



Clinical Group

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## Short Communication

# 2017 AHA Heart Science Forum Innovation Challenge Award 1<sup>st</sup> Place Winner and the 1<sup>st</sup> Annual Samsung Digital Health Summit Technology Pitch Contest Award 1<sup>st</sup> Place Winner

## Introduction

Multifunction Cardiogram Technology or the MCG was engineered to answer a fundamental question and solve a critical problem. The question was if we could apply the mathematic principals of *Lagrangian Mechanics* to build an objective machine powered digital diagnostic paradigm to forever change the face of the future of diagnostic medicine, as we know it. The problem we wanted to solve once and for all was the intractable dilemma of poor diagnostic accuracy caused by the deeply flawed system designs of the conventional imaging and EKG/EEG tools used throughout the industry. Thus, starting from the very first moment, we had to learn from where others failed.

During the design phase of the first generation of our technology, our team performed an extensive review of all existing technology that currently works via the processing of ECG signals. We reviewed the methods designed to improve the traditional 12-lead ECG, from the exotic signal average EKG (failed clinically), vector EKG (also failed) all the way to mapping using 86 EKG leads (never entered clinical use, too cumbersome). Following the meta-analysis of over one million published papers, we concluded that the traditional ECG waveform analysis has fundamental, fatal design flaws which doom those who attempt to improve its performance with dismal failures in the real world settings. *We believe that the traditional "expert dependent" ECG waveform analysis had arrived at a dead-end.*

In our research in the early 1990s, we also discovered another unpleasant, and frankly disturbing truth: most, if not all, of the published peer review journal articles we had to sift through were based on multitudes of biases, fraudulent claims, and flat out wrong self-fulfilling conclusions [1-3], that lack the independent, unpaid verification and validation

process that we absolutely insisted on to validate the MCG Technology through to break out of that trend. In the words of *Dr. Marcia Angell*, a physician and editor in chief of the *New England Medical Journal*: *"It is simply no longer possible to believe much of the clinical research that is published, or to rely on the judgment of trusted physicians or authoritative medical guidelines. I take no pleasure in this conclusion, which I reached slowly and reluctantly over my two decades as an editor of the New England Journal of Medicine"* [4]. This new perspective we gained also led to us discovering that cardiologists armed with the most expensive cardiac imaging tests the world has to offer are only correct 40% of the time, translating in unnecessary coronary angiograms that routinely performed 60% of the time for patients everywhere. In 2010, Manesh R Patel et al., performed a meta-analysis of ~400,000 patients that underwent coronary angiograms independent of our own analysis, and by the end of the study, the overall diagnostic yield was 38% [5]. In 2014, another large study of ~600,000 patients underwent coronary angiogram in more than 224 US hospitals, also independent of us, providing an overall yield of 40% [6]. Even the highly regarded Functional MRI has not been spared of criticism [7]. *The Institute of Medicine* published the results of their independent investigations on their website, stating that \$750 billion dollars are wasted on unnecessary medical tests and procedures a year [8]. This does not even mention the very real suffering and the number of deaths inflicted by these practices, what have been ranked as the third leading cause of deaths in America [9]. In short, a better-designed tool and diagnostic modality are desperately needed. In fact, Patel et al., concluded the following: *"In this study, slightly more than one-third of patients without known disease who underwent elective cardiac catheterization had obstructive coronary artery disease. Better strategies for risk stratification are needed to inform decisions and to increase the diagnostic yield of cardiac catheterization in routine clinical practice"* [5].

Armed with this knowledge, we decided to explore new ways to analyze ECG signals based on *Professor Norbert Wiener's Cybernetics Theory*. Instead of the usual process of analyzing each conventional EKG signal as a single vector, MCG Technology adopts mathematics principals of *Euler and LaGrange Coordinates* expressed via *Lagrangian Mechanics* to explore the interactions and communication between two EKG signal sources, *Lead V5 and Lead II*, via multiple non-linear functions (Figure 1). We believe that this is the best, most rational, method to understand the physics of the extremely complicated and dynamic relationship between the heart muscle and blood flow throughout the cardiovascular system. Our discovery has proven that the non-linear mathematical transformations of a pair of digitized resting electrical signals (Lead V5 and Lead II) can express a plethora of never before seen information embedded between these two signal sources, completely unavailable to the conventional ECG waveform analysis. These were discovered empirically from large volumes of digitized EKG signal data recorded from both animals and humans. This new, generative discovery opens up an entirely unprecedented path that allows our team to explore hidden dimensions of the cardiovascular system in a new domain of discipline we call: *Computational Electrophysiology*.

The Multifunction Cardiogram (MCG) takes a systems theory approach to the mathematic models based on *Euler – La Grange Coordinates* by combining the results of 6 non-linear mathematical transformations derived from the fusion of both coordinates via a *Laplace Transformation* (Figure 2).

