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Boosting comprehensive two-dimensional chromatography with artificial intelligence: Application to food-omics

Andrea Caratti [a,1], Simone Squara [a,1], Carlo Bicchi [a], Erica Liberto [a], Marco Vincenti [b], Stephen E. Reichenbach [c,d], Qingping Tao [d], Daniel Geschwender [d], Eugenio Alladio [b,**], Chiara Cordero [a,*]

[a] Dipartimento di Scienza e Tecnologia del Farmaco, Università di Torino, Via Pietro Giuria 9, I-10125, Torino, Italy
[b] Dipartimento di Chimica, Università di Torino, Via Pietro Giuria 7, I-10125, Torino, Italy
[c] Computer Science and Engineering Department, University of Nebraska – Lincoln, 104E Avery Hall, Lincoln, NE, 68588-0115, USA
[d] GC Image, PO Box 57403, Lincoln, NE, 68505-7403, USA

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ABSTRACT

The unceasing evolution of analytical instrumentation determines an exponential increase of data production, which in turn boosts new cutting-edge analytical challenges, requiring a progressive integration of artificial intelligence (AI) algorithms into the instrumental data treatment software. Machine learning, deep learning, and computer vision are the most common techniques adopted to exploit the information potential of advanced analytical chemistry measures. In this paper, our primary focus is on elucidating the remarkable advantages of leveraging AI tools for comprehensive two-dimensional gas chromatography data (pre)processing. We illustrate how AI techniques can efficiently explore the complex datasets derived from multidimensional platforms combining comprehensive two-dimensional separations with mass spectrometry in the challenging application area of food-omics.

Pattern recognition based on image processing, computer vision, and AI smelling are discussed by introducing the principles of operation, reviewing available tools and software solutions, and illustrating their potentials and limitations through selected applications.

1. Introduction

Artificial intelligence (AI) is an exponentially expanding field poised to transform the landscape of analytical chemistry [1]. Within this expansive domain, various specialized branches have emerged to confront intricate challenges. One way to divide AI into branches is based on the type of learning involved [2]. Machine learning (ML) represents the cornerstone of AI, since it empowers computers to learn and predict from large amounts of data (Big Data) [3]. ML models and algorithms are trained on the data collected in the lab and then used to make predictions on novel samples. Another significant field of AI is deep learning (DL), an advanced facet of ML, which harnesses artificial neural networks (ANN) inspired by the complexity of the human brain, enabling tasks such as nuanced image recognition [4]. Other AI tools involve natural language processing (NLP), which facilitates seamless communication between computers and human languages, fuelling advancements in speech recognition and machine translation [3], computer vision (CV), which imparts machines with the ability to comprehend images and videos [5], and robotics, a pivotal arm of AI, is dedicated to the design and operation of robots, utilizing algorithms to handle tasks ranging from navigation to sophisticated manipulation [6]. These specialized branches collectively sculpt the intriguing terrain of AI, reshaping industries and heralding the future of technology. It is important to note that these branches of AI are not mutually exclusive. For example, many deep learning algorithms are also machine learning algorithms. Additionally, many AI applications use techniques from multiple branches of AI such as, for instance, open-source or commercial software [7], which might use DL algorithms to identify regions of interests (ROIs) contour images within the data acquired from comprehensive two-dimensional gas chromatography coupled to mass

* Corresponding author.
** Corresponding author.
E-mail addresses: eugenio.alladio@unito.it (E. Alladio), chiara.cordero@unito.it (C. Cordero).
[1] Andrea Caratti and Simone Squara, listed in alphabetical order, equally contributed to this work.

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spectrometry (GC × GC-MS) [8], CV algorithms to evaluate the chromatographic fingerprint of the acquired samples images [9,10], and ML algorithms to develop supervised predictive models. All these strategies find applications in several research fields, such as environmental monitoring [11], exposome profiling [12], pharmaceutical research [13] and food quality [14–16], thus facilitating informed decision-making and accelerating the identification of innovative target compounds (*e.g.*, biomarkers).

Dividing AI into branches is useful for organising and understanding the different types of AI techniques. However, it is essential to remember that these branches are not mutually exclusive and that many AI applications use techniques from multiple branches of AI [17].

Undoubtedly, the most promising application of AI in analytical chemistry is ML, whose algorithms and models are exploited for data (pre)processing [18], unsupervised data analysis (explorative models) [19,20], supervised data analysis (classification [21] and regression models [22]) and design of experiment (DoE) [23,24].

AI algorithms serve as powerful tools, automating tasks, enhancing the precision of analytical methods, and pioneering novel techniques, especially in the *-omics* research [25]. Foodomics, in particular, is a complex field that analyses a wide range of food components, including primary metabolites, secondary/specialized metabolites, and other non-nutrient compounds (metabolomics) [26] to connect with biological outcomes in the nutrition and food science domains [27]. Multidimensional chromatography (MDC) techniques are powerful tools for separating and identifying these components, but it generates large and complex datasets whose interpretation can be challenging [26]. Therefore, AI algorithms are usually exploited to ease or possibly automate the analysis of these datasets and identify patterns and trends that would be substantially impossible to detect by manual inspection.

In the domain of MDC, the targeted and untargeted approaches delineate methodological disparities, both designed with specific objectives and scientific applications. The targeted strategy is meticulously crafted to precisely examine predetermined compounds or compound classes within a given sample, necessitating calibration curves or standards tailored to the specific compounds under exam [28]. In contrast, the untargeted approach adopts a more expansive stance, enabling the comprehensive exploration of the entire chromatographic domain devoid of predefined targets [9,16]. This methodology involves the judicious selection of ROIs in both dimensions of the chromatogram, facilitating the discovery of unforeseen compounds or intricate patterns within the data [8,29]. ML techniques shine in this domain, leveraging their ability to recognize patterns and correlations within large datasets. ML algorithms, particularly those in unsupervised learning such as principal component analysis (PCA) [30,31] or t-distributed stochastic neighbour embedding (t-SNE) [32], can uncover previously unidentified biomarkers or unique biological patterns, enhancing our understanding of complex biological systems. In contrast, while it is invaluable for confirming hypotheses and specific biological investigations, targeted approaches require fewer advanced computational methods due to their narrower focus, typically devoted to regression or classification tasks. Therefore, the selection between targeted and untargeted approaches, as well as the use of specific ML algorithms, is contingent upon the research objectives, wherein targeted methods offer precision and specificity, while untargeted approaches provide versatility and the opportunity for discovery novel target markers.

In this paper, our primary focus is not on ML *per se*. Instead, we focus on elucidating the remarkable advantages of leveraging AI tools for data (pre)processing. Our aim is to illustrate how AI techniques can efficiently explore the complex datasets derived from comprehensive two-dimensional chromatography (C2DC) in the application area of foodomic. By harnessing the power of AI, we highlight the potential for streamlined and insightful data analysis which includes data preprocessing, data processing based on different kind of features, and data mining as illustrated in the schematic diagram of Fig. 1. Through this exploration, we showcase the transformative impact of AI in deciphering the complexities of GC × GC data, emphasizing efficiency and precision in data processing.

The application of data mining and ML to collected peak features and peak-region features proves immensely useful in foodomics. This integration of techniques adds significant value to the analysis of complex datasets generated from advanced analytical technologies. One primary advantage lies in pattern recognition and classification, where these methods help identify distinctive peak features or patterns serving as

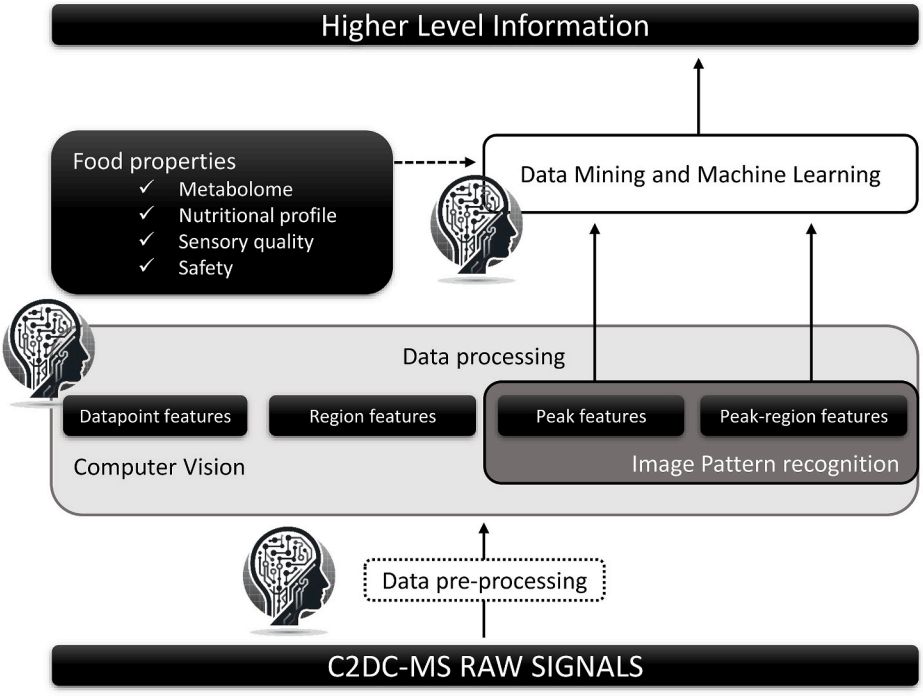


Fig. 1. Logic workflow to access higher level information. Domains where AI tools are adopted: data mining and machine learning; data processing, data preprocessing. Further details are provided in the text.

biomarkers for specific food components or contaminants. This capability is particularly vital for quality control, authentication, and safety assessment within the food industry. Additionally, ML algorithms play a crucial role in feature selection, focusing on the most relevant peak features or regions and effectively reducing dimensionality. This not only streamlines the analysis process, but also enhances the efficiency of subsequent modeling efforts. Furthermore, ML techniques enable predictive modeling for quantitative analysis, allowing for the accurate prediction of the quantity of specific compounds present in food samples, contributing to a more in-depth understanding of food composition, quality, and safety through the extraction of meaningful insights from complex molecular datasets.

