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SPOTLIGHT

Integration of imaging biomarkers into systems biomedicine: a renaissance for medical imaging

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Abstract
Systems biomedicine consists in the integration of biosciences, medicine and computer sciences. Systems biomedicine is supposed to allow a holistic approach to the human subject and its disease states. This paper outlines the basic concepts and open issues in this field and provides an outlook for the integration of medical imaging procedures in the growing area of systems biomedicine. The terms "Systems biomedicine", "Systems medicine" were used for bibliographic search in Pubmed and Web of sciences. Most relevant papers were selected for inclusion in this paper; a synthesis of the papers is presented. An integration of methods is required to best exploit the potential of the multi-'omics biobanks, in which imaging biomarker data represent an added value. To obtain such integration, imaging biomarker data from different "systems" should be in a manageable format. The recent evolution of AI and the hardware improvements by parallel and fast computing are bringing us towards a new age of molecular and morphologic imaging. Although there will always be a qualitative aspect to imaging, AI and quantitative metrics will supplement and complement the current "human" methods of interpretation of imaging data in a holistic approach to individual patient management.

Introduction

In a short abstract published in July 1991, Takenobu Kamada launched the visionary concept of systems biomedicine envisaging the integration of biosciences, medicine and computer sciences; in his abstract, he stated that: "*Objectives in medicine have recently expanded from treatment of disease to human comfort and wellbeing* […] *Biomedical engineering (BME) should make possible understanding of human being under the holonism theory and comprehensive circuits from genes to human communication will be established. BME hopefully will unify directions in molecular biology, medical engineering and medico-sociology to provide the new paradigm, 'system biomedicine"* [1]. This concept was further expanded in his following paper [2]. Probably, although visionary, he was not really aware of the future of such a process of integration, although he must have been aware of the rapid evolutions in the field of medical imaging.

The multidisciplinary integration of medicine, physics and informatics was indeed a fact in the last quarter of the past century; CT, PET, SPET and MRI were already substantially contributing to the advancement of patient's management, as acknowledged by the Nobel prize awards for Physiology or Medicine to Allan Cormack and Godfrey Hounsfield in 1977 and to Paul Lauterbur and Peter Mansfield in 2003, none of them being a physician.

The statement of Kamada was, however, predictive of the integration between the various fields of medicine, aiming at the improvement of healthcare, and non-clinical experimental sciences, based on advances in the fields of computational sciences applied to biological data mining/elaboration, and bioinformatics. Nowadays, more than ever it is transparent that the integration of biology, medicine and computational sciences is not only well grounded, but also deeply needed for both research and clinical applications.

Through an in-depth revision of the literature, Schleidgen et al. have developed a definition of systems biomedicine

Giovanni Lucignani and Emanuele Neri contributed equally to planning and writing this paper.

This spotlight aims to highlight the content of previously published papers on systems biomedicine and draws extensively on the texts and summaries of the articles referenced.

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as: "*An approach seeking to improve medical research (i.e., the understanding of complex processes occurring in diseases, pathologies and health states as well as innovative approaches to drug discovery) and health care (i.e., prevention, prediction, diagnosis and treatment) through stratification by means of Systems Biology (i.e., data integration, modeling, experimentation and bioinformatics)*" [3].

Systems biomedicine is supposed to allow a holistic approach to the human subject and its disease states founded on two concepts: (1) the human body has complex and dynamic biological properties that are based on the interaction of molecular agents sustaining the physiological functioning of the entire organism as well as the pathogenesis of diseases; (2) whereas complex interaction cannot be understood or processed by conventional analytical methods; such interactions can be analyzed using the power of bioinformatics and artificial intelligence (AI). This paper outlines the basic concepts and open issues in this field, using the words of a few leaders in the field of systems medicine, and provides an outlook for the integration of medical imaging procedures in the growing area of systems biomedicine.

According to Apweiler et al. [4], systems biomedicine is inducing rapid changes in preclinical, translational and clinical research with an impact on the health care systems. The future of systems biology and medicine hinges on the circular process "bedside–bench–bedside" determined by a clinical demand and followed by investigation and data elaboration by biologists, biostatisticians, computer science specialists, mathematicians, for delivering information for clinical use. These authors emphasize the role of "*systems medicine as a multilevel and multidisciplinary methodological framework for informed data acquisition and interdisciplinary data analysis to extract previously inaccessible knowledge for the benefit of patients*". Furthermore, Wang et al. [5] remark that "*systems biology allows also to use predictive computational modeling to (1) understand biological functions, providing new perspectives to understand diseases, (2) identify diagnostic biomarkers (characteristics that are objectively measured and evaluated as indicators of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention), and (3) develop disease treatments at a system's level*" [6].

