Assessing the Severity of Dehydration of Children in Low-Resource Settings

- Research Paper -

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Abstract

Introduction: *Diarrhoea is currently the second major cause of child mortality, which mostly affects children in developing countries. Dehydration is the major risk involved with diarrhoea, which is therefore the actual cause of death in most cases. Currently there are no cheap and reliable methods for assessing dehydration, while dehydration assessment is key for determining proper treatment. In this research two digitally measured diagnostic variables will be investigated: skin turgor and capillary refill time.* ***Research Question:*** *Does the severity of dehydration significantly correlated with increased capillary refill time and decreased skin turgor, when these variables are measured objectively using digital methods?* ***Methods:*** *To objectively measure skin turgor and capillary refill time, two experimental devices were used: the Cutometer and a prototype using green-light photoplethysmography (respectively). An experiment was conducted where subject volunteers were dehydrated. The loss of body-mass was used as the gold-standard for measuring dehydration. A regression analysis was conducted to determine the adjusted coefficients of determination ($\bar{R}^2$).* ***Results:*** *$\bar{R}^2$ for most parameters of interest show arbitrary results. One parameter that stood out was R2 of the Cutometer, which represents skin elasticity. This parameter showed relatively high consistency in terms of high $\bar{R}^2$ and trends, although still it seems to be subject to noise.* ***Discussion:*** *Most results showed to be quite unexpected and arbitrary. It is believed that this might be primarily due to some considerable limitations of the experiment and equipment. Most importantly, it is believed that the dehydration achieved with the subjects was not high enough to have effect on the measurements.* ***Conclusions:*** *In general, no significant relations have been detected between the variables of interest and the severity of dehydration. The results should be interpreted with care, due to the major limitations of the experiment and the equipment.* ***Recommendations:*** *Future research should focus on building a set prototypes based on different technological principles and diagnostic variables. Also, using these prototypes, a data-collection study in the field should be conducted in areas where child-dehydration is frequent. Data collected will be much more representative. All collected data should be used for building a regression model for future diagnostic devices.*

1 Introduction

Even though infants consist of about 73% water [1], slight changes in their total body water contents can have severe consequences on their health, and could be fatal if not treated in time. *Dehydration* may occur whenever fluid output from the body exceeds fluid input over a prolonged period of time. The first signs of (mild) dehydration include thirst, sticky oral mucosa, dry skin and decreased urine output. Prolonged (more severe) dehydration could lead to significant weight loss, fever and mental confusion. Decreased plasma volume is another potential consequence, and may lead to inadequate blood volume to maintain circulation, resulting in hypovolemic shock. Especially young children rely on a stable fluid input/output, because of their large total body water content in healthy conditions, and as they depend on relatively more fluid input due to their higher metabolic rates [2].

One major condition that can significantly destabilize the balance of fluid input/output is *severe gastroenteritis*, more commonly known as diarrhoea. Diarrhoea has been identified by WHO as the second biggest cause of child mortality. In 2012 an estimated 622 165 children under the age of five (post-neonatal) died globally because of the consequences of diarrhoea [3]. 80% of all these child deaths occur in Africa and South Asia, with India far on top of the list of countries with most child deaths [2]. It is known that children who die from diarrhoea, actually die from the resulting severe dehydration [4].

The World Health Organisation (WHO) has defined three degrees of dehydration: *no dehydration*, *some dehydration* and *severe dehydration* [5]. The degree of dehydration is a measure of the amount of water lost in terms of mass, relative to total body mass in percentages. See table 1.

The *first priority* for the *Community Health Worker* (CHW) is to manage the potential dehydration, before treating the diarrhoea itself. If a child is suspected by the CHW of suffering from dehydration, proper diagnostic tests should be done to assess the degree of dehydration. Accurately assessing the degree of dehydration is an important step in management of dehydration, since the outcome of the diagnosis be key in determining the most appropriate treatment plan. Patients with *no signs of dehydration* (but who are still at risk) will be educated how to prevent dehydration with a home-therapy plan. Patients with *some dehydration* should be treated with Oral Rehydration Therapy, by drinking an Oral Rehydration Salts (ORS) solution [5]. Whenever the patient is *severely dehydrated*, rapid intravenous rehydration should be the preferred treatment. Providing the right treatment plan that corresponds to the patient's degree of dehydration is considered very important, since choosing the wrong treatment can either lead to over-utilisation of the already scarce treatment resources or harm to the patient.

Due to the importance of accurate dehydration assessment, a few diagnostic scales have been developed: the *WHO scale* [5], *Gorelick scale* [6], and *Clinical Dehydration Scale* [7]. These scales consist of the execution of several quick and manual diagnostic tests that combined would provide a solid assessment for the severity of dehydration. Yet, none of these scales have been proven to be sufficiently accurate [8] [9]. Additional issues are the socio-cultural and individual factors that undermine the credibility of health-workers in resource-limited settings. Although the variety of cultures across Sub-Saharan Africa and South-Asia are impossible to generalize, it has been found that in some areas health-workers have a high authority, whereas in some other areas the assessment of such health-workers is often questioned by the health-receiver (or parent), which leads to over-subscription of unnecessary (or even damaging) treatment resources [10], while the use of ORS is often neglected since it is not seen as a sufficing treatment for dehydration by some parents [11]. Therefore, in order to be able to further decrease the preventable child-deaths due to diarrhoea, *new and more reliable methods for assessing the degree of dehydration have to be developed.*

Two of the manual individual tests that are currently used to quickly assess dehydration are Capillary Refill Time (CRT) and the skin pinch test in order to assess Skin Turgor (ST). Both of these tests have a relatively high diagnostic performance in terms of *sensitivity* (58% for ST and 60% for CRT) and *specificity* (76% for ST and 85% for CRT) [12]. Although these numbers vary somewhat between different studies, there is a general consensus that these diagnostic variables perform best in assessing dehydration in young children.

CRT is assessed by using the index-finger to apply a moderate pressure on the skin of the subject (often the index-finger, or chest). This process blanches that piece of skin, which is actually the process of blood in the dermal capillaries being pushed out. When the pressure is released, the process of the capillaries refilling with blood can be observed by watching the pink colour return to the skin. The longer this process takes, the higher the severity of dehydration. ST is assessed by using the thumb and index-finger to pinch the skin of the subject (often done at the abdomen at infants). When releasing the skin, the longer it takes to recoil, the more skin-turgor is decreased. Decreased skin-turgor is inversely related to increased dehydration.

It is hypothesized that the main causes of inaccuracy of these tests are: a lacking programme for *training* CHW's appropriately for performing and interpreting these tests, *external influences* that cause variability of the outcome of these tests, and *subjectivity* involved with these tests that cause inter-observer variability [8]. In terms of the main external influence that cause variability in the outcome of these tests, for both ST and CRT *temperature* has been defined as the main cause of variability when assessing young children. In CRT it has been found that core-temperature, skin surface temperature and ambient temperature [13] [14] are all of influence on the reading (although these factors could be interdependent), while ST has been determined to be influenced by temperature in general [15].

