BIOTECHNO 2020

The Twelfth International Conference on Bioinformatics,

Biocomputational Systems and Biotechnologies

September 27, 2020 to October 01, 2020 - Lisbon, Portugal

BIOLOGICAL DIGITAL SIGNAL PROCESSING INTERPRETATION AND COMBINATION

Authors: Ionescu Marius

Supervisor: Grigore Ovidiu

Doctoral School of Electronics, Telecommunications and Information Technology

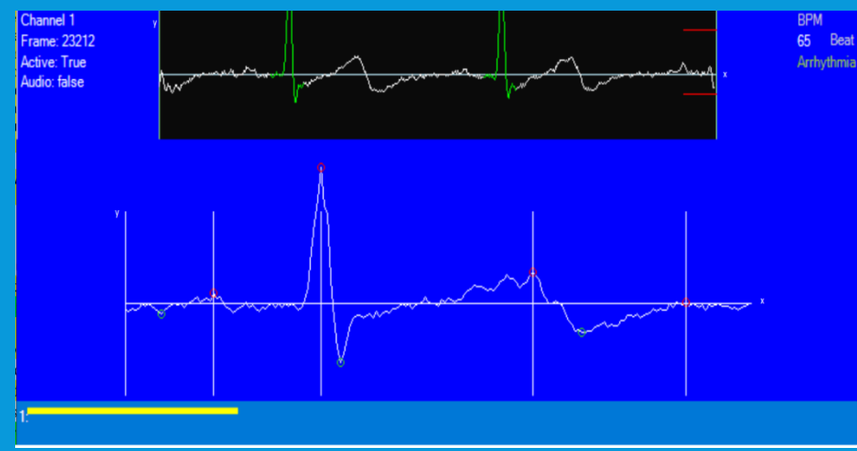
Bucharest, Romania

INTRODUCTION

- In this work, we will discuss methods, filters and algorithms for processing of biological signals, as well as the interpretation and display of the results. Biological signals can help us diagnose certain diseases, and their combination and interpretation can provide us with relevant information about our health. The discussed problem is related to how biological signals can be processed, combined, interpreted and displayed in order to make accurate diagnoses.
- The article illustrates a new prototype based on spectroscopic methods which uses near infrared sensors to monitor blood glucose levels. The prototype combines the spectroscopic methods with other methods, such as Electrocardiography or Electromyography. The work focuses on light absorbance in matter and on non-invasive blood glucose detection using near infrared technology by colorimetric interpretation of the values transmitted.

ELECTROCARDIOGRAPHY AND ELECTROMIOGRAPHY SIGNAL PROCESSING, COMBINING AND DISPLAYING

- The Electrocardiography signals can be combined with other signals, or signals can be extracted from the same information that would be of other nature, such as the Electromyography or near infrared, spectroscopic signal.
- The acquisition of Electrocardiography signals uses the latest new generation of microprocessors, that before being forwarded are extensively processed. At the moment, the acquisition of Electrocardiography signal is investigated with silver chloride.
- Ag / AgCl (silver chloride) electrode is used in common ECG systems and has a maximum offset voltage of ± 300 mV. ± 0.5 mV desired signal is superimposed on the electrode offset. In addition, the system also takes the noise 50/60 Hz power lines forming common mode signal. The amplitude of power line noise could be very large and also must be filtered



SIGNALS - HAAR AND BUTTERWORTH FILTER

- For processing and filtering graphics, there were used two filters. Haar filter used in mathematics for waves, form a wavelet family. Wavelet analysis is similar to Fourier analysis, because it allows a target function to be represented as an orthonormal basis. Using the wavelets for Electrocardiography representation is quite useful if the sampled signal is continuous and has sudden transitions

- The advantages of using Haar filter for Electrocardiography graphical representation help us represent any sample time as a continuous function, uniformly, approximated by linear combinations. Thus, this algorithm is extended to those areas where any function of this type can be uniform approximated by continuous functions.

SIGNALS - HAAR AND BUTTERWORTH FILTER

- Butterworth had a reputation for solving mathematical problems "impossible". At the time, this filter design requires a considerable amount of experience designer because of the limitations of the theory in use. The filter has not been used for more than 30 years after its publication.
- Such an ideal filter cannot be achieved, but Butterworth has shown that close successive approximations were obtained by increasing the number of screening the correct values. At the time, filters waves generated substantial low-pass filter. Butterworth has shown that a low-pass filter can be designed with a cutoff frequency normalized to 1 radian per second

$$G(\omega) = \frac{1}{\sqrt{}}$$

- where ω is the angular frequency in radians per second, and n is the number of poles in the filter equal to the number of reactive elements in a passive filter. If $\omega = 1$, the magnitude of this type of filter passband is $1 / \sqrt{2} \approx 0.707$, which is half power or -3 dB. Butterworth filters work only with an even number of poles in his work. He can ignore that these filters can be designed with an odd number of poles. He built his higher order filters, the filters with two poles separated by vacuum tube amplifiers. Its frequency response plot of 2, 4, 6, 8 and 10 pole filters it is shown as A, B, C, D and E in its original chart.

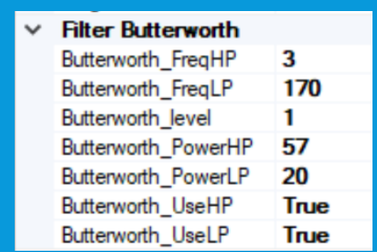
SIGNALS - HAAR AND BUTTERWORTH FILTER

- The Butterworth filtering algorithm can be transformed with the Haar filter used for Electrocardiography graphics, that can help to sample the Butterworth signal processing, where the algorithm has a defined number of low and high pass Butterworth filters with three poles, and which works on a certain frequency threshold [17]. A band-pass filter can be implemented by applying sequential algorithms to filter high-pass and low-pass

- Butterworth solved the equations of two or four-pole filters, that shows how the latter could be in waterfall when they are separated by vacuum tube amplifiers, allowing the construction of higher order filters despite the losses.
  In 1930, Butterworth used forms of coil diameter of 1.25 and 3 cm long, with plug-in terminals, capacitors and resistors associated contained inside a coil. Coil resistance forms part of the load plate. Two poles were used for each vacuum tube and RC coupling was used to the electric grid of the next tube.

SIGNALS - HAAR AND BUTTERWORTH FILTER

- In this application, we will have Butterworth type filters with the following settings:
- Butterworth_FreqHP - frequency high-pass which has the default 3 dB;
- Butterworth_FreqLP - low-pass frequency is 170 dB default value;
- Butterworth_Level - up crossing that has the default 1;
- Butterworth_PowerHP - high-pass power that has the default 57;
- Butterworth_PowerLP - low-pass power that has the default 20;
- Butterworth_UseHP - to enable high-pass, default is true;
- Butterworth_UseLP - to enable low-pass, default is true;



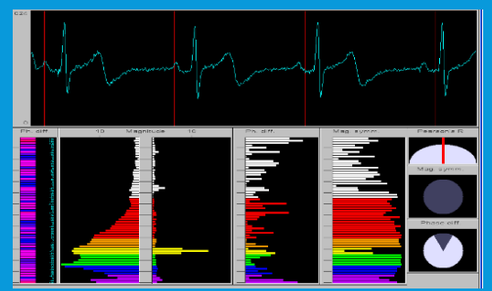
SETTINGS AND USING CHANNELS FOR ARRHYTHMIA

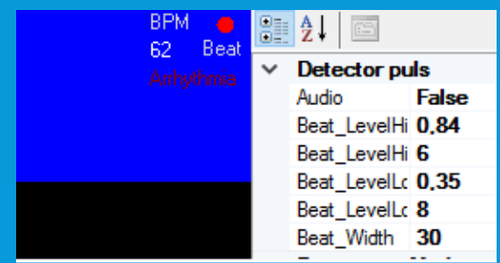
- Current application for processing biological signals can set and use multiple channels simultaneously, which can receive different signals. Each channel has its settings. For example, heart rate settings can be used:
- Beat Level High;
- Beat Level High Limit;
- Beat Level Low;
- Beat Level Low Limit;
- Filter Haar;
- Filter Butterworth