Machine learning is seamlessly integrated into the field of data mining, playing a crucial role in various stages of the process. In terms of data pre-processing, machine learning algorithms contribute to handling missing data by predicting and filling values, and they assist in data cleaning through techniques like clustering and anomaly detection. Moreover, feature selection benefits from ML's statistical prowess, employing algorithms to identify the most relevant features for predictive models. Dimensionality reduction, often achieved through methods like principal component analysis (PCA) and unsupervised algorithms, utilizes machine learning to reduce complexity while preserving essential information. Furthermore, ML involves the application of classifiers and regressors to categorize and predict data in a supervised way. Therefore, ML's role extends to addressing the interpretability of models, with features integrated to enhance transparency in the data mining process. Consequently, the integration of ML into data mining amplifies the capacity to extract meaningful insights from vast and complex datasets.

1.1. Nature's complexity and analytical system dimensions

As intriguing test bench for AI tools and concepts, food applications offer many challenges due to the compositional complexity of samples (*e.g.*, primary metabolites, secondary/specialized metabolites, processing derivatives, exogenous compounds from microbial communities, presence of xenobiotics and contaminants etc.) and the properties connected to specific yet unique chemical patterns. Multidimensional analysis (MDA) systems, combining physico-chemical discrimination of individual components by chromatography with the structure-elucidation potential of MS, are the ultimate solutions for comprehensive investigations. However, the analytical data generated by MDA platforms have to be fully exploited by applying non-conventional approaches supported by the AI potential, to make a further step ahead and generate new knowledge on food properties, going beyond current quality indexes.

Biological systems are characterized by a high degree of complexity due to multi-level interactions of molecular patterns on multiple targets [33]. To reveal and understand the higher-order network structures and relationships between conditions that generate biological phenomena, system biology has developed and validated investigation strategies and tools capable of tackling Nature's complexity while giving access to higher-level information [16,34]. The so-called *integrationist approach* of system biology necessitates MDA systems to perform untargeted analysis [33] while requiring dedicated yet effective data processing to fully exploit the information potential and generate new knowledge.

Food science can take great benefits by implementing such comprehensive investigations (*i.e.*, *integrationism*) since the generation of new knowledge would overcome current protocols/markers used in quality and authenticity assessment [35,36], sometimes ineffective or unreliable, by defining new robust markers capable of predicting key properties of food (*e.g.*, origin, sensory features, quality level, nutritional density, bioactivity, *etc.*) [9,37,38].

Nowadays, we can affirm that analytical platforms adopted in *omics* have reached the maturity and effectiveness foreseen by R. Wilson in 1991 "*A persistent research frontier is the analytical chemistry of the mixtures of chemical substances generated by living organisms. The problems of separation, molecular identification, and quantification of these mixtures are enormous. They are the ultimate molecular mishmash. The challenges they offer have demanded, and produced, many new concepts in chemical measurement science*" [39].

In the field of GC, the conceptualization and realization of the first system for GC × GC marked a turning point in the approach to volatiles and semi-volatile mixtures analysis, while also revolutionized the means to process and interpret the resulting data. In 1991 Liu and Phillips showed the first comprehensive 2D separation of a mixture by connecting in-series two capillary columns. The system, equipped with a modulator operating on a thermal principle (*i.e.*, open tubular capillary modulator), adopted a first dimension (^{1}D) polyethylene glycol (PEG) column [21 m × 0.25 mm id × 0.25 μm d_f] connected to a second dimension (^{2}D) apolar column with dimethyl polysiloxane stationary phase [1 m × 0.10 mm id × 0.10 μm d_f] [40]. The analytical run lasted 2.5 min and the modulation period (P_M) was set at 2 s. The resulting chromatogram was displayed in a 2D time domain and authors could state that "*each substance forms a peak on the two-dimensional plane at a location determined by the interaction of the substance with the two different stationary phases*" paving the way toward new concepts of chromatographic interpretation and investigation, *i.e.*, 2D chromatographic fingerprinting [34]. Moreover, the potential of the new technique was immediately evident, since the authors commented in their concluding remarks that "*potential applications for this method take advantage of its speed, its power to separate complex mixtures, or its more reliable identification of substances through two independent retention times*".

It took a while to overcome the skepticism of some experts, but then the technique was adopted in several fields as a complement to one-dimensional (1D)GC or by replacing it [41–50]. The improved separation capacity due to greater efficiency and resolution was accompanied by a significantly enhanced sensitivity, especially when platforms implement cryogenic modulation which produces band compression *in-space* [51]. These combined improvements made GC × GC the analytical tool of choice for investigating highly complex samples [52]. Fig. 2 compares the 1D-GC profile (2 A) *vs.* GC × GC contour plots (2 B and 2C) of the volatile fraction of a Colombian cocoa sample. Volatiles, sampled by headspace solid-phase micro extraction (HS-SPME) with a validated protocol [53], were analyzed in close-to optimal conditions by 1D-GC and GC × GC with loop-type thermal modulation and reverse-inject differential-flow modulation. The GC × GC methods were mutually translated to keep the original method resolution and preserve elution order [54]. The separation power and sensitivity can be roughly evaluated by the number of detectable peak features with a threshold resolution (*R)* of 1.5 above a signal-to-noise ratio (S/N) of 50. By 1D-GC, 180 chromatographic peaks were detected (**2A**); 1130 in the GC × GC with loop-type thermal modulation (**2B**); and 290 in the GC × GC with reverse-inject differential-flow modulation with translated conditions (**2C**).

To achieve suitable information capacity, MDA should nevertheless include MS detection, as it provides orthogonal information on the properties of the analytes. It supports structure elucidation [55], identity confirmation, and accurate quantification in presence of authentic or surrogated standards completing the information inferred by the differential retention in the C2DC system. MS, operating at unit-mass resolution or by exact mass assignments (*i.e.*, high-resolution MS - HRMS), allows access to fundamental molecular features and provides additional selectivity and specificity for data processing.

1.2. Food – omics domains and the role of comprehensive two-dimensional chromatography

The term "omics" describes the collective characterization and quantification of pools of biological molecules that translate into the structure, function, and dynamics of an organism or many organisms [56]. The first omics field was genomics, which was theoretically