There have been studies that attempted to prototype technological solutions that measure either ST [16] or CRT [16] [17] based on optical measurements while mitigating these main issues that cause variability in the measurements. Specifically for CRT, one proposed technological principle that really stands out is the use of *photoplethysmography* (PPG) [18] [19] [20] [21] [22] [23] [24] [25], although no results are published that reveal the diagnostic performance of CRT measurements using PPG when assessing dehydration.

This research builds upon the current state of research into measuring ST and CRT using technologically novel tools, which will enable digital anal-

Assessment	Fluid deficit as % of body weight	Fluid deficit in ml/kg body weight
No dehydration	<5%	<50 ml/kg
Some dehydration	5-10%	50-100 ml/kg
Severe dehydration	>10%	>100 ml/kg

Table 1: Degrees of dehydration as formulated by the WHO [5].

ysis of these variables in order to predict the severity of dehydration with a significantly improved diagnostic performance compared to current standard methods. The main additional requirement for such technologies is the potential to eventually produce a diagnostic tool which has a very minimal bill of materials, and enables quick point-of-care diagnostics. This research paper is a compacted report of this research assignment, derived from the more elaborate eponymous thesis report.

2 Research Question

In this research, the aim is to validate whether or not using novel technology enabled ways of assessing ST and CRT could be used to diagnose the severity of dehydration. The idea is that using tools and digital analysis of these diagnostic variables will mitigate the influence from subjectivity and lack of training of the observer, while clever design considerations should mitigate the influence from temperature. The known expected behaviour of ST is to decrease (skin takes longer to recoil) with higher levels of dehydration, while CRT becomes longer with higher levels of dehydration. The central research question for this research is therefore:

"Does the severity of dehydration significantly correlated with increased capillary refill time and decreased skin turgor, when these variables are measured objectively using digital methods?"

3 Methods

In order to validate the use of digitally measured ST and CRT, a lab experiment was conducted. The approach of the experiment was to stimulate loss of fluid through sweating at volunteering subjects, whilst denying access to rehydration for a considerable amount of time. This approach should ensure an accelerated fluid output with zero fluid input, and this will eventually lead to dehydration. The researcher will take measurements of ST and CRT and other external factors of influence over the course of the experiment as the subject loses more and more of its total body water. Once all the the measurements were done, data was processed and statistically analysed using Matlab.

3.1 Variables & equipment

The main variables that were measured at each subject over the course of each run consisted of (excluding any vital signs monitoring):

1. **CRT**, as measured using green-light photoplethysmography (PPG). A prototype was built specifically for this experiment (the PPG-CRT prototype), which will be elaborated further in section 3.3. Measurements will be taken from the following body locations:
   (a) Pulp of the index finger
   (b) Sternum
   (c) Midpoint of the forehead
2. **ST**, as measured using the *Cutometer*. The Cutometer is a experimental device, used often for studying elastic properties of the skin by the cosmetic industry. The Cutometer sensory component consists of a probe which is held against the skin. The probe applies a negative pressure on that section of the skin, pulling the skin up into the hollow air chamber (see figure 1). The negative pressure is than released to relax the skin, and repeats this cycle two more times at every measurement. The displacement of the skin into the probe is measured every 10 milliseconds, with an accuracy of 1 μm. A software package on a PC will transform the displacement data into 19 different meaningful parameters, which all are related to the viscous or elastic response of the skin to the applied force-changes. These parameters will be directly used in the retrospective analysis of the experimental results. For a quantitative explanation of each of the parameters, and a more detailed explanation of the device in general, please be referred to the brochure of the Cutometer [26]. Measurements will be taken from the following body locations:
   (a) first dorsal interosseus (the back of the hand)
   (b) Anterior fore arm

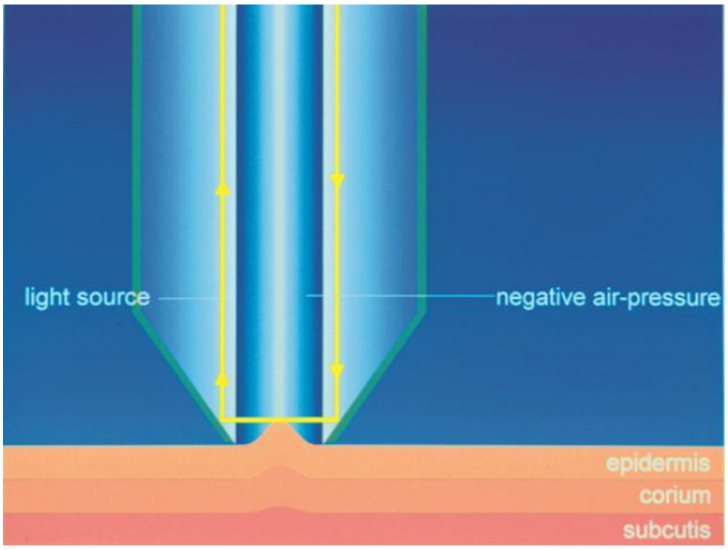


Figure 1: Working principle of the Cutometer. [26]

(c) Sternum

3. **Total body mass**, since the current golden standard for exactly determining dehydration is the short term loss of body mass. This variable will be measured in Kg's using a weighing scale, which has an accuracy of 0.1Kg. This measurement will function as the definition of dehydration (% loss of body mass), and will be the main independent variable in the retrospective regression analysis.

4. **Core temperature**, since it is one of the identified potential sources of external influence on both ST and CRT. This variable will be measured using the HuBDIC Thermofinder FS-300 Non-Contact Infrared Thermometer. The variable will be used as an independent variable in the multivariate regression analysis in combination with degree of dehydration, in order to detect its relation to both ST and CRT.

5. **Skin surface temperature**, which will be used for the same goals as core temperature.

6. **Ambient temperature,**, which will be used for the same goals as core temperature and skin surface temperature.

3.2 Experiment protocol

Five subjects were recruited to volunteer in this experiment, of which one was used as a control-subject. All non-control group volunteers are instructed to exercise, using a spinning-bike, in order to stimulate sweating. To further stimulate the sweating, the experiment takes place in a climate chamber with a constant ambient temperature of 35°C, and a constant ambient relative humidity of 10%. Over the course of the experiment, after every 30 minutes of exercise a measurement moment (a "hydration snap-shot") was executed, which was meant to collect all data regarding the variables described earlier. Each (non-control group) experiment-run should continue until the subject lost 4% of its body mass, or after a duration of 4 hours, which was the restricted time-window per subject. All data was be stored on a PC for retrospective analysis.

3.3 PPG-CRT Prototype

A prototype of a PPG device has been developed specifically for this experiment, in order to use an experimental device which is optimized specifically for measuring CRT. The device consisted of an Arduino ZERO micro-controller as the central processing unit, with two prototyped PPG probes connected to it, a few LED's as a visual feedback interface for the user, and a Micro-SD card module for data storage (see figure 2).