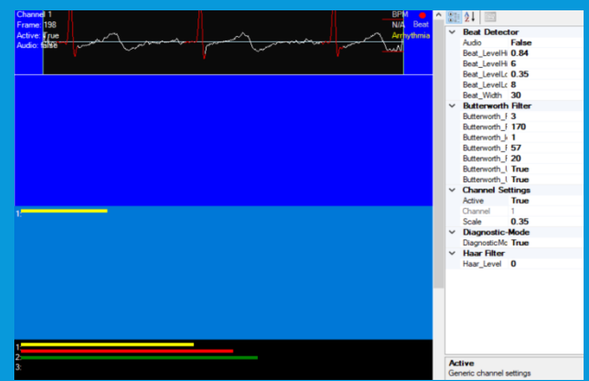
- The application allows diagnosis mode that draws axis PQST based on filters used at some point. The goal is to save at certain intervals, PQST state.
- The signals based on flows and electric excitations of body, detected and transmitted by electrodes, can display, process and sets various diagnoses, prognoses and can interpolate the obtained informations, so that the area of diagnostics includes batch jobs related to other regions (organisms) or functions of the biological body, such as Electrocardiography or Electromyography

ARRHYTHMIA

- Arrhythmia is an irregular heart beat, an irregular rhythm, too slow or too fast. Below 60 beats too slow we have a rhythm called bradycardia and over 100 beats tachycardia.
- Arrhythmia algorithm calculation is based on data from sampling difference every 6 beats. If a heartbeat is detected within 6, an anomaly will exceeds known standards and the software will make alerts.





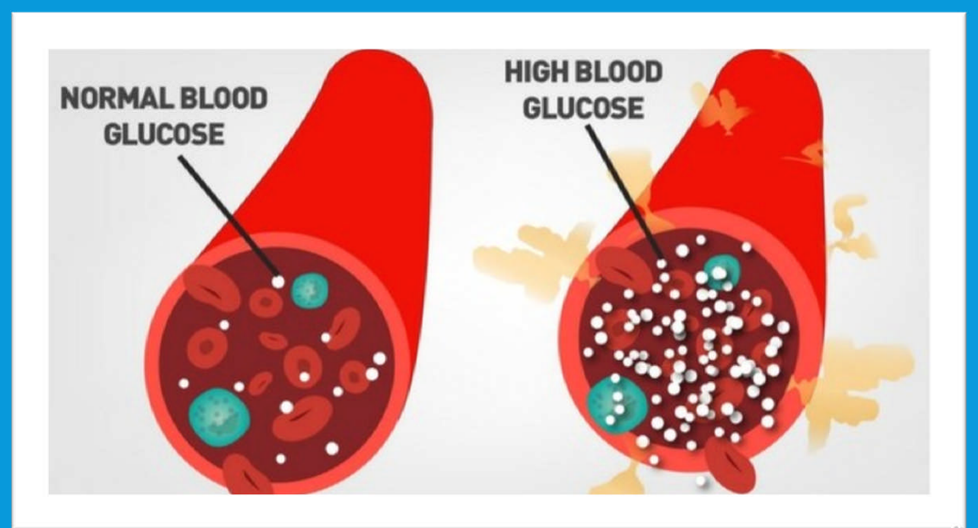


NEAR INFRARED SPECTROSCOPY SIGNAL IN MEASURING GLUCOSE

This chapter aims to discuss the:

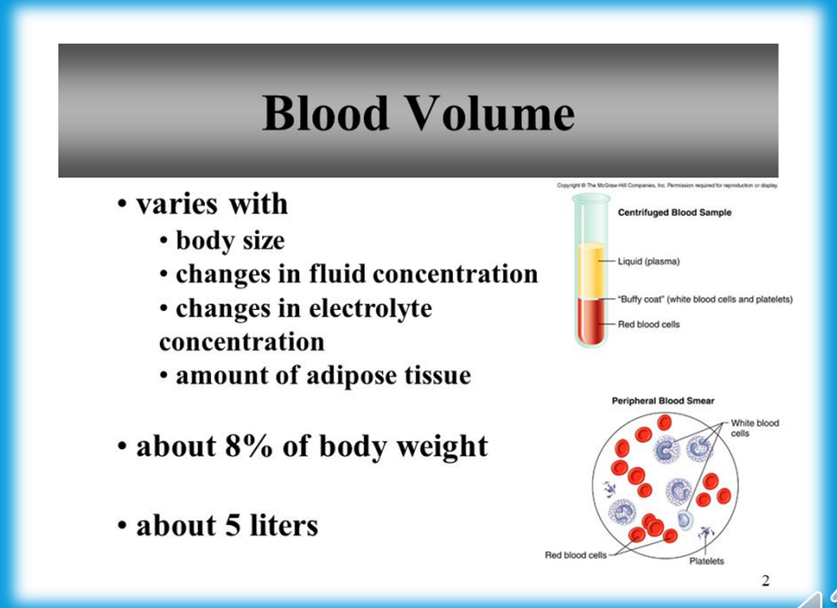
- detection and measurement of blood glucose by non-invasive methods
- absorption of infrared light through the skin, muscle, bone and venous blood
- current and future research

Non-invasive methods aim to measure blood glucose without taking blood samples. We will discuss in this article about old invasive methods and new non-invasive methods as well as about contributions to new non-invasive methods.



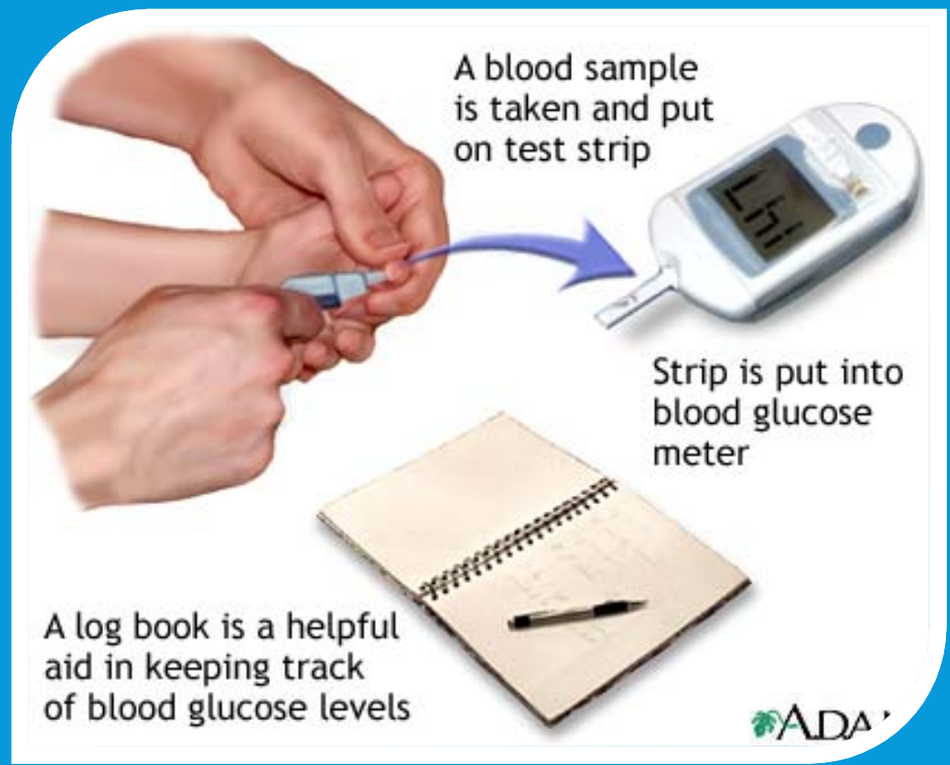
TECHNIQUES AND CHARACTERISTICS FOR GLUCOSE MEASUREMENT

- There are a number of useful features in measuring blood glucose such as:
- • Blood volume for the sample - if the test is based on blood samples. This volume may vary between 0.3 and 1 µl;
- • Test strips - contain chemical supplies that react with glucose from the drop of blood;
- The size of the tissue area on which blood glucose (finger, ear lobe) is measured;
- • Measurement intervals and a history based on which advanced diagrams can be made;



