Leman Micro Devices

FLYING BLIND OR TAKING CONTROL?

OPPORTUNITIES AND REQUIREMENTS FOR PERSONAL SENSORS THAT MEASURE OUR HEALTH

A White Paper from Leman Micro Devices SA, Lausanne, Switzerland

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SUMMARY

The first generation of sensors were aimed at tracking fitness, making simple measurements of inputs (what have I done) such as how many steps have I taken today rather than outputs (how is my health). The second generation picked off easier health-related targets like pulse rate (heart rate) but have struggled to find a use for the results.

The third generation is emerging, measuring what we really need to know: the Vital Signs, as used by doctors everywhere. These are not toys, they are regulated medical devices: accurate, credible and safe.

This White Paper examines such devices using LMD's V-Sensor as a model.

It starts with those basic Vital Signs – blood pressure, temperature, blood oxygen, pulse rate, respiration rate, all of which must be measured to high accuracy.

After that, it considers some of the other clinical measurements that it has been shown to make, including a 1-lead ECG, arterial stiffness (both general and peripheral), Cardiac Output, Aortic Systolic Pressure and the identity of the user. This section ends by showing how it can also find the timing of the valves and muscles of the heart.

The next section speculates on what a fourth generation sensor might do, either one derived from the V-Sensor or following its design principles.

The underlying message is clear – medically accurate and regulated sensors will become ubiquitous, costing only a few dollars and integrated with or connected to the device that almost everyone already carries, the smartphone.

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CONTEXT

In the 50 or so years since the emergence of micro-electronics, we have transformed the way we communicate with each other and interact with the world.

Banking, dating, booking a taxi and finding the way in an unknown town have been with us for hundreds of years but personal communications have made them easier, more efficient and cheaper.

Interactions with the world rely on sensors and measurements of everything from the remote doorbell so I can see the delivery to my home while I'm sitting on the beach to real-time reporting by jet engines to their makers.

Our cars are full of sensors – we've come a long way from only checking fuel and oil pressure, now every feature is instrumented and logged so we can not only diagnose faults after they occur but also anticipate them.

Increasingly we do the same with smarthomes that automatically check the weather forecast to optimise the heating before it turns cold.

But we've been slow to do the same for our bodies and their health.

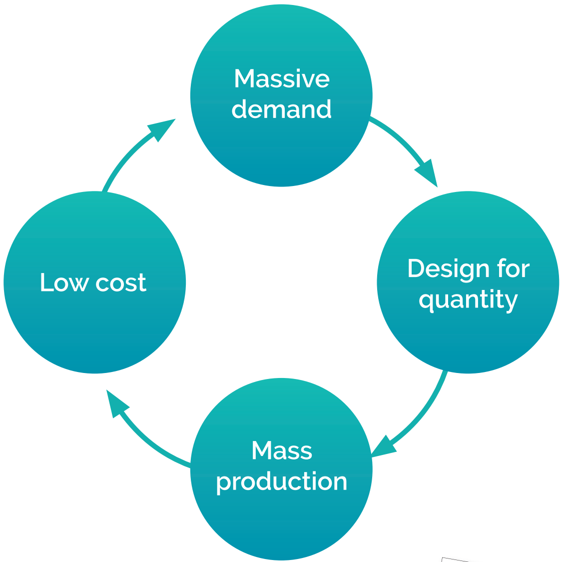
This White Paper is concerned with sensors as part of the growth of personal medicine, towards a world in which patients take responsibility for their care and where that care is tailored to their needs.

Medical technology has traditionally been trapped in a vicious circle – it is expensive so there are few devices and they are owned by the "white coats", held centrally and shared between many patients. The aim is to diagnose what has gone wrong, not to anticipate and prevent it happening.

Our model for the future

This White Paper looks at how we will monitor our own health with accurate, reliable, inexpensive and ubiquitous sensors. They will be ubiquitous because they will exploit the platform of our mobile phones, the powerful computer that is always with us, and will be either integrated like the camera or connected wirelessly from a watch or pocket device.

Micro-electronics offers this opportunity – the vicious circle is replaced by a virtuous circle that starts by assuming that there is massive demand because we all want to take control of our health.