Two PPG probes were used in this prototype: one for measuring CRT, and one for measuring a reference signal in parallel. Both probes consist of a 3D-printed PLA housing, which contain an off-the-shelve green reflective PPG probe (Pulse Sensor Amplified, `http://pulsesensor.com/`). Green reflective PPG has been identified as the most optimal type of PPG for CRT measurements, due to its optimal depth of modulation and SNR [27]. In order to measure CRT with PPG, the non-pulsatile component of the signal (the DC-component) is of main interest. Therefore, an extra wire was soldered onto the PCB of the Pulse Sensor just before the signal is be high-pass filtered. This enabled the recording of a "raw"

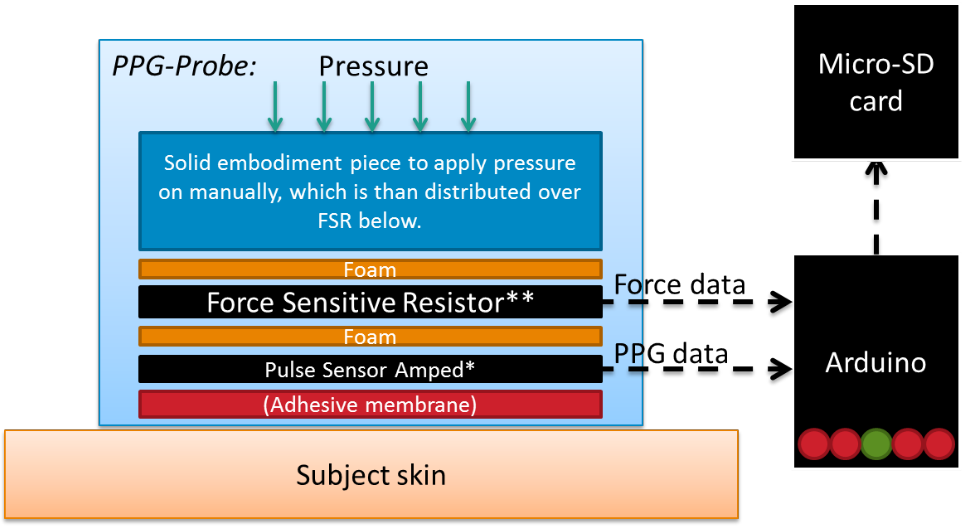


Figure 2: Schematic view of the CRT prototype (excluding the reference probe).

PPG signal which still includes a DC-component and an AC-component (the pulsating component of the signal, commonly related to heart-rate).

One of the probe, the one used to measure CRT, also houses a force sensitive resistor (FSR), which is used for force feedback to the user. The CRT measurement consists of 3 phases: a *pre-compression phase*, a *compression phase* and the *capillary refill phase*. During the compression phase, the user manually applies a force on the CRT-probe. To make this compression phase as consistent as possible when done manually, the force as sensed by the FSR inside the probe will be used to provide visual feedback to the user by LED's. These LED's give the user information about whether the applied force is within the predetermined boundaries considered optimal for CRT measurements (between 14N and 16N), and when the user may release the force (after 5 seconds of compression).

3.4 Data processing

All but the PPG data will be used as-is in the regression analysis.

To be able to convert a typical capillary refill curve as seen as the blue line in figure 3, it was chosen to apply a parameter estimation method. Matlab was used to run a curve-fitting algorithm to the CRT data, using the model in eq. 1 as the model.

$$\hat{y} = \mathbf{A} * (-e^{\frac{-x}{\mathbf{B}}} + 1) \qquad (1)$$

This model is a modified version from the suggested model by Kviesis et al. [25]. An exponential function is used for the model, as the typical CRT sample seems to show a natural growth curve. This model returns two estimated parameters: A and B. A only represents the mean value of the steady state after complete refill, while B varies as the capillary refilling process varies in speed. Therefore parameter B is considered most interesting for this experiment. The red line in figure 3 represents the fitted model. As can be seen, the model fits well, but not perfectly. This residual error can be explained by two reasons: The transient response of the CRT data shows a slight s-curve, and the pulsating component also still affects the data. In order to cancel out the s-curve, the midpoint of the capillary refill process (halfway from the origin to the mean steady state value) is taken as the origin in a second version of the same sample. In order to also cancel any influence from the pulsating component, the reference PPG waveform which is measured with the reference probe is fitted onto the pulsating component of the CRT data (as seen in figure 4). The pulsating component is than cancelled out by either division or subtraction of the reference data from the CRT data. Taking all of the previously explained methods into account, the set of parameters displayed in table 2 was used in the regression analysis.

3.5 Data analysis

It was chosen to perform a (multivariate) regression analysis using Matlab, since it will return information on how well the experimental parameters of interest could be used to predict the severity of dehydration (% loss of body mass). More specifically, the *coefficient of determination* (R^2) was of main interest here, as it represents the percentage of variation of the dependent variable (in this case the experimental parameters related to

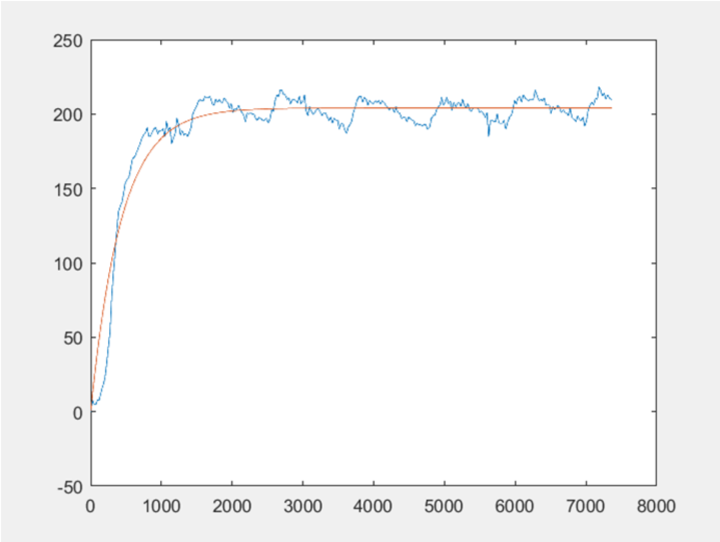


Figure 3: A plot of a typical CRT sample with the fitted exponential model from eq. 1.

