Discussion of “Computational Electrocardiography: Revisiting Holter ECG Monitoring”

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Summary
This article is part of a For-Discussion-Section of Methods of Information in Medicine about the paper “Computational Electrocardiography: Revisiting Holter ECG Monitoring” written by Thomas M. Deserno and Nikolaus Marx. It is introduced by an editorial. This article contains the combined commentaries invited to independently comment on the paper of Deserno and Marx. In subsequent issues the discussion can continue through letters to the editor.

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With these comments on the paper “Computational Electrocardiography: Revisiting Holter ECG Monitoring”, written by Thomas M. Deserno and Nikolaus Marx [1], the journal seeks to stimulate a broad discussion on new methodological approaches for ECG monitoring and data analysis. An international group of experts has been invited by the editor of Methods of Information in Medicine to comment on this paper. Each of the invited commentaries forms one section of this paper.

1. Comment by C. Baumgartner

In the survey article written by Deserno and Marx [1], the great successes and innovations of ECG-gated cardiovascular diagnostics of the past 100 years are nicely reviewed, and new directions and challenges of the era of “computational” electrocardiography, which arrived in the early nineteen nineties, are thoroughly discussed. In particular, the upcoming new soft- and hardware technologies for ECG recording, signal analysis and interpretation opens unlimited possibilities for future applications, not only in a clinical setting, but also for wellness and home use.

Standard ECG devices are declared by the European Medical Directive 93/42/EEC as class Ila/IIB low-medium/high risk medical devices or class II according to the FDA classification (21 CFR Part 870.2340), respectively. Also medical device or stand-alone software with measurement or extended alert functions is defined and classified as low, medium or high risk medical product. Therefore, medical apps such as ECG apps, if they are “intended for use in performing a medical device function (i.e., for diagnosis of disease or other conditions, or the cure, mitigation, treatment, or prevention of disease) are medical devices, regardless of the platform on which they are run” (FDA Guidance Document-Mobile Medical Applications, 02–2015; see also European General Guidance Documents-Manual in Borderline and Classification in the Community Regulatory Framework for Medical Devices, Version 1.17, 09–2015). As a consequence, mobile apps intended to run on smart phones, analysing and interpreting ECG waveforms to detect heart function abnormalities, need to be treated in a similar way to software running on a desktop computer, which is essential for mobile medical app manufacturers, pursuing a conformity assessment process.

With regard to these regulatory challenges, home- or self-monitoring of physiological parameters such as blood pressure, heart rate and physical activity, including feedback reports of these parameters via smart phone apps, has especially become an accepted tool for the mobile rehabilitation of patients e.g. with cardiovascular disease [2, 3]. To prevent myocardial (re-)infarction in this group of patients, life-long medical therapy, lifestyle modifications, and regular follow-up examinations are necessary. Integrative telemonitoring systems have already been introduced, where (medical) devices used by the patient typically communicate via Near Field Communication (NFC) with smart phones, on which mobile apps are run. Collected data is transmitted and synchronised automatically via secure protocols with the central server. Clinicians have access to all this information via web-interfaces or, in case of life-threatening
cardiac events, they are notified through an alert on their phone which allows for prompt clinical action to be taken.

As pointed out by Deserno and Marx, multiple steps towards computational electrocardiography (CECG) brought about by new developments in microelectronics and sensing, big data handling and exploitation as well as biomedical signal processing and interpretation have boosted new diagnostic concepts and innovations in this field. One of these developments is the non-invasive imaging of cardiac electrophysiology, which allows for the visualization of ventricular electrical activation in patients with electrical excitation abnormalities with up to 250 electrode leads. In a study which we performed in 2011, ten patients with congestive heart failure (CHF) undergoing cardiac resynchronization therapy (CRT) and the same number of patients without structural heart disease (control group) were examined, using 65-lead high-resolution electrode array registrations [4]. This array was coupled with a patient’s individual cardiothoracic anatomic model, considering compartments of different conductivity (heart, blood mass, lung and chest surface), generated from MRI scans. Beat-to-beat endocardial and epicardial ventricular activation sequences were computed during native sinus rhythm and ventricular pacing. A bidomain theory-based heart model was used by solving the inverse problem. Using this approach, the control group showed a deterioration of the ventricular activation sequence during right ventricular pacing, similar to the intrinsic activation pattern of CHF patients. To enhance the clinical usability of this approach, a further reduction of the number of electrodes to a standard 12-lead electrode configuration, e.g. by using active electrodes with optimized signal-to-noise ratio, highlights a possible research direction.

