Graduate thesis

NTNU
Norwegian University of Science and Technology

Jacob Askeland Schärer

Analysis of circadian temperature and bioimpedance rhythms using a body-worn sensor

Graduate thesis in Medical Studies
Supervisor: Ellen Jaatun
Co-supervisor: Anne Dragøy Hafstad, Solfrid Romundstad
January 2023

NTNU
Norwegian University of
Science and Technology

Jacob Askeland Schärer

Analysis of circadian temperature and bioimpedance rhythms using a body-worn sensor

Graduate thesis in Medical Studies
Supervisor: Ellen Jaatun
Co-supervisor: Anne Dragøy Hafstad, Solfrid Romundstad
January 2023

Norwegian University of Science and Technology

NTNU
Norwegian University of
Science and Technology

Introduction

The number of elderly and frail people in the population is increasing, so is also the number of patients with chronic diseases living at home. For many of these patients, the symptoms of deterioration show up late in the disease trajectory. Delayed management of symptoms and chronic diseases pose increased suffering and is costly to reverse. The current state of the art to assess these patients are both invasive and less accurate than desired. Because of these diagnostic and healthcare domain challenges, digital sensor patches have been developed to assess and monitor patients in a healthcare setting.

Both external (heat, trauma), physiological (intake, aging, pregnancies, exercise) and pathological stressors such as cancer, renal failure, heart failure, endocrine disorders, gastrointestinal diseases and surgery may induce fluid imbalances. In an aging population, dehydration may lead to hypotension, electrolyte imbalances, renal failure, medical intoxications, tachycardia, fatigue, heat- stress and stroke. Fluid overload is also a common complication associated with several conditions such as hypertension, oedemas, renal and heart failure. Fluid imbalances are therefore a massive cost for the society. Monitoring of the hemodynamic changes in the human body is important but challenging. According to an article by Scheeren and Ramsay (2019), there is an ongoing shift from more invasive methods to less or non-invasive methods. In the article they discuss the accuracy of these methods and conclude that many of these non-invasive methods are inaccurate when measured statically, but the accuracy will increase when using dynamic or continuous methods (Scheeren & Ramsay, 2019).

When monitoring a physiological response or pathological changes over time, the physiological changes have to be taken into account. Most living organisms have built-in biological clocks which control their physiology and behaviour (Mehling & Fluhr, 2006). These clocks help produce biological rhythmical activities such as gene expression, secretion of hormones and behaviour. The rhythms manifest at different time periods, like daily, monthly and seasonally. (Ince, 2022). A good example of a seasonal biological rhythm is shedding and changing of the coat in the animal kingdom, which is due to a endogenous biological rhythm in the fur follicles, that again is affected by numerous factors in the body. (Stenn & Paus, 2001) A good example of a monthly rhythm may be the menstrual cycle in humans (Ince, 2022).

The daily cycle is called a circadian rhythm, derived from Latin “circa diem” which means “about a day”, and lasts about 24 hours (Vitaterna et al., 2001). These are present in most of the organs in the human body (Zhu & Zee, 2012), and persist due to genetical expression in the cells (Sand et al., 2014). They affect a lot of physiological processes, like sleep, temperature, hormones and blood pressure (Brodal, 2013). The circadian rhythms are endogenous, and will persist even without time cues from the environment (Zhu & Zee, 2012). Typically, the circadian rhythms last a little longer than a day, in adults the average circadian rhythm is about 25 hours (Czeisler et al., 1999).

The suprachiasmatic nucleus (SCN) is located in the hypothalamus and can override the endogenous biological clocks. Therefore, it works like a “pacemaker” for the rest of the body (Zhu & Zee, 2012). The SCN gets signals by exogenous factors or time cues, so called “Zeitgebers” which is German for “time-givers” (Vitaterna et al., 2001). This means that the body can synchronise its circadian rhythm with the surroundings. The main Zeitgeber is light, which again affects the levels of melatonin (Zhu & Zee, 2012). The production of melatonin is inhibited by light, and increases in a dark environment, this increase leads to sleepiness. Other Zeitgebers might be sound, smell, the temperature of surroundings, meals (Sand et al., 2014) and activity (Brodal, 2013).

In addition to affecting sleep, the circadian rhythms play a role in several other processes in the body, like changes in body temperature and blood pressure. About two hours before natural awakening, the body has its lowest temperature, this point is called the nadir (Zhu & Zee, 2012). In an article from (2006), Johnsson and Moan wrote that human beings with nadir at 4:30 will have their highest temperature at about 19:00.

The body is also displaying a circadian rhythm in blood pressure, which is increasing rapidly in the morning, reaching its highest level in the evening (Johnsson & Moan, 2006), and then again decreasing during the night (Zhang et al., 2021). The two main factors deciding blood pressure are cardiac output (CO) and the systemic vascular resistance.

About 60% of the body weight in a healthy adult is water and the fluid is distributed into two compartments: the intracellular fluid (ICF) and extracellular fluid (ECF, Figure 1). The ICF is located inside the cells, mainly as cytoplasm, and makes up about 40% of the total body

weight. The rest of the water is ECF and consists of plasma and interstitial fluid (Brinkman et al., 2022). An increase in the ECF will increase the cardiac preload, resulting in an increased CO and consequently higher blood pressure and *vice versa* if the preload is reduced The total peripheral resistance is affected by several factors, among these, vasoconstriction is playing an important role (Karppanen, 1991).

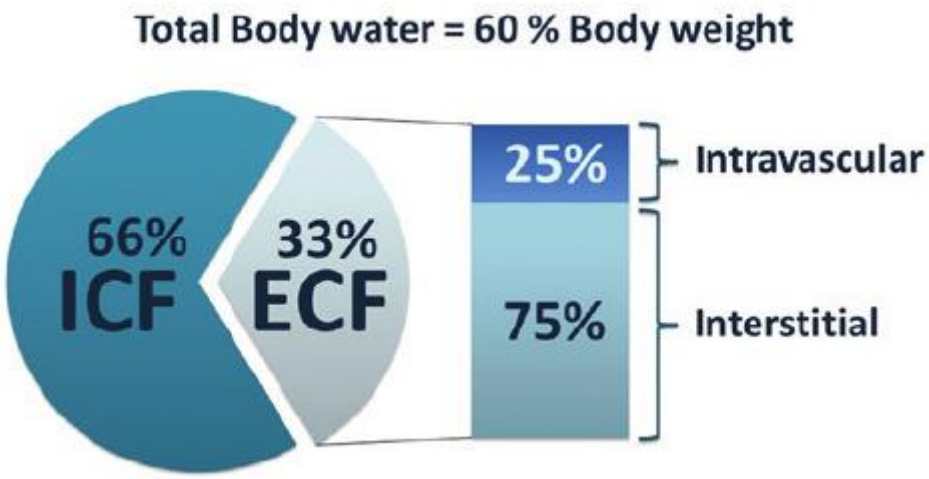


Figure 1: The distribution of fluids in the body. (Chan & Stanzani, 2014)

