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Causal inference based cuffless blood pressure estimation: A pilot study

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Abstract

Enabled by wearable sensing, e.g., photoplethysmography (PPG) and electrocardiography (ECG), and machine learning techniques, study on cuffless blood pressure (BP) measurement with data-driven methods has become popular in recent years. However, causality has been overlooked in most of current studies. In this study, we aim to examine the feasibility of causal inference for cuffless BP estimation. We first attempt to detect wearable features that are causally related, rather than correlated, to BP changes by identifying causal graphs of interested variables with fast causal inference (FCI) algorithm. With identified causal features, we then employ time-lagged link to integrate the mechanism of causal inference into the BP estimated model. The proposed method was validated on 62 subjects with their continuous ECG, PPG and BP signals being collected. We found new causal features that can better track BP changes than pulse transit time (PTT). Further, the developed causal-based estimation model achieved an estimation error of mean absolute difference (MAD) being 5.10 mmHg and 2.85 mmHg for SBP and DBP, respectively, which outperformed traditional model without consideration of causality. To the best of our knowledge, this work is the first to study the causal inference for cuffless BP estimation, which can shed light on the mechanism, method and application of cuffless BP measurement.

Keywords: Cuffless blood pressure; Causal inference; Pulse transit time; Amplitude alteration of PPG

1. Introduction

Cardiovascular diseases (CVDs) have gradually become an important public health problem, which led to 17.7 million deaths in 2017 increasing 14.5 percent compared with a decade earlier [1]. Hypertension, or high blood pressure (BP), is the most significant contributory factor of CVDs, and severe hypertension could increase the risk of having CVDs dramatically. So it is indispensable to monitor continuous BP accurately for prevention and intervention of hypertension and related CVDs.

Cuffless BP estimation is a research hotspot for its noninvasiveness and convenience, currently, in the field of accurate evaluation of continuous BP. Cuffless BP measurement can be achieved with models built to translate cardiac signals acquired with noninvasive and unobtrusive wearable sensors to BP values. The conventional cuffless BP measurement methods are either physiology knowledge based [2] or data-driven based [3].

The physiological method, or heuristic regression method, has been proposed usually based on one or several features extracted from wearable signals, such as PTT-based approaches. For purpose of achieving accurate continuous estimation, periodic individual calibration usually is inevitable for physiological method due to individual difference. What is more, the establishment of models generally rely on many assumptions of physiological knowledge such as hemodynamics, and the selection of feature usually depends on feature engineering or experience, and therefore the precision of BP estimation is not guaranteed.

On the other hand, the data-driven BP estimation model [4] is usually black-box and less interpretable. Although the data-driven method has excellent performance sometimes, it is difficult to understand the

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The internal mechanism of cardiovascular system and make corresponding interventions in the regulation of BP.

That is, current methods are blinded because of either the implausible hypothesis of physiological models or the black-box nature of data-driven models within limits. Using wearable signals for continuous cuffless BP estimation urgently needs new insight to break through these barriers now. Causal inference that allows drawing causal conclusions based on data, is potential to shed light on cuffless BP estimation by identifying causal new relationships rather than correlation and building causal models between wearable features and BP.

Causal inference is the process of drawing conclusions about causal links based on the conditions under which a certain event occurred [5]. In other words, causal inference leads to the conclusion that something is (or maybe) the cause of something else. Generally, a directed acyclic causality diagram can be used to describe the causal relationship among multiple random variables, that is, the result of causal inference. In a dynamic as complex as the cardiovascular system, it can be easily misled by false relationships that further affect the accuracy of cuffless BP estimation, for example, Simpson’s Paradox [6], if the causal links are ignored within it. The application of causal inference methods for inferring causal features of BP variance, and building corresponding causal-based regression model could be a potential approach to achieve cuffless BP estimation precisely.

