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Solutions are solutions, and gels are almost solutions*

Hervé This[1,2,‡]

[1]INRA, UMR 1145, Group of Molecular Gastronomy, 16 rue Claude Bernard, 75005 Paris, France; [2]AgroParisTech, UFR de chimie analytique, 16 rue Claude Bernard, 75005 Paris, France

Abstract: Molecular gastronomy is the scientific discipline that looks for mechanisms of phenomena occurring during dish preparation and consumption. Solutions are studied because most foods, being based on animal and plant tissues, are gels, with a liquid fraction and a continuous solid phase. This is why food can be studied in situ using liquid NMR spectroscopy in the frequency domain (isq NMR). Using such tools, processes of the kind F@M $\rightarrow$ F′ @ M′ (where F stands for the food matrix, M for its environment, and @ for inclusion) were investigated for various processes as classified using the complex disperse system/nonperiodical organization of space formalism ("disperse systems formalism", DSF). As an application of these studies, "note by note cuisine" was promoted as a new paradigm for culinary activities.

Keywords: analytical chemistry; aqueous solutions; bioactivity; colloids; disperse systems formalism; food chemistry; molecular gastronomy; NMR.

Before considering a general framework for the description of the bioactivity of physical systems, this article will discuss how this topic is central to the scientific discipline called "molecular gastronomy". It will also be shown that this discipline is part of physical chemistry, and that a relationship exists between science and its applications, in particular, technical applications, through the activity of technology. A novel method for the exploration of bioactivity and "matrix effect" will be discussed as well. As a conclusion, the novel idea of "note by note cuisine" is presented in both scientific and artistic contexts.

SCIENCE AND FOOD SCIENCE

The creation of a new scientific field such as molecular gastronomy (definition: "looking for the mechanisms of phenomena occurring during dish preparation and consumption"), in 1988 [1], was an opportunity to discuss its precise content and also its relationship with other existing fields of science (chemistry, physics, biology, etc.).

Before explaining this, the intellectual status of the "mother science", chemistry, needs to be considered. Indeed, in past centuries, chemistry evolved from technique to technology and to science [2]. Even today, chemical science is not entirely separated from chemical technology... as the name of IUPAC makes it clear: it contains the expression "applied chemistry", which is strange, because if

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‡E-mail: herve.this@agroparistech.fr

chemistry is a science (*philosophia naturalis* [3]), "pure chemistry" is a pleonasm, and "applied chemistry" is no longer chemistry, and does not deserve this name. Technical activities called "chemical arts" were indeed at the origin of the development of chemistry (below, we are using this word in order to designate chemical science only). For example, concerning drugs, in 1560 the French physician Ambroise Paré introduced the word "emulsion" (from the Latin word *emulgere*, "to draw milk") to describe milky systems, which were indeed often colloidal dispersions of fat droplets in an aqueous solution [4]. Concerning food, in 1783 Antoine-Laurent de Lavoisier published the result of his technological studies (he was interested in the application of his results, i.e., feeding people in hospitals) of aqueous solutions obtained by thermal processing of muscular tissues of animals in water ("meat stock") [5]; in the article giving his results, he acknowledged that he was following Claude Joseph Geoffroy, who had done a similar study, although more scientific in nature, as early as 1730 [6]. Concerning metallurgy, Michael Faraday devoted a lot of work to steel alloys with James Stodart around 1830 [7]. In still another field, the studies of soaps and candles by Michel-Eugène Chevreul led him not only to the discovery of triglycerides constitution, but also to a new way of making candles (patent with Louis-Joseph Gay-Lussac) [8]. Concerning dyes, William Henry Perkin obtained mauvein in 1855 while trying to make quinine from aniline [9], etc.

In most early studies of chemical arts, and for food in particular, science (it is proposed that we use here the definition: looking for the mechanisms of phenomena using the "scientific" method [10]) was mixed with technology (it was rightly recognized by the Belgian Academy of Sciences to be: studying techniques in order to improve them [11]), but slowly the differences between the two fields appeared more clearly.

For food also, there was and still is much confusion between science and technology. But first, what is "food" really? One dictionary definition is: "any substance that can give to living beings the elements necessary for their growth or for their preservation" [12]. According to this definition, raw plant or animal tissues should be considered as food as well as dishes; but this option would be confusing, as human beings very seldom eat non-transformed tissues or natural products [13]. Raw materials are transformed, so that chemical and physical changes determine the final composition of all food as well as its "bioactivity" (we propose to call "bioactive" any compound having sensory effects, as well as nutritional value, possible toxic effects, etc.). During food preparation, plant or animal tissues are at the very least washed and/or cut, and most foods are thermally processed. Even for a carrot salad, which does not involve thermal processing, there is a big difference between the raw product in the field, and the preparation that is consumed, i.e., grated carrots in a plate, because cutting the tissue triggers enzymatic reactions at the surface [14] and also because compounds can be exchanged between the dressing and the plant tissue. This analysis leads to the first conclusion that reagents and products of "culinary transformations" should not be called food indifferently; the former are food ingredients, while only dishes are food.

Making a clear distinction between science and technology is particularly important for molecular gastronomy because there is much confusion between science and cooking, and also because the public unduly fears "chemistry in its plate" [15]. First, let us observe that Lavoisier was indeed right to write, in his article about meat stocks, that the two fields of science and technology "do not meet": making stock is not to be confused with studying it. Later, the French chemist and biologist Louis Pasteur, who was both successful in science and technology, was also a fierce opponent to the expression "applied sciences" [16]. This led us to consider that there is a key difference between the science *based on* food transformations and the technology *of* food transformations. The technology of food is not the same as the scientific study of phenomena occurring during culinary transformations, what we named "molecular gastronomy". Let us add that expressions such as "culinary science" [17] are wrong, strictly speaking, except if "science" means "knowledge" in general, rather than a science of nature. Also, there are no "scientific chefs", contrary to what is sometimes published in the media since applications of "molecular gastronomy" have been popular.

Finally, are there different sciences which would justify the plural in "food sciences", so that molecular gastronomy could be one of them [18]? Yes, because whereas the "experimental" (or "hypothetico-deductive", or "scientific") method is common to all sciences of nature, objects can be different, and "models" cannot be extended to other scales than those for which they were obtained. Toxicology and nutrition, for example, are different from physical and chemical studies of food phenomena. And finally, molecular gastronomy is one food science in particular, with relationships to chemistry, physics, and biology [19].

MOLECULAR GASTRONOMY IS 25 YEARS OLD

Molecular gastronomy had ancestors [20], as many chemical phenomena occurring during culinary transformations had been studied before its creation in 1988. However, it is a fact that in the 1980s food sciences had neglected culinary processes. For example, textbooks such as the classic *Food Chemistry* [21] contained almost nothing on culinary transformations (it is still true in the last, more recent, edition): less than 0.5 % of the chapter on meat described "culinary phenomena" (meat shrinkage during heating because of collagen denaturation); most of the chapter described meat composition and structure, or industrial products (sausages, meat extracts…); and the same textbook contains nothing about thermal processing of wine, in spite of the large use of "cooked wine" in culinary activities (48 % of French classical sauces include wine [22]).

Probably because culinary transformations are complex and also because the food industry did not fund studies outside its field, food science drifted slowly toward the science of ingredients on one hand and food technology on the other hand, neglecting phenomena which occur during the making of cassoulet, goulash, hollandaise sauce, etc. It was considered an eccentricity when a paper on Béarnaise sauce was published in a scientific journal in the 1970s [23]. This is why the late Nicholas Kurti (1908–1998) [24], former professor of physics in Oxford, and I decided that a "new discipline" had to be introduced.

