Intra-Subject Blood Pressure Tracking Using an Innovative Cuffless Laser-Based Technology

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Key Takeaways

- Intra-subject tracking of blood pressure is critical, and the existing standard reporting metrics are insufficient
- Protocols to assess cuffless device performance must include significant variations in each subject's blood pressure
- Intra-subject best-fit regression slope is a critical indicator of performance to demonstrate clinical utility and differentiate results from the null hypothesis (repeating calibration value) or chance
- Regression slope is affected by reference error, which highlights the importance of minimizing reference error to the greatest extent possible and adjusting expectations accordingly
- Rockley's laser-based signal captures intra-subject blood pressure tracking using the pulse waveform alone and does not rely on subject demographics as demonstrated in hold-out subjects

The Importance of Blood Pressure and Measuring its Change

Blood pressure is an important indicator of heart health as evidenced by measurement of this vital sign at each clinical visit. Chronic high blood pressure (hypertension) is the most significant risk factor for the development of heart disease, and heart disease accounts for roughly 20% of deaths in the United States.[1] Hypertension is prevalent in 46% of adults in the United States.[2] The most recent guidelines for classification of hypertension status published by the American Heart Association are shown in Table 1.

Table 1. Hypertension status guidelines from the American Heart Association.

Blood Pressure Category	Systolic (mmHg)		Diastolic (mmHg)
Normal	Less than 120	and	Less than 80
Elevated	120-129	and	Less than 80
High Blood Pressure (Hypertension Stage 1)	130-139	or	80-89
High Blood Pressure (Hypertension Stage 2)	140 or higher	or	90 or higher
Hypertensive Crisis (consult your clinician immediately)	Higher than 180	and/or	Higher than 120

Blood pressure is a relatively dynamic vital physiological indicator, where changes in pressure respond acutely or chronically to a variety of physical and psychological stimuli, lifestyle choices, illness and disease, as well as congenital or hereditary risk factors. Annual blood pressure readings at a regular

checkup are limited to providing a snapshot of an individual's cardiovascular health. Not only are measurements typically taken infrequently on an annual basis, but patients may experience a common phenomenon known as "white coat syndrome," defined as an acute increase in blood pressure due to anxiety brought on in a clinical setting. This momentary increase in blood pressure may falsely inflate a true reading and is acknowledged by current practice guidelines.[2] The opposite effect, where clinical readings are normal and day-to-day readings are high, is known as "masked hypertension."

A variety of other scenarios may also cause both acute and chronic deviations in blood pressure from an individual's baseline, such as a postural change (eliciting orthostatic hypotension), periods of acute or chronic stress, diet, and physical activity. (Table 2) Hypohydration also poses an impact on blood pressure stability due to changes in plasma volume, sodium concentration, sympathetic outflow, and vascular function. [3]

Regular physical activity is inarguably associated with improvements in cardiovascular health, decreasing the risk and age of onset of cardiovascular disease. Acute bouts of exercise and chronic adaptations to training elicit a variety of hemodynamic, vascular, and myocardial responses, all of which impact blood pressure in the short and long-term. Systolic blood pressure (SBP) is mediated by changes in cardiac output.[4] Further, a correlation exists between changes in HR and systolic pressure during both static and dynamic exercise; the product of these is known as the rate-pressure product (RPP), which reflects a person's myocardial oxygen consumption. Diastolic blood pressure (DBP), on the other hand, remains relatively unchanged during exercise, as the effects of systemic vasoconstriction and local vasodilation around working muscle essentially cancel each other out.

In addition, the blood pressure response to acute bouts of resistance exercise is markedly higher and more profound compared to aerobic activity.[4] This is due mainly to the differences in cardiac output and vascular resistance, the latter greatly having an impact on mean arterial pressure (MAP). The higher the relative effort, the larger the change in blood pressure from baseline. In fact, increases in blood pressure during resistance exercise can exceed 300/200 mmHg.[4,5,6] Upon ceasing a bout of exercise, blood pressure decreases to baseline levels relatively quickly, and typically dips lower for a period of time (an effect known as postexercise hypotension). With both resistance and aerobic training, small but meaningful changes in baseline blood pressure can manifest.

Table 2. Typical blood pressure ranges and fluctuations based on scenario [4-11]

Indication	**Baseline Range (SBP/DBP mmHg)** ***and/or***	**Deviation from Baseline (mmHg)**
Healthy Adult	90-<120/60-<80	
Acute moderate intensity aerobic exercise (60% VO_2max)		Increase 20-25 SBP correlated with HR Negligible decrease in DBP
Chronic aerobic training		Decrease 4.4 SBP Decrease 6.6 DBP
Acute strength training (95% 1RM, double-leg press)	>300/240	
Valsalva maneuver	>320/250	
Chronic resistance training		Decrease 3-4 SBP and DBP

Indication	Baseline Range (SBP/DBP mmHg) *and/or*	Deviation from Baseline (mmHg)
Postexercise hypotension		Decrease 8 SBP and 9 DBP
Diurnal fluctuation (overnight ABPM)	100-<120/65-<80	Decrease 0-≤19 SBP Decrease 0-≤14 DBP
Diurnal fluctuation (24 hr ABPM)	115-120/75-<80	Decrease 5 SBP and DBP
Mild dehydration (≥2% fluid loss)		Systolic drop upon standing >20 SBP
Episodic Hypertension **White Coat Syndrome**		Increase 10-30 SBP Increase 5 DBP
Hypertensive Adult **Postexercise hypotension**		Decrease 10 SBP and 7 DBP
Meditation (transcendantal)		Decrease 10-13 SBP Decrease 6-8 DBP
Progressive muscle relaxation		Decrease 4.7 SBP and 3.3 DBP
Hypertensive Crisis (malignant hypertension)	>180 and/or >120	
Hypotension	<90 or <60	
Orthostatic / postural hypotension		Decrease >20 SBP or >10 DBP within 1 minute from laying or sitting to standing is abnormal

Current methods of measuring blood pressure during the variety of scenarios stated above are lacking, and it is also difficult to administer a reliable measurement that can reflect trending changes that are important in gathering an individualized snapshot of someone's cardiovascular health and the related responses to medical treatment and lifestyle choices. Daily blood pressure readings using an at-home monitor provide a more detailed picture of overall cardiovascular health and alleviate limitations associated with clinical visits such as white coat syndrome.