METHODS OF CLASSIC SPECTROSCOPIC MEASUREMENT

- There are types of sensors that measure heart rate, SPO2 blood level, temperature or glucose in the tear or sweat of the body
- Continuous glucose monitoring or implantable systems currently in use are invasive and require blood samples and replacements after a few days, and there is an urgent need to replace invasive classical methods with new glucose measurement devices noninvasive that are easy to use, have a low cost, mobility and a high degree of safety in their use for patients or non-patients

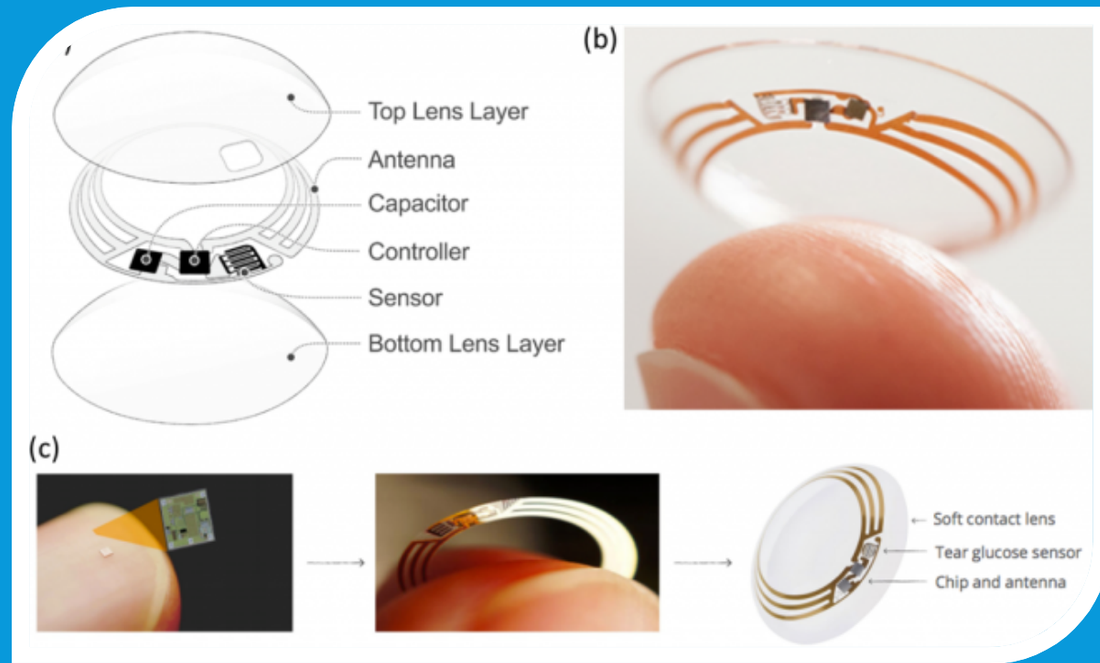


MODERN METHODS

- The first device to measure glycemia without needle was **GlucoTrack**;

This device is intended for people who are in pre-diabetes and type 2 diabetes. The device is attached to the earlobe and has a sensor that measures glucose;

- Another modern method for measuring blood glucose was developed by the company **Nemaura Medical** in the UK, who measure blood glucose by placing a patch every day on the skin and a sensor placed on this patch;



- **NovioSense**, a Dutch company, proposes to measure blood glucose through a sensor consisting of a 15mm metal coil covered by a hydrophilic gel and attached to the lower eyelid that analyzes the eye fluids and measures the concentration of glucose in the tears;
- **Google Lens**, in collaboration with Novartis, proposes a contact lens that contains a microchip that measures blood glucose directly from the tear fluid and transmits information to a mobile device;

BLOOD COMPOSITION

- Blood consists of:

- 55% plasma

- 45% formed elements.

- Plasma is made up of:

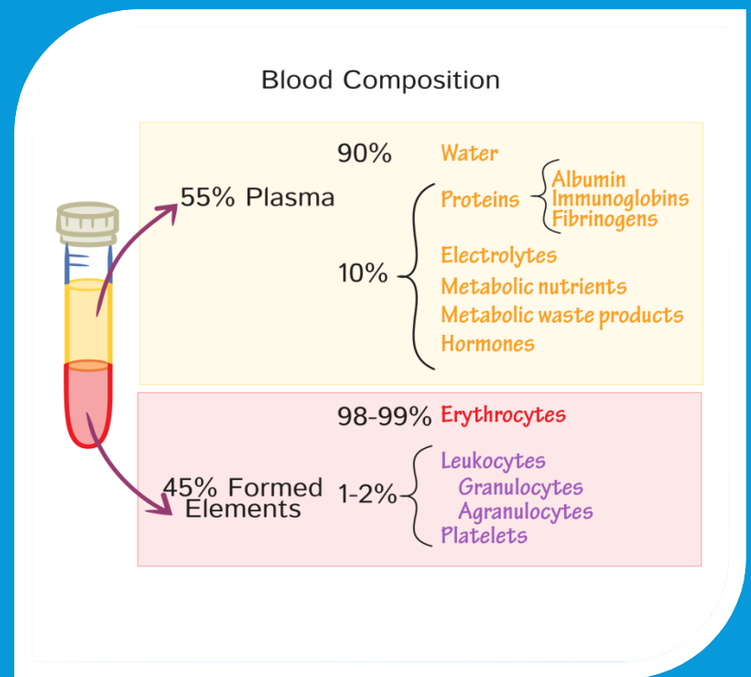
- 90% water

- 10% other elements

The formed elements are composed largely of:

- 99% erythrocytes

- the rest formed elements such as: leukocytes, platelets etc.



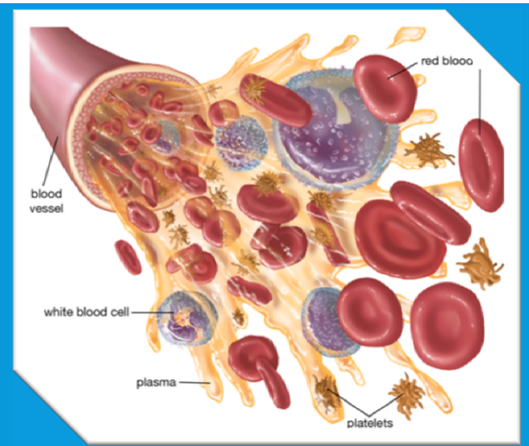
FORMED ELEMENTS OF BLOOD (45%)

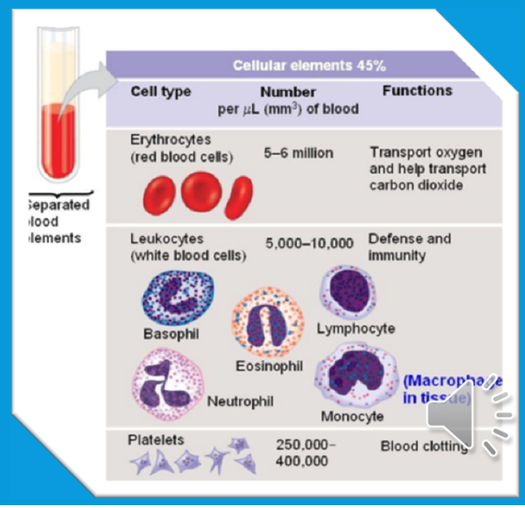
- ***Erytrocytes***

- They are devoid of the nucleus and represent the largest population of blood cells (4 - 5 million / cubic millimeter of blood). When evaluated with an optical microscope, they are described on the blood smear: round-oval cells of pink color (due to the coloration commonly used in hematology

- ***Leukocytes***

- Nuclear cells, which are also called white blood cells, due to the absence of staining on the blood smear. Normal value is 4000 - 8000 per cubic millimeter of blood. The role of leukocytes is to protect the body against infections, inflammation, neoplasia or allergies.