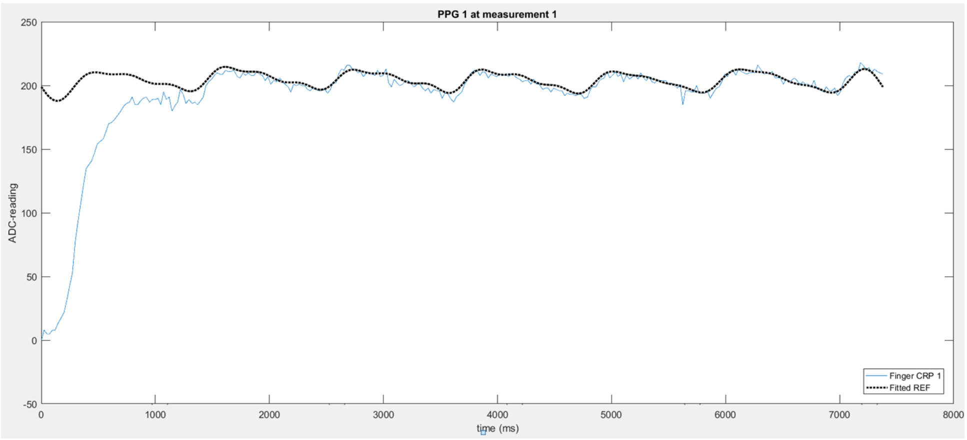


Figure 4: A plot of a CRT sample with a filtered reference signal fitted to it.

	Original CRT data	CRT data / Reference data	CRT data - Reference data
Origin at start of capillary refill phase	O	O/R	$O-R$
Origin halfway refilling process	$\frac{1}{2}O$	$\frac{1}{2}O/R$	$\frac{1}{2}O-R$

Table 2: All different versions per CRT sample, which will be included in the analysis.

ST or CRT) that can be explained by the independent variable(s) (in this case loss of body weight, which may or may not be in combination with one of the temperature variables). This R^2 is defined by the error of the (linear) regression model from the actual data. This means that if the error is small, R^2 will be close to 1, which means that the regression model could be a good representative model to use for future diagnostic devices. Yet, in this case there is a relatively small number of degrees of freedom (DOF), especially when performing a multivariate regression analysis, since a relatively small amount of samples per subject has been collected. Therefore, it has been chosen to use the *adjusted coefficient of determination* ($\bar{R}^2$), as it takes a small DOF into account when defining $\bar{R}^2$, as explained in eq. 2.

$$\bar{R}^2 = 1 - (1 - R^2)\frac{n-1}{n-k-1} \tag{2}$$

$\bar{R}^2$ will be examined per experimental parameter of interest, per body location, per subject. It has been chosen to not combine all results into one final $\bar{R}^2$, as it is expected that results will vary substantially between individual subjects and body locations. The aim is to see if there is any consistence in predictive value for all options, which will be assessed by plotting the mean and standard-deviation of each group of $\bar{R}^2$ for all subjects, per body location, parameter of interest, and per type of regression analysis as multiple analyses will be performed using different independent variables.

4 Results

In figures 5 to 7 the $\bar{R}^2$-plots are shown. The closer $\bar{R}^2$ is to 1, the better the parameters of interest which are described in the caption of each plot can be used for predicting dehydration. The plots are divided in body location per column (finger, chest and head, in that order). Shown per row are the consecutive measurements per snap-shot, as at every snap-shot 3 measurements are taken. The bottom row represents a mean of the raw data of those three samples, which is a way of averaging and filtering out noise. Per plot six lines represent the mean and standard deviations from all subjects, divided per sample processing method as shown in table 2. These 6 differently processed samples thus represent from left to right: the original sample (O), the sample with the origin half-way of the refill process ($\frac{1}{2}O$), the original sample with the AC-component filtered out by dividing it by the reference data (O/R) and with the half-way origin ($\frac{1}{2}O/R$), and the version with the AC-component filtered out by subtracting the reference data(O/R), together with the half-way origin ($\frac{1}{2}O - R$). Each figure represents the regression analysis using different variables, where figure 5 represents the regression analysis of CRT vs. % loss of body mass, figure 6 represents the analysis of CRT vs. % loss of body mass and local skin temperature, and figure 7 represents the analysis of CRT vs. % loss of body mass and core temperature.

A similar way of plotting the results has been done for the results of the Cutometer, which can be seen in figures 8 to 10. These results are organised in different plots per body location (Hand, arm and chest, respectively), while every different plot illustrates the results per Cutometer parameter. Figure 8 represents the analysis results of all Cutometer parameters vs. % loss of body mass, while figure 9 represents the results of all Cutometer parameters vs. % loss of body mass combined with local skin surface temperature. Figure 10 represents the results of all Cutometer parameters vs. % loss of body mass combined with core temperature.

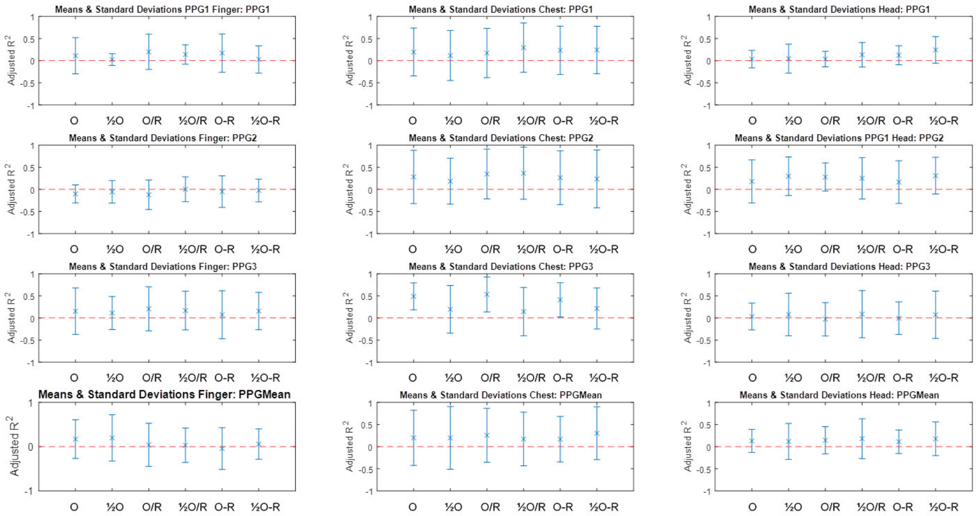


Figure 5: Regression analysis PPG-CRT: $\bar{R}^2$ of parameter B vs. % loss of body mass.

