Smart Health from Big Data to System Medicine: the Network Physiology Paradigm

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Abstract—The technological development of the last years and recent advances in scientific research have favoured the emergence of new models of healthcare in smart cities. Fostered by the decentralization of clinical practice outside hospitals and the massive amount of physiological data that are recorded daily, new approaches that aim to go beyond traditional medicine are emerging. At the forefront of numerate disciplines, biological research and clinics, Network Physiology is a new field in science that proposes to take the distance from traditional segregation and look at human physiology from a holistic perspective. According to this approach, systems composing the human body are studied in their interactions, through newly developed theoretical frameworks and cutting edge data analysis tools. The aim is to introduce new biomarkers of physiological functioning that will improve our knowledge about the human body, help clinicians in diagnoses and enhance prevention of critical events. This white paper elaborates on the impact of Network Physiology in future smart cities and presents how diversified fields of science are implementing this paradigm to help scientific and clinical progress.

I. INTRODUCTION

The application of the Smart City concept have become a trend in today’s urban environments, favored by recent advances in information and communication technologies (ICTs) and fostered by the increasing number of people living in cities [1]. In this context, the smartness challenge implies that the latest technological improvements are used at the service of the citizens, with the purpose of improving their daily living and their quality of life.

Of broad relevance, the rapid technological development of the last years have seen the use of wearable sensors to become widespread in our daily activities, coming either in the form of self-contained devices or as an integrating part of mobile phones [2]. Wearables are usually small and light high-tech devices, implementing a wide range of functions and often representing pieces of design, such as bracelets, glasses or necklaces. Mostly, they are used for fitness purpose, so to monitor personal physical performance and tune exercise to reach personalized goals. However, their potentials are much wider and new configurations of wearable devices are starting to enter very diversified applications [3]. Let us mention for instance movement data capturing devices that allow rehabilitation to be performed at home [4], elderly people monitors that favor remote assistance [5], heart rate sensors that allow immediate emergency alerting for people suffering from cardiac disease [6] and insulin pumps that deliver insulin by continuous infusion mimicking physiological demands [7]. The massive use of wearable monitors results in the daily collection of a huge amount of data, so that it is possible to talk about a new type of big data: physiological big data.

At the same time, a trend is developing within the clinical setting, that aims to shift from a traditional reductionist approach to a modern system approach, known as system medicine [8]. The idea behind system medicine is to consider the human organism as part of an integrated whole, where interactions among different constituents are studied in the attempt to provide a wider perspective on the holistic nature of physiological conditions of health or disease. Contrarily to modern medicine, that focuses on single organ systems as separated entities, system medicine aims to consider dynamic interactions between different elements composing the human body in the attempt to understand how they affect the system as a whole. Indeed, according to this perspective, existing networks manifest emergent properties that define the whole that are not simply the sum of features of the component parts.

Physiological big data constituted by recordings from diversified physiological districts would represent an invaluable source of information for system medicine to improve our knowledge about the functioning of the human body, however, there is the need to develop advanced tools that are able to deal with a wide variety of data types, happening at different time scales, showing non linear interactions and representing very different mechanisms. This is the main goal of Network Physiology, a new interdisciplinary field at the forefront between scientific research and clinical practice, whose aim is to develop a theoretical framework and practical analytic tools for the treatment of big data acquired from the human body, shifting the focus from single organ systems to networks of organ interactions, in the attempt to better understand human physiology in an integrated way and predict clinical events and diseases [9].

II. NETWORK PHYSIOLOGY: ORIGIN AND FOCUS

Network Physiology was introduced as a new field in science by Professor Plamen Ivanov and its research group at Boston University as a result of an innovative study regarding the communication between organ systems across sleep stages [10]. They analyzed full-night sleep recordings from 36 subjects consisting of the measurements of the electrical activity of the heart and the brain, the ventilation of the lungs and the movements of eyes, legs and chin (Figure 1). They looked at correlations between the activity coming from different body parts, and what they found was quite revolutionary. While during deep sleep the physiological systems appeared to be
somehow disconnected, stronger coupling appeared as soon as the subjects transitioned to REM sleep, and even stronger going to light sleep and finally to awake, in contrast to the traditional indices computed on the dynamics of individual systems, that show high similarity between wake and REM sleep, compared to non-REM sleep. Even more surprisingly, the network reorganized very fast (within seconds) during the transitions from one sleep stage to another, showing an amazing flexibility of the mechanism involved in the optimization and coordination of organs behavior. Whereas it was known that sleep regulation influenced the control mechanisms of individual physiological systems, this study further revealed that sleep stages are able to modify topology and coupling strength of the physiological network composed by all the observed systems, in a way that cannot be directly inferred by individual dynamics, thus setting the ground for the development of new and revolutionary approaches to look at the human body from an integrated perspective.

