Non-Invasive Estimation of Blood Pressure through Genetic Programming
Preliminary Results

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Abstract: The hypothesis underlying this paper is that a nonlinear relationship exists between Electrocardiography (ECG) and Heart Related Variability (HRV) parameters, plethysmography (PPG), and blood pressure (BP) values. If this hypothesis is true, rather than continuously measuring the patient's BP, a wearable wireless PPG sensor can be applied to patient's finger, an ECG sensor to his/her chest, HRV parameter values can be computed and, through regression, both systolic and diastolic BP values can be indirectly measured. Genetic Programming (GP) automatically both evolves the structure of the mathematical model and finds the most important parameters in it. Therefore, it is perfectly suited to perform regression task. As far as it can be found in the scientific literature of this field, until now nobody has ever investigated the use of GP to relate parameters derived from HRV analysis and PPG to BP values. Therefore, in this paper we have carried out preliminary experiments on the use of GP in facing this regression task. GP has been able to find a mathematical model expressing a nonlinear relationship between heart activity, and thus ECG and HRV parameters, PPG and BP values. The approximation error involved by the use of this method is lower than 2 mmHg for both systolic and diastolic BP values.

1 INTRODUCTION

Arterial blood pressure can be continuously measured in real time and with no patient's body cannulation by means of the continuous non-invasive arterial pressure (CNAP) method.

This method shows the positive features of two clinical "gold standards": firstly, blood pressure (BP) is continuously measured in real time as it takes place in the invasive arterial catheter system (IBP), secondly it is non-invasive as it is the case for the standard procedure based on upper arm sphygmomanometer (NBP). Recently, results have been promising in this field as concerns the features of ease of use, accuracy, and clinical acceptance.

Currently a high demand exists for accurate and easy-to-use CNAP-systems. Because of this, there is an increasing focus on these devices by researchers, practitioners and the related industry of medical devices. The development of efficient BP measurement instruments is facilitated by the use of small yet powerful microcomputers, and by that of digital signal processors as well. Small, cheap devices of this kind allow for an easy processing of complex and computationally intensive mathematical functions. Researchers (Maguire, 2011) (von Skerst, 2008) have reported that invasive catheters are used to continuously measure BP in only a small fraction, between 15% and 18%, of inpatient surgeries. The practical standard of care for all the remaining inpatient surgeries, and for outpatient surgeries as well, is, instead, constituted by intermittent, non-invasive blood pressure monitoring. Unfortunately, this latter monitoring type has the feature of being discontinuous, which implies possibly missing some dangerous hypotensive episodes. As an example, when monitoring women undergoing Caesarean section, hypotensive phases were detected by CNAP in 39% of the cases, but only in 9% by non-invasive methods. As a further example, (Ilies, 2012) reports that, when CNAP was used to measure systolic BP values higher than 100mmHg, dangerous foetal acidosis did not occur. Moreover, (Dueck, 2006)

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reports that more than 22% of hypotensive episodes were missed, thus leading to delayed treatments or even no treatments at all.

Of course, it is very difficult to detect in-artery pressure changes from outside the arteries themselves, while it is quite easy to measure changes in artery volume and flow. This can be accomplished through the use of e.g. echography, light, impedance, and so on. The problem is that there is no linear correlation between these changes in volume and the arterial pressure, especially when the measurement takes place in the periphery, where it is easier to access the arteries.

As a consequence, non-invasive devices must be able to transform the volume signal measured at the periphery into a corresponding for the arterial pressure. Some techniques are based on vascular unloading, tonometry, pulse transit time (PTT). This latter relies on the fact that, each time a heart ejects stroke volume towards arteries, the BP wave reaches the periphery after a given transit time. PTT has an indirect dependence on BP, namely it is known that the higher the pressure, the faster PTT is. The non-invasive detection of blood pressure changes can be carried out thanks to this phenomenon (Sotera wireless). The method has to be calibrated in order to get absolute values. PTT-based techniques are good examples of indirect ways for continuously measuring blood pressure. In them, a measure is continuously taken of other parameters, and a non-linear relationship is hypothesized.