Circadian rhythms of blood pressure and fluid balance are controlled by numerous processes. One factor is the circadian rhythms in the kidneys, which will speed up the diuresis in an active phase during the day, and slow down to an inactive phase during the night (Firsov & Bonny, 2018). Another factor is the activity of hormones controlling body fluid and vascular reactivity. One of these hormones is vasopressin, also known as antidiuretic hormone (ADH) (Halse, 2022), this affects the kidneys, making them retain fluid, which will raise ECF and blood pressure. Cortisol is also a hormonal regulator of the blood pressure, increasing it when released. It is activated by the body to tolerate stress. The body also has an important regulatory system in the renin-angiotensin-aldosterone system (RAAS). Activation will lead to sodium retention and higher blood pressure in addition to stimulating ADH production (Patel et al., 2017).

Most of the endocrine system exhibit circadian rhythms. An important example is cortisol which peaks in the early morning before awakening. ADH, given a normal daily rhythm, will have its highest level around 8:00 and lowest at about 20:00 (Johnsson & Moan, 2006). The

high levels of ADH and cortisol in the late night and morning are explaining the rapid rise in blood pressure in the morning hours. Another example from the endocrine system is testosterone, which follows the same rhythm as cortisol. The changes in blood pressure, diuresis and hormonal system indirectly and directly affect the sodium concentration on an intra- and extra-cellular level.

Sodium is quantitatively the most important electrolyte when it comes to the osmolality in the ECF. The body is regulating the osmolality through excretion and intake of both salts and water by diuresis or inducing thirst. The cells have water channels (aquaporines), which makes it possible for water to diffuse freely between the extracellular space and the intracellular space, making the osmolality approximately the same. This means that changes in osmolality will change the volumes of ECF and ICF, and the changes of these can indicate changes in the hydration levels. (Joergensen et al., 2019). Bioimpedance is a measuring method that is simple in use, non-invasive and can detect small changes in sodium concentrations.

This technology measures the electrical resistance in the tissue and may be applied in many ways and for different purposes. It is often used to estimate body fat percentage through a whole body bioimpedance measurement. It can also be used for monitoring changes in electrolytes in the tissue compartments. This can indicate changes in hydration levels.

By applying a spectrum of frequencies from high (typically above 50 kHz) to low (below 20 kHz) frequencies, more detailed information about extra and intracellular tissue can be displayed (Grimnes & Martinsen, 2015). The high frequencies will pass the cell membranes, and will measure the bioimpedance for both the ECF and ICF (Grimnes & Martinsen, 2015). Low frequencies are not able to pass the cell membranes and will only measure the bioimpedance for the ECF. (Grimnes & Martinsen, 2015; Khalil et al., 2014). When measuring bioimpedance through a segment of the body, it is possible to calculate changes in the bioimpedance for ECF, ICF and total fluid in the specific segment. Continuous measurements can be utilized to gather important information about physiological and pathological changes in the body segment over a period of time.

Monitoring of temperature may also be useful in several situations. Temperature changes can give us information about many processes in the human body, such as predicting ovulation

and the menstrual cycle (Yu et al., 2022) and measuring fever in patients with an infection (Nakamura, 2011). Continuous measurements of the temperature will also give us information about the circadian rhythms in the body (Zhu & Zee, 2012).

The most common way of measuring temperature is using the core temperature. According to Norsk Elektronisk Legehåndbok (2019), the diagnostic criteria for fever is a temperature of 38°C or above, measured rectally. The arguments for this are that superficial measurements like orally, axillary or in the ear canal are more exposed to temperature changes from the environment. This makes the results less reliable for point-measurements. This project is using continuous measurements from a body worn sensor patch placed on the skin. As mentioned, peripheral sensors are exposed to changes from the environment, like temperature changes or moisture. Wearable sensor technology may offer a possibility to continuously monitor and transmit data from the patient's home. A reliable bioimpedance sensor patch with high quality data may enable us to provide a better healthcare service to patients living at home. The aim of this pilot study is to assess whether bioimpedance and skin temperature data can provide accurate information about people's circadian rhythms.

The research question is therefore: Are peripheral measurements with a body-worn sensor over a period accurate enough to give us reliable information about the circadian rhythm of the body temperature and bioimpedance?

Objectives

1. Present a circadian rhythm for both temperature and bioimpedance.
2. Analyse the rhythms and correlate with theoretical and measured variations through the day.

Material and method

The sensor was provided by Acme corporation.[1] The study location was above the arctic circle. The participants were included from a group of healthy individuals, and were supposed to live their normal lives, with the only restriction was not to go swimming in the ocean during the study. The original exclusion criteria were kidney disease, neurological disease,

[1] Pseudonym for the company providing the sensor.

cardiac disease, endocrinological disease, hypertension, eating disorder or allergies to medical adhesives or gels.

During analysis of this project, participants with missing files or time stamps during the period were excluded. Sensor patches that fell off during the data collection, and participants who did not have a normal sleep-wake cycle were also excluded. In the end, individuals who had data with interpolation which lasted for more than six hours straight were excluded.

The process is presented in Figure 2.

