Computational Electrocardiography: Revisiting Holter ECG Monitoring

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Summary
Background: Since 1942, when Goldberger introduced the 12-lead electrocardiography (ECG), this diagnostic method has not been changed.
Objectives: After 70 years of technologic developments, we revisit Holter ECG from recording to understanding.
Methods: A fundamental change is foreseen towards "computational ECG" (CECG), where continuous monitoring is producing big data volumes that are impossible to be inspected conventionally but require efficient computational methods. We draw parallels between CECG and computational biology, in particular with respect to computed tomography, computed radiology, and computed photography. From that, we identify technology and methodology needed for CECG.
Results: Real-time transfer of raw data into meaningful parameters that are tracked over time will allow prediction of serious events, such as sudden cardiac death. Evolved from Holter's technology, portable smartphones with Bluetooth-connected textile-embedded sensors will capture noisy raw data (recording), process meaningful parameters over time (analysis), and transfer them to cloud services for sharing (handling), predicting serious events, and alarming (understanding). To make this happen, the following fields need more research: i) signal processing, ii) cycle decomposition; iii) cycle normalization, iv) cycle modeling, v) clinical parameter computation, vi) physiological modeling, and vii) event prediction.
Conclusions: We shall start immediately developing methodology for CECG analysis and understanding.

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1. Introduction

A long time has gone since in 1895, Willem Einthoven turned electrocardiography into a diagnostically applicable medical device (►Figure 1a) delivering the leads I, II, and III [1]. Einthoven also assigned the letters P, Q, R, S, and T to the various deflections of the curve's pattern. In 1924, he was awarded the Nobel Prize in Medicine for his discovery. In 1934, Wilson defines the unipolar limb leads VR, VL and VF, where V denotes voltage [2]. Shortly thereafter, in 1938, the American Heart Association and the Cardiac Society of Great Britain have defined the standard positions and the wiring of the chest leads V1 to V6 [3]. In 1942, Emanuel Goldberger increased the voltage of Wilson's unipolar leads by 50% and created the augmented limb leads aVR, aVL and aVF [4, 5]. When added to Einthoven's three limb leads and the six chest leads, we have arrived at the 12-lead electrocardiography (ECG) that is used today. Slightly thereafter in 1949, Norman J. Holter has developed a mobile backpack that records the ECG of its wearer and transmits the signals [6]. Starting at 75 pound, this system has been greatly reduced in size and weight while increased in performance. Recent technology allows for continuous 12-lead ECG recordings over days thus providing physicians with valuable information on arrhythmias in high risk patients.

However, the core principles of recording and analysis remained unchanged over all the years: Today in 2015, continuous ECG monitoring is performed following the same paradigms as it has been done in 1949. Therefore, it is time to revisit these paradigms with respect to today's technology.

2. Methods

2.1 Relation to Computational Biology

Within the past 75 years, enormous technological developments have been made, in particular regarding computer systems and their applications in medicine. We particularly refer to the 'computed' or 'computational' terminology that aims at indicating the substitute of a system's core processes by data processing techniques (computation) such as data-analytical and theoretical methods, mathematical modeling, and simulation techniques. Some examples are:

- Computed tomography (CT): In the 1970s, the first CT device was installed at Mayo Clinic, Rochester, Minnesota, USA, resulting in three-dimensional (3D) volumetric data. Invented by Godfrey Hounsfield, digital geometry processing is used to obtain large series of two-dimensional (2D) radiographic images taken around a single axis of rotation [7, 8].
- Computed radiology (CR): In the 1980s, Fujifilm Medical Systems introduced CR, initially limited to a few selected veterinary colleges and specialty private veterinary practices because of its high cost [9]. This 2D imaging technology makes use of intensive computation when reading out excitation states of recording plates by laser beam.
- Computational photography (CP): In the 1990s, another 10 years after CR invention, CP was born by several technological inventions including in-camera computation of digital panoramas and mosaicking [10, 11], high-dynamic range images [12, 13], and light field rendering [14], which uses optical and computational elements to capture 3D scene information which, for example, can then be used for selective focusing [15], also referred to as post focus, e.g., available with the Google camera app for Android. A more recent CP example is the visual microphone [16], where subtle deformations of objects from sound are visually monitored, emphasized, and decomposed into frequencies to reconstruct the sound waves that have induced these mechanic alternations.

More generally, the National Institutes of Health (NIH), Bethesda, MD, USA, have defined 'computational biology' as the development and application of data-analytical and theoretical methods, mathematical modeling, and computational simulation techniques to study biological, behavioral, and social systems [17]. With respect to the presented time line, one-dimensional (1D) imaging, in other words, medical signal recording shall be revisited next by introducing computational power to substitute device limitations.