In the knowledge discovery area any problem as this latter, in which a relationship between some variables, called independent, and another one, called dependent, is supposed, and the aim is to search for the explicit form of the mathematical model connecting them, is termed as a *regression* problem. The term "independent" simply means that these variables are the input variables to the problem, and this does by no way imply that they are not correlated one another. In traditional regression analysis the user must specify the structure of the mathematical model. Hypothesizing or experimentally finding a good model is a very laborious and time-consuming trial-and-error procedure, and human minds may experience difficulties in guessing which the most important independent variables affecting the dependent one are, and which the best formula relating them is.

Genetic Programming (GP) (Koza, 1992), instead, automatically both evolves the structure of the mathematical model and finds the most important parameters in it. Therefore, it is perfectly suited to perform regression task.

Nowadays wearable sensors are becoming more and more widespread and cheap. Among them, chest sensors able to capture electrocardiographic (ECG) signals are frequently used. Starting from an ECG signal, Heart Rate Variability (HRV) analysis can easily extract a wide set of parameters describing ECG activity of a patient. Moreover, wearable wireless sensors can be applied to a patient's finger to compute plethysmography (PPG) values.

The hypothesis underlying this paper is that a nonlinear relationship exists between PPG and heart activity (and thus ECG and HRV parameters), and blood pressure. If this hypothesis is true, rather than continuously measuring the patient's blood pressure, a wearable wireless PPG sensor can be applied to patient's finger, a wearable wireless ECG sensor to his/her chest, HRV parameter values can be computed and, through regression, systolic and diastolic blood pressure can be indirectly measured.

As far as it can be found in the literature of this field, until now nobody has ever investigated the use of GP to relate parameters derived from HRV analysis and PPG to BP values. Therefore, in this paper we carry out some preliminary experiments on the use of GP in facing this regression task.

2 RELATED WORKS

Some papers exist in which the aim is the investigation of the relationship between the blood pressure and some other variables. In the following, some of those papers are shortly described.

In (Meigas, 2007) the BP estimation method relies on the hypothesis that a relationship exists between the pulse wave velocity (PWV) in the arteries and BP. Measuring PWV requires registering two time markers. The first marker depends on ECG R peak detection, whereas the second on detecting the pulse wave in peripheral arteries. Their experimental device for BP monitoring is made of two analogue modules for the acquisition of signals, namely one for ECG and another for PPG signal. Namely, the ECG electrodes are positioned on patient's wrists, while a pulse oximetry finger to register PPG is placed on a finger.

In (Najjar, 2008) the aim was the evaluation of whether PWV can reliably predict the longitudinal changes in systolic BP (SBP), and the incident hypertension. The authors measured PWV at baseline in 449 volunteers, partly normotensive and partly untreated hypertensive. Their average age was 53±17. BP measurements were repeatedly carried out during an average follow-up of 4.9 ± 2.5 years.

By considering covariates such as body mass index, age, and mean arterial pressure, the authors applied linear mixed effects regression models, and concluded that PWV can independently determine the longitudinal SBP increase.

In (Inajima, 2012) an attempt was made to design and build a wearable sensor for BP measurement. This sensor should have the features of placing a lower burden on the examinees, of being less influenced by patient's physical movements, and of being usable to continuously measure BP. They modified the existing Moens-Korteweg BP equation by hypothesizing that the following relation exists: $P_s = b_1 / T_{PTT}^{\ 2} + b_2$, where *TPTT* is the pulse-wave transit time, *Ps* is the systolic BP, and coefficients $b1$ and $b2$ can be derived by using measured values of an examinee's BP and measured values of T_{PTT} . They implemented a new system for the calculation of patient's systolic BP. This system made use of electrocardiography and ear-lobe pulse waves. Through this system they were able to estimate patients' BP, and to also directly measure patient's arterial pressure. They found that their methodology was able to correctly capture trends in the variations in BP.

