Article

Pulse Wave Harmony: Ancient Wisdoms for Modern Age

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Abstract: Background: This research presents the use of photoplethsmography combined with Traditional Tibetan Pulse reading for the estimation of the three energies of a person: Activity, Transformation and Stability. The growing interest to revive traditional finger pulse reading attests of the need to find alternative ways to approach complex multi-source diseases as well as individualised diagnostic wearable or portable cost effective systems. Method: Our work is presented in two studies. The first study presents the development of the technique of photoplethsmography to classify the three energies. The second study presents a validation of this methodology on mental stress and relaxation. Results: Energies classification achieved a sensitivity above 85% and specificity above 72%. Mental stress and relaxation could be significantly discriminated from baseline condition. Harmonic analysis gave further insights into the dynamic of the pulse wave under stress/relaxation. Conclusion: The photoplethsmogram contains information pertaining to the mental and physiological state of a person as interpreted with the Eastern energies concepts. The implication of this work points towards a holistic understanding and impact of human activities, health and its environment.

Keywords: Pulse wave analysis; Traditional Tibetan Medicine; Harmonic analysis; Mental stress; Holism; Environment

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1. Introduction

Western medical practice and science has progressed rapidly since 100 years to reach unprecedented accuracy in diagnostic instruments and surgical practices. Intelligent robots are helping surgeons to perform faster and better operations. Medical data are analysed by artificial intelligent algorithms and help physicians to take better decisions regarding therapeutic treatments. We however see a resurgence of complementary and so-called alternative medicine, including ancient traditional medicinal systems. Indeed the price to pay for a sophisticated instrumented diagnostic arsenal, is the loss of a holistic view on the patient's problems. Traditional medicine systems offer a natural way to counterbalance the analytical approach with a synthetic one. Chronic multiple-sources illnesses such as cancer, multiple-sclerosis and fibromyalgia or even hypertension are less well treated and sometimes diagnosed by Western medicine. One common cause of these diseases originate in stress. Stress can have multiple origins such as internal and external to our body as well as mental. Mental stress is particularly interesting to study in our epoch as it is a common health issue, associated with increased cardiovascular mortality and morbidity [1]. It also has a great impact on both professional and private lives as it has been associated with negative mood [2], immunosuppression [3], impacts on physical and mental health and increased occurrence of illnesses [4].

Methods to assess mental stress have been primarily focused on questionnaires. More objective techniques have emerged based on neurophysiological sensors such as electroencephalogram and heart inter-beat intervals analysis. Among the most popular sensors are those based on photoplethysmography (PPG) [5,6] due to their low cost and relative ease of use. The PPG signal is a surrogate of the blood pulse pressure wave which contains information about the neuro-cardio-vascular system [7–9] thus offering a potential powerful tool to assess mental stress as manifested in neuro-physiological responses. Mental stress has indeed been quantified using PPG analysis [10–15].

Pulse wave reading as a long history in both Western and Eastern medicinal systems and offers a powerful diagnostic method. It is thus a legitimate question to ask if traditional pulse reading methods can be linked to modern pulse wave sensing and processing techniques. As Eastern empirical medicinal knowledge are slowly transformed into evidence based medicine, Eastern pulse reading method is indeed currently under rapid modernization using digital techniques [16–23].

In this work, we present for the first time a method based on PPG analysis to interpret some aspects of Traditional Tibetan pulse reading. This method is further used in a mental stress laboratory experiment. The concepts of traditional pulse reading are verified and analysed in terms of Western medicine concepts. Additional insights into the use of pulse wave harmonic analysis is presented and discussed in correlation with time domain pulse wave analysis.

The paper is organized as follows. Section 2 presents the basic understanding of Eastern philosophy together with Traditional Tibetan Medicine concepts and their relationship with Western concepts. Section 3 describes our two separate data collection protocols and pulse wave sensing instruments. The first study is presented in Section 4.1 and describes the classification of the three energies. The second study is presented in Section 4.2 and validate our energies classification together with a harmonic analysis in the assessment of mental stress. The two studies were independently performed. Section 5 discusses the results and Section 6 concludes this work.

2. Eastern and Western Pulse Reading

2.1. Traditional Tibetan Pulse Reading: The Three Energies

Sowa Rigpa, the Traditional Tibetan Medicine [24] is essentially based on medical texts originating from Central Asia and Tibet [25] and derives from a collection of texts known as the Four Tantras [26]. The two major contribution to the Traditional Tibetan Medicine came from India [27] and China [28,29]. We can thus say that Traditional Tibetan Medicine is an integration of local Tibetan healing knowledge with Ayurveda and Chinese medicine.

At the core of ancient medical and cosmological knowledge, both from Western and Eastern cultures, stands the philosophy of the elements [27]. These elements were thought to pervade all of animate and inanimate objects, perceivable and not. The elements are commonly known as Air/Wind, Fire, Water and Earth. The elements are not to be conceived as static building blocks but rather as functional entities or elemental energies that reflect their stability, and their dynamic and transformative nature. The concept of energy is central in both Western and Eastern sciences and is thus a good base for making the bridge between the two systems. In order to ease the way from Western to Eastern thoughts when reading this article, we should keep in mind the following definition of energy: a measure of a system's ability to cause change or maintain its structure.

When concerned with our body, the elements are further reduced to the three energies known as: Wind (*Lung*), Bile (*Tripa*) and Phlegm (*Beken*). In order to make the bridge with Western concepts easier, we have tentatively introduced a new terminology. It has to be noticed however that to grasp the full concept and meaning of these energies in their original context, one should consult specialized books or have a clear explanation from a Tibetan doctor.

- Phlegm (Beken) = Earth + Water = **Stability**
- Wind (Lung) = Wind = **Activity**
- Bile (Tripa) = Fire = **Transformation**

Stability is associated with foundational structure. Thus, it is linked with bone and marrow, flesh and liquids on the body side, and mental quality of calmness and focus. **Activity** is linked to movements. It can be the nervous system activity, blood flow, physical movement as well as movements of thoughts and emotions. **Transformation** is linked with heat and clarity. Thus it is linked with metabolic processes as well as sense perception and mental clarity.

Each person possesses a specific *typology* from birth, that is to say a certain proportion of these three energies. These energies slowly evolves with time and ageing depending on external (environment) and internal (physiology and mind) conditions. For example, these energies manifest differently in our body functions according to the four seasons, sun and moon activities (i.e. night and day). They also varies according to our breathing pattern, cardiovascular condition and cell level functional states. Pathologies reflect the fact that the three energies at a certain time are in a state of imbalance with respect to the typology of the person. Thus, the typology is the reference point for the doctor, from which any departure represents a state of imbalance. A few examples of imbalance are discussed below. Usually, a mix of these condition appears as the energies are dependent on each other.

- Elevated **Stability** energy result in obesity due to inactivity, dullness of mind or depression, flu and immune system dysfunction,
- Elevated **Activity** energy can manifest as anxiety, mental and physical hyperactivity, hearing problems, dysautonomia, constipation, or breathing disorders,
- Elevated **Transformation** energy tends to increase excitability, over joyful state or anger, tendency towards hypertension and cardiovascular problems.

The typology is the natural condition of the person and has to be determined in precise conditions [24]. To each organ corresponds a predominance of an element and is thus also correlated with a typology. There is a correspondence between the three energies and physiological, psychological, energy functions and the senses/sense organs. These correspondences are helpful to cross the bridge between Eastern and Western way of thinking and their essential correspondences are shown in Table 1.

Table 1. The Three Energies and their Western Correspondences

	Activity (Lung)	*Transformation (Tripa)*	*Stability (Beken)*
Physiology	Nervous system, Blood circulation, Lymphatic circulation, Tissue growth, Reproduction, Excretion	Digestion, Skin coloring	Immune system, Bone structure, Joint lubrication
Psychology	Cognition, Anxiety, Distress, Fear, Instability	Creativity, Intuition, Desire, Anger, Joy, Impulsiveness, Extraversion	Tolerance, Generosity, Tranquility, Introversion, Sensation, Feeling
Sense/Organ	Touch (Skin), Hearing (Ears)	Vision (Eyes)	Taste (Tongue), Smell (Nose)
Energy	Movement, Creation, Birth, Aging, Death	Transformation, Discrimination	Structure, Stability, Construction/Cohesion
Pulse	Rough, quick, empty, floating with intermittent beats	Sharp, rolling, strong, fast, overflowing with taut beats	Sunken, slow with very weak beats
Elements	Wind	Fire	Water and Earth

The exceptional discovery by ancient physicians that the pulse wave characteristics can be mapped to the three energies led to great progresses in the art of diagnosis. Pulse reading is one diagnosis method among others such as urine, tongue or eyes analysis, but pulse diagnosis is the preferred technique. Tibetan Medicine qualifies the pulse wave using a descriptive method with lots of analogies of animal features and behaviors [24]. Certain qualities of the pulse are more prominent at certain locations of the bodies: radial artery at the wrist, carotid artery, forehead arteries (especially at the temporal sites), ankle arteries (such as lateral tarsal artery). In most cases, the radial artery is used by the doctor. The traditional doctor position three fingers (index, middle and ring) alongside the artery on each wrist to perform the diagnosis [30] using various pressure levels on the fingers. Figure 2 illustrates the finger position. This technique involved a physical contact between the patient and the doctor whereby the doctor uses his respiration when analysing the patient's pulse. The main challenge that took us about ten years was to translate the Eastern concepts to something that could be used using modern pulse sensing such as PPG. The Section 2.2 describes such a translation.