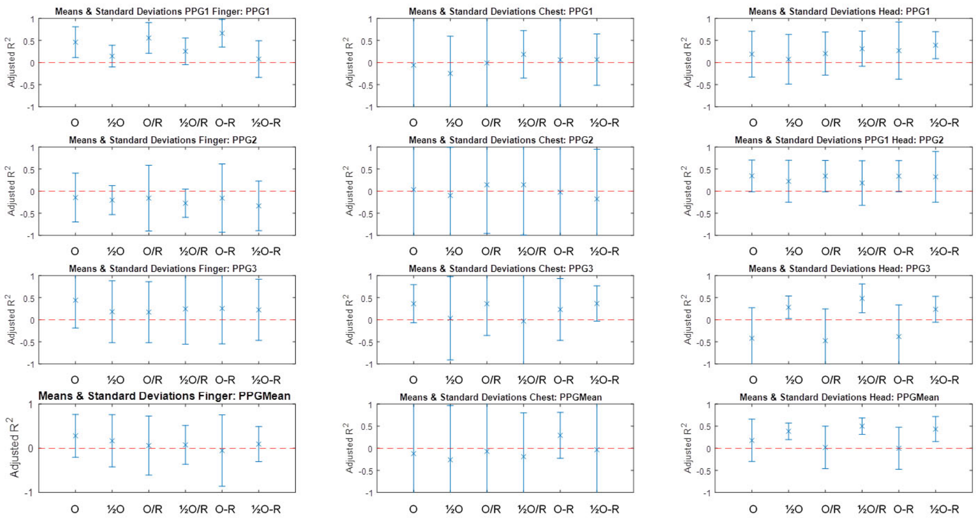


Figure 6: Multivariate regression analysis PPG-CRT: $\bar{R}^2$ of parameter B vs. % loss of body mass & local skin surface temperature.

5 Discussion

5.1 Results from the PPG-CRT Prototype

Looking at the overall results of the regression analysis, a lot of inconsistency in the data can be observed. Due to bad skin-contact, the measurements from the chest are considered to be unreliable, and are therefore neglected. Looking at the remaining results, the regression $\bar{R}^2$ coefficients of the single-variate regression analysis between degree of dehydration and the estimated parameter of the exponential model don't seem to show any significant predictive properties. When local skin-temperature is introduced as an independent variable, the $\bar{R}^2$ seem to benefit from it, especially the samples taken from the forehead which are processed using the "half-way" method. Also in the finger there seems to be some effect, yet this is rather inconsistent. This could be explained by the difficulties that existed with taking skin temperature from the index-finger. Other attempts at introducing other independent variables such as core temperature, or even core- and skin temperature simultaneously did not result in any improvements in $\bar{R}^2$.

Based on these results, CRT as measured with

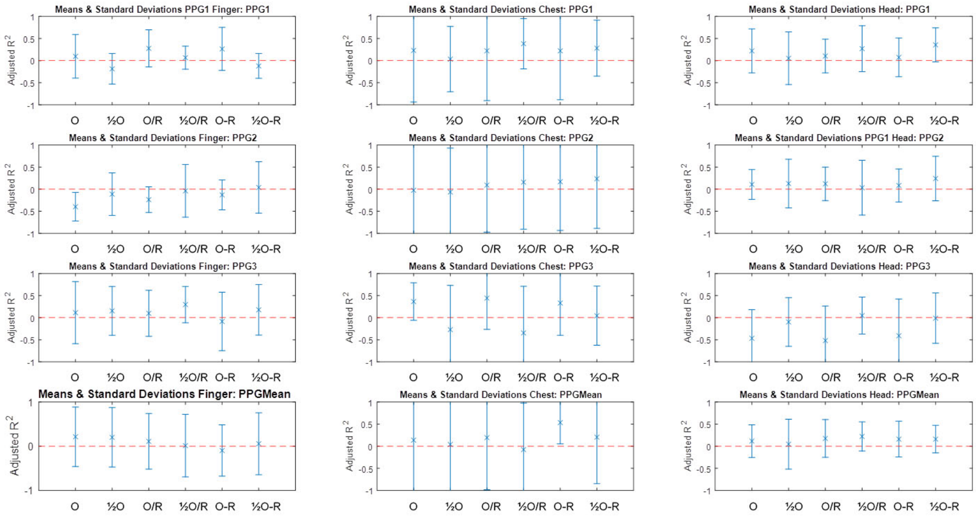


Figure 7: Multivariate regression analysis PPG-CRT: $\bar{R}^2$ of parameter B vs. % loss of body mass & core temperature.

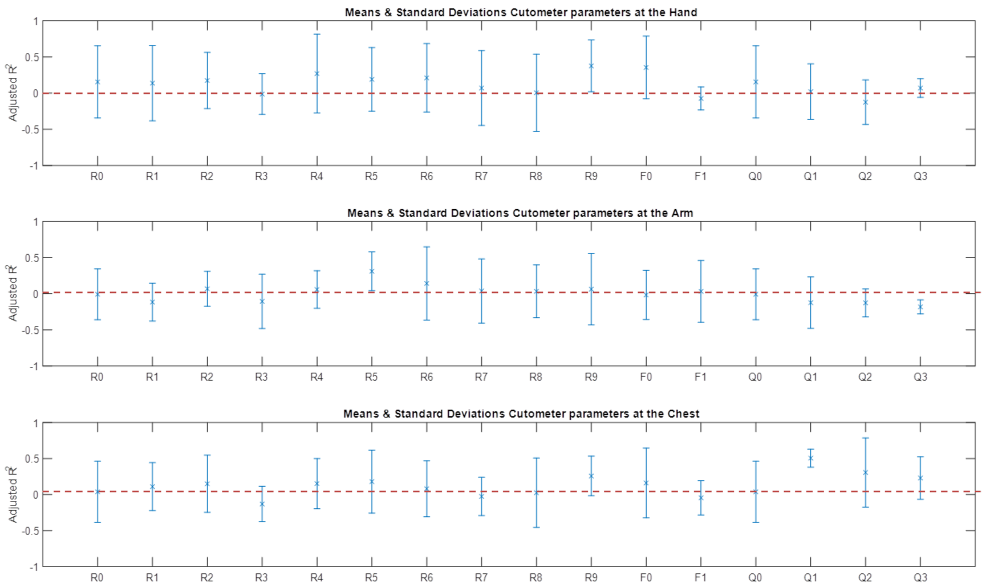


Figure 8: Regression analysis Cutometer: $\bar{R}^2$ of all Cutometer parameters vs. % loss of body mass.

PPG would be most optimal when measured on the forehead, and should be adjusted by local skin temperature on the forehead in order to improve the diagnostic performance.

