Proceedings of the Canadian Society for Mechanical Engineering International Congress 2020
CSME Congress 2020
June 21-24, 2020, Charlottetown, PE, Canada

Intermittent Pneumatic Compression: Towards Optimal Timing for Enhancing Lower Limb Blood Flow

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Abstract— **Intermittent pneumatic compression (IPC) systems are generally used as a prophylactic for venous insufficiency (e.g., deep vein thrombosis) in the lower limbs by emulating the action of the muscle pump. Recent studies have demonstrated that compressing and releasing the calf within each heartbeat enhances blood flow compared to typical "slow" compression methods. However, each individual's hemodynamics can be sensitive to the compression timing within the heartbeat. Assessing the optimal compression timing is a complex process, since it changes from one individual to another, but also for every heartbeat. Therefore, a good understanding of the relationship between the hemodynamics and compression timing is required. The aim of this study is to assess whether blood flow in the femoral artery is predictable when external pressure is applied to the calf at different times within the cardiac cycle. Four participants wore a custom IPC device and the timing of the compression within the cardiac cycle was randomly varied for one hour. The following measurements were collected: femoral blood velocity (BV), electrocardiogram (ECG), and the applied pressure. Predicting the BV is a two-step process. (1) ECG is predicted one sample ahead by a nonlinear auto-regressive (NAR) model. (2) The femoral blood velocity is predicted by a NAR with exogenous inputs (NARX) model using the ECG and the measured external pressure as external inputs. Our NAR and NARX models consist of artificial neural network models that were trained to predict the blood flow one sample ahead (~10 ms). Once trained, those models were used in a closed-loop form to predict the ECG and the blood velocity (BV) traces of the next heartbeat. Even though the models failed to predict the next ECG R-wave, the prediction of the ECG and the BV was accurate between two successive R-waves, showing that the BV can be predicted for one heartbeat ahead.**

Keywords-component; Intermittent pneumatic compression, deep vein thrombosis, blood flow, machine learning

I. INTRODUCTION

The calf muscle is the motive force promoting the return of venous blood from the lower limbs to the heart. Veins are compliant conduits containing one-way valves to prevent backflow. When the calf muscle contracts, blood is forced through the vessel towards the heart. Compression devices mimic such action by applying external pressure to the calf, which has been shown to reduce venous stasis and thus mitigate the risk of venous disorders [1] and suggested as a mechanism for improving recovery from exercise [2], [3]

External compression devices principally employed as in-patient medical devices. The most common use is for deep vein thrombosis (DVT) prevention [1], a disorder that had an estimated health care cost of $39.5 billion in the United States in 2010 [4]. DVT is the generation of blood clots in the deep veins, which can lead to edema (swelling), ischemia (local cell death), and on occasion, the clot can dislodge and cause a stroke or heart attack. Principal causes of DVT are localized vascular injuries, surgeries, reduced mobility, and medications, which can all cause poor blood circulation [5]. In such flow conditions, compression devices can enhance blood flow and mitigate the risks of developing a DVT by 60% [6].

The standard in active compression is intermittent pneumatic compression (IPC) devices, which comprise inflatable bladders that enclose the leg and inflate and deflate to apply external pressure to the limb. IPC devices differ widely in their coverage (foot, calf, and thigh), compression sequence (simultaneous or sequential inflation of cuffs), number of cuffs, the applied pressure level, and the actuation timing, mainly due to the lack of mechanistic knowledge of the treatment [7]. Most of the commercially available devices use sequential compression, where the pressure applied to the limb progresses distal to proximal. With regards to pressure levels, some devices use uniform pressure (same pressure levels for all cuffs), whereas others use graded pressure, normally reducing from distal to proximal [8]. IPC devices typically apply pressures ranging from 65 to 120 mmHg [9]. Though there is no gold standard for IPC design or strategy, intermittent application of pressure to the lower limbs results in elevated blood flow for healthy subjects and for people with venous insufficiency in comparison with no compression [1], [8].

There is evidence suggesting that timing compression with the individual's cardiac cycle increases lower limb blood flow in comparison with non-cardiac-gated timing [10], [11]. For example, the device by Tochikubo et al. [10] uses a photoplethsmography (PPG) sensor clipped to the earlobe to trigger the compression in the diastolic phase of the cardiac cycle (compression for each heartbeat). In their study, the lower limb blood flow was measured without compression, with compression but without synchronization, and with cardiac-

synchronized compression; the increases in blood flow with respect to baseline were 100%, 123%, and 165% respectively. Blood flow was significantly increased using synchronization with the pulse, however, the actual timing with the local flow was not reported.

