Chapter

# Integrated Cyber-Physical System to Support Early Diagnosis and Prevention of Prediabetes and Complications of Type 2 Diabetes

*Zsolt P. Ori*

## Abstract

Dietary and exercise interventions are the mainstay of prevention, and they constitute important part in the treatment of type 2 diabetes (DM2) and its complications. Automated, continuous, individualized non-invasive measurement of pathological processes leading to DM2 and complications are needed in terms of self-explaining metrics for improved individualized lifestyle management. Our company, the Ori Diagnostic Instruments, LLC is using tools of Medical Cybernetics (MC) to monitor non-invasive indicators of insulin resistance, exercise capacity, and autonomic dysfunction. The MC approach utilizes mathematical process and measurement models which are connected to a wearable sensor system. This chapter has the purpose to show how already widely available information technologies like smart phones, cloud computing, and sensor devices of the fitness industry could be put together into an integrated cyber-physical system (ICPS) to support fitness goals like fighting cardiometabolic conditions including high insulin resistance and low level of cardiorespiratory fitness and help building resilience with improved physiological reserve capacity. We want to demonstrate also how ICPS can be not only used for fitness self-management but can be extended to become a platform of noninvasive monitoring devices and become a medical software to support person-centered, outcome driven treatments for DM2 and complications in primary care.

**Keywords:** medical cybernetics, non-invasive monitoring, insulin resistance, exercise capacity, cardiorespiratory fitness, cardio-vegetative stress, metabolic syndrome, atherosclerotic disease, autonomic dysfunction, anemia, heart failure

## 1. Introduction

This chapter envisions the possibility of continuous risk assessment with non-invasive monitoring using tools of Medical Cybernetics (MC) facilitating early diagnosis and prevention of type 2 diabetes (DM2) and its complications including cardiovascular disease (CVD), chronic kidney disease (CKD) and heart failure (HF). MC offers a suitable conceptual framework to make the pathological processes of DM2, CVD, CKD, and HF observable and controllable through

appropriate interventions facilitated by mathematical modeling. Utilizing principles of MC has the potential to enable primary care to help more beyond current standard of care and to make Digital Health more accessible to our patients. Moving away from traditional reductionism and embracing holistic approaches will certainly help fulfill the promise of Medical Cybernetics (MC) and help find workable solutions to tackle the ever growing health related challenges of humanity and introduce new approaches to manage and self-manage chronic non-communicative conditions or diseases in the 21st century. Already available information technologies like smart phones, cloud computing and the widely available sensor devices of the fitness industry could be put together into a cyber-physical system (CPS) to gain needed data and tools and to provide a holistic approach. The principle idea behind using MC [1–9] and developing a CPS [5, 6] is to gain deep insight and make so far unmeasurable phenomena indirectly calculable in the users' natural environment and put these unknown phenomena in the appropriate context for improved control. The plethora of new data gained with such CPS will lead to the creation of needed metrics and open opportunities for optimized self-control and dynamic behavior interventions based on the targeted metrics, leading to self-healing and cyber-therapy supervised by health care providers.

Ori Diagnostic Instruments, LLC (ODI) has been conducting R&D [1–11] and recently we introduced a CPS [5, 6]. CPS is a mobile technology integrating sensory data from various mobile devices into individualized dynamic mathematical models of physiological processes allowing for analysis and prediction using the models and allowing for quasi-real time feedback to the user (and optionally the primary provider). We have developed several technical and medical innovations allowing for creation of a CPS: 1. Self-adaptive models of the human energy metabolism (SAM-HEM) [1–11]; 2. Self-improving measurement models to amend validity, reliability, consistency, and accuracy of bioelectrical measurements [7–9]; 3. Using the minimum variance Kalman filter along with state space modeling technique [1–11] where process models of state variables work in unison with measurement models, mutually updating each other's *a priori* and *a posteriori* model calculations with the help of the minimum variance Kalman filter; 4. Utilizing principles of "least action/ stationary action" to obtain essential practically unmeasurable parameters of the human energy metabolism [5–6]; 5. Applying principles of "maximum information entropy" to evaluate stochastic processes and perform parameter estimations with constraints or subsidiary conditions [7–10]; 6. Feasibility demonstration of our process modeling technologies in simulation studies using published trial data [1–6, 11]; 7. Innovations using a CPS to reenergize primary care and facilitate goals of Global Health [4, 10, 11].

Some important advantages of ODI's innovations to combat noncommunicable cardiometabolic diseases are the following. 1. An important aspect of ODI's innovations is the integration of self-adapting models into a cloud based cyber-physical system [5, 6] that provides user feedback and allows for truly individualized patient-oriented approaches. 2. Further it is anticipated that ODI's holistic and data driven individualized diagnostic approach will allow not just to help prevention and improve management and self-management of chronic conditions related to DM2 but also to lend help during emerging medical emergencies [7, 10]. 3. It is envisioned here that as more and more wearable physiological sensors become available, the sensors can be integrated with our cyber-physical system platform and their respective self-adaptive pathophysiological process models and self-learning measurement models [10, 11]. 4. A user's individual dynamic mathematical models provide feedback and prediction to assist behavior modification by supporting and maximizing control [10, 11]. 5. A CPS can realize not just a complex adaptive system at the individual level, but also through interconnections a network

of individualized cyber-physical systems can be realized, allowing for network analysis and machine learning/artificial intelligence. Global Health goals [10, 11] could be approached at a community or even societal level.

This chapter consists of two parts. In part I, we will show how already widely available information technologies like smart phones, cloud computing, and sensor devices of the fitness industry could be put together into an integrated cyber-physical system (ICPS) to support fitness goals like fighting increased insulin resistance and low level of cardiorespiratory fitness and help in building resilience with improved physiological reserve capacity. This form of ICPS supports fitness goals without the wider scope of a "medical software "i.e. without the intention of medical treatment. This non-medical software ICPS focuses on three interlinked physiological/pathophysiological processes: 1. Cardiometabolic Functioning and Disease (CMD), 2. Cardiovascular Functioning and Disease (CVD), and 3. Cardio-vegetative Functioning and Stress (CVS). We will show how representative metrics reflecting health in these areas of physiological functioning and early disease can be created using MC modeling using data from a wearable sensor system (SS). Regarding CMD, the reader will be informed about how the non-invasive measurement of insulin resistance is possible with the R- or Rw-ratio which follows changes of the invasively measured HOMA-IR. R- or Rw-ratio related estimates are derived from serially measured weight, fat weight by bioimpedance measurement, and energy balance related data [3–6]. The CVD health status is assessed by indirectly estimating maximal oxygen uptake (VO2max) from daily physical activity and heart rate related data [5]. Indices of CVS health are obtained from time and frequency domain analysis of heart rate variability (HRV) [12, 13].