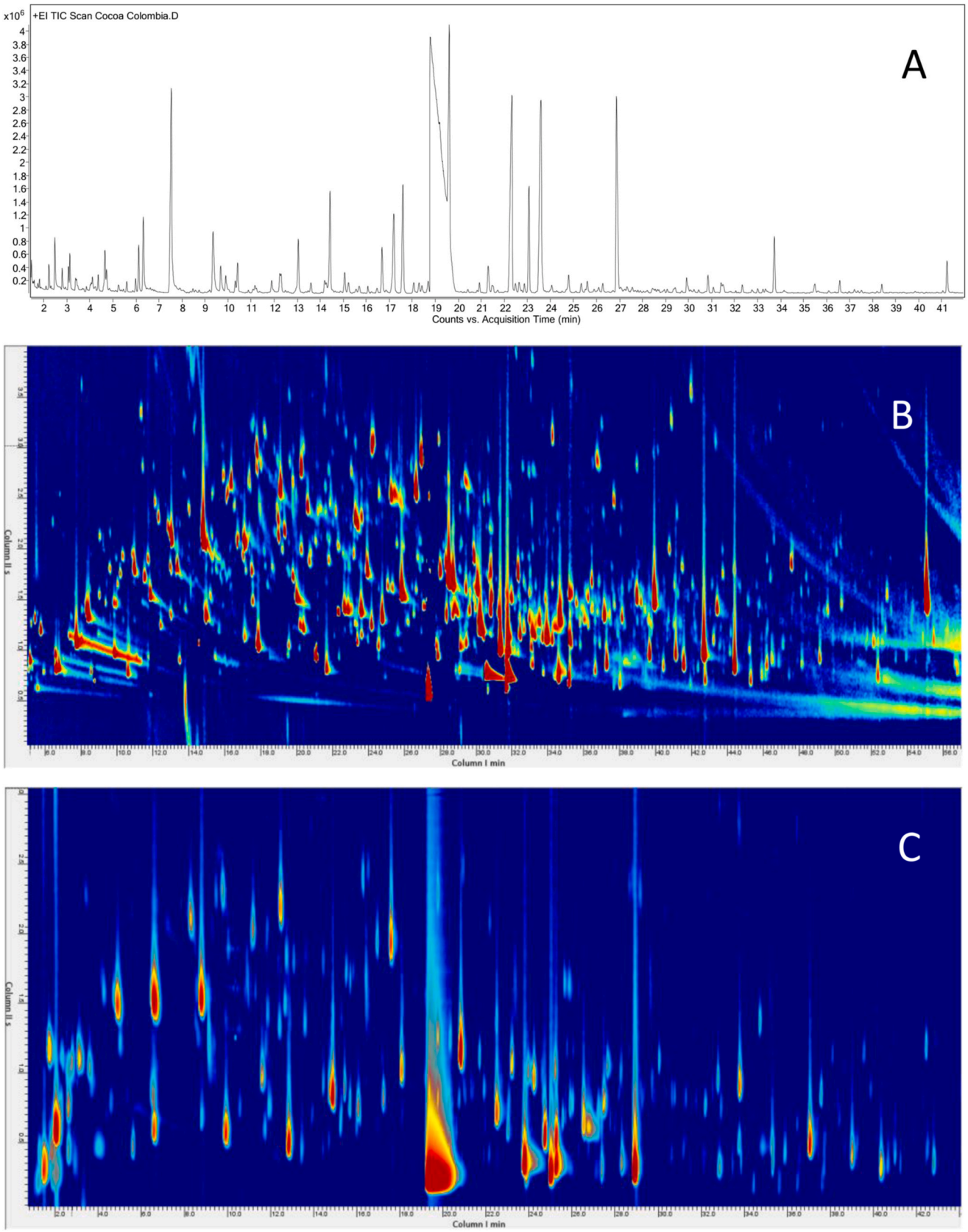


Fig. 2. 1D-GC profile (**2A**) and GC × GC contour plots (**2B** and **2C**) of volatile compounds from roasted cocoa beans from Colombia origin. Sampling was by HS-SPME with a DVB/CAR/PDMS fiber on 1.50 g of finely grounded sample in 20 mL HS vial kept at 50 °C for 40 min. Split/splitless injection was with a 1:20 split ratio in all analytical systems. Further details on the application and analytical set-up can be retrieved in reference study by Magagna et al. [53]. Detected peaks (resolution threshold 1.5) above a S/N of 50 were: 180 in the 1D-GC (**2A**); 1130 in the GC × GC with loop-type thermal modulation (**2B**); and 290 in the GC × GC with reverse-inject differential-flow modulation with translated conditions (**2C**).

opposed to genetics and focused on examining individual variations or single genes rather than complete genomes. Numerous omics have been described to date, spanning a wide range of genetics, biology, and chemical domains. It's interesting to note that the majority of food-related omics attempt to link chemical patterns and composition with biological aspects of food, such as nutrient content and how it affects humans, sensory qualities, biological activity, and reactions to external stimuli, including climate change on crops, processing methods on semi-finished and finished goods, plant pathologies, and effects of bacterial and mold metabolism [56].

With a thorough and reliable definition of the chemical code of food, various phenomena are better understood, including (i) quality – by markers in raw materials and finished products, (ii) bioactivity - by patterns of nutrients and active ingredients, (iii) sensory perception - by taste and odor-active compounds that are receptor ligands, and (iv) safety - by contaminants and toxic compounds with concentrations exceeding predetermined limits.

Within the general concept of *foodomics* [27], a discipline that investigates the interrelations between food and nutrition domains by applying omics technologies, more specific omic-related disciplines have been conceptualized in the last decade [57]. They have common investigation approaches inasmuch as all looks for the interrelation between chemical patterns and different biological phenomena.

Food metabolomics, for example, studies the impact of external stimuli/variables on the primary metabolome that, for an edible crop, has relevance concerning nutritional density and sensory features (*e.g.*, the presence of taste-active primary metabolites or aroma precursors) [58–60] or might have diagnostic capacity in relation to genetic and phenotype traits. A good understanding of the effect on food composition of climate variations, harvesting practices, post-harvest treatments, storage conditions, and shelf-life, enables pro-active strategies to drive quality toward desirable targets [28,37,61]. Food metabolomics has implemented GC × GC-MS as an essential technique, complementary to liquid chromatography (LC-MS) and nuclear magnetic resonance (NMR).

Food volatilomics focuses the investigation on the volatilome [62], also referred to as volatome [63], the fraction that includes volatile metabolites and all the other volatile organic and inorganic compounds originating from an organism [64] super-organism, or ecosystem. Volatile metabolites are part of the sample's metabolome, although degradation compounds and/or exogenous metabolites (*e.g.,* environmental contaminants, compounds formed by bacteria and molds - *microbial cloud* [65]) may also be present within this fraction. Better understanding of primary materials phenotyping and adaptation/-reaction mechanisms is achieved by integrating the information brought by both volatilome and metabolome. Due to the physico-chemical properties of volatile metabolites, volatilomics is crucial in many food applications [49]. The easy access to the volatile fraction by gas sampling techniques and the availability of complete automation solutions for sample preparation steps have boosted the investigations in this area [37,66,67].

When nutrition sciences intercept the trajectory of food metabolomics, the nutrimetabolomics perimeter is delineated. Within its boundaries, the impact exerted by specific dietary patterns on human health is investigated [68]. By nutrimetabolomics, the impact of diet and food components/nutrients patterns on the human physiology [68] are deepened and better mechanistic understanding of the phenomena is likely achieved by providing nutritionists with effective predictive tools for early diagnosis or preventive strategies. Nutrimetabolomics focuses on both: (i) nutrients and essential nutrients influencing the metabolic response in humans, and (ii) non-nutrients having various bio-activities and impacting the human metabolism with various effects.

As an essential quality component, food hedonic properties are a challenging bench for analytical chemistry. Besides the actual potential of analytical platforms in terms of sensitivity and information capacity, human senses should be integrated into the analytical workflow. Olfaction, taste, and trigeminal perception should drive the investigation toward ligands (*i.e.,* sensory active compounds) screening and targeting, while validating the outcomes by recombination and omission experiments, as the final stage. Sensomics is the discipline that "*molecularizes flavor entities of nature*" by identifying the unique yet peculiar pattern of odorants and tastants that evoke food sensory identity [69]. Sensomics and flavoromics [70] provide solid foundations for predicting food hedonic quality by rationalizing the chemoreceptive events occurring in our noses and oral cavity [71].

Food safety and authenticity are other crucial elements of food quality, although they have not yet been established as omics-related disciplines. Food safety is a prerequisite and a mandatory criterion for all food items intended for human consumption. Due to the current role played by GC × GC in safety evaluations of food (*e.g.*, mineral oil contamination assessment [72] and non-intentionally added substances detection [73]) and its information capacity for food *identitation* [74], food safety and quality will be also covered by this review article.

2. Machine learning techniques: general overview

Machine learning techniques can be broadly categorized into two primary groups: (i) pattern recognition techniques and (ii) regression/calibration models. In a nutshell, pattern recognition models further break down into two types: (i) unsupervised models (where *a priori* classification information for each object under examination is absent) and (ii) supervised/classification models (where the *a priori* classification of each object under examination is known). Well-known unsupervised methodologies, also referred to as exploratory analyses, include PCA [75], cluster analysis [76], t-distributed stochastic neighbour embedding (t-SNE) [77], and uniform manifold approximation and projection (UMAP) [78]. Conversely, supervised/classification modeling techniques can be subdivided into discrimination methods and class modeling techniques. Discrimination models, such as Fisher ratio [79], k-nearest neighbours (kNN) [80], logistic regression [81], naïve Bayes [82], linear discriminant analysis (LDA) [83], quadratic discriminant analysis (QDA) [84], and partial least squares – discriminant analysis (PLS-DA) [85], aim to distinguish objects within their respective classes by assessing features specific to each class. For instance, models like kNN evaluate distances between objects to estimate class boundaries, while LDA, QDA, and PLS-DA calculate new class boundaries in multidimensional space to separate objects within their classes. These models consistently yield outcomes related to object classification. Furthermore, they can also be categorized as probabilistic (parametric) methods because their classification algorithms rely on estimating parameters describing probability density functions, such as arithmetic mean, variance, and covariance, along with their respective distributions. Another set of supervised models for classification tasks relies on experience-based approaches. Specifically, these models employ iterative classification strategies, minimizing classification errors based on specific training sets used to construct the models. Traditionally labeled as ML techniques, examples include support vector machines (SVM) [4], random forest (RF) [86], eXtreme gradient boosting (XGBoost) [87], and ANN [88].

In contrast, class modeling techniques assess the similarity among objects within the same class. Consequently, different categories are modeled individually, allowing objects to be assigned to one, more than one, or even no category. Examples of class modeling techniques, also known as distance-based techniques, include soft-independent modeling of class analogy (SIMCA) [89] and unequal dispersed class (UNEQ) [90]. SIMCA and UNEQ classify objects based on different distance metrics, considering a measure of multivariate outlying placement of observations.

On the other hand, the primary goal of supervised regression/calibration modeling is to examine relationships between a matrix X of predictors/variables and one or more responses in a matrix Y. ML regression techniques include multivariate linear regression (MLR) [91],

principal component regression (PCR) [92], and partial least squares regression (PLS-R) [93], but also most of the models mentioned previously for supervised classification can be converted to solve regression tasks (such as, for instance, kNN, SVM and RF).

It's important to note that sometimes data cannot be structured into a matrix X but rather into an N-dimensional (N-way) array. This situation arises, for example, when considering information about sampling times or the opinions of different judges. A 3-way array, for instance, can be organized as follows: observations × parameters × sampling times. To explore such complex arrays, various N-way chemometric procedures can be applied, with parallel factor analysis (PARAFAC) [94] and Tucker3 [95] being the most popular. These models serve both classification and calibration purposes.

A concise description of all the mentioned models is reported in the Supplementary Material.