Structure of this White Paper

This paper considers many different medical measurements, most if not all of which are traditionally made and owned by the "white coats".

For each one, it describes the measurement and what it means, what is needed for it to be democratised, and our solution. Not all of those solutions exist now – some do, some have been demonstrated in research and some are still speculation – but together they form a map for the future of personal medical technology.

BASIC CAPABILITY – THE FIVE VITAL SIGNS

> *Hypertension is one of the world's most neglected killers, affecting a quarter of the adult population. It's easily treated if you know that you've got it; a reliable BP measuring device costing less than $5 would save many lives.*

Sir George Alleyne, Director Emeritus of the Pan American Health Organisation

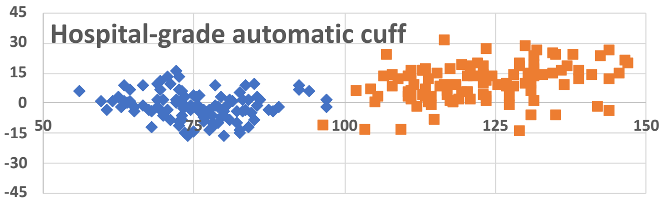
Hypertension

Hypertension (high blood pressure), is the #1 risk, affecting over 1.1 billion people and causing 10.4 million deaths per year[1]: 1 every 3 seconds. It is a "silent killer" - usually asymptomatic - and easily treated using cheap drugs and lifestyle changes if you know that you have it. A study by a health economist found that a readily available blood pressure monitor would add on average 6 months to the life of a young adult[2].

A reliable device like Sir George Alleyne called for would have three important qualities:

• **Absolute** – there are many devices that measure the change in BP which have to be calibrated using a cuff and recalibrated every few days or weeks. Advice that can only tell you the change in your blood pressure since you last measured it with a cuff will not help to detect hypertension – after you've used the cuff you have no need of the device. It can be useful for detailed diagnosis but does nothing for the billion people who have asymptomatic hypertension. The only absolute solution currently available to the general public is the automatic cuff.

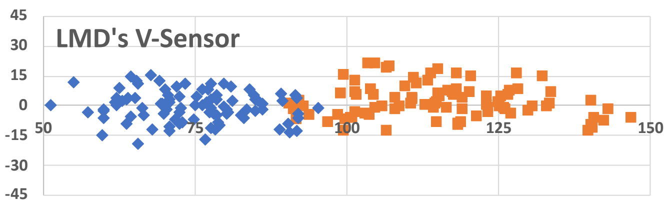
• **Accurate** – there is an ISO standard for the accuracy of blood pressure meters, if they do not meet that, they are not credible. The main requirement of the ISO standard is that 90% of the results are within 15 mm of value measured by two trained medics using a manual cuff, mercury column and stethoscope. Here's a carefully controlled test of a hospital-grade automatic cuff.



- o Vertical axis - difference between the values from the automatic cuff and the nurses
- o Horizontal axis – average of the two values, for systolic and diastolic BP

• **Comfortable** – if the measurement is not easy, quick and painless, people will not make it. Blood pressure varies from minute to minute and with time of day, with general health and even how you are sitting. Frequent measurements are needed to give a significant indication.

LMD's patented V-Sensor works in the same way as a cuff, by balancing the pressure inside the artery with a pressure applied outside the artery and detecting when the artery wall collapses or occludes. The difference from a cuff is that it uses the arteries in the fingertip and asks the user to press harder or softer to create the pressure. Here are the results of similar trial of the V-Sensor.



BASIC CAPABILITY – THE FIVE VITAL SIGNS

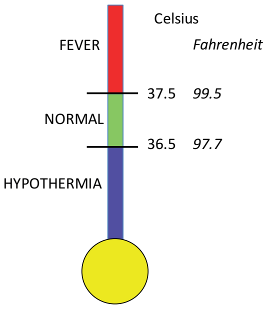
I believe in evidence. I believe in observation, measurement, and reasoning, confirmed by independent observers.

Isaac Azimov

Temperature

A raised temperature is a reliable sign of infection or inflammation and a very low temperature (hypothermia) shows excessive exposure to cold air or water. Tracking temperature is also used to help women know when they are most fertile and likely to conceive a baby.