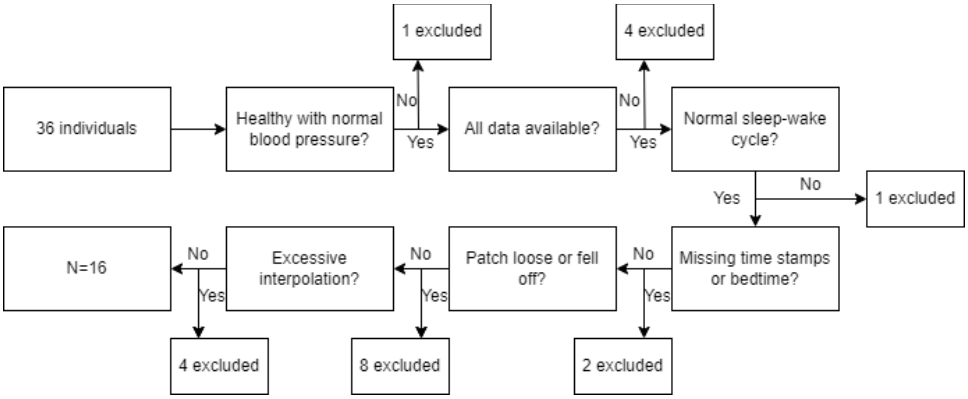


Figure 2: Flow chart showing exclusion of participants.

The patch contained a battery-powered sensor with four electrodes. It was placed vertically on the back, on the left or right side of the columna, either on top of musculus trapezius or erector spinae and at the level of the heart. Every 30 seconds a small current was transmitted between the electrodes and the data was stored in a flash drive in the patch. The duration of the collection was 5 days. During the same period, temperature was recorded from a separate sensor on the same patch. The activation time for each sensor was saved for later use. The collection was done between May and June 2021.

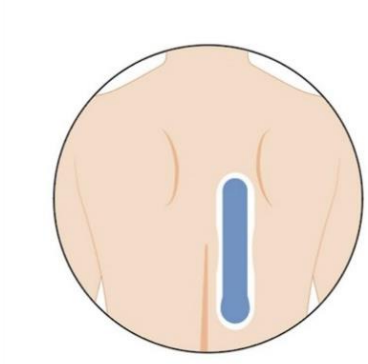


Figure 3: Sensor patch placement

Every participant was handed a diary on the activation day of the sensor. In this diary they recorded wake-up time, bedtime, meals and exercise every day. It also included information about which test substance to consume each day and the amount of it. During the 5 days with the sensor, they were supposed to consume 4 different substances. They were fasting and were not allowed to drink nor eat until 90 minutes after intake of the test substance. From day 2 through 5 the participants consumed respectively salt (8g/70kg body weight through soy sauce), water (2% weight gain or 1,7L/70kg body weight), isotonic sports drink (2% weight gain) and sugar (1,3g/kg body weight through jelly candy). The participants registered thirst on a numeric rating scale (NRS) for 90 minutes after consumption of the test substance. They also measured blood glucose for 120 minutes after consumption of jelly candy. This intervention was not part of the present project, but a part of the initial study.

Analysed data is based on cole-cole parameter R0 [Ω] and R∞ [Ω]. The bioimpedance and temperature data were meaned to 5-minute bins and normalised by dividing all the values by the first value of the same day. This means that every day, the first value was 1 for each participant. This was done due to an individual variation of values. Using the activation time of the patch, all the data were synchronised in a data set. Afterwards the data were sorted by the time the participants went to sleep. Each day was defined by when the participant went to sleep and lasted for 24 hours. This meant there were three days of data for both bioimpedance and temperature out of the 5 initial days. When an individual did not record the bedtime, the average bedtime for this individual was used instead, calculated using an online calculator.

All the data were then transferred to SPSS, where a two-tailed Pearson correlation analysis of the normalised data was performed and presented in three tables (Table 2, Table 3, Table 4). In this analysis, the correlation between bioimpedance and temperature from the same day was analysed. In addition to this, bioimpedance and temperature were compared to the same variables from the other days. There was also made a scatter plot for each day presenting both temperature and bioimpedance. The values were rounded off to the closest hour, and there was added a cubic best fit line for each of these (Figure 4, Figure 5, Figure 6).

The study is completed, and data has been collected in an acceptable way: The project has a REK-approval (REK 201027 Hydra 1) and approval from the Norwegian Medicines Agency (ref21/03725-8) and the Data Protection Officer at UiT – The Arctic University of Norway.

Results

In this study we analysed data from 16 unique, healthy individuals. The descriptive statistics are presented in Table 1. The plasma sodium concentration ($P\text{-}Na^+$) is missing for 4 of the participants due to haemolysis in 3 of the samples, and the 4th did not deliver a blood sample, making N=12 in this case.

4 participants were excluded because of missing data files. The reason for this might be missing storage of data because of an error in the product, or it might have been lost in the transferring process from the patch to the computer application because of human error, software error or software version error.

Table 1: Patient population. The p-NA^+ is missing for 4 of the participants due to haemolysis in 3 of the samples, and the 4th did not deliver a blood sample, making N=12 in this case. The population contains 10 female and 6 male participants.*

	N	Unit	Minimum	Maximum	Mean ± 2x std. deviation
Age	16	years	26	59	42 ± 20
Weight	16	kg	54	135	77 ± 45
Height	16	m	158	188	171 ± 20
Waist	16	cm	72	131	89 ± 34
Systolic blood pressure	16	mmHg	100	165	127 ± 36
Diastolic blood pressure	16	mmHg	63	104	81 ± 22
$P\text{-}Na^+$	12*	mmol/L	135	142	139 ± 4

The scatter plots of bioimpedance and temperature with fitlines (Figure 4, Figure 5, Figure 6) are presented below. For these, a lot of the individuals had interpolated bioimpedance data, seen as straight lines in a scatter plot on an individual level. However, on group level, there is a clear circadian rhythm for the bioimpedance for all three days. The nadir is at about 4 to 5 hours after going to bed for all the days, and it peaks at about 18 to 19 hours after going to sleep. For temperature, the first day shows a circadian rhythm. However, in day 2 and 3 the fitlines do not display a clear nadir nor a peak. The nadir for the first day was at about 7 hours after going to sleep. The peak is at about 19 hours after going to sleep, making the circadian rhythm slightly shifted to the right compared to the bioimpedance.