Unless continuous or specifically timed measurements are taken, they do not capture the natural diurnal and prandial swings in blood pressure that provide essential information about cardiovascular risk.

Notably, measuring ambulatory and nighttime changes in blood pressure is superior to clinical measurements of blood pressure for predicting cardiovascular mortality.[12] Unfortunately, nighttime acquisition of blood pressure utilizing cuff-based techniques disrupts sleep, and automated cuffs may leave bruising on the arm. Subject discomfort often reduces compliance. In addition, accurate representation of the true delta between waking and sleeping periods is heavily dependent on the measurement technique itself, as well as a person's quality and length of sleep.

While there are many cuffless devices on the market that purport to measure blood pressure at the wrist, few garner both consumer and FDA confidence due to inherent performance inaccuracy and/or usability issues. FDA regulates devices that provide noninvasive blood pressure readings as Class II medical devices (product code DXN) and the vast majority of available devices are not cleared by FDA.

Assessing device accuracy: standards and metrics

The required accuracy of noninvasive blood pressure devices is described in ISO 81060-2. However, ISO 81060-2 was written specifically for cuff-based oscillometric blood pressure devices (typical automated cuffs). Strict adherence to this standard may be inappropriate for devices that rely on a calibration (or initialization) blood pressure measurement. An initialization measurement is needed for techniques that do not directly measure pressure but instead measure changes in a signal associated with pressure. Currently, most optical, RF, electrical, and acoustic techniques fall into this category.

ISO 81060-2 is inappropriate for indirect measurement techniques because it requires an individual subject to only be measured at a single blood pressure plateau. A plateau is a stable blood pressure state that varies less than 12 mmHg systolic and 8 mmHg diastolic over the time needed for multiple cuff inflations (e.g., the reference and device under test). Therefore, it is difficult to assess whether the device adequately tracks intra-subject changes in blood pressure. This evidence is essential to prove utility for a cuffless measurement device.

Meeting the ISO-2 standard does not indicate ability to accurately track a person's blood pressure

To illustrate the problem assessing intra-subject tracking, consider two of the primary accuracy metrics specified in ISO 81060-2:

- Mean difference (MD) or bias, defined as the average difference between the reference pressure and the pressure reported by the device under test.
- Standard deviation of the differences (SDD), the standard deviation of the differences between reference and test pressures.

ISO 81060-2 specifies that MD should be within ±5 mmHg of 0, and that SDD should be <8 mmHg.

As a thought experiment, suppose we know the average blood pressure of a person, and we supply them with a cuffless device that always reports this average blood pressure. If we measured the error between this device and the true blood pressure, the mean of those errors would be zero, and the standard deviation would depend on how much the person's blood pressure fluctuates. This relationship is shown in Table 3, which is generated by assuming that the true blood pressure fluctuates uniformly about the indicated range in Column 1. The standard deviation of the errors from the device that predicts a constant number is just the standard deviation of the uniform distribution, $\sqrt{range^2/12}$, as calculated in Column 2. If a person's overall change in blood pressure is under 30 mmHg, the device will technically meet the ISO 81060-2 accuracy standard.

Table 3. Standard deviation of errors if blood pressure varies uniformly over the given range and we predict a constant average value. For a dynamic range less than 30 mmHg, the ISO 81060-2 accuracy requirement is met.

BP Dynamic Range [mmHg]	Standard Deviation of Constant Predictor
20	**5.77**
25	**7.22**
30	**8.66**
35	10.10
40	11.55

Given that many people experience daily deviations less than 30 mmHg, a device that delivers readings on or about a constant value could meet the standard without providing actionable data.

Within the US, FDA has adopted another consensus standard, IEEE 1708, for cuffless blood pressure devices. Notably, IEEE 1708 calls for measurements on subjects with blood pressure changes from the initial calibration point as well as measurements at times after calibration. However, there are some outstanding issues regarding the exact amount of required blood pressure change, induced versus natural changes, and how often the device should be challenged between calibration points. Therefore, engagement with FDA in Q-subs will be necessary to ensure a proposed clinical validation protocol would be acceptable.

IEEE 1708 calls for an additional metric, mean absolute difference (magnitude) (MAD) as opposed to the mean difference in ISO 81060-2. The IEEE standard also attempts to address the importance of changes in blood pressure by requiring separate accuracy reporting for different levels of change. Specifically, for every 15 mmHg of change, a separate set of MAD, MD, and SDD results should be reported. While an improvement, this granulation falls short of demonstrating intra-subject tracking. Notably, the requested scatter plots are still at population level, without subject identification. Data presented in this way can be misleading, as discussed in later sections.