A thermometer is the medical device that is most likely to be found in the home. Unfortunately, that's often where it is, not with you when you need it. Many home thermometers have poor accuracy or require contact with the body. A big step forward would be a thermometer that is:



- **Convenient and easy to use** – always with you, quick and simple
- **Hygienic** – non-invasive and preferably non-contact
- **Accurate** – ±0.5˚C for diagnosis, repeatability ±0.2˚C for successive measurements by one person

LMD's V-Sensor has a non-contact infra-red thermopile and uses other sensors in the module and the processing power of the phone to make an accurate reading on the forehead.

It takes 2 seconds to move it up to the forehead and take it away. The result is displayed instantly and meets the ISO standard for accuracy.

A second mode works over a much wider range of temperatures, allowing you to check that your pizza is cooked or that the freezer is operating properly.

Blood oxygen

Oxygen is transported from our lungs to the whole of the body by the haemoglobin in red blood cells. They change colour when they are rich in oxygen – arterial blood is bright red, the blood in veins, after the oxygen has been used by the body, is darker.

The colour indicates the fraction of available oxygen capacity in the blood (SpO2). SpO2 is normally 95% to 100%. It falls with altitude because the pressure of oxygen in the air falls – typically it is around 85% to 90% in an aircraft and around 75% when 5,000m up a mountain. The ISO standard demands accuracy of ±4% for measuring SpO2 between 70% and 100%.

SpO2 is an effective early warning of hypoxia – the condition where the body is short of oxygen – brought about by a lack of oxygen in the air or a respiratory condition such as Chronic Obstructive Pulmonary Disease, asthma or a respiratory infection such as Covid-19. It is very important for checking new-born babies. Specialist sports trainers use SpO2 to monitor intense interval training.

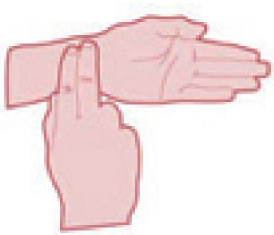
Finger clip devices that detect the colour of the blood in the finger artery are routinely used in hospitals and are often carried by mountain guides to check that their clients are fit to continue. The V-Sensor uses this standard technique but, with the V-Sensor, you need no extra device – it is measured automatically with blood pressure.

BASIC CAPABILITY – THE FIVE VITAL SIGNS

Pulse rate

Pulse rate (or heart rate) is the number of times that your heart beats per minute (bpm). Even if you're not an athlete, knowledge about your pulse rate can help you monitor your fitness level — and it might even help you spot developing health problems. If you're sitting or lying and you're calm, relaxed and not ill, your pulse rate is normally between 60 (beats per minute) and 100 (beats per minute). A lower pulse rate is also common for people who have a lot of physical activity or are very athletic. Pulse rate is affected by many factors, including air temperature, body position, emotions and medications, and can indicate infection and inflammation.

The usual way to measure pulse rate is by holding the patient's wrist and counting pulses while 15 seconds pass on the watch, then multiplying by 4. Many mobile devices measure pulse rate using the camera and flash because it is easy to do.



We measure pulse rate with the V-Sensor at the same time as measuring blood pressure. Because we have several sources of accurate data and a powerful computer, we can check that the pulse rate is sufficiently stable. If it varies too much, especially if it falls, we assume that the user has not taken time to become calm and relaxed so the blood pressure might be wrong. If it is stable, we display that average bpm.

Respiration rate

Respiration rate is the number of breaths taken per minute, typically 12 to 16. It is usually estimated by counting the chest movements while timing one minute or, in hospital, monitoring with a clip attached to the nose.

Respiration rate is an important indicator of many different conditions, from predicting cardiac arrest to diagnosing respiratory diseases.

Outside the hospital, the time that it takes for the respiration rate to return to normal after a period of aerobic exercise can be an indicator of fitness.

The V-Sensor allows a quick and simple measurement of the respiration rate that is useful for routine health monitoring. When we breathe in and out, we change our pulse rate and blood pressure. The V-Sensor detects these small changes and finds the respiration rate, at the same time as measuring blood pressure.