An in-house developed IPC device (Fig. 1a) has been employed to study the efficacy of cardiac-gated compression on lower limb blood flow during light exercise [11] and walking [12]. The device comprises 5 independently controlled pressure bladders that inflate in the sequence shown in Fig. 1b. Compression is triggered in the *local* diastolic phase of each cardiac cycle at the calf, that is, after cessation of the forward flow in the popliteal artery, and completes within the diastolic phase of the cycle. This is achieved by continuously monitoring the participants' ECG signal and correcting for the pulse wave transit time from the heart to the peripheral compression application site. Using this technique, enhanced blood flow was achieved for healthy subjects performing plantar flexion exercise in comparison with the same test protocol without external compression. Similarly, when applied during and after walking, compression improves lower limb blood flow significantly during exercise recovery [12]. It has recently been shown that the CGC device is an effective countermeasure to orthostatic stress [13]. Comparison with commercial IPC devices has demonstrated that the employed local cardiac-gated compression significantly enhances average blood flow [14].

To date, it has been demonstrated that IPC is capable of elevating blood flow, with improved device performance achieved by timing compression with the individual's cardiac cycle. However, pilot studies have suggested that optimal compression timing may differ from person to person, and may change over the duration of an extended therapy session. There are currently no existing tools that enable determination of optimal parameters for an individual in a given state (seated, prone, etc.). Considering there are many different operational parameters for IPC devices, such as the external pressure of each cuff, timing of each cuff compression, etc., modeling tools are needed to facilitate optimization. The goal of this paper is to develop a modeling approach for the lower limb blood flow when using a CGC device, which is a first step towards optimizing the compression protocol for a given user. Machine learning is employed to develop a model capable of predicting blood velocity (BV) for the next cardiac cycle with and without compression, thus enabling exploration of optimal timing parameters for an individual user.

II. METHOD

A. *Experiment*

The CGC device detailed in Fig. 1 was employed to apply lower limb compression to four subjects (2 men and 2 women). The sequence of cuff inflation (Fig. 1b) and the timing of the compression cycles within a heartbeat were controlled electronically using LabVIEW software (National Instruments, Austin, TX). During experiments, compression timing was changed each minute; however, the delay between the compression of each sequential cuff was kept constant at 30 ms. Compression delays from 10% to 100% in 5% increments of the RR interval were considered; the same range was repeated a second time with increments of 10% (see Fig. 2). For the two portions of the test (A and B in Fig. 2), each compression delay was kept constant for 1 min and the sequence of compression delays were randomly shuffled for each participant. Data were collected at the beginning and the end of each session for 5 min without compression. Portions A and B were also separated by 5 min without compression.

Interface pressure between the compression cuffs and the lower leg was determined using four pressure sensors located under the four top compression cuffs on the posterior surface of the left leg. The pressure sensors consisted of a Picopress bladder (Microlab Electronica) connected to an Omega PX390 pressure transducer (Omega Engineering, Laval, Quebec, Canada). At the start of testing, the compression system was adjusted to apply an approximate pressure of 100 mmHg.

A standard three-lead ECG (Pilot 9200; Colin Medical Instruments, San Antonio, TX) was continuously monitored and recorded to compute the R-R interval for assessing heart rate and to time the compressions. Blood velocity was measured in the superficial femoral artery (SFA) using a 4-MHz Doppler probe (WAKIe; Atys Medical, Soucieu en Jarrest, France) that was held in place with medical tape. All collected data were recorded at 1000 Hz (LabVIEW software) for later analysis.

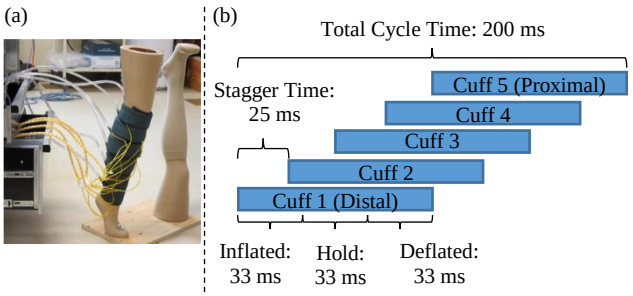

Fig. 1 – (a) In-house intermittent pneumatic compression (IPC) device; and (b) its cardiac-gated cycle.