Recognized need for intra-subject tracking

Multiple published articles have called for transparency in presenting blood pressure results and demonstration of intra-subject tracking. Two recent review articles are quoted as follows:

"While these methods have been extensively studied and cuff-calibrated devices are now on the market, there is no compelling proof in the public domain indicating that they can accurately track intraindividual BP changes."[13]

"Furthermore, the results of cuff-calibrated devices are sometimes pooled over the individual subjects, which typically yields remarkable correlations. However, because of the calibration, these results merely reflect the interindividual differences in the reference BP levels. As a result, the accuracy of these devices in tracking short-term or long-term BP changes within an individual often remains unclear."[14]

Rockley's Approach

For years, the primary focus of optical, cuffless blood pressure measurements has been LED-based photoplethysmography (PPG) due to its relatively inexpensive components and existing uses for monitoring heart rate and oxygen saturation. Nevertheless, PPG signal quality at the wrist is subject to multiple noise sources such as skin tone, venous pulsations, and vasoconstriction that obscure its blood pressure sensing capabilities.[15] Owing to these challenges, Rockley has opted to further develop a potentially more powerful, laser-based technique for monitoring blood pressure. Rockley's adopted technique could provide a much larger and sharper trace with more visible pulse reflections. At this time, Rockley has completed an initial study using a pre-Alpha device for the purposes of assessing our ability to track intra-subject changes in induced blood pressure. The calibration/ initialization was performed on the same day as the induced changes; we have not yet assessed the duration over which calibration holds. Critically, we took a deep dive into what governs intra-subject

tracking results and calculated a bevy of statistical parameters to better evaluate the findings and ensure they are meaningful.

Study Description

A total of 104 subjects participated in the study, which was reviewed for safety and ethics and approved by the Western Copernicus Group Institutional Review Board (WCGIRB). Data were collected at two sites: the Irvine and Pasadena offices of Rockley Photonics. Eligible subjects for this study were any willing adult participant (age >18) without scarring, tattoos, or other impediments that would attenuate the optical signal in the region of interest. Additional exclusion criteria were sensitive populations (i.e., pregnant women and prisoners) and individuals whose systolic blood pressure exceeded 180 mmHg.

The protocol utilizes isometric exercise as a means of modulating study participants' blood pressures. Exercise is known to increase systolic blood pressure through increased cardiac stroke volume but maintains diastolic blood pressure near resting levels through vasodilation. Therefore, systolic pressures span a larger induced range than diastolic. Figure 1 shows the distribution of the reference blood pressure cuff measurements for each of the subjects analyzed. The plot is organized by increasing baseline systolic pressure, plotted in blue circles. The diastolic pressures for a subject are directly under their corresponding systolic measurements and the baseline diastolic pressures are plotted in orange circles. It is observed that diastolic blood pressure is generally higher for subjects with higher systolic blood pressures, though not a strong correlation.

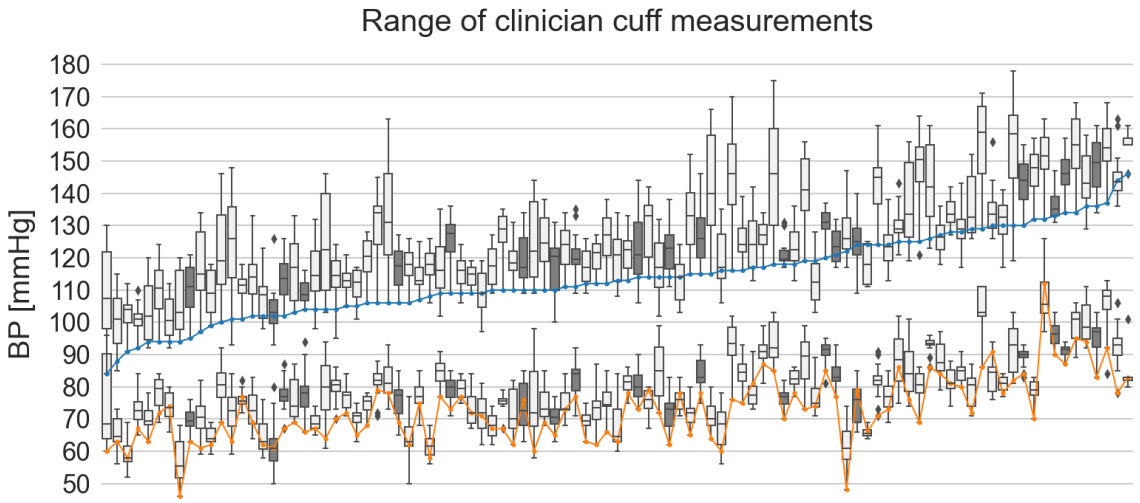

Figure 1. Blood pressure range as measured by the trained observer (auscultatory cuff measurement) for each subject (in a column). Subjects are organized by increasing systolic baseline pressure, in blue points. Diastolic values are under the corresponding systolic values, with baseline reading in orange points. Approximately 16 reference cuff measurements were collected per subject. The boxes show interquartile range (IQR), the midline shows the median, whiskers extend to 2 IQR, and outliers are shown as black dots. The boxes shaded in gray are the randomized hold-out subjects

At the start of the protocol, blood pressure was measured with the subject resting in a seated position, with feet flat on the floor. A second blood pressure measurement was acquired after the subject raised their feet and rested in an elevated position for three minutes. The subject then completed at least

four serial isometric leg press sets with increasing weight. For each set, the given weight was held for five minutes, with two blood pressure measurements acquired during that time, approximately two minutes apart. The subject then released the weight and rested their feet in an elevated position for three minutes, with another blood pressure measurement acquired near the end of that time. To conclude the set, the subject lowered their feet to the floor and rested in a neutral position while the weight was modified. After the sets were completed, the subject rested with their feet flat on the floor for five minutes and repeated the first step, with blood pressure measurements acquired with feet down and then feet up again.

Approximately 16 reference blood pressure measurements were acquired for each subject during the protocol, which spanned about 90 minutes. The reference blood pressure measurements were acquired via manual auscultation with a trained observer. In lieu of a second trained observer, an acoustic transducer recorded the Korotkoff sounds, and a pressure transducer recorded the cuff pressure to a BIOPAC data acquisition system for future playback and additional observer analysis. In addition to Korotkoff sounds and cuff pressure, the BIOPAC system was utilized to collect ECG and respiratory strap readings from each subject at 1000 Hz.