National Early Warning Score (NEWS)

The UK NHS has adopted a scoring system to assess the severity of a Covid-19 infection. It combines some qualitative observations, with the sum of 5 quantitative scores

Systolic BP		Temperature		Pulse rate bpm		Respiration rate		SpO2**	
<90	+3	<35	+3	<41	+3	8	+3	<91%	+3
91-100	+2	35 - 36	+1	41 - 50	+1	9 - 11	+1	92% - 93%	+2
101-110	+1	36 - 38	0	51 - 90	0	12 - 20	0	94% - 95%	+1
111-219	0	938 - 39	+1	91 - 110	+1	21 - 24	+2	>96%	0
>220	+3	>39	+2	111 - 130	+2	>25	+3		
				>131	+3				

** Used for original NEWS score but not in revised NEWS2

LMD'S V-SENSOR

Function – how does it work?

The V-Sensor has 3 sensing systems and its ASIC "brain":

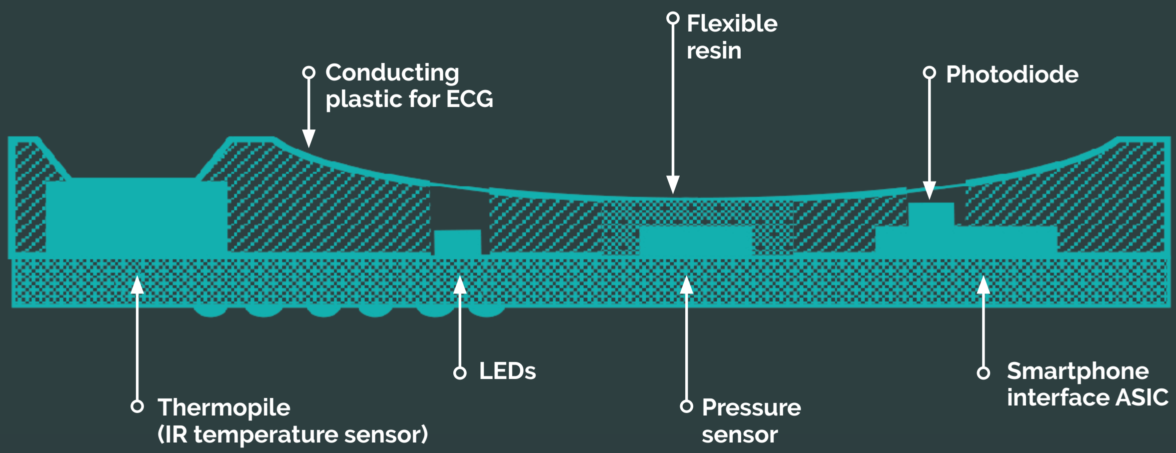
- **Pressure sensor** – a MEMS device embedded in a flexible resin to transmit the pressure from the surface of the skin
- **Optical sensor** – two LEDs and a photodiode constitute a classic pulse oximeter
- **Temperature sensor** – a MEMS thermopile with an integral silicon window
- **ASIC** – LMD's custom Application Specific Integrated Circuit that conditions and digitises the signals from the sensors, drives the LEDs and communicates via I^2C

Design philosophy

The V-Sensor was designed for mass production, in quantities of hundreds of millions.

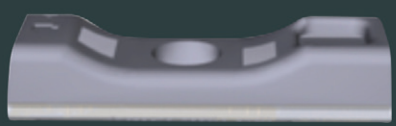
The ASIC is made in one of the biggest fabs in the world and the V-Sensor is built by leading chip assemblers.

Assembly is fully automated and every device goes through a 100% test and characterisation cycle in which the sensor outputs are measured at a range of temperatures and pressures - the results are coded in a set of calibration laws unique to that device.



Materials and structure

The cover is injection-moulded carbon-reinforced plastic to give strength and electrical conduction. The optical windows are waterproof transparent plastic or silicon.



It is 15 mm long, 5 mm wide and 2.7 mm high

V-Sensor in mobile & wearable devices

V-Sensor integrates easily with a wide range of devices. The I^2C interface is standard in Smartphones and it can equally be integrated with a smart watch, a stand-alone device or even with a device with some other function like a computer mouse or TV remote control.

DEMONSTRATED CAPABILITY – WITH THE CURRENT SENSOR

The V-Sensor collects around 1 MB of data during every blood pressure measurement, yielding much more information than just blood pressure.