FORMED ELEMENTS OF BLOOD (45%)

- ***Lymphocytes***

Lymphocytes - are the most numerous mononucleate, they play a role in the defense against viral, tuberculosis and neoplasm infections. They can be classified into:

- B lymphocytes - role in antibody production (humoral immunity)

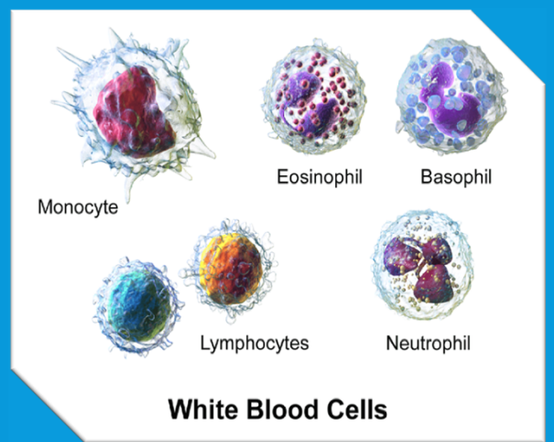
- T lymphocytes, of which the NK (natural killer) lymphocytes - a role in antitumor defense - also belong to this category

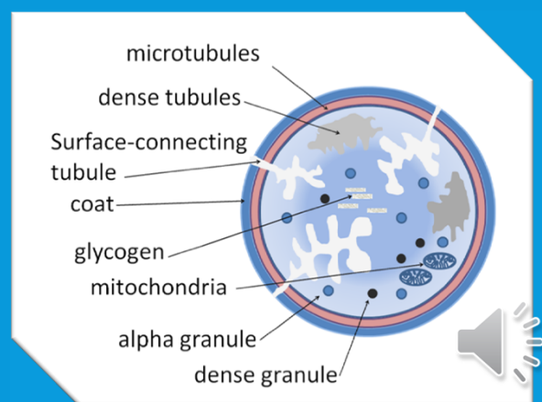
- ***Platelets***

- Plasmocytes represent a more evolved population of lymphocytes that are found in the marrow and play a role in antibody production.

- Monocytes are less numerous. Some of them migrate to tissues where they are called macrophages (role of elimination of debris, antiviral and antiparasitic defense).

- The normal value of platelets is: 150000 - 370000 / cubic millimeter of blood





BLOOD COUNT (HEMOGRAM)

- The hemogram is a basic laboratory medical analysis, being one of the most frequently requested tests, providing important information about various hematological and non-hematological conditions.
- The blood count consists of the automatic measurement of the following parameters:

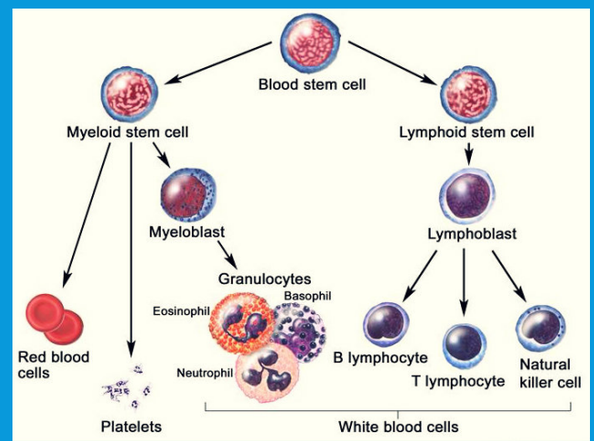
- Red blood cell number

- Hemoglobin (Hb)