2.1. Current applications of AI in correlating analytical data and food properties

Artificial intelligence algorithms (particularly ML and DL models) emerged as a powerful tools in food science, especially by correlating analytical data with various food properties (*i.e.*, data mining in Fig. 1). In mass spectrometric and spectroscopic data, AI models can decipher intricate patterns associated with food composition, aiding in identifying specific compounds, additives, or contaminants [9]. By correlating this information with sensory attributes, nutritional content, or shelf life, researchers gain valuable insights into food products' quality, safety, and authenticity [96]. In particular, GC × GC-MS experienced rapid evolution under the boost of AI improvements. In data processing, the ROIMCR approach (regions of interest multivariate curve resolution), developed by the R. Tauler group [97], represents a sensitive and versatile technique to identify and quantify a wide range of metabolites in complex samples using comprehensive two-dimensional liquid chromatography (LC × LC) [98]. Specific ROIs are identified in the mass spectrum to highlight metabolites present at low levels, resolve overlapping peaks, discover new biomarkers and for the study of metabolic pathways [29].

In the discovery of new markers, multiple hypotheses testing is used to compare the levels of several metabolites between two sample groups and notice the significant differences, surpassing the limits of univariate testing. The Bayesian approach proposed by de Sousa et al. [99] explicitly incorporates the compositional constraint of metabolomic data, consisting in minor variations in numerous small-molecule metabolites within the investigated biological material, by representing them in tems of metabolite ratios. A new Bayesian parameter (b-value) was introduced, measuring the distance between a posterior distribution and the null distribution. The b-value can be used to rank the metabolites according to the strength of evidence against the null hypothesis (no significant differences) [100].

Also spectroscopic methods like Fourier transform infrared (FTIR) [101,102], Raman [103,104], and NMR [105,106], when used to investigate complex food compositions, develop their true potential when coupled with ML and DL algorithms [107,108]. Once trained on big data, ML models distinguish subtle spectral patterns enabling rapid and accurate predictions of critical food properties, such as moisture content, fat composition, and protein levels [109], certifying origin and quality across diverse food products, from agriculture [110] to beverages [111].

Spectroscopic imaging technologies like hyperspectral imaging (HSI) provide detailed visual insights into foodomics [112,113]. In the food industry, AI-driven imaging technologies pinpoint defects [114], contaminants [115], and even predict fruit ripeness [116]. For instance, in fruit sorting processes, hyperspectral images are scrutinized by AI models to assess sugar content and peel features, facilitating precise sorting and quality control [117,118]. AI integration into real-time monitoring and quality control systems on food processing lines revolutionized the food industry [119], by prompt signalling deviations from quality standards, thus minimizing waste and assuring reliable answers/results.

3. AI and comprehensive two-dimensional chromatography data processing

Artificial Intelligence algorithms are currently used in many steps of an analytical workflow that has C2DC as core platform. Signal pre-processing is primarily concerned with individual chromatographic signals. Its focus is to refine raw data from the instrument, dealing with issues like modulation-phase adjustment [17,18], peak detection [120,121], noise removal [122], correction of baseline drifts [122–124] and peak distortions [24]. Therefore, these algorithms are expected to be applied directly to the signals of each sample, ensuring the accuracy of individual peaks. Several AI tools have been developed to perform and optimize signal pre-processing strategies, enhance the quality of individual signals before any data integration or analysis, and address the intricacies within each chromatographic trace, preparing them for subsequent processing steps [7,20,123,125]. One fundamental aspect of signal pre-processing is the precise identification of peaks within the raw chromatographic data, commonly known as peak detection, whose goal is to recognize those peaks that signify distinct compounds or analytes separated by the chromatographic system. Peak detection algorithms, employing techniques such as thresholding, derivative-based methods, and wavelet transforms, are instrumental to the accurate peaks location, forming the foundation for subsequent analyses [126,127]. In parallel, chromatographic signals often exhibit a baseline drift, a phenomenon induced by temperature fluctuations or detector noise: baseline correction algorithms come into play to eliminate or reduce it [123,128]. A clear and stable signal is obtained by removing this unwanted variation, providing a solid foundation for further in-depth analysis. Furthermore, random or systematic noise might arise from electronic or environmental sources, obscuring the genuine peaks within the data and hampering accurate analysis. Effective noise reduction techniques, including algorithms like smoothing, sparsity correction, and wavelet denoising are employed to this purpose [21,122,129]. These methods selectively diminish the noise levels while preserving the integrity of the actual signal, ensuring a more straightforward and accurate representation of the underlying data.

2D chromatography offers new opportunities for data exploration and interpretation, due to the high degree of multidimensionality of the data arrays collected during the analytical run. For the scope of this review, the potential of AI in the different data processing approaches is analyzed in detail.

C2D chromatograms may be represented as digital images by rasterizing, *i.e.*, arranging the detector data values from individual modulation periods (or cycles) as a column of pixels (picture elements). It should be noted that when MS is adopted as the detector, each pixel corresponds to a spectrum, providing information on feature identity and amount, generating a 3D/4D data matrix [34]. Rasterized pixel columns are then arranged from left to right along the X-axis of a Cartesian plane according to ^{1}D retention time, while the ^{2}D data and related retention times are plotted from bottom to top on the Y-axis [130]. Chromatographic images can then be processed in a variety of ways, using multiple feature types and associated tools [34,130–133] as well as by applying image pattern recognition (PR) and CV tools [5,134,135].

Data arrays and fingerprints (*e.g.*, images, signals, textual data, or chemical features) can be effectively explored by PR to extract information about their chemical properties. Moreover, neural networks, ML or other AI algorithms can then support data classification into categories [136]. When applied to chromatographic data, PR drives sample discrimination and classification on the basis of the differential distribution of common chemical features or the presence of unique yet distinctive features [16,131,136].

Computer vision, a subfield of AI and computer science, extracts meaningful information from visual data (*e.g.*, digital images) and enables computer or systems to take actions or make recommendations [137]. CV applies techniques such as image processing, ML, and 3D image reconstruction [138]. Image PR and CV are, therefore, two strongly interconnected fields that share common algorithms and tools, and are possibly integrated into hybrid systems.

As hybrid systems, CV and image PR offer a new perspective in the "observation" of the compositional differences between samples (*i.e.,* augmented visualization [139]) which is more intuitive and immediate than any other classical approach applied in chromatographic data analysis. Their integration in dedicated software and commercial platforms facilitates comparative analysis of large sets of samples while reducing the computational time even for high information density data such as those collected with HRMS.

3.1. Image pattern recognition and computer vision applied to C2DC data: approaches and tools

Image PR algorithms for 2D peak patterns matching in C2DC were implemented in commercial software many years ago [140,141]. Inspired by fingerprint recognition technology used in forensics, image PR based on template matching considers 2D chromatograms as the sample's unique fingerprint. Fingerprint verification systems localize and extract *minutiae* information (*i.e.*, ridge endings and bifurcations) from digitalized images of human fingertips and then perform cross-matching with stored templates for identification [142]. In C2DC, 2D peaks or other kinds of features (*e.g.*, datapoint or regions – Fig. 1) are treated as *minutiae* features located over the 2D temporal space by tracking them across multiple images. When comparative analysis is aimed at samples discrimination or classification, it is referred to as chromatographic fingerprinting [34] which makes the process of sample *identitation* possible as previously conceptualized for 1D chromatographic fingerprinting [74].

Independently from the feature type adopted, chromatographic fingerprinting could also provide visual evidence of compositional differences between samples, by comparative visualization [143]. In this perspective, it can be accounted a CV approach.

3.1.1. Computer vision by datapoint features

Comparative visualization was one of the earliest approaches adopted to highlight compositional differences between pairs of chromatograms. As for other CV tools, it provides prompt evidence of pattern differences by comparing datapoint feature responses between pairs of chromatogram images. This pixel-by-pixel comparison could lead to erroneous conclusions when it is performed without any image/pattern re-alignment and transformation. Earlier applications based on datapoint features explored single-channel detector responses (*e.g.* flame ionization detector FID) with Fisher's *f* ratio and PCA [144]. Later, the same approach was extended to multi-channel detectors (*e.g.*, MS) by selecting specific *m/z* signals (mass-chromatograms) from the available spectra [31,145,146].