Time Alignment

The Rockley pre-Alpha device collected optical data at 122 Hz. To time-align the BIOPAC system data to the pre-Alpha device data, a microcontroller with a synchronization LED was utilized for triggering and acquisition confirmation. The LED was strobed every 300 optical data points. After time alignment, the strobe signal was deleted from the optical data without impact to signal quality. However, on occasion, the strobe signal would fail to be captured. Of the 104 subjects, 5 had missing strobes that prevented baseline blood pressure time alignment and required removal from further analysis. In future studies, Rockley will implement more robust time synchronization techniques with reference measurements.

Subject Demographics

Demographics for the remaining 99 study participants are shown in Table 4.

Table 4. Analyzed subject demographics by category. (a) kg/m2. (b) Fitzpatrick scale, calculated from Mexameter-reported skin melanin content.

Total	**Sex**		**Age**		**BMI[a]**		**Skin Color[b]**	
99	Male	44	**18 – 35**	36	**≤ 18.5**	5	**I**	16
	Female	55	**36 – 50**	26	**18.5 – 24.9**	45	**II**	17
			50 +	37	**25.0 – 29.9**	30	**III**	36
					> 30.0	19	**IV**	14
							V	6
							VI	10

Split into Training, Validation, and Test Sets

The 99 subjects with usable reference data were split into five bins based on their baseline systolic blood pressure measurements as shown in Table 5. The bin width was 5 mmHg up to a baseline blood pressure of 115 where it increased to 10 mmHg to capture a roughly equal number of subjects in each bin.

Table 5. Histogram data of number of subjects per specified systolic blood pressure (SBP) range. Four hold-out subjects were randomly selected from each bin.

SBP Bin Range	Number of Subjects
BP ≤ 105	25
105 < BP ≤ 110	19
110 < BP ≤ 115	15
115 < BP ≤ 125	20
125 < BP	20

Four subjects were selected at random from each bin to constitute the hold-out (test) set of 20 subjects, with 79 remaining for training and validation.

The classification for subjects in the training/validation and test sets by hypertension status are shown in Figure 2 and Table 6.

Table 6. Number of subjects total and in hold-out set for each hypertension status listed in column 1.

Hypertension Status	Total	In Test Set (Hold-out)
Normal	66	13
Elevated	9	2
Stage 1	16	4
Stage 2	8	1

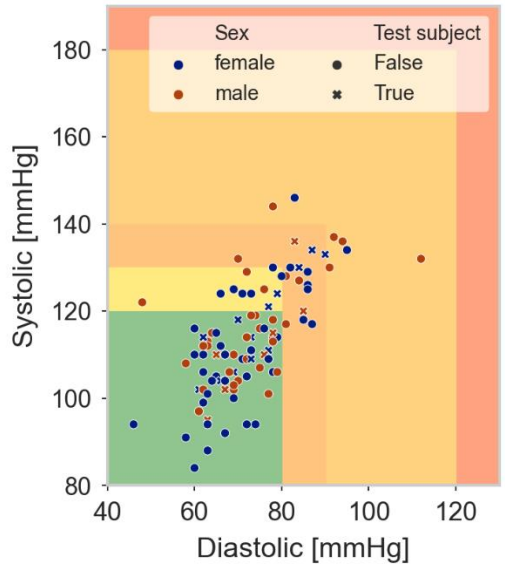

Figure 2. Distribution of subject blood pressures with colored regions indicating hypertension stages. Green region is normal, yellow is elevated, orange is Stage 1 hypertension, and gold is Stage 2 hypertension. Subjects in the red region were ineligible for the study. A marker (dot or cross) represents a subject, with a cross indicating a hold-out subject. A blue marker is a female subject, and a red marker is a male subject.

Use of population demographics in a model can be misleading

Demographics including a person's age, sex, and BMI are generally correlated with average blood pressure. This leads to broad assertions such as a male with high BMI in his sixties is likely to have a higher blood pressure than a female with low BMI in her twenties. Population-based scatter plots can seem to provide reasonable correlation with blood pressure using this data alone. However, there is little clinical utility in such blanket assumptions. Moreover, other physiological signals, such as heart rate, may be strongly correlated with blood pressure in some cases like aerobic exercise, but not in others. Devices based on sophisticated acquisition techniques run the risk of unwittingly fitting to heart or respiration rate – a spurious correlation that will not reliably track with blood pressure across different activities (such as resistance training versus interval training).

To illustrate these issues, we constructed an L2-regularized linear regression model that includes the subject's sex, age, height, weight, BMI, and heart rate (derived from Rockley's signal in the -30 to -5 second window before the reference cuff was inflated) and uses a calibration blood pressure, and fit it to the reference blood pressure. Although isometric exercise protocols like ours avoid large changes in heart rate, long periods of exercise may still increase an individual's heart rate.

Figure 3(left) shows the predictions of this model on our 79-subject training data set fit with 5-fold cross validation. The pooled data shows strong correlation with blood pressure and with mean error close to zero and a standard deviation of error approaching the required limit, the results appear quite promising. However, as we stress above, and as discussed by Mukkamala et al.[14], pooled statistics conceal important intra-subject behavior. Figure 3(middle) shows identical data to Figure 3(left), but now color-coded according to subject, and with best-fit regression lines shown for every subject, making it clear that however accurate this demographic model might become at the population level, it could not be suitable for cuffless blood pressure monitoring as it has virtually no tracking with intra-subject blood pressure changes.