Moving from the organ level to a cellular description, ECG recordings in in-vitro experiments of cardiomyocytes using multi electrode arrays (MEA) have become essential for investigating modulations of electrical excitation under (patho)physiological conditions. MEA systems – provided as low resolution TiNi electrode arrays or in high-density CMOS technology with up to several thousand electrodes per square millimeter – facilitate the registration of extracellular field potentials (FPs) on the bottom of a cardiomyocyte cell culture (see Figure 1). Data can be registered with a sampling rate of up to 25 kHz on all channels simultaneously. This technique enables the investigation of electrophysiological alterations in a myocardial cell layer by studying parameters such as the spread of electrical excitation or the conduction velocity with extremely high spatial and temporal resolution. It is important to note that the shape of extracellular field potentials differ significantly from those of a body surface ECG because of the divergent morphological structure of a cellular (mono)layer. In a recent study, we investigated electrophysiological abnormalities under hypothermal conditions of randomly grown embryonic chicken cardiomyocytes, which interestingly formed multiple randomly distributed pacemaker centres [5]. However, a dominant pacemaker centre forces the cell layer to a synchronized regular contraction with definite direction of electrical excitation propagation. Our experiments demonstrated significant spread-direction-dependent variations of intrinsic FP parameters which could be measured between the different endogenous pacemakers. Thus, MEA is an emerging tool for basic research in electrophysiology, urgently needed for drug design and investigating therapy control in cardiac excitation disorders. In addition, MEAs serve as an excellent platform for evaluating and validating in-silico models of cardiac electrophysiology e.g. to study changes of electrical excitation in a selected cardiac tissue wedge or the whole heart. Ion current models of the cardiac cell provide the basis for the calculation of the pseudo ECG (pECG) as a bipolar measurement of the electric field of a myocardial tissue wedge, where the computed signals show a similar morphology and shape characteristics to those of a body surface ECG. In this application, the wavefront propagation time between two defined points can be measured to estimate the conduction velocity, a crucial electrophysiological parameter, representing the electrical conduction between connected cardiac cells determined by the gap junc-

Figure 1
Top: Cardiomyocyte cell layer on a multi-electrode array (MEA) with 60 TiNi electrodes (diameter 10 μm, inter-electrode distance 100 μm), Bottom: Registered field potentials of the spontaneous beating cell layer, showing a positive and negative peak and a small repolarization wave.
Discussion of “Computational Electrocardiography: Revisiting Holter ECG Monitoring”

The use of mobile devices that potentially allow long-term continuous monitoring has become a key aspect of patient empowerment. These technologies have opened many opportunities to research new and challenging topics in molecular, cellular and systemic electrocardiology, as the authors outlined in their conclusion.

2. Comment by E. G. Caiani

The paper of Deserno and Marx [1] revisits continuous ECG monitoring original paradigms with respect to today’s technology allowing long-term continuous monitoring and big data generation, thus suggesting the need for further research on several aspects of computational electrocardiography (CECG), including signal pre-processing, cycle decomposition, normalization and modelling, extraction of clinical parameters for the development of physiological models, to be used for event prediction.

While I fundamentally agree on what has been described here in the context of long-term monitoring, in this commentary I would like to offer a different viewpoint, based on technology that is available today to the layperson.

In the last decade, two relevant behavioral changes have to be considered:

- the use of mobile devices that potentially allow data collection in real time is increasing ubiquitously, widely adopted across demographic and ethnic groups;
- patient empowerment has become a key priority for policy-makers, under the premise that it would increase the sustainability of present paradigms of care delivery [6].

These factors lead to empowering individuals to assume a more active role in monitoring and managing their chronic conditions and therapeutic regimens, as well as their health and wellness.

To this aim, new technological solutions that transform the mobile device, or even a smartphone, into an approved medical device capable of acquiring 1-lead [7] to 22-leads [8] ECG monitoring systems are currently available, even over-the-counter. In this way, everyone is potentially provided with the ability to acquire themselves an ECG for a short-term (about 30 sec), everywhere and exactly when this is needed without the presence of a physician, and to obtain an immediate response about ECG normality or abnormality, thanks to the on-board approved processing and interpretation software.

The spectrum of cardiac abnormalities that could be observed as support to diagnoses with these mobile ECG devices will depend on progress in CECG for short-term recordings: feature extraction, machine learning algorithms and risk prediction.