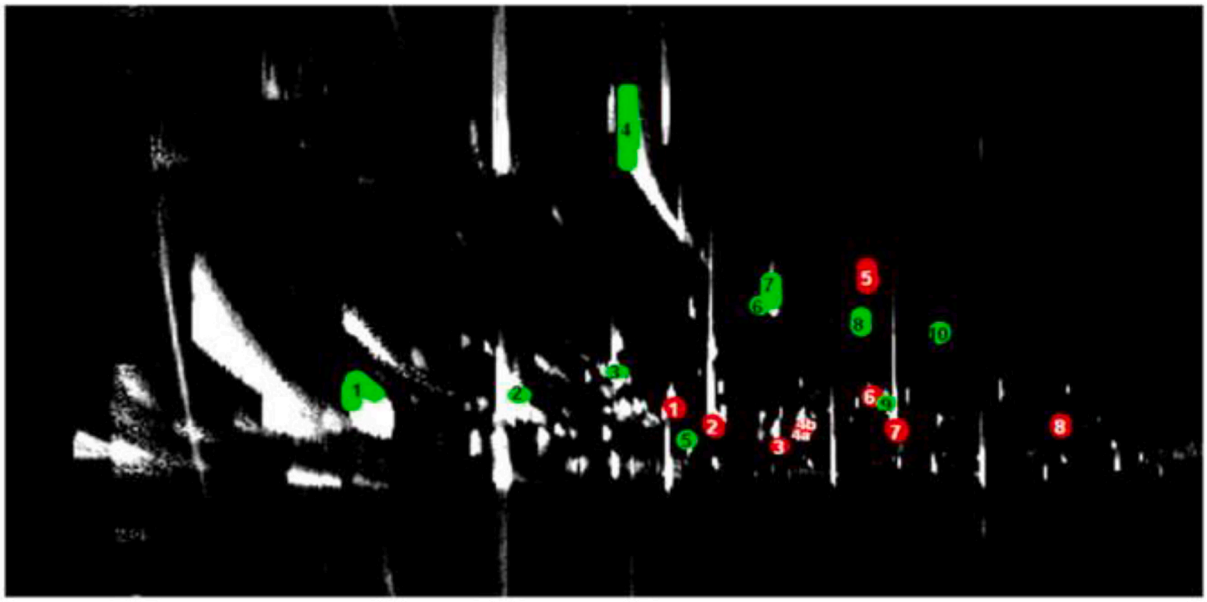
CV based on datapoint features without image re-alignment was adopted by Bordiga et al. [135] in a study focused on the evolution of the volatile fraction of "Asti Spumante" and "Moscato d'Asti" during aging. Based on Muscat grapes, both wines were screened by HS-SPME to comprehensively map odorants and non-odorants across 6 months of storage at different temperatures (5, 15, and 25 °C). Objective of the research was the detection of variations in the distribution of potent odorants and the identification of haloanisoles which impart off-flavors to the wine. To enable effective comparative visualization of the 2D pattern differences, authors developed a Mathematica™ software (Wolfram Research Inc., Champaign, IL, USA) carrying out a multi-step process consisting of a first graphical reconstruction of the contour plot from raw data recorded by the GC instrument. The pixels size of resulting 2D-chromatogram images was 251 × 673. In the second step, chromatograms alignment on the time domain was checked by locating the internal standard reference pixels. The authors did not detect any "dimensional shifts" in the GC chromatograms, therefore the alignment was not applied. On the other hand, a logarithmic scaling on the intensity domain was applied to better appreciate the different pixel contrasts in the graphical representation. In the last step, re-scaling was performed by arbitrarily choosing a *reference vs.* a *test* sample, to produce comparable chromatogram pairs. The scaling based on a pixel-by-pixel correction intensity dependent generated a differential image illustrated in Fig. 3 for Asti spumante wines. By colorization, it was possible to highlight pattern differences between *reference* and *test* chromatograms, one of which corresponds to a wine classified as *perfect*, the other showing off-flavors and classified as *imperfect*. Differences are visualized in green for analytes with an increasing trend in the *perfect* class, and red for components with decreasing trends in wines with sensory defects (*i.e., imperfect*).

As shown for the wine aroma application, datapoint features are comprehensive and provide the highest precision for fingerprint comparative visualization. However, many duplicative features per analyte might result in greater computational complexity while random shifts in retention times complicate consistent feature matching between pairs of chromatograms. These issues compromise the systematization of CV into decision-making processes; misinterpretation of compositional differences between sample pairs could produce wrong actions.

Vial et al. proposed a method named *the discriminant pixel approach*, combining peak features with datapoint features discrimination for comparative analysis of a large set of samples [147]. The application on tobacco extracts, rich in volatiles and odor-active compounds, was a challenging test bench for their tool completed on Matlab™ and C platforms. It consisted of a pre-processing step with background correction and raw data intensity normalization. Then, normalized signals were aligned on the temporal domain by dynamic time warping (DTW) applied with some constraints on the slope of the warping pipe and centering on the matrix diagonal using a windowing of 40 pixels. The temporal alignment was performed on each column of the matrix corresponding to each chromatogram as illustrated in Fig. 4. For each class of the three tobacco types investigated (*i.e.*, Burley, Virginia, and Oriental), one chromatogram was taken as a reference for the alignment. As the last step, the discriminant pixels were revealed by applying supervised PR models. Working in analogy to the Fisher Ratio method, first proposed by Pierce et al. [146], the authors were able to rank pixels corresponding to over-represented (or under-represented) compounds in each of the analyzed classes *vs.* all the others.

Very recently Ferreira et al. [10] proposed a comparative approach for the authentication of cachaça samples, a Brazilian distillate obtained from sugarcane, based on the detectable volatilome. In particular, the approach included a pre-processing of the raw total ion current (TIC) signals for response normalization and retention times fluctuations compensation. The latter worked on the shift of the absolute retention times in both temporal axes and pattern transformation by affine linear functions available in commercial software (*i.e.*, GC Image [148]). After re-alignment, the chromatograms were converted into grayscale images and imported in Matlab™ for unfolding into vectors. Samples authentication, by brand and by adulteration, was achieved by applying data-driven soft independent modeling of class analogies (DD-SIMCA) with good performances. In particular, the model specificity achieved 98% for cachaça adulteration and 100% for branding distinction; in both cases, model sensitivity was 100% with no false negatives found (0.05 significance).

A step ahead in making these hybrid systems (*i.e.*, combining image PR and CV) more specific was achieved by exploring the GC × GC-MS data array of regions and the corresponding peak region features. Higher specificity can be achieved by actively using the MS spectral signature during the comparative analysis or the CV. MS metadata can be exploited for discrimination - using the tile-based Fisher ratio analysis [149–151] - or effective re-alignment of the chromatographic patterns in



	% down			% up
1	isoamyl acetate (banana)	25	1	nerol oxide (green)	25
2	hexyl acetate (fruit)	15	2	ethyl octanoate (waxy)	25
3	linalool (flower, muscat)	15	3	2,6-dimethyl-1,7-octadiene-3,6-diol (bergamot)	20
4	2-phenylethyl alcohol (honey)	25	4a	geranyl ethyl ether (green)	20
5	4-terpineol (herbal)	15	4b	vitispirane (floral)	20
6	β-phenethyl acetate (honey)	15	5	decanoic acid (rancid)	30
7	2-phenylethyl formate (rose)	25	6	[A]1,2-dihydro-1,5,8-trimethylnaphthalene (kerosene)	25
8	2-phenylethyl propionate (floral)	15	7	ethyl decanoate (waxy)	25
9	ethyl dec-9-enoate (fruity)	15	8	ethyl laurate (waxy)	25
10	2-phenylethyl butanoate (musty)	15			

Fig. 3. Computer Vision approach based on datapoint features. Comparative visualization among bidimensional chromatograms of Asti spumante wines (perfect one *vs.* imperfect one). Pixels in green correspond to analytes with decreasing trends wile in red are represented those with increasing content. From Ref. [135].

the time domains, followed by features matching, as with the combined untargeted and targeted (*UT*) fingerprinting based on image PR algorithms [152–154].

3.1.2. *Computer vision by region features*

Regions are typically identified as small rectangular tiles overimposed on the contour plot of a 2D chromatogram. They were employed by Marney et al. [150] and Parsons et al. [149] to generate features for cross-sample analysis. Summing the *m/z* signal within a defined number of datapoints on the first and second chromatographic dimensions into a single tile resulted in some advantages with respect to datapoint feature approaches, including reduced computational time and better compensation for temporal misalignments. These studies showed that PR operated with region features (*i.e.*, tiles) increased the rate of true positive matches and decreased the chance of false positives. Whenever MS constraints imposed no selectivity, the same approach showed limitations both in cases where tiles are populated by multiple analytes (*e.g.*, tiles larger than 2D peaks footprint) and when the analytes were split across multiple tiles. Tiles (*i.e.*, bins) are sized according to the chromatographic performances (*e.g.*, peak widths) while also considering possible random fluctuations of the retention times in the two dimensions. To improve the performance of the tile-based analysis, a four-grid tile scheme is used, as illustrated in Fig. 5, with which each detected peak is likely to be included/captured within a tile rather than split into multiple tiles. The process, now implemented in the commercial software ChromaTOF™Tile (LECO, St. Joseph, MI, USA), overlaps a four-grid tile scheme over a chromatogram to enable signal binning on each tile on the basis of *m/z* values. The redundant hits generated by the four overlapped grid tiles are then removed by a "pinning and clustering" process, which is fully automated in the software. Once the "pin location" corresponding the 2D peak apex is determined, pins with similar retention in the 2D space are re-aligned and consolidated at the position of the pin with the highest intensity or response. The process is then repeated for all features and redundant hits are removed before peak centering. Details on tile-based analysis and its performances in case of signal saturation and co-elutions are provided in a recent review paper by Synovec and co-workers [155].