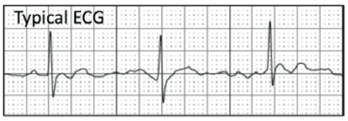
The ECG sensor integrated into the device provides both precise timing of the initiation of the pulse and insight into many conditions that can be diagnosed from a 1-lead signal between the two arms.

The V-Sensor may be used with other sensors that are already integrated with the host smartphone or wearable to derive even more information.

This section summarises some of the future capabilities that have been tested without any change to the V-Sensor hardware – all can be implemented using only additional software.

ECG – signal and its uses

The ECG is obtained by measuring the voltage between the finger resting on the V-Sensor and a finger of the other hand resting on a second electrode.



There is extensive research[3] into the use of 1-lead ECG for diagnosing atrial fibrillation and other conditions such as bundle branch block.

Either the PPG or ECG signals may be used to detect arrhythmias, including tachycardia, bradycardia and atrial fibrillation. The measurements may be made either at random times or in response to other symptoms such as palpitations, anxiety, fatigue, and breathlessness.

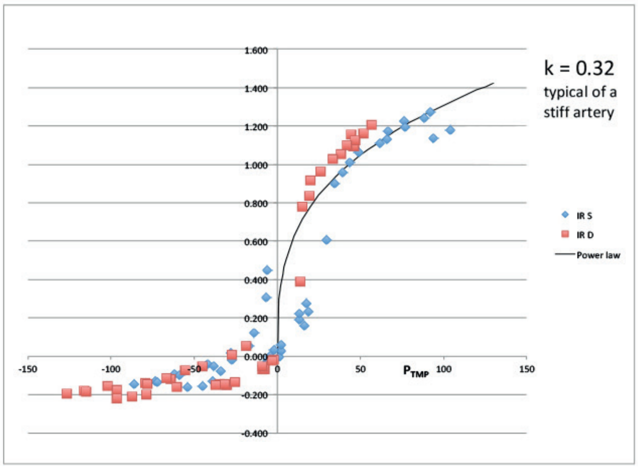
Arterial stiffness

The stiffness of the arteries is a valuable cardio-vascular diagnostic. The V-Sensor offers two ways of measuring it: peripherally in the finger and extensively between the heart and finger. There is some evidence that the difference between peripheral and general arterial stiffness is an early indicator of diabetes[4].

The change in PPG from diastole to systole is proportional to the change in luminal area and the measured pressure outside the artery allows us to find the trans-mural pressure P_{TMP} (difference between the systolic or diastolic pressure and the pressure surrounding the artery). We plot luminal area against P_{TMP}.

A power law of the form $A \propto P_{TMP}^{k}$ gives a close approximation to the measured values of Langeworters[5] and Drzewiecki[6], and thus

$$\frac{\Delta P}{\Delta A} \propto 1/k.$$



Arterial stiffness can also be found from the time interval between the ECG signal initiating a pulse and the PPG signal indicating its arrival at the finger. The Pulse Wave Velocity is found by making assumptions about the Pre-Ejection Period and arm length.

From PWV, arterial stiffness is found using the Moens-Korteweg equation[7]:

$$PWV = \sqrt{\frac{A}{\rho} * \frac{\Delta P}{\Delta A}}$$

Cardiac output

Total systemic compliance can also be found from PWV using Bramwell–Hill equation[8,9]

$$C_T = 37 * \frac{1}{PWV^2}$$

From total systemic compliance, Cardiac Output (CO) is found using Systolic Volume Balance[10].

