

Technical White Paper

Edited by Dr. Abraham B. Bornstein, F.A.C.C Assistant Professor of Medicine/Weill Medical College of Cornell University

3DMP: Applied Systems Analysis of Surface ECG

The 3DMP (Digital Database-Driven Multiphase) ECG analysis product is part of an emerging trend in medicine: the clinical application of advances in computational biology. By combining mathematical modeling with probabilistic diagnosis based on an extensive empirical digital database, 3DMP is able to deliver the detection of ischemia within 90% of the accuracy of an angiogram¹, using a method that is immediate, non-invasive, and does not expose the patient to radiation or physical stress.

The technology works by sampling an ECG signal from 2 left ventricular leads (V₅ & II) and performing a series of digital signal analysis operations. The operations produce a sequence of indexes, which quantify abnormalities in the ECG; clusters of these indexes represent potential diagnoses. A statistical analysis is then performed to determine the probability that a cluster is positive, and a final diagnosis is produced.

Systems Analysis and ECG Signals

The Cardiascan approach is based on systems *theory*, in which mathematical modeling is used in the analysis of complex systems. The mathematical modeling of organ systems is based on computational physiology research such as the Physiome project. This approach is becoming increasingly popular as advances in computer processing power make the analysis of large datasets, such as those produced by medical devices, more feasible. Efforts in computational physiology, such as the Physiome Project, and computational electrophysiology, such as 3DMP for surface resting ECG, have proven useful in academia or clinical practice.

An analog signal such as an ECG can be digitized and then processed by digital signal processing algorithms. When two signals are recorded from the same source, these algorithms can be used to examine the relationships between the signals and infer information about the source. This allows a complex system emitting signals to be modeled as mathematical functions, where one signal is the input, and the other is the output of the system. The functions represent a virtual or *idealized* system that embodies the relationship between the two signals, and is used to examine the relationship as a meaningful component of the more complex system.

The system modeled by such a function could be a series of cardiac cycles, a flow of blood from chamber to chamber, or a depolarization and repolarization cycle from one part of the heart to another part of the heart³. The conventional 2-D ECG plot is the summation of all of the complex periodic electrical activity throughout a cardiac cycle of a human heart, and can be broken down into discernible components in systems analysis approach. Once the complex waveform is broken into simpler mathematical functions, it can be studied quantitatively by obtaining and examining the functional characteristics not visible from the conventional ECG plots of signals sampled from healthy and diseased patients.

The mathematical model of the system can be used to determine which digital signal processing methods are appropriate, and where in the output significant characteristics are likely to be found. For example, any system derived from a pair of input and output signals can be analyzed with the **impulse response** operation, while ECG data itself is particularly suited to **power spectrum** analysis, with the most significant discoveries near the fundamental frequency of the heart rate and its multiples or *harmonic*.

Digital ECG Signal Processing and Analysis

In traditional 12-lead ECG, 6 limb and 6 precordial leads represent the vectors of the heart as an electrical power-generating source, reduced to a dipole. Conventionally, each lead is sampled at a rate of 200-500Hz, and then analyzed individually and sequentially in the time domain. This neglects the dynamic multidimensional electrical field changes due to the stress and strain of the interaction between the myocardium and the blood circulating through the cardiac cycle of the heart⁴.

In the 3DMP system, only two leads are used: the V₅ lead, a precordial lead that represents electrical activity in the left ventricle, and lead II, a limb lead that represents electrical activity from right arm to left ankle along the left ventricular axis. The sampling rate is calculated to target frequency domain components that fall between 1 Hz (a 60 bpm heart rate) and 35 Hz⁵. Multiple cardiac cycles for the 2 leads are sampled to encompassing all the activities of five to ten cycles, then analyzed in both the time and the frequency domains.

The **frequency domain** is commonly used in signal analysis to detect component wear or deterioration in a signal by monitoring for changes in amplitude at a specific frequency. This approach can be applied to biological signals by treating the biological system as a mechanism whose components oscillate at specific frequencies. In the heart, these components would be the left and right atria and ventricles.

The ECG is a periodic waveform, and therefore can be represented in the frequency domain as a Fourier series in which the fundamental frequency, or **first harmonic**, is the heart rate. The harmonics of the heart rate frequency are the basis of further analysis: as with any periodic waveform, each harmonic component has a characteristic amplitude and phase angle. **Correlation analysis** uses the amplitudes and phase angles of the harmonics of two ECG leads to determine the systemic relationship between those leads.