In part II an upgraded version of ICPS to medical software will be outlined which still has to be developed and clinically tried and properly examined and verified according to applicable rules and regulations by FDA. The major reason for distinction between non-medical software and FDA approved medical software is that the former primarily serves the purpose of prevention of prediabetes, DM2 and complications as opposed to the latter where medical diagnosis is made requiring active therapeutic interventions by health professionals. The part II subchapter is inspired also by the most recent summary recommendation for person-centered, outcomes-driven treatments of DM2 in primary care by leading academic authors [14]. One of the key points of this article is to call for "a patient-centered approach that addresses patients' multimorbidities, needs, preferences, and barriers and includes diabetes education and lifestyle interventions as well as pharmacologic treatment...". The medical software version of ICPS could be complementary to key points in [14]. We introduce here to the reader how the following comorbid conditions could be observed non-invasively and how metrics can be created to see outcomes objectively. We will discuss here the following pathological processes as targets of monitoring, tracking and metric creation for outcome measures: 1. CMD and Metabolic Syndrome (MS), 2. Atherosclerotic Cardiovascular Disease (ASCD), 3. Autonomic Dysfunction (AD), 4. Chronic Anemia due to CKD, and 5. Heart failure (HF). Here we want to point out that [14] puts great emphasis on ASCD, CKD and HF as a targeted outcome measure for interventions. It is envisioned here that self-explaining metrics regarding disease processes 1–5 can be displayed quasi real time on the patient's smart phone app giving tremendous opportunity for patients to educate themselves and learn more about their diseases and ask appropriate questions. The feedback of information may help improve self-management in a non-judgmental manner. The self-explaining nature of metrics may also point out individual responsibilities to fight modifiable risk factors. Having quantifiable metrics allows for dynamic lifestyle interventions which could be managed, self-managed or helped with automated feedback of information. Further, the response

to pharmacological interventions could be gauged, helping to track results of treatment and recognize inadvertent side effects.

To our knowledge there is no noninvasive tool or monitoring device available to measure increased oxidative stress, inflammation, or insulin resistance in the user's natural environment. However, these pathological processes are strongly interlinked, leading to among others DM2, CMD, MS, CVD, ASCD, AD, Chronic Anemia of CKD, and HF. Importantly, ICPS is built on the holistic modeling approach of considering the entire human energy metabolism and insulin resistance. The latter can be viewed also as a surrogate marker for whole body oxidative stress and inflammation [15]. The bio-physical principle behind the proposed conceptual framework of ICPS and for process models is the recognition that the changes of the body composition (lean mass and fat mass) and the energy flow in and out of the body are governed by the fat vs. carbohydrate burning ratio and are strongly linked to insulin resistance [16, 17]. The significance of this is that an impaired mitochondrial lipid oxidation is a major anomaly in the chain of metabolic events leading to obesity and increase of insulin resistance [18]. High insulin resistance is associated with high respiratory quotient (RQ) reflecting lower fat burning than normal [19]. We have no non-invasive measuring technique for Oxidative Stress. However, there is a strong connection between Oxidative Stress and Insulin Resistance [20]. Similarly, there are strong connections between inflammation and insulin resistance [21] but there is no non-invasive tool available currently to monitor whole body inflammation. Therefore, we intend to use the R- and Rw ratio to give at least a qualitative signal tool if the trends of changes in the metabolism are in the right or wrong direction in terms oxidative stress and inflammation. *Our central hypothesis is that by improving insulin resistance with the use of ICPS, we can ameliorate the condition of oxidative stress, overall inflammation, fat vs. carbohydrate oxidation, and cardiovascular disease progression*.

To our knowledge ODI is the first in using the principle of "least action/stationary action" as a principle for finding key physiological parameters of the energy metabolism [5, 6]. This is instrumental to estimate noninvasively the HOMA- IR linked marker of insulin resistance R- or Rw-ratio which are defined as $R = \Delta L/\Delta F$ and $Rw = \Delta W/\Delta F$ where $\Delta L$, $\Delta W$ and $\Delta F$ are lean mass, weight and fat mass change over 24 hrs. For monitoring of insulin resistance, we were able to prove the feasibility of this concept [5–6]. Further, we have shown that our Weight, Fat weight, Energy Balance (WFE) model can estimate changes of Rw without mandatory calorie counting by serially measuring weight, fat weight, and energy balance [6]. Our extended model of WFE calculation is called WFE-DNL-AT [6] and allows also for estimating for the first time noninvasively in the user's natural environment the otherwise difficult or impossible to measure changes of state variables (SV's) of the metabolism such as 24 h nonprotein respiratory quotient (24hRQ), utilized macronutrient energy intake, fat vs. carbohydrate oxidation rate (Fox/Cox), de novo lipogenesis (DNL), and adaptive thermogenesis (AT). However, WFE-DNL-AT calculations require knowledge of the daily macronutrient calorie intake.

For measuring daily changes of fat mass F, lean body mass L, the measurement of intracellular water mass (ICW) as well as extracellular water mass (ECW) are also needed. Unfortunately, bioimpedance measurement technologies are not suitable for clinical use in current form due to significant interindividual variations mainly due to lack of reliable bio-electrical modeling of electrical properties of a body segment. On the other hand, bioimpedance measurements are quite well suited for individualized measurements or serial measurement as the intraindividual variation is small. The electrical modeling issue can be improved with using the principle of "maximum information entropy" [9, 10]. Therefore, ODI developed

a Body Composition and Hydration Status Analyzer stand up scale (BC-HS-A) [7–10]. We use here several innovations for creating individualized bioimpedance measurement models [7–10].

A general principle of the development of ICPS as medical software is that we want to connect the calculated SV's to morbidity and mortality risks. An example is given in [22] where cumulative incidence of various CVD events is compared in people with and without diabetes. The hazard ratio for CVD in view of HOMA-IR is published in [23]. CVD mortality and all-cause mortality is investigated with low cardiorespiratory fitness according to weight categories in [24]. Waist circumference is connected to mortality in [25]. Mortality is evaluated according to weight status with incidence of diabetes in [26]. CVD and mortality as a function of BMI is published in [27]. Heart Rate Variability and Risk of All-Cause Death and Cardiovascular Events are investigated in [28]. All these published morbidity/mortality studies allow us to assess the time trajectory of likelihood of morbidity and mortality as a function of the individually calculated SV's.

ICPS generates SV's and metrics in each domain of use (1–5) and displays the results quasi real time on the screen of a mobile app, the Metabolic Health Monitoring (MHM) Mobile app or on the Metabolic Manager Software Tool (MST) Web app. MHM is designed for displaying the SV's quasi real time and for entering input data and providing feedback that is either machine generated or from MST by personal trainer or primary provider. MST is a web app designed for use by personal trainer/primary provider (s) or the user himself/herself for analysis and prediction of the calculated SV's and metrics. MST enables also planning for lifestyle change and evaluating progress and outcome.

## 2. ICPS non-medical software (ORI FIT-MET™)

### 2.1 Description of the process models

Here we introduce ICPS ORI FIT-MET™ for the purpose to achieve fitness and prevent prediabetes, DM2 and complications such as CVD and AD. Uniquely, ICPS can construct trajectories of SV's (metrics) quasi real time in three domains of health: 1. Cardiometabolic Functioning and Disease (CMD), 2. Cardiovascular Functioning and Disease (CVD), and 3. Cardio-vegetative Functioning and Stress (CVS) with major implications to morbidity/mortality risks. Each of these domains have their mathematical process models to estimate the SV's (metrics). ICPS uses the predictive Kalman filter to predict future changes based on serially measured input data and using the respective predictive model calculation.