In (Gesche, 2012) the aim was the creation of a function able to link SBP and PWV, and the testing of its reliability in determining suitable absolute SBP values by using a non-linear algorithm and a one-point calibration. They asked 63 volunteers to exercise to induce BP increase, and obtained this nonlinear function: $BP_{PTT} = P1 * PWV * e^{(P3*PWV)} + P2 * PWV^{P4} – (BP_{PTT,cal} - BP_{cal})$, with P1 = 700, P2 = 766,000, P3 = -1, and P4 = 9. $BP_{PTT,cal}$ is the BP value, computed from PTT, corresponding to the BP value measured by the reference method, while BP_{cal} is the BP measured by the reference method (cuff) at experiment beginning. This non-linear function was used to compute BP values. Comparing SBP values using the PTT-based method and those measured by cuff resulted in a significant correlation.

This brief review shows that researchers are striving to find a suitable relationship between independent and dependent variables, yet this is done at a high cost in terms of labour, time, and experiments to find the values of the coefficients.

3 SIGNAL PROCESSING

The regulation of BP is traditionally described in terms of homeostasis (Vukovich & Knill, 1980). This is regulated by the autonomic nervous system (ANS) due to two opposing divisions: the sympathetic division and the parasympathetic division. Heart rate variability (HRV) is a tool that represents the balance between the sympathetic and parasympathetic branches of the autonomic nervous system. As shown in many studies (Berntson et al., 1997; Electrophysiology et al., 1996; Karapetian, Evaluation, & Research, 2008), HRV is considered one of the most studied non-invasive biomarkers of ANS activities, and it can be extracted by using a wearable ECG sensor.

Furthermore, as demonstrated in (Golparvar, Naddafnia, Saghaei, & Mahmood, 2002), the PPG is a simple and low-cost optical technique that can be used to detect blood volume changes in the micro-vascular bed of tissue. The PPG is a physiological waveform related to the sympathetic nervous system activity (Allen, 2007), and it can be monitored by using a wearable non-invasive finger pulse oximeter. For these reasons we investigate here the associations among HRV and PPG measurements and the Systolic BP (SYS) and Diastolic BP (DIA) to propose a mathematical model to calculate the SYS and the DIA by using only a wearable ECG sensor and a pulse oximeter.

To realize the mathematical model, the MIMIC database (Goldberger et al., 2000), available on physionet.org, was used. The MIMIC Database includes data recorded from over 90 ICU patients. The data include signals and periodic measurements obtained from a bedside monitor as well as clinical data obtained from the patient's medical record. The files include *qrs* (ECG beat labels, all beats labelled normal), *al* (annotations for alarms related to changes in the patient's status), *in* (annotations related to changes in the functioning of the monitor), *abp* (arterial blood pressure), *pap* (pulmonary arterial pressure), *cvp* (central venous pressure), and *ple* (fingertip plethysmograph) annotations.

3.1 ElectroCardioGraphy

ECG signal is pre-processed by using Kubios (Niskanen, Tarvainen, Ranta-Aho, & Karjalainen, 2004; Tarvainen, Ranta-Aho, & Karjalainen, 2002), a Matlab-based software package for event-related bio-signal analysis developed by the University of Kuopio, Finland. Kubios is an advanced computer program to extract and analyse HRV.

Standard linear HRV analysis is performed according to the guidelines of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (Electrophysiology et al., 1996). Additionally, nonlinear features are computed according to the literature (Melillo,

Bracale, & Pecchia, 2011; Rajendra Acharya, Paul Joseph, Kannathal, Lim, & Suri, 2006). All the computed measures are summarized in Table 1.

3.2 Plethysmography and Arterial Blood Pressure Pulse Waveform

PPG signal and the Arterial Blood Pressure (ABP) pulse waveform are processed using a Matlab script developed to automatically calculate the minimum and the maximum values of PPG and the systolic and diastolic blood pressure values from the ABP waveform, as shown in Fig. 1.