Among current clinical applications, atrial fibrillation (AF) represents a major public health problem and is the most common cardiac arrhythmia, with a lifetime risk of 1 in 4 for adults [9]. True prevalence of AF is underestimated because episodes are often sporadic, even in symptomatic patients: this represents a challenge to detect and record an occurrence of AF in a “real world” setting, where important implications include (dis)continuation of therapies aimed at preventing AF-related complications (e.g. stroke).

To this purpose, current guidelines [10, 11] suggest the use of prolonged noncontinuous recording to facilitate AF detection in paroxysmal AF, where a 7-day Holter ECG recording, or daily and symptom-activated event recordings, may document the arrhythmia in about 70% of AF patients, with a negative predictive value for the absence of AF between 30 and 50% [12].

In this context, the use of mobile device as ECG monitor could allow rapid, real-world, on-demand, ubiquitous cardiac monitoring in pts, to confirm AF when symptomatic, allowing for more timely treatment and management, and performing community AF screening in aging population at risk (> 65 yo), with impact on reducing stroke burden [11].

Indeed, some examples of deployment of this technology into preventive medicine have already been shown successfully. Specifically, in 1000 pharmacy customers aged ≥ 65 years old, newly identified AF was found in 1.5%, all with CHA2DS2-VASc score ≥ 2, with 98.5% sensitivity and 91.4% specificity [13]. Also, the ability to detect heart rhythm defects in general population was tested in 381 participants, where smartphone ECG was compared with 12-leads ECG interpretation: sensitivities ranged from 72% (QRS delay) to 94% (atrial fibrillation), with specificities larger than 94% [14].

Instead of the needle-in-the-haystack search by hand, this technology is updating this paradigm by providing a “magnet”. The probability of capturing AF (i.e., the needle) is increased by using anytime available inexpensive handheld technology (i.e., the magnet) with no need of physician intervention, everywhere the patient experiences potential symptoms, with instant and accurate diagnosis of atrial fibrillation [15].

This new opportunity can be considered as a no-turning point in the field of medicine and cardiology, probably like when the first digital blood pressure monitor for home-use (HEM-77, Omron healthcare Ltd, Japan) was launched in 1978, about 80 years after the Italian internist Scipione Riva-Rocci introduced the first blood pressure monitor – a sphygmomanometer with the pneumatic cuff. However, medical professionals defined that the blood pressure measurement should be conducted at a hospital, so the idea of home monitoring was not well received until the first international guidelines in 2000 [16].

In this scenario, it could be predicted that in the next 5–10 years home-monitoring ECG would become a common tool available in every home, like the blood pressure monitoring device and thermometer. And, as these two medical devices, it will be used by everyone to check their health status, confirm or disconfirm symptoms, activate for a physician’s consultation or take immediate action. It is the role of the CECG community to actively participate to this changing path, by focusing on the improvement of processing techniques related to mobile ECG applications that will have a direct and effective impact on clinical diagnoses, providing high specificity and sensitivity in abnormality detection, by leaving in the backstage those techniques that have not become part of the clinical diagnostic tools available to the cardiologist.

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3. Comment by H. Dickhaus

As one of the proven and established standard techniques in current cardiological diagnosis Holter ECG-Monitoring is subject to continuous development.

The article Computational Electrocardiography by Deserno and Marx [1] describes the successful history of long-term recording of the electrical activity of the heart developed by J. Holter in the middle of last century. It presents current methodical approaches and technologies made possible through the increased use of computers and appropriate software. However, the article does not only underline the typical advantage of long-term recording originally characterizing the Holter ECG, but also outlines the current automatic evaluation of 12 lead short-term recordings and its potential for future developments.

Computational Electrocardiography (CECG) is the key word in their article, and its implementation is expected to bring about fundamental changes in cardiological diagnosis. The authors speak of "revisiting" the Holter ECG Monitoring and call for more efficient hardware technologies, modern software engineering, current storage concepts and intelligent methods of analysis to be stronger considered in research and development which should finally lead to a better clinical outcome for diagnosis and therapy.

As Deserno and Marx reported in their article [1], industry has obviously successfully adapted to these developments. There are numerous systems, new electrode types and storage media with differing specifications on the market that already continuously record and save data with up to 12 channels over a period of several weeks. The question of a clinically feasible application, however, often remains unanswered. Signals recorded by textile embedded electrodes and recorders from wearables are often distorted by interference from electrical devices and body motion which does hardly allow any reliable assessment. The storage and evaluation already commercially available in clouds is sometimes more expensive and particularly problematic with regard to data security and privacy. Nevertheless, the technical requirements are already available although they still need some improvement.