5.2 Results from the Cutometer

Like with the PPG-CRT data, a lot of unexpected inconsistency is observed in the results of the regression analysis of the parameters that were returned by the software of the Cutometer at each measurement. In the single-variate regression analysis where changes in each Cutometer parameter are compared with changes in degree of dehydration, the only parameter that seemingly shows a consistent and relatively significant coefficient of determination can be seen at the chest with parameter Q1, with an $\bar{R}^2$ of approximately 0.6. Q1 stands for the relative elastic recovery in relation to the total displacement of the skin during the "suction-phase", which is considered to be an representative parameter for ST. This strong $\bar{R}^2$ is

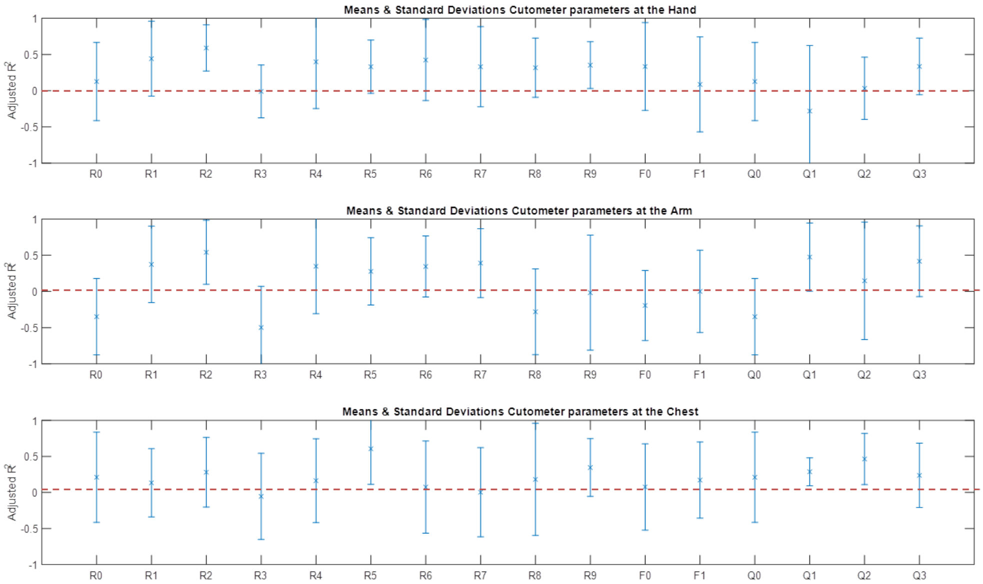


Figure 9: Multivariate regression analysis Cutometer: $\bar{R}^2$ of all Cutometer parameters vs. % loss of body mass & local skin surface temperature.

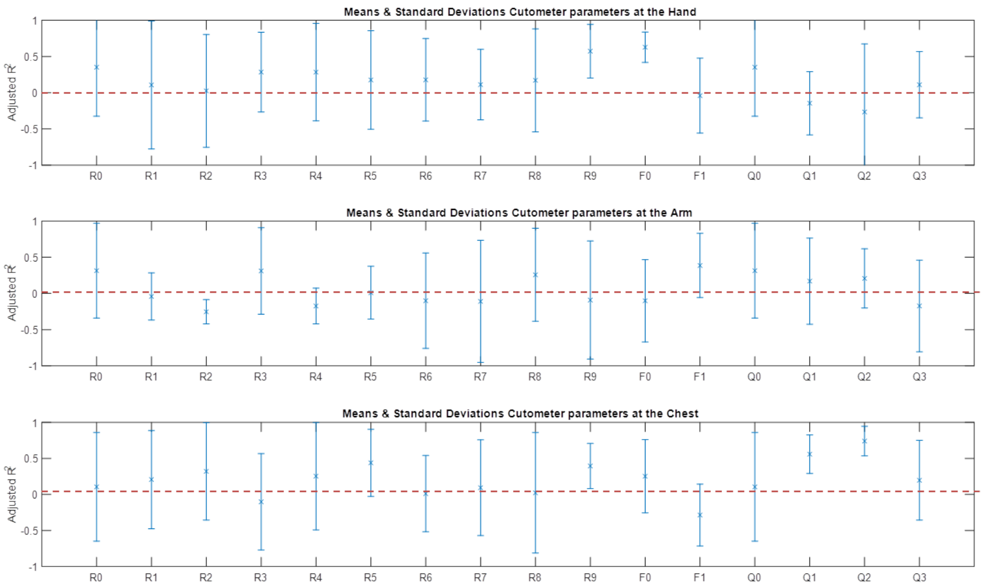


Figure 10: Multivariate regression analysis Cutometer: $\bar{R}^2$ of all Cutometer parameters vs. % loss of body mass & core temperature.

therefore expected. Yet, looking at the individual trend-lines of the changing Q1 parameter over time, it can be seen that the trend lines move up in subjects 4 and 6, while the trend lines move down in subjects 2 and 3. It is a reminder that performing a regression analysis on measurements at individual subjects may indicate how well the regression model fits to data on individual level, but it does not mean it is thereby applicable to a larger population. These differences can be explained by the significant biological differences in mechanical properties of the skin in adults.

In a multivariate regression analysis where local skin temperature is introduced as an independent variable, it can also be seen that $\bar{R}^2$ is reduced for Q1 at the chest. On the other hand, Q2 (representing viscous recovery) at the chest, Q1 at the arm, and R2 (representing gross elasticity) at both the hand and the arm seem to be improved in terms of $\bar{R}^2$. R2 remarkably also shows a decreasing trend with increasing dehydration at every subject in both the hand and the arm (accept in the hand of subject 2). Observing all trend-lines of R2 in the chest, these also almost all of them show a decreasing trend, although the variability is much higher compared to the hand and the arm, which may be due to the larger motion artefact, which explains the lower $\bar{R}^2$. Altogether it can thus be said that R2, as a parameter representing gross skin elasticity, is showing expected behaviour in by far most cases.

When using core-temperature instead of skin-temperature in the multivariate regression analysis, the resulting $\bar{R}^2$'s change again. Now Q1 and Q2 in the chest show high $\bar{R}^2$ values again, along with R9 (representing tiring effects after repeated suction) and F0 (representing elastic and viscous response to negative pressure) in the hand. R9 indeed shows a consistent trend upwards with increasing dehydration for all subjects, although showing some variability as well. The effect of dehydration on tiring of repeated deformation of the skin has not been anticipated yet, but suggest rethinking the way ST could be assessed, such as looking at tiring of the skin after repeated perturbations.

5.3 Limitations

Although it is believed that the way this experiment was conducted was to most optimal given the prior knowledge, the available resources and restrictions, there still were some considerable limitations to this experiment which have to be taken into account before interpreting the results. There were both limitations to the overall experimental design, as well as to the equipment, which will all be mentioned in this section.

Experiment limitations

- *The number of subjects*: The ICBE gave a restriction to only experiment on a maximum of five subjects in total. This eventually meant that only 4 dehydration subjects could be included, and only 1 control subject. This limits the statistical power of the acquired data.
- *The number of samples per subject*: There were only 4 to 6 hydration snap-shots per subject where the experimental equipment was used. The reason for this was the limited amount of time per subject (max. 4 hours as restricted by the ICBE), and the fact that taking many different measurements at a single hydration snap-shot with just 1 researcher in the room can be very time consuming. It would have been better if less measurement actions had to be taken during each hydration snap shot, so that more time is left for more hydration snap-shots. The low number of samples also was the reason for a very low DOF, which limits the amount of variables that can be used in a multivariate analysis and causes an unreliable coefficient of determination.

