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MINI-REVIEW

The NMR added value to the green foodomics perspective: Advances by machine learning to the holistic view on food and nutrition

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Abstract

Food is a complex matter, literally. From production to functionalization, from nutritional quality engineering to predicting effects on health, the interest in finding an efficient physicochemical characterization of food has boomed in recent years. The sheer complexity of characterizing food and its interaction with the human organism has however made the use of data driven approaches in modeling a necessity. High-throughput techniques, such as nuclear magnetic resonance (NMR) spectroscopy, are well suited for omics data production and, coupled with machine learning, are paving a promising way of modeling food–human interaction. The *foodomics* approach sets the framework for omic data integration in food studies, in which NMR experiments play a key role. NMR data can be used to assess nutritional qualities of food, helping the design of functional and sustainable sources of nutrients; detect biomarkers of intake and study how they impact the metabolism of different individuals; study the kinetics of compounds in foods or their by-products to detect pathological conditions; and improve the efficiency of in silico models of the metabolic network.

KEYWORDS

^{1}H NMR, biomarkers, data analysis, green foodomics, kinetics, simulation, sustainability

1 | INTRODUCTION

The 21st century has imposed a decisive acceleration on the shift from mass production to the improvement of the nutritional quality of the food available to the entire world population. Nevertheless, a healthy-eating renaissance is complicated by the three most great phenomena of these last years, which are market globalization, climate changes, and the most recent SARS-CoV-2 or COVID-19 pandemic.[1] The latter raised the attention of consumers towards **functional foods** (FFs), enriched by bioactive compounds with immune-boosting and functional properties.[2] From this point of view, food is considered an affordable way to prevent a broad range of diseases.[3] However, the consumption of such FFs enriched with bio-active compounds implies the ingestion and the consequent digestion and breakdown of complex matrices where bioactive molecules are found together with other molecules that can act synergistically or antagonistically.[4]

The ability to design new foods aimed at improving health must consider the availability of raw materials at affordable and sustainable costs, an aspect threatened by climate change that is increasingly critical today. For this reason, alternative sources of proteins, and other important nutrients, are designed to reduce the impact of the exploitation of the planet's resources in a perspective that is ever closer to the circular economy, converting waste products into second-life products,[5] creating a so-called "green food". Again, the choice must consider the nutritional quality of the selected ingredients once they are used to prepare new and more sustainable products. The impact on human health of these choices must consider the fate of nutrients once consumed in a meal, according to dietary habits that are also changing due to the fusion of cultures consequent to globalization.

This new way of conceiving foods forces scientists to demonstrate the healthiness of food by revealing the mechanisms underlying its effects on the human metabolome, looking at the problem with a different approach, defined as the "foodomics approach".[6] A first definition of the term *foodomics* appears in 2009,[7] underlining its holistic approach on the investigation of all the possible connections among food (including composition, quality, and safety), diet, and the individual, including food impact on health/illness. In 2013, a new definition of *foodomics* was written, considering food as a highly complex mixture that affects the whole human organism.[6] According to the new definition, *foodomics* is the comprehensive, high-throughput approach for the exploitation of food science in the light of an improvement of human nutrition.[6] Recently, *foodomics* showed the potential not only of foods but also of their related by-products, as sources of compounds with human health benefits.[8] For example, the anti-inflammatory potential of the aqueous extract of olive pomace (which is one of the main by-products of olive oil production) was evaluated by supplementing Caco-2 human intestinal cells in culture.[9,10] This aspect is important also in the light of the "green" perspective known as the circular economy, included in "The 2030 Agenda for Sustainable Development adopted by all United Nations Member States in 2015". If from one side foods are becoming greener and greener, also analytical methods are assuming this color; green chemistry and green analytical chemistry principles have been promoting the development of environmentally friendly processes to achieve a more sustainable society.[11,12] In parallel, the 2030 Agenda is also promoting dietary patterns, like the Mediterranean diet, with low environmental impact, and at the same time, healthy, accessible, affordable, safe, and fair.[13] This is the reason why *foodomics* nowadays is shifting toward a **greener foodomics**.