This study aims to investigate the feasibility of causal inference in cuffless BP estimation. In order to explore the causal mechanism of BP variation within the cardiovascular system, the causal graph between BP and wearable features taken from ECG and PPG is inferred firstly. Then the causal indicators in causal graph connected with SBP and DBP is identified. To verify if these causal indicators play a key role in evaluating BP changes, we analyze and compare the power spectrum of SBP, DBP with their corresponding causal indicators. We then explore the feasibility of integrating causal features identified with BP estimation. Time-lagged causal links identified from causal graph, motivated by Granger causality, are employed to establish the causal-based cuffless BP estimation model. To further evaluate the efficiency of causality in cuffless BP estimation effectively, the PTT-based regression model serves as a control experiment in this study.

2. Methodology

2.1. Experiment and feature extraction

This study used the data collected from our previous study [7], which includes 62 subjects (36 males) with the average age of 26.7 ± 4.5 (range from 21 to 42 years). The data contains wearable signals, namely ECG and PPG signals collected by a multi-channel physiological parameter monitoring system (Biopac system). The experiment also synchronously measured continuous BP as reference with Finapres® NOVA, SMART Medical, UK, a noninvasive ambulatory arterial BP measurement device. The signal acquisition process lasted for 10 min at the sampling rate of 1000 Hz while each subject maintaining a seated state. The overall mean systolic BP (SBP) was 114.0 ± 13.4 mmHg for all subjects, and the corresponding mean of diastolic BP (DBP) was 67.0 ± 10.6 mmHg. Before the experiment, all subjects provided their informed consent according to the criteria of the institutional research ethics board.

In order to infer causal mechanisms of BP variation as much as possible within the cardiovascular system, we has extracted as many features as possible from PPG and ECG, following our previous work [8]. Based on process of filtered PPG and ECG signals, 222 features in 7 categories were extracted for the following process of causal inference. The classification and detailed definition of 222 features are depicted in Table 1.

Before calculating the corresponding features, the fiducial points of ECG, PPG, first derivative PPG (dPPG) and second derivative PPG (sdPPG) signals in each cardiac cycle were identified initially, as illustrated in Fig. 1. Further, complete mathematical definitions of all features are elaborated as below:

- **Fiducial Point of PPG (FP, 1~10)**: (PPG_valley, sdPPG_a, dPPG_peak, sdPPG_b, PPG_peak, sdPPG_c, sdPPG_d, dPPG_valley, sdPPG_e, sdPPG_f, PPG_valley_next)
- **Pulse Transit Time (PTT)**: FP(i) – P_peak, i = 1~10
- **Time Duration (TD)**: [RRI, (FP(i)−FP(j), 1 ≤ i < j ≤ 10]
- **Pulse Width (PW)**: pulse width of PPG at 50%, 60%, 70% amplitude or fiducial points

**Amplitude alteration (AA)**: = PPG(FP(i)) – PPG(FP(j)), 1 ≤ i < j ≤ 10

**Absolute Intensity of PPG (AI_PPG)**: = PPG(FP(i)), i = 1~10

**Absolute Intensity of dPPG (AI_dPPG)**: = dPPG(FP(i)), i = 1~10

**Absolute Intensity of sdPPG (AI_sdPPG)**: = sdPPG(FP(i)), i = 1, 2, 4, 7~10

**Area under PPG curve (AR)**: Area between [FP(j), FP(i)] under PPG curve, 1 ≤ i < j ≤ 10

**Physiological Ratio Index (RI):**

- dicrotic diastolic ratio, relative rising time, inflection point area ratio, augmentation index, slope transit time, PPG intensity ratio, ratio of sdPPG (b/a, c/a, (c−d−b)/a, etc.), perfusion index [9].

### 2.2. Algorithm and strategy of causal inference

This subsection begins with a brief introduction to the fast causal inference (FCI) algorithm. Further, for subject-to-subject specificity, this work proposes a majority strategy of causal inference to obtain a universal causal graph.

