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Novel approaches for medication compliance and effectiveness analysis and support in cardiovascular disease patients

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Abstract— **HeartCycle is an integrated project aiming to provide a disease management solution for cardiovascular disease patients, by developing technologies, algorithms to interpret data and services to facilitate the remote management of patients at home. In this paper an overview of part of the algorithmic work package, oriented at motivating the patients to be compliant to treatment regimes and to adopt a beneficial lifestyle, will be given. A concept allowing further education of the patient on the effect of medication on their vital signs, as well as the prediction of medication effect and a possible way to check compliance using vital signs measurements will be presented.**

I. Introduction

MEDICATION therapy is a major component in the successful treatment of both Heart Failure (HF) and Coronary Artery Disease (CAD) patients.

In the context of eHealth services and focusing on medication therapy, it is important for the professional to optimize treatment via decision support systems (DSS) and receive treatment support in clinical practice, i.e. to know what medication/physical therapy to prescribe, in order to have a desirable impact on the patient vitals and wellbeing. A possible solution is to accurately model the impact of medications on vitals, in order to monitor therapy effectiveness and outcome by checking whether the therapy is having the desired effect in an individual patient. Furthermore, professionals have to be ready for patient counseling, i.e. know how to communicate the importance of complying to the therapy to the patient so that therapy achieves desired effects, and have access to services that facilitate the process of patient education/motivation about the impact of medications and lifestyle on his/her vitals.

The patient's responsibility in successful treatment lies in following the therapy as prescribed by the professional, i.e. being compliant. Knowing why a medication is prescribed and understanding how medications affect one's vitals are related with increased compliance. It is therefore important for the clinician to address the patient on the reasons for medication administration and the risks of discontinuation [1].

Medication misconceptions about expected medication effects, time needed to experience the effect, side effects and dosing can all be alleviated by presenting clear and concrete cause-effect examples. This causal attribution can then be translated into a perceived responsibility by the patient and this could lead to a readiness to comply with the treatment regimen, eventually paving the way for lasting behavioural change.

Ideally, such therapy effect counseling sessions should be carried out by a range of medical personnel including nurses and GPs (i.e. non-experts), who should be familiar with the dynamic treatment process and its expected effectiveness for the patient, including the interpretation of the actual patient's vitals timeseries as regards treatment and other factors. However, this is not a trivial task, as continuing professional education is required to develop this clinical expertise – and even then, it may be difficult to fully keep track of the different effects of a wide range of possible medications a patient might be prescribed. Clinical scenarios and interactive simulated cases are seen as a means to support physician training and decision-making activity, as SimCare for diabetes management [2].

Within HeartCycle, we aim to encourage patient compliance to medication by creating an interactive education tool showing the predicted effects on vital measurements for different treatments, thus providing an experiential learning environment. Furthermore, an initial approach is proposed within HeartCycle, towards interpreting the actual vital signals timeseries and potentially highlighting incompliance periods. This dual functionality is made available in a framework, which incorporates realistic and medically sound evidence on treatment effects, potentially useful to medical professionals for treatment decision support in clinical decision making.

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II. METHODS

A. Medication Effectiveness and Compliance Concepts and Functionality

With respect to medication effect on vital signs (blood pressure BP and resting heart rate HR), the basic pieces of information that are considered relevant and useful for the cardiac patients to receive education on are:

-- Which drugs affect which vital signs, i.e. drugs & HR/ BP models

-- Gradual effect on vital signs, and time to peak effect

-- Range of reference (population or subgroup average) peak effect, including uptitration gradual effect

-- Consequence of incompliance and range of average effect of medication discontinuation

-- Combined effect of multiple medications

These pieces of information can be presented and discussed with the patient during a patient-professional encounter, and help in better understanding the reasons for medication prescription and the realistic expectations from this treatment.

While this treatment prediction functionality may be of use for the clinician, he/she might also benefit from tools that allow for the analysis of past treatment effect on the vital signs timeseries, with respect to medication effectiveness, patient (in)compliance, or other factors affecting the vitals. This option might support the medical decisions for personalized therapy optimizations.