2.2. Western Pulse Wave Analysis: The Three Principles

It is nowadays well known from digital pulse wave analysis that the pulse waveform varies depending on the body location and contains information about the organs and tissues 'visited' by the travelling wave from the heart to the periphery [31,32]. Additionally, research started to appear on the effect of mental processes and emotions using features contained in the pulse wave [10,11,33,34] which correlates with the Tibetan Medicine approach shown in Table 1. The pulse wave description of Table 1 can be explained according to the following three principles: **Rhythm** (Quick, slow, fast, rolling, intermittent, (in)coherent), **Force** (Sunken, strong, empty, weak) and **Complexity** (Rough, sharp). These three principles can be interpreted using signal processing terminologies with the following physiological interpretation:

- **Rhythm**: is the way the heart beat intervals are distributed, fast or slow and regular or irregular, mainly as a manifestation of the autonomic nervous system activity. This quality can be reasonably well described using *heart rate*, *heart rate variability* and *breathing frequency* analysis [35–37],
- **Force**: is the strength of the blood pressure felt under the fingers. Our PPG sensor capture the changes in blood oxygenated red cell volumes. These changes are also correlated with increased diameter at the systole and reduced diameter at diastole. The peak-to-peak *amplitude* of the PPG signal is thus an indirect measure of the blood pressure [38]. The modulation depth is also felt under the finger as a varying force. This modulation depth can be measured using well known techniques of signal modulation for example as used when measuring the periodic breathing in cardiac patients [39],
- **Complexity**: are the details of the pressure wave shape felt under the fingers within each heart beat [40,41]. This behavior can be related to local vasoconstriction and/or dilation of the vessels as well as the arterial branching system which influences the location of the dicrotic notch as well as the amplitude of the dicrotic wave. It can be described using spectral entropies and location and bandwidth of the harmonics of the pulse wave. The shape of the pulse wave can have low, average or high *complexity* [42,43].

Table 2 shows a **qualitative** interpretation of the three energies in function of the three principles above which are directly connected to the physiological parameters described above. The goal of this Table is to give the reader an intuitive interpretation of the energies. Each of these principles are further linked with **quantitative** measures as shown in the Table 3 and described in detail in the Section 4.1.1..

The physiological processes involved in the quantification of the three energies can be quite complex as a nonlinear mix of inter beat intervals variability and pulse wave shape [44]. As a result, the qualitative interpretation from Table 2 must be turned into a quantitative one using machine learning techniques as exposed in Section 4.1. The complete flow chart of our work is shown in

Table 2. Relationship between the three energies and principles in terms of physiological parameters

	Stability	Activity	Transformation
Rhythm	Low, Variable	Average, Variable	High, Stable
Force	High	Low	Average
Complexity	Low	High	Average

Figure 1 where we clearly distinguish the TTM qualitative path (Traditional Eastern medicine) and the digital pulse wave analysis path (Technological Western medicine). The true three energies are the one diagnosed by the Tibetan physician, while the estimated ones are those derived from our algorithm.

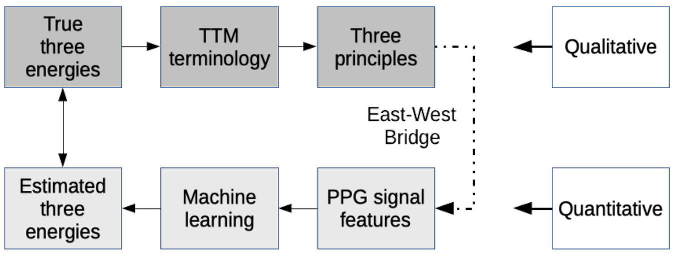

Figure 1. East-West bridge flow chart

3. Methods

The paper presents two studies that were conducted in two different countries at different times. The first study was conducted in Italy between 2008 and 2010. The purpose of the study was to investigate the use of PPG signals as a tool for analyzing the pulse wave in a similar way as a Tibetan doctor does. The final aim was to develop a PPG-based classification of the three energies. The second study was elaborated and realized at St Thomas Hospital in London in 2018 and was designed for the analysis of the pulse wave during periods of mental stress and relaxation. This second study served as a validation of the first study and additional analysis of the pulse wave harmonics.

Both studies conform with the seventh declaration of Helsinki (2013) on ethical principles regarding human experimentation developed for the medical community by the World Medical Association (WMA).

3.1. Study 1: Digital Tibetan Pulse Reading

3.1.1. Subjects

The subject pool consisted in 34 healthy participants (between 18 and 65 years of age, Male (13), Female (21)) engaged in studies at the Lama Tzong Khapa (Pomaia, Italy). Each participant gave an informed consent to this study and received an identification code (ID) to preserve privacy, and data from each subject was kept anonymously. This ID is used to identify the doctor assessment sheets, pulse wave recordings and clinical measurements. Amongst the 34 subjects, we have the following fairly equally distributed typology: Activity (14), Transformation (8) and Stability (12). The inclusion criteria were as follows: Healthy subjects, having a relation with the Institute Lama Tzong Khapa and/or living in the residential area close by, and willing to be enrolled for the entire duration of this study. Physical and mental health was ascertained by the medical doctor and psychologist in charge of this project. Exclusion criteria were as follows: Hypertension level 2 (Systolic >160 $mmHg$ and/or

Diastolic > 95 $mmHg$ without medication), Cardiovascular problems, Cancer, Diabetes, Breathing disorders, Mental illness such as schizophrenia, phobias, etc. Participants were given clinical advice after the study period, so that they are compensated for having participated in the study.

3.1.2. Protocol

At the time of the enrolment, participants were asked to complete a questionnaire with their background relevant data, such as age, gender, height and weight. Data were anonymised. According to Tibetan Medicine, the typology assessment requires the medical doctor and the patient to respect certain rules such as: diet and behavior the day before the reading and the time of the day which is traditionally early morning or at dawn when the outer and inner elements are the most balanced. Due to logistical constrains and the number of participants, we had to adapt these traditional rules by relaxing the time of day. The Tibetan doctor can slightly adjust his pulse diagnosis according to the time of when the assessment is done. The participants were asked to behave calmly and avoid eating spicy food and excitants the day prior to the recording. Routine subject information were recorded and done continuously during the study. When the participants visited the Tibetan doctor, they had a Tibetan pulse reading, which was immediately followed by our pulse wave sensor recording as described in Section 3.1.3. The total recording session were 30 minutes: 15 minutes for the Tibetan finger pulse reading and 3 to 5 minutes for the pulse wave recording. We used such a short recording time in order to avoid muscle tension, movement and sweating artefacts as much as possible.

1. Physiological measurements: blood pressure was measured using a standard automatic commercial oscillometric system (Omron IA2): systolic, diastolic and heart rate were reported and recorded on the Tibetan Doctor File (see Section 3.1.3),
2. Self-report: participants were asked to regularly fill a multiple choice report on temporary non-compliance, exercise, personal meditation practice, diet, work or study load.

The Tibetan doctor file was prepared with the help of Dr. Tsewang Tamdin director of the Men Tsee Khang Institute (Dharamsala, India) and his collaborators, and Dr. Nida Chenagtsang (director of the International Academy for Traditional Tibetan Medicine). The file contained information about the pulse reading as well as any information that the doctor felt necessary and useful for this study such as sleep and environment/social problems. This was important as this study lasted for a long period of time.

3.1.3. Pulse Wave Recording and Preprocessing

The Tibetan pulse information can be measured sequentially with one finger at a time as well as simultaneously with the three fingers as shown in Figure 2 and is traditionally assessed by the fingers' feeling of the doctor, placed along the radial artery. Each fingertip, index, middle and ring, assess different parts of the body: upper, middle and lower respectively. The index finger position is called *Tson* and corresponds to the Activity energy, the middle finger is called *Kan* and corresponds to the Transformation energy, and the ring finger is called *Chag* and corresponds to the Stability energy. The index is always placed toward the thumb in a flat position so that each side of the fingertip can sense the pulse wave. Left and right wrist pulse reading were taken.