Ad 1. For CMD we use our Cardiometabolic Function Model (CMFM) which utilizes our Self-Adaptive Model of the Human Energy Metabolism (SAM-HEM) [1–4]; the Weight, Fat weight, Energy Balance model calculation (WFE); and the de novo lipogenesis, adaptive thermogenesis, and 24 hr. respiratory quotient model calculation WFE-DNL-AT [6]. The metric for insulin resistance in terms of R- or Rw-ratio carries the power of allowing to estimate the fat vs. carbohydrate burning and it is reflective of overall oxidative stress and inflammation. The CMFM modeling can calculate and predict the following physiological SV's: weight, fat mass, lean mass, ECW, ICW, R-ratio, Rw-ratio, Fat vs. Carbohydrate Oxidation, and 24 h non-protein respiratory quotient. With precise calorie counting the estimations of utilized macronutrient energy intake, de novo lipogenesis DNL and adaptive thermogenesis AT is possible.

Ad 2. For CVD process modeling ODI uses a cardiovascular fitness model (CVFM) in which the maximum oxygen uptake capacity ($VO_2max$) is estimated

from heart rate and measuring maximal activity energy expenditure (aEEmax) during graded exercise. The $VO_2$max calculation model uses multiple linear regression with data on age, sex, height, percent body fat, aEEmax, and the slope between HR and physical activity as in [29]. CVFM is self-adapting (self-learning) from the daily incoming data and assesses changes of $VO_2$max, exercise capacity, and heart rate reserve. We adopted the Critical Power model from [30] which is defined as the maximal sustainable aerobic power not causing "fatigue" to measure exercise capacity.

Ad 3. For CVS modeling ODI uses its Cardio-vegetative Stress Model (CVSM) which calculates the state variables (SV's) measuring functioning of the autonomous nervous system and estimating imbalance between sympathetic vs. parasympathetic activity. The time domain measure is the standard deviation of R-R intervals (SDNN) and the frequency domain power spectrum indicators are the low frequency spectral power of HRV (LFr), the high frequency spectral power of HRV (HFr), and their ratio LFr/HFr [12–13, 28].

### 2.2 Data flow

The usage of ICPS ORI FIT-MET™ is centered around data flowing in and out of the system. ICPS works with a wearable Sensor System (SS) to provide input data for the process models to arrive at metrics regarding CMD, CVD, CVS. The heart rate and physical activity energy expenditure related input data come from a wearable wristwatch-type fitness tracker like Garmin's smart watch. The body composition and hydration status related input data come from Garmin's Index scale. Alternatively, ODI developed its own fitness tracker, the sensor belt (SB) [7], and the BC-HS-A stand up scale [8, 9]. During regular use, ICPS updates every day the SV's and creates metrics allowing for trend prediction. The input and result data can be displayed on MHM or MST.

### 2.3 Analysis and interpretation

ODI's proposition is that MC modeling can provide special insight into physiological/ pathophysiological processes. MC modeling gives the expected direction of change of a variable in the future i.e. by connecting the data points and drawing a trajectory of the predicted changes. The benefit is that instead of comparing the user's data against a group average, the individualized modeling and data trajectory creation allows for self-comparison to historical data, capturing individual characteristics and facilitating individualized interventions. The MC models are generating metrics and trajectories allowing for tracking progress and facilitating dynamic behavioral changes. The undeniable advantage of modern portable electronics is that they can provide the resources and powerful data for self-healing in a non-judgmental way. The self-explaining context of SV's have the potential to raise self-awareness and draw attention to risk reduction and individual responsibility in the fight against modifiable noncommunicative disease processes. The derived metrics provided by ICPS have the potential to give the opportunity for education and learning about risks for health, development of new skills to fight risks, building motivation, as well as measuring self-efficacy in the fight against modifiable risks. The same ICPS metrics can be used by a personal trainer/primary provider for teaching and guiding needed changes of lifestyle or behavior. Importantly, it must be emphasized that the most important tool in our armamentarium to enhance insulin sensitivity and along with-it fat burning is endurance training [31] and it works even if no weight loss is achieved.

## 3. ICPS medical software

### 3.1 Description of the process models

Inspired by the call for person-centered, outcome-driven treatment as a new paradigm for treatment of type 2 diabetes in primary care [14] we present here our vision of how MC type approaches could significantly help goals set forth by the academic authors in [14]. Target points for outcome in [14] are ASCD, CKD, and HF. For a practicing primary physician, it is desirable to offer non-invasive monitoring for patients in their natural environment not just for early detection of deterioration but also to improve patients' handling of rising issues with appropriate behaviors.

Here we offer a preview about ICPS as a Medical Software and show how we can construct trajectories of SV's quasi real time in five domains of disease processes: 1. CMD and Metabolic Syndrome (MS), 2. Atherosclerotic Cardiovascular Disease (ASCD), 3. CVS and Autonomic Dysfunction (AD), 4. Chronic Anemia due to CKD, and 5. Heart failure (HF). It appears natural to extend the use of ICPS non-Medical Software with the areas of Chronic Anemia due to CKD and Heart failure. The respective process models are the following:

Ad1. The MC model for CMD and MS remains the same Cardiometabolic Function Model (CMFM) as in ICPS ORI FIT-MET™. Response to the therapies of metabolic syndrome could be tracked and compared with baseline for de novo lipogenesis DNL, Fat vs. Carbohydrate Oxidation, and 24 h non-protein respiratory quotient. These metrics can supply valuable feedback in terms of ongoing diet and exercise habits with implications to spur needed change.

Ad 2. For ASCD we want to extend CVFM. In the modeling of the maximum oxygen uptake capacity ($VO_2$max) we also want to consider modeling oxygen delivery which depends on hemoglobin concentration (Hb), total hemoglobin mass due to chronic anemia of CKD and cardiac output. For modeling of oxygen delivery and oxygen consumption we use the model equations in [32]. For process modeling of hemoglobin concentration, total hemoglobin mass, and cardiac output see also Ad 4. and 5.

Ad 3. For CVS modeling ODI uses CVSM. For quantifying AD, the rationale is that there are strong associations between central adiposity (which is a marker of insulin resistance) and autonomic dysfunction [33] and there is an increased sympathetic system activity in metabolic syndrome [34]. We plan on using promising markers beyond SDNN, LFr, and HFr to recognize AD such as heart rate recovery time [33]. For the prediction of sudden cardiac death, we want to also use the correlation dimension of R-R intervals D2 [35].