B. Modelling Medication Treatment Effect

Medication effect on vital signs has a component of magnitude, which relates to the prescribed dose via "dose response" tables, available as medical evidence, when a new medication is investigated. Population-based medication responses for various medication dosages are available in medical literature, including publications that have reported on randomized clinical trials [3]. These sources constitute the basis for the medication model responses, along with clinical sources, i.e. clinical guidelines, and expert physician opinion. The effect of intermediate doses is calculated via interpolation.

A second component is the time response of the medication, i.e. the time until converging to the maximum effect (time to peak effect), and the shape of the gradual effect (the effectiveness fraction over time), as in (1).

$$E_{\alpha,\beta}(t)=\left(1+\left(\frac{1}{\alpha}-1\right)\exp\left(\frac{-t}{\beta}\right)\right)^{-1} \quad (1)$$

Note that $E_{\alpha,\beta}(t)\in[0,1], E_{\alpha,\beta}(0)=\alpha$ and $E_{\alpha,\beta}(\infty)=1$. The parameter α is the immediate effect of the medication, and β is the speed at which the maximum decrease in BP is reached [2]. Then, the decrease in vital sign over time (*dE*), e.g in BP, can be expressed as in (2)

$$dE(t)=Total\_dE\times E_{\alpha,\beta}(t) \quad (2)$$

where the maximum effect *Total_dE* is calculated based on the dose-response information.

Based on these general assumptions, separate models were built for medication effects on average diastolic and systolic blood pressure (DBP and SBP) and for resting HR, and for various relevant medication categories.

Personalization parameters were introduced for each model, as multiplicative parameters on the average response of (2). The approach followed, based on medical evidence, was the particularization of models for patient subcategories. For SBP and DBP the personalization factors were the pretreatment value [3], race, and age [4]. The model is a combination of: 1) an analytical model which takes as input the pretreatment value, and 2) a fuzzy model, which takes as inputs two factors that affect response to each medication group, i.e. age for which a fuzzy subset is formed, and race as a qualitative variable with two discrete values (Black, Caucasian).

For HR, the pretreatment value was the only personalisation factor initially incorporated, with a separate modelling approach per drug, as proposed in [5]-[7]. For example, the basic idea for modelling the effect of Diltiazem-SR is the fuzzification of the four (crisp) categories of pretreatment HR, as follows: <=65 beats/min, 65-74 beats/min, 75-84 beats/min and >=85beats/min as Baseline HR={Low, Slightly Low to Normal , Normal to Slightly Elevated, Elevated}, leading to different effects correspondingly.

C. Analysis of the Past Effectiveness and Compliance

Medication effectiveness refers to the actual change of vital signs as a result of medication treatment, with respect to the expected change. Additionally, medication compliance refers to patient's behaviour as regards the extent to which the prescribed medicines are taken as agreed with the medical professional.

Based on the modeling of average (per subgroup) medication effects, an initial algorithm for the analysis of these concepts was developed. The basic assumption employed is that after a period (time to peak effect) the affected vital should statistically converge to a value, at a proximity with the expected value, and stay statistically stable, while any divergence should be attributed to a cause, be it an acute medical condition, or a period of non-adherence to medication, etc. As suggested in [8], multiple vital signs measurements along with knowledge of therapy actions are assessed, for robustness.

A hybrid approach is followed for the interpretation of past vitals, consisting of:

1) Step 1: vital signs are segmented into periods of different statistical behaviour, i.e. "steady", "trend" and "transient" segments. For each steady segment is assigned a *treatment effect deviation index* (TEDI) is calculated, as the relative error between real and expected effect.

TEDI is an indicator of good or poor treatment effect, and more importantly, changes in this index can help the clinician trace back the causes, i.e. effectiveness, compliance or other reasons. Steady segments are characterized as "*expected effect*" if abs(TEDI) < 0.5, otherwise lower or higher effect depending on TEDI value.