The situation at that time was more or less the same as for molecular biology some decades before [25]. As what Kurti and I had in mind was more or less the same, but concerned another field of knowledge, the name "molecular and physical gastronomy" was first chosen. The choice of "gastronomy" in this title was obvious, as it does not mean "haute cuisine" but rather "intelligent knowledge of whatever concerns man's nourishment" [26]. When Kurti died in 1998, the name was abbreviated to "molecular gastronomy", and Kurti's name was given to the international meetings of the discipline.

The interest of this new discipline was and remains scientifically clear: if one wants to discover new phenomena or new mechanisms, the exploration of a new field is probably a safe choice. Of course, as always when new knowledge is produced, there is the possibility of making important technological applications, and indeed since the year 2000 "innovations" based on molecular gastronomy have been introduced every month (frequently, names of famous chemists of the past are given to new "dishes") [27].

However, the initial program of the discipline was inappropriate because it mixed science and technology. Even as late as 2001, in an article published in *Angewandte Chemie* [28], it was written (after earlier discussions with Kurti) that molecular gastronomy had five goals: (1) explore old wives' tales; (2) explore recipes; (3) introduce new tools, ingredients, and methods into the kitchen; (4) invent new recipes; (5) use the appeal for food to show that chemistry is wonderful [19]. It was later recognized that if goals 1 and 2 are scientific, goals 3 and 4 are technology, and goal 5 is communication. At the same time, it was realized that any recipe has three main parts: a technically useless part, a "definition", and "culinary precisions", the last term applying to technical information that is not absolutely needed to make the dish (culinary precisions include old wives' tales, proverbs, tips, methods…) [29]. Then, some years later, it was understood that "cuisine" involves an artistic activity of fundamental importance: a cheese soufflé is not consumed (and then it is not really "food") if the flavor is not appropriate for a specific consumer, but this appreciation is a question of art, not of technique. It was recognized that a "social link" is also very important in culinary activities: a soufflé is not "good" if it is

thrown at the face of guests. All this led to the proposal for a new program for molecular gastronomy: (1) model recipes ("culinary definitions"); (2) collect and test "culinary precisions"; (3) explore (scientifically) the art component of cooking; and (4) explore (scientifically) the "social link" of cuisine [30].

BIOACTIVITY AND MATRIX EFFECT

With this clearer scientific program, it is convenient to come back now to the question of "bioactivity". Most formulated products, and in particular food, are systems (often of colloidal nature [31]) which display "bioactivity": this means that they can exchange "bioactive" compounds (bc), i.e. compounds that have the potentiality to interact with biological receptors. In some cases, a physical binding is needed to trigger physiological effects (olfaction, taste, trigeminal effects...) but for vision the effect is indirect, and for receptors inside tissues, a transfer into the blood system is needed, sometimes after modifications during digestion. Here let us remark that even compounds that would be trapped by the swallowed bits of food are encompassed by the given definition, such as tasty ions adhering surfaces, complexed salivary proteins on some compounds in food; after all, absorption is a negative release.

Bioactivity is different from bioavailability, a widely recognized concept [32,33], defined by the Food and Drug Administration as the rate and extent to which the active substances or therapeutic moieties contained in a drug are absorbed and become available at the site of action [34]. Absolute bioavailability is defined as the quantity and rate that characterize the transfer of the drug in blood, and relative bioavailability measures the quantity and speed that characterize the transfer of a drug when many forms are compared to a reference form, for example. This definition also applies to active substances (nutrients) present in foods: in nutrition science, it is the proportion of a nutrient that is absorbed by the body. However, even today, nutrient bioavailability is an important but often imprecise concept associated with the efficiency of absorption and metabolic utilization of an ingested nutrient [35]. Another term that is commonly used is bioaccessibility, which is defined as the amount of an ingested nutrient that is available for absorption in the gut after digestion [36]. Thus, it is not equivalent to speak of bioavailability or bioaccessibility. If the amount of recovered nutrient after digestion is of relevance, then the term to use is "bioaccessibility". On the other hand, bioavailability of nutrients is usually measured in the blood plasma of humans (in vivo assay), so factors such as individual variability, physiological state, dose, and presence of other meal components come into play [37]. Although all of a nutrient is potentially bioaccessible, in reality almost no nutrient is totally converted during digestion into a potentially absorbable form. In almost every case, bioaccessibility and bioavailability of a nutrient are governed by the physical properties of the food matrix, which affect the efficiency of the physical, enzymatic, and chemical digestion processes [38].

With bioactivity, the main goal is not nutrition, but to describe the exchange of bc between food systems and their environment. As molecular gastronomy seeks to characterize and understand the effect on how food exchanges bc, we define the first notion using quantitative parameters such as "absolute bioactivity" (B) for the description of the total release of bc over time, and "dynamic bioactivity" (b) for the time course release of bc from food systems.

Let us start from a simple case of a food system F containing a mass m of a bc C. Concerning absolute bioactivity, a difference is introduced between "potential absolute bioactivity" (B_p) and "actual absolute bioactivity" (B_a) because the presence of a bc in a matrix is not a guarantee that all the molecules of the bc will be able to leave the matrix and to interact with receptors. We propose to call "potential absolute bioactivity" the possibility to bind to receptors, and to measure this property as the mass of bc present in the food matrix. On the other hand, "actual absolute bioactivity" is the real quantity (mass) of bc that would be released between the onset of release and time infinite; of course, $0 < B_a < B_p$.

This definition goes along with a definition of an "absolute matrix effect" E, defined in such a way that $E = 0$ when $B_a = B_p$ (no effect of the matrix on the release of the bc), and $E = 1$ when $B_a = 0$ (the matrix completely traps the bc) [39–41]. A simple definition can be (if the matrix effect is chosen as a dimensionless parameter):

$$E = \frac{\left(B_p - B_a\right)}{B_p} \tag{1}$$

In general, the food system F is an object of complex shape inside an environment M. Let S be its surface, and let t be the contact time of F and M. A mass flux (mass exchanged through the surface S by time unit) can be defined algebrically as

$$\frac{dm(t)}{dt} = \int\int \mathbf{j}(t)\cdot\mathbf{ds} \tag{2}$$

where **ds** is an area element through which a quantity $\mathbf{j}(t)$ of bc is exchanged between the food system F and its environment, the integration being taken over the entire surface S of F. Using this definition, the released quantity of bc is equal to

$$B_a = \int \frac{dm}{dt} dt \tag{3}$$

where the integration is taken between the contact time considered 0 and $+\infty$.

Using this definition, we can now consider a definition of dynamic bioactivities. When the matrix effect is of physical nature (no molecular modification of bc during the transfer), a dynamic bioactivity can be defined for each bc. Let us first observe that one could calculate dynamic bioactivity as the variation of the released quantity as a function of time, but the new parameter would not have the same dimension as absolute bioactivity. This is why we propose to define dynamic bioactivity after "releasability" $l(t)$

$$l(t) = \frac{dm(t)}{dt} \tag{4}$$

Using this function, dynamic bioactivity $b(t)$ can be defined as

$$b(t) = \int l(t)\, dt \tag{5}$$

where integration is taken between 0 and t. Using this definition, dynamic bioactivity for $t \to +\infty$ is equal to the actual absolute bioactivity B_a.