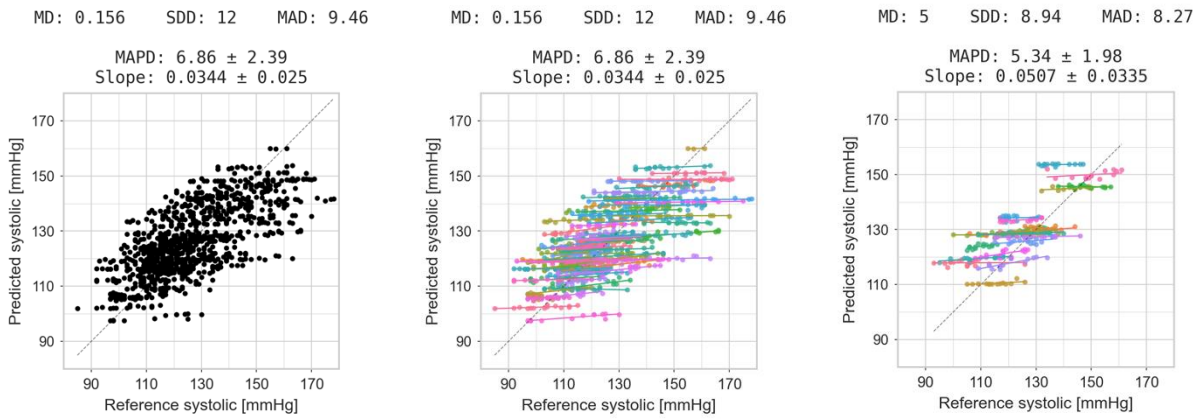

Figure 3. Blood pressure predictions utilizing subject demographics and heart rate, along with a calibration value. (left) Cross-validated results on training data; (middle) Same as (left), but color-coded per subject and with intra-subject best-fit regression lines; (right) Results on 20 hold-out test subjects.

These considerations motivate us to define and report additional cuffless assessment metrics, beyond what is described in the ISO and IEEE standards. Mukkamala, et al.[14] suggest making a per-subject correction for the calibration pressure, and then using pooled population statistics (Pearson's *r* given as an example). We note that such a per-subject correction (shifting every group of colored points

independently but along the diagonal) will not actually have any effect on population metrics that are based on error (reference – prediction); instead, we suggest reporting both pooled metrics and the distribution of per-subject metrics. The metrics we present at the top of each scatter plot are described in Table 7.

Table 7. Metrics reported above each scatter plot and their corresponding definitions. RP (reference pressure) is the clinician-determined pressure from the reference cuff; PP (predicted pressure) is the pressure predicted from Rockley's instrument and calibrated algorithm. The total number of cuff measurements is K; the number of cuff measurements taken from subject s is k_s. We write RP_{s, i} to indicate the i-th cuff measurement from subject s. The per-subject slope is simply the slope of the best fit linear regression line of the predicted pressures (y-axis) against the reference pressures (x-axis), where we perform a separate regression for each subject. The formula for the slope for a subject is the sample correlation coefficient of the predicted vs reference pressures, scaled by the ratio of the uncorrected sample standard deviation of the predicted pressures over the reference pressures.

	Abbreviation	Definition	Mathematical Definition
Population statistics, presented as single value	MD	population mean difference	$\frac{1}{K} \times \sum_{i=1}^{K} (\mathrm{RP}_i - \mathrm{PP}_i)$
	SDD	population standard deviation of the differences	$\sqrt{\frac{1}{K-1} \times \sum_{i=1}^{K} (\mathrm{PP} - \mathrm{MD})}$
	MAD	population mean absolute difference	$\frac{1}{K} \times \sum_{i=1}^{K} \lvert \mathrm{RP}_i - \mathrm{PP}_i \rvert$
Per-subject statistics, presented as median value ± median absolute deviation	MAPD	subject mean absolute percent difference	$\mathrm{MAPD}_s = \frac{100}{k_s} \times \sum_{i=1}^{k_s} \left\lvert \frac{\mathrm{RP}_{s,i} - \mathrm{PP}_{s,i}}{\mathrm{RP}_{s,i}} \right\rvert$
	Slope	slope of the best-fit regression line for intra-subject data	$\mathrm{Corr}[\mathrm{RP}_s, \mathrm{PP}_s] \times \frac{\mathrm{SD}[\mathrm{PP}_s]}{\mathrm{SD}[\mathrm{RP}_s]}$

Data preprocessing

We examined the ability of Rockley's laser signal to capture information about blood pressure by studying two families of regression model of increasing complexity. The first is based on simple linear regression and the second is an advanced model based on deep learning. Although the architectures and training methodologies for the linear and advanced models are quite different, we pre-process our laser-based signal in a similar way for both. Common pre-processing steps include smoothing with bandpass filters to focus on physiologically relevant frequency bands, pulse segmentation and alignment, and per-pulse signal quality filtering. For all models, we use data recorded from -30 s to -5 s before the beginning of a cuff measurement to derive model inputs. In addition, the basic and advanced models both use a per-subject blood pressure calibration measurement, which is taken from the subject while sitting normally before the exercise protocol began. In all cases, model predictions are reported only for non-calibration data.

To minimize reference error during model development, the blood pressure value recorded by the trained observer was compared to an automated measurement derived from the cuff pressure. If the values differed by more than 15 mmHg, that blood pressure reading was considered suspect, and its associated data removed from further analysis. In addition, a signal quality threshold was used to analyze Rockley's signal quality for further processing. Figure 4 outlines the number of subjects and blood pressure recordings used for each portion of data analysis.