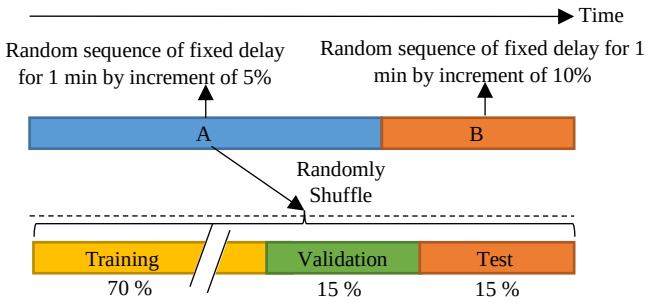

Fig. 2- Schematic showing how each dataset was subdivided. Part A was randomly split into training, validation, and test datasets. Part B is the sub dataset used for comparing the model performance in one heartbeat-ahead prediction.

B. *Model Architecture and Training*

Two Artificial Neural Network (ANN) models were used in cascade to predict the BV one heartbeat ahead. The first was a nonlinear autoregressive model to predict the ECG (NAR_{ECG}), and the second a nonlinear autoregressive with exogenous inputs (NARX) model to predict the BV ($NARX_{BV}$). $NARX_{BV}$ used the ECG signal and the measured applied pressure on the lowest cuff (AP) as exogenous inputs. All models were trained as feedforward ANNs, as seen in Fig. 3a,b. Once each model was trained, they were assembled ($NARX_2$) as seen in Fig. 3c.

In this study, the $NARX_2$ model was used offline for multi-step-ahead prediction from one R-wave to the next. When detecting an ECG R-wave, the first predictions $\widehat{\mathrm{ECG}}(k)$ and $\widehat{BV}(k)$ were made using the data from the previous heartbeats (*k*-1, *k*-2, …, *k*-200). Those predictions were then fed back into the input layer and used to predict the next values. This process continued until the next R-wave was detected.

To find inputs (frequency and time lags) of the $NARX_{BV}$ model, the maximum time lag was varied from 0 to 2000 ms and the sampling period was tested for 5 ms, 10 ms, and 20 ms (resampled from the original sampling frequency of 1000 Hz). The final configuration used a sampling frequency of 100 Hz where the BV dynamics was well characterized by a second-order system ($\mathrm{BV}(k-1)$ and $\mathrm{BV}(k-2)$). The ECG and AP were used as the input signals; however, there was a delay between inputs and the response of the BV, i.e., the first 9 time-steps carried no information. The input delays from 10 to 40 time-steps drove the dynamics of the BV. The higher delays (*k*-40, *k*-44, …, *k*-200) were kept as it was observed that they minimized the model bias in a one-heartbeat-ahead prediction configuration. That portion of the input was resampled every 4 time-steps to minimize the ANN size. NAR_{ECG} was set to use the same sampling frequency as $NARX_{BV}$. Time-step delays from 0 to 100 were used as inputs to the NAR_{ECG} as one second is a normal resting RR interval.

Typical ECG, AP, and BV signals are shown in Fig. 4 illustrating the character of the inputs of the $NARX_{BV}$ model and showing the delays between peaks in the various measures. In this study, the compression delay was defined as when the compression was triggered in the software in percentage of the previous RR interval. A delay of 160 ms was observed between the trigger and the peak applied pressure (Mech. delay), which is the mechanical time for the cuff to inflate.