- Hematocrit (Ht) - the mass of red blood cells in a certain volume of blood

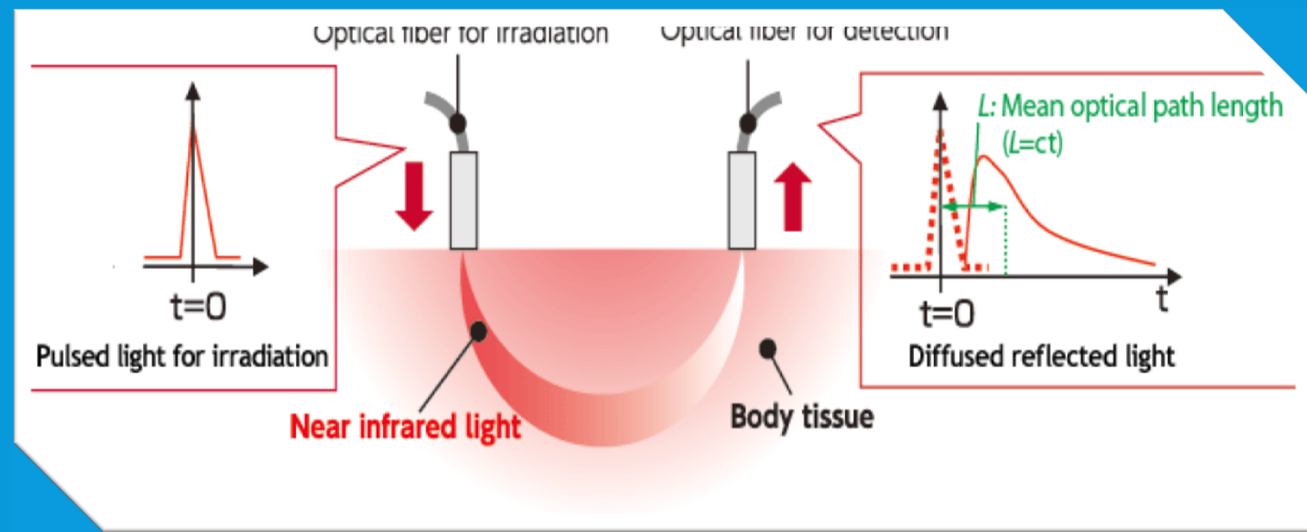
- Number of platelets

- Leukocyte number



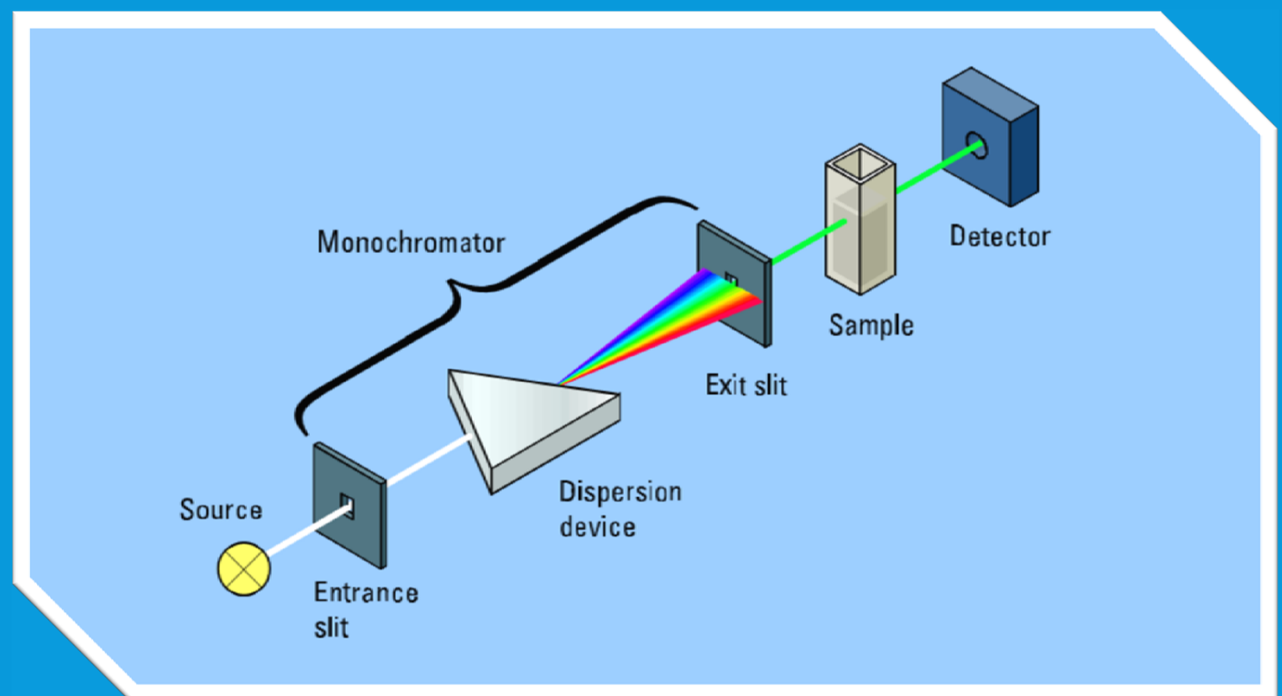
NON-INVASIVE MEASUREMENT OF BLOOD

- Near-infrared spectroscopy is a method that uses the infrared region of an electromagnetic spectrum with values between 700-2500 nm. Applications using this technology are in the field of medical and physiological diagnostics and research, such as glucocorticoid, pulsoximetry, neuroimaging, sports medicine, ergonomics, rehabilitation, neonatal research, urology, neurology.



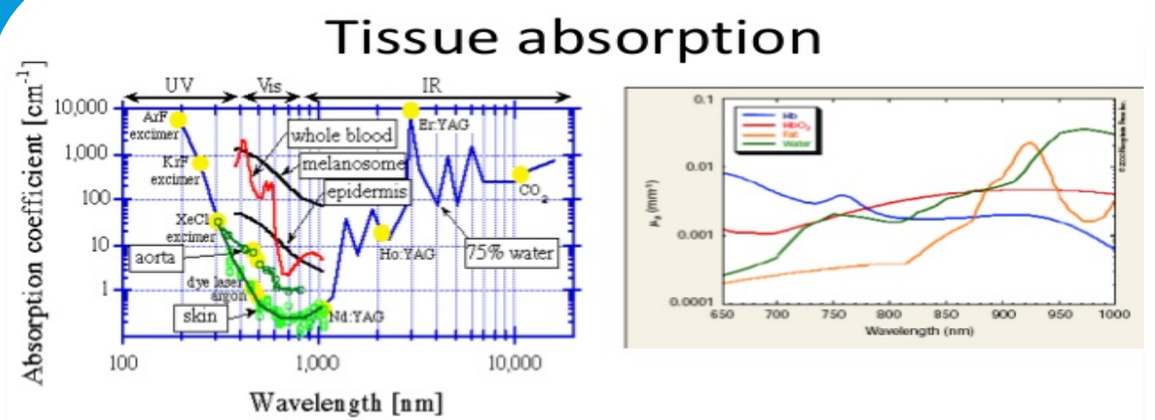
NEAR INFRARED SPECTROSCOPY

- Near infrared spectroscopy is based on combined and subtle vibrations in molecules. Such transitions are forbidden by the rules of quantum mechanics selection. As a result, molar absorbance in the near infrared region is usually quite low. An advantage is that short-wave infrared (NIR) radiation can typically penetrate much more into a sample than short-wave infrared radiation. Nearby infrared spectroscopy is therefore not particularly sensitive, but it can be very useful in probing multiple sets of samples.



ABSORPTION OF NIR LIGHT IN HUMAN BODY TISSUES

- Spectroscopically near infrared (NIR) instruments are similar to visible UV and IR instruments. There is a source, a detector and a dispersion element (such as a prism or, more commonly, a diffraction pattern) to allow the intensity at different wavelengths to be recorded. In this sense the transformed Fourier is applied using an interferometer, especially for wavelengths above ~ 1000 nm.

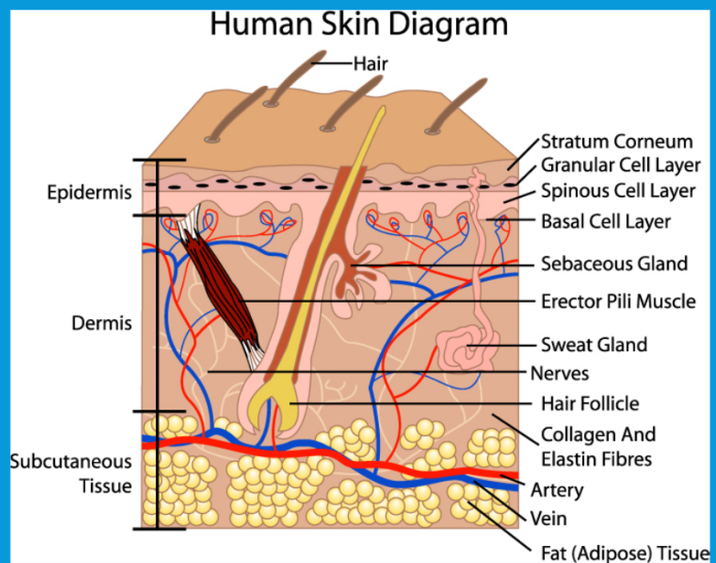


Major tissue absorbers include: **Hemoglobin, lipids (beta carotene), melanin, water, proteins, blood components, body fluids**
Oxy and deoxy hemoglobin have distinct spectra. **Optical measurements can provide information on tissue oxygenation, oxygen consumption, blood hemodynamics**

- Primary application of near-infrared (NIRS) waves on the human body is based on the fact that the transmission and absorption of NIR light in human body tissues contains information about changes in hemoglobin concentration.

HUMAN SKIN DIAGRAM

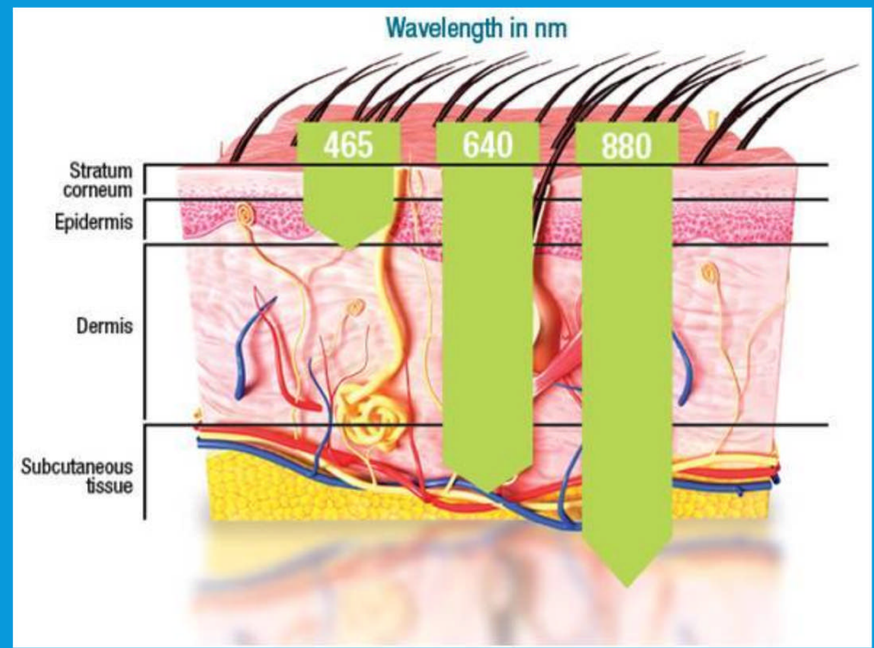
- The skin has a complex structure consisting of three layers: epidermis, dermis and hypoderm.