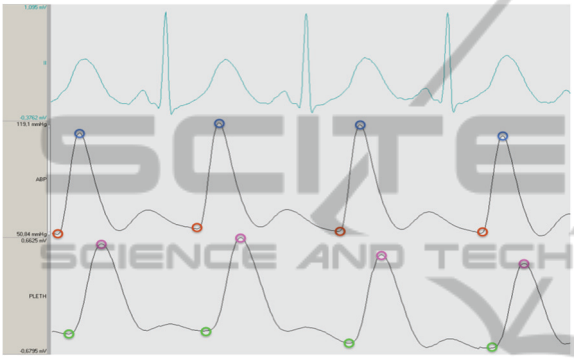

Figure 1: An example of a record contains the ECG, the ABP waveform and the PPG. The blue circles indicate the systolic BP values; the red circles indicate the diastolic BP values; the pink circles indicate the maximum PPG values; the green circles indicate the minimum PPG values.

3.3 The Database

Starting from the MIMIC database (Goldberger et al., 2000) a new dataset has been built to develop the mathematical model.

The new database contains the HRV measures, the BP measurements and the PPG measurements.

It is composed by 50 instances for each subject. Each instance i in the new database is constituted by the following information:

- sub_id: a number value to identify the subject;
- SYS_BP_i: the average of the Systolic BP computed in the i-th 1-minute time slot;
- DIA_BP_i: the average of the Diastolic BP computed in the i-th 1-minute time slot;
- $Pleth\_max_i$: the average of the maximum values of PPG signal computed in the i-th 1-minute time slot;
- $Pleth\_min_i$: the average of the minimum values of PPG signal computed in the i-th 1-minute time slot;
- f : a vector containing the 35 HRV measures reported in Table 1;

Table 1: Linear and non Linear HRV features.

Measure	Description (Unit)
Time Domain	
Mean RR	The mean of RR intervals (ms)
STD RR	Standard deviation of RR intervals (ms)
Mean HR	The mean heart rate (1/min)
STD HR	Standard deviation of instantaneous heart rate value (1/min)
RMSS	Square root of the mean squared differences between successive RR intervals (ms)
NN50	Number of successive RR interval pairs that differ more than 50 m (count)
pNN50	NN50 divided by the total number of RR intervals (%)
RR tri index	The integral of the RR interval histogram divided by the height of the histogram
TINN	Baseline width of the RR interval histogram (ms)
Frequency Domain	
Peak freq. VLF	VLF band peak frequencies (Hz)
Peak freq. LF	LF band peak frequencies (Hz)
Peak freq. HF	HF band peak frequencies (Hz)
Absol. Pow. VLF	Absolute powers of VLF band (ms^2)
Absol. Pow. LF	Absolute powers of LF band (ms^2)
Absol. Pow. HF	Absolute powers of HF band (ms^2)
Rel powers VLF	Relative powers of VLF bands (%)
Rel powers LF	Relative powers of LF bands (%)
Rel powers HF	Relative powers of HF bands (%)
Normalized powers LF	Powers of LF bands in normalized units
Normalized powers HF	Powers of HF bands in normalized units
Total power	Total Value for the spectral power (ms^2)
LF/HF ratio	Ratio between LF and HF band powers
EDR	Electrocardiogram Derived Respiration (Hz)
NonLinear Domain	
SD1	The standard deviation of the Poincarè plot perpendicular to the line of identity (ms)
SD2	The standard deviation of the Poincarè plot along to the line of identity (ms)
ApEn	Approximate entropy
SampEn	Sample entropy
D_2	Correlation Dimension
α_1	Short-term fluctuation slope in Detrended Fluctuation Analysis
α_2	Long-term fluctuation slope in Detrended Fluctuation Analysis
Mean line length	Mean line length in RP (beats)
Max line length	Maximum line length in RP (beats)
REC	Recurrence Rate (%)
DET	Determinism (%)
ShEn	Shannon Entropy

Therefore, each instance is defined as follows:

$$i = sub_{id}; SYS_{BP_i}; DIA_{BP_i}; Pleth_{Max_i}; Pleth_{Min_i}; f$$

In this paper we have considered four patients, so our database contains 200 instances in total.