2 | NUCLEAR MAGNETIC RESONANCE (NMR) AND GREEN FOODOMICS

Considering the background described previously, the development of sustainable analytical methodology is challenging for the green *foodomics*, which has to integrate the green analytical chemistry principles, in each of the omics platforms, to determine food constituents and nutrients at the molecular level.[11] Among all the omics platforms, NMR spectroscopy can be defined as a "green analytical method" in *foodomics* studies.[14] Differently from other techniques, NMR spectroscopy makes possible the substitution of organic solvents, for the extraction and separation of different classes of molecular species from foods and ingredients, by only aqueous solutions or minimal amounts of alcohols. Thus, NMR spectroscopy contributes to the chemical "green" transition, especially when methods based on aromatic compounds are avoided.[14,15] Of course, the lower environmental impact is not the only advantage linked to such a methodology. Other peculiar characteristics make NMR spectroscopic methods very attractive for the analysis of metabolites in complex biological samples: (i) It is a high-reproducibility technique, (ii) its coupling with separation techniques is less necessary than in mass spectrometry (MS), and (iii) there is simplicity in the preparation of samples from biological materials.[16,17] Despite many advantages, NMR also has weaknesses, such as limited sensitivity and resolution of the spectra. Although low sensitivity is the main limitation of NMR spectroscopy, significant developments have been made to enhance the sensitivity, including microprobes, cryogenically cooled probes, and the dynamic nuclear polarization (DNP) approach.[1]

The capability of NMR in *foodomics* has been largely documented in several research papers and reviews, above all in what concerns quality, traceability, and food safety.[18–20] NMR spectroscopy is particularly suitable for the investigation of extra virgin olive oil (EVOO), as it allows the characterization and quantification of minor components, like phenolic bioactive compounds, and the preparation of the sample consists in just adding a few hundred microliters of deuterated chloroform directly to the oil.[21–23] NMR-based *foodomics* has been also adopted for the definition of the molecular fingerprint of Pachino cherry tomato, which is an important Italian Protected Geographical Indication (PGI), deserving robust traceability methods, such as those based on NMR spectroscopy.[24,25]

Another perspective from which foods must be evaluated for being defined as "green" is the cost/benefit ratio of their production. The environmental impact caused by the unsustainable exploitation of natural resources and the waste of products caused by poor management of the

supply chain are part of the costs that must be reduced. On the other hand, there is a growing interest in maximizing the benefit of consuming foods enriched with important nutrients and bioactive compounds, derived from the refining of by-products that otherwise would become waste impacting on the planet's resources. In this case, since new ingredients and foods are designed, it is necessary to ensure that the nutritional quality of these fortified foods is guaranteed by the effective bioavailability of the healthy molecules. Indeed, constituents of the food matrix could aid or hinder the bio-accessibility and bioavailability of the relevant molecules.[26] An NMR-based *foodomics* approach, analyzing human serum samples, has been applied to evaluate the metabolomics effects of docosahexaenoic acid (DHA) supplementation, alone or in combination with oat beta-glucan (from bran), and anthocyanins (from grape skin), as ingredients of different fortified foods. Using this approach, it has been demonstrated that DHA induces positive perturbations in the lipoprotein profile of consumers that are modulated by the food matrix.[27] It is worth noting here that for assessing the actual concentration of nutrients, or other healthy food molecules, in blood and urine, those methods based on target analysis are not suitable. In fact, the intrinsic metabolome of food is different from what is detected after digestion and metabolization by the gut microbiota.[28,29] For this reason, in the last decade, NMR together with advanced chemometric tools has been employed for identifying urinary and blood metabolite profiles able to discriminate among food intake associated to specific dietary intervention.[30–37] From this point of view, NMR-based *foodomics* has been also suggested as one of the methods for gathering scientific evidence from clinical trials in dietary intervention studies, by discovering dietary biomarkers.[38] In vivo intervention studies are extremely expensive, and protocols based solely on this approach, for any newly developed fortified food, would be unaffordable to food companies. For this reason, in vitro digestion systems have been developed and validated by the international INFOGEST consortium.[39] So far, several studies have been published, concerning the release of nutrients and bioactive molecules during in vitro digestion experiments, both on single food products and on their combinations as in a meal.[40–42] They include cheese, processed meat, fish, vegetables, olive oil, vinegar, and eggs, as a few examples of applications of the NMR spectroscopy in this field.[43–51]

3 | THE FOOD BIOMARKER ALLIANCE (FOODBALL)