Based on the faithfulness and Markov property assumption [10], constraint-based algorithms could infer causal graph satisfying the conditional independence hidden in the data. There are three structures for unshield triple composed of random variables X, Y and Z, namely chain (X ← Z → Y), fork (X → Z ← Y) and collider (X → Z → Y). The independence and conditional independence relation of unshield triple are shown in Table 2, which is the fundamental idea for causal inference behind constraint-based algorithm.

By identifying the structure of unshield triple, the constraint-based algorithm could infer the causal relationship from observed data. For example, if X ⊥ Y and X ⊥ Y | Z, there is no causal relationship between X and Y even though they are not independent. The conventional constraint-based algorithms, such as Peter-Clark (PC) algorithm [11], complete causal inference processing in a two-step fashion. Firstly, the algorithm infers an undirected skeleton by gradually deleting the edges from an initial complete graph, and then it orients the direction of edges of the skeleton. Moreover, FCI algorithm [12] took unobserved confounders and selection bias into consideration through additional statistical tests with set of Possible D Separation (PDS). The universal process of causal inference with FCI algorithm is depicted as following:

1. **Get initial skeleton**
   Through conditional independence test, the initial skeleton of the causal graph is obtained by deleting edges of a complete graph composed of all random variables. That is, for variable X, Y and conditional variable set Z, if X ⊥ Y | Z, the edge connecting X and Y is deleted.

2. **Recognize colliders**
   For the unshield triple X-Z-Y in the initial skeleton, if X ⊥ Y and X ⊥ Y | Z, then X-Z-Y is identified as a collider, i.e., X → Z ← Y.

3. **Recognize PDS**
   The definition of PDS: For the graph G obtained in step 2, node X_i ∈ PDS(G, X_i), if and only if there is a path, for every subpath(X_i, X_j, X_k), X_j is the collider of the subpath or the subpath forms a triangle.

4. **Get final skeleton**
   For every node X in the initial skeleton, PDS(G, X) is used as the conditional set to test the independence of X on its adjacent nodes. The edge deletion operation is performed again to obtain the final skeleton of the causal graph.
5. Orienting

The colliders are identified from the final skeleton, and other rules [13] are used to calibrate the direction of the causal graph as much as possible.

To detect the nonlinear causal link between random variables, Randomized Conditional Independence Test (RCIT) [14] was utilized in this work to perform the iteration of FCI algorithm. Though non-parametric kernel-based RCIT could partly overcome the curse of dimension in the big datasets, the challenge of huge computational cost remains due to the large number of features extracted. What is more, different causal graphs would be inferred if the causal inference algorithm was performed independently for each subject since individual specificity in physiology. Therefore, it is unwise and computationally consuming to execute causal inference individually for each subject.

Obtaining a general and universal causal graph, applicable to all subjects, is what this work expects, from which some general causal conclusions could be drawn providing new insight for continuous cuffless BP estimation further. With the compromise between the cost of computation and accuracy of causal inference, this paper suggests a strategy of causal inference below. By means of the majority rule of conditional independence tests’ results, this strategy helps to infer a general causal graph that is universal to all subjects.

**Strategy of causal inference:** With the iteration of constraint-based (such as FCI) algorithm, if the algorithm needs to determine whether \( X \perp Y \mid Z \), then do the test \( X \perp Y \mid Z \) separately for each subject. Suppose there are M subjects in the dataset totally, and the strategy will test for M subjects respectively. Finally, the strategy takes “majority rule” to obtain a general conclusion for this test. When more than half of the subjects (\( \frac{M}{2} + 1 \)) agree that \( X \perp Y \mid Z \), the strategy concludes \( X \perp Y \mid Z \) is true within a general scale, otherwise vice versa.

With the strategy, FCI algorithm could quickly identify a general causal graph of BP and a large number of wearable features extracted from ECG and PPG. The causal graph may give new inspiration for the mechanisms of BP changes and prompt better accuracy of cuffless BP estimation further.

### 2.3. Bridge the gap between causality and regression

The causal-based regression model of BP estimation was built inspired by Granger causality [15]. Granger infers the causality of two time series based upon whether the lagged values of one time series could provide statistically significant knowledge for the regression of another time series’ current values. What the core hides in Granger causality is utilizing regression equations to draw causal conclusion, where regression equations were established through time-lagged links.