But are the clinical applications also defined? Are the applied procedures and methods validated with regard to their clinical significance? It is obvious that computational electrocardiography is still primarily driven by technological developments and industry rather than being initiated by cardiologists. Still, it has to be mentioned that established data repositories and data warehouses such as MIT data base Physionet [17] or telemetric and Holter ECG Warehouse supported by FDA [18] are significant and helpful data repositories and poolings that are best suited for research and development in this field, also for the pharmaceutical industry.

Deserno and Marx discuss the development of computer-based ECG evaluation in the light of computational biology where Big Data processing provides a better understanding of complex biological and medical processes as well as of social systems [19]. There are certainly similarities to be observed between the two fields. Nevertheless, the question arises whether the development of computer-assisted ECG evaluation began a long time ago and has given substantial importance to Holter Monitoring.

It still remains to be seen whether or not the required development of computational electrocardiography, as far as its innovative nature and prospective diagnostic potential is concerned, continues to be comparable to what is beginning to emerge through accumulation and networking in the fields of biology, systems medicine, social networks and many other areas of our lives. Nonetheless, it is worth casting a glance at the field of Big Data that generate data base Physionet [17] or telemetric and Holter ECG Warehouse supported by FDA [18] are significant and helpful data repositories and poolings that are best suited for research and development in this field, also for the pharmaceutical industry.

Thus, there will be no reliable prediction yet for sudden cardiac death [23]. It is also questionable whether increased computational power and new technical and methodical options in the field of signal acquisition, data storage, signal analysis and visualisation will make this possible. Nevertheless, the sense of these efforts and their partial benefit for clinical interpretation as suggested by Deserno and Marx is still unequivocal. Whether or not, however, this will lead to a change of paradigm and an important milestone for diagnostics is hardly possible to predict today.

In the context of computational electrocardiography with regard to Big Data processing there are, according to the authors, other important aspects apart from Big Data volumes caused by many recording leads over long periods of time and their constant availability through wearables and textile electrodes [24, 25]. These aspects exceed previous approaches and their technical upgrades, namely the inclusion of i) multimodal data sources through e.g. other mechanical or physiological impacts such as ejection fraction or different pressure ratios, ii) inclusion of genetic predispositions for certain clinical conditions, iii) the individual quantitative documentation of the cardiological patient history and a complex modelling of the electromechanical cardiovascular system under
changing conditions that is adapting dynamically over time and is suitable for prediction.

Hypothesis-driven research and development with computer-assisted methods should always aim at improving clinical outcomes with regard to lower mortality, safe predictions and selective definitions of risk groups or diagnosis. Exploiting the existing technical and methodological potential must always be subject to clinical evaluation and not be an independent objective of action. Another point worth mentioning in conclusion is that also future-focused developments must follow economic conditions and adapt to the financial viability of the health care system.

4. Comment by C. A. Kulikowski

The paper by Deserno and Marx [1] is quite original in proposing a broad expansion of computational models for Holter ECG monitoring when this is recorded over a large number of heart cycles (days or even months) to summarize and interpret this "Big Data" of long-term or short-term electrocardiography signals within the context of individual patient characteristics for the purposes of personalized and more precise diagnosis and treatment. The paper is both a review of past results and a proposal for what the authors see as the challenges of obtaining better analytical and predictive results from such large multi-cycle Holter electrocardiographic data.

Deserno and Marx first describe some analogies to past data integration and reconstruction methods as CT, CR, and computed photography (CP), and then proceed to describe how almost all current approaches to ECG interpretation – even for multi-cycle large data sets, still adheres to the traditional "needle-in-a-haystack" paradigm of selectively looking at small subsets of the data in using well-known ECG curve features, to determine heart rhythm, rate, conductive intervals, heart axis, P wave morphology, QRS and ST morphology. They point out some of the difficulties in integrating the analysis and obtaining a clear picture of a patient's heart function for what is almost always an un-normalized set of time-intervals reflecting the very different signals and their patterns that the different leads provide.

The authors make it very clear that technologies of data recording and handling (such as ambulatory 14-day ECGs, their non-invasive body attachments, mobile services-to-cloud computing storage, and so on) and are not a major challenge, but rather that the methods of analysis, and summarization across heterogeneous signals that will detect multiple clinically significant events (such as predictive markers for Sudden Cardiac Death, or SCD) and the software that implement these are what pose the greatest scientific and data analysis and interpretation obstacles to progress.