Whereas dynamic bioactivity describes the exchange of the bc as a function of time, the dynamic matrix effect $e(t)$ must describe the variation of the rate at which the bc is released (because of matrix). For the same reasons as before, the dynamic matrix effect has to be a dimensionless function of time, and a reference has to be chosen. It is proposed that the dynamic matrix effect is nil when no matrix is present, so that releasability $l(t)$ has to be compared to releasability without matrix (pure diffusion)

$$e(t) = \frac{f(t) - l(t)}{f(t)} \tag{6}$$

where $f(t)$ is releasability without matrix (simple molecular diffusion in the considered environment). Of course, in order to determine this function, one has to consider an object having the same shape as the food system F (same surface), with

$$f(t) = \int\int \mathbf{j}(t)\cdot\mathbf{ds} \tag{7}$$

the integration being taken over the entire surface S.

As the physical matrix effect describes the molecular interaction of some bc with the matrix, the "chemical matrix effect" is used when some molecular transformation occurs between a bc and the matrix, during culinary transformations (thermal treatment, i.e., indeed "cooking", being a particular case of such transformations). In order to define a chemical matrix effect, one considers a bc that is

modified during the F–M interaction. Chemical processes reduce the quantity of released bc. The absolute matrix effect E describes both the chemical as well as the physical matrix effects, but the dynamic matrix effect only indicates an influence of the matrix on the overall release of bc, without taking into account the molecular transformations. In order to introduce a chemical dynamic matrix effect, one has to make assumptions on the independence of the compounds and their reaction products. When chemical transformations occur, the release of bc is reduced [releasability $l'(t)$ instead of $l(t)$] by processes which make a quantity $r(t)$ (per time unit) disappear. One can write

$$l'(t) = l(t) - r(t) \tag{8}$$

Here again, the dynamic chemical matrix effect $e_c(t)$ an be introduced as a dimensionless function as

$$e_c(t) = \frac{r(t)}{l(t)} \tag{9}$$

Using this definition, the chemical dynamic matrix effect is nil when there is no chemical transformation at any time, and equal to 1 when the bc is entirely transformed within the matrix [$r(t) = l'(t)$]. Depending on the experimental situations, the other definition can be used

$$e_c(t) = \frac{l(t) - l'(t)}{l(t)} \tag{10}$$

BIOACTIVITY AND DSF

Bioactivity being defined, one of the main issues of molecular gastronomy (and other scientific disciplines) can be investigated, i.e., the relationship between the modifications of the structure of food and the actual bioactivity of food (Fig. 1). In order to study this question, a formal description ("disperse systems formalism", DSF) of the structure of food systems was proposed [42]. Recently, modifications of this formalism were introduced as shown below.

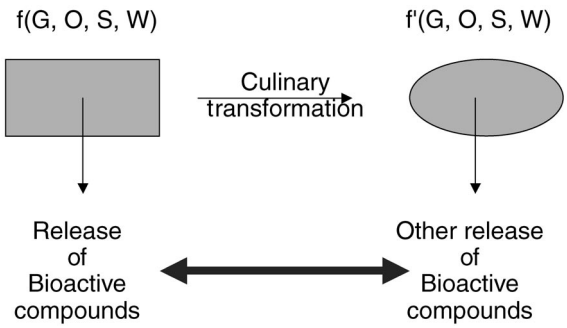

Fig. 1 One issue of molecular gastronomy is to find a relationship between the bioactivity changes of food systems when these systems (they can be described using DSF) are processed.

Let us first observe that formulated products are frequently highly organized systems, made of many parts but with no regular organization (contrary to crystals, e.g.). This organization influences bioactivity: for example, the transfer of some hydrophilic compound C in a gelatin gel, where diffusion of C molecules can occur, is very different from the transfer of the same compound in a plant tissue, where the molecules would be enclosed in cells [43]. As crystallographic descriptions apply only for

periodical organization, they cannot be used for the description of man-made systems, which are non-periodic in space, or even irregular.

In order to give a formal description of formulated products, DSF considers "objects" and "operators", after the definition of a "reference size" (*rs*), as an order of magnitudes of considered objects (the same kind of description can be made at any order of magnitude for sizes) [44]. For example, if the diameter of a plate is chosen as *rs* (~3×10^{-1} m), then only the various food items of diameter (defined as the largest dimension) between *rs*/5 and 5 *rs* should be considered, all objects of different diameters being excluded from the description.

"Objects" can be of various "physical dimensions": D_0, D_1, D_2, and D_3. Here, D_0 stands for objects of physical dimension equal to 0 ("dots"), i.e., objects whose size in the three directions of space is more than one order of magnitude lower than *rs*; D_1 stands for "lines" (with only one dimension of the same order of magnitude as *rs*), D_2 for surfaces (with two dimensions of the same order of magnitude as *rs*), D_3 for volumes (all dimensions of the same order of magnitude as *rs*). If necessary, D_x objects could be considered, *x* being non-integer, and these objects then being fractals [45].

If necessary, the *rs* can be explicitly added in brackets at the end of the formula (units should of course be in International System of Units). For example, $D_1[10^{-5}]$ would indicate a linear structure whose length is of the order of magnitude of 10^{-5} m (and, accordingly, whose radius is more than one order of magnitude lower).

The organization of a system at a particular scale is then described from the various parts D_k ($k \in \{1,2,3\}$) with some spatial relationships between these parts described using operators: the operator "/" represents random dispersion; the operator "×" represents intermixing of two continuous phases; the operator "+" represents coexistence of phases; the operator "@" represents inclusion; geometrical operators such as "σ_x", "σ_y", "σ_z" represent respectively superposition in the directions *x*, *y*, and *z* (but any particular direction could be given by the Cartesian coordinates of a vector, such as in (*u*, *v*, *w*), or even other coordinates systems such as {*r*, θ, φ} for spherical organization). Other operators may be added when needed.

Using this formalism, only topology is considered, and the geometrical shape of formulated products is not described: a square has the same "formula" as a disk. This topological description can be increased with an indication of the nature of the phases of the various parts, added between parentheses. Indeed, many formulated products such as food, paints, cosmetics, or drugs, are colloids [46]: they are made of many parts, each composed of many phases that physical chemists name "water" (aqueous solutions), "oil" (lipids in a liquid state), gas, solids. Their properties are in particular due to the organization of the molecules in these phases, and of the organization among the phases. More precisely, IUPAC decided that the word "colloid" applies to material systems that contain molecules or molecular associations in which one dimension is of the order of 1 nm to 1 μm, or to systems that include discontinuities with distances of this order of magnitude [47]. It is not necessary that all dimensions be of this order of magnitude: fibers have only two dimensions of this order, and thin films only one. It is not necessary either that the units of a colloidal system be separated: structures with subunits of colloidal dimensions (porous solids, gels, and foams) are also considered as colloidal. Such systems are frequent in food [48], in particular because plant and animal tissues, made of cells whose smallest dimension is of the order of 1 μm, are colloids according to IUPAC definition: cell aggregation in tissues makes formally non-connected gels, contrary to gelatin gels, which are connected gels, water forming a continuous phase in the continuous solid phase due to collagen molecular associations by triple helixes. Emulsions are also frequent in the kitchen (mayonnaise, aioli, wine sauces with butter…) [49].