Ad 4. We want to build a modeling platform for Chronic Anemia due to CKD. The main rationale is that anemia is a recognized risk factor for cardiovascular disease [36]. This is potentially important because iron deficiency anemia, if corrected, may in fact improve endothelial function and potentially improve morbidity and mortality [36]. Not surprisingly, anemia and insulin resistance and type 2 diabetes are interlinked [37] through various inflammatory processes which play crucial roles in the development of insulin resistance. There is also an inverse correlation between iron levels and HbA1c [38]. The reasons for this include kidney complications, neuropathy, and malabsorption occurring in the setting of advanced DM2. The elevated blood sugar will, over time, damage small blood vessels in the kidneys leading also to CKD. The erythropoietin production by the kidney goes down and along with it the production of red blood cells by bone marrow. Several studies show that diabetics with reduced renal function are more likely to end up with iron deficiency anemia than those without reduced

renal function [38]. The significance of monitoring hemoglobin concentration and mass is that it determines exercise performance, surgical outcome [39], and impacts heart failure [40].

The self-adapting process model of anemia of CKD (SAM-AC) will predict future hemoglobin concentration and total hemoglobin mass based on non-invasively measured hemoglobin concentration (Hb), extracellular water (ECW), and intracellular water (ICW). The ECW and ICW comes from ICPS ORI FIT-MET™. For capturing and predicting dynamics of changes of hemoglobin concentration ( $Hb_k$ ) and hemoglobin mass ( $tHbmass_k$ ) for day $k$ we use the following process models (Eqs. (1–3 and 5)) and measurement model (Eq. (4)). Hb concentration measurement comes from a non-invasive hemoglobin concentration measuring device like in [41, 42]. Data of daily *a posteriori* estimates of $ECW_k^{(+)}$ and $ICW_k^{(+)}$ will come from ODI's ICPS ORI FIT-MET™. We assume that 7.4% of the total body water constitutes the plasma volume (PV). Further we assume that the plasma albumin concentration is semi-constant, and it is not changing as rapidly as ECW and ICW, then the following formula could be used for plasma volume as in Eq. (1):

$$PV_k^{(+)} = \left(ECW_k^{(+)} + ICW_k^{(+)}\right).0.074; \tag{1}$$

The initial hemoglobin mass is calculated as $tHbmass_0 = Hb_0 . PV_0$ . The process equation for *a priori* (denoted as ( – )) hemoglobin mass on day $k$ is in Eq. (2):

$$tHbmass_k^{(-)} = Hb_{k-1}^{(+)} . PV_k^{(+)} + u_k; \tag{2}$$

The process equation for *a priori* (denoted as ( – )) hemoglobin concentration prediction is in Eq. (3):

$$Hb_k^{(-)} = \frac{tHbmass_k^{(-)}}{PV_k^{(+)}} + w_k; \tag{3}$$

The measurement model with the measured hemoglobin concentration $Hb_k$ on day $k$ is in Eq. (4):

$$Hb_k = Hb_k^{(-)} + v_k; \tag{4}$$

The process equation for *a posteriori* (denoted as ( + )) hemoglobin concentration is in Eq. (3):

$$Hb_k^{(+)} = Hb_k^{(-)} + K_k . \left(Hb_k - Hb_k^{(-)}\right); \tag{5}$$

Here $K_k$ symbolizes the Kalman gain provided by the Kalman filter. The random terms $u_k$ , $w_k$ , and $v_k$ represent errors and are assumed to be normally distributed with expectancy value and initial value of zero and estimated variance values with assumed non-zero initial value which is updated throughout the time of observation by the Kalman filter algorithm. Applying the Kalman filter guarantees minimum variance for errors. We use the maximum information entropy principle with

Lagrange multipliers and the Kalman filter with constraint as in (1) for minimizing error in Eqs. (4) in the estimation/ prediction process. The modeling calculation allows recognition of the significant deviation between measured and expected/ predicted values for Hb. A sudden significant change (determined by statistical testing) can be either from sudden change of total water content or change of hemoglobin mass change or both.

Ad5. Non-invasive monitoring of Heart failure (HF) for flair ups and avoidance of admissions or readmission to the hospital has been the core element of cost reduction programs [43]. Frequently used strategy to reduce readmission rate includes behavior related recommendations: 1) Take medications as prescribed, 2) Monitor daily weights, 3) Stay active every day, 4) Follow low salt, fluid restricted diet, and 5) Recognize symptoms of heart failure and how to respond early. Our proposition regarding this issue is that the recommendations 2–5 could be helped with an ICPS Medical Software with appropriate sensor device. The bioimpedance measurement of ECW and ICW comes handy because of convenience and safety. As mentioned in Section 1. Introduction ODI has created BC-HS-A and gathered significant experience with this technology and improved the modeling and measurement technique by individualization of the measurement models [7–10]. The personalization can make bioelectric measurements extremely useful not just under physiological but also under pathophysiological conditions. For measuring cardiac function, we want to use Impedance Cardiography (ICG). Regarding accuracy of ICG it is stated in [44] that when ICG is used for intra-subject measurements with same device for continuous monitoring of cardiac stroke output the performance and accuracy is better and surpasses those of inter-subject measurements. The usage of ICG has been verified in clinical studies [45]. ICG can provide calculated SV's such as Cardiac Output, Cardiac Index, and other hemodynamic parameters. Our self-adapting process model of HF (SAM-HF) will capture metrics of HF in terms of cardiac output, weight, ECW, ICW, $VO_2$max, heart rate variability, Hb, oxygen delivery, and other hemodynamic indices by ICG. All these metrics can be integrated to an individualized HF score improving interpretation and facilitating clinical use.

### 3.2 Data flow

The flow of data in and out of ICPS as a Medical Software is like that one of ICPS ORI FIT-MET™. The sensor system consists of the following parts: 1. The heart rate and physical activity energy expenditure related data come from a wearable wristwatch-type fitness tracker or ODI's Sensor Belt (SB). 2. The body composition and hydration status related data come from our specialized Body Composition and Hydration Status Analyzer (BC-HS-A) and stand up scale [7–10]. 3. For noninvasive hemoglobin concentration measurement, one could use a smart phone app [41] or measuring device with lap top connection [42]. 4. Regarding Impedance Cardiography (ICG), development kits are available [46]. ODI has the vision to develop its own hemoglobin concentration measuring sensor device and ICG device and integrate all these sensors via Bluetooth wireless communication to BC-HS-A which serves also as a base unit communicating directly to ICPS Medical Software. The incoming data from the sensor system (SS) is processed by the ICPS Medical Software.

ODI wants to use the SV's and metrics of change from baseline and determine the physiological reserve of the variables on a continuum for preventive purposes before reaching significant disease, decompensation, or death. This concept is visualized in **Table 1**. entitled, "ICPS Medical Software".