The recent focus on relatively easily computed indexes such as those for Heart Rate Variability (HRV) is brought up as a useful, but very preliminary approach to summarizing within-patient and between-patient data patterns. The authors paint a vision of how in a few years we ought to be able to have continuous ECGs – possibly for a lifetime, and be able to tell apart those who are at high risk from those who are at lower risk for SCD, which affects not only patients with chronic disease, but also many undiagnosed younger patients who may be vulnerable due to genetic or life-style and environmental prior exposure factors.

Deserno and Marx then point out that such new work will be needed to come up with novel techniques for signal processing of the large collections of patient ECG data (such as the 8GB of uncompressed data that accumulated per week of a Swiss device), new methods for cycle decomposition, data normalization to allow comparative analyses which are based less on the characteristics of the measuring device, and simple signal sampling considerations, and more on their interpretation in terms of physiological models of the conditions that may be afflicting a particular patient (such as respiratory rhythm, glucose physiology, cardiovascular pressure and other such). The authors are in effect making a plea to consider how such models can help predict potentially dangerous change in heart function over time and for important conditions – like patient sleep and exercise – that are not often incorporated explicitly in an analytical model. A question that arises is whether sufficient predictive events will be detected from the much larger data sets that can help avoid SCD. The authors give a simple example of the contrast between conventional ECG recordings, and the summary averages for multiple patients and their regression analysis.

While this is suggestive of what can be done across patients, the authors do not give a good example or address the question of how one might filter and extract meaningful predictive cardiac risk events from the very large month-or-year-long data sets for a single patient, where determining baseline "steady-state" ECG patterns for an individual's "normal" vs. "abnormal" risk-predictive patterns presents a major challenge for spatio-temporal time-series analysis, and the detection of "change-of-system-state" events that can be indicative of serious risk vs. those that merely reflect non-pathological changes within the range of biological variability.

The reference to surrogate markers for predicting SCD in patients with diabetes mellitus and end-stage renal disease suggest the authors are aware and are tackling the problem, but this is not made sufficiently clear in terms of the new data analysis and visualization methods that will be needed. The lack of further detail on how these surrogate markers are extracted is a weakness of the paper, as it lays itself open to the critique that the authors might still be using a "needle-in-a-haystack" approach, now elevated to the level of integrating features of combined patterns of large ECG sets summarized in the form of such surrogate markers. It would be interesting to find out whether deeper and more systematic mathematical models extracting low-dimensional manifolds from the high-dimensional, non-linear ECG data might reveal predictively useful markers for the "prospective risks" of SCD onset before these are detectable by any of the single-signal analyses. This conjecture is motivated by observing successful results from manifold analysis in extracting biologically constrained parameters for visual human motion tracking [26], a problem with some superficial similarities in terms of "style vs. content" to the present one, but where musculo-skeletal constraints apply quite
Discussion of “Computational Electrocardiography: Revisiting Holter ECG Monitoring”

5. Comment by J. H. van Bemmel

5.1 Introduction

Information systems for the interpretation of electrocardiograms are increasingly in routine use at thousands of locations in the world. The annual turnover in ECG interpretation systems amounts to several hundred millions of dollars. By all means, this must be a reason for success!

A fundamental question is, however, whether fully automated ECG interpretation systems have really been completely accepted in health care. Are these systems in clinical use in the way the early developers had in mind? Has this situation improved even after 50 years of R&D in this field? The answer is less positive than originally anticipated.

Examples of successful clinical support systems are imaging systems (scintigraphy, CT, MRI, ultrasound); ancillary systems (laboratory, pharmacy, radiology); and patient-monitoring systems (ICU, CCU, peri-operative). In some instances such processing systems are extended by decision support. Examples of developments of decision-support systems in the past were, e.g., Internist/QMR [27], DXplain [28], and HELP/Iliad [29]. The latter systems are not in clinical use, with few exceptions only.

The article of Deserno and Marx [1], to be discussed below, belongs partly to the first, successful group of systems, and marginally to the second, less profitable group. Yet, the authors claim that time has come that, with the help of wearable systems and virtually infinite memories in the cloud, it will be possible to fundamentally improve the present generation of ECG interpretation systems. This, however, is perhaps too optimistic, as will be explained below.

5.2 Medical Support Systems

The success of a research project to develop a medical support system can be measured in (1) the number of refereed publications, (2) ongoing financial support from sponsoring institutions and perhaps interesting commercial partners and, most important, (3) the number of users of the resulting systems. In the field of medical imaging, for instance, all three types of successes were scored. No doubt, imaging systems are a success story in health care. The developers of imaging systems had, most probably, a clear view on the requirements of end-users: presentation of pictorial data on anatomy (CT) or function (MRI, ultrasound, scintigraphy). And what is of no less importance: already very early, industry became involved in the R&D of imaging systems, so that soon prototypes were produced for later marketing. However, it is the experience of all developers that it takes a long time to develop a system in such a way that it can be transferred to third-party users, let alone that it can be handed over to industry to be marketed to end-users.