Measurements performed by our pulse wave recording system rely on the photoplethysmogram (PPG). PPG is an optical non-invasive technology allowing the assessment of information related to subcutaneous blood circulation. By illuminating a living tissue with a light source, PPG can measure both arterial blood volume changes and blood content [45]. PPG measurements setups consist in a light source, a photo-diode and the electronics for signal conditioning and filtering. Our optical probe included a Light Emitting Diode (LED) emitting at 940 nm, and a photodiode located 1 cm apart. The electronic box includes an analog front-end (performing the continuous removal of ambient light reaching the photo-diode, and acquiring the raw optical signals 50 times per second (sampling frequency $F_s = 50Hz$) via a 24 bits Analog to Digital Convertor). Raw optical signals were transmitted

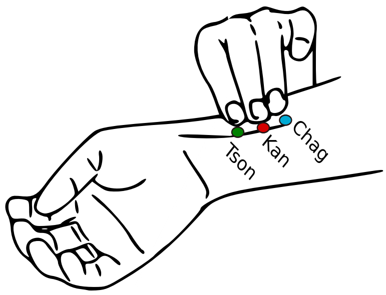

Figure 2. TTP doctor fingers position.

via an USB cable to a laptop where data were displayed and stored for further processing. The PPG signal was further upsampled to 100 Hz for further analysis. Left and right wrist PPG signals were recorded sequentially.

The sensor was made for single finger position measurement at a time and we used the index finger position. The index finger location is the one proximal to the thumb as can be seen in Figure 2. This location is particularly suited to analyze the properties related to the heart, lungs, small and large intestines. The sensor was then positioned on the radial artery in a similar way a Tibetan doctor would sense the pulse until the signal showed some stability as displayed on the screen of the computer running the recording software. Once an optimal position was found, the sensor was maintained with a wrist band during the duration of the recording. The PPG signals were analyzed off-line using Matlab software (MathWorks, Inc., Natick, Massachusetts, United States).

The PPG signal contained a large DC offset, slow drift and movement artefacts despite the instruction to the subject not to move the hand. Additionally, infrared sensor signals are known to be more susceptible to deep tissue structure which act as noise sources. The preprocessing consists in reducing these effects while keeping the main features of the pulse wave [46–48]. We used a quadratic detrending followed by Principal Component Analysis in State Space (PCA-SS) [49,50] with an additional frequency selection. The quadratic detrending was performed by removing a piecewise 2nd order polynomial fit to the data by block length of 10s. The PCA-SS was performed using a state space embedding of the time series with an embedding dimension of $m = 40$ and reconstruction lag $l = 1$ sample [**?**]. We selected the first 8 components corresponding to the largest eigenvalues of the trajectory matrix, thus reducing the amplitude of the high frequencies. We further selected from these components those for which the spectral content had a maximum between 0.05Hz and 12Hz. This choice of the frequency band corresponds to the physiologically plausible content of the pulse wave main harmonics. We have further used a wavelet based noise reduction method [48,51] which finally resulted in the preprocessed pulse wave signal $DPW(t)$.

3.2. Study 2: Mental Stress

The mental stress protocol has been presented in details in [11] and is briefly reproduced here for sake of ease of reading of this article.

3.2.1. Subjects

Ten young, healthy participants (4 males and 6 females, age range 23 – 31 *years*, BMI range 17.6 – 33.8 $kg\ m^{-2}$) participated in the study at St Thomas' Hospital, London. All participants completed a preliminary questionnaire about cardiovascular and mental health as well as any medications that could influence the results. Exclusion criteria were: diagnosed hypertension, heart arrhythmias, cognitive impairments. The *NRES Committee London – Westminster* approved the study IRAS ID

(168545) and REC reference (15/LO/1173). Participants could ask to withdraw or pause at any time during the study. Subjects received an ID code to preserve anonymity.

3.2.2. Protocol

The study protocol consisted of six phases as illustrated in Figure 3: instrumentation, baseline measurements, Stroop test 1, relaxation phase, Stroop test 2, and recovery. Blood pressure (BP) measurements and subjective stress assessment using a visual analog scale (VAS) were performed before and after each protocol phase. The study was conducted in a dedicated room, isolated from noise and other visual disturbances. The study phases are described next.

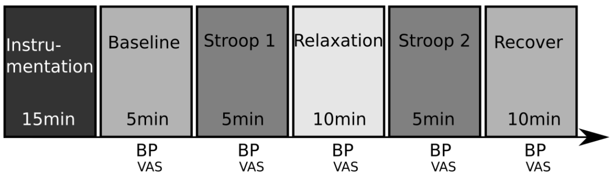

Figure 3. The six phases of the stress study. BP: Cuff blood pressure measurement; VAS: Visual analog scale for subjective stress assessment

During the *Instrumentation phase*, participants were provided with instructions on how to perform the Stroop test and relaxation phases, and measurement instruments were attached (as explained in the next section). As part of the routine clinical protocol at the hospital, participants completed the Patient Health Questionnaire (PHQ-9) [52]. The *Baseline phase*, consisted of acquiring measurements from participants whilst lying on a bed, head tilted up slightly, for five minutes whilst breathing spontaneously. In the *Stroop test 1 phase*, stress was induced using the color word Stroop test [53]. This test has been shown to provide reasonable results in terms of controlled induced stress and is widely used in psychology research. The test was performed for five minutes while subjects were lying down in the bed looking at a computer screen where the Stroop test was running. Participants were asked to answer simple word-color-matching questions, at an increasingly faster pace as the test progressed to compensate for the known adaptation process that participants undergo. In the *Relaxation phase*, participants used the Resperate system (Resperate, Inc) for ten minutes, which is designed to lower blood pressure through device-guided slow-paced breathing [54]. The breathing frequency range was adjusted for each individual according to his comfort zone. In the *Stroop test 2 phase*, a second Stroop test was conducted lasting five minutes. In the *Recovery phase*, participants relaxed, unaided and in silence, for ten minutes whilst isolated by a curtain. Reference assessments of stress were obtained at the end of each phase by asking participants two questions: (i) do you feel any pain or discomfort?; and (ii) how would you rate your stress level? Subjects provided responses using a VAS ranging from 0 to 10. The VAS has been successfully used in many psychological studies and has the great advantage of being very simple, especially during experiments when subjects are psychologically stressed [55].

3.2.3. Pulse Wave Recording and Preprocessing

PPG signals for pulse wave analysis were acquired using OH1 sensors (Polar Electro Oy) placed on the lateral site of the of the left upper arm. The OH1 device complies with electro-magnetic radiation safety, has been tested for skin biocompatibility. The OH1 sensor consists of a hexagonal arrangement of green light sources and measures PPG signals at 135 Hz. The digitalized PPG signal was further band passed filtered with a linear 4th order Butterworth filter with cutoff frequencies 0.2Hz - 15Hz. The quality of the PPG signal was far superior to the one used in the first study and thus required less preprocessing. The preprocessed PPG is called $DPW(t)$.

4. Results

4.1. Study 1: Digital Pulse Wave Classification

4.1.1. Feature Extraction

The PPG signal processing flow is summarised in Figure 4. It contained information about the **Rhythm**, **Force** and **Complexity** as described in Table 3. The features were computed from both the heart inter-beat intervals and the preprocessed PPG signal. All features were extracted using a rectangular sliding window of 30s with 50% overlap.

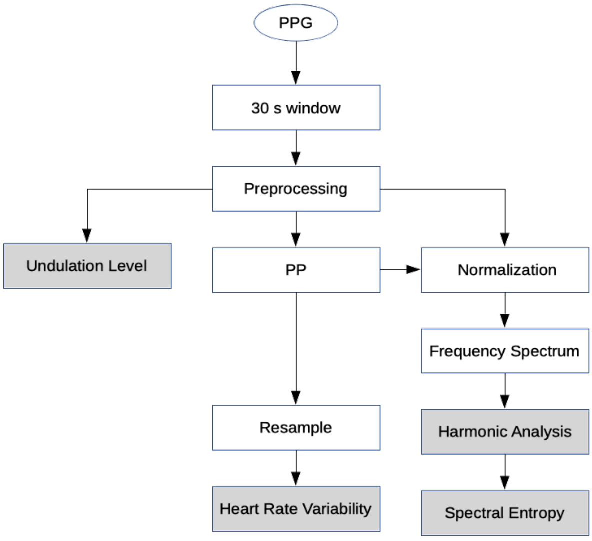

Figure 4. Pulse wave algorithm

Heart rate and linear heart rate variability: The PPG signal displayed fluctuations both in the frequency and amplitude domains. The fluctuations in the frequency domain are linked with known phenomena originating from the neuro-cardiovascular system such as respiration or emotions [56].