The increasing risk of major morbidity/ mortality is represented by a thickening red stripe as the physiological reserve capacity diminishes. The tapering arrow in blue symbolizes diminishing reserve capacity and represents the target

| Domains of health and MC models | Pathophysiological range metrics and possible interventions | | Major morbidity with crisis |
|---|---|---|---|
| Morbidity mortality |  | | |
| Physiological reserve |  | | Organ failure and crisis |
| Cardio-Metabolic Health, CMFM & Metabolic Syndrome | W, L, F, WCF, R-, Rw-ratio, Fox/Cox, 24hRQ, DNL, Metrics & Risk Scoring | Behavior modification/ Lifestyle Change/ Dynamic behavioral modification with ICPS | Metabolic catastrophe with need for urgent intervention |
| Cardio-vascular Health CVFM & ASCD | $VO_2$max, Exercise Capacity, heart rate reserve Metrics & Risk Scoring | Cardiopulmonary exercise/ Dynamic exercises planning with ICPS | Cardiorespiratory failure with need for urgent intervention |
| Cardio-vegetative Stress CVSM & AD | HR, SDNN, LFr, HFr, Metrics & Risk Scoring | Care by cardiologist/ Dynamic planned interactions supported with metrics from ICPS | Nerve exhaustion/ pending sudden cardiac death needing urgent intervention |
| Chronic Anemia due to CKD & SAM-AC | Hb concentration Hb mass Metrics & Risk Scoring | Care by provider and supplementation of needed factor(s), Automatic alert by ICPS | Symptomatic anemia with need for urgent intervention |
| Heart Function& SAM-HF | Cardiac Output Cardiac Index Metrics & Risk Scoring | Care by provider and following guidelines Automatic alert by ICPS | Symptomatic Heart Failure with need for urgent intervention |

**Table 1.**
*ICPS medical software.*

for improvement. The diagram shows also major tools for how vanishing physiological reserve in each health category could be improved and potentially help restore health. ODI's leap ahead innovation is *to use ICPS to collect highly impactful data, compress them into MC models, and determine and predict the model parameters which become the target for optimization of physiological functioning to reduce risk for morbidity/mortality.*

**Table 1** also shows the MC models and the respective SV's which are used to calculate metrics of change and Risk Scores (see second column from the left in **Table 1**). The possible intervention types for each MC models are listed as well (see third column from the left in **Table 1**). Handling recognized major morbidities and crisis is shown in the rightmost column of **Table 1**.

### 3.3 Analysis and interpretation

MC modeling can provide special insight into physiological or pathophysiological processes alike, giving the expected direction of change of a data point in the future i.e. connecting the dots or putting them on a model trajectory and explaining the changes. The benefit is that instead of comparing the user's data against a group average, the individualized modeling and data trajectory creation allows for individualized interventions and support goals of person-centered, outcome-driven

treatment as outlined by [14]. The MC models with trajectories and predictions allow for quantifying progress and for providing metrics for dynamic behavioral interventions supported by smart portable devices. The self-explaining context of SV's (metrics) have the potential to raise self-awareness and draw attention to risk reduction and individual responsibility in the fight against modifiable noncommunicative disease processes. The derived metrics provided by the MC models of ICPS have the potential to give the opportunity for education and learning about risks for health, development of new skills to fight risks, building motivation, as well as measuring self-efficacy in the fight against modifiable risks. The same ICPS metrics can be used by primary provider for teaching and guiding needed changes of lifestyle or behavior. A specialized sensor system such the Sensor Belt might provide important information to help manage also emerging emergency situations.

It is ODI's vision to develop its point-based risk-scoring system to summarize the relationship between SV's and the risk of the occurrence of a major morbidity event and have a Risk Score related to the five domains of functioning (in leftmost column of **Table 1**). The Risk Score calculation systems are popular among physicians and can facilitate evidence based clinical decision making [47]. The proposed Risk Score may permit effective risk stratification and assessing patient prognosis when the focus is on non-fatal outcomes because of specific causes [47].

Use of ICPS allows for machine learning to optimize the MC models to fit the best to the available data and enhance the accuracy and predictive value of the derived metrics and help maximize the control over results. **Table 2**. Entitled, "The Pathways to Maximize Control" gives a conceptual summary of how the collected data can be analyzed by ICPS and how the derived metrics can facilitate interventions across lifespan. In the future, an ICPS as a Medical Software could allow for Cyber-therapy i.e. to become a medical device allowing for diagnosis and therapy. Under such a scenario, an automated self-adaptive model will assess SV's at baseline and throughout pathophysiological changes. It is foreseen that autonomous computer-generated optimal control could be enabled to maximize improvements and realize individualized "precision" medicine with strict supervision by a health professional [10]. When the disease processes(es) enter crisis stage in a

| **Intervention type** | **Physiological range methods of choice** | **Pathophysiological range possible interventions** | **Major morbidity with crisis** |
|---|---|---|---|
| Self Care | Self-education, learning, following guidelines for healthy lifestyle | Self-healing with behavior modification and using ICPS | Optimized learned behaviors to secure survival until rescue |
| Managed Care/ therapy using information from ICPS medical device | Teaching/ learning how to improve health with use of ICPS | Interventions by health care provider/ team to guide therapy also using information from ICPS | Lifesaving interventions by rescue team using data also from ICPS |
| Cyber-therapy (ICPS medical device allowing for diagnosis and therapy) | Machine Learning of healthy baseline functioning | Autonomous computer-generated optimal control to maximize results and realize individualized "precision" medicine with strict supervision by health professional | Autonomous machine directed therapies which can be overruled by physician |

**Table 2.**
*The pathways to maximize control.*

home environment one can foresee the possibility of remote autonomous machine directed therapies which can be overruled by a physician.

## 4. Discussion

From person-centered, outcomes-driven treatment point of view of type 2 diabetes the innovation of the Integrated Cyber-Physical System Medical Software is that it can capture metrics in 5 intertwined domains of physiological or pathophysiological functioning in the user's natural environment non-invasively. Data can be obtained in the metabolic, cardiovascular, cardio-vegetative, hematological (circulating hemoglobin mass), and cardiac functioning health domains.

The ICPS non-Medical Software (ORI FIT-MET™) realizes already now the observation of metrics in the metabolic, cardiovascular, and cardio-vegetative health domains with preventative purpose. Input data regarding heart rate and physical activity energy expenditure come from a watch-type fitness tracker such as Garmin smart watch and from serially measured body composition and hydration data such as the Garmin Index scale. ICPS allows a quasi-real time monitoring of metrics of functioning for the user and personal trainer/primary provider and allowing for self-healing and directed lifestyle interventions. Analysis, prediction, and planning for change can be performed either at home or optionally in the personal trainer/primary provider's office through a web app and display of results on the user's smartphone. Unique to our effort is that our suggested state variables are connected to risks of morbidity and mortality and allow risk assessment continuously over a lifespan, raising self-awareness, enhancing motivation, and underscoring self-responsibility to reduce modifiable risks as much as possible. Metabolic health goals, like improved metabolic flexibility, improved insulin resistance along with greater lean mass and optimized fat versus carbohydrate burning can be approached with the help of ICPS ORI FIT-MET™ through feedback of information from a personalized self-adaptive mathematical model of the energy metabolism. ICPS can also help optimize cardiorespiratory fitness level by providing feedback of indirectly estimated maximum oxygen uptake from heart rate and measuring maximal activity energy expenditure. Knowing the fitness level by $VO_2$max can help set the optimal training loads for endurance training leading to improved resilience, fat oxidation and insulin sensitivity [31]. Cardio-vegetative stress level is estimated by time domain and frequency domain analysis providing metrics for the overall activation of the sympathetic system which is a non-specific marker of vegetative state and should not be interpreted without appropriate clinical context, but it has significant prognostic value for overall health status and change of it.