2.2 Reflecting the State of the Art

So far, clinical use of ECG signals follows the needle-in-the-haystack paradigm. Four to six cycles are plotted on a scale paper and manually measured for clinically meaningful parameters, which, however, are fairly well standardized [18–23]. ECG pattern inspection is basically composed of seven steps: 1) rhythm, 2) heart rate, 3) conduction intervals (PQ, QRS, QT), 4) heart axis, 5) P wave morphology, 6) QRS morphology, and 7) ST morphology. Meaningful measures include the PQ duration, which is normally between 120 ms and 200 ms, QRS duration, which should be less than 120 ms, and the QT time, usually normalized by the square root of the heart rate in seconds (QTc) and below 450 ms.

2.2.1 Hardware and Protocols for Recording and Handling

Today's Holter monitoring is usually recorded on 3 or 12 leads over 24 hours, since short-term intervals (< 10 min) are not reliable [24]. The limitations due to the shortness of the 24 hours have already been addressed [25] and answered by devices such as the Zio Patch (iRhythm Technologies, Inc, San Francisco, CA, USA), which is an FDA-cleared, single use, non-invasive, water-resistant, 14-day, ambulatory ECG monitoring adhesive patch [26]. Nonetheless, the needle-in-the-haystack paradigm is followed since only a small number of events are considered. Recent research coupling the recordings to 1-min epochs [27] does not change that paradigm in general. Contrarily, technology for cloud-sharing of mobile recordings is already available, but has not yet been used for Holter monitoring.

2.2.2 Software for Analysis and Understanding

The field of automated ECG analysis was one of the earliest topics in Medical Informatics and is still representing rank 13 of MeSH (U.S. National Library of Medicine Medical Subject Headings) topics discussed in Methods articles in the last 50 years [28]. In previous works, ECG data is parsed for just a few irregular events, i.e., arrhythmias, such as extra-systoles [29]. Today, 'Computing in Cardiology' (CinC) has been established as annual (since 1974) scientific conference (http://www.cinc.org/). Within the last 25 years, almost 350 papers have addressed the heart rate variability (HRV), which is computed over several ECG cycles. The intervals are ranging from ultra-short-term (< 60 sec) to long-term e.g., 6 hours [30] or 24 hours [31]. Recently, a comprehensive list of 70 HRV indices has been compiled that produce a finite number out of 30 beats [32]. The indices have been evaluated [33] and dynamic analysis has been suggested for clinical consideration [33, 34]. However, shape analysis of cycles in several leads is certainly more important as just considering the pulse rate. For instance, the QT dispersion has been identified as indicator for stroke [35].

2.3 Foreseeing Computational Electrocardiography

In future, such type of data processing will become standard in ECG analysis, and raw data will be recorded continuously (up to the full lifetime). Wellness industry and sportive consumers who like monitoring their body performance and sharing it in social networks will open economical markets that allow low cost hardware, for instance embedded in smart clothes (▶ Figure 1b). More meaningful use of this technology will start with high-risk patients, for instance in ambient assisted living (AAL) or as security method in public transportation on roads, railways, or airways, before applied to all humans. Computational ECG (CECG) aims at predicting and preventing serious adverse events, such as the sudden cardiac death (SCD) [36], which remains a major public health problem worldwide, e.g., causing more than 300,000 deaths per year in the United States [37]. SCD affects not only patients with chronic diseases [38, 39] or obstructive sleep apnea [40, 41] but also athletic and sportive young people [42]. Medical Informatics is seen as key component for improvements.