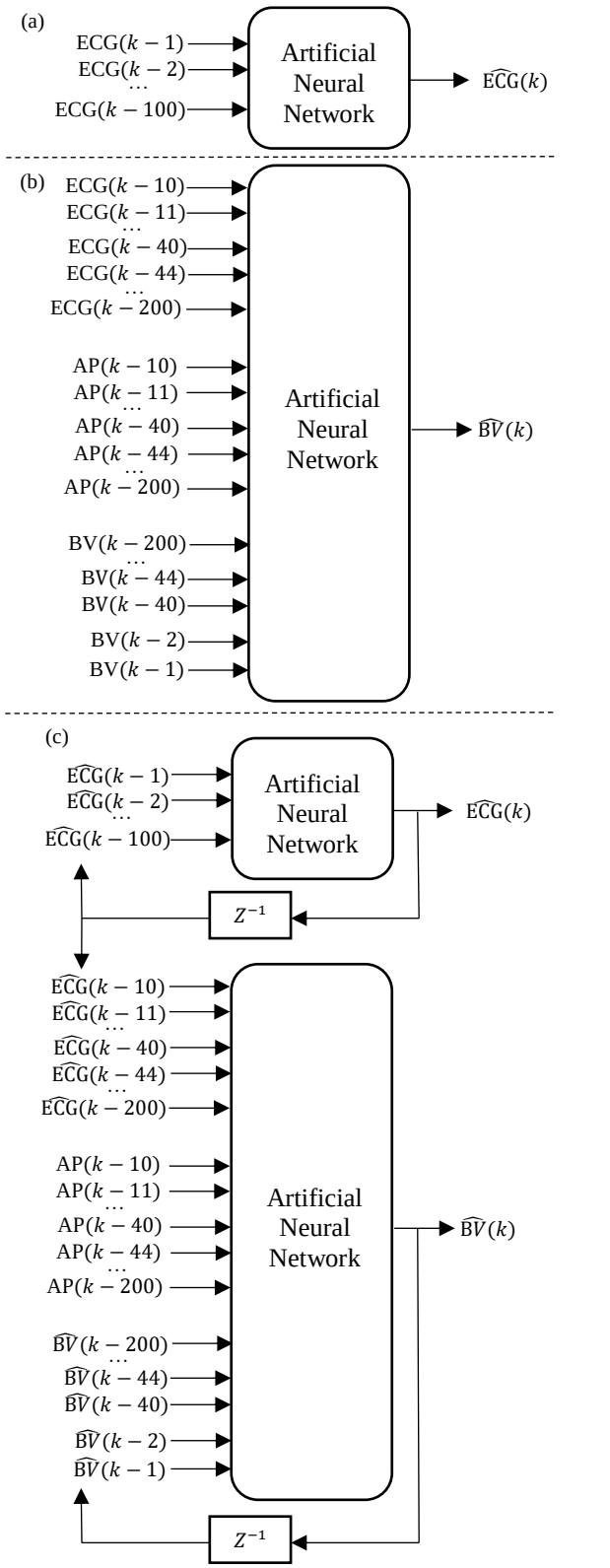

Fig. 3- Schematic of the model used for (a) training of the ANN as a feedforward for the NAR_{ECG}, (b) for the $NARX_{BV}$, and (c) estimation and testing of the BV using a recurrent ANN $NARX_2$.

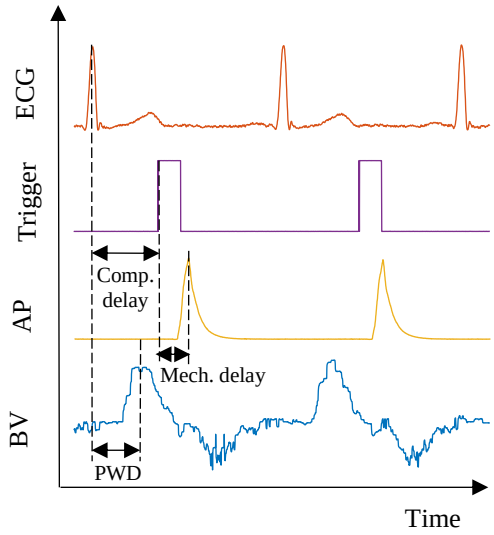

Fig. 4– Typical ECG, trigger, AP, and BP signals illustrating the potential temporal delays between the peaks for a compression delay of 35%

C. *Data Analysis*

For each subject, a cross-correlation analysis was performed to quantify any delay between the predicted and the measured BV. The model was developed for optimizing the compression timing of compression devices, where the goal is to maximize the overall flow that goes into the lower limb, an important performance metric for an IPC [1]. Therefore, assuming that the flow in the artery is proportional to the blood velocity, the beat-by-beat mean velocity (BBMV), defined as the BV mean velocity between two R-waves, is used as the performance metric for the model. A comparison of the predicted and measured BBMV was graphically visualized as a function of the compression delay to see if the prediction trends were similar to the measured trends. Next, the scatterplots of the predicted and measured BBMV were used to assess the correlation.