A peak detection algorithm was used to detect each diastolic point $P(k)$ from $DPW(t)$ at the heart beat k, and then derive the peak to peak intervals $PP(k) = P(k) - P(k-1)$. The peak detection algorithm consists in three steps: a Butterworth 4th order band-pass filter with cutoff frequencies 0.3Hz and 3Hz is applied to $DPW(t)$ followed by a first order derivative filter and an adaptive peak detection method. The Butterworh filter removes most of the high and low frequency noise. The slope of the $DPW(t)$ during the systole phase is characteristically high which results in a sharp peaked signal after the derivative. The adaptive peak detection method described in [57] was used to finally find the peaks. Spline interpolation around the detected peaks was further used to increase the peaks location accuracy. Please note that the location of the derivative peaks are not the location of the $DPW(t)$ systolic foot which can be easily located by looking backward to the next local minima. We have used a technique to automatically detect and eventually correct non-physiological PP intervals or ectopic beats [58]. The fluctuations of these PP intervals have been shown to be similar to the electrocardiogram peak R-wave intervals variability [59] for healthy subjects at rest and are thus suitable for our analysis. The interbeat intervals PP were quantified using their average value and variability: 1) the average pulse PPm, 2) the variance Rv, 3) the normalised Low Frequency (LF) Power (LFn: power in 0.04 Hz to 0.15 Hz) and 4) the normalised High Frequency (HF) Power (HFn: power in 0.15 Hz to 0.4 Hz). The normalisation of the LF and HF was performed by dividing them by the total power of the DC free PPG segment under analysis. Breathing is an important modulation factor both in the PPG amplitude and frequency, i.e.

the so-called Respiratory Sinus Arrhythmia (RSA). The RSA is usually measured from the PP interval in the frequency band from 0.1 Hz to 0.25 Hz when the person is in a calm spontaneous breathing state as typically the case when visiting a doctor. The breathing frequency BF was thus estimated as the frequency corresponding to the maximum frequency spectrum peak in this band.

Harmonic analysis: The pulse wave contains a rich spectrum which is essentially related to the different functions of the heart, vascular, autonomic nervous and respiratory systems, as well as other components from the different organs visited by this wave. In order to isolate the vascular part contained in the shape of each heart beat without the 'interference' of the heart beat variability, we have implemented a technique to normalise each heart beat pulse wave so that they have the same peak to peak amplitude of 1 and same duration of 1s [38]. From the knowledge of the peak wave instant $P(k)$, the procedure was performed in three steps: 1) to detrend each heart beat so that each diastolic points have zero amplitude, 2) to resample each heart beat wave using a linear interpolation method, and 3) to normalise each heart beat to an amplitude of 1. Once this procedure is performed on each heart beat pulse wave, we performed a spectral analysis and derive the power spectral density $P(\omega)$. We have used a Welsh method to estimate the power spectrum density. The number of harmonics Nb^H contained in $P(\omega)$, their amplitudes A_k^H, locations f_k^H, phases ϕ_k^H and bandwidths Δ_k^H, $k = 1, \dots, Nb^H$, were the main used spectral features. The fundamental frequency f_0^H corresponds to the heart beat average frequency: i.e. the heart rate. The bandwidth Δ_k^H of a signal x, centred around the frequency f_k^H, was computed as follows:

$$\Delta_k^H = \sqrt{\int_\Omega \tilde{P}(\omega) \left(\omega - 2\pi f_k^H)\right)^2 d\omega} \tag{1}$$

where Ω is the bandwidth of interest and $\tilde{P}(\omega)$ is an estimation of the energy-normalised power spectral density of $DPW(t)$: $\tilde{P}(\omega) = P(\omega) / \int_\Omega P(\omega) d\omega$. The bandwidth of the fundamental frequency is $BW = \Delta_0^H$. The parameter BW is thus proportional to the variance of the PP intervals, while $\Delta_{k>0}^H$ measure the variability of the smaller waves composing the heart pulse wave $DPW(t)$. The frequencies $f_{k>0}^H$ and phases $\phi_{k>0}^H$ are modulated by the arterio-venous tree properties such as branching (anatomy) and wall (i.e. endothelium) structures. These aspects are known to influence the shape of the pulse wave such as the crest time, dicrotic notch location and amplitude and dicrotic wave amplitude. Thus the frequency domain analysis is an other way to measure the influence of the anatomical, functional and local nervous system properties of the vessels. Mathematically, the Fourier transform of a signal contains exactly the same information as the time domain which further justify the use of the frequency analysis of the pulse wave. This harmonic frequency analysis has been studied by Chinese medical doctors [43,60,61] and scientists since years and are known to correlate with organ function as well. The amplitude of the PPG signal is usually not calibrated thus limiting the use of the absolute amplitude or power of such signal. However, the relative power using ratios of harmonics is relevant and indeed contains known health information [43,61–63]. In our work we will limit the number of harmonics to $Nb^H = 4$ and we use the harmonic power ratios as features: $H_{i,j} = A_i^H / A_j^H$ for $i, j = 0, .., Nb^H$ with $j > i$. One of the main advantage of using the harmonic analysis is that it is more easy and robust to compute than time domain parameters in the presence of noise.

Order analysis: A well known measure of regularity or order is entropy. The regularity of the pulse wave shape is relevant for our study and can be quantified using spectral entropy. Typically, narrow frequency band signals will have a small entropy as compared to broadband signals. The normalised Spectral Entropy (SE) in Ω is defined as:

$$SE = -\left(\int_\Omega \tilde{P}(\omega) \log(\tilde{P}(\omega)) d\omega \right) / \Omega \tag{2}$$

Table 3. Digital Pulse Wave Qualities and Features

DPW Qualities	DPW Features
Rhythm	Normalized PP Low Frequency (LFn)
	Normalized PP High Frequency (HFn)
	PP Variance (Rv)
	PP Average (Rm)
	Breathing Frequency (BF)
Force	Undulation Level (UL)
Complexity	Normalized Bandwidth (BW)
	Normalised Spectral Entropy (SE)
	Harmonic Ratios ($H_{i,j}$)

The regularity of the pulse wave in the time domain is characterised in first approximation by an Undulation Level (UL). The pulse wave is indeed modulated in amplitude due to various factors such as respiration, the autonomous nervous system or heart pacemaker dysrhythmias. The UL is also well adapted to measure the depth of modulation during RSA, and thus the influences of the respiration on the pulse wave amplitude fluctuations. The concept of the modulation depth used in this context is borrowed from the domain of telecommunication where the modulation depth is defined from the following equation:

$$x(t) = K(1 + UL\ Cos(\omega_{AM}t))\ Cos(\omega_{FM}t) + n(t) \quad (3)$$

where $\omega_{AM,FM}$ is the angular frequency of the (Amplitude,Frequency) modulated part of $x(t)$ and $n(t)$ is some zero mean noise. The modulation depth UL varies between 0 and 1. The estimation of UL can be performed using demodulation methods.

4.1.2. Features Selection and classification

Features Selection: In Table 3, the $9 + Nb^H(Nb^H)/2$ features are summarized. I order to condition our feature space in the best way, we have proceeded to a feature selection procedure. A method developed by Peng *et al.* [64] called mRMR (minimum Redundancy Maximum Relevance Feature Selection) has been chosen and applied to our feature set. The mRMR method need the feature values to be converted to symbols. In order to do this, we have quantized the features using a standard quantization method on 5 bits. Each quantized level is then assigned an integer value, which together with the classes are the input to mRMR. The result of mRMR is summarized as follows where the features have to be read from left to right and are in order of decreasing minimum redundancy. Progressively grouped features from left to right also have decreasing minimum redundancy.

$$\mathbf{Rv} \rightarrow \mathbf{SE} \rightarrow \mathbf{H_{2,4}} \rightarrow \mathbf{H_{1,2}} \rightarrow UL \rightarrow Rm$$

Due to the limited number of subjects and $DPW(t)$ signal duration, the number of feature points is quite limited. In order to improve the robustness of the classification, we have decided to make use of surrogates of the features. The way to produce high quality surrogates is explained in detail in [65]. Using Schreiber method as a first step, we have improved the surrogate by making them probability density function invariant as well. This second step guarantees that the surrogates' pdfs are preserved. This surrogate method is further used in this work to test the performance of the classifier by using Monte Carlo simulations of the classifier (see Section 4.1.2). In order to further ease the work of the classifier, we have performed a Principal Component Analysis in State Space (PCA-SS). The parameters for the nonlinear embedding are: dimension $m = 4$ and lag $l = 1$. The first 4 Principal Components have been retained.

