Living Condensed Matter Biosensor Technology

In Prevention and Management of Chronic Disease

Next generation Lifestyle and Healthcare Device

Executive summary

Company	R&D Intercell invented the unique breakthrough biosensor technology, allowing to monitor blood glucose levels and blood pressure noninvasive continuously in real time, applicable in healthcare and wellbeing.
Problem	The global challenge – Prevention and Management of Diabetes and related Cardiovascular Disease; noninvasive continuous glucose monitoring (CGM) technology.
Solution	We have discovered the biomarker unknown before – osmotic pressure of intercellular substance of human living tissue, characterizing the tissue cells metabolism, and invented the breakthrough LCM biosensor technology allowing to monitor blood glucose levels and blood pressure noninvasive and continuously by high accuracy real time measurement of intercell osmotic pressure by sensors placed on the skin surface.
Current status	Our solution has been validated in a proof-of-concept clinical study with 50 patients, including 42 diabetic subjects with total 252 tests with 30 minutes duration of each test. 8 prototypes manufactured and tested to continue clinical validation. Miniaturization of protype is in progress: 3D Model is ready.
Next steps	Finalize miniaturization of prototype, prototyping MVP and start MVP production.

The Global Challenge.

Diabetes and related Cardiovascular Disease are the biggest global threats today.

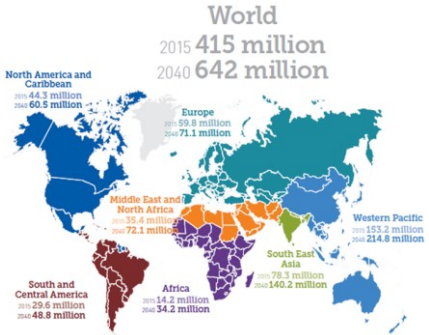
For pre-diabetes, it is estimated that 88% of patients are unaware of their condition and it takes less than five years for it to progress to full fledged disease.

But Type 2 diabetes is a fully preventable disease. This is good news driving us toward discovery biomarker for diabetes and breakthrough technology that will allow to build a next generation lifestyle and medical device for early diagnoses of this chronic disease.

At last, but not a least, one more global problem related to diabetes challenge is the invention of noninvasive continuous glucose sensing technology to build monitoring device for diabetes treatment complementary to conventional finger - prick glucometers.

Market

- A large number of companies are active in non-invasive glucose monitoring R&D. However, despite a rapidly growing number of worldwide patents, none of these techniques has generated reliable results.
- The currently available consumer devices only provides nonspecific information on physical activity and heart rate. But the consumers require something that is actionable in early prevention of chronic disease.



	dexcom	OptiScan	CNOGA MEDICAL	Senseonics
Post-Valuation ($M)	$340	$211	$217	$187
Last Investment ($M)	$56	$29	$50	$20

Market leaders and newcomers

Roche, BAYER, Abbott, LIFESCAN, Panasonic, SANOFI, Walmart, TARGET

Source: *Dow Jones, venturesource database*

SAMSUNG

BIOSTRAP

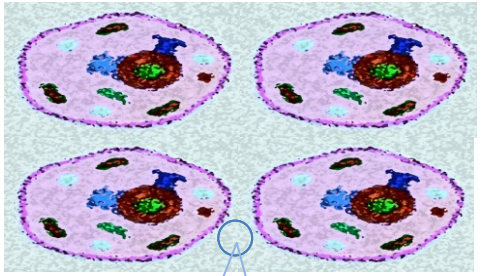
The non-invasive glucose monitoring device has a global market targeting more than 415 million diabetic patients.

According to a 2021 market research report by Grand View Research, the global wearable medical devices market was an estimated $16.6B in 2020 and is expected to reach $111B by 2028, representing a very high forecast CAGR of 26.8% from 2021 to 2028 .

The consumer version of device – lifestyle device has a global market exceeding the multi billions diabetics market at least 10 times.