The graphs are presented below:

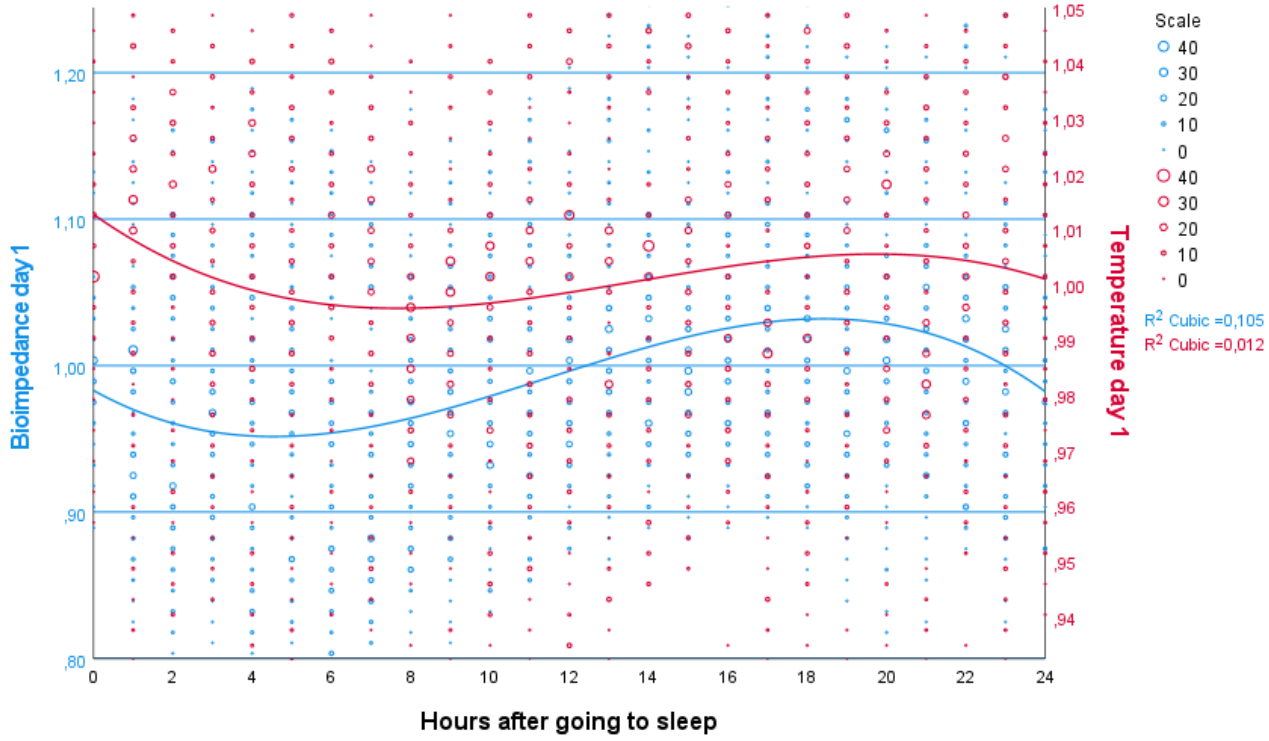


Figure 4: Scatter plot with fitlines showing the normalised bioimpedance and temperature during the first day.

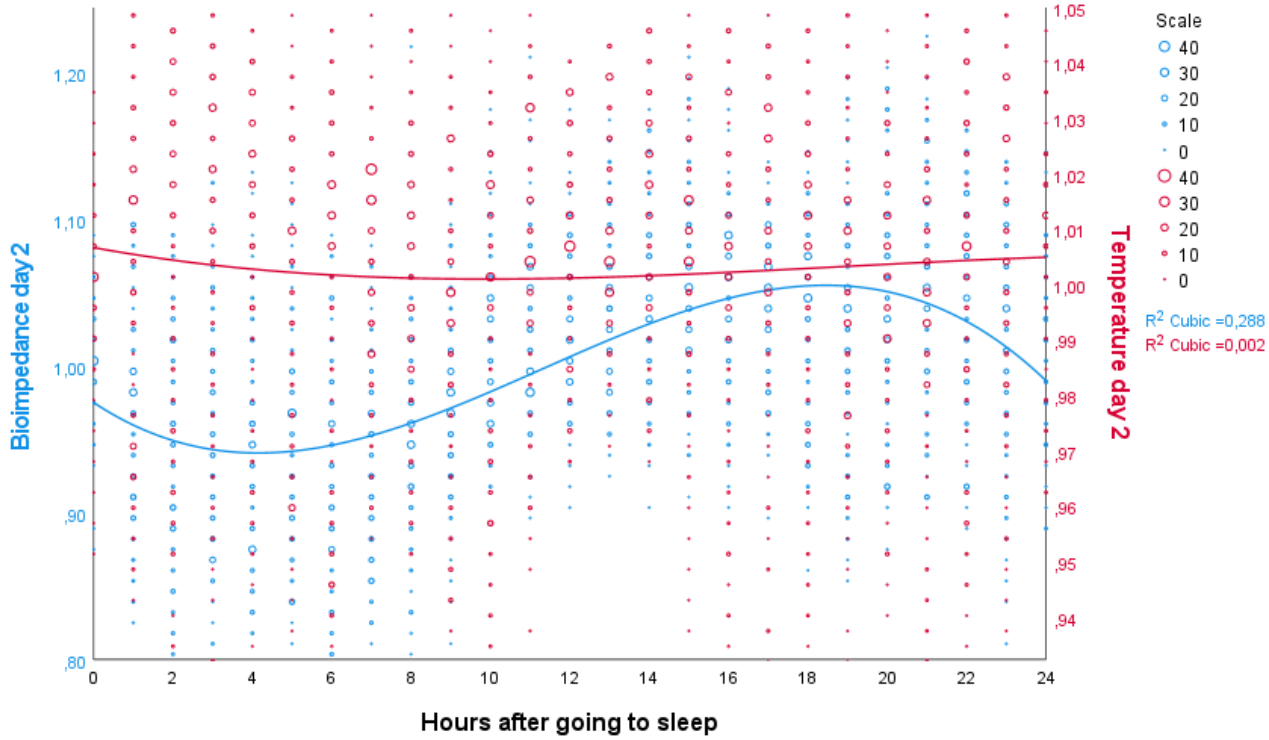


Figure 5: Scatter plot with fitlines showing the normalised bioimpedance and temperature during the second day.