The tile-based approach was applied by Sudol et al. in a study focused on wine volatilome [156]. The geographical-based differences of "Grillo" wines from Sicily (Italy) were investigated by profiling the volatile organic compounds after HS-SPME sampling followed by differential-flow modulated GC × GC combined with time-of-flight MS (FM GC × GC-TOFMS). The analytes' discriminant for the five wine classes were discovered by tile-based Fisher ratio analysis. For the specific application based on the actual ^{2}D peak widths generated by the system, tile sizes were [7 s × 300 ms] corresponding to 10 modulations on the ^{1}D and 45 spectra on the ^{2}D, respectively. ANOVA test with a *p*-value threshold of 0.01 was applied to retain the most important

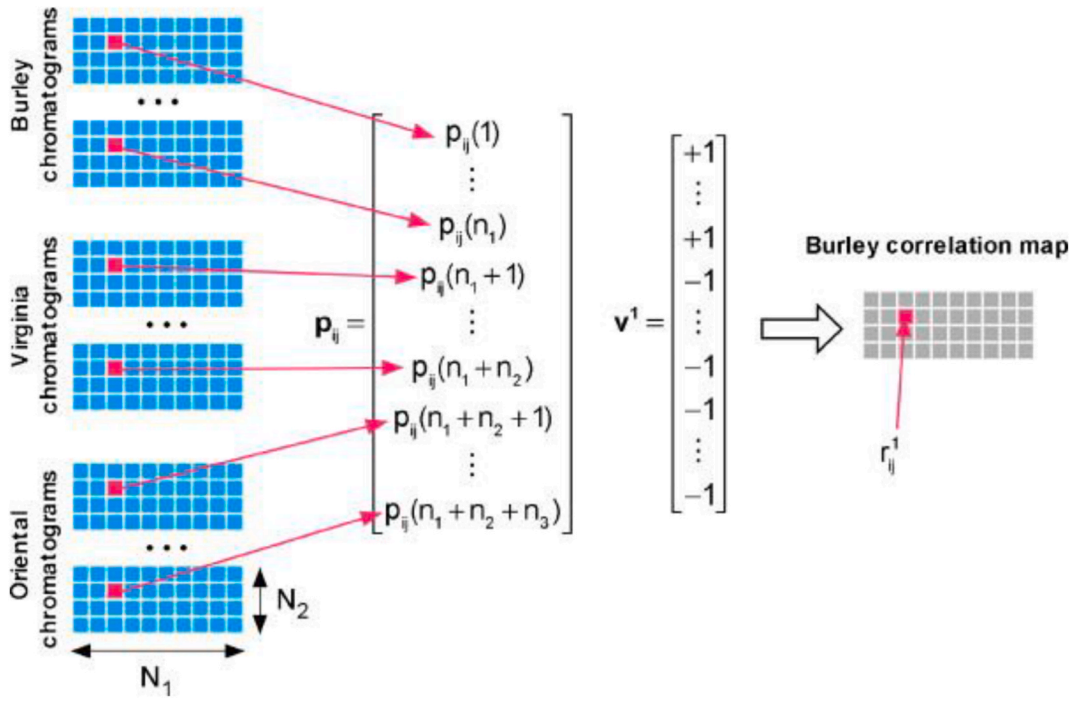


Fig. 4. Example of the computation for one of the pixels of Burley tobacco correlation map. The ability of a pixel to discriminate between classes was defined as Pearson's linear correlation coefficient; if the correlation is close to 1, the pixel corresponds to a compound over-represented in Burley tobacco extracts, and if it is close to −1, the pixel corresponds to a compound under-represented in Burley samples. Details are available in Ref [147] where the original figure was reported.

class-distinguishing analytes, which were then used for unsupervised analysis with PCA. The PCA revealed the natural clustering of wine samples according to their geographical origin, supporting the adoption of tile-based analysis in challenging applications where the components span over a wide dynamic concentration range in the samples.

In food safety applications, contaminants consisting of complex fractions of chemicals are challenging for 1D chromatography-based methods. GC × GC with its capability of generating rational retention patterns for homologs and structurally related compounds, has great potential in groups/classes quantification and fingerprinting, as it is required for some contamination sources. Mineral oil hydrocarbon (MOH) contamination [73] is an example where CV based on region features was successfully applied. Grob and collaborators adopted for the first time on-line and off-line GC × GC coupled to LC to detect mineral oil-saturated hydrocarbons (MOSHs) and mineral oil-aromatic hydrocarbons (MOAHs) in food samples [157]. By applying a medium polar × apolar column combination (OV-17 in the ^{1}D and PS-255-dimethylpolysiloxane in the ^{2}D) different classes of contaminants result separated within the 2D retention space with a retention logic driven by their volatility/polarity. Class distribution over the 2D space facilitates the identification of the contamination source [158]. Diagnostic patterns of contaminant mixtures were included in a contour (*i.e.*, region feature) which was stored as a template for comparative analysis. In this case, CV facilitated the identification of the source of contamination as long as it showed a unique yet distinctive fingerprint. Recently Ursol et al. tracked the MOH contamination in extra-virgin olive oil production by characterizing the MOSH/MOAH fractions fingerprint on process intermediates [159].

Although effective from a computational viewpoint, region features are challenged by retention times inconsistencies and co-elutions. Moreover, work-flows occasionally do not provide visual evidence of pattern differences, possibly preventing prompt diagnosis of sample similarities and differences, as for most of the datapoint features methods.

3.1.3. *Computer vision by peak-region features*

Peak-region features based on template matching have been introduced in image PR to overcome some malfunctioning of peak feature approaches in scenarios characterized by pattern misalignment and detector response fluctuations [160]. Likewise, peak features approaches, they achieve the one-feature-to-one-analyte selectivity, but also implicitly match the same peak region across chromatograms, a task that peak features do not necessarily accomplish in all patterns. Peak-region features provide a hybrid concept between regions and peaks by delineating one region in the 2D retention-times plane for each analyte peak detected in the data set. By precisely defining a 2D contour (*i.e.*, region) around 2D peaks footprint on the retention time plane, peak-regions are more specific than rectangular tiles and their re-alignment across chromatograms takes the benefit of the smart templates matching procedure [140].

Peak-region approaches were developed by Reichenbach et al. [160–162] and Schmarr et al. [163,164] with similar procedures. Raw data signal pre-processing (*i.e.*, rasterization, background noise subtraction, deconvolution, peak detection and integration) is the first step of an automated process applied to the source chromatograms of a samples set. After pre-processing, chromatograms are aligned on the temporal domain before their combination (fusion) to form a single composite chromatogram [165]. Then from 2D peaks detected in the composite chromatogram, a contour region is recorded and stored in a *feature template*. The feature template is then matched to all source chromatograms for geometrical remapping and transformation in the temporal domain. Once the process of feature template matching is completed for all chromatograms of a set, peak region features are tracked across all samples for a truly comprehensive mapping of the chemical diversity.

Since peak regions implicitly match all peaks in all chromatograms, they could be challenged by co-elutions and retention times variability. Whenever MS detection is available, co-eluting peaks falling within the same regions can be recognized by selecting quantitative/discriminant ions or resolved by incorporating deconvolution [153]. On the other hand, random or systematic retention-times variations are effectively

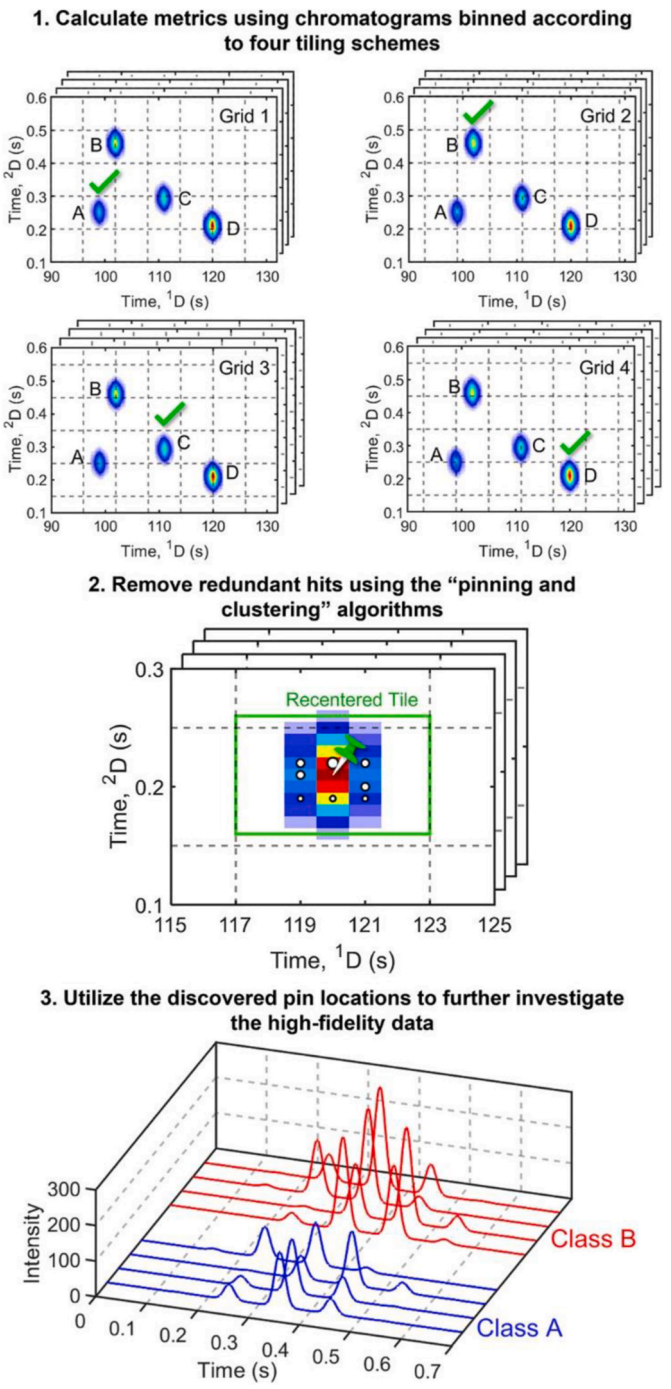


Fig. 5. Computer Vision by tile-based analysis. Details are discussed in the text. From Ref. [136].

addressed by geometric transformations in the retention-times plane [148,166,167]. Peak regions are implemented in a commercial software called "GC Image GC × GC and LC × LC" (GC Image, LLC, Lincoln NE, USA) by Smart Templates™.