Pain Point: A New Approach

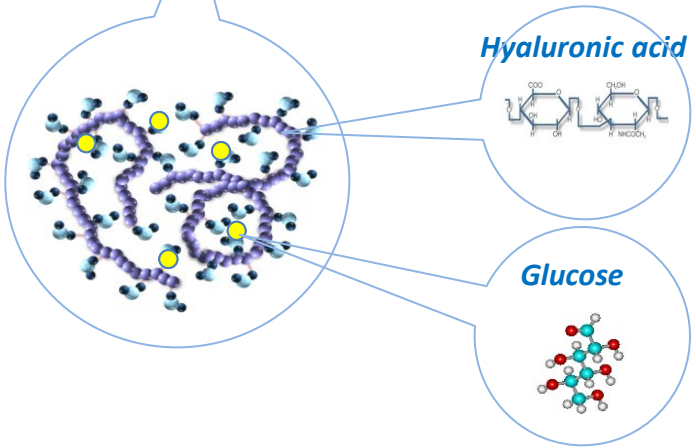
Living Tissue Structure

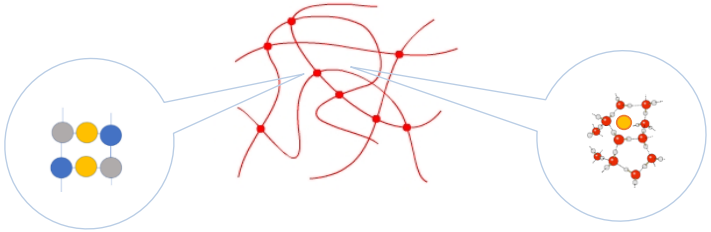


What is the pain point of this problem and what is deterring the progress in noninvasive glucose monitoring R&D?

We figured out that the deterrent is the underdevelopment of the scientific basics of Living Tissue Biophysics that in turn results in the lack of progress in discovery of biomarkers of tissue cells metabolism.

We decided to take a different approach by first re-examining the basic physics of glucose interaction with the living tissue. It took years to build the scientific groundwork of living tissue biophysics that is the *Physics of intercellular substance – Living Condensed Matter (LCM) Physics that describes the thermodynamics of Living Condensed Matter that finally resulted to* the technology breakthrough (International patent application # PCT/RU 2020/05324, 10.02.2021).

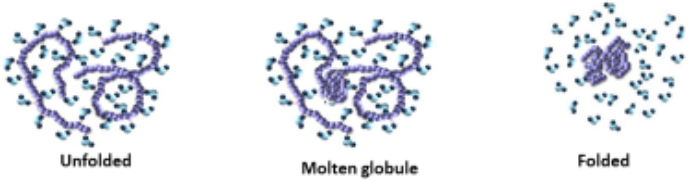




LCM Physics describes non-covalent weak interactions of glucose molecules with hyaluronic acid

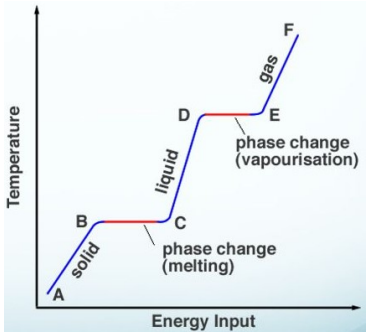
Technology Basics: Living Condensed Matter Physics

It was discovered that the intercellular substance at physiological conditions is in a heterophase condensed state, in which globular (crystalline) and melted globule (liquid) phases are coexist in thermodynamic equilibrium, analogous to the coexistence of condensed phases of water at triple point 0^0C.

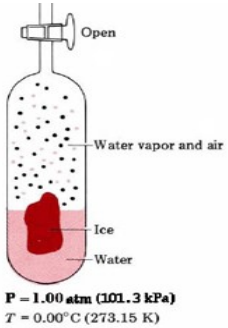


Heterophase region of intercellular LCM corresponds to Physiological Norm

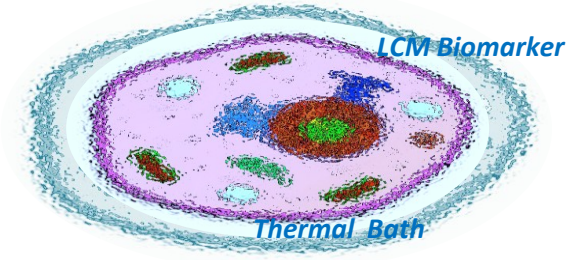
Temperature:	36,45	^{0}C
Blood glucose :	3,7 – 11,4	mmol/L
Capillary pressure:	30,0 – 8,5	mmHg
[Na] – [Cl]	40,256	mmol/L