$$Q_{SVB} = \frac{C_T * PP}{T - \frac{P_{SM} * T_S}{P_{Mean}}}$$

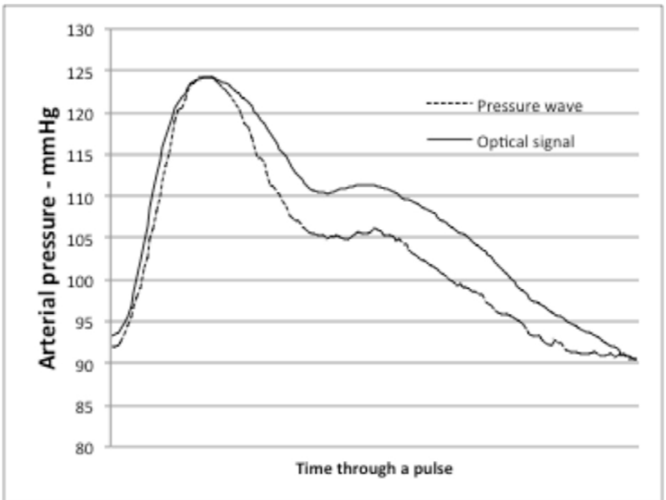
The V-Sensor measured CO for healthy subjects at between 4.5 and 6.5 litres per minute[11].

DEMONSTRATED CAPABILITY – WITH THE CURRENT SENSOR

Aortic Systolic Pressure

Measurement of the arterial stiffness allows the instantaneous blood pressure to be found throughout the pulse, not just at diastole and systole.

A typical measured PPG optical signal and the corresponding reconstructed pressure wave are shown. From this it is possible to estimate the augmentation index and Aortic Systolic Pressure[12].



Identification of the user

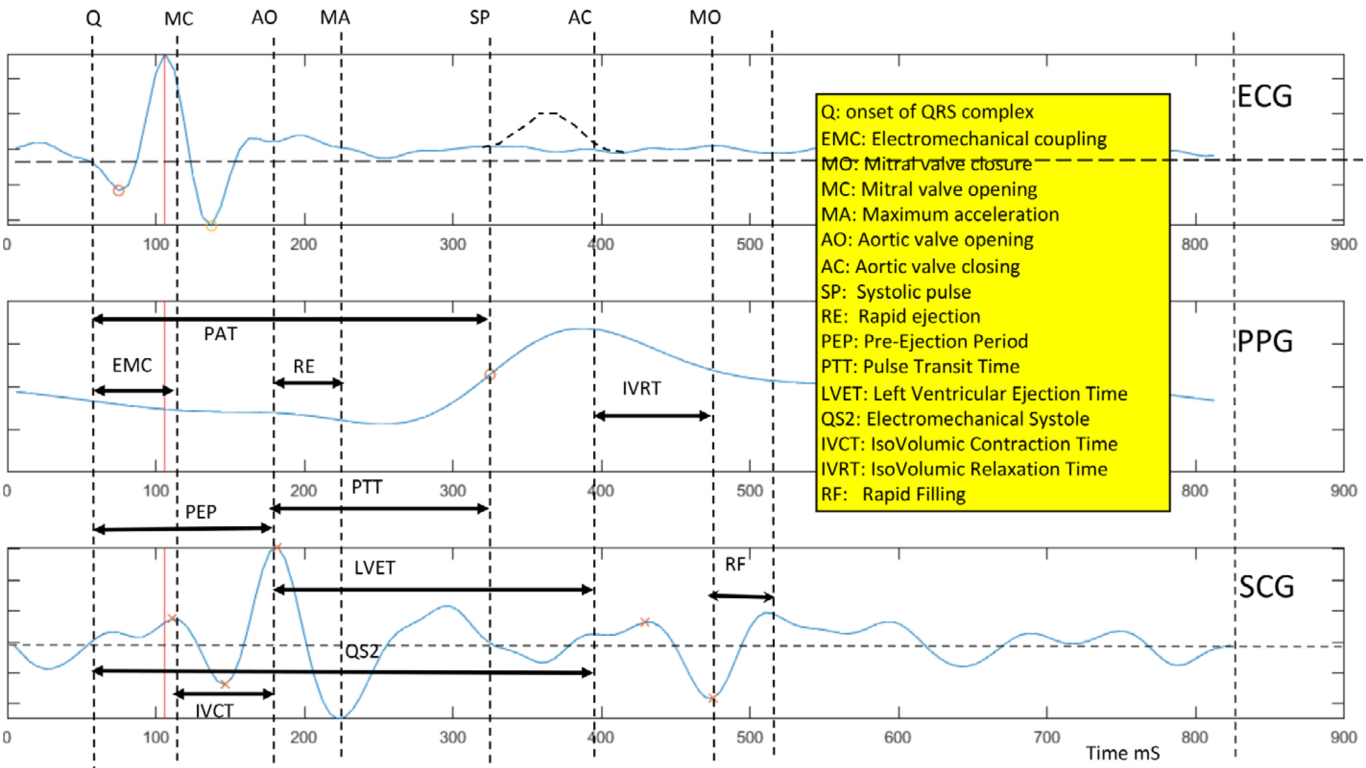
Even without the ECG signal, the data collected by the V-Sensor can recognise a user from a group of 10 with a certainty of around 90%[13]. With ECG, the accuracy can be over 98%[14].