Network Physiology is presented as an interdisciplinary field, that combines efforts of scientists in statistical physics, applied mathematics, computer and data science, in the attempt to unravel the complex mechanisms that regulate the communications between organ systems. In other works, Network Physiology aims to study the horizontal integration that exists between systems that are commonly treated vertically (Figure 2). Whereas it is common practice to study organs from the molecular composition all the way up to the anatomical structure (vertical perspective), the relationships that exists between different organs (horizontal perspective) are almost never taken into account by modern medicine: the cardiologist studies the heart, the pneumologist studies the lungs, and so on. However, it is argued that a lot of information about the functioning of our body may be lost if interactions between organs are not considered. Paradigmatically, one may think at multiple organs failure, a clinical condition in which critically ill people die, without any organ being directly responsible. The lack of a single point of failure suggests that the cause of the system breakdown may be a dysfunction of the mechanisms that organs use to synchronize themselves. According to the Network Physiology perspective, if the focus is shifted to the study of the interactions among organs, it might be possible in the future to predict critical events such as multiple organs failure, and hopefully prevent them from happening.

III. Future Perspectives

Drawing inspiration by existing atlases of human anatomy, mapping bones, muscles, nerves and vasculature, the final goal of Network Physiology would be to map the information being circulated in the human body and build an atlas of the dynamical interactions between organ systems under healthy conditions, pathological and physiological states, differentiated by age or population group. This atlas will be constituted by a catalogue of reference maps of dynamical organs interactions extracted from continuous parallel recordings of organ systems. The availability of such an atlas would dramatically change the way in which physiological regulatory mechanisms are understood and revolutionize and innovate many aspects of health provision. First, new biomarkers related to organ network interactions could be defined in order to provide clinicians with a wider picture of the physiological status of patients. Then, the atlas may be a helpful resource for new types of physicians, having expertise in the field of system medicine. Moreover, a comprehensive assessment of the effects of drugs of pharmaceuticals on the whole human organism might be also favored by knowing how organs reciprocally affect each other. Finally, algorithms extracting maps of physiological interactions or indicators of system functioning may be implemented in next generation ICUs and, in a later future, in personalized health monitors, allowing a comprehensive evaluation of the patient status based on several innovative physiological indices.

IV. Current Developments in Research and Clinical Practice

If the future perspectives that Network Physiology offers are very appealing, it is also true that at the present time efforts
in various fields are being made in order to take concepts that belong to fields such as complex systems theory, non-linear systems and complex network analysis to mention some, and apply them to the study of the behaviors that emerge from networks of physiological systems. Prominent examples representing current developments in the field of Network Physiology will be presented in the following.

A. Cardiorespiratory interactions

Following a research line that started in the 80s [11], [12], the study of the dynamical interactions between heart rate and respiration is a prominent example of how the behavior of a systems may be strongly influenced by the dynamics of another. This type of coupling can be probed by everyone of us, simply measuring the pulse during one whole respiration cycle (inspiration and expiration). This simple experiment will make it possible to verify that during inspiration the heart rate accelerates a bit, while during expiration it slows down again. This phenomenon is known as respiratory sinus arrhythmia (RSA), and explains the presence of oscillatory components at the respiratory frequencies that are found in the spectrum of the heart rate variability signal (Figure 3).

However, the physiological mechanisms that drive RSA are very complex and not fully understood yet. They comprise the action of the autonomic nervous system as a mediator, possible mechanical effects of the rib cage and may also be affected the activity of higher brain centers. Most importantly, the interaction between respiration and heart rate varies across physiological states and may be impaired as a consequence of pathological conditions [13]. A typical example is the study of the response to an orthostatic stress, that results in a strong reduction of RSA with a concomitant simplification of the heart rate dynamics as a result of autonomic effects. This healthy behavior is not observed in patients suffering from orthostatic syncope [14].

Going beyond the interaction between heart and lungs, recent approaches make use of extended set of signals recorded from different districts (thorax, fingers, limbs, head) in order to shed light on the neuroautonomic regulation of cardiovascular and cardiorespiratory activity. Different body parts are modelled as interdependent on one another as nodes of an underlying network and analyzed in an integrated fashion [15].