4 GENETIC PROGRAMMING

4.1 The General GP Framework

Genetic Programming (GP) (Koza, 1992) is a heuristic optimization technique based on mimicking in a computer mechanisms that are typical of the evolution in natural populations. GP relies on a set, called population, of solutions to a given problem. In the population, individuals are programs that are represented by tree structures, typically differing in shape and size. In each individual the internal nodes represent the functions, while the leaves represent terminals, meaning with this both problem variables and constant values. The program can be obtained by reading the tree in *pre-order* (see Figure 2).

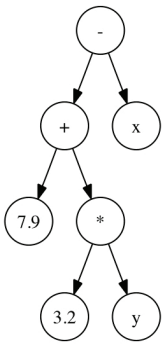

Figure 2: An example of a tree in Genetic Programming.

This example tree encodes for the following in-order expression: 7.9 + (3.2 *y) –x.

A very delicate issue of GP is the choice of a *fitness* function, i.e. a criterion which may represent quantitatively the degree of goodness of any solution at solving the problem faced. Of course, the choice of a type of fitness depends on the problem at hand.

The search procedure executed by a GP tool is described by the following pseudo-code:

- load the problem data (e.g. regression values);
- generate randomly an initial population of a number of *Pop_size* individuals, each of which represents a regression model;
- evaluate each individual through the use of a suitable *fitness function*;
- at each generation repeat the following steps until a new population is obtained:
  - choose an operator among *crossover*, *mutation,* and *copy*;
  - *select* a number of individuals in current population suited to the chosen operator;
  - apply the operator chosen in order to generate an offspring;
  - insert the offspring in the new population;
  - evaluate the new offspring through the use of the *fitness* function;
- repeat the above step until a maximum number of generations *Max_gen* is reached.

As the number of generations increases, better and better solutions in terms of better *fitness* values) to the original problem will very likely be found.

Selection is a mechanism that chooses the individuals that will undergo the reproduction process among those contained in the current population. It should favour individuals with better fitness values to be chosen more frequently, yet allowing also worse individuals to be selected, though with lower probability. For the experiments described in this paper, the widely used tournament selection has been used. In it, a number of *tourn_size* individuals contained in the current population is chosen in a random way, and the best among them in terms of fitness is the one that is selected.

The three genetic operators work as follows:

Crossover. Two parent individuals are chosen, are in each of them a subtree is randomly selected. Then crossover swaps those subtrees from one parent individual to the other. The respect of the limit on the maximal depth allowed should be ensured by this operator. If this condition is not respected, then the too-deep offspring is discarded, and one of the two parents, randomly selected, becomes the new offspring.

Copy. One individual is randomly selected from the current population and is copied in the new one.

Mutation. A node in the tree is randomly selected, and starting from it a new subtree is generated. The check is carried out that the depth limit is not violated by this replacement. If this takes place, this new offspring is discarded and the original tree is copied into the new generation.

Each time an operator must be chosen, this choice takes place on the basis of three probability values for them: *p_mutate* is that for mutation, *p_cross* for crossover, and *p_copy* for the direct copy. The sum of these three values must be equal to 1. A random real value in [0.0, 1.0] is generated and its value determines the operator that will be used.

4.2 GP for Regression

The goal of the use of GP for the regression problem relies in automatically finding the modelling of the relationship between the independent variables and a dependent one, in this case the blood pressure. Thus, given a fitness function, facing the regression problem by GP consists in searching the model that best describes the essential characteristics of this relationship. Of course, an exhaustive search performed by the complete enumeration of all the possible models unviable from a computational point of view. As a consequence, we make reference here to GP. Being GP a heuristic method, it does not guarantee that the global optimum will be achieved yet it typically finds a suboptimal solution in a computation time that is reasonable for the users.

The evolving population is composed by 'formulas', each of which represents one potential regression model. These models are encoded as trees with variable depth, and each of them is composed by elementary functions and terminals. The function set contains 11 well-known elementary functions, and is reported in Table 2. In it, Arity is the number of arguments a function has.

Table 2: The set of the symbols representing the elementary functions, their description, and their arity.