Heating curve of substance



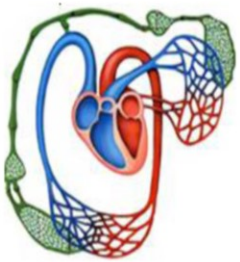
Triple point of water 0,0^0 C



*Spontaneous deviations of physiological parameters from the norm lead to a phase transition of intercell LCM into a homogeneous phase, with changes in volume and osmotic pressure. Therefore, intercell **osmotic pressure** , which characterizes the thermodynamic phase state of a intercellular substance, is a sensitive indicator- **biomarker of the physiological state of the body**.*

The Solution

We have discovered the LCM *biomarker* unknown before – osmotic pressure of intercellular substance of human living tissue, characterizing the physiological state and cells metabolism. The State Equation of intercellular substance F(C, P, W, Posm) ≡ 0 that describes the relationships between *osmotic pressure* Posm and physiological parameters - *blood sugar* C, *blood pressure* P and *cell metabolism rate* W has been proved by clinical proof of concept study.



BLOOD PRESSURE P

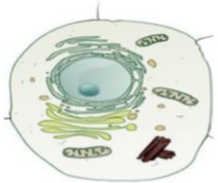
BLOOD SUGAR C

Intercellular substance itself at its heterophase region at physiological conditions acts as a nature biosensor with the selectivity to glucose molecules & extremely high sensitivity to heat flow that in turn results in dependence of osmotic pressure of intercellular substance vs glucose concentrations and heat input.

OSMOTIC PRESSURE P_{osm}

INTERCELLULAR SUBSTANCE

Our solution allows to isolate blood glucose concentration (C) by high accuracy measurement of intercellular *osmotic pressure* (P_{osm}) by sensors placed on skin surface.

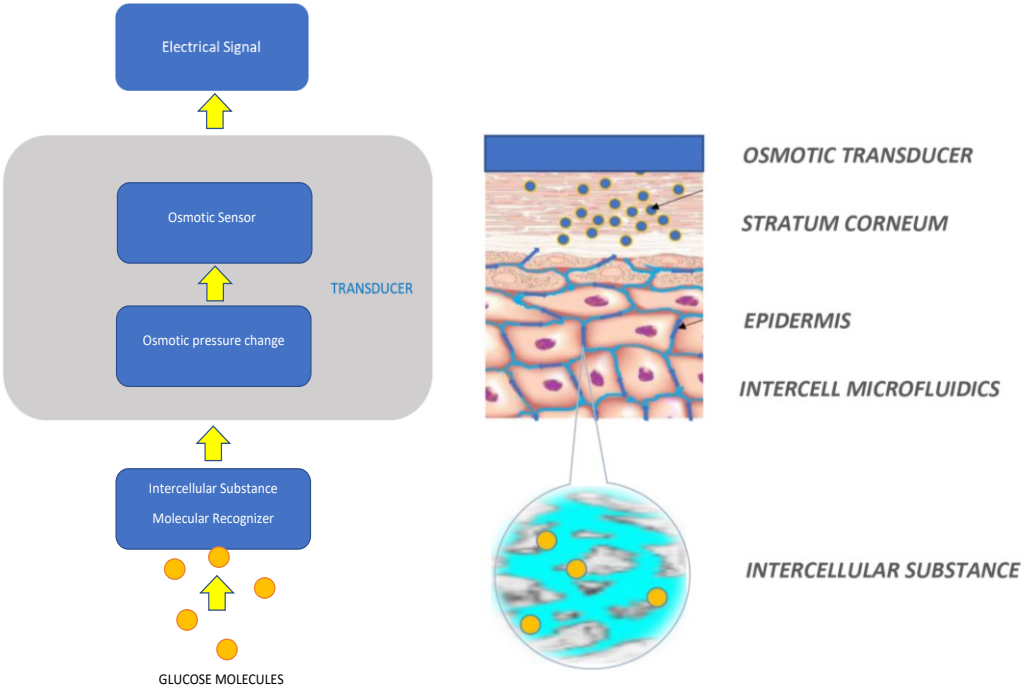


CELL METABOLISM RATE W

The Working Principle

The skin epidermis itself acts as a natural *glucose biosensor* that transforms glucose concentration change into an osmotic pressure change what in turn leads to change in intercellular microfluidics flow via epidermis towards the skin surface.