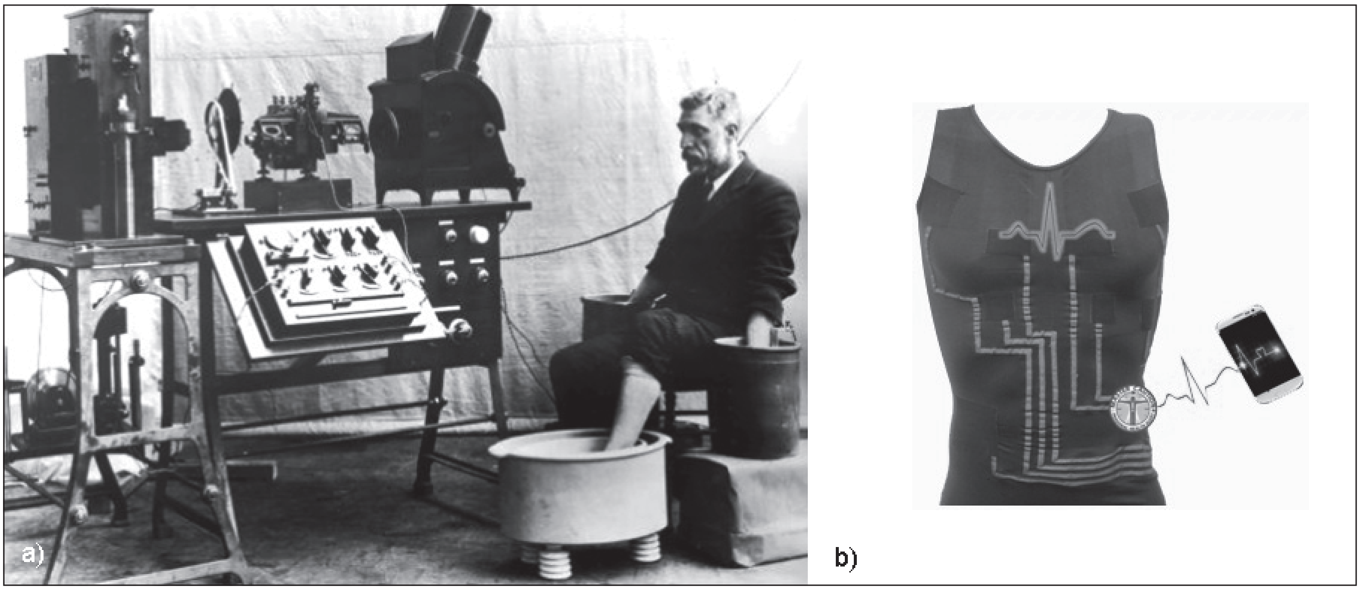

Figure 1 ECG recording hardware. a) In 1903, the Eindhoven device delivered three leads (health.howstuffworks.com). b) In 2014, the HealthWatch Company of Tel Aviv, Israel has applied its 12-lead embedded T-shirts coupled with a smartphone for FDA approval (http://mobihealthnews.com/32774/healthwatch-seeks-fda-clearance-for-its-12-lead-ecg-tshirt).

3. Results

3.1 Technology and Methodology Needed

Data transfer from mobile devices to cloud services is available already. As the recording hardware is becoming available (►Figure 1b), remaining obstacles hindering our vision to turn to reality are signal analysis and understanding methods as well as standards for biodata interfacing – all in the core competences of medical informaticians. The following fields need more research:

- *Signal preprocessing:* Big data results from continuous ECG monitoring. Novel Holter devices deliver 12 leads, each at 1000 Hz sampling rate and 10 bit coding, ending up with 8 GB of uncompressed data per week (e.g., Medilog FD 12 plus, Schiller, Switzerland). Textile-embedded electrodes and consumer market products are expected to deliver noisy signals and there might be disconnected or shifted periods. These must be detected robustly, and the user needs feedback to check the hardware components and their interconnection.
- *Cycle decomposition:* It is commonly acknowledged that ECG is decomposed into the cycles for further analysis. R-wave detection is used, and several algorithms have been suggested, which usually are based on leads I or II. For instance, high-pass filters [43], spectral analysis [44], template matching [45], and wavelet decomposition [46] are applied. Advanced methods use the vector cardiogram, which is composed from the six chest leads [47]. However, more recent research has indicated already the limitations of existing approaches when applied to noisy signals [48] or recordings of multi-morbid patients [49].
- *Cycle normalization:* To apply big data analysis methods, one need to cope with the problem that the human heart rate is changing abruptly and frequently, and hence, all cycles are sampled with different effective rates, i.e., represented by a different number of samples. Since the ECG cycle pattern is changing non-linearly, simple resampling is not an option but non-linear stretching is required [50].
- *Cycle modeling:* As a core component of any real time ECG understanding, each cycle needs representation by a small set of model parameters. So far, heart model construction is used primarily for ECG simulation rather than analysis [51]. Matching models onto recordings usually is based on curve fitting [52, 53], and Gaussians are the preferred curve. However, existing methods do not cope with multi-lead recording, and computational efficiency is required, which calls for further research [54].
- *Clinical parameters:* Data reduction into parameter curves is the next step following consequently. Various ECG risk markers for SCD have been identified, which are far beyond the heart rate and its variability. Cardiac rhythm abnormalities, AV block, QT length, QT dispersion, T-wave alternas, late potentials, as well as left- (LBBB) or right-bundle branch blocks (RBBB) are important [55]. These medical concepts need to be transformed into mathematical expressions using the cycle model parameters. Then, they can be computed automatically, visualized in real time, and substitute the native ECG curve inspections.
- *Physiological models:* Such risk markers need to be combined for the development of physiological models. The physiological models must be enhanced including traditional (e.g., body temperature, respiratory rhythm) as well as more advanced (e.g., glucose level, cardiovascular pressure) physiological measures. Engineering approaches are needed to model cardiovascular physiology [56]. Such models will be based