The 3DMP analysis server performs standard DSP transformations on the Fourier series of the two leads, including auto and cross power spectra, cross-correlation, phase shift, and impulse response. The output of each transformation has an associated set of empirically derived indexes whose values are calculated by proprietary signal analysis algorithms.

These quantifiable and reproducible indexes (not observed in 2-D conventional ECG graphic output) represent significant abnormal characteristics of the waveform, which have been identified and quantified through empirical research. The individual indexes have no clinical meaning, but *patterns* or clusters of indexes have been found to have a high probability of indicating a specific disease.

The results of this analysis can indicate abnormalities of the heart that have been found empirically to represent early (i.e., sub-critical coronary artery narrowing due to atherosclerosis of as little as 40% in single vessel disease) to later (severe multiple vessel disease due to critical stenosis) stages of myocardial pathologies. In particular, the power spectra analysis, impulse response, phase shift, and cross correlation data have been found to be highly sensitive to the changes in heart mechanical and/or electrical functions as a result of ischemia due to coronary supply and myocardium demand imbalances.

Statistical Analysis

The statistical analysis phase uses the indexes generated during signal analysis to generate probabilities for each disease diagnosis. These probabilities are derived from a clinical database population with a set of index patterns for each disease diagnosis.

The probabilities are then used to produce a diagnosis. The disease diagnoses are ordered by probability, and all diagnoses with a probability that exceeds a threshold are reported.

A 3DMP report consists of three classes of diagnosis (primary, secondary, and tertiary) and a *disease severity score*, which represents the overall risk of heart disease for the patient. The secondary and tertiary diagnosis classes contain diagnoses whose accuracy have not been formally validated in clinical trials, and should therefore be considered as suggestions.

The primary diagnosis produces a result for ischemia, which can be negative, borderline, local, or global. The secondary diagnosis produces a positive or negative result for myocardial infarct, ventricular hypertrophy, congenital heart disease, myocarditis, rheumatic heart disease, ventricular fibrillation, atrial fibrillation, cardiomyopathy, and pulmonary heart disease. The tertiary diagnosis produces a positive or negative result for power failure, ejection fraction, bradycardia, tachycardia, increased and decreased myocardial compliance, myocardial remodeling, and local or global asynchrony.

The database server maintains 3 overlapping populations of patient data:

- 1) The *general* population contains every test in the database, and is used to generate the other populations.
- 2) The *quantitative* or statistical population contains tests whose results have been confirmed by two independent physician experts, and is used to generate the statistical weights used in diagnosis. The current population includes 35,000 patients between the ages of 14 and 95, of which 20% are clinically normal and the remaining 80% have been diagnosed with various pathologies.
- 3) The *qualitative* or verified population contains tests, which have been exhaustively reviewed, and is used for improving the mathematical model and the analysis algorithms.

This allows for the accumulation of a large body of clinical data on which to base the statistical analysis. By permitting only verified diagnoses in the generation of probabilities for disease diagnosis, the accuracy of the technology will continually improve. Furthermore, the qualitative population can be mined to develop additional analysis algorithms for the diagnosis of additional diseases.

Clinical Trial Results

In recent years, Cardiascan's 3DMP technology has been clinically validated in three prospective studies comprising more than 1000 patients. In all three studies, the reference method to establish the diagnosis of coronary artery disease (CAD) was coronary angiography. In addition, 3dmp was compared against a 12-lead ECG in one study (Westchester Medical Center, USA⁵), against the predicted risk for CAD from established risk factors in another (Siegburg Heart Center, Germany^{6,7}) and in a multi-center trial conducted in 6 Asian countries.

Table1: Trial Summary 2001-2007

Statistics	Number of Patients	True (+)	True (-)	False (+)	False (-)	Sensitivity	Specificity	(+) Predictive Value	(-) Predictive Value
------------	--------------------	----------	----------	-----------	-----------	-------------	-------------	----------------------	----------------------

Early Stage CAD Ischemia Detection: 30-40% Lumen Narrowing

USA	136	84	38	8	6	0.933	0.826		
Asia	222	76	97	15	4	0.950	0.870		
Multicenter									

Critical Stage CAD Ischemia Detection: >70% Stenosis for Pre/Post Intervention

EU Pre-revascularization	545	18	250	7	0	0.890	0.842	0.832	0.893
EU Post-revascularization	213	6	126	6	5	0.930	0.887	0.805	0.960
Total EU Patients	758	84	367	3	5	0.890	0.856	0.818	0.915