The causal graph of BP has already been identified by FCI algorithm, so there must be corresponding regression equations for BP estimation behind the causal graph. What bridge the gap between causal graph and BP regression models is time-lagged causal links.

Therefore, from causal graph, we detected the time-lagged causal links by PCMCI algorithm, which could provide statistically significant information for BP estimation. With the time-lagged causal links, we could cross the gap between causality and regression of cuffless BP estimation naturally.

Peter and Clark & momentary conditional independence algorithm (PCMCI) [16], a variant of Granger causality, was utilized to identify the time-lagged causal links of BP in this work. PCMCI algorithm could scale with large nonlinear multiple time series, and it consists of a two-step fashion: First of all, the adapted PC algorithm identifies initial time-lagged causal links, a superset of parents for each variable. Secondly, the momentary conditional independence step deletes the false-positive causal links for highly interdependent case. For example, \( \hat{P}(X_j^i) \) is the superset parents of random variable \( j \) detected by PC algorithm. Supposing there is \( X_{i-r} \in \hat{P}(X_j^i) \), MCI do the test of \( \hat{P}(X_j^i) \) vs. \( \hat{P}(X_j^i) \) by \( \hat{P}(X_j^i) \), and only if the MCI test is statistically significant, then \( X_{i-r} \) is removed from \( \hat{P}(X_j^i) \), otherwise vice versa.
Causal graph, inferred in the previous subsection, has actually completed partial work for the first step of PCMCI algorithm, since it has already contained the information of superset of parents for each variable. On this basis, PCMCI algorithm further identified the time-lagged causal links of BP, which were utilized to build the causal-based regression model.

Inspired by Granger causality, the time-lagged causal identified links could provide statistically significant information for BP regression. For simulating the regression process in Granger causality, multiple Linear regression and XGBoost, taking the time-lagged causal links as input, were adopted to build regression models of cuffless BP estimation in this study. Multiple Linear regression is a typical linear regression method in machine learning, and XGBoost has good performance in dealing with nonlinear problems. They were utilized to fit the linear and nonlinear causal dependencies between wearable features and BP respectively.

In addition to the causal-based regression model, our work also built the other regression models (PTT-based) which only take PTT(R-dPPG \(_{\text{peak}}\)) as the sole input. The PTT-based regression model serves as a control experiment to compare with the causal-based model. Standardization and outlier removal were taken before feeding the time-lagged causal links of BP into the ML models for training. In order to avoid data overfitting, this study used the leave-one-subject-out cross-validation (LOOCV) strategy to evaluate the performance of regression models according to clinical practice.

### 3.2. Spectral analysis of BP components and its causal indicators

As can be seen in Fig. 2, PTT(R-dPPG \(_{\text{peak}}\)) is the descendant of SBP and DBP, while PTT(R-dPPG \(_{\text{peak}}\)) has no direct link with SBP or DBP in the causal graph. Except for the PTT, causal graphs provide a novel inspiration on wearable features of Amplitude Alteration (AA), where AA stands for amplitude alteration of PPG between PPG valley and sdPPG, \(\Delta_t\) means the first extreme point after the peak of the second derivative PPG. Analogously, AA(PPG \(_{\text{valley}}\) - sdPPG) is defined as amplitude alteration of PPG between PPG valley and sdPPG, where \(\Delta_t\) means the first extreme point after the peak of the second derivative PPG. AA(dPPG \(_{\text{peak}}\) - sdPPG) refers to the amplitude alteration of PPG between dPPG peak and sdPPG, where dPPG means the first derivative PPG. PTT(R-dPPG \(_{\text{peak}}\)) refers to the pulse transit time between the R peak of ECG and the dPPG peak. And PTT(R-dPPG \(_{\text{peak}}\)) refers to the pulse transit time between the R peak of ECG and the peak of PPG. Cycle Area, Systolic Area and Diastolic Area stand for the area under the PPG curve in one cardiac cycle, the systolic period and diastolic period, respectively. \(\delta_{\text{PPG}}(c+d-b)/a\) means the relative ratio of \(\Delta_t\) of PPG, where \(\Delta_t\) stands for the absolute intensity of the second derivative PPG. \(\Delta_t\) refers to the absolute intensity of PPG on sdPPG.