When complex systems are considered (e.g., multiple emulsions), physics generally focuses on the interface [50], i.e., local descriptions of macroscopic systems, or on some thermodynamic properties. However, this has two main disadvantages. First, the global description of the systems is lost. Then, in more complex—but familiar—systems, such as potato tissue or ice cream, the denominations are rather complex. Potatoes, for example, are mainly "suspensions dispersed in gels", as amyloplasts (solid

starch granules having a radius lower than 20 μm), are dispersed in the cytoplasm of cells (water or gel, depending on the description level), this phase being itself dispersed in the network of cell walls responsible for the "solid" behavior of the whole potato [51,52]. Ice cream is another example of a complex food system that should be called "multiple suspension/foam/emulsion", as gas (air) bubbles, ice crystals, protein aggregates, sucrose crystals, fat (either crystals or liquid droplets), etc. (depending on the "recipes" and on the process used) are dispersed in an aqueous solution [53]. On the other hand, the names "potato" or "ice cream" are probably not admissible names in physics textbooks because they are imprecise and restricted to a particular food.

This is why DSF was introduced, based on the same idea as the one proposed by Lavoisier for chemistry [54]. In colloids, the phases are gases, solids, or liquids, and in food, liquids are mostly water and mixtures of triacylglycerols. Accordingly, the symbols G, O, W, S, respectively, stand for "gas", "oil", "water", "solid"; of course, other symbols such as E (for ethanol) could be added if necessary (this would be useful in fields other than food).

Adding some rules gives more coherence to the formalism. First, some formula can be simplified. For example, $D_0(G)/D_3(G)$ or $D_1(W)/D_3(W)$ are respectively reduced to $D_3(G)$ or $D_3(W)$. Then, the various components of a sum (operator +) must be written in alphabetical order. For example, custard {which is not an emulsion $D_0(O)/D_3(W)$, contrary to what is frequently published in culinary textbooks [55]} is made of oil droplets O (from milk), air bubbles G (introduced during the initial whipping of sugar and egg yolks) and small solid particles S (due to egg coagulation during thermal processing), and should be described as $[D_0(G) + D_0(O) + D_0(S)]/D_3(W)$. This rule is the key to the uniqueness of formulas associated with physical systems. Repetitions can be described by exponents. For example, egg yolks are made of concentric layers called light and deep yolk, deposited, respectively, during the day and the night; their number is about 9, as shown on ultrasound scan pictures. As each layer is composed of granules (S) dispersed into a plasma (W) [56], the full yolk could be described as $[D_0(S)/D_2(W)]^{@9}$.

The basic formalism can be enhanced to give more precise descriptions of systems. For example, the quantity of each phase can be added as a subscript. For example, $D_0(O)_{200}/D_3(W)_5$ would describe an oil into water emulsion at the limit of failure, with 95 g of oil dispersed in 5 g of water (the oil droplets would have a polyhedral shape) [57]. Using such subscripts, conservation laws can be used. For example, the overall making of a mayonnaise could be written as

$$O_{95} + W_5 - E_W \rightarrow O_{95}/W_5 \tag{11}$$

where E_W stands for mechanical energy.

Finally, it is of course possible to make up longer formulas, adding descriptions at various scales. Until now, all the food systems considered could be described using this formalism, but do all formulas correspond to possible systems? The question is difficult because many disperse systems are only metastable and not thermodynamically stable. In emulsions or in suspensions, for example, creaming and sedimentation rates depend on the size of structures or on the nature of surfactants [50], but these systems are not stable thermodynamically and it is therefore a question of smartness to make most colloidal systems.

APPLICATIONS AND RATIONALIZATION OF STUDIES

How helpful is DSF for studying real biological structures with a high level of complexity? First, the reference to a *rs* is one way to bring some order into the complexity of real systems. Then even when a complex object such as a living cell is considered, the fact that some particular structures are detected with various observational tools demonstrates that the formalism applies. Of course, the description can sometimes be cumbersome, such as for the Golgi apparatus [43], but the use of "random distribution operators" such as "/" is a way to get at least a partial description of such complex systems. Moreover,

the number of operators could be increased when new particular cases are encountered (up to now, even in such complex fields as sauces, only the four operators given above were useful).

Specifically for food and solutions, DSF has value in differentiating the various kinds of gels. This is important because, as said before, plant tissues and animal tissues are gels, as well as gelatin or pectin gels. However, gelatin gels are very different from plant tissues, as their liquid phase is continuous, which is not the case for the liquid phase of plant tissues, where it is localized in the cells (of course, this is an approximation: some continuous liquid phase exists in the vascular tissues); and plant tissues are very different from animal tissues in muscles, as muscle fibers are elongated cells of length up to 20 cm. The formulae for these three different gels are therefore different: $D_3(W) \times D_3(S)$ for gelatin gels; $D_0(W)/D_3(S)$ for plant tissues; $D_1(W)/D_3(S)$ for muscular tissues.

The usefulness of DSF has been shown many times for the description of systems and for inventing new systems, but how is it useful for science, specifically for the study of bioactivity and matrix effects? A good way to use it is first to consider that bioactivity can be considered as phenomena occurring in the F @ M or F σ M. As one should have rational reasons to study particular systems, ranking systems according to the "complexity" of their formula in DSF is a strategy.

Of course, the number of different phases is to be considered first for this ranking, but also the organization of phases within the system. This organization is described by the various operators, which means that a ranking of operators by order of "complexity" is needed. In order to do this, the determination of a free energy can be used, assuming, for example, simply an interface energy γ_{AB} between the phases A and B.

Considering two phases which do not mix at a temperature T such as oil and water, the ratio of free energy (or more precisely free enthalpy) between superposition and inclusion can be calculated simply. Let us assume two material substances A and B (A being less dense than B) with respective volumes V_A and V_B. The surface energy between A and air is neglected, and the two phases have a $c \times c$ contact surface (where c is the length of the edge of A, assuming it has a cubic shape). Then the free enthalpy is equal to $\gamma_{AB}\ {V_A}^{1/3}$. For inclusion, it would be equal to $6\gamma_{AB}\ {V_A}^{2/3}$, showing that the free enthalpy for inclusion is about one order of magnitude higher than for superposition.

To compare the free enthalpy for mixture (intermixing operator ×) and dispersion (operator /), the calculation was made on a network. Let us assume that for the system A × B, the phase A is around the edges of a cubic cell with n elementary cells per side of the total volume. The free enthalpy would then be $4 \cdot \sqrt{3} \cdot \gamma_{AB} n \cdot {V_A}^{1/2} (V_A + V_B)^{1/6}$. For the dispersion, n^3 elementary cubes of A are considered dispersed in B, and the total free enthalpy is $\gamma_{AB} \cdot 6 \cdot n \cdot {V_A}^{2/3}$. Numerical comparison (with γ_{AB} chosen to be 80, n = 100 000, T = 300 K, V_A = 1, V_B = 1) shows that intermixing needs about 1.3 times more free energy than dispersion.

IN SITU QUANTITATIVE NMR

Now, with a means of ranking the various systems by order of "complexity", the question arises: how can the transfers of bc in matrices be followed? Recently, a new analytical method called in situ quantitative NMR (isq NMR) was proposed for this purpose. It is based on the fact that gels enclose a liquid component. This new method was first studied for the analysis of saccharides and amino acids, and organic acids of plant tissues [58,59], and it was compared to the classic method for the determination of the saccharide content of plant tissues devised by Davis, Terry, Chop, and Faul [60] after O'Donoghue, Omerfield, Bendall, Hedderly, Eason, and Sims [61] and others [62,63]. In the "modified O'Donoghue" (MOD) method, plant tissues are lyophilized, heated under reflux in a mixture of methanol and water (62.5:37.5, w:w) for 15 min at 55 °C; after filtration, solvent evaporation and lyophilization, the resulting product is analyzed using various analytical techniques, such as quantitative proton NMR spectroscopy (q ^{1}H NMR) [64,65]. However, analyses done by this MOD method are long, destructive, and need manipulations with toxic solvents. As metabolites from plant tissues, includ-

ing saccharides, are supposed to be dissolved in an aqueous cytosolic environment [66], we wanted to know how much of them could be detected using isq ^{1}H NMR of whole tissues.