All Trials Combined

All Trials Combined	1116	455	523	87	51	0.899	0.857	0.839	0.911
---------------------	------	-----	-----	----	----	-------	-------	-------	-------

In all studies and all subgroups 3DMP showed a better performance than that reported of other resting EGG methods, exercise EGG tests, stress echocardiography, GT Angiography or MRI in numerous, previously published studies. Although a direct comparison between 3DMP and these other methods, with the exception of 12 lead resting EGG, has not yet been done, it appears justified to conclude from the study results that 3DMP provides a sensitivity and specificity for hemodynamically relevant coronary stenosis at least equally as good as (if not better) that of stress EGG, or of stress echocardiography.

The results show a high a level of stability for the 3DMP methodology. Moreover, the fact that the results were comparable between seven centers on three continents indicates that the performance of 3DMP is independent of different age, gender, clinical practices and racial origins.

All studies were approved by the respective ethics committees and followed the principles of the Helsinki declaration. Patients were only included if they were scheduled for coronary angiography. 3DMP data acquisition and analysis was always done shortly before the angiography.

Angiographers and staff at the study sites were blinded to all 3DMP findings. The 3DMP technicians and all Cardiascan staff were blinded to all clinical data, including pre-test probabilities for GAD or angiography findings from the study patients. An independent study monitor verified the double-blindness of the studies and monitored the data acquisition process, all angiography reports, and all 3DMP test results.

Edited by Dr. Abraham B. Bornstein, Assistant Professor of Medicine/Weill Medical College of Cornell University

Fellow/American College of Cardiology

Fellow/American College of Angiology

American Board of Internal Medicine/subspecialty in cardiovascular diseases.

Faculty Member, Division of Cardiovascular Physiopathology, Cornell University

Faculty Member, Weill Cornell Howard Gilman Institute for Valvular Heart Diseases, Cornell University

Dr. Bornstein is a board-certified cardiologist who is currently an Assistant Professor of Medicine in Pediatrics at the Weill Cornell Medical College, serving in the divisions of both Cardiovascular Pathophysiology, as well as Pediatric Cardiology in the area of adult congenital heart disease. He has more than 25 years of clinical practice experience in invasive and interventional cardiology, as well as critical care medicine.

References:

- 1) The Physiome project is located at <http://www.physiome.org>
- 2) Examples of this approach used in clinical research include Sawson SL, Robinson TG, Youde JH, et al. "Older subjects show no age-related decrease in cardiac baroreceptor sensitivity", *Age Aging* 1999; and Kocsis B, "Basis for differential coupling between rhythmic discharges of sympathetic efferent nerves-", *Am J Physiol/ Regu/Integr Comp Physiol*/1994.
- 3) Traditional ECG methods have poor (20%) sensitivity in detection of myocardial abnormality as a result of hemodynamically significant ischemia, and equally poor (-50%) sensitivity in detecting myocardial infarction. Source: Welch RD, Zlenski RJ, Frederick PO, et al. "Prognostic value of a normal or nonspecific initial electrocardiogram in acute myocardial infarction", *JAMA* 2001.
- 4) Feng G. EKG and EEG Multiphase Information Analysis (A collection of unpublished notes, thesis, papers and published articles from mid seventies to the late eighties translated into English from Chinese). First Edition. New York: American Medical Publishers; 1992.
- 5) Weiss MB, Narasimhadevara SM, Feng GO, Shen JT. Computer-enhanced frequency-domain and 12-lead electrocardiography accurately detect abnormalities consistent with obstructive and non-obstructive coronary artery disease. *Heart Dis.* 2002; 4:2-12.
- 6) Grube E, Bootsvelde A, Yucel S, Shen JT, Imhoff M. Computerized two-lead resting ECG analysis for the detection of coronary artery stenosis. *Int J Med Sci* 2007; 4:249-263. Empirical findings of Premier Heart research show that 85-90% of the power output for a normal human heart occurs below 35 Hz.
- 7) Eberhard Grube, Andreas Bootsvelde, Lutz Buellesfeld, Seyrani Yucel, Joseph T Shen, Michael Imhoff. Computerized two-lead resting ECG analysis for the detection of coronary artery stenosis after coronary revascularization *Int. J. Med. Sci.* 2008, 5 (2):50-61