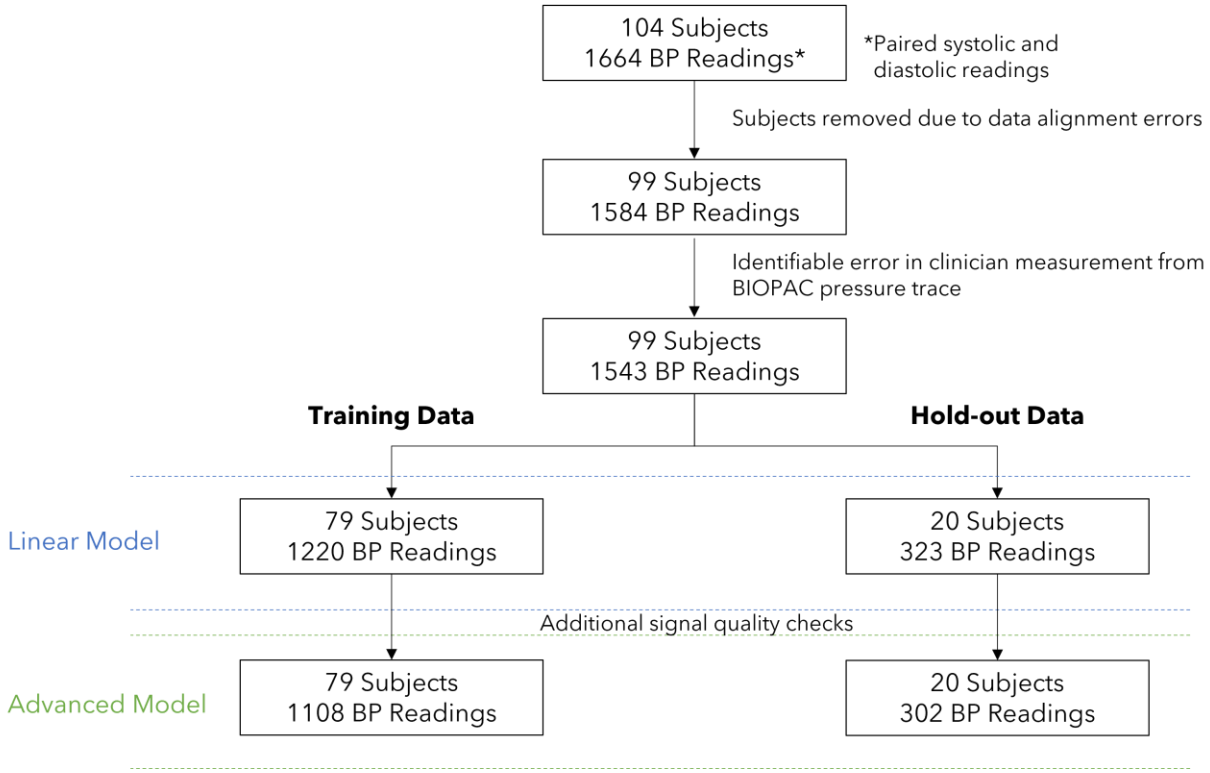

Figure 4. 104 subjects participated in the study with a total of 1664 paired systolic and diastolic blood pressure (BP) readings. 5 subjects and their corresponding BP readings were removed from the data analysis due to data alignment errors. 41 BP readings were removed due to identifiable errors from the BIOPAC recordings. The remaining data were separated into training data and hold-out data. For the advanced model, additional signal quality checks reduced the number of BP readings in each set.

Blood Pressure Results

Basic model with laser waveforms

To examine the inherent blood-pressure-related information within the Rockley laser signal waveform, we built a relatively simple linear model using L2-regularized linear regression (ridge regression). The model was trained on the data from 79 subjects, with model inputs including calibration blood pressure measurements, pulse shape parameters, and the individual pulse waveforms from the -30 to -5 second window before the reference cuff was inflated. Heart rate and demographic information was not utilized in any way. The predicted systolic blood pressures for the 20 hold-out subjects are plotted in Figure 5.

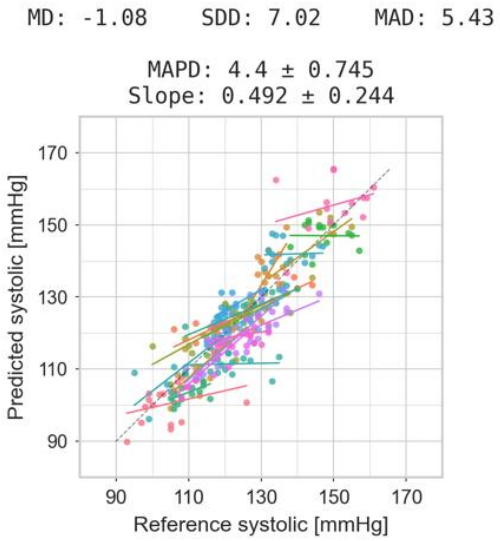

Figure 5. Basic linear model systolic predictions on 20 hold-out subjects with individual subject colors and best-fit lines. Only the Rockley laser signal information and a single calibration measurement was utilized. No heart rate or demographic information is utilized.

It is important to note that Figure 5 looks very different from Figure 3(right). Critically, the majority of subjects show strong intra-subject tracking. The intra-subject slope is 0.49 ± 0.24, with 95% confidence interval of the median between 0.31 and 0.65.

Advanced model with laser waveforms

After obtaining confidence from the linear model that meaningful signal is encoded in the Rockley laser signal waveform, we investigated the ability of more advanced models based on convolutional neural networks (CNN) to improve the predictions. Figure 7 (left) shows the results of this advanced model when it is provided with only the laser signal waveform and reference blood pressure measurement. As with the linear model, no subject demographic information is utilized. Interestingly, at first glance the results seem inferior to the linear model. Upon closer inspection, we see a trade in an increase in MAPD (4.40 to 6.22 mmHg) for an increase in per-subject slope (0.492 to 0.677). In other words, the model's ability to track intra-subject changes improves on average, but at a cost of increased per-subject variance.

Throughout the analyses in this paper, we have specifically avoided the use of subject demographics as inputs to the model because doing so does not on its own contribute to intra-subject tracking and could be misleading. However, there is a more nuanced approach that can be taken here. It is strongly understood that aging is associated with increased arterial stiffness/decreased vascular compliance, physiological differences exist between sexes, and BMI strongly correlates with the health status of the cardiovascular system. Indeed, the ISO 81060-2 standard calls out validation requirements on different subsets of individuals, such as age under 50 and over 50 treated as separate populations. [Note that we did not separate subjects by age due to the limited sample pool for this initial study.]

