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Principles of Continuous Risk Monitoring of Body Composition, Insulin Resistance, Endothelial Dysfunction and Nutrition to Improve General Health and Prevent Cardiovascular Disease and Cancer

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Abstract
This paper presents a leap ahead innovation: a cloud based Cyber-Physical System, a mobile technology to integrate sensory data from various mobile devices of a user into individualized dynamic mathematical models of physiological processes, allowing for analysis and prediction by mathematical models combined with machine learning and maximizing control of physiological metrics by the user. This paper describes several bio-physical principles for realizing a Cyber-Physical System (CPS). A CPS allows for collection of a large amount of data for continuous risk monitoring and to support the creation of suitable metrics for dynamic behavioral interventions. The innovative concepts include using the following principles: 1. Holistic principle to connect different domains of physiological functioning which are directly and independently linked to morbidity and mortality like metabolic, cardiorespiratory, cardio-vegetative, oxygen delivering, endovascular and hemodynamic functioning; 2. Estimation of the parameters of the human energy metabolism using principles of "least action" or stationary action; 3. Estimation of daily changes of body composition and hydration status by using the "maximum information entropy" principle; 4. Using state space modeling where process models are connected to measurement models via the minimum variance Kalman filter/ predictor realizing principles of Medical Cybernetics including optimal control theory; 5. Principle of individualized risk predictions realized by direct measurement and long-term observation of subclinical disease (screening) to allow early corrective action; 6. Utilizing principles of precision medicine and precision nutrition for primary prevention of cardiovascular disease and cancer.
The main innovation of this paper is to consider physiological state variables of modifiable risks over a lifetime and connect them to calculations of morbidity and mortality, offering a self-explaining context to raise self-awareness to reduce cardiometabolic risks, oxidative stress and endothelial dysfunction to prevent cardiovascular disease and cancer with appropriate behavior modification supported using CPS. In conclusion a CPS with machine learning using principles of optimal control theory supervised by physician can provide a truly individualized strategy for estimation, continuous monitoring, and prediction of physiological state variables for self-therapy, guided therapies, and mobile health interventions or cyber-therapy. CPS facilitated interventions allow for improving health, fitness, resilience and chance of survival of an acute illness.

Keywords
cardiometabolic health, cardiorespiratory fitness, cardio-vegetative stress monitoring, endothelial dysfunction, cardiovascular disease prevention, cancer prevention, machine learning, modifiable risks, continuous risk assessment and monitoring, mobile health interventions, cyber-therapy, digital health

Introduction

Moving away from traditional reductionism and embracing holistic approaches will certainly help fulfill the promise of Digital Health (DH) supported by tools of Medical Cybernetics (MC) and find workable solutions to tackle the ever growing health related challenges of humanity and introduce new approaches to prevent, manage and self-manage chronic non-communicative conditions such as cardiovascular disease and cancer in the 21st century.

Obesity or excess fat mass with associated insulin resistance is directly associated with shorter longevity and significantly increased risk of cardiovascular morbidity and mortality [1]. Furthermore, when a surrogate index of insulin resistance such as waist circumference is used to predict mortality, an elevated waistline was strongly predictive of an increased mortality rate among patients with cardiovascular disease [2], and it is an independent risk factor for cardiovascular disease (CVD) mortality [3, 4]. 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 [5]. High insulin resistance is associated with high respiratory quotient (RQ) reflecting lower fat burning than normal [6]. Similarly, there are strong connections between oxidative stress, endothelial dysfunction, endovascular inflammation and insulin resistance [7, 8]. Further, there is a causal relationship between insulin resistance and development of cancer [9]. It is recognized that the increased risk of cancer among insulin-resistant patients can be due to overproduction of reactive oxygen species (ROS) that can damage DNA contributing to mutagenesis and carcinogenesis [10]. An important example is that increased markers of ROS are independently linked to development of colorectal cancer [11]. Cancer patients with diabetes and insulin resistance are more likely to be sarcopenic, with higher incidence of malnourishment and compromised survival [12]. Importantly, lifestyle intervention with weight loss lowered incidence of obesity related cancers by 16% [13].