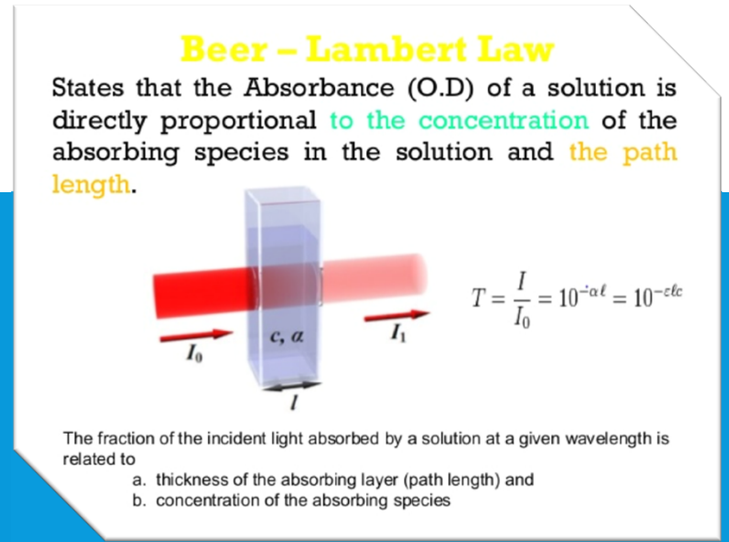
- ***Epidermis:*** it is a pluristrated epithelial layer, corneal, avascular, crossed by hair, excretory channels of sweat glands and free nerve endings.
- ***Derma:***The dermis is a layer of connective tissue in which the blood vessels are found, the nerve endings we feel, feel the temperature and pain.
- ***Hypodermis:***Hypoderm is found right beneath the dermis and is also a conjuctive layer and combines the skin of the muscles or bones.

WAVELENGTH SPECTROSCOPY SKIN IN NM

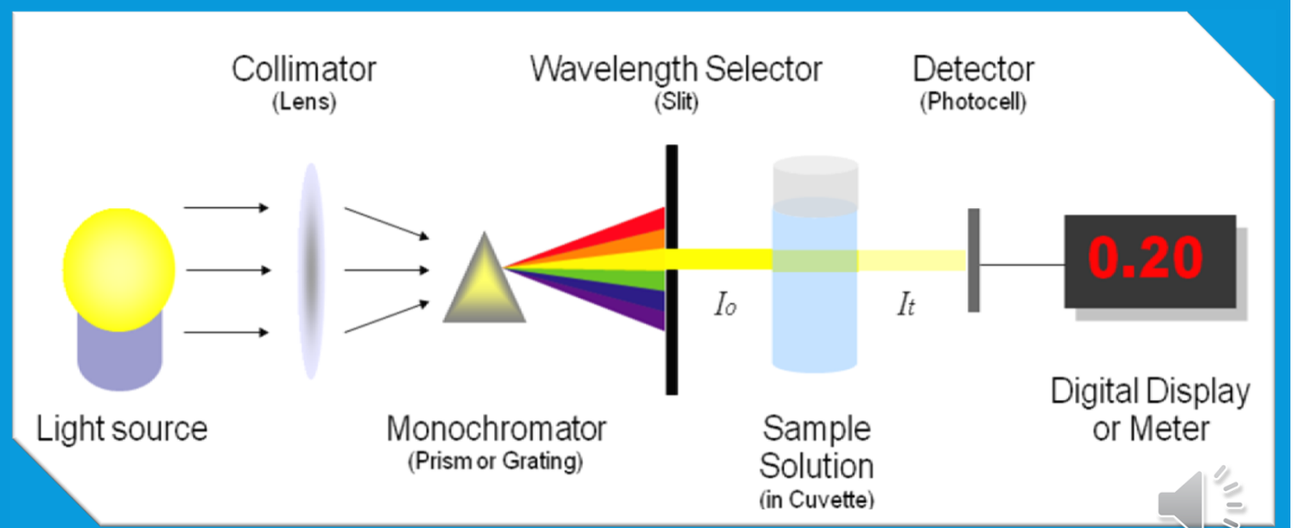
- As can be seen in Figure, the wavelength of **465** nm can penetrate to the epidermis layer, the wavelength of **640** nm to the dermis, and **880** nm can reach up to the subcatanated tissue.When the heart pumps blood, the blood circulates regularly, and the blood volume in the arteries will have cyclical changes. When the body is in the systolic phase, the heart's blood is supplied to the whole body, and the arterial blood in the finger will be at its maximum volume. At this point, the absorption of infrared light is the strongest, and the electrical signals in the photoelectric sensors are weaker. On the contrary, the absorption of near-infrared light is stronger.



THE BEER-LAMBERT LAW



- The Beer-Lambert Law offers a mathematical formula of the method that allows the calculation of light absorption through material to provide information on the concentration and thickness of the sample. The value of the absorption is also related to the transmission, and the transmission is related to the optical depth and the absorption of the light passing through the matter.
- (a)the transmitted light intensity decreases exponentially as the concentration of the substance in the solution increases;
- (b) the transmitted light intensity decreases exponentially as the distance traveled by the substance increases ;