III. RESULTS

The NAR_{ECG} was used to predict ECG signal starting from an R-wave up to the next R-wave minus one time-step. The reason is that the next R-wave cannot be accurately predicted with the model, as shown in Fig. 5, presumably due to slight variations in heart rate from beat to beat. Therefore, the BV prediction horizon in this study was limited to the R-R period minus one time-step, limited by the NAR_{ECG}.

Representative samples of predicted BV using $NARX_2$ of subject 1 are benchmarked with the measured BV in Fig. 6 without compression (NoComp) and with 20%, 50% and 80% compression delays. A delay of one time-step (10 ms) of the one-hearbeat-ahead predicted time series compared to the measured BV time series was observed for all four subjects when using cross-correlation analysis. However, when shifting the predicted time series by 10 ms, the Pearson correlation coefficient changed from 0.895 to 0.905 for subject 1, which is substantial as it should not affect the prediction of the BBMV. The prediction on other subjects yield similar results.

The predicted BBMV (expected value and standard deviation) is compared with the measured BBMV for subject 1 (Fig. 7.a) and for subject 3 (Fig. 7.b) as a function of the previous heartbeat period. The previous heartbeat period was used since the current heartbeat period is unknown during the experiment. In Fig. 7a-1 and b-1, the results are shown for the training dataset (portion A), whereas a-2 and b-2 shows the results from the test dataset (portion B). It is observed that the BBMV curves changed from portion A to portion B.

Fig. 8 presents scatterplots of the measured versus estimated BBMV for each subject predicted with $NARX_2$ on portion B of the dataset. Each compression delay is color-coded. The linear fit between estimated and measured BBMV shows coefficients of determination ranging for R^2=0.66 to R^2=0.88.

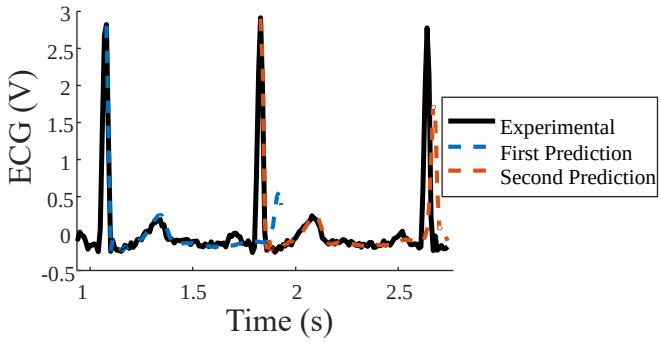

Fig. 5 – Prediction starting from the R-wave showing good accuracy up to the next R-Wave, which it not accurately predicted.

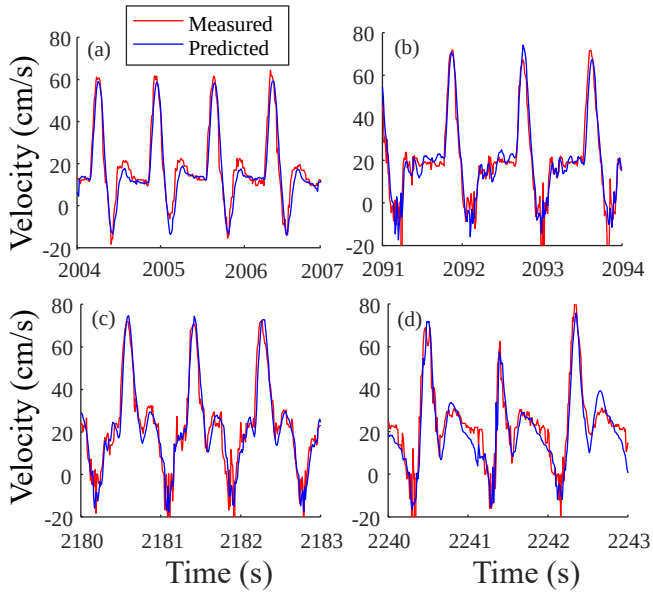

Fig. 6 - Comparison of actual versus predicted BV waveforms for subject 1 for (a) NoComp (b) 20%, (c) 50%, and (d) 80% compression delay. The BV waveforms show considerable qualitative differences in shape for different compression delays, but there is an agreement between the model prediction and the measurements in every case.