Based on this observation, we extended our advanced model by adding subject-specific fine tuning with carefully selected data. Before predicting on a hold-out subject, the model is fine-tuned using an additional segment of data from the subject along with its associated reference blood pressure value and data from a subset (n=30) of subjects from the training data who are demographically similar to the subject being predicted. The model still does not receive demographic information as an input,

instead it sees only demographically similar waveform data during the final stage of training. This type of approach, which is less extreme than building separate models for different demographic subsets, allows a single model to share the majority of its features learned across a diverse subject population, while helping to up-weight those features that are more useful in a particular subject's demographic region. Because the fine-tuning step requires a second reference blood pressure measurement, we opted to select the measurement closest in time to the first reading (legs up, no weight) as it would be more practical in a real use case for a person to take two calibration measurements back-to-back.

The results of this technique are shown in Figure 7(right). Again, comparing the basic linear model to the CNN with personalization, we now see the MAPD is comparable (4.40 to 4.92) while retaining much of the improved per-subject tracking of the initial CNN model (0.492 to 0.586).

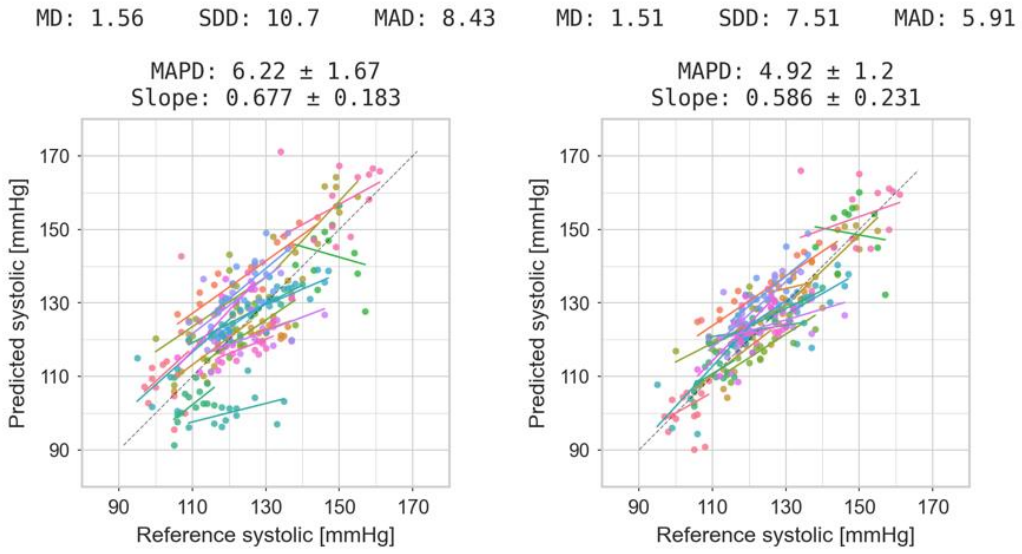

Figure 6. Convolutional neural network model showing predicted systolic blood pressure on the 20 hold-out subjects. (left) Model trained without demographic inputs, and without personalized fine-tuning, (right) Model trained without demographic inputs, and with demographically based personalization.

Consolidated results for each of the models presented are listed in Table 8, including cross-validated training results and diastolic pressure results (scatter plots not shown for brevity).

Table 8. Consolidated accuracy metric for the models discussed here. The metrics in Column 1 are defined in Table 7. CV is the cross-validated training data and Test is the complete model applied to the set of 20 hold-out subjects.

			Demographics + HR (Plotted in Figure 3)	**Linear** (Test plotted in Figure 5)	**Advanced** (Test plotted in Figure 6a)	**Advanced + Personalization** (Test plotted in Figure 6b)
Metric	**Marker**	**Dataset**				
MD	Diastolic	CV	-0.0254	-1.52	0.17	-0.634
		Test	0.642	-1.92	-3.56	-0.0789
	Systolic	CV	0.156	-2.47	-1.88	-3.15
		Test	5	-1.08	1.56	1.51

			Demographics + HR (Plotted in Figure 3)	Linear (Test plotted in Figure 5)	Advanced (Test plotted in Figure 6a)	Advanced + Personalization (Test plotted in Figure 6b)
SDD	Diastolic	CV	7.42	8.03	8.22	7.44
		Test	6.24	6.76	6.97	6.27
	Systolic	CV	12	11.6	12.3	9.47
		Test	8.94	7.02	10.7	7.51
MAD	Diastolic	CV	5.8	6.34	6.6	5.81
		Test	4.83	5.31	6.22	4.88
	Systolic	CV	9.46	9.01	9.58	7.71
		Test	8.27	5.43	8.43	5.91
MAPD **(per subject, median)**	Diastolic	CV	6.53	6.66	7.77	6.39
		Test	5.1	5.69	6.59	5.83
	Systolic	CV	6.86	5.54	6.42	5.78
		Test	5.34	4.4	6.22	4.92
Slope **(per subject, median)**	Diastolic	CV	0.0418	0.28	0.385	0.391
		Test	0.0369	0.263	0.402	0.33
	Systolic	CV	0.0344	0.444	0.527	0.513
		Test	0.0507	0.492	0.677	0.586

Challenges of assessing intra-subject tracking: reference error and trend lines

To assess intra-subject tracking, we compute the best-fit regression line for a subject and check that the slope is close to 1. This is similar to the SpO_2 FDA guidance and consensus standard. During our analysis, we noted the potential ability of Rockley's innovative breakthrough technology to provide a signal that consistently and significantly tracks with intra-subject blood pressure changes.
While the intra-subject slope is significant, the median is not centered around 1. We believe this is at least partially explained by regression dilution: a feature of linear regression that causes the slope of the best-fit line to move towards 0 when there is error in the x-axis variable, even when the true relationship is perfectly linear and the errors are independent. Figure 7 illustrates this effect with simulated data. As in our other scatter plot figures, the reference blood pressure values are on the x-axis. In this case, the y-axis blood pressure values are perfect, true values with no error. The black dots show the case in which the reference (x-axis) also has no error. The best-fit regression line (dashed) lies exactly on the diagonal. The blue dots have introduced error in the reference values by adding normally distributed random numbers with a standard deviation of 5 mmHg to the true values, randomly shifting each point's x-coordinate. This causes the best fit regression line's slope to decrease (dashed blue).