Recognizing that obesity, DM2, insulin resistance with associated endothelial dysfunction combined with poor nutrition poses an increased risk for development of CVD and cancer and the presence of these factors reduces survival chance is an important first step in forming a plan of interventions. Laboratory testing for insulin resistance, endothelial dysfunction and nutritional status can show early deviations from normal and could be used for screening. However, this one point in time screening is not likely to give enough persisting motivation for lifestyle change and continuous observation and monitoring is needed for risk factors of CVD [14, 15] and cancer. Current recommendations to prevent and treat obesity, DM2, insulin resistance, and CVD come from leading academic authors [16]. One of the key points 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…". However, traditional recommendations for lifestyle change as in [16] seems to be ineffectual in view of prevalence of obesity, insulin resistance and DM2 [17, 18]. Specifically, the perceived needs to overcome barriers are: 1. Tools to gauge *individual characteristics of the metabolism* for a prescribed individualized lifestyle change to help set cardiovascular fitness goals, weight goals, track progress, and provide feedback to both patients and physicians during a weight-loss intervention [19, 20]. 2. There is a need for *healthy lifestyle interventions* using mobile health and DH technology combined with a team to prevent and treat non-communicable diseases linked to insulin resistance and obesity [21-23]. Clearly, there is a need also to facilitate efforts to reduce metabolic, cardiovascular and stress related risks with healthy lifestyle and to improve cardiometabolic and cardio-vegetative health and longevity with both self-management and guided therapy.

Method

Ori Diagnostic Instruments (ODI) has been conducting R&D [24-31] and recently we introduced a Cyber-Physical System (CPS) [24, 25]. 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) to allow for control in 3 domains of physiological functioning: 1. metabolic (MF), 2. cardiorespiratory (CR), and 3. cardio-vegetative (CV). Our technology is capable of continuously monitoring, through model predicted values based on direct measurements, the following state variables in these domains:

Ad 1. MF: Closely mimicking HOMA-IR (a practical laboratory measurement of insulin resistance) is our metric allowing for the noninvasive observation of insulin resistance changes by estimating R- or Rw-ratio which are defined as $R=\Delta L/\Delta F$ and $Rw=\Delta W/\Delta F$ where ΔL, ΔW and ΔF are lean mass, weight and fat mass change over 24hrs. We can estimate R- or Rw-ratio either with use of our Self-Adaptive Model of the Energy Metabolism (SAM-HEM) [27-31] demanding precise calorie counting or with our Weight, Fat weight, Energy Balance (WFE) model [25] without mandatory calorie counting by serially measuring weight, fat weight, and energy balance. The verification of this concept was performed using data from 12 clinical studies with 39 clinical study arms and with total number of patients n=2010. In our simulation study, the correlation between changes of HOMA-IR and changes of daily WFE calculated Rw-ratio was -0.6745 with a P value of 0.0000024 [25].

Ad 2. CR: We calculate the maximum oxygen uptake capacity (VO_2max) which is estimated from heart rate and measuring maximal activity energy expenditure (aEEmax) during graded exercise.

Ad 3. CV: We use measures of heart rate variability (HRV) such as the time domain and frequency domain measures.

CPS is designed for noninvasively tracking, drawing trajectories, and indirectly measuring daily changes and predicting the otherwise very-difficult- or impossible-to-measure slow changes of the daily state variables such as insulin resistance, estimated maximum oxygen uptake capacity and activity of the autonomic nervous system. CPS captures the state variables for the first time noninvasively in freely moving humans in their natural environment to allow for prevention and for supporting treatment of cardiometabolic risks. CPS has been realized in MATLAB and will be transitioned to the cloud as a mathematical software enterprise called ORI FIT-MET™.

We want to emphasize the use of the R- and Rw ratio which can serve as a qualitative signal tool to show if the trends of changes in the metabolism are in the right or wrong direction in terms of changes of insulin resistance/ endothelial dysfunction and endothelial inflammation. This is supported by the strong association between insulin resistance and whole-body endothelial dysfunction and inflammation [32]. To quantify this relationship, we plan on taking total arterial compliance index (TAC) measurements by impedance cardiograph. The justification is that TAC independently predicts mortality [33]. Connecting WEF model to TAC would allow for noninvasively assessing the state of endothelial dysfunction/ endothelial dysfunction.