Classification of the Three Energies: As explained in Section 2.1 each individual possesses a dominant Typology and sometimes manifest the other two in different proportions. The classification of the typology must thereby take this into account, which impose a classifier with continuous output values rather than binary. Fuzzy classifiers thus seems the most appropriate. Amongst the fuzzy classifiers, a special type of Artificial Neural Networks called Quantum Neural Networks (QNN) have shown promising properties [66]. These QNNs are a class of feedforward neural networks which can handle uncertain inputs and have a very flexible structure of hidden nonlinear layer in the form of a superimposition of sigmoidal functions with flexible amplitude, slope and shift. The hidden layer can focus or relax its *data representation* by concentrating or spreading around regions of certainties or uncertainties of the feature space more like a quantum wave function localize or spread out around certain or uncertain states bearing some resemblance to quantum systems and networks. Forty surrogate PCA-SS components are generated to train the QNN with one hundred batch iteration. We have validated the trained network using additional independent surrogated data. These validation surrogates are then used to compute the Receiver Operating Curves (ROC) of the QNN in a Monte Carlo simulation and an optimal threshold is found using the Youden index [67]. The confusion matrix is then computed from these Monte Carlo simulations at the Youden optimal point. The confusion matrix C expressed in percent is given as:

$$C = \begin{pmatrix} C_{1;1} & C_{1;2} \\ C_{2;1} & C_{2;2} \end{pmatrix} \tag{4}$$

The diagonal entries $C_{1(2);1(2)}$ are related to the percent of samples which are correctly classified in the respective Class 1(2). The off-diagonal entries in C have the following meaning: $C_{1(2);2(1)}$ is the percentage of samples from Class 1(2) which are classified as Class 2(1). The confusion matrix (4) has the following standard statistical meaning: for Class 1(2), $C_{1(2);1(2)}$ are the True Positive Rates (respectively True Negative Rates), and $C_{1(2);2(1)}$ are the False Negative Rates (respectively False Positive Rates) such that $C_{1(2);1(2)} + C_{1(2);2(1)} = 100$. The Sensitivities and Specificities for Class 1(2) are thus $Sen_{1(2)} = C_{1(2);1(2)}$ and $Spec_{1(2)} = C_{2(1);2(1)}$ respectively. Please note that in our 2-class problem, Sensitivity and Specificity are symmetrical. When assessing the performance of the classifier, we aim at maximizing the diagonal elements, while minimizing the off diagonal elements, ideally 100% and 0% respectively.

The classification is performed in two steps using two classifiers: Step 1: Separation of *Activity* from *Transformation* and *Stability* and Step 2: Separation of *Transformation* from *Stability*. This has proved to be the best strategy to maximize the classifier performances. The first classifier is called QNN First Pass (FP): QNN^{FP}. By assumption we assign Class 1 to *Activity*, while Class 2 is the union of *Transformation* and *Stability*: (*Transformation* - *Stability*). The confusion matrix at the optimal ROC point C^{FP} of the QNN^{FP} is given as:

$$C^{FP} = \begin{pmatrix} C^{FP}_{1;1} = 85(2) & C^{FP}_{1;2} = 15(2) \\ C^{FP}_{2;1} = 28(2) & C^{FP}_{2;2} = 72(2) \end{pmatrix} \tag{5}$$

The second classifier is called QNN Second Pass (SP): QNN^{SP}. By assumption we assign Class 1 to *Transformation*, while Class 2 is *Stability*. The confusion matrix at the optimal ROC point C^{SP} of the QNN^{SP} is given as:

$$C^{SP} = \begin{pmatrix} C^{SP}_{1;1} = 90(2) & C^{SP}_{1;2} = 10(2) \\ C^{SP}_{2;1} = 14(2) & C^{SP}_{2;2} = 86(2) \end{pmatrix} \tag{6}$$

Our classificaion results are summarized in Table 5

Table 5. Average Sensitivity and Specificity

	Stability	Activity	Transformation
Sensitivity	86%	85%	90%
Specificity	90%	72%	86%

4.2. Study 2: Mental Stress

Distributions of parameters across subjects were summarized using the median and inter-quartile range in box plots. Significant differences between parameters were identified using paired *t*-Tests (significance level $\alpha = 0.05$).

4.2.1. The Three Energies

Figure 5 shows the three energies computed according to the methodology presented above in each phase of the protocol for the 10 participants. Please note that the humours/energies have no units as they are the likelihood of each class and are bounded between 0 and 1. Activity and Transformation increased significantly from baseline to Stroop 1, while Stability stayed almost unchanged. During the breathing relaxation period, Stability increased significantly with an associated large dispersion across subjects, while the Activity and Transformation decreased significantly back to baseline. Stroop 2 manifested in a slight nonsignificant increase of Activity and Transformation with respect to baseline, while Stability decreased significantly from relaxation showing a reduced capacity to cope with stress. During the recovery period, Activity, Transformation and Stability came back to baseline with a noteworthy low dispersion of Stability.

The statistical analysis is summarized in Table 6 where the significance value $p_{m,n}$ is displayed with the following index convention: $n, m = 1$ for Baseline, $n, m = 2$ for Stroop 1, $n, m = 3$ for Relaxation, $n, m = 4$ for Stroop 2 and $n, m = 5$ for Recovery.

Table 6. Statistics for the three energies

Transformation	$p_{1,2} = 1.16\ 10^{-6}$; $p_{2,3} = 5.43\ 10^{-4}$; $p_{2,4} = 5.79\ 10^{-4}$; $p_{2,5} = 2.57\ 10^{-5}$
Activity	$p_{1,2} = 9.45\ 10^{-5}$; $p_{2,3} = 1.14\ 10^{-3}$; $p_{2,4} = 2.77\ 10^{-3}$; $p_{2,5} = 1.62\ 10^{-4}$
Stability	$p_{1,3} = 2.36\ 10^{-2}$; $p_{3,4} = 1.33\ 10^{-2}$; $p_{3,5} = 2.50\ 10^{-2}$

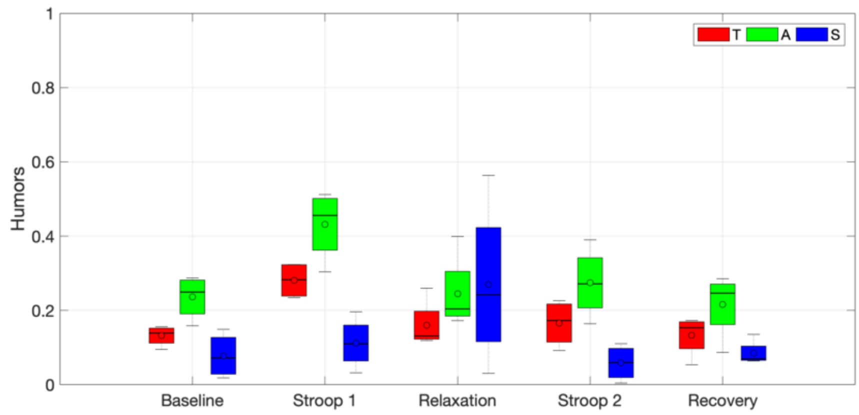

Figure 5. The three energies during the mental stress protocol

4.2.2. Harmonics

It has been suggested in [11] that the complexity of the pulse wave contour could be a further parameter able to discriminate the states of stress. In this continuation, the complexity of a wave can be quantified by its Fourier spectrum, and thus its harmonic content if this wave is periodic or quasi-periodic. As it was introduced in Section 4.1.1, the harmonic analysis proved to be a very efficient way to extract pulse wave structure parameters [43,61,68]. In order to further assess this hypothesis, we have analyzed the behavior of the harmonic ratios $H_{i,j}$ as defined in Section 4.1.1. Figure 6 shows the behavior of $H_{i,j}$ across the stress protocol. The harmonic ratios $H_{i,j}$ are unit-less. From Figure 6, we can observe that the harmonic ratios are changing during the various phases of the protocol, confirming that they contain information according to the stress/relaxation level as manifested by the vascular system. The second striking observation is a clear separation between the low and high harmonic ratios as indicated in Figure 6 by the red and green colored bars respectively. This indicate that the higher the harmonic frequencies the less differences between their amplitude. Visual inspection indicates that the relaxation procedure affect mostly $H_{1,2}$ and $H_{2,4}$ and that mental stress affects $H_{2,4}$ primarily. The highest harmonic ratio $H_{3,4}$ tend to decrease during the protocol.

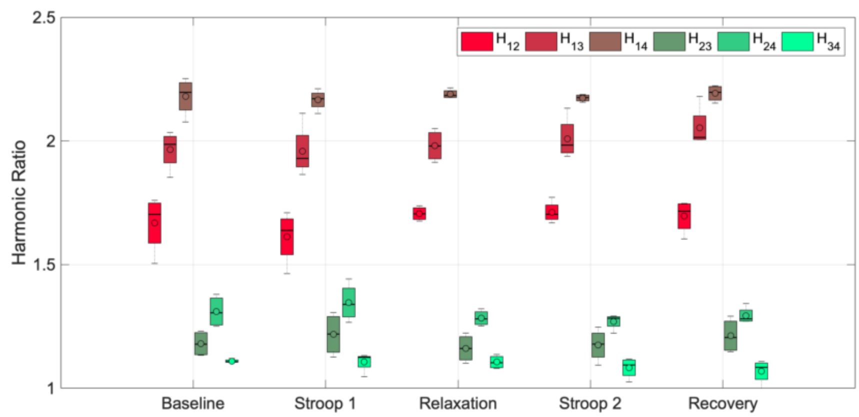

Figure 6. The harmonic ratios during the mental stress protocol

The statistical analysis is summarized in Table 7 with the same convention as above. $H_{2,4}$ and $H_{2,4}$ are thus good candidates for monitoring stress and relaxation. It was also selected by our feature selection algorithm in Section 4.1.1.