As can be seen in Fig. 2, PTT(R-dPPG \(_{\text{peak}}\)) is the descendant of SBP and DBP, while PTT(R-dPPG \(_{\text{peak}}\)) has no direct link with SBP or DBP in the causal graph. Except for the PTT, causal graphs provide a novel inspiration on wearable features of Amplitude Alteration (AA), where AA stands for amplitude alteration of PPG between two reference points, as can be seen in Fig. 1. The identified causal graphs reveal that AA(PPG \(_{\text{valley}}\) - sdPPG) is the effect of SBP, and AA(PPG \(_{\text{valley}}\) - sdPPG) and PTT(R-dPPG \(_{\text{peak}}\)) are the effects of DBP.

### 3.2. Spectral analysis of BP components and its causal indicators

As shown in causal graph, the feature AA(PPG \(_{\text{valley}}\) - sdPPG) connects with SBP, while both AA(PPG \(_{\text{valley}}\) - sdPPG) and PTT(R-dPPG \(_{\text{peak}}\)) connect with DBP directly. These three features were identified as causal indicators of corresponding BP components, and then we analyzed power spectrum of these indicators and BP.

As can be seen in Fig. 3(a), the continuous BP signal consists of fast variability and slow variability. Correspondingly, the beat-to-beat SBP and DBP are illustrated in Fig. 3(b). Notably, SBP and DBP have
different amplitude, with SBP featuring both fast variability and slow variability, DBP mainly displaying slow variability. It could be further illustrated with the power spectral density (PSD) of SBP and DBP, which varies between 0–0.1 Hz at low frequency (LF) domain and concentrates on 0.4 Hz during high frequency (HF), as depicted in Fig. 3. And this is fit with previous study on BP variation [19].

Furthermore, time series of the SBP causal indicator AA(PPG_valley–sdPPG_b) and PTT(R–dPPG_peak) with their corresponding spectrums are illustrated in Fig. 4. Compared with Fig. 3(c), the spectrum of PTT(R–dPPG_peak) only contains the HF component, which is almost identical to the fast variation pattern of SBP. But the direct causal indicator of SBP, AA(PPG_valley–sdPPG_b) could better reflect both the HF and LF components of SBP. There is also a good match between the spectrum of DBP and its causal indicator AA(PPG_valley–sdPPG_b), as depicted in Figs. 3(b) and 4(f).

The results of PSD are well-matched with the causal graph. In other words, the spectral analysis proves that the identified causal graph is reasonable partly.

### Table 3

<table>
<thead>
<tr>
<th>Index</th>
<th>SBP</th>
<th>DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AA(PPG_valley–sdPPG_b)[0]</td>
<td>AA(PPG_valley–sdPPG_b)[0]</td>
</tr>
<tr>
<td>2</td>
<td>PTT(R–dPPG_peak)[0]</td>
<td>PTT(R–dPPG_peak)[0]</td>
</tr>
<tr>
<td>3</td>
<td>Cycle Area[0]</td>
<td>AI_65(sdPPG_b)[0]</td>
</tr>
<tr>
<td>4</td>
<td>Systolic Area[0]</td>
<td>Cycle Area[0]</td>
</tr>
<tr>
<td>5</td>
<td>=</td>
<td>Diastolic Area[0]</td>
</tr>
</tbody>
</table>

### 3.3. Establishment and evaluation of BP regression model

Taking features inferred in causal graph as inputs of PCMCI algorithm, time-lagged causal links are identified and illustrated in Table 3. There are 4 causal links of SBP and 5 links of DBP inferred, where all links were with the time lag of 0. The number in [] refers to lags of time. This means the current state of features has a stronger causal link with BP components than their past states.
With the help of multiple linear regression and XGBoost methods, this study further took the time-lagged causal links in Table 3 to establish causal-based estimation models for SBP and DBP correspondingly. As the benchmark, the PTT-based models only took PTT(R-dPPG) as input of multiple linear regression and XGBoost.