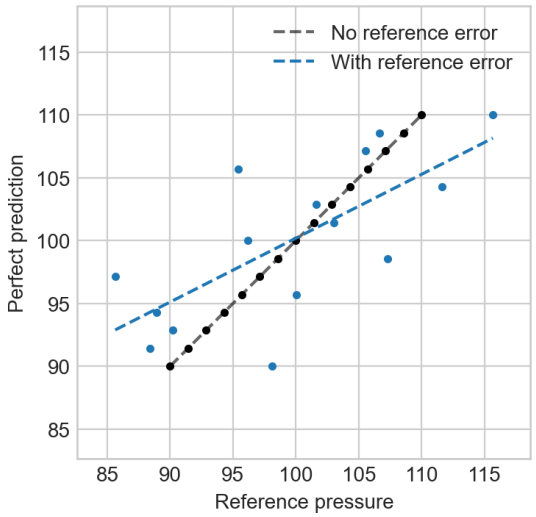

Figure 7. Scatter plot illustrating regression dilution. A perfect prediction with no error is plotted versus reference readings with no error (black dots, black dashed regression line) and with 5 mmHg random error (blue dots, blue dashed regression line). When error is introduced to the reference readings, the slope of the regression line is reduced.

Reference error is particularly important for cuffless blood pressure devices because consensus standards require the use of cuff-based sphygmomanometers as reference devices for intermittent measurements, which are known to have large error compared to arterial line pressure sensors. Published comparisons provide varying measurements of the standard deviation of cuff – arterial line errors in various patient populations, but all report the SD is *at least* 5 mmHg, and normally higher.[16,17,18,19] We illustrate the effect of reference error on the average trend line slope in Figure 8, which shows this effect at work on a simulated data set with 100 subjects, each with 15 blood pressure readings. As we add increasing amounts of noise to the reference values, the average slope decreases. The shaded region indicates the size of noise reported in the real-world studies, mentioned above, that compare cuff-based blood pressure measurements with arterial line pressure sensors. We note that, if we assume that the error in Rockley's cuff-based reference measurements is 5 mmHg, the average slope in this simulated population would be about 0.6, slightly better than we achieved in our advanced model with personalization.

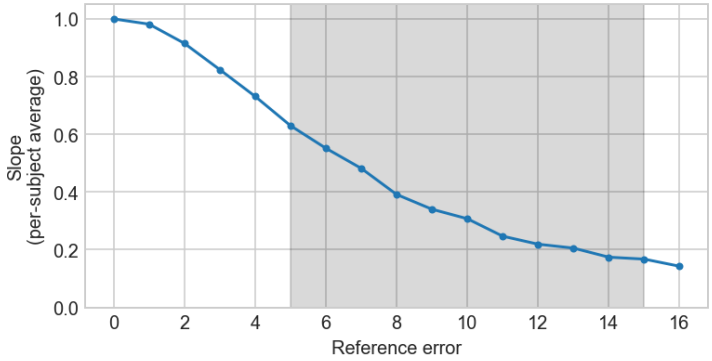

Figure 8. Simulated per-subject average slope as a function of increasing reference error. The simulation is based on 100 subjects, each with 15 blood pressure reference readings. The shaded area indicates the expected reference error from cuff-based measurements as compared to arterial in-line pressure sensors.

In future studies, Rockley will look to reduce reference cuff error. Unfortunately, common approaches to reference error reduction still face inherent limitations. Utilizing two observers for cuff readings reduces error, but it does not eliminate sequential error because, if the device under development is on the same arm as the cuff, there will be a temporal delay between signal acquisition and the occlusive blood pressure reading. On the other hand, paired lateral measurements (e.g., placing the device under development on the opposite arm of the cuff and estimating a constant correction factor) removes the temporal delay but introduces error if the lateral difference fluctuates, which is expected during natural perturbations of blood pressure. These constraints suggest that, while still important, the slope of the best fit regression line for a subject may not tell the whole story regarding blood pressure tracking. Potentially, a combination of metrics (slope + rank correlation) or averaged same-time, same-site blood pressure readings (auscultatory + oscillometric) will enhance future work.

Conclusions

Rockley has successfully demonstrated prediction of hold-out subjects' blood pressures with strong intra-subject tracking following same-day calibration. A fully wireless, wearable Alpha device is in the final stages of assembly and testing. This Alpha wireless device is designed for use in upcoming human studies on over 200 participants later this year. The studies will include isometric and aerobic exercise-based protocols using manual auscultation for reference, as well as an in-line arterial protocol with a catheter-based pressure transducer for reference. Importantly, longitudinal data will also be collected to evaluate natural diurnal and prandial changes in blood pressure and to ascertain the time period for which calibration holds.

We believe that assessing intra-subject tracking is an essential part of evaluating any cuffless blood pressure device. Additional research is required to establish the optimal metrics for this assessment. A simple approach based on trendline slope (used in this paper) is biased by a small number of outlier measurements and subject to the reference errors highlighted above. Other approaches might include rank correlation metrics, although this would highlight directionality rather than accuracy of the trend. A higher standard of accuracy for the reference measurements would also prove beneficial.

Authors and Contribution

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Siddharth Jain – *Linear model*

Mohsen Naji – *Signal quality and parameterization*

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