Symbol	Arity	Description
+	2	addition
-	2	subtraction
*	2	multiplication
/	2	protected division (returns 1 if the denominator is 0)
psqroot	1	protected square root (returns 0 for negative operands)
plog	1	protected logarithm (rlog(0) is 0)
sqr		square
tanh	1	hyperbolic tangent
sin	1	sine
cos	1	cosine
exp	1	exponential

The terminal set, instead, consists of 37 symbols (the generic x_i represents the i-th independent variable in the database), plus the *Const* symbol, representing a random constant value in a suitable range. All these terminals have arity equal to 0.

In order to find the model, the available data is suitably divided into three sets: the train, the test, and the validation sets. The train set contains the items onto which the approximation of the actual output values will be carried out in the learning phase. The generalization ability of the model achieved is, instead, evaluated on the test set. Finally, the real evaluation of algorithm's performance is carried out over the validation set.

If we denote by S the model represented by a generic individual in the GP evolution, and if f is the function that represents a regression model over n instances, the fitness function Φ we use in this paper is the Root Mean Square Error (RMSE), i.e.:

$$\Phi = \frac{\sum_{i=1}^{n}(S(i) - f(i))^2}{n}$$

where $S(i)$ is the value forecasted by the model on the i-th item of the problem. In this way the regression becomes a minimization problem.

5 EXPERIMENTS

We have empirically set the GP parameters values at: *Pop_size* = 500, *Max_gen* = 200, *tourn_size* = 7, *p_mutate* = 0.10, *p_cross* = 0.85, and *p_copy* = 0.05.

The database described in Section 3.3, composed by 50 instances for each of the four patients, has been divided into train, test, and validation sets. Namely, for each patient, each item has been randomly and exclusively assigned to one of the three sets in this way: 44% for the train set, 32% for the test set, and 24% for the validation set.

GP is a nondeterministic algorithm, which means that its execution and its results depend on the initial value assigned to a random seed. In order to get rid of this feature, the GP algorithm has been run over the database 25 times. Among the 25 runs, we consider as the best one that in which the lowest RMSE value over the validation set has been achieved. In fact, the model found in that run shows the best ability to correctly get totally unknown data, so it has the highest generalization capability.

The formula achieved in the best run for the systolic blood pressure is:

$$\begin{aligned} &SYS\_BP \\ &= 0.5064\, cos\left(\frac{0.6095\, Mean\ HR}{plog(Mean\ HR)}\right) \\ &- 0.5947 \tanh\left(cos\left(\frac{Pleth\_max}{Mean\ HR}\right) - RR\ tri\ index\right) \\ &- 0.7316\, e^{Pleth\_min} 0.7316 \sin(Pleth\_min) \\ &+ \frac{0.5857 \sin(\sin(\sin(EDR)))}{e^{Pleth\_min} - \sin(Pleth\_min)} + 1.112 \end{aligned}$$

Figure 3 reports how this formula allows fitting the real systolic BP values over the three sets. Namely, the top pane shows the behaviour over the train set, the middle pane that over the test set, and the bottom pane that over the validation set.

Figure 3: Results for systolic blood pressure.

The results over the validation set, i.e. over data never learned by the GP algorithm, are very good, and the RMSE is 3.3679. This means that, on average, over previously unseen data any actual systolic blood pressure value and the corresponding computed one differ by $\pm\sqrt{3.3679} = \pm 1.8352$ mmHg, which is an excellent approximation.

A very important result of the methodology used is that it has allowed performing the automatic selection, out of the 37 present in the database, of the most important parameters for predicting the values of the systolic blood pressure.
They have turned out to be five: Pleth_min, Pleth_max, Mean HR, RR tri index, and EDR. This task is extremely difficult for a human being, however expert he can be of the field.

Similarly, the formula achieved in the best run for the diastolic blood pressure is:

$$\begin{aligned} &DIA\_BP \\ &= 0.3132\ EDR - 2.142\ Pleth\_min \\ &+ 2.899 \tanh\big(tanh(Pleth\_min + 0.6855)\big) \\ &+ 0.8554\ plog(\sin(\sin(Mean\ HR)))) \\ &+ 1.829 \tanh(e^{Pleth\_min}) - 1.386 \end{aligned}$$

Figure 4 reports how this formula allows fitting the real diastolic BP values over the three sets. Namely, the top pane describes the behaviour over the train set, the middle pane that over the test set, and the bottom pane refers to the validation set.