  Due to both the small number of subjects and the small sample size, the *p-value* for testing statistical significance of the data is not regarded in the analysis, as it can already be presumed that given the amount of samples, the statistical significance of the experiment should be rather low (meaning $p > 0.05$). Any observed (causal) relations in this experiment should therefore be considered nothing more than a suggestive insight for further research.
- *The maximum severity of dehydration*: The maximum allowed severity of dehydration was chosen to be 4%, to keep it safe. Yet, this relatively low degree of dehydration does have the disadvantage that the effects on CRT and ST could be very small. This could cause any effects to be unnoticeable, even when measured with the used equipment. It is hypothesized that any effects of dehydration would've been much more noticeable in a regression analysis when a dehydration of for instance 10% could have been achieved. It would on the other hand be difficult to increase the max. severity of dehydration, since within the 4 hour time-window the subjects rarely succeeded to reach the 4% limit. More time would've been needed, and combined with a more severe degree of dehydration this would be very straining on the subjects. Therefore it is considered to be difficult to achieve higher levels of dehydration within a lab setting.
- *The age of the subjects*: The group of focus for this assignment is children under the age of five, and it has already been established that CRT and ST are affected differently by dehydration within this age group when compared to adults, as these diagnostic variables become less predictive in older age. The subjects were all between 20 and 25, which is significantly older than young children. This could have caused a lot of unexplainable biological variability between measurements.
- *The control group*: Only one subject was picked to play the role of the control group,

due to the strict restriction in maximum allowed subjects. Ideally, the control group is the same size as the experimental group. Another limitation of this control group was that it consisted of the researcher himself. As measurements were conducted by himself, and had to be stored on the PC during this experiment run, there was no time to exercise in between these measurements. Ideally, the control subject should also have exercised, while in contrast to the other subjects the control subject would have gotten enough water to rehydrate.

Equipment limitations

PPG-CRT Prototype:

- *Timing of the measurements*: These measurements were relatively time-consuming, as every time the strap had to be attached to the subject, and a good skin contact had to be validated. Also, skin-temperature measurements had to be taken with other dedicated equipment, which caused extra time delays. Also, this resulted in skin- and core temperature measurements to be taken on a slightly different moment, causing time-difference between these measurements. Ideally, these measurements are taken simultaneously.
- *Motion artefact*: In a number of data samples considerable artefacts have been found, most of which could be attributed to relative motion of the sensor in relation to the skin of the subject. Better ways of stabilizing the sensor should thus be found.
- *Manual pressure*: The assumption before the start of the experiment was that manual pressure application with feedback from a FSR would result in a sufficiently consistent pressure application. Yet is showed to be quite difficult still to keep the compression force within the predefined boundaries, and some variation can be seen in the data recorded from the FSR. In addition, in hindsight it was found that a FSR is actually quite unsuitable to use for accurate force measurements, due to many significant variations in the sensory response of the component to force. Variations are for instance caused by temperature, force duration, humidity and many more factors. A more suitable and accurate sensor is preferred.
- *Pulse Sensor*: The Pulse Sensor showed to be very suitable for heart-rate monitoring, yet for this application there are some limitations to the component. Apart from the fact that a small hack had to be made in order to receive the un-amplified signal, the brightness of the led was relatively low compared to similar sensors. Also, the size of the photo-detector was small when compared to similar sensors. This could have caused a sub-optimal SNR. When calibrating the PPG probe for the minimum amount of force needed in order to blanch the skin, it was found that the force had to be quite substantial (at least 14N). The subjects notably experienced it as quite uncomfortable, let alone if this would have been applied to neonates. It is hypothesized that the reason behind this is due to the somewhat large and flat surface of the Pulse Sensor. It is believed that with a smaller contact area, less force has to be applied in order to blanch the skin. It was also already established in literature that smaller compression forces result in more consistent CRT values [21]. Another observation was that blanching the skin with the PPG probe often still left a pink-dot in the middle of the blanched area, which is assumed to be an accumulation of blood in that spot and is therefore considered to be an ineffective blanching result. It is believed that using a dome-shaped PPG probe in the future would solve this problem.
- *Unstable sampling rate*: The used microcontroller (Arduino ZERO) didn't have a very stable sampling rate, which caused difficulties during signal processing. In future prototypes, the coding of the device should be made more efficient, whilst using a more powerful processor.
- *Bad skin-contact on the chest*: Due to different shapes of the chest at the level of the sternum, the PPG-probe did not always make good skin-contact at the chest. This resulted in a lot of rejected samples, and overall bad signal quality. For this reason, the PPG samples taken from the chest should not be regarded as a reliable result.
- *Inconvenient data storage*: The data was stored in such a way that it needs a lot of processing before it can be analysed. This resulted in a very time-consuming data processing phase after the experiment. In future devices, the data should be labelled more conveniently, so that it can more easily be sorted for automated processing using Matlab scripts, which saves a lot of time. Also, the points where there is a change between the three phases is quite ill-defined. This should be improved when automated compression is used.

Cutometer:

- *Aperture size*: As already established, the area where ST should be defined is at the dermis. For the Cutometer it is known that a larger aperture size causes a deeper penetration depth. Yet, it is ill-defined what the exact contribution of the skin layers are on the readings when using different aperture sized. There is a good chance that the used aperture size (8 mm) was either too small or too wide.
- *Motion artefact*: On many measurements some motion artefact can be seen due to relative motion between the examiner and the skin of the subject, especially at the chest, since the hand or arm can easily be stabilized on a table surface. Sometimes the motion even caused loss of skin contact, which caused loss of negative pressure.

Skin surface temperature measurements:
Apart from the fact that time delays were caused as the skin-surface temperature had to be measured separately from the PPG and Cutometer measurements, instead of simultaneously, the use of this device for skin-temperature measurements is not the intended use of this device. The object temperature function is mainly intended for other warm objects such as a warm bottle of milk. Therefore the reliability of these measurements cannot be guaranteed. Also, some variations can be seen in subsequent skin measurements.

6 Conclusions

First of all, it has been established based on literature that child mortality due to dehydration is a severe problem, which accounts for a very large proportion of all child deaths in low resource settings, since diarrhoea is known to be the second biggest killer of (post-neonatal) children under the age of five. It has been identified that assessing dehydration is currently a problem based on literature reviews and interviews with health workers in low-resource settings, as children suffering from diarrhoea are often diagnosed with an inaccurate severity of dehydration. This misdiagnosis causes preventable deaths, as underestimation leads to delayed treatment of the condition, which in turn leads to severe (fatal) dehydration. The problems with diagnosis also can contribute to unnecessary high cost of healthcare in low resource settings, as ORS is often out of stock due to over-subscription, while this lack of ORS then leads to administration of the more expensive intravenous fluids to patients who would have been fine with only ORS. In addition, regardless of the actual diagnostic performance of the current standard tests for dehydration assessment, parents or guardians often seem to distrust the assessment of the community health worker. This distrust in turn also leads to over-subscription of treatment resources that the patient does not benefit from. Therefore, finding cost-effective solutions that could solve the problem of dehydration assessment is considered to be both beneficial for reducing child mortality and for reducing the cost of healthcare in low-resource settings.