For several decades, computers have now been in use in cardiology for the interpretation of the ECG. It is typical for such systems that they support all routine tasks in a clinic or a screening centre, from the application of the electrodes up to the printed document; computer-assisted ECG interpretation can be viewed as a chain of processing steps, each with its own task, such as signal pre-processing, waveform recognition, and diagnostic classification (e.g., [30]). In this last step, parameters are computed that serve as inputs for rhythm classification and diagnostic waveform classification. The ECG is classified into different categories such as hypertrophy (LVH, RVH), infarcts (AMI, IMI), bundle-branch blocks (RBBB, LBBB), or Normal. Besides the processing of “routine” ECGs, much attention has also been paid to exercise ECGs (XECGs), ECG monitoring in CCUs, and Holter monitoring. In all instances, computers play a role in processing, interpretation, and serial comparison.

Routine ECG decision support is fully integrated with transmission of signals and interpretation results, and with documentation and storage. In that way ECG systems are comparable to laboratory support systems, with the addition that they are able to deliver a fully interpreted final document, which is usually to be reviewed by the treating physician.

5.3 Validation

Only very few decision-support systems in health care have been assessed as extensively as ECG interpretation systems, such as in the so-called CSE study (Common Standards for Quantitative Electrocardiography), supported by the European Union [31, 32]. The first part of CSE, dealing with the accuracy of waveform recognition in ECG interpretation systems, was completed in 1985 [31], and the second stage, on diagnostic interpretation, in 1990. The last stage was published in the NEJM [32]. At the start of the two-stage evaluation study, in 1980, there existed about 15 systems for ECG interpretation worldwide of which 6 systems were commercially available.

One of the outcomes of the first stage was that several interpretation systems appeared to be much more accurate and stable than others. This sometimes resulted in major changes in the current systems and, in a few cases, even withdrawal of the system from further evaluation and thus from routine utilization.

The second stage revealed that cardiologists (on average) perform no better than the best systems, and that a combination of diagnostic results from different cardiologists is better than the diagnostic results from any individual expert. The latter also applies, however, to the combined result of interpretation systems.

1 This commentary is partly based on earlier publications by the author of this section, which appeared in the past decades in different books and journals.
Some of the conclusions that can be drawn from the validation studies of ECG interpretation systems are:

1. The development and optimization takes a long time (for ECG systems more than 25 years) and requires a large investment in multidisciplinary manpower;
2. Evaluation should be conducted in a multi-centre study, and the principal investigators should not partake in the collection of the patient material nor in the processing of the results of the study;
3. The collection of large validated databases is a prerequisite but it is expensive and should, therefore, preferably be done on a multi-institutional scale. Independent Referees should validate the material.

CSE underlined that an ECG interpretation system can enhance the diagnostic performance of clinicians. The best interpretation systems reached a diagnostic accuracy, approaching that of the best experts.

5.4 Article by Deserno and Marx

Before coming to some main comments in view of the preceding paragraphs, I want to give some minor remarks on what was written.

- In par. 2.2 the interpretation of a short ECG recording, be it manually and/or by computer, is compared to a haystack paradigm. However, one should not forget that a clinician asks for an ECG recording only when he has already phrased a certain hypothesis about a possibly underlying disease. Only in case of population surveys, the haystack paradigm might be appropriate, but even then, the ECG recording might later be used for serial comparison.
- In par. 3.1 the authors refer to continuous recording of 12-lead ECGs with a 1000 Hz sampling rate. In case of recording with wearable electrodes the results are very noisy ECGs. Correctly they state that more research is needed. In that respect they should also take into account the experience with XECGs, where not only different electrode positions are applied, with much less noisy ECGs, but also a comparison is possible with standard 12-lead ECGs, using an individual transformation matrix.
- In the same par. 3.1 under ‘cycle normalization’ the term ‘non-linear’ is used for both changes in the ECG and stretching of the ECG. However, nothing in the ECG is ‘linear’ in the sense of systems theory. A different term might be more appropriate.
- Again in par. 3.1., the authors appear to be optimistic about the use of physiological models to predict abnormalities. However, an in-depth study of cardiovascular as well as electrophysiological modelling, already started in the 1960s, does not give rise to such optimism. This is, however, a much larger and more fundamental problem than the one discussed in this article.
- Given the very large experience with substantial validation studies in electrocardiology, the publication of the results of 5 cases on just one parameter, QRS duration, seems very immature. A study with many more clinically evident parameters on a far larger database would have been more appropriate.