B. Sleep regulation

Besides being elucidatory on the role of sleep stages in changing the topology of the physiological network, the study of physiological systems’ interactions during sleep also proved to be useful for the evaluation of the consequences of sleep disorders. As an example, we report the results of a study on sleep apnoea, a sleep disorder characterized by repetitive cessations of respiratory flow for at least 10 seconds [16] (Figure 4). The study shows that the cardiorespiratory coupling that is commonly observed in deep sleep is lost with apnoea. This is particularly critical because a function of deep sleep is physical recreation in a low-energy consumption setting, that is favored by a high degree of synchronization between respiration and heart beat. If this synchronization is lost with apnoeas, it is possible that physical recreation is impaired, thus increasing the possibility to develop very serious consequences in the mid-long term [17].

C. Brain connectivity

Founding concepts that set the basis of Network Physiology see their applicability for the study of the most complex organ of our body, that is the human brain. Understanding the
mechanisms that govern information processing in the brain is one of the biggest challenges of our century, favored by the development and improvement of investigation methods that allow to study this organ with an increasing level of detail. Among the most commonly used techniques it is worth mentioning EEG, fMRI, MEG, NIRS, fNIRS, PET (Figure 5). Signals recorded using one or a combination of these techniques allow to build what is known as a functional connectivity map, that is a special type of graph, where the nodes represent brain areas, while the links represent the dynamical interactions between them [19].

Although functional networks partly reflect the properties of the underlying structural network that composes the brain, it is important to point out that nodes in a functional network can be linked even though there is no physical structure connecting them, thus reflecting a common functionality. Unlike structural connections, functional links are highly dynamics and subject to changes that depend on the level of attention or arousal, on the emotional state, on the task that is performed and also on pathological conditions.

The study of the functional connectivity maps allows to shed light on neurodegenerative diseases: it was discovered that regions of high connectivity in the human brain, called hubs, are more likely to be affected by Alzheimer’s disease, probably because of their continuous high baseline activity [20]; moreover, recent evidence regarding the study of epilepsy suggests the existence of an epileptic network in contrast to the traditional epileptic focus hypothesis, arguing that seizures are not relegated to a circumscribed area of the brain, but rather large functionally and anatomically connected brain structures may be involved [21].

D. Cardiovascular networks

Cardiovascular network health is of paramount importance for the life and function of all systems composing the human body. The functioning of the cardiovascular network can be probed by measuring blood perfusion, that is also an indicator of hormonal, circulatory and tissue health in humans. However, providing a reliable measurement of this quantity can be challenging. Different non-invasive monitoring systems are available, relying on mechanical (plethysmography), optical (photoplethysmography, laser Doppler flowmetry), acoustic (ultrasound) or thermal (infrared thermography) physical principles. Whereas optical and acoustic techniques are particularly effective in terms of spatio-temporal mapping, they show an extreme sensitivity to motion, requiring immobilization of the subjects during the measurements. On the other hand, thermal techniques, that measure blood flow from the thermal response of the skin, are less sensitive to motion, thus providing a valid alternative in scenarios that require movement. A further advantage is that these techniques allow to map the functional architecture of cutaneous and subcutaneous vessels simultaneously (Figure 6).

Thermography has been applied to a range of different studies as a novel means to provide additional information with respect to more common practice indicators. In [22], thermography has been successfully used during brain surgery on the exposed cerebral cortex, in order to map the distribution of cortical activation during language and motor tasks, going above and beyond the information provided by standard functional imaging techniques. In [23], infrared imaging is employed during renal transplant in order to assess noninvasively kidney reperfusion, as a novel objective means to evaluate the effects of ischemia in real time. This is a particularly critical indicator because ischemia results in an increased risk of rejection after transplant as a consequence of ischemic damage. In [24], thermography is used to evaluate vascular dysfunction as an indicator of sickle cell disease.
E. Genomics, metabolomics and transcriptomics

While structural networks characterize physical connections between units (vascular tree, brain connectome, airway tree) and functional networks reveal the temporal correlations between the activity of the nodes under study (cardiovascular and cardiorespiratory interactions, brain function), there exist classes of biological data that lack both physical and time dependencies, for which it does not make sense to compute structural or functional connectivity. One may think for example at blood test results, genes or metabolites. For this type of data, adopting a network approach might be helpful in order to unveil the presence of relationship between nodes. Recently, a new type of network for the representation of isolated and heterogeneous values was defined, called parenclitic network, in which nodes represent features extracted from data, whereas links quantify the deviation (parenclisis) of the two connected features from a reference model [25]. The topology of the resulting network is then informative about the system under study.