Importantly, CPS is built on the holistic modelling approach of considering the entire human energy metabolism including insulin resistance and endothelial dysfunction from endothelial dysfunction. ***Our central hypothesis is that by improving insulin resistance with lifestyle interventions supported by using CPS we can ameliorate the condition of endothelial dysfunction, overall inflammation, fat vs. carbohydrate oxidation, cardiovascular disease progression and development of cancer.***

Conceptual Framework

It appears useful to formalize the principles on which a Cyber Physical System (CPS) could be built with goals of cardiometabolic risks prevention along with fighting cancer risk and lending support to patients at risk and to those who already have cancer and are suffering also from obesity, DM2, insulin resistance, sarcopenia, poor nutritional status, and CVD. Our suggested approach includes using cloud computing, wearable sensors either of those of the fitness industry or newly developed ones, and utilize tools of MC. The principles are:

1. Holistic principle. This means here that we want to connect different domains of physiological functioning which are directly and independently linked to morbidity and mortality like metabolic (MF), cardiorespiratory (CR), cardio-vegetative (CV), oxygen delivering (OD), endovascular and hemodynamic functioning (HD). The metrics for MF, CR, and CV are explained in the introduction. The hemoglobin concentration can be non-invasively measured by photo sensors attached to the fingertip. We have created a model for OD [34] to estimate and predict changes of hemoglobin concentration and total hemoglobin mass using photosensor data. OD will use information on daily *a posteriori* estimates of extracellular water $ECW_k^{(+)}$ and intracellular water $ICW_k^{(+)}$ which will come from ODI's ORI FIT-MET™. We plan on fully developing HD modelling [34] which will use non-invasively measured data like TAC obtained from Impedance Cardiography.

2. Estimation of the parameters of the human energy metabolism using principles of "least action" or stationary action. Here we give an example of how we use this principle well known in physics to estimate unknown system parameters of the human energy metabolism using Lagrange multipliers [24, 25]. We consider the energy balance EB_k i.e. energy in minus out for each day with equation (1).

$$EB_k = \left(\varrho_{W_k} \cdot Rw_k + \varrho_F \right) \cdot \Delta F_k; \qquad (1)$$

Here ϱ_{W_k} is the unknown energy density of bodyweight change at the end of day $_k$; Rw-ratio is calculated as $Rw_k = \Delta W_k / \Delta F_k$ with weight change velocity ΔW_k (body weight change in 24 hours) and fat mass change velocity ΔF_k (fat mass change in 24 hours). ϱ_F is the known daily energy density of the fat mass change which is estimated to be $\varrho_F \approx 9.4$ Kcal/g. Rw_k is estimated as $Rw_k \approx \alpha w_k / F_k$, where αw_k is the unknown first-order term coefficient in the Taylor series expansion of the weight-fat logarithmic relationship as in (2):

$$W_k = \alpha w_k \cdot \ln(F_k); \quad (2)$$

Daily W_k and F_k and energy balance measurements allow for estimation of the unknown system parameters ϱ_{W_k} and αw_k using the Lagrange functional for the human energy metabolism [24, 25] as shown in (3). The use of the principle of "least action/ stationary action" will predict that the energy metabolism works with the minimum consumption of fuel and would not waste energy unnecessarily. The sum of energies $\boldsymbol{\mathcal{L}}$ for each day from day $k = 1$ to day $k = N$ should go to minimum:

$$\boldsymbol{\mathcal{L}} = \sum_{\boldsymbol{k=0}}^{\boldsymbol{k=N}} \left[\left(\varrho_{W_k} \cdot Rw_k + \varrho_F \right) \cdot \Delta F_k \right]^{\mathbf{2}}$$

$$+\lambda \alpha w_k \cdot [\Delta W_k - \alpha w_k \cdot (\ln F_k - \ln F_{k-1})]$$

$$+ \lambda \varrho_{W_k} \cdot \left[EB_k - \varrho_{W_k} \cdot \Delta W_k - \varrho_F \cdot \Delta F_k \right] \qquad (3)$$