My main comments are:
1. The article is a typical example of a technology-driven approach.
2. A project like this should start from sound clinical and biomedical hypotheses.
3. Before publishing ideas as phrased in this article, a more comprehensive study would have been recommendable.

6. Comment by H. Witte and K. Schiecke

The review “Computational Electrocardiography: Revisiting Holter ECG Monitoring” by Deserno and Marx [1] is a valuable contribution to the current discussion on methodological advances in the field of automated ECG analysis (e.g. analysis of a 12-lead Holter ECG). We agree with the authors that ECG analysis “is still a hot topic in research providing challenging tasks in the near future”. From the viewpoint of a discipline which uses the (single-lead) ECG as an important add-on for clinical monitoring, in our example as an add-on for EEG (electroencephalography) epilepsy monitoring, the challenges for ECG analysis are not fewer, however, rather different. Long-term EEG monitoring (scalp, basal extracranial, and intracranial recordings) can be done as out-patient ambulatory or as in-patient video-EEG monitoring for investigating seizures and for classification of epilepsy [33]. Video-EEG monitoring is carried out e.g. for pre-surgical localization of the seizure onset zone (‘zone concept’) and combines EEG and video recording, where the video allows an objective record of behavior in correlation with EEG changes. At a minimum, patients undergoing video-EEG monitoring should likely have a single-channel ECG monitor with resources available to address any life-threatening abnormalities detected” [34]. Consequently, cardiac telemetry monitoring and monitoring of pulse oximetry are frequently used in epilepsy monitoring units.

Here we would like to address the question of how computer-aided ECG analysis can provide additional information for a better understanding of physiological events that give rise to seizures and perhaps to alter them before they can disrupt normal function [35]. We focus here on a specific challenging methodological goal, namely seizure prediction.

In patients with uncontrollable seizures a reliable seizure prediction may eventually lead to a triggering of therapy, such as local electrical or magnetic stimulation, drug infusion, or cooling, which could possibly limit or even prevent the spread of the seizure [35]. The ability to control or diminish epileptic attacks could significantly improve the patient’s quality of life (extended family, social, educational, and professional activities) and could prevent irreversible damage of brain structures associated with frequent and long, uncontrollable seizures. Algorithms (devices) for seizure prediction are at a relatively early stage of development [36]. The predictability of an imminent seizure depends on the seizure type and is strongly associated with the reliable existence of seizure-advertising signal changes or signal patterns during the preictal period, e.g. in the EEG. It can be assumed that parameters derived from ECG.
and/or from heart rate variability (HRV) courses can be used to improve the prediction reliability. This assumption is based on the fact that epileptic seizures affect the autonomic control of the heart rate and respiration, and of the whole autonomic nervous system (ANS), which can be indicated by means of appropriate ECG/HRV parameters during, and even before the EEG seizure onset [37, 38]. Analysis of long-term ECG recordings enables valuable interpretation of the cardiac situation [39]: Is the rhythm regular or irregular? Are all QRS complexes similar, and are they narrow? Are all P waves similar and are PR intervals normal? Is the rate normal? Do waves and complexes proceed in normal sequence? Are the waves and complexes proceeding in normal sequence? Parameters of the HRV are most frequently used in order to investigate the long-term and short-term alterations of the ANS in response to the type of epilepsy and to the evolution of the epileptic seizure [40]. A seizure prediction only based on ECG/HRV could be used in daily life, because the ECG can be measured easily by using a wearable sensor. For such a device, adaptive, artifact-resistant and real-time capable algorithms must be available.

Seizure prediction can also reduce sudden unexpected death in epilepsy (SUDEP), which can be seen as an early postictal, centrally mediated breakdown of the cardiorespiratory system. The risk of sudden death is about 20 times higher in people with epilepsy than in the general population, and SUDEP is the leading cause of death in people with chronic refractory epilepsy [41].