One of the issues related to the exploitation of the large amount of data collected with the aim of taking advantage of the potential impact of systems biomedicine in clinical practice is the development of methods and technologies for storage, retrieval and interpretation of data useful for the identification of biological variables associated with disease states.

Saqi et al. have defined "*three computational challenges associated with systems medicine: (1) disease subtype discovery using integrated datasets, (2) obtaining a mechanistic understanding of disease, (3) development of an informatics platform for the mining, analysis, and visualization of data emerging from translational medicine studies*" [7].

A computational framework for complex disease stratification from multiple large-scale datasets has been proposed by the U-BIOPRED Study Group and the eTRIKS Consortium [8]. "*The framework is divided into four major steps: (1) dataset subsetting, (2) feature filtering, (3) 'omics-based clustering and (4) biomarker identification. The authors of the study show that the analysis generates a higher number of stable and clinically relevant clusters than previously reported, and enables the generation of predictive models of patient outcomes*".

Saqi et al. [9] focus their attention also on the fact that "*the contextualization of these patterns is important for obtaining mechanistic insight into the pathophysiology associated with a disease, involving the integration of multiple and heterogeneous high-throughput data*". They discuss knowledge representations that can be useful to explore the biological context of molecular signatures. In particular, they discuss the utility of three paradigms, *i.e. "(1) pathway mapping approaches, (2) molecular network centric approaches and (3) approaches that represent biological statements as knowledge graphs"*.

With respect to "*the challenges for integration of data due to a mix of complexity together with rich semantics*", Lisenko et al., describe *"how graph databases provide a powerful framework for storage, querying and envisioning of biological data.* These authors show how *"graph databases are well-suited for the representation of biological information, which is typically highly connected, semi-structured and unpredictable. They conclude that graph databases provide a flexible solution for the integration of multiple types of biological data and facilitate exploratory data mining to support hypothesis generation"* [10].

Like other "omics", also radiomics is part of systems biomedicine [11]. In their recent paper, Neri et al. [12] sustain that the "*multiparametric pattern analysis of radiomics, combined with molecular information obtained from liquid biopsy (i.e., the analysis of biomarkers circulating in blood), may aid decision-making in clinical practice. Furthermore, they sustain that the concept of biobanks usually employed for repositories of biological samples and records can be used also as repositories of data obtained by any imaging method or combination of methods* [13, 14]. *In 2015, the working group of the European Society of Radiology defined imaging biobanks as "organized databases of medical images, and associated imaging biomarkers (radiology and beyond), shared among multiple researchers, and linked to other bio-repositories", and suggested that biobanks (which focus only on the collection of genotype data) should simultaneously come with a system to collect related clinical or phenotype data"* [15].

To be integrated in systems biomedicine, the imaging biomarkers stored in the biobanks must be linked to the other types of qualitative or categorical and quantitative biomarkers, where categorical are those that cannot be expressed using quantity values (i.e., all ordinal biomarkers including pathological grading systems, methods for categorical classification of reports such as BI-RADS, LI-RADS, etc.), and quantifiable biomarkers, whose magnitude is expressed in numbers (e.g., volume, diameter, density, intensity, perfusion, diffusion, radiomics features, as well as variables from PET and SPET metrics, etc.).

The integration is required to best exploit the potential of the multi-'omics biobanks, in which imaging biomarker data represent an added value [16]. To obtain such integration, imaging biomarker data from different "systems" should be in a manageable format (e.g., standardized quantitative MRI and PET protocols and measures, obtained and combined by either two separate or concurrent acquisitions) to be integrated with other 'omics, including the genomic profile of the same lesion and/or of the patient.

To this end, bioinformatics plays a key role, not only at the standardization level, but also at the computational level, where the large amount of biomarker big data cannot be analyzed, correlated and interpreted solely based on the capabilities of the human mind. Complex interpretations, that may allow predicting disease behavior, such as aggressiveness of the disease and response to treatment, need the computational power of machine/deep learning methods to analyze data sets from large populations or from a single subject's multiple biomarkers.