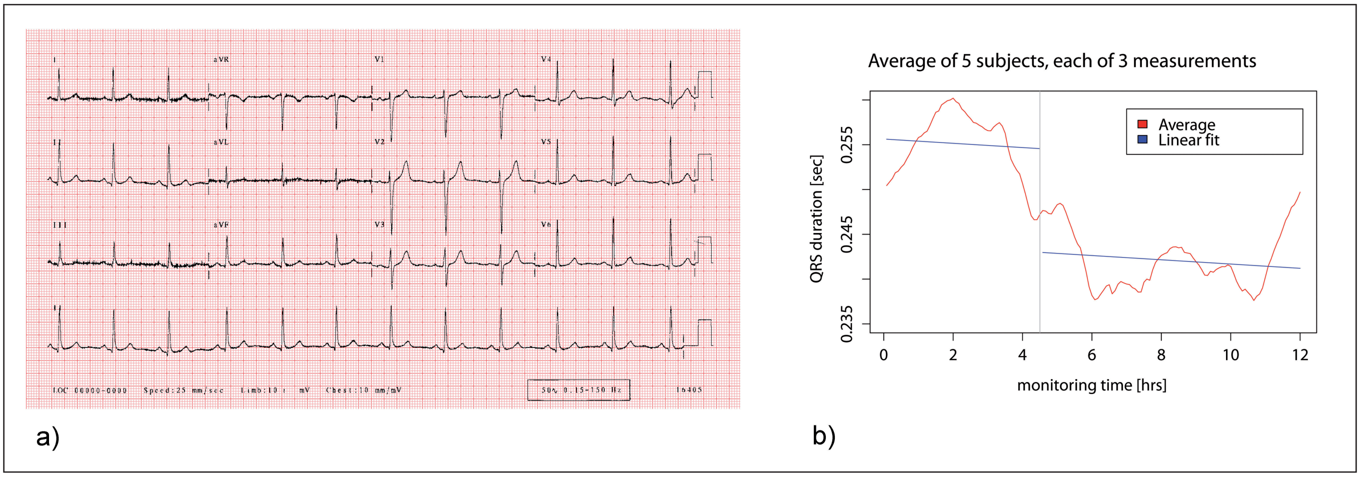

Figure 2 Conventional vs. computational ECG. a) Commonly, ECG is plotted over a short period and a few measurements are done manually by counting the scales on the normalized plot (http://www.ecglibrary.com/norm.php). b) In computational ECG, long time recordings are processed automatically and visualized by parameter over the time plots. Note that panel b is an average of 15 recordings (the high values of 0.25 s are due to a systematical offset when transforming model parameters to clinical measures and subject to improvement).

on clinical parameters rather than ECG potential samples.

- *Event prediction:* Event prediction in patients with risk factor or those with existing cardiovascular disease is one of the major tasks in cardiology today [57]. So far, these parameters are often assessed from standard rest ECGs and extended analyses over a longer period of time as well as under different conditions in daily life (e.g. sleep, exercise) are missing. Knowledge must be gained and meta-models must be established to allow in time alerts and event prevention. At this end, the CECG wearer is alerted and takes action such that SCD will not happen [58]. So far, the subject's age is roughly predictable on HRV signals [31] but work on predicting events has not yet published. In addition, event prediction models need to cope with signal changes due to physical body movement [59, 60].

3.2 First Steps Towards CECG

In some of these points, first steps have already been reported in the literature and further research is ongoing. As an example, we illustrate our CECG vision with respect to the identification of surrogate markers for SCD in patients with diabetes mellitus and end stage renal disease (ESRD). In an ongoing controlled clinical trial (ClinicalTrials.gov: NTC02001480), which has been approved by the Ethics Committee of the RWTH Aachen University, the study subjects are continuously monitored over a 24/7 interval. The recording period covers three dialysis cycles and delivers about 800,000 cycles per person. A vector cardiogram-based R-spike detection is applied [54]. The ECG model fitting is based on Gaussians. Mean and standard deviation of the Gaussians describing Q- and S-wave are used to compute the QRS duration in each of the cycle.

So far, data from five individuals is available. ▶Figure 2b visualizes the QRS-duration averaged over 15 measurements which have been synchronized on the start of the dialysis (monitoring time = 0). A 12-hour period is plotted (red) and the end of the dialysis is indicated by the vertical grey line. In both periods (during and after the dialysis), a linear regression model has been fitted (blue lines). The offset in both parts differ significantly (Student's t-test, $p << 0.001$).