Our studies were done using carrot (*Daucus carota* L.) roots, in which the mean water content is about 88 % of fresh weight [67]. In these tissues, as in most plant tissues, the cytoplasm of plant cells is a jellified system [68], where metabolites and ions are in an aqueous, liquid environment that can be described by the DSF formula $D_0(W)/D_3(S)$. Indeed, in the cytoplasm, the cytoskeleton forms a network which includes an aqueous solution of metabolites (cytosol) where organelles are dispersed. Moreover, some free aqueous solution makes up the sap filling the vessels called xylem and phloem; saccharides are dissolved in the elaborated sap [43].

The isq NMR method was compared with extraction followed by quantitative NMR spectroscopy of extracts (q NMR): nontreated samples of plant tissues were introduced in a 5-mm glass NMR tube with enough D_2O for locking (in practice, about 0.05 g). Experiments validated the assumption that plant tissues could be directly studied by the application of liquid q ^{1}H NMR spectroscopy to whole, nontreated tissues, in spite of a large quantity of ordinary (i.e., nondeuterated) water in the tissues. In particular, even if the baseline is sometimes somehow deformed, saccharides can be easily determined in the aqueous environment of cells and of conducting tissues (for the latest results, a 1/1000 precision was obtained). NMR spectra obtained by direct determination have the same general appearance as NMR spectra obtained with solutions of saccharides, including solutions made by the MOD method. Moreover, with both MOD/q ^{1}H NMR and isq ^{1}H NMR methods, a quantification of the major saccharides (glucose, fructose, sucrose) in carrots was possible with minimal mathematical treatment. The main resonance of spectra obtained by both methods was due to water; it is surrounded by resonances of various metabolites, including primarily saccharides and amino acids [59]. As well, saccharides are not the only metabolites that can be quantitatively determined, and in particular many resonances associated with amino acids can also be studied with some mathematical treatment. One difference between the spectra in the two methods was the intensity of the resonances: using isq NMR, resonances are smaller than with the MOD/q ^{1}H NMR method (but still more than 10 times the noise level), because the mass of plant tissue used for the direct determination (0.2 g) is about 50 times less than the mass of fresh tissue used in the MOD/q ^{1}H NMR method (7–10 g). Of course, water resonance is huge with isq NMR, but it does not prevent the determination of the important metabolites. As the characteristic resonance of glucose at a chemical shift of 5.24 ppm was partly covered by the water resonance, the other characteristic resonance at 3.25 ppm was used for the direct determination. Figure 2 shows the general shape of spectra.

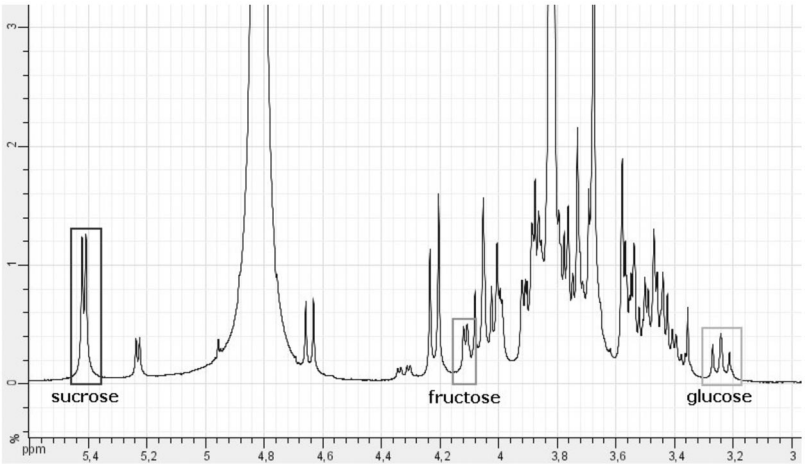

Fig. 2 An isq ^{1}H NMR spectrum for a carrot (*Daucus carota* L.) root sample.

In some spectra obtained by the in situ method, the multiplicity of the sucrose and fructose resonances was not observed and some analyses gave irregular spectra, where the singlet of 3-(trimethylsilyl)propionic-2,2,3,3-d_4 acid, sodium salt (TSP, used as a chemical shift reference, and also for quantitative determination) was split into a doublet. These poor spectra were generally associated with a bad shim that could not be corrected easily. As the shim gives information about the homogeneity of the magnetic field in the analyzed sample, it is an important factor for the quality of the spectra. The solution we found to overcome this irregularity was to partially dry the tissues before analyses. Thus, both the water resonance is minimized and the glucose resonance at 5.24 ppm ($H_{1\alpha}$) is more visible in the spectra (however, the glucose resonance at 3.25 ppm was used for quantification because it gives better results).

In general, the direct determination shows a higher saccharide content than the MOD/q ^{1}H NMR method. However, this trend is statistically significant only for glucose and sucrose (one-way ANOVA test, significance level of 1 %). Of course, the isq NMR method is much faster and easier than the MOD/q ^{1}H NMR method: whereas sample preparation takes 6 days for the MOD method (because of double lyophilization), only a few hours are needed with the isq NMR method. Moreover, methanol is not used in the direct method. Also, the isq NMR method shows less tissue homogeneity (larger standard deviations) than the MOD/q ^{1}H NMR method, probably because the smaller quantity of tissue used allows for distinction between samples, with or without conductive tissues, the latter having a different saccharide content than parenchyma cells.

A CLASSIFICATION OF BIOACTIVITIES CAN BE STUDIED

With a rational way to study bioactivity, and methods for the determination of bc release from colloidal systems, let us now consider theoretically what the matrix effect could be. Indeed, such an effect is due both to structure and to particular chemical details of the binding of bc to molecular details of the matrices. Such interactions can be ranked in order of energy [69]. At the low-energy end of the interaction energy spectrum, van der Waals interactions can limit the autodiffusion coefficient of compounds; this is the case for most solutions. At higher energies, hydrophobic forces or hydrogen bonds can play a role. At even higher energies, we can envision the effect of disulfide bridges, with the ability to rearrange, as in dynamers [70]. At the highest end of the energy scale, covalent and electrostatic bonds are important. One important question is to know whether the matrix effect in complex disperse systems can or cannot be described as a result of elementary interactions between the various phases.

In our group, this question was addressed first by analyzing the processing of "vegetable stocks", i.e., aqueous solutions obtained by thermal processing of plant tissues in water [64]. In spite of extensive use of carrot root stock in homes, restaurants, or in the food industry, very little was known about metabolites found in the stock and their kinetics during the extraction process in water. The release of saccharides from carrot root samples thermally processed in water (stock) was studied for various reasons [71]: identification of stock composition [72,73], loss of vitamins [74], nitrates release in food products [75]. The mechanism of saccharide release was studied. Solutes are present either in phloem sap or in intra- and inter-cellular spaces [76]. Hence, saccharides can be released from any of these compartments.