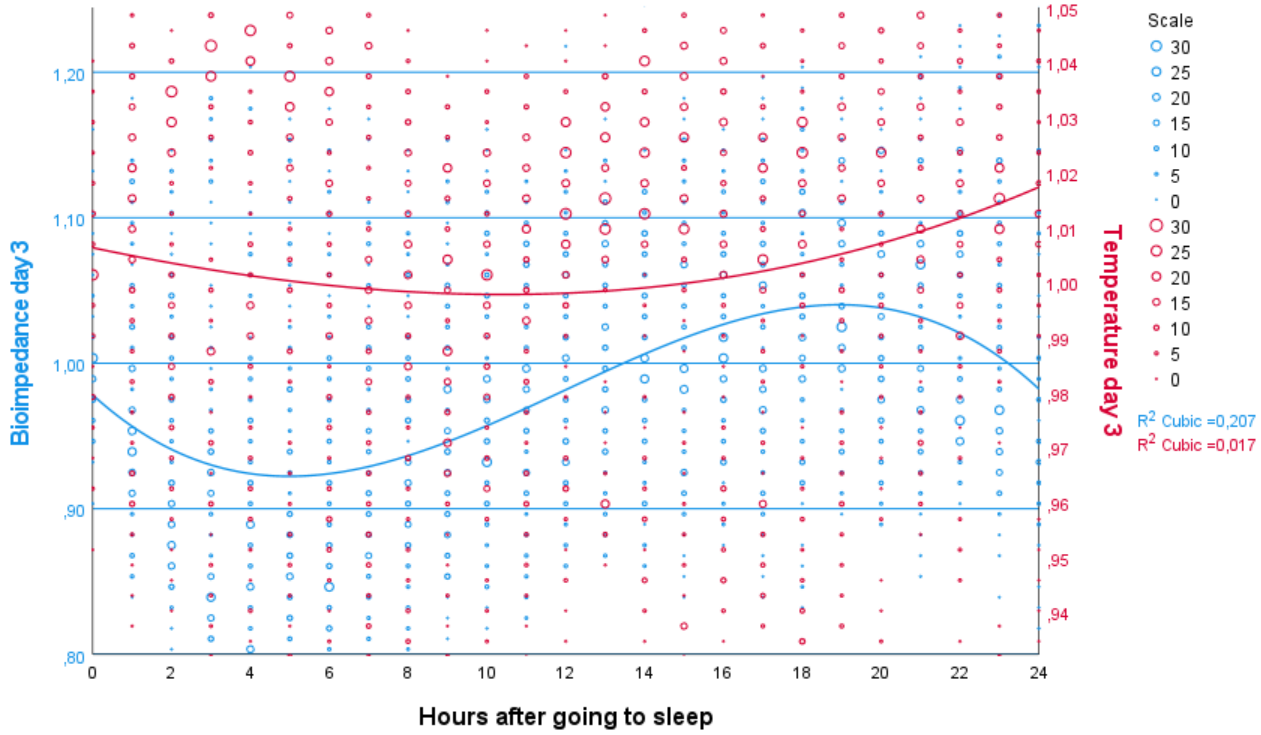


Figure 6: Scatter plot with fitlines showing the normalised bioimpedance and temperature during the third day.

The tables (Table 2, Table 3, Table 4) from the Pearson correlation analysis are listed below. The Pearson correlations are all significant (P<0,01) with a P-value of 0.001. For the analysis of day-to-day, Pearson correlation of bioimpedance (Table 2), values stay quite even. The day-to-day Pearson correlation of temperature (Table 3), the values are varying slightly more. In Table 4 where bioimpedance and temperature are correlated to each other for the same day, the Pearson correlation is also quite even.

Table 2:

Correlations between the bioimpedance from different days

		Bioimpedance day 1	Bioimpedance day 2	Bioimpedance day 3
Bioimpedance day 1	Pearson Correlation		,354**	,289**
	Sig. (2-tailed)		<,001	<,001
	N		4608	4608
Bioimpedance day 2	Pearson Correlation	,354**		,389**
	Sig. (2-tailed)	<,001		<,001
	N	4608		4608
Bioimpedance day 3	Pearson Correlation	,289**	,389**	
	Sig. (2-tailed)	<,001	<,001	
	N	4608	4608	

**. Correlation is significant at the 0.01 level (2-tailed).

Table 3:

Correlations between the temperature from different days

		Temperature day 1	Temperature day 2	Temperature day 3
Temperature day 1	Pearson Correlation		,343**	,290**
	Sig. (2-tailed)		<,001	<,001
	N		4608	4608
Temperature day 2	Pearson Correlation	,343**		,126**
	Sig. (2-tailed)	<,001		<,001
	N	4608		4608
Temperature day 3	Pearson Correlation	,290**	,126**	
	Sig. (2-tailed)	<,001	<,001	
	N	4608	4608	

**. Correlation is significant at the 0.01 level (2-tailed).

Table 4:

Correlations between temperature and bioimpedance from the same day

		Temperature day 1	Temperature day 2	Temperature day 3
Bioimpedance day 1	Pearson Correlation	-,291		
	Sig. (2-tailed)	<,001		
	N	4608		
Bioimpedance day 2	Pearson Correlation		-,352	
	Sig. (2-tailed)		<,001	
	N		4608	
Bioimpedance day 3	Pearson Correlation			-,308
	Sig. (2-tailed)			<,001
	N			4608

Discussion

The main finding in this study was the presence of a bioimpedance circadian rhythm detected by a sensor patch. The low correlation indicates a large individual spread, as expected. This was mostly caused by the anthropometric spread. For the temperature there was a clear circadian rhythm the first day. The following days the temperature was not displaying a circadian rhythm, with no clear nadir nor a peak.

In clinical practice, the ability to detect a circadian rhythm is important and should be possible to detect in healthy individuals. If the physiological rhythms are presented, deviations from it might indicate a change in the course of disease. For example, a deviation of the circadian rhythm in a patient with suspected delayed sleep phase disorder can indicate the disorder (Zhu & Zee, 2012). In other organ systems, such as the cardiovascular system, changes in CO affect RAAS, leading to changes in the extracellular sodium and water concentration, which again affect bioimpedance measurements. This also means deterioration of heart failure would lead to changes in extracellular fluid (Malik et al., 2022) which can be displayed as a deviation from the normal bioimpedance circadian rhythm.