Our device isolates this signal by *osmotic transducer* placed on the skin surface that converts osmotic pressure of intercellular substance into analog electrical signal.



INTERCELLULAR OSMOTIC BIOSENSOR ASSAY

The Product

Here is our product LCM Biosensor resulting from our solution above.

We have invented the breakthrough LCM biosensor technology allowing to monitor *blood glucose and blood pressure* noninvasive and continuously by high accuracy real time measurement of the *osmotic pressure* of intercellular substance of living tissue by sensors placed on the skin surface. The product is a smart integrated multi - sensor device with integration of unique *biosensor technique* into *isothermal phase transition microcalorimeter*.

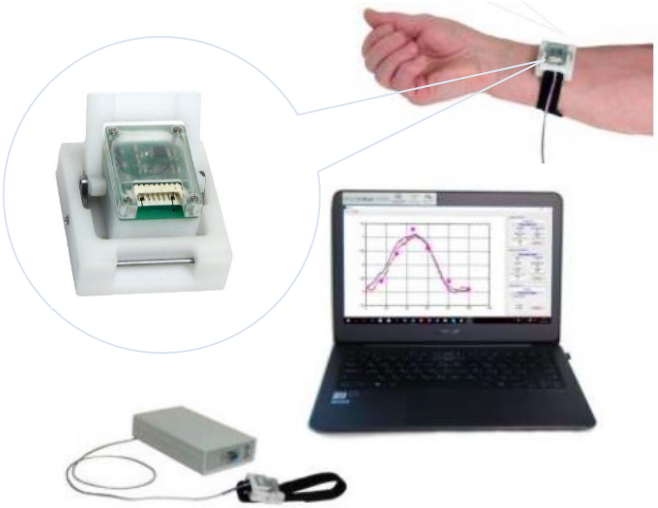
The Product: 3D Model Preview

***Unlike currently available consumer devices*, such as Fitbit, Apple Watch and Biostrap, that only provide nonspecific information on physical activity and heart rate, *our noninvasive LCM Biosensor collects molecular level data that is actionable in early prevention of chronic disease - cardiovascular, renal and metabolic* (CVRM) *diseases*.**

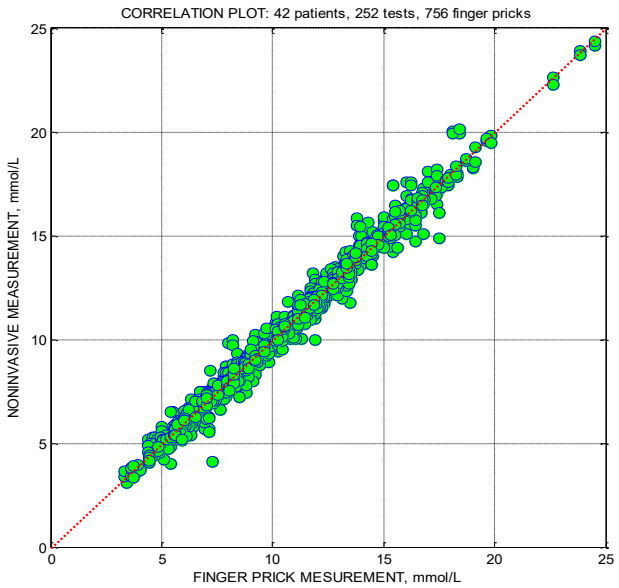
The Product: 3D Model Preview

The holy grail of prevention and treatment of chronic disease – *breakthrough product LCM Biosensor perfect* for both treatment and early diagnostics of CVRM (*cardiovascular, renal and metabolic*) diseases.

The Prototype



The prototype device that has been used in clinical proof of concept study with diabetic and healthy subjects.