Recently Caratti et al. proposed a novel approach referred to as *augmented visualization* to highlight pattern differences in butter samples analyzed along the production process [5]. The dataset consisted of 84 chromatograms (7 butter processing steps × 2 inocula × 2 biological replicates × 3 analytical replicates) plus additional quality control samples (QCs). Samples were grouped in seven classes as a function of the food processing stage: from raw sweet cream to cultured butter, then analyzed at four ripening stages (after 0-8-20-40 days). By automated UT fingerprinting available in GC Image Investigator™ (GC Image™, GC Image LLC), the chromatograms were re-aligned by feature template objects. This alignment was at first achieved within chromatograms belonging to the seven classes, whose workflow is illustrated in a schematic diagram depicted in Fig. 6. The six chromatograms (2 biological replicates × 3 analytical replicates) were pre-processed before comprehensive pair-wise peak matching in each class. Reliable registration peaks (n ≈ 1000 per class), peaks that were matched in at least 50% + 1 of the chromatograms, were used as anchor points for template matching, image transformation, and registration. A composite chromatogram (Class Image) was then generated (last operaton of Step 1 – Fig. 6) by combining all registered images (*i.e.*, all analytical runs for samples belonging to the same class) in a single image. The Class Images were then matched over the reliable template and graphic objects (*i.e.*, peak region features) generated and included in a *feature template* used later to match, transform, and align all Class Images chromatograms before their fusion into a cumulative Reference Class Image (right side of Fig. 6) chromatogram. The process generates a feature template collecting all reliable peaks from Class Images and delineating the contour of all detected peak regions. A comprehensive alignment and registration of Class Images was possible; unique identifiers for peak and peak regions features were assigned enabling effective cross-comparison of features responses across many chormatograms (single chromatograms or Class Image chromatograms). By solving the temporal misalignment issue, the comparative visualization is facilitated and augmented visualization (AV) is achieved. AV refers to "*computational techniques for visualizing what cannot be seen with raw image input*" [139]. With the CV based on UT fingerprinting process, comparative visualization was directly linked to feature metadata and resulted *augmented* by molecular information that gives access to higher-level information about the phenomenon under study.

CV was used by Stilo et al. to highlight patterns of volatile organic compounds diagnostic of some spoilage phenomena in raw halzelunts (*Corylus avellana* L.) [9]. Researchers analyzed samples selected among different cultivars, geographical origins, shelf-life and storage conditions and characterized by perceivable sensory defects (*mouldy*, *rancid, solvent-like, stale*, and *general unpleasant notes*). The workflow generated composite Class Images from samples grouped by sensory qualification of spoilage with an operative procedure similar to that proposed by Caratti et al. [5]. The results were validated against a chromatographic UT fingerprinting workflow based on image PR, providing proof of evidence of CV effectiveness and robustness in complex patterns analysis.

Classical CV techniques can be used to realign chromatograms with significant retention time shifts. Geschwender et al. demonstrated an automated two-step approach to alignment of chromatograms from samples of cocoa acquired on two different instruments, *i.e.,* a differential-flow modulated GC × GC-qMS (Fig. 7A left chromatogram) and a cryogenic-modulated GC × GC-TOF MS (Fig. 7A right chromatogram) without translation of the chromatographic conditions [53,168]. The first step, coarse alignment, aims to establish an initial match in scale and location as illustrated in Fig. 7B. The enhanced correlation coefficient (ECC) is used, which is an image similarity metric that is robust to photometric distortions [169]. Multiscale image pyramids [170] are used in conjunction with the ECC to extend the range of ECC optimization search. The second step (Fig. 7C), fine alignment, focuses on achieving peak-to-peak retention time correspondence. It initializes peak matching algorithms from the coarse alignment, and uses high-order global or local transform functions derived from matched peaks.

Examples provided here demonstrate how strategic is the adoption of AI tools at the data processing level and suggest that hybrid approaches which combine different AI concepts (*e.g.*, image PR and CV) could result also very intuitive and easily accessible for prompt identification of compositional differences that originate samples discrimination and classification.

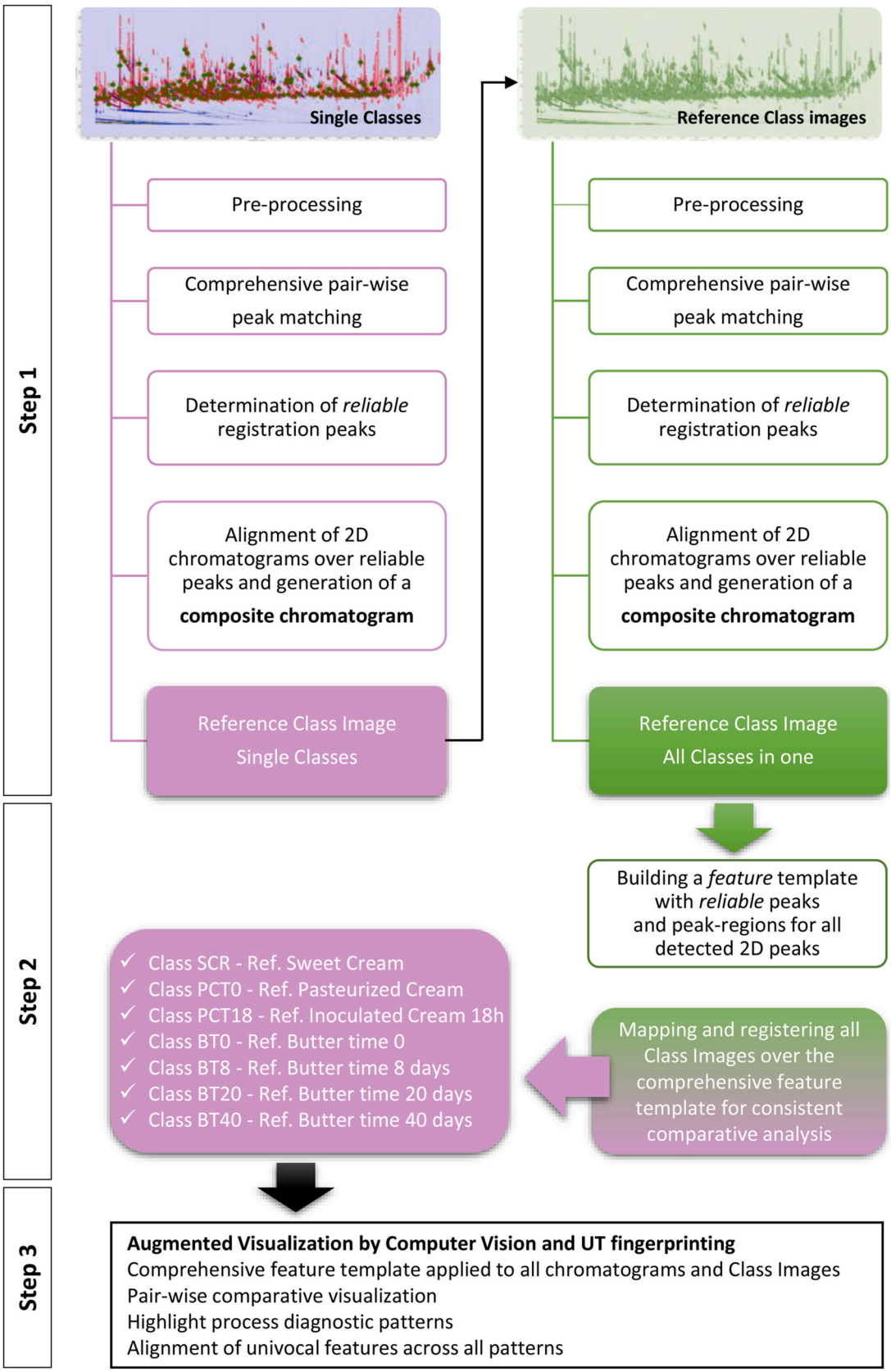


Fig. 6. Schematic diagram of the computer vision approach based on image pattern recognition and images fusion. Details are discussed in the text. From Ref. [5].