Developments in the field of epilepsy research are characterized by a shift from the ‘zone concept’ (helpful in epilepsy surgery) to the ‘network concept’ of epilepsy (more relevant for the treatment), where epilepsy is considered as a disorder of “functionally and anatomically connected, bilaterally represented set[s] of cortical and subcortical brain structures and regions in which, activity in any part affects activity in all the others” [42]. Consequently, basic and clinically-related research is increasingly targeted at interrelations (couplings) between cortical networks (EEG) and the ANS (ECG and/or HRV) which can be con-

**Figure 2** (A) Grand mean results of Morlet wavelet coherence (MWC) analysis between HRV and envelopes of EEG-IMF for the electrode site T4 achieved by averaging over the corresponding 9 children with TLE (right focus group). Seizure onset at 300 s is designated by the vertical arrows. An overlay of MWC between HRV and two IMF envelopes is represented (black – envelope of IMFa: lower delta range, grey – envelope of IMFb: upper delta range). Statistical thresholds are computed as the mean over time of the 95th – red line (90th – green line) percentile by using surrogate data (phase randomization). This diagram was adopted from [44] in a modified form. (B) Grand mean results of time-variant Convergent Cross Mapping (CCM) analysis based on the same data set as used for MWC analysis. The black course designates the direction EEG → HRV and the red course the direction HRV → EEG for the envelope of IMFb. The shadowed tubes designate the 95% confidence intervals of a bootstrapping approach.
sidered as coupled networks. Time-variant analysis approaches open up the possibility to study the time evolution of couplings before (preictal), during (ictal) and after (postictal) the seizure. We would like to illustrate this by a time-variant coupling analysis between EEG-envelopes (in particular delta activity) and HRV in children and adolescents with temporal lobe epilepsy (TLE), where the underlying recordings encompass 300 s before and 300 s after the seizure onset.

The data preprocessing can be summarized as follows: By means of a multivariate empirical mode decomposition the natural EEG oscillations (so-called intrinsic mode functions – IMF) were extracted, i.e. without arbitrary frequency range definitions by filtering, followed by an envelope computing (Hilbert transform) of the EEG-IMFs which cover different frequency ranges. The QRS events of the ECG were marked by using a QRS detection algorithm and the resulting impulse-frequency modulated series of events was demodulated by the French-Holden algorithm which provides the HRV representation. The sampling frequencies of both the EEG envelope and HRV were adjusted. In order to achieve time-variant, bivariate coupling information, the Morlet wavelet coherency (MWC – linear correlating coupling parameter) and the time-variant (moving window) Convergent Cross Mapping (CCM – nonlinear coupling on the basis of phase space embedding [43]) were applied to EEG-IMF envelope(s) and HRV. The results of a 10-min-analysis (grand mean, N=9, right focus group) are depicted for one electrode (T4) of the focus side in Figure 2. The median seizure duration is 90 s (seizure onset at 300 s), i.e. the early postictal (recuperation) period is covered by the analysis interval (600 s). It is important to note here that the investigated TLE seizures are preceded by an acceleration of the HRV (starts 60 s before seizure) and that after EEG seizure onset an ictal tachycardia can be observed. An interpretation of the coupling courses in Figure 2 must consider that both courses provide different (complementary) information about coupling: MWC stands for ‘correlation’ (undirected coupling) and CCM for ‘causation’ (directed coupling). The MWC courses (Figure 2A) show segments with statistically significant coherence (synchronization) between HRV and EEG-IMF envelopes (black: envelope of IMFa = lower delta range; grey: envelope of IMFb = upper delta range) before seizure onset. About 20 s before the onset the correlation breaks down for the lower delta range, decreases for the upper delta range, and both remain low during the seizure and non-significant afterwards. The CCM courses (Figure 2B) express that the coupling of the directional IMF-EEG envelope (upper delta range) to HRV (EEG→HRV) is stronger than the coupling of the reverse direction during the entire analysis interval. During the seizure the coupling strength of the direction HRV to IMF-EEG envelope (HRV→EEG) reaches the values of the EEG→HRV coupling, i.e. a balanced bi-directional coupling can be observed. In a nutshell, synchronization collapses/decreases and HRV→EEG coupling increases shortly before and during the seizure. The first result can be discussed in connection with the breakdown and the second with a counter regulation of the ANS. For a clarification of these hypotheses, intensified research efforts are necessary.

Deserno and Marx also highlight that a widespread expansion of ECG analysis through the ‘wellness’ or healthcare industry is imminent. Indeed, also in the field of seizure prediction great efforts are being made to establish health care services in connection with smartphone and smartwatch devices. For self-monitoring of epileptic seizures and seizure prediction several innovations exist. Viewed from a positive perspective, this could help epilepsy research by enhancing the ability to share data on seizures, to explore whether future ‘apps’ can predict a seizure, to control it and/or prevent accidents, or to extend the time window to contact relatives or healthcare professionals, etc.

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