Our findings from the first day of temperature recordings correlate well with a study performed on individuals with narcolepsy (Mosko et al., 1983), including a group of healthy controls featuring 5 men and 4 women. The study used a rectal probe to measure the temperature every hour for 24 hours, and each individual's values were shifted so that their sleep onset was at the same time. In the presented mean values from the study, there seems to be a circadian rhythm with nadir at about 4-6 hours after sleep onset. The highest point seems to be at about 8-9 hours before sleep onset. The mean amplitude for the cosine fit curve was reported to be 1,00 ± 0,14°F. The presence of a circadian rhythm for temperature is not surprising given the fact that it is natural to have lower activity during the night and higher activity during the day. It also persist in sleep-deprived subjects as demonstrated by Krauchi and Wirz-Justice (1994) where 7 healthy male participants had to go to bed for a regular time between 23:00 and 01:00 (average bedtime 23:48) during the last work week before being monitored for daily core temperature. The individuals studied were kept awake for 36 hours, with controlled temperature, environment and calorie intake. The temperature was both recorded rectally and on the skin several places on the body. The nadir seemed to be somewhere between 05:00 and 06:00, and there was a peak value between about 21:00 and

22:00. As the average bedtime presented by Krauchi and Wirz-Justice (1994) was close to midnight, the findings of nadir between 6 and 7 hours after going to bed and a peak about 19 hours after bedtime correlate well with the findings in the present study.

Based on extensive search I have found limited evidence in literature in the field of continuous bioimpedance measurements by body worn sensors and circadian rhythms of bioimpedance. The circadian rhythm for bioimpedance is less intuitive than the circadian rhythm of temperature. However, it clearly persists through the three days of recording with the body-worn sensor patch in the present study. The observed rhythm is most likely a consequence of mechanisms controlling the ECF and the concentration of sodium. If we look into the endocrine control of the fluid balance and blood pressure and their circadian rhythms, it is reported that ADH has its highest point at about 8:00 and lowest point at about 20:00 (Johnsson & Moan, 2006). The high morning ADH contributes to retention of fluid and rising blood pressure the following hours (Moon et al., 2004). Both cortisol and RAAS share roughly the same rhythm as ADH by peaking in the early morning. Cortisol leads to urine and sodium retention, which is increasing both plasma sodium and volume, which again increases the CO and the blood pressure. The rise in plasma volume may also lead to changes in bioimpedance. RAAS is inducing a general vasoconstriction, fluid retention and sodium reabsorption (Hurwitz et al., 2004; Patel et al., 2017). These endocrine factors might explain the previous reported fast rise in blood pressure in the morning, and the rise throughout the day until reaching the peak in the afternoon, before falling again (Zhang et al., 2021), similar to our bioimpedance measurement curve. There are several theories as to why bioimpedance decreases in the night. According to Sachdeva and Weder (2006), the sodium excretion is decreasing during the night in most normotensive individuals, which again will increase the sodium concentration in the ECF, and lead to a decrease in bioimpedance measurement, leading to a nadir in the morning.

In the present study, we presented a circadian rhythm for extracellular bioimpedance, with a nadir at about 5-6 hours after bedtime, and a peak at about 19 hours. We compared these findings with another study (Kirchner et al., 2015), which was on 53 individuals with heart failure, monitored with thoracic impedance. They presented a sine function with nadir at about 6:00 and a peak at about 17:00-18:00. Their median bedtime was around 22:00, making the time between bedtime and nadir close to 8 hours, and the time between bedtime and peak

about 19-20 hours. This means the nadir in the present study comes a bit earlier than the one presented by Kirchner et al. (2015), but the peak shows up at about the same time.

There could be several reasons causing our results to differ from Kirchner et al. (2015). The population is not the same, as the present study was on healthy individuals while Kirchner's study was done on heart failure patients. Studying patients with heart failure leads to more confounding factors than healthy patients, their decreased CO leads to RAAS activation and fluid retention, leading to oedemas, and they are often treated with both diuretics and RAAS inhibitors as well (Malik et al., 2022). As the present study was performed on healthy individuals without the same number of confounding factors, and with more data points, our results could give more reliable results for circadian rhythms. There were also a few technical differences. Kirchner et al. (2015) have used thoracic impedance measured by implants while in our study, a small body worn sensor placed on the skin was used to measure thoracic bioimpedance.

There were no clear findings from the intake of nutrient substances in the fitlines presented. There could be numerous reasons for this. Firstly, the test substances were taken in doses that should not require substantial compensation mechanisms. Instead, the body was supposed to reach homeostasis soon after ingestion. Therefore, it would not likely be affecting the "slow" circadian rhythm of bioimpedance. In addition to this, the test substances were not taken at the same time of the day and the participants' days were also shifted according to their bedtime, making a relatively large spread in time for intake.

The sensor was placed in a hydrostatic neutral segment to avoid large postural changes. It was placed on the back which has a lot of type 1 muscle fibres, meaning the activity in the muscle is quite even during the day compared to type 2 fibres (McCuller et al., 2022). In addition to this, elderly people are prone to loss of type 2 fibres (Talbot & Maves, 2016). In order to test a placement that can be applied for both young and old participants, the erector spinae was selected.

Limitations

Although we were able to demonstrate circadian rhythms both for temperature and bioimpedance in the present study, the study has several limitations that may influence our

results. The participants were living their normal lives, with a varying rhythm of sleep, light, meals and activity, meaning several Zeitgebers will influence the circadian rhythms of the body. The only Zeitgeber that was adjusted for in the data set was bedtime. This means the results are affected by several environmental factors. An important example to mention is that the data was collected between May and June above the arctic circle, which means that most of the collection period happened while it was midnight sun with little variation in natural light. The sensor, which was placed on the skin, was also exposed to environmental factors like quick temperature changes, and sweating (moisture) which may have led to changes in adherence and contact with the skin.

The study was performed using a protype. This early model of the patch was not designed nor tested for daily use. On an individual level, there was a large amount of interpolation. This is possibly because the electrodes lost contact with the skin. This happened at some degree for most of the participants, but usually for a short period of time. Because the circadian rhythms change direction about every 6 hours, it was decided to exclude those with interpolation lasting for more than 6 hours straight. This was done to prevent the amplitude from decreasing. At the same time, there is still a lot of interpolated values in the data set, but for shorter time periods.

An explanation for the interpolation might be technical problems in the patch such as loss of contact, or increased insulation between the skin and the temperature sensor. In this version of the patch, the temperature sensor was directed away from the skin. This might not be the best design, because we cannot control all factors affecting the temperature measurements. This deviation might also be the reason for the decrease of Pearson correlation for temperature the last 2 days. However, at an individual level, there was still a significant correlation between bioimpedance and temperature at day two and day three.

The analysis method that was used in the present study did not adjust for individual differences. More advanced methods could be utilized to adjust for individual difference. For example the Cosinor and Fourier methods that was performed by Kirchner et al. (2015).