For the diastolic pressure the results over the validation set, never learned by the GP algorithm, yield an RMSE value of 2.6692. In this case the approximation of any actual diastolic blood pressure value with its corresponding computed value over previously unseen data is even better than that for the systolic case, since their difference is now equal to $\pm\sqrt{2.6692} = \pm 1.6338$ mmHg.

Here the automatic selection of the most important independent parameters has resulted in three of them, i.e.: Pleth_min, Mean HR, and EDR.

By looking at the two formulae, it can be seen that some parameters are present in both, so they strongly influence both pressure values. These parameters are: Pleth_min, Mean HR, and EDR. Also Pleth_max and RR tri index are important, since they are contained in one of the two rules. A result from these preliminary experiments is that both PPG values and ECG-related ones are very important to indirectly estimate BP values.

6 CONCLUSIONS

Continuous blood pressure measurement is an important issue in the medical field. Of course, a sphygmomanometer cannot be used to fulfil this task, and alternative ways should found. One way

Figure 4: Results for diastolic blood pressure.

consists in indirectly measuring blood pressure through the measurement of others among the patient's vital parameters, if a relationship between the former and these latter exists.

This paper has tested the hypothesis that a nonlinear relationship exists between heart activity, and thus ECG and HRV parameters, PPG and BP values. Genetic Programming (GP) is able to automatically both evolve the structure of the mathematical model and find the most important parameters in it. Therefore, it is perfectly suited to perform a regression task such as that involved by the above hypothesis.

Preliminary experiments on a real-world database have been performed. The numerical results achieved have confirmed that this non-linear relationship indeed exists, and GP has been able to find a mathematical model expressing it. A result from these preliminary experiments is that both PPG values and ECG-related ones are very important to indirectly estimate BP values. This implies that, rather than continuously measuring the patient's BP, a wearable wireless PPG sensor can be applied to patient's finger, a wearable wireless ECG to his/her chest, HRV parameter values can be computed and, through regression, both systolic and diastolic BP values can be indirectly measured. The approximation error involved by the use of this method is lower than 2 mmHg for both systolic and diastolic BP values.

As a future work we will perform an experimental phase in which 10-fold cross-validation will be used. Moreover, we will investigate to determine which the maximal number of items in the database is, and cases from a much higher number of patients will be considered in the creation of the database. Finally, our model will be compared with other approaches from the literature.

REFERENCES

Allen, J. (2007). Photoplethysmography and its application in clinical physiological measurement. *Physiological Measurement, 28*(3), R1.

Berntson, G. G., Bigger, J. T., Jr., Eckberg, D. L., Grossman, P., Kaufmann, P. G., Malik, M., . . . van der Molen, M. W. (1997). Heart rate variability: origins, methods, and interpretive caveats. *Psychophysiology, 34*(6), 623-648.

Dueck, R., Jameson, L. C. (2006). Reliability of hypotension detection with noninvasive radial artery beat-to-beat versus upper arm cuff BP monitoring. *Anesth Analg, 102*, Suppl:S10.

Electrophysiology, Task, Force, of, the, European, . . . Pacing. (1996). Heart Rate Variability: Standards of Measurement, Physiological Interpretation, and

Clinical Use. *Circulation, 93*(5), 1043-1065. doi: 10.1161/01.cir.93.5.1043.

Gesche, H., Grosskurth, D., Kuechler, G., Patzak, A. (2012). Continuous blood pressure measurement by using the pulse transit time: comparison to a cuff-based method. *Eur J Appl Physiol, 112*, 309-315.

Goldberger, A. L., Amaral, L. A. N., Glass, L., Hausdorff, J. M., Ivanov, P. C., Mark, R. G., . . . Stanley, H. E. (2000). PhysioBank, PhysioToolkit, and PhysioNet: Components of a New Research Resource for Complex Physiologic Signals. *Circulation, 101*(23), e215-e220. doi: 10.1161/01.CIR.101.23.e215.