In one of our studies (before isq NMR was set up), we used q ^{1}H NMR for the direct quantitative determination of saccharides found in carrot stocks prepared at three temperatures: 50, 75, and 100 °C. Using the same protocol as in [64], carrot roots were peeled, and the bottoms and tops were removed. Then the samples were cut into cylinders of a specific size, and heated in demineralized water at a determined temperature. The aqueous solution samples were centrifuged, filtrated, double freeze-dried, and dissolved in D_2O with pH adjustment to 7 (using solutions of DCl). For the spectroscopy, an Ultra Shield Bruker 500 MHz spectrometer was used, at T = 21 °C (± 0.1 °C); 64 scans of 65 K (300 MHz), spectral width 6 kHz, aq 5.3 s, D1 25 s, zg 90°. The main compounds found in carrot stocks are: saccharides, amino acids, and organic acids. Three regions could be identified corresponding to the amino

acid region (0–3 ppm), the saccharide region (3–6 ppm), and the phenolic region (6–10 ppm). Each major metabolite of the different extracts was identified after resonance assignment using ^{1}H NMR spectra from pure compounds associated with comparison of published data [77,78]. Twenty-one metabolites were identified on each spectrum including 3 saccharides, 11 amino acids, 7 organic acids, and other compounds. Experimental details are given in [65].

The thermal processing caused significant enrichment of the water environment in saccharides (Fig. 3). For all three studied saccharides, extraction is less important at 50 °C than at the two other temperatures. As optimal temperature for carrot pectin methyl esterase (PME) activity is in the 40–60 °C range for the pH conditions (between 4.5 and 7) [79], we propose to explain this difference by enzymatic activity: at 50 °C, cell membranes remain intact in spite of some protein denaturation and loss of nutrients occurs mainly due to osmosis [80,81]. Carrot PME activity is responsible for pectin linking through calcium cations, and diffusion through a cell wall is more difficult than diffusion through a cell wall with hydrolyzed pectic material in the high-temperature regime. Alzamora et al. [82] showed that in order to minimize leaching losses of vitamins during water blanching of peas, it is preferable to have a high temperature in "static" water and the biggest peas as possible. On the contrary, to maximize saccharide recovery in a water solution, higher temperatures than 60 °C are to be chosen.

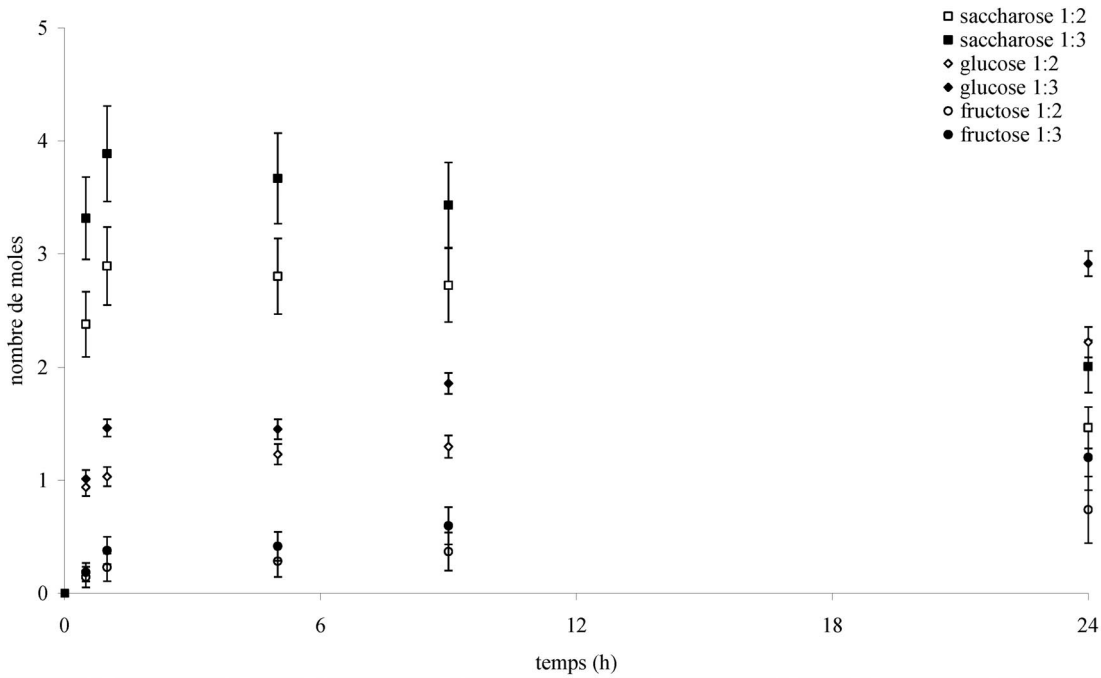

Fig. 3 Time course release of three saccharides (sucrose, glucose, and fructose) detected in carrot stocks for two different experimental set-ups (plant tissue:water, 1:2 and 1:3).

To explain the increase in glucose and fructose concentration at 100 °C associated with a decrease in sucrose at the same temperature, sucrose hydrolysis can be proposed. In theory, this assumption could be checked by correlating the sucrose to the glucose + fructose concentrations. However, Maillard reactions occur with reducing saccharides and amino acids, so glucose and fructose are probably consumed by those reactions at the same time that they are extracted or issued from sucrose hydrolysis.

MODELING SACCHARIDES

The quantitative study of the time course evolution of saccharides concentration in carrot stocks led us to some assumptions about the mechanisms of this evolution. Using a mathematical system, we tried to study the various hypotheses. In Fig. 4, the left rectangle stands for the inside of the plant tissue. Here S, G, F, and HMF represent respectively sucrose, glucose, fructose, and 5-hydroxymethylfurfural; the second letter (c or b) indicates the carrot tissue or the stock.

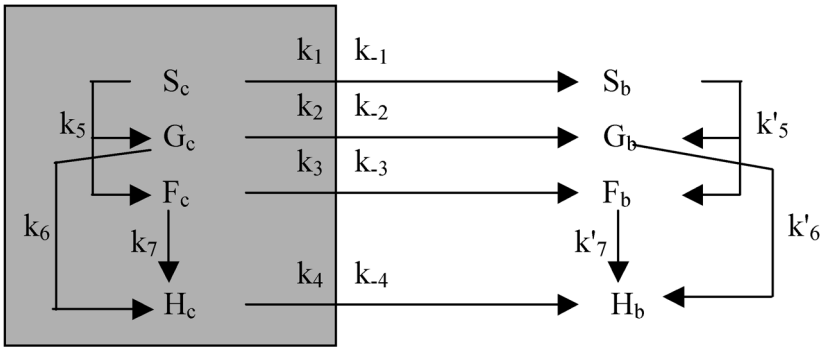

Fig. 4 Model of saccharides during carrot stock making.

Given measured initial conditions, a differential system assuming linearity can lead, with simplifying assumptions, to a solution such as in Fig. 5. Indeed, no difficult calculation is needed to solve such a linear differential system. From the initial equations, sucrose, glucose, and fructose have to decrease in the plant tissue, and to increase in the stock. Sucrose in the stock should, however, decrease because of hydrolysis. Only the exact shapes of the various curves can change.