A proposal for the development of imaging biobanks and biomarkers within the domain of systems biomedicine: a step forward in mind

Tomographic imaging procedures, including PET, SPET, MRI, CT and combinations thereof (PET/CT, PET/MRI, SPET/CT), represent ideal tools for the identification of morphologic, functional, and molecular biomarkers; their full exploitation should be firmly pursued for the development of quantitative analytical methods and their clinical use in systems medicine. However, this is possible only on the condition that imaging specialists become aware, with a new and broad perspective, of the contribution of medical imaging methods in the 'omics world. In fact, in the context of 'omics sciences, imaging modalities are likely to become a substantial component of systems biomedicine, essential for phenotyping individuals as well as large populations of humans subjects, for clinical and research purposes; the full exploitation of the potentials of imaging procedures is key in this endeavor of integrating radiomics with other 'omics.

The progressive application of quantitative methods to the analysis of imaging biomarkers has produced already, and is likely to further produce, a large amount of clinical information, even for a single patient; the paradigm of radiomics is a clear example of how the analysis of a lesion/tumor can produce thousand of features in a single patient.

Although medical imaging data must be correlated with the other 'omics to achieve a better understanding of key processes and their expressions, it is worth noting that the understanding of these correlations is also expected to lead to the emergence of new biomarkers as well. The correlation and the interpretation of data, the stratification of data from each patient, the prediction of aggressiveness and response to treatment, based on individual and population datasets, can be approached only to a limited extent by the human mind, whereas computational methods, with appropriate human cognitive functions, using deep learning tools, allow the performance of a type of analysis that is systematic, objective and reproducible.

The recent evolution of AI, with the introduction of more efficient convolutional neural networks as a basis for deep learning tools, and the hardware improvements by parallel and fast computing, are bringing us towards a new age of molecular and morphologic imaging [17].

AI is, therefore, needed not only for image analysis, to extract and interpret complex quantitative data, but also at the systems medicine level, allowing us to interpret the multi-'omics environment, to build patient's models, digital twins or avatars, to be used to simulate, in a virtual environment, risk factors and/or susceptibility to treatment.

Systems biomedicine is an original construct, a new scientific domain, a discipline aimed at unraveling the complexity of molecular biology and clinical medicine. Systems medicine has been made possible, thanks to the achievements of bioinformatics and to the collection of large biochemical, molecular and cellular datasets; the integration of such data with clinical measurements is already having an impact on the understanding of the molecular basis of complex disease states and their present and future management. In principle, systems biomedicine may allow the development of genuine strategies for a new approach to healthcare based on the development of computing algorithms. With this perspective in mind, the medical imaging community should seriously consider the possibility of joining other scientific communities worldwide in this endeavor, by developing guidelines for establishing biobanks that may further advance the role of imaging within the domain of systems biomedicine. In particular, molecular imaging has, due to the heterogeneity of processes measurable using specific radiopharmaceuticals with PET and SPET, a key role in providing, non-invasively, *"the visualization, characterization, and measurement of biological processes at the molecular and*

cellular levels in humans and other living systems" [18] to be integrated with any of the other available 'omics. It is remarkable that this definition can be extended also to MRI procedures with dedicated sequences and contrast agents, with the advantage of offering unique morphological information as well. In this perspective, a gap between nuclear medicine and radiology specialists should be overcome, as what is usually called "hybrid imaging" is not only a matter of tools but also the result of "hybrid minds".

In view of the future developments and applicability of systems biomedicine, also a few but very relevant challenges must be addressed and overcome: (1) the need to expand the size and availability of standardized and very well-labeled datasets, (2) the intra- and inter-laboratory validation of such standardized datasets, based on much larger sample size research data, possibly collected by multicentric laboratories, and last but not least, (3) the need to deal with different regulatory and ethical standards among USA, EU and the rest of the world, regarding the use of patients data [19].

We are at the beginning of a new age, similar to what happened with the invention of CT, MRI, PET and SPET, when planar imaging was substituted by tomography. As quantitative methods for assessing the status of imaging biomarkers are entering the diagnostic workflow, most likely, the human visual interpretation of images will become insufficient and possibly inadequate for good clinical practice and research.

Although there will always be a qualitative aspect to imaging, AI and quantitative metrics will supplement and complement the current "human" methods of interpretation of imaging data in a holistic approach to individual patient management.

May be that the time is coming for an irreversible breakthrough due to an unavoidable generational turnover; "digital naïve" medical imaging specialists, educated to use a mix of visual and quantitative interpretation, will be substituted by "digital native" specialists, who are eager to use quantitative methods for analyzing imaging biomarkers, in the patient's everyday workflow, and ready to correlate such data with patient's clinical signs and 'omics data, with the help of AI. A renaissance for medical imaging is on the way.

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Compliance with ethical standards

Conflict of interest Giovanni Lucignani declares that he has no conflict of interest. Emanuele Neri declares that he has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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