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Titolo dell’assegno di ricerca: A

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Obiettivi della ricerca:

Study of a new ECG-based parameter, the V-index, for risk stratification of cardiac events (Part I)

1. Background and Introduction
   1.1. Physiological background
       In 2011, Sassi and Mainardi developed a new ECG-based parameter, i.e., V-index, sensitive (at least theoretically) to the spatial heterogeneity of the ventricular repolarization (known pro-arrhythmic aspect). The parameter estimates the standard deviation of the repolarization times of the myocytes, i.e., $s_G$, a quantity measurable at the cellular level, from the macroscopic standard surface ECG through the combination of one mathematical and one statistical model.

   1.2. Methodological background
       In order to compute the V-index, it is necessary to fit a model for each cardiac beat. The model is defined as the linear combination of $T$ scalars (with $T$) called lead factors ($w_i$, with $i$ from 1 to $T$) with the derivatives of a function ($T_d(t)$) called dominant T-wave. The model is $Y(t) = \sum_{i=1}^{T} w_i \frac{d^{i-1}}{dt^{i-1}} T_d(t)$. The model fitting has several degrees of freedom such as model order $T$, basis expansion for $T_d(t)$, separate or shared $T_d(t)$ across beats, boundary conditions etc. Moreover, there are a plenty of possible feasible optimization algorithms capable to minimize the error between the real data and the model $Y(t)$.

2. Goals
   During the first year of work, we (BISP Lab colleague and I) focused on three different tasks. First, we implemented two new algorithms for estimating the V-index (goal 1). Second, we investigated on the possible correlation between $s_G$ and the action potential duration (APD) dispersion (APDD; see below for its definition), that are quantities measurable only on cardiac tissue preparation, using an in-silico high-resolution human left-ventricular wedge model (goal 2). Third, we prospectively analysed a real dataset composed by subjects with suspected acute myocardial infarction (goal 3).

2.1. Goal 1
Two new algorithms have been developed and tested; they were based on:
1) Euler-Lagrange equations with a common $T_d(t)$ across beats (M1);
2) sinusoidal basis functions with periodic boundary conditions for modelling $T_d(t)$ (M2).

M1 was an extension of previous validated algorithm (M0) based on the Euler-Lagrange equations with a different dominant T-wave for each beat. M1 instead assumed that the dominant T-wave must be a single function shared among all the beats. Both methods were based on a numerical approximation scheme of the derivatives and only two lead factors were considered ($T=2$).

M2 modelled the dominant T-wave using a Truncated Fourier Series. The number of sinusoidal basis functions and the number of lead factors were selected to have the best trade-off between model error and model overfitting via synthetic simulations.

Both M1 and M2 were tested using both synthetic and real data, and compared with M0. In particular, synthetic data were generated using a forward model composed by 257 nodes. This model linked the transmembrane action potential of each cardiac cell to the in-silico standard 12 ECG lead system located on a virtual chest model. On the other hand, a dataset composed by 68 subjects was retrospectively analyzed using all the three methodologies, i.e., M0, M1 and M2. Each subject underwent two 24-hours Holter ECG recordings when either a placebo or moxifloxacin (drug supposed to increase the heterogeneity of the ventricular repolarization) was administered.

The objective of these two analysis was twofold. First, we needed to understand whether the V-index computed through the new methodologies could be a reliable estimate of $s_\theta$ (selected in the model). Second, we assessed the capability of the new algorithms to be sensitive to the effects of a real drug, known to increase the heterogeneity of the ventricular repolarization.

2.2. Goal 2
The second goal was related to the in-silico assessment of the relationship between $s_\theta$ and APDD. APDD is a known measure sensitive to the heterogeneity of the ventricular repolarization. It is defined as the difference between the longest and shortest APD measured on a cardiac tissue preparation. However, such quantity is not directly available from the surface ECG. Also, it is not known whether it is related with $s_\theta$ (the quantity that V-index is supposed to estimate).

For such assessment, we employed an in-silico high-resolution human left-ventricular wedge model. The in-silico wedge model was previously extracted from an anatomical model of the human left ventricle by using cryosectional images stored in the Visible Human Project of The National Library of Medicine. Its dimensions were 32x35x32mm (35mm was the transmural length) with a spatial resolution of 0.2 mm. The model was comprised of approximately 4 million cells (or nodes). For each node, a cell type selectable from three possible options has to be assigned. Moreover, each of these three cells had several model parameters (we selected to use only 5 of them and to keep the others fixed). The main difference among these three cell types was their APD.

Three set of synthetic simulations were run using a supercomputer (BlueGene/Q from IBM) located at the University of Rochester (NY, USA). In order to perform the tests, we developed an user-interface (Matlab and C) capable to set the wedge model’s millions of parameters.

The main objective was to understand how the wedge model behaved using different settings of cell distributions for the 4 millions of nodes and to compute the correlation between $s_\theta$ and APDD.

2.3. Goal 3
Twelve lead ECG's of five minutes duration were recorded on 582 subjects at presentation in the emergency department at the University Hospital Basel, Switzerland, for suspected acute myocardial infarction (AMI). Sixteen percent of the total population presented AMI at time of presentation and 18 out of 582 died within two years from the recruitment.

The main goal was to compute the diagnostic and prognostic V-index's values in determining the occurrence of AMI and all-cause mortality within two years. ROC analysis and Survival analysis were then performed to obtain such quantities.

V-index was estimated using M2 method.

**Risultati della ricerca:**

**Goal 1** [1]
Both M1 and M2 provided V-index's values sensitive to a wide range $s_T$ (from 10 to 70ms). In particular, we noticed that M2, having higher model order $T$ than M0 and M1, obtained smaller bias between V-index and $s_T$, especially for large values.

However, all the three methods were capable to detect the effects of the drug in a real dataset with comparable performance.

**Goal 2** [2]
The in-silico simulations of the wedge model resulted on having high correlation between APDD and $s_T$. This means that when V-index is a good estimator of $s_T$, then it is also a good estimator of the dispersion of the ventricular repolarization.

**Goal 3** [3]
V-index's diagnostic value was similar to other ECG-based parameters. However, when used in combination with these other parameters, the AMI detection rate increased from 41% to 85% (p<0.001). The prognostic value of V-index was found to be independent from other population characteristics as age and was higher than 90%.

**Sviluppi futuri:**

There are mainly three different researches planned for the next year. First, we will implement a new V-index estimation algorithm based on a Truncated Discreet Fourier Series. Such formalism will permit to remove the constraint of the periodicity at the boundaries of M2: assumption that does not hold for real cases. Second, we will investigate more on the relationship between $s_T$ and the other parameters of the in-silico high-resolution wedge model. Such simulations would suggest which subjects would benefit the use of V-index (for example, some of the biophysical quantities modelled using those model's parameters are highly altered by genetic mutations and can cause ventricular arrhythmias). Third, we will retrospectively analyse several dataset in which an alteration of the normal dispersion of the ventricular repolarization is present. So far, three real dataset have been used to verify the capability of V-index to be sensitive to the dispersion of the ventricular repolarization.

**Conclusione:**

The on-going research on V-index is a multidisciplinary work meant to foster technical improvements in the Computer Science and Biomedical Engineering field as well as to provide advancement in the Clinical and Medical knowledge.
Up to date, the work involves collaborations spread all over the world, including both universities and companies.

**Prodotti della ricerca conseguiti:**


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Firmato (in Stampatello) **NOME** .......................... **COGNOME** ..........................

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