The availability of accurate information on the fate of the nutrients embedded in different food matrices, when they are subjected to digestion, is not sufficient to create links with the health effects resulting from the ingestion of even well-characterized foods. The link between nutrition and health must be based on correlations between nutrients or bioactive molecules, made bio-accessible and bio-available by digestive processes, and the human metabolome. For this reason, the search for biomarkers of food consumption as well as of the individual health status is of fundamental importance, and NMR spectroscopy plays a decisive role. Based on their intended use, six subclasses for biomarker classification are suggested: food compound intake biomarkers, food or food component intake biomarkers, dietary pattern biomarkers, food compound status biomarkers, effect biomarkers, physiological, or health state biomarkers.[52] The ultimate goal of modern nutritionists is to rely on mathematical models capable of predicting the impact of those biomarkers describing the molecular composition of food and diet on the last two subclasses of health effect biomarkers. Currently, a great effort is being made to acquire as many biomarkers as possible with respect to food intake.[53] NMR spectroscopy has been exploited to discover or validate food intake biomarkers through human acute intervention studies specifically designed to avoid unwanted sources of variance, like those occurring in observational studies at population levels. Interestingly, none of the urinary biomarkers for milk and cheese intake previously reported in the literature have been confirmed by such an intervention study, but more robust new ones were proposed, although limited to the consumption of the studied foods.[32] The concentration of most metabolites in urine, generated by food intake, varies by up to 350%, mainly due to interindividual variability and analytical variability.[54] Intersubject variability may be due to differences in genetics, lifestyle including dietary habits, and gut microbiota composition. NMR-based metabolomics is the approach of choice for minimizing the analytical source of variance, provided that a standard protocol is adopted by the whole scientific community, aiming at discovering robust biomarkers. Recently, a collection of detailed instructions for the whole pipeline, from sample collection to data analysis, has been also made available to the metabolomics community, also for the NMR-based approach.[55]

Even if food products are correctly defined at the correct resolution, intersubjective variability still remains an important source of confounding errors in any simple model of correlation between diet and health status. Simple models consider food as a static source of nutrients, poorly defined by its composition. For modern food scientists and nutritionists, it is clear that the underestimation of the kinetics of nutrient release from the food matrix, and subsequent absorption into the digestive

tract, is by far the most important cause of the failure to find links between diet, characterized at the molecular level, and the health status described through metabolomic descriptors. For this reason, attention must be paid to the design of in silico experiments capable of simulating the kinetics of digestion and absorption, with the result of being able to identify, through metabolic flows analyses, different human phenotypes that, once correctly classified, can be parameterized in more effective predictive models.

4 | KINETIC SIMULATION FOR NUTRIMETABOLOMICS WITH NMR DATA

The sheer complexity of food–human interactions involves a high number of phenomena happening at very different observational scales: from food structure breakdown to digestive functions, all the way down to effects on enzymatic activities. Linking these interdependent phenomena to reach a holistic physiological model of such interactions is thus a very hard task. However, the advent of omics data production, which stems from the use of high-throughput sources such as NMR spectroscopy, coupled with ever-increasing computational power, has opened the way for data-driven approaches and simulation-based modeling in the field. Within this picture, the role of machine learning is that of finding links between complex patterns of molecular data, through classification, clustering, features discovery, and integration. At present, machine learning is the branch of artificial intelligence (AI), a term that groups a broad set of methods and paradigms, that majorly impacted data-driven modeling in the field. Machine learning frameworks act on two main levels when applied to NMR metabolomics data: (i) dimensionality reduction of spectral data, through single value decomposition of the covariance matrix (principal components analysis, factor analysis, partial least square discriminant analysis); (ii) classification and clustering of spectral data in latent feature spaces (with linear classifiers, hierarchical clustering, decision trees, random forests ...). When combined in a pipeline, these two steps can help etiological findings from studies and experiments by (i) detecting and representing sources of variance in the data and (ii) analyzing latent structures to ultimately link spectral features (and thus molecules) to physiological outcomes, through classification tasks. On the other hand, true deep learning approaches are still missing from these types of frameworks due to the requirement of a huge amount of suitable data for proper training (which are currently not available in the field) and a general higher difficulty in the interpretation of results, except for classification performances, from complex deep architectures (the black box problem). Overall, even at the early stage, data-driven approaches are helpful to link some of the levels of complexity of the food–human interaction problem. In this section, ways of tackling some of the problematics using NMR spectroscopy and MS data alike will be outlined.

