotechnology, all of which have proposal due dates of March 3. Another possible NSF source is the Interdisciplinary Research (IDR) program. As discussed above, the NSF has recently funded some of the joint research of the investigators, which speaks well of the NSF’s interest in intelligent algorithms for ECG analysis.

American Heart Association: The American Heart Association is one of the main beneficiaries of our research results. The due dates for proposals are January and July. We plan to target AHA’s Clinical Research Program, the Fellow-to-Faculty Transition Award, and the Scientist Development Grant.

Commercial Sponsors: There are several local biomedical companies that may be interested in funding and commercializing a diagnostic system based on the technology described in this proposal. Some local biomedical companies will be approached for additional funding and collaboration, including Valtronic Technologies, with whom we have had preliminary discussions. We will discuss the possibility of straight-through funding from these companies, and also the possibility of SBIR or STTR funding from the NIH or NSF.

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Budget and Budget Justification

The effort for the Cleveland Clinic PI is within 5% and will thus be supported by the Clinic. The budget includes funding for two graduate students at Cleveland State University. Both students will be funded for 40 hours per week during the summer. Both students will be funded with a graduate assistantship (nine credit hours of tuition and a stipend) during the academic year, working 20 hours per week. Tuition has been calculated by adding 6% to the spring 2011 tuition for resident graduate students (masters or doctoral level). The travel funds are for one or more conferences: for example, the AMA-IEEE Medical Technology Conference, October 16–18, 2011, in Boston.

Student summer salary (two students, \$13/hour, 11 weeks, 40 hours/week)	\$ 11,440
Tuition (two resident graduate students for two semesters each)	\$ 17,907
Student stipends (two students for two semesters each)	\$ 26,000
Fringes (5.5% of salary and stipend)	\$ 2,060
CCF travel (conferences)	\$ 2,000
Total	\$ 59,407