The MCG not only analyzes the heart but the whole of the electronic network, or the entire cardiovascular “intranet”, that controls the cardiovascular system in its entirety, interacting with all these internal and external factors using multiple mathematical functions to extract and analyze the interactions or communications that occur throughout the system. Each function represents a unique functional aspect of the system that the other functions do not describe.

The MCG Delivers the computational power that analysis of the complex dynamic phenotypical expressions of an individual's Cardiovascular System as a whole demand, rating at a numerical complexity of 10 to the 168th power (or ten quinquagintillion), via the 168 mathematical elements from the six functions extracted empirically from the large clinical database.

In order to teach the machine to recognize all the various forms of heart disease, we first embarked on a two-decade-long journey of research and development via digital signal processing, empirical clinical data collection, data mining, supervised machine learning, neural network development, A.I. algorithm development and countless iterations of optimization and improvement. In this period, two million individuals were tested on MCG and more than 100,000 people had their data strategically added to the system with various common cardiac diseases to build a production database for system software development. All our data sets used in analysis and the proposed statistical models have to satisfy the tests of both Null Hypothesis and Alternative Hypothesis. The extremely carefully verified and thoroughly validated data sets were used in the discovery of the estimated 200+ mathematical elements from the six non-linear functions. We ensured that the development of the machine learning algorithms for the quantitative automatic heart disease pattern classification and differentiation was based purely on thoroughly vetted and trusted empirical evidence. Our aim is to systematically explore, define, express, measure, quantify and differentiate the hidden NORMAL and ABNORMAL expressions of *electro-mechanical, electro-structural, electro-biochemical, electro-hematics, electro-neuroendocrine or neurohormonal, electro-immunological, and the highly elusive, yet vitally important diverse expressions of electro-myocardial perfusion pattern of the cardiovascular system*. Such information is beyond what the cardiologists armed with expensive imaging machines can provide for much faster, much more reliably accurate, independent, objective, widely accessible via the worldwide web, and affordable diagnostic decision-making.

To achieve this, MCG has been put through vigorous internal verification and external independent clinical validation trials using real-world patient data collected from eight countries in three continents by investigators performing *without quid pro quo* since 2002. We decided to validate MCG system in a completely unconventional fashion to steer clear of the mainstream practices that have deeply tainted the world of peer review publishing. Our principles and methods are as follows:

1. The principals of MCG External Validation Methods: Opening new dimensions on objective, honest, unbiased, and transparent high-quality evidence-based clinical validations to reestablish public trust and rebuild confidence.

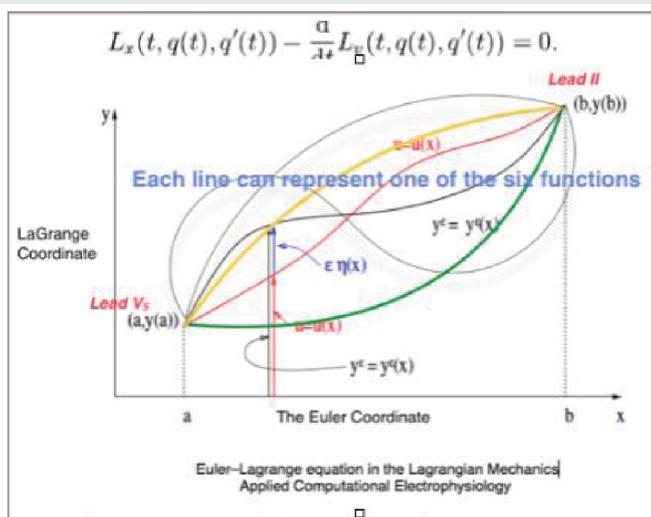


Figure 1: Lagrangian Mechanics to explore the interactions and communication between two EKG signal sources, Lead V5 and Lead II, via multiple non-linear functions.

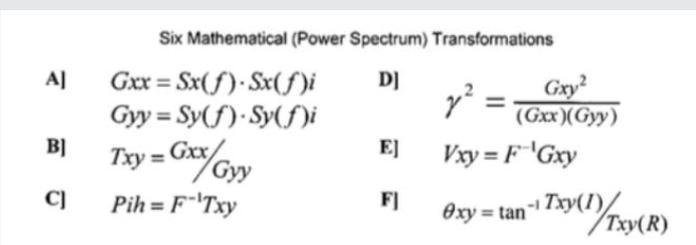


Figure 2: Six mathematical (power spectrum) transformation.

2. Trial design and guiding ethical principles: Compare MCG only to the Gold Standard Interventional Diagnostic tools with *the eight quality criteria advocated by Professor John Ioannidis* (10) and beyond to ensure integrity, objectivity without cherry picking the data and completely void of any bias.

3. No quid pro quo (or money changing hands with any of the investigators) for double-blinded, independently monitored by a third party trial monitor, replicable trial design and protocols with reproducible data analysis.