Identification becomes important in some of the possible future applications of medical sensors considered in the next section.

Heart valve timing

Before the development of ultrasound, there was considerable interest in SeismoCardioGraphy (SCG). This is the detection of small vibrations of the body caused by the movements of the heart and its valves[15]. It has largely fallen out of use until recently, when the availability of inexpensive and very sensitive 3-axis accelerometers again made it interesting.

Mobile phones include such accelerometers[16]. LMD measured the accelerometer signals when the phone is held against the sternum while simultaneously recording PPG and ECG from the V-Sensor. Typical results are shown below: the top trace is the ECG, the second the PPG at the finger and the third the principal axis of the accelerometer signals. The recorded signals have been marked with the events with which they are associated.



SPECULATION – WHAT MIGHT BE POSSIBLE?

> *Healthcare will make the smartphone market look small.*

Tim Cook, Apple

This section explores some other clinical uses of sensors similar to the V-Sensor, either derivatives of it or new devices that use similar components and the same design philosophy.

Continuous blood pressure

The are many devices that estimate changes in blood pressure using either PWV or the form of the PPG curve. All suffer from the need to be calibrated and frequently recalibrated for the absolute blood pressure of each user.

The V-Sensor can be used to make an absolute calibration measurement of blood pressure then estimate the change from the calibration using Pulse Wave Analysis[17] or Pulse Wave Velocity[18]. The V-Sensor thus provides the benefit of absolute, frequent and easy measurements of blood pressure and pulse-to-pulse variations in blood pressure without needing any external device.

Arrythmias

The detection and classification of arrhythmias, particularly Premature Ventricular Contraction, might be made more reliable using the ECG and PPG[19]. A premature beat causes the volume of blood pumped by that beat to be reduced. A missed beat causes the volume of blood pumped on the next beat to be increased. The illustration shows a premature beat in the ECG and PPG traces.

It might be possible to use this to characterise arrhythmias. They are associated with other symptoms such as fainting (syncope) when not enough blood reaches the brain because pulse rate is too low (<20 bpm) or too high (>200 bpm). It remains to be investigated if there is sufficient peripheral circulation to allow the arrhythmia to be assessed, even if the patient is unable to use the device and a friend or health specialist holds the device against the patient.

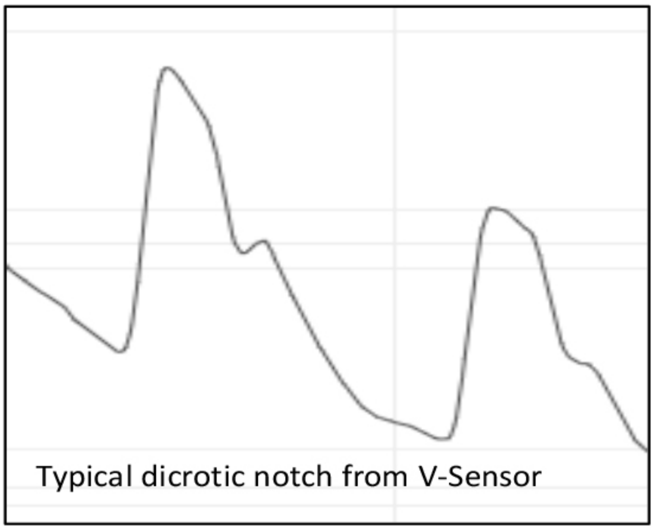
Arterial glucose and other analytes

Cuffless and calibration-free blood pressure is one of the two "Holy Grails" of health sensing. The V-Sensor already has that one; the other is non-invasive measurement of arterial glucose and LMD has a solution. Like the original Holy Grail, many people have searched widely. There is extensive literature and many patent applications but none of the ideas have worked. In this crowded field, LMD's invention has been recognised as novel and granted a patent in 8 countries including Europe, China and the USA.