Golparvar, M., Naddafnia, H., Saghaei, & Mahmood. (2002). Evaluating the Relationship Between Arterial Blood Pressure Changes and Indices of Pulse Oximetric Plethysmography. *Anesthesia & Analgesia, 95*(6), 1686-1690 1610.1097/00000539-200212000-200200040.

Ilies, C., Kiskalt, H., Siedenhans, D., Meybohm, P., Steinfath, M., Bein, B., Hanss, R. (2012). Detection of hypotension during Caesarean section with continuous non-invasive arterial pressure device or intermittent oscillometric arterial pressure measurement. *British Journal of Anaesthesia*, 3-9.

Inajima, T., Imai, Y., Shuzo, M., Lopez, G., Yanagimoto, S., Iijima, K., Morita, H., Nagai, R., Yahagi, N., Yamada, I. (2012). Relation Between Blood Pressure Estimated by Pulse Wave Velocity and Directly Measured Arterial Pressure. *Journal of Robotics andMechatronics, 24*(5), 811-821.

Karapetian, G. K., Evaluation, W. S. U. E., & Research. (2008). *Heart Rate Variability as a Non-invasive Biomarker of Sympatho-vagal Interaction and Determinant of Physiologic Thresholds*: Wayne State University.

Koza, J. (1992). *Genetic Programming: On the Programming of Computers by Means of Natural Selection*: MIT Press, Cambridge, MA.

Maguire, S., Rinehart, J., Vakharia, S., Cannesson, M. (2011). Technical communication: respiratory variation in pulse pressure and plethysmographic waveforms: intraoperative applicability in a North American academic center. *Anesthesia and analgesia, 112*(1), 94-96.

Meigas, K., Lass, J., Karai, D., Kattai, R., Kaik, J. (2007). *Pulse Wave Velocity in Continuous Blood Pressure Measurements.* Paper presented at the IFMBE.

Melillo, P., Bracale, M., & Pecchia, L. (2011). Nonlinear Heart Rate Variability features for real-life stress detection. Case study: students under stress due to university examination. *Biomed Eng Online, 10*, 96. doi: 10.1186/1475-925x-10-96.

Najjar, S., Scuteri, A., Shetty, V., Wright, J.G., Muller, D.C:, Fleg, J.L., Spurgeon, H.P., Ferrucci, L., Lakatta, E.G. (2008). Pulse Wave Velocity Is an Independent Predictor of the Longitudinal Increase in Systolic Blood Pressure and of Incident Hypertension in the Baltimore Longitudinal Study of Aging. *J Am Coll Cardiol, 51*(14), 1377-1383.

Niskanen, J. P., Tarvainen, M. P., Ranta-Aho, P. O., & Karjalainen, P. A. (2004). Software for advanced HRV analysis. *Comput Methods Programs Biomed, 76*(1), 73-81. doi: 10.1016/j.cmpb.2004.03.004.

Rajendra Acharya, U., Paul Joseph, K., Kannathal, N., Lim, C. M., & Suri, J. S. (2006). Heart rate variability: a review. *Med Biol Eng Comput, 44*(12), 1031-1051. doi: 10.1007/s11517-006-0119-0.

Sotera wireless. http://www.soterawireless.com.

Tarvainen, M. P., Ranta-Aho, P. O., & Karjalainen, P. A. (2002). An advanced detrending method with application to HRV analysis. *IEEE Trans Biomed Eng, 49*(2), 172-175. doi: 10.1109/10.979357.

von Skerst, B. (2008). Market survey, N=198 physicians in Germany and Austria. Dec.2007 - Mar 2008: InnoTech Consult GmbH, Germany.

Vukovich, R., & Knill, J. (1980). Blood Pressure Homeostasis. In D. Case, E. Sonnenblick & J. Laragh (Eds.), *Captopril and Hypertension* (pp. 3-13): Springer US.