4.1 | Food structure and digestion: An overview on complexity

The growing interest in understanding the effect of food on human health has led to an inevitable demand for modeling and computational tools to predict food–human interactions. However, many intertwined compartments must be modeled and connected, making holistic in silico approaches a hard goal to reach. Food–human interaction modeling revolves around two main stages: food structure and breakdown, transit, and absorption of nutrients in the gastrointestinal tract (GIT). While physiologically based kinetic models (mainly used in pharmacokinetics) exist to predict overall exposures to macronutrients, they are not capable of taking food structure effects into account. As a matter of fact, of the main issues of modeling, real food is simulating the structure and its breakdown in the oral phase and how they affect the activation of digestive function through the GIT. A complete overview of the state of the art of tools for in silico simulations available for the different compartments of the GIT is given by le Feunteunet al.[56]

4.2 | Characterization of food as an ensemble of patterns of biomolecules

Food can be considered a complex overlap of soft matter structures over different length scales. As such, when investigating food intake effects through biomarkers detectable in serum or urine, one can rarely expect to be able to characterize foods using a single or a small cluster of biomolecules. Furthermore, biomarkers of intake require extensive and dedicated studies to be validated. However, spectral data from human biofluids coupled with machine learning can help disentangle the patterns of detected compounds to characterize food. A successful example of such an approach is given by Reisdorphet al.[57] in a recent paper. This study aimed to detect specific food compounds related to blood pressure in individuals following Dietary Approaches to Stop Hypertension (DASH). To do this, the metabolome of the various food constituting the diet was investigated using MS. Spectra of food metabolome were decomposed using

projection on latent variables methods (principal component analysis) and clustered, to obtain patterns of compounds (both identifiable and unknown) as food signatures. The metabolomic signatures were compared with pre-diet urines and post-diet urines metabolomes. In this way, food specific compounds and post-diet unique compounds patterns could be discriminated and identified (when possible). The comparison yielded two main results: a detailed characterization of food in the diet using food-specific patterns and the individuation of intervention diet food by-products and endogenous compounds in post-diet urines significantly associated with changes in blood pressure.

Spectral data allow complex food characterization, and with carefully designed experiments, it can be joined with spectral data of human biofluids to investigate interactions and health-related effects at systemic levels.

4.3 | Characterization of pathological conditions using food-related kinetics

The human metabolome is characterized and affected by individual variability, lifestyle, dietary habits, and pathological conditions. As such, studying how nutrients and biomolecules are metabolized in different individuals using spectral data can help to engineer personalized nutritional interventions. In their recent study, Bütikoferet al.[58] suggested that postprandial response of the ingestion of high fat meals can be used to discriminate between obese and healthy subjects.[58] The authors isolated patterns of high-fat meals administration dose-dependent metabolites in serum using decomposition on latent structure and clustering, in a cohort with healthy and obese subjects. By studying the kinetics of such compounds, mostly amino acids and amino acids derivatives, the authors were able to classify healthy and obese subject. Approaches of these types are helpful in discriminating dose-dependent and interindividual dependent patterns in metabolomic spectra, characterize sets of food-related compounds and their kinetics, and shed light on food–human interactions associated with clinical and physiological conditions.

4.4 | Systemic data integration and in silico simulations at cellular levels

Systemic spectral data obtained from biofluids (serum, urine) can also be used to build constraint based models with metabolic control and flux balance analysis. This type of modeling originates from mapping the metabolic pathways of different cells and evaluating the evolution of the fluxes of reactions at fixed starting conditions. This means that abnormal metabolites presence (in example associated with a certain health condition) observed at the systemic level can be used to set the parameters for the model and predict changes in the overall cellular metabolism and enzymatic activity. Savoglidis et al.[59] developed an extension of this type of modeling, by reverse-engineering the matrix of reactions of sphingolipid metabolism to predict lipidomic kinetic data.[59] The authors used metabolites from spectral data to input the inverse matrix of the network of enzymatic activities. In this way, they used metabolite imbalances from a class of mutated cells to predict changes in enzymatic activities. These changes have been used to create the input parameters for traditional metabolic control analysis that computes metabolite levels from a starting set of parameters regarding enzymatic activities, allowing them to predict new perturbations in expression levels of metabolites and confirm the observed ones. This type of back-and-forth approach between simulations and data allows to simultaneously refine metabolism modeling (optimizing computational efficiency) while focusing the search for important patterns in spectral data. In a similar fashion, Simonettiet al.[60] integrated NMR metabolomics and genomics data with a machine learning pipeline and fed them to a flux balance model, to extract metabolic fingerprints of leukemia mutated cells and predict possible target pathways for treatment.[60] NMR spectral data are particularly suitable for such approaches, thanks to their reproducibility and high-throughput nature, which are key features for semi-stochastic modeling and machine learning algorithms. Furthermore, these approaches are capable of linking the systemic and cellular scale: a key aspect when exploring the complex nature of food–human interaction. Thus, translating data integration and these types of in silico models to *foodomics* studies can be a crucial step in solving certain modeling problems in the field.[61]

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