2) Step 2: available information about the patient's medical status in each time segment (as defined above) and the adjacent ones is employed, for the detailed characterisation of each segment as associated with medication (in)compliance or a specific medical or lifestyle situation. Context information and knowledge about possible effects on vitals of different factors have been provided by medical experts. This information has been formed as rules, helping to better filter possible incompliance or effectiveness problems. Rules employ information on a) changes in the TEDI between consecutive segments (candidate points of behavioral change), b) factors that may be alternatively responsible for the observed deviations in vital signs, rather than incompliance, such as acute diseases/infection, fever, NSAIDs or cortisone intake, adverse drug events, changes in lifestyle, and c) patterns that are related to incompliance or specific drugs. An example rule combining these pieces of information is "*if diuretic medication, and BP has increased, accompanied by symptoms but not other medical factors, then possible diuretic incompliance*".

III. Results

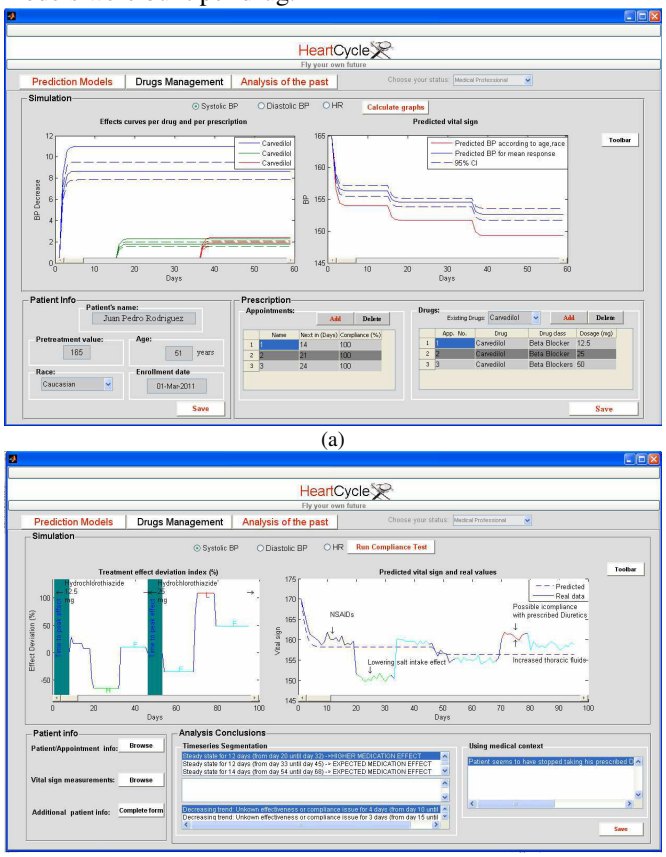
A. Medication management Tool (MMtool)

A tool has been built (MMtool) for the management of the medical knowledge as regards medication effect, holding the necessary parameters for the medication modeling, i.e. average dose-response tables and time to peak effect per medication or medication category.

This information is stored in a structured form in a scheme of linked xml files:

1) OutcomeType, including the relevant vitals, i.e. HR, SBP, DBP,
2) DrugClass, i.e. "BetaBlocker", 'AceInhibitor", etc,
3) Drug, e.g. "Carvedilol", "Irbesartan", etc, each one belong to a drug class,
4) Dosages, including reasonable dosages per drug,
5) Responses, including response information per dosage and vital sign, i.e. *<Response response_id="5" dosage_id="5" outcome_id="1" effect="-6.9" />*
6) "TimeToPeakEffect", i.e. time to peak effect, per drug.

Medication management supported by the Matlab user interface, is available for all 3 vital signs, i.e. SBP, DBP and HR. The SBP and DBP information concerns the medication categories: "ACE Inhibitors", Beta Blockers", "Diuretics", "ARB Agents", and "Calcium Channel Blockers", with models per medication category, and equivalent dosages among drugs of a category. For HR, drug classes include "Beta Blockers", "Calcium Channel Blockers", "Ivabradine", "Central a2 antagonists", while separate models were built per drug.