Comparing ▶Figure 2a and ▶Figure 2b, the different approaches become obvious. The ECG in ▶Figure 2a shows 12 cycles on 4 leads, while the CECG in ▶Figure 2b is based on 5 subjects times 3 period times 12 hours times 3,600 cycles per hour ~ 650,000 cycles on 12 leads. The change in QRS duration is manifested averaging over same periods of different individuals. Such computations need medical explanations, which require comprehensive research and further experiments as well as conduction of controlled clinical trials.

4. Discussion

SCD remains the leading cause of mortality in developed nations [61]. It is consensus that increasing the number of leads while increasing the duration of monitoring is required for a better understanding of SCD and other pathologic heart failures. Ideally, computer algorithms for risk analysis are applied that process the significantly increased amount of ECG monitoring data (big data [62, 63]), and forecasting as well as prevention strategies are developed taking into account subject-specific circumstances (personalized medicine [64]).

After decades, the ancient paradigm of ECG recording, handling, analysis, and understanding is changing towards what we have named 'computational ECG' (CECG). In our vision of CECG, continuous monitoring is achieved using inexpensive hardware (recording), big data is preprocessed on mobile devices to form meaningful indicators over the time (analysis), which are transferred into the cloud and shared (handling), and further analyzed for alarming before adverse events, such as SCD, are happening (understanding).

Roughly 25 years ago, the medical informatics community already aimed at changing the ECG paradigm [65]. At that time, the goal was to define common standards for quantitative electrocardiography (QECG) based on digital recordings and to validate ECG-based diagnostic decision support [66]. In total, 14 different 12-lead ECG analysis programs from Belgium [67], Canada [68], France [69], Germany [70], Italy [71], Japan [72], The Netherlands [73], Portugal [74], United Kingdom [75], and United States [76] including research systems as well as commercial products from major industrial companies have been compared based on the same dataset. However, the entire campaign was based on patient recordings of 8 or 10 seconds [77], thus following the ancient paradigm.

Stepping forward, some examples of CECG are available already. For instance, HRV analysis has developed from about 0 to almost 1000 (PubMed-registered publications per year) from 1990 to 2012, respectively [34], which is in line with our analysis of the CinC conference. In the already mentioned QECG campaign, the value of scatter-graphs for the assessment of computer-based ECG measures has been emphasized [78]. These plots condense measures from several cycles into a non-signal like format. As another example, electrocardiographic imaging (ECGI), a noninvasive method for mapping the electric activity of the heart in humans in real-world conditions [79, 80] is based on up to 250 electrodes (leads). The enormous data is visualized in 3D by pseudo-coloring an MRI-based heard shape. Furthermore, Marques has recently suggested a changed paradigm of diagnosis towards molecular genetics [81], emphasizing the personalized component of CECG.

However, more research is required that shall start by today. Then, in five years from now, we expect the wellness industry to offer hard- and software technology for continuous ECG recording and handling for less than 100 US$, which will open a huge and international consumer market. The data is preprocessed and analyzed on the smart device via complementary apps for computational ECG, hosted in cloud-based vendor-specific proprietary repositories, but shared with friends via social networks. However, more serious applications in medicine and for ambient assisted living (AAL) are already in development, profiting from low cost hardware and already established consumer markets.

Table 1 Key issues for discussion

- Reading of ECG has remained unchanged over more than 70 years: From clinical recordings individual cycles are plotted on scale paper and manually annotated and analyzed, while in long term Holter monitoring, the numbers of irregularities are counted.
- A 7 day 24 hour recording yields 15.6 km printout; most of the recorded cycles remain uninspected.
- In near future, textile-embedded electrodes coupled with smartphones will continuous monitor individual heart activities, producing personalized big data volumes that require automatic analysis.
- Identifying individual cycles, mapping models to each of the cycles, where the model parameters allow computing medical meaningful ECG readings and plotting them in curves over the time will revolutionize ECG in medicine.
- Such computational ECG (CECG) supports prediction of serious adverse events and allows preventing actions to be taken in time applying cloud-based big data analytics.
- In parallel to the hardware development that is currently ongoing, we urgently need to revisit ECG reading and focus research on data analysis and modelling.

5. Conclusion

The field of automated ECG analysis was one of the earliest topics in Medical Informatics and may be regarded as a model for both, computer-assisted medical diagnosis and evaluating medical diagnostic programs [82]. Nonetheless, it is still a hot topic in research providing challenging tasks in near future (▶Table 1).

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