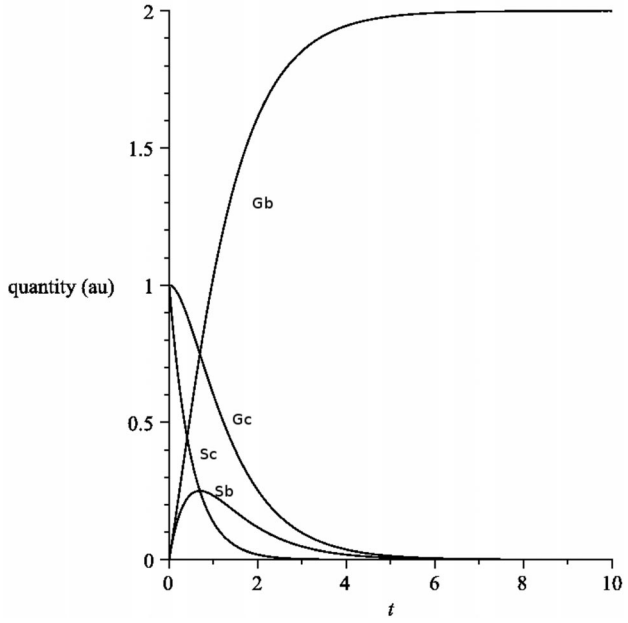

Fig. 5 Modeling saccharide evolution during carrot stock processing.

Also, of course, fitting experimental data with the functions obtained in solving general cases can give constants for transfers and various chemical processes occurring during thermal treatment, but it is unlikely, due to uncertainties in experimental data, that any new scientific result is obtained using this strategy. On the other hand, use of a different model provides other information, for example, where tissues are considered to be made of channels (xylem, phloem) and parenchymous tissues, such as in Fig. 6 (model based on microscopy pictures such as Fig. 7).

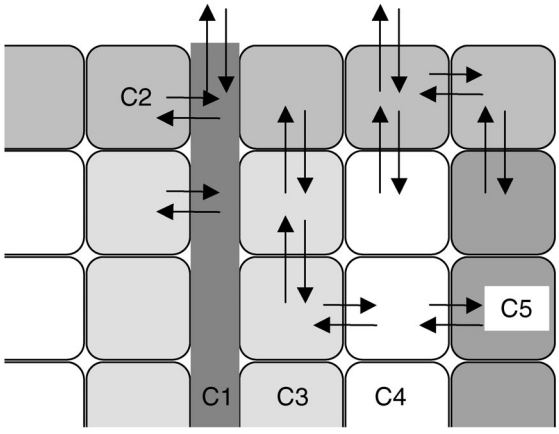

Fig. 6 A model of plant tissues with various compartments allowing for saccharide exchange.

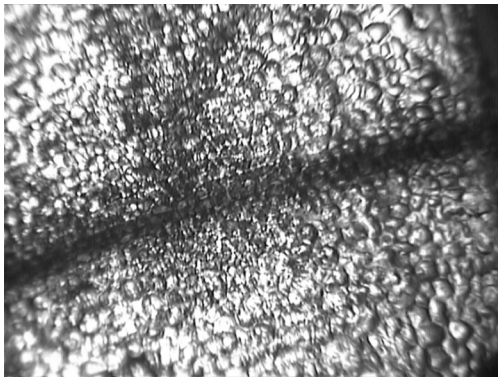

Fig. 7 An onion (*Allium cepa* L.) bulb sample soaked in methylene blue shows some colorant inside channels, and very little colorant inside plant cells.

Such pictures (onion bulb sample soaked in methylene blue, 3,7-bis(dimethylamino)-phenothiazin-5-ium chloride) indicate that saccharides and other solutes can migrate from some aqueous solutions toward the inside of plant tissue. If this phenomenon is molecular diffusion, it could also occur the opposite way, from plant tissues toward an aqueous environment, such as in many culinary processes.

In order to model the extraction of water-soluble compounds from onion bulb tissues in an aqueous environment, these compounds have to be identified, and their concentration has to be estimated in the aqueous solution at different times. The phenomenon of extraction of solutes from plant tissues to the soaking solution was investigated experimentally, and the data were studied analytically for bulbs of onions (*Allium cepa* L.). We considered a larger amount of solutes located either in channels or in

parenchyma cells, in order to explain the time course extraction features. Short and long times of extraction were studied.

Here modeling can give useful indications. First, only two compartments were considered: channels and parenchyma cells. Two main limit profiles for metabolites can be considered: quantity in cells >> quantity in channels, quantity in channels >> quantity in cells. For each case, there are two possibilities: release from cells faster than release from channels, or release from channels faster than release from cells. Another case could be: quantity in cells ~ quantity in channels, with two transfer rates being equal or different (Fig. 8).

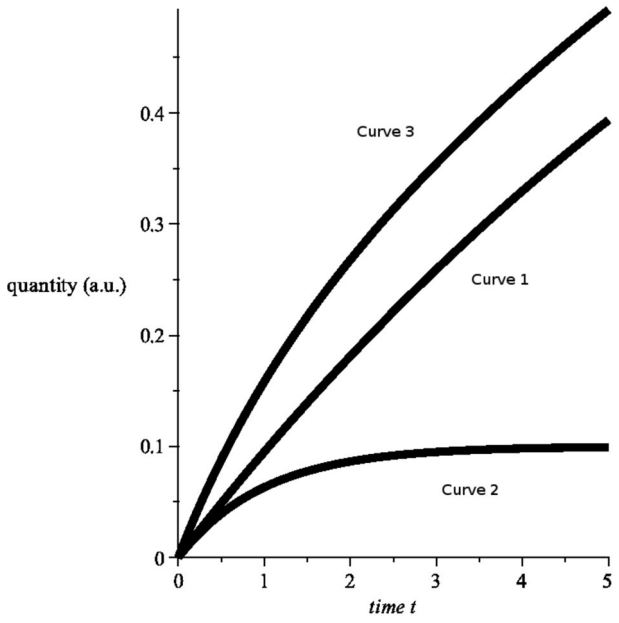

Fig. 8 One particular behavior that can be obtained for the model of Fig. 8 restricted to two compartments ("cells" and "channels"). Curve 1 corresponds to the compartment richest in metabolites; curve 2 to the compartment with the lowest concentration in metabolites; curve 3 to the sum of the two phenomena.

Fitting curves of the dry matter vs. time measured during experiments indicates that about the same quantity of saccharides is extracted from cells and from channels with a large difference in transfer rate (0.048 for the former, 0.876 for the latter, arbitrary units). At this point, we do not know which compartment releases bc the fastest, but if pure molecular diffusion occurs from channels, it is likely that this compartment is responsible for exchanges faster than the other.

NOTE BY NOTE CUISINE

Experiments and modeling show how poor traditional ways of cooking are: a large quantity of saccharides remains in tissues, even after very long thermal processing. This is why a first modernization of culinary activities was first proposed in the 1980s under the name "molecular cuisine" (definition: cooking using new tools, new ingredients, new methods, "new" meaning what was not used in kitchens of the 1980s). More recently, a more radical modernization of culinary activities was proposed under the name "note by note cuisine".

This second proposal has its origin in 1994 [83], but the name "note by note cuisine" was given only in 1999, during a lecture [84]. The idea of this new way of cooking is to "constitute" entire dishes

from pure compounds. The principle of this new cuisine is the same as for synthesizers in music, by which one can in principle produce any possible sound. In cuisine, the choice and particular use of well-chosen compounds can create virtually any food. Of course, all aspects of dishes have to be designed and made: the general organization of the parts, the particular shape, consistency, color, brilliancy, odor, and taste of the various parts, not forgetting nutrition!