Future Work

The promising results from this study may in future work provide even better data given a different study design and analysis method. The sensor patch was an early prototype version which may need some improvements before use in clinical practice and research. Possible improvements suggested for the sensor:

- To mitigate interpolation:
    - It is recommended to use technically mature bioimpedance device (preferably medical device approved or similar) for reliable multi-frequency data collection.
    - Assessing bioimpedance frequencies (e.g. 50kHz-100kHz) which are not that affected by measurement artifacts, such as sweat, movement, skin-electrode contact (and not cole-cole parameters which requires reliable measurements across the frequency spectrum).
- Improvements for the temperature sensor:
    - Use of a temperature sensor validated to monitor core body temperature.
- Study design improvements:
    - Design and execute a controlled study with more volunteer restrictions and procedures suited to answer the research questions.

Conclusion

My findings suggest that continuous bioimpedance and skin temperature data measured by a body-worn sensor, can be a useful method to assess people's circadian rhythms and disturbances which can be useful in detecting diseases.

Acknowledgement

I would like to thank all volunteers that have contributed with data and insight in this study, and I would like to thank Acme Corporation[1] for providing me with data.

Literature

Brinkman, J. E., Dorius, B., & Sharma, S. (2022). Physiology, Body Fluids. In *StatPearls*. StatPearls Publishing

Copyright © 2022, StatPearls Publishing LLC.

Brodal, P. (2013). *Sentralnervesystemet* (5. utg. ed.). Universitetsforl.

Chan, D., & Stanzani, G. (2014). Controversies in Fluid Therapy. *Eur J Comp Anim Pract*, *24*, 14-23.

Czeisler, C. A., Duffy, J. F., Shanahan, T. L., Brown, E. N., Mitchell, J. F., Rimmer, D. W., Ronda, J. M., Silva, E. J., Allan, J. S., Emens, J. S., Dijk, D. J., & Kronauer, R. E. (1999). Stability, precision, and near-24-hour period of the human circadian pacemaker. *Science*, *284*(5423), 2177-2181. https://doi.org/10.1126/science.284.5423.2177

Firsov, D., & Bonny, O. (2018). Circadian rhythms and the kidney. *Nat Rev Nephrol*, *14*(10), 626-635. https://doi.org/10.1038/s41581-018-0048-9

Grimnes, S., & Martinsen, Ø. G. (2015). *Bioimpedance and bioelectricity basics* (3rd ed.). Academic Press.

Halse, J. (2022, 22.10.2020). *ADH - antidiuretisk hormon*. Retrieved 22.01 from https://sml.snl.no/ADH_-_antidiuretisk_hormon

Hurwitz, S., Cohen, R. J., & Williams, G. H. (2004). Diurnal variation of aldosterone and plasma renin activity: timing relation to melatonin and cortisol and consistency after prolonged bed rest. *J Appl Physiol (1985)*, *96*(4), 1406-1414. https://doi.org/10.1152/japplphysiol.00611.2003

Ince, L. M. (2022). Introduction to biological rhythms: A brief history of chronobiology and its relevance to parasite immunology. *Parasite Immunol*, *44*(3), e12905. https://doi.org/10.1111/pim.12905

Joergensen, D., Tazmini, K., & Jacobsen, D. (2019). Acute Dysnatremias - a dangerous and overlooked clinical problem. *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine*, *27*(1), 58. https://doi.org/10.1186/s13049-019-0633-3

Johnsson, A., & Moan, J. (2006). [Rhythms, depressions and light]. *Tidsskr Nor Laegeforen*, *126*(8), 1044-1047. (Rytmer, depresjoner og lys.)

Karppanen, H. (1991). Minerals and blood pressure. *Ann Med*, *23*(3), 299-305. https://doi.org/10.3109/07853899109148064

Khalil, S. F., Mohktar, M. S., & Ibrahim, F. (2014). The theory and fundamentals of bioimpedance analysis in clinical status monitoring and diagnosis of diseases. *Sensors (Basel)*, *14*(6), 10895-10928. https://doi.org/10.3390/s140610895

Kirchner, J., Paule, S., Beckendorf, C., Achenbach, S., & Arnold, M. (2015). Circadian and circaseptan rhythms in implant-based thoracic impedance. *Physiol Meas*, *36*(7), 1615-1628. https://doi.org/10.1088/0967-3334/36/7/1615

Krauchi, K., & Wirz-Justice, A. (1994). Circadian rhythm of heat production, heart rate, and skin and core temperature under unmasking conditions in men. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *267*(3), R819-R829. https://doi.org/10.1152/ajpregu.1994.267.3.R819

Malik, A., Brito, D., Vaqar, S., & Chhabra, L. (2022). Congestive Heart Failure. In *StatPearls*. StatPearls Publishing

Copyright © 2022, StatPearls Publishing LLC.

McCuller, C., Jessu, R., & Callahan, A. L. (2022). Physiology, Skeletal Muscle. In *StatPearls*. StatPearls Publishing

Mehling, A., & Fluhr, J. W. (2006). Chronobiology: biological clocks and rhythms of the skin. *Skin Pharmacol Physiol*, *19*(4), 182-189. https://doi.org/10.1159/000093113

Moon, D. G., Jin, M. H., Lee, J. G., Kim, J. J., Kim, M. G., & Cha, D. R. (2004). Antidiuretic hormone in elderly male patients with severe nocturia: a circadian study. *BJU Int*, *94*(4), 571-575. https://doi.org/10.1111/j.1464-410X.2004.05003.x

Mosko, S. S., Holowach, J. B., & Sassin, J. F. (1983). The 24-Hour Rhythm of Core Temperature in Narcolepsy. *Sleep*, *6*(2), 137-146. https://doi.org/10.1093/sleep/6.2.137

Nakamura, K. (2011). Central circuitries for body temperature regulation and fever. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *301*(5), R1207-R1228. https://doi.org/10.1152/ajpregu.00109.2011

Norsk Elektronisk Legehåndbok. (2019, 19.09). *Temperaturmåling*. Retrieved 20.01 from https://legehandboka.no/handboken/kliniske-prosedyrer/pasientinformasjon/diverse-undersokelser/temperaturmaling

Patel, S., Rauf, A., Khan, H., & Abu-Izneid, T. (2017). Renin-angiotensin-aldosterone (RAAS): The ubiquitous system for homeostasis and pathologies. *Biomed Pharmacother*, *94*, 317-325. https://doi.org/10.1016/j.biopha.2017.07.091

Sachdeva, A., & Weder, A. B. (2006). Nocturnal Sodium Excretion, Blood Pressure Dipping, and Sodium Sensitivity. *Hypertension*, *48*(4), 527-533. https://doi.org/doi:10.1161/01.HYP.0000240268.37379.7c

Sand, O., Sjaastad, Ø. V., Haug, E., & Toverud, K. C. (2014). *Menneskets fysiologi* (2. utg. ed.). Gyldendal akademisk.