Table 7. Statistics for the harmonic ratios

$\mathbf{H_{1,2}}$	$p_{2,3} = 2.08\ 10^{-3}$; $p_{2,4} = 1.92\ 10^{-2}$
$\mathbf{H_{1,3}}$	$p_{1,5} = 3.45\ 10^{-2}$
$\mathbf{H_{2,4}}$	$p_{2,3} = 3.38\ 10^{-2}$; $p_{2,4} = 1.29\ 10^{-2}$
$\mathbf{H_{3,4}}$	$p_{1,5} = 2.52\ 10^{-2}$

We have further tested our hypothesis of the relationship between the time domain pulse wave analysis as presented in [10,11,69] and the harmonic ratios presented here. For this purpose, we have produced a simulated PPG based on a linear superposition of two bandpass filtered (Butterworth filter 2nd order with cutoff frequencies 0.3Hz and 4Hz) asymmetric sawtooth signals (shape is shown in Figure 6(a)). The asymmetrical sawtooth shape controls the systolic and diastolic heart contraction and relaxation phases, and noteworthy the crest time: i.e. the time from the foot to the peak systole. We have simulated different PPG with increasing crest time (CT), i.e. the the time delay between the onset of a pulse wave and the peak of the wave also called tidal wave peak, in the range of our clinical measurements [11] and performed a Fourier analysis to compute the $H_{1,2}$ and $H_{2,4}$ (continuous curves in Figure 7(b)). Figure 6(b) shows a very good agreement between the simulation and the clinical measurement harmonic ratios (color circles in Figure 7(b)).

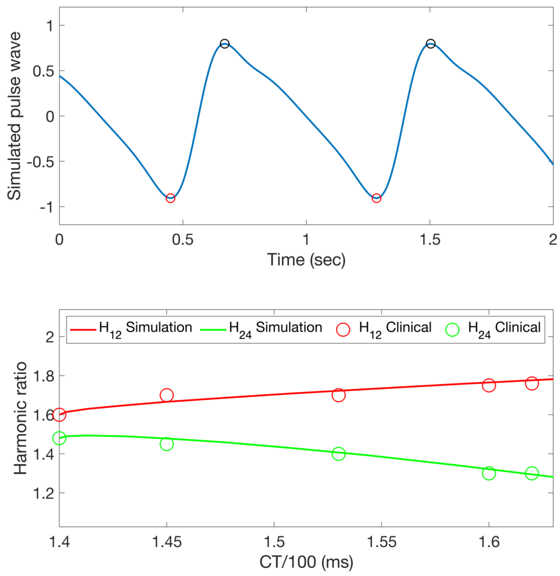

Figure 7. ((a) An example of a synthetic PPG signal with peak systole and diastole. (b) The relationship between the crest time (CT) and the harmonic ratios $H_{1,2}$ and $H_{2,4}$ from Figure 6

5. Discussion

The three energies. We have developed a methodology based on photoplethysmogram (PPG) pulse wave analysis to estimate the three fundamental energies of Traditional Tibetan Medicine (TTM). The three fundamental energies or humours described in TTM have been characterized using modern techniques of PPG analysis, both in time and frequency domains. The TTM pulse reading is essentially qualitative and holistic like all ancient medicinal systems. This synthetic view of health has been lost in modern analytical techniques which tend to view health and disease using compartmental approaches. Despite the success of the diagnostic techniques developed by Western science, there is a resurgence of integrative approaches viewing health in a more holistic way. There is thus a growing demand for using modern techniques of digital processing and machine learning based on ancient knowledge. Practiced by an experienced physician trained in TTM, it is quite challenging to assess the results of the method using quantitative modern techniques. In this work, we have been able to express the TTM pulse reading using the three principles of Rhythm, Force and Complexity. Each of these principles having a direct interpretation in terms of physiological processes as explained in Section 2.2. Moreover, these three principles can be implemented using PPG signals. The signal processing techniques used in this work are not novel by themselves, but their combination gives interesting insights has we combine two different approaches: 1) the beat to beat heart intervals and 2) the pulse wave shape. Both of these aspects are usually analysed separately in the literature for historical and research field application reasons. Similar approaches and aims have been developed from a Chinese pulse reading perspective [21,22] and noteworthy the work of Tang et al. [44] which uses an eight element approach similar to our three principles. The three TTM energies of Stability, Activity and Transformation are derived from the three principles which allowed us to have a holistic view on the human body function: namely the autonomic nervous system, the breathing system and the vascular system. An other approach based on time characteristics of the pulse pressure wave has been applied from an Ayurvedic point of view [17] and was proven useful in relation to arterial stiffness.The use of our approach can specifically be applied to chronic diseases or dysfunctions originating from multiple sources such as stress or sleep disorders, fibromyalgia, multiple sclerosis or mental problems such as ADD/ADHD or chronic stress.

Mental stress and the three energies. According to TTM, stress is primarily an Activity disorder associated with Transformation imbalance and manifest primarily in the nervous system with high impact on blood pressure and the vascular system. In a previous study, we have shown that time domain pulse wave analysis can be a complimentary tool for the analysis of mental stress specifically the crest time and the diastolic time of the pulse wave [10,11]. Both of these aspects are now mostly encoded in the principle of Complexity whereby a shortened diastolic time and crest time are reflected by an increased Complexity, i.e. increased BW and SE, which according to Table 2 reflect an increased Activity energy. This study further shows that in a state of stress, not only the Activity is increased but the Transformation energy which correspond to an increase of metabolic heat, heart rate and decreased heart rate variability as shown in Table 2. Ayurveda expert Lad [30] also relates the Activity energy (Vata in Ayurveda) to increased artery stiffness. The counter aspect of a stress state is a relax state. Relaxation is dominantly manifested as an increase in Stability energy and decrease in both Activity and Transformation. This is also mentioned by Lad whereby soft arteries related to Kapha: i.e. Stability. Increased levels of Activity and Transformation correspond to increased pulse wave velocity, whle normal to low level of Stability energy corresponds to reduced pulse wave velocity. Both pulse wave velocity and arterial stiffness have been shown to correlate with high blood pressure [69**? ?**]. Figure 5 illustrate this point clearly. On a physiological level, this corresponds to a decreased heart rate, increased heart rate variability, decreased arterial stiffness and blood pressure (especially systolic) and increased diastolic time as well as pulse transit time (timing between the main pulse peak and the dicrotic peak) [10,11]. This is again illustrated in our Table 2. The interesting finding is also the adaptation process to stress as shown in the Stress 2 and the recovery phase where the Activity and Transformation energies do not increase as significantly as in Stroop 1, and remain close or slightly decrease to that Stroop 2 state in the recovery phase. This indicates that a laboratory stress test is only a short term exploration of the stress phenomena. Further longer term recording of stressed people is needed to validate any stress quantitative metrics.

Mental stress and the harmonic ratios. Harmonic ratios have been studied in [43,61] in relationship with the Chinese medicine framework and the organs' function. It would be premature to draw conclusions from our study in relation to the energy/humor theory, but we can however mention that the harmonic ratios $H_{1,2}$ and $H_{2,4}$ could indeed be linked to the relationship between the heart and the lungs, and between the lungs and smaller organs involved in digestion respectively [43]. The harmonic ratios $H_{2,4}$ and $H_{1,2}$ were selected as a salient features for our classifier, thus also showing their relevance in the determination of the energies.

Our study further showed that the behaviour of $H_{1,2}$ and $H_{2,4}$ are related to the crest time from our previous analytical and clinical studies [10,11], thus making a bridge between time and frequency domain analysis of the pulse wave. As the crest time is also a good indicator of arterial stiffness [70–72], we can infer that the harmonic analysis can also gives insights into the health of the vascular system. The harmonic analysis can be a very useful tool to assess mental stress as it does not requires the task of detecting the various pulse wave features which can prove to be difficult in some situations [72] such as slight micro-movements, skin condition and perfusion. Additionally, it has been shown that this harmonic analysis is relevant for detecting pathological conditions such as coronary artery disease [63], hypertension [61], myocardial ischemia, decrease of heart function in type II diabetes patients [63].

6. Conclusion

In this work we have developed an algorithm based on photoplethysmogram for the estimation of the three humors known to be the essential energies governing our body and mind following the Traditional Tibetan Medicine system. In order to facilitate the understanding of these energies, we have tentatively defined Western terms such as Activity, Transformation and Stability. We have developed a strategy to translate the ancient Tibetan terms into three principles that guided us to implement our signal processing analysis. We have further used a classifier to estimate the three energies. The algorithm showed reasonable performances on a small selected set of pulse wave features.