Tables 4 and 5 display the evaluation of these regression models on AAMI, IEEE 1708 and BHS standard. It can be seen that the causal-based XGBoost model performs best, with ME ± SDE being 0.43 ± 6.44, 0.57 ± 3.89 mmHg, and MAD of 5.10, 2.85 mmHg for SBP and DBP, respectively. In comparison to PTT-based models, causal-based regression models showed a significant (p < 0.05) better performance. Further from Table 5, we can see that the causal-based regression models achieved higher Grades and accuracy than PTT-based regression models.

Furthermore, this study analyzes the importance of features in causal-based XGBoost model, where feature importance is calculated by the normalized average gain across all splits the feature is used by. For causal-based XGBoost model of DBP, the feature importance of AA(PPG_va{l}l{e}y) is 5.10. For causal-based XGBoost model of SBP, the feature importance is 6.44.

Table 5
<table>
<thead>
<tr>
<th>Model</th>
<th>Grade</th>
<th>ME (mmHg)</th>
<th>SDE (mmHg)</th>
<th>MAD (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTT-based multi-linear</td>
<td>&lt;5 (%)</td>
<td>67.85</td>
<td>89.03</td>
<td>96.44</td>
</tr>
<tr>
<td>PTT-based XGBoost</td>
<td>&lt;5 (%)</td>
<td>79.70</td>
<td>94.51</td>
<td>95.67</td>
</tr>
<tr>
<td>Causal-based multi-linear</td>
<td>&lt;5 (%)</td>
<td>94.51</td>
<td>52.74</td>
<td>87.20</td>
</tr>
<tr>
<td>Causal-based XGBoost</td>
<td>&lt;5 (%)</td>
<td>80.27</td>
<td>93.84</td>
<td>99.04</td>
</tr>
<tr>
<td></td>
<td>&lt;5 (%)</td>
<td>57.56</td>
<td>49.23</td>
<td>99.04</td>
</tr>
<tr>
<td></td>
<td>&lt;5 (%)</td>
<td>85.05</td>
<td>96.92</td>
<td>99.23</td>
</tr>
</tbody>
</table>

Note: BHS standard requires minimum cumulative frequency (% of error):
- Grade A: 60% (<5 mmHg) 85% (<10 mmHg) 95% (<15 mmHg)
- Grade B: 50% (<5 mmHg) 75% (<10 mmHg) 90% (<15 mmHg)
- Grade C: 40% (<5 mmHg) 65% (<10 mmHg) 85% (<15 mmHg)

4.1. Causal inference

Considering individual physiological difference, the proposed strategy of causal inference that the minority obeys the majority helps us get one general causal graph. The causal graph is essentially a statistical result of conditional independence test, so there will be different statistical result for different individuals evidently. In other words, the general causal graph is the result of a majority vote, which may be imprecise for the minority. This phenomenon is common in the field of cuffless BP estimation due to the fact that human body is an extremely specific and complex individual. For example, PTT and SBP are negatively correlated for most subjects, but they are not correlated or even positively correlated for a few subjects [20]. Nevertheless, this does not prevent PTT from being widely used to estimate cuffless BP.

In this study, SBP and DBP were considered separately for causal inference, which were not used together with wearable features to obtain one causal graph. Otherwise, the connected branch containing SBP will not include other wearable features, except DBP, because the causal interdependence between SBP and DBP is particularly high. As the FCI algorithm iterates for conditional independence test, the test of SBP ⊥ wearable features | DBP is statistically significant so that SBP will not connect with any features besides DBP. This study attempts to identify the key wearable indicators causing BP changes, so that causal graph containing merely two nodes of SBP and DBP is not a result expected.