Paper studies have shown that it is capable of accurate sensing using an optical technique and that it could equally be used for other substances in the artery such as alcohol.

Detecting sepsis

Sepsis is a major killer – more than 1 million Americans get severe sepsis each year, and it is fatal for 28-50% - often because it is recognised too late for effective treatment. There is growing evidence [20,21,22,23] that biomarkers such as those measured by the V-Sensor and its future derivatives can make effective early detection.



Analysis of dicrotic notch

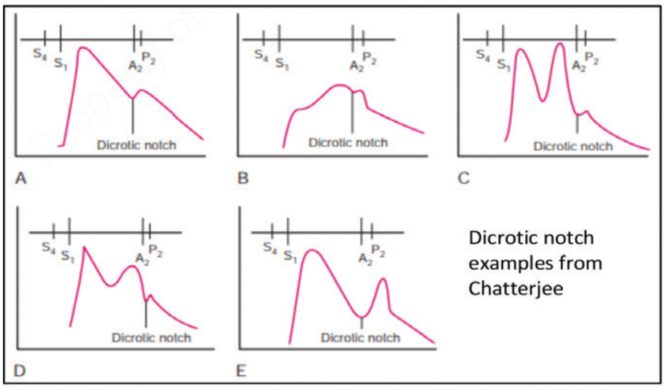
The dicrotic notch is created when the aortic valve closes. Its form might be indicative of the state of that valve, or other properties of the heart. Because the applied pressure is known and controlled, the V-Sensor can give a more stable notch than many other devices.

Chatterjee[25] cites five examples of forms of the aortic dicrotic notch and associated waveform;

A Normal (similar to example from V-Sensor)

B Suggests fixed left ventricular outflow obstruction

C Pulsus bisferiens, suggests aortic regurgitation



D Pulsus bisferiens, suggests hypertrophic obstructive cardiomyopathy

E Suggests sepsis or severe heart failure

The dicrotic notch changes as the pressure wave passes towards the peripheral arteries[24]. The technique used to reconstruct Aortic Systolic Pressure might also be used in the opposite direction to correct for this.

Tissue stiffness and hydration

It has been found to be necessary to take account of the measured properties of the tissue surrounding the arteries in order to develop algorithms to measure blood pressure accurately. Those properties change between subjects and with time. It is believed that the change is related to the state of hydration of the tissue, in part because of the similarity to the hydration test that indicates skin turgor[26]. If this is correct, it should be possible to make an objective measure of hydration.

Anticipating sudden cardiac arrest

Marijon[27] has reported that there are markers in the vital sign data that can warn of incipient Sudden Cardiac Arrest up to one month before the event. Survival rate is low (~7%) but rises to 32% if the warning signs are used to call timely intervention by the emergency services.

The sensitivity and specificity of the warnings identified by Marijon might be enhanced by precise, quantified and frequent measurements.

Integration with diagnostic systems and health records

The V-Sensor can be integrated with systems that exploit artificial intelligence, both to create new interpretations of its data and to feed its analyses directly into diagnostic decision algorithms.

As telehealth grows in importance, its measurements can also be integrated into a remote consultation and its results merged into the user's health records. This will require a reliable way of identifying the user (mentioned earlier) to ensure that the records are accurate.

Insurers have a strong interest in promoting the health of their customers but this raises issues of privacy. One approach might be for the V-Sensor, or more accurately the device that hosts it, to inform the insurer that the user has, for example, checked her/his blood pressure but not report the result. This will ensure that the user benefits from early detection and warning without compromising confidential data.

DEFINITIONS AND REFERENCES

Definitions

- ECG – Electrocardiogram – the electrical signal between the two hands (1-lead version)
- ISO - International Standards Organisation - sets requirements for accuracy & safety
- PPG – Photoplethysmogram or photoplethysmography – optical sensing of the artery
- MEMS - Micro-Electro-Mechanical Systems
- SpO2 - a measure of the amount of oxygen-carrying hemoglobin relative to that not carrying oxygen
- I^2C – a standard bus for connecting sensors to a processor

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