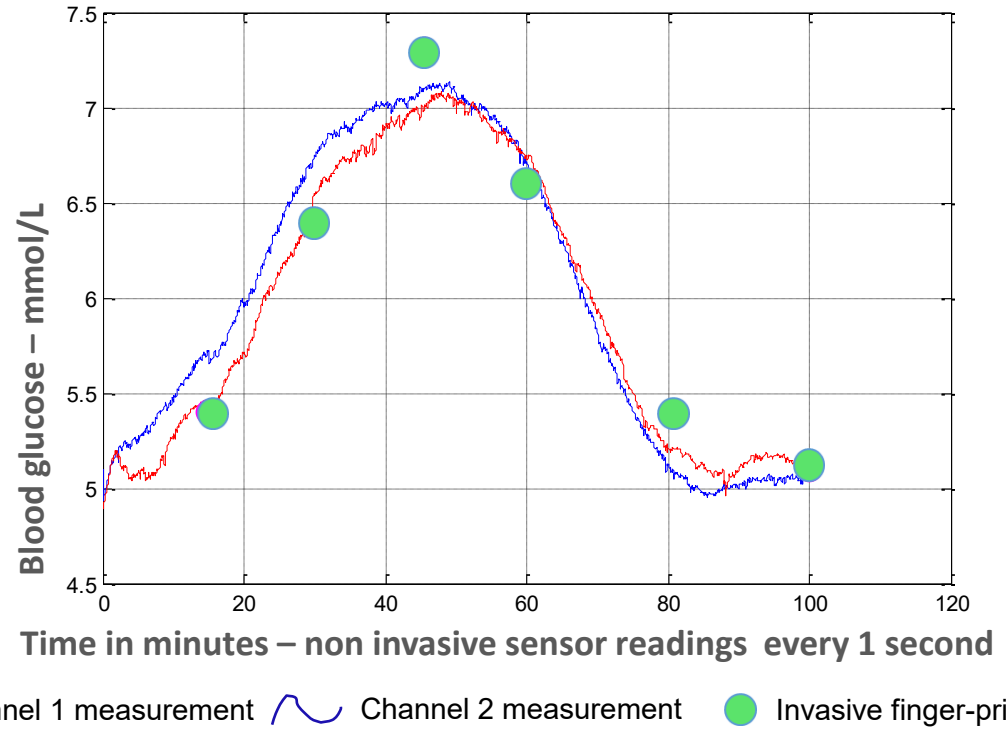
Our solution has been validated in a proof-of-concept clinical study with 42 diabetic subjects with total 252 tests with 30 minutes duration of each test, which compared performance of our device prototype to that of FDA-approved conventional finger-prick glucometers.

Proof - of - Concept Study: Method Comparison

Here is an example of comparison measurements during Glucose Tolerance Test of healthy patient.

We can see good correlation between non-invasive sensor readings of 2 channels prototype and finger prick measurements.

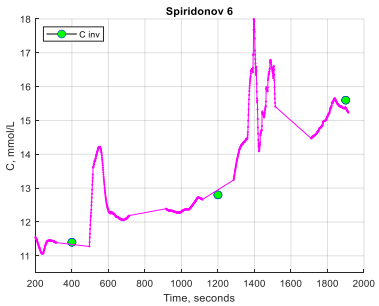
Oral Glucose Tolerance Test (OGTT) of healthy patient.

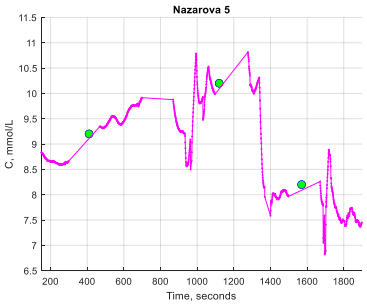


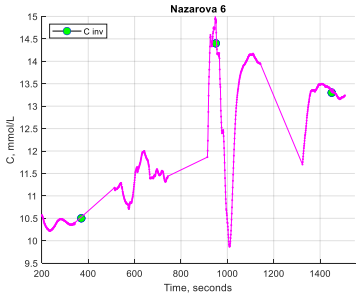
Channel 1 measurement Channel 2 measurement Invasive finger-prick*

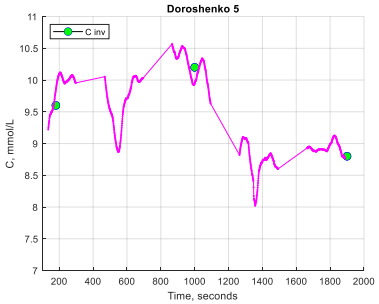
* Using a commercial device "Accu Check active" to detect sample glucose level