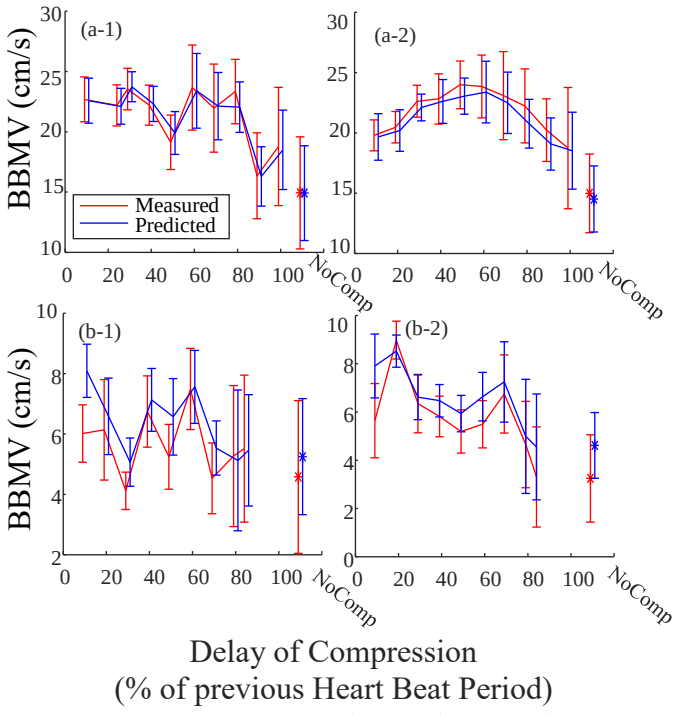

Fig. 7 – Beat-by-beat mean velocity as a function of the delay of compression for the predicted and measured velocity for (a) subject 1, and (b) subject 3. In a-1 and b-1, the results are shown for portion A of the data, whereas a-2 and b-2 show it for portion B.

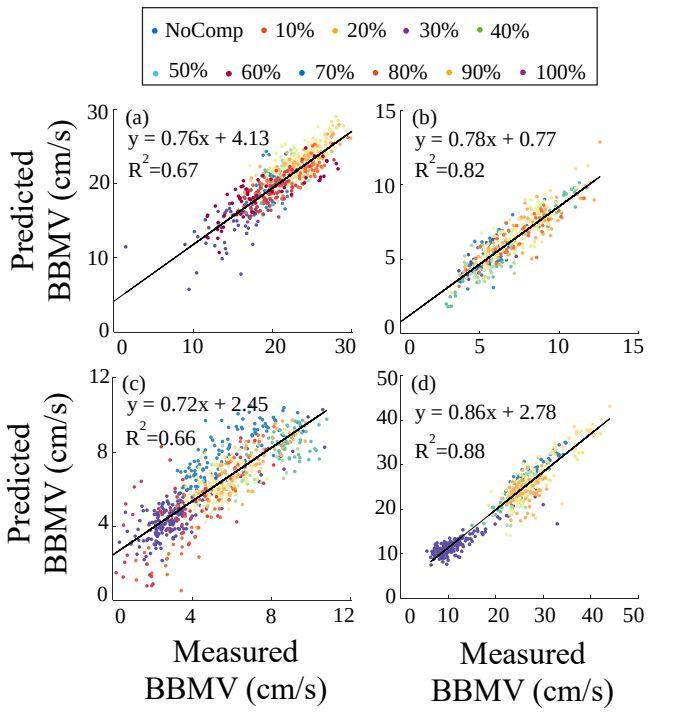

Fig. 8 - Scatterplots of BBMV for (a) subject 1, (b) subject 2, (c) subject 3, and (d) subject 4. The solid line is a regression line through all data. The coefficient of determination and the equation are shown near each regression line. Compression delays are color-coded.