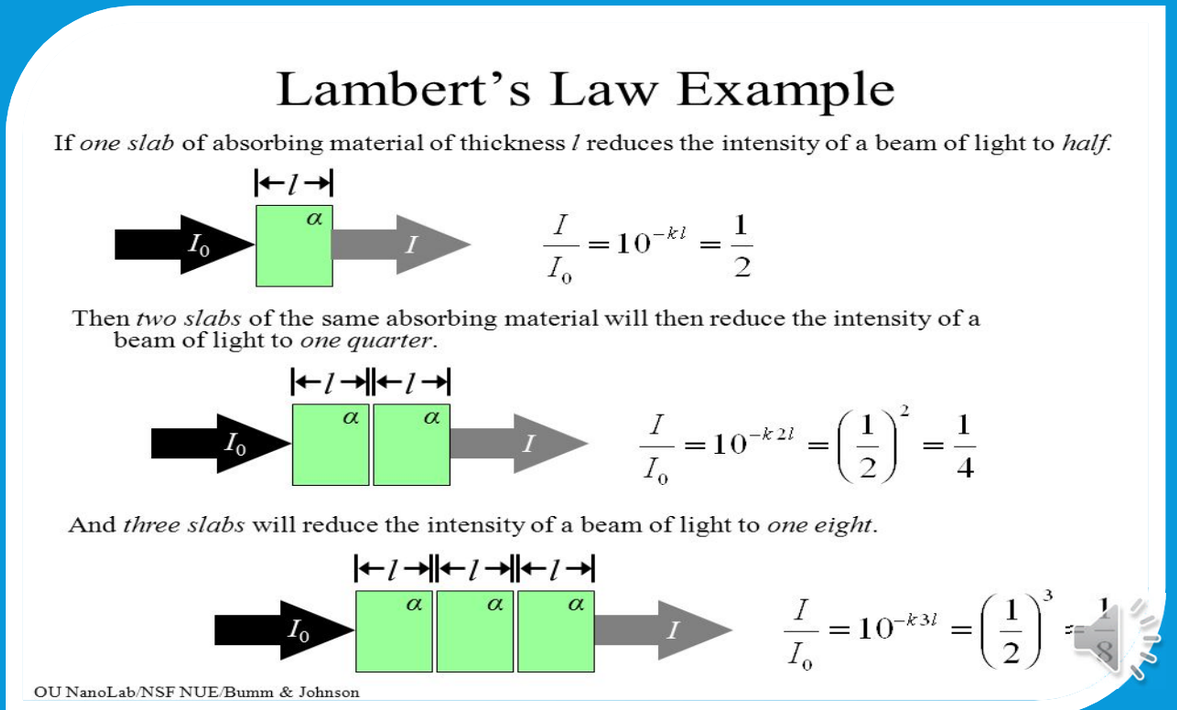


THE TRANSMISSION OF THE MATERIAL SAMPLE IS RELATED TO IT'S OPTICAL DEPTH *T*

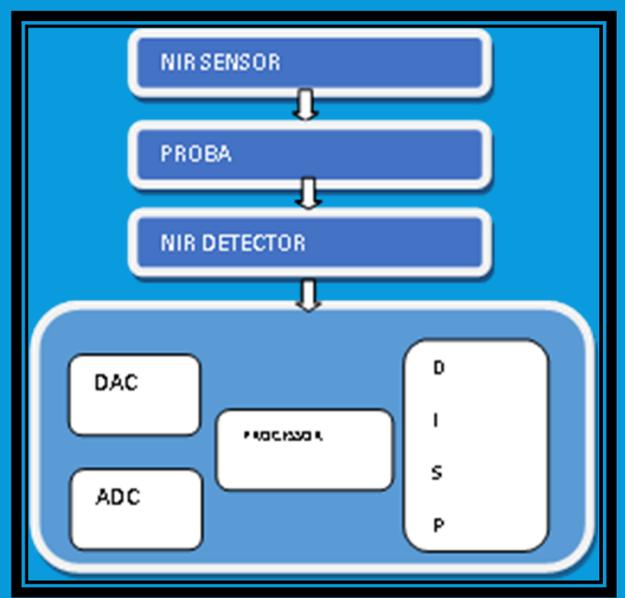
$$T = \frac{\theta_e^t}{\theta_e^i} = e^{-\tau} = 10^{-A}$$

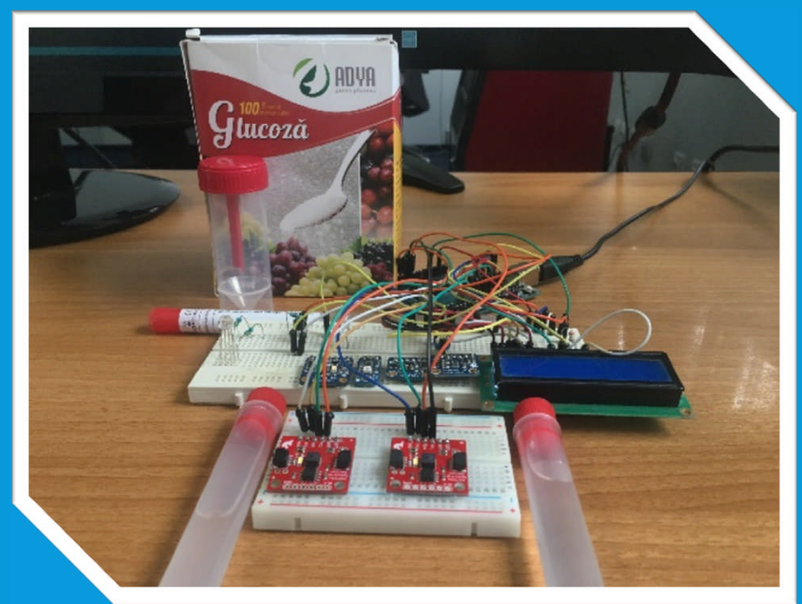
- A is Absorption
- T is Transmission
- τ is optical depth
- ϕ^t_e represents the radiant flux transmitted by the surface of the sample
- ϕ^i_e is the radiant flux received by the sample surface
- I_o is the intensity of the light entering the sample
- I_t is the intensity of the light leaving the sample

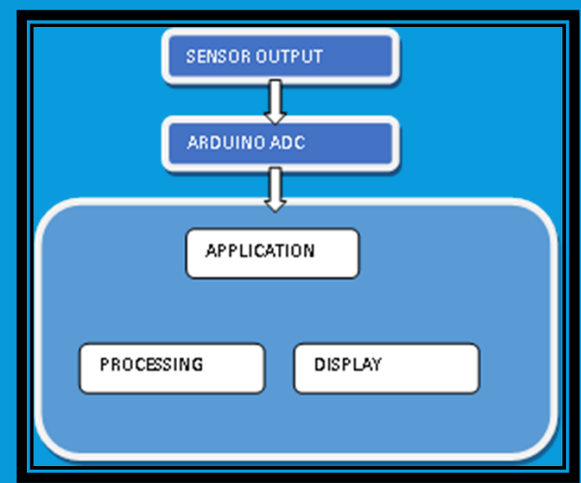
- This demonstrates that the Beer-Lambert law clearly establishes a correlation between the absorbance of light by a sample and the concentration of the sample.



THE BLOCK DIAGRAM & PROTOYPE

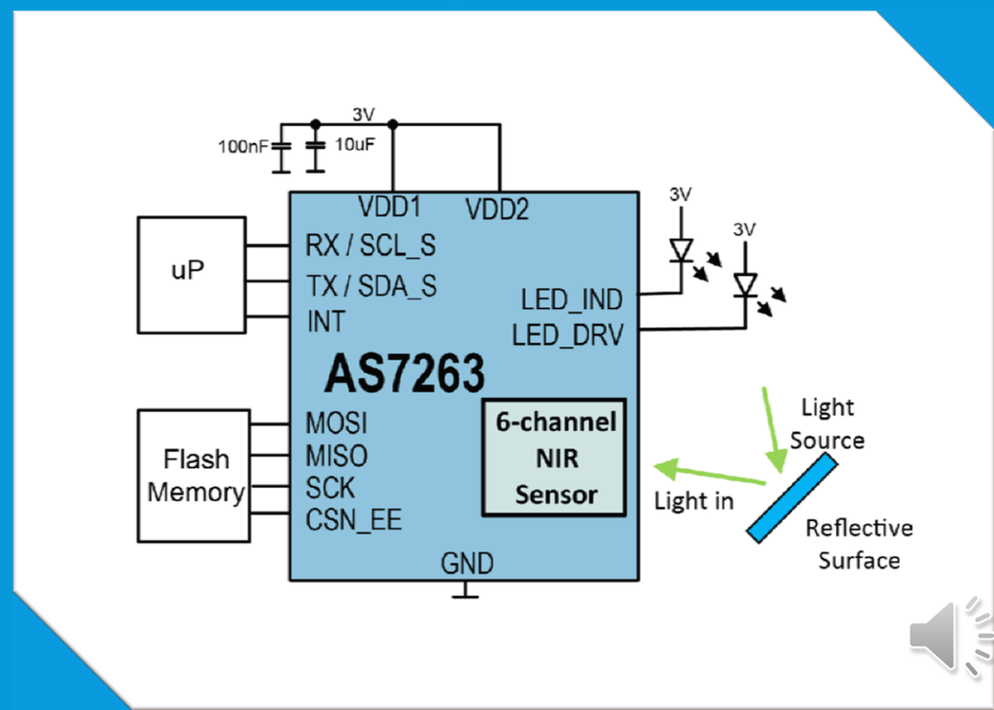






SENSOR: ABSORBANCE AND COLORIMETER(AS7262 - AS7263)

- . The absorption pattern of these active absorbents is less sensitive to near infrared. In this study a light is chosen at an operating wavelength of 610~880 nm.
- **AS7263** is the NIR version of the spectral sensor capable of measuring 610, 680, 730, 760, 810 and 860 nm of light, each with a maximum detection error of 20nm. The 6 light channels have the following wavelengths:
- R = 610 nm; S = 680 nm; T = 730 nm; U = 760 nm;
- V = 810 nm; W = 860 nm;
- **AS7262** is the NIR version of the spectral sensor capable
- of measuring and transmitting on 6 channels the
- values for:
- V = violet; B = blue; G = green; Y = yellow; O = orange;
- R = red;



TESTING AND RESULTS

- For tests we have taken into account 6 channels. The first channel runs to a depth of 480 nm (dermis), the second channel 560 nm to the hypoderm and the third to 680 nm hypoderm. The values in these channels are low from the 6 channel of 940 nm which reaches the capillary area.
- Suppose we have the following data acquired on several samples as can be seen in the table below:

E	R-610	S-680	T-730	U-760	V-810	W-860
E1	7797.68	3150.99	874.13	416.04	387.01	291.97
E2	7894.71	2573.4	897.28	424.99	305.84	296.62
E3	8011.66	3247.07	901.92	427.98	388.00	298.95
E4	7888.06	3186.12	882.23	419.0	389.98	294.29
E5	7739.20	3184.05	874.13	415.04	392.95	290.80
E6	7937.24	3175.79	882.23	420.02	391.96	295.46