Proof - of - Concept Study: Method Comparison









Non-invasive measurement

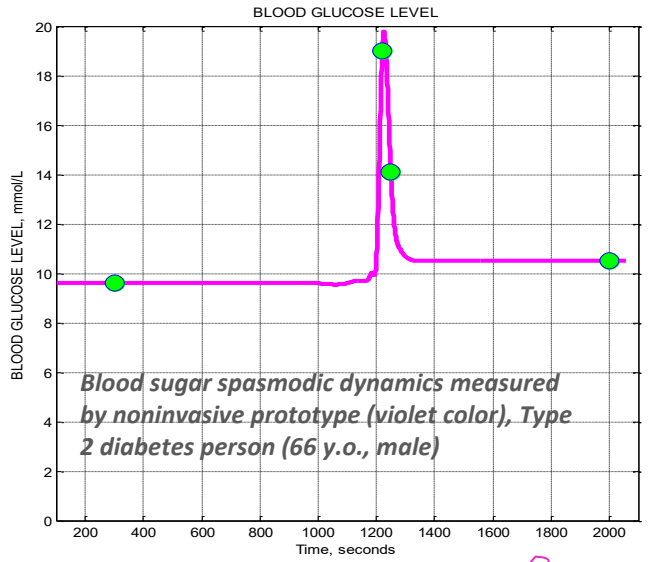
Invasive finger-prick*

* Using a commercial device “One Touch Verio Pro” to detect sample glucose level

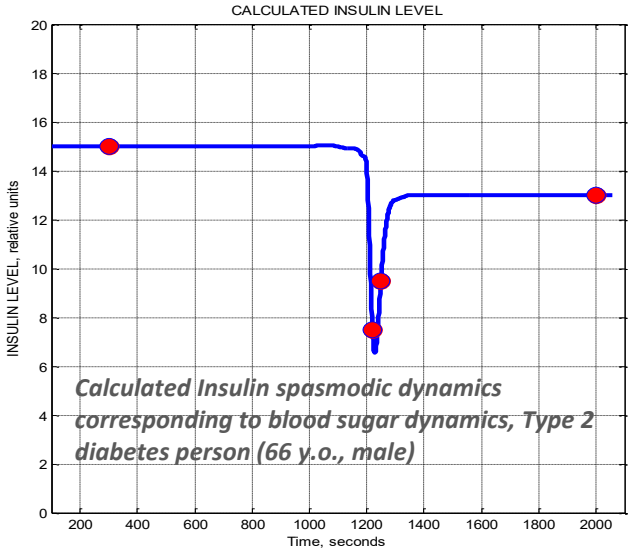
Here are examples of comparison measurements with diabetic subjects. Unlike the smooth monitoring dynamics of blood sugar of healthy patients, the dynamics of diabetics has a spasmodic nature with possible jump changes of blood sugar level.

Diagnostic Utility

Our device allows to detect the short-term jump changes of blood sugar in the form of a single pulse signal. This "*jump changes*" specificity of diabetic sugar dynamics was unknown before. Now we can determine the blood *insulin* dynamics by calculations based on blood sugar dynamics that in turn leads to possibility of real time assessment of insulin resistance of individuals.



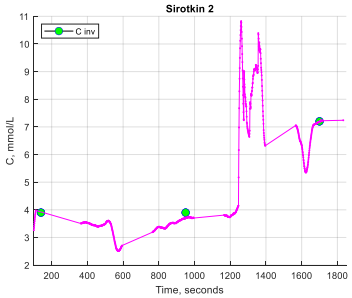
CALCULATED INSULIN DYNAMICS



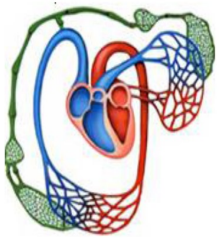
Non-invasive measurement Invasive finger-prick* Calculated insulin dynamics

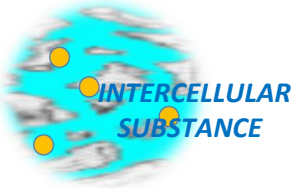
Diagnostic Utility

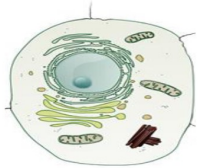
At last, but not a least, it was clinically proved, the intercellular osmotic pressure is a biomarker of human diabetes state: our product can distinguish healthy, pre-diabetic and diabetic individuals based on the volatility of blood sugar dynamics and osmotic pressure without the need to calibrate the device by finger-prick measurements.



High volatility and step wise temporary dynamics of blood sugar and intercell osmotic pressure are a characteristic feature of Type 2 diabetes.