Here the minimum solution of $\boldsymbol{\mathcal{L}}$ is sought for very slow changing semi stable αw_k and ϱ_{W_k} for known ΔF_k, ΔW_k, and EB_k. This could be obtained with numerical methods to minimize the Lagrange energy functional $\boldsymbol{\mathcal{L}}$**.** The Lagrange multipliers $\lambda \alpha w_k$ and $\lambda \varrho_{W_k}$ are non-zero variables and are part of the minimization procedure and they multiply the constraints for conservation of mass and energy respectively.

3. Estimation of daily changes of body composition and hydration status changes by using the "maximum information entropy" principle. Using this principle and the Lagrange multiplier method we are able to estimate the most likely changes of fat mass ΔF_k, lean body mass ΔL_k, intracellular water mass ΔICW_k as well as extracellular water mass ΔECW_k by bioimpedance measurements. In general, bioimpedance measurements show random variations and are fraught with a multitude of other sources of errors. Currently, the bioelectric modeling of the human body is a major challenge which remains unsolved. Heuristic measurement models like the Cole model along with personalized models for ECW_k (5) and ICW_k (6) of Moissl et al [35] and for lean mass by Jaffrin et al [36] have been used mainly in research settings. ODI is the first to our knowledge to combine metabolic process modeling like in (1) with self-calibrating measurement models, taking advantage of serial measurements during use of CPS in which process models and measurement models are feeding each other with *a priori* and *a posteriori* information, thereby enabling regular clinical use of bioimpedance measurements [30, 31]. Briefly, the Cole model in (4) contains R_0 and R_∞ for resistance of a measured human body segment at zero and infinite frequency; τ is the characteristic time of relaxation; α is the exponential symbol of relaxation time dispersion; f_i is the measuring frequency; $kECW_{ref}$ and $kICW_{ref}$ are the reference values related parameters to calculate extra and intracellular water mass; and H is height.

$$Z_i^{COLE}(R_0, R_\infty, \tau, \alpha) = R_\infty + (R_0 - R_\infty)/(1 + (j \cdot 2\pi f_i \cdot \tau)^\alpha) \qquad (4)$$

$$ECW_k = kECW_{ref} \cdot \left(\frac{H^2 \cdot \sqrt{W_k}}{R_0}\right)^{2/3} \qquad (5)$$

$$ICW_k = kICW_{ref} \cdot \left(\frac{H^2 \cdot \sqrt{W_k}}{R_\infty}\right)^{2/3} \qquad (6)$$

$$0.732 \cdot L_k = ECW_k + ICW_k \qquad (7)$$

In equation (8) we show an example of how we use nonlinear least-squares technique with Lagrange multipliers for considering also constraints [37]. The goal of minimization of S is to find solutions for unknown $R_0, R_\infty, \tau, \alpha$, ECW_k, ICW_k, L_k and F_k.

$$S = \sum_{i=1}^{N} \frac{1}{\sigma_i^2} \cdot \left|Z_i^* - Z_i^{COLE}\right|^2 + \lambda_1 \cdot h_1 + \lambda_2 \cdot h_2 \qquad (8)$$

Here σ_i^2 stands for known variance of the measured impedance at f_i, the Z_i^* denotes the measured average impedance at frequency f_i, λ_1, and λ_2 are Lagrange multipliers for constraints, h_1 is the constraint for total water mass $ECW_k + ICW_k$ which has to add up to 73.2% of lean mass L_k as in (7) and h_2 is the weight constraint $W_k = L_k + F_k$. We use the scalar problem Kalman filter solution as on page 140 in [38] to update the quasi-stable parameters $kECW_{ref}$ and $kICW_{ref}$. Though the Kalman filter lends relative stability to the measuring system, it may require reference calibration to tabulated reference values from time to time which can be found in the international literature such as [39].