This chapter outlined the scope of an ICPS Medical Software which still must be built. The significance of this outlined plan is to show that with already existing technology, goals of [14] can be supported. The exciting perspective is that ICPS Medical Software or a similar device will undoubtedly allow for big data collection and data mining and thereby provide the foundation for truly individualized "precision" medicine. ICPS in its fully developed form could provide information about primary interlinked pathological processes of whole-body oxidative stress, inflammation, and insulin resistance. Multiple observational studies have demonstrated already that these primary pathological processes are intricately linked to metabolic syndrome, atherosclerotic disease, sympathetic nerve activation, anemia of chronic kidney disease, and heart failure. ICPS with its state variables and derived metrics & Risk Scoring can potentially give the opportunity to calculate risks of non-fatal major morbidity outcomes in the 5 studied domains and define clear targets for specific individualized interventions. Even treatments of complications of heart

failure could be feasible at home, potentially avoiding frequent readmissions to the hospital.

Before making ICPS non-Medical Software (ORI FIT-MET™) available to the public several important problems need to be addressed. The technical hurdle is to create a scalable versatile mobile and cloud computing platform for ICPS which can potentially be used with a variety of mobile health products on the market. While ODI wants to make ICPS potentially usable with various mobile health products, this effort may be stifled because of a lack of interoperability of various fitness devices and because data are stored in "data silos," preventing users and health professionals from getting an integrated view of health and fitness data [48]. The current practice is for third-party developers to retrieve the data via an open API with permission of the owner of the API and the user. The key risk and challenge are to make users' data accessible for cloud computing systems like ICPS. A short list of other problems to be overcome is as follows: data privacy and security, to create a marketable product which is only a fitness device at this stage of development and remains a non-medical device category, creating tools for easy calorie intake counting, creating tools for visceral fat mass measurement, and educating future users and also physicians about the complex science behind ICPS.

To create an ICPS Medical Software would pose even more challenges. The needed sensor hardware components must be developed and interfaced with ICPS. The main reason for ODI developing its own hardware for ICPS Medical Software is to avoid the 3rd party API issues and to guarantee top security for data flow with the latest and possibly most up to date technology. The other reason to have self-developed hardware is to have information regarding errors of measurements. ODI uses intensively the Kalman filter technology which works best if the standard deviation of the error of the measuring instrument is known. This allows "tuning" the Kalman filter to have the best performance. The seemingly daunting proposition for ODI to build its own hardware is mitigated by the fact that major electronic device companies offer their sensors with fully developed reference designs for hardware and software. This should help to build the needed sensors such as the watch-type fitness tracker, the Sensor Belt for ECG and waist circumference monitoring, the body composition and hydration status measuring standup scale [9], the hemoglobin concentration measuring finger sensor, and the Impedance Cardiography which could be also designed as a wearable sensor belt for continuous use or it could be integrated into the afore mentioned stand up scale for one point in time use. Phase I clinical study is needed to verify accuracy and certify analytical performance and safety. Phase II study is desirable to demonstrate utility and create user guide for patients and physicians. Reimbursement for the use of ICPS is also an issue as insurance companies may want to have proof that ICPS is able to save cost and improve clinical outcome.

After proper consenting, secondary analysis of metabolic data could help not only clinical research and pursuing goals of Global Health [11], but also insurance companies to calculate costs and potentially reimburse the treatment/self-treatment and improvement of risk factors for prevention, treating type 2 diabetes and complications. A value-based health delivery system holds potential to incentivize participants to improve their lifestyle, especially if insurance companies would honor participants with a discount on the premiums for those who were successful in lowering their cardiometabolic, cardiovascular, and cardio-vegetative risk.

## 5. Conclusion

In conclusion, ICPS can serve as an appropriate quasi real-time tool to monitor and optimally adjust modifiable risk factors. The trends/trajectories of metabolic values

calculated by the mathematical models can serve as tools, allowing for planning and executing dynamic changes of behavior for optimization and control of these values. All-encompassing Risk Scores calculated by the mathematical models can serve as outcome measures to be tracked by the user and personal trainer/primary provider to prevent and fight burdens of type 2 diabetes and optimize lifestyle quasi real-time.

## Acknowledgements

We would like to express our gratitude for the valuable related discussions with Professor Dr. John Buse, UNC-Chapel Hill. Further, we would like to thank Ilona Ori, JD, Ori Diagnostic Instruments, LLC, for editorial help.

## Conflict of interest

The author declares that there is no conflict of interest regarding the publication of this paper. No specific funding was provided for this research. This research was performed as part of the author's employment with Ori Diagnostic Instruments, LLC. The author is the inventor on patents [8, 9] and the patents are owned by Ori Diagnostic Instruments, LLC.

## Abbreviations

*System Variables:*

| | |
|---|---|
| aEEmax | maximal activity energy expenditure |
| AT | adaptive thermogenesis/thermal loss |
| DNL | de novo lipogenesis |
| ECW | extracellular water |
| F | fat weight |
| Fox/Cox | fat vs. carbohydrate oxidation |
| HFr | high frequency spectral power of heart rate variability |
| Hb | hemoglobin concentration |
| ICW | intracellular water |
| $K_k$ | Kalman gain provided by the Kalman filter |
| L | lean mass |
| LFr | low frequency spectral power of heart rate variability |
| PV | plasma volume |
| R | R-ratio |
| Rw | Rw-ratio |
| tHbmas | Total Hemoglobin Mass |
| 24hrRQ | 24 hr. respiratory quotient |
| SDNN | standard deviation of R-R intervals |
| $u_k$ | zero mean white noise sequence |
| $VO_2$max | maximum oxygen uptake |
| $v_k$ | zero mean white noise sequence |
| W | weight |
| $w_k$ | zero mean white noise sequence |
| AD | Autonomic Dysfunction |

| | |
|---|---|
| ASCD | Atherosclerotic Cardiovascular Disease |
| BC-HC-A | Body Composition and Hydration Status Analyzer |
| CKD | Chronic Kidney Disease |
| CMD | Cardiometabolic Functioning and Disease |
| CMFM | Cardiometabolic Function Model |
| CVD | Cardiovascular Functioning and Disease |
| CVFM | Cardiovascular Fitness Model |
| CVS | Cardio-vegetative Functioning and Stress |
| CVSM | Cardio-vegetative Stress Model |
| CPS | Cyber-physical System |
| DM2 | type 2 diabetes |
| HF | Heart Failure |
| ICG | Impedance Cardiography |
| ICPS | Integrated Cyber-Physical System |
| MC | Medical Cybernetics |
| MHM | Metabolic Health Monitoring |
| MS | Metabolic Syndrome |
| MST | Metabolic Manager Software Tool |
| ODI | Ori Diagnostic Instruments, LLC |
| SAM-AC | Self-adaptive Model of Anemia of CKD |
| SAM-HF | Self-adaptive Model for Heart Failure |
| SAM-HEM | Self-adaptive models of the human energy metabolism |
| SB | Sensor Belt |
| SV | State Variable |
| WFE | Weight, Fat weight, Energy Balance calculation model |
| WFE-DNL-AT | WFE extended version |