Scheeren, T. W. L., & Ramsay, M. A. E. (2019). New Developments in Hemodynamic Monitoring. *J Cardiothorac Vasc Anesth*, *33 Suppl 1*, S67-s72. https://doi.org/10.1053/j.jvca.2019.03.043

Stenn, K. S., & Paus, R. (2001). Controls of hair follicle cycling. *Physiol Rev*, *81*(1), 449-494. https://doi.org/10.1152/physrev.2001.81.1.449

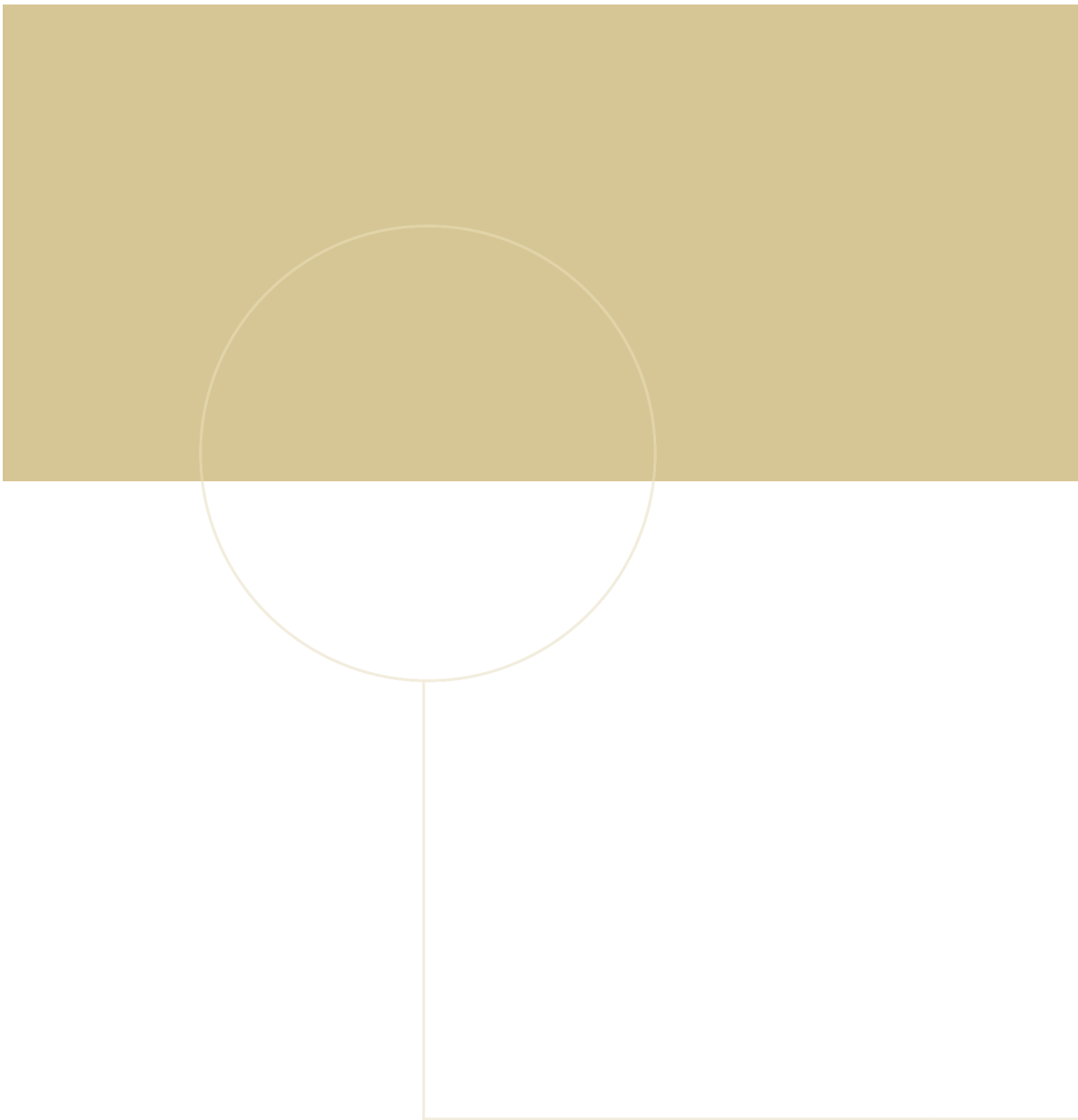
Talbot, J., & Maves, L. (2016). Skeletal muscle fiber type: using insights from muscle developmental biology to dissect targets for susceptibility and resistance to muscle disease. *Wiley Interdiscip Rev Dev Biol*, *5*(4), 518-534. https://doi.org/10.1002/wdev.230

Vitaterna, M. H., Takahashi, J. S., & Turek, F. W. (2001). Overview of circadian rhythms. *Alcohol Res Health*, *25*(2), 85-93.

Yu, J. L., Su, Y. F., Zhang, C., Jin, L., Lin, X. H., Chen, L. T., Huang, H. F., & Wu, Y. T. (2022). Tracking of menstrual cycles and prediction of the fertile window via measurements of basal body temperature and heart rate as well as machine-learning algorithms. *Reprod Biol Endocrinol*, *20*(1), 118. https://doi.org/10.1186/s12958-022-00993-4

Zhang, J., Sun, R., Jiang, T., Yang, G., & Chen, L. (2021). Circadian Blood Pressure Rhythm in Cardiovascular and Renal Health and Disease. *Biomolecules*, *11*(6). https://doi.org/10.3390/biom11060868

Zhu, L., & Zee, P. C. (2012). Circadian rhythm sleep disorders. *Neurol Clin*, *30*(4), 1167-1191. https://doi.org/10.1016/j.ncl.2012.08.011



NTNU

Norwegian University of
Science and Technology