4. Using state space modeling where process models are connected to measurement models via the minimum variance Kalman filter/ predictor utilizing principles of Medical Cybernetics. We published already our SAM-HEM model utilizing Kalman filter/ predictor together with simulation studies [26-31].

5. Principle of individualized risk predictions realized by direct measurement and long-term observation of subclinical disease (screening) to allow early corrective action. Central to the mission of

primary care is fighting the burden of noncommunicable disease and among them the most prominent one: cardiovascular disease (CVD) [16]. Currently, the paradigm for primary prevention is to use traditional risk factors to estimate cardiovascular risk and calculate for example the Framingham Risk Score. These risk estimates are based on prediction models derived from prospective cohort studies and are incorporated into guideline-based initiation algorithms for commonly used preventive pharmacologic treatments, such as aspirin and statins [14]. We feel that our approach using CPS and individualized MC modeling is responding to the criticisms of current risk stratification of CVD raised by academic authors [14, 15] and may offer a paradigm shift. The criticisms are: "(1) predictions of risk are accurate at the level of populations but do not translate directly to patients, (2) perfect accuracy of individual risk estimation is unobtainable …., (3) direct measurement of subclinical disease (screening)…" is needed. McEvoy et al. [14] conclude that we must come from "prediction of events to detection of disease" i.e. *observing CVD in its evolution to improve personalized decision-making and outcomes*. McEvoy et al. [14] call for "innovative future strategies for risk estimation and treatment…". The general idea behind CPS and individualized MC modeling is to collect a plethora of data during continuous monitoring from sensors and compress them into compact form of individualized process models with state variables to observe processes leading to CVD and provide metrics which are easily understandable, self-explaining, and completely describing processes with implications to morbidity and mortality. Unique to ***our effort is the continuous observation of state variables and metrics leading to morbidity and mortality by CVD and allowing for risk assessment continuously over a lifespan***, raising self-awareness, enhancing motivation, and underscoring self-responsibility to reduce modifiable risks as much as possible.

6. Utilizing principles of "precision medicine" (PM) and "precision nutrition" (PN) for primary prevention of DM2, CVD, and cancer. The goal of PM is individualized care i.e. to find and exploit clinically actionable individual features about risk of disease, optimal treatment, disease course, and response to treatment. Instrumental towards this goal the creation of individualized MC diseases process models which are connected to non-invasive monitoring sensors. The huge potential of PM goals this way could be realized not just in academic centers but also at primary care offices. In this regard we recently outlined our vision for an Integrated Cyber-Physical System ICPS which describes already the MC disease process modelling in the MF, CR, CV, OD, and HD domains [34]. The needed data come from wearable sensors. A fully developed ICPS can realize also goals of individualized PN as defined by NIH [40].

Discussion

Prodigious scientist of mathematics and founder of cybernetics like Norbert Wiener and John von Neumann showed the direction how we can find workable solutions and build Cyber-Physical Systems utilizing principles of Medical Cybernetics to address increasing major public health issues which could be applicable in Primary Care, Corporate & Public Health, and Academic Research. The current paper lays out a pragmatic conceptual framework of how CPS could be put together for continuous risk assessment and for preventing morbidities like prediabetes, obesity, insulin resistance, DM2, CVD, cancer, and for supporting lifestyle changes and medical therapies. The here introduced principles of continuous risk monitoring of insulin resistance, endothelial dysfunction and nutrition could be the foundation on which future mobile health interventions and Digital Health related products can be built.