## Author details

Zsolt P. Ori
Ori Diagnostic Instruments, LLC, Durham, NC, USA

*Address all correspondence to: ori.zsolt@oridiagnosticinstruments.com

## References

[1] Öri Z, Öri I. (2015). Self-directed weight management by feedback from a self-adaptive metabolic health monitoring system. Self-Adaptive and Self-Organizing Systems (SASO), 2015 IEEE 9th International Conference on. doi: 10.1109/SASO.2015.28

[2] Őri Z. (2017). Parametric recursive system identification and self-adaptive modeling of the human energy metabolism for adaptive control of fat weight. Medical and Biological Engineering and Computing. 2017 May 1; Volume 55, Issue 5: 759-767. DOI: 10.1007/s11517-016-1552-3

[3] Ori Z, Ori I. (2016). Canonical representation of the human energy metabolism of lean mass, fat mass, and insulin resistance. 2016 IEEE 7th Annual Ubiquitous Computing, Electronics & Mobile Communication Conference (UEMCON); 2016 Oct 20-22; New York, NY. IEEE; 2016 Dec 12. p. 1-8; DOI: 10.1109/UEMCON.2016.7777862. https://ieeexplore.ieee.org/Xplore/home.jsp4

[4] Ori Z, Ori I. (2016). Fighting weight problems and insulin resistance with the metabolic health monitor app for patients in the setting of limited access to health care in rural America. 2016 IEEE Global Humanitarian Technology Conference (GHTC); 2016 Oct 13-16; Seattle, WA. IEEE ISBN: 1-5090-2433-6, 978-1-5090-2433-9; 2017 Feb 16. p. 547-554. DOI: 10.1109/GHTC.2016.7857334. IEEE Xplore Digital Library https://ieeexplore.ieee.org/Xplore/home.jsp

[5] Ori, Z. (2018). Cyber-Physical System for Management and Self-Management of Cardio-metabolic Health. Published on-line and accepted for publication in "Type 2 Diabetes" by IntechOpen, DOI: http://dx.doi.org/10.5772/intechopen.84262

[6] Ori, Z. (2019). Metabolic Health Analysis and Forecasting with Mobile Computing. Published on-line in "Mobile Computing" by IntechOpen, https://www.intechopen.com/online-first/metabolic-health-analysis-and-forecasting-with-mobile-computing DOI: 10.5772/intechopen.88872

[7] Öri, Z. (2009). Portable Metabolic and Trauma Monitoring System. Leonard Wood Institute Research. Project Final Report [Unpublished final report]. "Phase 0" fund from the Leonard Wood Institute (197 Replacement Avenue, Fort Leonard Wood, Missouri 65473) subaward number: LWI-000-006, as part of a Prime Award of the Army Research Laboratory No.: W911NF-07-2-0062U

[8] Öri Z. (2018). "An Apparatus and Method for the Analysis of the Change of Body Composition and Hydration Status and for Dynamic Indirect Individualized Measurement of Components of the Human Energy Metabolism," U.S. Patent No.: 9,949,663 B1 Date: 4/24/2018, U.S. Patent No.: 10,716,491 B2 Date: 7/21/2020

[9] Ori Z. (2020). "Systems and methods for high frequency impedance spectroscopy detection of daily changes of dielectric properties of the human body to measure body composition and hydration status." U.S. Patent No.: US 10,653,333 B2. Date of Patent: May 19, 2020.

[10] Ori Z. (2020) Principles of Continuous Risk Monitoring of Insulin Resistance, Oxidative Stress and Nutrition for Cardiovascular Disease and Cancer Prevention in Primary Care [Forthcoming].

[11] Ori Z. (2020). Reaching for Cardio-Metabolic Fitness and Resilience through Self-Healing and Guided Individualized Cyber-Therapy – an

Opportunity to Reenergize Primary Care, Healthy Aging Research, Accepted for Publication, August 26, 2020. OPEN ACCESS Freely available online.

[12] Öri Z et al. (1992). Heart rate variability: Frequency Domain Analysis. Cardiology Clinics 1992. vol. 10, No 3, pp 499-537.

[13] Singer DH, Öri Z. (1995). Changes in heart rate variability associated with sudden cardiac death. In:nMalik M, Camm AJ, editors. Heart Rate Variability. Armonk, NY: Futura Publishing Company, Inc.; 1995. pp. 429-448.

[14] 100. Harris SB, Cheng AYY, Davies MJ, Gerstein HC, Green JB, Skolnik N. Person-Centered, Outcomes-Driven Treatment: A New Paradigm for Type 2 Diabetes in Primary Care. Arlington, Va., American Diabetes Association, 2020 (https://doi.org/10.2337/db2020-02)

[15] Ceriello A, Motz E: Is Oxidative Stress the Pathogenic Mechanism Underlying Insulin Resistance, Diabetes, and Cardiovascular Disease? The Common Soil Hypothesis Revisited. Arterioscler Thromb Vasc Biol. 2004; 24:816-823. DOI: 10.1161/01.ATV.0000122852.22604.78

[16] David E. Kelley: Skeletal muscle fat oxidation: timing and flexibility are everything. J. Clin. Invest. 115:1699-1702 (2005). doi:10.1172/JCI25758.

[17] Jose E. Galgani, Cedric Moro, and Eric Ravussin: Metabolic flexibility and insulin resistance. Am J Physiol Endocrinol Metab 295: E1009–E1017, 2008. First published September 2, 2008; doi:10.1152/ajpendo.90558.2008.

[18] Mary Madeline Rogge: The Role of Impaired Mitochondrial Lipid Oxidation in Obesity. Biological Research for Nursing, Volume 10 Number 4, April 2009 356-373 (2009). doi.org/10.1177/1099800408329408.

[19] Shook RP, Hand GA, Paluch AE, et al.: High respiratory quotient is associated with increases in body weight and fat mass in young adults. European Journal of Clinical Nutrition, 24 Nov 2015, 70(10):1197-1202. DOI: 10.1038/ejcn.2015.198

[20] Park K, Gross M. et al.: Oxidative Stress and Insulin Resistance. Diabetes Care 2009 Jul; 32(7): 1302-1307.https://doi.org/10.2337/dc09-0259

[21] Li Chen, Rui Chen, HuaWang, and Fengxia Liang: Mechanisms Linking Inflammation to Insulin Resistance. Hindawi Publishing Corporation. International Journal of Endocrinology, Volume 2015, Article ID 508409, 9 pages http://dx.doi.org/10.1155/2015/508409

[22] Shah AD, Langenberg C, Rapsomaniki E, et al. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1.9 million people. Lancet Diabetes Endocrinol 2015; 3:105-113; doi: 10.1016/S2213-8587(14)70219-0

[23] Bonora E, Kiechl S, Willeit J, et al. Insulin resistance as estimated by homeostasis model assessment predicts incident symptomatic cardiovascular disease in caucasian subjects from the general population: the Bruneck study. Diabetes Care. 2007; 30(2):318-324. doi:10.2337/dc06-0919

[24] Wei M, Kampert JB, Barlow CE et al: Relationship Between Low Cardiorespiratory Fitness and Mortality in Normal-Weight, Overweight, and Obese Men. JAMA. 1999;282(16):1547-1553. doi:10.1001/jama.282.16.1547

[25] Cerhan JR, Moore SC, Jacobs EJ, et al. A pooled analysis of waist circumference and mortality in 650,000 adults. Mayo Clin Proc.