To this effect, multiple double-blind independent prospective clinical trials conducted in Eight Countries, USA, Germany, Japan, India, China, Singapore, Myanmar, and Malaysia from Three Continents to Validate MCG thousands of patients, since 2002. The final results placed MCG's overall accuracy at a reproducible rate of over 90%. When the results of MCG are combined with serum biomarkers such as HbA1c, hBNP, Abnormal Glucose levels, or LDL levels, the accuracy approaches 100% for the detection of coronary artery ischemia from very early stages to the very severe late stages, as well as the natural recovery stages of the disease. This along with reported negative predictive values between 95% to 99% (References of independently published clinical validation trial articles available upon request).

To demonstrate what we have accomplished to thoroughly verify and validate MCG, most recently, our colleagues from Japan and many other countries have conducted independent meta-analysis of the data of thousands of patients collected over the past five years from multiple centers, and concluded the following in "A Phase Five Post Market Surveillance Data Meta-Analysis Concludes" (pending publication):

- MCG is 3 to 5 times more accurate than conventional ECG
- MCG is 2 to 3 times more accurate than echocardiogram
- MCG is 2 to 3 time more accurate than nuclear, echo, ECG, and pharmacological stress tests
- MCG is reproducibly "compatible" with the current platinum standard - *Coronary Angiography plus Functional Fractional Reserve, Classical Syntax Score or Functional Syntax Scores* with replicable results. However, they also concluded that MCG may be much better in areas that coronary angiography cannot detect, such as small vessel micro vascular disease and metabolic heart disease due to type two diabetes.

Below are some examples of the unique capabilities of MCG the physician communities have discovered over the past five years:

- MCG can quantify the degrees of functional loss of the myocardium and its interaction with other factors such as blood supply, metabolic disorders, such as diabetes, heart failure of any cause, and many inflammatory, infectious, or neural hormonal systemic disorders, etc.
- MCG can detect low, intermediate and high degrees of ischemia due to all stages of coronary artery disease from

very early (as little as 30% coronary artery narrowing to 100% occlusion with or without the collaterals).

- MCG is just as accurate for people with low risks as it is for people with intermediate or high risks for CAD. (The conventional imaging tools can only detect late-stage disease at poorer accuracies than MCG).
- *MCG is just as accurate for women as it is for men, or people's EKG output shows LBBB (Left Bundle Branch Block), RBBB (Right Bundle Branch Block), or simple BBB (Bundle Branch Block).*
- MCG can predict increased myocardial ischemia due to post-interventional restenosis. (The evidence shows that MCG is correct 100% of the time!) The reverse is also true - MCG can directly measure the functional reversal of metabolic heart disease due to Type II Diabetes and/or Coronary Artery Disease.
- MCG can predict recurrent Atrial Fibrillation post ablation procedures, also at 100% of the time. (This is unheard of in the history of medicine, BTW.)
- MCG can predict "INCIPIENT" Atrial Fibrillation or potentially lethal ventricular arrhythmia BEFORE they are visible by the conventional EKG.
- MCG's capability to detect abnormal expressions of the aspects of the myocardial system is beyond the conventional ECG, echo, all stress imaging tests and coronary angiogram can provide. The possibility of human predicting sudden cardiac death has become a reality using MCG.

### The current technology embodiment is ready to serve the public

MCG benefits from more than two decades of dedicated work by two generations of mathematicians, physiologists, bioengineers, computer engineers, and physicians, and is absolutely ready to assist diagnosticians efficiently, non-invasively, and cost-effectively to detect and monitor heart disease at any stage anywhere there is the Internet, satellite, or cellular network access. With this, primary prevention as the first line of defense not only gains increased viability but also lowers health care costs and saves lives in ways that an expert armed with expensive imaging scanners simply cannot provide. A.I.-based MCG Technology is unconventional, and often times considered unbelievable, but it is now a new reality (virtually speaking, perhaps?) in the brave new world of digital medicine.

Additionally, because MCG's analytical software platform is designed to be an A.I. driven, supervised machine learning algorithm we are set to at any time develop the next generation system using a version of my new, seven categories based discriminative analysis in conjunction with an automated generative model to develop into an automated self-learning system. Our development work will enable a real-time cloud A.I. system for data-mining and deep learning for globally available, objective clinical data analysis.

In truth, with all of this being considered, one can say that we here stand at the precipice of potentially eliminating human bias from cardiovascular diagnosis and clinical trial data analysis reporting for the good of both doctors and patients the world over. When *Professor John Ioannidis* asked where the practice of evidence-based medicine could be undeniably helpful to human beings and society at large, he questioned what remote corner of the world he'd have to go to see it happen in person. In truth, the answer was much simpler than he likely thought. It is here, with us, with this company, with this technology. *In fact, we believe that our peer review published clinical validation work is one of the very rare and few examples amongst 30+ million articles published in the medical literature in the past 10 to 15 years!* All that needs to happen now is its wider adoption into the open market so that all may reap its benefits.

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