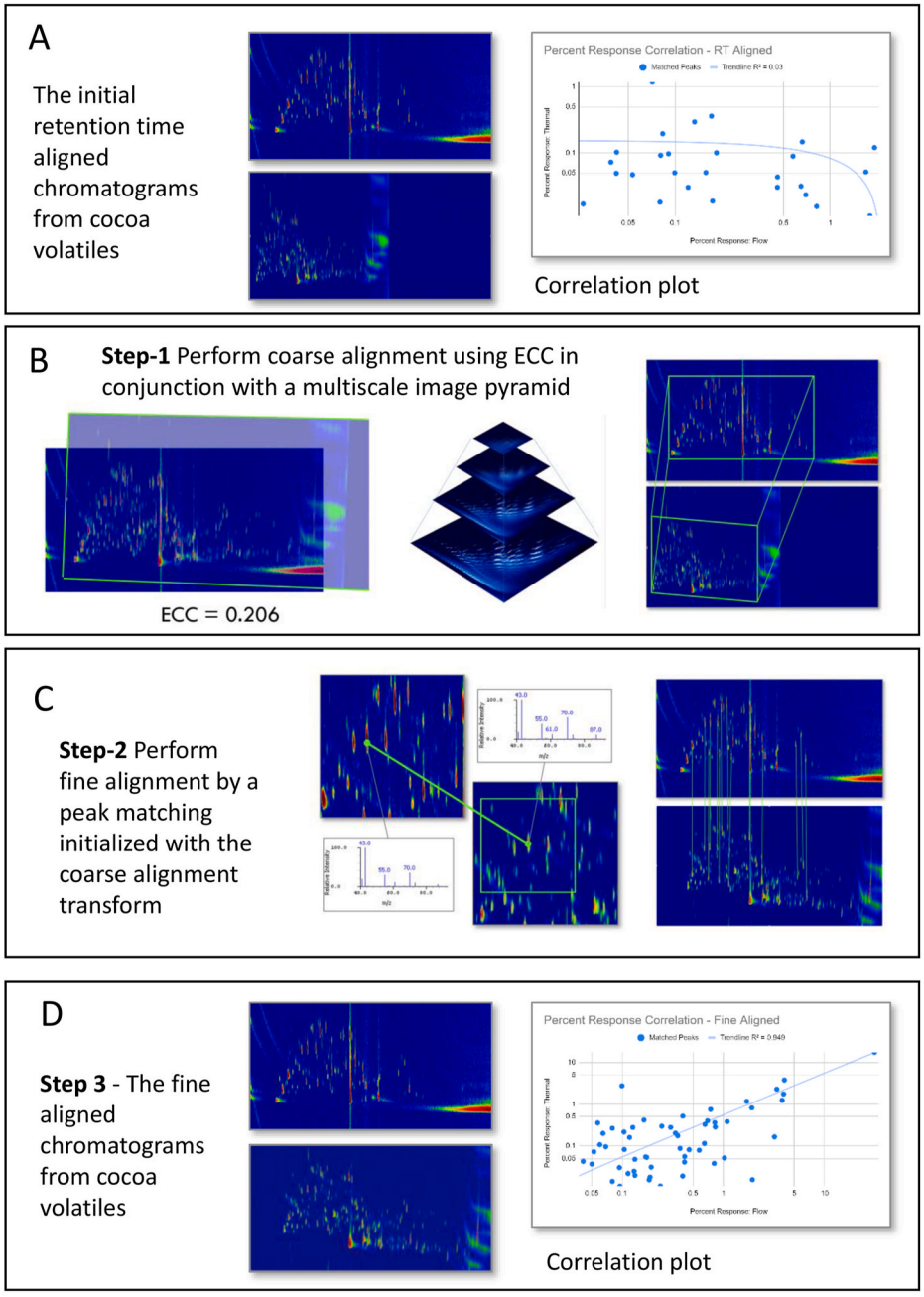


Fig. 7. Schematic diagram illustrating the workflow for chromatogram images re-alignment in presence of severe retention-time shifts. Cocoa volatiles patterns were analyzed with a differential-flow modulated GC × GC-qMS (upper chromatogram **7A**) and with a cryogenic-modulated GC × GC-TOF MS (lower chromatogram **7A**). Re-alignment is obtained by enhanced correlation coefficient (ECC) and multiscale image pyramids. Details are reported in the text. Details on cocoa volatiles profiling are reported in reference literature [53,148].

4. Artificial intelligence smelling based on sensomics: concept and tools

In this last section, the concept of *AI smelling* based on sensomics is discussed as it was conceptualized in an integrated workflow thanks to the unique features of GC × GC [71]. The food aroma alone contributes about 80% of the whole flavor [69]; it is generated by the interaction of odorants (*i.e.*, odor active volatiles) with odorant receptors (ORs) located in the olfactory epithelium. Potent odorants, even when present at trace and sub-trace level (mg/kg or μg/kg), activate a complex pattern of signals (*i.e.,* the Receptor Code) which integration by the nervous system produces olfactory perceptions [69]. The odor code, also referred to as *aroma blueprint* [69], evokes the unique identity traits of a food enabling its recognition and discrimination among others. To identify the molecular code of olfaction, sensomics has established a protocol that combines multiple, discrete steps aimed at isolating, extracting, and concentrating odor-active compounds before their qualification (odor characterization and description), accurate quantification and validation in aroma recombinates [171].

GC × GC became a central analytical tool for sensomics due to its separation power and enhanced sensitivity compared to 1D-GC or heart-cut 2D-GC. Marriott and co-workers designed and realized many *multi-multidimensional* platforms [172–174] implementing efficient separation of volatiles with olfactory screening by GC-olfactomerty (GC-O). Various systems enable to switch between GC × GC and targeted MDGC [175] to operate in critical regions of the separation space with the maximum chromatographic resolution. Although attractive, the direct coupling of GC × GC with olfactometry (GC × GC-O) is quite challenging due to the very narrow bands produced by the ^{2}D separation. D'Acampora et al. [176] explored the possibility of odor fingerprint acquisition by GC × GC-O/MS in the field of fragrance analysis. Their attempts remained pioneering as the complexity of execution is limiting. The sense of smell and neuronal integration of signals in humans requires a physiological recovery period that is not compatible with the speed and resolution typical of GC × GC.

On the other hand, off-line GC-O screenings open to some opportunities. They can drive or focus fingerprinting toward odor-active elution regions of the 2D chromatogram supporting ML to effectively discriminate samples based on features likely correlated to peculiar olfactory qualities. An example was provided by Gabetti et al. who investigated the unique aroma traits of Piemonte peppermint essential oils by combining GC-O, performed as aroma extract dilution analysis (AEDA), with GC × GC-TOF MS and variable ionization energy (Tandem Ionization™) [177]. By targeting specific regions of the chromatographic space with intense *creamy* and *sweet* notes, still perceivable at higher dilution factors, the classification performances of PLS-DA models improved. Authors argued that an AI-smelling tool based on GC × GC would be capable of making decisions driven by samples' sensory features without the use of a human sensory panel.

Nicolotti et al. [71] developed a sensomics-based expert system – SEBES capable of predicting food aroma features by accurately quantifying key-aroma compounds in a simplified methodological workflow. As a proof-of-concept supporting the SEBES effectiveness, the accurate quantification of about 100 compounds out of the 226 key-food odorants (KFOs) listed by Dunkel et al. [69] was achieved and their conversion in odor activity values (OAV; ratio of concentration to odor threshold) was demonstrated. GC × GC was fundamental to achieve an extended dynamic range of the method covering the actual concentration range of KFOs in real-world samples. SEBES validation was compared with reference sensomic protocol [49]; in particular, accuracy was very satisfactory with a maximum quantification error of ±20%. As a conclusive remark, the authors stated that "*it was successfully shown that it is possible to characterize key food odorants with one single analytical platform and without using the human olfactory system, that is, by artificial intelligence smelling*".

The AI smelling concept was further expanded to enable aroma blueprint prediction in different food products. For extra-virgin olive (EVO) oil, blueprinting was possible by exploiting the quantification features of the flame ionization detector (FID) with the application of predicted relative response factors (RRFs) based on combustion enthalpies [15,38,166,178]. Methods designed for accurate quantification of volatiles with multiple headspace extraction (MHE) combined with SPME could replace traditional extraction/distillation procedures speeding up the sample preparation step and making it fully automated [171,179]. The system realized with a differential-flow modulator with reverse-inject dynamics, and set for parallel detection by MS and FID, extends the quantification capabilities to all detectable volatiles showing HS linearity (i.e., without saturation of the HS) with benefits for high-throughput screenings as those supporting industrial research.

Recently, the AI smelling machine concept was integrated into a decision-making tool for confectionery industry [37]. The analytical method, completed by automated MHS-SPME combined with GC × GC-MS/FID, was applied to accurately quantify key-aroma compounds, rancidity and spoilage markers in premium quality hazelnuts (*Corylus avellana* L.) over 12 months of method application. By accurate quantification, chemical quality traits for incoming materials were confidently assessed with results transferability over time and across laboratories supporting objective decisions and reliable prediction of sensory features (*i.e.*, AI smelling based on sensomics), geographical origin of samples, and storage time.

5. Concluding remarks

Artificial Intelligence concepts based on image PR and CV have been successfully applied to advance multidimensional data array interpretation to derive information and predict samples' properties. The compositional complexity of food challenges conventional data processing approaches, but the multidimensional nature of C2DC data offers unique possibilities for CV and augmented visualization. Robust AI tools are capable of (i) compensating for retention-time shifts that cause image distortion, thereby facilitating comparative visualization and related strategies; (ii) specifically targeting *unknown-knowns,* actively exploiting mass spectral signatures in the presence of co-elutions and misalignments; (iii) identifying the source(s) of contamination in complex mixtures by analysing chromatographic fingerprints; and (iv) predicting aroma signatures by systematically identifying key food-odorants in presence of interferents.

The most powerful systems are those integrating multiple concepts and facilitating analyst access to embedded information using intuitive tools available in commercial software platforms. In-depth exploitation of the information content of every single analysis from C2DC benefits from AI and soon we expect further advancements through the adoption of generative learning which could explore the full information content from different sources and link it to additional, not necessarily correlated, properties [180].

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CRediT authorship contribution statement

Andrea Caratti: Writing – review & editing, Methodology, Writing – original draft. **Simone Squara:** Writing – review & editing, Writing – original draft, Methodology. **Carlo Bicchi:** Supervision, Writing – review & editing. **Erica Liberto:** Writing – review & editing. **Marco Vincenti:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing. **Stephen E. Reichenbach:** Writing – review & editing, Software, Methodology, Conceptualization. **Qingping Tao:** Writing – review & editing, Software, Methodology. **Daniel Geschwender:** Writing – review & editing, Software, Methodology. **Eugenio**

Alladio: Writing – review & editing, Writing – original draft, Supervision, Conceptualization, Methodology. **Chiara Cordero:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Data availability

No data was used for the research described in the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.trac.2024.117669.

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