A prominent result was obtained for the early diagnosis of obstructive neuropathy from metabolites and regulators [26]. Obstructive neuropathy is a complex disease affecting children, that is characterized by a partial or total obstruction of urinary tract that may result in kidney damage. Despite the gravity of this disease, the pathological mechanisms are not fully understood yet. Parenclitic networks allow a further insight into the genetic and metabolic elements that are responsible for the malfunction: whereas the topology of the parenclitic network of control subjects was amorphous, patients suffering from obstructive neuropathy showed star-like topologies centred on the most abnormal metabolite or regulator (Figure 7).

In another study, a different approach based on linear algebra techniques for dimensionality reduction was applied to transcriptomic data from adipocytes (fat cells) in order to study the alterations in regulatory and metabolic activities in obesity [27]. In order to provide a more robust and significant result, different transcriptomic datasets in literature were combined, so to remove the bias deriving from single experiments. The dimensionality reduction technique applied on transcriptomic big data allowed to find a signature of 38 genes that was able to discriminate between obese and lean subjects, even when tested on independent databases. Interestingly, the genes in the signature were involved in typical dysfunctions that are associated with obesity, such as those related to the central nervous system (anxiety, depression), digestive system (salivary secretion, digestive problems), diabetes or fertility. In addition, a similar transcriptomic signature was found when comparing data from healthy breast tissue with data from breast cancer tissue, validating the strong association between obesity and breast cancer.

V. Conclusion

This white paper illustrated the role of the emerging field of Network Physiology in fostering and shaping innovative models of healthcare in smart cities. Relying on the availability of big data coming either from hospital recordings or from physiological measurements performed by wearable devices, and following the lines of system medicine in treating the human organism as a connected whole, Network Physiology is proving the effectiveness of its distinctive approach in a variety of different clinical settings, ranging from cardiovascular impairments to neurological diseases, from sleep disorders to genetic diseases. Current efforts in developing theoretical frameworks and practical analytical tools will give the possibility to revolutionize the way in which the functioning of the human body is understood, fostering a more informed treatment of diseases, a more effective prediction of critical episodes and new ways of prevention.

GLOSSARY

Network Physiology A new interdisciplinary field of science that is emerging at the forefront of statistical physics, biomedical engineering, applied physiology and clinical medicine, that aims to develop a theoretical framework and system-wide analysis tools to study how different organ systems, each characterized by its own regulatory mechanism and physiological functioning, dynamically interact with each other and change their interconnected behaviors in conditions of health and disease.

hubs A hub is a concept belonging to network theory that indicates a node characterized by high connectivity, i.e. with a number of links that is much larger than the average.

infrared thermography Infrared thermography is an imaging technique that detects the infrared radiation emitted from objects, converts it to temperature and outputs an image of the heat distribution.

metabolites Metabolites are the intermediate products of metabolic reactions that occur within cells. Primary metabolites are indispensable for the cells growth and include amino acids, vitamins, alcohols, organic acids, nucleotides. Secondary metabolites are not required for primary metabolic processes, but are involved in other functions such as protection, competition, species interaction.

orthostatic stress A type of physiological stress that is caused by assuming the standing position. It is characterized by a lowering of the arterial blood pressure that in turn triggers the autonomic nervous system response. Orthostatic stress is induced in laboratory experiments via the head-up tilt (HUT) test.

parenclitic network A parenclitic network is a novel network representation of a set of items that unveils the presence of relationships between features of these items. Nodes in parenclitic networks represent features, while links encode the deviation from a reference model.

physiological big data Big data consisting of recordings of human body function from a variety of districts, acquired either in hospitals or through the use of modern portable systems that incorporate...
sensors into wearable devices. Physiological big data is characterized by a high degree of heterogeneity in terms of physical quantities, timescales and activity patterns.

**sleep stages** The different stages of sleep that cyclically repeat during sleep. Sleep stages are identified by the corresponding predominant frequency of brain wave activity that occurs during each stage. Five different sleep stages are commonly identified: light sleep 1 and 2, deep sleep 1 and 2 and rapid eye movement (REM).

**system medicine** A newly-proposed holistic approach to medical education and practice, that aims to take the distance from the reductionist framework of modern medicine, by studying interactions among different body parts to provide a wider perspective on physiological functioning in conditions of health or disease.

**transcriptomic data** The transcriptome is the set of all RNA molecules in one cell or in a population of cells, reflecting all the genes that are being actively expressed at any given time.

**ACKNOWLEDGMENT**

This project is supported by the IEEE Smart Cities Trento, Student Grant Program (Second Call, May 2016).

**REFERENCES**