2014;89(3):335-345. doi: 10.1016/j.mayocp.2013.11.011

[26] Carnethon MR, De Chavez PJ, Biggs ML, et al. Association of weight status with mortality in adults with incident diabetes [published correction appears in JAMA. 2012 Nov 28;308(20):2085]. JAMA. 2012;308(6):581-590. doi:10.1001/jama.2012.9282

[27] Khan SS, Ning H, Wilkins JT, et al. Association of Body Mass Index With Lifetime Risk of Cardiovascular Disease and Compression of Morbidity. *JAMA Cardiol*. 2018;3(4):280-287. doi:10.1001/jamacardio.2018.0022

[28] Fang SC, Wu YL, Tsai PS: Heart Rate Variability and Risk of All-Cause Death and Cardiovascular Events in Patients With Cardiovascular Disease: A Meta-Analysis of Cohort Studies. Biol Res Nurs. 2020 Jan; 22(1):45-56. doi: 10.1177/1099800419877442.

[29] Kwon SB, Ahn JW, Lee SM, et al. Estimating Maximal Oxygen Uptake From Daily Activity Data Measured by a Watch-Type Fitness Tracker: Cross-Sectional Study. JMIR Mhealth Uhealth. 2019;7(6):e13327. Published 2019 Jun 13. doi:10.2196/13327

[30] Clarke DC and Skiba PF: Rationale and resources for teaching the mathematical modeling of athletic training and performance. Adv Physiol Educ 37: 134-152, 2013; doi:10.1152/advan.00078.2011.

[31] Venables MC, Jeukendrup AE: Endurance Training and Obesity: Effect on Substrate Metabolism and Insulin Sensitivity. Medicine & Science in Sports & Exercise: March 2008 - Volume 40 - Issue 3 - p 495-502, doi: 10.1249/MSS.0b013e31815f256f

[32] McLellan SA and Walsh TS: Oxygen delivery and haemoglobin. Continuing Education in Anaesthesia, Critical Care & Pain | Volume 4 Number 4 2004. DOI 10.1093/bjaceaccp/mkh033

[33] Fidan-Yaylali G, Yaylali YT: The Association between Central Adiposity and Autonomic Dysfunction in Obesity. Med Princ Pract 2016; 25:442-448, DOI: 10.1159/000446915

[34] Tentolouris N, Liatis S: Sympathetic System Activity in Obesity and Metabolic Syndrome. Ann. N.Y. Acad. Sci. 1083: 129-152 (2006). New York Academy of Sciences. doi:10.1196/annals.1367.010

[35] Skinner JE, Pratt CM, Vybiral T. A reduction in the correlation dimension of heartbeat intervals precedes imminent ventricular fibrillation in human subjects. Am Heart J. 1993;125(3):731-743. doi:10.1016/0002-8703(93)90165-6

[36] Pereira AA, Sarnak MJ. Anemia as a risk factor for cardiovascular disease. Kidney Int Suppl. 2003;(87):S32-S39. doi:10.1046/j.1523-1755.64.s87.6.x

[37] Rehman, K., Akash, M.S.H. Mechanisms of inflammatory responses and development of insulin resistance: how are they interlinked? J Biomed Sci 23, 87 (2016). https://doi.org/10.1186/s12929-016-0303-y

[38] Christy AL, Manjrekar PA et al: Influence of Iron Deficiency Anemia on Hemoglobin A1C Levels in Diabetic Individuals with Controlled Plasma Glucose Levels. Iran Biomed J. 2014 Apr; 18(2): 88-93. doi: 10.6091/ibj.1257.2014

[39] Otto JM, Montgomery HE, Richards T. Haemoglobin concentration and mass as determinants of exercise performance and of surgical outcome. Extrem Physiol Med. 2013;2(1):33. Published 2013 Nov 26. doi:10.1186/2046-7648-2-33

[40] Cattadori G, Agostoni P, Corrà U, et al. Heart failure and anemia: Effects

on prognostic variables. Eur J Intern Med. 2017; 37:56-63. doi:10.1016/j.ejim.2016.09.011

[41] Wang EJ, Li W et al: HemaApp: HemaApp: Noninvasive Blood Screening of Hemoglobin Using Smartphone Cameras. UBICOMP '16, September 12-16, 2016, Heidelberg, Germany. DOI: http://dx.doi.org/10.1145/2971648.2971653

[42] Timm U, McGrath D et al: Sensor System for Non-Invasive Optical Hemoglobin Determination. SENSORS, 2009 IEEE, 25-28 Oct. 2009, IEEE Xplore: 22 January 2010, DOI: 10.1109/ICSENS.2009.5398321

[43] Ziaeian B, Fonarow GC. The Prevention of Hospital Readmissions in Heart Failure. Prog Cardiovasc Dis. 2016;58(4):379-385. doi: 10.1016/j.pcad.2015.09.004

[44] Miller JC, Horvath SM: Impedance Cardiography. Psychophysiology. Volume15, Issue1, January 1978. Pages 80-91, https://doi.org/10.1111/j.1469-8986.1978.tb01340.x

[45] Yancy C, Abraham WT. Noninvasive hemodynamic monitoring in heart failure: utilization of impedance cardiography [published correction appears in Congest Heart Fail. 2004 May-Jun;10(3):139]. *Congest Heart Fail*. 2003;9(5):241-250. doi:10.1111/j.1751-7133.2003.tb00021.x

[46] Hafid A, Benouar S, Kedir-Talha M, Abtahi F, Attari M, Seoane F. Full Impedance Cardiography measurement device using Raspberry PI3 and System-on-Chip biomedical Instrumentation Solutions. IEEE J Biomed Health Inform. 2018;22(6):1883-1894. doi:10.1109/JBHI.2017.2783949

[47] Austin PC, Lee DS, D'Agostino RB, Fine JP. Developing points-based risk-scoring systems in the presence of competing risks [published correction appears in Stat Med. 2018 Apr 15;37(8):1405]. *Stat Med*. 2016;35(22):4056-4072. doi:10.1002/sim.6994

[48] Gay V and Leijdekkers P: Bringing Health and Fitness Data Together for Connected Health Care: Mobile Apps as Enablers of Interoperability. J Med Internet Res. 2015 Nov; 17(11): e260. Published online 2015 Nov 18. doi: 10.2196/jmir.5094