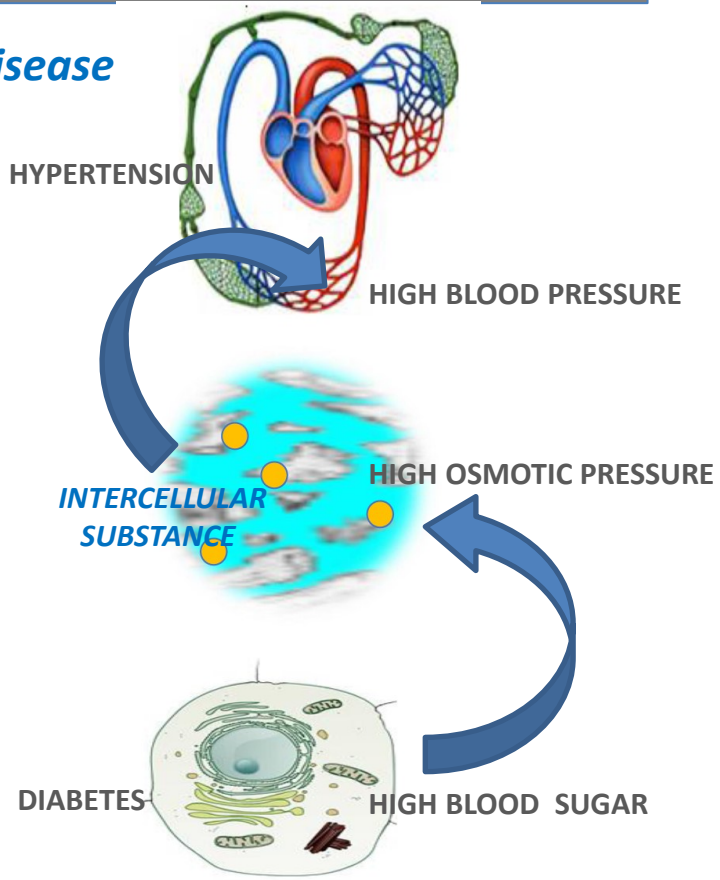


Examples of stepwise temporary dynamics of blood sugar and osmotic pressure of diabetic subjects.

Diagnostic Utility: Cardiovascular and Metabolic Diseases

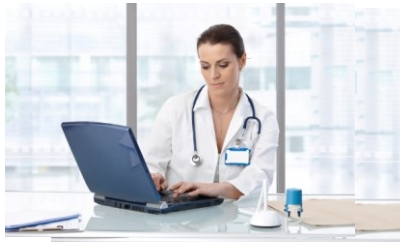
The Link Between Diabetes and Cardiovascular Disease

Living Condensed Matter (LCM) Physics that** describes the* relationships between intercellular osmotic pressure and physiological parameters - blood sugar and blood pressure and allows to understand the basics of the ***Link between Diabetes and Cardiovascular Disease. The deviation of the characteristics of the intercellular substance from the physiological norm due to high blood sugar levels in diabetes leads to high blood pressure resulting from the intercellular osmotic pressure change and in turn leads to cardiovascular disease.



Instability and spikes in blood sugar level leads to osmotic pressure spikes and as a result to the blood pressure spikes.

Cloud-based telemedicine for healthcare and wellbeing



The device connects – through a wireless connection – with the computer for analysis and review of the near real time visualization of monitoring data by doctors.

Using the cloud platform, it is able perform in real time a thorough analysis of diabetes and healthy persons data to monitor diagnostics results that lead to better decision making and an increased health data equity.

Intellectual Property

Patents & Academic Publications:

1. US patent application, USPTO # 16303371, 2018

2. European patent application, EP #16903293.5, 2108

2.1. Method;

2.2. Multi – Sensor Device

https://worldwide.espacenet.com/publicationDetails/originalDocument?CC=EP&NR=3466320A1&KC=A1&FT=D&ND=3&date=20190410&DB=EPODOC&locale=en_EP

3. Patent RU application, # 2019136897/14(072952), 18.11.2019

4. International patent application, PCT/RU 2020/05324, 10.02.2021.

4.1. Calorimeter Spectrometer;

4.2. Diabetes Diagnostics;

4.3. Protein Folding & Biocatalysts.

5. Academic publications, in progress