We further applied the classifier to the test case of mental stress and active relaxation using paced breathing. Results showed consistent statistics with respect to both Tibetan Medicine interpretation and Western medicine physiological processes. We finally showed interesting results on harmonic analysis of the pulse wave and related our results with the crest time pulse wave feature which is known to be related to arterial stiffness and pulse wave velocity. Eastern medicine is holistic by nature and in our work we have shown the potential use of Traditional Tibetan medicine pulse reading for the assessment of mental stress and breathing relaxation techniques. Our digital sensing and processing approach is not aimed at replacing a qualified traditional physician but rather to give an additional tool for his assessment.

Several stress management interventions have been shown to be effective in both the workplace and personal settings [73]. This provides great incentive for developing wearable sensing and processing techniques to recognise elevated stress levels, prompting interventions to reduce stress levels, and potentially improve health. Eventually, our approach can be useful to this purpose, and also to complex chronic multi-source illnesses as well as a preventative tool for monitoring the quality of life.

Both traditional and modern medical systems have advantages and drawbacks, and certainly can benefit from each other. Specifically, traditional medicine would benefit from the technological advances of modern diagnostic tools.

7. Patents

A patent named: A method and system for determining the state of a person on the classification of the three humours, has been filed under EP2874539 and WO 2014/012839.

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Conflicts of Interest: P. Celka was an employee of Polar Electro Oy at the time of the mental stress study and declare no conflict of interests. Other authors declare no conflict of interests.

1. Brotman, D.J.; Golden, S.H.; Wittstein, I.S. The cardiovascular toll of stress, 2007.
2. Bolger, N.; DeLongis, a.; Kessler, R.C.; Schilling, E.a. Effects of daily stress on negative mood. *Journal of personality and social psychology* **1989**.
3. Khansari, D.N.; Murgo, A.J.; Faith, R.E. Effects of stress on the immune system, 1990.
4. McGrady, A. Psychophysiological mechanisms of stress. *Principles and practice of stress management* **2007**, *3*, 16–37.
5. Allen, J. Photoplethysmography and its application in clinical physiological measurement. *Physiological measurement* **2007**, *28*, R1.
6. Tuchin, V. *Handbook of Optical Biomedical Diagnosis*; SPIE Press, 2002.
7. Cavalcante, J.L.; Jac, L.; Redheuil, A.A.M. Aortic stiffness current understanding and future directions. *J Am Coll Cardiol* **2011**, *57*, 1511–1522.
8. Heffernan, K.S.; Karas, R.H.; Patvardhan, E.A.; Jafri, H.; JT, K. Peripheral arterial tonometry for risk stratification in men with coronary artery disease. *Clin Cardiol* **2010**, *33*, 94–98.
9. Prince, C.T.; Secrest, A.M.; Mackey, R.H.; Arena, V.C.; Kingsley, L.A.; others. Pulse wave analysis and prevalent cardiovascular disease in type 1 diabetes. *Atherosclerosis* **2010**, *213*, 469–474.
10. Charlton, P.H.; Celka, P.; Farukh, B.; Chowienczyk, P.; Alastruey, J. Assessing mental stress from the photoplethysmogram: A numerical study. *Physiological Measurement* **2018**, *39*, 054001.
11. Celka, P.; Charlton, P.; Farukh, B.; Chowienczyk, P.; Alastruey, J. Influence of mental stress on the pulse wave features of photoplethysmograms *The Institution of Engineering and Technology, Healthcare Technology Letters*, **2019**, under review
12. Zangróniz, R.; Martínez-Rodrigo, A.; López, M.; Pastor, J.; Fernández-Caballero, A. Estimation of Mental Distress from Photoplethysmography *Applied Sciences*, **2018**, *8* 69–84.
13. Madhan Mohan, P.; Nagarajan, V.; Das, S. R. Stress measurement from wearable photoplethysmographic sensor using heart rate variability data *In International Conference on Communication and Signal Processing, ICCSP 2016*, **2016**, *2016* 11141–1144.
14. Minakuchi, E.; Ohnishi, E.; Ohnishi, J.; Sakamoto, S., Hori; M., Motomura, M.; Hoshino, J.; Murakami, K.; Kawaguchi, T. Evaluation of mental stress by physiological indices derived from finger plethysmography *Journal of Physiological Anthropology*, **2013**, *32* 17–28.
15. Kageyama, Y.; Odagaki, M.; Hosaka, H. Wavelet analysis for quantification of mental stress stage by finger-tip photo-plethysmography *In Annual International Conference of the IEEE Engineering in Medicine and Biology*, **2007**, *2007* 1846–1849.
16. Nelson, M.; Stepanek, J.; Cevette, M.; Covalciuc, M.; Hurst, R.; others. Noninvasive measurement of central vascular pressures with arterial tonometry: Clinical revival of the pulse pressure waveform? *Mayo Clin Proc* **2010**, *85*, 460–472.
17. Nelson, M.; Stepanek, J.; Cevette, M.; Covalciuc, M.; Hurst, R.; others. Significance of arterial stiffness in Tridosha analysis: A pilot study *Journal of Ayurveda and Integrative Medicine* **2017**, *8*, 252–256.
18. Zarshenas, M.M.; Abolhassanzadeh, Z.; Faridi, P.; Mohagheghzadeh, A. Sphygmology of ibn sina, a message for future. *Heart views: the official journal of the Gulf Heart Association* **2013**, *14*, 155.
19. Nasser, M.; Tibi, A.; Savage-Smith, E. Ibn Sina's Canon of Medicine: 11th century rules for assessing the effects of drugs. *Journal of the Royal society of Medicine* **2009**, *102*, 78–80.
20. Chudakova, T. The Pulse in the Machine: Automating Tibetan Diagnostic Palpation in Postsocialist Russia. *Comparative Studies in Society and History* **2015**, *57*, 407–434.

21. Velik, R. An objective review of the technological developments for radial pulse diagnosis in Traditional Chinese Medicine. *European Journal of Integrative Medicine* **2015**, *7*, 321–331.
22. Luo, C.H.; Chung, Y.F.; Hu, C.S.; Yeh, C.C.; Si, X.C.; Feng, D.H.; Lee, Y.C.; Huang, S.I.; Yeh, S.M.; Liang, C.H. Possibility of quantifying TCM finger-reading sensations: I. Bi-sensing pulse diagnosis instrument. *European Journal of Integrative Medicine* **2012**, *4*, e255–e262.
23. Kim, H.; Kim, J.Y.; Park, Y.J.; Park, Y.B. Development of pulse diagnostic devices in Korea. *Integrative medicine research* **2013**, *2*, 7–17.
24. Donden, Y. *Health through balance: An introduction to Tibetan medicine*; Motilal Banarsidass Publ., 2003.
25. Norbu, N. *On Birth and Life - A Treatise on Tibetan Medicine*; Shang-Shung Edizioni, 1983.
26. Clark, B. *The Quintessence Tantras of Tibetan Medicine*; Snow Lion Publications, 1995.
27. Lad, V. *Ayurveda: The science of self-healing: A practical guide*; Lotus press, 1984.
28. Ni, M. *The Yellow Emperor's Classic of Medicine: A new translation of the Neijing Suwen with commentary*; Shambhala Publications, 1995.
29. Wang, Y.Y.L.; Wang, S.H.; Jan, M.Y.; Wang, W.K. Past, Present, and Future of the Pulse Examination. *Journal of traditional and complementary medicine* **2012**, *2*, 164–177.
30. Lad, V. *Secrets of the Pulse: The Ancient Art of Ayurvedic Pulse Diagnosis*; Motilal Banarsidass,; 2nd edition, 2007
31. Nichols, W.W. Clinical measurement of arterial stiffness obtained from noninvasive pressure waveforms. *American journal of hypertension* **2005**, *18*, 3S–10S.
32. Couceiro, R.; Carvalho, P.; Paiva, R.; Henriques, J.; Quintal, I.; Antunes, M.; Muehlsteff, J.; Eickholt, C.; Brinkmeyer, C.; Kelm, M.; others. Assessment of cardiovascular function from multi-Gaussian fitting of a finger photoplethysmogram. *Physiological measurement* **2015**, *36*, 1801.
33. Goshvarpour, A.; Goshvarpour, A. Poincaré's section analysis for PPG-based automatic emotion recognition. *Chaos, Solitons & Fractals* **2018**, *114*, 400–407.
34. Li, F.; Yang, L.; Shi, H.; Liu, C. Differences in photoplethysmography morphological features and feature time series between two opposite emotions: Happiness and sadness. *Artery Research* **2017**, *18*, 7–13.
35. Choi, A.; Shin, H. Photoplethysmography sampling frequency: pilot assessment of how low can we go to analyze pulse rate variability with reliability? *Physiological measurement* **2017**, *38*, 586.
36. Shaffer, F.; Ginsberg, J. An overview of heart rate variability metrics and norms. *Frontiers in public health* **2017**, *5*, 258.
37. Charlton, P.; Birrenkott, D.A.; Bonnici, T.; Pimentel, M.A.; Johnson, A.E.; Alastruey, J.; Tarassenko, L.; Watkinson, P.J.; Beale, R.; Clifton, D.A. Breathing Rate Estimation from the Electrocardiogram and Photoplethysmogram: A Review, 2017.
38. Millasseau, S.C.; Guigui, F.G.; Kelly, R.P.; Prasad, K.; Cockcroft, J.R.; Ritter, J.M.; Chowienczyk, P.J. Noninvasive assessment of the digital volume pulse: comparison with the peripheral pressure pulse. *Hypertension* **2000**, *36*, 952–956.
39. Fernandez Tellez, H.; Pattyn, N.; Mairesse, O.; Dolenc-Groselj, L.; Eiken, O.; Mekjavic, I.B.; Migeotte, P.F.; Macdonald-Nethercott, E.; Meeusen, R.; Neyt, X. eAMI: a qualitative quantification of periodic breathing based on amplitude of oscillations. *Sleep* **2015**, *38*, 381–389.
40. Elgendi, M.; Norton, I.; Brearley, M.; Abbott, D.; Schuurmans, D. Detection of a and b waves in the acceleration photoplethysmogram. *BioMedical Engineering Online* **2014**.
41. Elgendi, M. Detection of c, d, and e waves in the acceleration photoplethysmogram. *Computer methods and programs in biomedicine* **2014**, *117*, 125–136.
42. Powell, G.; Percival, I. A spectral entropy method for distinguishing regular and irregular motion of Hamiltonian systems. *Journal of Physics A: Mathematical and General* **1979**, *12*, 2053.
43. Huang, C.M.; Wei, C.C.; Liao, Y.T.; Chang, H.C.; Kao, S.T.; Li, T.C. Developing the effective method of spectral harmonic energy ratio to analyze the arterial pulse spectrum. *Evidence-Based Complementary and Alternative Medicine* **2011**, *2011*.
44. Tang, A.C.; Chung, J.W.Y.; Wong, T. K. S. Digitalizing Traditional Chinese Medicine Pulse Diagnosis with Artificial Neural Network *Telemedicine and E-Health*, **2012**, *18* 446–453.
45. Allen, J. Photoplethysmography and its application in clinical physiological measurement. *Physiol Meas* **2007**, *28*, 1–39.