For the Cutometer, the R2 parameter stands out as a diagnostic parameter for dehydration, especially when combined with local skin temperature. This parameter represents the gross elasticity of the skin (the total skin displacement during suction divided by the total skin recovery after release), and is regarded by the manufacturer of the Cutometer as a "very important parameter" [26]. It suggests that skin elasticity measurements in combination with local skin surface temperature could be a possible diagnostic variable for dehydration assessment.

Regarding the CRT measurements which were made using the PPG prototype, it seemed that measurements on the forehead resulted in measurements that could in general be used best to predict dehydration, especially when combining the measurements with local skin temperature.

Apart from a few very specific outliers, the parameters which have been included in this regression analysis for both ST and CRT show very unexpected results overall, with not much predictive value or consistency among these results. Also with the outliers described above, none of them show a unanimous $\bar{R}^2$ that comes close to 1, meaning there is still a lot of variations which are not yet accounted for by any variable. Based on the results of this experiment, the experimental hypothesis can therefore not be confirmed yet.

It also has to be mentioned that are a number of significant limitations to the used equipment and the over experimental set-up. Especially the age-group of the participants and the range of dehydration are believed to have significantly contributed to variability in the results. If more severe dehydration was to be achieved, the contribution of unaccounted noise on the data would have probably been for less. It is also expected, based on literature, that children under the age of five will generate much more consistent and expected results. As for the equipment, also considerable limitations were identified, which should be addressed in any future studies.

7 Recommendations

Based on the insights that have been identified up to now, there are a few key recommendations that should be given away for any future research regarding this topic.

1. Based on the identified limitations of the used equipment in this experiment, a new set of prototypes should be developed as functional prototypes which are suitable for use as data-collection devices. Key should be that no user related variability should be allowed when using these prototypes, meaning all processes (including kinetic processes) should be automated. Prototypes should be developed based on CRT and ST, as these are still proven to have the best overall diagnostic performance. Yet, preferably more research should be conducted into more direct ways of measuring dehydration, such as directly measuring the water content of a large piece of tissue. Altogether a set of at least 3 prototypes should be developed, which could all be used by researchers for data-collection studies

2. The next step should then be to conduct a data-collection study, indeed using the set of prototypes which is suggested above for comparison. In this experiment a learning point was that measuring only a small number of up to 4% dehydrated adults will not generate any statistically significant results. A suggestion is therefore to perform a child study, where the effects of severe dehydration in children are measured using the different prototypes. It is obvious that conducting a similar lab test with actively stimulating dehydration in young children would ethically be an issue, and should therefore not be considered as a feasible next step. Performing data collection tests on children that already suffer from severe dehydration (due to diarrhoea) in a clinical setting is therefore preferred. Yet, such patients are very rare to find in high-quality healthcare systems such as in the Netherlands, based on conversations with neonatologist Prof. dr. Sidarto Bambang Oetomo. It is therefore recommended to, after having done small validation tests with the prototypes, already go with the functional data-collection prototypes to low-resource settings, in areas where the prevalence of dehydration is known to be high. It is recommended to cooperate with local health-workers who cope with dehydrated children on a daily basis. These health workers could use these prototypes (one at a time) in parallel to their normal work-flow, on the condition that this extra action does not interfere with their normal work-flow in a damaging way. The data collected with the devices should be compared with the degree of dehydration, by letting the health worker monitor the weight gain of the patient. The initial degree of dehydration at the time of first contact with the patient can than be derived retroactively, by defining the weight of the patient when he/she is considered to be fully rehydrated.

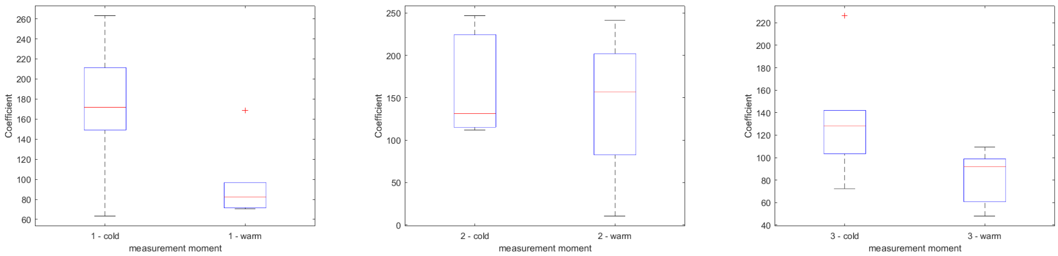
   The collected data can then be analysed in a similar way using multivariate regression analysis. If needed, for instance when a lot of different parameters need to be analysed for their relation to different degrees of dehydration, *machine learning algorithms* is a suggested method for defining a definitive predictive model for use in future diagnostic tools for dehydration assessment. This definitive predictive model should then not be limited to a single diagnostic variable with any confounding factors taken into account. The feasibility and diagnostic performance increase of using a combination of diagnostic variables, such as CRT an ST, should thus also be investigated, as it is hypothesized that any combination of diagnostic variables could improve the performance of any eventual diagnostic device.

As a first step to already start realizing these recommendations, an improved prototype for the CRT-PPG prototype has been developed based on the learnings from this study. The prototype features:

- A fully automated measurement protocol, which uses a linear actuator with force feedback-control using a more accurate force-sensor.

- An improved PPG probe design which has a smaller contact area and a slight dome-shape in order to optimise the blanching process. With the smaller contact area also a smaller amount of force is needed to blanch the skin, which was found to be beneficial for the consistency of the measurement results.

- An array of integrated IR temperature sensors can measure skin-temperature in parallel to the CRT measurement. This is expected to be more accurate compared to the previous method, and less time-consuming as no extra actions are needed for measuring skin-temperature with this prototype.



(a) Boxplot results day 1 (b) Boxplot results day 2 (c) Boxplot results day 3

Figure 11: All results after processing the data for each day, grouped per ambient temperature.

- A more stable and increased sampling rate of 100Hz.
- A more convenient way of storing data, with data labelling. Each sample is for instant now labelled regarding its measurement phase. This labelling makes the analysis much more efficient.
- Optimized analogue filters and higher quality PPG reflective sensors (Osram SFH 7051, with brighter LED's and a photodetector with a bigger surface) are integrated into the circuit, which optimized SNR and overall signal strength.

Validation tests have already been executed, to test if the prototype detects minor differences in CRT due to differences in ambient temperature. Indeed comparing results taken in a cold room (10°C) and a warm room (20°C), with a repeated measurements over the course of three days, showed to result in significantly different results after conducting an analysis of variance ($F(1, 35) = 6.15, p < .05$). The results from a the warm room showed in general a smaller parameter B from the fitted exponential model as seen in figure 11, which corresponds to the expected shorter CRT compared to CRT from the cold room. This suggests that this prototype is able to measure differences in CRT, and similar embodiments may be used in future studies regarding this topic.

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