In the causal graph, PTT(R-dPPG_peek) is the descendant of SBP and DBP, while PTT(R-PGG_peek) has no direct link with the BP component. This is consistent with most of previous studies that use PTT(R-dPPG_peek) to estimate cuffless continuous BP rather than PTT(R-PGG_peek). Notably, we have not identified other indicator such as photoplethysmogram intensity ratio (PIR) that we reported in our previous study [21] in the causal graph of BP. The main reason is that the PPG signal in this dataset [7] contains only alternative component. This makes it not possible to calculate PIR correctly. As shown in Fig. 2, a set of equivalent Markov class are obtained after causal inference, where the directions of some edges in the causal graph are not determined and the direct cause of BP change is not discovered. Currently the direction of the edge of the causal graphs can only be oriented by the collider structure’s recognition and related rules suggested by Zhang [13], so that indeterminate orientation of some edges is due to the theory flaw of constraint-based algorithm.

To validate the efficiency of the BP causal indicators identified from the causal graphs, the power spectrum analysis is used to evaluate the capability of features to track BP changes. The result of power spectrum analysis shows that the BP component and the feature directly linked to it in the causal graph matched well in the frequency domain.
Fig. 5. Correlation, Bland–Altman plots of SBP (a), (c) and DBP (b), (d) of causal-based XGBoost regression model.

Fig. 6. Estimated beat-to-beat SBP (a) and DBP (b) of causal-based XGBoost regression model with corresponding reference Finapres BP.

4.2. Regression of cuffless BP estimation

How to build the causal-based regression model with causal graph is another piece of the puzzle this work tackled. The identification of Granger causality is done by several regression equations and corresponding statistical tests relying on time-lagged links, so our work made good use of this core idea. For Granger causality, causal relation is unknown initially, which is deduced by statistical test on the error of two regression equations based on time-lag. Therefore, reversing the process, from result of causal inference to deducing statistically
significant time-lag for BP regression, is enough to establish the causal-based BP regression model. It is time-lagged links that plays a key role in connecting causality and regression. After detecting the time-lagged causal links between BP components and features in the causal graph, building regression models of cuffless BP estimation becomes natural through several machine learning methods.

PTT-based regression model was chosen in this study as the contrast method. PTT(R-dPPG\textsubscript{peak}) has been extensively studied for continuous cuffless BP estimation for its physiological interpretability. It is obvious that the inferred time-lagged causal links with BP components could explain the dynamic change of BP better, so causal-based regression model achieved more excellent prediction results in different evaluation standards. From the perspective of causal inference, this work made a good attempt to estimate cuffless BP instead of PTT.

4.3. Limitations

There are several limitations about this study. First, we only analyzed the power spectral density of AA(PPG\textsubscript{valley},sdPPG\textsubscript{d}) and AA(PPG\textsubscript{valley},sdPPG\textsubscript{b}) with corresponding BP components, but the work is lack to explain how they cause BP change from the view of physiological mechanism. Second, though time-lagged causal links helped us build the causal-based model logically, topological information in causal graphs was not well utilized. Finally, our method causal inference in cuffless BP estimation only experimented on seated position, where other maneuvers of ambulatory BP estimation were not considered, such as deep breathing, supine and active standing.

5. Conclusion and future work

We explored the feasibility of causal inference for cuffless BP estimation in this study. With identified features that were causally related with BP, we detected time-lagged causal links between the features and BP, and further developed regression model for BP estimation. We found new features that can better track BP changes than PTT in frequency domain, and the estimation model performs well for BP estimation. To the best of our knowledge, this study is the first attempt considering causal inference for cuffless BP estimation. Future causal inference study of cuffless BP estimation should provide more new perspectives to understand the mechanisms underlying BP changes, and contribute to achieving a better performance for cuffless BP estimation. In future work, the knowledge of physiological mechanisms will take causal-based cuffless BP estimation further persuasively. In addition, making causal inference on different states of subjects other than seated position may give us new inspiration for cuffless BP estimation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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