46. Renevey, P.; Vetter, R.; Krauss, J.; Celka, P.; Depeursinge, Y. Wrist-Located Pulse Detection using {IR} Signals, Activity and Nonlinear Artifact Cancellation. *Proceedings of IEEE EMBS 2001* **2001**, pp. 1–4.
47. Celka, P.; Vetter, R.; Renevey, P.; Verjus, C.; Neuman, V. Wearable biosensing: signal processing and communication architecture issues. *Journal of Telecommunications and Information Technology, Special Issue on e-Health: Wearable devices, Personal Health Management Systems and Services based on biosensors* **2005**, *4*, 90–104.
48. Celka, P.; Vetter, R.; Gysels, E.; Hine, T. Dealing with randomness in biosignals. In *Winterhalder M*; Schelter, B.; Timmer, J., Eds.; Wiley-CVH Verlag GmbH & Co, Berlin: Handbook of Time Series Analysis. Recent Theoretical Developments and Applications, 2006; pp. 101–141.
49. Vetter, R.; Vesin, J.M.; Celka, P.; Renevey, P.; Krauss, J. Automatic Nonlinear Noise Reduction Using Local Component Analysis and {MDL} Parameter Selection. *EMBS 2003, Cancun, Mexico* **2003**, *1*, 491–496.
50. Cutmore, T.; Celka, P. Composite noise reduction of ERps using wavelets, model-based and principal component analysis subspace methods. *J of Psychophysiology* **2008**, *22*, 111–120.
51. Mallat, S. *A Wavelet Tour of Signal Processing*; Academic Press, 1998.
52. Kroenke, K.; Spitzer, R.L. The PHQ-9: A New Depression Diagnostic and Severity Measure. *Psychiatric Annals* **2002**,*32*, 509–515.
53. Scarpina, F.; Tagini, S. The stroop color and word test, **2017**, *8*, 557.
54. Brook, R.D.; Appel, L.J.; Rubenfire, M.; Ogedegbe, G.; Bisognano, J.D.; Elliott, W.J.; Fuchs, F.D.; Hughes, J.W.; Lackland, D.T.; Staffileno, B.A.; Townsend, R.R.; Rajagopalan, S. Beyond medications and diet: Alternative approaches to lowering blood pressure: A scientific statement from the american heart association. *Hypertension* **2013**.
55. McCormack, H.M.; Horne, D.J.; Sheather, S. Clinical applications of visual analogue scales: a critical review. *Psychological medicine* **1988**.
56. Saul, J.; Kaplan, D.; Kitney, R. Nonlinear interactions between respiration and heart rate: a phenomenon common to multiple physiologic states. *Comp. Cardiol.* **1988**, *15*, 12–23.
57. Arberet, S.; Mathieu, L.; Renevey, P.; Sola, J.; Grossenbacher, O.; Andries, D.; Sartori, C.; Bertschi M. Photoplethysmography-based ambulatory heartbeat monitoring embedded into a dedicated bracelet *IEEE Conference, Computing in Cardiology*, **2013**, *40* 935–938.
58. Lippman, N.; Stein, K.M.; Lerman, B.B. Comparison of methods for removal of ectopy in measurement of heart rate variability. *American Journal of Physiology-Heart and Circulatory Physiology* **1994**, *267*, H411–H418.
59. Moraes, J.; Rocha, M.; Vasconcelos, G.; Vasconcelos Filho, J.; de Albuquerque, V. Advances in photopletysmography signal analysis for biomedical applications. *Sensors* **2018**, *18*, 1894.
60. Wang, Y.; Chang, S.; Wu, Y.; Hsu, T.; Wang, W. Resonance. The missing phenomenon in hemodynamics. *Circulation research* **1991**, *69*, 246–249.
61. Wang, Y.Y.L.; Hsu, T.L.; Jan, M.Y.; Wang, W.K. Theory and applications of the harmonic analysis of arterial pressure pulse waves. *Journal of Medical and Biological Engineering* **2010**, *30*, 125–131.
62. Wang, Y.Y.L.; Jan, M.Y.; Shyu, C.S.; Chiang, C.A.; Wang, W.K. The natural frequencies of the arterial system and their relation to the heart rate. *IEEE Transactions on Biomedical Engineering* **2004**, *51*, 193–195.
63. Chang, C.W.; Liao, K.m.; Chang, Y.T.; Wang, S.H.; Chen, Y.c.; Wang, G.C. The First Harmonic of Radial Pulse as an Early Predictor of Silent Coronary Artery Disease and Adverse Cardiac Events in Type 2 Diabetic Patients. *Cardiology research and practice* **2018**, *2018*.
64. Peng, H.; Long, F.; Ding, C. Feature selection based on mutual information: Criteria of max-dependency, max-relevance, and min-redundancy. *IEEE Trans on Pattern Analysis and Machine Intelligence* **2005**, *27*, 1226–1238.
65. Schreiber, T.; Schmitz, A. Surrogate time series. *Physica D* **2000**, *142*, 346–382.
66. Menneer, T. Quantum Artificial Neural Networks. PhD thesis, Faculty of Science, University of Exeter, 1998.
67. Youden, W.J. Index for rating diagnostic tests *Cancer* **2009**, *3*, 32–35.
68. Wang, L.; Pickwell-Macpherson, E.; Liang, Y.P.; Zhang, Y.T. Noninvasive cardiac output estimation using a novel photoplethysmogram index. *Conference proceedings : Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Conference* **2009**.
69. Alty, S. R.; Angarita-Jaimes, N.; Millasseau, S. C.; Chowienczyk, P. J. Predicting arterial stiffness from the digital volume pulse waveform *IEEE Transactions on Biomedical Engineering*, **2007**, *54* 2268–2275.

70. Sheng, C. S.; Li, Y.; Huang, Q. F.; Kang, Y. Y.; Li, F. K.; Wang, J. G. Pulse Waves in the Lower Extremities as a Diagnostic Tool of Peripheral Arterial Disease and Predictor of Mortality in Elderly Chinese *Hypertension*, **2016**, *18* 527–534.
71. Hsu, P. C.; Wu, H. T.; Sun, C. K. Assessment of Subtle Changes in Diabetes-Associated Arteriosclerosis using Photoplethysmographic Pulse Wave from Index Finger *Journal of Medical Systems*, **2018**, *42* 43.
72. Wu, H. T.; Liu, C. C.; Lin, P. H.; Chung, H. M.; Liu, M. C.; Yip, H. K.; Liu, A. B.; Sun, C. K. Novel application of parameters in waveform contour analysis for assessing arterial stiffness in aged and atherosclerotic subjects *Atherosclerosis*, **2010**, *213* 173–177.
73. Khoury, B.; Sharma, M.; Rush, S.E.; Fournier, C. Mindfulness-based stress reduction for healthy individuals: A meta-analysis, 2015.