CPS is designed to support achieving general health including normal body composition, normal insulin resistance with age adequate endothelial functioning, and normal nutritional status along with exercise tolerance, normal autonomic functioning, and resilience against mental and physical harm. Achieving age adequate health goals becomes particularly important not just for DM2, CVD and cancer prevention but also to fight any acute illness. A particular example is given to us by the epidemic of Covid-19 which meets the pandemic of obesity/insulin resistance and people afflicted with metabolic conditions with associated high endothelial dysfunction levels have a reduced chance to survive [41]. It is well documented now that obesity and associated insulin resistance worsen the outcome of Covid-19 [42]. The most important link is the state of metabolic inflammation that predisposes patients to an enhanced release of cytokines. Metabolic inflammation will also compromise the immune system, reducing the body's ability to tackle the infection, impairing the healing process, and prolonging the recovery [43]. Improvement of sugar control and insulin resistance are key in the battle to reduce the proinflammatory state leading to morbidity and mortality [43]. This event is further stressing the need for strategic planning to improve not just individual health but health at corporate, community and societal level. Currently NIH nutritional research initiative "precision nutrition" [40] is calling for solutions that "advance understanding of the vitality of food in health". Stepping up to the challenges it appears that a CPS like product with its continuous monitoring and predicting risks and providing metrics associated with insulin resistance, endothelial dysfunction and nutrition could support NIH goals and primary care effort to improve the dismal statistics of prevalence of obesity and insulin resistance.

From primary health care point of view the innovation is that the current CPS can capture metrics of physiological functioning in 3 intertwined domains in the user's natural environment: metabolic, cardiorespiratory, and cardio-vegetative health. The metrics are centered around the common pathological pathway of obesity, insulin resistance, endothelial dysfunction [44], CVD and cancer [45]. An all-encompassing risk assessment by CPS allows a quasi-real time monitoring for the user and the primary care giver. Analysis, prediction, and planning for change can be performed either at home or in the primary provider's office through a Metabolic Health Monitor (MHM) mobile and web app and display of results on the user's smartphone [46]. As physical activity remains the main tool to fight insulin resistance and endothelial dysfunction [47] an MHM like device with its metrics for physical activity along with metrics of metabolic, cardiorespiratory, and cardio-vegetative health could play a central role to guide user to personal best achievable results.

The 'leap ahead' innovation and significance of CPS is the continuing observation of important disease markers and allows for using this information for self- and guided management of modifiable risk factors with lifestyle and behavioral modification. The paradigm shift is here the extension of the current practice of using one point in time risk assessment with continuous individualized estimation of progress of various disease processes real time. ODI's *idea is to use CPS, which collects highly impactful physiological data, compresses it into MC models, and determines and predicts the model parameters, which become the target for optimization of physiological functioning to reduce risk for morbidity/ mortality*. CPS provides metrics which are easily understandable, self-explaining, and completely describing processes increasing morbidity and mortality. Unique to our effort is the continuous observation of state variables in the users' natural environment raising self-awareness, enhancing motivation, and underscoring self-responsibility to reduce modifiable risks as much as possible. This could lead to reducing disease burden for the entire nation with implication for reducing societal costs to deal with them when they reach decompensated or catastrophic stage. The large volume of impactful data gathered together may find usage at different levels such as personal, community, corporate, and public health levels to fight non-communicative diseases in general.

CPS could be upgraded from a support software to achieve fitness goals to an FDA approved and medically tested software to realize an Integrated Cyber-Physical System (ICPS) [34]. The medical software version could monitor progress of disease processes of metabolic (MF), cardiorespiratory (CR), cardio-vegetative (CV), oxygen delivering (OD), endovascular and hemodynamic (HD) functioning [34].

Cancer prevention strategy with constant monitoring for changes of insulin resistance by metrics of R- and Rw- ratio has been provided. It is envisioned that even the most vulnerable cancer patients with risk factors of obesity, sarcopenia, poor nutrition status, insulin resistance, DM2, and CVD could be supported with guided therapies by primary physician.

CPS and ICPS support the goals of “precision medicine” and “precision nutrition”.
The individualized nature of precision medicine helps health care providers to have a holistic and functional understanding. An integrated approach considering among others environment, lifestyle, and heredity factors could be adopted. Information gained by CPS/ ICPS lets providers more accurately predict which treatments will be most effective and safe, or possibly how to prevent the illness from starting in the first place.

Conclusion

In conclusion use of a CPS with machine learning using principles of optimal control theory with supervision by a physician can provide a truly individualized strategy for estimation, continuous monitoring, and prediction of physiological state variables for self-therapy, guided therapies, and cyber-therapy. CPS follows the principles of “precision medicine” and “precision nutrition”.

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