(a)

(b)

Fig. 1. (a) FYOFtool example use for medication effect prediction with a betablocker prescription. (b) MCEtool for analysis of a patient's medication effect and compliance.

B. Fly your future Tool (FYOFtool)

Fly your Own Future (FYOFtool) is a tool developed to be used during the patient – health professional encounter. FYOFtool is meant for use in all stages of treatment, either during initiation of new treatment, in uptitration or after reaching a steady state, to help the patient realize the expected effects of treatment and the benefits of being compliant, alleviating barriers due to lack of knowledge, or misbeliefs, negative attitude etc.

Based on MMtool functionality, which specifies the magnitude of a drug's effect and the manifestation of that effect over time, the simulation allows a full set of treatment "moves" from a set and takes into account the cumulative effect of past moves. As a first step towards integration with the medical professional's applications and patient records, an xml scheme has been developed to hold the necessary patient information as regards: a) patient information, b) consecutive patient appointments/visits, and c) prescriptions per appointment.

The healthcare professional enters/loads personal information about the patient, gender, age, race, medication and dosage, the vital signs value prior to treatment. The predicted signal evolution (BP and HR) are graphically

shown, illustrating in a concrete and quantitative manner the effect of medications on patients' vitals, for one or a series of appointments/prescription changes. An example is depicted in Fig1a.

C. Medication compliance-effectiveness tool(MCEtool)

The purpose of MCEtool is twofold:

-- to characterize actual treatment effect over time in terms of vital signs improvement

-- to further analyse vital signs and medical context and characterize in detail the treatment effect, i.e. highlight changes and causal factors such as incompliance.

The MCEtool is built on top of the MMtool and FYOFtool functionality, and uses the same knowledge base, i.e. the same xml structure and medication models. The additional xml files for MCEtool (MedicalHistory.xml, Symptoms.xml, Factors.xml, Segments.xml) refer to the patient medical history, and to the outcome of the analysis and user validation.

A user interface is being developed (Fig 1b) allowing the user to add information, visualize the biosignals and the characterization/interpretation of segments, with medical information overlapped, and to confirm or reject the interpretation (for the professionals). The visualisation tab includes two plotting areas. The TEDI per time segment is depicted in the left one, along with patient's prescriptions (information included in the Appointments.xml and Prescriptions.xml). The initial (transient) medication days are also depicted. The steady time segments are characterised as 'E', 'L' or 'H', referring to "expected",, "low' or 'high' effect correspondingly. On the right, the actual measurements are shown, along with the expected vital signs effect according to prescription. Prescription dose and appointments are also depicted. Medical context information applying to the patient and potentially related to the signal's variation is marked on the relevant locations. The comments are the result of the rules applied (e.g. if a factor has an effect on patient's response to therapy this is marked, otherwise only the facto, e.g. fever, is shown). In the lower part, there is more information in textual form, regarding the characterisation of timeseries segments (left), and the medical rules applied (right).

IV. Discussion

This work constitutes a first approach on a framework addressing medication effectiveness and compliance, in terms of modeling, as well as analysis of the past; the former is considered as a part of the patient-professional encounter, serving as a tool for patient education and motivation, while the latter is aimed as a support tool for the clinician during treatment decision making.

While the approaches have been developed following medical experts' advice, extended qualitative and quantitative validation will follow, including various aspects, i.e. the soundness and accuracy of the models and algorithms, the usability of the tools as communication means and the perceived impact on the patient.

The domain addressed is quite challenging and a series of future steps are foreseen for the improvement of the proposed framework, such as the improvement of medication models, the incorporation of further personalisation factors, the I/O interface or binding with the medical patient record for the retrieval of the information necessary for each model, the improvement of the medical context for compliance, and the extension of knowledge base to include the context information.

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