V	B	G	Y	O	R
22.14	34.23	25.71	24.11	27.61	40.14
20.23	32.72	23.56	20.22	27.11	39.94
19.84	31.52	23.71	23.58	26.66	39.77
14.88	20.55	19.20	18.67	25.68	37.00
13.64	20.55	18.07	18.67	24.69	37.00

TESTING AND RESULTS

- We know that red blood cells represent 4 ~ 5 million / cubic millimeter of blood) blood cells. They contain a pigment called hemoglobin (Hb), which determines the red color of the blood. Hb is made up of heme (red dye, which contains iron and which has the role of fixing oxygen) and globin (protein from the albumin group). The reference value is between 4.30-5.90 / 106 µL. Leukocytes are white cells and have a reference value of 4 ~ 10/103 µL, and platelets between 150 ~ 450/103 µL.
- The main process that helps us in spectroscopic measurement of erythrocytes is related to the phenomena related to the absorption of NIR excitation by hemoglobin and the primary photochemical process of photo-dissociation of oxyhemoglobin from deoxymoglobin. When the heart pumps blood through arteries loaded with oxygen, we can say that we have a great absorption of light through oxyhemoglobin. This absorption gradually decreases as we go through deoxiglobination. To calculate the amount of absorption in the hemoglobin, we will take the results on the R channel of the sensor, the red one with the wavelength of 860 nm. From this we will decrease the absorptions on the lengths 480, 560 and 610 nm which represent the absorption through the skin.
- $\beta_n = \Delta_c - \phi_n$
- where:
- Δ_c is the rate of absorption through the three layers of skin calculated above;
- ϕ_n is the absorption rate on the Red 860 nm channel;
- β_n is the absorption rate in hemoglobin

R
40.14
39.94
39.77
37.00
37.00

TESTING AND RESULTS

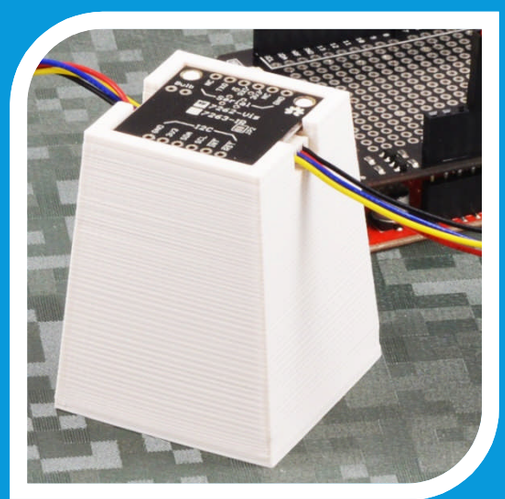
- We know that normal values for erythrocytes are 4-5 million / µL, for leukocytes is 4000-800 per µL, and for platelets of 150000-40000 per µL. From the absorption rate through hemoglobin we have to decrease the absorption rate through leukocytes and platelets. Suppose that on 1 µL we have a total of 4404000 of which 4 million are red blood cells, 6000 leukocytes and the rest platelets. We will have the following percentages:
- erythrocytes – 90,00 %
- leukocytes – 0,99 %
- platelets – 9,01 %

$\beta_n = \Delta_c - \phi_n$	Erythrocytes 90%	Leukocytes 0,99%	Platelets 9,01%
291,97 - 40.14	226,65	2,49	22,69
296,62 - 39.94	231,01	2,54	23,13
298,95 - 39.77	233,26	2,57	23,35
294,29 - 37.00	231,56	2,55	23,18
295,46- 37.00	232,61	2,56	23,29

- Based on the percentages and formulas above, we will have the following absorption rate results:

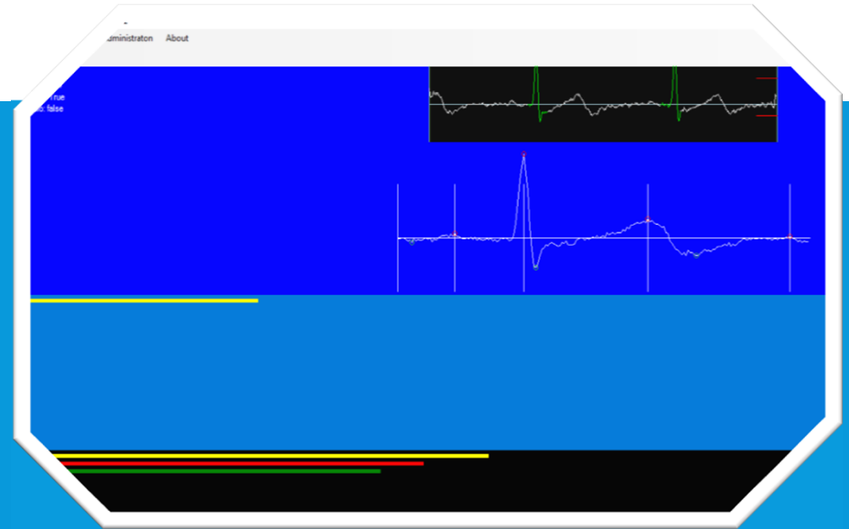
PROTOTYPE & SENSOR

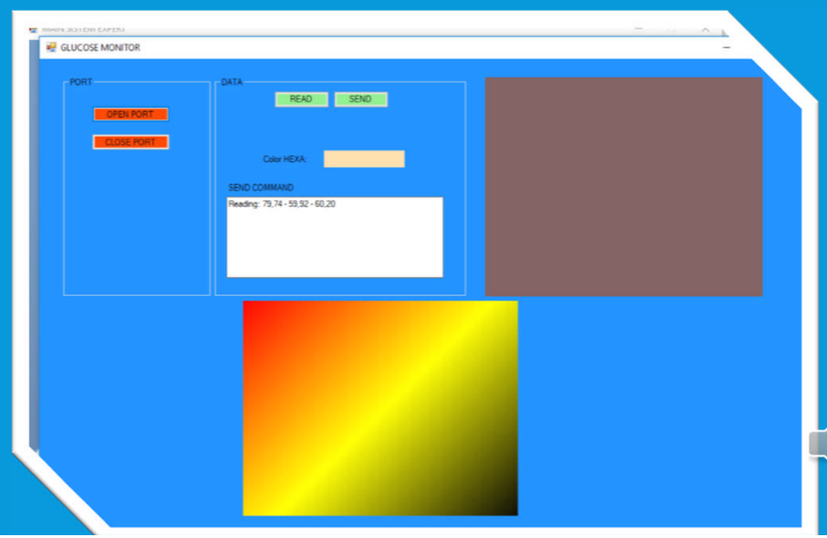
- A non-invasive commercial NIR sensor, Qwiic NIR AS726x (Figure 9), used to measure how different materials absorb or reflect infrared light, was used for the tests.



- Protoype at work: communications between sensor and Arduino, data transmission and display.

SOFTWARE APPLICATION PROCESSING





CONCLUSIONS AND FUTURE WORK

- The NIR spectroscopy experiment demonstrates great potential for the non-invasive continuity of elements levels in the human body blood. There are other possible variables that have not been included in this proposed model such as skin roughness that can cause light scattering, concentration of various body fluids, etc. could have an impact on system performance.
- Calculation of plasma in the blood can cause errors in the transmission of light absorption data, because we do not have any precise data related to how much water and nutrients are in this plasma
- To further improve system calibration and sensitivity, in our next study, we will investigate the impact of these variables on the performance of the sensor system.
- Multivariate regression will be implemented to make the system more robust for in-vitro testing. This would have a major impact on the monitoring of personal health and the history of patients with diabete
- The invasive method of measuring the elements formed in the blood is done by taking a blood sample, using the centrifugation process and anticoagulants.

THANK YOU!
QUESTIONS?