One could think that note by note dishes would be more difficult to make than just cooking plant or animal tissues, but the same comment was made about music three or four decades ago (it was said that it would be very difficult, if not impossible, to build the notes wave by wave) and it did not prevent synthesizer music from developing quickly, because modern composers and musicians succeeded in finding their own, new shortcuts. Building dishes note by note is difficult when one works from pure compounds, but why not adopt the same approach taken for music? Why not use mixtures of compounds, such as music did with waves? After all, this is how perfumes are created, from the various extracts of the flavoring industry (concretes, essences, supercritic dioxyde extracts...).

Of course, this proposal raises many issues. Technically, first, chefs will have to consider how to select and then assemble compounds into dishes. As food is primarily made from water and many organic compounds are poorly soluble in water, emulsification and gel-making are obviously very important processes for food in the future, in particular in note by note cuisine. More generally, all dispersion techniques will be useful.

During this assembly, the various biological properties of food will have to be considered. Of course, the nutritional content is important, but it would be a mistake to forget that food has to stimulate the various sensory receptors: vision, odor, taste, trigeminal system, temperature... Many questions now arise. For example, while we know how to determine the light absorption spectrum of a mixture of compounds in a mixture, even if we know the individual absorption spectrum of each compound, we cannot predict the "color" of the resulting mixture. Also, when odorant compounds are mixed in proportions near the perception threshold, unpredictable odors are obtained. Worse still, when only two odorant compounds are mixed, is the result a "chord" or a fusion?

With respect to tastes, the question is even more serious, because on the whole their receptors and their substrate are not known, and it was only less than 10 years ago that it was discovered that the tongue also includes receptors for fatty acids with long unsaturated chains [85]. This means that there are still other important discoveries to be made! In the meantime, one can use citric, malic, tartaric, acetic, ascorbic, or lactic acids... Or saccharides such as glucose, fructose, lactose, etc., and not only the old familiar sucrose. For trigeminal effects, some "fresh" or "pungent" compounds are known, such as eugenol (in cloves), menthol (one of its enantiomers only), capsaicin (for chilli), piperine (for pepper), ethanol, sodium bicarbonate... and many others.

From the consistency point of view, again technological work can be done, because making colloidal materials has not been studied enough. Making simple emulsions is sometimes considered difficult, but more generally one should not consider that texturization of formulated products is a solved issue, even if we now have surimi and analogous systems. Who will succeed in creating a food with the consistency of a green apple? Or a pear? Or a strawberry? Not only is the question of laboratory prototypes not solved, but also the question of mass production has not been considered (and this is why fruit companies providing products for the yogurt industry are so upset).

As a whole, much remains to be done, a lot of questions have to be studied by science and by technology. Let us finish this paragraph with an important observation: it would be uninteresting to "reproduce" already existing food ingredients. As synthesizers can make the sounds of a piano or violin, note by note cuisine could obviously reproduce wines, carrots, meats..., but why? Except for astronauts travelling for a long time, it is probably useless to make what already exists, and it is much more exciting to investigate flavors and dishes which were never envisioned using traditional food ingredients.

A simple calculation shows the immensity of the world to be discovered. If we assume that the number of traditional food ingredients is about 1000 and if we assume that a traditional recipe uses 10

food ingredients, the number of possibilities is 1000 to the power 10, or 10 to the power 30. However, if we assume that the number of compounds present in food ingredients is about 1000, and if we assume that the number of compounds that will be used in note by note cuisine is of the order of 100, then the number of possibilities is about 10 to the power 3000... And, in this calculation we did not consider that the concentration of each compound can be adjusted, which indeed means that a whole new flavor continent can be discovered. Why reproduce our small world, then?

However, producing note by note dishes has proven difficult up to now; the cooks who tried were unfamiliar with the vocabulary building blocks and so were unable to create sentences with meaning. It is difficult, but not impossible, and I have guided Pierre Gagnaire (with restaurants in Paris, London, Tokyo, Dubai, Hong Kong, Moscow, Courchevel, Berlin, Las Vegas, and Seoul) so that he would be the first cook in the history of cooking to produce a fully note by note dish: after many months of work with technology help, he presented a note by note dish during a special dinner in Hong Kong on 24 April 2009.

Fig. 9 This "note by note" dish was served on 15 April 2012 during a demonstration at the Institut de Tourisme et d'Hôtellerie du Québec (ITHQ, Montreal, Canada). It was prepared by chef Ismael Osorio with the help of the scientist Erik Ayala-Bribiesca, from fish proteins and fractions of cucumber, plus some definite compounds.

Then, during the summer of 2010, the Alsatian cooks Hubert Maetz (Rosheim, France) and Aline Kuentz (Strasbourg, France) created note by note dishes that they demonstrated during the JSPS meeting (French-German-Japanese alumni), in Strasbourg. Later, in October 2010, the professors of the Cordon Bleu School, in Paris, made a complete note by note meal for a group of 20 participants in the Hautes Etudes du Goût (Advanced Studies in Gastronomy) program. In January 2011, the day before the official launching of the International Year of Chemistry, Jean-Pierre Biffi and his team of the catering company Potel & Chabot made a note by note meal for more than 100 people, and more recently, in May 2011, the same meal was served in Paris to all chefs that had won a Michelin star.

On each occasion, the cooks sought out compounds that they did not know, and they learned to use them to make remarkable dishes with new flavors. Of course, it is difficult to explain the flavor of these dishes: how do you explain the color blue to someone who cannot see? Then there is the question of naming these dishes; the world of perfumes provided an answer: Chanel no. 5, etc. (Fig. 9). For all those who are afraid of losing the stew, cassoulet, or choucroute named in their honor, as is the case in the art world, there is no replacement, but only addition, more freedom, more choice. Debussy did not make Mozart or Bach disappear; Picasso or Buffet did not stop us from admiring the works of Rembrandt or Brueghel. And molecular cuisine did not kill nouvelle cuisine or traditional cuisine. In the same way, note by note cuisine will be an artistic addition.

How much will note by note cuisine cost? Will it be more expensive than current cooking? Here the energy issue has to be considered because the next increase in the cost of energy will perhaps be the key to the success of note by note cuisine. Today, in order to "reduce" wine or bouillon when making

a sauce, cooks evaporate water primarily (losing many odorant compounds to steam evaporation). If we assume a reduction such as professionals do (e.g., by 2/3), a simple calculation shows that the energy consumed is 0.417 kWh, which means 0.05 euros per sauce.

More generally, the question of energy has not been considered by traditional cuisine. Traditionally, meat is heated to more than 200 °C in order to produce compounds, the same compounds that note by note cuisine can get directly and mass-produced compounds could be made at a much lower cost (roasting 10 chickens in the same oven does not cost more than roasting one, which means that the cost per chicken drops).

On the other hand, it will not be necessary to synthesize the compounds used by cooks. Frequently, they will be extracted, from plant material, such as chlorophylls today. Chemists fully recognize that hundreds of chemist-years were necessary to synthesize vitamin B12, so that agriculture and extraction remain the most efficient, particularly and in the absence of an efficient method. Note by note cuisine can then use either synthesized products or extracted products, no matter where they come from...

The first tests of note by note cuisine inescapably created fear, based on the bizarre notion that we would be eating "chemicals". Here, as for genetically modified organisms, for example, political ideas are confusedly mixed up with other matters under discussion. How would farmers survive when, although most unlikely, all food would become note by note? These questions are more than chemists can answer, but they call for the following answer: as some people become rich by making wine rather than selling grapes, farmers could become richer than they are today if they were to produce fractions of plants, instead of selling the raw materials.

Finally, having considered some questions about note by note cuisine, the scientific question remains. This is not new in the history of chemistry, which has many times grown out of the "chemical arts". A new opportunity is now here.

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