I. Discussion

The model architecture presented in this paper showed that the dynamics of the BV when using a compression device can be modeled using a second-order nonlinear dynamics model, similar to the blood pressure model discussed in [15]. It can be argued that the model is not second-order, but a higher-order model as the higher time-step delays of the BV were used as inputs, i.e., the 44 to 200 time-steps by increments of 4 time-steps. However, those time-steps were added only to better model the BBMV, as they connected the model to the previous heartbeat with measured data. This resulted in a lower bias of the BBMV estimates compared to a model that did not use the higher time-step delays of the BV as inputs. It was qualitatively observed, however, that the dynamics of the BV itself can be well modeled using only the inputs of the ANN from 1 to 40 time-steps, i.e. ECG(k-10), ECG(k-11), …, ECG(k-40), AP(k-10), AP(k-11), …, AP(k-40), BV(k-1), and BV(k-2).

In the real application setting, the NARX model can be trained on data at the beginning of a compression therapy session. Once trained, the model can be used for predicting the BBMV one-heartbeat-ahead for different simulated compression delay and the one that maximizes the BBMV can be applied. However, in this study, the prediction horizon of the $NARX_2$ was limited to one heartbeat ahead minus one time step because the NAR_{ECG} was not able to predict the next R-wave. This is probably due to the underlying system being chaotic which affects the ECG signal [16]. This means that the heart rate variability may not be predictable using a NAR model, but should be predicted by another model that is trained for that [17]. This was left for future work.

It can be observed from Fig. 6 that the experimental blood velocity measurements contain noise. Most of the noise was caused by the leg shaking from the compression. No filter was applied remove the noise, since it was difficult to distinguish between high frequency noise from the vibration of the leg and high frequency blood velocity caused by the fast compression. Future work should include accelerometers on the thigh and on the ultrasound probe to better understand compression-induced leg vibration. This information could be used to design a filter that minimizes noise without altering the high frequency velocity signal. The error caused by the noise applies to the model as well, as it is data driven, i.e., when training the ANN, the noise is included in the training dataset. This can lead to a larger variance of the model, which could be minimized if the noise was filtered out of the measurements.

It was shown that the BBMV as a function of the compression delay changes over time (Fig. 7), which makes it difficult to identify which delay was optimal. This is due to the fact that in addition to the dependency of the BBMV to compression delay, BBMV is also a function of the ECG, AP and BV history. It was shown that the BBMV can be modeled using a nonlinear function of the ECG, the AP, and the BV previous states, which makes it difficult to understand which input caused the change in the BV. This means that, if a fixed

delay has to be chosen only from experiments, choosing the delay that maximized the flow during testing could be misleading, as this flow could have been caused by the heart (ECG) or the previous state of BV, and not by the external compression (AP). This justifies the need for a model capable of predicting the changes over time (Fig. 7-1 versus Fig. 7-2), caused by either input.

The scatterplots showed important results. First, the coefficient of determination R2 showed what percentage of change in blood flow the model can predict. An R^2 value of 0.67 is quite reasonable; as observed in Fig. 5, the blood flow signals are noisy, which affects the coefficient of determination. One problem was that the application of external pressure made the legs vibrate, which influenced the Doppler blood flow measurement. This phenomenon could explain why subject 1 and 3 correlations were lower as maybe the ratios of vibration to blood velocity signal were higher. Further investigation using an accelerometer is needed.

The second important result from the scatterplots is the BBMV bias for each compression delay was similar, i.e. the centroids for each set of compression delay data points were close to the regression line. This is an important parameter as all predictions must be equally proportional to the actual value when using this model to optimize the flow. Otherwise, the model would bias the choice of compression timing.

The last observation from the scatterplots was how the distribution of the data around the regression line was similar for all compression delays and for the full range of BV. This might indicate that the portion that was not predicted by the model affected equally all predictions. That implies that even if the change in blood flow is not always proportional to the measured value (low R^2), the decision of choosing a compression delay over another from the prediction remains the best choice.

The impact of not knowing when is the next R-wave on the optimization of the compression timing when using $NARX_2$ for online optimization was not assessed and is left for future work.

II. Conclusion

It was shown that the complete BV waveform can be predicted one heartbeat ahead from the ECG and the AP signals with a NARX model using ANNs. The model was developed for optimizing the timing of compression devices where the performance metric is the average flow. The optimization of the timing only based on experimental data is however difficult since the BBMV is a nonlinear function of the ECG and the AP. The focus of this manuscript was to demonstrate that the BV can be predicted one heartbeat ahead in presence of the compression, which is the core foundation for the optimization of the compression timing; which is left as future work. In addition, effort should be made in order to better understand the impact of the prediction horizon on the selected optimal timing.

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